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A support vector machine based pharmacodynamic prediction model for searching active fraction and ingredients of herbal medicine: Naodesheng prescription as an example

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ABSTRACT

The complex chemical composition of herbal medicine leads to the lack of appropriate method for identifying active compounds and optimizing the formulation of herbal medicine. One of the most commonly used method is bioassay-guided fractionation. However, if the herbal medicine was divided into many fractions, it would cost much money and time in carrying out such a full bioassay. So, can we just perform the bioassay of a few fractions, and then develop a method to predict the bioactivities of other fractions? This study is designed to try to answer the question.

In this work, a support vector machine (SVM) pharmacodynamic prediction model was introduced to search active fraction and ingredients of Naodesheng prescription. The prescription was first divided into five extracts, yielding a total of $2^5 = 32$ combinations. Anti-platelet aggregation experiment with SD rats was just carried out on 16 combinations. The effects of the remained $32 - 16 = 16$ combinations were then predicted by the SVM model. The prediction quality was evaluated by both the rigorous jackknife test and the independent dataset validation test. Furthermore, the present method was compared with the frequently used MLR, PCR and PLSR.

The present method outperforms the other 3 methods, yielding: RMSECV = 2.40, $R = 0.895$ by the jackknife test and RMSEP = 7.41, $R = 0.910$ by the independent dataset test. It indicates that the SVM prediction model has good accuracy and generalization ability. The active fraction and ingredients of Naodesheng prescription were then predicted by the model. It is believed that the present model can be extended to help search the active fraction and ingredients of other herbal medicines.

1. Introduction

In recent years, herbal medicine has been successfully applied in clinical for prevention and treatment of various illnesses, especially in East Asian countries such as China, Japan and Korea [1]. In China, almost half of the commercial drugs are botanical drugs, which are developed from herbal medicines and widely applied in the treatment of various chronic diseases including cardiovascular disease and cancer. Unlike modern drugs in the form of a single active chemical ingredient, herbal medicine is usually prepared from aqueous extracts of a few herbs and contains hundreds of chemical compounds [2]. Some constituents are useless or even toxic and should be eliminated. Thus, discovering active compounds is of help to ensure the safety and availability of herbal medicine. However, the complex chemical composition of herbal medicine leads to the lack of appropriate method for identifying active compounds and optimizing the formulation.

One of the most commonly used method is bioassay-guided fractionation, which has gained definite success in discovering novel biologically active structures [3]. In this process, herb medicine was first extracted by various solvents, and separated into many fractions (single extracts or their combinations). Then, bioassay of each fraction was performed to determine which of them should be subjected to further separation step. Through the circle of separation and bioactivity assay, some active compounds ('leads') may be discovered. However, for example, if a herbal medicine was extracted by five kinds of solvents, the number of total fractions would be $2^5 = 32$. As a result, it would cost much money and time

Abbreviations: DAD, diode array detector; HPLC, high performance liquid chromatography; MAR, macroporous absorbent resin; MLR, multiple linear regression; PCR, principle component regression; PLSR, partial least square regression; PRP, platelet-rich plasma; *R*, correlation coefficient; RMSECV, root mean square error of cross validation; RMSEP, root mean square error of prediction; SVM, support vector machine; TCM, traditional Chinese medicine.

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in carrying out such a full bioassay. So, can we just perform the bioassay of a few fractions, and then develop a method to predict the bioactivities of other fractions? This study is designed to try to answer the question.

In this paper, support vector machine (SVM), first proposed by Cortes and Vapnik [4], was used as the prediction engine. Compared with other machine learning systems, the SVM has many attractive features, including the absence of local minima, its speed and scalability and its ability to condense information contained in the training set. In the past decade, the SVM has performed well in diverse research fields [5,6]. A sample traditional Chinese medicine (TCM) prescription, called Naodesheng, was processed in this paper. The prescription consists of Sanchi (*Panax notoginseng*), Chuanxiong (*Rhizoma Ligustici chuanxiong*), Safflower (*Flos Carthami*), Kudzu Root (*Radix Puerariae*) and stoned Hawkthorn (*Crataegus pinnatifida* Bge.), and has functions of promoting blood flow to dissipate stasis, dredging channel meridians and waking up brain. In order to demonstrate the validity and superiority of the present SVM model, both the rigorous jackknife test and independent dataset test were performed. The frequently used models including multiple linear regression (MLR), principle component regression (PCR) and partial least square regression (PLSR) were compared.

2. Materials and methods

2.1. Animals and chemicals

Adult male SD rats weighing 180–200 g were purchased from Experimental Animal Center of Guangdong Province, PRC (Certificate no. 2007A003), and were housed in a controlled room with a 12 h light–dark cycle and temperature of 25 ± 2 °C. The medical materials of Sanchi, Chuanxiong, Safflower, Kudzu Root and Hawkthorn were all purchased from Zhi-xin Medical Materials Company of Guangzhou City, and authenticated by Professor Shuyuan Li from Guangdong Pharmaceutical University. Aspirin was purchased from Lu-wang Pharmaceutical Co. Ltd of Jilin Province (Batch no. H22025784). Chromatographic grade acetonitrile was purchased from Fisher Scientific Inc., and all other chemicals and solvents were of analytical grade.

2.2. Preparation of extracts

According to the formulation of Naodesheng, the medical materials of 7.8 g Sanchi, 7.8 g Chuanxiong, 9.1 g Safflower, 26.1 g Kudzu Root and 15.7 g Hawkthorn were smashed into crude powder, and then divided into two parts for further extraction step. The powder of Safflower was denoted as Part II, and the others were denoted as Part I. Part I was extracted twice with 70% ethanol, purified with macroporous absorbent resin (MAR), and then divided into three parts: (a) 0% and 10% ethanol elution wash, (b) 70% ethanol elution wash, and (c) 95% ethanol elution wash. Part II was extracted twice with distilled water, purified with MAR, and also divided into three parts: (d) 0% ethanol elution wash, (e) 30% ethanol elution wash, and (f) 95% ethanol elution wash. Part (a) and (d) were then combined, and consequently the original prescription was divided into five extracts: A(a + d), B(c), C(b), D(e) and E(f). The whole fractionation process can be graphed in Fig. 1. Based on L12(2^5) orthogonal table [7], 12 combinations of extracts were formed (see Table 1). The extracts were dried up by evaporation in a water bath, and dissolved by appropriate amount of saline water. The yielded solution contained 33.25 g medical materials per liter.

2.3. HPLC analysis

HPLC analysis of the extracts were carried out on a Waters (2695) LC apparatus with a diode array detector (DAD) using a Hyspersil ODS-2 reverse phase analytical column (250 mm × 4.6 mm, particle size 5 μm). Extract (10 μL) was separated at 30 °C at a flow rate of 1 mL/min using the following gradient of aqueous phosphoric acid (0.05%) (A) and acetonitrile (B): 0–5 min: 5–10% B; 5–60 min: 10–20% B; 60–80 min: 20–40% B; 80–120 min: 40–60% B; 120–150 min: 60–5% B. The detection wavelength is 203 nm. This procedure was repeated in triplicate.

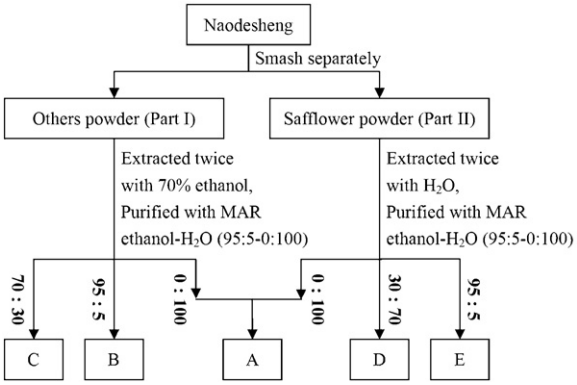

Fig. 1. Flowchart of the fractionation process.

2.4. Animal treatment

The animals were randomly divided into eighteen experimental groups (8 rats per group): (1) a negative control group receiving normal saline (10 mL/kg, group 12 in Table 1); (2) a positive control group receiving aspirin (0.4 g/kg); and (3) sixteen extracts combination groups (1.01 g/kg, groups 1–11 and five single extracts). The animals were administered by gavage once a day, and continuously for 5 days.

2.5. Platelet aggregation assay

2.5.1. Platelet preparation

Adult male SD rats were anaesthetized with 10% chloralhydrate (300 mg/kg) 60 min after the last administration. The blood was removed from the common carotid under an anti-coagulant solution containing citric acid 130 mM, trisodium citrate 170 mM and dextrose 4%. The blood was centrifuged at 160 × *g* for 10 min at room temperature. The resulting platelet-rich plasma (PRP) was then centrifuged at 2200 × *g* for 10 min to obtain the platelet pellets. After washing, platelets were resuspended in a buffer solution at pH 7.4 (NaCl 137 mM, KCl 2.6 mM, $MgCl_2$ 0.9 mM, glucose 5.5 mM, gelatin 0.25%, Hepes 5 mM, $CaCl_2$ 1.3 mM) to adjust the platelet concentration to 5×10^5 cells/mm^3. The protocol was approved by the Ethic Committee of Guangdong Pharmaceutical University.

Table 1
L12(2^5) table designed by orthogonal principle.

Group	Numbers	Subscripts	Characters
1	11111	$A_1B_1C_1D_1E_1$	ABCDE
2	11122	$A_1B_1C_1D_2E_2$	ABC
3	11222	$A_1B_1C_2D_2E_2$	AB
4	12112	$A_1B_2C_1D_1E_2$	ACD
5	12211	$A_1B_2C_2D_1E_1$	ADE
6	12221	$A_1B_2C_2D_2E_1$	AE
7	21121	$A_2B_1C_1D_2E_1$	BCE
8	21212	$A_2B_1C_2D_1E_2$	BD
9	21211	$A_2B_1C_2D_1E_1$	BDE
10	22112	$A_2B_2C_1D_1E_2$	CD
11	22121	$A_2B_2C_1D_2E_1$	CE
12	22222	$A_2B_2C_2D_2E_2$	–

Table 2
Origination of 13 representative peaks.

Peak no.	Origination	Retention time (mean ± SEM) (min)
7	Kudzu Root	17.40 ± 0.21
8	Kudzu Root	18.06 ± 0.16
10	Safflower	19.75 ± 0.29
11	Hawkthorn	20.37 ± 0.37
13	Kudzu Root	25.26 ± 0.42
14	Kudzu Root	25.96 ± 0.19
15	Chuanxiong	27.67 ± 0.20
16	Kudzu Root	28.56 ± 0.33
33	Sanchi	65.32 ± 0.48
34	Sanchi	68.03 ± 0.52
36	Sanchi	78.47 ± 0.34
40	Chuanxiong	90.35 ± 0.29
42	Chuanxiong	92.30 ± 0.44

2.5.2. Platelet aggregation

Platelet aggregation was performed at 37 °C and 1000 rpm using an aggregometer. Washed platelets (250 μL) were stimulated with ADP (10 μL) as the aggregating agent at a final concentration of 5.6 μg/L. Platelet aggregation was recorded during 5 min after platelet stimulation.

The percentage of platelet aggregation inhibition by the extracts was calculated by the following formula [8]: $[(X-Y)/X] \times 100$. X is the maximum aggregation of the negative control group; Y is the maximum aggregation of the extracts combination group.

2.6. Statistical analysis

Data were reported as a mean value ± SEM (standard error of the mean). The difference between the groups was assessed by using Student's t-test and the values of $P < 0.05$ were considered to be statistically significant.

3. Results and discussion

3.1. Assessment of the validity of the HPLC method

After a careful comparison, 48 well-separated peaks were chosen, among which 13 representative peaks have definite origination as illustrated in Table 2. As an example, the chromatogram of the ABCDE combination was illustrated in Fig. 2. In order to assess the validity of the HPLC method, the ABCDE combination was used as the sample solution. Method precision was based on six-replicated analysis of samples, with reported relative standard deviations

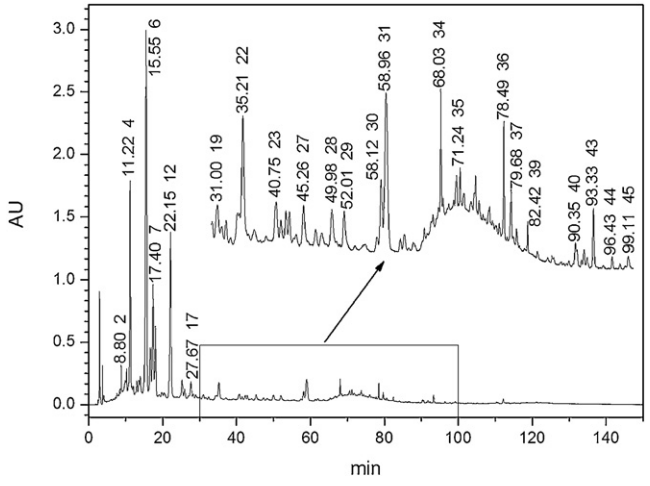

Fig. 2. Chromatogram of the ABCDE combination.

Table 3
Effect of the extracts against platelet aggregation (mean ± SEM).

Group	Dose (g/kg)	Inhibition (%)
Negative, saline	–	–
Positive, aspirin	0.4	23.45 ± 0.22*
ABCDE	1.01	22.85 ± 0.27*
ABC	1.01	21.02 ± 0.21*
AB	1.01	9.51 ± 0.33
ACD	1.01	22.77 ± 0.19*
ADE	1.01	16.47 ± 0.29
AE	1.01	8.87 ± 0.23
BCE	1.01	19.18 ± 0.23*
BD	1.01	10.51 ± 0.28
BDE	1.01	12.78 ± 0.19
CD	1.01	22.48 ± 0.23*
CE	1.01	20.32 ± 0.28*
A	1.01	8.42 ± 0.26
B	1.01	3.68 ± 0.17
C	1.01	19.35 ± 0.21*
D	1.01	10.89 ± 0.24
E	1.01	3.34 ± 0.28

* $P < 0.05$ compared with negative control.

(RSDs) of less than 1.12 and 2.94% for relative retention and peak area of all peaks, respectively. The method reproducibility was studied through six-replicated sample solutions extracted from a single batch of Naodesheng prescription. The corresponding RSDs of relative retention and peak area were reported less than 1.16 and 1.54%. The stability test was performed with a sample solution over 24 h of standing period. The RSDs of the relative retention and peak area were found less than 1.15 and 2.52%, respectively. The results indicated that the developed method was validated and applicable for sample analysis.

3.2. Classes of the 48 constituents

Some related work has revealed that the major effective constituents in the 5 medical materials of Naodesheng prescription belong to polysaccharide, saponins and flavonoids [9–11]. Others such as hydroxysafflor yellow A and ferulic acid are also reported [12]. It has been found that some of them have specific effects against platelet aggregation [13]. According to the preparation of extracts (combination) and the retention mechanism on reverse phase chromatographic column, these 48 constituents may in turn correspond to the compounds of polysaccharide, saponins, and flavonoids.

3.3. Anti-platelet aggregation effect of the extracts

Compared to negative control group, significant difference ($^*P < 0.05$) was observed for seven combination groups and positive control group in Table 3, indicating that these eight groups have anti-platelet aggregation effect.

3.4. Pharmacodynamic prediction model

In Table 3, the 11 extracts combination groups were taken as the training set, and the 5 single extracts groups were as the validation set. The areas of 48 peaks were used as the inputs of the SVM, and the expected outputs were the average anti-platelet aggregation effects. Note that before inputting the values to the SVM, they all are subjected to the following conversion:

$$x(i) = \frac{x_0(i) - \mathrm{Min}(x_0)}{\mathrm{Max}(x_0) - \mathrm{Min}(x_0)}$$

where $x_0(i)$ is the original value of $x(i)$, and the operators of Max/Min mean taking the largest/smallest one among the vector of x_0, respectively. So, each value is in the range of 0 and 1. The pub-

Table 4
Comparison with other popular methods.

Method	Training set		Validation set	
	RMSECV[a]	R^2[b]	RMSEP[a]	R
MLR	3.46	0.798	5.50	0.719
PCR[c]	3.28	0.866	3.97	0.912
PLSR[c]	3.29	0.838	5.02	0.916
SVM[d]	2.40	0.895	7.41	0.910

[a] RMSECV, root mean square error of cross validation; RMSEP, root mean square error of prediction. They both are defined as: $\sqrt{\sum(x^{\text{predicted}} - x^{\text{observed}})^2/N}$, where $x^{\text{predicted}}$, x^{observed} and N denote the predicted value, the experimental value and the sample size, respectively.
[b] Correlation coefficient.
[c] The number of principle components was optimized by resulting the small errors. In PCR it is set at 3 and in PLSR it is 2.
[d] The kernel parameter $\gamma = 2^{-5}$, and the regularization parameter $C = 1$.

licly available LIBSVM software [14] was used to process the SVM computation with the radial basis function as the kernel.

A rigorous jackknife test, also known as leave-one-out-cross-validation (LOOCV) test, was carried out on the training set, and an independent dataset test was performed on the validation set. For demonstrating the priority of the current method, a further comparison with the frequently used models, such as multiple linear regression (MLR), principle component regression (PCR) and partial least square regression (PLSR), was carried out. The detailed results were listed in Table 4, including the root mean square errors and the correlation coefficients. As is well known, better methods often yield lower errors and higher correlation coefficients. From Table 4, it can be easily found that the performance is SVM > PCR > PLSR > MLR. As for our method, frankly speaking, the RMSEP value being equal to 7.41 is a bit higher, whereas the R value of 0.910 is much better. In addition, the lowest RMSECV of 2.40 and the highest R value of 0.895 on the training set were obtained by our method. Therefore, we can conclude that the present SVM model has well grasped the hidden relationship between the peak areas and the pharmacodynamic effects, and can be utilized to predict the pharmacodynamic effects of other combinations.

Table 5
Predicted effects of different extracts combinations.

Combination scheme	Predicted effect
ABC	22.2
CE	21.77
ABCDE	21.08
CD	20.41
BCE	20.26
ACD	20.06
CDE	17.45
C	17.45
BCDE	17.45
BCD	17.45
BC	17.45
ACE	17.45
ACDE	17.45
AC	17.45
ABCD	17.45
ABD	16.26
ABDE	16.19
AD	15.96
ABE	15.79
A	15.29
DE	14.72
D	14.71
E	14.41
BD	13.44
BE	13.03
B	13.00
AE	12.49
BDE	12.45
AB	11.95
BD	11.69
ADE	11.59

Table 6
Values of the weight vector for the 48 peaks.

Peak no.	Value
27	2.30
12	2.26
46	2.14
43	2.06
30	2.03
7	1.99
36	1.96
37	1.96
41	1.88
22	1.84
35	1.82
44	1.80
13	1.80
10	1.73
8	1.70
14	1.70
15	1.69
23	1.60
33	1.59
25	1.59
9	1.58
16	1.56
17	1.54
19	1.50
39	1.48
34	1.46
29	1.44
6	1.40
28	1.32
5	1.31
21	1.25
38	1.23
20	1.20
24	1.17
11	1.14
31	1.07
3	0.95
18	0.88
2	0.85
4	0.83
26	0.72
1	0.60
32	0.32
40	−0.26
47	−0.88
42	−1.36
45	−1.63
48	−2.02

3.5. Active fraction and ingredients of Naodesheng

The above reported results indicate that the present SVM model has a good accuracy, and can be used to predict the pharmacodynamic effects of other combinations once their peak areas were provided. As for the current five single extracts, the number of full combinations is $2^5 = 32$. Except the 11 combinations in the training set, the 5 single extracts (combination) in the validation set and the one combination in the negative control group, the remained $(32 - 11 - 5 - 1 = 15)$ combinations were determined by HPLC to obtain the peak areas information. Due to the space limitation, all the detailed peak areas were provided in the supplementary materials. When the peak areas were input to our SVM model, the pharmacodynamic effects can be predicted. The detailed results were listed in Table 5, with the predicted effects in descending order. The active fraction of Naodesheng prescrip-

tion must be among the combinations with top 10% or 15% effects (noting that the combination with maximal effect is not always the active fraction due to variance of animals test). Subsequently, the experimental confirmation can be made in such a narrowed range, and of course lots of cost and time can be saved.

Furthermore, we are always interested in identifying the active compounds. Cheng et al. reported some pioneering work and introduced computational methods for discovering active compounds of the herbal medicines [15,16]. In this paper, the SVM model can also be applied to searching the active ingredients of Naodesheng prescription. The weight vector is $w^* = \sum_{i=1}^{l} y_i \alpha_i^* x_i = (w_1^*, \ldots, w_n^*)$ in the decision function $f(x) = sgn(w \cdot x_i + b)$ of the SVM, which can indicate the correlation level of each dimension regarding to the specific classification criteria [17]. Therefore, the bigger weight vectors the peaks have, the more the corresponding ingredients correlate with the effect of anti-platelet aggregation. From Table 6 one can see that Peaks 27, 12, 46, 43 and 30 (top 10%) have the biggest weight vectors, and to a greater extent correspond to the active ingredients.

4. Conclusion

In this paper, a SVM model was constructed for pharmacodynamic prediction of Naodesheng prescription. Its accuracy was evaluated by both the rigorous jackknife test and the independent dataset validation test. The much lower errors and much higher correlation coefficients indicate that the present SVM model has well grasped the relationship between the peak areas and the pharmacodynamic effects. Although the active fraction and ingredients must be confirmed by pharmacodynamic experiments, the confirmation can be made in a much more narrowed range. Therefore, the present model may be of great use to be extended to help search active fraction and ingredients of other TCM prescriptions in their re-developments based on active compounds, and save lots of cost and time in performing pharmacodynamic experiments.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jpba.2011.05.010.

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