Statistical Models of Plant Functions in Jamu Medicines

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NAIST-IS-DD0961210

Doctoral Dissertation

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August 8, 2012

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A Doctoral Dissertation

submitted to the Graduate School of Information Science,

Nara Institute of Science and Technology

in partial fulfillment of the requirements for the degree of

Doctor of Science.

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Farit Mochamad Afendi

Abstract

This study is intended to develop statistical models of plants utilization in Jamu medicines. Exploration using Biplot reveals many plants are rarely utilized while some plants are highly utilized toward specific efficacy. Furthermore, I modeled the ingredients of Jamu formulas using Partial Least Squares Discriminant Analysis (PLS-DA) in order to predict their efficacy. The plants used in each Jamu medicine served as the predictors, whereas the efficacy of each Jamu provided the responses. This model produces 71.6% of correct classification in predicting efficacy. Permutation test then is used to determine plants serve as main ingredients in Jamu formula by evaluating the significance of the PLS-DA coefficients. By performing 1,000 permutation processes I found 231 plants are significant and many of them are supported by scientific papers. Next, in order to explain the role of plants serve as main ingredients in Jamu medicines, information of pharmacological activity of the plants is added to the predictor's block. Then N-PLS-DA model, multiway version of PLS-DA, is utilized to handle the three-dimensional array of the predictor's block. The resulting N-PLS-DA model reveals that the effect of some activities are specific for certain efficacy and the other activities are diverse toward many efficacies.

Keywords: Jamu, efficacy, Biplot, outlier, RobustPCA, PLS-DA, Permutation test, N-PLS-DA

[1]Doctoral Dissertation. Department of Bioinformatics and Genomics, Graduate School of Information Science, Nara Institute of Science and Technology, NAIST-IS-DD0961210

Acknowledgements

In the name of Allah, the Most Gracious and the Most Merciful. Alhamdulillah, all praises to Allah for the strengths and His blessing in completing this dissertation.

Special appreciation goes to my supervisor, **Professor Shigehiko Kanaya**, for his supervision and constant support. His invaluable help of constructive comments and suggestions throughout the analysis and dissertation works have contributed to the success of this research.

I would like to thank to **Associate Professor Md. Altaf-Ul-Amin** for all his valuable comments, suggestions, and reviewing my papers and this dissertation. I also would like to thank to **Professor Naotake Ogasawara** and **Professor Kotaro Minato** for their support and knowledge regarding this topic and reviewing this dissertation.

I thank my fellow labmates in **Computational Systems Biology Laboratory** for the stimulating discussions, and for all the fun we have had in the last three years. In particular, I am grateful to **Mrs. Aki Morita** for her support in developing **KNApSAcK Jamu Database** and also for taking care most of my administration matters. To those who indirectly contributed in this research, your kindness means a lot to me. Thank you very much.

Last but not the least, I would like to thank my family: **my parents and my parents in law**, for giving birth to me at the first place and supporting me spiritually throughout my life. And, my special thank to my wife: **Euis Siti Aisyah** for her endless love, prayers, encouragement, and understanding during my doctorate works.

July 2012

Afendi Farit Mochamad

List of abbreviations

AUC	Area Under Curve
CPCA	Classical Principal Component Analysis
DMB	Disorders of mood and behavior
DOA	Disorders of appetite
Eq-E	Equal prior - Empirical distribution
Eq-N	Equal prior - Normal distribution
FPR	False Positive Rate
FML	Female reproductive organ problems
GST	Gastrointestinal disorders
MCD	Minimum Covariance Determinant
MD	Mahalanobis Distance
MSC	Musculoskeletal and connective tissue disorders
NA-DFC	The National Agency of Drug and Food Control
N-PLS	Multiway Partial Least Square (here, N refers to the dimension of predictor's block which can be 3 or larger)
N-PLS-DA	Multiway Partial Least Square Discriminat Analysis (here, N refers to the dimension of predictor's block which can be 3 or larger)
PCA	Principal Component Analysis
PIN	Pain and inflammation
PLS	Partial Least Square
PLSR	Partial Least Square Regression
PLS-DA	Partial Least Square Discriminant Analysis
PP	Projection Pursuit

PRESS	Prediction Error Sum of Square
Pr-E	Proportional prior - Empirical distribution
Pr-N	Proportional prior - Normal distribution
RD	Robust Distance
ROBPCA	Robust Principal Component Analysis
ROC	Receiver operating characteristic
RSP	Respiratory diseases
SVD	Singular Value Decomposition
URI	Urinary-related problems
WND	Wounds and skin infection

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Chapter 1

Introduction

1.1 Background

Jamu is the common name for Indonesian herbal medicines; each Jamu is prepared from a single plants or mixture of several plants. In making Jamu, however, not all parts of the plant are used. Ginger (*Zingiber officinale*) for example, only its rhizome is used. Another example is Tamarind (*Tamarindus indica*) whose fruit is only used. Other plants might be utilized for their leaf, flower, seed, bark, timber, etc. However, in order to simplify notation, I will use the term plants to refer plants as ingredients in Jamu medicines regardless of the part of the plants that is used in making Jamu.

Besides being useful in curing diseases, Jamu remedies help for health maintenance and are used for cosmetic purposes (Beers, 2001; Pramono, 2007). To prepare Jamu, several plants are selected and mixed such that the concoction has the desired efficacy. Traditionally, plants are chosen using previous experiences, which is passed down from generation to generation, and the efficacies of Jamu medicines have been empirically demonstrated (Adnyana & Soemardji, 2007; Pramono, 2007). In curing a particular dis-

ease, each ethnic group in Indonesia may have its own formulas, whose specific nature depends strongly on the local plant resources in the region where a given population lives (Adnyana & Soemardji, 2007; Sangat et al., 2000).

Nowadays, many Jamu remedies are produced commercially on an industrial scale in Indonesia. Although individual producers have their own Jamu formula, it is clear that the efficacy is determined by the composition of the plants used (Pramono, 2007). Thus, it may be helpful to model the ingredients of Jamu, i.e. the constituent plants, and use this model to predict efficacy.

Among the ingredients of Jamu formulas are plants used as main ingredients, which contribute primarily to the medicines' efficacies; other plants are used as supporting ingredients (Pramono, 2007). Investigating which plants are main ingredients and which are supporting is important in order to comprehensively understand the mechanisms by which specific plants achieve desired efficacies. A statistical model can be helpful in this regard, by relating plants utilization in Jamu as the predictors and Jamu efficacies as the response. Plants serve as main ingredients will have significant effects on the resulting model.

1.2 Objectives

The objectives of this research are developing a statistical model that captures a systematic utilization of plants in Jamu medicines to achieve desired efficacies. It is expected that, once developed, we can use the model to predict the efficacy of Jamu medicine given the information of the ingredients, i.e. the plants used. In addition, we can also use the model to determine plants perform as main ingredients in Jamu formula by testing the plant's

significance in the resulting model, that is, plants serve as main ingredients will have significant effects on the resulting model. Next, the roles of the plants serve as main ingredients will be explored further so that the mechanisms of Jamu medicines to achieve desired efficacy can be described.

1.3 Dissertation outline

This dissertation is organized as follows. In Chapter 2, relationship between Indonesian herbal plants and the efficacy of Jamu is explored using Biplot, a multivariate exploration tool that provides a plot of plants and Jamu efficacy simultaneously.

Chapter 3 describes the efficacy prediction of Jamu formulations by Partial Least Square (PLS) modeling. In this model, the plants used in each Jamu medicine served as the predictors, whereas the efficacy of each Jamu provided the responses.

Chapter 4 is devoted to determine plants serve as main ingredients in Jamu formula by evaluating the significance of the regression coefficient of PLS model obtained in Chapter 3. Permutation test is proposed for evaluation of significance due to the absence of parametric testing on the coefficient of PLS model. Chapter 4 also proposes the simplification of Jamu formula by utilizing only plants serve as main ingredients.

Chapter 5 explores the degree distribution of Jamu formulation network, i.e. bipartite connection between Jamu and plants. The exploration involving the Jamu out-degree and plant in-degree properties of Jamu formulation network.

Next, in order to explain the role of plants serve as main ingredients in Jamu medicines, information of the reported pharmacological activity of the plants is added to the predictor's block, which can be represented

by three-dimensional array, indexed by Jamu, plants, and pharmacological activity. To handle this three-dimensional array of predictor's block, the N-PLS model, an extension of PLS model to deal with multidimensional data, is utilized and the details are discussed in Chapter 6.

Finally, Chapter 7 gives concluding remarks of this dissertation.

Chapter 2

Relationship between Plants and Jamu Efficacy

In this chapter, the relationship between plants and Jamu efficacy is explored. Note that, one plant may be used in many Jamu with varying efficacies. Hence, it is interesting to find out the most significant effects of specific plants by analyzing their usage in Jamu, and considering that the more useful a given plant in having certain effect, the more frequently the plant will be used in Jamu when that effect is desired. Biplot, a multivariate exploration tool, is suitable for this purpose because it provides a plot of observations and variables simultaneously (Gabriel, 1971). Considering plants as observations and efficacy groups as variables, the relationship between them can be explored using a biplot.

2.1 KNApSAcK Jamu Database

In Indonesia, all commercial Jamu must be registered at The National Agency of Drug and Food Control (NA-DFC) in order to have its ingre-

dients inspected and evaluated regarding safety for use in humans. In their website (http://www.pom.go.id/nonpublic/obattradisional/default.asp), this agency provides information about all registered Jamu, along with their ingredients. This information provided the main source of data for this analysis. However, NA-DFC did not provide information regarding the efficacy of registered Jamu. This information were obtained from other sources mainly from the producers.

As of February 2010, 6,533 Jamu produced by local industries in Indonesia were registered at NA-DFC. Among them, 1,223 Jamu are redundant i.e. one Jamu formula from one industry with more than one registration number due to multiple forms of packaging (pills, capsules, powder, volume in one pack, etc). Furthermore, among the remaining 5,310 Jamu, only 3,138 Jamu could be evaluated for their efficacy. These 3,138 Jamu were used for our analysis. In total, these 3,138 Jamu are using 465 plants. To simplify and to obtain more meaningful results, the efficacies of Jamu was classified into 9 groups (see Table 2.1). According to this classification, most Jamu are useful for relieving gastrointestinal disorders, musculoskeletal and connective tissue disorders, and female reproductive organ problems. All data used for this analysis can be accessed at http://kanaya.naist.jp/Jamu/top.jsp integrated in the KNApSAcK database.

Fig. 2.1 depicted the illustration of the usage of KNApSAcK Jamu Database. It starts from KNApSAcK Family Database (Fig. 2.1A), that can be accessed at http://kanaya.naist.jp/KNApSAcK_Family/, by clicking the Jamu icon provided at the KNApSAcK Family Database page to get the KNApSAcK Jamu Database page, which featured in a new window (Fig. 2.1B). Finding Jamu formula in this database can be done either by clicking the 'Herb list', to find Jamu formula based on the herb utilized in

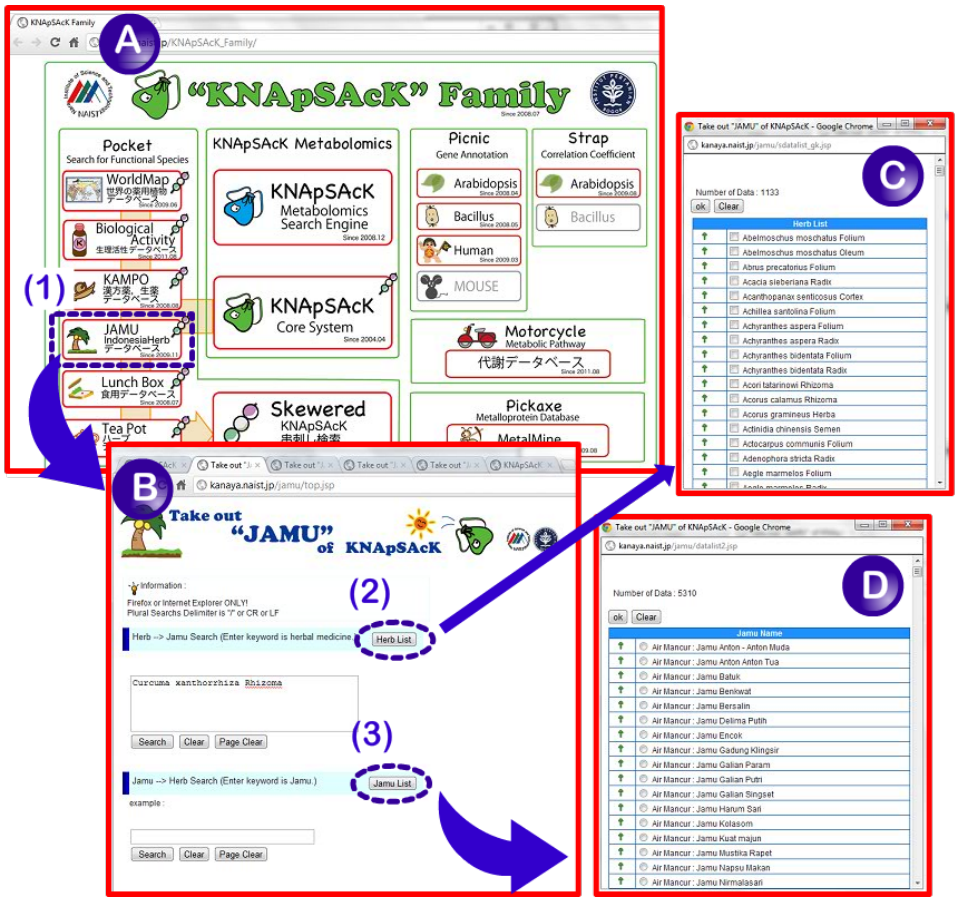


Figure 2.1. *Accessing KNApSAcK Jamu Database. (A) Main window for the KNApSAcK family. Users can access the Jamu Database by clicking the Jamu icon (1). (B) Jamu medicine database. List of medicinal plants (C) and formulae (D) can be obtained from Jamu medicine database by clicking the Herb List (2) and Jamu List (3), respectively.*

the formula, or by clicking the 'Jamu list', to find the Jamu formula based on the name of the Jamu product. In KNApSAcK Jamu Database, we provide 1,133 herbs (Fig. 2.1C) and 5,310 Jamu product (Fig. 2.1D).

In Fig. 2.1B, I provide illustration of finding Jamu formula that utilized the rhizome of Javanese Turmeric (*Curcuma xanthorriza*). The result of this finding is depicted in Fig. 2.2A. It is recorded that 1,474 Jamu medicines are using this plant in their formula. We can click one of these Jamu to obtain

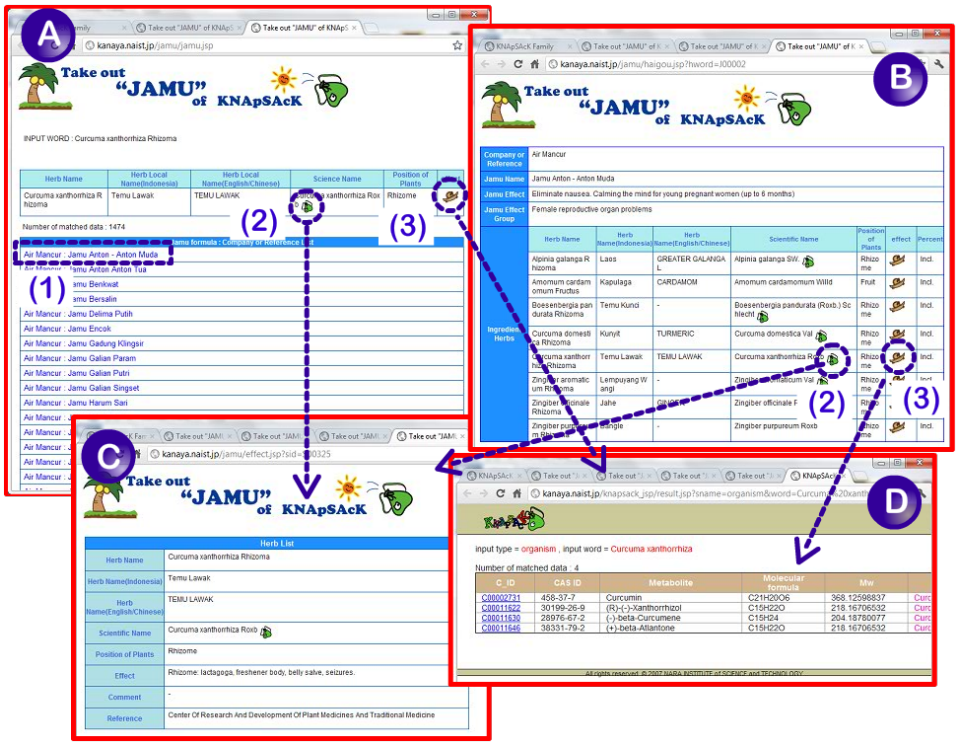


Figure 2.2. *Illustration of accessing information provided by KNApSAcK Jamu Database. (A) List of Jamu medicines utilized Curcuma xanthorrhiza. User can obtain further information for specific Jamu medicine (B) by clicking the name of the Jamu (1). Further information for the medicinal plants (C) as well as plants' metabolite (D) can be obtained by clicking plant button (2) and metabolite button (3), respectively.*

a complete list of plants utilized in the formula as well as other information such as the efficacy of the Jamu. Fig. 2.2B provides illustration for 'Jamu Anton - Anton Muda' produced by Air Mancur company. The KNApSAcK Jamu database also provide the effect of plant which can be accessed by clicking the green icon near the name of the plant. Illustration for the effect of *Curcuma xanthorriza* is depicted in Fig. 2.2C. In addition, the secondary metabolite reported for the plant also can be accessed via this database. See Fig. 2.2D for the illustration of the secondary metabolite recorded for *Curcuma xanthorriza*.

Table 2.1. *Distribution of Jamu and plant utilized in Jamu for each efficacy*

Efficacy	Number of Jamu	Number of plants utilized in Jamu formulas
Urinary-related problems (URI)	72	80
Disorders of appetite (DOA)	249	148
Disorders of mood and behavior (DMB)	22	47
Gastrointestinal disorders (GST)	980	290
Female reproductive organ problems (FML)	398	182
Musculoskeletal and connective tissue disorders (MSC)	840	270
Pain and inflammation (PIN)	311	183
Respiratory diseases (RSP)	107	105
Wounds and skin infection (WND)	159	120

Table 2.2. *Illustration of data structure relating efficacy-plant obtained from network in Figure 2.3*

Plant	Efficacy			
	E_1	E_2	...	E_9
P_1	1	0	...	2
P_2	0	1	...	1
P_3	1	0	...	0
P_4	1	1	...	0
...	...	...	...	...
P_J	0	1	...	1

2.2 Data set for Biplot analysis

The data structure used in Biplot analysis are as follows. Each Jamu is classified into one efficacy group. In accordance with its ingredients, each Jamu is then assigned to plants it contains. For example, Jamu M_1 whose efficacy is grouped into E_1 use plants P_1, P_3, and P_4. If we draw this relation into a network, as can be seen in Fig. 2.3, node E_1 is connected with M_1 which then is connected with P_1, P_3, and P_4. The other relations, for example Jamu M_2 with efficacy E_9 use P_1 and P_2 in its formula, can be drawn similarly. In the Fig. 2.3, I is equal to number of Jamu ($I = 3,138$) whereas J is the number of plants ($J = 465$).

By utilizing this network, relationship between efficacy and plants can be obtained. If we ignore other nodes not shown in the network, Plant P_1 is used by 2 Jamu (M_2 and M_I) and both Jamu have efficacy E_9. Tracing the other relations, we can summarize as illustrated in Table 2.2. Thus, applying this idea to our data, we will generate a data matrix $\mathbf{M}$ with 465 rows and 9 columns, and each cell m_{ij} contains the number of Jamu with efficacy j and use plant i.

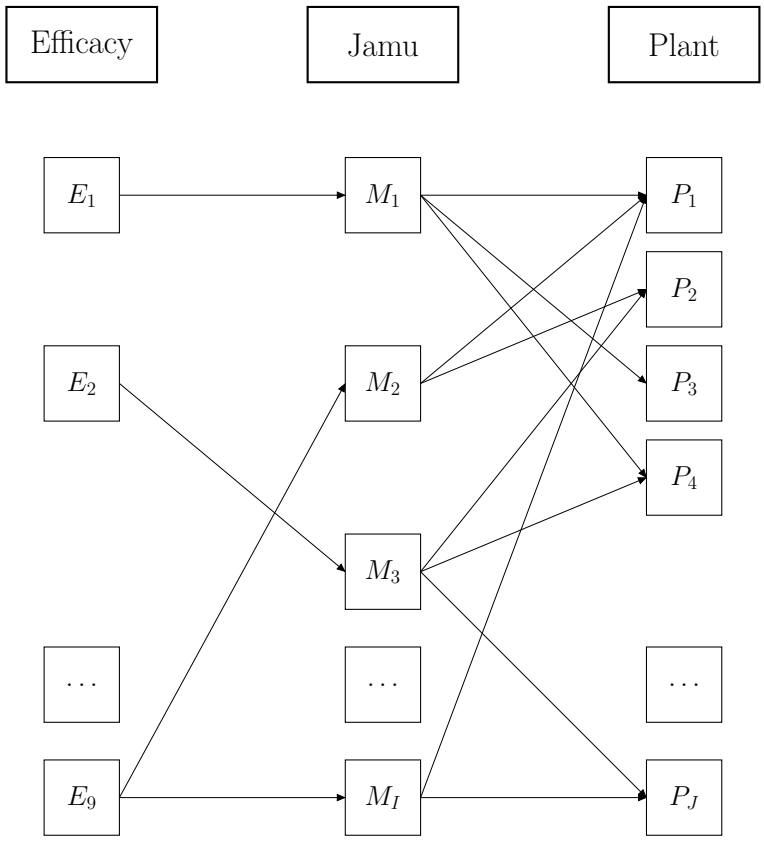


Figure 2.3. *Illustration of network connecting efficacy-jamu-plant. Efficacy-Jamu connection exhibits the efficacy of Jamu medicines. Each Jamu is connected to one efficacy only. On the other hand, Jamu-plant connection represents the plants utilization in Jamu formula.*

2.3 Visualizing Multivariate Data with Biplot

A biplot is an exploration tool in multivariate data analysis that provides a simultaneous plot of observations and variables. Observations are usually represented as points, and variables as vectors. From the plot we can examine relationships among variables, among observations, and the positions of observations relative to variables (Gabriel, 1971).

2.3.1 Classical Biplot

A biplot starts with Singular Value Decomposition (SVD) that decomposes data matrix $\mathbf{M}$ based on its singular values

$$\mathbf{M} = \mathbf{ULA}^t, \tag{2.1}$$

where $\mathbf{U}$ ($\mathbf{A}$) is the orthonormal basis of $\mathbf{MM}^t$ ($\mathbf{M}^t\mathbf{M}$), and $\mathbf{L}$ is the diagonal matrix whose diagonal values are singular values (square root of eigenvalues) of matrix $\mathbf{MM}^t$ or $\mathbf{M}^t\mathbf{M}$ where $r(\mathbf{L}) = r(\mathbf{M}) = r$. Matrix $\mathbf{U}$ ($\mathbf{A}$) can also be regarded as basis for the observation (variable) space of $\mathbf{M}$, respectively. In creating the plot, we take

$$\mathbf{M} = \mathbf{UL}^\theta\mathbf{L}^{1-\theta}\mathbf{A}^t. \tag{2.2}$$

Usually $\theta = 0.5$ to give equal weight between plot of observations and variables. By taking

$$\mathbf{G} = \mathbf{UL}^\theta \text{ and } \mathbf{H} = \mathbf{AL}^{1-\theta} \tag{2.3}$$

we obtain

$$\mathbf{M} = \mathbf{GH}^t. \tag{2.4}$$

$\mathbf{G}$ ($\mathbf{H}$) contains information about coordinate values of observations (variables). The biplot is then obtained by taking 2 columns of $\mathbf{G}$ and 2 corresponding columns of $\mathbf{H}$. Usually the first two columns, which correspond to the first two largest singular values, are chosen.

On the other hand, conducting Principal Component Analysis (PCA) on $\mathbf{M}$ proceeds as follows. If we work with the covariance matrix $\mathbf{\Sigma}$ of $\mathbf{M}$,

the principal component of $\mathbf{M}$ can be obtained by

$$\mathbf{P} = \mathbf{MV}, \tag{2.5}$$

where $\mathbf{P}$ is a matrix of score components, and $\mathbf{V}$ is a matrix of eigenvectors of $\mathbf{\Sigma}$. From this, we can obtain $\mathbf{M}$ from $\mathbf{P}$ by

$$\mathbf{M} = \mathbf{PV}^t. \tag{2.6}$$

If on SVD of $\mathbf{M}$ we start by centering the variables, then $\mathbf{V} = \mathbf{A}$ and $\mathbf{P} = \mathbf{UL}$.

2.3.2 Robust Biplot based on ROBPCA

It is well known that mean and variance of variables are highly affected by outliers. If an outlier occurs, the mean and variance no longer represent the center and variability of the data. Many attempts have been proposed for dealing with outliers such as excluding them from the analysis; or, if we still want to retain all observations, we give less weight on outlier so that the effect of outliers is reduced.

The previous section connects SVD and Classical PCA (CPCA). Because CPCA is based on covariance, it is affected by outliers. CPCA will yield unreliable results because the first components will be attracted by outliers and will not capture variations of regular observations. Subsequently, SVD and its biplot configuration are also unreliable if outliers are present.

One of the solutions for dealing with outliers in PCA is to replace the classical covariance matrix by a robust one, e.g. by using the Minimum Covariance Determinant (MCD) method (Rousseeuw & Driessen, 1999). In essence, this method tries to find a subset of h observations from the whole

data set n whose covariance matrix has the smallest determinant. However, this method can be applied only for small-to medium dimensions because if $h < q$ (q denotes number of variables), the covariance matrix of any subset h has a zero determinant.

Another solution for robust PCA is concerned with obtaining robust estimates of eigenvectors and eigenvalues without replacing the covariance matrix with the robust one. This method is based on Projection Pursuit (PP) as developed in previous studies (Croux & Ruiz-Gazen, 2005; Li & Chen, 1985). This method can be applied to datasets with many variables and/or many observations.

Hubert et al. (Hubert & Engelen, 2004; Hubert et al., 2005) proposed the Robust PCA (ROBPCA) approach which combines the advantages of both approaches. The principle of PP is used in initial dimension reduction, and then the MCD estimator is applied to this lower-dimensional data space. The four major steps in ROBPCA are as follows.

1. SVD is performed on the data to project all observations onto space spanned by n observations.

2. A measure of 'outlyingness' is computed for every point. This is obtained by projecting all the observations on many univariate directions through two data points. At most 250 random directions are taken in this step. For every direction, a robust center and scale of the projected data point is computed. Next, the standardized distance of each observation to the center is measured. For each data point the largest distance, which is called 'outlyingness', is considered. The h points with smallest outlyingness are then retained.

3. Based on the empirical covariance matrix Σ_1 of this h-subset, the

number of principal components to retain, k, is selected.

4. In this stage, the data points are projected onto the k-dimensional subspace spanned by the k largest eigenvectors of Σ_1. Then their center and covariance matrix are computed by means of a reweighted MCD estimator. The eigenvectors of this scatter matrix then determine the robust principal components.

Let $\tilde{\mathbf{P}}$, $\tilde{\mathbf{L}}$, and $\tilde{\mathbf{V}}$ respectively denote a matrix of scores, a diagonal matrix whose entries are singular values, and a matrix of eigenvectors all obtained from ROBPCA. If we take $\theta = 0.5$, then we have the robust version of Eq. (2.3) as follows

$$\tilde{\mathbf{G}} = \tilde{\mathbf{P}}\tilde{\mathbf{L}}^{-0.5} \text{ and } \tilde{\mathbf{H}} = \tilde{\mathbf{A}}\tilde{\mathbf{L}}^{0.5}. \tag{2.7}$$

Taking 2 columns in $\tilde{\mathbf{G}}$ and 2 corresponding columns in $\tilde{\mathbf{H}}$ we obtain a robust biplot based on ROBPCA.

2.3.3 Testing For Outlier in Multivariate Case

In the univariate case, checking for outliers can be performed by computing the distance between each observation x_i to the center of the data $\bar{x}$ which is then scaled in units of standard deviation s as shown below

$$z_i = \frac{x_i - \bar{x}}{s}. \tag{2.8}$$

Assuming that data is normally distributed, an observation x_i is regarded as outlier if $|z_i| > z_{\alpha/2}$ for some significance level α.

For the multivariate case, the analog of computing the distance of observation $\mathbf{x}_i$ to the estimated centroid $\bar{\mathbf{x}}$ takes the form of the Mahalanobis

Distance (MD)

$$d_i = \sqrt{(\mathbf{x}_i - \bar{\mathbf{x}})\mathbf{S}^{-1}(\mathbf{x}_i - \bar{\mathbf{x}})}, \tag{2.9}$$

where $\mathbf{S}$ is the sample covariance matrix. If $\mathbf{X}$ is multivariate normal $(\mu, \mathbf{\Sigma})$ with q variables, then d_i^2 will have a chi-square distribution with degrees of freedom equal to q. Thus, an observation $\mathbf{x}_i$ is regarded as outlier if $d_i^2 > \chi^2_{(q,\alpha/2)}$.

However, it is well known that $\bar{\mathbf{x}}$ and $\mathbf{S}$ are not robust: single extreme observations, or groups of observations, departing from the main data structure will attract $\bar{\mathbf{x}}$ and will inflate $\mathbf{S}$ in its direction. Thus the MDs need to be estimated by a robust procedure in order to provide reliable measures for the recognition of outliers. The MCD estimator is probably most frequently used in practice, partly because a computationally fast algorithm is available (Rousseeuw & Driessen, 1999).

Rousseeuw & Van Zomeren (1990) proposed a Robust Distance (RD) by replacing $\bar{\mathbf{x}}$ and $\mathbf{S}$ with the estimator obtained from MCD, that is, $\bar{\mathbf{x}}_{MCD}$ and $\mathbf{S}_{MCD}$, respectively, as the following

$$d_i^* = \sqrt{(\mathbf{x}_i - \bar{\mathbf{x}}_{MCD})\mathbf{S}_{MCD}^{-1}(\mathbf{x}_i - \bar{\mathbf{x}}_{MCD})}, \tag{2.10}$$

and used these RDs for multivariate outlier detection. The cutoff value for these RDs is $\chi^2_{(q,\alpha/2)}$ (Rousseeuw & Van Zomeren, 1990). However, the cutoff value $\chi^2_{(q,\alpha/2)}$ is based on the asymptotic distribution of the robust distances, and often flags too many observations as outlying (Hubert & Debruyne, 2010). Therefore, Hardin & Rocke (2005) recommended a scaled F-distribution in approximating the true distribution of the robust distances.

Table 2.3. *Distribution of Jamu by number of plant contained in the formula*

Number of plant used in Jamu	Count of Jamu	Percentage
1	454	14.5
2	180	5.7
3	297	9.5
4	487	15.5
5	672	21.4
6	384	12.2
7	208	6.6
8	133	4.2
9	99	3.2
10	75	2.4
> 10	149	4.8
Total	3138	100.0

2.4 Results

Among 3,138 Jamu, 14.5% of them are extracts of one plant only. The other 85.5% use extracts from at least two plants and most of them use 4 to 6 plants in their formula. I also found Jamu that contain more than 10 plants in the ingredients, but they represent less than 5% of the total (Table 2.3). On the other hand, I found 112 plants, almost a quarter of the total 465 plants, are used by only one Jamu; and approximately half of the 465 plants are used by at most 4 Jamu (Table 2.4). In contrast to these plants, whose frequencies of usage in Jamu are very low, approximately one third of plants are used by more than 10 Jamu.

Fig. 2.4 depicts the RD against the plant index. The red line is the cutoff based on F-distribution following Hardin & Rocke (2005). Clearly, this figure exhibits some plants are outliers because their RDs are larger than the cutoff. Thus, the biplot configuration should be created based on the ROBPCA instead of the CPCA.

Table 2.4. *Distribution of plant according to their usage in Jamu formula*

Plant usage in Jamu formula	Count of plant	Percentage
1	112	24.1
2	59	12.7
3	55	11.8
4	24	5.2
5	13	2.8
6	15	3.2
7	15	3.2
8	13	2.8
9	5	1.1
10	3	0.6
> 10	151	32.5
Total	465	100.0

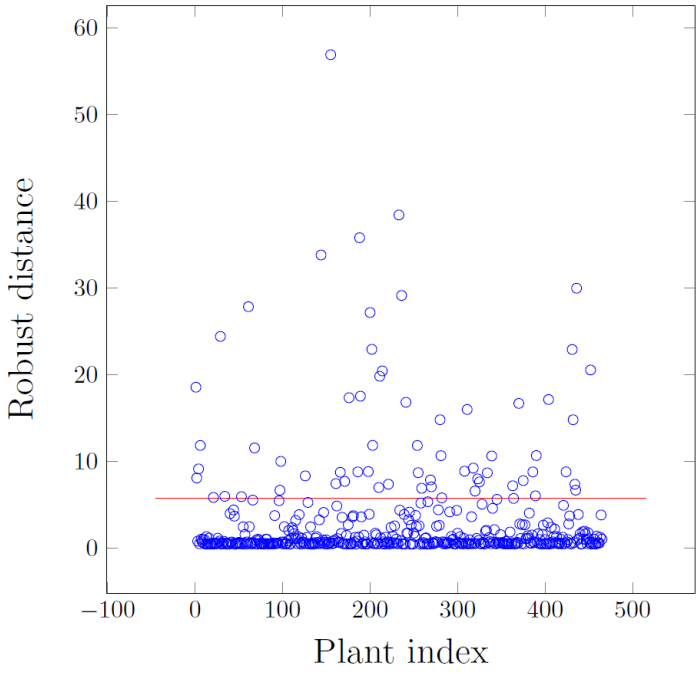


Figure 2.4. *Plot of robust distance versus plant index. The red line is the cutoff for detecting outliers, that is, plants with RD larger than the cutoff are considered as outliers.*

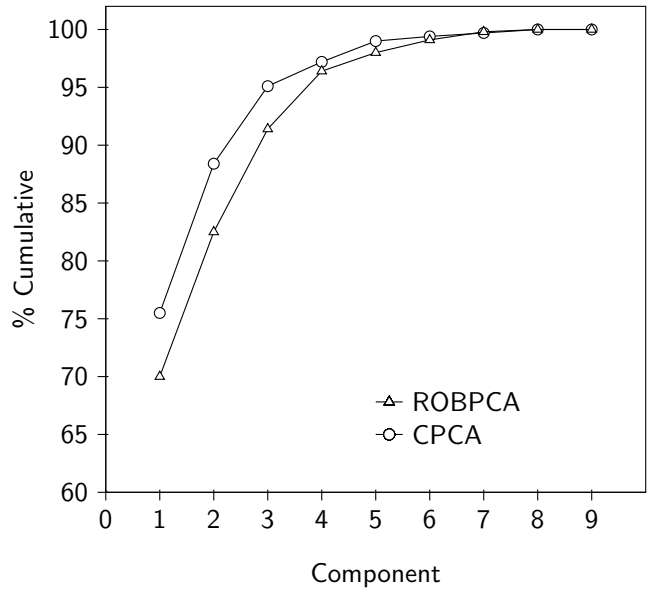


Figure 2.5. *Cumulative percentage of eigenvalue for CPCA and ROBPCA*

Applying CPCA and ROBPCA to the dataset gives us eigenvalues whose cumulative percentage is shown in Fig. 2.5. The differences between eigenvalues obtained from CPCA and ROBPCA for the first 3 components are large, whereas the differences for the next 6 components are negligible. We can conclude that these large differences are due to outliers in the dataset. These outliers will attract the first components in CPCA and make them inflate.

Biplot configuration using the first two components of ROBPCA is shown in Fig. 2.6. In the figure, plants are represented as points while Jamu efficacies as vectors. The length of a given efficacy line showing the variability of plants usage for the corresponding efficacy, that is, the longer the efficacy line the larger the variability of plants usage for that efficacy. From Fig. 2.6, it is obvious that efficacy MSC has the largest variability of plant usage, followed by efficacy GST and FML. On the other hand, efficacy DMB has the

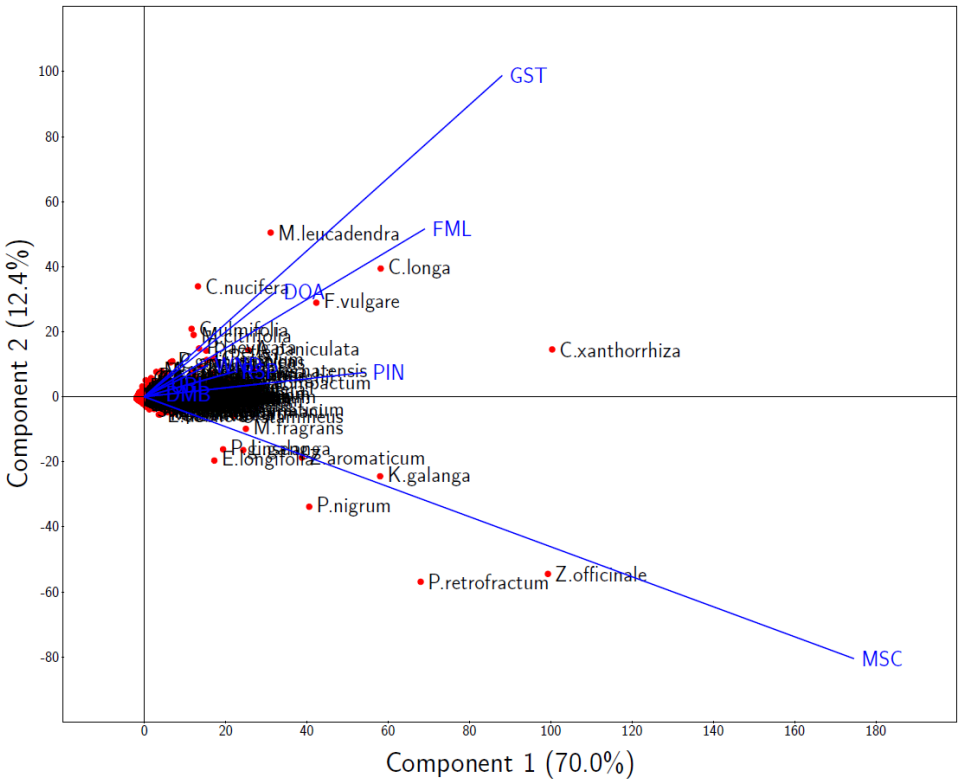


Figure 2.6. *Biplot configuration based on ROBPCA. Plants and Jamu efficacy are represented as points and vectors, respectively.*

smallest variability of plant usage, followed by efficacy URI and RSP. This finding can be addressed due to two factors, that is, the number of Jamu as well as the number of plant utilized in the corresponding efficacy (see Table. 2.1). Efficacies with large variability of plants usage (MSC, GST, and FML) have large values for both factors; in contrast, efficacies with small variability of plants usage (efficacy DMB, URI, and RSP) have small values for both factors.

In the configurations, many plants are clustered in the center. Note that, the projection value of plants' point on a given efficacy line is the prediction of the frequency of plants usage on that efficacy. So, these clustered plants are basically plants whose frequencies of usage in Jamu are very low. In con-

trast to the clustered plants, some plants are spread out and located near the efficacy for which the plants are highly utilized. For example, Ginger (*Zingiber officinale*) is located near the efficacy MSC. Ginger is well known for its function of refreshing body, and for this reason many Jamu use Ginger for efficacy MSC which can easily be identified from biplot configuration. Another example is Turmeric (*Curcuma longa*) which located near the efficacy FML. Due to its analgesic and antimicrobial activity, this plant is well known and highly utilized in Indonesia as ingredient of Jamu formula for women during menstruation, which is a problem that classified into efficacy FML. Thus, the biplot configuration exhibits useful information in exploring the relationship between plants and the efficacy of Jamu.

2.5 Summary

In this chapter, relationship between plants and efficacy of Jamu is explored using Biplot, which provides plot of plants and efficacy of Jamu simultaneously. The biplot is closely related to PCA, where, in this case, plot of plants is analog to plot of score of components and plot of efficacy of Jamu is analog to plot of eigenvectors. Due to outliers on plant-efficacy data, the biplot configuration is created based on Robust PCA method. In the biplot configurations, many plants are clustered in the center, which are basically plants whose frequencies of usage in Jamu are very low. In contrast to the clustered plants, some plants are spread out and located near the efficacy of which the plants are highly utilized. Thus, the biplot configuration exhibits useful information in exploring the relationship between plants and the efficacy of Jamu.

Chapter 3

Modeling Ingredients of Jamu to Predict Efficacy

As explained in the previous chapter, Jamu is prepared from a mixture of several plants. The plants are chosen so that the Jamu has the desired efficacy. As a result, the composition of the plants used in Jamu formula determines the efficacy. Thus, it is interesting to model the ingredients of Jamu, i.e. the constituent plants, and use this model to predict efficacy. Partial Least Squares Discriminant Analysis (PLS-DA), a statistical model for classification and discrimination based on Partial Least Square Regression (PLSR), is suitable for this analysis because a large number of plants are used in Jamu, whereas Jamu efficacies can be grouped into categories or classes. In this method, the plants used in each Jamu medicine served as the predictors, whereas the efficacy of each Jamu provided the responses.

3.1 Data set for PLS-DA model

Fig. 3.1 schematically depicts the relationship between Jamu and efficacy. The data matrix $\mathbf{X}$ in X-block contains plant usage status. The dimension of matrix $\mathbf{X}$ is $(I \times J)$, where I is the number of Jamu (in this case, 3,138), and J is the number of plants (in this case, 465). Because of the availability of information about Jamu products, which are generally not state in detail the mixing ratio of the plants used, then the predictors $\mathbf{X}$ is constructed only in binary data. Each cell x_{ij} is set to 1 if Jamu i uses plant j, and is set to 0 otherwise. In the present study, nine indicator variables, which correspond to the efficacies listed in Table 2.1, perform as the Y-block in PLS-DA modeling. Thus, the dimension of data matrix $\mathbf{Y}$ is $(I \times 9)$. Each cell y_{il} is set to 1 if Jamu i is classified into efficacy group l, and is set to 0 otherwise. Note that $\sum_{l=1}^{9} y_{il} = 1$ because each Jamu is classified to one efficacy only.

3.2 PLS-DA

PLS-DA model is a special case of PLSR in which the response variable has the properties of categories or classes; such models are used for classification and discrimination. The group membership of the response variable is transformed into a dummy matrix, which provides the response block for the PLS-DA model. PLS-DA is superior to PCA for reducing dimensionality with the goal of achieving group separation because PLS-DA is guided by among-groups variability, whereas the PCA is guided only by total variability (Barker & Rayens, 2003). Thus, PLS-DA is suitable for this study: Jamu efficacy, which serves as the response, is categorical; the large number of plants used in Jamu formulas serve as the predictors.

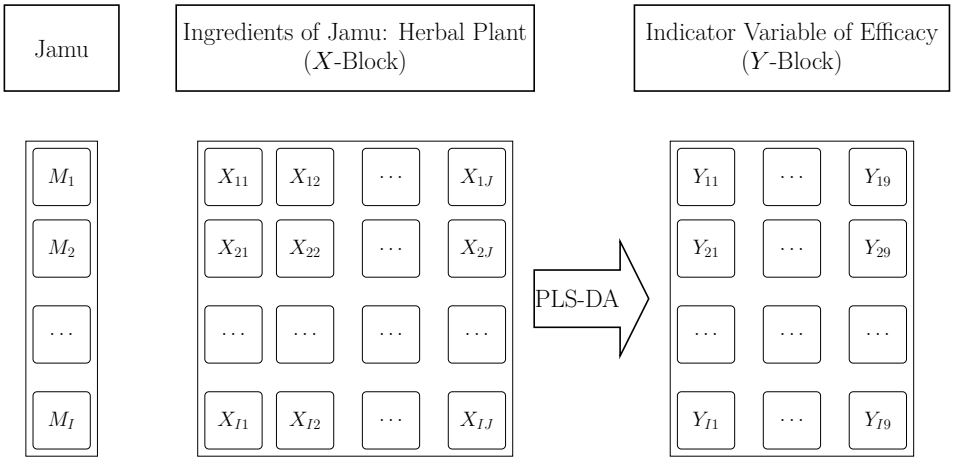


Figure 3.1. *Schematic diagram of the data structure used in the PLS-DA model. Due to the absence of the mixing ratio of the plants used in Jamu, the X-block is constructed only in binary data: each cell x_{ij} is set to 1 if Jamu i uses plant j, and is set to 0 otherwise. The Y-block also is constructed in binary data formed by nine indicator variables correspond to the 9 efficacies: each cell y_{il} is set to 1 if Jamu i is classified into efficacy group l, and is set to 0 otherwise.*

The details of the PLS-DA modeling are as follows (Barker & Rayens, 2003; Wold et al., 2001). It consists of two steps: decomposition and regression step. In decomposition step, both predictors and responses are decomposed into factors such that the factors of predictors have maximum covariance with the corresponding factors of responses. Fig. 3.2 illustrates the decomposition of PLS-DA model. Let $\mathbf{T}$ $(I \times C)$ be a matrix of the underlying factors of $\mathbf{X}$, obtained by maximizing its covariance with the corresponding matrix of the underlying factors of $\mathbf{Y}$:

$$\mathbf{T} = \mathbf{XW} \tag{3.1}$$

where $\mathbf{W}$ $(J \times C)$ is a matrix of weight, and C is the number of factors extracted. Matrix $\mathbf{T}$ thus is a good predictor of $\mathbf{Y}$ and replaced the original

predictors $\mathbf{X}$ during the regression step

$$\mathbf{Y} = \mathbf{T}\mathbf{Q}^t + \mathbf{D} \tag{3.2}$$

where $\mathbf{Q}$ $(9 \times C)$ is a matrix of regression coefficients in terms of $\mathbf{T}$ as the predictor. The Y-residuals $\mathbf{D}$ $(I \times 9)$ express the deviation between the observed and the predicted responses. Substituting Eq. (3.1) into Eq. (3.2), we obtain the multiple regression model of PLS-DA

$$\mathbf{Y} = \mathbf{X}\mathbf{W}\mathbf{Q}^t + \mathbf{D} = \mathbf{X}\mathbf{B} + \mathbf{D} \tag{3.3}$$

where the PLS-DA coefficient matrix $\mathbf{B}$ $(J \times 9)$, the regression coefficients in term of $\mathbf{X}$ as the predictor, is calculated as

$$\mathbf{B} = \mathbf{W}\mathbf{Q}^t \tag{3.4}$$

Note that each plant has a set of coefficient containing 9 values, one for each efficacy.

3.2.1 Selection of the number of components

In PLS-DA, the number of components must initially be determined. In this analysis, the number of components in PLS-DA is determined by a five-fold cross-validation. The steps are as follows.

1. Data is randomly divided into five groups so that each group contains 20% of data, ensuring that each efficacy group is well represented in each of these five groups.

2. One of these five groups is chosen as the testing data, and the other four groups are merged and serve as the training data. Next, PLS-DA

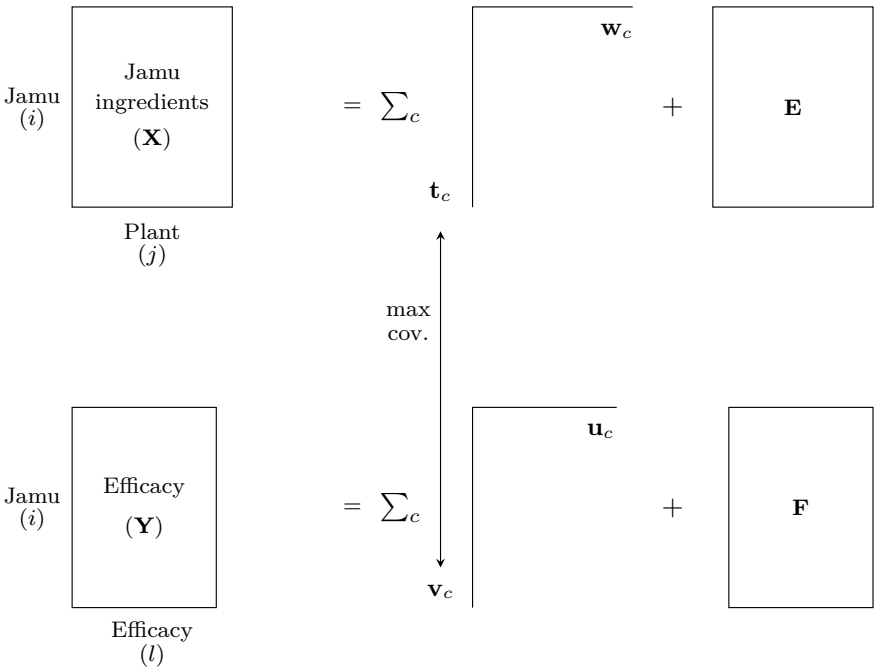


Figure 3.2. *Schematic diagram of the decomposition of both predictor and response blocks for PLS model. The* $\mathbf{X}$ *and* $\mathbf{Y}$ *are decomposed into* $\mathbf{T}$ *and* $\mathbf{V}$*, respectively, such that the covariance among* $\mathbf{T}$ *and* $\mathbf{V}$ *are maximized. The* $\mathbf{W}$ *and* $\mathbf{U}$ *are weights for* $\mathbf{X}$ *and* $\mathbf{Y}$*, respectively, while* $\mathbf{E}$ *and* $\mathbf{F}$ *are residuals for* $\mathbf{X}$ *and* $\mathbf{Y}$*, respectively, during this decomposition step of PLS model.*

is performed on training data using $c = 1$ component.

3. The model obtained from Step 2 is used to predict the Y-block value of the testing data.

4. Steps 2 and 3 are repeated by selecting another group as the testing data. This step is repeated until all the groups have been selected once as the testing data.

5. Steps 2 to 4 are repeated by increasing c to $c + 1$ in every iteration.

Let $\hat{y}_{(-i,l)c}$ denote the prediction of response variable l using the PLS-DA model obtained without observation i, i.e. i is within the testing data,

and using c components. After the five-fold cross-validation is performed, Prediction Error Sum of Square (PRESS) using c components for efficacy group l is calculated as

$$\mathrm{PRESS}(c)_l = \sum_{i=1}^{I} \left(y_{il} - \hat{y}_{(-i,l)c} \right)^2 . \tag{3.5}$$

This statistic is then plotted as a function of c. The number of components is selected such that the addition of more components does not significantly decrease the PRESS value.

3.2.2 Utilization of $\hat{y}_{il}$ to predict the efficacies of Jamu remedies

In PLS-DA, the efficacy of a particular Jamu can be predicted by utilizing the prediction value of the indicator variable of the efficacy, i.e. $\hat{y}_{il}$. In this work, I employ two methods using $\hat{y}_{il}$ to predict efficacies: the *'maximum $\hat{y}_{il}$'* and *'maximum probability'* methods. The former method directly determines the efficacy. As explained in the previous section, the larger the value of $\hat{y}_{il}$, the more useful Jamu i is for efficacy l. Thus, a given Jamu i is predicted to have efficacy l if the $\hat{y}_{il}$ value is the largest across $l = 1$ to 9 for Jamu i. The second method utilizes $\hat{y}_{il}$ to calculate the probability of Jamu i belong to efficacy l, and then this probability is used to predict the efficacy of a particular Jamu. Then, I predicted that a given Jamu i has efficacy l if the probability of belonging to efficacy l is the largest across $l = 1$ to 9 for Jamu i.

The procedure to calculate the posterior probability of Jamu i belong to efficacy l utilizing $\hat{y}_{il}$ is described below. Here I employ Bayes Theorem as

in Bylesjö et al. (2006)

$$P\left(Class_{il}|\hat{Y}_{il}\right) = \frac{P\left(\hat{Y}_{il}|Class_{il}\right)P\left(Class_{il}\right)}{\sum_{l=1}^{q} P\left(\hat{Y}_{il}|Class_{il}\right)P\left(Class_{il}\right)} \tag{3.6}$$

where q is the number of response classifications, which equals nine in this case. In the formula, $P(Class_{il})$ is the prior probability of Jamu i belonging to efficacy l. There are two options to determine this prior probability; the probability can be equal across all classes (i.e. equal to 1/9 for all efficacies) or proportional to the frequency of each efficacy class. Furthermore, $P(\hat{Y}_{il}|Class_{il})$ is the probability of Jamu i with the predicted indicator variable up to $\hat{y}_{il}$ given that Jamu i belongs to efficacy l. It is assumed that $(\hat{Y}_{il}|Class_{il})$ has a normal distribution with mean μ_l and variance σ_l^2 (Bylesjö et al., 2006). To avoid overfitting, Bylesjö et al. (2006) has suggested not to directly use the distribution of $\hat{y}_{il}$ obtained from PLS-DA to estimate mean μ_l and variance σ_l^2, but to generate a distribution using cross-validation as follows.

1. A random sample without replacement with size $t < I$ is drawn from the data as the training set to be used to calculate the PLS-DA model.

2. The remaining observations are used as the testing set. The PLS-DA model obtained from Step 1 is used to calculate the prediction of the indicator variable of efficacy for the testing set, which is denoted as $\hat{y}_{il,test}$.

3. Steps 1 and 2 are repeated s times. The values of $\hat{y}_{il,test}$ across s rounds cross-validation are saved into $\hat{y}_{il,CV}$.

The parameters for mean μ_l and variance σ_l^2 are estimated as

$$\hat{\mu}_l = \frac{1}{p}\sum_{i=1}^{p} \hat{y}_{il,CV} \tag{3.7}$$

$$\hat{\sigma}_l^2 = \frac{1}{p-1}\sum_{i=1}^{p} \left(\hat{y}_{il,CV} - \hat{\mu}_l\right)^2 . \tag{3.8}$$

where p is the number of elements in $\hat{y}_{il,CV}$, which is equal to the sample size of testing set for each cross-validation round, i.e. $(I - t)$, multiplied by the number of cross-validation rounds s. Moreover, class-conditional probability $P(\hat{Y}_{il}|Class_{il})$ is calculated in the form of a normal cumulative distribution function as

$$P\left(\hat{Y}_{il}|Class_{il}\right) = P\left(\hat{Y}_{il} \leq \hat{y}_{il}|Class_{ij}\right) = \int_{-\infty}^{\hat{y}_{il}} \frac{1}{\sqrt{2\pi\hat{\sigma}_l^2}} e^{-(x-\hat{\mu}_l)/(2\hat{\sigma}_l^2)} dx. \tag{3.9}$$

Hence, in posterior probability $P(\hat{Y}_{il}|Class_{il})$, the likelihood of an observation belonging to class l increases (to a maximum value of 1) as the $\hat{y}_{il}$ value increases.

3.3 Results

3.3.1 Determination of the number of PLS-DA components

The number of components for the PLS-DA model is selected using PRESS. Fig. 3.3 shows the PRESS plot of a five-fold cross-validation. For all indicator variables, the plots remain nearly constant from $C = 10$ onward. Consequently, the number of components is set to ten. Analysis of PLS-DA using ten components shows the percentage variation accounted during the decomposition step for predictors and responses are equal to 5.5% and

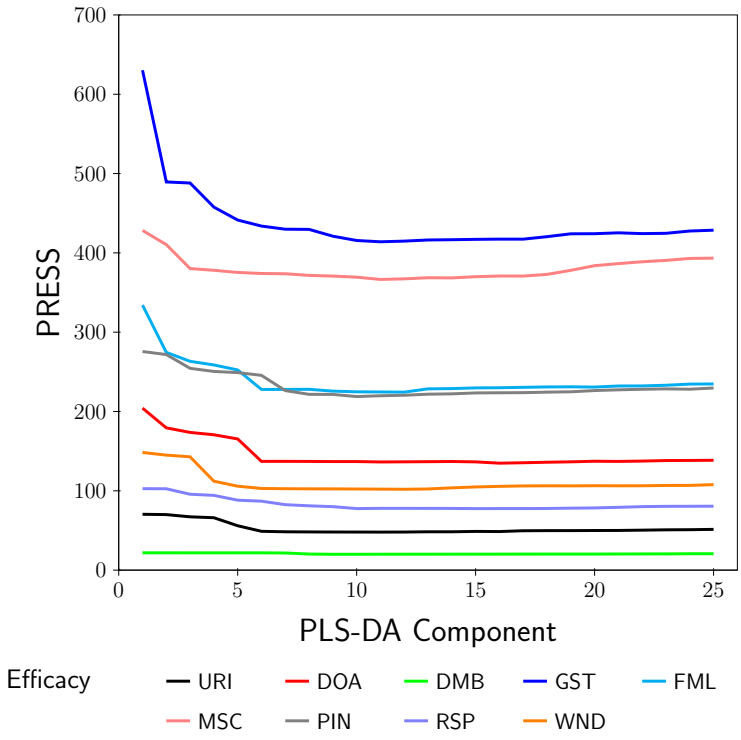


Figure 3.3. *PRESS plot of five-folds cross-validation for PLS-DA model. The number of components is set to ten because all plots remain nearly constant from* $C = 10$ *onward.*

40.5%, respectively. The small amount of predictor variation accounted in PLS-DA model is reasonable considering that more than 500 companies produce the 3,138 Jamu remedies used in this analysis. Although several Jamu medicines, which have different manufacturers, are useful for identical symptoms, each manufacturer has its own Jamu formula because a given plant may be useful as either the main ingredient or as a supporting ingredient (Pramono, 2007). Plants that act as supporting ingredients might be replaced with other plants without affecting the efficacy of the Jamu formula, which makes Jamu formula varies.

3.3.2 Prediction of Jamu efficacy

Matrix **T** or factor scores of predictors in PLS can be regarded as a predictors' summary. Plotting these scores can aid in exploring the performance of PLS in predicting responses. Fig. 3.4 plots the first two predictors' scores, and many points from different efficacies overlap. This overlap also occurs for other scores (results not shown), indicates that no specific information regarding the Jamu efficacy can be obtained from each component. It is because many plants are used not specific to one efficacy only but varies to many efficacies. Then the predictors' scores, which summarized the plants usage in Jamu ingredients, also reflecting this non unique usage to many efficacies. Hence, all ten scores must be used simultaneously to predict Jamu efficacy.

From the PLS-DA model, I obtain nine sets of $\hat{y}_{il}$, one for each efficacy indicator variable. Fig. 3.5 shows the distribution of $\hat{y}_{il}$ corresponding to $Y_l = 0$ and $Y_l = 1$ for each efficacy. It is observed that the averages of $\hat{y}_{il}$ corresponding to $Y_l = 0$ and $Y_l = 1$ are well separated for all efficacies; the averages of $\hat{y}_{il}$ for $Y_l = 1$ are always larger than those for $Y_l = 0$. The t-test for each efficacy confirms that both averages are well separated. The p-values obtained from this test are less than 0.01 for all efficacies.

Although the averages of $\hat{y}_{il}$ corresponding to $Y_l = 0$ and $Y_l = 1$ are well separated, Fig.3.5 indicates that the efficacies have overlapping regions where both $Y_l = 0$ and $Y_l = 1$ have the same $\hat{y}_{il}$. However, the Area Under Curve (AUC) statistics of the ROC Curve for all efficacies exceed 0.9. Note that the maximum value of AUC is 1 which corresponds to perfect discrimination. Thus, the AUC indicates that $\hat{y}_{il}$ is a good candidate to discriminate $Y_l = 0$ and $Y_l = 1$.

Meanwhile, the distribution of $\hat{y}_{il,CV}$ is obtained using $s = 200$ rounds of

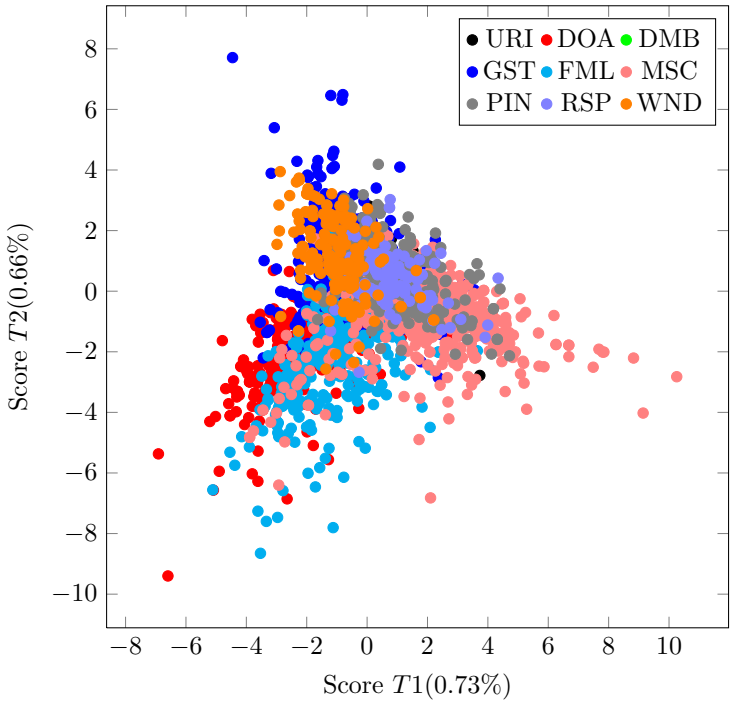


Figure 3.4. *Plot of predictor's scores* (**T**) *for component 1 vs. component 2. The overlaping among points from different efficacies, which also occur for other scores (results not shown), indicates that no specific information regarding the Jamu efficacy can be obtained from each component. Thus, all ten scores must be used simultaneously to predict Jamu efficacy.*

cross-validation. Checking the normality of these distributions using Anderson Darling Normality Test, the p-values are less than 0.005 for all efficacies, indicating the distributions of $\hat{y}_{il,CV}$ for all efficacies are non-normal. Hence, I employed two analysis options to calculate $P(\hat{Y}_{il}|Class_{il})$. The first option assumes that the distributions of $(\hat{Y}_{il}|Class_{il})$ are normal, and calculates $P(\hat{Y}_{il}|Class_{il})$ in the form of a normal cumulative distribution function, as in Eq. (3.9). In this option, the distributions of $\hat{y}_{il,CV}$ are generated only to estimate the parameters for the mean μ_l and variance σ_l^2 of the normal distribution. The second option assumes that the distributions of $(\hat{Y}_{il}|Class_{il})$ are non-normal, and calculates $P(\hat{Y}_{il}|Class_{il})$ in the form of the empirical

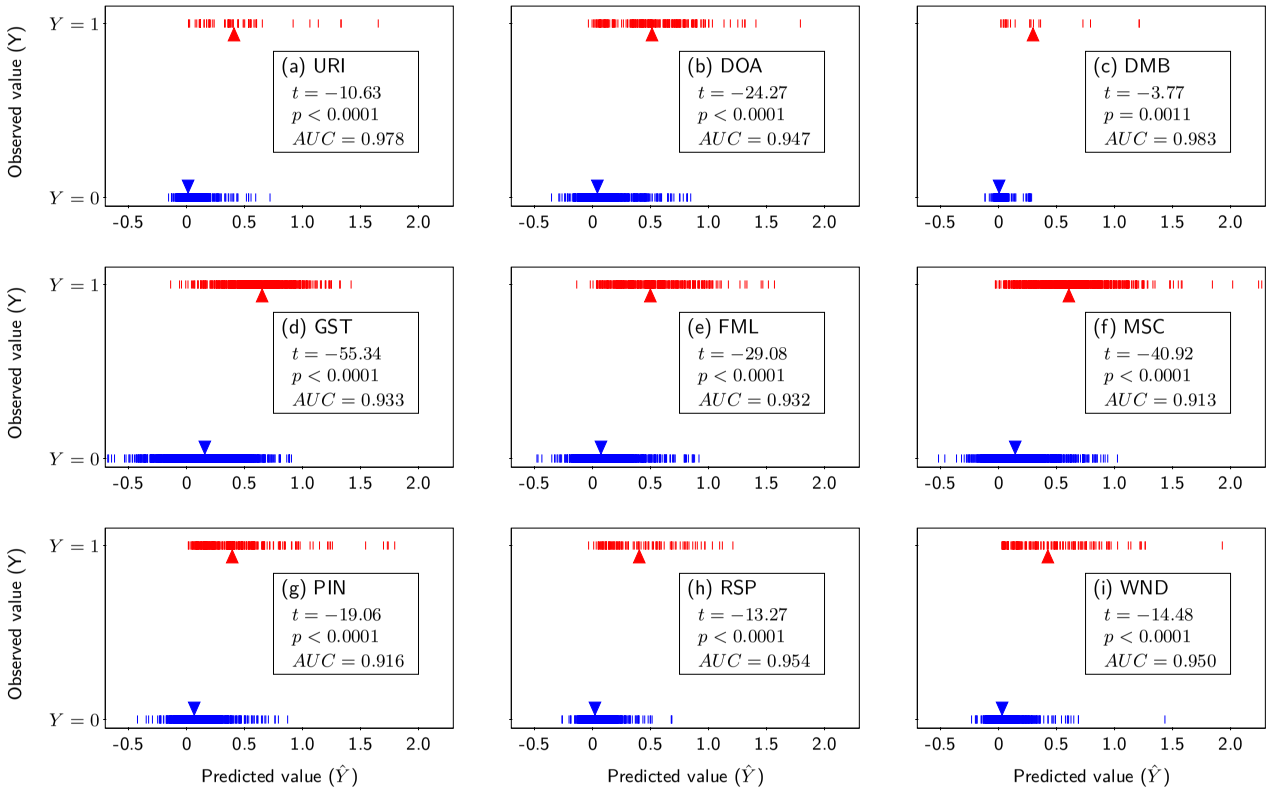


Figure 3.5. *Distribution of $\hat{y}_{il}$ corresponding to $Y_l = 0$ and $Y_l = 1$ for all nine efficacies. The red and blue triangles showing average values of $\hat{y}_{il}$ corresponding to $Y_l = 1$ and $Y_l = 0$, respectively. The plots exhibit that $\hat{y}_{il}$ is a good candidate in predicting efficacy: the averages of $\hat{y}_{il}$ corresponding to $Y_l = 0$ and $Y_l = 1$ are well separated (the t-test confirms that the averages are significantly different), and all AUCs are larger than 0.9.*

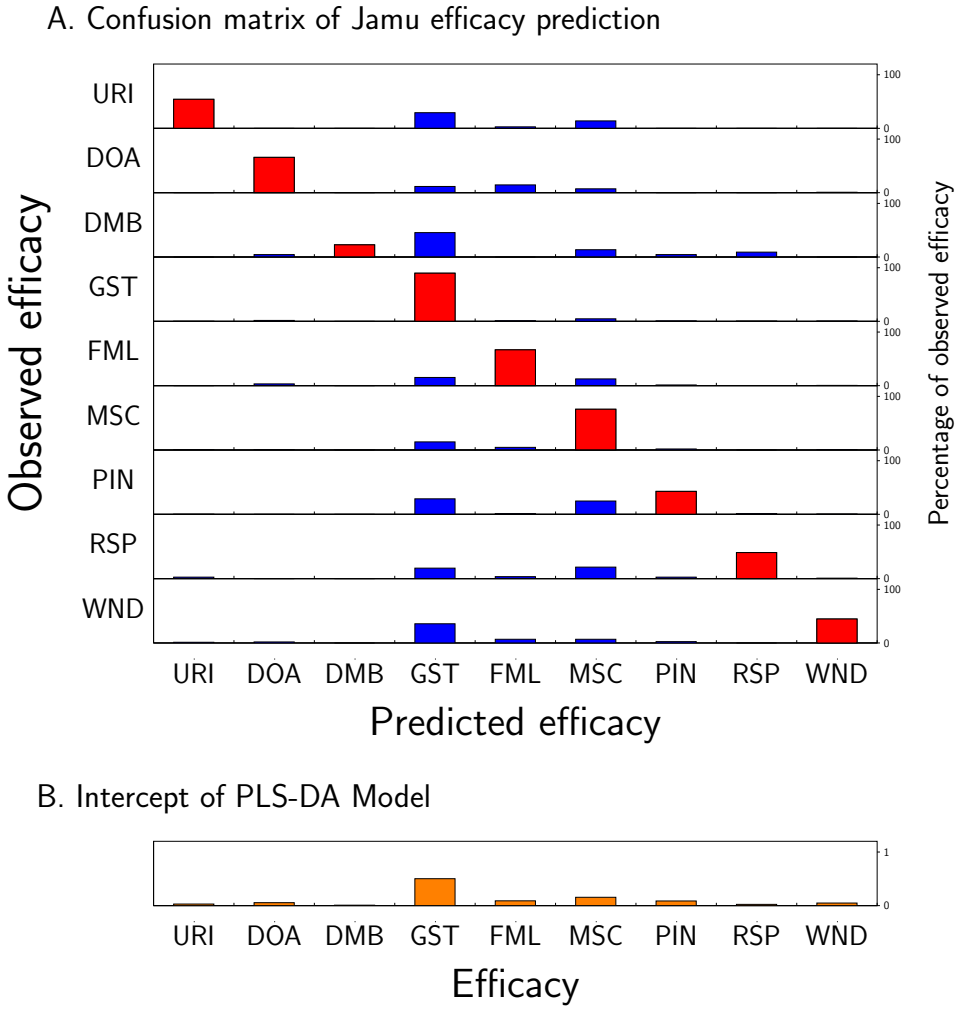


Figure 3.6. *Results of the PLS-DA model. (A) Confusion matrix of the prediction of Jamu efficacy using the maximum $\hat{y}_{il}$ method. Red bars indicate correctly predicted Jamu; blue bars denote incorrectly predicted Jamu. (B) Intercept of the PLS-DA Model for all nine efficacies. The height of the bars is proportional to the intercept value for the corresponding efficacy.*

cumulative distribution function based on the $\hat{y}_{il,CV}$, as follows

$$P\left(\hat{Y}_{il}|Class_{il}\right) = P\left(\hat{Y}_{il,CV} \leq \hat{y}_{il}|Class_{il}\right). \tag{3.10}$$

Thus, in the second option, $P(\hat{Y}_{il}|Class_{il})$ is proportional to $\hat{y}_{il,CV}$ whose

Table 3.1. *False positive rate in predicting Jamu efficacy*

Prediction method	False positive rate
Maximum $\hat{y}_{il}$	0.284
Maximum probability	
Eq-N	0.328
Eq-E	0.439
Pr-N	0.417
Pr-E	0.434

values are less than or equal to $\hat{y}_{il}$.

Note that we considered two options to determine the prior probability $P(Class_{il})$: (1) the equal prior and (2) the proportional prior, and another two options to calculate the class-conditional probability $P(\hat{Y}_{il}|Class_{il})$: based on (1) the normal cumulative distribution and (2) the empirical cumulative distribution based on $\hat{y}_{il,CV}$. If we combine these pairs of options, there are four possible combinations to calculate the posterior probability $P(\hat{Y}_{il}|Class_{il})$. These four combinations are: (i) equal prior - normal distribution (Eq-N), (ii) equal prior - empirical distribution (Eq-E), (iii) proportional prior - normal distribution (Pr-N), and (iv) proportional prior - empirical distribution (Pr-E). The False Positive Rates (FPRs) in predicting Jamu efficacy for the maximum $\hat{y}_{il}$ method as well as the maximum probability methods are shown in Table. 3.1. FPR for the maximum $\hat{y}_{il}$ method is smaller than the four maximum probability methods. Hence, the maximum $\hat{y}_{il}$ method is used to predict the Jamu efficacies, and the result of prediction for each efficacy is shown in Fig. 3.6A.

Among the 3,138 Jamu medicines, the efficacies of 2,248 Jamu medicines (71.6%) can be assigned to an individual efficacy reported. Hence, the efficacy in most Jamu medicines can be predicted on the basis on medicinal plants used. The percentage of correct prediction for each efficacy vary

from 22.7% for efficacy DMB to 89.8% for efficacy GST. The low percentage of correct prediction for efficacy DMB can be addressed due to the small number of Jamu for this efficacy, which is only 22 out of 3130 Jamu (see Table 2.1).

Furthermore, beside showing correct prediction, Fig. 3.6A also shows incorrect prediction which most of the incorrect prediction are predicted to efficacy GST, FML, and MSC. This is because, like other regression models, PLS-DA model has a constant or intercept in the regression equation, which in this analysis representing the number of Jamu for the corresponding efficacy. The intercepts for GST, FML, and MSC are larger than those for the other six efficacies (Fig. 3.6B), which consistent with the distribution of Jamu in Table 2.1. The large intercepts for GST, FML, and MSC makes the $\hat{y}_{il}$ for efficacy GST, FML, and MSC are tend to be larger than the $\hat{y}_{il}$ for the other six efficacies, which in turn make some of the prediction of the efficacy are classified to efficacy GST, FML, and MSC regardless the original efficacy of the predicted Jamu.

Another source of error in the prediction of Jamu efficacy is that the plant usage in Jamu is not unique for certain efficacy. As noted previously, many plants are used for more than one efficacy. In particular, medicinal plants for GST and MSC are diverse because poor physical conditions of gastrointestinal, musculoskeletal, and connective tissue systems are derived from many different symptoms, including lifestyle-related diseases such as infectious disease, excessive drinking, overeating and strain, malfunction of liver and renal functions, etc.

3.4 Summary

This chapter discussed about the modeling of the ingredients of Jamu formulas using Partial Least Squares Discriminant Analysis (PLS-DA) in order to predict their efficacy. The plants used in each Jamu medicine served as the predictors, whereas the efficacy of each Jamu provided the responses. Because of the availability of information about Jamu products, which are generally not state in detail about the mixing ratio of the plants used, then the predictors x_{ij} is constructed only in binary data, which are x_{ij} is set to 1 if plant j is used in Jamu i and x_{ij} is set to 0 otherwise.

Utilizing response predictions $\hat{y}_{il}$ obtained from PLS-DA, I predicted the efficacies of Jamu formulations using two methods: maximum $\hat{y}_{il}$ and maximum probability. In predictions of Jamu efficacy, the maximum $\hat{y}_{il}$ method produced a smaller error than that of the maximum probability method. Further exploration on the predictions reveals that intercepts for GST, FML, and MSC are larger than intercepts for the other six efficacies due to large number of Jamu for those three efficacies. It makes some of the prediction of the efficacy are classified to efficacy GST, FML, and MSC regardless the original efficacy of the predicted Jamu.

Chapter 4

Determining Plants as Main Ingredients in Jamu Formulas

Previous chapter employs PLS-DA model to capture systematic utilization of plant in Jamu medicine to achieve desired efficacy. Hence, the PLS-DA coefficients can be used to investigate which plants are main ingredients and which are supporting by considering that plants serve as main ingredients will have significant effects on the resulting model. Furthermore, due to the absence of parametric testing for the PLS-DA coefficients, the evaluation for significance is performed using permutation testing, in which the distribution of coefficients under the null hypothesis is generated via resampling of the existing data (Good, 2005).

The resampling is performed by permuting the order of the responses (in this case, Jamu efficacies) while maintaining the order of the predictors (in this case, plant utilization as Jamu ingredients) so that the existing relationship between the predictors and the response is destroyed and a new data set is generated under the null hypothesis, i.e., plant utilization in Jamu does not affect Jamu efficacy. If we perform such resampling many

times and apply the PLSDA model on the new data generated from the resampling, the accumulation of the PLSDA coefficients obtained from this process generates a distribution, against which a p-value can be calculated and subsequently evaluated for significance.

4.1 Permutation Test

Permutation testing is a resampling method intended to provide an underlying distribution of a test statistic under a null hypothesis (denoted as null distribution), which then can be used to calculate the p-value. Unlike conventional statistical testing, which assumes that the null distribution follows some theoretical distribution, permutation testing generates the null distribution empirically through resampling of the data sample at hand. The idea of permutation testing in PLS-DA is illustrated in Fig. 4.1. The details of the steps are as follows.

1. Resampling of Jamu data. In this step, we generate a new Jamu data set under the null hypothesis, i.e., that plants are not affecting the Jamu efficacy, by resampling the existing Jamu data set. The resampling process is performed as follows.

   (a) For each row i in the response block Y_{il}, a uniform random number is generated.

   (b) The rows in the response block then are sorted according to the value of the uniform random number. Let $\tilde{Y}_{il}$ denote the response after the sorting process.

   (c) The new response $\tilde{Y}_{il}$ is then merged with the original, i.e., unsorted, predictors X_{ij} to form a new Jamu data set to be used in PLS-DA modeling in Step 2.

The process of permuting the order of the response while maintaining the order of the predictors ensures that any relationship between the predictors and the response in the original Jamu data set will be destroyed. The result of this resampling is a new Jamu data set generated under null hypothesis.

2. PLS-DA modeling on the new Jamu data set. PLS-DA model is performed on the new Jamu data set obtained from Step 1. The matrices $\mathbf{X}$ and $\tilde{\mathbf{Y}}$ provide the predictors and responses, respectively. The coefficient matrix obtained is denoted by $\tilde{\mathbf{C}}$. Steps 1 and 2 are then repeated R times. In the present study I performed $R = 1,000$ permutations.

3. Accumulation of PLS-DA coefficients. After all permutation rounds R are performed, the PLS-DA coefficient in each round $\tilde{\mathbf{C}}_r$ is accumulated into the coefficient distribution $\mathbf{C}$, which is the distribution of PLS-DA coefficient under null hypothesis. Let $C_{jl,r}$ denote the coefficient for plant j with respect to efficacy l on permutation round r.

After obtaining the distribution of PLS-DA coefficients under the null hypothesis, the p-value for the effect of plant j on efficacy l is calculated as follows. Note that the hypothesis to be tested is

$$H_0 : \beta_{jl} \leq 0 \; vs. \; H_1 : \beta_{jl} > 0.$$

The null hypothesis states that plant j is *not* affecting the efficacy j while the alternative hypothesis states that plant j is affecting the efficacy j. Thus,

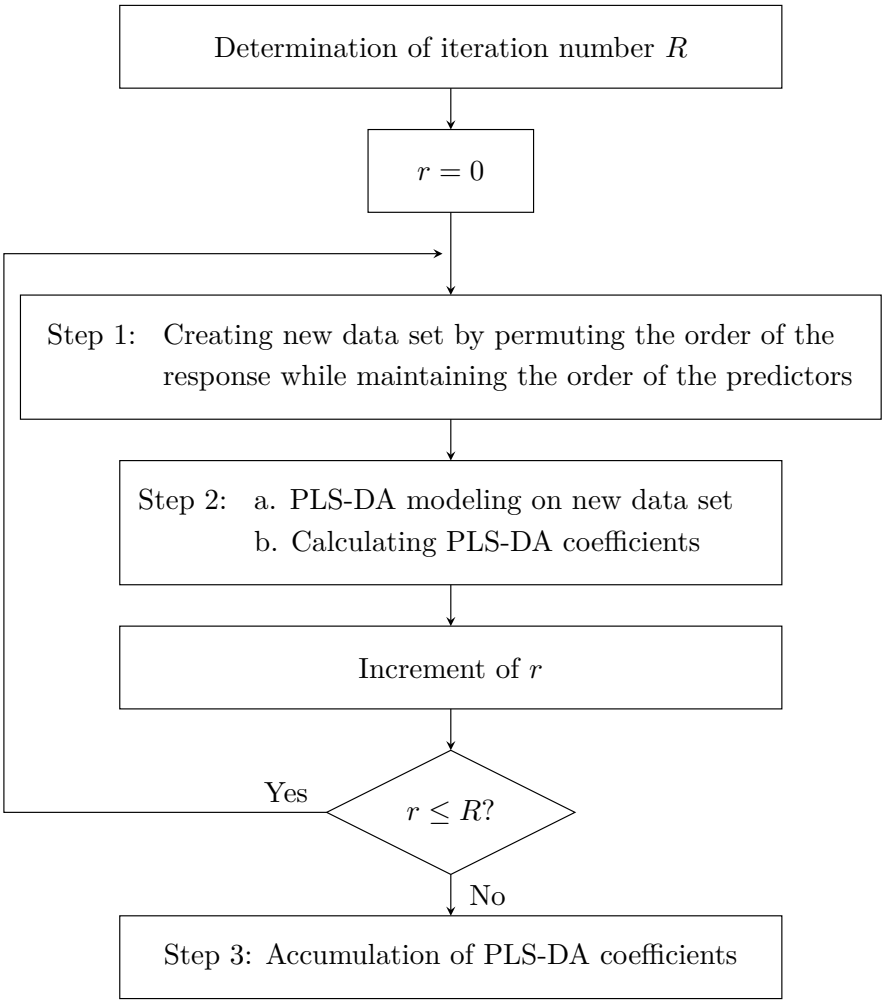


Figure 4.1. *The schematic diagram of the permutation steps used in this study*

the p-value is calculated as

$$p_{jl} = \frac{1}{R+1}\left\{\left(\sum_{r=1}^{R} I(C_{jl,r} \geq B_{jl})\right) + 1\right\} \tag{4.1}$$

where B_{jl} is the coefficient of plant j on efficacy l obtained from the original data set and $I(C_{jl,r} \geq B_{jl})$ is an identity function that is equal to 1 if the argument is fulfilled, and 0 otherwise. The null hypothesis is rejected if the

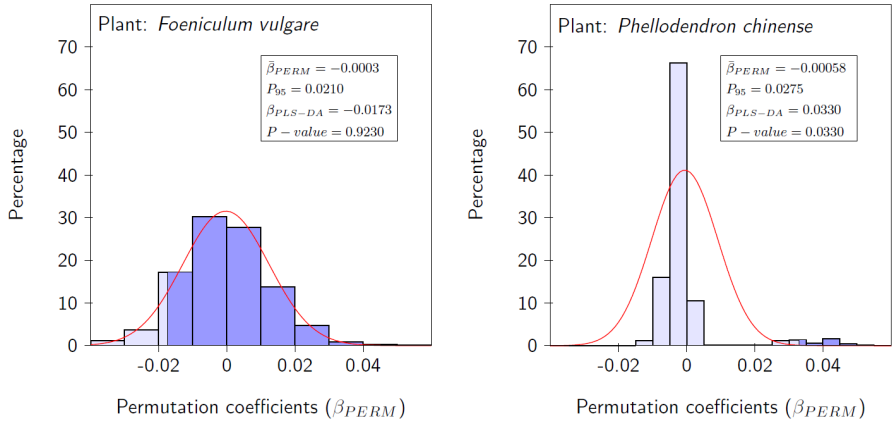


Figure 4.2. *Illustration of the coefficient distribution under the null hypothesis, obtained using the permutation process*

p-value is smaller than the significance level α.

4.2 Results

Fig. 4.2 illustrates the coefficient distribution under the null hypothesis, obtained from the permutation process. In this illustration, both plants are evaluated according to their use in Jamu formulas with efficacy URI. The means of the two distributions (and also for all other distributions) are very close to 0, as expected, indicating that the distributions were generated under null hypothesis. The normal curves were sketched onto both distributions in order to show that not all permutation distributions can be approximated with a normal distribution. This result supports the p-value calculation performed using an empirical distribution, as formulated in Eq. (4.1). Using significance level $\alpha = 5\%$, in this illustration we can conclude that *Phellodendron chinense* significantly affects the Jamu efficacy URI, whereas *Foeniculum vulgare* does not.

The results of the significance testing of all plants used in each of the 9

Table 4.1. *Number of significant plants for each efficacy*

Efficacy	Total	Support from scientific papers	
URI	20	15	(75.0%)
DOA	21	20	(95.2%)
DMB	12	6	(50.0%)
GST	26	23	(88.5%)
FML	40	30	(75.0%)
MSC	40	39	(97.5%)
PIN	39	37	(94.9%)
RSP	36	33	(91.7%)
WND	43	38	(88.4%)

efficacies are shown in Table 4.1. Note that one plant may be used for more than one efficacy. From the testing, it is observed that 234 plants (50.3% among all 465 plants) with no significant status for any of the 9 efficacies; however, 231 other plants have significant status: 189 plants (40.6%) are significant only for 1 efficacy; 38 plants (8.2%) are significant for 2 efficacies; and the other 4 plants (0.9%) are significant for 3 efficacies. Exploration on the significant plants in terms of their usage frequency in Jamu medicines as depicted in Figure 4.3 indicates that the significant plants for a given efficacy are usually the plants utilized most intensively in Jamu medicines for that efficacy relative to the usage for other efficacies.

Besides testing plant usage statistically, furthermore, I also determined which of the significant plants have been associated with the corresponding efficacy in the scientific literature. These results are shown in Table 4.1. I found that many of the testing results are supported by scientific papers.

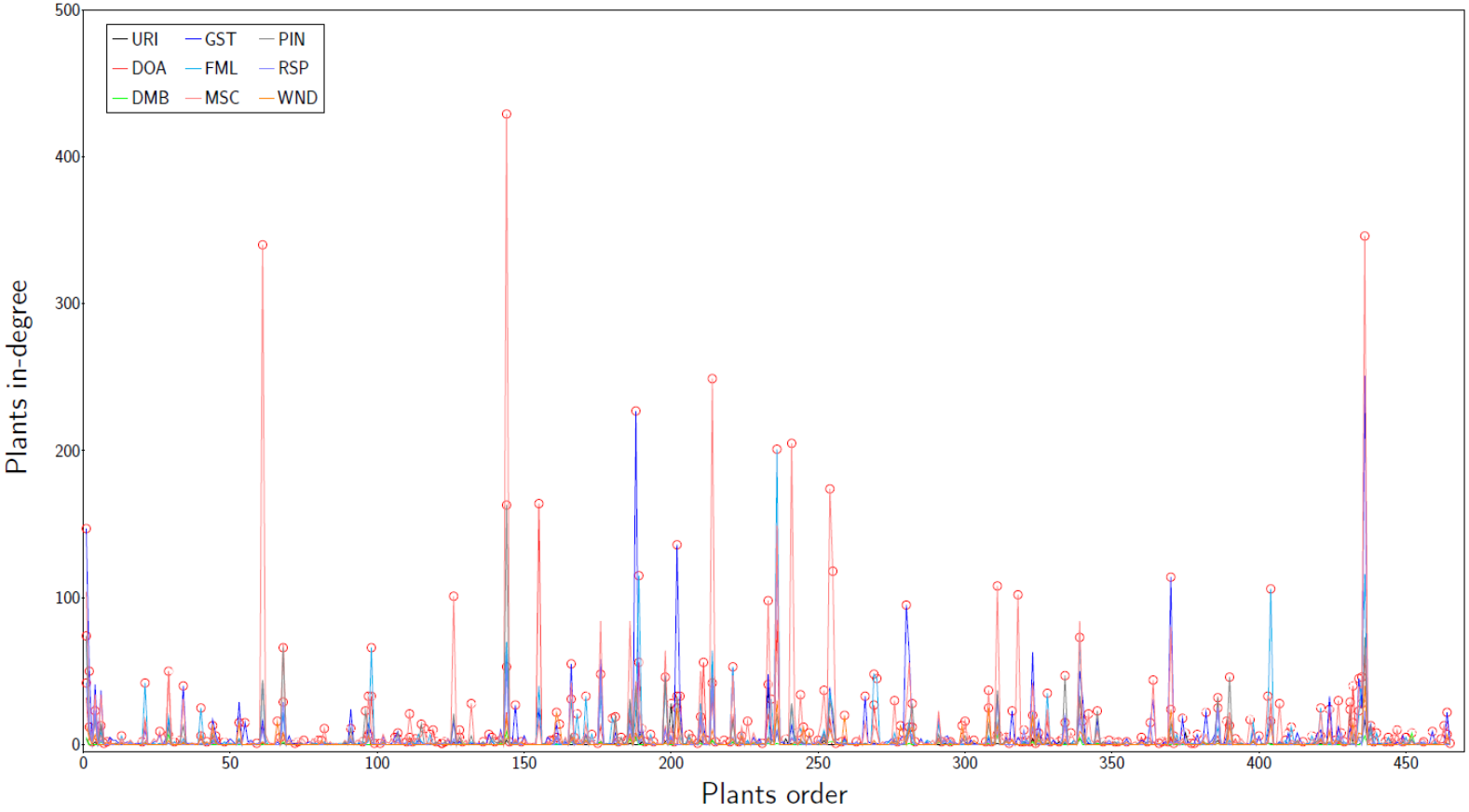


Figure 4.3. *Plot of frequency of plant usage in Jamu medicines (plant in-degree) versus plants order. The red circle emphasize the significant plant for a given efficacy. The figure indicates that the significant plants for a given efficacy are usually the plants utilized most intensively in Jamu medicines for that efficacy relative to the usage for other efficacies.*

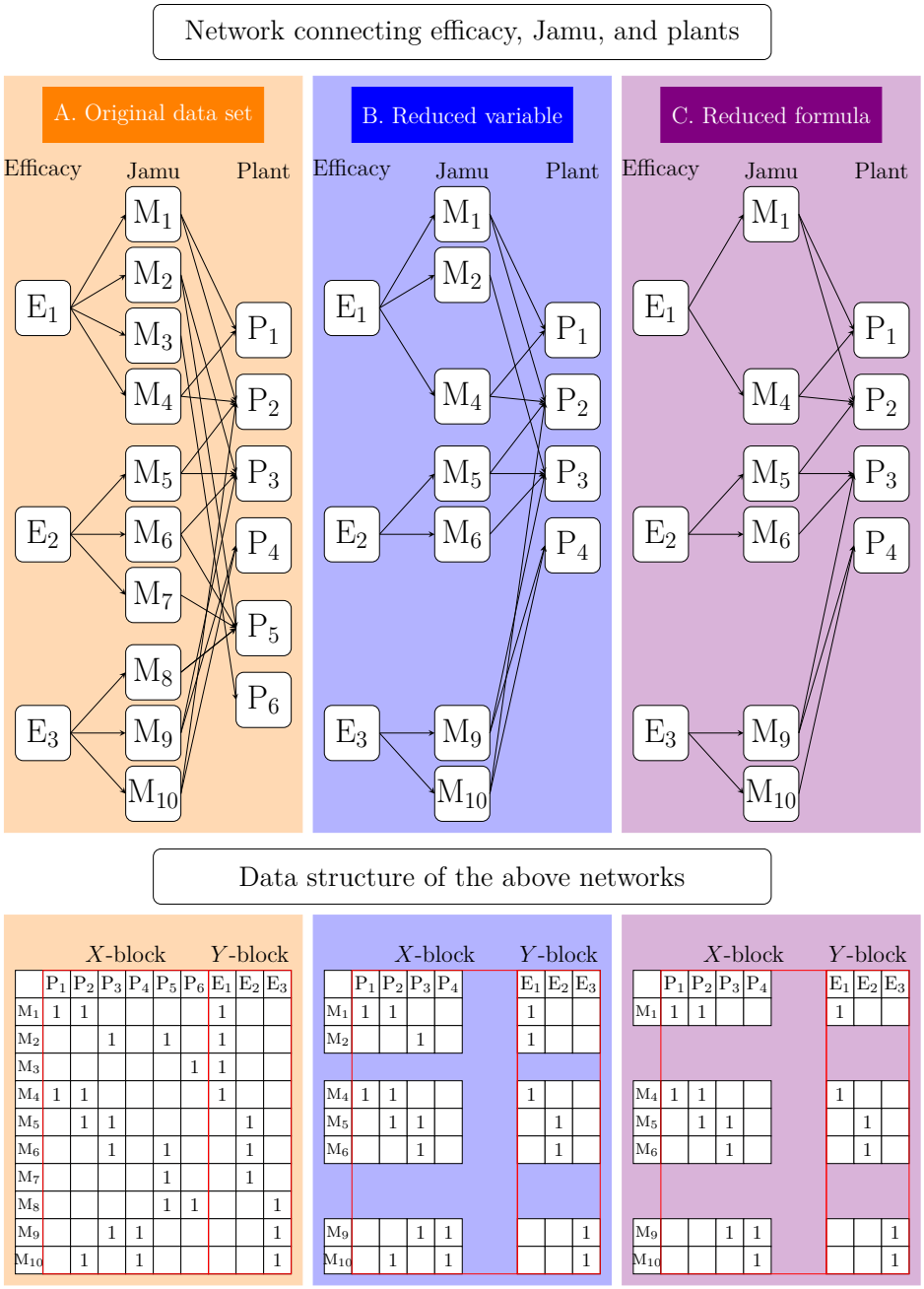
Table 4.2. *Comparison of the performance of the PLS-DA model between all data, reduced variables, and reduced formulas scenario*

PLS-DA model	# Jamu	# plant	% variation accounted for		% correct classification
			X-block	Y-block	
All data	3,138	465	5.5	40.5	71.60
Reduced variables	3,110	231	9.3	39.8	70.64
Reduced formulas	2,748	231	11.1	70.9	94.21

4.2.1 PLS-DA of the reduced data

As noted previously, from permutation testing I was able to determine 231 significant plants. In this section I further explored the performance of a PLS-DA model on reduced data containing only these 231 significant plants, i.e., the other 234 non-significant plants are dropped from the data set. I call this scenario *'PLS-DA for reduced variables'*. See Fig. 4.4B for the illustration of the network and data structure for this scenario. As with the PLS-DA model for the original data set, I used 10 components for the reduced-variable scenario. Table 4.2 provides the results of the PLS-DA model for the reduced-variable scenario; Fig. 4.5a shows the results of the efficacy prediction. The PLS-DA model for the reduced-variable scenario performs similarly to PLS-DA on the original data set. The correlations between the PLS-DA coefficients in the original and reduced-variable data sets (see Table 4.3) also confirm that the PLS-DA model for reduced variables exhibits similar performance to that of the PLS-DA model for the original data set. It indicates that the dropped variables, i.e. the non-significant plants, contribute little on the PLS-DA Model so that removing them did not affecting the performance of the PLS-DA model.

Next, the performance of the PLS-DA model was investigated when the Jamu formulas is simplified so that they contain only the main ingredients.



So, in this scenario, besides dropping the non-significant plants from the data set, any plants not significant for a specific efficacy was also dropped, even if they are significant for another efficacy. This scenario is called as

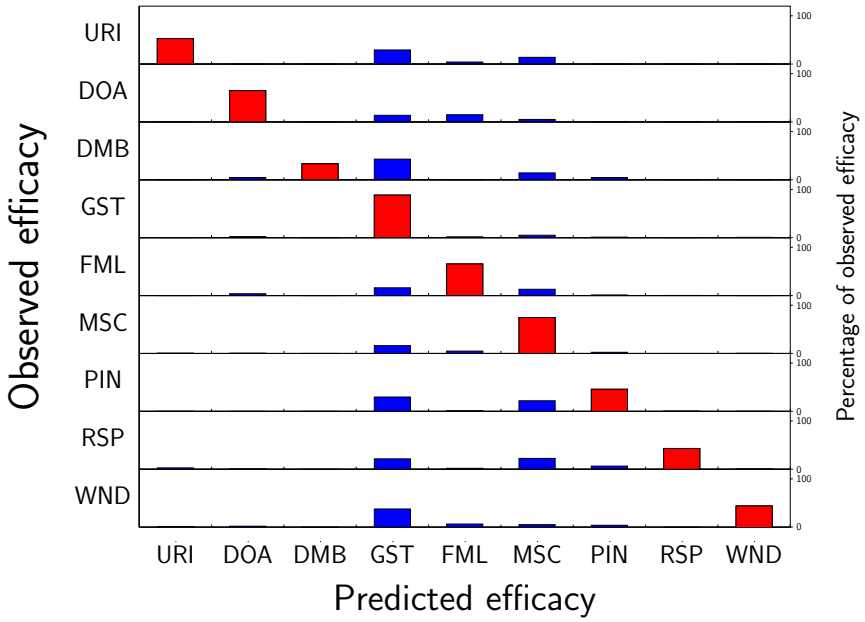
Figure 4.4 ***(previous page).*** *Networks connecting Jamu efficacy, Jamu, and plants utilized in Jamu formulas. Here, 10 Jamu are categorized into 3 efficacies (M_1 to M_4 for efficacy E_1, M_5 to M_7 for efficacy E_2, and M_8 to J_{10} for efficacy E_3). From permutation testing, P_1 and P_2 are the main ingredients for E_1, P_2 and P_3 are the main ingredients of E_2, and P_3 and P_4 are the main ingredients for E_3. In the reduced-variable scenario, all non-main ingredients (P_5 and P_6 in this illustration) are dropped from the analysis but kept the main ingredients. For the reduced-formula scenario, the formulas is simplified by using only main ingredients for the corresponding efficacy. In these two reduced scenarios, Jamu that no longer connected to the remaining plants were dropped from the analysis. I also illustrate the data structure for each network: each row corresponds to Jamu, and the columns in the X-block and Y-block correspond to plant and efficacy group, respectively. Each connection between two objects is denoted by 1 in the corresponding cell.*

Table 4.3. *Correlations between PLS-DA coefficients*

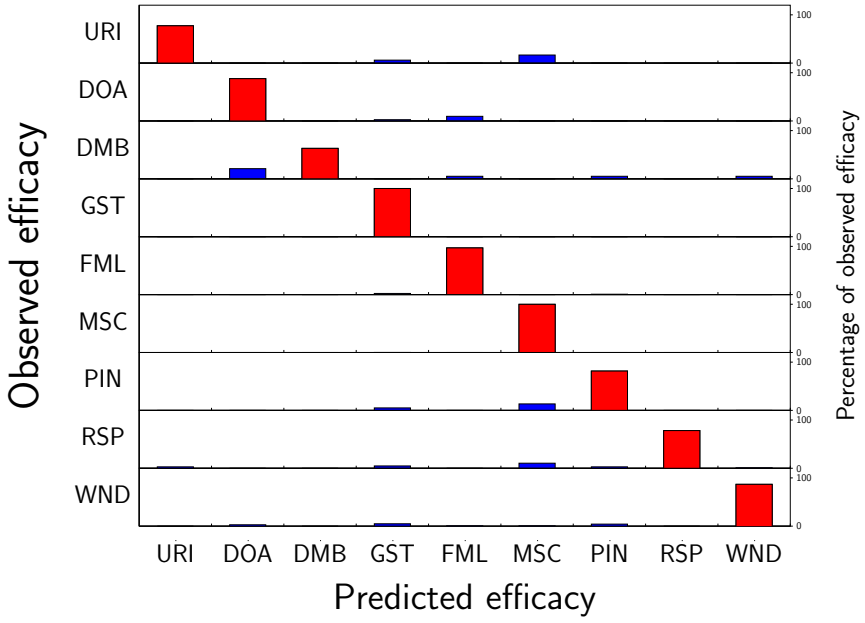
Efficacy	Original data set vs. Reduced variable	Original data set vs. Reduced formula
URI	0.998	0.704
DOA	0.999	0.955
DMB	0.996	0.517
GST	0.991	0.790
FML	0.993	0.743
MSC	0.984	0.835
PIN	0.948	0.663
RSP	0.977	0.630
WND	0.992	0.739

'PLS-DA model for reduced formulas'. See Fig. 4.4C for the illustration of the network and data structure for this reduced-formula scenario. Using 10 components, as for the previous PLS-DA models, it is obtained that the PLS-DA model for reduced formulas exhibited superior performance in predicting Jamu efficacy relative to the PLS-DA model of the original data set (see Table 4.2 and Fig. 4.5b).

This findings can be understood as follows. In Chapter 3 it is explained



(a) *Reduced variable*



(b) *Reduced formula*

Figure 4.5. *Results of the Jamu efficacy prediction: (a) Reduced variable, and (b) Reduced formula. Red bars indicate correctly predicted Jamu; blue bars denote incorrectly predicted Jamu.*

that one source of error in the prediction of efficacy is the use of plants in many efficacies. It is because the inclusion of all uses of the plants, regardless of plant functions whether as main or supporting ingredient, would obscure the main functions of the plant. So, simplifying the Jamu formula using only the main ingredients led to the use of plants in Jamu become more compact, i.e. concentrated only in certain efficacy where these plants serve as main ingredients. This simplification reduces the noise caused by the use of plants serve as supporting ingredients with no significant role in efficacy and subsequently increase the correct prediction of Jamu efficacy produced by PLS-DA model for the reduced formulas scenario compared to PLS-DA model for the original data set. Thus, statistically, it is an indication that Jamu formulas can be simplified by utilizing main ingredients only without losing efficacy.

This simplification greatly reduced the number of plants utilized in each Jamu. Apart from original formula that using one plant only, the number of plants used in simplified formula are reduced between 1 to 22 plants compared to the original formula. Consequently, this simplification will reduces the effort in studying the mechanism of Jamu efficacy by concentrating on fewer plants. In addition, as depicted in Figure 4.6, in simplified formula many Jamu now contain one plant only, although many others are contain two until four plants. It indicates that interaction among plants also plays important role in Jamu to achieve desired efficacy.

4.3 Summary

Plants serve as main ingredients in Jamu formula is determined in this chapter by testing the significance of PLS-DA coefficients obtained in Chapter 3. The idea is that plants serve as main ingredients in a given efficacy should

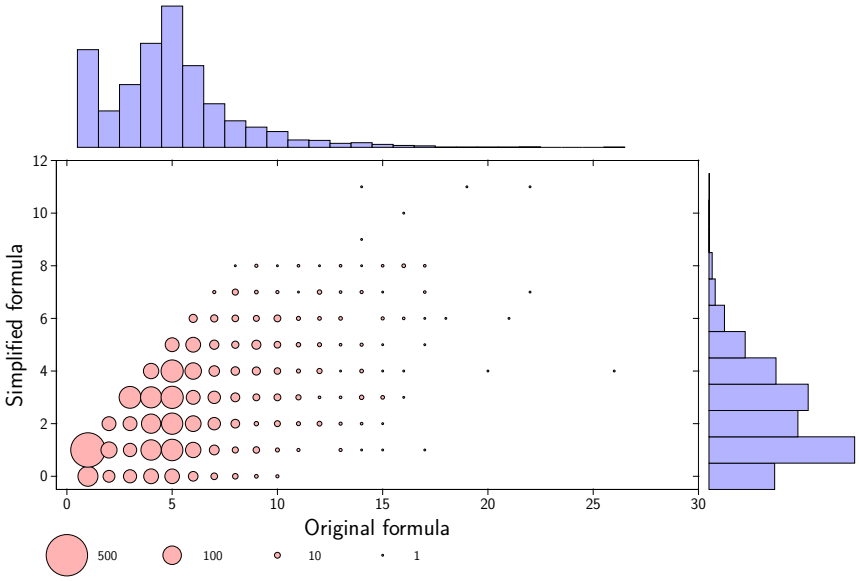


Figure 4.6. *Plot of number of plant utilized in Jamu medicines between original formula versus simplified formula. The size of the bubbles is proportional to the number of Jamu in the corresponding coordinates. The marginal distribution of the number of plant used in Jamu medicines for original formula and simplified formula are depicted at the top and right side of the scatter plot, respectively.*

have significance coefficient on that corresponding efficacy. Due to the absence of parametric testing for the coefficients in PLS Regression, permutation testing is proposed. The procedure for permutation test is similar to parametric test only that the underlying distribution for the testing is generated through a resampling process. In each resampling round, the order of the response is permuted while the order of the predictors is maintained. Then the PLS-DA model is applied and the regression coefficients is calculated. After repeating the resampling process many times, accumulation of the calculated coefficients form the underlying distribution for the permutation testing. By performing 1,000 permutation process and using 5% significance level, I found 231 plants are significant for a given efficacy and usually they are utilized most intensively in Jamu medicines for that efficacy

relative to the usage for other efficacies, and many of them are supported by scientific papers.

Moreover, the idea of simplifying the Jamu formula by utilizing only plants serve as main ingredients is proposed. PLS-DA model of reduced variable, i.e. removing the non-significant plant, showing similar performance compared with PLS-DA model of the original data set. It indicates that the dropped variables, i.e. the non-significant plants, contribute little on the PLS-DA Model so that removing them did not affecting the performance of the PLS-DA model. Moreover, PLS-DA model of reduced formula, i.e. simplifying the Jamu formula using only the main ingredients, showing better prediction performance compared with PLS-DA model of the original data set. It is because the simplification make the plant usage in Jamu become more compact, i.e. concentrated only in certain efficacy where these plants serve as main ingredients. It reduces the noise caused by the use of plants serve as supporting ingredients with no significant role in efficacy and subsequently increase the correct prediction of Jamu efficacy produced by the PLS-DA model. Thus, it indicates that, statistically, Jamu formula can be simplified by utilizing main plants only without losing its efficacy.

Chapter 5

Degree Distribution of Jamu Formulas

In this chapter, a bipartite network connecting Jamu and plant is used to explore the properties of Jamu formulation. The exploration involving the Jamu out-degree and plant in-degree properties of Jamu formulation network.

5.1 Degree Distribution

In the study of networks, the degree of a node is the number of connections or edges the node has to other nodes; the degree distribution is the probability distribution of these degrees over the whole network. If the network is directed, as in our case of Jamu-plant connections, then each node has two different degrees, the in-degree and the out-degree, which represent the numbers of incoming and outgoing connections, respectively.

To characterize the relationships between Jamu and plants, a power-law analysis of this network is performed; Fig. 5.1 shows the procedure for

this power-law analysis. The counts of Jamu corresponding to numbers of plants utilized in the formula (Jamu out-degree), and counts of plants corresponding to numbers of Jamu utilizing those plants (plant in-degree) are obtained as the core for the power-law analysis.

5.2 Results

For original data set, a clear linear decreasing trend of plant in-degree distribution (Fig. 5.2a) was observed demonstrating that plant utilization in Jamu follows a scale-free property. This means that the majority of plants are not widely used in Jamu formulas, whereas some plants are utilized frequently. Thus, the mechanism of plant utilization in Jamu can be explained by growing bipartite graphs (Guillaume & Latapy, 2006; Ohkubo et al., 2005) corresponding to the Barabási and Albert (BA) model (Barabási & Albert, 1999). In this model, each formulation of new Jamu medicine represents addition of a new plant or removal of a pre-existing one from a prior formula, using preferential attachment. Preferential attachment means that there is a higher probability to utilize a specific plant with larger utilization in Jamu formulas, a phenomenon called rich-get-richer (Barabási & Albert, 1999).

From Chapter 4 it is observed that the plants serve as main ingredients are the plants utilized most intensively in Jamu medicines. So, the preferential attachment of the scale-free pattern observed in plant in-degree distribution indicates that the Jamu formulation is started by choosing plants serve as main ingredients and then, if necessary, additional plants as supporting ingredients are added to the formula. Meanwhile, a scale-free property is not observed in the Jamu out-degree distributions for the original data set as well as for the reduced-variable and reduced-formula scenarios (Fig. 5.2b).

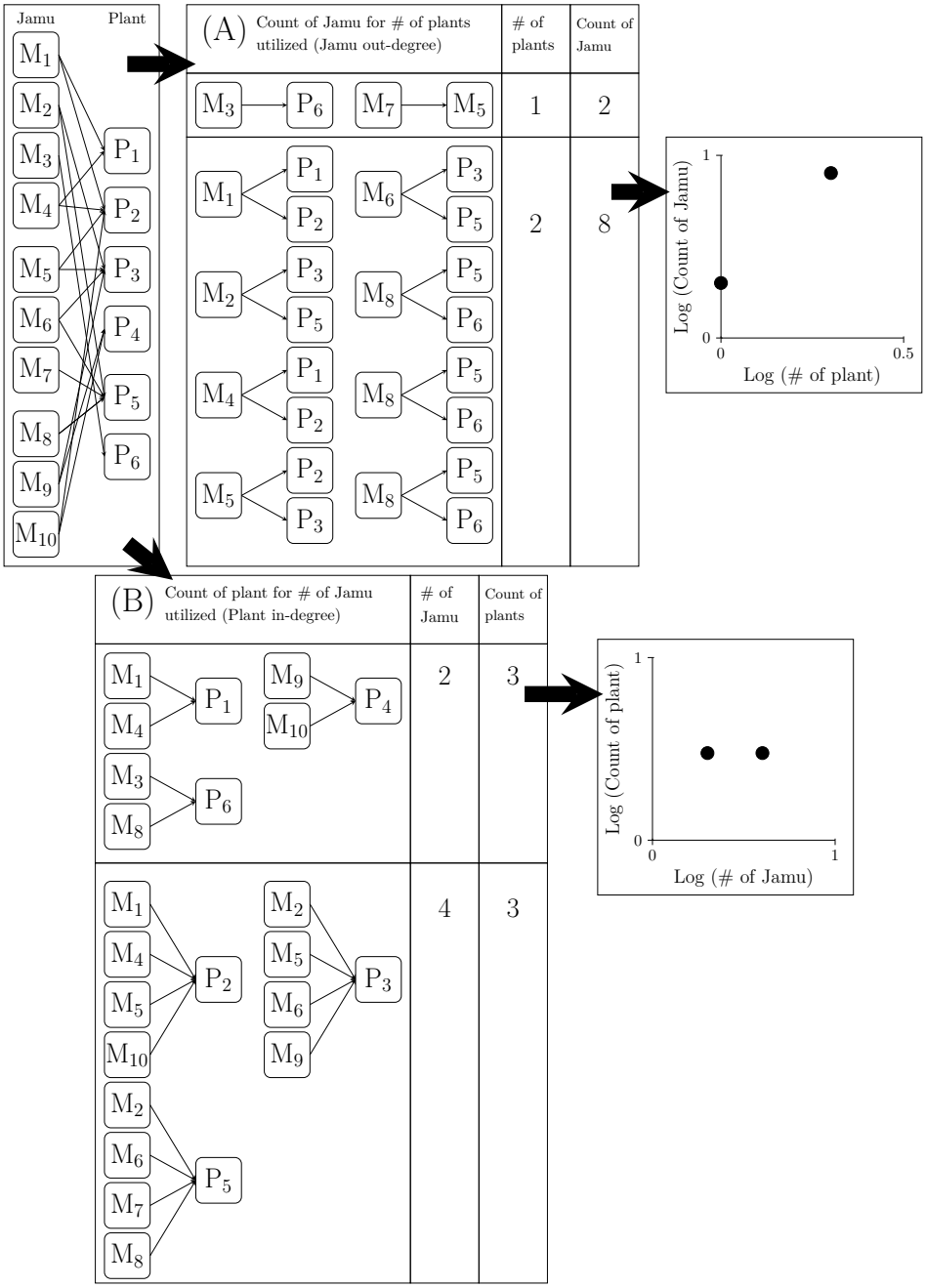
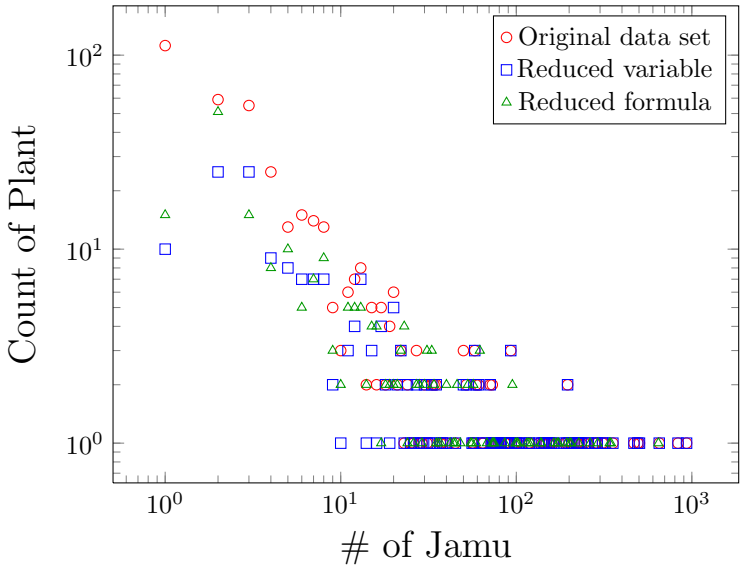
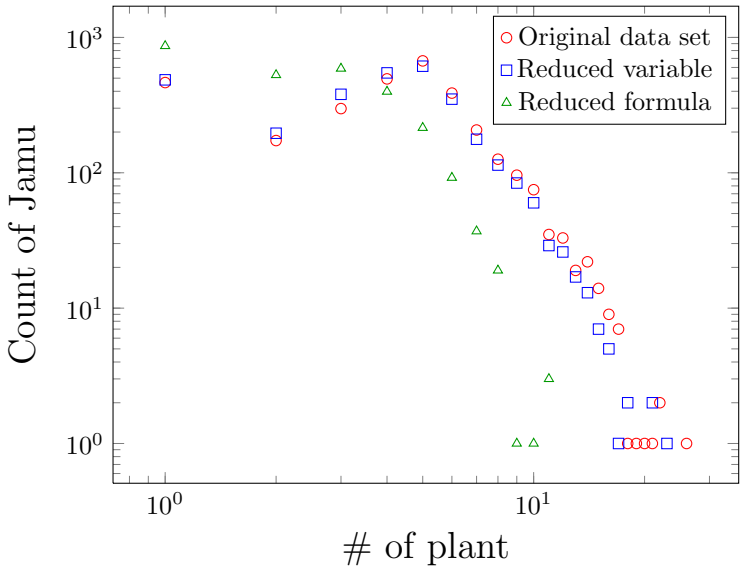


Figure 5.1. *Illustration of degree-distribution calculation for the bipartite graph connecting Jamu and plants. Part (A) showing process for Jamu out-degree, while part (B) for plant in-degree.*



(a) *Plant in-degree*



(b) *Jamu out-degree*

Figure 5.2. *Degree distribution of networks connecting Jamu and plants. (a) Plant in-degree, and (b) Jamu out-degree*

On the other hand, a scale-free pattern is not observed in the plant in-degree distribution of the reduced-variable and reduced-formula scenario

(Fig. 5.2a). This is because some points on the upper left part of the scatter plot of both reduced scenarios are dropped which make the linear pattern of both scatter plots are not as smooth as the scatter plot for the original dataset. The points on the upper left part of plant in-degree distribution are those for plants with low frequency of usage in Jamu medicines. From Chapter 4, these plants are regarded as supporting ingredients. So, dropping them during simplification of Jamu formulas destroys a scale-free pattern which previously observed in the original data set.

Interestingly, destruction of a scale-free pattern is also observed in plant in-degree distribution in Kampo medicines (Afendi et al., 2012), which was originally imported from China. The modern version of Kampo can be viewed as a reduced version of Chinese medicines, resulting from the seclusion of Japan from the outside world during the Edo period from 1600 onwards, leading to a reduction in the number of medicinal plants relative to the thousands of crude drugs used in traditional Chinese medicines. Thus, the simplification in fact happen in real situation as observed in modern Kampo medicines.

5.3 Summary

This chapter explores the plant in-degree distribution of Jamu formula. For original data set the distribution shows a scale-free pattern, meaning that there is a higher probability to utilize a specific plant with larger utilization in Jamu formulas. Regarding that the plants serve as main ingredients are the plants utilized most intensively in Jamu medicines then it indicates that the Jamu formulation is started by choosing plants serve as main ingredients and then, if necessary, additional plants as supporting ingredients are added to the formula. However, the plant in-degree distributions of the reduced

version, due to the simplification process of dropping the supporting ingredients, are showing a destroyed scale free pattern, a similar pattern which also found in Kampo medicines that can be viewed as a reduced version of the Chinese medicines.

Chapter 6

Multiway Model of Jamu Medicines

In previous section, PLS-DA model has been developed to capture systematic utilization of plants in Jamu medicines to achieve desired efficacy. Plants serve as main ingredients also have been determined by testing the significance of coefficients in the resulting PLS-DA model. The next question arise is then what are the roles of the plants that serve as main ingredients in Jamu medicines. In order to answer this question, the reported pharmacological activity of the plants is added to the predictor's block. The pharmacological activity itself describes the beneficial or adverse effects of a plant on living matter. Thus, the additional of this new information is suitable for describing the roles of the plants in Jamu medicines which in turn useful in explaining the mechanism of Jamu medicines to achieve desired efficacy.

6.1 Data set for multiway model

The present study utilized 2,748 Jamu medicines that have been reduced so that the formula uses only the main ingredients. On the whole, these

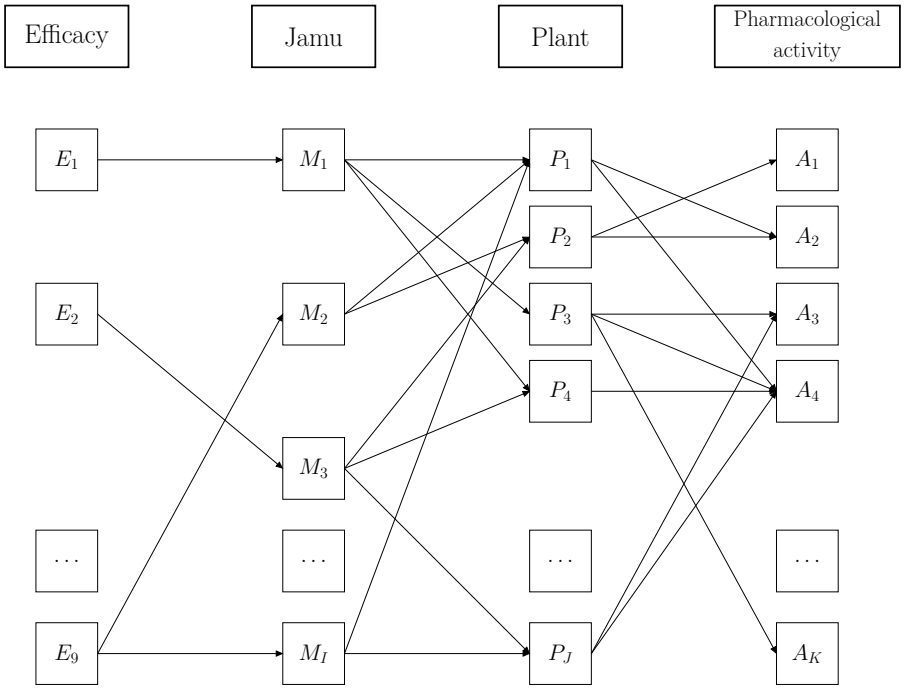


Figure 6.1. *Illustration of a network connecting Jamu efficacy, Jamu, plant, and pharmacological activity of plant*

2,748 Jamu use 231 plants while the number of the reported pharmacological activity of these 231 plants is equal to 46. On the other hand, each Jamu is classified into one of nine efficacy grouping. Fig. 6.1 illustrates the network connecting the efficacy of Jamu, Jamu medicine, plant, and pharmacological activity, while Table 6.1 describes the distribution of Jamu according to the nine efficacy grouping as well as the number of plant utilized in the corresponding efficacy and the number of pharmacological activity of the plants. In addition, Table 6.2 provides the list of pharmacological activity correspond to each efficacy.

Table 6.1. *Distribution of Jamu, plant, and pharmacological activity based on Jamu efficacy for reduced formula scenario*

Efficacy	Number of Jamu	Number of plants used in the corresponding efficacy	Number of pharmacological activity of the corresponding plants
URI	66	20	20
DOA	228	21	23
DMB	19	12	19
GST	720	26	32
FML	377	40	33
MSC	798	40	32
PIN	292	39	32
RSP	105	36	32
WND	143	43	34

Table 6.2. *List of pharmacological activity correspond to each efficacy. In this table,* '1' *and* '-' *indicates connection and no connection, repectively, between pharmacological activity and Jamu efficacy.*

Pharmacological activity	URI	DOA	GST	FML	MSC	PIN	RSP	WND
Adaptogen	-	-	1	1	1	-	-	1
Analgesic	1	1	1	1	1	1	1	1
Antacid	-	-	1	1	-	1	1	-
Anthelmintic	-	1	1	-	-	1	1	1
Antiarthritic	1	1	1	1	1	1	1	1
Antiasthmatic	-	-	1	1	1	1	1	1
Antimicrobial	1	1	1	1	1	1	1	1
Antibilious	-	-	-	-	-	1	-	1
Anticholesterolemic	-	1	-	1	-	-	-	-
Antidermatosic	-	-	-	1	-	-	-	1
Antiemetic	-	-	-	-	1	1	1	1
Antihaemorrhoidal	-	-	1	-	1	-	-	-
Antiinflammatory	1	1	1	1	1	1	1	1
Antipruritic	-	-	-	1	-	-	-	1

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Table 6.2 – continued from previous page

Pharmacological activity	URI	DOA	GST	FML	MSC	PIN	RSP	WND
Antipyretic	1	1	1	1	1	1	1	1
Antirheumatic	1	1	-	1	1	1	1	1
Antispasmodic	1	1	1	1	1	1	1	1
Antitumor	-	-	1	1	1	1	1	1
Antitussive	1	-	1	1	1	1	1	1
Laxative	1	1	1	1	-	1	1	-
Aphrodisiac	1	-	1	-	1	1	1	1
Astringent	1	-	1	1	-	1	1	1
Bitter	1	1	1	1	1	1	1	1
Cardiotonic	-	1	1	1	1	1	1	1
Carminative	-	1	1	1	-	-	-	-
Cholagogue	-	1	1	1	-	1	1	1
Decongestant	1	1	1	1	1	1	1	1
Demulcent	1	-	-	1	1	1	1	1
Depurative	-	1	1	-	1	1	-	1
Diaphoretic	-	-	-	1	1	1	1	1
Digestive	-	1	1	1	-	1	1	1
Diuretic	1	1	1	1	1	-	1	1
Emetic	-	-	-	-	1	1	1	-
Emmenagogue	-	-	1	1	1	1	1	1
Expectorant	1	-	1	-	1	1	1	-
Galactogogue	-	1	-	1	-	-	-	-
Hepatic	-	-	1	-	-	-	-	-
Hypnotic	1	-	-	1	1	-	-	-
Hypoglycaemic	-	-	1	-	1	-	-	-
Hypotensive	-	-	1	1	-	-	1	1
Kidney	-	-	-	-	1	-	-	-
Nervine	-	1	-	-	1	-	-	1
Rubefacient	1	-	-	-	1	1	1	1
Sedative	1	1	1	1	1	1	1	1
Stimulant	-	1	1	1	1	1	1	1
Vulnerary	1	1	1	1	1	1	1	1

During the modeling process, the ingredients of Jamu provide the predictor while the Jamu efficacy serves as the response. In order to identify the function of the plants in Jamu to achieve specific efficacy, the reported

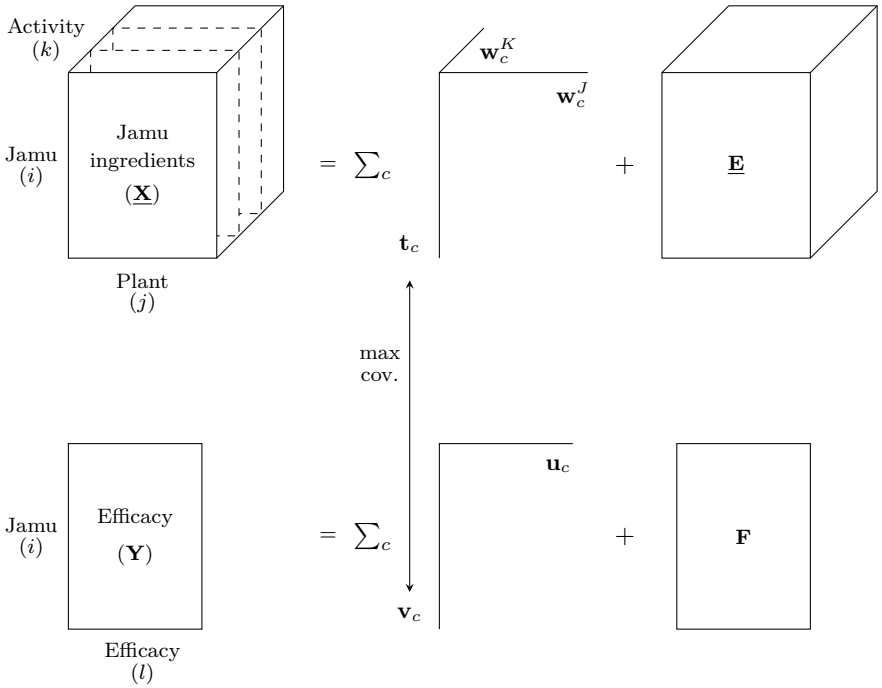


Figure 6.2. *Schematic diagram of the decomposition of both predictor and response blocks based on N-PLS model. Similar to PLS model, the* $\underline{\mathbf{X}}$ *and* $\mathbf{Y}$ *are decomposed into* $\mathbf{T}$ *and* $\mathbf{V}$*, respectively, such that the covariance among* $\mathbf{T}$ *and* $\mathbf{V}$ *are maximized. However, now the predictor's block has two weights instead of one, that is,* $\mathbf{W}^J$ *and* $\mathbf{W}^K$ *which are correspond to plant and pharmacological activity, respectively.*

pharmacological activities of the plants are added to the predictors block. Thus, the predictors block can be represented as a three-dimensional array $\underline{\mathbf{X}}$ $(I \times J \times K)$ indexed by Jamu medicine (i), plant (j), and pharmacological activity (k) as depicted in Fig. 6.2. Furthermore, the response block is represented as matrix $\mathbf{Y}$ $(I \times 9)$. The detail about the elements of array $\underline{\mathbf{X}}$ and matrix $\mathbf{Y}$ is as the following.

Let x_{ijk} $(i = 1, 2, \ldots, I; j = 1, 2, \ldots, J; k = 1, 2, \ldots, K; I = 2,748; J = 231; K = 46)$ denotes the usage status of plant j with pharmacological activity k in Jamu i, where $x_{ijk} = 1$ if the plant j with pharmacological activity

k is used in Jamu i, and $x_{ijk} = 0$ otherwise. On the other hand, let y_{il} $(l = 1, 2, \ldots, 9)$ represents the status of Jamu i on efficacy l, where $y_{il} = 1$ if Jamu i is classified into efficacy l, and $y_{il} = 0$ otherwise.

6.2 N-PLS-DA

An extension of PLSR to deal with multidimensional data known as Multiway Partial Least Squares has been developed by Bro (1996) and is called as N-PLS. In this model, the same principle of PLSR for two dimensional data is utilized, that is, both predictor and response blocks are decomposed successively into multilinear model such that the pairwise scores have maximal covariance. The score of the predictor is then regressed to the response variable. Fig. 6.2 illustrates the decomposition of N-PLS model. Moreover, N-PLS model can also be used for discrimination purpose, which is called as N-PLS-DA, that is the multiway version of PLS-DA, by utilizing the dummy matrix of group membership as the response variable.

Consider the three-dimensional array $\underline{\mathbf{X}}$ of the ingredients of Jamu extended with the information of reported pharmacological activity of the plants and the matrix $\mathbf{Y}$ of the Jamu efficacy as defined in the previous section. The decomposition of both the predictor and the response block based on N-PLS model are as follows

$$X_{ijk} = \sum_{c=1}^{C} T_{ic} W_{jc}^{J} W_{kc}^{K} + E_{ijk} \tag{6.1}$$

$$Y_{il} = \sum_{c=1}^{C} V_{ic} U_{lc} + F_{il} \tag{6.2}$$

The array $\underline{\mathbf{X}}$ is decomposed into a tri-linear model consists of one score vector for Jamu called $\mathbf{t}_c$ $(I \times 1)$, and two weight vectors, one for plant

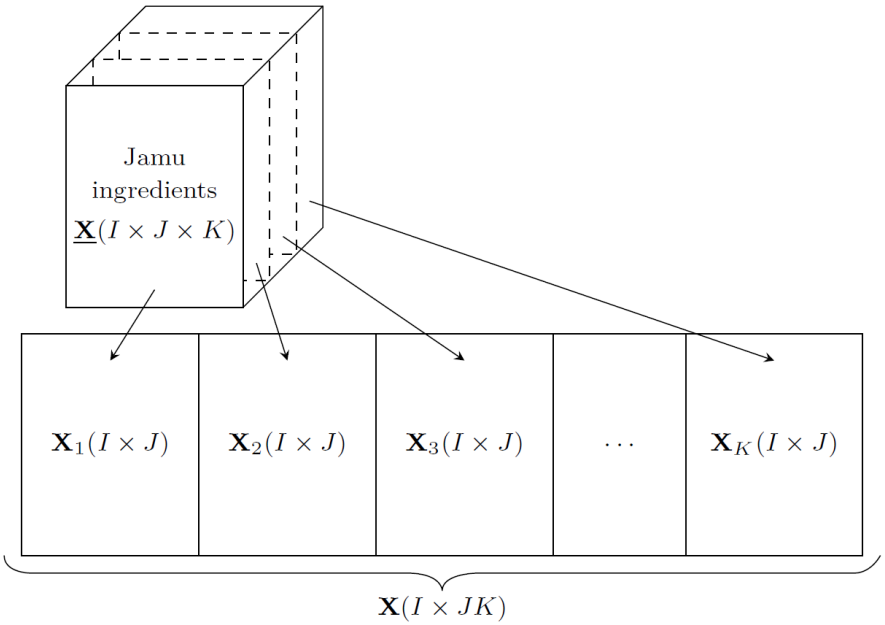


Figure 6.3. *Illustration of matricizing three-dimensional array* $\underline{\mathbf{X}}$ $(I \times J \times K)$ *into matrix* $\mathbf{X}$ $(I \times JK)$

called $\mathbf{w}_c^J$ $(J \times 1)$ and one for pharmacological activity called $\mathbf{w}_c^K$ $(K \times 1)$. Similarly, a bi-linear model is used in decomposing the matrix $\mathbf{Y}$ into one score vector $\mathbf{v}_c$ $(I \times 1)$ and one weight vector $\mathbf{u}_c$ (9×1). The decomposition is conducted such that the covariance among the score of predictor $\mathbf{t}$ and the corresponding score of the response $\mathbf{v}$ is maximized. All scores and weights are indexed with c showing that they correspond to cth multiway component, while C represents the total number of multiway components used in N-PLS model. Moreover, $\underline{\mathbf{E}}$ and $\mathbf{F}$ are the residuals of the decomposition of the three-dimensional array $\underline{\mathbf{X}}$ and matrix $\mathbf{Y}$, respectively.

Furthermore, let $\mathbf{X}_k$ $(I \times J)$ be the kth slice of $\underline{\mathbf{X}}$ $(I \times J \times K)$ for the corresponding kth pharmacological activity, then matricizing three-dimensional array $\underline{\mathbf{X}}$ into matrix $\mathbf{X}$ $(I \times JK)$ is performed as follows (Smilde et al., 2004)

$$\mathbf{X} = [\mathbf{X}_1 | \mathbf{X}_2 | \ldots | \mathbf{X}_K] \tag{6.3}$$

Fig. 6.3 depicts this unfolding process of array $\underline{\mathbf{X}}$ into matrix $\mathbf{X}$. Using this notation, the score $\mathbf{t}_c$ of the cth component can be calculated as (Smilde, 1997)

$$\mathbf{t}_c = \mathbf{X}(\mathbf{w}_c^K \otimes \mathbf{w}_c^J) \text{ or } t_{ic} = \sum_{j=1}^{J}\sum_{k=1}^{K} x_{ijk} w_{jc}^J w_{kc}^K \tag{6.4}$$

From Eq. (6.4), the weight corresponding to cth component, $\mathbf{w}_c$ $(JK \times 1)$, can be defined as

$$\mathbf{w}_c = (\mathbf{w}_c^K \otimes \mathbf{w}_c^J) \tag{6.5}$$

Smilde (1997) also described that, due to the deflation in $\mathbf{X}$ during the decomposition, the weight matrix $\mathbf{W}$ $(JK \times C)$ that can be applied directly to the original unfolded matrix $\mathbf{X}$ is defined as

$$\begin{aligned}\mathbf{W} = [\mathbf{w}_1 | (\mathbf{I}_{JK} - \mathbf{w}_1\mathbf{w}_1^t)\mathbf{w}_2 | \ldots | \\ (\mathbf{I}_{JK} - \mathbf{w}_1\mathbf{w}_1^t)(\mathbf{I}_{JK} - \mathbf{w}_2\mathbf{w}_2^t)\ldots(\mathbf{I}_{JK} - \mathbf{w}_{Q-1}\mathbf{w}_{Q-1}^t)\mathbf{w}_Q]\end{aligned} \tag{6.6}$$

Hence, the scores in $\mathbf{T}$ $(I \times C)$ expressed directly in terms of the X-columns is

$$\mathbf{T} = \mathbf{XW} \tag{6.7}$$

After the decomposition procedure, the next step is to regress $\mathbf{Y}$ on the component scores $\mathbf{T}$

$$\hat{\mathbf{Y}} = \mathbf{TB} \tag{6.8}$$

with

$$\mathbf{B} = (\mathbf{T}^t\mathbf{T})^{-1}\mathbf{T}^t\mathbf{Y} \tag{6.9}$$

From Eq. (6.7) and (6.8) we have

$$\hat{\mathbf{Y}} = \mathbf{XWB} \tag{6.10}$$

Therefore, the regression coefficients $\mathbf{B}_{NPLS}$ $(JK \times 9)$ needed to predict $\mathbf{Y}$ from $\mathbf{X}$ are obtained as

$$\mathbf{B}_{NPLS} = \mathbf{WB} \tag{6.11}$$

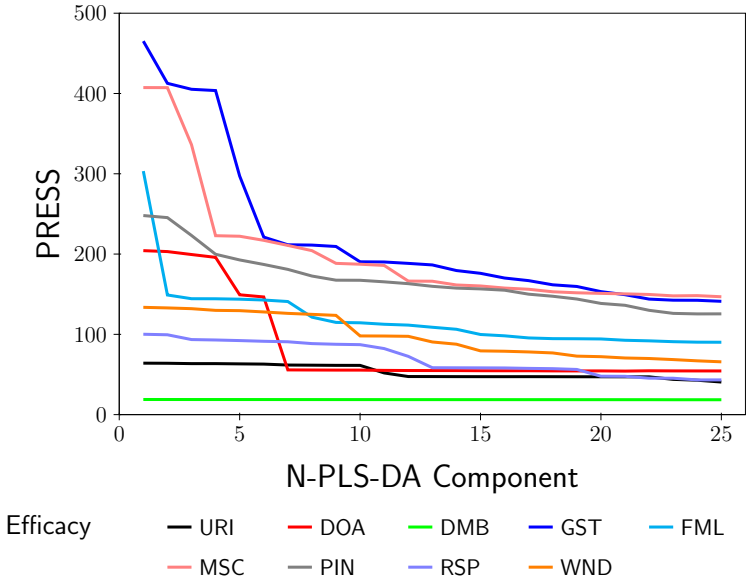
6.3 Results

6.3.1 Selection of the number of component in N-PLS-DA model

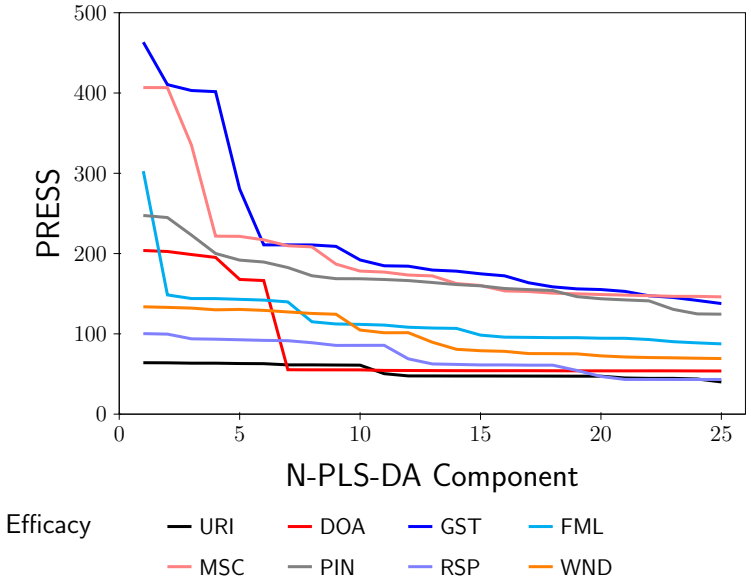
In this work, the number of component in N-PLS-DA model is selected using 5-folds cross-validation as in PLS-DA model, that is, the data set is splitted randomly into 5 sets, and, for a given number of component, each set is once selected as testing set and the other four are merged as training set. Next, the N-PLS-DA model is applied to the training set and use the obtained model to predict the response of the testing set. Prediction Error Sum of Squares (PRESS) for efficacy l using number of component c is then calculated as

$$PRESS(c)_l = \sum_{i=1}^{I} \left(y_{il} - \hat{y}_{(-i,l)c}\right)^2$$

where $\hat{y}_{(-i,l)c}$ is the prediction of the response for the testing set using number of component c. Fig. 6.4a shows the plot of the PRESS statistic against the number of component. As the number of component increased, some efficacy show a large decrease on their PRESS statistic (efficacy GST, FML, MSC, and DOA), while the other showing a moderate decrease (efficacy PIN) and small decrease (efficacy URI, RSP, WND, and DMB). However, from this figure it is obtained that the plot nearly constant from $c = 23$ onward. Using 23 components the N-PLS-DA model produces 56.5% and 67.9% in explaining variation of the predictor block and the response block, respectively.



(a) *Using all 9 efficacies*



(b) *Without efficacy DMB*

Figure 6.4. *PRESS plot of the N-PLS-DA model obtained using 5-folds cross-validation*

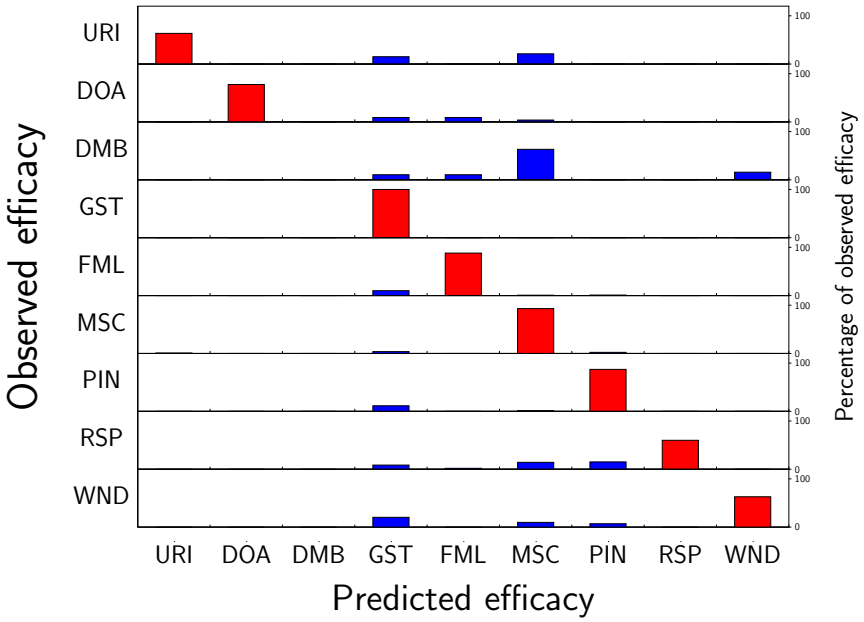
6.3.2 Prediction of Jamu efficacy using N-PLS-DA model

Furthermore, I utilized the N-PLS-DA model to predict the Jamu efficacy as follows. Note that the N-PLS-DA model produces matrix $\hat{\mathbf{Y}}$ $(I \times 9)$ as the

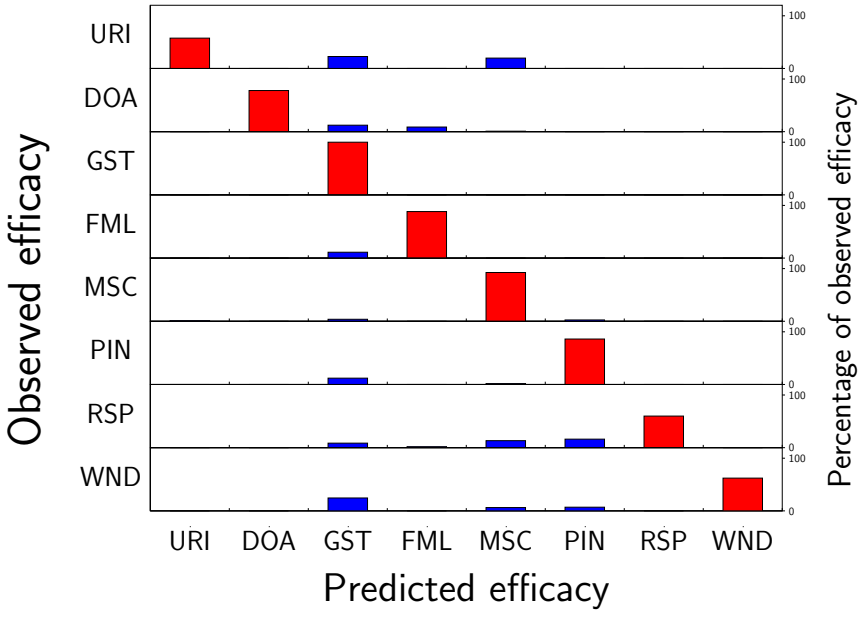
prediction of the response, i.e. the dummy matrix of Jamu efficacy group. So, each Jamu has a set of prediction consisting of nine values and each one corresponds to a specific efficacy, that is $\hat{y}_{il}$; $l = 1$ to 9. On the other hand, because each Jamu is classified into one efficacy group only, then for a given Jamu i, the maximum value of the row of the dummy matrix is 1 on the column which corresponds to the observed efficacy of Jamu i. Thus, a given Jamu i is predicted to have efficacy l if the $\hat{y}_{il}$ value is the largest across $l = 1$ to 9 for Jamu i.

Using this procedure, I obtained the total correct classification of Jamu efficacy is 88.1%, while the detail of the results of the classification for each efficacy is depicted in Fig. 6.5a. The performance of the N-PLS-DA model in predicting the Jamu efficacy vary across the efficacy groups, from 0% of correct classification for efficacy DMB to 100% of correct classification for efficacy GST. Furthermore, I found a large positive correlation ($r = 0.726$) between the percentage of correct classification and the number of Jamu classified to the corresponding efficacy. Thus, the poor performance of N-PLS-DA on efficacy DMB can be addressed due to the small number of Jamu in efficacy DMB. Therefore, I drop Jamu with efficacy DMB from our analysis, resulting new dimension of the array $\underline{\mathbf{X}}$ ($2729 \times 225 \times 46$) and the matrix $\mathbf{Y}$ (2729×8).

Fig. 6.4b shows the PRESS plot of the 5-folds cross-validation for the new data set, i.e. without the efficacy DMB. Based on this plot, I use 23 components for the N-PLS-DA model which produces 57.0% and 67.7% in explaining variation of the predictor block and the response block, respectively. Moreover, utilizing the N-PLS-DA model to predict the Jamu efficacy, I obtain 88.4% of total correct classification while the detail of the results of the classification for each efficacy is depicted in Fig. 6.5b.



(a) *Using all 9 efficacies*



(b) *Without efficacy DMB*

Figure 6.5. *Prediction status of Jamu efficacy*

Note that the percentage of total correct classification for N-PLS-DA model is smaller compare to PLS-DA model for reduced formula, although

the dataset for N-PLS-DA model is the extension, by adding the pharmacological activity, of the dataset for PLS-DA model for reduced formula. So, adding complexity of the dataset, which is expected would increase the predicting performance of the model, even reduce the total correct classification in predicting Jamu efficacy. However, in this analysis, adding complexity to the dataset by adding the reported pharmacological activity also adding noise to the dataset in form of pharmacological activity that not affecting a given efficacy. This noise then reduces the predicting performance of the N-PLS-DA model compare to PLS-DA model for reduced formula. Thus the N-PLS-DA model will be used only as means for evaluating which pharmacological activity affecting Jamu efficacy and *not* for predicting Jamu efficacy.

6.3.3 Characterization of N-PLS-DA components

Fig. 6.6 showing plot of the response weight, i.e. vector **u** obtained from the decomposition process of N-PLS-DA model, against the number of components. This plot is useful to characterize the information extracted on each component regarding the efficacy of Jamu. Note that for a given component, the vector **u** consists of 8 values and each corresponds to a specific efficacy. Thus, a component with large weight on a specific efficacy means that the component contains useful information in predicting that efficacy.

Many methods have been proposed in considering the loadings or weights of a component differ significantly from zero (Peres-Neto et al., 2003; Richman, 1988; Hair et al., 2010). In this work, however, I adopt the guidelines from Hair et al. (2010) that all weights (in absolute values) of 0.3 or above are significant for sample sizes of 350 or greater. As an example, for component 1, only the two largest weights, which are 0.766 and -0.499 for efficacy

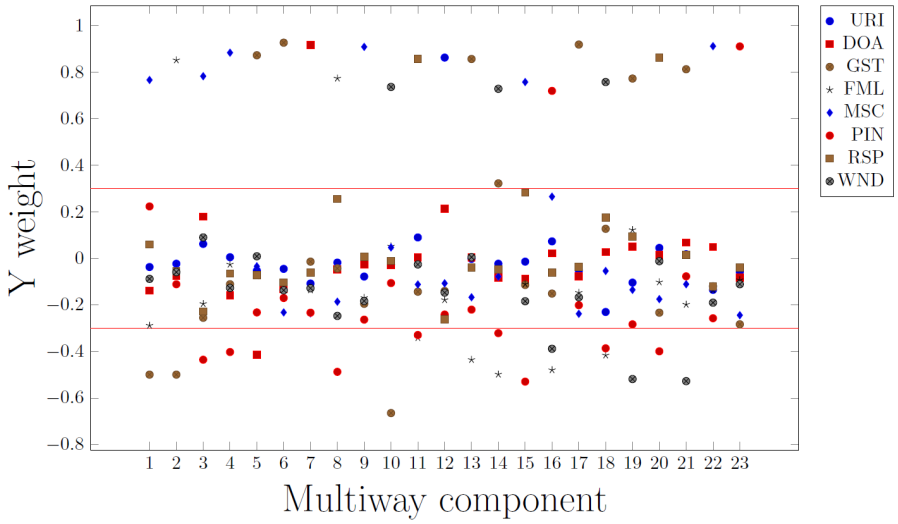


Figure 6.6. *Plot of response weight* (**u**) *against number of N-PLS-DA component. The red line is created at 0.3 and -0.3 as threshold for significancy. Any point beyond threshold is regarded as significant.*

Table 6.3. *List of component significantly related with the efficacy*

Efficacy	Component related with the corresponding efficacy	
	Positive contribution	Negative contribution
URI	12	-
DOA	7	5
GST	5, 6, 13, 14, 17, 19, 21	1, 2, 10
FML	2, 8	11, 13, 14, 16, 18
MSC	1, 3, 4, 9, 15, 22	-
PIN	16, 23	3, 4, 8, 11, 14, 15, 18, 20
RSP	11, 20	-
WND	10, 14, 18	16, 19, 21

MSC and GST, respectively, that larger than the threshold of 0.3. Thus, component 1 primarily comprises of information that positively related with efficacy MSC, and negatively related with efficacy GST. The results for all 23 components are summarized in Table 6.3.

Having the components significantly related with the efficacy as listed

in Table 6.3 allows us to concentrate on much fewer than 23 components in evaluating the pharmacological activity that significantly affecting a given efficacy. As an example, in investigating significant pharmacological activity for efficacy URI only component 12 is needed, while for efficacy DOA only component 7 and 5 are needed.

Note that in N-PLS-DA, the component in predictor block is obtained by maximizing the covariance with the component in response block. Therefore, we can expect a consistency between the result of the response components and the predictor components. Plot of the score of the predictor, i.e. vector $\mathbf{t}$, against the number of component is shown in Fig. 6.7. Taking component 1 as an example, it is obvious from Fig. 6.7 that large scores in $\mathbf{t}_1$ are corresponding to efficacy MSC while the small scores correspond to efficacy GST. On the other hand, in $\mathbf{u}_1$, the weight for efficacy MSC is 0.766, so the value can be considered as large; while the weight for efficacy GST is -0.499, so the value can be considered as small. Thus, the pattern in $\mathbf{t}$ is consistent with $\mathbf{u}$, that is, large score in $\mathbf{t}$ corresponds with positive weight in $\mathbf{u}$, while small score in $\mathbf{t}$ corresponds with negative weight in $\mathbf{u}$. So, the performance of the score of predictor $\mathbf{t}$ in discriminating the efficacies is consistent with the result of the response weight $\mathbf{u}$.

Having this consistency allows us to explore the predictor weight, and subsequently the pharmacological activity, that corresponds to a specific efficacy using the result of the response weight $\mathbf{u}$ as summarized in Table 6.3. For instance, as indicated previously, from Table 6.3 the efficacy DOA is best described using component 5 and 7, and we expect that Jamu with efficacy DOA has large score in component 7 and small score in component 5. Consequently, the predictor weight $\mathbf{w}$ that best describes the efficacy DOA should be positive with large magnitude on component 7 and negative

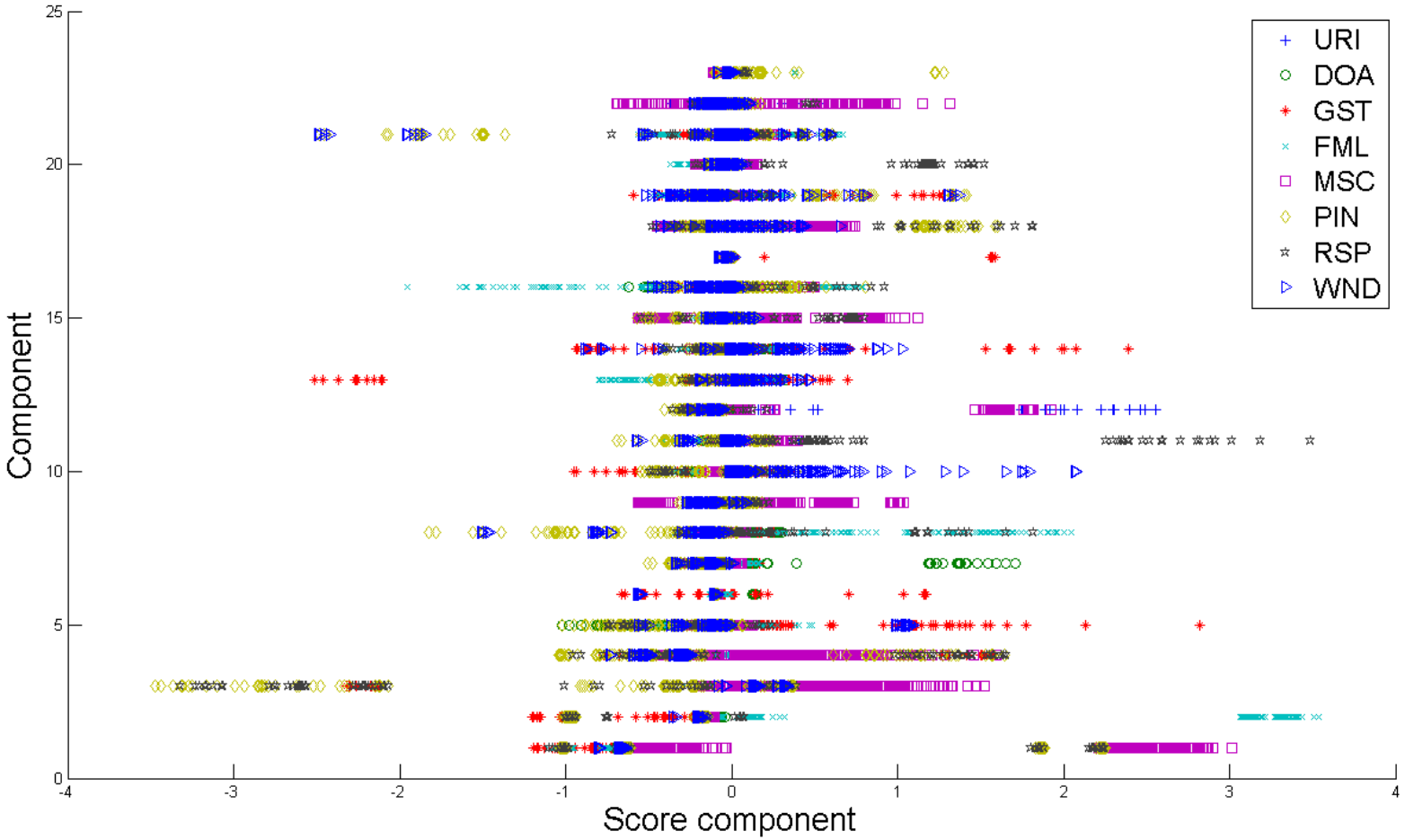


Figure 6.7. *Plot of predictor's scores* (**t**) *against number of N-PLS-DA component*

with large magnitude on component 5. Fig. 6.8 gives plot of weight of plant $\mathbf{w}^J$ for the corresponding component that best describe a given efficacy. So, for efficacy DOA, only the weight of plant for component 5 and 7 are provided. It is observed that most of the weights $\mathbf{w}^J$ for component 7 are positive while for component 5 are negative. This result is also applies to the other efficacies, that is, the sign of most of the weight $\mathbf{w}^J$ agree with the component contribution on the corresponding efficacy. On the other hand, all weights of pharmacological activity $\mathbf{w}^K$ are non-negative. Because the weight of the predictor $\mathbf{w}$ is a product of $\mathbf{w}^J$ and $\mathbf{w}^K$ (see Eq. (6.5)), then the sign of the weight $\mathbf{w}$ is determined by the sign of $\mathbf{w}^J$ while the magnitude of the weight $\mathbf{w}$ is determined both by $\mathbf{w}^J$ and $\mathbf{w}^K$.

Fig. 6.9 depicts the weight of pharmacological activity $\mathbf{w}^K$ for the corresponding component that best describe a given efficacy. A threshold line is created at 0.3 in order to identify the pharmacological activity that is significantly related with the efficacy, that is, the weight $\mathbf{w}^K$ of the significant pharmacological activity should be larger than 0.3. Table 6.4 provides the list of significant pharmacological activity for each efficacy.

In order to help identify the relationship between Jamu efficacy and the pharmacological activity, Fig. 6.10 depicts the clustergram of Jamu efficacy and the pharmacological activity based on the results shown in Table 6.4. The cluster of Jamu efficacy and the pharmacological activity was performed using Ward Linkage based on the Euclid Distance among the entities. The clustering of the pharmacological activity side clearly exhibits two groups. The first group consists of activities useful for one or two efficacies only. This group can be regarded as a group of specific activity because the effect of the activities are specific for certain efficacy. For example the diuretic activity, which from the clustergram, is useful for efficacy URI and DOA. Diuretic is

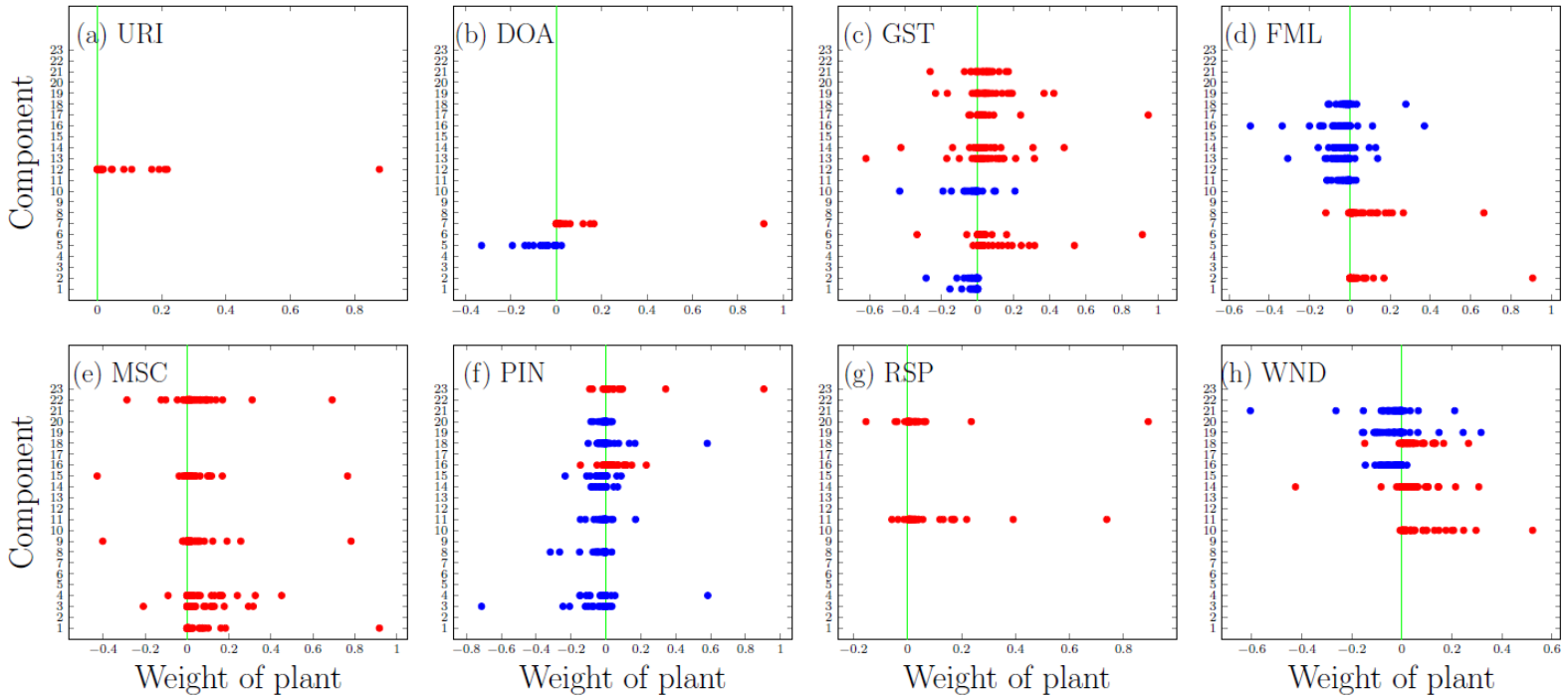


Figure 6.8. *Plot of weight of plant against number of N-PLS-DA component*

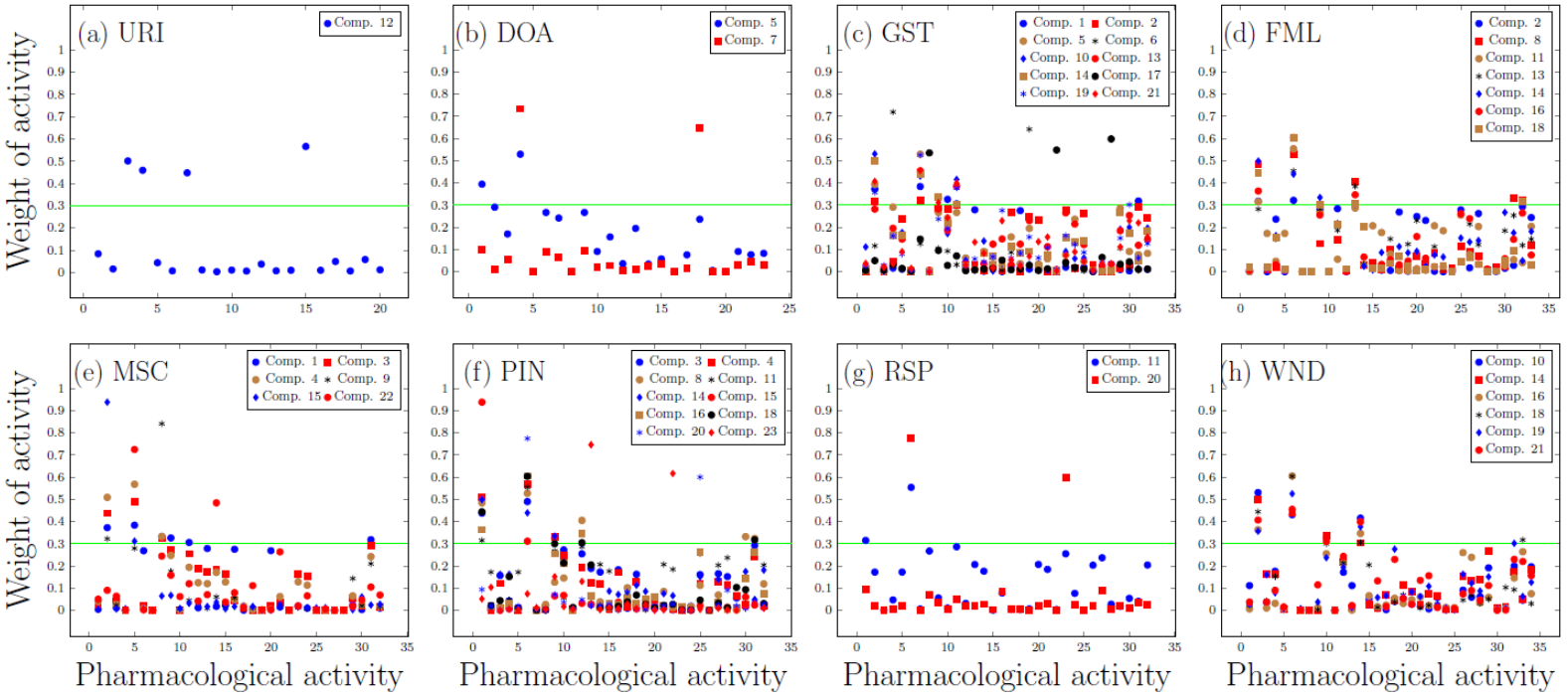


Figure 6.9. *Plot of weight of activity against pharmacological activity index*

Table 6.4. *List of pharmacological activity significantly related with Jamu efficacy*

Efficacy	Pharmacological activity
URI	Antimicrobial, Antiinflammatory, Antispasmodic, Diuretic
DOA	Analgesic, Antimicrobial, Diuretic
GST	Analgesic, Anthelmintic, Antimicrobial, Antihaemorrhoidal, Antiinflammatory, Antipyretic, Antispasmodic, Carminative, Depurative, Hypoglycaemic, Sedative, Stimulant
FML	Analgesic, Antimicrobial, Antiinflammatory, Antispasmodic, Sedative, Stimulant
MSC	Analgesic, Antimicrobial, Antiinflammatory, Antipyretic, Antispasmodic, Aphrodisiac, Stimulant
PIN	Analgesic, Antimicrobial, Antiinflammatory, Antispasmodic, Antitumor, Demulcent, Digestive, Sedative, Stimulant
RSP	Analgesic, Antimicrobial, Digestive
WND	Analgesic, Antimicrobial, Antiinflammatory, Antispasmodic, Sedative, Stimulant

an agent that increases the secretion and elimination of urine from the body (Hoffmann, 2003). Obviously, this activity is beneficial for the efficacy URI. Diuretic also help the body eliminate waste and support the whole process of inner cleansing, which is an action that is useful for efficacy DOA especially related with a slimming purpose. Another example is the activities antihaemorrhoidal, carminative, hypoglycaemic, depurative, and anthelmintic which are specifically related with efficacy GST. Antihaemorrhoidal means an activity that treats haemorrhoids (piles), while the carminative is defined as an activity that eases discomfort caused by flatulence. Hypoglycaemic activity help reduce the levels of sugar in the blood, whereas the depurative eliminates toxins and purifies the system especially the blood, and the anthelmintic helpful in expels parasites from the gut. Thus, all of these activities are helpful for the problem related with the digestive system, i.e.

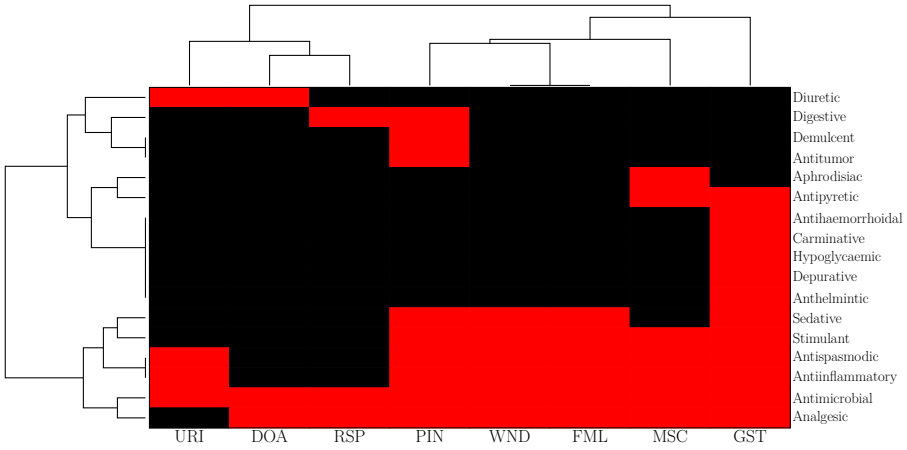


Figure 6.10. *Clustergram of pharmacological activity against Jamu efficacy*

the efficacy GST.

Furthermore, the second group of activity revealed by the clustergram consists of activities useful for at least four efficacies. In contrast to the first group, this group can be regarded as the general activities because of the diverse efficacies related to this group. Among all activities clustered to this group, antimicrobial activity is significantly related with all 8 efficacies. We can interpret this result as follows. Due to the environmental conditions, hygiene, and its location as a tropical country which led to many microbes that are harmful to health, then it is reasonable that antimicrobial activity is important and should be available in many Jamu formulas in Indonesia. No wonder that many popular medicinal plants in Indonesia such as Temulawak (*Curcuma xanthorriza*), Ginger (*Zingiber officinale*), Turmeric (*Curcuma longa*) or Kencur (*Kaempferia galanga*) have content of this activity (Duke et al., 2002).

Next, antiinflammation, antispasmodic, analgesic, sedative, and stimulant are also clustered into this general activity group. The reasons are as follow. Since many health problems or diseases are often accompanied

with inflammation or spasm, then the plants with antiinflammation and/or antispasmodic activity are chosen in many Jamu formulas. Those health problems or diseases are also often creating pain or other discomforts, which causing plants with activity analgesic, i.e. pain killer, or sedative, i.e. gently calms, reducing nervousness, distress and irritation, are often chosen in many Jamu medicines. Finally, stimulant activity, which excites or quickens activity of the physiological processes, is important for the recovery reason after one experiencing those health problems or diseases.

From the previous explanation regarding the grouping of pharmacological activity, it can be concluded that in formulating Jamu the plants are selected so that, beside curing the targeted diseases or health problems as indicated by the specific activities, the plants also should overcome the other discomforts caused by the targeted diseases or health problems as indicated by the general activities. It is in accordance with the process of making the Jamu medicines that involving whole part of plant and not only the specific active components. Hence, all the active components, which then become the specific or the general activities, are involved during the curing process of Jamu medicines toward the targeted diseases or health problems.

6.4 Summary

This chapter is intended to explore the role of plants serve as main ingredients by adding information of reported pharmacological activity of the plants into the predictors block, which can be represented by three-dimensional array, indexed by Jamu, plants, and pharmacological activity. To handle this three-dimensional array of predictor's block, multiway version of PLS-DA (N-PLS-DA) model is utilized. The N-PLS-DA model has the same principles as PLS-DA, which are decomposition of predictors and responses block

into factors subject to the factor of predictors has maximum covariance with the corresponding factor of responses and then the factor of predictors is regressed to the responses. The difference is that N-PLS-DA has two weights correspond to plants and activities, respectively. Exploration on weights of the pharmacological activity of the resulting N-PLS-DA model reveals that the effect of some activities are specific for certain efficacy and the other activities are diverse toward many efficacies. As a result, in formulating Jamu the plants are selected so that, besides curing the targeted diseases or health problems as indicated by the specific activities, the plants also should overcome the other discomforts caused by the targeted diseases or health problems as indicated by the general activities.

Chapter 7

Conclusions

By utilizing biplot configuration, I explored the relationship between Indonesian herbal plants and efficacy of jamu. Due to outliers, the biplot configuration is created based on robust PCA method. In the biplot configurations, many plants are clustered in the center, which are basically plants whose frequencies of usage in Jamu are very low. In contrast to the clustered plants, some plants are spread out and located near the efficacy of which the plants are highly utilized.

PLS-DA is used to model Jamu ingredients, which are a mixture of plants, to predict efficacies. Data regarding the usage of plant ingredients provide the predictors, whereas Jamu efficacies are the responses. I utilized $\hat{y}_{il}$ obtained from the PLS-DA to predict Jamu efficacy using two methods: maximum $\hat{y}_{il}$ and maximum probability. The prediction of Jamu efficacy using maximum $\hat{y}_{il}$ produced smaller errors than prediction using the maximum probability method. Hence, I used the maximum $\hat{y}_{il}$ method to predict Jamu efficacy, and this method resulted in 71.6% correct classification. Further exploration on the predictions reveals that intercepts for GST, FML, and MSC are larger than intercepts for the other six efficacies due to large

number of Jamu for those three efficacies. It makes some of the prediction of the efficacy are classified to efficacy GST, FML, and MSC regardless the original efficacy of the predicted Jamu.

Permutation tests can be used to identify the plants serve as main ingredients for a given efficacy; these are usually the plants utilized most intensively in Jamu medicines for that efficacy relative to the usage for other efficacies. I also found that many of the main ingredients identified by the permutation test in the present study are supported by scientific papers. Furthermore, compared with PLS-DA model using original data, PLS-DA model for reduced variables exhibits similar performance, and PLS-DA model for reduced formulas exhibits better performance in predicting Jamu efficacy. It is because, the dropped variables in PLS-DA model for reduced variables, i.e. the non-significant plants, contribute little on the PLS-DA Model so that removing them did not affecting the performance of the PLS-DA model. In addition, the simplification in PLS-DA model for reduced formulas make the plant usage in Jamu become more compact, i.e. concentrated only in certain efficacy where these plants serve as main ingredients. It reduces the noise caused by the use of plants serve as supporting ingredients with no significant role in efficacy and subsequently increase the correct prediction of Jamu efficacy produced by the PLS-DA model. Thus, it indicates that, statistically, Jamu formulas can be simplified by utilizing only the main plants, without losing efficacy.

Moreover, in the original data set, the pattern of plant in-degree distributions exhibits a scale-free property. Regarding that the plants serve as main ingredients are the plants utilized most intensively in Jamu medicines then it indicates that the Jamu formulation is started by choosing plants serve as main ingredients and then, if necessary, additional plants as supporting

ingredients are added to the formula. However, the plant in-degree distributions of the reduced version, due to the simplification process of dropping the supporting ingredients, are showing a destroyed scale free pattern, a similar pattern which also found in Kampo medicines that can be viewed as a reduced version of the Chinese medicines.

The relationship between ingredients of Jamu formula, which consist of plants, along with plant's pharmacological activity and Jamu efficacy can be modeled via N-PLS-DA model, i.e. the multiway version of PLS-DA model, in order to understand the mechanism of Jamu medicines to achieve desired efficacy. Exploration on weights of the pharmacological activity of the resulting N-PLS-DA model reveals that the beneficial of some activities are specific for certain efficacy and the other activities are diverse toward many efficacies. As a result, in formulating Jamu the plants are selected so that, besides curing the targeted diseases or health problems as indicated by the specific activities, the plants also should overcome the other discomforts caused by the targeted diseases or health problems as indicated by the general activities.

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Achievements

Reviewed publications

1. **Farit Mochamad Afendi**, Taketo Okada, Mami Yamazaki, Aki Hirai-Morita, Yukiko Nakamura, Kensuke Nakamura, Shun Ikeda, Hiroki Takahashi, Md. Altaf-Ul-Amin, Latifah K. Darusman, Kazuki Saito and Shigehiko Kanaya, 2012, Knapsack family databases: Integrated metabolite-plant species databases for multifaceted plant researches. Plant and Cell Physiol, Vol. 53(2), e1 doi:10.1093/pcp/pcr165 (in Chapter 5).

2. **Farit Mochamad Afendi**, Tetsuo Katsuragi, Akira Kato, Noritaka Nishihara, Kensuke Nakamura, Yukiko Nakamura, Ken Tanaka, Aki Hirai Morita, Altaf-Ul-Amin, Hiroki Takahashi and Shigehiko Kanaya, 2012, Systems Biology Approaches and Metabolomics for Understanding Japanese Traditional Kampo Medicine, Current Pharmacogenomics and Personalized Medicine, Vol. 10, 110-124 (in Chapter 4).

3. **Farit Mochamad Afendi**, Latifah K Darusman, Aki Hirai Morita, Md Altaf-Ul-Amin, Hiroki Takahashi, Kensuke Nakamura, Ken Tanaka, and Shigehiko Kanaya, 2012, Efficacy Prediction of Jamu Formulations

by PLS Modeling, Current Computer-Aided Drug Design (in Chapter 3).

4. **Farit Mochamad Afendi**, Latifah K Darusman, Masato Fukuyama, Md Altaf-Ul-Amin, and Shigehiko Kanaya, 2012, A Bootstrapping Approach for Investigating the Consistency of Assignment of Plants to Jamu Efficacy by PLS-DA Model, Malaysian Journal of Mathematical Sciences, Vol. 6(2), 147-164 (in Chapter 4).

5. Taketo Okada, **Farit Mochamad Afendi**, Md Altaf-Ul-Amin, Hiroki Takahashi, Kensuke Nakamura, and Shigehiko Kanaya, 2010, Metabolomics of Medicinal Plants: The Importance of Multivariate Analysis of Analytical Chemistry Data, Current Computer-Aided Drug Design, Vol. 6, 179-196 (in Chapter 2).

International conferences

1. **Farit Mochamad Afendi**, Latifah K Darusman, Aki Hirai, Md Altaf-Ul-Amin, Hiroki Takahashi, Kensuke Nakamura, and Shigehiko Kanaya, 2010, System Biology Approach for Elucidating the Relationship between Indonesian Herbal Plants and the Efficacy of Jamu, IEEE International Conference on Data Mining Workshops, ICDM 2010 (December 14-17 2010, University of Technology Sydney, Sydney, Australia) (in Chapter 2)

2. **Farit Mochamad Afendi**, Sulistiyani, Aki Hirai, Md Altaf-Ul-Amin, Hiroki Takahashi, Kensuke Nakamura, and Shigehiko Kanaya, 2011, Bootstrapping Jamu Dataset to Examine Assignment Consistency of Plants to Jamu Efficacy, The 2nd International Symposium on Temulawak (May 25-27 2011, Bogor Agricultural University, Bogor, Indonesia) (in Chapter 2)

3. **Farit Mochamad Afendi**, Md Altaf-Ul-Amin, and Shigehiko Kanaya, 2011, Permutation Test in Evaluating the Significance of Plants in PLS-DA Model of Jamu Ingredients, The 7th Asian Crop Science Association Conference, ACSAC 2011 (September 27-30 2011, Bogor Agricultural University, Bogor, Indonesia) (in Chapter 4)

Appendices

Appendix A

List of plants serve as main ingredients

This appendix provides the list of plants serve as main ingredients based on permutation test of PLS-DA coefficients along with the paper that support the usage of the plants on a given efficacy.

No	Scientific Name	Paper's title	Author's name	Journal's name
Efficacy: Urinary-related problems				
1	Alisma orientalis	Guaiane-type sesquiterpenoids from Alisma orientalis.	Peng GP, Tian G, Huang XF, Lou FC.	Phytochemistry. 2003 Aug;63(8):877-81.
2	Borreria hispida	Efek Infus Borreria hispida Schum terhadap Batu Kandung Kemih Buatan pada Tikus Putih (Rat)	Yun Astuti, B. Wahjoedi, Lucie Widowati	Kongres Biologi Nasional III, Oktober 1987, Purwokerto, Indonesia

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No	Scientific Name	Paper's title	Author's name	Journal's name
3	Cucurbita pepo	Inhibition of testosterone-induced hyperplasia of the prostate of sprague-dawley rats by pumpkin seed oil.	Gossell-Williams M, Davis A, O'Connor N.	J Med Food. 2006 Summer;9(2):284-6.
4	Imperata cylindrica	Chemical interaction in the invasiveness of cogongrass (Imperata cylindrica (L.) Beauv.).	Xuan TD, Toyama T, Fukuta M, Khanh TD, Tawata S.	J Agric Food Chem. 2009 Oct 28;57(20):9448-53.
5	Merremia mammosa	-	-	-
6	Orthosiphon stamineus	Evaluation of the genotoxicity of Orthosiphon stamineus aqueous extract.	Muhammad H, Gomes-Carneiro MR, Poa KS, De-Oliveira AC, Afzan A, Sulaiman SA, Ismail Z, Paumgartten FJ.	J Ethnopharmacol. 2011 Jan 27;133(2):647-53. Epub 2010 Oct 29.
7	Paeonia suffruticosa	Platelet anti-aggregatory and blood anti-coagulant effects of compounds isolated from Paeonia lactiflora and Paeonia suffruticosa.	Koo YK, Kim JM, Koo JY, Kang SS, Bae K, Kim YS, Chung JH, Yun-Choi HS.	Pharmazie. 2010 Aug;65(8):624-8.
8	Phellodendron chinense	-	-	-
9	Phyllanthus urinaria	Antioxidative and cardioprotective effects of Phyllanthus urinaria L. on doxorubicin-induced cardiotoxicity.	Chularojmontri L, Wattanapitayakul SK, Herunsalee A, Charuchongkolwongse S, Niumsakul S, Srichairat S.	Biol Pharm Bull. 2005 Jul;28(7):1165-71.
10	Plantago major	Hepatoprotective and anti-inflammatory activities of Plantago major L.	Trel I, Ozbek H, Erten R, Oner AC, Cengiz N, Yilmaz O.	Indian J Pharmacol. 2009 Jun;41(3):120-4.

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No	Scientific Name	Paper's title	Author's name	Journal's name
11	Prunus cerasus	Diuretic effect of powdered Cerasus avium (cherry) tails on healthy volunteers.	Hooman N, Mojab F, Nickavar B, Pouryousefi-Kermani P.	Pak J Pharm Sci. 2009 Oct;22(4):381-3.
12	Pygeum africanum	The natural compounds atraric acid and N-butylbenzene-sulfonamide as antagonists of the human androgen receptor and inhibitors of prostate cancer cell growth	Roell D, Baniahmad A.	Mol Cell Endocrinol. 2011 Jan 30;332(1-2):1-8. Epub 2010 Oct 19.
13	Serenoa repens	Long-Term Efficacy of Serenoa repens Treatment in Patients with Mild and Moderate Symptomatic Benign Prostatic Hyperplasia.	Sinescu I, Geavlete P, Multescu R, Gangu C, Miclea F, Coman I, Ioiart I, Ambert V, Constantin T, Petrut B, Feciche B.	Urol Int. 2011 Feb 8. [Epub ahead of print]
14	Smilax zeylanica	-	-	-
15	Solanum lycopersicum	Toxicological evaluation of 10% Solanum lycocarpum St. Hill fruit consumption in the diet of growing rats: hematological, biochemical and histopathological effects.	Soares-Mota MR, Schwarz A, Bernardi MM, Maiorka PC, Spinosa Hde S.	Exp Toxicol Pathol. 2010 Sep;62(5):549-53. Epub 2009 Aug 11.
16	Sonchus arvensis	Prevention of CCl4-induced nephrotoxicity with Sonchus asper in rat.	Khan RA, Khan MR, Sahreen S, Bokhari J.	Food Chem Toxicol. 2010 Aug-Sep;48(8-9):2469-76. Epub 2010 Jun 13.
17	Soya max	-	-	-

Continued on next page

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No	Scientific Name	Paper's title	Author's name	Journal's name
18	Strobilanthes crispus	Anticancer activity of a sub-fraction of dichloromethane extract of Strobilanthes crispus on human breast and prostate cancer cells in vitro.	Yaacob NS, Hamzah N, Nik Mohamed Kamal NN, Zainal Abidin SA, Lai CS, Navaratnam V, Norazmi MN.	BMC Complement Altern Med. 2010 Aug 5;10:42.
19	Wolfiporia extensa	-	-	-
20	Zea mays	[An orientational examination of the effects of extracts from mixtures of herbal drugs on selected renal functions].	Masteikov R, Klimas R, Samura BB, Savickas A, Samura BA, Belaij SI, Samura IB, Rabiskov M, Chalupov Z, Bernatoniene J.	Ceska Slov Farm. 2007 Apr;56(2):85-9.
Efficacy: Disorders of appetite				
1	Caesalpinia sappan	Toxicity evaluation of sappan wood extract in rats.	Sireeratawong S, Piyabhan P, Singhalak T, Wongkrajang Y, Temsiririrkkul R, Punsrirat J, Ruangwises N, Saraya S, Lerdvuthisopon N, Jaijoy K.	J Med Assoc Thai. 2010 Dec;93 Suppl 7:S50-7.
2	Cassia angustifolia	Portal vein thrombosis related to Cassia angustifolia.	Soyuncu S, Cete Y, Nokay AE.	Clin Toxicol (Phila). 2008 Sep;46(8):774-7.
3	Cassia fistula	Antiulcer activity of ethanol leaf extract of Cassia fistula.	Karthikeyan S, Gobianand K.	Pharm Biol. 2010 Aug;48(8):869-77.
4	Crataegus pinnatifida	Synergetic effect and structure-activity relationship of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors from Crataegus pinnatifida Bge.	Ye XL, Huang WW, Chen Z, Li XG, Li P, Lan P, Wang L, Gao Y, Zhao ZQ, Chen X.	J Agric Food Chem. 2010 Mar 10;58(5):3132-8.

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No	Scientific Name	Paper's title	Author's name	Journal's name
5	Curcuma aeruginosa	Efektivitas Ekstrak Temu Hitam (Curcuma Aeruginosa,) Dan Temu Lawak (Curcuma Xanthorhiza) Sebagai Kontrol Helminthiasis Terhadap Packed Cell Volume (Pcv) Pada Anak Kambing Peranakan Etawah	Rositawati Indrati	Jurnal Universitas Brawijaya
6	Curcuma heyneana	Zedoarondiol isolated from the rhizoma of Curcuma heyneana is involved in the inhibition of iNOS, COX-2 and pro-inflammatory cytokines via the downregulation of NF-kappaB pathway in LPS-stimulated murine macrophages.	Cho W, Nam JW, Kang HJ, Windono T, Seo EK, Lee KT.	Int Immunopharmacol. 2009 Aug;9(9):1049-57. Epub 2009 Apr 24.
7	Galla lusitania	-	-	-
8	Garcinia cambogia	Attenuation of colitis injury in rats using Garcinia cambogia extract.	dos Reis SB, de Oliveira CC, Acedo SC, Miranda DD, Ribeiro ML, Pedrazzoli J Jr, Gambero A.	Phytother Res. 2009 Mar;23(3):324-9.
9	Guazuma ulmifolia	The anti-diabetic properties of Guazuma ulmifolia Lam are mediated by the stimulation of glucose uptake in normal and diabetic adipocytes without inducing adipogenesis.	Alonso-Castro AJ, Salazar-Olivo LA.	J Ethnopharmacol. 2008 Jul 23;118(2):252-6. Epub 2008 Apr 12.

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No	Scientific Name	Paper's title	Author's name	Journal's name
10	Kaempferia pandurata	Kaempferia pandurata Roxb. inhibits Porphyromonas gingivalis supernatant-induced matrix metalloproteinase-9 expression via signal transduction in human oral epidermoid cells.	Yanti, Anggakusuma, Gwon SH, Hwang JK.	J Ethnopharmacol. 2009 Jun 22;123(2):315-24. Epub 2009 Mar 9.
11	Laminaria japonica	Luteolin isolated from the flowers of Lonicera japonica suppresses inflammatory mediator release by blocking NF-kappaB and MAPKs activation pathways in HMC-1 cells.	Kang OH, Choi JG, Lee JH, Kwon DY.	Molecules. 2010 Jan 18;15(1):385-98.
12	Litsea chinensis	Ethnobotanical Investigation of Some Medicinal Plants Availed by Gond Tribe of Naoradehi Wild Life Sanctuary, Madhya Pradesh	Dinesh Kumar Tiwari and Ashok Yadav	Anthropologist, 5(3): 201-202 (2003)
13	Murraya paniculata	The in vitro antigiardial activity of extracts from plants that are used for self-medication by AIDS patients in southern Thailand.	Sawangjaroen N, Subhadhirasakul S, Phongpaichit S, Siripanth C, Jamjaroen K, Sawangjaroen K.	Parasitol Res. 2005 Jan;95(1):17-21. Epub 2004 Nov 18.
14	Parameria laevigata	Pengaruh ekstrak kulit kayu rapat (Parameria Laevigata) terhadap nafsu makan dan bobot badan tikus putih jantan	Lydia Irawati Soesilo	Undergraduate theses of Unika Widya Mandala Surabaya, Indonesia

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No	Scientific Name	Paper's title	Author's name	Journal's name
15	Phyllanthus acidus	Effects of Phyllanthus acidus (L.) Skeels fruit on carbon tetrachloride-induced acute oxidative damage in livers of rats and mice.	Jain NK, Lodhi S, Jain A, Nahata A, Singhai AK.	Zhong Xi Yi Jie He Xue Bao. 2011 Jan;9(1):49-56.
16	Polygonum multiflorum	Antimutagenic property of an herbal medicine, Polygonum multiftorum Thunb. detected by the Tradescantia micronucleus assay.	Zhang H, Jeong BS, Ma TH.	J Environ Pathol Toxicol Oncol. 1999;18(2):127-30.
17	Punica granatum	Antidiabetic effect of Punica granatum flowers: effect on hyperlipidemia, pancreatic cells lipid peroxidation and antioxidant enzymes in experimental diabetes.	Bagri P, Ali M, Aeri V, Bhowmik M, Sultana S.	Food Chem Toxicol. 2009 Jan;47(1):50-4. Epub 2008 Oct 4.
18	Rheum tanguticum	The beneficial effect of Rheum tanguticum polysaccharide on protecting against diarrhea, colonic inflammation and ulceration in rats with TNBS-induced colitis: the role of macrophage mannose receptor in inflammation and immune response.	Liu L, Guo Z, Lv Z, Sun Y, Cao W, Zhang R, Liu Z, Li C, Cao S, Mei Q.	Int Immunopharmacol. 2008 Nov;8(11):1481-92. Epub 2008 May 28.
19	Terminalia catappa	Antidiabetic activity of Terminalia catappa Linn fruits.	Nagappa AN, Thakurdesai PA, Venkat Rao N, Singh J.	J Ethnopharmacol. 2003 Sep;88(1):45-50.

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No	Scientific Name	Paper's title	Author's name	Journal's name
20	Theae sinensis	Natural products: A safest approach for obesity	Vasudeva N, Yadav N, Sharma SK	Chin J Integr Med. 2012 Jun;18(6):473-80. Epub 2012 Jul 22
21	Zingiber purpureum	Inhibition of human pathogenic fungi by members of Zingiberaceae used by the Kenyah (Indonesian Borneo).	Ficker CE, Smith ML, Susiarti S, Leaman DJ, Irawati C, Arnason JT.	J Ethnopharmacol. 2003 Apr;85(2-3):289-93.
Efficacy: Disorders of mood and behavior				
1	Baeckea frutescens	-	-	-
2	Brassica nigrae	Preliminary studies on antihyperglycemic effect of aqueous extract of Brassica nigra (L.) Koch in streptozotocin induced diabetic rats.	Anand P, Murali KY, Tandon V, Chandra R, Murthy PS.	Indian J Exp Biol. 2007 Aug;45(8):696-701.
3	Carica papaya	Anticonvulsant activities of nutmeg oil of Myristica fragrans.	Wahab A, Ul Haq R, Ahmed A, Khan RA, Raza M.	Phytother Res. 2009 Feb;23(2):153-8.
4	Eleutherococcus senticosus	Effects of various Eleutherococcus senticosus cortex on swimming time, natural killer activity and corticosterone level in forced swimming stressed mice.	Kimura Y, Sumiyoshi M.	J Ethnopharmacol. 2004 Dec;95(2-3):447-53.
5	Euphorbia hirta	-	-	-
6	Ipomoea reptana	-	-	-
7	Leucas lavandulifolia	-	-	-
8	Moschosma polystachium	-	-	-

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No	Scientific Name	Paper's title	Author's name	Journal's name
9	Myristica fragrans	AMP-activated protein kinase (AMPK) activators from Myristica fragrans (nutmeg) and their anti-obesity effect.	Nguyen PH, Le TV, Kang HW, Chae J, Kim SK, Kwon KI, Seo DB, Lee SJ, Oh WK.	Bioorg Med Chem Lett. 2010 Jul 15;20(14):4128-31. Epub 2010 Jun 10.
10	Polygala glomerata	Benzophenone C-glucosides from Polygala glomerata Lour.	Li CJ, Zhang DM, Yu SS.	J Asian Nat Prod Res. 2008 Mar-Apr;10(3-4):329-36.
11	Valeriana javanica	-	-	-
12	Zingiber purpureum	Phenylbutenoid dimers isolated from Zingiber purpureum exert neurotrophic effects on cultured neurons and enhance hippocampal neurogenesis in olfactory bulbectomized mice	Matsui N, Kido Y, Okada H, Kubo M, Nakai M, Fukuishi N, Fukuyama Y, Akagi M.	Neurosci Lett. 2012 Mar 28;513(1):72-7. Epub 2012 Feb 11
Efficacy: Gastrointestinal disorders				
1	Allium sativum	Compared ability of garlic (Allium sativum) extract or a-tocopherol + magnesium association to reduce metabolic disorders and oxidative stress in diabetic rats.	0	Phytother Res. 2010 Nov 17. doi: 10.1002/ptr.3344. [Epub ahead of print]
2	Andrographis paniculata	Undetectable antibacterial activity of Andrographis paniculata (Burma) wall. ex ness.	Leelarasamee A, Trakulsomboon S, Sittisomwong N.	J Med Assoc Thai. 1990 Jun;73(6):299-304.
3	Apium graveolens	Gastric antiulcer, antisecretory and cytoprotective properties of celery (Apium graveolens) in rats.	Al-Howiriny T, Alsheikh A, Alqasoumi S, Al-Yahya M, ElTahir K, Rafatullah S.	Pharm Biol. 2010 Jul;48(7):786-93.

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No	Scientific Name	Paper's title	Author's name	Journal's name
4	Citrus amblycarpa	Analisis GC-MS dan daya anti bakteri minyak atsiri Citrus amblycarpa (Hassk) Ochse	Sri Mulyani, Susilowati and Maslan Maniur Hutabarat	Majalah Farmasi Indonesia, 20(3), 127 132, 2009
5	Clausena anisum-olens	-	-	-
6	Cocos nucifera	Evaluation of the use of Cocos nucifera as antimalarial remedy in Malaysian folk medicine.	Al-Adhroey AH, Nor ZM, Al-Mekhlafi HM, Amran AA, Mahmud R.	J Ethnopharmacol. 2011 Jan 26. [Epub ahead of print]
7	Curcuma aeruginosa	Antimicrobial activity and essential oils of Curcuma aeruginosa, Curcuma mangga, and Zingiber cassumunar from Malaysia	Kamazeri TS, Samah OA, Taher M, Susanti D, Qaralleh H.	Asian Pac J Trop Med. 2012 Mar;5(3):202-9.
8	Daucus carota	Antispasmodic activity of the tertiary base of Daucus carota, Linn. seeds.	Gambhir SS, Sen SP, Sanyal AK, Das PK.	Indian J Physiol Pharmacol. 1979 Jul-Sep;23(3):225-8.
9	Euphorbia thymifolia	Antioxidant and antiviral activities of Euphorbia thymifolia L.	Lin CC, Cheng HY, Yang CM, Lin TC.	J Biomed Sci. 2002 Nov-Dec;9(6 Pt 2):656-64.
10	Foeniculum vulgare	Beneficial effects of Foeniculum vulgare on ethanol-induced acute gastric mucosal injury in rats.	Birdane FM, Cemek M, Birdane YO, Glin I, Bykokuroglu ME.	World J Gastroenterol. 2007 Jan 28;13(4):607-11.
11	Grewia salutaris	-	-	-
12	Magnolia officinalis	Protective effect of a polyphenolic rich extract from Magnolia officinalis bark on influenza virus-induced pneumonia in mice.	Wu XN, Yu CH, Cai W, Hua J, Li SQ, Wang W.	J Ethnopharmacol. 2010 Dec 10. [Epub ahead of print]

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No	Scientific Name	Paper's title	Author's name	Journal's name
13	Melaleuca leucadendra	Efek Analgetika Ekstrak Etanol Daun Kayu Putih (Melaleuca leucadendron L) pada Mencit Jantan	Pratita Febri Setyo Tuhu	Undergraduate thesis Universitas Muhammadiyah Surakarta
14	Momordica charantia	Anti-hyperglycemic and anti-oxidative effect of aqueous extract of Momordica charantia pulp and Trigonella foenum graecum seed in alloxan-induced diabetic rats.	Tripathi UN, Chandra D.	Indian J Biochem Biophys. 2010 Aug;47(4):227-33.
15	Morinda citrifolia	Effects of Morinda citrifolia aqueous fruit extract and its biomarker scopoletin on reflux esophagitis and gastric ulcer in rats.	Mahattanadul S, Ridtitid W, Nima S, Phdoongsombut N, Ratanasuwon P, Kasiwong S.	J Ethnopharmacol. 2010 Dec 14. [Epub ahead of print]
16	Nigella sativa	Phytochemical and biological investigation of the extracts of Nigella sativa L. seed waste.	Michel CG, El-Sayed NS, Moustafa SF, Ezzat SM, Nesseem DI, El-Alfy TS.	Drug Test Anal. 2011 Feb 9. doi: 10.1002/dta.225. [Epub ahead of print]
17	Olea europaea	Olive (Olea europaea L.) leaf extract elicits antinociceptive activity, potentiates morphine analgesia and suppresses morphine hyperalgesia in rats.	Esmaeili-Mahani S, Rezaeezadeh-Roukerd M, Esmaeilpour K, Abbasnejad M, Rasoulian B, Sheibani V, Kaeidi A, Hajializadeh Z.	J Ethnopharmacol. 2010 Oct 28;132(1):200-5. Epub 2010 Aug 14.
18	Pandanus amaryllifolius	Aktivitas Senyawa Antidiabetes Ektrak Etil Asetat Daun Pandan Wangi (Pandanus Amaryllifolius Roxb.)	Dede Sukandar, Sandra Hermanto, Imamah Al Mabrur	Jurnal Valensi Vol 1, No 6 (2010)

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No	Scientific Name	Paper's title	Author's name	Journal's name
19	Pandanus conoideus	Uji hambatan tumorigenesis sari buah merah (Pandanus conoideus lam.) terhadap tikus putih betina yang diinduksi 7,12 dimetilbenz(a)antrasen (dmba)	Abdul Munim, Retnosari Andrajati, Heni Susilowati	Majalah Ilmu Kefarmasian, Vol. III, No. 3, Desember 2006, 153 - 161
20	Phaleria papuana	Pengaruh Pemberian Ekstrak Buah Phaleria papuana terhadap Aktivitas Fagositosis Makrofag Mencit Balb/c	R.R. Dyah Ayu Nopitasari	Undergraduate thesis Universitas Diponegoro Indonesia
21	Psidium guajava	Ethyl acetate extract of Psidium guajava inhibits IgE-mediated allergic responses by blocking FceRI signaling.	Han EH, Hwang YP, Kim HG, Park JH, Choi JH, Im JH, Khanal T, Park BH, Yang JH, Choi JM, Chun SS, Seo JK, Chung YC, Jeong HG.	javascript:AL_get(this, 'jour', 'Food Chem Toxicol.');
22	Schisandra chinensis	[Phytotherapeutic aspects of diseases of the circulatory system. 7. Schisandra chinensis (Turcz.) Baill.): its composition and biological activity].	Opletal L, Krenkov M, Havlckov P.	Ceska Slov Farm. 2001 Jul;50(4):173-80.
23	Silybum marianum	Silymarin treatment reduces granuloma and hepatic fibrosis in experimental schistosomiasis.	Mata-Santos HA, Lino FG, Rocha CC, Paiva CN, Castelo Branco MT, Pyrrho Ados S.	Parasitol Res. 2010 Nov;107(6):1429-34. Epub 2010 Aug 7.
24	Spirulina	The effects of Spirulina on anemia and immune function in senior citizens.	Selmi C, Leung PS, Fischer L, German B, Yang CY, Kenny TP, Cysewski GR, Gershwin ME.	Cell Mol Immunol. 2011 Jan 31. [Epub ahead of print]

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No	Scientific Name	Paper's title	Author's name	Journal's name
25	Symplocos odoratissima	-	-	-
26	Syzygium cumini	Alpha-glucosidase inhibitory activity of Syzygium cumini (Linn.) Skeels seed kernel in vitro and in Goto-Kakizaki (GK) rats.	Shinde J, Taldone T, Barletta M, Kunaparaju N, Hu B, Kumar S, Placido J, Zito SW.	Carbohydr Res. 2008 May 19;343(7):1278-81. Epub 2008 Mar 18.
Efficacy: Female reproductive organ problems				
1	Achillea santolina	Chemical composition and antioxidant, antimicrobial, and antifungal activities of the essential oil of Achillea ligustica all.	Tuberoso CI, Kowalczyk A, Coroneo V, Russo MT, Dess S, Cabras P.	J Agric Food Chem. 2005 Dec 28;53(26):10148-53.
2	Allium fistulosum	Anti-ischemia steroidal saponins from the seeds of Allium fistulosum.	Lai W, Wu Z, Lin H, Li T, Sun L, Chai Y, Chen W.	J Nat Prod. 2010 Jun 25;73(6):1053-7.
3	Areca catechu	Antiovulatory and abortifacient effects of Areca catechu (betel nut) in female rats.	Shrestha J, Shanbhag T, Shenoy S, Amuthan A, Prabhu K, Sharma S, Banerjee S, Kafle S.	Indian J Pharmacol. 2010 Oct;42(5):306-11.
4	Artemisia cina	Studies on monieziasis of sheep I. Prevalence and antihelminthic effects of some plant extracts, a light and electron microscopic study.	Bashtar AR, Hassanein M, Abdel-Ghaffar F, Al-Rasheid K, Hassan S, Mehlhorn H, Al-Mahdi M, Morsy K, Al-Ghamdi A.	Parasitol Res. 2011 Jan;108(1):177-86. Epub 2010 Sep 24.
5	Baeckea frutescens	Phloroglucinols from Baeckea frutescens.	Fujimoto Y, Usui S, Makino M, Sumatra M.	Phytochemistry. 1996 Feb;41(3):923-5.
6	Canangium odoratum	-	-	-

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No	Scientific Name	Paper's title	Author's name	Journal's name
7	Cimicifuga racemosa	Gene expression profiling reveals effects of Cimicifuga racemosa (L.) NUTT. (black cohosh) on the estrogen receptor positive human breast cancer cell line MCF-7.	Gaube F, Wolfl S, Pusch L, Kroll TC, Hamburger M.	BMC Pharmacol. 2007 Sep 20;7:11.
8	Coriandrum sativum	Post-coital antifertility activity of the seeds of Coriandrum sativum in rats.	Al-Said MS, Al-Khamis KI, Islam MW, Parmar NS, Tariq M, Ageel AM.	J Ethnopharmacol. 1987 Nov;21(2):165-73.
9	Curcuma longa	Curcumin and genistein, plant natural products, show synergistic inhibitory effects on the growth of human breast cancer MCF-7 cells induced by estrogenic pesticides.	Verma SP, Salamone E, Goldin B.	Biochem Biophys Res Commun. 1997 Apr 28;233(3):692-6.
10	Curcuma zedoaria	[Effect of Curcuma zedoaria (Berg.) Bosc on the myoelectric activity of uterus in rats and study of its mechanisms]	Xu XB, Qin XM, Xu JD, Pang JJ.	Zhongguo Zhong Yao Za Zhi. 2001 May;26(5):334-7.
11	Elaeocarpus grandiflora	-	-	-
12	Elephantopus scaber	-	-	-

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No	Scientific Name	Paper's title	Author's name	Journal's name
13	Ficus deltoidea	Ficus deltoidea (Mas cotek) extract exerted anti-melanogenic activity by preventing tyrosinase activity in vitro and by suppressing tyrosinase gene expression in B16F1 melanoma cells.	Oh MJ, Abdul Hamid M, Ngadiran S, Seo YK, Sarmidi MR, Park CS.	Arch Dermatol Res. 2010 Oct 28. [Epub ahead of print]
14	Galla lusitania	-	-	-
15	Garcinia atroviridis	Atrovirisidone B, a new prenylated depsidone with cytotoxic property from the roots of Garcinia atroviridis.	Permanaa D, Abas F, Maulidiani, Shaari K, Stanslas J, Ali AM, Lajis NH.	Z Naturforsch C. 2005 Jul-Aug;60(7-8):523-6.
16	Hemigraphis colorata	-	-	-
17	Kaempferia angustifolia	Deteksi Kandungan Kimia dan Efek Oksitosik Fraksi Tidak Larut Etanol Infusa Daun Kaempferia angustifolia Roscue terhadap Uterus Marmut Terpisah	Pramono S and Sumastuti R	Majalah Farmasi Indonesia, 14(3), 114 - 118, 2003
18	Kaempferia pandurata	Cytotoxic mechanism of flavonoid from Temu Kunci (Kaempferia pandurata) in cell culture of human mammary carcinoma.	Sukardiman, Darwanto A, Tanjung M, Darmadi MO.	Clin Hemorheol Microcirc. 2000;23(2-4):185-90.

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20	Lepiniopsis ternatensis	-	-	-
21	Ligusticum acutilobum	-	-	-
22	Nigella sativa	Effect of Nigella sativa (N. sativa L.) and oxidative stress on the survival pattern of MCF-7 breast cancer cells.	Farah IO, Begum RA.	Biomed Sci Instrum. 2003;39:359-64.
23	Nyctanthes arbortritis	Tranquilizing, antihistaminic and purgative activity of Nyctanthes arbor tristis leaf extract.	Saxena RS, Gupta B, Lata S.	J Ethnopharmacol. 2002 Aug;81(3):321-5.
24	Ocimum sanctum	Antifertility screening of plants. 3. Effect of six indigenous plants on early pregnancy in albino rats.	Vohora SB, Garg SK, Chaudhury RR.	Indian J Med Res. 1969 May;57(5):893-9.
25	Parameria laevigata	Uji khasiat analgetika infus Kayu Rapet (Parameria Laevigata (Juss.) Moldenke) pada mencit putih	Sundari, Dian; Nuratmi, Budi and Gusmali, Desy M.	Media Penelitian dan Pengembangan Kesehatan vol. 15 no. 04 (2005)
26	Phaseolus radiatus	-	-	-
27	Piper betle	Antifertility effect of Piper betle Linn. extract on ovary and testis of albino rats.	Adhikary P, Banerji J, Chowdhury D, Das AK, Deb CC, Mukherjee SR, Chatterjee A.	Indian J Exp Biol. 1989 Oct;27(10):868-70.

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28	Pluchea indica	Isolation of pure compound R/J/3 from Pluchea indica (L.) Less. and its antiamoebic activities against Entamoeba histolytica.	Biswas R, Dutta PK, Achari B, Bandyopadhyay D, Mishra M, Pramanik KC, Chatterjee TK.	Phytomedicine. 2007 Aug;14(7-8):534-7. Epub 2006 Dec 15.
29	Prunus persica	Evaluation of oriental medicinal herbs for estrogenic and antiproliferative activities.	Kang SC, Lee CM, Choi H, Lee JH, Oh JS, Kwak JH, Zee OP.	Phytother Res. 2006 Nov;20(11):1017-9.
30	Psophocarpus tetragonolobus	Antimicrobial activities of Psophocarpus tetragonolobus (L.) DC extracts.	Sasidharan S, Zuraini Z, Yoga Latha L, Sangetha S, Suryani S.	Foodborne Pathog Dis. 2008 Jun;5(3):303-9.
31	Punica granatum	Chemopreventive and adjuvant therapeutic potential of pomegranate (Punica granatum) for human breast cancer.	Kim ND, Mehta R, Yu W, Neeman I, Livney T, Amichay A, Poirier D, Nicholls P, Kirby A, Jiang W, Mansel R, Ramachandran C, Rabi T, Kaplan B, Lansky E.	Breast Cancer Res Treat. 2002 Feb;71(3):203-17.
32	Quercus lusitanica	-	-	-
33	Sauropus androgynus	Effect of Sauropus androgynus leaf extracts on the expression of prolactin and oxytocin genes in lactating BALB/C mice.	Soka S, Alam H, Boenjamin N, Agustina TW, Suhartono MT.	J Nutrigenet Nutrigenomics. 2010;3(1):31-6. Epub 2010 Aug 26.
34	Sesbania grandiflora	Evaluation of anticancer activity of ethanol extract of Sesbania grandiflora (Agati Sesban) against Ehrlich ascites carcinoma in Swiss albino mice.	Sreelatha S, Padma PR, Umasankari E.	J Ethnopharmacol. 2011 Jan 18. [Epub ahead of print]

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36	Sparganium stoloniferum	Inhibitory effects of Oriental herbal medicines on IL-8 induction in lipopolysaccharide-activated rat macrophages.	Lee GI, Ha JY, Min KR, Nakagawa H, Tsurufuji S, Chang IM, Kim Y.	Planta Med. 1995 Feb;61(1):26-30.
37	Tamarindus indica	Antimicrobial activity of extracts from Tamarindus indica L. leaves.	Escalona-Arranz JC, Pres-Roses R, Urdaneta-Laffita I, Camacho-Pozo MI, Rodrguez-Amado J, Licea-Jimnez I.	Pharmacogn Mag. 2010 Jul;6(23):242-7.
38	Terminalia bellirica	Evaluation of antidepressant-like activity of aqueous and ethanolic extracts of Terminalia bellirica Roxb. fruits in mice.	Dhingra D, Valecha R.	Indian J Exp Biol. 2007 Jul;45(7):610-6.
39	Tetranthera brawas	-	-	-
40	Trifolium pratense	Seasonal variation of red clover (Trifolium pratense L., Fabaceae) isoflavones and estrogenic activity.	Booth NL, Overk CR, Yao P, Totura S, Deng Y, Hedayat AS, Bolton JL, Pauli GF, Farnsworth NR.	J Agric Food Chem. 2006 Feb 22;54(4):1277-82.
Efficacy: Musculoskeletal and connective tissue disorders				
1	Alpinia galanga	Alpinia galanga extracts downregulate interleukin-1-induced matrix metalloproteinases expression in human synovial fibroblasts.	Pothacharoen P, Choocheep K, Phitak T, Pompimon W, Kongtawelert P.	In Vitro Cell Dev Biol Anim. 2010 Dec 4. [Epub ahead of print]

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3	Atractylodis Macrocephala	[Effects of lactone I from Atractylodes macrocephala Koidz on cytokines and proteolysis-inducing factors in cachectic cancer patients].	Liu Y, Ye F, Qiu GQ, Zhang M, Wang R, He QY, Cai Y.	Di Yi Jun Yi Da Xue Xue Bao. 2005 Oct;25(10):1308-11.
4	Cibotium barometz	Antioxidative, tyrosinase inhibiting and antibacterial activities of leaf extracts from medicinal ferns.	Lai HY, Lim YY, Tan SP.	Biosci Biotechnol Biochem. 2009 Jun;73(6):1362-6. Epub 2009 Jun 7.
5	Cinnamomum sintok	-	-	-
6	Cistanches salsa	(2E,6R)-8-hydroxy-2,6-dimethyl-2-octenoic acid, a novel anti-osteoporotic monoterpene, isolated from Cistanche salsa.	Yamaguchi K, Shinohara C, Kojima S, Sodeoka M, Tsuji T.	Biosci Biotechnol Biochem. 1999 Apr;63(4):731-5.
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8	Cola acuminata	Content of polyphenolic compounds in the Nigerian stimulants Cola nitida ssp. alba, Cola nitida ssp. rubra A. Chev, and Cola acuminata Schott & Endl and their antioxidant capacity.	Atawodi SE, Pfundstein B, Haubner R, Spiegelhalder B, Bartsch H, Owen RW.	J Agric Food Chem. 2007 Nov 28;55(24):9824-8. Epub 2007 Nov 3.

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10	Cordyceps sinensis	Water extract of Cordyceps sinensis (WECS) inhibits the RANKL-induced osteoclast differentiation.	Mizuha Y, Yamamoto H, Sato T, Tsuji M, Masuda M, Uchida M, Sakai K, Taketani Y, Yasutomo K, Sasaki H, Takeda E.	Biofactors. 2007;30(2):105-16.
11	Curcuma xanthorrhiza	Antiinflammatory effect of Curcuma xanthorrhiza Roxb, and its active principles.	Ozaki Y.	Chem Pharm Bull (Tokyo). 1990 Apr;38(4):1045-8.
12	Cyperus rotundus	Antifatigue effect of Rubus coreanus Miquel extract in mice.	Jung KA, Han D, Kwon EK, Lee CH, Kim YE.	J Med Food. 2007 Dec;10(4):689-93.
13	Dioscorea opposite	Evaluation of the nanofibrillar structure of Dioscorea oppositeextract for cell attachment	Xia L, Lenaghan SC, Wills AB, Chen Y, Zhang M.	Colloids Surf B Biointerfaces. 2011 Nov 1;88(1):425-31. Epub 2011 Jul 18.
14	Epimedium brevicornum	Epimedium brevicornum Maxim extract relaxes rabbit corpus cavernosum through multitargets on nitric oxide/cyclic guanosine monophosphate signaling pathway.	Chiu JH, Chen KK, Chien TM, Chiou WF, Chen CC, Wang JY, Lui WY, Wu CW.	Int J Impot Res. 2006 Jul-Aug;18(4):335-42. Epub 2006 Jan 5.
15	Equisetum debile	Chemical constituents of Equisetum debile	Tan JM, Qiu YH, Tan XQ, Tan CH, Xiao K.	J Asian Nat Prod Res. 2011 Sep;13(9):811-6.

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17	Eurycoma longifolia	The anti-osteoporotic effect of Eurycoma Longifolia in aged orchidectomised rat model.	Shuid AN, Abu Bakar MF, Abdul Shukor TA, Muhammad N, Mohamed N, Soelaiman IN.	Aging Male. 2010 Sep 28. [Epub ahead of print]
18	Justicia gendarussa	Anti-arthritic potential of the plant Justicia gendarussa Burm F.	Paval J, Kaitheri SK, Potu BK, Govindan S, Kumar RS, Narayanan SN, Moorkoth S.	Clinics (Sao Paulo). 2009;64(4):357-62.
19	Kaempferia galanga	Antinociceptive activity of the methanolic extract of Kaempferia galanga Linn. in experimental animals.	Ridtitid W, Sae-Wong C, Reanmongkol W, Wongnawa M.	J Ethnopharmacol. 2008 Jul 23;118(2):225-30. Epub 2008 Apr 11.
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21	Massoia aromatica	Tinjauan beberapa sifat dan manfaat tumbuhan masoyi (Massoia aromaticum BECC.)	Iskandar, M.I.;Ismanto, Agus	Warta tumbuhan obat Indonesia, Vol 5 No.2: 7-8

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23	Orthosiphon stamineus	In vitro effects of active constituents and extracts of Orthosiphon stamineus on the activities of three major human cDNA-expressed cytochrome P450 enzymes.	Pan Y, Abd-Rashid BA, Ismail Z, Ismail R, Mak JW, Pook PC, Er HM, Ong CE.	Chem Biol Interact. 2011 Mar 15;190(1):1-8. Epub 2011 Jan 27.
24	Oryza sativa	Molecular mechanisms of anti-inflammatory action of the flavonoid, tricin from Njavara rice (Oryza sativa L.) in human peripheral blood mononuclear cells: Possible role in the inflammatory signaling.	Shalini V, Bhaskar S, Kumar KS, Mohanlal S, Jayalekshmy A, Helen A.	Int Immunopharmacol. 2012 Sep;14(1):32-8. Epub 2012 Jun 15.
25	Panax ginseng	Panax ginseng.	Kiefer D, Pantuso T.	Am Fam Physician. 2003 Oct 15;68(8):1539-42.
26	Panax pseudoginseng	Trilinolein preserves mitochondria ultrastructure in isolated rat heart subjected to global ischemia through antioxidant activity as measured by chemiluminescence.	Chan P, Niu CS, Cheng JT, Tsao CW, Tsai SK, Hong CY.	Pharmacology. 1996 Apr;52(4):216-25.

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28	Pimpinella pruatjan	Status Penelitian Purwoceng (Pimpinella alpina Molk.) di Indonesia	Ireng Darwati and Ika Roostika	Buletin Plasma Nutfah Vol.12 No.1 Th.2006
29	Piper nigrum	Pharmacological basis for the medicinal use of black pepper and piperine in gastrointestinal disorders.	Mehmood MH, Gilani AH.	J Med Food. 2010 Oct;13(5):1086-96.
30	Piper retrofractum	Chemical constituents of peppers (Piper spp.) and application to food preservation: naturally occurring antioxidative compounds.	Nakatani N, Inatani R, Ohta H, Nishioka A.	Environ Health Perspect. 1986 Aug;67:135-42.
31	Plantago major	Hepatoprotective and anti-inflammatory activities of Plantago major L.	Trel I, Ozbek H, Erten R, Oner AC, Cengiz N, Yilmaz O.	Indian J Pharmacol. 2009 Jun;41(3):120-4.
32	Sida rhombifolia	Anti-arthritic activity of various extracts of Sida rhombifolia aerial parts.	Gupta SR, Nirmal SA, Patil RY, Asane GS.	Nat Prod Res. 2009;23(8):689-95.
33	Sonchus arvensis	Sesquiterpene lactones from Sonchus arvensis L. and their antibacterial activity against Streptococcus mutans ATCC 25175.	Xia Z, Qu W, Lu H, Fu J, Ren Y, Liang J.	Fitoterapia. 2010 Jul;81(5):424-8. Epub 2009 Dec 16.

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35	Syzygium polyanthum	Biological activity and phytochemical analysis of three Indonesian medicinal plants, Murraya koenigii, Syzygiumpolyanthum and Zingiber purpurea.	Kusuma IW, Kuspradini H, Arung ET, Aryani F, Min YH, Kim JS, Kim YU.	J Acupunct Meridian Stud. 2011 Mar;4(1):75-9.
36	Talinum paniculatum	Khasiat dan Keamanan Som Jawa (Talinum paniculatum Gaertn) dan Kolesom (Talinum triangulare wild)	Yun Astuti Nugroho	Litbang Depkes Indonesia
37	Tribulus terrestris	Effect of Tribulus terrestris L. saponin mixture on some smooth muscle preparations: a preliminary study.	Arcasoy HB, Erenmemisoglu A, Tekol Y, Kurucu S, Kartal M.	Boll Chim Farm. 1998 Dec;137(11):473-5.
38	Zingiber aromaticum	Antitumor activity of extract of Zingiber aromaticum and its bioactive sesquiterpenoid zerumbone.	Kirana C, McIntosh GH, Record IR, Jones GP.	Nutr Cancer. 2003;45(2):218-25.
39	Zingiber officinale	Effects of ginger (Zingiber officinale Rosc.) on decreasing the production of inflammatory mediators in sow osteoarthrotic cartilage explants.	Shen CL, Hong KJ, Kim SW.	J Med Food. 2003 Winter;6(4):323-8.

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Efficacy: Pain and inflammation				
1	Allium cepae	Antibacterial and antioxidant activities of quercetin oxidation products from yellow onion (Allium cepa) skin.	Ramos FA, Takaishi Y, Shirotori M, Kawaguchi Y, Tsuchiya K, Shibata H, Higuti T, Tadokoro T, Takeuchi M.	J Agric Food Chem. 2006 May 17;54(10):3551-7.
2	Alstonia scholaris	Pharmacological evaluation of Alstonia scholaris: anti-inflammatory and analgesic effects.	Shang JH, Cai XH, Feng T, Zhao YL, Wang JK, Zhang LY, Yan M, Luo XD.	J Ethnopharmacol. 2010 May 27;129(2):174-81. Epub 2010 Feb 26.
3	Angelica sinensis	Antiinflammatory effect of tetramethylpyrazine and ferulic acid.	Ozaki Y.	Chem Pharm Bull (Tokyo). 1992 Apr;40(4):954-6.
4	Asarum sieboldii	Mechanism of antinociceptive effects of Asarum sieboldii Miq. radix: potential role of bradykinin, histamine and opioid receptor-mediated pathways.	Kim SJ, Gao Zhang C, Taek Lim J.	J Ethnopharmacol. 2003 Sep;88(1):5-9.
5	Blumea balsamifera	Anti-obesity effect of Blumea balsamifera extract in 3T3-L1 preadipocytes and adipocytes.	Kubota H, Kojima-Yuasa A, Morii R, Huang X, Norikura T, Rho SN, Matsui-Yuasa I.	Am J Chin Med. 2009;37(5):843-54.

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7	Cinchona succirubra	Antimalarial activity of Cinchona-like plants used to treat fever and malaria in Brazil.	Andrade-Neto VF, Brando MG, Stehmann JR, Oliveira LA, Krettli AU.	J Ethnopharmacol. 2003 Aug;87(2-3):253-6.
8	Cinnamomum camphora	[Study on antiinflammatory effect of different chemotype of Cinnamomum camphora on rat arthritis model induced by Freund's adjuvant].	Li H, Huang L, Zhou A, Li X, Sun J.	Zhongguo Zhong Yao Za Zhi. 2009 Dec;34(24):3251-4.
9	Cinnamomum cassia	Antiproliferative Activity of Cinnamomum cassia Constituents and Effects of Pifithrin-Alpha on Their Apoptotic Signaling Pathways in Hep G2 Cells.	Ng LT, Wu SJ.	Evid Based Complement Alternat Med. 2009 Dec 28. [Epub ahead of print]
10	Cinnamomum cullilawan	The Croonian Lectures on the Relationship between Chemical Structure and Physiological Action	T. Lauder Brunton	Br Med J. 1889 June 22; 1(1486): 13891397.
11	Cocos nucifera	Characterization of the antinociceptive and anti-inflammatory activities from Cocos nucifera L. (Palmae).	Rinaldi S, Silva DO, Bello F, Alviano CS, Alviano DS, Matheus ME, Fernandes PD.	J Ethnopharmacol. 2009 Apr 21;122(3):541-6. Epub 2009 Feb 7.

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12	Coleus scutellarioides	Aktivitas antibakteri ekstrak daun Jawer Kotok (Coleus scutellarioides (L.)Benth.)	Bintang, Maria; Kustaman, Eman	Undergraduate thesis, Bogor Agricultutal University
13	Commiphora myrrha	Anti-inflammatory and analgesic activity of different extracts of Commiphora myrrha.	Su S, Wang T, Duan JA, Zhou W, Hua YQ, Tang YP, Yu L, Qian DW.	J Ethnopharmacol. 2010 Dec 15. [Epub ahead of print]
14	Curcuma zedoaria	Inhibition of inducible prostaglandin E2 production and cyclooxygenase-2 expression by curdione from Curcuma zedoaria.	Oh OJ, Min HY, Lee SK.	Arch Pharm Res. 2007 Oct;30(10):1236-9.
15	Cymbopogon nardus	Comparative chemical and analgesic properties of essential oils of Cymbopogon nardus (L) Rendle of Benin and Congo.	Abena AA, Gbenou JD, Yayi E, Moudachirou M, Ongoka RP, Ouamba JM, Silou T.	Afr J Tradit Complement Altern Med. 2007 Feb 16;4(3):267-72.
16	Echinacea purpurea	Bactericidal and anti-inflammatory properties of a standardized Echinacea extract (Echinaforce): dual actions against respiratory bacteria.	Sharma SM, Anderson M, Schoop SR, Hudson JB.	Phytomedicine. 2010 Jul;17(8-9):563-8. Epub 2009 Dec 29.
17	Foeniculum vulgare	Antiinflammatory, analgesic and antioxidant activities of the fruit of Foeniculum vulgare.	Choi EM, Hwang JK.	Fitoterapia. 2004 Sep;75(6):557-65.
18	Gaultheria punctata	-	-	-
19	Graptophyllum pictum	Antiinflammatory effect of Graptophyllum pictum (L.) Griff.	Ozaki Y, Sekita S, Soedigdo S, Harada M.	Chem Pharm Bull (Tokyo). 1989 Oct;37(10):2799-802.

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21	Hedyotis corymbosa	Hepatoprotective studies on Hedyotis corymbosa (L.) Lam.	Sadasivan S, Latha PG, Sasikumar JM, Rajashekaran S, Shyamal S, Shine VJ.	J Ethnopharmacol. 2006 Jun 30;106(2):245-9. Epub 2006 Feb 21.
22	Helicteres isora	Antioxidant and Antidiabetic Activity of Helicteres isora (L.) Fruits.	Suthar M, Rathore GS, Pareek A.	Indian J Pharm Sci. 2009 Nov;71(6):695-9.
23	Mentha arvensis	Inhibition of immunologic and nonimmunologic stimulation-mediated anaphylactic reactions by the aqueous extract of Mentha arvensis.	Shin TY.	Immunopharmacol Immunotoxicol. 2003 May;25(2):273-83.
24	Mentha piperita	Antispasmodic effect of Mentha piperita essential oil on tracheal smooth muscle of rats.	de Sousa AA, Soares PM, de Almeida AN, Maia AR, de Souza EP, Assreuy AM.	J Ethnopharmacol. 2010 Jul 20;130(2):433-6. Epub 2010 May 19.
25	Moschosma polystachium	Repellency of volatile oils from Moschosma polystachyum and Solanum xanthocarpum against filarial vector Culex quinquefasciatus say.	Rajkumar S, Jebanesan A.	Trop Biomed. 2005 Dec;22(2):139-42.
26	Notopterygium incisum	Analgesic component of Notopterygium incisum Ting.	Okuyama E, Nishimura S, Ohmori S, Ozaki Y, Satake M, Yamazaki M.	Chem Pharm Bull (Tokyo). 1993 May;41(5):926-9.

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28	Parkia roxburghii	Two novel lectins from Parkia biglandulosa and Parkia roxburghii: isolation, physicochemical characterization, mitogenicity and antiproliferative activity.	Kaur N, Singh J, Kamboj SS, Agrewala JN, Kaur M.	Protein Pept Lett. 2005 Aug;12(6):585-95.
29	Pinus merkusii	-	-	-
30	Pistacia lentiscus	Antiinflammatory and antioxidant activities of gum mastic.	Mahmoudi M, Ebrahimzadeh MA, Nabavi SF, Hafezi S, Nabavi SM, Eslami Sh.	Eur Rev Med Pharmacol Sci. 2010 Sep;14(9):765-9.
31	Rubia cordifolia	Evaluation of nitric oxide scavenging activity, in vitro and ex vivo, of selected medicinal plants traditionally used in inflammatory diseases.	Basu S, Hazra B.	Phytother Res. 2006 Oct;20(10):896-900.
32	Ruta angustifolia	[Alkaloids from Ruta angustifolia Pers., Ruta chalepensis L., Ruta-graveolens L. and Ruta montana Mill].	Vasudevan TN, Luckner M.	Pharmazie. 1968 Sep 9;23(9):520-1.
33	Sanguisorba officinalis	Anti-asthmatic effect of Sanguisorba officinalis L. and potential role of heme oxygenase-1 in an ovalbumin-induced murine asthma model.	Lee NH, Lee MY, Lee JA, Jung DY, Seo CS, Kim JH, Shin HK.	Int J Mol Med. 2010 Aug;26(2):201-8.

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35	Syzygium aromaticum	Anti-nociceptive and anti-inflammatory activities of ethanol extract of syzygium aromaticum flower bud in Wistar rats and mice.	Tanko Y, Mohammed A, Okasha MA, Umar AH, Magaji RA.	Afr J Tradit Complement Altern Med. 2008 Jan 22;5(2):209-12.
36	Typhonium flagelliforme	[Pharmacological study on the extracts from Typhonium flagelliforme Blume].	Zhong Z, Zhou G, Chen X, Huang P.	Zhong Yao Cai. 2001 Oct;24(10):735-8.
37	Usnea misaminensis	Aktivitas Antibakteri Fraksi Metanol Kayu Angin (Usnea misaminensis (Vain) Not) terhadap Mycobacterium Tuberculosis H37Rv	Sutiningsih, Dwi and . Sulistyani	Undergraduate Thesis University Diponegoro
38	Zingiber officinale	Repeated oral administration of a squeezed ginger (Zingiber officinale) extract augmented the serum corticosterone level and had anti-inflammatory properties.	Ueda H, Ippoushi K, Takeuchi A.	Biosci Biotechnol Biochem. 2010 Nov 23;74(11):2248-52. Epub 2010 Nov 7.

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39	Zingiber officinale	Comparative antioxidant and anti-inflammatory effects of [6]-gingerol, [8]-gingerol, [10]-gingerol and [6]-shogaol.	Dugasani S, Pichika MR, Nadarajah VD, Balijepalli MK, Tandra S, Korlakunta JN.	J Ethnopharmacol. 2010 Feb 3;127(2):515-20. Epub 2009 Oct 13.
Efficacy: Respiratory diseases				
1	Abrus precatorius	Potent antiplatelet, anti-inflammatory and antiallergic isoflavanquinones from the roots of Abrus precatorius.	Kuo SC, Chen SC, Chen LH, Wu JB, Wang JP, Teng CM.	Planta Med. 1995 Aug;61(4):307-12.
2	Amomum compactum	Anti-asthmatic effects of an Amomum compactum extract on an ovalbumin (OVA)-induced murine asthma model.	Lee JA, Lee MY, Seo CS, Jung da Y, Lee NH, Kim JH, Ha H, Shin HK.	Biosci Biotechnol Biochem. 2010 Sep 23;74(9):1814-8. Epub 2010 Sep 7.
3	Blumea balsamifera	Anticancer activities and mechanisms of Blumea balsamifera extract in hepatocellular carcinoma cells.	Norikura T, Kojima-Yuasa A, Shimizu M, Huang X, Xu S, Kametani S, Rho SN, Kennedy DO, Matsui-Yuasa I.	Am J Chin Med. 2008;36(2):411-24.
4	Borreria hispida	Potential role of Borreria hispida in ameliorating cardiovascular risk factors.	Vasanthi HR, Mukherjee S, Lekli I, Ray D, Veeraraghavan G, Das DK.	J Cardiovasc Pharmacol. 2009 Jun;53(6):499-506.
5	Ceiba pentandra	Two new sesquiterpene lactones from Ceiba pentandra.	Rao KV, Sreeramulu K, Gunasekar D, Ramesh D.	J Nat Prod. 1993 Dec;56(12):2041-5.

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6	Citrus aurantium	Chinese Guidelines for Diagnosis and Treatment of Influenza	Nan-shan Zhong, Yi-min Li, Zi-feng Yang, Chen Wang, You-ning Liu, Xing-wang Li, Yue-long Shu, Guang-fa Wang, Zhan-cheng Gao, Guo-hua Deng, Li-xian He, Xiu-ming Xi, Bin Cao, Kun-ling Shen, Hao Wu, Ping-an Zhou, Qing-quan Li, Influenza Diagnosis and Treatment Expert Panel of the Chinese Ministry of Health	J Thorac Dis.2011 December;3(4): 274289.doi:10.3978/j.issn.2072-1439.2011.10.01
7	Clausena anisum-olens	-	-	-
8	Clerodendron squamatum	Isolasi 5,7,4' trihidroksi flavon (apigenin) dari tumbuhan obat sipanggie-panggie (Clerodendron squamatum Vahl).	Mon, Irma	Eksakta, 2002, Vol 2: 8-13
9	Costus speciosus	Antituberculosis potential of some ethnobotanically selected Malaysian plants.	Mohamad S, Zin NM, Wahab HA, Ibrahim P, Sulaiman SF, Zahariludin AS, Noor SS.	J Ethnopharmacol. 2011 Feb 16;133(3):1021-6. Epub 2010 Nov 19.
10	Echinacea purpurea	Bactericidal and anti-inflammatory properties of a standardized Echinacea extract (Echinaforce): dual actions against respiratory bacteria.	Sharma SM, Anderson M, Schoop SR, Hudson JB.	Phytomedicine. 2010 Jul;17(8-9):563-8. Epub 2009 Dec 29.

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11	Elephantopus scaber	Evaluation of antiasthmatic activity of ethanolic extract ofElephantopus scaber L. leaves.	Sagar R, Sahoo HB.	Indian J Pharmacol. 2012 May;44(3):398-401.
12	Eriobotrya japonica	Anti-inflammatory and antinociceptive properties of the leaves of Eriobotrya japonica.	Cha DS, Eun JS, Jeon H.	J Ethnopharmacol. 2010 Dec 21. [Epub ahead of print]
13	Euphorbia hirta	Analgesic, antipyretic and anti-inflammatory properties of Euphorbia hirta.	Lanhers MC, Fleurentin J, Dorfman P, Mortier F, Pelt JM.	Planta Med. 1991 Jun;57(3):225-31.
14	Foeniculum vulgare	Activity against drug resistant-tuberculosis strains of plants used in Mexican traditional medicine to treat tuberculosis and other respiratory diseases.	Camacho-Corona Mdel R, Ramrez-Cabrera MA, Santiago OG, Garza-Gonzlez E, Palacios Ide P, Luna-Herrera J.	Phytother Res. 2008 Jan;22(1):82-5.
15	Forsythia suspensa	Antioxidant and antibacterial activity of two compounds (forsythiaside and forsythin) isolated from Forsythia suspensa.	Qu H, Zhang Y, Wang Y, Li B, Sun W.	J Pharm Pharmacol. 2008 Feb;60(2):261-6.
16	Fritillaria cirrhosa	Identification of bulb from Fritillaria cirrhosa by PCR with specific primers.	Li YF, Li YX, Lin J, Xu Y, Yan F, Tang L, Chen F.	Planta Med. 2003 Feb;69(2):186-8.
17	Glochidion rubrum	Penapisan Aktivitas Farmakologi dan Penentuan LD50 Ekstrak Etanol Daun Gambiran (Glochidion rubrum Bl.)	Rahmadewita	Undergraduate Thesis, 2006, University of Andalas

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18	Glycyrrhiza uralensis	Preparative purification of glycyrrhizin extracted from the root of liquorice using high-speed counter-current chromatography.	Jiang Y, Lu HT, Chen F.	J Chromatogr A. 2004 Apr 9;1033(1):183-6.
19	Harpagophytum procumbens	Analgesic, antiinflammatory and antidiabetic properties of Harpagophytum procumbens DC (Pedaliaceae) secondary root aqueous extract.	Mahomed IM, Ojewole JA.	Phytother Res. 2004 Dec;18(12):982-9.
20	Illicium verum	Antimicrobial properties of star anise (Illicium verum Hook f).	De M, De AK, Sen P, Banerjee AB.	Phytother Res. 2002 Feb;16(1):94-5.
21	Kaempferia galanga	Antinociceptive and anti-inflammatory activities of the aqueous extract of Kaempferia galanga leaves in animal models.	Sulaiman MR, Zakaria ZA, Daud IA, Ng FN, Ng YC, Hidayat MT.	J Nat Med. 2008 Apr;62(2):221-7. Epub 2007 Nov 29.
22	Mentha arvensis	Anti-Candida activity of Brazilian medicinal plants.	Duarte MC, Figueira GM, Sartoratto A, Rehder VL, Delarmelina C.	J Ethnopharmacol. 2005 Feb 28;97(2):305-11. Epub 2005 Jan 5.
23	Merremia mammosa	Uji Daya Hambat Mycobacterium Tuberculosis Dari Umbi Bidara Upas (Merremia mammosa Hall)	Mangestuti Agil, Noor Erma Sugianto, Rr. Retno Widyowati, Neny Purwitasari	DIPA-RM STRATNAS, 2010
24	Messua ferrea	Antibacterial potentiality of Mesua ferrea Linn. flowers.	Mazumder R, Dastidar SG, Basu SP, Mazumder A, Singh SK.	Phytother Res. 2004 Oct;18(10):824-6.

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25	Nasturtium indicum	-	-	-
26	Piper betle	The effect of betel quid chewing on the Achilles tendon reflex time	Harrison O, Linjim W, Adeniyi KO.	P N G Med J. 2006 Mar-Jun;49(1-2):47-51.
27	Piper cubeba	Tablet Hisap Ekstrak Kemukus (Piper cubeba L.f) Sebagai Ekspektoran pada Penyakit Bronkitis	Hilda Ismail, Fajri Nugroho, Khafidoh Kurniasih	Program Kreativitas Mahasiswa Gagasan Tertulis Didanai DIKTI 2010
28	Plantago major	Pengaruh Pemberian Ekstrak Daun Sendok (Plantago mayor L.) terhadap Hitung Sel Mast Intestinum pada Mencit Balb/C Model Asma Alergi	Rinny Oktafiani Arief	Undergraduate Thesis, 2010, Universitas Negeri Surakarta.
29	Prunus armeniaca	Antinociceptive effect of amygdalin isolated from Prunus armeniaca on formalin-induced pain in rats.	Hwang HJ, Kim P, Kim CJ, Lee HJ, Shim I, Yin CS, Yang Y, Hahm DH.	Biol Pharm Bull. 2008 Aug;31(8):1559-64.
30	Salix alba	[A short history of anti-rheumatic therapy. II. Aspirin].	Pasero G, Marson P.	Reumatismo. 2010 Apr-Jun;62(2):148-56.
31	Stachytarpheta jamaicensis	Antinociceptive and anti-inflammatory effects of Stachytarpheta jamaicensis (L.) Vahl (Verbenaceae) in experimental animal models.	Sulaiman MR, Zakaria ZA, Chiong HS, Lai SK, Israf DA, Azam Shah TM.	Med Princ Pract. 2009;18(4):272-9. Epub 2009 Jun 2.
32	Strobilanthes crispus	-	-	-

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33	Syzygium aromaticum	[Cytomegalovirus infection and its possible treatment with herbal medicines].	Shiraki K, Yukawa T, Kurokawa M, Kageyama S.	Nippon Rinsho. 1998 Jan;56(1):156-60.
34	Thymus vulgaris	Relaxant effect of Thymus vulgaris on guinea-pig tracheal chains and its possible mechanism(s).	Boskabady MH, Aslani MR, Kiani S.	Phytother Res. 2006 Jan;20(1):28-33.
35	Vitex trifolia	Flavonoids from Vitex trifolia L. inhibit cell cycle progression at G2/M phase and induce apoptosis in mammalian cancer cells.	Li WX, Cui CB, Cai B, Wang HY, Yao XS.	J Asian Nat Prod Res. 2005 Aug;7(4):615-26.
36	Zingiber officinale	Ginger attenuates acetylcholine-induced contraction and Ca2+ signalling in murine airway smooth muscle cells.	Ghayur MN, Gilani AH, Janssen LJ.	Can J Physiol Pharmacol. 2008 May;86(5):264-71.
Efficacy: Wounds and skin infection				
1	Aleurites moluccana	Anti-microbial activity and anti-complement activity of extracts obtained from selected Hawaiian medicinal plants.	Locher CP, Burch MT, Mower HF, Berestecky J, Davis H, Van Poel B, Lasure A, Vanden Berghe DA, Vlietinck AJ.	J Ethnopharmacol. 1995 Nov 17;49(1):23-32.
2	Aloe vera	Influence of Aloe vera on the glycosaminoglycans in the matrix of healing dermal wounds in rats.	Chithra P, Sajithlal GB, Chandrakasan G.	J Ethnopharmacol. 1998 Jan;59(3):179-86.
3	Anacardium occidentale	Effects of Anacardium occidentale stem bark extract on in vivo inflammatory models.	Olajide OA, Aderogba MA, Adedapo AD, Makinde JM.	J Ethnopharmacol. 2004 Dec;95(2-3):139-42.

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4	Andrographis paniculata	Anti-malarial activity of some xanthones isolated from the roots of Andrographis paniculata.	Dua VK, Ojha VP, Roy R, Joshi BC, Valecha N, Devi CU, Bhatnagar MC, Sharma VP, Subbarao SK.	J Ethnopharmacol. 2004 Dec;95(2-3):247-51.
5	Aquilaria sinensis	Laxative effects of agarwood on low-fiber diet-induced constipation in rats.	Kakino M, Tazawa S, Maruyama H, Tsuruma K, Araki Y, Shimazawa M, Hara H.	BMC Complement Altern Med. 2010 Nov 15;10:68.
6	Canangium odoratum	Sensitization to fragrance materials in Indonesian cosmetics.	Roesyanto-Mahadi ID, Geursen-Reitsma AM, van Joost T, van den Akker TW.	Contact Dermatitis. 1990 Apr;22(4):212-7.
7	Carica papaya	Topical Antimicrobials for Burn Wound Infections	Tianhong Dai, Ying-Ying Huang, Sulbha K. Sharma, Javad T. Hashmi, Divya B. Kurup, Michael R. Hamblin	Recent Pat Antiinfect Drug Discov. 2010 June 1; 5(2): 124151.
8	Cassia alata	In vitro antifungal activity of indirubin isolated from a South Indian ethnomedicinal plant Wrightia tinctoria R. Br.	Ponnusamy K, Petchiammal C, Mohankumar R, Hopper W.	J Ethnopharmacol. 2010 Oct 28;132(1):349-54. Epub 2010 Aug 5.
9	Cassia siamea	Synthesis and structure-activity relationships of cassiarin A as potential antimalarials with vasorelaxant activity.	Morita H, Tomizawa Y, Deguchi J, Ishikawa T, Arai H, Zaima K, Hosoya T, Hirasawa Y, Matsumoto T, Kamata K, Ekasari W, Widyawaruyanti A, Wahyuni TS, Zaini NC, Honda T.	Bioorg Med Chem. 2009 Dec 15;17(24):8234-40. Epub 2009 Oct 13.

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10	Citrus aurantium	Suppressive Effect on Lipopolysaccharide-Induced Proinflammatory Mediators by Citrus aurantium L. in Macrophage RAW 264.7 Cells via NF-?B Signal Pathway.	Kang SR, Han DY, Park KI, Park HS, Cho YB, Lee HJ, Lee WS, Ryu CH, Ha YL, Lee do H, Kim JA, Kim GS.	Evid Based Complement Alternat Med. 2011;2011. pii: 248592. Epub 2010 Sep 21.
11	Citrus hystrix	Chemical composition and antimicrobial activity of the essential oils from New Caledonian Citrus macroptera and Citrus hystrix.	Waikedre J, Dugay A, Barrachina I, Herrenknecht C, Cabalion P, Fournet A.	Chem Biodivers. 2010 Apr;7(4):871-7.
12	Citrus sinensis	Chemical profile, antifungal, antiaflatoxigenic and antioxidant activity of Citrus maxima Burm. and Citrus sinensis (L.) Osbeck essential oils and their cyclic monoterpene, DL-limonene.	Singh P, Shukla R, Prakash B, Kumar A, Singh S, Mishra PK, Dubey NK.	Food Chem Toxicol. 2010 Jun;48(6):1734-40. Epub 2010 Apr 9.
13	Cocos nucifera	Evaluation of the use of Cocos nucifera as antimalarial remedy in Malaysian folk medicine.	Al-Adhroey AH, Nor ZM, Al-Mekhlafi HM, Amran AA, Mahmud R.	J Ethnopharmacol. 2011 Jan 26. [Epub ahead of print]
14	Cucumis sativus	Inhibitory effect of Cucumis sativus on melanin production in melanoma B16 cells by downregulation of tyrosinase expression.	Kai H, Baba M, Okuyama T.	Planta Med. 2008 Dec;74(15):1785-8. Epub 2008 Nov 13.

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15	Curcuma heyneana	Zedoarondiol isolated from the rhizoma of Curcuma heyneana is involved in the inhibition of iNOS, COX-2 and pro-inflammatory cytokines via the downregulation of NF-kappaB pathway in LPS-stimulated murine macrophages.	Cho W, Nam JW, Kang HJ, Windono T, Seo EK, Lee KT.	Int Immunopharmacol. 2009 Aug;9(9):1049-57. Epub 2009 Apr 24.
16	Cymbopogon nardus	Comparative chemical and analgesic properties of essential oils of Cymbopogon nardus (L) Rendle of Benin and Congo.	Abena AA, Gbenou JD, Yayi E, Moudachirou M, Ongoka RP, Ouamba JM, Silou T.	Afr J Tradit Complement Altern Med. 2007 Feb 16;4(3):267-72.
17	Dioscorea opposite	The effect of Chinese herbal medicines on TNF-a induced matrix metalloproteinase-1, -9 activities and interleukin-8 secretion	Mei-Hsien LEE, Yi-Yuan YANG, Yu-Hui TSAI, Yueh-Lun LEE, Po-Yuan HUANG, I-Jen HUANG, Kur-Ta CHENG, and Sy-Jye LEU	Botanical Studies (2008) 49: 301-309.
18	Eclipta prostrata	Leishmanicidal activity of saponins isolated from the leaves of Eclipta prostrata and Gymnema sylvestre.	Khanna VG, Kannabiran K, Getti G.	Indian J Pharmacol. 2009 Feb;41(1):32-5.
19	Elettaria speciosa	-	-	-
20	Hibiscus sabdariffa	Hibiscus sabdariffa L. water extract inhibits the adipocyte differentiation through the PI3-K and MAPK pathway.	Kim JK, So H, Youn MJ, Kim HJ, Kim Y, Park C, Kim SJ, Ha YA, Chai KY, Kim SM, Kim KY, Park R.	J Ethnopharmacol. 2007 Nov 1;114(2):260-7. Epub 2007 Aug 19.

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21	Hydrocotyle asiatica	Cardioprotective activity of Hydrocotyle asiatica L. in ischemia-reperfusion induced myocardial infarction in rats.	Pragada RR, Veeravalli KK, Chowdary KP, Routhu KV.	J Ethnopharmacol. 2004 Jul;93(1):105-8.
22	Jasminum sambac	Sensitization to fragrance materials in Indonesian cosmetics.	Roesyanto-Mahadi ID, Geursen-Reitsma AM, van Joost T, van den Akker TW.	Contact Dermatitis. 1990 Apr;22(4):212-7.
23	Lavandula angustifolia	Lavandula angustifolia Miller: English lavender.	Denner SS.	Holist Nurs Pract. 2009 Jan-Feb;23(1):57-64.
24	Melaleuca alternifolia	Tea tree oil in the treatment of tinea pedis.	Tong MM, Altman PM, Barnetson RS.	Australas J Dermatol. 1992;33(3):145-9.
25	Mentha piperita	Anti-nociceptive and anti-inflammatory effects of some Jordanian medicinal plant extracts.	Atta AH, Alkofahi A.	J Ethnopharmacol. 1998 Mar;60(2):117-24.
26	Olea europaea	Wound repair potential of Olea europaea L. leaf extracts revealed by in vivo experimental models and comparative evaluation of the extracts' antioxidant activity.	Koca U, Sntar I, Akkol EK, Yilmazer D, Alper M.	J Med Food. 2011 Jan-Feb;14(1-2):140-6. Epub 2010 Dec 4.
27	Oryza sativa	Anti-inflammatory effects of peptide fragments of H2A histone and Oryza Sativa Japonica protein.	Schussheim Y, Aschner M, Brodsky B, Proscura E, Erlanger-Rosengarten A, Feldman R, Shapira E, Wormser U.	Peptides. 2011 Jan;32(1):125-30. Epub 2010 Nov 3.

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28	Pachyrrhizus erosus	Studies on the constituents of seeds of Pachyrrhizus erosus and their anti herpes simplex virus (HSV) activities.	Phrutivorapongkul A, Lipipun V, Ruangrungsi N, Watanabe T, Ishikawa T.	Chem Pharm Bull (Tokyo). 2002 Apr;50(4):534-7.
29	Phyllanthus emblica	Amla (Emblica officinalis Gaertn), a wonder berry in the treatment and prevention of cancer.	Baliga MS, Dsouza JJ.	Eur J Cancer Prev. 2011 Feb 10. [Epub ahead of print]
30	Pluchea indica	-	-	-
31	Pogostemon cablin	Analgesic and Anti-Inflammatory Activities of the Methanol Extract from Pogostemon cablin.	Lu TC, Liao JC, Huang TH, Lin YC, Liu CY, Chiu YJ, Peng WH.	Evid Based Complement Alternat Med. 2009 Nov 20. [Epub ahead of print]
32	Portulaca oleracea	Characterization of structures and antiviral effects of polysaccharides from Portulaca oleracea L.	Dong CX, Hayashi K, Lee JB, Hayashi T.	Chem Pharm Bull (Tokyo). 2010;58(4):507-10.
33	Rosa chinensis	Fungitoxic properties of Rosa chinensis Jacq.	Tripathi SC, Dixit SN.	Experientia. 1977 Feb 15;33(2):207-9.
34	Salvia coccinea	-	-	-
35	Santalum album	Chemopreventive effects of sandalwood oil on skin papillomas in mice.	Dwivedi C, Abu-Ghazaleh A.	Eur J Cancer Prev. 1997 Aug;6(4):399-401.
36	Strychnos ligustrina	-	-	-
37	Tagetes erecta	In vitro antiplasmodial and antimicrobial potential of Tagetes erecta roots.	Gupta P, Vasudeva N.	Pharm Biol. 2010 Nov;48(11):1218-23. Epub 2010 Sep 6.

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39	Tinospora tuberculata	Inhibition of nitric oxide release by an aqueous extract of Tinospora tuberculata.	Yokozawa T, Wang TS, Chen CP, Hattori M.	Phytother Res. 2000 Feb;14(1):51-3.
40	Trigonella foenum-graecum	Anti-hyperglycemic and anti-oxidative effect of aqueous extract of Momordica charantia pulp and Trigonella foenum graecum seed in alloxan-induced diabetic rats.	Tripathi UN, Chandra D.	Indian J Biochem Biophys. 2010 Aug;47(4):227-33.
41	Vanilla planifolia	Inhibition of bacterial quorum sensing by vanilla extract.	Choo JH, Rukayadi Y, Hwang JK.	javascript:AL_get(this, 'jour', 'Lett Appl Microbiol.');
42	Vetiveria zizanioides	Evaluation of antioxidant activity of vetiver (Vetiveria zizanioides L.) oil and identification of its antioxidant constituents.	Kim HJ, Chen F, Wang X, Chung HY, Jin Z.	J Agric Food Chem. 2005 Oct 5;53(20):7691-5.
43	Zanthoxylum acanthopodium	-	-	-