

## RESEARCH ARTICLE

**PRIMARY QUALITIES IN PHYTOTHERAPY AND TRADITIONAL MEDICINES:  
A STATISTICAL STUDY****\*Ramezany Farid<sup>1,2</sup>; Jafari Samineh<sup>3</sup>; Tofiqhi, Zahra<sup>3</sup>; Farsam, Hassan<sup>4</sup>; Shams Ardakani Mohammad Reza<sup>1,3</sup>**<sup>1</sup>Department of Traditional Pharmaceutics, Faculty of Traditional Medicine, Tehran University of Medical Sciences, Tehran, Iran<sup>2</sup>Institute of Environmental Research (INFU), Faculty of Chemistry, Technical University of Dortmund, Dortmund, Germany<sup>3</sup>Department of Pharmacognosy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran<sup>4</sup>Department of Medicinal Chemistry, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran*\*Corresponding Author's Email: [f.ramezany@infu.tu-dortmund.de](mailto:f.ramezany@infu.tu-dortmund.de), [framezany@razi.tums.ac.ir](mailto:framezany@razi.tums.ac.ir)***ABSTRACT**

**Objectives:** The significance of principles of traditional medicines in research protocols are emphasized by World Health Organization. Primary qualities, traditionally referred to as "hot", "cold", "dry" and "wet", are fundamental concepts of many medical traditions of antiquity such as Persian, Chinese, Greek, and Indian. In Humoral-based traditional medicines, these qualities are regulating factors and act in dynamic balance to maintain health. Therefore, understanding of the primary qualities of body humors and drugs is decisive for treatment, self-care and prevention of diseases in many traditional medicines. The main goals of this study are to consider the relationships among primary qualities and botanical or phytochemical profiles of the traditional Iranian medicinal herbs.

**Method:** A number of 489 medicinal plants were accommodated with proposed scientific names and the corresponding primary qualities were extracted from old Persian pharmacopeias. Based on literatures, two data sets screened for statistical study. To ensure consistency and similarity of screened samples, they were examined by Chi-square ( $\chi^2$ ) test. Influences of botanical families on primary qualities were studied by screening of 339 plants in 29 botanical families tested with  $\chi^2$  test. In the second stage, major phytochemicals of 192 herbs were categorized based on existence of 23 groups of phytochemicals and a model based on traditional medicine concepts was made using logistic regression.

**Results:** Statistical outcomes revealed that although a few botanical families tend to correlate in specific primary qualities, most others displayed no significant relationship. The proposed phytochemical model was able to estimate the relationship between primary qualities and phytochemical classes in more than 77% of the cases. The findings were in accordance with old literatures.

**Conclusion:** The botanical family classification is not an empirically acceptable indicator of primary qualities in medicinal plants. On the other hand, phytochemical profile of a plant is an authentic indicator of primary qualities.

**Keywords:** Primary qualities, Phytotherapy, Traditional Medicine, Botanical family, Phytochemicals.

**INTRODUCTION**

Humoral-based traditional medicines such as Iranian (Persian), Greek (Unani) and Islamic as well as other disciplines like Indian, Chinese etc have many common aspects. Classical elements and primary qualities are belonging to these concepts. Trends for bringing traditional medicine up to date were considered by the world health organization (WHO)<sup>1</sup>. Discernment and identification of relationships among the concepts of traditional and contemporary medicine, in light of our present day knowledge can greatly help us in usage of such seemingly encrypted data in modern medicine and make traditional medicine up to date. In addition, WHO stated that regarding the principles of the traditional systems of medicine in a research study is a priority<sup>2</sup>. Therefore, traditional knowledge and experience of the use of drugs should be considered when a study is proposed, prepared and conducted. The concepts of primary qualities and temperaments are one of dichotomies that negate the possibility of matching traditional medicine studies with contemporary medicine.

The Humoral theory is related to Empedocles theory of four classical elements. In this theory the nature consists of mixtures these elements which come into being through combination of their four primary qualities namely hot, cold, dry and wet. The elements are governed the materials

and humors in return<sup>3, 4</sup>. According to old traditional literatures, primary qualities are able to counteract and influence each others to reach a new equilibrated level called temperaments<sup>5</sup>. Usually, temperaments described as a pair, one from each opposite primary qualities (eg. Hot and dry, cold and wet, etc.)

In Humorism, primary qualities are concepts which used as an effective method on self-care and preventive medicine. They are regulating factors in the human dynamic balance to maintain health<sup>6, 7</sup>. Imbalance in the humors temperaments could be compensated by using drugs with opposite one<sup>3</sup>. Therefore, it is not surprising that primary qualities and temperaments not only are used to describe pharmacologic behaviors drugs, but also play an important role in compounding medicaments<sup>5, 8</sup>.

In the Old Persian traditional medicine Pharmacopeias, as well as in the other disciplines, one often encounter to description of primary qualities, referred as "nature" in simple drugs<sup>9</sup>. Normally, they were stated at the beginning of each monograph accompanied by a degree from 0 (temperate) to 4 (very strong action or toxic) which regarded as a measure for efficacy of drugs.

Recently, few researchers attempted to find out the relationship(s) among primary and physical, botanical or

phytochemical characteristics of the plants<sup>10, 11</sup>. Yet, the lack of statistically validated proof necessitates further research in authentic empirical and statistical evidence. Different results were obtained from these studies which primary qualities attributed to botanical family<sup>11</sup> or the major phytochemical constituents of medicinal plants<sup>10</sup>. In addition, the results were not discussed based on notes and criteria found in old literatures, a prerequisite for any research plan on traditional medicine<sup>2</sup>. The main goal of this study was to find out relationship(s) among botanical family and phytochemical characteristics of medicinal plants and the primary qualities statistically; followed by comparison of the results by traditional medicine literature to validate the observed results. Finally, evaluation of the parameters to describe the primary qualities was considered.

## MATERIALS AND METHODS

A number of 489 medicinal plants were accommodated with their known scientific names and the corresponding primary qualities were extracted from Old Persian pharmacopeias<sup>12, 13</sup>, regarded as reference sample. Based on availability of data, two samples screened for statistical study as mentioned later. Data analysis was done using Statistical Package for the Social Sciences (SPSS version 16). First, screened samples were examined to ensure consistency and similarity of them with reference sample by  $\chi^2$  test. To study of botanical family intervention on primary qualities, families which contain at least 4 plants in the reference sample were screened (339 plants in 29 families, figures 1 and 2) and difference between pairs of opposite primary qualities (hot vs. cold and dry vs. wet) were examined by  $\chi^2$  test. Phytochemicals influences were studied by selection of herbs with known profiles (192 herbs), checked for similarity with reference sample and the major ingredients of them were categorized based on existence of 23 groups of phytochemicals (table 1)<sup>14-17</sup>. These data were analyzed, using logistic regression method to obtain a polynomial equation describing the probability of presence or absence of each primary quality. Then, the contribution of each phytochemical groups in introducing a specific primary quality were determined based on the coefficients of related term of them (logits<sup>1</sup>) in the equation.

## RESULTS

In preliminary study of the frequency of primary qualities in the reference sample, it was noticed that a few plants hold any opposite pair primary qualities (considered as temperate based on traditional medicine literatures). On the other hand, a few herbs are attributed both of an opposite pair (dual quality). At first glance, questions were arisen about the significance of difference and relationship between opposite primary qualities in the reference sample and the other sample sets. Chi-square test results on studied and screened plants showed significant difference ( $p<0.01$ ) in all three sample sets. Phi measurements (-0.780 to -0.910) of the tests demonstrated strong negative relationship between opposite primary qualities in all

sample sets in accordance with opposite relationship of them in old literatures. Therefore, it was concluded that all sample sets are in agreement with traditional medicine concepts of primary qualities opposition and the statistical outcomes could be attributed to all plants used in traditional medicine.

### Primary qualities based on the botanical families:

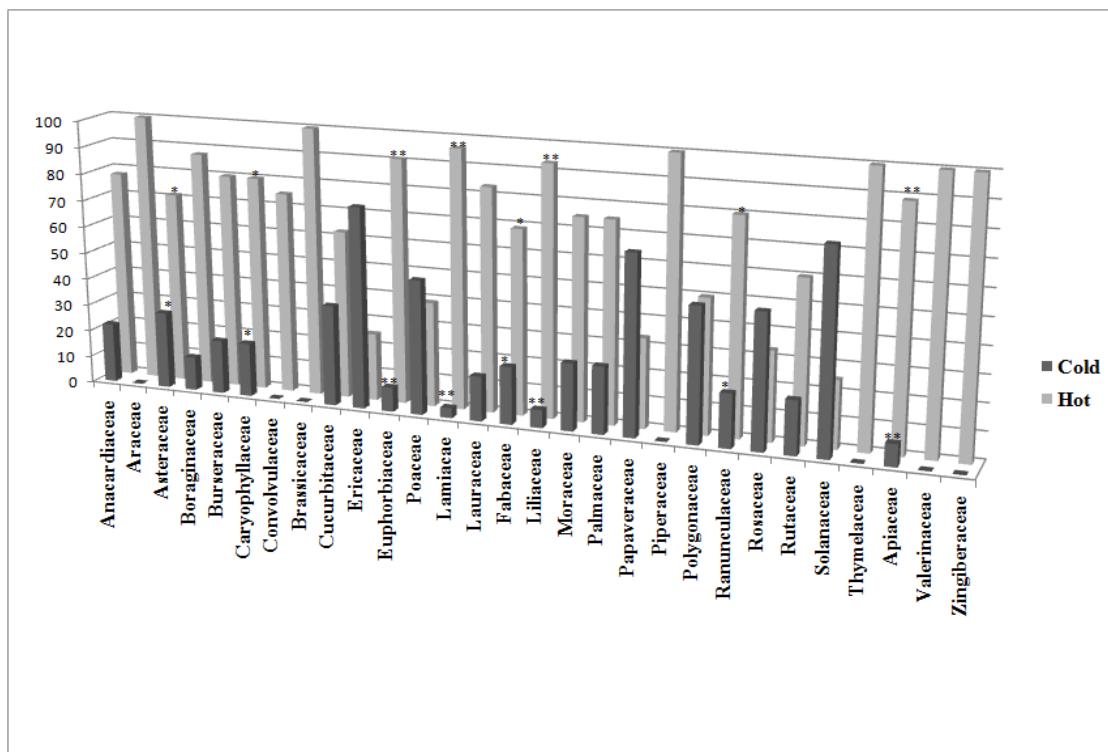
To study the influence of botanical characteristics on the existence or absence of primary qualities, the sample were examined by  $\chi^2$  test. The results were represented in figure 1 (Hot and Cold) and figure 2 (Dry and Wet). It is noticeable while significant relationship were observed in a few families, the majority of them showed no significance.

### Primary quality based on phytochemical class:

Table 1 shows the logit values of 23 groups of phytochemicals applying logistic regression on 191 herbs which the phytochemical profiles were found in contemporary literatures. On the basis of these assessments, one can conclude the relative contribution of each class in primary qualities outcomes. Due to counteraction of opposite primary qualities in traditional medicine concepts, logit values differences of two pairs of opposite primary qualities ( $\text{logit}_{\text{Hot}} - \text{Logit}_{\text{Cold}}$  and  $\text{Logit}_{\text{Dry}} - \text{Logit}_{\text{Wet}}$ ) were considered as criteria for temperament assignment for each class. Arbitrarily, Hot and Dry primary qualities were assigned positive and cold and wet negative sign. Net logit values were categorized based on cut off and  $P_{\text{out}}^2$  values as insignificant (0.0 - 0.2) temperate (0.2 - 0.5), and significant (more than 0.5). The measure of net logit values were considered as an indicator for contribution of a chemical class to a particular temperament. Based on the data on table 1, Glucosinolates and Sulfur-containing phytochemicals were estimated hottest while Fruit acids, Flavonoids, Phenolic acid esters and Polyene-carotenoides coldest. Similar estimations were performed for dry and wet primary qualities showed Glucosinolates and Resins as driest and Anthraquinones and Iridoides wettest phytochemicals.

<sup>1</sup> In logistic regression variables expressed as the log of the odds ratio. Or in math speak,  $\ln(p/(1-p))$  which  $p$  is the probability.

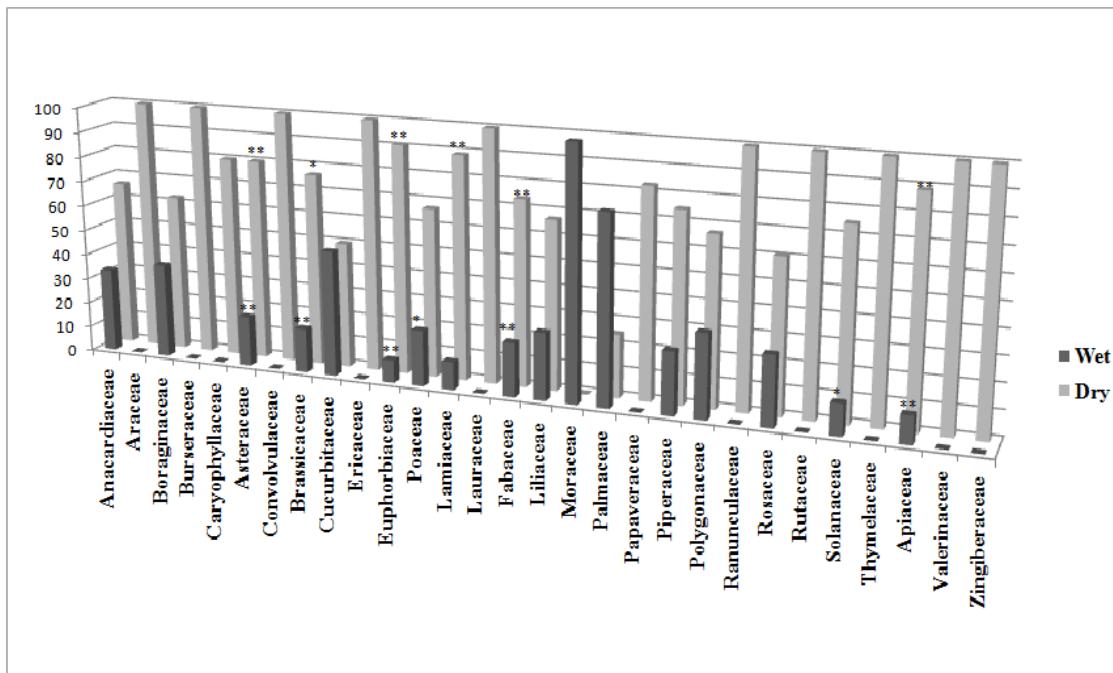
<sup>2</sup>  $P_{\text{out}}$  values considered as measurement of error and the errors were added to represent more accurate results (cf. Table 1)



**Figure 1: The percentage of the existence of Hot and Cold primary qualities in some botanical families found in Persian Traditional Pharmacopeias.**

\* =  $P<0.05$ , \*\* =  $P<0.01$

*Plants with dual reported primary qualities are not considered.*



**Figure 2: The percentage of the existence of Dry and Wet primary qualities in some botanical families found in Persian Traditional Pharmacopeias.**

\* =  $P<0.05$ , \*\* =  $P<0.01$

*The Plants with dual reported primary qualities are not considered.*

Table 1: Primary qualities and Temperament assignment of Phytochemical classes

Name	<i>Logit</i> <sub>Hot</sub> <sup>3</sup>	<i>Logit</i> <sub>Cold</sub> <sup>4</sup>	<i>Logit</i> <sub>Dry</sub> <sup>5</sup>	<i>Logit</i> <sub>wet</sub> <sup>6</sup>	<i>Δlogit</i> <sub>Hot-Cold</sub>	<i>Δlogit</i> <sub>Dry-Wet</sub>	Temperament <sup>7</sup>
Alkaloids	-0.563	0.161	0.297	-0.357	-0.724	0.654	Cold - Dry
Flavenoids	-1.135	1.018	-0.004	0.009	-2.153	-0.013	Cold - NS <sup>8</sup>
Volatile oils	1.551	-1.520	1.012	-0.793	3.071	1.805	Hot - Dry
Phenolic acids	-0.43	-0.474	0.926	-0.466	0.044	1.392	NS - Dry
Terpenes (nonvolatile)	1.039	-0.770	0.031	0.147	1.809	-0.116	Hot - NS
Saccharides, Polysaccharides	0.295	-0.532	-0.360	0.485	0.827	-0.845	Hot - Wet
Fruit acids	-1.296	0.837	-0.906	0.383	-2.133	-1.289	Cold - Wet
Fats and Oils	-0.602	0.388	-0.104	-0.504	-0.99	0.4	Cold - Temperate
Anthraquinones	0.041	-0.086	-1.076	1.041	0.127	-2.117	NS - Wet
Coumarins	0.333	0.203	0.059	-0.083	0.13	0.142	NS - NS
Steroids	0.174	-0.249	-0.376	0.321	0.423	-0.697	Temperate - Wet
Saponins	0.518	-0.933	-0.422	1.169	1.451	-1.591	Hot - Wet
Tannins	-01.015	0.648	-0.015	-0.055	-1.663	0.04	Cold - NS
Cardiac Glycosides	-0.246	-0.137	-0.364	0.131	-0.109	-0.495	NS - Temperate
Sesquiterpene lactones	-0.005	-0.452	0.273	-0.275	0.447	0.548	Temperate - Dry
Sulfides	19.064	-19.428	-1.350	-0.759	38.492	-0.591	Hot - Wet
Glucosinolates	19.858	-20.428	20.138	-19.861	40.286	39.999	Hot - Dry
Resins	-0.245	-0.275	19.573	-19.579	0.03	39.152	NS - Dry
Lignans	0.794	-0.382	-0.099	-0.212	1.176	0.113	Hot - NS
Phenols	1.692	-1.727	-0.155	-0.374	3.419	0.219	Hot - Temperate
Polyenes and Carotenoids	-1.571	1.018	-0.597	-0.208	-2.589	-0.389	Cold - Temperate
Iridoids	0.266	-0.545	-1.029	0.682	0.811	-1.711	Hot - Wet
Phenolic acid esters	-1.311	0.917	-0.118	-0.668	-2.228	0.55	Cold - Dry

## DISCUSSIONS

Based on traditional medicine literatures, primary qualities of drugs specially herbals were determined by studying the effects on human and in some cases on animals or by consideration of some physical or organoleptic characteristics such as taste, aroma, shape, color etc. In this paper the authors focused on study primary qualities in two features, botanical aspect which reflects the shape similarity of herbal drugs and phytochemicals for taste, aroma and colors.

Although botanical family introduced as criterion for primary qualities description in one study, based on our statistical results, it is not possible to make a clear conclusion among botanical families and them. In addition, the primary qualities in some cases could not be explained by this point of view, especially in some families such as Cucurbitaceae and Rutaceae. Colocynth (*Citrullus colocynthis* (L.) Schrad.) and watermelon (*Citrullus vulgaris* Schrad.) are typical examples which have completely same family and genus even shape, but the primary qualities of their fruits (Hot and Dry vs. Cold and Wet respectively) are completely different. In addition, drastic differences of primary qualities in particular plant organs could not be described by botanical family classifications. For example, the pulp of the Citron (*Citrus medica* L.) fruit is cold and dry but its pith is cold and wet, while the seeds are hot and dry<sup>12</sup>. Consequently, contrary to a previous study that regarded botanical families for primary qualities assessment<sup>11</sup>, they could not be considered as a criterion.

Description of primary qualities was also considered in previous studies based on phytochemical constituents. Some authors claimed traditional Iranian medicine is more chemically related compared to other alternative medicines<sup>18</sup>. Others tried to explain primary qualities by the main pharmacological component of the herbs<sup>10, 11</sup>.

Owing to multiplicity and diversity of phytochemicals in a particular plant, we try to make a model based on a concept found in the old literatures<sup>5, 8</sup>. In compound medicines the primary qualities of the simple drugs interact to each other yield new temperaments<sup>8, 19</sup>. The new primary quality degree of a compound medicament can be calculated by the following formula.

$$Pt = \frac{\sum_{i=1}^n \frac{Pi \times Mi}{Di}}{n} \quad (1)$$

<sup>3</sup> Constant= 1.449, Nagelkerke R<sup>2</sup>= 0.338, Overall percentage correct= 78.1%

<sup>4</sup> Constant= -0.578, Nagelkerke R<sup>2</sup>= 0.309, Overall percentage correct= 77.1%

<sup>5</sup> Constant= 1.383, Nagelkerke R<sup>2</sup>= 0.244, Overall percentage correct= 81.8%

<sup>6</sup> Constant= -1.217, Nagelkerke R<sup>2</sup>= 0.222, Overall percentage correct= 81.2%

<sup>7</sup> Cut off value= 0.5, P out= 0.1

<sup>8</sup> Not Significant

Where  $P_t$  is the total primary quality degree of compound drug,  $P_i$ ,  $M_i$ ,  $D_i$  are the primary qualities degree, mass and dose coefficient<sup>9</sup> of the ingredient  $i$  respectively and  $n$  is the number of ingredients.

It could be concluded from the equation 1 that primary qualities and its degree are related to the amount, degree, dosage and number of constituents of a compound drug. Owing to dependence of pharmacological effects of herbs to the same factors of their phytochemicals, it is reasonable to postulate that the primary qualities of a herb are the average of primary qualities of its pharmacologically active components.

In order to overcome data acquisition limitations for the amount, lack of traditional dosage coefficients and degree of phytochemicals, we focus on the logit ( $P$ ), which reflects the probability, of presence of primary quality in herbs based on the sum of the logits of phytochemical constituents ( $P_i$ ). Consequently, the equation 1 was summarized to polynomial equation 2.

$$P = \sum_{i=1}^n P_i \quad (2)$$

Where the  $P$  is the logit for a herb to have a particular primary quality and  $p_i$  is the logit of the phytochemical constituents. Using logistic regression, we are able to calculate the  $P_i$  coefficients of the proposed model which represented in table 1.

Many conflicts and paradoxical reports of primary qualities such as previous examples could be explained logically by differences and variations of phytochemicals in plants. For instance, hotness of Colocynth could be explained by presence of cucurbitacin terpenes which are hot according to  $P_i$  values. Comparison of outcomes of table 1 with literatures and previous works showed considerable agreement with traditional medicine concepts. The hotness-wetness of saccharides and polysaccharides, coldness of fruit acids and tannins and hotness-dryness of essences were prominent. Alkaloids are cold and dry, which is in accordance with previous article<sup>11</sup>. Furthermore, the capability of the model to estimate 77.1%-81.8% cases implies the decisive value of phytochemicals, especially secondary metabolites, on primary qualities. Persian pharmacopeias provide clues which are in accordance with the model. Factors such as region, season of harvesting, freshness, storage conditions and ripeness play roles in the primary qualities variations<sup>20</sup>. Obviously, these biotic and abiotic conditions influence the presence and quantity of phytochemicals in plants<sup>21</sup>.

Based on the model, primary qualities of a herb are not related to the only one pharmacologically active constituent and depend on the pharmaco-phytochemical profile of it. This consequence is in accordance with current knowledge of synergy and metabolomics that

<sup>9</sup> This coefficient is related to dosage, but not exactly. For example, the dosage coefficient of opium is as much as high that can leads to toxic reactions even death. There are many interpretations about the dose coefficient. The amount of a drug which is able to induce effects in the body equal to the degree of primary quality seems to be the best description.

rejects the so-called "magic bullet" theory for medicinal herbs and functional foods<sup>21-23</sup>.

## CONCLUSION

Primary qualities of herbs in Persian traditional medicine and other traditional medicines are the least understood concept in terms of our knowledge. Statistical results of our data demonstrated the primary qualities of the herbs are not related to their botanical families, thus this approach is not applicable in their classification. However, there are indications based on relationship of them with phytochemicals present in the medicinal herbs. As discussed before, despite the modicum of information about the quantity and variation of phytochemical constituents in literatures, logistic regression of presence of phytochemicals in herbs is a viable statistical tool to verify the relationships. Nevertheless future studies are required, integrating other factors such as genus and sub-genus, quantity of constituents and primary qualities degree of herbs to advance our understanding about primary qualities.

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