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The components transitive regularity of three dosage forms of Liuwei Dihuang Fufang

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ABSTRACT

Objective To explore the transitive regularity of holistic constituents from the crude slices of the medicinal raw materials (MCS) to the formula granules (FG), fufang decoction (FD), and finally, the concentrated pills (CP) of Liuwei Dihuang Fufang (六味地黄复方, LWDHF).

Methods Samples for MCS, FG, FD, and CP of LWDHF were obtained, and a fingerprint database was established using high-performance liquid chromatography (HPLC), by separating the samples in an XB-C18 column and analyzing the transitive regularity of components using the total quantum statistical moment (TQSM), including total quantum zero moment (AUC_T), total quantum first moment (MRT_T), total quantum second moment (VRT_T), and its similarity approach. The AUC_T, MRT_T, and VRT_T were calculated based on the representative HPLC chromatograms of FG, FD, and CP of LWDHF.

Results AUC_T of FG, FD, and CP of LWDHF was 71 804, 46 553, and 144 646 μV·s, respectively; MRT_T was 14.43, 14.54, and 18.85 min, respectively; and VRT_T was 106.98, 112.84, and 269.12 min^2, respectively. Comparing the similarity of FG/FD, FG/CP and FD/CP of LWDHF, the TQSM similarity values were 98.66%, 76.62%, and 75.37%, respectively, whereas the traditional similarity evaluation values were 98.68%, 85.43%, and 85.60%, respectively.

Conclusion The results perform little distinction in the total composition between FG and FD, whereas some distinction existed between FD and CP. Experimental evidence, therefore indicates that FG could be used as the alternative of MCS in clinical applications.

1. Introduction

Liuwei Dihuang Fufang (六味地黄复方, LWDHF), a well-known representative of the Chinese materia medica formulae (CMMF), is generally used to treat kidney deficiency syndrome (referring to "kidney Yin" in China) under the traditional Chinese medicine (TCM) theory [1, 2]. LWDHF is composed of Shudihuang (Rehmanniae Radix Praeparata), Shanyao (Dioscoreae Rhizoma), Shanzhuyu (Corni Fructus), Zexie (Alismatis Rhizoma), Fuling (Poria), and Mudanpi (Moutan Cortex) [3]. The formula possesses functions of nourishing Yin and tonifying the liver,

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spleen, and especially the kidney Yin. Modern pharmacological studies have revealed many comprehensive regulatory functions, such as maintaining neuroendocrine immunomodulation balance and improving cognitive effectiveness [4, 5].

Currently, LWDHF is often flexibly modified according to different clinical symptoms based on the basic theory of TCM [5, 6]. This means that plus or minus LWDHF prescriptions are always used in different patients to achieve syndrome differentiation characteristics and comprehensive TCM effects [7]. Moreover, to flexibly apply CMMF in the clinic, many scientists have proposed research on formula granules (FG). FG is a modern idea in which medicinal raw materials (MCS) are decocted separately in each vessel, and then each decoction or extraction is granulated and assembled according to the corresponding CMMF; this satisfies the need for personalized medicine in TCM clinics [8]. Previous studies have shown that there are some differences in the peak quantity or peak area of HPLC fingerprints among the MCS, FG, fufang decoction (FD), and concentrated pills (CP) of LWDHF [9, 10]. Therefore, accurately analyzing the differences would not only benefit the dynamic quality control (DQC) of LWDHF but will also provide a basis for the difference in the curative effect of different dosage forms.

To address this requirement, an analytical method coupled with high-performance liquid chromatography (HPLC) fingerprints for MCS, FG, FD, and CP of LWDHF was developed. This method can determine a distinct HPLC fingerprint and discriminate between different dosage forms [11, 12]. Analysis of these fingerprints can thus provide substantial information on the active compounds for MCS, FG, FD, and CP of LWDHF and can be applied to ensure its DQC. Furthermore, the total quantum statistical moment (TQSM) and its similarity can be used to analyze the differences in the active compounds [13]. A preliminary study on the differences between dosage forms was based on the supramolecular phenomena [14]. Therefore, in this study, we used TQSM and a similarity approach to evaluate transitive qualitative regularity in this example of a CMMF.

2 Materials and methods

2.1 Reagents and materials

Shudihuang (Rehmanniae Radix Praeparata), Shanyao (Dioscoreae Rhizoma), Shanzhuyu (Corni Fructus), Zexie (Alismatis Rhizoma), Fuling (Poria), Mudanpi (Moutan Cortex) and CP were purchased from Jiuzhitang Co., Ltd. (China). All of the decocting herbs were authenticated and verified by Professor LIU Wenlong; samples were deposited in the herbarium of the Department of Pharmacy of Hunan University of Chinese Medicine.

HPLC-grade acetonitrile (AS-1122) and formic acid (FS-0630) were obtained from TEDIA. Ultrapure water was obtained from a Milli-Q system (Millipore, Bedford).

2.2 Sample preparation

The LWDHF was composed of Shudihuang (Rehmanniae Radix Praeparata) 80 g, Shanyao (Dioscoreae Rhizoma) 40 g, Shanzhuyu (Corni Fructus) 40 g, Zexie (Alismatis Rhizoma) 30 g, Fuling (Poria) 30 g, and Mudanpi (Moutan Cortex) 30 g. Six MCS of LWDHF were decocted in each vessel separately, LWDHF was decocted in one container, and all the decoctions were concentrated for extraction. All of the extracts were preserved at 4 °C for the HPLC analysis.

Samples of MCS: the extractions were taken out according to the corresponding ratios in LWDHF into 2.0 mL methanol, subjected to 30 min ultrasound at 28 °C, then centrifuged for 15 min at 12 000 r/min, filtered through a 0.22 μm membrane filter, and reserved for detection.

Samples of FG: six extractions were taken out in ratios corresponding to LWDHF and mixed into 2.0 mL methanol; the samples were then treated as for MCS, and reserved for detection.

Samples of FD: extracts were mixed with 2.0 mL methanol; the samples were then treated as for MCS, and reserved for detection.

Samples of CP: CP were placed in 2.0 mL methanol proportionately; the samples were then treated as for MCS, and reserved for detection.

All samples were extracted in parallel in three batches, and two samples were prepared in each batch.

2.3 Chromatographic analysis

HPLC analysis were performed using an Agilent 1260 system (Palo Alto). The samples were separated on an XB-C18 column (4.6 mm × 250 mm, 5 μm) at a temperature of 30 °C. Mobile phase A was 0.1% formic acid and mobile phase B was acetonitrile. The gradient program was as follows: 0 – 30 min, linear gradient 2% – 25% B (98% – 75% A); 30 – 39 min, linear gradient 25% – 100% B; 39 – 45 min, linear gradient 100% – 2% B; 45 – 55 min, isocratic 2% B; flow rate, 1.0 mL/min; absorbance was monitored at 277 nm; and the injection volume of each sample was 12.0 μL.

2.4 Data processing

Raw mass data were processed using Progenesis QI v1.0 software (Waters Corporation) for peak alignment and

peak selection. The TQSM method and its similarity were used to assess the differences between the separated and combined decoction and concentrated pills of LWDHF. The expression formulae are as follows.

2.4.1 Total quantum zero moment (AUC_T) AUC_T: the area under the curve of total quantum, reflecting the total amount of the multi-component population, is expressed as following Equation (1) and (2).

$$AUC_T = \int_0^{\infty} \sum_{i=1}^{r} M_i e^{-\alpha_i t} dt = \sum_{i=1}^{r} \frac{M_i}{\alpha_i} \tag{1}$$

$$AUC_T = \frac{k_m c_0}{V_m} + \frac{c_0^2}{2V_m} \tag{2}$$

Where Equation (1) is the AUC_T of the linear drug, and Equation (2) represents the AUC_T of a nonlinear drug.

2.4.2 Total quantum first moment (MRT_T) MRT_T ($\bar{\lambda}_T$): the mean chromatographic retention time of the total quantum, reflects the overall apparent residence time of the multi-component, and the formula is Equation (3).

$$\bar{\lambda}_T = \frac{\sum_{j=1}^{m} \int_0^{\lambda} \lambda R j d\lambda}{\sum_{j=1}^{m} \int_0^{\lambda} R j d\lambda} = \frac{\sum_{j=1}^{m} A j \lambda j}{\sum_{j=1}^{m} A j} \tag{3}$$

Where Rj is one of the Gaussian curves for peak j in the chromatographic fingerprint.

2.4.3 Total quantum second moment (VRT_T) VRT_T ($\bar{\sigma}_T^2$): the variance of chromatographic retention time of the total quantum, reflects the dispersion degree of the multicomponent, and the formula is given by Equation (4).

$$\bar{\sigma}_T^2 = \frac{\sum_{j=1}^{m} \int_0^{\lambda} (\lambda - \lambda T)^2 R j d\lambda}{\sum_{j=1}^{m} \int_0^{\lambda} R j d\lambda} = \frac{\sum_{j=1}^{m} A j (\sigma_j^2 + \lambda_j^2)}{\sum_{j=1}^{m} A j} - \lambda_T^2 \tag{4}$$

Where σ_j^2 is the variance for peak j.

2.4.4 TQSM similarity The TQSM parameters of MRT_T and VRT_T are converted into a representation of the normal distribution probability density function with respect to time, as shown in Equation (5).

$$F(t) = \int_{-\infty}^{+\infty} \frac{1}{\sqrt{2\pi}\sigma} e^{-\frac{(t-\bar{t})^2}{2\sigma^2}} dt \quad (-\infty < t < +\infty) \tag{5}$$

Where t is the retention time of the fingerprint, $\bar{t}$ is the average MRT (n ⩾ 3), and σ^2 is the average VRT (n ⩾ 3) for the two fingerprint profiles $\bar{t}_a$, $\bar{t}_b$, and σ_a^2, σ_b^2, respectively. The similarity of the TQSM for fingerprints can be defined by the overlapped area of the cross-curve, which is converted into probability density functions surrounding the λ-axis.

$$S_T = 1 - \left| \int_{t_1}^{t_2} \frac{1}{\sqrt{2\pi}\sigma_a} e^{-\frac{(t-\bar{t}_a)^2}{2\sigma_a^2}} dt - \int_{t_1}^{t_2} \frac{1}{\sqrt{2\pi}\sigma_b} e^{-\frac{(t-\bar{t}_b)^2}{2\sigma_b^2}} dt \right| \quad (-\infty < t < +\infty) \tag{6}$$

There are three situations as follows: when $\sigma_a = \sigma_b$, $\bar{t}_a \neq \bar{t}_b$, $\bar{t}_a > \bar{t}_b$, two normal curves have an intersection point; the cross-point, t, is shown in Equation (7) (Figure 1A). t_1 and t_2 are represented as the intersections of the two normal distribution curves. The similarity of TQSM for fingerprints is shown in Equation (8).

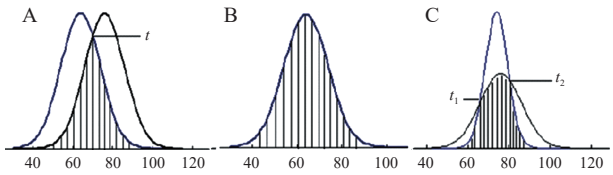

Figure 1 The normal distribution diagram of TQSM similarity
A, a point of intersection. B, overlap. C, two intersection points.

$$t = (\bar{t}_a + \bar{t}_b)/2 \tag{7}$$

$$S_T = 1 - \left| \int_{-\infty}^{t_1} \left(\frac{1}{\sqrt{2\pi}\sigma_a} e^{-\frac{(t-\bar{t}_a)^2}{2\sigma_a^2}} dt - \frac{1}{\sqrt{2\pi}\sigma_b} e^{-\frac{(t-\bar{t}_b)^2}{2\sigma_b^2}} \right) dt \right| \tag{8}$$

When $\sigma_a = \sigma_b$ and $\bar{t}_a = \bar{t}_b$, the two normal curves completely overlap (Figure 1B). The similarity value of the TQSM is 1. When $\sigma_a \neq \sigma_b$, $\bar{t}_a \neq \bar{t}_b$, and $\sigma_a > \sigma_b$, there are two intersections of the two normal curves [Equation (9), Figure 1C]. The similarity can be calculated using Equation (6).

$$t_{1(2)} = \frac{(\bar{t}_a \sigma_b^2 - \bar{t}_b \sigma_a^2)}{\sigma_b^2 - \sigma_a^2} \pm \frac{\sqrt{(\bar{t}_a \sigma_b^2 - \bar{t}_b \sigma_a^2)^2 - (\sigma_b^2 - \sigma_a^2)(\sigma_a^2 \sigma_b^2 \ln \frac{\sigma_a^2}{\sigma_b^2} + \sigma_b^2 \bar{t}_a^2 - \sigma_a^2 \bar{t}_b^2)}}{\sigma_b^2 - \sigma_a^2} \tag{9}$$

The result of the TQSM similarity was compared with the similarity evaluation system for the chromatographic fingerprint of TCM (version 2004 A) recommended by the State Pharmacopoeia Committee of China.

3 Results

3.1 Optimization of analytical conditions

The conditions for sample pretreatment were optimized by investigating the type of mobile phase (methanol/water and acetonitrile/water), formic acid concentration in water (0.1%, v/v), and extraction time (10, 15, 20, 25, and 30 min). Considering the types and quality of the samples, acetonitrile was an ideal extraction solvent that effectively extracted all compounds. The results of the extraction time test showed that most of the compounds were extracted within 15 min. Thirty minutes were sufficient for ultrasonication extraction.

Several chromatographic parameters, including the chromatographic column, mobile phase composition, wavelength, and column temperature, were optimized for HPLC analysis to achieve high resolution as quickly as possible. Acetonitrile-water [1], gradient elution for 15 min, and a wavelength of 277 nm was deemed to be optimal.

3.2 TQSM analysis of the HPLC data

The representative HPLC chromatograms of FG, FD, and CP of LWDHF are shown in Figure 2; the results of the calculation of AUC_T, MRT_T, and VRT_T are listed in Table 1 and Figure 3; the results of TQSM similarity of FG, FD, and CP of LWDHF are listed in Table 2; and the results from the similarity evaluation system for the chromatographic fingerprint of TCM (version 2004 A) are listed in Table 3.

The AUC_T of FG was larger than that of FD, and AUC_T of both was less than that of CP; MRT_T of FG was similar to FD, the MRT_T of CP was slightly higher than others; VRT_T of FD was similar to FG, and VRT_T of CP was the highest (Table 1). Tables 2 and 3 show that the TQSM similarity of FG and FD was 98.66%, the similarity evaluation was 98.68%, the TQSM similarity of FD and CP was

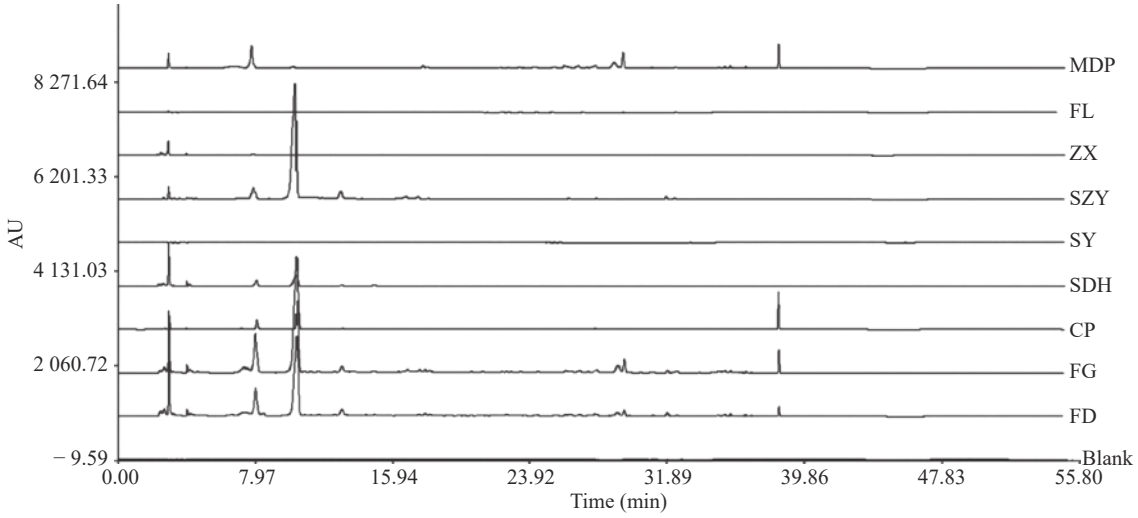

Figure 2 Chromatographic fingerprint of LWDHF

FD represents fufang decoction; FG represents formula granules; CP represents concentrated pills; SDH represents Shudihuang (Rehmanniae Radix Praeparata); SY represents Shanyao (Dioscoreae Rhizoma); SZY represents Shanzhuyu (Corni Fructus); ZX represents Zexie (Alismatis Rhizoma); FL represents Fuling (Poria); MDP represents Mudanpi (Moutan Cortex).

Table 1 The TQSM data of FG, FD, and CP for LWDHF

Parameter	AUC_T (μV·s)	MRT_T (min)	VRT_T (min²)
FG	71 804	14.43	106.98
FD	46 553	14.54	112.84
CP	144 646	18.85	269.12
SDH	7 655	12.90	81.82
SY	55	3.09	36.40
SZY	47 806	11.29	26.95
ZX	730	8.33	31.24
FL	128	10.30	1.39
MDP	25 389	20.46	256.24

FG represents formula granules; FD represents fufang decoction; CP represents concentrated pills; SDH represents Shudihuang (Rehmanniae Radix Praeparata); SY represents Shanyao (Dioscoreae Rhizoma); SZY represents Shanzhuyu (Corni Fructus); ZX represents Zexie (Alismatis Rhizoma); FL represents Fuling (Poria); MDP represents Mudanpi (Moutan Cortex).

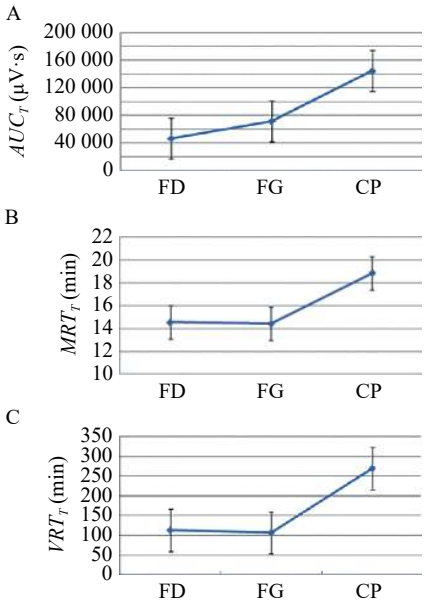

Figure 3 TQSM of FD, FG, and CP of LWDHF

A, AUC_T of FD, FG, and CP. B, MRT_T of FD, FG, and CP. C, VRT_T of FD, FG, and CP.

Table 2 The TQSM similarity of FG, FD, and CP of LWDHF (%)

Item	FG	FD	CP
FG	100.00	98.66	76.62
FD	98.66	100.00	75.37
CP	76.62	75.37	100.00

Table 3 The similarity of evaluation system for the chromatographic fingerprint of TCM (version 2004 A) (%)

Item	FG	FD	CP
FG	100.00	98.68	85.60
FD	98.68	100.00	85.43
CP	85.60	85.43	100.00

75.37%, the similarity evaluation was 85.43%, the TQSM similarity of FG and CP was 76.62%, and the similarity evaluation was 85.60%.

4 Discussion

Overall, our study serves as a proof of concept that TQSM can be a novel method for discovering the transitivity of all components and distinctions among FG, FD, and CP for CMMF. Thus, TQSM is similar to describing and comparing pharmacokinetic behavior of multiple ingredients separately and in combination. This is based on drug pharmacokinetic parameters that are inconsistent with the integral effects [15]. TQSM was performed to synthesize all fingerprint peaks with no segmentation and to analyze the intrinsic features of fingerprints by statistical methods. This reflects the macroscopicity of fingerprints and considers the ambiguity of fingerprints. AUC_T, MRT_T, and VRT_T were additive in calculating raw data and in dynamically monitoring changes in the TCM components. Specifically, AUC_T can be used for quantitative analysis, whereas MRT_T and VRT_T can be used for qualitative analysis. TQSM is being widely applied in the analysis of multi-component TCM [16]. TQSM can accurately reflect the fingerprint characteristics of the multi-component system of CMMF because of its anti-interference, additivity, and coupling characteristics.

Compared with the other evaluation methods of HPLC fingerprints, TQSM focuses more on evaluating fingerprints as a whole, and not from the components. Therefore, for the fingerprint of the same TCM (fufang and its formulations), the TQSM performs consistently as long as the overall chemical composition is stable, even if the single peak information in the fingerprint changes. In addition, as long as their integrity components or composition ratios are similar, they reflect a similar response in AUC_T, MRT_T, and VRT_T. Therefore, TQSM, AUC_T, MRT_T, and VRT_T can be used to analyze the differences between the chemical properties and different formulations of LWDHF. Based on TQSM in this study, we can conclude that the AUC_T of FG was larger than that of FD, but both were less than that of CP. The total quantity of the methanol-dissolving part (TQMP) in FG exceeded that in FD, and both were less than that in CP. The MRT_T of FG was similar to that of FD, and the MRT_T of CP was slightly higher than that of the others, suggesting that the apparent polarity of TQMP was similar. The VRT_T of the combined decoction was similar to that of FG, and the VRT_T of CP was the highest, which reflected that the degree of dispersion of the multicomponents of FG and FD was similar, and the dispersion degree of CP was the highest. The TQSM similarity of FG and FD was 98.66%, while the traditional similarity evaluation was 98.68%. The TQSM similarity of FD and CP was 75.37%, while the traditional similarity evaluation was 85.43%, indicating that there was no significant difference between FG and FD, but there was a considerable distinction between FD and CP.

The mechanisms and factors influencing the distinctions among different formulations are traditionally thought to be linked to the solubility of the chemical composition [16]. The solubility changes when ingredients are compatibly mixed, such as a combination of glycosides, organic acids, anthraquinones, alkaloids, and their derivatives; surface-active agents and pH are also considered to be influencing factors. Hundreds of TCM ingredients exist in the form of molecular and supramolecular chemistry [17]; therefore, supramolecular chemical reactions should be considered in addition to simple chemicals. Recent researches show that CMMF is viewed as an aggregate of supramolecules composed of host and guest molecules [16, 17]. For instance, proteins, organs, and tissues act as host molecules; glycosides, terpenes, anthraquinones, alkaloids, and tannins act as guest molecules. In this study, the quality characteristics and supramolecules formed between the same dosage forms (FG and FD) were the same, but the dosage forms of FD and CP were different. Supramolecular chemistry phenomena could be the principal reason why there are considerable distinctions between different formulations, whose transitivity can be described by TQSM. The FD and CP of LWDHF and the similarities of different dosage forms was different. When both decoctions are used, the compatibility of decoctions is different, but the similarity is very high. The graphical abstract is shown in Figure 4.

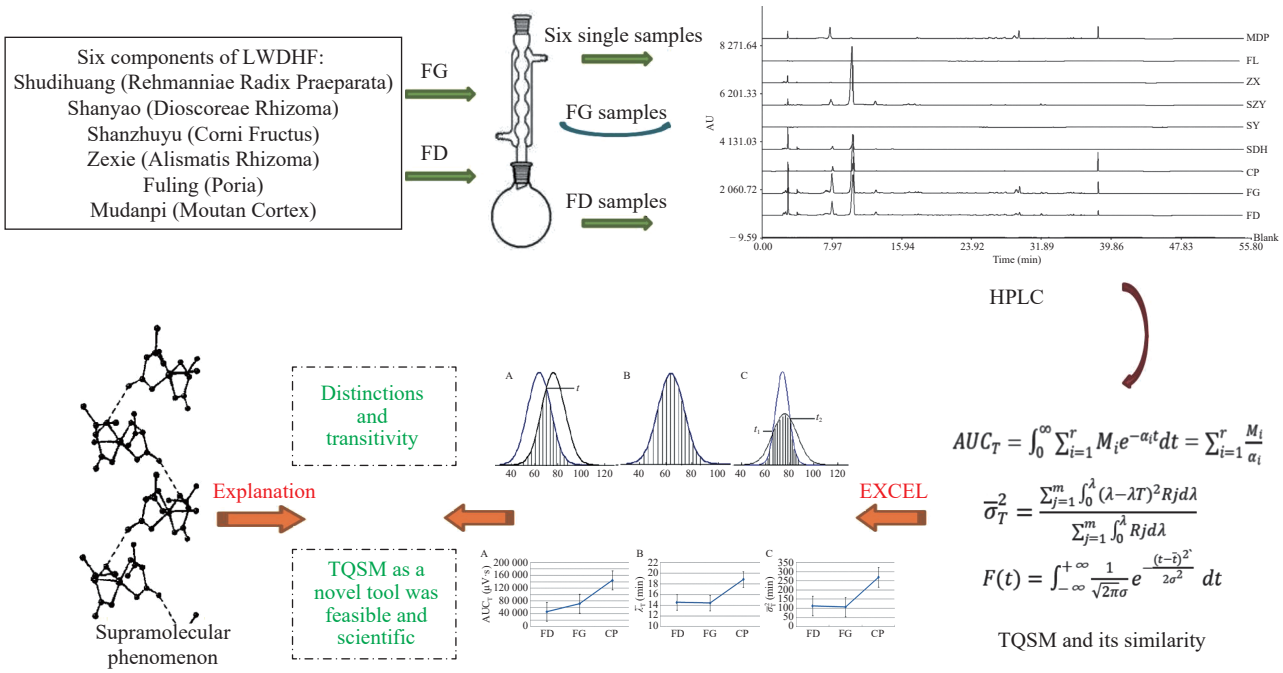

Figure 4 Graphical abstract of the study

5 Conclusion

In summary, our results indicate that the transitivity of the compositions can be described by TQSM. There was little distinction of the total composition between FG and FD, but some distinction existed when different dosage forms, such as FD and CP, were used; the distinctions between different dosage forms cannot be neglected. The mechanism of distinction and transitivity can be explained by the supramolecular phenomena of TCM. TQSM was used to analyze the quality differences between FG and FD, and the other formulations were feasible and scientific. The current study offers a viable strategy to study the transitivity of MCS in CMMF and the distinctions between the different dosage forms of the same prescription. It also provides a basis for FG to replace MCS in clinical applications. TCM diagnosis and treatment should pay attention not only to compatibility, but also to the role of dosage forms in diseases.

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Competing interests

The authors declare no conflict of interest.

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六味地黄复方三种不同剂型之间的组分传递规律研究

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【摘要】目的 本文旨在探讨六味地黄复方 (LWDHF) 原料粗片 (MCS) 至配方颗粒 (FG)、方汤 (FD)、浓缩片 (CP) 的整体组分传递规律。**方法** 处理 LWDHF 不同剂型提取物后，得到 LWDHF 的 MCS、FG、FD 和 CP 样品。通过使用高效液相色谱（HPLC）建立指纹图谱数据库，使用 XB-C18 色谱柱分离各组分后，采用总量统计矩法 (TQSM) 计算各样品的总量零阶矩（AUC_T）、总量一阶矩（MRT_T）和总量二阶矩（VRT_T），基于计算结果分析整体组分的传递规则及其相似性方法。基于 LWDHF 的 FG、FD 和 CP 的 HPLC 指纹图谱，计算各自的 AUC_T、MRT_T 和 VRT_T。**结果** LWDHF 的 FG、FD 和 CP 的 AUC_T 分别为 71 804、46 553 和 144 646 μV·s，MRT_T 分别为 14.43、14.54 和 18.85 min，VRT_T 分别为 106.98、112.84 和 269.12 min^2。通过比较 LWDHF 的 FG/FD、FG/CP 和 FD/CP 的相似性，得出 TQSM 相似性值分别为 98.66%、76.62% 和 75.37%，而传统的相似性评估值分别为 98.68%、85.43% 和 85.60%。**结论** FG 和 FD 的整体组分之间无明显区别，而 FD 和 CP 之间存在一定的差异。故六味地黄复方配方颗粒可以作为原料粗片的可替代物在临床应用中使用。

【关键词】六味地黄复方；配方颗粒；方汤；浓缩片；总量统计矩；高效液相色谱；组分传递规律