Physicochemical Studies on Decoctions of Kampo Prescriptions. III.[1] Effect of the Volume Ratio of the Crude Drug *vs.* Extractant on the Transfer Ratio of Crude Drug Components into a Model Decoction

Kaoru NAKAJIMA,* Tomoko HORIUCHI, Heihachiro TAGUCHI, Koji HAYASHI, Minoru OKADA, and Masao MARUNO

Tsumura Central Research Laboratories, Tsumura & Co., 3586 Yoshiwara, Ami-machi, Inashiki-gun, Ibaraki 300-11, Japan. Received March 3, 1994; accepted June 16, 1994

Using a model decoction of Schisandrae Fructus, the effect of the volume ratio of the crude drug *vs.* extractant was studied. On changing the alteration ratio of the volume ratio according to a two-fold geometric series, the transfer ratios of each lignan into model decoctions generally decreased with increasing alteration ratio. However, the transfer ratios of the high hydrophobic lignans increased partially with the high alteration ratios. As a result, a comprehensive equation involving to the transfer ratios of all the low molecular weight organic components of Schisandrae Fructus in the model decoctions was derived from the analyses of the variant alteration ratios. This equation might be applicable to other crude drug components in kampo decoctions.

Keywords transfer ratio; lignan; Schisandrae Fructus; decoction; HPLC; hydrophobic parameter

In our previous study on the transfer ratio (r_T, %) of organic components of crude drugs into kampo decoctions,[1] we found that log $(100/r_T - 1)$ is correlated with the hydrophobicity parameter or related parameters, such as the partition coefficient (log P) and the capacity factor (log k') from reverse-phase HPLC. However, the actual transfer ratio of an extremely hydrophobic component, such as 1,3-ditrichosanoyl-2-linoleoylglycerol from Trichosanthis Semen, was higher than the value estimated from the basic equation for model decoctions. In the case of highly hydrophobic components, more than the predicted amount is considered to be transferred by adsorption in the form of "Ori (Japanese for dregs)," which is transferred to the decoction without dissolution, or by suspension and emulsification of the components themselves. Therefore, a decoction cannot be simply regarded as a water solution.

The fact that the transfer ratio of a crude drug component is dependent on its hydrophobicity suggests that it is affected by factors related to the Belthelot–Nernst law of partition.[2] One such factor in the decoction is the volume ratio between the two phases, *i.e.*, the crude drug and the extractant (water). A different volume of extractant may be used to make a decoction of the same kampo prescription in different textbooks or in different countries.[3] It is of interest to see how these differences affect the components in a decoction.

In the present study, we used a model decoction of Schisandrae Fructus cut on its own into pieces of size 0.5—1.0 mm in order to examine the effect of the volume of water used to make a decoction of Schisandrae Fructus on the transfer ratios of lignans. We also theoretically evaluated the transfer of the lignans by dividing the process into transfer with and without dissolution; we also studied the effect of the volume ratio of the crude drug *vs.* extractant on the measured transfer ratio.

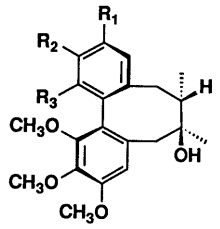
Experimental

Measurement of the Transfer Ratios of Lignans into Single-Drug Decoctions Using Schisandrae Fructus. Crude Drug and Its Preparation Schisandrae Fructus purchased from Uchida Wakanyaku, Co., Ltd. was cut up finely with a knife, and the fragments 0.5—1.0 mm were collected by sifting.

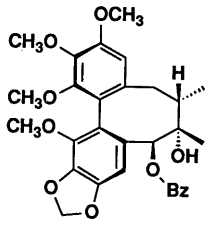
Components Analyzed The following lignans[4] and previously unidentified components of Schisandrae Fructus were analyzed (Chart 1, Fig. 1): Schizandrin (**1**), gomisin A (**2**), angeloylgomisin H (**3**), gomisin G (**5**), deoxyschizandrin (**8**), (±)-γ-schizandrin (**9**), gomisin N (**10**) and wuweizisu C (**11**).

Unidentified components (**4**, **6**, **7**) were analysed using HPLC and a three-dimensional UV detector (Multi-330, JASCO) and found to be biphenyl lignans belonging to the same group as the other 8 lignans.

Preparation of Single-Drug Decoctions An aliquot (0.500—8.000 g) of Schisandrae Fructus was transferred to a 1 or 0.5-l beaker by changing the volume ratio of the crude drug *vs.* extractant according to a two-fold geometric series, and decocted with 600 or 300 ml water on



	R_1	R_2	R_3
1	OMe	OMe	OMe
2	-OCH_2O-		OMe
3	OMe	OMe	OAng



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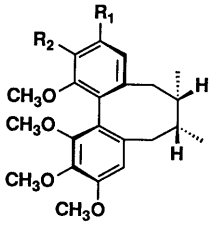
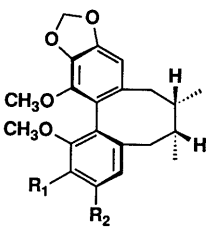


	R_1	R_2
8	OMe	OMe
9	-OCH_2O-	



	R_1	R_2
10	OMe	OMe
11	-OCH_2O-	

Me = methyl
Ang = angeloyl
Bz = benzoyl

Chart 1

TABLE I. Transfer Ratios of Lignan into Model Decoctions Using a Small Size Preparation of Schisandrae Fructus

Component	$\log k'$ [a]	Transfer ratio (%) (S.D., $n=3$)					
		Decoction no.					
		$1_{n=-1}$	$2_{n=0}$	$3_{n=1}$	$4_{n=2}$	$5_{n=3}$	$6_{n=4}$
		S. Fructus wt. (g)					
		0.500	1.000	1.000	2.000	4.000	8.000
		Initial water vol. (ml)					
		600	600	300	300	300	300
		Decoction vol. (ml)					
		300	300	150	150	150	150
1	0.5540	95.6 (3.9)	88.2 (4.8)	82.9 (3.3)	74.3 (4.7)	61.6 (3.9)	46.5 (0.7)
2	0.6919	92.6 (4.4)	82.7 (5.0)	73.5 (3.9)	62.2 (1.2)	45.8 (2.0)	32.9 (1.2)
3	0.8218	93.8 (4.0)	82.4 (1.3)	70.0 (2.7)	60.7 (1.9)	43.6 (0.4)	30.8 (2.4)
4	0.8838	81.8 (3.7)	78.6 (5.9)	66.9 (2.0)	58.1 (1.4)	41.4 (1.8)	30.0 (1.4)
5	0.9583	92.3 (11.9)	73.3 (10.4)	59.7 (6.6)	45.6 (5.0)	27.9 (4.9)	22.2 (6.3)
7	0.9946	76.4 (5.9)	58.9 (3.0)	48.3 (1.5)	34.6 (2.1)	21.4 (1.3)	19.9 (1.6)
6	1.0395	82.4 (5.1)	68.0 (2.1)	54.6 (2.1)	41.1 (5.3)	29.0 (3.2)	22.0 (0.6)
8	1.3065	22.9 (2.6)	17.0 (1.4)	14.9 (1.1)	10.9 (1.3)	12.2 (0.4)	13.8 (1.0)
10	1.4492	20.4 (1.9)	14.9 (2.8)	12.4 (2.2)	12.5 (1.0)	14.8 (1.7)	16.0 (2.7)
9	1.4797	19.2 (1.2)	14.9 (2.3)	11.4 (2.0)	12.5 (0.8)	15.2 (2.0)	16.1 (2.0)
11	1.6001	13.3 (1.7)	10.8 (1.2)	9.8 (1.8)	12.0 (1.2)	15.5 (1.5)	16.3 (2.1)

a) HPLC conditions: equipment, ALC/GPC 244 (Waters); column, μ Bondapak C_{18} (10 μm, 3.9 mm i.d. × 30 cm, Waters); mobile phase, 50%CH_3CN; flow rate, 1 ml/min; detection, UV 254 nm.

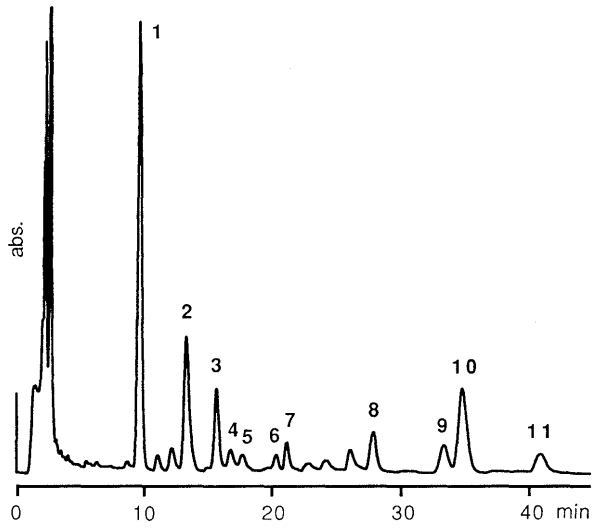


Fig. 1. High Performance Liquid Chromatogram of a Methanolic Extract of Schisandrae Fructus

HPLC conditions: see Experimental.

an electric heater (National NK-685SG; 300—600 W) for about 70 min until the volume was reduced to about 300 or 150 ml, respectively. The decoction was filtered through 2 layers of gauze while still hot, adjusted to a volume of 300 ml with water after cooling, and used as a single-drug decoction to evaluate the effects of the alteration ratio on the volume ratio (Table I).

Preparation of Sample Solutions for HPLC An aliquot (50—75 ml) of the single-drug decoction was mixed with 50 ml butanol, and the mixture was concentrated under reduced pressure. The residue was extracted with 50 ml methanol by refluxing for 30 min. The residue was treated again with 50 ml methanol. The extracts were combined and concentrated under reduced pressure, and adjusted to a fixed volume.

Preparation of Standard Solutions for HPLC Exactly 1.000 g of Schisandrae Fructus was extracted with 50 ml methanol for 30 min under reflux. After filtration, the residue was treated similarly with a further 50 ml methanol. The extracts were combined, concentrated under reduced pressure, and adjusted to 20 ml with methanol.

TABLE II. Water Content in Crude Drug Residue of Model Decoctions Using Small Size Preparation of Schisandrae Fructus and Specific Gravity of the Residue

	Weight of crude drug residue (g)/weight of crude drug (g)	Water content (ml)/ weight of crude drug residue (g)	Specific gravity of crude drug residue
Ave.	49.54%	3.55 (ml/g)	1.12 (g/ml)
S.D.	2.42%	0.68 (ml/g)	0.22 (g/ml)
C.V.	4.89%	19.19%	19.78%
n	18	18	18

C.V., coefficient of variation.

HPLC Assay After passing the sample and standard solutions through a 0.45 μm filter, a fixed volume was applied to HPLC. The transfer ratio (%) of each lignan was determined by comparison of the peak area with that of the corresponding standard solution for HPLC. The HPLC conditions are shown below: equipment, ALC/GPC 244 (Waters); column, μ Bondapak C_{18} (10 μm, 3.9 mm i.d. × 30 cm, Waters); mobile phase, CH_3CN–CH_3OH–H_2O (11 : 11 : 16)→(10 : 10 : 10) (stepwise gradient, 10 min); flow rate, 1 ml/min; detection, UV 254 nm.

Measurement of the Volume of Decoction in the Drug Residue and the Specific Gravity of the Drug Residue Volume of decoction in the residue of the crude drug: The moist residue of the crude drug was weighed, then freeze-dried and weighed again, and the volume of water contained in the moist residue was calculated from the weight difference before and after drying.

Specific gravity of the residue of the crude drug: A fixed amount of methanol was added to a measuring cylinder, the dried residue of a crude drug was placed in the methanol and the increase in volume was taken as the volume of the residue (Table II).

Results and Discussion

Effects of the Alteration Ratio on the Transfer Ratio. The Transfer Ratios into Single-Drug Decoctions Using Schisandrae Fructus Table I shows the transfer ratios of each lignan into single-drug decoctions using Schisandrae Fructus. The transfer ratios of each lignan decreased

with increasing hydrophobicity or alteration ratio in the volume ratio of the crude drug *vs.* extractant. However, the transfer ratio increased for highly hydrophobic lignans **8**—**11** in decoctions with high alteration ratios such as decoctions No. 5 and No. 6, and this tendency was most notable in the very highly hydrophobic lignans. Moreover, a model decoction was more turbid; its alteration ratio was greater when it was diluted to the same concentration for a qualitative comparison. These findings suggest that this phenomenon is caused by components transferred without dissolution.

Effects of the Alteration Ratio on the Transfer Ratio with Dissolution Equation 4, described in a previous report[1b] shows the relationship between the transfer ratio (r_T) of the component to the decoction and the volume (v) of the decoction (W) or the residue (C) of the drug and the concentration (c) of the component in the decoction or the residue.

$$\frac{c_C}{c_W}=\frac{v_W}{v_C}\left(\frac{100}{r_T}-1\right) \tag{4}$$

Since the left term c_C/c_W corresponds to the partition coefficient ($P_{Dec.}$) of a crude drug component in that system, the following Eq. 10 is obtained if the transfer ratio of the component with dissolution, under given decoction conditions, is defined as r_{Ts}:

$$P_{Dec.}=\frac{v_W}{v_C}\left(\frac{100}{r_{Ts}}-1\right) \tag{10}$$

In the same system, when the transfer ratio with dissolution of a decoction with different drug and extractant volumes is expressed as r'_{Ts}, and a complete partition equilibrium is assumed to be reached, the $P_{Dec.}$ of the component is constant, hence:

$$P_{Dec.}=\frac{v'_W}{v'_C}\left(\frac{100}{r'_{Ts}}-1\right) \tag{11}$$

In Eq. 11, v'_W represents the volume of decoction when the volume of the extractant (water) is different, and v'_C represents the volume of the residue of the crude drug when the amount of crude drug is different. When the alteration ratio in the volume ratio of the crude drug *vs.* extractant of the other decoction on a given standard decoction is defined as α, the following, Eq. 12, is obtained:

$$\frac{v'_C}{v'_W}=\alpha\frac{v_C}{v_W} \tag{12}$$

From Eqs. 10, 11 and 12, the following, Eq. 13, is derived:

$$\frac{100}{r'_{Ts}}-1=\alpha\left(\frac{100}{r_{Ts}}-1\right) \tag{13}$$

Furthermore, when $\alpha=2^n$, Eq. 13 can be converted to:

$$\log\left(\frac{100}{r'_{Ts}}-1\right)=\log\left(\frac{100}{r_{Ts}}-1\right)+n\log 2 \tag{14}$$

When the values of $\log(100/r'_{Ts}-1)$ are plotted along the y axis and those of $\log(100/r_{Ts}-1)$ along the x axis, and when n is an integral number, the y intercept occurs at fixed intervals, and changes in the soluble transfer ratio associated with changes in the α can be determined (Fig. 2).

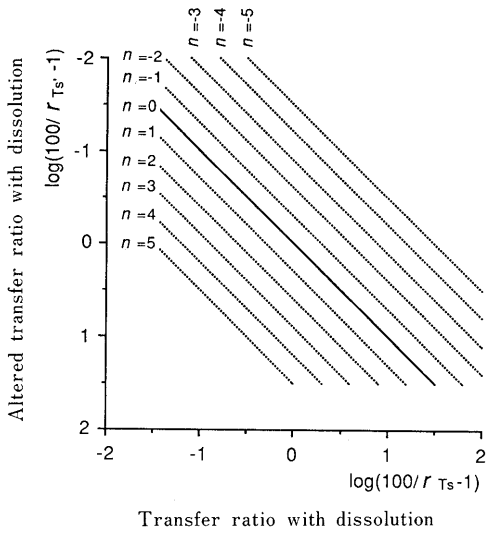


Fig. 2. Alteration of Transfer Ratio with Dissolution

Transfer without Dissolution When the mole number of a given crude drug component transferred by complete dissolution is n_{Ws}, that of the component transferred without dissolution as a suspension and/or emulsion is n_{Wi}, and that remaining in and/or readsorbed to the residue of the crude drug is n_C; the total moles of component transferred into the decoction (n_{Wt}) is the sum of n_{Ws} and n_{Wi}:

$$n_{Wt}=n_{Ws}+n_{Wi} \tag{15}$$

Moreover, if n_C is divided by n_{Wt}, then Eq. 15 is transformed into the following, Eq. 16:

$$\frac{n_C}{n_{Wt}}=\frac{(n_C+n_{Wi})}{n_{Ws}}\cdot\frac{n_{Ws}n_C}{(n_{Ws}+n_{Wi})(n_C+n_{Wi})} \tag{16}$$

When the total transfer ratio is r_{Tt}, n_C/n_{Wt} is expressed as $100/r_{Tt}-1$. Moreover, if $(n_C+n_{Wi})/n_{Ws}$ is expressed as $100/r_{Ts}-1$, the following, Eq. 17, can be derived:

$$\log\left(\frac{100}{r_{Tt}}-1\right)=\log\left(\frac{100}{r_{Ts}}-1\right)-\log\left[\left(\frac{n_{Wi}}{n_{Ws}}+1\right)\left(\frac{n_{Wi}}{n_C}+1\right)\right] \tag{17}$$

$\log(100/r_{Ts}-1)$ in Eq. 17 is the term related to the transfer ratio with dissolution and the remaining $-\log[(n_{Wi}/n_{Ws}+1)(n_{Wi}/n_C+1)]$ corresponds to transfer without dissolution. This suggests that transfer with dissolution involves a complex balance involving the completely soluble phase, the insoluble phase such as a suspensoid and/or emulsoid, and the residue of the crude drug in the decoction. However, it is difficult to directly evaluate the changes in transfer without dissolution.

Effects of the Alteration Ratio on Transfer without Dissolution. i) Analysis of Measured Values As part of the decoction remained in the residue of the crude drug, an increase in the alteration ratio (α) leads to an increase in the proportion of unrecovered decoction. To reduce the effect of the unrecovered decoction on the transfer ratio, we estimated the volume of unrecovered decoction from the water content in the residue of the crude drug by correction of the transfer ratios to the single-drug

decoctions (Table III).

Figure 3 shows the relationship between the transfer ratio of each lignan and the capacity factor ($\log k'$) of those lignans on reverse-phase HPLC. In comparison with decoction No. 2, the transfer ratio of highly hydrophobic lignans was reversed in decoction No. 6, but the relationship between both decoctions was unclear. Since this was primarily due to the fact that the transfer ratio and the capacity factor are not exactly correlated (correlation coefficient $r \neq 1$), other methods were tested. If the transfer ratio is correlated with the hydrophobic parameter, it can be used as a substitute for that parameter. Therefore, a transfer ratio in a weak model decoction which scarcely contains any insoluble components can be regarded as equivalent to the hydrophobic parameter in this system. Moreover, this weak model decoction of standard (standard decoction) shows an exact correlation (correlation coefficient $r=1$), and changes in other model decoctions can be evaluated in detail using the standard decoction. On the basis of this hypothesis, we defined the transfer ratio of each lignan in the weak decoction No. 2 as standard $r_{\mathrm{Tstd.}}$ and plotted the $\log(100/r_{\mathrm{T}}-1)$ of various lignans in other model decoctions on the ordinate axis against $\log(100/r_{\mathrm{Tstd.}}-1)$ as abscissa (Fig. 4). This graph showed the transfer ratios of the model decoctions as curves compared with the straight line obtained for the decoction No. 2. This graph allows the estimation of changes in the transfer ratio without dissolution associated with changes in α.

ii) Estimation of the Effect of the Alteration Ratio on Transfer without Dissolution Since Eq. 17 suggests that it is difficult to directly evaluate the effect of α on transfer without dissolusion, we attempted to estimate it from the measured values of the transfer ratio in the single-drug decoction. Firstly, Eq. 17 can be simplified to:

$$Y_{\mathrm{t}} = Y_{\mathrm{s}} + Y_{\mathrm{i}} \tag{18}$$

by expressing the total transfer $\log(100/r_{\mathrm{Tt}}-1)$ as Y_{t}, the transfer with dissolution $\log(100/r_{\mathrm{Ts}}-1)$ as Y_{s}, and the transfer without dissolution $-\log[(n_{\mathrm{Wi}}/n_{\mathrm{Ws}}+1)(n_{\mathrm{Wi}}/n_{\mathrm{C}}+1)]$ as Y_{i}.

The equation involving the relationship between changes in α and in the transfer ratio without dissolution, *i.e.* Eq. 14, is valid when the size of the drug is negligible and complete partition equilibrium is present between the residue of the drug and the decoction. However, the size of the drug cannot be ignored in actual decoctions. Also, a factor involving the morphology of the drug that serves as a standard is required when complete partition equilibrium is reached. The relationship between this factor (f) and $\log(100/r_{\mathrm{Tstd.}}-1)$ (X) is expressed as:

TABLE III. Corrected Transfer Ratios of Lignan into Model Decoctions Using a Small Size Preparation of Schisandrae Fructus

	Corrected transfer ratio (%)					
	Decoction no.					
	$1_{n=-1}$	$2_{n=0}$	$3_{n=1}$	$4_{n=2}$	$5_{n=3}$	$6_{n=4}$
	S. Fructus wt. (g)					
Component	0.500	1.000	1.000	2.000	4.000	8.000
	Initial water vol. (ml)					
	600	600	300	300	300	300
	Decoction vol. (ml)					
	300	300	150	150	150	150
1	95.8	88.7	83.9	76.0	64.5	50.8
2	92.9	83.2	74.3	63.7	48.0	36.0
3	94.1	82.9	70.9	62.2	45.7	33.7
4	82.0	79.0	67.7	59.4	43.3	32.8
5	92.6	73.7	60.4	46.7	29.2	24.3
7	82.6	68.4	55.2	42.0	30.3	24.0
6	76.6	59.2	48.8	35.4	22.4	21.8
8	23.0	17.1	15.1	11.2	12.8	15.1
10	20.5	15.0	12.5	12.8	15.5	17.5
9	19.3	15.0	11.6	12.8	16.0	17.6
11	13.3	10.8	9.9	12.2	16.2	17.8
	Correction factor[a]					
	1.0029	1.0059	1.0117	1.0235	1.0470	1.0938

a) Correction factor = 1 + (water content in the crude drug residue)/(decoction volume).

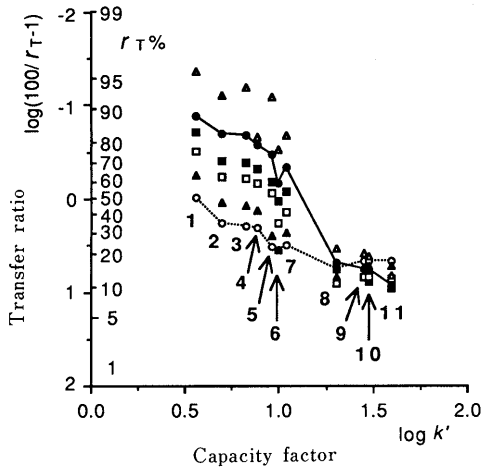


Fig. 3. Relationships between Capacity Factors of Lignan and Their Transfer Ratios to Each Model Decoction

HPLC conditions: equipment, ALC/GPC 244 (Waters); column, μ Bondapak C_{18} (10 μm, 3.9 mm i.d. × 30 cm, Waters); mobile phase, 50% CH_3CN; flow rate, 1 ml/min; detection, UV 254 nm. Decoction No.: △, $1_{n=-1}$; ●, $2_{n=0}$; ■, $3_{n=1}$; □, $4_{n=2}$; ▲, $5_{n=3}$; ○, $6_{n=4}$.

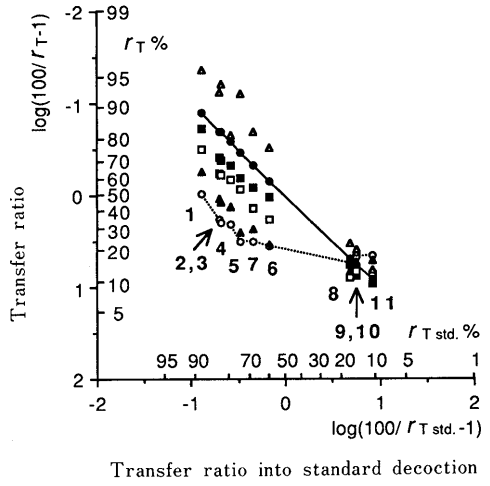


Fig. 4. Relationships between Transfer Ratios of Lignan to Standard Decoction and to Each Model Decoction

Symbols are the same as in Fig. 3.

TABLE IV. Values of Portion of Transfer without Dissolution (Y_i)

Component	$X^{a)}$	Value of $Y_i^{b)}$					
		Decoction no.					
		$1_{n=-1}$	$2_{n=0}$	$3_{n=1}$	$4_{n=2}$	$5_{n=3}$	$6_{n=4}$
1	−0.8944	−0.1961	0	−0.0939	−0.1548	−0.1800	−0.2077
2	−0.6926	−0.1535	0	0.0035	−0.0953	−0.0881	−0.1450
3	−0.6843	−0.2437	0	0.0264	−0.0753	−0.0561	−0.1104
4	−0.5875	0.1996	0	−0.0061	−0.1219	−0.1112	−0.1882
5	−0.4740	−0.3339	0	0.0164	−0.1377	0.0466	−0.1092
7	−0.3352	−0.0878	0	−0.0281	−0.0692	−0.1175	−0.2524
6	−0.1624	−0.0808	0	−0.0888	−0.1204	−0.1126	−0.3702
8	0.6843	0.1127	0	−0.2054	−0.3291	−0.6658	−1.0234
10	0.7533	0.1064	0	−0.1420	−0.4624	−0.7475	−1.1697
9	0.7550	0.1409	0	−0.1815	−0.4641	−0.8335	−1.1702
11	0.9160	0.1694	0	−0.2274	−0.6041	−1.0180	−1.3404

a) $X=\log(100/r_{\text{T std.}}-1)$. $r_{\text{T std.}}$, transfer ratio of lignan into standard decoction. *b)* Y_i, portion of transfer without dissolution of lignan into each model decoction.

$$Y_s = X + nf\log 2 \tag{19}$$

and the equation:

$$Y_i = Y_t - (X + nf\log 2) \tag{20}$$

can be derived from Eqs. 18 and 19.

Equation 20 is described changes in the portion of transfer without dissolution (Y_i) as changes in α. Table IV and Fig. 5 show the values of measured Y_i. Since the value of f is difficult to determine theoretically, it was estimated in the following manner. When the transfer ratios of various lignans to the decoctions Nos. 3—6 are displayed in a graph where the transfer ratios to the standard decoction are plotted along the x axis, the line resembles a quadratic curve (Fig. 4). When the values of Y_t and X were subjected to quadratic regression, and tangents parallel to $Y_t = X$ were determined, they occurred at nearly equal intervals. The mean value of the intervals was 0.8071 log 2 (C.V. = 3.45%, $n=4$). Factor f has to be equal to 1 if the size of the crude drug is assumed to be negligible in a system where there is complete partition equilibrium. Since an f value between 0.8071 and 1 is appropriate in this experiment, the f was approximated by 0.9036 as a median value. The value of f relating to the form of the crude drug can also be estimated by making a comparison between the single-drug decoction and the mixed-drug decoction using small size preparations (0.5—1.0 mm) of the crude drugs in previous studies[1b]; this was done and its value was found to be 0.8563—1. Therefore, the estimated f value (=0.9036) used in this study is appropriate. Figure 5, showing changes in the transfer ratio without dissolution, indicates that α has little effect on the transfer ratio without dissolution for the moderately hydrophobic lignans even if high. On the other hand, the transfer ratio without dissolution increases with α in the case of highly hydrophobic lignans. This suggests that highly hydrophobic components are also related to transfer without dissolution in general kampo decoctions (Fig. 5).

The transfer ratios of crude drug components other than these lignans must be taken into consideration. Therefore, the following hypotheses are proposed.

i) The participation of transfer without dissolution

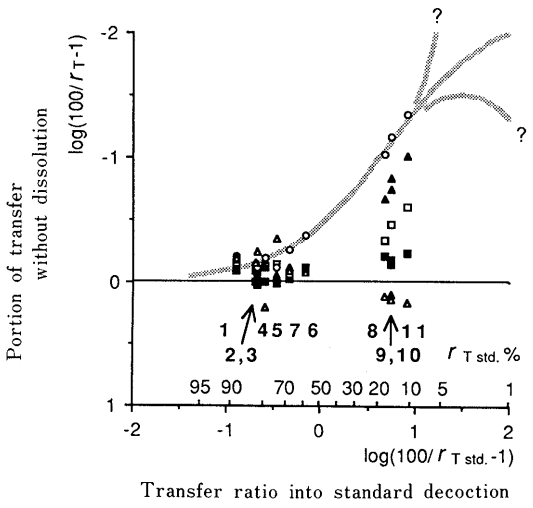


Fig. 5. Alteration of Portion of Transfer without Dissolution of Lignan
Symbols are the same as in Fig. 3.

increases with the increase in hydrophobicity of the components.

ii) If the transfer ratio into the standard decoction is 100% for an extremely hydrophilic component, its transfer ratio will always be 100% under all decoction conditions. On the other hand, if, for an extremely hydrophobic component, the transfer ratio to the standard decoction is 0%, the transfer ratio will always be 0% under all decoction conditions.

iii) The relationship of $n+1$ to n in α becomes equal to that of $n+2$ to $n+1$ as the relationship among decoctions become relative.

Figure 5 shows a gradual increase in the relationship between the transfer without dissolution and the hydrophobicity of lignans. If these increases are assumed to be exponential, the transfer ratio of a component whose transfer ratio is 0% in the standard decoction becomes 100% when α is increased infinitely. Since this is contradictory to actual fact, the exponential function equation is inappropriate for this estimation. If the transfer ratio is assumed to decrease at higher hydrophobicities, it will be difficult for hydrophobic components to be distributed

TABLE V. Values of $\log(-1.8072n\cdot\log 2/Y_i-1)$

Component	X	Value of $\log(-1.8072n\cdot\log 2/Y_i-1)$					
		Decoction no.					
		$1_{n=-1}$	$2_{n=0}$	$3_{n=1}$	$4_{n=2}$	$5_{n=3}$	$6_{n=4}$
1	−0.8944	NC	NC	0.6806	0.7802	0.9067	0.9767
2	−0.6926	NC	NC	NC	1.0177	1.2436	1.1463
3	−0.6843	NC	NC	NC	1.1287	1.4486	1.2721
4	−0.5875	0.2369	NC	1.9454	0.8990	1.1360	1.0238
5	−0.4740	NC	NC	NC	0.8389	NC	1.2771
7	−0.3352	NC	NC	1.2639	1.1680	1.1102	0.8820
6	−0.1624	NC	NC	0.7098	0.9051	1.1301	0.6882
8	0.6843	0.5829	NC	0.2171	0.3629	0.1617	0.0516
10	0.7533	0.6141	NC	0.4519	0.1313	0.0731	−0.0653
9	0.7550	0.4565	NC	0.3004	0.1285	−0.0186	−0.0657
11	0.9160	0.3447	NC	0.1437	−0.0964	−0.2196	−0.2052

NC: non-calculable.

TABLE VI. Regression Equations between X and $\log(-1.8072n\cdot\log 2/Y_i-1)$

Decoction no.	Regression equation	
$1_{n=-1}$	$\log(1.8072\log 2/Y_i-1)=0.1933X+0.3970$	$(r=0.5627, n=5)$
$2_{n=0}$	—	
$3_{n=1}$	$\log(-1.8072\log 2/Y_i-1)=-0.6302X+0.8030$	$(r=-0.7339, n=8)$
$4_{n=2}$	$\log(-3.6144\log 2/Y_i-1)=-0.5782X+0.6224$	$(r=-0.9027, n=11)$
$5_{n=3}$	$\log(-5.4216\log 2/Y_i-1)=-0.8058X+0.6772$	$(r=-0.9316, n=10)$
$6_{n=4}$	$\log(-7.2288\log 2/Y_i-1)=-0.8129X+0.5814$	$(r=-0.9657, n=11)$
Total	$\log(-1.8072n\cdot\log 2/Y_i-1)=-0.8094X-0.0958n+0.9646$	

in the organic phase such as a suspensoid and/or emulsoid, which also contradicts what actually happens. If the transfer ratio must increase with the hydrophobicity over a finite range, the equation must approach infinity to some degree. Therefore, an equation for the estimation is considered to be an asymptotic one, which approaches $Y_i=0$ and $Y_i=m$ (m is a certain constant) in low and high hydrophobic regions, respectively. In addition, as factors for the transfer without dissolution are included to some extent in the standard decoction, equations for the estimation in various model decoctions must be related. Therefore, m should be negative n, and the relationship can be expressed as an equation that gradually approaches $Y_t=X+nf\log 2$ in the low hydrophobic region and $Y_t=X-nf\log 2$ in the high hydrophobic region. The relationship between Y_i and X is similar to that between r_T and $\log(100/r_{Tstd.}-1)$. Thus it is represented as:

$$\log\left(\frac{-2nf\log 2}{Y_i}-1\right)=aX+bn+c \tag{21}$$

where a, b, and c are constants. If a is regarded as a variable, transfer without dissolution decreases as the alteration ratio (α) increases, which contradicts what actually happen. A segment where the transfer ratio remains constant, in spite of changing α, occurs unless $bn+c$ is a function of n. Table V shows the values of $\log(-2nf\log 2/Y_i-1)$ determined by the experiment. When linear regression by the least squares method is applied to the values of $\log(-2nf\log 2/Y_i-1)$ and X, the regression equations shown in Table VI are obtained. The values of the constants a, b and c and Y_i were determined from the regression equations for decoctions No. 5, and No. 6, in which the regression equations were accurate, and hence Eq. 22:

$$Y_i=-1.8072n\log 2(10^{-0.8094X-0.0958n+0.9646}+1)^{-1} \tag{22}$$

was obtained. This can be expressed as a general equation:

$$Y_i=-2nf\log 2(10^{aX+bn+c}+1)^{-1} \tag{23}$$

This Eq. 23 is useful for estimating changes in the portion of the transfer without dissolution associated with changes in α. In this case, Y_i does not mean the transfer ratio without dissolution itself.

Effects of the Alteration Ratio on the Total Transfer Ratio The total transfer Y_t is calculated from the portion of transfer with dissolution Y_s and the portion of transfer without dissolution Y_i. Therefore, changes in the total transfer ratio of each lignan associated with changes in the alteration ratio (α) can be estimated by Eq. 24 (Fig. 6):

$$Y_t=X+0.9036n\log 2-1.8072n\log 2(10^{-0.8094X-0.0958n+0.9646}+1)^{-1} \tag{24}$$

This Eq. 24 estimates the transfer ratios of all the lignans examined here from Schisandrae Fructus to single-drug decoctions prepared at various alteration ratios with a standard deviation of 3.06%. Therefore, changes in the transfer ratios of all components into a decoction associated with changes in α can be expressed comprehensively as:

$$Y_t=X+nf\log 2-2nf\log 2(10^{aX+bn+c}+1)^{-1} \tag{25}$$

where:

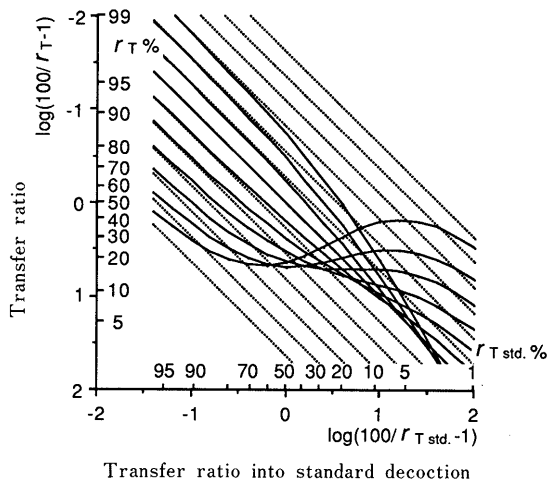


Fig. 6. Alteration of Transfer Ratios of Lignan to Model Decoctions Using a Small Size Preparation of Schisandrae Fructus

Regression equation: $y=x+0.272n-0.544n\ (10^{-0.809x+0.096n+0.965}+1)^{-1}$, $n=-2, -1, 0, 1, 2, 3, 4, 5, 6$.

$$Y_t=\log(100/r_{Tt}-1)$$
$$X=\log(100/r_{Tstd.}-1)$$
$$n=\log\alpha/\log 2$$

r_{Tt}, total transfer ratio; $r_{Tstd.}$, transfer ratio into a weak standard decoction in parallel with the hydrophobic parameter; f, factor related to the form and size of the crude drug; α, alteration ratio in the volume ratio of the crude drug *vs.* extractant of the other decoction with respect to a given standard decoction; a, b and c are constants.

Since Eq. 25 is a relative equation for the transfer ratios of given crude drug components in the decoctions when the alteration ratio is changed compared with the standard decoction, it is valid for estimating the transfer ratio for a wide range of organic components in a decoction prepared with crude drugs minced into small fragments of a fixed size. Therefore, the validity of this is considered to be unaffected by whether the component is volatile or non-volatile, ionic or non-ionic.

Conclusion

From these studies including those in previous papers,[1] the basic mechanisms concerning the transfer of organic crude drug components into decoctions can be summarized as follows.

As for as the ordinary low molecular organic components in crude drugs are concerned, some are transferred with dissolution in water and others are transferred without dissolution to kampo decoctions.

The transfer with dissolution is dependent on their relative solubilities in terms of the residue of the crude drug, insoluble materials, and water during the decoction. In the case of relatively highly hydrophobic components, it is strongly affected by their hydrophobicity. In addition, the higher the volume ratio of the crude drug *vs.* extractant, the lower its transfer ratio.

The transfer without dissolution is performed by adsorption and/or partition of components to the insoluble phase such as a suspensoid and/or emulsoid resulting from the deposition of other insoluble components and the finely disintegrated crude drug residue, or by suspension and/or emulsification of the components themselves.

The transfer ratio without dissolution is determined by a balance of the amount of each components among the drug residues, the insoluble phase, and the soluble phase in the decoction. Because of the uncertainly of these factors, they cannot be accurately predicted by the extent of the transfer ratio or the hydrophobicity of the component. However, the concentration of dissolved organic materials increases with an increase in the volume ratio, and increased contact and collision among the drug residues increase the amount of finely disintegrated residues, which results in the easy formation of a suspensoid and/or emulsoid, which assists the transfer of much higher hydrophobic components without dissolution.

These arguments lead to the conclusion that the compositions of components in decoctions vary under different decoction conditions and that the transfer ratio of an organic crude drug component is controlled by these basic mechanisms under the influence of particular reactions occurring during the decoction as well as by other factors.

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