Theoretical pharmacological effects in single herb and polyherbal therapies: influences of processing on the constituents, and their synergistic/modulatory interactions

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The formulations of traditional medicines used in China, India and Japan have been constructed to expect desirable treatment of diseases. The principles are based on the interaction of several crude drugs or several ingredients even in a single crude drug. Therefore, the apparent combined effects are equivalent to the sum of effects of those components which underwent addition, potentiation, subtraction and modulation. Here we provide hypothetical mathematical formulas to explain the theory of combinatorics, which successfully proved the pharmacological effects of processed single herbs and the basis of polyherbal therapies. The constructed formulas will contribute to designing new formulations together with seeking novel patterns of pharmacological actions of traditional medicines or with understanding of the mechanisms behind them.

Key words Traditional medicines, combinatorics, polyherbal therapies, Yin-Yang ingredients interaction, processed single herb.

Introduction

Clinicians in traditional Chinese and ayurvedic medicines have been frequently prescribing polyherbal formulation depending on *Sho*-syndrome (metabolic, gastrointestinal, respiratory, and water and mineral-balance disorder) of patients. There are numerous descriptive reports explaining the potentiating, additive, subtractive, and other modulatory effects in traditional and new formulations using multi-herb drugs or multiple ingredients in the same herb, and a large number of experiential data are accumulated. Yet, very few theoretical bases in the polyherbal and multi-ingredients approach have been proposed. Synergism in biological responses to traditional Chinese medicines has been explained by chemical and physical interaction among some component compounds: solubility improvement due to formation of complex compounds with new compounds decocted.[1] We attempted to construct a theoretical basis of polyherbal and multi-ingredients therapies, using the experimental results that we have previously reported.[2-5] A paradigmatic account of the uses of mathematic formula in the combinatrics comes, in deliberately oversimplified fashion, from the classic experience. In this review, mathematical formulas based on pharmacological effects of processed single herbs and on polyherbal therapies are proposed to explain the theory of combinatorics.

Benefit of processing

A toxic ingredient is altered to a less-toxic ingredient, when processed with steaming, flaming, and boiling in alkaline solution. That is a case of aconite root. Because raw aconite root is highly toxic, it is used only after processing during which aconitine and other toxic component compounds are converted to the less toxic and pharmacologically effective compounds.

Another case is ginger rhizome. The simply dried ginger is described as dried ginger in Japan (*Shokyo*). Processing with steaming of ginger causes the dehydration of the main effective ingredient gingerol; as a result, the amount of shogaol increases in the steamed and dried ginger (*Kankyo*) which is rarely used in traditional Chinese medicines. *Kankyo* has a quite different pharmacological profile from those of *Shokyo* as shown in Table 1.[2]

Table 1 Effects of extracts of dried ginger (*Shokyo*) and steamed and dried ginger (*Kankyo*) on the contractions induced by prostaglandin (PG) $F_{2\alpha}$ and noradrenaline (NA) in the isolated mesenteric veins of mice[a]

	μg/ml	EC50[b] (95% confidence limit)		% maximal contraction[c]	
		$PGF_{2\alpha}$	NA	$PGF_{2\alpha}$	NA
	0	13 (11-14)	0.7(0.6-0.8)	100	100
Dried ginger (*Shokyo*)	10	6.1 (4.9-7.4)		134±2[d]	98±5
Steamed and dried ginger (*Kankyo*)	10	45 (27-75)		77±6[e]	101±2

[a]Referred to Pancho *et al.* (1989).[2] EC50: fifty percent effective concentration. [b]The contraction induced by $PGF_{2\alpha}$ (0.3 μM - 0.3 mM) or NA (60 nM - 60 μM) without the above extracts was used as the control, and the values are expressed as concentrations inducing 50% response with confidence limits. All EC50 values were significantly different from the control value at $p<0.01$ by the unpaired Student's *t*-test. [c]The contraction induced by $PGF_{2\alpha}$ (0.3 mM) or NA (60 μM) without the above extracts was used as the control (100%) and the values are expressed as mean percentages ±S.E.M. (n = 3 - 5). Statistical analysis was made using paired Student's *t*-test. [d,e]: $p<0.01$, 0.05.

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Benefit of synergy

The synergisms in pharmacological effects are frequently observed among ingredient compounds in polyherbal formulation of traditional Chinese medicines, dissimilar to the additive effects expected from the combination drugs of Western medicines. One example is "*Keishikajutubuto*" in which there is synergy among peony root, licorice root, aconite root, and *Atractyrodes lancea* as shown in Table 2. For example, the synergistic effects of neuromuscular blocking in skeletal muscles are explained by synergistic interactions among constituent compounds: paeoniflorin (a desensitizer of nicotinic acetylcholine receptor), glycyrrhizin (a K^+ channel blocker, and a phospholipase A_2 inhibitor), aconitine (a Na^+ channel activator), and β-eudesmol (a nicotinic receptor channel blocker).[3] The sites of action of these four ingredients are completely different. Consequently, resultant neuromuscular blockade was caused by complementary interaction among them.

Table 2 50% Neuromuscular blocking dose (mg/kg, intraarterial) (95% confidence limit) of decocted extracts of *Shakuyakukanzoto*-related *Kampo hozai* and the formulation of combined crude drugs in diabetic KK-A^y mice *in situ*[a]

Keishikajutubuto	0.0679 (0.0559 - 0.0825)
(peony:licorice:aconite:*Atractylodes lancea*:cassia: ginger:jujube = 4 : 2 : 1 : 4 : 4 : 1 : 4)	
Keishito	0.46 (0.40-0.52)
(peony:licorice:cassia:ginger:jujube = 4 : 2 : 4 : 1.5 : 4)	
paeony + licorice (3:3)	89.8 (72.2 - 112)
+ aconite (3:3:1)[b]	32.7[c] (15.6 - 67.1)
+ *Atractylodes lancea* (3:3:1)	36.2[d] (26.6 - 49.1)

[a]Referred to the data by Kimura *et al.* (1987).[3] [b]Corresponded to 3:3:1 of the crude drug weight ratio. [c,d]$p<0.05$ and 0.01 as compared with the effect of (peony + licorice) by unpaired *t*- or Welch test (n = 3 - 8).

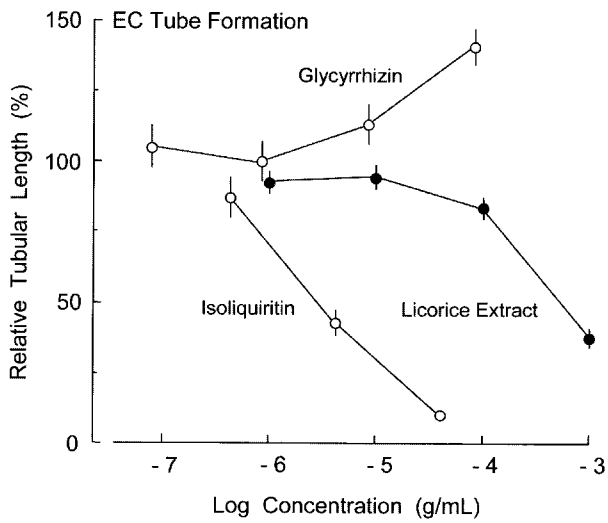

Figure 1 Inhibitory effects of licorice extract and its constituents, isoliquiritin and glycyrrhizin, on tube formation in cultured endothelial cells (EC) of rat thoracic aorta. Modified, with permission, from Ref. 4.

Modulation of pharmacological effects in polyherbal prescription

The combination of constituent crude drugs in polyherbal preparations are prescribed and adjusted to the *Sho*-syndrome (metabolic, gastrointestinal, respiratory, and water and mineral-balance disorder), and the ingredients often contribute to opposite activities to achieve balanced overall effects. For example, as shown in Figure 1, treatment of cultured rat aortic endothelial cells with licorice extract (1 mg/ml) caused the inhibition of the tube formation, as shown previously.[4] Yet, among the ingredients of licorice root, glycyrrhizin (82 μg/ml) enhanced the tube formation, whereas isoliquiritin (0.42-42 μg/ml) inhibited this endothelial function in a concentration-dependent manner.

Therefore, it may be rational that clinicians in traditional Chinese and ayurvedic medicine select the prescription combined with other crude drugs which could antagonize unfavorable effects.

Pharmacological theory of polyherbal therapies

Polyherbal formulations have long been prescribed to a great number of patients, according to their *Sho*-syndromes. The principles in the polyherbal formulations have not been sufficiently adopted in pathopharmacology, but it should be extremely important to develop individual therapy. Interestingly, mutually opposite actions, the so-callled *Yin-Yang* actions, are produced by components of a single crude drug. When some herbs or a single crude drug are prescribed, the unfavorable activities of the ingredient compounds are often eliminated by the other ingredient compounds contained in the same herb or single crude drug. Thus, it is likely that the crude extract or the polyherbal formulations exert an overall beneficial action on the targeted disease, rather than a pure compound or a single herb.

The pharmacological principles of polyherbal formulation are partly explicable with mathematical formula as shown in Table 3, and they can serve as the reason why some crude drugs need to be combined. First, we can anticipate the benefit of processing of crude drugs. The processing (steaming, flaming, and boiling in alkaline solution) converts a toxic ingredient a into a less-toxic one ***a***, and sometimes changes the spectra of pharmacological activities from A to **B**, which is totally different from A, through the conversion of ingredient compound from a to **b**. Thus, the processing frequently changes the unfavorable effects into more favorable ones, which are beneficial for treating the targeted disease. In Table 3, ***u*** and ***u′*** were obtained by processing u, where u is a single herb or crude drugs. The ***u*** and ***u′*** were less toxic than, and thus used differently from, original u, respectively.

Second, we illustrated how synergistic actions of several crude drugs can be represented by mathematical formula (Table 3). If single crude drugs d_1 and d_2 consist of effective ingredient compounds a_1 and a_2, and if respective compounds have similar weak effects A_1 and A_2 via different mode of actions, the apparent effect **A** will be greater

Table 3 Theoretical pharmacological effects of processed single herb or polyherbal combinatrics

	Herb or single crude drug	Effective ingredient compounds	Effect
Processing:			
1	u	a	toxic A
	u	***a***	***less-toxic A***
2	u	a	**A**
	u'	**b**	**B different from A**
Synergy:			
	d_1	a_1	weak A_1
	d_2	a_2	weak A_2
	.	.	.
	.	.	.
	d_n	a_n	weak A_n
	Σ	$a_1 \times a_2 \times ..... \times a_n$	**more potent A**
Modulation:			
	d_0	$a_1 \times a_2 \times ..... \times a_n$	no/weak
	d_1	a_1^{-1}	anti-A1
	d_2	a_2^{-1}	anti-A2
	d_3	a_3^{-1}	anti-A3
	$\Sigma(d_0 + d_1)$	$a_2 \times a_3 \times ..... \times a_n$	**X**
	$\Sigma(d_0 + d_2)$	$a_1 \times a_3 \times ..... \times a_n$	**Y**
	$\Sigma(d_0 + d_3)$	$a_1 \times a_2 \times a_4 ..... \times a_n$	**Z**

The a and a^{-1} antagonize each other. ***u*** is a processed u.

than A_1 or A_2. In that case, the synergistic effect **A** can be expressed as the product of a_1 and a_2 ($a_1 \times a_2$).

Third, we considered the case of modulatory interactions among some crude drugs. A main crude drug is often combined in several kinds of formulations depending on *Sho*-syndromes. If a single crude drug d_0 is mainly composed of several effective ingredient compounds ($a_1 \times a_2 \times ..... \times a_n$), and if the other drugs d_1, d_2 and d_3 demonstrate anti-A_1, anti-A_2, and anti-A_3 effects, respectively, the polyherbal combination will produce **X**, **Y** and **Z** effects by disinhibiting a_1, a_2 and a_3, respectively (Table 3). Probably, traditional medicines-clinicians empirically prescribe $d_0 + d_1$, $d_0 + d_2$, $d_0 + d_3$ to predict the **X**, **Y** or **Z** effects, depending on the patient's *Sho*-syndrome.

Theoretical basis of polyherbal formulation has not yet been established despite accumulated pharmacological data. For the clinical use, after determination of *Sho*-syndrome, traditional Chinese and ayurvedic clinicians first determine the *Sho*-syndrome of individual patients and then choose polyherbal formulations best fitted to the *Sho*-syndrome. Chemical and physical interactions among crude drug constituents have been proposed to account for the modification of the effect of each constituent, which include acceleration of hydrolysis, improvement of solubility, detoxication by chemical modification of a constituent compound, complex formation between constituent compounds, and formation of a new compound during decoction.[1] The formulations had been largely descriptive until recently. The present mathematical trials will contribute to designing new formulations together with seeking novel patterns of pharmacological actions of traditional medicines or with understanding the mechanisms behind them. May (2004) has recently mentioned that various conjectures about underlying mechanisms can be made explicit in mathematical terms, and the consequences can be explored and tested against the observed patterns.[6] The virtue of mathematics in such a context is that it forces clarity and precision upon the conjecture, thus enabling meaningful comparison between the consequences of basic assumption and empirical facts.[6] The actual reassembling of the constituent crude drugs, to obtain more effective formulation, is being investigated with both computational power and complex software. From the pharmacological point of view, we strongly suggest the use of a mathematical formula to explain the rationale of polyherbal approach and processing in traditional Chinese and ayurvedic medicines.

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Japanese abstract

漢方方剤やアユルベーダ薬の薬理作用における，修治，相乗作用，組み合わせの科学的根拠を明らかにするため，著者らによる公表論文の実験データを用いて，数式による理論化を試みた。

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