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Review Article

A study on the Compatibility of Crude Drugs Comprising Kampo Medicines

Tetsuya Isobe*, Koichi Yoneyama, Mikako Kaijima and Hirotsune Kaijima

Kawasaki Satellite of Minatomirai Yume Clinic: Roundcross Kawasaki 8F Ekimaehonnmachi 26-4 Kawasaki, Kawasaki, Kanagawa, Japan

Abstract

Introduction: An herbal formulation typically consists of several crude drugs, and their unique combinations have therapeutic effects. The combination of these constituent crude drugs in herbal medicines has been naturally selected over a long period of time into good compatibility. The compatibility of pairs of the crude drugs in herbal medicines has not been elucidated.

Subjects and Methods: The compatibility of crude drugs in 324 herbal formulations that are frequently used was investigated. Non-coexisting pairs of crude drugs were examined using Excel.

Results: Based on the current results, bellflower, pinellia tuber, and bupleurum root were identified as crude drugs that may be incompatible with aconite. Schizonepeta spike was identified as a crude drug that is potentially incompatible with ginseng. Polyporus and perilla herb were identified as crude drugs that are potentially incompatible with peony. Pinellia tuber may be most incompatible with rehmannia root. There were no crude drugs that were incompatible with licorice or ginger.

Discussion: When one wishes to add powdered aconite extract to a formulation for its "warming and analgesic action," it should probably not be taken at the same time the formulation which include bellflower, pinellia tuber, or bupleurum root. When one wishes to add powdered red ginseng extract to a formulation for its "action to promote digestive function" and "supplement 'qi'," it should probably not be taken at the same time the formulation which include schizonepeta spike. Shakuyaku-kanzo-to consists of licorice and peony.

*Corresponding author: Tetsuya Isobe, Kawasaki Satellite of Minatomirai Yume Clinic: Roundcross Kawasaki 8F Ekimaehonnmachi 26-4 Kawasaki, Kawasaki, Kanagawa, Japan, E-mail: iso12-7@blue.ocn.ne.jp

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peony has "antispasmodic and analgesic action." When one wishes to add powdered Shakuyaku-kanzo-to to another formulation for its "antispasmodic and analgesic action." it should probably not be taken at the same time the formulation which include Polyporus or perilla herb. Kikyo-to consists of licorice and bellflower. Bellflower has "detoxifying and pus-draining action." When one wishes to add powdered Kikyo-to to another formulation for its "antispasmodic and analgesic action." it should probably not be taken at the same time the formulation which include dry ginger or aconite.

Conclusion: The current results may provide a basis for considering the appropriateness of mixing different formulation like Kampo extract or adding a crude drug to a formulation.

Keywords: Compatibility; Crude Drug; Herbal medicines; Kampo Extracts; Powdered Aconite

Background and Objective

Typically, an herbal formulation consists of multiple crude drugs of natural origins (denoted here simply as "crude drugs"), and these medicines are efficacious because of the specific combinations of those crude drugs. Formulations consisting of crude drugs were developed over a long period of time based on the compatibility of crude drugs. Even if a person in a certain era devised a new formulation consisting of crude drugs and named it, that herbal medicine's efficacy was subsequently determined over a long period of time. If it was inefficacious, it disappeared through natural selection. Only those Herbal formulations that many people feel are efficacious have been passed down to the present day. Currently, approximately 150 types of Kampo medicines are used in traditional Japanese medicine in Japan, while about 300 types are stringently selected and used in Chinese medicine in modern China, including those with the same constituents as Kampo medicines. In Japan, 148 types of Kampo formulations are currently covered by health insurance. In addition, approximately 100 types of crude drugs are covered by health insurance. In Japan, many Kampo formulations from several companies are used in daily practice. packaged as an instant extract, these formulations are boiled or provided in the form of a dry powder in advance. As example, aconite [1,2] (an extract with action "to warm and relieve pain") and red ginseng [3] (an extract with action to "supplement 'qi' and relieve fatigue and malaise") are available as extracts of a single crude drug from Tsumura.

Typically, a single crude drug has several types of action, so the action of a herbal formulation as a whole often differs from the additive actions of the individual crude drugs that comprise it. When different formulations are taken simultaneously, the crude drugs that comprise them mix in the stomach.

The compatibility of pairs of the crude drug in herbal medicines has not been elucidated. Accordingly, when taking several different types of herbal formulations on the same day, the formulations may need to be taken after a certain interval to prevent them from mixing in the stomach. If incompatible crude drugs mix, the efficacy of each

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150 Japanese Kampo formulations			174 Ch	inese herbal formulatio	ons
Makyo-yokukan-to	Saiboku-to	Hainosankyu-to	Seikoryuko-to	Gonin-gan	Tennohoshin-tan
Makyo-kanseki-to	Sairei-to	Bakumondo-to	Akyokeishio-to	Eppi-to	Iko-san
Kanbaku-taiso-to	Sannoshashin-to	Hachimijio-gan	Keibuunkyu-gan	Etsukiku-gan	Tenmmachoto-in
Anchu-san	Sansonin-to	Hacchin-to	Shinka-koju-san	Saikakujio-gan	Tokinentsu-to
Irei-to	Jiinshiho-to	Hangekoboku-to	Shinka-oryu-to	Saisen-sen	Tokihoketsu-to
Inchin-gorei-san	Jiinkoka-to	Hangeshashin-to	Kanroshodoku-in	Saiko-ka-bosho-to	Tokiryuso-gan
Inchinko-to	Shiun-ko	Hangebyakujutsutemma-to	Angyugoou-gan	Saikosokan-san	Tokirokuo-to
Unkei-to	Shigyaku-san	Byakko-ka-ninjin-to	Seika-to	Saizo-san	Dokkatsukisei-to
Unsei-in	Shishihakuhi-to	Bukuryo-in	Ikkan-sen	Teikan-gan	Shiso-san
Eppika-jutsu-to	Shichimotsukoka-to	Bushirichu-to	Shomyaku-san	Teizen-to	Shichihoubihatsu-tar
Ogi-kenchu-to	Saihaku-to	Heii-san	Ubai-gan	Sankofukumyaku-to	Seika-to
Orengedoku-to	Saiso-in	Boiogi-to	Uzu-to	Sannin-to	Kyogai-to
Oren-to	Shimotsu-to	Bofutsusho-san	Ekio-gan	Sanmotsubikyu-gan	Nimyo-san
Otsuji-to	Shakanzo-to	Hochuekki-to	Eppi-to	Sanyo-to	Ninjingokai-san
Kakkonka-jutsubu-to	Shakuyakukanzobushi-to	Mao-to	Ogikeishigomotsu-to	Jio-inshi	Shokan-to
Kakkon-to	Shakuyakukanzo-to	Maobushisaishin-to	Odo-to	Jippi-in	Shoyoekii-to
Kakkonto-ka-senkyushinni	Juzentaiho-to	Mashinin-gan	Hohaiakyu-to	Saikatsugeki-to	Haidoku-san
Keima-kakuhan-to	Jumihaidoku-to	Sanmotsuogon-to	Hyokango-to	Chibakujio-gan	Baimokarou-san
Keikyo-soso-oshinnbu-to	Juncho-to	Nyoshin-san	Untan-to	Saihaku-to	Hakushiyoshin-gan
Keishaku-chimo-to	Shoma-kakkon-to	Yokuinin-to	Unpi-san	Shakuyaku-to	Hassho-san
Kamikihi-to	Shokenchu-to	Yokukan-san	Unpi-to	Jakoshoki-san	Kagai-san
Kamishoyo-san	Shosaiko-to	Shikunshi-to	Kaiyokyukyu-to	Jukai-san	Saki-in
Senkyuchacho-san	Shosaiko-to-ka-kikyosekko	Shirei-to	Kosharikkunshi-gan	Shushaanjin-gan	Sakin-gan
Kikyo-to	Shoseiryu-to	Rikkunnshi-to	Koren-gan	Shokankyo-to	Byakugokokin-to
	-		Kakukachikuo-to	Shokyoshashin-to	
Ogon-to Kihi-to	Shohange-ka-bukuryo-to Shofu-san	Ryutanshakan-to		Shokei-inshi	Fukugenkakketsu-to
Mokuboi-to	Shinniseihai-to	Ryokankyomishingenin-to	Kagenfukumyaku-to Kosho-to	Jotan-to	Fukuhodaijoki-to
Kumibinro-to	Jinso-in	Ryokeijutsukan-to Ryokyojutsukan-to	Kakkonnogonoren-to	Seifu-to	Bukuryo-gan Fuseishodoku-in
Kyukikyogai-to	Shinpi-to	Renju-in	Keiryokannro-in	Shofukuchikuo-to	Bushi-to
Kyukichoketsu-in	Shinbu-to	Rokumi-gan	Kamiuyaku-san	Hakutoo-to	Boibukuryo-to
seishoeki-to	Seijobofu-to	Kokuliii-gali	Shinsui-tan	Jingyoryuko-san	Bofu-to
Seishinrenshi-in Keigairengyo-to	Seihai-to Sessho-in		Kantai-to Kanzokankyobukuryobyaku-	Shinka-koju-san Ryokaku-san	Hogen-to Borei-san
			jutsu-to	-	
Keishi-ka-ogi-to	Sokeikakketsu-to		Kanzoshashin-to	Senfukudaiseki-to	Jinbu-to
Keishi-ka-kakkonn-to	Daiokanzo-to		Ogon-to	Senpokatsumei-in	Jinryobyakujutsu-sai
Keishi-ka-kobokukyonin-to	Daiobotanpi-to		Kijitsushohi-gan	Zoekijoki-to	Ekii-to
Keishi-ka-shakuyakudaio-to	Daikenchu-to		Kijitsudotai-gan	Sogoko-gan	Shinjinyozo-to
Keishi-ka-shakuyaku-to	Daisaiko-to		Kumikyokatsu-to	Soshikoki-to	Doseki-san
Keishi-ka-jutsubu-to	Daisaiko-to-kyo-daio		Kyusen-san	Shasei-gan	Dotan-to
Keishi-ka-ryukotsuborei-to	Daijoki-to		Seii-san	Daiseiryu-to	Shintsuchikuo-to
Keishi-ka-ryojutsubu-to	Daibofu-to		Kyokatsushoshitsu-to	Daiobushi-to	Shisetsu-tan
Keishinieppi-itto	Chikujountan-to		Kyoso-san	Daihoin-gan	Mokkobinro-gan
Keishininjin-to	Rikko-san		Seiei-to	Daikankyo-to	Shisei-gan
Keishibukuryo-gan	Jiziso-ippo		Seitai-to	Daiteifuju-to	Tokoshimotsu-to
eishibukuryogan-ka-yokuinin	Jidaboku-ippo		Seiunhaidoku-san	Daijingyo-to	Yoinseihai-to
Keishi-to	Choijoki-to		Seikiketan-to	Chikuyosekko-to	Taizanbanjaku-san
Keihi-to	Choto-san		Seisokyuhai-to	Chikuyoryubo-to	Yowa-to

6.1	at t	G:		att t
Goko-to	Chorei-to	Gingyo-san	Kippichikujo-to	Shigyaku-to
Goshaku-san	Tokakujoki-to	Sokyo-to	Gyokueki-to	Richu-gan
Goshajinki-gan	Tokikenchu-to	Sokiku-in	Gyokujo-sen	Ryokangomikyoshin-to
Goshuyu-to	Tokishakuyaku-san	Sohyosho-san	Gyokubyobu-san	Reikakuchoto-to
Shojoki-to	Toki-inshi	Keibohaidoku-san	Gyokushin-san	Renju-in
Gorin-san	Toki-to	keppuchikuo-to	Howa-gan	Rokuwa-to
Gorei-san	Tokishigyaku-ka-goshuy- ushokyo-to	Kenhi-gan	Dankan-sen	
Saikan-to	Tsudo-san	Kogonseitan-to	Tsukyokakketsu-to	
Saikoseikan-to	Nijutsu-to	Kobokuunchu-to	Tsusha-yoho	
Saiko-ka-ryukotsuborei-to	Nichin-to	Oryu-to	Boi-gan	
Saikokeishikankyo-to	Ninjin-to	Gohi-san	Zokumei-to	
Saikokeishi-to	Ninjinyoei-to	Kokei-gan	Chokoshitei-to	

Table 1: The formulations studied (150 Kampo formulations + 174 Chinese herbal formulations).

formulation may presumably decrease compared to when each formulation is taken alone. Taking the compatibility of crude drugs into account may allow added crude drugs to have an effect without decreasing overall efficacy. When considering whether to add powdered aconite extract or powdered red ginseng extract or when contemplating taking different Kampo extracts at the same time, the appropriateness of the types of formulations to add is a concern. If pairs of incompatible crude drugs can be identified by the current study, then the effects of adding certain crude drugs or combining formulations may be determined in routine practice.

Materials and Methods

This study examined the compatibility of crude drugs comprising herbal formulations, with a focus on the TOP 40 crude drugs most often contained in Kampo extracts. A total of 324 formulations were studied, including 150 formulations often used in Japan and 174 formulations that are often used in modern China as listed in a textbook from a university of traditional Chinese medicine (Table 1).

To identify pairs of crude drugs that do not coexist in any of the formulations studied, the following procedures (1) and (2) were performed in sequence. Procedure (1): Crude drugs comprising all of the formulations studied were entered in Excel. Formulations were sorted in descending order by the crude drugs they consisted of. Formulations containing crude drug A were selected, and those not containing crude drug B were identified. Procedure (2): Formulations containing crude drug B were selected, and they were checked to see whether or not they contained crude drug A.

Through procedures (1) and (2), pairs of crude drugs (AB) were identified, i.e., "crude drug B is not present in formulations containing crude drug A, and crude drug A is not present in formulations containing crude drug B." When the conditions above were satisfied, pairs of crude drugs (AB) that did not coexist were identified and designated "non-coexisting pairs" of crude drugs. Non-coexisting pairs of crude drugs are likely to be incompatible.

This study was approved by the ethics review board of this facility.

Results

Non-coexisting pairs are shown in table 2. Based on the current results, there were no crude drugs that were incompatible with licorice [4] or ginger. bellflower [5], pinellia tuber, and bupleurum root [6,7]

were identified as crude drugs that may be incompatible with aconite. Schizonepeta spike was identified as a crude drug that is potentially incompatible with ginseng. Polyporus and perilla herb were identified as crude drugs that are potentially incompatible with peony [8]. The following pairs of crude drugs may be incompatible. Peach kernel [9] and coptis chinensis [10,11], rhubarb [12,13] and astragalus membranaceus [14], angelica acutiloba [15] and japanese yam, ephedra herb [16] and coptis chinensis, anemarrhena [17] and dried ginger [18], magnolia officinalis [19] and plaster, poria [20] and sodium sulfate, and pinellia tuber and rehmannia root [21]. In regard to non-coexisting pairs AB which are shown in table 2, number of formulations included crude drug A or B is respectively shown in table 3. The higher number of formulations included A×number of formulations included B is, the higher a possibility of existence of non-coexisting pair AB. Accordingly, most incompatible pair is thought to be pinellia tuber rehmannia root.

Non-coexisting pears					
	×	Gardenia fruit			
	×	Moutan bark			
5.1.	×	Anemarrhena			
Dried ginger	×	Fruit			
	×	Ophiopogon japonicus			
	×	Bellflower			
	×	Japanese yam			
	×	Schizonepeta spike			
Jujube	×	Peach kernel			
	×	Phellodendron bark			
	×	Anemarrhena			
	×	Moutan bark			
	×	Plaster			
Magnolia officinalis	×	Anemarrhena			
	×	Ophiopogon japonicus			
	×	Windbreak fence			
	×	Moutan bark			
	×	Plaster			
Astragalus membranaceus	×	Almond kernel			
	×	Fruit			

	×	Peach kernel		
	×	Plaster		
Coptis chinensis	×	Almond kernel		
	×	Atractylodes rhizome		
	×	Pinellia tuber		
Aconite	×	Bellflower		
	×	Bupleurum root		
	×	Poria		
Sodium sulfate	×	Citrus unshiu peel		
	×	Atractylodes rhizome		
	×	Moutan bark		
Ephedra	×	Coptis chinensis		
	×	Ophiopogon japonicus		
	×	Rehmannia root		
Pinellia tuber	×	Japanese yam		
	×	Peach kernel		
	×	Astragalus membranaceus		
Rhubarb	×	Anemarrhena		
a.r. 1.	×	Japanese yam		
Cnidium rhizome	×	Almond kernel		
	×	Polyporus		
Peony	×	Perilla herb		
Ginseng	×	Schizonepeta spike		
Huang jin	Huang jin × Japanese yam			
Baizhu	×	Almond kernel		
Atractylodes rhizome	×	Almond kernel		
Alismatis rhizome	×	Ophiopogon japonicus		
Angelica acutiloba	×	Japanese yam		

Table 2: The non-coexisting pairs in the formulations studied.

	Number of Formula- tions			Number of Formula- tions	(1)×(2)
Crude drug A	including Crude drug A (1)		Crude drug B	including Crude drug B (2)	
Pinellia tuber	54	×	Rehmannia root	60	3240
Atractylodes rhizome	42	×	Coptis chin- ensis	37	1554
Cnidium rhizome	53	×	Almond kernel	27	1431
Jujube	66	×	Anemarrhena	21	1386
Sodium sulfate	15	×	Poria	91	1365
Pinellia tuber	54	×	Aconite	25	1350
Jujube	66	×	Phellodendron bark	19	1254
Jujube	66	×	Peach kernel	18	1188
Coptis chinensis	37	×	Ephedra	31	1147
Atractylodes rhizome	42	×	Almond kernel	27	1134
Japanese yam	14	×	Angelica acutiloba	81	1134

Baizhu	41	×	Almond kernel	27	1107
Astragalus mem- branaceus	30	×	Rhubarb	36	1080
Coptis chinensis	37	×	Almond kernel	27	999
Pinellia tuber	54	×	Peach kernel	18	972
Ophiopogon japonicus	30	×	Ephedra	31	930
Peony	93	×	Polyporus	10	930
Peony	93	×	Perilla herb	10	930
Bupleurum root	37	×	Aconite	25	925
Japanese yam	14	×	Jujube	66	924
Schizonepeta spike	11	×	Ginseng	84	924
Dried ginger	30	×	Bellflower	30	900
Ophiopogon japonicus	30	×	Magnolia officinalis	30	900
Ophiopogon japonicus	30	×	Dried ginger	30	900
Coptis chinensis	37	×	Plaster	24	888
Windbreak fence	28	×	Magnolia officinalis	30	840
Japanese yam	14	×	Huang jin	58	812
Astragalus mem- branaceus	30	×	Almond kernel	27	810
Gardenia fruit	27	×	Dried ginger	30	810
Japanese yam	14	×	Pinellia tuber	54	756
Rhubarb	36	×	Anemarrhena	21	756
Bellflower	30	×	Aconite	25	750
Fruit	25	×	Astragalus membranaceus	30	750
Fruit	25	×	Dried ginger	30	750
Ephedra	31	×	Moutan bark	24	744
Japanese yam	14	×	Cnidium rhizome	53	742
Sodium sulfate	15	×	Citrus unshiu peel	49	735
Jujube	66	×	Schizonepeta spike	11	726
Magnolia offic- inalis	30	×	Moutan bark	24	720
Magnolia offic- inalis	30	×	Plaster	24	720
Dried ginger	30	×	Moutan bark	24	720
Astragalus mem- branaceus	30	×	Moutan bark	24	720
Astragalus mem- branaceus	30	×	Plaster	24	720
Coptis chinensis	37	×	Peach kernel	18	666
			Alismatis	22	660
Ophiopogon japonicus	30	×	rhizome		
	42	×	rhizome Sodium sulfate	15	630
japonicus Atractylodes					630

 $\textbf{Table 3:} \ Number \ of formulations included \ crude \ drug \ A \ or \ B \ in \ regard \ to \ non-coexisting \ pairs \ AB \ which \ are shown in \ table \ 2.$

Discussion

Pairs of crude drugs that are incompatible are presumed to have been eliminated from formulations through natural selection over a long period of time. As a result, the combinations of crude drugs in the 324 formulations studied have stood the test of time.

The non-coexisting pairs shown in table 2 were systematically organized, yielding the following findings. When one wishes to mix one formulation with the other or when one wishes to add a crude drug to a formulation, "right or wrong" should be taken into consideration based on the current results to avoid mixing of incompatible crude drug in the stomach.

The crude drugs comprising Kampo formulations tended to contain jujube [22], ginger, and licorice in comparison to traditional Chinese medicine formulations. Licorice has action to "harmonize various drugs," ginger has action to "promote digestion". there were no crude drugs that were incompatible with licorice or ginger. In case of taking the formulation that include jujube, it should probably not be taken at the same time the formulation which include the crude drugs like gardenia fruit, moutan bark, anemarrhena, Ophiopogon japonicus, and bellflower.

White atractylodes (Baizhu) is often used in traditional Chinese medicine formulations (white atractylodes: atractylodes rhizome = 27: 5), while atractylodes rhizome is often used in Kampo formulations (white atractylodes: atractylodes rhizome = 14: 35). Both atractylodes and white atractylodes are often found to be incompatible with almond kernel [23]. In case of taking the formulation that include atractylodes or white atractylodes, it should probably not be taken at the same time the formulation which include almond kernel.

When one wishes to add powdered aconite extract to a formulation for its "warming and analgesic action," it should probably not be taken at the same time the formulation which include bellflower, pinellia tuber, or bupleurum root. When one wishes to add powdered red ginseng extract to a formulation for its "action to promote digestive function" and "supplement 'qi'," it should probably not be taken at the same time the formulation which include schizonepeta spike.

Shakuyaku-kanzo-to consists of licorice and peony. peony has "antispasmodic and analgesic action." When one wishes to add powdered Shakuyaku-kanzo-to to another formulation for its "antispasmodic and analgesic action." it should probably not be taken at the same time the formulation which include Polyporus or perilla herb. Kikyo-to consists of licorice and bellflower. Bellflower has "detoxifying and pus-draining action." When one wishes to add powdered Kikyo-to to another formulation for its "antispasmodic and analgesic action." it should probably not be taken at the same time the formulation which include dry ginger or aconite.

Considering above, when several different formulations are taken, it may be safe to leave a time interval required for digestion to take medicine.

Conclusion

The current results may provide a basis for considering the appropriateness of mixing different formulations like Kampo extract or adding a crude drug to a formulation.

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