

Scientific Analysis of Formulation Theory of Chungpesagan-tang; The purgative Action of Chungpesagan-tang

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Abstract – To analyze scientifically the fundamental formulation theory and drug interaction on the purgative action of Chungpesagan-tang, which is one of the traditional Korean medical prescriptions that has been most frequently used for stroke, water extracts of herbal medicines with Rhei Rhizoma were administered into mice and the purgative action was measured. Water extracts of Raphani Semen or Cimicifugae Rhizoma with Rhei Rhizoma had more potent purgative activity than Rhei Rhizoma alone, although Raphani Semen alone displayed no purgative action. However, Platycodi Radix and Puerariae Radix inhibited the purgative action of Rhei Rhizoma. When Rhei Rhizoma with Raphani Semen or Cimicifugae Radix was extracted with water, sennoside A content in the water extract was increased. However, Puerariae Radix and Platycodi Radix decreased the content of sennoside A in the extracted water. The transforming rate of sennoside A of Rhei Rhizoma was inhibited by Puerariae Radix and Platycodi Radix. The transforming rate of sennoside A of Chungpesagan-tang to rheinanthrone by human intestinal microflora and its purgative activity were similar to those of Rhei Rhizoma. Finally we thought that the purgative action of Chungpesagan-tang could be controlled by the addition and subtraction of Chungpesagan-tang-composing herbal medicines.

Key words – Chungpesagan-tang, Rhei Rhizoma, purgative action, drug interaction

Introduction

The herbal medicinal polyprescription is composed of several herbal medicines. In Korea, this herbal medicinal polyprescription has been formulated according to the four regular components theory of Oriental medicines, which consisted of King, Minister, Assistant and Laborer. However, this theory has not been elucidated by the scientific research method until now. If this theory could be understood through the experiment, new polyprescription could be developed. To scientifically understand the fundamental formulation theory of traditional herbal medicinal polyprescription, we tried to investigate herbal medicinal interaction on the purgative action of Chungpesagan-tang. The Chungpesagan-tang was developed from Yuldahasotang, which consisted of Puerariae Radix, Scutellariae Radix, Angelicae Tenussimae Radix, Platycodi Radix, Platycodi Semen, Cimicifugae Rhizoma and Angelicae Dahuricae Radix (Table 1) (Lee, 1996). Therefore this Chungpesagan-tang is

composed of 8 crude herbs, which include original Yuldahasotang and Rhei Rhizoma. We thought that Chungpesagan-tang had better purgative action than Yuldahasotang. Therefore, it was frequently used for patients who suffer from stroke with constipation, and proved to have valuable clinical effects.

Here we investigated the effect of Chungpesagan-tang-composing herbal medicines on the purgative

Table 1. Composition of Chungpesagan-tang and Yuldahasotang

Herbal Medicine	Weight (g)	
	Chungpesagan-tang	Yuldahasotang
<i>Pueraria thunbergiana</i> (root)	15	15
<i>Scutellaria baicalensis</i> (root)	7.5	7.5
<i>Angelica tenussima</i> (root)	7.5	7.5
<i>Platycodon gradiflorum</i> (root)	3.75	3.75
<i>Raphanus sativus</i> (seed)	3.75	3.75
<i>Cimicifuga heracleifolia</i> (root)	3.75	3.75
<i>Angelica dahurica</i> (root)	3.75	3.75
<i>Rheum palmatum</i>	3.75	

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action of Rhei Rhizoma and on the metabolism of sennoside A of Rhei Rhizoma.

Experimental

Materials – Rhei Rhizoma, Puerariae Radix, Scutellariae Radix, Angelicae Tenuissimae Radix, Platycodi Radix, Raphani Semen, Cimicifugae Rhizoma and Angelicae Dahuricae Radix were purchased from Kyung-Dong traditional herbal medicinal market (Seoul, Korea). Media for human intestinal bacteria were purchased from Difco, Co., (U.S.A.). The other chemicals were of analytical reagent grade.

Extraction and sennoside A determination of polyprescriptions – Fifty grams of each Chungpesagan-tang-composing herbal medicine, were extracted with 450 ml of water in a boiling water bath, filtered, concentrated and dried with a freezing dryer. The combination of each herbal medicine composing Chungpesagan-tang with Rhei Rhizoma (0.5:1, 1:1, 1:2) were also extracted with water. Chungpesagan-tang was also extracted. All extracts were dried with a freezing dryer and used if necessary.

One hundred milligrams of each dried extract of all polyprescriptions was dissolved and made to 10 ml with methanol. The quantity of sennoside A assayed with a HPLC. HPLC (Younglin system, Korea) was carried out as follows: column, μ -Bondapak C18 3.8 \times 300 mm; solvent, 30% acetonitrile-0.02% acetic acid; wavelength of detector, 280 nm.

Metabolism of sennoside A of each polyprescription by human intestinal bacteria – Human intestinal bacteria (10 g of fresh human feces) were suspended with 100 ml of the anaerobic dilution medium according to the previous method (Kim *et al.*, 1998). The supernatant (10 ml) were inoculated into 90 ml of the anaerobic dilution medium containing the above polyprescription extracts and then anaerobically incubated at 37°C. 5ml of each of the cultured media was aseptically and periodically taken out at 3, 6, 12, 18 and 24 h. Into the periodically taken media, 5 ml of methanol was added and the quantity of sennoside A and its metabolites were assayed by TLC scanner (Shimadzu CS-920, Japan).

Animals, treatment and sampling – Male mice (ICR 20-25 g) were purchased from Daehan Animal Co (Korea), and maintained for two weeks before use and then kept in metabolic cages for the experiments: Pellet foods (Samyang Co., Korea) and water were freely available. All animal experiments carried out

on 20~22°C and 50 \pm 10% humidity. Rhei Rhizoma or its containing polyprescriptions were orally administered to 10 mice, and saline to 10 mice as the control. Fresh feces were compulsively obtained just before and at 2, 3.5, 4.5 and 6 h after the administration, and their moisture content (%) was determined according to the following formula.

Moisture content (%) = (fresh feces weight-dry feces weight)/fresh feces weight \times 100

Results and Discussion

Effect of herbal medicines on the purgative action of Rhei Rhizoma – To investigate the fundamental formulation theory and drug interaction on the purgative action of Chungpesagan-tang, water extract of herbal medicines with Rhei Rhizoma were administered into mice and the fecal moisture of mice was measured (Fig. 1). Fecal moisture of normal control group was 45%. When water extract of Rhei Rhizoma alone was administered on mice, the fecal moisture was 63% at 4h after its administration. Water extract of Raphani Semen, Angelicae Tenuissimae Radix or Cimicifugae Rhizoma with Rhei Rhizoma increased the fecal moisture. Particularly, Raphani Semen potently induced the purgative action of Rhei Rhizoma, although Raphani Semen alone displayed no purgative action. This synergism was dependent on the dose of Raphani semen. However, Platycodi Radix and Puerariae Radix inhibited the purgative action of Rhei Rhizoma. The other herbal medicines, Angelicae Dahuricae Radix, Scutellariae Radix did not affect the purgative action of Rhei Rhizoma. The

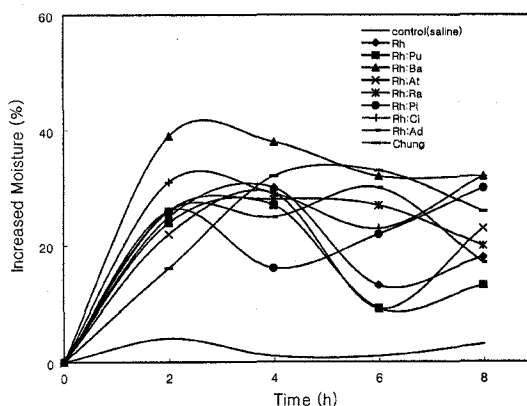


Fig. 1. The purgative activity of water extract of polyprescriptions on mice.

purgative action of Chungpesagan-tang was similar to that of Rhei Rhizoma. Chungpesagan-tang have been frequently used for CVA patients in Korea traditional medicine (Bae *et al.*, 1987; Kwon *et al.*, 1996). This polyprescription should be considered to improve stroke because constipation is relieved.

Effect of herbal medicines on sennoside A content in water extract from Rhei Rhizoma containing polyprescriptions – To understand why the purgative action of Rhei Rhizoma was induced by herbal medicines such as Raphani semen and Cimicifugae Rhizoma, yield and sennoside A content of water extract of each polyprescription were determined (Table 2). Yield of water extract of Rhei Rhizoma was 20% and sennoside A content was 0.3%. Yield of water extract of Chungpesagan-tang was 20% and sennoside A content was 4.3%. Although yield of water extract of Puerariae Radix, Angelicae Dahuricae Radix or Platycodi Radix with Rhei Rhizoma

was not affected by increasing the amount of Rhei Rhizoma added, sennosides A content was significantly decreased. Yield and sennosides A content of water extract of Scutellariae Radix or Angelicae Tenuissimae Radix with Rhei Rhizoma was slightly changed, but was not significant. Yield of water extract of Raphani Semen, Cimicifugae Rhizoma with Rhei Rhizoma was decreased by increasing the amount of Rhei Rhizoma added, and sennosides A content was significantly increased. Sennoside A is a genuine purgative compound in Rhei Rhizoma (Yaki *et al.*, 1971; Oshino *et al.*, 1972; Oshino *et al.*, 1978; Ko *et al.*, 1991; Miyawaki *et al.*, 1993). Therefore, these results suggested that Raphani Semen could induce the purgative action, because Raphani Semen or Angelicae Tenuissimae Radix increased the extract level of sennoside A from Rhei Rhizoma. These actions, synergism and antagonism of sennoside A extraction rate from Rhei Rhizoma by herbal medicines, could affect the purgative action of Chungpesagan-tang. By the addition and subtraction of Chungpesagan-tang-composing herbal medicines, we thought, the sennoside A extract level was controlled and the potency of the purgative action could be also controlled.

Table 2. Sennoside A content of water extract of Rhei Rhizoma and its containing polyprescription

Polyprescription	Sennoside A Content (%)				
	0:1	1:0.5	1:1	1:2	1:4
Rh ^{a)}	0.30				
Rh:Pu		0.23	0.25	0.25	0.26
Rh:Sc		0.17	0.25	0.26	
Rh:At		0.20	0.43	0.47	
Rh:Ra		0.43	0.50	0.35	
Rh:Pl		0.33	0.33	0.29	
Rh:Ci		0.36	0.39	0.44	
Rh:Ad		0.30	0.26	0.25	
Chung	0.43				

^{a)}Rh, Rhei Rhizoma; Pu, Puerariae Radix; Sc, Scutellariae Radix; At, Angelicae Tenuissimae Radix; Ra, Raphani Semen; Pl, Platycodi Rhizoma; Ci, Cimicifugae Radix; Ad, Angelicae Dahuricae Rhizoma; Chung, Chungpesagan-tang.

^{b)}Ration of Rhei Rhizoma to the other herbal medicine composing Chungpesagan-tang.

Effect of herbal medicine on the metabolism of sennoside A in polyprescriptions by human intestinal bacteria – Sennoside A is a prodrug which can be activated to rheinanthrone, a genuine purgative component, by human intestinal bacteria (Fig. 2) (Kobashi *et al.*, 1980). Therefore, to evaluate herbal drug interaction and the purgative action of Rhei Rhizoma in Chungpesagan-tang, the activity transforming sennoside A in each polyprescription to rheinanthrone was measured (Fig. 3). When Rhei Rhizoma was anaerobically incubated with human intestinal bacteria, 90% sennoside A in Rhei Rhizoma was transformed to rheinanthrone within 12 h. This transforming activity of sennoside A to rheinanthrone

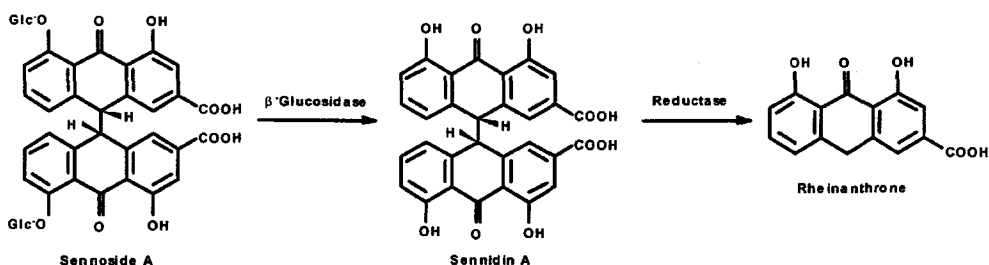


Fig. 2. Proposed metabolic pathway of sennoside A by human intestinal bacteria.

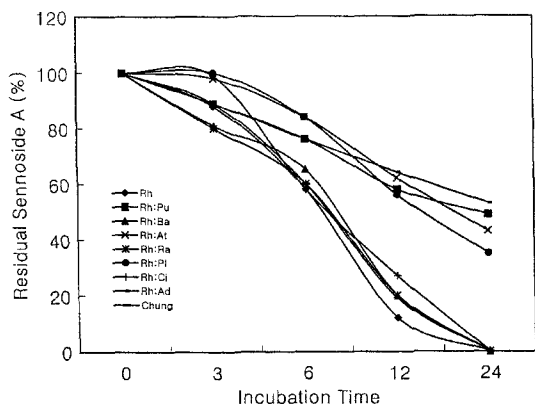


Fig. 3. Time course of the metabolism of sennoside A of water extract of polyprescriptions by human intestinal microflora.

throne was inhibited by *Angelicae Tenussimae Radix*, *Angelicae Dahuricae Radix*, *Puerariae Radix* and *platycodi Radix*. *Puerariae Radix* and *Platycodi Radix* had the most potent inhibitory activity. *Scutellariae Radix* and *Cimicifugae Rhizoma* did not affect the transforming activity of sennoside A to rheinanthrone. However, *Raphani Semen* weakly activated the transforming activity of sennoside A to rheinanthrone. The transforming activity of sennoside A in *Chungpesagan-tang* to rheinanthrone was 86% within 12 h. Sennoside A of *Chungpesagan-tang* was transformed to rheinanthrone as much as that of *Rhei Rhizoma* alone. These results suggested that *Raphani Semen* could induce the purgative action, because *Raphani Semen* induced the transforming activity of sennoside A of *Rhei Rhizoma* to rheinanthrone as well as the extraction level of sennoside A from *Rhei Rhizoma*. This transforming activity and the extraction efficacy of sennoside A from *Rhei Rhizoma* could be affected by herbal medicines. By the addition and subtraction of *Chungpesagan-tang*-composing herbal medicines, we thought, the purgative action of *Chungpesagan-tang* could be controlled.

In this point of view, even if *Rhei Rhizoma* is not a Monarch of *Chungpesagan-tang*, the purgative action of *Rhei Rhizoma* could be controlled in CVA patients by the addition and subtraction of herbal medicines. With a better understanding of these results, new polyprescriptions could be scientifically developed.

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