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원 저

실소산가미 및 그 구성약물이 세포내독소로 인한 혈전증 흰쥐에 미치는 영향

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Effects of *Silsosangami*-extract on Endotoxin-induced Experimental Thrombosis in Rats

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목적: 한의학에서 어혈증으로 야기되는 여러 가지 증상의 개선에 사용되는 실소산가미의 범발성혈관내응고증 및 혈전증에 미치는 영향을 연구하는 것이다.

방법: 동물은 Wistar-King strain Rats(150-200g)를 사용하였고, 혈전증은 세포내독소로 유발하였다. 측정은 실소산가미와 각 구성약물들에 대한 혈소판, 섬유소원, 프로트롬빈시간, 섬유소섬유소원분해산물에 미치는 영향을 연구하였다.

결과: 항혈전의 특성에 관한 것은 실소산가미와 구성약물중 포황, 오령지, 적작약, 도인 그리고 울금에서 억제특성이 나타났으며, 또한 실소산가미와 구성약물은 정상쥐에서 범발성혈관내응고증에서 혈소판과 섬유소원의 감소가 억제되었고, 섬유소분해산물의 증가가 억제 되었다. 실험관 실험에서 실소산가미와 구성약물은 트롬빈에 의해 섬유소원에서 섬유소로 전환이 억제되었으며, 플라스미노겐 또는 플라스민의 활성을 억제하였다.

결론: 실소산가미가 세포내독소로 유발된 혈전증에 대한 억제작용을 보이므로, 혈전증으로 야기되는 심혈관계질환등의 치료 및 예방에 응용가능성이 있을 것으로 사료된다. *(J Korean Oriental Med 2002;23(4):105-112)*

중심단어: 실소산가미*(Shi xiao-san jia wei)*, 혈전증, 혈소판, 섬유소원, 프로트롬빈시간, 섬유소섬유소원분해산물

Introduction

The herbal medical system known as "Hanbang medicine" is a traditional Korean therapeutic system. Silsosangami(SSG, Shi xiao-san jia wei) has been reported to have a hypolipidemic effect in patients[1,2,3]. SSG is consisted of *Typhae Pollen, Pteropi Faeces, Paeoniae Radicis rubra, Cnidii Rhizoma, Persicae Semen, Carthami Flos, and Curcumae Tuber*[1].

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According to the Korean and Chinese medicinal and herbal literature, SSG is effective for the treatment of inflammation, hyperlipemia and arteriosclerosis[1,2,3]. The SSG is a formula of Hanbang herbal medicines applied in Korea as an effective biological response modifier for augmenting host homeostasis of body circulation[1]. The pharmacological action of SSG has been limitedly studied in regard to ischemic infarction[1]. This herbal medicine has been shown to express diverse activities such as immunomodulating, anti-infarction, anti-allergic and anti-inflammatory effects[1,2,3]. Antisclerotic effects of SSG in experimentally induced atherosclerosis in rabbits have also been reported[1,2,3]. However, pharmacological mechanisms of SSG on lipid metabolism and atherosclerosis formation are poorly understood.

Although the effectiveness of SSG for ischemic infarction and inflammatory lung diseases has been widely demonstrated by clinical administration, the scientific and acting mechanisms for those are not understood and elucidated. It is generally known that inflammation, hyperlipemia and atherosclerosis induce disseminated intravascular coagulation (DIC). Therefore, anti-inflammatory activity may be assessed by the effect on DIC.

The present paper reports the effect of extracts obtained from SSG on endotoxin-induced experimental DIC in rats. Also, these were tested for their effect on endotoxin-induced blood platelet aggregation, thrombin-induced conversion of fibrinogen and fibrinolysis in *in vitro* experiments with aspirin as a positive agent.

Materials and Methods

1. Animals

Animals were maintained in the animal facility (room temperature: 23.2℃, relative humidity: 55.10%, all fresh air ventilation: 15-20times/h, 12hrs light and 12hrs dark) and subjected to the experiment after a 7-day quarantine period.

For DIC animal, male Wistar-King strain rats weighing 150-200 g were used. They were fed on a standard diet for at least 7days. They were fasted for 24hrs before the start of the experiments.

2. Drugs

Silsosangami(失笑散加味, SSG)[1] : *Typhae Pollen*(蒲黃) 4g, *Pteropi Faeces*(五靈脂) 4g, *Paeoniae Radicis rubra*(赤芍藥) 4g, *Cnidii Rhizoma*(川芎) 4g, *Persicae Semen*(桃仁) 4g, *Carthami Flos*(紅花) 4g and *Curcumae Tuber*(鬱金) 4g were used as SSG prescription.

SSG is a dried decoctum of a mixture of 7 herbal drugs. A total of 28 g of SSG was added in 500 *ml* of water and boiled for 2 hrs, filtered and then concentrated to 200 *ml*. This decoction was spray-dried to give a powdered extract. The yield was 5.2g, which represents one human dose/day.

The aqueous extracts of SSG and its seven composed herbs, which was massproduced as for clinical use, were kindly supplied by the Oriental Medical Hospital of Dongguk University (Kyungju, Korea).

Endotoxin (*Escherichia coli*; 055:B5) was from Difco Lab. (USA). Thrombin, adenosine diphosphate (ADP) disodium salt, Plasminogen-containing fibrinogen and urokinase were purchased from Sigma Co. (USA).

3. Method of endotoxin-induced DIC and process of drug treatment

Experimental DIC was induced by a modification of the method of Kubo[4]. Extracts (400 or 800 ㎎/㎏) was administered orally to healthy rats 1 hour before the injection of endotoxin (0.1 ㎎/㎏) into the tail vein. Four hours after the injection of endotoxin, the rats were

abesthetized with pentobarbital. And blood samples were taken from the heart with a plastic syringe. As an anticoagulant, 10 mM sodium ethylenediaminetetraacetic acid (EDTA) was used for platelet counts and a 1:9 volume of 3.8% sodium citrate for prothrombin time and fibrinogen determination.

The number of platelets was countered with an automatic blood counter (Coulter Counter, model S-Plus, Coulter Co., USA). Fibrinogen count was determined according to the method of Nishio[5]. The prothrombin time was measured with a COAG-A-Mate dual-channel device (General Diagnostic, Warner-Lambert Co., USA). Content of fibrin degradation product (FDP) was determined by means of the latex aggregation test (FDPL test U, Teikoku Zoki, Japan).

4. Blood platelet aggregation test

Whole blood samples were collected from heart of pentobarbital-anesthetized rats. Nine *ml* of the blood and 1 *ml* of heparin solution (10 U/*ml*) were transferred into a plastic tube. And centrifuged at 1,000 rpm for 10 min to give platelet-rich plasma (PRP). PRP was removed with a siliconized pipet, to be stored in a plastic test tube with a screw cap. The remaining red cell precipitate of the blood samples was further centrifuged at 3,000 rpm for 30 min to give platelet-poor plasma (PPP), which was used as a maximal transmittance standard [6].

Platelet aggregation test described by Ekimoto et al.[7] was modified and performed with collagen (500 *μg/ml*) and ADP (0.05 *μM*) used as aggregation agents. A 0.2 *ml* aliquot of PRP was placed in a test tube and the content was stirred at 1,200 rpm, at 37℃, for 1 min to which was added a 10 *μl* aliquot of a test solution. After 1 min, an aggregation agent was added to the reaction mixture. Changes in the light transmittance of the reaction mixture was continuously recorded with a Husm System platelet aggregometer (Rika Electric Co., Japan) and the transmission at the maximal aggregation after the addition of an aggregating agent was recorded. Then platelet aggregation was expressed as the percent increase in the transmittance taking the transmittance of a control mixture containing no test solutions zero.

5. Thrombin-induced conversion of fibrinogen to fibrin

Fibrinogen (500 ㎎) was dissolved in 100 *ml* of 150 mM NaCl containing 50 mM Tris-Acetate buffer (pH 7.4). A test solution (0.1 *ml*) was added to 1.8 *ml* of the fibrinogen solution with stirring. After 1 min, 0.1 *ml* of thrombin solution (0.2 U/*ml*) was added to the mixture and the whole was gently stirred until a fibrin clot appeared. The time required for clotting was recorded.

6. Fibrin plates

Fibrin plates were prepared by the method of Astrup and Mullertz [8]. One % agarose solution in phosphate buffered saline (10 mM phosphate buffer, pH 7.8, in 150 mM NaCl) was kept at 45-50℃ in a water bath. Agarose solution of plasminogen-containing fibrinogen and of plasminogen free-fibrinogen was prepared by dissolving 166 ㎎ of plasminogen-fibrinogen and 200 ㎎ of plasminogen free-fibrinogen in 100 *ml* of agarose solution at 31℃. A 10 *ml* aliquot of the mixture and 0.1 *ml* of thrombin (10 U/*ml*) solution were quickly mixed in a test tube, and the contents were immediately poured into a petri dish. The five wells of diameter 5 mm were made into each fibrin-agar plate.

7. Inhibition of plasminogen

A test solution (0.1 *ml*) and urokinase solution (0.1 *ml*, 100 U/*ml*) were mixed, and 200 *μl* of the mixture was added to each of the wells in the plasminogen-containing fibrin plate. Twenty *μl* of a mixture of phosphate buffer (0.1 *ml*) and urokinase solution (0.1 *ml*, 100 U/*ml*) was used as a control mixture. The plates

were incubated at 31℃ for 20 hrs. Then parent rings appeared where the fibrin lysis had occured. Two diameters of such rings were measured and the area was calculated. The inhibitory effect of test samples in this fibrinolytic system was assessed by comparing the lysed area with that of the control. The activity was expressed as an concentration which inhibited the lysis by 50% (IC50: ㎎/㎖)

8. Inhibition of plasmin

Urokinase solution (0.5 ㎖, 100 U/㎖) and plasminogen solution (0.5 ㎖, 0.5 ㎎/㎖) were mixed and incubated at 28℃ for 30 min. To the incubated solution (0.1 ㎖) was added a test solution (0.1 ㎖) of an appropriate concentration. Then 20 ㎕ of the mixture was put into each well in the plasminogen-free fibrin plates. Twenty ㎕ of phosphate buffer was used as control. The plates were incubated at 37℃ for 18 hrs. Two diameters of the lysed area were measured and the area was calculated. The inhibitory effect of samples was assessed by comparison of the lysed area with that of the control. The activity was expressed as the concentration which inhibits plasmin activity by 50% (IC50: ㎎/㎖)

9. Statistical analysis

The statistical significance was established as follows. The ANOVA one-way analysis of variance followed by pairwise comparisons using the Scheff test was used for the multigroup comparisons. The statistical analysis between two groups was evaluated by the F-t test. A probability value of 5% or less was considered indicative of a significant effect.

Data are expressed as mean±standard error. The differences were considered significant at $p<0.01$.

Results

1. Effects of SSG on endotoxin-induced DIC in normal rats (*in vivo*)

The injection of endotoxin (0.1㎎/500g) into the tail vein may induce DIC accompanied by a decrease in the number of blood platelets and fibrinogen, prolongation of prothrombin time and an increase in FDP. Oral administration of 200 or 500㎎/100g of SSG or 20㎎/100g of aspirin before the injection of endotoxin prevented endotoxin-induced DIC as shown in Table 1,2,3,4.

1) Effects of the SSG on the blood platelets of endotoxin-induced DIC in normal rats

The platelet count was $72.1\pm8\times10^4/mm^3$ in normal rats only with saline and $18.4\pm3\times10^4/mm^3$ in rats injected with 0.1㎎/500g of endotoxin control rats. Oral administration of 200 or 500㎎/100g of SSG counteracts the endotoxin-induced decrease in the platelet count significantly (Table 1).

2) Effects of the SSG on the fibrinogen of endotoxin-induced DIC in normal rats

The level of fibrinogen was 226±25㎎/㎖ in normal rats treated only with saline and 90.1±9㎎/㎖ in DIC rats control. Oral administration of 200㎎/㎖ and 500㎎

Table 1. Effects of the SSG and Aspirin on the Blood Platelets of Endotoxin-induced DIC in Normal Rats

Dose (㎎/100g)	Number of rats	Blood platelets count ($\times10^4/mm^3$)
Normal	5	72.1±8
Control	6	18.4±3
SSG 100	7	29.3±4
SSG 200	6	42.3±4[a]
SSG 500	8	50.2±3[b]
Aspirin 5	5	51.2±3[b]
10	6	53.4±6[b]
20	7	59.4±6[b]

[a] Significantly different from control, $p<0.05$.
[b] Significantly different from control, $p<0.01$
Each value represents the mean ± S.E.

Table 2. Effects of the SSG and Aspirin on the Fibrinogen of Endotoxin-induced DIC in Normal Rats

Dose (㎎/100g)	Number of rats	Fibrinogen (㎎/㎖)
Normal	5	226.0±25
Control	6	90.1± 9
SSG 100	7	118.0±12
SSG 200	6	138.0± 5[a]
SSG 500	8	160.2±16[b]
Aspirin 5	5	170.0±17[b]
10	6	186.0±17[b]
20	7	188.0±18[b]

[a] Significantly different from control, p<0.05.
[b] Significantly different from control, p<0.01
Each value represents the mean ± S.E.

Table 3. Effects of the SSG and Aspirin on the Prothrombin Time of Endotoxin-induced DIC in Normal Rats

Dose (㎎/100g)	Number of rats	Prothrombin time (sec)
Normal	5	10.4±0.5
Control	6	16.8±2.1
SSG 100	7	15.1±1.4
SSG 200	6	14.9±1.2[a]
SSG 500	8	13.2±1.1[b]
Aspirin 5	5	14.1±1.5[a]
10	6	14.9±1.3[a]
20	7	15.3±1.3[a]

a) Significantly different from control, p<0.05.
b) Significantly different from control, p<0.01
Each value represents the mean ± S.E.

Table 4. Effects of the SSG and Aspirin on the FDP of Endotoxin-induced DIC in Normal Rats

Dose (㎎/100g)	Number of rats	FDP (㎍/㎖)
Normal	5	0.2±0.01
Control	6	6.1±0.50
SSG 100	7	2.5±0.40[a]
SSG 200	6	3.6±0.30[a]
SSG 500	8	3.2±0.30[a]
Aspirin 5	5	3.0±0.40[a]
10	6	4.2±0.40[b]
20	7	4.7±0.50[b]

[a] Significantly different from control, p<0.05.
[b] Significantly different from control, p<0.01
Each value represents the mean ± S.E.

/100g of SSG countereacted the endotoxin-induced decrease in fibrin level significantly (Table 2).

3) Effects of the SSG on the prothrombin time of endotoxin-induced DIC in normal rats

The prothrombin time was 10.4±0.5sec in normal rats and 16.8±2.1sec in DIC rats. In rats treated with oral administration of 200㎎/100g or 500㎎/100g of SSG, the prothrombin time was found to be shorter than that of control animals (Table 3).

4) Effects of the SSG on the FDP of endotoxin-induced DIC in normal rats

The FDP level was 0.2±0.01㎍/㎖ in normal rats and 6.1±0.5㎍/㎖ in DIC rats control. Administration to 200㎎/100g and 500㎎/100g of SSG for 1hr before the injection of endotoxin counteracted the endotoxin-induced elevation of FDP level significantly. A marked preventive effect of aspirin, which was used as a standard drug, was observed on endotoxin-induced blood platelets decrease and fibrinogen decrease, however, little effect on endotoxin-induced prothrombin time increase or FDP increase (Table 4).

2. Effects of SSG' s 7 herbs on endotoxin-induced DIC in normal rats (*in vivo*)

1) Effects of the SSG' s 7 herbs on the blood platelets of Endotoxin-induced DIC in normal rats

Oral administration of 500㎎/100g of each herb before the injection of endotoxin prevented endotoxin-induced DIC as shown in Table 5,6,7,8. Oral administrations of 500㎎/100g of *Persicae Semen, Paeoniae Radicis rubra, Typhae Pollen, Curcumae Tuber* and *Pteropi Faeces* counteract the endotoxin-induced decrease in the platelet count significantly (Table 5).

2) Effects of the SSG' s 7 herbs on the fibrinogen of Endotoxin-induced DIC in normal rats

Oral administrations of 500㎎/100g of *Persicae Semen, Paeoniae Radicis rubra* and *Pteropi Faeces* countereacted the endotoxin-induced decrease in fibrin level significantly (Table 6).

3) Effects of the SSG' s 7 herbs on the prothrombin time of Endotoxin-induced DIC in normal rats

Table 5. Effects of the SSG's 7 Herbs on the Blood Platelets of Endotoxin-induced DIC in Normal Rats

Dose (500㎎/100g)	Number of rats	Blood platelets count ($\times 10^4/mm^3$)
Normal	5	72.1±8
Control	6	18.4±3
Persicae Semen	5	46.3±4[b]
Paeoniae Radicis rubra	6	48.3±5[b]
Typhae Pollen	7	40.2±4[a]
Curcumae Tuber	5	41.5±5[a]
Pteropi Faeces	6	42.3±6[b]
Carthami Flos	6	23.2±2.5
Cnidii Rhizoma	5	24.3±4

[a] Significantly different from control, p<0.05
[b] Significantly different from control, p<0.01
Each value represents the mean ± S.E

Table 7. Effects of the SSG's 7 Herbs on the Prothrombin Time of Endotoxin-induced DIC in Normal Rats

Dose (500㎎/100g)	Number of rats	Prothrombin time (sec)
Normal	5	10.4±0.5
Control	6	16.8±2.1
Persicae Semen	5	10.8±1.4[b]
Paeoniae Radicis rubra	6	15.2±1.6[b]
Typhae Pollen	7	11.2±1.5[a]
Curcumae Tuber	5	12.2±1.6[a]
Pteropi Faeces	6	12.1±1.5[b]
Carthami Flos	6	16.2±2.2
Cnidii Rhizoma	5	16.8±3.2

[a] Significantly different from control, p<0.05
[b] Significantly different from control, p<0.01
Each value represents the mean ± S.E

Table 6. Effects of the SSG's 7 Herbs on the Fibrinogen of Endotoxin-induced DIC in Normal Rats

Dose (500㎎/100g)	Number of rats	Fibrinogen (㎎/㎖)
Normal	5	226.0±25
Control	6	90.1±9
Persicae Semen	5	158.3±13[b]
Paeoniae Radicis rubra	6	162.1±14[b]
Typhae Pollen	7	143.0±16[a]
Curcumae Tuber	5	138.0±15[a]
Pteropi Faeces	6	158.4±16[b]
Carthami Flos	6	123.0±13.0
Cnidii Rhizoma	5	116.0±12.4

[a] Significantly different from control, p<0.05
[b] Significantly different from control, p<0.01
Each value represents the mean ± S.E.

Table 8. Effects of the SSG's 7 Herbs on the FDP of Endotoxin-induced DIC in Normal Rats

Dose (500㎎/100g)	Number of rats	FDP (㎍/㎖)
Normal	5	0.2±0.01
Control	6	6.1±0.5
Persicae Semen	5	2.9±0.3[a]
Paeoniae Radicis rubra	6	2.7±0.3[a]
Typhae Pollen	7	2.8±0.3[a]
Curcumae Tuber	5	3.3±0.4[a]
Pteropi Faeces	6	3.3±0.4[a]
Carthami Flos	6	4.9±0.4
Cnidii Rhizoma	5	4.3±0.5

[a] Significantly different from control, p<0.05
[b] Significantly different from control, p<0.01
Each value represents the mean ± S.E

In rats treated with oral administration of 500㎎/100g of *Persicae Semen, Paeoniae Radicis rubra, Typhae Pollen, Curcumae Tuber* and *Pteropi Faeces*, the prothrombin time was found to be shorter than that of control animals (Table 7).

4) Effects of the SSG's 7 herbs on the FDP of Endotoxin-induced DIC in normal rats

Although the FDP level was 0.2±0.01㎍/㎖ in normal rats and 6.1±0.5㎍/㎖ in DIC rats control, administration to 500㎎/100g of *Persicae Semen, Paeoniae Radicis rubra, Typhae Pollen, Curcumae Tuber and Pteropi Faeces* for 1hr before the injection of endotoxin counteracted the endotoxin-induced elevation of FDP level significantly (Table 8).

Discussion

In oriental medicine, the thrombosis is the category of blood stasis. Blood stasis is a pathological state resulting from the reverse or impeded flow of blood in the body or the stagnation of blood flow in local parts as well as abnormal blood outside of the vessles which remains in the body and fails to disperse[9]. As soon as blood stasis is formed, it can further affect the circulation of blood and lead to new pathological changes, causing a variety of diseases and syndromes[9]. Blood stasis is formed in two ways. In one way, it results from the impeded circulation of blood causesd by deficiency of qi(氣虛), stagnation of qi(氣滯), blood-cold(血寒) and blood-heat(血熱), etc. In the other way, blood stasis is caused

by abnormal blood outside of the vessels due to trauma or other reasons which fails to disperse and remains in the body[9]. Blood stasis has different clinical manifestations in accordance with its stagnation in different parts of the body and the various reasons for its formations[9]. Though diseases caused by blood stasis are many and diverse, their clinical manifestations can be summed up as follows, stabbing pain, cyanosis, tumour, bleeding(dark purplish blood with blood clots), dark complexion, squamous and dry skin, purplish dark tongue or with petechiae, ecchymosis, thready and uneven pulse, knotted pulse or intermittent pulse[9].

Moreover, the drugs for invigorating blood circulation and eliminating blood stasis or drugs for removing blood stasis are used for all kinds of syndrome through the blood stasis and atherosclerosis[10,11].

SSG has been considered as an effective agent for the treatment of inflammation, hyperlipemia and arteriosclerosis[2,3]. A syndrome referred to as DIC (closely related to arteriosclerosis and hyperlipemia) is an hemorrhagic disorder apparently caused by simultaneous activation of blood coagulation, fibrinolysis and kinin generation, accompanied by consequent fibrin deposition in the microcirculation[2,3]. The pathophysiological aspects of DIC produced by infusion of endotoxin in animals have been fully described[2,3,12].

SSG was reported that it was increased of depressor hypoxia tolerance and resolved the unbalanced supply of myocardial oxigen in mice[1]. Also SSG is used for angina pectoris of coronary heart disease in man[1].

In this studies, extracts of SSG and its 7 herbs were tested for its effect on experimental DIC, which is considered to be closely related to thrombosis. SSG is composed *Typhae Pollen, Pteropi Faeces, Paeoniae Radicis rubra, Cnidii Rhizoma, Persicae Semen, Carthami Flos, Curcumae Tuber*[1].

The extract of SSG and its herbs of *Typhae Pollen, Pteropi Faeces, Paeoniae Radicis rubra, Persicae Semen* and *Curcumae Tuber* prevented the endotoxin-induced experimental DIC and thrombosis in rats. A significant preventive effect on experimental DIC was noted in three parameters (excepting for prothrombin time) in rats when they were treated orally with 200 ㎎-500 ㎎ /100 g of the extract. Thus, SSG may be useful for the prevention of DIC in man. However, there is no evidence as to whether SSG is effective or not when used after the onset of DIC.

The extract derived from SSG and its herbs were then used for its effect on blood platelet aggregation, thrombin action and fibrinolytic action *in vitro*. The results show that the extracts of SSG and its herbs of *Typhae Pollen, Pteropi Faeces, Paeoniae Radicis rubra, Persicae Semen* and *Curcumae Tuber* effectively inhibited the platelet aggregation induced by various aggregating agents, such as ADP and collagen and that the extract inhibited conversion of fibrinogen to fibrin. In fibrinolytic system, this extract had inhibitory effect of plasminogen and plasmin action. Further work is in progress on the effect of main components, flavonoids of SSG, on blood coagulative and fibrinolytic system.

Conclusion

The inhibitory effects of the traditional herbal medicine SSG on the anti-thrombosis in rats which were induced by endotoxin. The anti-thrombic properties of SSG were also investigated by means of analytical parameters of bood composition. The extracts of SSG and its herbs of *Typhae Pollen, Pteropi Faeces, Paeoniae Radicis rubra, Persicae Semen* and *Curcumae Tuber* inhibited the endotoxin-induced DIC and thrombosis in rats. Also the extract inhibited the endotoxin-induced decrease in blood platelets and fibrinogen, and endotoxin-induced increase in fibrin

degradation products (FDP) on disseminated intravascular coagulation in normal rats.

In conclusion, the protection of extracts of SSG and its herbs on the ischemic infarction induced artificially might be related to their inhibitory effects on DIC, platelet coagulation and thrombic action.

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