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Original article

Comparative Study for Pharmacological Action of *Corydalis Rhizoma* before and after Processing

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ABSTRACT

Objective To clarify the rationality and to provide reasonable usage references of processed *Corydalis Rhizoma* (CR) in clinic by comparing respectively pharmacological actions including analgesic, anti-inflammation, antiplatelet aggregation and spasmolysis of Yuanhu Zhitong Tablet (YZT) and Yanhusuo Decoction (YD) constituted with raw CR (RCR) or processed CR (PCR). **Method** The hot-board, acetic-acid-induced twisting experiments and mouse auricular swelling model by injecting xylene in the abdomen of mouse were adopted to investigate the analgesic and anti-inflammatory effects of the four formulas on Kunming mice; The experiment of contractile activity on isolated rat intestine smooth muscle on Wistar rats was applied to observe the spasmolysis effect of the four formulas; The experiments of platelet aggregation induced by ADP or collagen on Wistar rats by turbidimetry method were used to observe the anti-platelet aggregation effect of the four formulas. **Results** Compared with RCR in two prescriptions, PCR displayed better analgesic effect ($P < 0.05$, 0.01), while there was no difference on anti-inflammatory effect; Inhibition of smooth muscle spasm of the two prescriptions was presented well, and the prescription YD with PCR was remarkable ($P < 0.05$, 0.01); Compared with the blank group, the two prescriptions showed outstanding effects on anti-platelet aggregation ($P < 0.01$), but no difference between RCR and PCR in two prescriptions. **Conclusion** PCR can improve the analgesic effect of prescription YZT and intensify the spasmolysis effect of prescription YD, which can be explained by the Chinese medicine processing regulation. Therefore, PCR is suggested to be chosen in YZT and YD to cure pain symptoms.

Key words

Corydalis Rhizoma; pharmacological action; processing; Yanhusuo Decoction; Yuanhu Zhitong Tablet

1. Introduction

Corydalis Rhizoma (CR) is the dried tuber of *Corydalis yanhusuo* W.T. Wang. It is usually collected in early summer, when the leaves and fibrous roots are wilted removed. After cleaned with water, it was boiled to yellow, sundried, cut into pieces, and utilized as medicine after it was ready. The prescription Yuanhu Zhitong Tablet (YZT) recorded in *Chinese Pharmacopoeia 2010* are constituted of CR with *Angelicae Dahuricae Radix* (ADR), which could not only

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promote circulation of *qi*, blood circulation and pain relief effects, but also cure the stomach pain, flank pain, headaches and dysmenorrhea caused by *qi*-stagnancy and blood stasis. The prescription Yanhusuo Decoction (YD) from ancient medical records MingJiaFangXuan, which constituted with only promote, *Angelicae Sinenisis Radix*, *Cinnamomi Ramulus*, and *Zingiberis Rhizoma*, can be used to cure the irregular menses of females and some arrhythmic abdominal pain.

The main chemical composition of CR is alkaloids, including tertiary amine (0.65%), quaternary ammonium alkali (0.3%), alkaline phenolic amine alkaloid alkali, etc (He et al, 2007). The alkaloids in CR, tetrahydrocorysamine, tetrahydrocoptisine, corydaline, tetra-hydropalmatine, dehydrocorydaline, oxoglaucine, noroxy-hydrastinine, tetrahydroberberine, behenic acid, β sitosterol, daucosterol, vanillic acid, and p-hydroxybenzoic acid had been extracted and separated by Zhang et al (2008). In the history of traditional Chinese medicine (TCM), CR was widely used as it could activate blood, move *qi* and relieve pain, and cure the stagnation of *qi* and blood stasis causing pain (Pharmacopoeia Committee of P. R. China, 2010). Over the years, with the further study of CR, some pharmacological actions were confirmed by using advanced healthcare technology, and the study showed that CR had analgesic and sedation effects, and could improve myocardial ischemia and relax coronary artery and smooth muscle, etc (Tang et al, 1962; Liu et al, 1993; Jing et al, 2011; Ma et al, 2011; Xu et al, 2007).

Over the years, the main processing methods of CR included stir-frying, stir-baking with vinegar, stir-baking with wine, boiling with vinegar, stir-baking with salt, etc (Ma, 2005; Lei et al, 2013), in which the stir-frying and stir-baking with vinegar as processing ways were adopted widely. The study demonstrated that in CR after processing with vinegar, the dissolution of tetrahydropalmatine and fumarine would be improved. In particular, the effect of stir-frying was more protruding (You et al, 2009). The content of dehydrocorydaline in fresh CR processed by vinegar-boiling, vinegar-frying and alcohol-frying was high, and the content of tetrahydropalmatine in purchased CR which was processed by water-boiling at production place was high (Cao et al, 2009). From above substance, it may suggest that pharmacological difference will exist when raw CR (RCR) or processed CR (PCR) was applied in prescription. By consulting amount of references, we found that the study about CR was concentrated primarily on single drug, and the discussion of pharmacological action changing in the level of prescription was deficient. In addition, from the TCM history, the usage of Chinese medicine with the form of prescription was more extensive in clinic, but there usually existed more confusion when using RCR or PCR in prescription, many hospital staffers scarcely distinguish the difference of RCR and PCR, ignoring the otherness of pharmacological action. As a result, it often induced some errors on using RCR or PCR, which made the pharmacological actions of CR were weak or strong, and even no effect. Therefore, we choose the prescription YZT and prescription YD as our study objects, by using CR and CR processed with vinegar in prescriptions separately to investigate the differences in pharmacodynamic actions, and hope that it can provide research foundation for the usage of CR in clinic.

2. Materials and Methods

2.1 Main instruments

Perfusion system (*in vitro*) was purchased from Zander Apparatus Co., Ltd. (USA). Platelet Aggregation was provided by CHRONO-LOG Company (USA). Low Speed Automatic Balancing Centrifuge was obtained from Jingli Centrifuge Company (batch No.: LDZ5-2, China).

2.2 Drugs and reagents

Aspirin was purchased from Bai'ao Pharmaceutical Co., Ltd. (batch No.: 20070501, China). Acetylcholine chloride was provided by Sinopharm Chemical Reagent Co., Ltd. (batch No.: WL20080102, China). Atropine sulphate injection was purchased from Tianjin Pharmaceutical Group Xinzheng Co., Ltd. (batch No.: 1212061, China). Adenosine-5′-diphosphate disodium (ADP) and collagen (stored at 4 ^{o}C) were obtained from CHRONO-LOG Company (batch No.: 34073408, USA). Sodium citrate was purchased from Tianjin Chemical Reagents Company. Adrenaline Hydrochlaride injection was purchased from Yuanda Pharmaceutical Co., Ltd. The drugs used in this experiment came from Tianjin Chinese Medicine Factory Co., Ltd. (The bath numbers of CR, ADR, *Angelicae Sinenisis Radix*, *Cinnamomi Ramulus*, and *Zingiberis Rhizoma* are 1105010, 1105019, 1211233, 1211236, and 1212027).

2.3 Animals

Kunming mice weighing 20–22 g (Certificate No.: 0001750) and Wistar rats weighing 200−220 g (Certificate No.: 0001751) were supplied by Tianjin Shanghong Laboratory Animal Science and Technology Co., Ltd.

2.4 Processing of CR

RCR was soaked by 20% vinegar (20 mL vinegar added to 100 g RCR), then it was fried with slow-fire to dry in the frying vessel.

2.5 Preparation of liquid drugs

RCR and ADR were mixed together with equal quantities, and the method of water extraction and alcohol precipitation was used to get the liquid drugs, then concentrated the liquid to reach the final concentration standard of 1 g/mL. The same method was used to obtain the prescription YZT with PRP and prescription YD with RCR or PCP. By using UPLC, the result of chromatographic fingerprint analysis of RCR and PCR was performed in Figure 1, which showed that the tetrahydropalmatine

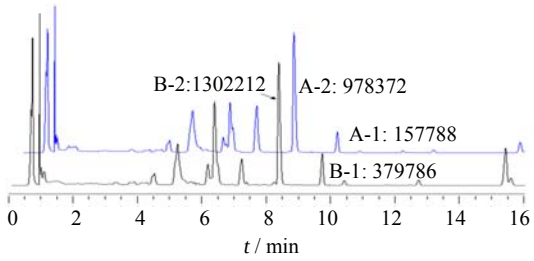

Figure 1 Chromatographic fingerprint analysis of RCR (A) and PCR (B)

A1 and B1: tetrahydropalmatine A2 and B2: dehydrocorydaline A

of CR when processed with vinegar was more easily dissolved, and dehydrocorydaline had the same phenomenon.

3. Experimental methods

3.1 Heat conduction caused pain reaction

Kunming mice (170 mice) weighing 20−22 g were divided into 14 groups randomly, including blank, positive medicine (aspirin, 0.1 g/kg), prescription YZT with RCR (10, 20, and 40 g/kg), prescription YZT with PCR (10, 20, and 40 g/kg), prescription YD with RCR (10, 20, and 40 g/kg), and prescription YD with PCR (10, 20, and 40 g/kg) groups, then weighed and numbered. After ig administration for 7 d, we investigated the pain threshold of mice in hot-board (Qiu et al, 2009).

Percentage of improving pain threshold = (pain threshold before giving drugs−pain threshold after giving drugs) / pain threshold before giving drugs.

3.2 Chemical stimulation caused pain reaction

All methods of administration and grouping were same as described above. Acetic-acid-induced twisting experiments (Qiu et al, 2009) were used to observe the frequency of body twisting, and calculate the analgesia percentage.

Analgesia percentage = (average frequency of body twisting of blank group−average frequency of body twisting of treating group) / average frequency of body twisting of blank group

3.3 Xylene-induced mouse ear swelling

The methods of administration and grouping were same as described above. The model of xylene-induced mouse ear swelling (Cao et al, 2009) was made to calculate the swelling degree and resistant rate.

Swelling degree = weight of left ear –weight of right ear.

Resistant rate = (average swelling degree of blank group – average swelling degree of treatment group) / average swelling degree of blank group.

3.4 Spasmolysis effect

The small intestine was isolated at first, and then put to *in vitro* tissue perfusion system (Zhang et al, 2009). We recorded a normal waveform of smooth muscle spontaneous activity when the small intestine generated stable contractions. ① Drugs were given in different doses (6, 12, and 24 g/L). ② About 100 μL Ach (0.01%) was added to water-bathing at constant temperature. When the trend of waveform kept stabilization and the intestinal spasm model was set up successfully, we began to add the drugs (the doses were same above), then the change of tension was observed and recorded. ③ Giving drugs (the doses were same above) after giving about 100 μL atropine (0.01%), the method was same as described above.

Resistant rate = (average tension before giving drugs – average tension after giving drugs) / average tension before giving drugs

Resistant rate = (average tension after giving Ach – average tension after giving drugs) / average tension before giving drugs

Increasing resistant rate = (average tension after giving atropine – average tension after giving drugs) / average tension before giving drugs

3.5 Platelet aggregation test

The model of ice-adrenergic blood stasis model on rats was set up first, then anti-coagulant samples were made (Bai et al, 2005). Appropriate mount of anti-coagulant sample was centrifuged at 800 r/min for 10 min to obtain platelet-rich plasma (PRP). Afterwards, the liquid supernatant was collected, and the remaining samples continued to be centrifuged on the condition of 3000 r/min for 10 min to obtain platelet-poor plasma (PPP). PPP and PRP of 200 μL were added respectively to cuvettes, then put to corresponding channels after incubation for 5 min, adding ADP (5 μmol/L) or collagen (2 μg/mL) of 2 μL, then recorded the maximal platelet aggregative rate.

Resistant rate = (maximal platelet aggregative rate of model group − maximal platelet aggregative rate of giving drugs group) / maximal platelet aggregative rate of model group

3.6 Statistical analysis

All the data were analyzed by SPSS 15.0. The measurement data were expressed as $\bar{x} \pm s$, and one-way analysis of variance (ANOVA) was used. The variance of comparisons between groups can use LSD method, and also can use Dunnett's T3 method if missing variance.

4. Results

4.1 Analgesic effect of two prescriptions on pain reaction caused by heat conduction

With respect to the blank group, the high dose of prescription YZT with RCR and the three doses of prescription YZT with PCR in four time-points had an obvious difference ($P < 0.01$), the mid- and high-dose prescription YD with RCR or PCR in 1.5 and 2 h after administration had a statistical difference ($P < 0.05$, 0.01), it

suggested that RCR or PCR applied in prescription YD had a late analgesic effect. With the same dose level (20 g/kg, 40 g/kg), the prescription YZT with PCR and prescription YZT with RCR had a statistical difference ($P < 0.05$, 0.01), it was clarified that PCR applied in prescription YZT outperformed RCR on rapid analgesic. However, the every dose of prescription YD with PCR and corresponding prescription YD with PCR had no difference, which showed that it played the same role in prescription YD regardless of choosing RCR or PCR on pain reaction caused by heat conduction (Table 1).

4.2 Analgesic effect of two prescriptions on pain reaction caused by chemical stimulation

The high-dose prescription YZT with RCR and low-dose prescription YZT with PCR had an obvious difference ($P < 0.01$), compared with blank group, the all doses of prescription YD with RCR and prescription YD with PCR also had a statically difference ($P < 0.01$). In addition, the mid- and high-dose prescription YZT with RCR and corresponding prescription YZT with PCR had obvious difference ($P < 0.01$), and it also clarified that PCR applied in prescription YZT outperformed RCR on rapid analgesic. However, the analgesic effect of prescription YD presented a same phenomenon as described above (Figure 2).

4.3 Anti-inflammatory effect

Compared with blank group, all treatment groups had a statically difference ($P < 0.01$), which suggested that there existed anti-inflammatory effects in two prescriptions regardless of choosing RCR or PCP. However, the three doses of prescription YZT and corresponding prescription YD with RCR or PCP had no difference; It showed that RCR or PCP applied in prescriptions played the same role on anti-inflammation. From the resistant rate of swelling degree (Figure 3), every dose of prescriptions with PCR were higher than RCR applied in prescriptions, it suggested that PCR in prescriptions had a good advantageous on anti-inflammation.

Table 1 Analgesic effect of two prescriptions on pain reaction caused by heat conduction ($\bar{x} \pm s$, $n = 12$)

Groups	Doses / ($g \cdot kg^{-1}$)	Threshold before administration /s	Threshold after administration /s			
		0 h	0.5 h	1 h	1.5 h	2 h
Blank	20 $mL \cdot kg^{-1}$	21.00 ± 5.83	18.83 ± 3.33	20.92 ± 5.02	22.25 ± 5.75	22.08 ± 7.32
Aspirin	0.1	17.60 ± 2.86	24.70 ± 5.62*	29.60 ± 7.73*	30.10 ± 8.20*	29.20 ± 7.30*
PY(RCR)	10	21.95 ± 4.19	20.20 ± 4.52	20.90 ± 4.36	24.50 ± 4.25	23.60 ± 6.06
YZT(RCR)	20	22.74 ± 1.86	25.00 ± 3.78*	30.13 ± 4.67*	26.63 ± 5.78	26.88 ± 6.29
YZT(RCR)	40	25.19 ± 3.97	27.25 ± 3.62**	33.25 ± 8.41**	36.75 ± 6.90**	32.88 ± 4.12**
YZT(PCR)	10	18.83 ± 4.31	26.38 ± 7.95$^{**▲}$	25.88 ± 7.30	24.13 ± 6.66	21.38 ± 5.68
YZT(PCR)	20	21.29 ± 3.23	37.88 ± 5.72$^{**▲▲}$	43.00 ± 14.81**	48.63 ± 12.57$^{**▲▲}$	42.75 ± 8.58$^{**▲▲}$
YZT(PCR)	40	20.36 ± 3.79	35.50 ± 12.78$^{**▲▲}$	45.38 ± 10.36**	47.50 ± 10.85$^{**▲}$	40.38 ± 6.99$^{**▲}$
YD(RCR)	10	16.69 ± 3.03	17.63 ± 3.50	21.38 ± 5.24	22.88 ± 5.08	22.63 ± 4.41
YD(RCR)	20	21.41 ± 2.64	25.75 ± 2.49*	29.88 ± 6.10*	39.38 ± 8.40**	35.75 ± 3.54**
YD(RCR)	40	16.00 ± 1.71	23.71 ± 4.65	26.00 ± 4.00	30.29 ± 6.09	31.14 ± 4.45**
YD(PCR)	10	20.44 ± 4.43	22.63 ± 4.90	25.50 ± 5.21	27.88 ± 5.25	25.75 ± 3.69
YD(PCR)	20	19.06 ± 3.22	22.00 ± 3.46	27.00 ± 5.83	38.00 ± 12.28**	34.25 ± 5.90**
YD(PCR)	40	14.56 ± 2.31	21.25 ± 3.37	25.75 ± 6.30	30.88 ± 7.94*	29.75 ± 5.47*

$^{*}P < 0.05$ $^{**}P < 0.01$ *vs* blank group; $^{▲}P < 0.05$ $^{▲▲}P < 0.01$ *vs* prescription with RCR

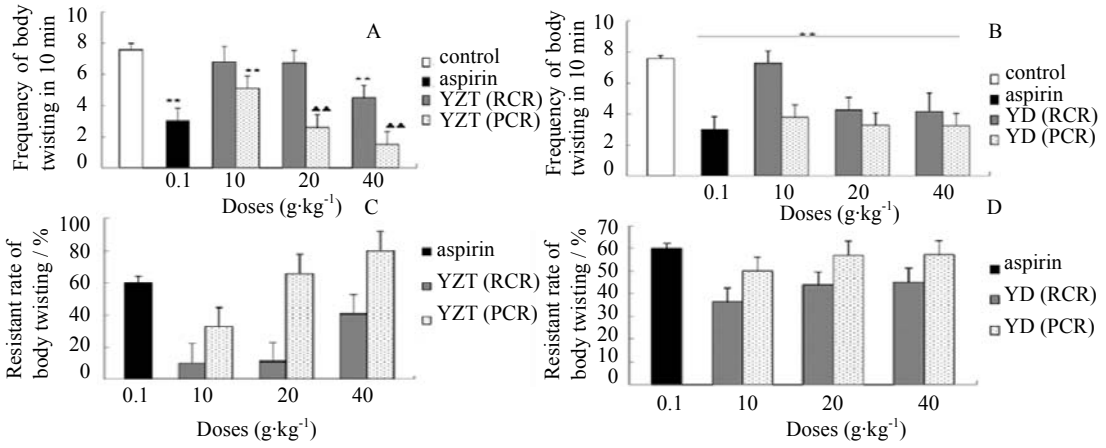

Figure 2 Analgesic effects of two prescriptions on pain reaction caused by chemical stimulation

$^{*}P < 0.05$ $^{**}P < 0.01$ *vs* control group; $^{▲}P < 0.05$ $^{▲▲}P < 0.01$ *vs* prescription with RCR

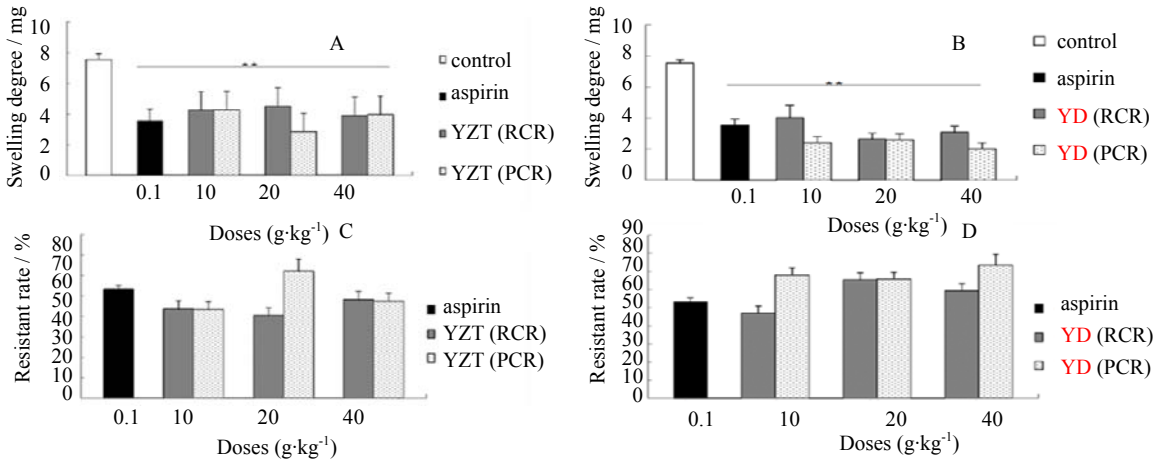

Figure 3 Anti-inflammatory effect

$^{*}P < 0.05$ $^{**}P < 0.01$ *vs* control group; $^{▲}P < 0.05$ $^{▲▲}P < 0.01$ *vs* prescription with RCR

4.4 Spasmolysis effect

4.4.1 Spontaneous activity on isolated small intestine

With respect to the tension before administration, between the mid- and high-dose prescription YZT with RCR and prescription YD with RCR as well as three doses of prescription YZT and YD with PCR had an obvious difference ($P < 0.05$, 0.01). All doses of prescription YD with PCR and corresponding prescription YD with RCR existed a statically difference ($P < 0.05$, 0.01), which suggested that PCR in prescription YD outperformed RCR on spasmolysis. However, there were no differences in prescription YZT regardless of choosing RCR or PCR (Figure 4).

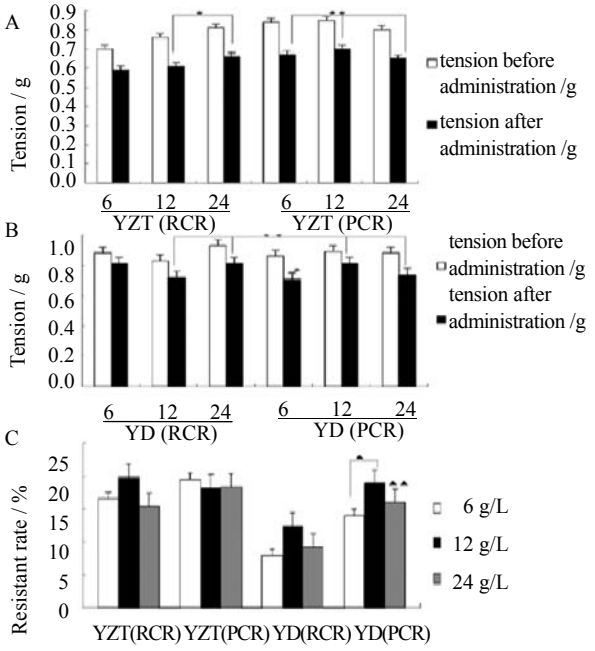

Figure 4 Spontaneous activity on isolated small intestine

$^{▲}P < 0.05$ $^{▲▲}P < 0.01$ *vs* prescription with RCR in same dose after administration

4.4.2 Contraction activity induced by acetylcholine (Ach) on isolated rat small intestine smooth muscle

Compared with the tension before giving Ach (Figure 5), all doses of two prescriptions with RCR or PCR had a statically difference ($P < 0.01$), it suggested that RCR or PCR in prescriptions played a good role on antispasmodic, while the every dose of prescription YZT with RCR and corresponding prescription YZT with PCP had no difference. However, compared with the prescription YD with RCR in the same dose after administration, the same pharmacological action of prescription YD with PCR on spasmolysis was presented ($P < 0.05$), and it clarified that choosing PCR in prescription YD had a better spasmolysis effect.

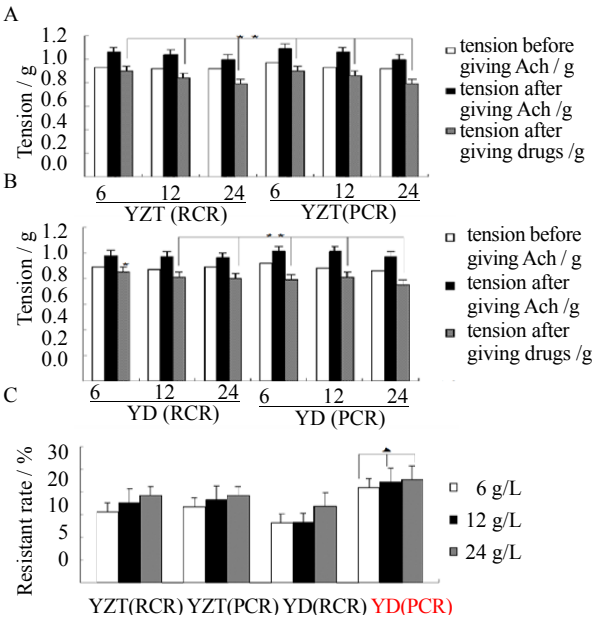

Figure 5 Contraction activity induced by Ach on isolated rat small intestine smooth muscle

$^{*}P < 0.05$ $^{**}P < 0.01$ *vs* tension before giving Ach; $^{▲}P < 0.05$ $^{▲▲}P < 0.01$ *vs* prescription with RCR in same dose after administration

4.4.3 Contraction activity induced by atropine on isolated rat small intestine smooth muscle

The three doses of prescription YZT with RCR and prescription YZT and YD with PCR (12 and 24 g/L) had an obvious difference ($P < 0.05$, 0.01), with respect to the tension before giving atropine. The three doses of prescription YZT with RCR and corresponding prescription YZT with PCP had no difference; This trend was the same as descried above.

Likewise, all doses of prescription YD with RCR and corresponding prescription YD with PCR had obvious difference ($P < 0.05$, 0.01), which showed that PCR in prescription YD had a synergistic effect well on relaxing intestinal smooth muscle contraction activity induced by atropine (Figure 6).

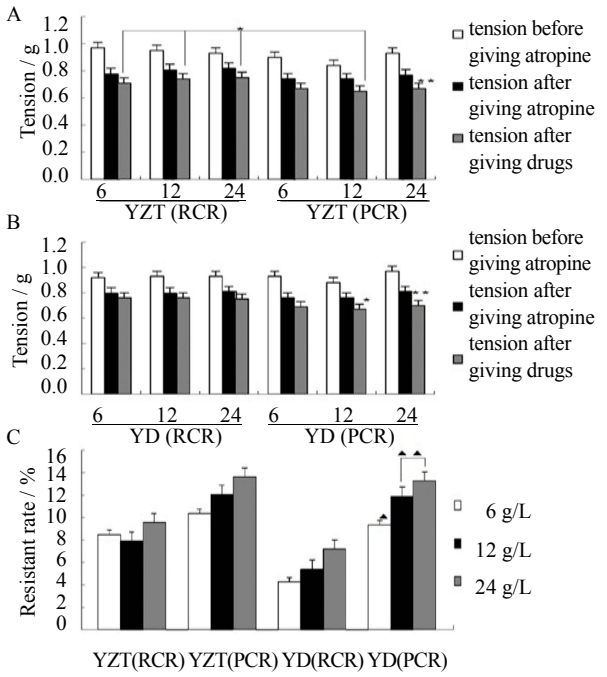

Figure 6 Contraction activity induced by atropine on isolated rat small intestine smooth muscle

$^{*}P < 0.05$ $^{**}P < 0.01$ *vs* tension before giving atropine; $^{▲}P < 0.05$ $^{▲▲}P < 0.01$ *vs* prescription with RCR in same dose after administration

4.5 Platelet aggregation test

4.5.1 Platelet aggregation induced by ADP

From the result of experiment (Figure 7), all doses of two prescriptions regardless of choosing RCR or PCR had a statically difference ($P < 0.05$, 0.01), compared with blank group, so it clarified that it had an anti-platelet aggregation effect for platelet aggregation induced by ADP. However, with the level of the same dose, the three doses of two prescriptions with RCR and two prescriptions with PCR had no difference, which showed that RCR or PCR applied in prescriptions had the same effect on anti-platelet aggregation.

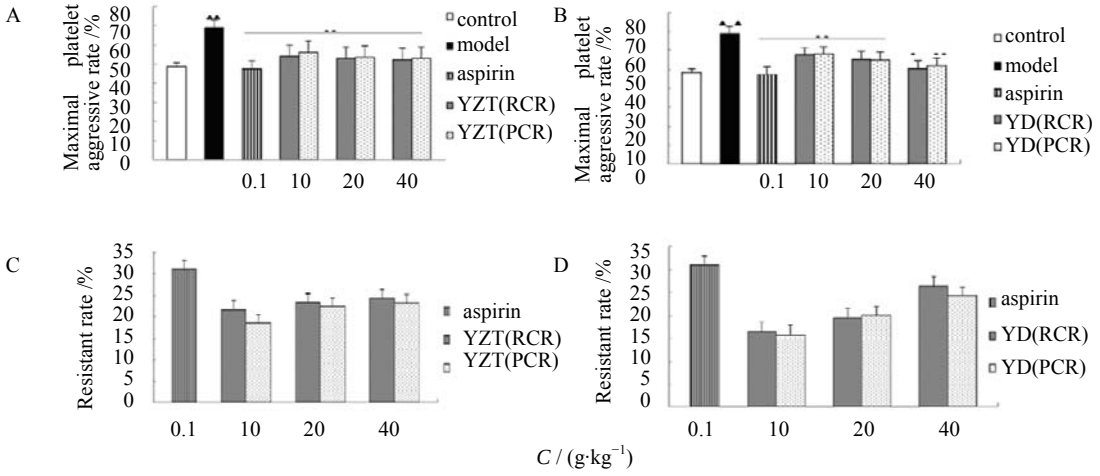

Figure 7 Platelet aggregation induced by ADP

$^{*}P < 0.05$ $^{**}P < 0.01$ *vs* model group; $^{▲}P < 0.05$ $^{▲▲}P < 0.01$ *vs* model group and blank group

4.5.2 Platelet aggregation induced by collagen

As is described above, the same trend was represented in Figure 8, the two prescriptions played a great role in anti-platelet aggregation for platelet aggregation induced by collagen ($P < 0.05$, 0.01), while no difference between RCR and PCR in two prescriptions.

5. Conclusion

Two prescriptions had good pharmacological actions such as analgesic, anti-inflammation, spasmolysis, and antiplatelet aggregation. The PCR in prescription YZT was better than that on analgesic while no difference in prescription YD. It had no obvious distinguish in two prescriptions whether the CR was precessed or not on anti-inflammation. CR processed with vinegar in prescription YD outperformed the RCR on spasmolysis while no difference in prescription YZT. Regardless of the RCR or PCR in two prescriptions, little difference was represented on inhibiting platelet aggregation that ADP or collagen induced separately. Above all, the pharmacological actions of CR after processing with vinegar had an otherness, especially on analgesic and

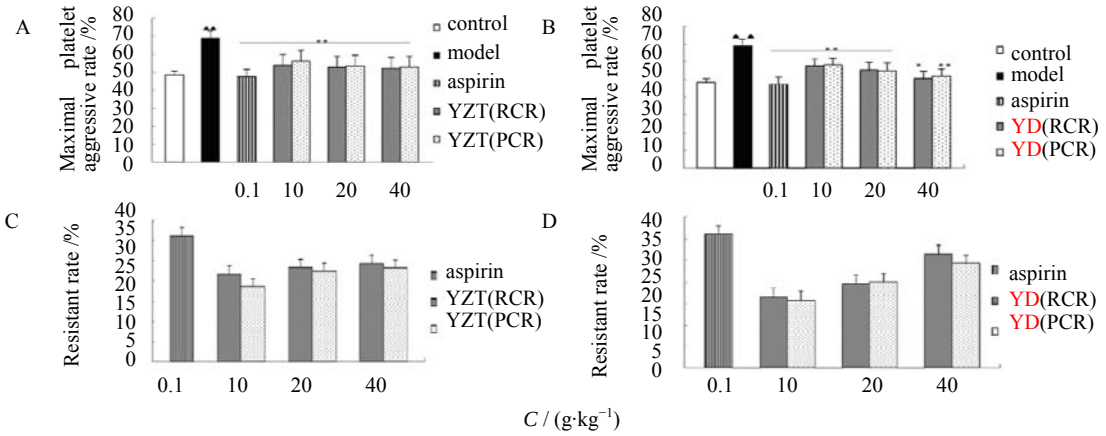

Figure 8 Platelet aggregation induced by collagen

$^{*}P < 0.05$ $^{**}P < 0.01$ *vs* model group; $^{▲}P < 0.05$ $^{▲▲}P < 0.01$ *vs* model group and blank group

spasmolysis, PCR should be applied in prescription YZT and YD to cure pain symptoms.

6. Discussion

The effective components in CR are all kinds of alkaloids, and total alkaloids, CR A, tetrahydropalmatine, and CR L had a strong analgesia effect, but the analgesic effect of tetrahydro-palmatine is more prominent (Jing et al, 1957). Tetrahydro-palmatine is known as levorotatory four hydrogen palmatine (1-THP), the studies have shown that 1-THP can block DA receptor to form stronger analgesic effect (Peng et al, 2005; Xu et al, 2009). In our experiments, the RCR or PCR applied in two prescriptions had an analgesic effect well on the pain reaction caused by head conduction and chemical stimulation, which suggested that its mechanism was likely related to DA receptor blocked. Moreover, it suggested that the analgesic effect of CR was related directly to the quantities of alkaloids dissolved (Zhao et al, 2007; Du et al, 2009). In prescription YZT, CR combined with ADR can inhibit the pain reaction well, and CR after processing with vinegar in prescription was better on analgesic. So, it suggested that CR after processing with vinegar could improve the quantities of alkaloids dissolved; CR and ADR have a synergistic function on analgesic.

The TCM theory held that *qi* was being transported in whole body as the basic of life activities. When some organs or main and collateral channels had a change in some circumstances, there was an adverse impact on dredging of *qi*, inducing stagnation and reversed flow of *qi*. From the perspective of modern medicine, stagnation and reversed flow of *qi* were closely related to digestive system diseases such as chronic gastritis, dyspepsia, peptic ulcer disease, enteritis, dysentery, biliary tract disease, and other syndromes. The contraction of intestinal smooth muscle can induce many pain syndromes, such as intestinal spasm and so on. Pharmacology researches studied that it can active the intestinal smooth muscle with the increase of Ca^{2+} in cytoplasm and form a strong contraction (Liang et al, 2008; He et al, 2010). In our experiment, the prescriptions YZT and YD played a good role on inhibiting intestinal spasm for spontaneous activity and contraction activity induced by Ach on isolated small intestine, it suggested that some active ingredients in two prescriptions were equal to antagonist of Ca^{2+} channel. Moreover, the result of experiment showed that the PCR in prescription YD outperformed RCR on spasmolytic, it conformed the regulation of Chinese medicine processing, and could provide some guidance for clinic.

At present, the incidence of thrombotic diseases has been increasing year by year in the world. Aspirin, clopidogrel, tirofiban, Proteinkinase-1 (PAR-1) antagonist, and other drugs were used commonly in clinic on treating thrombotic diseases (Tomasello et al, 2010), although it had acquired an obvious achievement, there were many adverse reactions. So, that should have not been used for a long time. In our experiments, the prescription YZT and prescription YD can activate blood, cure the stagnation of *qi* and blood stasis well, which the adverse reactions were less, and were more suitable to use permanently in clinic. The result of experiments showed that the RCR or PCR in two prescriptions can inhibit primly the platelet aggregation induced by ADP or collagen, corresponding to the regulation that ancient people thought that the prescription YZT and prescription YD had a promoting blood circulation and removing blood stasis effects well. But there were no difference between the RCR and PCR in prescriptions, it may be related to the way of giving drugs (Ancient people usually used CR with alcohol or boiling with vinegar, which could intensify the effect of prompting blood circulation.), the specific mechanism should be studied further.

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