ANTICOAGULANT EFFECT OF TRI BAO HOAN IN AN EXPERIMENTAL THROMBOSIS MODEL

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The purpose of this study was to evaluate the anticoagulant effects of Tri Bao Hoan in a lipopolysaccharide (LPS)-induced thrombosis model using Wistar rats. Tri Bao Hoan and rivaroxaban were administered orally for seven consecutive days. One hour after the final dose, LPS (3 mg/kg) was injected via the tail vein to induce thrombosis. Blood samples were collected four hours after LPS administration to assess the study parameters. Our findings indicated that Tri Bao Hoan at 0.36 pill/kg/day exerted significant anticoagulant effects by increasing platelet count and fibrinogen concentration, as well as prolonging prothrombin time (PT) and activated partial thromboplastin time (aPTT) compared with the vehicle-treated thrombosis group ($p < 0.05$). Tri Bao Hoan at 0.12 pill/kg/day did not show statistically significant changes in these parameters ($p > 0.05$). Regarding biochemical findings, Tri Bao Hoan at 0.36 pill/kg/day significantly reduced serum AST activity in the vehicle-treated thrombosis group ($p < 0.05$), whereas AST activity, urea and creatinine concentration remained statistically unchanged at both doses ($p > 0.05$). In conclusion, Tri Bao Hoan at 0.36 pill/kg/day demonstrated a significant anticoagulant effect in Wistar rats with LPS-induced thrombosis.

Keywords: Tri Bao Hoan, anticoagulant effect, lipopolysaccharide, *Wistar* rats.

I. INTRODUCTION

Coagulation is a crucial physiological process that prevents excessive blood loss following vascular injury. This process involves the sequential activation of coagulation factors, ultimately converting soluble fibrinogen into insoluble fibrin. The resulting fibrin network stabilizes the hemostatic plug and supports tissue repair.[1] However, when the coagulation system becomes excessively activated or unbalanced with the body's regulatory mechanisms, a hypercoagulable state may develop, leading to the formation of thrombus within the blood vessels. Thrombosis refers to the abnormal formation of blood clots that partially or completely obstruct blood flow. Such blockages can cause ischemia and damage to vital organs, such as the heart, brain, lungs, and kidneys, resulting in myocardial infarction, ischaemic stroke, pulmonary embolism, or other serious complications depending on the site of the thrombosis. This condition remains one of the major causes of morbidity and mortality worldwide.[2]

In the treatment and prevention of thrombosis, anticoagulant therapy plays a central role by inhibiting the activation of coagulation factors and preventing the formation of fibrin and thrombi. The main classes of anticoagulants currently in use include heparins, vitamin K antagonists, and novel oral anticoagulants.[3,4]

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Although these agents are highly effective, they still have several limitations, such as the risk of bleeding, drug–food interactions, the need for regular laboratory monitoring, and high treatment costs. Therefore, the search for safe and effective anticoagulant agents, particularly those derived from natural sources, has become an area of growing scientific interest.[5]

Tri Bao Hoan is formulated as a pill preparation containing main components with anticoagulant potential, including natokinase, lumbrokinase, extract of *Ginkgo biloba*, *Angelica sinensis*, and *Sophora japonica*, along with several other herbs known for their blood-activating and antioxidant properties. These bioactive ingredients have been reported to exhibit anticoagulant activity and reduce the risk of thrombosis through multiple mechanisms.[6-10] The combination of these anticoagulant components makes Tri Bao Hoan a promising formulation for the prevention of thrombosis. However, no experimental study has yet evaluated its anticoagulant effects. Therefore, this study was conducted to investigate the anticoagulant effect of Tri Bao Hoan using a lipopolysaccharide-induced thrombosis model in rats.

II. MATERIALS AND METHODS

1. Subjects

Preparation of test product

The test product used in this study was Tri Bao Hoan, manufactured by Napharco Pharmaceutical Co., Ltd. The formulation is in the pill form (traditional coated pellets). Each pill contains 1000mg of nattozyme phygic; 2100mg of herbal extract (equivalent to 3000mg of *Semen Platycladi orientalis*, 1000mg of *Albizia julibrissin cortex*, 1000mg of *Poria cocos*, 1000mg of *Radix Angelicae sinensis*, 1000mg of *Lycii fructus*, 1000mg of *Radix Rehmanniae glutinosae praeparata*, 1000mg of *Acori tatarinowii rhizoma*, 500 mg of *Flos Styphnolobii japonici imaturi*, 500mg of *Nelumbinis plumula*, and 500mg of *Glycyrrhizae radix)*; 300mg of Amber powder; 200 FU of Lumbrokinase; 120mg of *Ginkgo biloba* extract; 100mg of Gamma-aminobutyric acid; 50mg of Magnesium gluconate; 20mg of Alpha-lipoic acid; 15 mg of L-theanine; 3.5mg of Vitamin B6; and 3.5mg of Astaxanthin 5%. The product complies with internal quality standards (Certificate of Product Registration No. 3338/2024/DKSP). Batch no.: 03.2025; Manufacturing date: 12 March 2025; Expiry date: 11 March 2028.

The intended human dose is one pill daily. Using an interspecies dose conversion factor of 6 for rats, the corresponding experimental dose was 0.12 pill/kg/day in rats. The positive control drug was Rivaroxaban 20mg (Xarelto®, Bayer HealthCare Pharmaceuticals). Both the test product and the reference drug were fully dissolved in distilled water immediately before administration. Experimental animals received the freshly prepared solutions orally via a gavage needle at a dosing volume of 10 mL/kg/day.

Instruments and Chemicals

Lipopolysaccharides from Escherichia coli O55:B5 (L2880-25MG) were obtained from Sigma-Aldrich (USA).

Thromborel® S (containing thromboplastin and calcium) and Dade® Actin® FSL Activated PTT Reagent (containing phospholipids) were purchased from Siemens Healthineers, Germany, and imported by Sysmex Vietnam Co., Ltd. A 0.025 mol/L calcium chloride solution (Siemens, Germany) was also supplied by Sysmex Vietnam Co., Ltd.

Coagulation parameters were measured using a Sysmex CA-50 semi-automatic coagulation analyzer (Sysmex Corporation,

Japan).

Hematological parameters were analyzed using Horiba Medical reagents and the ABX Micros 60 ES hematology analyzer (Horiba Medical, France).

Serum biochemical parameters, including alanine aminotransferase, aspartate aminotransferase, urea, and creatinine, were determined using Erba diagnostic kits and analyzed with an Erba semi-automatic biochemical analyzer (Erba Mannheim, India).

Experimental animals

Healthy *Wistar* rats of both sexes, weighing 180 ± 20g, were used in this study. The animals were acclimatized for seven days in the animal facility under controlled environmental conditions with a temperature of 25 ± 1°C, appropriate humidity, and a 12-hour light/dark cycle. Rats had free access to water and were housed under standard laboratory conditions at the Department of Pharmacology, Hanoi Medical University.

2. Methods

In the LPS-induced thrombosis model, coagulation was experimentally triggered in *Wistar* rats by intravenously injecting lipopolysaccharide (LPS) at a dose of 3 mg/kg, administered slowly over three minutes through the tail vein.[11,12]

The rats were randomly divided into five groups (n = 10 per group) as follows:

- Group 1 (Sham): received distilled water orally and physiological saline intravenously.

- Group 2 (Vehicle-treated LPS-induced thrombosis): received distilled water orally and LPS 3 mg/kg intravenously.

- Group 3 (Rivaroxaban-treated LPS-induced thrombosis): received rivaroxaban 3 mg/kg orally for seven consecutive days, followed by intravenous injection of LPS 3 mg/kg.

- Group 4 (Tri Bao Hoan-treated LPS-induced thrombosis): received Tri Bao Hoan 0.12 pill/kg/day (*equivalent to the estimated human clinical dose, calculated using an interspecies conversion factor of 6*) orally for seven consecutive days, followed by LPS 3 mg/kg injection.

- Group 5 (Tri Bao Hoan-treated LPS-induced thrombosis): received Tri Bao Hoan 0.36 pill/kg/day (*three times the equivalent human dose*) orally for seven consecutive days, followed by LPS 3 mg/kg injection.

All rats received the test product or distilled water daily for seven days before LPS administration to induce thrombosis. On the seventh day, one hour after the final oral dose, rats in Group 1 were injected intravenously with physiological saline, while rats in Groups 2 – 5 received LPS (3 mg/kg) via slow tail vein injection over 3 minutes.

Blood samples were collected four hours after LPS injection to assess coagulation, haematological, and biochemical parameters, including platelet count; prothrombin time (PT), prothrombin activity (PT%), and PT-INR; activated partial thromboplastin time (aPTT) and aPTT ratio (sample/control); fibrinogen concentration; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels for hepatic injury assessment; and serum urea and creatinine concentrations for renal function assessment. All parameters were compared across the experimental groups.

Data analysis

Data were analyzed using SigmaPlot 12.0 (SYSTA Software Inc., Richmond, CA, USA). All data are expressed as the mean ± SD and analyzed by Student's t-test or one-way ANOVA followed by the post hoc Student-Newman-Keuls test. $p < 0.05$ was considered statistically significant.

III. RESULTS

1. Anticoagulant effect of Tri Bao Hoan in the LPS-induced thrombosis model

The anticoagulant effect of Tri Bao Hoan in rats with LPS-induced thrombosis was evaluated based on several coagulation parameters, including platelet count, fibrinogen concentration, prothrombin time (PT), and activated partial thromboplastin time (aPTT).

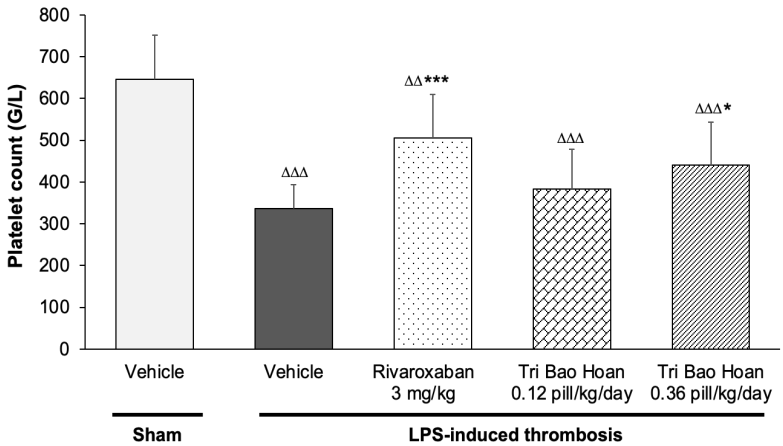

Chart 1. Effect of Tri Bao Hoan on platelet count in the LPS-induced thrombosis model

*Data were represented as mean ± SD (n = 10). $^{\Delta\Delta}p < 0.01$, $^{\Delta\Delta\Delta}p < 0.001$ vs. sham rats; *p < 0.05, ***p < 0.001 vs. vehicle-treated thrombosis in rats*

In the LPS-induced thrombosis model, the platelet count in the vehicle-treated group was significantly decreased compared to the sham group ($p < 0.001$). Rats treated with rivaroxaban (3 mg/kg) showed a notable increase in platelet count compared with the vehicle-treated thrombosis group ($p < 0.001$). Platelet count did not differ significantly between the Tri Bao Hoan 0.12 pill/kg/day group and the model group ($p > 0.05$). However, Tri Bao Hoan at 0.36 pill/kg/day significantly increased platelet count relative to the vehicle-treated thrombosis group ($p < 0.05$) (Chart 1).

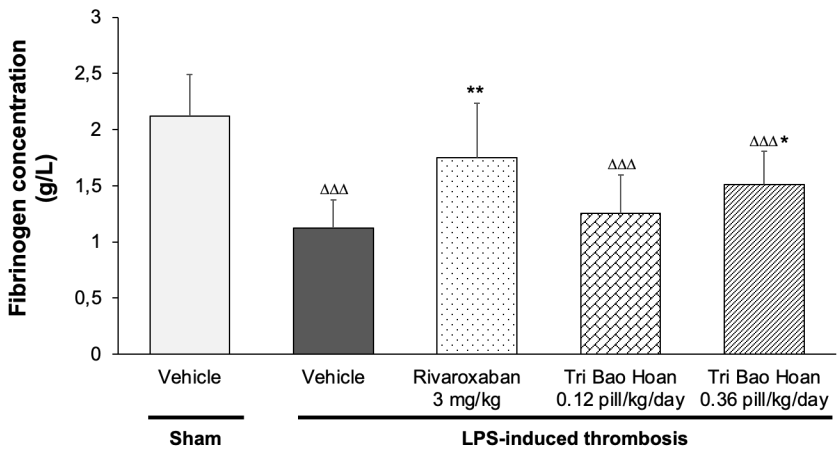

Chart 2. Effect of Tri Bao Hoan on fibrinogen concentration

*Data were represented as mean ± SD (n = 10). $^{\Delta\Delta\Delta}p < 0.001$ vs. sham rats; *p < 0.05, **p < 0.01 vs. vehicle-treated thrombosis in rats*

As shown in Chart 2, fibrinogen concentration in the vehicle-treated LPS group was significantly decreased compared with the sham group ($p < 0.001$). Rats treated with rivaroxaban (3 mg/kg) exhibited a significant increase in fibrinogen levels compared to the vehicle-treated thrombosis group ($p < 0.01$). Fibrinogen concentration did not differ significantly between the Tri Bao Hoan 0.12 pill/kg/day group and the model group ($p > 0.05$). However, Tri Bao Hoan at 0.36 pill/kg/day significantly increased fibrinogen concentration relative to the vehicle-treated thrombosis group ($p < 0.05$).

Table 1. Effect of Tri Bao Hoan on PT, PT%, and PT-INR

Operation	Treatment	PT (seconds)	PT%	PT-INR
Sham	Vehicle	15.25 ± 2.48	69.87 ± 24.98	1.34 ± 0.28
LPS-induced thrombosis	Vehicle	20.29 ± 2.06$^{\Delta\Delta\Delta}$	41.38 ± 5.26$^{\Delta\Delta}$	1.75 ± 0.18$^{\Delta\Delta}$
	Rivaroxaban	25.88 ± 3.15 $^{\Delta\Delta\Delta}$***	30.84 ± 4.67 $^{\Delta\Delta\Delta}$***	2.23 ± 0.27 $^{\Delta\Delta\Delta}$***
	Tri Bao Hoan 0.12 pill/kg/day	21.48 ± 2.54$^{\Delta\Delta\Delta}$	38.82 ± 6.66$^{\Delta\Delta}$	1.85 ± 0.22$^{\Delta\Delta\Delta}$
	Tri Bao Hoan 0.36 pill/kg/day	23.75 ± 4.56$^{\Delta\Delta\Delta}$*	34.97 ± 7.16$^{\Delta\Delta\Delta}$*	2.05 ± 0.40$^{\Delta\Delta\Delta}$*

*Data were represented as mean ± SD (n = 10). $^{\Delta\Delta}p < 0.01$, $^{\Delta\Delta\Delta}p < 0.001$ vs. sham rats; *p < 0.05, ***p < 0.001 vs. vehicle-treated thrombosis in rats*

As shown in Table 1, rats in the vehicle-treated LPS group exhibited a significant prolongation of PT, an increase in PT-INR, and a decrease in PT% compared with the sham group ($p < 0.01$). The rivaroxaban-treated group (3 mg/kg) showed a further prolongation of PT, an increase in PT-INR, and a reduction in PT% compared with the vehicle-treated thrombosis group ($p < 0.001$). PT, PT-INR, and PT% did not differ significantly between the Tri Bao Hoan 0.12 pill/kg/day group and the model group ($p > 0.05$). However, Tri Bao Hoan at 0.36 pill/kg/day significantly prolonged PT, increased PT-INR, and reduced PT% compared with the vehicle-treated thrombosis group ($p < 0.05$).

Table 2. Effect of Tri Bao Hoan on aPTT and aPTT ratio

Operation	Treatment	aPTT (seconds)	aPTT ratio (sample/control)
Sham	Vehicle	17.41 ± 2.76	0.65 ± 0.10
LPS-induced thrombosis	Vehicle	23.03 ± 3.49$^{\Delta\Delta\Delta}$	0.85 ± 0.13$^{\Delta\Delta\Delta}$
	Rivaroxaban	29.50 ± 4.89$^{\Delta\Delta\Delta}$**	1.09 ± 0.18$^{\Delta\Delta\Delta}$**
	Tri Bao Hoan 0.12 pill/kg/day	25.33 ± 5.62$^{\Delta\Delta\Delta}$	0.94 ± 0.21$^{\Delta\Delta\Delta}$
	Tri Bao Hoan 0.36 pill/kg/day	27.69 ± 4.91$^{\Delta\Delta\Delta}$*	1.03 ± 0.18$^{\Delta\Delta\Delta}$*

*Data were represented as mean ± SD (n = 10). $^{\Delta\Delta\Delta}p < 0.001$ vs. sham rats; *p < 0.05, **p < 0.01 vs. vehicle-treated thrombosis in rats*

According to the data presented in Table 2, rats in the vehicle-treated thrombosis group exhibited a significant prolongation of aPTT and an increase in the aPTT ratio (sample/control) compared with the sham group ($p < 0.001$). Treatment with rivaroxaban (3 mg/kg/day) further prolonged aPTT and increased the aPTT ratio compared with the vehicle-treated thrombosis group ($p < 0.01$). aPTT and aPTT ratio did not differ significantly between the Tri Bao Hoan 0.12 pill/kg/day group and the model group ($p > 0.05$). In contrast, Tri Bao Hoan at 0.36 pill/kg/day significantly prolonged aPTT and increased the aPTT ratio relative to the vehicle-treated thrombosis group ($p < 0.05$).

2. Effect of Tri Bao Hoan on hepatic cell damage and renal function in rats with LPS-induced thrombosis

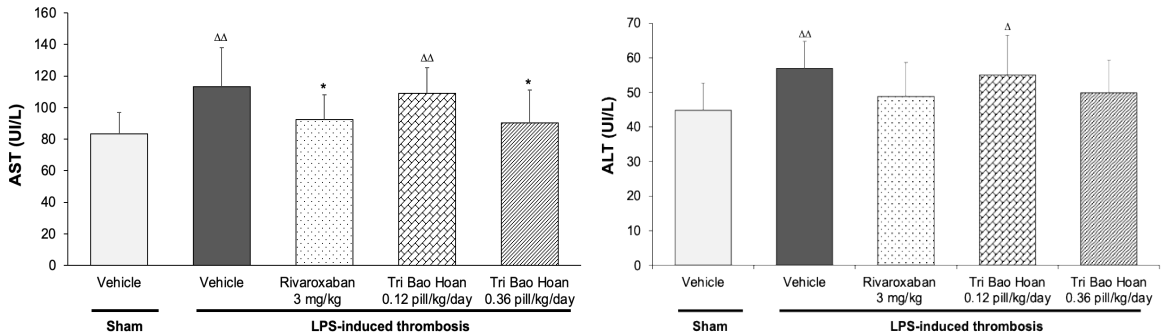

Chart 3. Effect of Tri Bao Hoan on serum AST and ALT activities in rats with LPS-induced thrombosis. *Data were represented as mean ± SD (n = 10). $^{\Delta}p < 0.05$, $^{\Delta\Delta}p < 0.01$ vs. sham rats; *p < 0.05 vs. vehicle-treated thrombosis in rats*

As illustrated in Chart 3, serum AST activity in the vehicle-treated LPS group was significantly increased compared with the sham group ($p < 0.01$). Treatment with rivaroxaban (3 mg/kg) and Tri Bao Hoan at 0.36 pill/kg/day significantly reduced serum AST activity compared with the vehicle-treated thrombosis group ($p < 0.05$), whereas Tri Bao Hoan at 0.12 pill/kg/day produced no statistically significant difference ($p > 0.05$).

Serum ALT activity in the vehicle-treated LPS group was also significantly elevated compared with the sham group ($p < 0.01$). However, rivaroxaban (3 mg/kg) and Tri Bao Hoan at both doses did not significantly alter ALT activity compared with the vehicle-treated thrombosis group ($p > 0.05$).

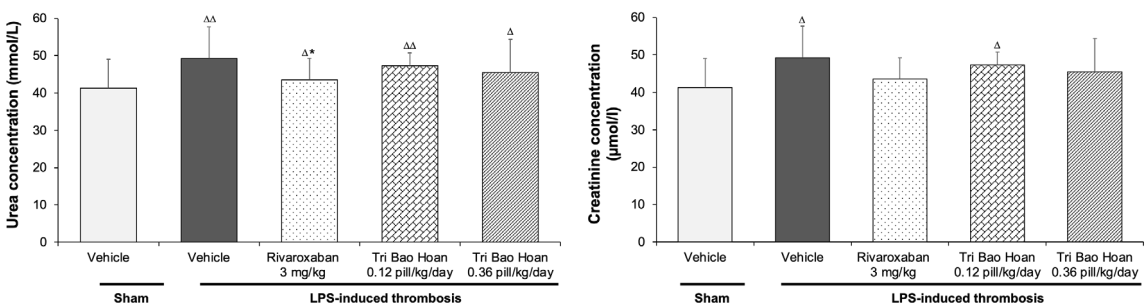

Chart 4. Effect of Tri Bao Hoan on serum urea and creatinine concentration in rats with LPS-induced thrombosis. *Data were represented as mean ± SD (n = 10). $^{\Delta}p < 0.05$, $^{\Delta\Delta}p < 0.01$vs. sham rats; *p < 0.05 vs. vehicle-treated thrombosis in rats.*

As shown in Chart 4, serum urea concentration in the vehicle-treated LPS group was significantly increased compared with the sham group ($p < 0.01$). Treatment with rivaroxaban (3 mg/kg) significantly reduced serum urea levels compared with the vehicle-treated thrombosis group ($p < 0.05$). In contrast, no significant difference in serum urea concentration was observed between the Tri Bao Hoan 0.12 and 0.36 pill/kg/day groups and the vehicle-treated thrombosis group ($p > 0.05$).

Serum creatinine concentration in the vehicle-treated LPS group was also significantly higher than in the sham group ($p < 0.05$). However, treatment with rivaroxaban (3 mg/kg) or Tri Bao Hoan at both doses did not significantly alter serum creatinine levels compared with the vehicle-treated thrombosis group ($p > 0.05$).

IV. DISCUSSION

In previous studies, LPS has commonly been used to induce a hypercoagulable state in experimental animals. It activates both the extrinsic and intrinsic coagulation pathways, leading to the consumption of coagulation factors in both cascades. Consequently, PT and aPTT are prolonged, accompanied by decreased platelet count and fibrinogen concentration due to their utilization in platelet aggregation and thrombus formation. Moreover, LPS also activates the fibrinolytic system, resulting in the degradation of fibrinogen and fibrin.[11,13] Therefore, LPS causes a decrease in platelet count and prolongs both PT and aPTT in rats. In the present study, the platelet count in the vehicle-treated group was markedly reduced compared with the sham group, while PT and aPTT were significantly prolonged. These findings indicate that the hypercoagulable model was successfully established using LPS in rats.

Rivaroxaban, a direct factor Xa inhibitor, is clinically used as an anticoagulant to prevent thromboembolic events, particularly in patients undergoing surgery.[3] According to the present results, platelet count in the rivaroxaban-treated group was significantly higher than in the model group. In addition, rivaroxaban markedly prolonged PT compared with the model group. These findings indicate that rivaroxaban exerted a preventive effect against thrombosis in the LPS-induced coagulation model. This result is consistent with the findings of Elisabeth Perzborn et al., who demonstrated the antithrombotic efficacy of rivaroxaban as a direct factor Xa inhibitor.[14]

The present study aimed to evaluate the anticoagulant effect of Tri Bao Hoan in an experimental thrombosis model in rats. The results showed that Tri Bao Hoan at 0.12 pill/kg/day had no significant anticoagulant activity. In contrast, the 0.36 pill/kg/day dose exerted an apparent anticoagulant effect by increasing platelet count and fibrinogen concentration, significantly prolonging PT and aPTT compared with the model group. The anticoagulant effect of Tri Bao Hoan may be attributed to the combined actions of its active herbal and biological ingredients.

Among these, nattokinase exerts anticoagulant effects by downregulating fibrin formation and inhibiting coagulation factors VII and VIII, thereby reducing thrombin generation and delaying clot development. In addition, it improves blood rheology and microcirculation by decreasing blood viscosity, which helps prevent hypercoagulability.[6] Similarly, lumbrokinase modulates both intrinsic and extrinsic coagulation pathways by inhibiting factors XIIa, XIa, and the activation of factor X, thereby reducing thrombin generation and prolonging PT and aPTT. It also protects vascular endothelium by attenuating oxidative stress and inflammation.[7] Both nattokinase and lumbrokinase are resistant to gastric acid and remain functionally stable in the

gastrointestinal tract, allowing for intestinal absorption and systemic bioactivity following oral administration.[6]

Radix Angelicae sinensis has also been demonstrated to possess anticoagulant properties. Its effects are mediated by inhibiting of thrombin generation and tissue factor expression, thereby reducing fibrin formation and clot stability. Lipophilic constituents such as ferulic acid and polysaccharides from *Angelica sinensis* exhibit potent anticoagulant activity, supporting the traditional use of this herb in improving blood circulation and preventing thrombosis.[8,9,15] *Flos Styphnolobii Japonici Imaturi* (immature flower buds of *Sophora japonica*) exhibits significant anticoagulant and antithrombotic effects primarily due to its flavonoid constituents, quercetin and isorhamnetin. These compounds inhibit thrombin and factor Xa activity, prolong PT and aPTT, and suppress tissue factor expression, thereby reducing fibrin formation and improving vascular function.[10,16,17] Collectively, these findings suggest that Tri Bao Hoan acts through multiple mechanisms to prevent hypercoagulability and thrombus formation, highlighting the synergistic contribution of its active constituents to its overall anticoagulant effect.

In addition to evaluating anticoagulant activity, the present study also assessed the effects of Tri Bao Hoan on hepatic cell injury and renal function. The liver plays a vital role in the body, performing multiple complex functions, particularly metabolism. Drug administration may cause hepatotoxicity and impair liver function. Therefore, evaluating the effect of a compound on hepatic function is essential when assessing its safety profile. Hepatocellular injury is typically evaluated by measuring the serum levels of liver-derived enzymes. Elevated levels of ALT and AST are commonly associated with drug-induced hepatotoxicity, reflecting hepatocyte damage.[18] It should also be noted that LPS-induced thrombosis or inflammation models can affect hepatic enzyme activity, as LPS triggers a systemic inflammatory response that may cause mild hepatocellular injury and transient increases in ALT and AST levels.[19] In addition, the kidneys are the primary excretory organs of the body. Renal parenchyma is highly susceptible to injury caused by both endogenous and exogenous substances. Since most drugs are eliminated through the kidneys, their administration may potentially induce nephrotoxicity and impair renal function.[18] The absence of hepatic or renal toxicity observed with Tri Bao Hoan suggests that its constituents are well-tolerated and do not interfere with normal metabolic or excretory pathways. Maintaining stable liver enzyme and renal biomarker levels under inflammatory and hypercoagulable conditions indicates that the formulation may possess protective or regulatory properties on these vital organs.

V. CONCLUSION

The study demonstrated that Tri Bao Hoan at 0.12 pill/kg/day did not exhibit significant anticoagulant effects in rats with experimentally induced coagulation. In contrast, the 0.36 pill/kg/day dose showed an apparent anticoagulant effect by increasing platelet count and fibrinogen concentration and significantly prolonging PT and aPTT compared with the vehicle-treated thrombosis group.

Administration of Tri Bao Hoan at both doses (0.12 and 0.36 pill/kg/day) did not cause significant changes in serum ALT activity, urea and creatinine concentration compared with the vehicle-treated thrombosis group. However, the 0.36 pill/kg/day dose significantly reduced AST activity compared with the model group. AST activity in rats treated with Tri Bao Hoan at 0.12 pill/kg/day showed no statistically significant difference compared with the model group.

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