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Bothrops jararaca snake venom: a reappraisal of its coagulant activity

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INTRODUCTION & AIM

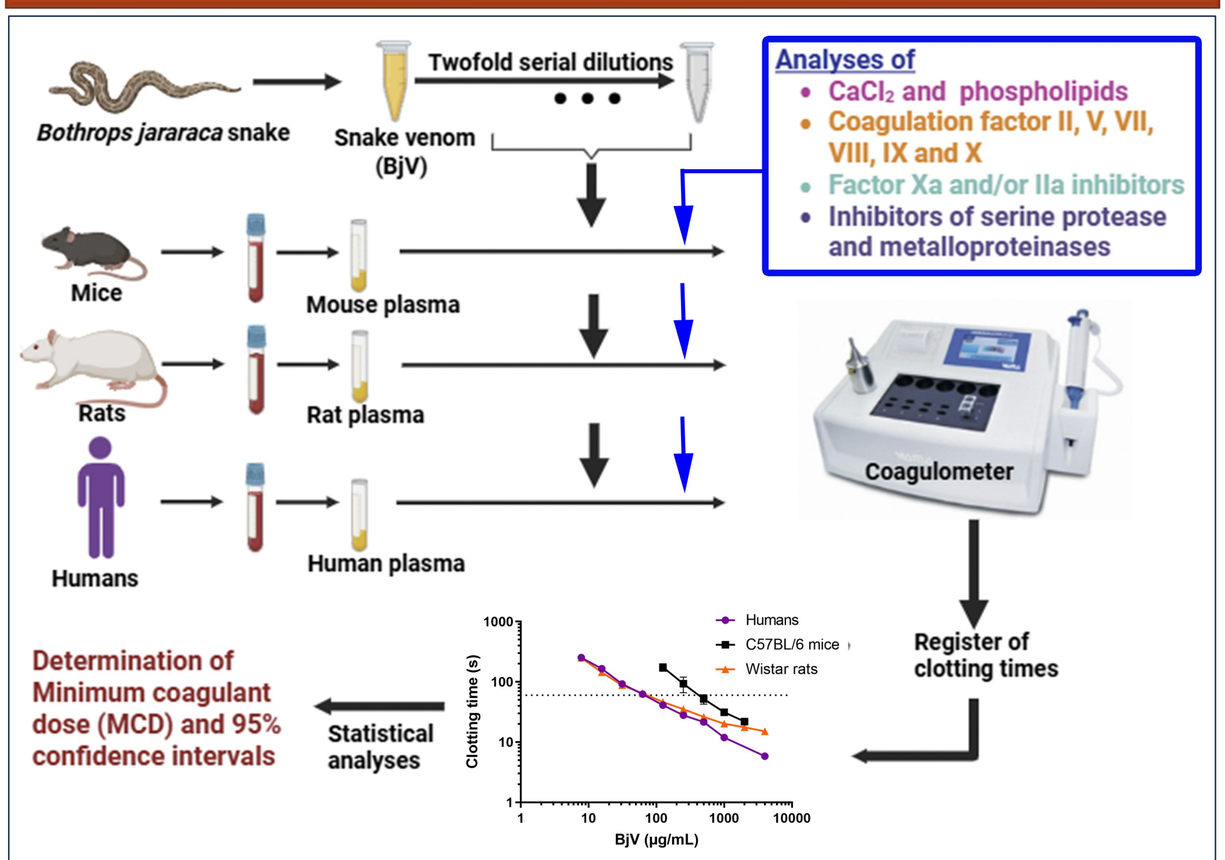
INTRODUCTION

Bothrops jararaca snake venom (BjV) contains toxins that activate and inhibit blood coagulation, induce thrombocytopenia, and promote endothelial dysfunction and secondary fibrinolysis in human and animal victims of snakebites.

AIM

To study the *in vitro* coagulant activity of BjV on human and murine plasmas.

METHOD



The coagulant activity of BjV was assessed in normal and coagulation-factor-deficient plasmas from humans, rats, and mice (C57BL/6, *F8*$^{-/-}$, *F9*$^{-/-}$, *Vwf*$^{-/-}$, and *Ap3b1*^{pe} (pearl mice)). The roles of calcium ions, phospholipids, and blood cells on the coagulant activity of BjV were evaluated. Pharmacological inhibitors were used to analyze the generation of factor Xa and/or thrombin, and their contribution to the coagulant activity of BjV.

CONCLUSIONS

1.Human plasma showed greater sensitivity to BjV than rat and mouse plasmas. Calcium ions and phospholipids influenced BjV's coagulant activity, and red blood cells and platelets further increased it. Pre-incubation of PPP with rivaroxaban and dabigatran demonstrated that BjV's activity in rodent plasmas primarily depended on prothrombin activation, while in human plasmas, it involved both thrombin-like enzymes and prothrombin activators.

2. This study highlights significant differences in BjV coagulant effects between human and rodent plasmas, underscoring the need to consider these disparities in comparative envenomation studies using animal models.

RESULTS & DISCUSSION

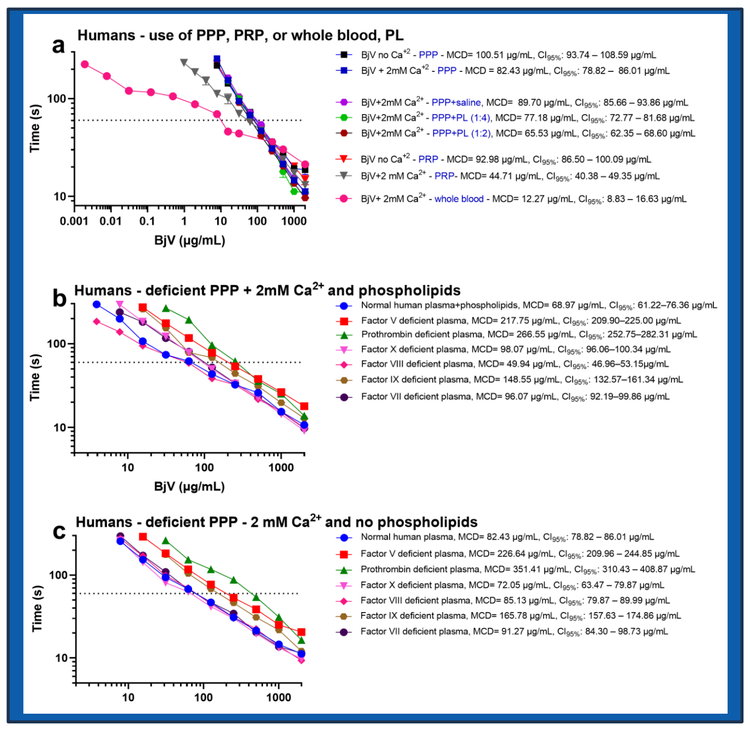


Fig. 1 - Minimum coagulant dose (MCD) curves of Bothrops jararaca venom (BjV) in citrated human plasma (PPP). BjV was two-fold serially diluted, and clotting times were recorded using a coagulometer. (a) The influence of calcium ions in the dilution solution (Tyrode's buffer) for BjV, and the presence of phospholipids, platelets (PRP – platelet rich plasma) and whole blood (including all blood cells) were evaluated on the coagulant activity of BjV. (b, c) The coagulant activity was further assessed using coagulation factor-deficient plasmas in the presence (b) or absence (c) of phospholipids in the clotting reaction. Each point in the plots represents the mean ± s.e.m. from at least three replicates. MCD values and 95% confidence intervals were estimated using inverse regression and bootstrapping.

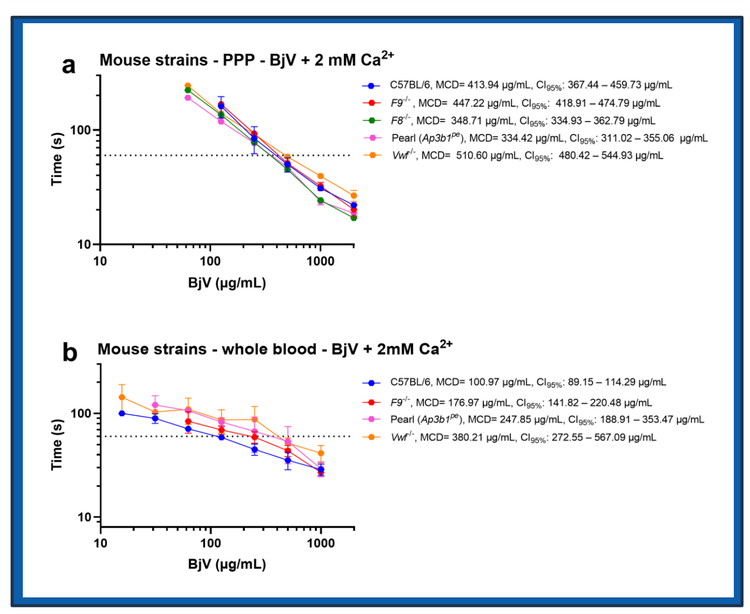


Fig. 2 – Minimum coagulant dose (MCD) curves of *Bothrops jararaca* venom (BjV) in citrated mouse plasmas (platelet poor plasma, PPP). BjV was two-fold serially diluted, and clotting times were recorded using a coagulometer. The influence of diverse mouse strains in the clotting activity in PPP (**a**) or whole blood (**b**) (containing all blood cells) were evaluated. Each point in the plots represents the mean ± s.e.m. from at least three replicates. MCD values and 95% confidence intervals were estimated using inverse regression and bootstrapping.

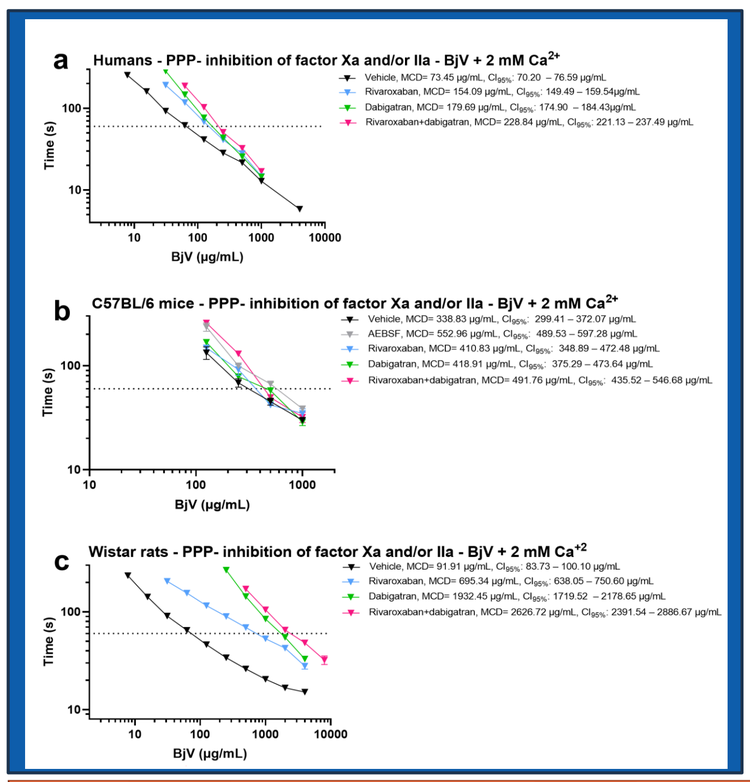


Figure 3 – Minimum coagulant dose (MCD) curves of *Bothrops jararaca* venom (BjV) in citrated plasmas (platelet poor plasmas, PPP) from humans (**a**), C57BL/6 mice (**b**), and Wistar rats (**c**). BjV was two-fold serially diluted, and clotting times were recorded using a coagulometer. (**a**) The influence of a factor-Xa inhibitor (rivaraxoban at 200 µg/mL, final concentration) and/or thrombin inhibitors (dabigatran at 40 µg/mL, final concentration) were evaluated on the coagulant activity of BjV. Each point in the plots represents the mean ± s.e.m. from at least three replicates. MCD values and 95% confidence intervals were estimated using inverse regression and bootstrapping.

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