Hemostatic disturbances and oxidative stress in experimental *Bothrops jararaca* envenomation: modulation by the natural antioxidant quercetin-3-rutinoside (rutin)

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INTRODUCTION

- **Snakebites are a major public health issue in Brazil** and *Bothrops jararaca* snakes are the principal causative agent of snakebites;
- *B. jararaca* envenomation causes **hemostatic disturbances**: thrombocytopenia, consumption of fibrinogen, and factors II e X and increased plasma levels of tissue factor (TF);
- **Oxidative stress occurs in patients bitten by *Bothrops* snakes, it is not neutralized by antivenom** and might be a indirect cause of the hemostatic disturbances;
- It is important to search for complementary therapies, such as the use of **rutin, a natural antioxidant that combats oxidative stress and inhibits PDI *in vivo***;
- Our aim was to characterize hemostatic disturbances, oxidative stress, as well as the protein expression of TF and PDI in mice injected with *B. jararaca* venom (BjV), and the possible modulatory activity of rutin on these parameters.

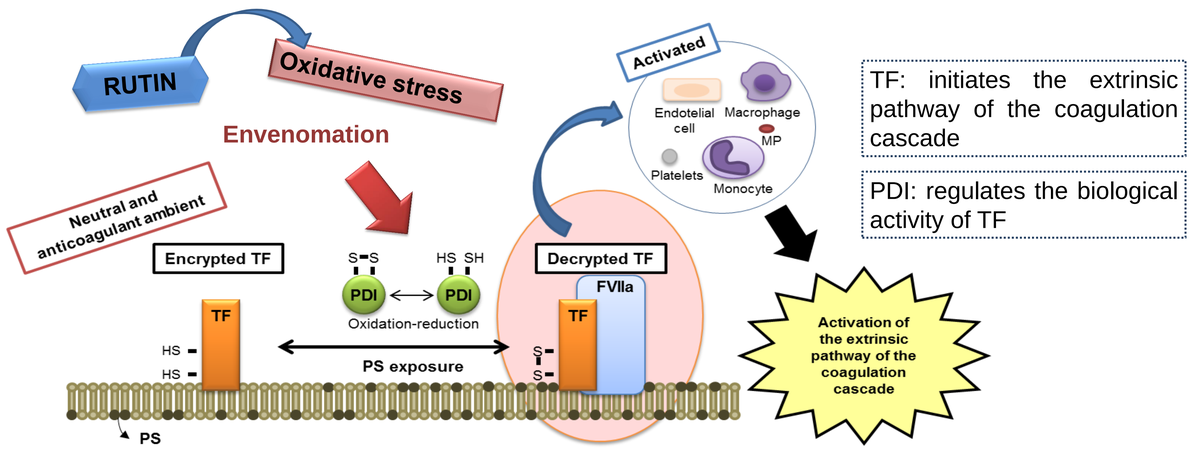
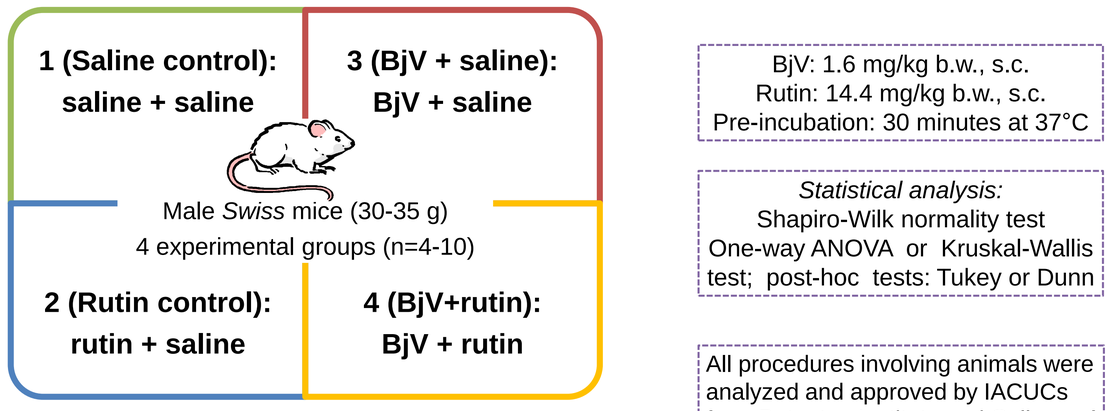


Figure 1: Representation of the possible influence of the envenomation on the decryption of TF by PS (phosphatidylserine) and PDI, which renders possible the binding of TF to factor VIIa. Modified: ref. Chen, Hogg, 2013.

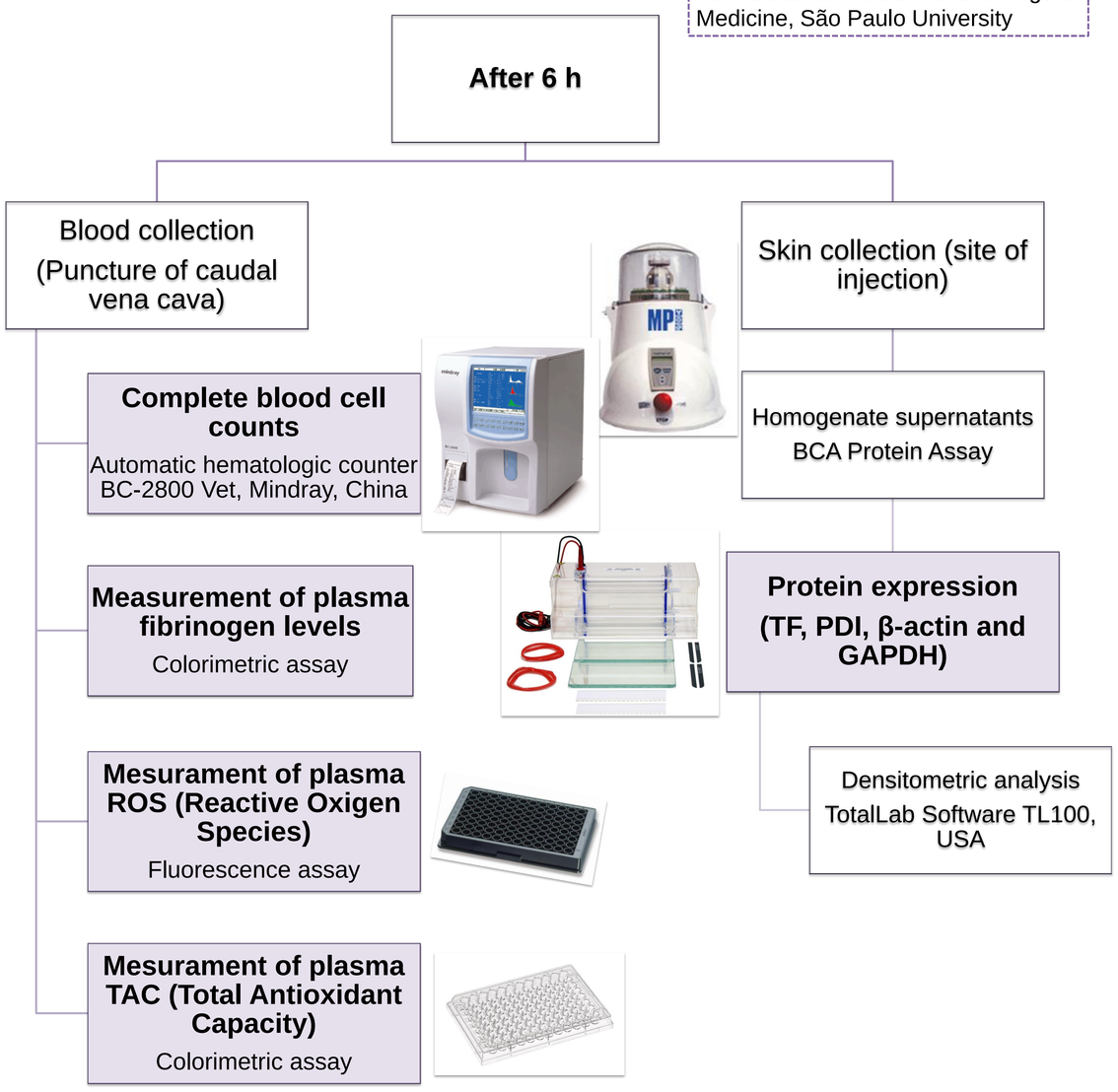
MATERIALS AND METHODS



BjV: 1.6 mg/kg b.w., s.c.
Rutin: 14.4 mg/kg b.w., s.c.
Pre-incubation: 30 minutes at 37°C

Statistical analysis:
Shapiro-Wilk normality test
One-way ANOVA or Kruskal-Wallis test; post-hoc tests: Tukey or Dunn

All procedures involving animals were analyzed and approved by IACUCs from Butantan Institute and College of Medicine, São Paulo University



RESULTS AND CONCLUSIONS

- ✓ ***Bothrops jararaca* envenomation induced important hemostatic disturbances**, such as thrombocytopenia, hypofibrinogenemia and an increase in the protein expression of TF.
- ✓ Raised ROS levels and decreased TAC levels indicate that ***Bothrops* envenomation leads to oxidative stress**.
- ✓ **Rutin restored ROS levels, acting as a promising antioxidant in the ancillary treatment for *Bothrops* snakebites.**

All data expressed as mean ± SEM.

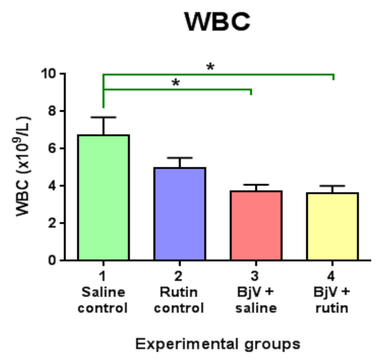


Figure 2: WBC counts, *p<0.05 (n=8-10/group).

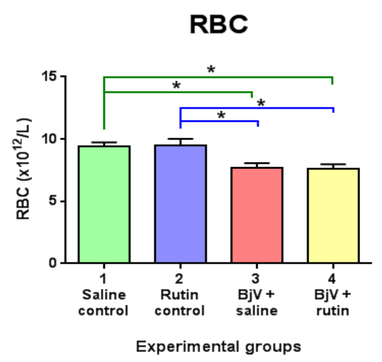


Figure 3: RBC counts, *p<0.05 (n=8-10/group).

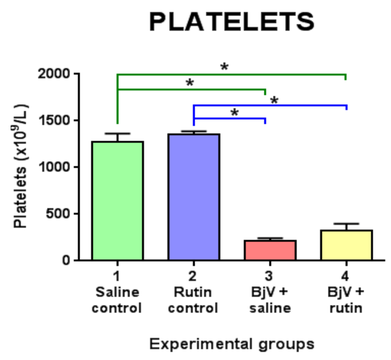


Figure 4: platelets counts, *p<0.05 (n=8-10/group).

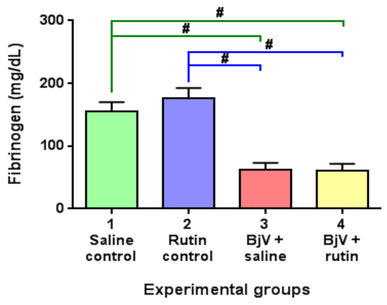


Figure 5: plasma fibrinogen levels, *p<0.001 (n=6-7/group).

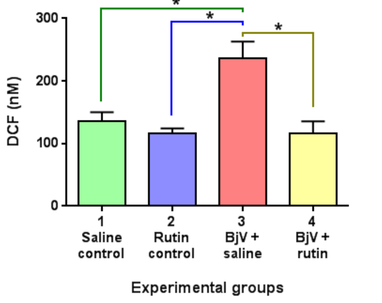


Figure 6: plasma ROS levels, *p<0.05 (n=5-6/group, triplicate).

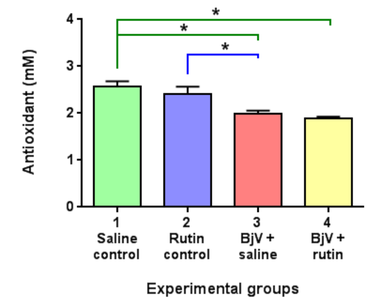


Figure 7: plasma total antioxidant capacity, *p<0.05 (n=4/group, duplicate).

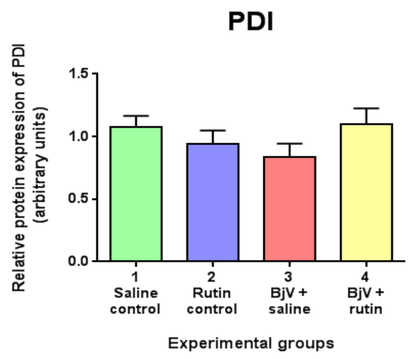


Figure 8: protein expression of PDI, p=0.127 (n= 5-7/group, triplicate).

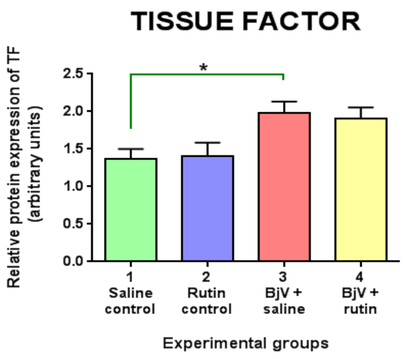


Figure 9: protein expression of TF, *p<0.05 (n= 5-7/group, triplicate).

The protein expressions of internal controls showed no statistically significant differences among groups. GAPDH (p=0.348) and β-actin (p=0.500).

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