
Effects of capsaicin on coagulation: Will this be the new blood thinner

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Abstract: *Background:* The effect of capsaicin (the active ingredient in *Capsicum frutescens* Linn. [Solanaceae] on coagulation was reported in several studies. Current research is being directed at elucidating if capsaicin has any effect on coagulation. *Objectives:* To investigate if either the ethyl acetate extract of *Capsicum frutescens* Linn. [Solanaceae] (CFE) or capsaicin (Fluka Biotechnika-CPF) on coagulation. *Methods:* The effects of ethyl acetate extract of *Capsicum frutescens* Linn. [Solanaceae] (CFE) and capsaicin (Fluka Biotechnika-CPF) was examined on rat hind paw. Ten animals in each of three treatment groups received 2.5, 5.0, 10 mg/kg (i.p.) capsaicin respectively. Data obtained were pooled and analysed using repeated ANOVA, in a general linear model with the CPSS software. *Results:* Compared to the control group, the mean INR was statistically significant ($P < 0.05$). *Conclusion:* Taken together, the use of capsaicin at therapeutic doses (2.5-10.0 mg/kg) may reduce thromboembolism without any clinically relevant alteration in platelets.

Keywords: *Capsicum Frutescens*, 'Chili', Ethylacetate Extract, Capsaicin, Coagulation

1. Introduction

Primary homeostasis is produced by the action of platelets and blood vessels (Petrovitch, 2002; Rubin, 2001). Secondary homeostatic mechanism is enhanced by the interaction of many plasma proteins known as "clotting factors" in various sequence to produce fibrin. Often, specific medications are used to enhance or inhibit individual step in coagulation cascade. Various phytochemicals have been shown to interact with these clotting mechanisms (Mohammed, 1986; Ariga, 1981; Boullin, 1981; Greuwald, 2000; Yuan, 2003; De Smet, 2002). The side-effects of uncontrolled use of these herbal remedies could be disastrous from severe bleeding episodes (Rose, 1990; Rowin, 1996; Fessenden, 2001); hepatotoxicity (Gebhardt, 1993), nephrotoxicity, and cardiopulmonary complications (Garges, 1998). *Capsicum spp.* constitutes a part of the oldest herbal medications known for more than 5000 years. Some of the beneficial effects of *Capsicum spp.* include anti-tumour and calminative effects, as well as their usefulness in the

treatment of acute and chronic pain (Weil, 1981). Recent study by Jaiarj *et al.* (1998) found that capsaicin acting on the heat sensitive vanilloid receptors had thrombolytic effects. Although this was a comment on the review of cardiovascular effects of capsaicin, the evidence was not strong enough. Jaiarj *et al.* (1998) also observed that individuals who consumed a large amount of *Capsicum* have lower incidence of thromboembolism. The objective of this study was to investigate the effect of capsaicin (which is the active vanilloid-sensitive agent in *Capsicum spp.*) on coagulation.

2. Materials and Methods

2.1. Animals

Experiments were performed on male Wistar rats (250-300 g). The rats were maintained under standard laboratory conditions of light, temperature, and relative humidity. The animals were fed with standard diet pellet and drinking tap water *ad libitum* and kept in the Biomedical Resource Unit of the University of KwaZulu-Natal, Durban.

2.2. Haematological Tests for Coagulation

In a pilot study, 10 Wistar rats (250-300 g) had oral treatments of 50 mg/kg of *Capsicum frutescens* fruit extract (CFE). The tissue's morphology was examined grossly from the oesophagus to the intra-abdominal organs.

In the definitive study, Wistar rats weighing 250–300 g were divided into two groups (A and B) of control and treated animals. They had similar demographics in terms of sex, age, and weight. All the animals were fed with standard diet pellet and drinking tap water *ad libitum*. Group A consisted of 10 untreated animals, which served as controls. Group B consisted of 3 treatment groups of 10 animals per group, treated with CFE, 2.5, 5.0, or 10.0 mg/kg *i.p.*, respectively. Following treatment, 1.5-2 ml blood was collected by intracardiac puncture, following deep halothane anaesthesia. The blood specimens were analysed for their platelets, as well as the internationalized normalised ratio (INR) of prothrombin time. In a parallel study, 3 groups of 10 Wistar rats per group were treated with 8 mg/kg of capsaicin extract daily for 2 weeks. From

each animal, 2 ml of blood was collected by intracardiac puncture, following deep halothane anaesthesia. The specimens were analysed for urea and creatinine.

3. Result

The results obtained show dose- and time-independent variations of INR in the treated groups, compared to the controls. The mean INR between the treated groups was statistically significant ($p < 0.05$), showing INR of 1 ± 0.1 , 1.4 ± 0.1 and 2.0 ± 0.3 , respectively, for the treated groups of CFE, 2.5, 5.0 and 10 mg/kg, respectively. Earlier pilot study showed macroscopic evidence of erosion, mucosal oedema, bleeding and ulceration, following oral administration of capsaicin extract at 50 mg/kg. In parallel studies, capsaicin did not show any renal complications in rats that were exposed to capsaicin treatments at therapeutic doses (8 mg/kg) daily for 2 weeks. The mean urea and creatinine were 5.4 ± 0.3 mmol/L and 45 ± 1 μ mol/L, respectively, in the rats.

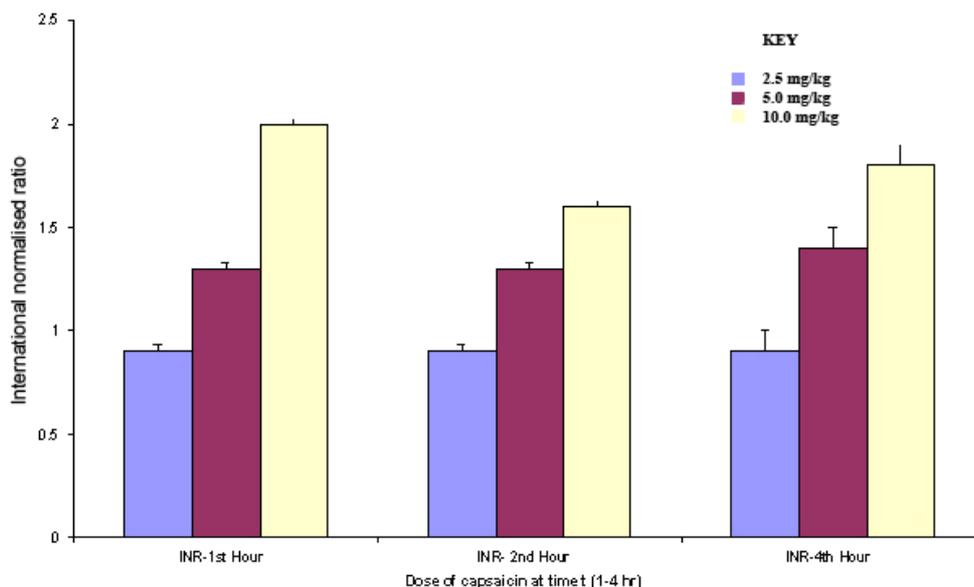


Figure 1. Shows dose-related increase in INR from 5-10 mg/kg *i.p.* capsaicin



Figure 2. Arrow showing gastric erosion following oral capsaicin at 50 mg/kg

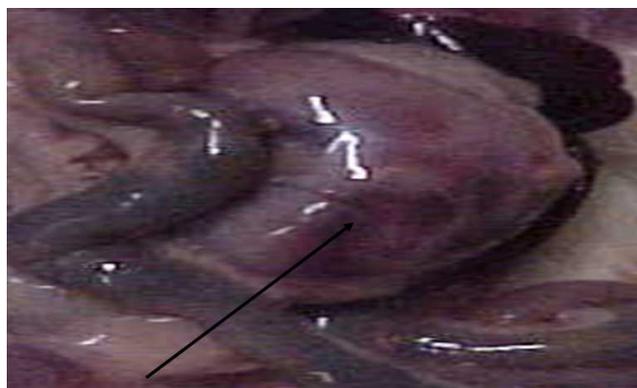


Figure 3. Arrow showing gastric ulceration from chemical burns following 50 mg/kg oral capsaicin.

4. Discussion

For a medication to impact on coagulation, it has to affect the Virchow's triad of the blood vessel, blood flow and blood viscosity (Virchow, 1856 and 1858, Brotman, *et al.*, 1981). The flow is influenced by the rheology of blood and the container. Considering Newtonian fluids, Fung reviewed the various factors influencing flow as represented below:

$$\text{Flow Rate} = (p_1 - p_2) \times d^4 \times \pi / 128 \times l \times \eta \text{ (Fung, 1993)}$$

Where p_1 = pressure at the entry of a vessel, p_2 = pressure at the exit of a vessel, and d^4 = double square of the diameter of the vessel, $p_1 - p_2$ = pressure gradient across a vessel, l = length of the vessel and the viscosity of the Newtonian fluid.

Considering this mathematical relationship, one will discover the interaction of the inner and the external diameters of the vessel, the pressure gradient in the flowing liquid, length of the vessel as well as the viscosity on the flow. To flow, the fluid has to overcome a resistive force, which is twice as great as the diameter of the vessel and frictional forces produced by viscosity. Although blood is a non-Newtonian fluid, the role of viscosity as well as vessel narrowing in the capillary and other microcirculation, is essential for the processes of diapedesis and platelet plugging in homeostasis (Chin, 2001; Byung, 1990). The platelets, microaggregates from white corpuscles and clotting factors, could be viewed as responsible for the viscosity, the pressure head being provided upstream by peripheral vascular resistance and the central pump of the heart, while the length and consistency of vessel calibre greatly relate the other variables in the formula.

Moreover, nature has provided a balance in the stream of innate anticoagulants such as heparin, Protein C, Protein S, antithrombin III, thrombomodulin, tissue factor pathway inhibitor among others. Likewise, there are procoagulant agents, such as factor V, VIII, FIX, FVII, VWF that prevent unopposed action of natural anticoagulants. Deficiencies of these agents could lead to a skewed pattern in favour of the opposing coagulation or anticoagulation pathways (Lipe B, *et al.*, 2011).

From time immemorial, man has always turned to nature to supplement inherited deficiencies; for example deficiencies leading to bleeding disorders. The knowledge of these phytochemicals is needed now than at any other time as the cost of healthcare becomes prohibitive in many parts of the world. Several phytochemicals have been found to increase the risk of unintentional bleeding. Besides, ginseng, ginkgo, ginger, garlic as well as St John's wart have been noted to cause bleeding in the individuals to whom they were administered. It is for this reason that the possibility of bleeding should be excluded in the patients who might be on these food additives and phytochemicals. The mechanisms of action of these agents are still open to further studies. Furthermore, their interactions with conventional anticoagulants (such as

warfarin), including the new oral anticoagulants –NOACs (dabigatran, rivaroxaban, and others), should be considered with a high index of suspicion. The question before us therefore is whether capsaicin could affect coagulation or not.

It is obvious that if capsaicin has to affect coagulation, it will have to influence one or more of the three notable variables of Virchow's triad; i.e., the flow, the vessel or the constituents. The role of capsaicin in the flow of blood has not been substantiated. Available evidence suggests that it may cause vasodilation, presenting as 'goose flesh' in Wistar rats following i.p administration. Jaiarj *et al.*, (1998) also observed that capsaicin does increase platelet adhesion. It is however debatable if this increase is statistically or clinically significant. Furthermore, the effects of capsaicin on clotting factors have received inconclusive evidence.

The standard methods of coagulation monitoring include measurements of bleeding time, prothrombin time (PT), or the measurement of Internationalised Normalised Ratio (INR). Bleeding time is the best estimate for platelets' qualitative function, but it lacks correlation with clinical bleeding, hence, the little value with its use. In addition, bleeding time estimates may be more difficult to assess in laboratory animals. But platelets count is useful for the estimation of quantitative function. However, the quantitative estimation of platelets has little to do with the function of platelets. The PT and INR are useful to estimate extrinsic and common pathways. The intrinsic and common pathways can be assessed by the partial prothromboplastin time (PTT), activated partial thromboplastin time (aPTT), and the activated clotting time. For the purpose of this study, the platelets counts, as well as the INR, were used as tests of extrinsic and common pathways. Intraperitoneal administration of capsaicin without any direct or intrinsic vessel injury was expected to affect intrinsic pathway, the extrinsic pathway, and the common pathway in a similar manner; hence the use of common indicators such as the platelets count and the INR.

The results obtained in this study show that platelets number was within normal range in the 'test' animal groups. Although platelet adhesion was found in the study by Jaiarj *et al.*, (1998), the present investigation could not document any platelet clumping, rouleaux formation or any increased adhesion in the 'test' animal groups. However, the trend of INR in the animals showed dose-dependent increase. This may reflect the tendency for capsaicin to influence the clotting factors through the common pathway, or the extrinsic coagulatory pathway. However, there have been reports of capsaicin affecting the release of Hageman factor-calcium. Calcium is a rate-limiting catalyst at various phases of coagulation (Stoelting *et al.*, 2002).

The discussion on coagulation and anti-platelet activity cannot be laid to rest without considering the role of prostaglandins in renal and gastro-intestinal functions. Inhibition of prostaglandin in the stomach and the kidneys has led to gastric ulcer or haemorrhage, and nephrotoxicity. This is because prostaglandin is a modulator of gastric

mucosal blood flow, and it is important for the maintenance of renal glomerular blood flow. Although INR is prolonged by capsaicin, renal function in a parallel study remained normal following prolonged exposure to capsaicin.

The effect of capsaicin on coagulation provides alternate non-antiprostaglandin mechanisms of thromboprophylaxis, without the inherent nephrotoxicity and gastropathy common with most currently used antithrombotic anti-platelet agents at therapeutic doses. Alternative non-oral and parenteral routes might improve the side-effect profile of capsaicin by the use of topical, subcutaneous, intramuscular, or as enteric-coated capsules.

Further studies are needed to elucidate the pharmacokinetic and pharmacodynamics interactions between capsaicin and the established oral (such as warfarin, dabigatran, apixaban, edoxaban and rivaroxaban), and parenteral (heparin and clexane) anticoagulants. Besides, the exact factor, or plasma proteins altered in the coagulation cascade by capsaicin is beyond the scope of the present study.

5. Conclusion

This study shows that capsaicin has dose-dependent prolongation on the INR. Platelet number appears to increase. This may be due to inhibition of platelet adhesion, or indirectly, due to haemoconcentration. This view supports the work of Jaiarj *et al.* (1998), which shows that capsaicin has antithrombotic effects. Unlike the report of Jaiarj *et al.* (1998), however, the present study suggests that the anti-thrombotic effect of capsaicin is related to its effects on the common and/or the extrinsic pathway, rather than any antiplatelet activity. Addition of capsicum to meals may achieve the required thromboprophylaxis, especially in the population at risk. However, high dose of oral *Capsicum frutescens* fruit extract (CFE) could lead to gastric erosion as seen in this study.

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