Novel antiplatelet properties of dietary cucurbitacins

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Cucurbitacins are naturally occurring tetracyclic terpenes, present in foods such as cucumber and pumpkin, which elicit a range of anti-tumour, anti-inflammatory and anti-atherosclerotic effects. These dietary compounds modulate cellular functions through a variety of mechanisms, including dysregulation of the actin cytoskeleton and disruption of integrin function. Integrin outside-in signalling and cytoskeletal rearrangements are critical for stable thrombus formation and clot retraction following platelet adhesion at the site of vessel damage. We investigated the effects of cucurbitacins on platelet function and thrombus formation using human washed platelets, platelet rich plasma and whole blood in *in vitro* platelet function assays.

We identified potent anti-platelet and anti-thrombotic effects of cucurbitacins B,E and I in human platelets. Treatment of platelets with cucurbitacins resulted in attenuation of platelet aggregation and fibrinogen binding evoked by ADP, TRAP6, collagen and CRP-XL. However, treatment with cucurbitacins did not significantly alter signalling events such as alpha granule secretion or mobilisation of intracellular calcium. We found that cucurbitacins potently inhibit integrin-mediated events, including adhesion and spreading on fibrinogen, fibronectin, collagen and laminin surfaces and cause a significant attenuation of clot retraction. Further investigation of cytoskeletal dynamics found treatment with cucurbitacins increased F actin polymerisation in a manner similar Jasplakinolide which has previously been shown to impair integrin activation, platelet spreading and clot retraction. The inhibitory effects of cucurbitacins on platelet integrin function and cytoskeletal dynamics resulted in the formation of highly unstable thrombi with reduced density under conditions of arterial shear.

Our research identifies, anti-platelet and anti-thrombotic effects of dietary cucurbitacins that are linked to dysregulation of platelet cytoskeletal dynamics and integrin activity.

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