## 1. Introduction

Snake venoms are a complex mixture of proteins and peptides exhibiting an array of biochemical and pharmacological functions [1]. These bioactive molecules have allowed for a trophic transition from a mechanical (constriction) to a chemical (venom) means of subduing prey [2] via the dysregulation of many homeostatic mechanisms simultaneously. Because venoms consist of 'usurped' regulatory compounds, many have also been subjected to detailed screenings in the search for novel compounds which may be utilized as biomedical tools and reagents [3e

[9]. Structur-

ally, disintegrins are classi ed based on their polypeptide length and number of disul de bonds [10]. Short disintegrins consist of 41e51 amino acid residues and 4 disul de bonds, whereas medium disintegrins are approximately 70 amino acids and have 6 disul de bonds. The vast majority of disintegrins that have been characterized and studied belong to this medium size class. The third group, long disintegrins, is composed of 84 amino acids and 7 disul de bonds. The fourth group, which consists of the homo- and heterodimeric disintegrins, has subunits of approximately 67 amino acids, including 10 cysteines which are involved in 4 intra-chain disul de bonds and 2 interchain cysteine linkages [10,11].

Despite the fact that disintegrins are relatively conserved, sig-

loop containing an RGD, KGD, MVD, MLD, MGD, WGD, VGD, KTS or RTS sequence[10,12e15]. Although the amino acid residues adja-



after 24 h incubation (both p  $\,$  < 0.001; Fig. 6). However, tzabcanin caused only a slight decrease in Colo-205 cell viability at concentrations of 1.75 mM and 3.5 mM (both p  $\,$  < 0.05) and at 14 mM

(p < 0.01); 7 mM tzabcanin also resulted in a decrease in cell survival, but this treatment level failed to reach signi cance (p > 0.05).

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Fig. 4.

high af nity to  $a_{IIb}b_3$  integrins, whereas RGDN show higher selectivity towards both  $a_5b_1$  and  $a_vb_3$  integrins [16,17,47]. Of the six disintegrins reported here, four contain an RGDW binding motif, and two, including tzabcanin, contain an RGDN binding region. Yet even with identical integrin-binding regions, structural discrep-

Similarly, the homodimeric disintegrin contortrostatin was found to lack cytotoxicity toward MDA-MB-435 cells in vitro [22]. However, recently Lucena et al. [30] showed that recombinant disintegrins r-virdistatin 2 and r-mojastin 1 induced apoptosis in approximately 20% of human pancreatic adenocarcinoma (BXPC-3) cells. Therefore, the slight decrease in Colo-205 cell viability in the presence of high concentrations of tzabcanin could be due to induction of apoptosis, or a loss of membrane integrity, ultimately leading to antiproliferative effects. On the other hand, the potent toxicity of crude venom towards both cell lines is likely due to the presence of LAAOS, SVMPs, and PLAS, which are abundant in C. s. tzabcan venom [51] and have been shown to exhibit a combination of cytotoxic and apoptotic activities [52e 54]. Similarly, Bradshaw et al. [38] also showed that C. s. tzabcan

Because many disintegrins have the capability to recognize an array of integrins, the relatively weak potency of tzabcanin suggest that this disintegrin may inhibit cell adhesion by binding to a more select group of integrins, leaving other receptors available for integrin-ECM interactions. Further, tzabcanin also contains an RGDN binding domain which has been shown to exhibit higher af nity to integrin  $a_v b_3$ 

[32] M.C. Brown, I. Staniszewska, L. Del Valle, G.P. Tuszynski, C. Marcinkiewicz,