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Snake envenomation represents a relevant public health crisis in Indian subcontinent. Even though, it is difficult to estimate incidence of snakebite, several reports claim 15,000 to 25,000 deaths and much more morbidity in India. Most accidents in India are inflicted by viper species such as *Echis carinatus* (EC) and *Vipera russelli* (VR). Viper venom is a complex mixture of enzymatic and non-enzymatic proteins, peptide toxins and small organic compounds. Viper bite is considered as subcutaneous/intramuscular injection of venom into the prey/human victims. Envenomation by viper species is characterized by rapid development of local manifestations such as edema, hemorrhage, blistering, dermonecrosis and myonecrosis. The systemic alterations induced by viper bite are renal malfunction, hemorrhage of vital organs, coagulation disturbances, hypotension and bradycardia. Till date, antivenom therapy is the only medically approved therapy currently available for the management of viper bite. It has proven successful in neutralizing systemically acting toxins and in reducing mortality rate. Nevertheless, the therapy has failed to offer protection against locally acting toxins owing to its high molecular mass which made extremely difficult to reach the envenomed tissues. Further an attempt to use low molecular weight antibody fragments such as F(ab)_2 and Fab was also found ineffective. In addition, the therapy is also associated with several limitations including anaphylaxis, serum sickness and poor availability in the distant regions. As a consequence, there is a need for designing focused and new therapeutic strategies to neutralize the dangerous local tissue destruction and life-threatening systemic toxicities of viper bite.

The mounting evidence on pathomechanism of viper venom suggests that Snake venom metalloproteinases (SVMPs) and Snake venom hyaluronidases
(SVHYs) are the major culprits of local tissue degradation. These are often called “Spreading Factors” as they facilitate diffusion of target specific toxins into the tissues of prey/victim by degrading the proteins and proteoglycans of basement membrane and connective tissues surrounding the blood vessels. SVMPs have been reported to reside close to capillary vessel through their disintegrin like and cysteine rich domains and hydrolyse the basement membrane components followed by disruption of blood vessels. Damage to the basement membrane, microvasculature, muscle fibres and nerves by the hemorrhagic SVMPs seems to be responsible for the poor regenerative response of muscle tissues. Further, microvasculature damage hinders the arrival of phagocytic cells to remove necrotic debris and also affects the provision of nutrients and oxygen supply required for tissue regeneration. In addition, deficient axonal regeneration is also likely to contribute to the poor regenerative outcome. This may end up with permanent tissue loss and deficient functional recovery, a common consequence of severe viper envenomation.

Thus, inhibition of these enzymes can be considered as a rate limiting step in the management of snakebite as it not only inhibits the local tissue damage, but also extends the survival time of the victim. In view of this, the venom researchers are much more focused on in situ administration of SVMPs and SVHYs inhibitors as an additional therapy to halt the progress of local tissue damage. Thus far, several studies independently reported the inhibition of SVMPs and SVHYs by different bioactive molecules, chelating agents and synthetic molecules. However, no studies claim a common inhibitor for SVMPs and SVHYs. In addition, the clinical trial of these inhibitors is highly complicated as it is difficult to have large number of snakebite victims to have enough statistical power. Instead, clinically approved compounds with inhibitory property against hydrolytic enzymes of viper venom could facilitate a
transit from preclinical to clinical scenario. In light of above, the present study is undertaken to evaluate the inhibitory potency of clinically approved compounds such as N-acetylcysteine (NAC) and citalopram derivative (DFD, 1-(3-Dimethylaminopropyl)-1-(4-fluorophenyl)-3-oxo-1,3-dihydroisobenzofuran-5-carbonitrile) against viper venom induced local manifestations.

Venom hydrolytic enzymes including SVMPs, SVHYs and Phospolipase A$_2$ (PLA$_2$) exhibit high degree of structural and functional homology with mammalian matrix metalloproteinases (MMPs), hyaluronidases and PLA$_2$s respectively. The inhibitory potential of NAC and DFD against mammalian enzymes is well demonstrated in several studies. NAC has been shown to inhibit MMP by interacting with active site zinc which block the catalytic cleft and thereby prevent the interaction with substrate. Further, recently it has been showed that citalopram can inhibit thrombin-induced platelet PLA$_2$ activation up to 24–35% and inhibition was found to be due to intercalation between the molecules of adjacent membrane phospholipids, thus causing changes in substrate availability for PLA$_2$. This prompted us to evaluate the potential of NAC and DFD to inhibit viper venom hydrolytic enzymes and venom induced pharmacological activities.