Snake venoms are complex mixture of proteins with various biological activities, such as neurotoxins, hemorrhagins, coagulants, anticoagulants and cardiotoxins[1]. The study of these venom proteins leads to our understanding of snakebite symptoms and also helps their rational treatments. In the last decade, many stimulants and inhibitors of platelet activation have been isolated from the snake venoms in our laboratory. In this paper, the effects of these venom proteins on platelet functions are reviewed. According to their biochemical properties and actions on platelets, they are classified into seven groups. The venom proteins of the first three groups accelerate or activate platelet aggregation, while those of the other four groups inhibit this process.

1. Thrombin-like Enzymes

Thrombin-like enzymes are found in most venoms of snakes from Crotalidae family[2,3]. Although they coagulate fibrinogen, their properties are found to be different from those of thrombin. Most thrombin-like enzymes release preferentially fibrinopeptide A, fail to activate Factor XIII and their coagulant activities are not inhibited by heparin and antithrombin III[4].

Three thrombin-like enzymes have been purified and their effect on fibrinogen and platelets were compared e.g. thrombocytin and batroxobin from B. atrox venom[5] and acutin from A. acutus venom[6]. The clotting activity of these venom proteins decreases in the following order: batroxobin > acutin > thrombocytin. However, their stimulatory effects on platelets are in the opposite order. A detailed comparison of the dose-response curve reveals that the aggregating activity of thrombin is $10^2$, $10^4$ and $10^5$ times more potent than those of thrombocytin, acutin and batroxobin, respectively. Platelet-activating potency of the thrombin-like enzymes is correlated with their effectiveness on the retractionility and elasticity of the clots[7].

The aggregating activity of thrombin-like enzymes could not be inhibited by indomethacin or platelet-activating factor (PAF) antagonists. Only small amount of thromboxane B$_2$ formed during platelet activation. However, ADP-scavenging system, creatine phosphate/creatine phosphokinase inhibited completely the aggregation caused by thrombin-like enzymes but not that by thrombin. Unlike thrombin, ADP-release mechanism induced by thrombin-like enzymes is dependent on the extracellular calcium[7]. Like thrombin, thrombin-like enzymes are serine
proteases, and their enzymatic and clotting activities can be inhibited by diisopropyl fluorophosphate, phenylmethanesulfonyl fluoride or tosyl-lysine chloromethylketone[2].

2. Noncoagulant, Nonenzymatic Inducers

Many noncoagulant platelet-aggregating proteins have been purified, and shown to be devoid of any recognized enzymatic activity found in the crude venoms. These include trimucytin isolated from T. mucrosquamatus venom[8] and triwaglerin isolated from T. wagleri venom[9]. These venom inducers cause aggregation, not agglutination, of platelets, because they do not clump the formaldehyde-fixed platelets. Their aggregating actions are calcium-dependent and accompanied with release reaction and thromboxane formation. Although indomethacin inhibits the release reaction and thromboxane formation, however, the aggregation is apparently not affected by indomethacin. This class of venom inducers cause "novel" aggregation which is thromboxane A₂-, ADP- and PAF-independent. The aggregation induced by triwaglerin is inhibited completely by mepacrine, imipramine and forskolin, and markedly by tetracaine and sodium nitroprusside. It was suggested that triwaglerin induced platelet aggregation possibly through phospholipase C-phosphoinositide mechanism[9].

Trimucytin caused morphological changes similar to thrombin or collagen even its action was thromboxane- and release- independent. Platelets exposed to trimucytin lost their discoid shape and developed irregular projections, which are devoid of organelles. Microtubules form a collar around the organelles which tend to shift toward the platelet center. Most α-granules and dense-bodies finally disappear and elements of tubular systems remain in the ballooned cytoplasm in the periphery of the aggregate[10].

3. Membrane-active Polypeptides

Membrane-active polypeptides are basic and devoid of enzymatic activity, existing in the snake venoms of Elapidae family. They induce a variety of pharmacological effects, such as muscle contracture, direct hemolysis and cytotoxic action. Cardiotoxin, a membrane-active polypeptide isolated from N. n. atra venom, potentiates platelet aggregation induced by ADP, thrombin, collagen and venom phospholipases A₂. However, cardiotoxin causes cell lysis at high concentrations. The potentiation of aggregation and increase of thromboxane B₂ formation are blocked by indomethacin and calcium of high (5 mM) or low (0.05 mM) concentration. Cardiotoxin does not potentiate thrombin-induced aggregation of p-bromophenacyl bromide-modified platelets, indicating activation of endogenous phospholipase A₂ is involved with its action. Arachidonic acid-induced platelet aggregation is not affected. So, cardiotoxin may augment the calcium-flux during the activation of platelets by the aggregation inducers and subsequently increase the activation of endogenous phospholipase A₂[11].

4. Phospholipase A₂ Enzymes

Platelet membrane phospholipids play important roles in blood coagulation and platelet aggregation. Phospholipases A₂ exist in almost every kind of snake venoms. Platelet