

## Modulation of Papain Structure by Interaction with Heparin Studied Through Molecular Dynamics

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Papain is an enzyme commonly used as model of human cysteine-proteases, such as, for example, those from cathepsin family. It has optimum activity at acid pH and presents low activity and higher inactivation probability at neutral and alkaline pH. At higher pH, the papain-heparin interaction inhibits the enzyme alkaline inactivation due to increase of  $\alpha$ -helical content. In this work, it was characterized the interaction between papain and heparin, a glucosaminoglycan model, using the following computational methods: Molecular Dynamic and the Generalized Simulated Annealing Docking. After long simulations of the complex, 100 ns, it was observed that the papain structure has a inherent dynamical characteristic: its two main domains oscillates periodically and alternately. The heparin binding site, found between the two main enzyme domains, showed to be a very dynamic region. The interaction with heparin imposes restrictions on the enzyme structure together with increase of  $\alpha$ -helical content. It was also observed that the interaction is responsible to maintain the alkaline pH papain structure very close to those observed at acid pH. The simulations suggest that papain can be modulated by glucosaminoglycans through a dynamic interference mechanism, which is able to maintain the enzyme functional conformation at alkaline or neutral pH. This work will contribute to the better understanding of the mechanisms involved in the cystein-proteases modulation by glucosaminoglycans, allowing the development of inhibitors of human proteases.