**Topic:** Chemistry of Phorbol Ester Toxicity: A Computer Modelling Approach

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**Abstract**

Phorbol esters are phytochemicals found in the Euphorbiaceae family, as the prime factors of toxicity in those plants. However, their degrees of toxicity vary from one compound to another, despite having closely similar structures.

The aim of this research project was to determine toxicity characteristics, reactivity and chemical detoxification methods for phorbol esters, using computer modelling. Chemical stability was evaluated by calculating single-point energy and optimization, with the use of Density Functional Theory. Prediction of sites of metabolism and intrinsic reactivity was done to ascertain biological stabilities of the substances. Selected phorbol esters and diacylglycerol were modelled by docking the ligands onto the binding site of protein kinase C- and analyzing the ligand-protein interactions, as well as carrying out bond rotation studies. However, the availability of only one computationally-prepared, protein-ligand complex in literature was a major limitation, as other phorbol-ester targets could not be successfully studied. Reactions between phorbol esters and a chosen detoxifying reagent were carried out using quantum mechanical calculations, to assess feasibility.

Findings from the study revealed that 12,13-phorbol esters are chemically more reactive, but biologically more stable than 13,16-phorbol esters. Although more toxic, the 12,13-phorbol esters would be easier to detoxify using chemical reagents than 13,16-phorbol esters. The toxicity of a phorbol ester is influenced by its ability to bind to the target protein, provide a hydrophobic cover on the binding site and its resistance to hydrolyze the ester linkages. Jatropha phorbol esters were found to be too big to fit into the binding pocket of the target protein under study and are predicted to interact with other phorbol-ester targets, by the same mechanism.

It can be concluded that computer modelling is an effective tool in determining the toxicity factors, stability and detoxification mechanisms of phorbol esters.