Molecular modeling of the inhibition of phospholipase A_2 by polyhydroxy phenolic compounds

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Introdução

Phosphlipases A_2 (PLA 2) are enzymes that act over cell membrane phospholipids and release arachidonic acid (AA), which is a precursor of pro-inflammatory eicosanoids (prostaglandins (PGs) and leukotrienes (LTs)).Non-steroidal anti-inflammatory drugs (NSAIDs) reduce the conversion of AA in PGs, but not LTs. The high levels of LTs are directly linked to adverse effects in the gastric and renal tracts as observed in patients that use NSAIDs. Some polyphenolic compounds have already been reported as presenting great capacity of PLA_2 inhibition. In this work we have tested five polyphenolic compounds on PLA_2 (1,3,5-trihydroxy benzene, 1,3-dihydroxy benzene, 2,4,6-trihydroxy acetophenone, 2,4-dihydroxy acethophenone and 2,6-dihydroxy acetophenone). The molecular modeling studies and the quantum-chemical calculations through DFT (Density Functional Theory), together with the experimental results obtained, make the proposition of a probable mechanism of enzyme inhibition possible.

Resultados e Discussão

In the concentration rate in which the inhibitors were tested, all compounds are able to inhibit the enzymatic activity of PLA_2. However, the compounds A, B and C (1,3,5-trihidroxi benzene, 1,3-dihidroxi benzene and 2,4,6-trihidroxi acetophenone, respectively) were more efficient in inhibiting PLA_2 than the other two acetophenone derivatives (compounds D and E, 2,4-dihidroxi acetophenone and 2,6-dihidroxi acetophenone, respectively). We can observe that the substrate concentration is very important in the kinetic behavior of PLA_2 and, probably, the increase of substrate concentration has provoked a cooperative conformational change in the enzyme that increased the substrate access to the active site. The IC_{50} calculated values (concentration able to inhibit 50% of the enzymatic activity) were: 6.39 µM, 6.68µM, 7.35µM, 16.16 µM and 17,54 µM, for compounds A, B, C, D and E, respectively. Once the catalytic site is well characterized and known, a very consistent

molecular model was obtained when compounds A to E were inserted inside the crystalline structure of PLA_2 from *C. atrox*. When the models were optimized through molecular mechanics utilizing the OPLS method. All compounds could be perfectly.

Conclusões

We have inferred that the presence of phenolic hydroxyl really plays an important role in the inhibition of the enzyme. Hence, the compounds A and B were the ones that showed the best results in the tests realized. The presence of an acetyl group in the polyhydroxy phenolic compounds C, D and E can reduce the efficiency in inhibition of the PLA_2 enzymatic activity. Thus the molecule potential is affecting the biological activities studied. The molecules with adequate potential (around 0.7 eV) and that have a non-sterically blocked hydroxyl cause the attenuation of both the enzymatic activity and the induction of edema formation by PLA_2.

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