STEM Scholars Program 2012

COMPUTATIONAL DRUG DESIGN

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ABSTRACT

Drug design is the process of finding or inventing new medications based on the knowledge of a biological target e.g. caspases (enzymes that degrade proteins and are involved in controlled cell death). From earlier research into caspases we believe caspases are inhibited competitively by some molecules known as flavonoids. These flavonoids interact with caspases with some affinity. But the strength with which the interactions occur was not optimal to function accordingly in cells. In other to acquire the necessary affinity between the caspases and flavonoids upon binding, we set out to study the interactions between flavonoids and caspases to enable us modify flavonoids to attain the desired affinity and work in a cell.

INTRODUCTION

The aim of this study was to look at the interaction between caspases and flavonoids using computer modeling software.

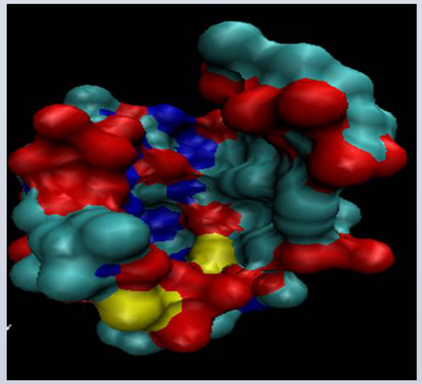
Caspases are cysteine aspartic proteases.

They cut proteins when a cysteine residue from them attaches to the second aspartic residue in a protein

C- because they use cysteine residues in the active site of the enzyme to cleave target proteins.

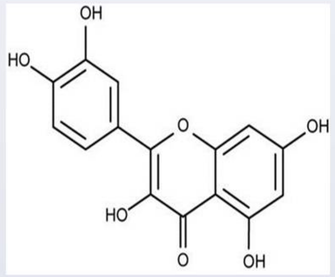
Asp- because they cleave the target protein next to the second aspartic acid in their chains.

ases- because of the cutting action it performs

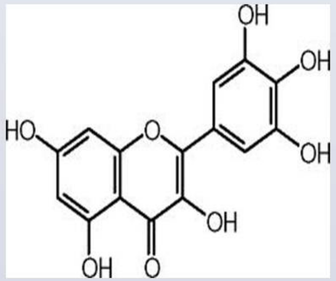


A visualization of caspase-3 using VMD

Flavonoids are a large family of compounds synthesized by plants that have a common chemical structure. They are plant pigments and are one of the reasons fruits and vegetables are so good for you. We used two flavonoids in our research; quercetin and myricetin



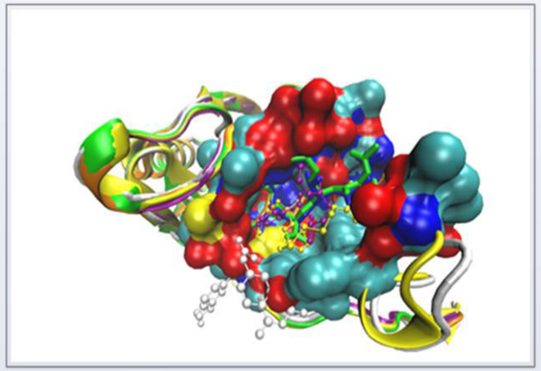
The structure of quercetin{flavonoid}



The structure of myricetin{flavonoid}

MATERIAL AND METHODS

VMD- (Visual Molecular Design) is a software program that is used for visualizing biological molecules. The software can be use to animate and analyze 3-Dimensional representations of various molecules. We used VMD to align six different crystallized structures of caspases-3 in order to test the hypothesis that they all posses the same active site.



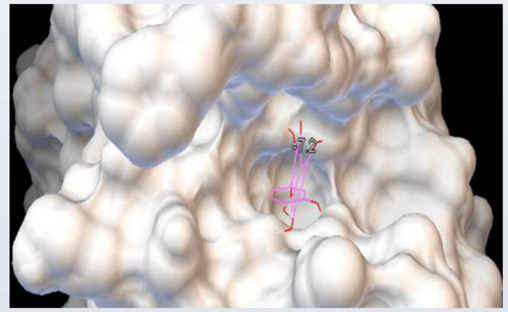
Six caspase-3 molecules aligned showing each one interacting with a ligand at the same position

Autodock is a molecular simulation computer software. It comprises of autodock 4 and autodock vina with a graphical interface, autodock tools. We used autodock tools to prepare the caspases and flavonoids for docking. Using Vina we run docking simulations of the flavonoids with the caspase-3. Vina gives us several values of internal energy from the interaction between the caspase and the flavonoids. Lowest value gives us the greatest caspase-flavonoid affinity.

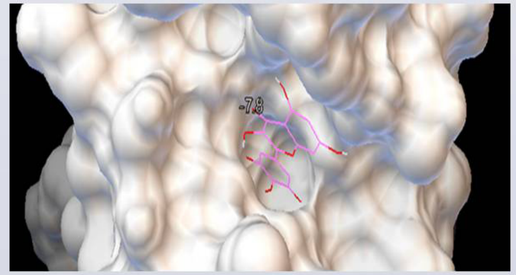
LIGAND	AFFINITY (kcal/mol)				
QUERCETIN	-7.2	-7.2	-7.0	-6.9	-6.6
MYRICETIN	-7.8	-7.7	-7.6	-7.4	-7.2

RESULTS

Caspases always interact with all the flavonoids at the same active site. The fact that the docking simulations gave us very low energy values indicates that the flavonoids can bind to the caspases with greater affinity. From these data we attempt to modify the flavonoid structures to obtain better affinity upon interaction.



Caspase-3 in complex with quercetin showing the energy



Caspase-3 in complex with myricetin showing the energy

REFERENCES

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