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Molecular Docking studies of Caspase -7 with the bioactive compound of *Erythroxylum Monogynum* Ecgonine, Hygrine, Erythroxidiol for Anti Inflammation

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***Abstract*: The most important compounds of the small tree *Erythroxylum monogynum* leaf extract are Ecgonine, Hygrine, Erythroxydiol were docked with the anti cancer protein like Caspase -7. The docking results showed best docking activity of compounds of *Erythroxylum monogynum* with this protein indicating the anti cancer activity.**

Key words : Erythroxylum monogynum, Caspase -7, Ecgonine, Hygrine, Erythroxidol, Anti inflammation.

INTRODUCTION

Erythroxylum monogynum Roxb (Roxburgh and Willium, 1978) is shrub or small tree about 7m to 9 m in the height. This species was placed under Sethia Section [1]. This was commonly found in India, Srilanka [2] America, Mayanmar. In India it mostly found in states like Kerala, Karnataka, Tamil Nadu and Andhra Pradesh. *Erythroxylum monogynum* shows great medicinal properties.The importanat bio active compounds of the *Erythroxylum monogynum* are Ecgonine, Hygrine, Erythroxidiol [3]. The Flavonoids contains antioxidant, antiplatelet, anti allergic, anti thrombic, anti inflammation properties [4],[5] The second largest common disease which is a major health burden is cancer [6],[7]. Plants are well used as medication for the cancer [8] From the natural resources about 60 percent of total anti cancer agents are derived the natural resources like plants as well as marine organisms and microorganisms [9]. According to the year 2009 the number of caspases identified are about eleven or twelve [10].The caspase activation leads to the cellular degradation without showing any effect on environment surrounded [11].They also play a great role in tumor supression,axon guidance[12] .They are very well known for the programmed cell death of cells that is generally called as the apoptosis.[13].The activation of csapases should be in the normal levels which much is required that only enough but on induction of heavy this leads to the over activation of the caspase and results in the over programmed cell death.as seen in neurodegenerative diseases.[14].Contrary to this the low dosage induction of the caspase lead to the low level natural cell deaths of infection which results the respective disorders[15]. Caspase -7 is a apoptosis-related cysteine peptidase, also known as CASP7, is a human protein encoded by the gene called *CASP7* , this is orthologs and have been notated in nearly in all the mammals for which genome complete data are available. Specific orthologs are also present in lizards, birds and teleosts. Two independent apoptotic signaling cascades are frequently distinguished, the extrinsic and intrinsic pathway. The extrinsic pathway is often triggered by binding of extracellular death receptor ligands such as Fas ligand (FasL) and TNF-related apoptosis-inducing ligand (TRAIL) to their respective transmembrane receptors. The death signal is transmitted to the cytosol by receptor clustering, which leads to recruitment and activation of caspase-8 and -10. On the other hand, DNA damage induced by UV irradiation and chemotherapeutic drugs triggers the release of mitochondrial cytochrome *c* into the cytosol, where the latter associates with the adaptor protein Apaf-1 to form the 'apoptosome'. This large (<700 kDa) protein complex mediates activation of caspase-9. Once activated, caspases-8,-9 and -10 process the executioner caspases-3 and -7. Mature caspases-3 and -7 cleave a large set of substrates ultimately resulting the charecterstic morphological and bio chemical hallmarks of apoptosis such as phospha tidylserine exposure,nuclear condensation and genomic DNA fragmentation. The maturation of proteolytic activity of the caspase-7 has also been seen under conditions of the inflamation. Interestingly, in macrophages stimulated with lipopoly saccharides (LPS) and ATP or infected with the Gram-negative pathogens *Salmonella typhymurium* and *Legionella pneumophila*, caspase-7 activation requires caspase-1 complexes named 'inflammasomes' rather than the caspase-8 and -9 protein complexes involved in apoptosis [16],[17]. Biochemical studies demonstrated that caspase-7 is a direct substrate of caspase-1 with maturation occurring after the canonical activation sites Asp23 and Asp198. In contrast to caspase-7, caspase-3 activation is not hampered in caspase-1 deficient macrophages, suggesting that activation of caspase-3 and -7 is differentially regulated during inflammation. This one of the best protein to analyse the anticancer activity or property of any compound choosen for the molecular docking studies.

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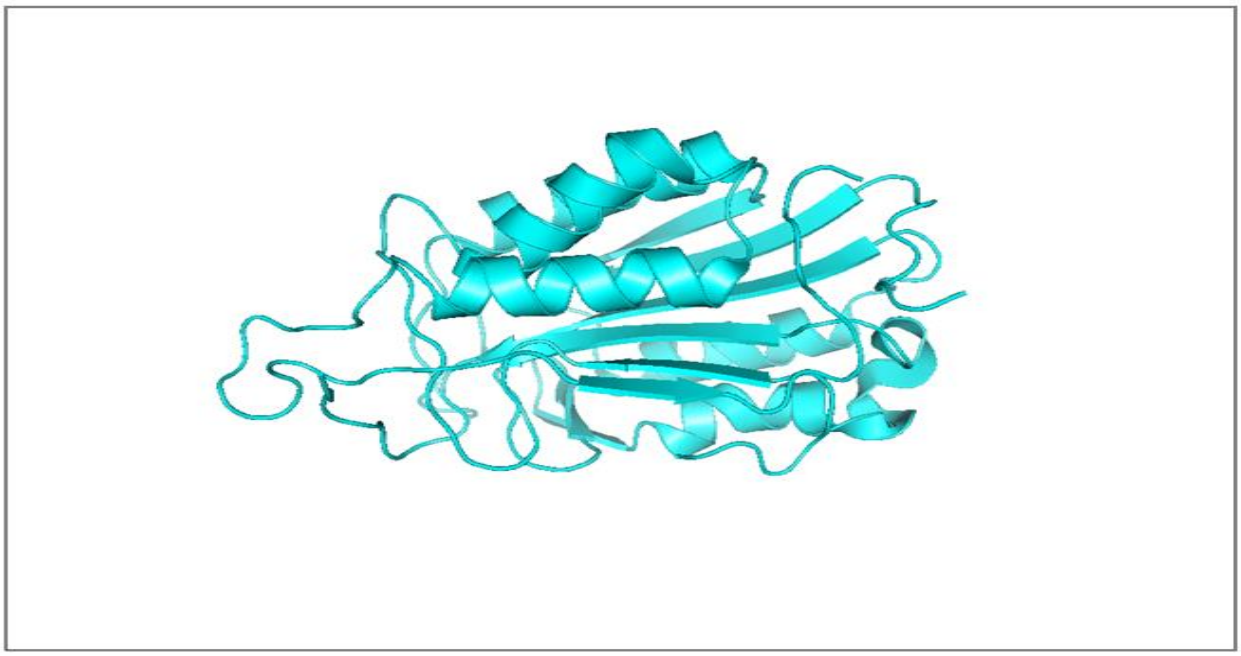

Figure 1: 3D Structure of the Caspase -7

Structures of Important Compounds of Erythroxylum monogynum : Ecgonine, Hygrine, Erythroxidol

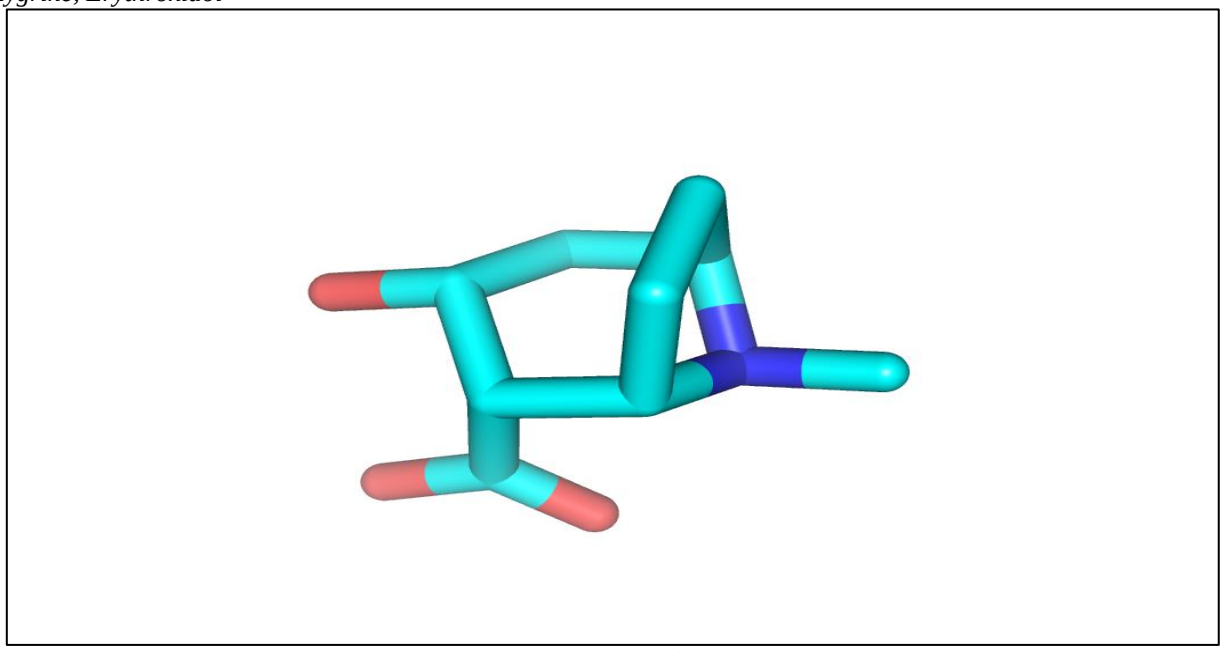

Figure 2 : 3D Structure of Ecgonine

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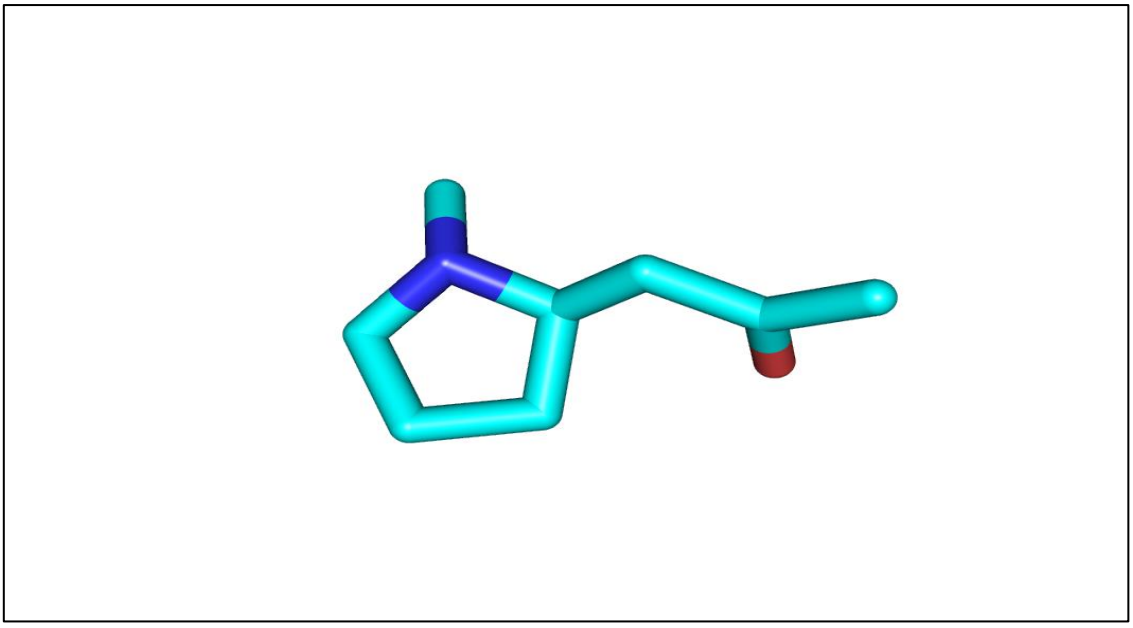

Figure 3 : 3D Structure of Hygrine

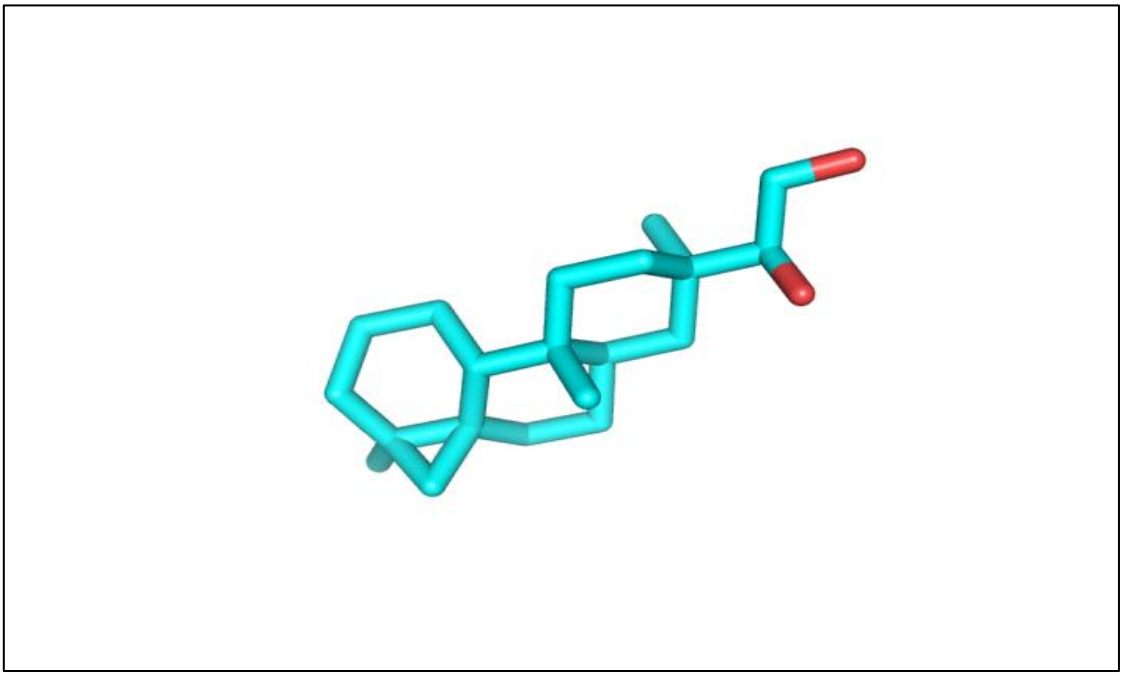

Figure 4 : 3D structure of Erythroxidol

METHODOLGY:

Molecular Docking method Caspase-7

It is apoptosis-related cysteine peptidase, also known as CASP7, is a human protein encoded the CASP-7 gene. CASP7 orthologs have been identified in nearly all mammals for which the complete genome data are available. Unique orthologs are also present in birds, lizards, and amphibians. Degradation of cellular components are ensured by activation of caspases .This took place in a controlled manner which carries out minimal effect on surrouds tissues proliferation, tumour suppression, cell differentiation, neural improvement, axon guidance and ageing are another roles of caspases PASS, and POCASA combined together to improve the prediction success rate [18]

a) Target protein preparation

Target selection is an important step and its correct choice is crucial to the success of drug discovery [19],[20].The Crystal structure of caspase- 7 (PDB ID:1K86) was downloaded from the protein data bank.

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b) Active site identification

Active site of caspase -7 was recognised by utilising the softwre called the meta pocket 2.0 server .This program MetaPocket 2.0 is a meta server to identify ligand binding sites on protein This is a consensus method, where the identified binding sites are of eight methods.They are

c) Docking method

The ligands, including all hydrogen atoms, were built and optimsed with Marvin sketch software suite. AutoDock is a molecular modeling simulation software. It is especially effective for protein-ligand docking. Inthese studies the interaction of the target and ligand observed. The best ligands screened were loaded in to auto dock and docking studies were carried out. Based on the binding energies and details from the histogram, the drug lead compounds were determined. The LIGSITE, Fpocket, GHECOM, ConCavity, Q siteFinder, SURFNE

Tble 1 : Determination of active site of the Caspase -7

Major active site
TRP_A^232^ PRO_A^235^ ARG_A^233^ TYR_A^230^ SER_A^234^ VAL_A^86^ ASN_A^88^ HIS_A^144^ ARG_A^187^ SER_A^231^ ARG_A^87^ GLY_A^89^ GLY_A^236^ GLY_A^85^ MET_A^84^ CYS_A^186^ GLN_A^184^ SER_A^239^ SER_A^224^ TRP_A^240^ THR_A^189^ PHE_A^282^ SER_A^277^ PHE_A^241^ VAL_A^269^ GLN_A^287^ ILE_A^288^ PRO_A^289^ ALA_A^270^ PHE_A^273^ SER_A^275^ LYS_A^286^ ASP_A^279^

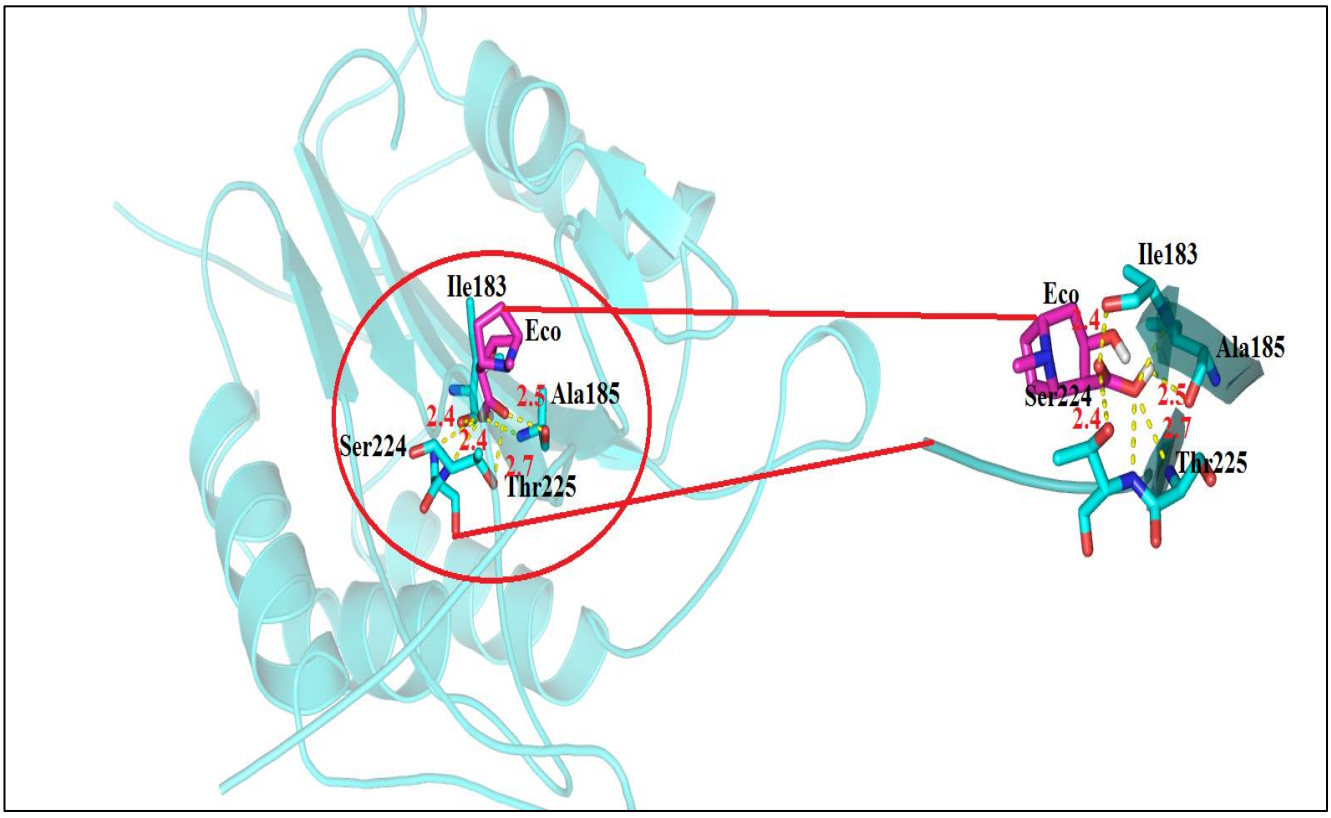

Figure 5 : Docking of Caspase -7 With the Ecgonine

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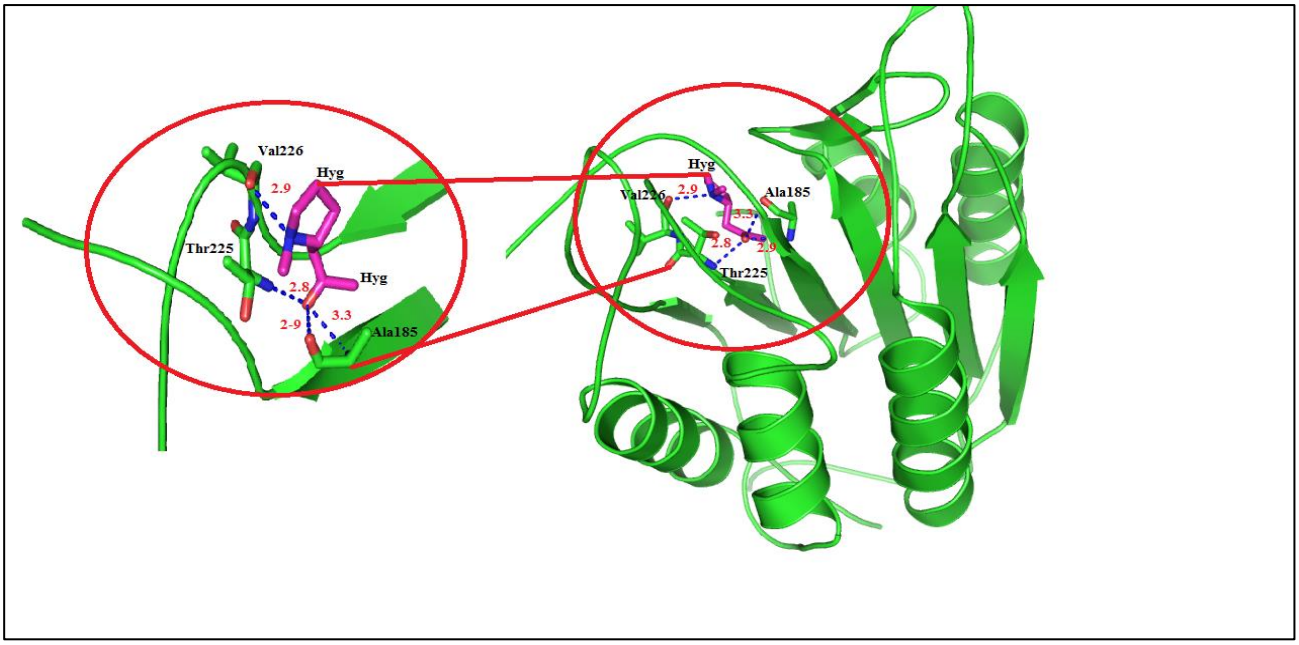

Figure 6: Docking results and interactions of Hygrine with caspase-7

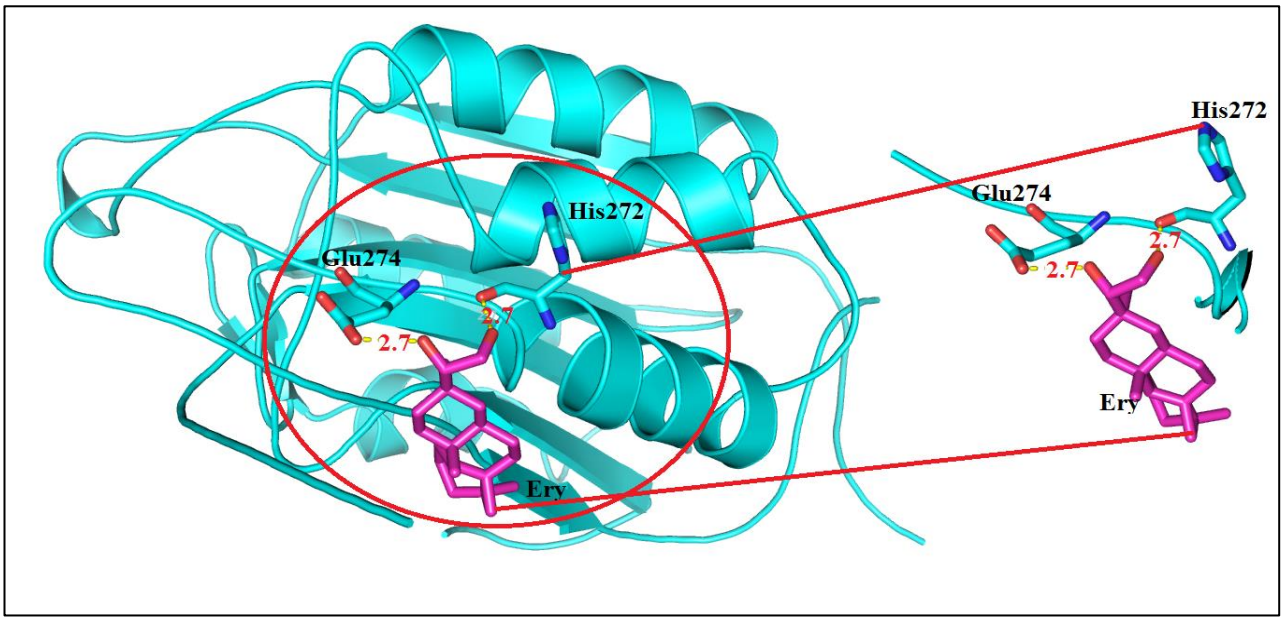

Figure 7: Docking results and Interactions of Erythroxydiol with caspase-7

RESULT:

The ILE183, ALA185, SER224, THR225, GLU274, HIS272 ILE183, ALA185, SER224, THR225 GLU274, HIS272,VAL226,of Caspase are important for strong hydrogen bonding interaction with the inhibitors. To the best of our knowledge ILE183, ALA185, THR225,GLU274,HIS272,VAL226 are conserved in this domain and maybe important for structural integrity or maintiaining the hydrophobicity of the inhibitor-binding pocket.

CONCLUSION:

The bioactive compounds of the *Erythroxylum monogynum* were docked with the antiinflammatory proeten like the caspase -7. The results gave good docking regions of possibility this indicates that the compounds of plant contains the anti inflammatory activities.

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