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MOLECULAR DOCKING STUDIES OF PERGULARIA *DAEMIA* BIOACTIVE COMPOUNDS WITH THERAPEUTIC TARGETS OF ARTHRITIS

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ABSTRACT

Natural remedies from medicinal plants are considered to be effective and safe alternative treatment for diseases. The present study was carried out to investigate the antiarthritic activity of *Pergularia daemia* through the docking simulation of specific target proteins with their bioactive compounds. The bioactive compounds of *Pergularia daemia* such as α-amyrin, β-amyrin, β-sitosterol, betaine, kaempferol, lupeol and quercetin whose structures were drawn using chemsketch software. The molecular targets of arthritis like Tumour necrosis factor(TNF-α), phospholipase-D, phospholipase-A_2 (sPLA_2), cyclooxygenases (COX-1 & COX-2) and crystallographic structures were obtained from PDB database for docking analysis by Hex 6.0. The molecular docking studies of these compounds showed that β-amyrin has energy value of docking and highest binding affinity with the targets and were considered to be best compared with ibuprofen in its binding affinity.

KEYWORDS: *Pergularia daemia*, α-amyrin, β-amyrin, β-sitosterol, betaine, kaempferol, lupeol and quercetin.

INTRODUCTION

Arthritis is one of the oldest diseases. It is a systemic inflammatory disease affecting mainly joints. It affects globally about 1-2% of the population. Arthritis is classified into rheumatoid arthritis and osteoarthritis. Gout is also a type of inflammatory disease caused by the deposition of uric acid crystals in joints and tissues. Conventional modern medicine is devoid of satisfactory treatment to severe cases of these diseases and to a large extent. These drugs have been treated symptomatically and the drugs used in the treatment have varying levels of toxic side effects. In the rheumatoid arthritis, a number of proinflammatory cytokines such as IL-1 and tumour necrosis factor-α (TNF-α) are responsible for the pathogenesis of RA. During the inflammation, it is characterized by the simultaneous destruction and healing of the tissues from the inflammatory process. The formation of important biological mediators called prostanoids, including prostaglandins, prostacyclin and thromboxane involves cyclooxygenase.[1] COX, an inducible enzyme abundant in activated macrophages and other cells at sites of inflammation catalyzes the formation of prostaglandins , the messenger molecules in the process of inflammation and thromboxane from arachidonic acid derived from the cellular phospholipid bilayer by Phospholipase A_2 (PLA_2). The suppression of inflammation may be by the inhibition of COX or prostaglandins. The non steroidal anti-inflammatory drugs become main COX inhibitors.[2] It is believed that such as lack of selectivity is caused by the dual insult of NSAIDS – direct irritation of the gastric mucosa and inhibition of prostaglandin synthesis by COX-1. Phospholipase A_2 (PLA_2) comprise a diverse family whose members share the capacity to hydrolyse the sn-2 position of membrane glycerophospholipids, releasing fatty acids and lysophospholipids. GroupII sPLA_2 has a proinflammatory role in arthritis. The mechanism of formulating medication for arthritis includes suppression of immune reactions, exerting anti-inflammatory action by one or more mechanisms such as inhibition of phospholipase A_2, phospholipase D, cyclooxygenases, lipoxygenases etc… *Pergularia daemia* belongs to a milky weed family of Asclepiadaceae, This plant has more magical application than medical application because it possesses a diverse potential for the treatment of various illnesses.[3] The most commonly found phytochemicals in the leaves are flavonoids, alkaloids, terpenoids, tannins, steroids and carbohydrates. The paste prepared from the leaves is mixed with castor oil and applied to the joints during inflammation, complaints of liver, spleen enlargement and the leaves also possess the hypoglycemic activity.[4] The leaf juice is also given for asthma and in combination with lime (or) ginger is applied on the rheumatic swellings. An oil prepared from the leaves possess medicinal property which is used in rheumatism, amenorrhea and dysmennorhoea.[5] The

dried leaves are used as antirheumatic agent and also for treating asthma, amenorrhea, dysmenorrheal, bronchitis, and whooping cough and also for healing of cuts and wounds. In the recent days, bioinformatics offers to find out the therapeutic targets for particular disease by using their software tools and it also used to identify the drugs from the bioactive compounds of medicinal plants by doing virtual screening. Molecular docking is a key tool in structural molecular biology and computer assisted drug design. The goal of ligand-protein docking is to predict the predominant binding model of a ligand with a receptor of known three dimensional structures.[6] The leaves and roots of *Pergularia daemia* were evaluated for the presence of various bioactive compounds and thus in this study the bioactive compounds α-amyrin(terpenoid),β-amyrin(terpenoid), etaine(alkaloid), β-sitosterol, kaempferol(flavonoid), quercetin(flavonoid), lupeol(terpenoid) were docked against the targets of arthritis such as Tumour necrosis factor(TNF-α), phospholipase-D,phospholipase-A_2(sPLA_2), cycloxygenases (COX-1 & COX-2).

MATERIALS AND METHODS

Insilico studies

Protein structure preparation

The crystal structures of the targets for arthritis like tumour necrosis factor-α (TNF-α), cyclooxygense-1, cyclooxygenase-2, phospholipase A_2 (sPLA_2 group II), phospholipase D whose crystallographic structures were downloaded from uniprot (www.uniprot.org) in the form of coordinate file and then the target proteins were converted to pdbqt format by open babel (version 10.1).

Ligand preparation

Bioactive compounds such as α-amyrin, β-amyrin, lupeol, β-sitosterol, betaine were drawn using ACD/chemsketch freeware version and coverted to pdbqt format by open babel (verson 10.1) as ligand for virtual screening.

Christopher lipinski's rule –of-five analyses helped to raise awareness about properties and structural features that make molecules more or less drug-like. The guidelines were quickly adopted by the pharmaceutical industry as it helped apply ADME considerations early in preclinical development and could help avoid costly late-stage preclinical and clinical failures. It predicts high probability of success or failure due to dryg likeness for molecules complying with 2 or more of the following rules. The drug structure properties have been analyzed under the rules of value which includes.[7]

- Molecular mass less than 500 Dalton
- High lipophilicity (expressed as log p less than 5)
- Less than 5 hydrogen bond donors
- Less than 10 hydrogen bond acceptors
- Molar refractivity should be between 40-130

Molecular docking

Molecular docking was performed using Hex (6.0) software downloaded from internet to identify the interaction between the target protein and ligand and also to identify the binding affinity between receptor and ligand.

RESULTS

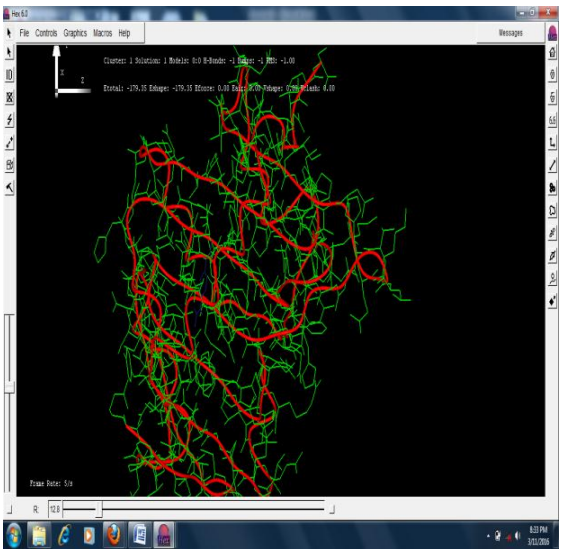
The target proteins of arthritis such as TNF-α, cyclooxygenase -1, cyclooxygenase-2, phospholipase A_2 (sPLA_2), phospholipase – D were docked against the ligands such as α-amyrin, β-amyrin, lupeol, β-sitosterol, betaine, quercetin.

Drug likeness determines whether particular molecule is similar to the known drugs or not defined as it is a complex balance of various molecular properties and stuructural features like hydrophobicity, electronic distribution and hydrogen bonding characteristics, molecule size and flexibility. This was done by Lipinski filters where the ligands (bioactive compounds of Pergularia *daemia)* were uploaded in pdbq file format and the results of drug likeness data were retrieved.

The hydrogen bond acceptor and hydrogen bond donor values of α-amyrin, β-amyrin, betaine, β-sitosterol, kaempferol, lupeol, includes 1, 1, 1, 1, 4, 1 whereas the quercetin has hydrogen bond acceptor value of 6 and hydrogen bond donor value of 4 respectively.

The molecular weights of the ligands such as α-amyrin, β-amyrin, betaine, β-sitosterol, kaempferol, lupeol, quercetin includes 408.0, 396.00, 409, 394.000, 292.0, 408.0, and 290.000 respectively.

Thus from the above docked results of all the ligands, the ligand β-amyrin showed highest binding energy value of -267.07 with phospholipase-D and log p value of 3.09 whereas the drug ibuprofen showed highest binding energy of -179.35 with COX-2 and phospholipase-D depicted in figure and log p value of 4. 42.



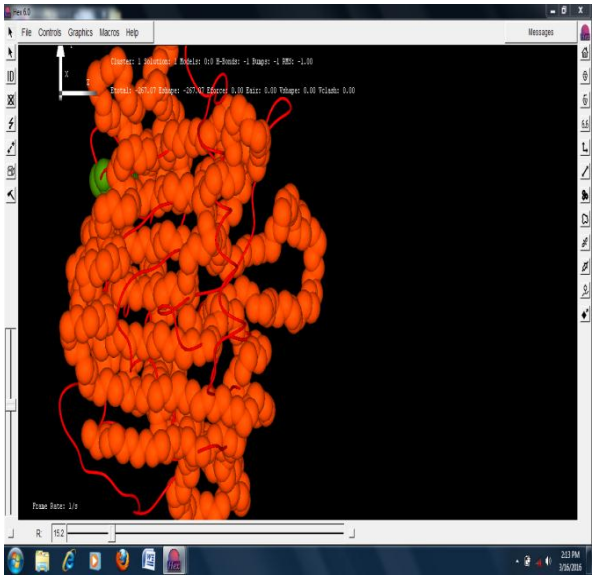


Fig illustrates the highest binding energy value of β-amyrin with phospholipase-D and ibuprofen with COX-1.

DISCUSSION

The current docking study for the evaluation of antiarthritic potential of *Pergularia daemia* on the target proteins of arthritis such as TNF-α, COX-1, COX-2, phospholipase A_2(sPLA_2) and phospholipase- D against the bioactive compounds of *Pergularia daemia* such as α-amyrin, β-amyrin, β-sitosterol, betaine, kaempferol, lupeol and quercetin where the β-amyrin showed the highest binding energy of -267.07 with phospholipase-D than that of ibuprofen and optimum log p value of 3.09 than that of ibuprofen. The same study was performed with different components from different plant[8] and reported that withaferin-A of withania somnifera has higher docking energy of -15.776 and optimum log p value of 3.85 which can be used as a anti-inflammatory drug[9] and reported the molecular docking studies on porcine phospholipase A_2 in which the caffeic acid served as an effective anti-inflammatory drug[10] and reported that the β-sitosterol having highest affinity with phospholipase A_2 and L-amino acid oxidase enzyme in snake venome which can be used against snake bites and[11] reported the ellagic acid of *Kiraginella reticulata* showed good dockinh energy and ligand efficiency with HIF-2α which is proved as an potent antiarthritic agent and[12] reported the eight non-synonymous deleterious mutations in ICAM1(intercellular adhesion molecule 1) protein leads to distruption of salt bridge between lys39 on ICAM1(chain A) and glu241 on LFA1(Chain B) which could reduce RA.

When the binding energy of the bioactive components was compared with ibuprofen, they were very much satisfactory and they support anti-inflammatory and antirheumatoid properties. In the previous studies the leaves of *Pergularia daemia* possess steroids which is responsible for anti-inflammatory activity[13] and doss *et al.*, (2012) reported that steroids, tannins, terpenoids, saponins of whole plant of *Pergularia daemia* contributes for anti-inflammatory activity, antispasmodic, analgesic property etc… and[14] reported the anti-inflammatory activity of leaves of *Pergularia daemia* in carrageenan induced paw edema in swiss albino rats and[5] reported the anti-inflammatory activity of *Pergularia daemia*. As the *Pergularia daemia* has the anti-inflammatory activity and thus to evaluate its antiarthritic potential through docking on receptor target proteins of arthritis such as TNF-α, COX-1, COX-2, Phospholipase A_2 and Phospholipase-D were docked against bioactive components such as α-amyrin, β-amyrin, β- sitosterol, betaine, kaempferol, lupeol and quercetin of *Pergularia daemia*. From these studies the β-amyrin can be used as a potential ligand for the treatment of arthritis based on the high docking energy, lesser log p value and hydrogen bond acceptor, this study proposes that β-amyrin can be treated as lead in the design of drug molecule against the target proteins of arthritis such as phospholipase-D and COX-2 when compared to other bioactive components (ligands).

CONCLUSION

The study concluded that the plant *Pergularia daemia* can be used in the treatment of arthritis. The bioactive compounds isolated can be purified and it can be used as a remedy for arthritis. In the present study the isolation and purification of the bioactive component was not performed which is the limitation of the study, instead of the structure was downloaded and research was carried out. Further research can be carried by isolating, purifying and elucidating the structure of the purified component and using the identified structure for docking study.

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