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Research Article

EVALUATION OF MEDICAL BENEFITS OF *COCCINIA INDICA* THROUGH *IN-SILICO* APPROACH

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ABSTRACT

Coccinia indica is a vine that majorly grows in tropical climates. It is commonly used in south Asian cuisine and is known to show various medicinal properties. Various parts of the plant are used as a medicine such as roots, fruits and leaves. It is commonly known to cure disease such as liver disease, asthma, ulcer, urinary infection, allergy, bronchitis. In the current study, we try to understand the hepatoprotective and anti-arthritis of the plant via *in-silico* docking methodologies. Firstly, the plant extract was subjected to GCMS analysis and the active components of the plant were obtained. The most reactive compounds amongst the result were chosen as ligands to conduct *in-silico* docking against the receptors of hepatoxicity and arthritis. Ligands like Pterin-6-carboxylic acid, 2r,3s-9-[[1,3-Dihydroxy-4-Fluoro-3-Butoxy]Methyl]Gu, D(17a)-Homo-C,18-dinorcard-20(22)-enolide, 14-hydroxy-17a-methylene-3-oxo-, (5.beta.) - Showed potential interaction against chosen receptors. *Coccinia indica* active compound has shown better binding affinity between hepatotoxicity and arthritis receptors. The potential active compound of *Coccinia indica* can be further studied in animal models to demonstrate its beneficial activities.

Keywords: *Coccinia indica*, hepatoprotective, anti-arthritis, *In-silico* docking, GCMS

INTRODUCTION

Coccinia indica, a perennial climber, has a high level of beta-carotene and is also often referred to as scarlet gourd, ivy gourd and kowai fruit and grows in tropical climate[1]. The leaves are about 5-10 cm long and wide and have 5 lobes. Our analysis aims to examine the possible behaviour of the *Coccinia indica* leaf extract by means of an in-silico method. *Coccinia indica* fruits and leaves are found to be used in many disease treatments, including anti-inflammatory, antipyretic, and analgesic operation. The fruits used to treat leprosy, fever, asthma, and jaundice in early medicine. The roots were found to be useful in treating scabies by the application of the root paste on the skin[2]. Through several experiments; it was found that the leaves show hepatotoxic nature and was also found that the *Coccinia indica* leaves work as a good agent against arthritis. Hepatotoxicity is associated to the liver damage which is generally caused due to a few drugs. The liver plays an important role in clearance of drugs and other toxins present in the body. Hepatotoxicity are caused due to drugs that causes acute or chronic liver damage[3]. Arthritis is a term used to describe the disorder that damages the joints, which have common symptoms such as joint pains, stiffness, swelling and decreased motion[4].

Gas Chromatography and mass spectroscopy, using two main techniques, gas chromatography (GC) and mass spectroscopy (MS) to analyze complex organic and biochemical mixtures, were performed. GC is used to distinguish volatile and non-volatile compounds; MS is used to provide structural details and to measure the compounds in the vapor state mixture. The specimen is passed through an inert gas and into a stationary phase called the column depending on the sample's volatility. Compounds are then collected by chromatographic column based on their spectra and transferred to mass spectroscopy. Based on their mass-to-charge ratio; compounds are identified and quantified by mass spectroscopy. For establish and test hypothesis, the *in-silico* method, which is a computational technique, is used. Such techniques include databases, modelling homology, data mining, data analysis, and other statistical approaches. This approach is mainly used to test and build the model in conjunction with the generation of *in vitro* data[5].

MATERIALS AND METHODS

Plant authentication

The *Coccinia indica* plant was authenticated by Prof. P. Jayaraman; the Director of Institute of Herbal Botany, Plant Anatomy Research Centre, Chennai, India. The authentication number is PRAC/2019/3961. The authenticated leaves where obtained and air dried in a dark room. The dried leaves where then grinded to a fine powder to obtain the leaf extract.

Gas Chromatography and Mass Spectroscopy

The leaf extract was then submitted for GCMS where the sample was run and different compounds present in the sample were obtained. GCMS works on the principle in which the mixture is separated by heat with the help of Helium. The compounds are identified by the mass of the molecules. The samples from the highest peak where taken and *In-silico* docking was done for those compounds. GCMS was carried out through Perkin-Elmer GC Clarus 500 system. The Gas chromatograph was with Mass spectrometer equipped with an Elite-I, capillary column fused with silica. The electron ionization energy of 70 eV and carrier gas Helium (99.999%) was used at constant flow rate of 1 mL/min. The injection volume of 2 µL was employed (split ratio of 10:1) with 250°C and 280°C Ion-source temperature. The oven temperature was from 110°C (isothermal for 2 min.), with an increase of 10°C/min, to 200°C, then 5°C/min to 280°C, ending

with a 9 min isothermal at 280°C. Mass spectra were taken at 70 eV; a scan interval of 0.5 seconds and fragments from 45 to 450 Da. Total. The relative % amount of each component was calculated by comparing its average peak area to the total areas, software adopted to handle mass spectra and chromatograms was a Turbomass.

Receptor Designing

The receptors for hepatotoxicity and arthritis which were reported to cause hepatotoxicity and arthritis in previous studies where used in the study. The PDB structures where acquired from Research Collaborator for Structural Bioinformatics (RCSB) protein data base. The PDB Ids of the receptors for hepatotoxicity are Apo Human Pregnane X Receptor- 1ILG, Nuclear bile acid receptor FXR-1OSH, Constitutive androstane receptor-1XNX, LXRalpha-5AVI, Nf-Kb-1NFK, Constitutive androstane receptor CAR/RXR heterodimer-1XVP. The PDB Ids of the receptors for arthritis are Interleukin-1 Beta- 1TWM, glucokinase regulatory protein complexed to fructose-1-phosphate- 4BB9, ABC transporter- 5NJ3, human TLR4 and hagfish VLRB.61-2Z62, Human milk xanthine oxidoreductase-2CKJ, Inactive Serum and Glucocorticoid- Regulated Kinase 1 - 2R5T, PDZ Domain Containing Protein 1- 2EEI, NLRP3 PYD- 2NAQ and Human phosphor ribosylpyrophosphatesynthetase- associated protein 39 - 2C4K.

Ligand Designing

The ligands where isolated from the highest peak from the GCMS results. These compounds were then used to study their interaction with the receptors. Each ligands canonical smile was obtained from PubChem database. The canonical smile was then pasted into Corina Molecular Network and their PDB structures where obtained. The ligand with their molecular formula, molecular weight and PubChem IDs have been tabulated below-

***In-silico* docking**

The interaction between the ligand and the receptor was checked by conducting *In-silico* docking. PDB files of the ligand and he receptor where posted on an online docking server called Patch Dock (http://bioinfo3d.cs.tau.ac.il/PatchDock/). The results were then sent to the users ID which was then analyzed for the interactions.

Analysis of docked complex

The results obtained from Patch Dock where then viewed and analysed in PyMol molecular viewer. The intermolecular interactions by means of hydrogen bonds where checked for the compounds and the bond length, number of bonds were noted. The interacting atom and the residues were also labelled.

RESULTS

GCMS analysis

The compounds of leaves were identified from the GCMS analysis (Figure 1). The plant compound found are: 5,8,11,14-Eicosatetraenoic Acid, Methyl Ester; 1-Hydroxy-1,7-Dimethyl-4-Isopropyl-2,7-Cyclodecadiene; 2-Phenanthrenol, 1,2,3,4,4a,4b,5,6,8a,9,10,10a-Dodecahydro-4a,7-Dimethyl-8-[3-Cyano-3-(Trimethylsilyloxy)Propyl]-, Acetate; 4-Pregnen-6.Beta.,11.Beta.,17.Alpha.,21-Tetraol-3,20-Dione; 12,15-Octadecadiynoic Acid Methyl Ester; D(17a)-Homo-C, 18-Dinorcard-20(22)-Enolide, 14-Hydroxy-17a-Methylene-3-Oxo-, (5.Beta.); 2,3-O-Benzal-D-Mannosan; 5-Pregnen-3.Beta.,9.Alpha.-Diol-20-One 3-Acetate; Bisnorallocholanic Acid; Pterin-6-Carboxylic Acid; 3 Beta.-Acetoxy-5-Cholenamide; 3-Isoxazolecarboperoxoic Acid, 4,5-Dihydro-5-Phenyl; 3-Azabicyclo (3.2.2) Nonane-3-Thiocarboxylic Acid, (1-(2-Pyridyl)Ethylidene) Hydrazide; 1,2,5,6-Di-O-Isopropylidene-3-O-Methanesulfonyl Glycol; Pregnane-3,11,20,21-Tetrol, Cyclic 20,21-[(1,1-Dimethylethyl)Boronate], (3.Alpha.,5.Alpha.,11.Beta.,20r); 2r,3s-9-[[1,3-Dihydroxy-4-Fluoro-3-Butoxy]Methyl]Gu and Butanol, 1-Dimethylphosphonate.

The online docking server Patch Dock yielded the results for the receptor and ligands submitted. Analysis of these results enabled the identification of ligands responsible for the hepatoprotective nature and anti-arthritis potential of the plant *C. indica*. Out of all the ligands, Pterin-6-carboxylic acid, D(17a)-Homo-C,18-dinorcard-20(22)-enolide, 14-hydroxy-17a-methylene-3-oxo-, (5.beta.), 1,2,5,6-Di-O-Isopropylidene-3-O-Methanesulfonyl Glycol, 3-Azabicyclo[3.2.2]Nonane-3-Thiocarboxylic Acid 2-[1, 2R,3S-9-[[1,3-Dihydroxy-4-Fluoro-3-Butoxy]Methyl]Gu proved to be the most effective ones.

Docking with Hepatotoxicity receptors

All the ligands obtained were docked against the 6 receptors which are known to be involved in the incidence of hepatotoxicity. The results obtained are as follows

Binding affinity of the compounds with 1ILG

The ligands like Bisnorallocholanic acid; Pterin-6-carboxylic acid; 3.Beta.-Acetoxy-5-Cholenamide; 3-Isoxazolecarboperoxoic Acid, 4,5-Dihydro-5-Phenyl; 1,2,5,6-Di-O-Isopropylidene-3-O-Methanesulfonyl Glycol And 2R,3S-9-[[1,3-Dihydroxy-4-Fluoro-3-Butoxy]Methyl] Gu has shown the interaction with the receptor. Obtained results suggest that the ligand 3 beta- acetoxy- 5 cholenamide binds stronger compared to all the others with bond length of 1.8 and 1.2 with ARG-410 and SER-208 respectively, the interacting atoms being O27 and O25 (Figure 2).

Binding affinity of the compounds with 1NFK

Against the receptor 1NFK, the ligand like 1-Hydroxy-1,7-dimethyl-4-isopropyl-2,7-cyclodecadiene; 2-Phenanthrenol, 1,2,3,4,4a,4b,5,6,8a,9,10,10a-dodecahydro-4a,7-dimethyl-8-[3-cyano-3-(trimethylsilyloxy)propyl]-, acetate; 12,15-Octadecadiynoic acid methyl ester; D(17a)-Homo-C,18-dinorcard-20(22)-enolide, 14-hydroxy-17a-methylene-3-oxo-, (5.beta.)-; Pterin-6-carboxylic acid; 3.Beta.-Acetoxy-5-Cholenamide; 3-Isoxazolecarboperoxoic Acid, 4,5-Dihydro-5-Phenyl; 3-Azabicyclo(3.2.2)nonane-3-thiocarboxylic acid, (1-(2-pyridyl)ethylidene)hydrazide; 1,2,5,6-Di-O-Isopropylidene-3-O-Methanesulfonyl Glycol; Pregnane-3,11,20,21-tetrol, cyclic 20,21-[(1,1-dimethylethyl)boronate], (3.alpha.,5.alpha.,11.beta.,20R); 2R,3S-9-[[1,3-Dihydroxy-4-Fluoro-3-Butoxy]Methyl]Gu and Butanol, 1-Dimethylphosphonate has shown the interaction. 2R, 3S-9-[[1,3-Dihydroxy-4-Fluoro-3-Butoxy]Methyl]Gu has shown a very strong interaction by forming 5 hydrogen bonds. The first one is a 2.5 long bond between the atom O13 and ARG-54 residue with a bond length of 2.5. The next one is between O12 and ASN-247 with a bond length of 2.3 followed by a 2.4 long bond between H30 and SER-240 and a 1.8 long bond between O19 and LYS-272. Finally, a bond of 2.6 can be seen between H33 and SER-246 (Figure 2).

Binding affinity of the compounds with 1XVP

Here, though the interactions aren't very strong. The ligands like 2-Phenanthrenol, 1,2,3,4,4a,4b,5,6,8a,9,10,10a-dodecahydro-4a,7-dimethyl-8-[3-cyano-3-(trimethylsilyloxy)propyl]-, acetate; 12,15-Octadecadiynoic acid methyl ester; D(17a)-Homo-C,18-dinorcard-20(22)-enolide, 14-hydroxy-17a-methylene-3-oxo-, (5.beta.)-; Bisnorallocholanic acid; Pterin-6-carboxylic acid; 3.Beta.-Acetoxy-5-Cholenamide; 3-Isoxazolecarboperoxoic Acid, 4,5-Dihydro-5-Phenyl and Pregnane-3,11,20,21-tetrol, cyclic 20,21-[(1,1-dimethylethyl)boronate], (3.alpha.,5.alpha.,11.beta.,20R). Pterin-6 carboxylic acid has shown a potential interaction. It has formed 2 bonds with the receptor 1XVP. The first one is between the atom O6 and residue ASN-306, the bond length being 3.4. The other one is seen between H18 and CYS-432 with a bond length of 2.5 (Figure 2).

Binding affinity of the compounds with 1XNX

The ligands like D(17a)-Homo-C,18-dinorcard-20(22)-enolide, 14-hydroxy-17a-methylene-3-oxo-, (5.beta.); Pterin-6-carboxylic acid; 3.Beta.-Acetoxy-5-Cholenamide; 3-Isoxazolecarboperoxoic Acid, 4,5-Dihydro-5-Phen; 3-Azabicyclo[3.2.2]Nonane-3-Thiocarboxylic Acid 2-[1]; Pregnane-3,11,20,21-Tetrol, Cyclic 20,21-(Butyl Boro And Butanol, 1-Dimethylphosphonato) has shown interaction between 1XNX receptor. D(17a)-Homo-C,18-dinorcard-20(22)-enolide, 14-hydroxy-17a-methylene-3-oxo-, (5.beta.) is the most actively interacting ligand against this receptor. Two bonds are formed with its residue HIS-213, the first by atom N9 with length 3.5 and the other by N11 with length 2.9 (Figure 2).

Binding affinity of the compounds with 5AVI

The ligands like 5,8,11,14-Eicosatetraenoic acid, methyl ester, (all-Z); 12,15-Octadecadiynoic acid methyl ester; D(17a)-Homo-C,18-dinorcard-20(22)-enolide, 14-hydroxy-17a-methylene-3-oxo-, (5.beta.); Pterin-6-carboxylic acid; 3.Beta.-Acetoxy-5-Cholenamide; 3-Isoxazolecarboperoxoic Acid, 4,5-Dihydro-5-Phen; 1,2,5,6-Di-O-Isopropylidene-3-O-Methanesulfonyl Gl; Pregnane-3,11,20,21-Tetrol, Cyclic 20,21-(Butyl Boro And Butanol, 1-Dimethylphosphonato) has shown interaction with the receptor. Pterin-6-carboxylic acid is the most actively interacting ligand again. It has formed 5 hydrogen bonds with the receptor. The bonds are as follows: 3.5 long bonds between O14 and GLN-,3S-9-[[1,3-Dihydroxy-4-Fluoro-3-Butoxy]Methyl]Gu And Butanol, 1-Dimethylphosphonate has shown interaction with the residue. Out of all the ligands, D(17a)-Homo-C,18-dinorcard-20(22)-enolide, 14-hydroxy-17a-methylene-3-oxo-, (5.beta.) has shown the strongest interaction. It has participated in 4 hydrogen bonds all of which are by oxygen atoms. First one is between O27 and ARG-4 residue having a bond length of 3.1. The next atom O24 formed two bonds of length 3.2 and 2.8 with the same residue, GLY-49. The last bond was seen between O6 and SER-5 with a bond length of 3.0 (Figure 3).

Binding affinity of the compounds with 2R5T

The receptor has shown interaction between the ligands like 2-Phenanthrenol, 1,2,3,4,4a,4b,5,6,8a,9,10,10a-dodecahydro-4a,7-dimethyl-8-[3-cyano-3-(trimethylsilyloxy)propyl]-, acetate; D(17a)-Homo-C,18-dinorcard-20(22)-enolide, 14-hydroxy-17a-methylene-3-oxo-, (5.beta.)-; Bisnorallocholanic acid; Pterin-6-carboxylic acid; 3.Beta.-Acetoxy-5-Cholenamide; 3-Isoxazolecarboperoxoic Acid, 4,5-Dihydro-5-Phenyl; 3-Azabicyclo(3.2.2)Nonane-3-Thiocarboxylic Acid, (1-(2-Pyridyl)Ethylidene)Hydrazide; 1,2,5,6-Di-O-Isopropylidene-3-O-Methanesulfonyl Glycol; Pregnane-3,11,20,21-Tetrol, Cyclic 375, 2.4 long bonds between O6 and GLU-379, 2.8 long bonds between N9 and SER-413, 2.6 long between H10 and SER-413 and finally a 2.8 long bond between H18 and MET-409 (Figure 2).

Binding affinity of the compounds with 1OSH

The ligands like 5,8,11,14-Eicosatetraenoic acid, methyl ester, (all-Z); 1-Hydroxy-1,7-dimethyl-4-isopropyl-2,7-cyclodecadiene; 2-Phenanthrenol, 1,2,3,4,4a,4b,5,6,8a,9,10,10a-dodecahydro-4a,7-dimethyl-8-[3-cyano-3-(trimethylsilyloxy)propyl]-, acetate; D(17a)-Homo-C,18-dinorcard-20(22)-enolide, 14-hydroxy-17a-methylene-3-oxo-, (5.beta.); Bisnorallocholanic acid; Pterin-6-carboxylic acid; 3-Isoxazolecarboperoxoic Acid, 4,5-Dihydro-5-Phen; 3-Azabicyclo[3.2.2]Nonane-3-Thiocarboxylic Acid 2-[1]; 1,2,5,6-Di-O-Isopropylidene-3-O-Methanesulfonyl Gl And 2R,3S-9-[[1,3-Dihydroxy-4-Fluoro-3-Butoxy]Methyl]Gu has shown interaction with the receptors. The best ligand against this receptor is 3-Isoxazolecarboperoxoic Acid, 4,5-Dihydro-5-Phen and has formed 2 hydrogen bonds with atom O18 and O19, residue TYR-365 and SER-336 and with bond length of 3.6 and 3.0 (Figure 2)

Docking with Arthritis receptors

Our study involved 9 receptors responsible for the manifestation of arthritis. To check for the effectiveness of *C. indica* as an arthritis suppressor, we docked the chosen ligands of the extract against these 9 receptors on PATCHDOCK.

Binding affinity of the compounds with 1TWM

The ligands like 2,3-O-Benzal-d-mannosan; 1-Hydroxy-1,7-dimethyl-4-isopropyl-2,7-cyclodecadiene; 2-Phenanthrenol, 1,2,3,4,4a,4b,5,6,8a,9,10,10a-dodecahydro-4a,7-dimethyl-8-[3-cyano-3-(trimethylsilyloxy)propyl]-, acetate 4-Pregnen-6.beta.,11.beta.,17.alpha.,21-tetraol-3,20-dione; 12,15-Octadecadiynoic acid methyl ester; D(17a)-Homo-C,18-dinorcard-20(22)-enolide, 14-hydroxy-17a-methylene-3-oxo-, (5.beta.); Pterin-6-carboxylic acid; 3-Isoxazolecarboperoxoic Acid, 4,5-Dihydro-5-Phenyl; 3-Azabicyclo(3.2.2)Nonane-3-Thiocarboxylic Acid, (1-(2-Pyridyl)Ethylidene)Hydrazide; Pregnane-3,11,20,21-Tetrol, Cyclic 20,21-[(1,1-Dimethylethyl) Boronate], (3.Alpha.,5.Alpha.,11.Beta.,20R); 2R 20,21-[(1,1-Dimethylethyl)Boronate], (3.Alpha.,5.Alpha.,11.Beta.,20r); 2r,3s-9-[[1,3-Dihydroxy-4-Fluoro-3-Butoxy]Methyl]Gu And Butanol, 1-Dimethylphosphonate. The strongest binding ligand is1,2,5,6-Di-O-Isopropylidene-3-O-Methanesulfonyl Glycol forming 5 hydrogen bonds with atom (O19, O19, O20, O11, O12), residue (ASN-227, LYS-245, LYS-127, PHE-109) and bond length (3.2, 3.0, 2.9, 3.3,2.9 respectively (Figure 3).

Binding affinity of the compounds with 2EEI

The interacting ligands are 2,3-O-Benzal-d-mannosan; 2-Phenanthrenol, 1,2,3,4,4a,4b,5,6,8a,9,10,10a-dodecahydro-4a,7-dimethyl-8-[3-cyano-3-(trimethylsilyloxy) propyl]-, acetate; D(17a)-Homo-C,18-dinorcard-20(22)-enolide, 14-hydroxy-17a-methylene-3-oxo-, (5.beta.); Pterin-6-carboxylic acid; 3-Isoxazolecarboperoxoic Acid, 4,5-Dihydro-5-Phenyl; 3-Azabicyclo(3.2.2)Nonane-3-Thiocarboxylic Acid, (1-(2-Pyridyl)Ethylidene)Hydrazide; 1,2,5,6-Di-O-Isopropylidene-3-O-Methanesulfonyl Glycol; Pregnane-3,11,20,21-Tetrol, Cyclic 20,21-[(1,1-Dimethylethyl)Boronate], (3.Alpha.,5.Alpha.,11.Beta.,20r); 2R,3S-9-[[1,3-Dihydroxy-4-Fluoro-3-Butoxy]Methyl]Gu. The best ligand against this

receptor is D(17a)-Homo-C,18-dinorcard-20(22)-enolide, 14-hydroxy-17a-methylene-3-oxo-, (5.beta.)-, forming 4 hydrogen bonds with atom (O25, O24, H57, H57) residue (ARG-95, ASP-53, LYS-94, ASP-93) and bond length (1.5, 1.4, 2.7, 2.6) respectively (Figure 3).

Binding affinity of the compounds with 2C4K

The receptor shown interacting residue with ligands like 2-Phenanthrenol, 1,2,3,4,4a,4b,5,6,8a,9,10,10a-dodecahydro-4a,7-dimethyl-8-[3-cyano-3-(trimethylsilyloxy)propyl]-, acetate; D(17a)-Homo-C,18-dinorcard-20(22)-enolide, 14-hydroxy-17a-methylene-3-Oxo-, (5.Beta.); Bisnorallocholanic Acid; Pterin-6-Carboxylic Acid; 3.Beta.-Acetoxy-5-Cholenamide; 3-Isoxazolecarboperoxoic Acid, 4,5-Dihydro-5-Phenyl; 3-Azabicyclo(3.2.2)Nonane-3-Thiocarboxylic Acid, (1-(2-Pyridyl)Ethylidene)Hydrazide; 1,2,5,6-Di-O-Isopropylidene-3-O-Methanesulfonyl Glycol; Pregnane-3,11,20,21-Tetrol, Cyclic 20,21-[(1,1-Dimethylethyl)Boronate], (3.Alpha.,5.Alpha.,11.Beta.,20r) and 2R,3S-9-[[1,3-Dihydroxy-4-Fluoro-3-Butoxy]Methyl]Gu. The best ligand against this receptor is D(17a)-Homo-C,18-dinorcard-20(22)-enolide, 14-hydroxy-17a-methylene-3-oxo-, (5.beta.)- and has formed 3 hydrogen bonds with atom (H57, O24, O24), residue (ARG-110, THR-86, VAL-148) and bond length (1.7, 3.2, 2.5) respectively (Figure 3).

Binding affinity of the compounds with 2Z62

The receptor has shown interaction with ligands like 5,8,11,14-Eicosatetraenoic acid, methyl ester, (all-Z); 1-Hydroxy-1,7-dimethyl-4-isopropyl-2,7-cyclodecadiene 4-Pregnen-6.beta.,11.beta.,17.alpha.,21-tetraol-3,20-dione; 12,15-Octadecadiynoic acid methyl ester; D(17a)-Homo-C,18-dinorcard-20(22)-enolide, 14-hydroxy-17a-methylene-3-oxo-, (5.beta.)-; Pterin-6-Carboxylic Acid; 3.Beta.-Acetoxy-5-Cholenamide; 3-Azabicyclo(3.2.2)Nonane-3-Thiocarboxylic Acid, (1-(2-Pyridyl)Ethylidene)Hydrazide; Pregnane-3,11,20,21-Tetrol, Cyclic 20,21-[(1,1-Dimethylethyl)Boronate], (3.Alpha.,5.Alpha.,11.Beta.,20r) and 2R,3S-9-[[1,3-Dihydroxy-4-Fluoro-3-Butoxy]Methyl]Gu. The best interaction were found between Pterin-6-carboxylic acid has shown the strongest interaction with this receptor by forming 5 hydrogen bonds with atom (O14, O6, O6, N9, H19) residue (LYS-278, ASN-279, LYS-282, TRP-275, PHE-246) and bond length (0.6, 3.0, 2.8, 3.3, 2.1) respectively (Figure 3).

Binding affinity of the compounds with 2NJ3

The receptor has shown interaction with ligand like 1-Hydroxy-1,7-dimethyl-4-isopropyl-2,7-cyclodecadiene; D(17a)-Homo-C,18-dinorcard-20(22)-enolide, 14-hydroxy-17a-methylene-3-oxo-, (5.beta.); Bisnorallocholanic acid; Pterin-6-carboxylic acid; 3.Beta.-Acetoxy-5-Cholenamide; 3-Isoxazolecarboperoxoic Acid, 4,5-Dihydro-5-Phen; 3-Azabicyclo[3.2.2]Nonane-3-Thiocarboxylic Acid 2-[1] and 2R,3S-9-[[1,3-Dihydroxy-4-Fluoro-3-Butoxy]Methyl]Gu. The most reactive ligand against this receptor is 2R, 3S-9-[[1,3-Dihydroxy-4-Fluoro-3-Butoxy]Methyl]Gu. It is seen to form 5 hydrogen bonds via the atoms N2, O12, O10, O13 and N5 with the residues ASP-419, LYS-610, SER-420, SER-420 and TRP-92 respectively with bond lengths of 3.3, 3.5, 3.6, 2.5 and 3.3 (Figure 3).

Binding affinity of the compounds with BB9

The receptor has shown interaction with ligand like 2-Phenanthrenol, 1,2,3,4,4a,4b,5,6,8a,9,10,10a-dodecahydro-4a,7-dimethyl-8-[3-cyano-3-(trimethylsilyloxy)propyl]-, acetate; D(17a)-Homo-C,18-dinorcard-20(22)-enolide, 14-hydroxy-17a-methylene-3-oxo-, (5.beta.); Bisnorallocholanic acid; Pterin-6-carboxylic acid; 3-Azabicyclo[3.2.2]Nonane-3-Thiocarboxylic Acid 2-[1]; 1,2,5,6-Di-O-Isopropylidene-3-O-Methanesulfonyl Gl; Pregnane-3,11,20,21-Tetrol, Cyclic 20,21-(Butyl Boro; 2r,3s-9-[[1,3-Dihydroxy-4-Fluoro-3-Butoxy]Methyl]Gu and Butanol, 1-Dimethylphosphonato). The most interactive ligand here is Pterin-6-carboxylic acid that formed 4 bonds with atom (O15, O14, N9, O6), residue (VAL-180, SER-179, ASN-512, SER-258) and bond length respectively 2.2, 2.0, 3.4, 2.3) respectively (Figure 3).

Binding affinity of the compounds with CKJ

The receptor has shown interaction with ligand like 2,3-O-Benzal-d-mannosan; 5,8,11,14-Eicosatetraenoic acid, methyl ester, (all-Z); 2-Phenanthrenol, 1,2,3,4,4a,4b,5,6,8a,9,10,10a-dodecahydro-4a,7-dimethyl-8-[3-cyano-3-(trimethylsilyloxy)propyl]-, acetate; D(17a)-Homo-C,18-dinorcard-20(22)-enolide, 14-hydroxy-17a-methylene-3-oxo-, (5.beta.); Bisnorallocholanic Acid; Pterin-6-Carboxylic Acid; 3-Isoxazolecarboperoxoic Acid, 4,5-Dihydro-5-Phen; 3-Azabicyclo[3.2.2]Nonane-3-Thiocarboxylic Acid 2-[1]; Pregnane-3,11,20,21-Tetrol, Cyclic 20,21-(Butyl Boro and 2r,3s-9-[[1,3-Dihydroxy-4-Fluoro-3-Butoxy]Methyl]Gu. D(17a)-Homo-C,18-dinorcard-20(22)-enolide, 14-hydroxy-17a-methylene-3-oxo-, (5.beta.)-has shown the strongest interaction with this receptor compared to all the others that has formed 5 hydrogen bonds with atom (H17, O6, O6, O24, O24), residue (ASP-829, SER-605, ARG-599, CYS-73, THR-25) and bond length (1.9, 2.9, 2.5, 1.8, 3.3) respectively (Figure 3).

Binding affinity of the compounds with NAQ

The receptor has shown interaction with ligand like 1-Hydroxy-1,7-dimethyl-4-isopropyl-2,7-cyclodecadiene; 12,15-Octadecadiynoic acid methyl ester; D(17a)-Homo-C,18-dinorcard-20(22)-enolide, 14-hydroxy-17a-methylene-3-oxo-, (5.beta.); Pterin-6-Carboxylic Acid; 3.Beta.-Acetoxy-5-Cholenamide; 1,2,5,6-Di-O-Isopropylidene-3-O-Methanesulfonyl Gl; Pregnane-3,11,20,21-Tetrol, Cyclic 20,21-(Butyl Boro) and 2R,3S-9-[[1,3-Dihydroxy-4-Fluoro-3-Butoxy]Methyl]Gu. Most of the ligands show weak interaction with the receptor. The strongest amongst all is 2R,3S-9-[[1,3-Dihydroxy-4-Fluoro-3-Butoxy]Methyl]Gu which formed 2 hydrogen bonds with atom (H31,N2), residue (GLU-89,ALA-65) and bond length (2.3, 3.0) respectively (Figure 3).

DISCUSSION

Coconica indica is known for its medicinal properties as a traditional Indian plant. We are attempting to assess its effectiveness as a hepatoprotective agent and as an anti-arthritis agent in our study. We found the active components of the plant's leaf extract through our GCMS study, which we believe to be potential ligands. Consideration was given to the highest peak obtained from our GCMS study and molecular docking was carried out using these molecules as ligands against receptors responsible for hepatotoxicity and arthritis.

1OSH acts as bile acids and lipid homeostasis, coordinates metabolism and vitamin and dietary fat absorption of cholesterol[6]. The FXR is encoded into humans by the gene NR1H4[7]. 1NFK helps to induce many biological processes such as immunity, inflammation, development of cells, differentiation and apoptosis[8]. 5AVI acts as a thyroid hormone activator. 1ILG is a nuclear orphan receptor translated by the NR1I2 gene[9]. PXR's main function is to detect foreign toxic particles and increase

protein expression which helps clear the particle from the body and to detoxify it[10]. 1XVP is predominantly human-specific and transcribes the gene NR1I31XNX is a xenobiotic that is necessary during cocaine and acetaminophen toxicity to clear drugs and billirubin[11].

4BB9 which is known as structure of glucokinase regulatory protein complexed to fructose-1-phosphate is also called as Glucokinase[12]. 5NJ3 receptors are found primarily in plants and belong to an omnipresent superfamily[13]. 2Z62 Assist in the development of NF-µB and inflammatory cytokine that activates the innate immune system[14]. 2R5T takes part in the controlling the epithelial ion transport and its proliferation and apoptosis[15]. 2EEI is actively transcribed by the gene PDZK1 in humans[16]. 2NAQ has shown that auto-inflammatory diseases such as periodic syndrome associated with cryopyrin and keratoendotheliitis fugax hereditaria are widely reported[17]. 2C4 K is commonly referred to as human phosphoribosylpyrophosphatesynthetase- related protein 39 (PAP39), an enzyme actively transcribed by the PRPSAP1 gene[15]. Ligands like 2R,3S-9-[[1,3-DIHYDROXY-4-FLUORO-3-BUTOXY]METHYL]GU, pterin-6 carboxylic acid, D(17a)-Homo-C,18-dinorcard-20(22)-enolide, 14-hydroxy-17a-methylene-3-oxo-, (5.beta.) have expressed high affinity towards the receptors responsible for hepatotoxicity as well as arthritis.

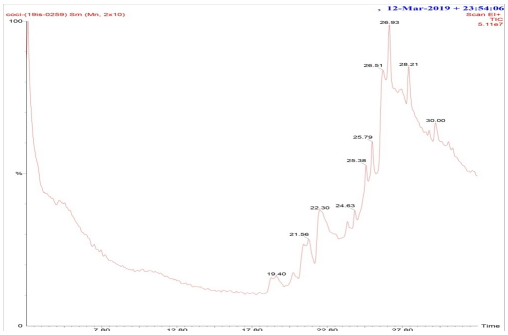
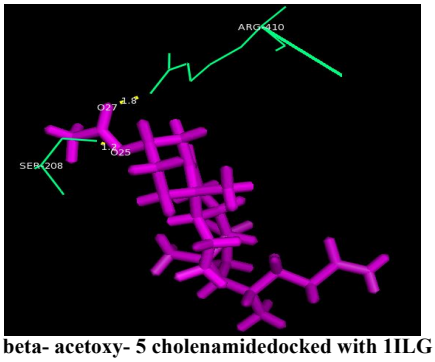
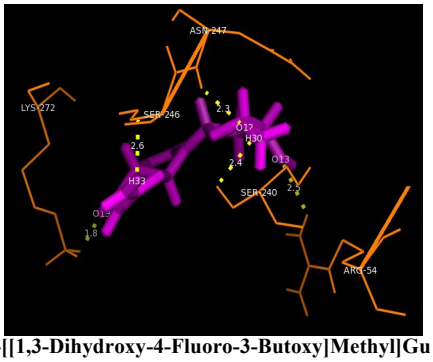


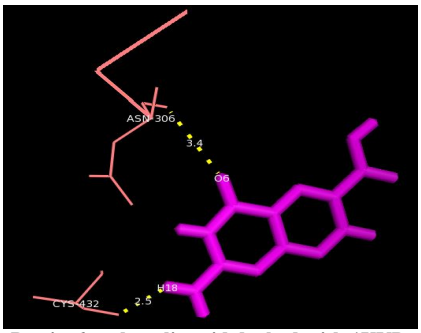
Figure 1: GCMS analysis of *Coccinia indica* leaf



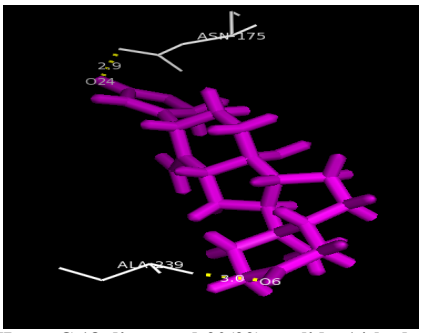
3 beta- acetoxy- 5 cholenamidedocked with 1ILG
Docked complex of Receptor (purple) and Ligand (green) with bonding (Yellow)



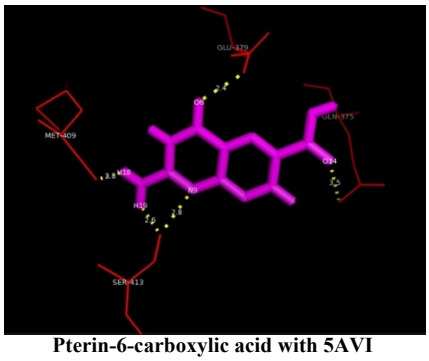
2R,3S-9-[[1,3-Dihydroxy-4-Fluoro-3-Butoxy]Methyl]Gu docked with 1NFK
Docked complex of Receptor (purple) and Ligand (orange) with bonding (Yellow)



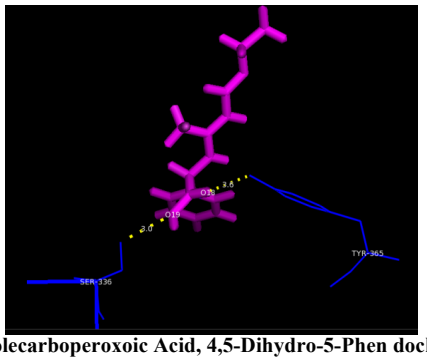
Pterin-6 carboxylic acid docked with 1XVP
Docked complex of Receptor (purple) and Ligand (salmon) with bonding (Yellow)



D (17a)-Homo-C,18-dinorcard-20(22)-enolide, 14-hydroxy-17a-methylene-3-oxo-, (5.beta.) docked with 1XNX
Docked complex of Receptor (purple) and Ligand (white) with bonding (Yellow)

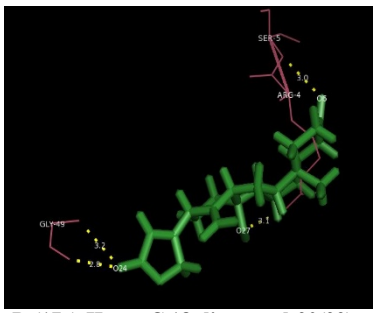


Pterin-6-carboxylic acid with 5AVI
Docked complex of Receptor (purple) and Ligand (red) with bonding (Yellow)

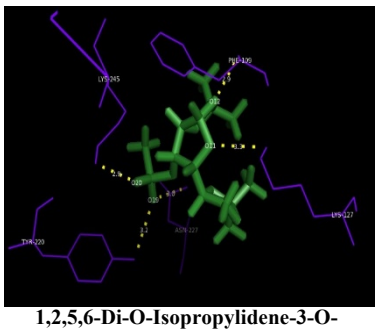


3-Isoxazolecarboperoxoic Acid, 4,5-Dihydro-5-Phen docked with 1OSH
Docked complex of Receptor (purple) and Ligand (blue) with bonding (Yellow)

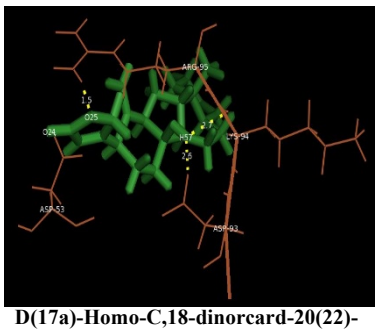
Figure 2: Docking result of ligands with hepatotoxicity receptor



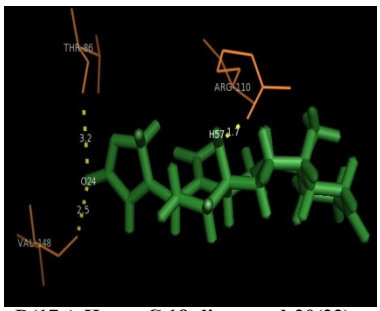
D (17a)-Homo-C,18-dinorcard-20(22)-enolide, 14-hydroxy-17a-methylene-3-oxo-, 5.beta with 1TWM
Docked complex of Receptor (green) and Ligand (salmon) with bonding (Yellow)



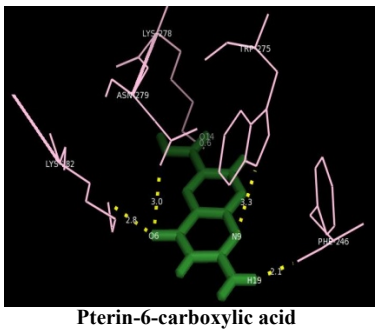
1,2,5,6-Di-O-Isopropylidene-3-O-Methanesulfonyl Glycol with 2RST
Docked complex of Receptor (green) and Ligand (purple) with bonding (Yellow)



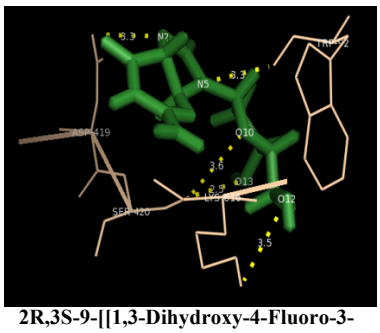
D(17a)-Homo-C,18-dinorcard-20(22)-enolide, 14-hydroxy-17a-methylene-3-oxo-, (5.beta.) with 2EEI
Docked complex of Receptor (green) and Ligand (brown) with bonding (Yellow)



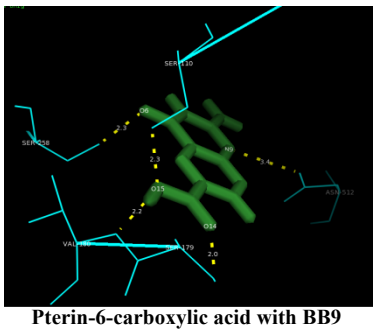
D(17a)-Homo-C,18-dinorcard-20(22)-enolide, 14-hydroxy-17a-methylene-3-oxo-, 5.beta with 2C4K
Docked complex of Receptor (green) and Ligand (salmon) with bonding (Yellow)



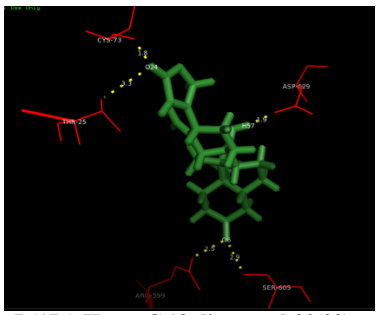
Pterin-6-carboxylic acid
Docked complex of Receptor (green) and Ligand (salmon) with bonding (Yellow)



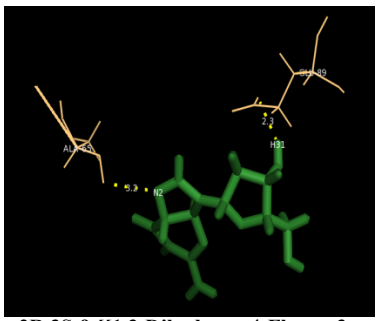
2R,3S-9-[[1,3-Dihydroxy-4-Fluoro-3-Butoxy]Methyl]Gu with 5NJ3
Docked complex of Receptor (green) and Ligand (salmon) with bonding (Yellow)



Pterin-6-carboxylic acid with BB9
Docked complex of Receptor (green) and Ligand (salmon) with bonding (Yellow)



D(17a)-Homo-C,18-dinorcard-20(22)-enolide, 14-hydroxy-17a-methylene-3-oxo-, (5.beta.) with CKJ
Docked complex of Receptor (green) and Ligand (salmon) with bonding (Yellow)



2R,3S-9-[[1,3-Dihydroxy-4-Fluoro-3-Butoxy]Methyl]Gu with NAQ
Docked complex of Receptor (green) and Ligand (salmon) with bonding (Yellow)

Figure 3: Docking result of ligands with arthritis receptor

CONCLUSION

Through our current *In-silico* study we were able to predict the better binding affinity of C*ocinia indica* against orphan nuclear receptor. The ligands 2R,3S-9-[[1,3-DIHYDROXY-4-FLUORO-3-BUTOXY]METHYL]GU, pterin-6 carboxylic acid, D(17a)-Homo-C,18-dinorcard-20(22)-enolide, 14-hydroxy-17a-methylene-3-oxo-, (5.beta.) were observed to show potential affinity against the receptors. Though the plant extract has shown good affinity towards hepatotoxicity receptors, it has shown better affinity and stronger binding with the arthritis receptors. We thereby conclude that *C.indica* is a good hepatoprotective agent and a better cure for arthritis.

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