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Research Article

A STUDY ON THE PHARMACOLOGICAL ACTIVITY OF THE SEEDS OF *ALOE VERA*: *IN-SILICO* AND GC-MS APPROACH

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ABSTRACT

Aloe vera is a succulent plant that is widely known for its medicinal properties. Though there are numerous suggestions for its utility, controlled trials are mandatory to govern its actual effectiveness. The aim of our study is to find the beneficial effects of *Aloe vera* seeds through *in-silico* studies with the help of GC-MS analysis. The freshly collected *Aloe vera* seeds were dried for two weeks in the absence of sunlight. Later the seeds powder is used for GC-MS. The active compounds obtained from GC-MS analysis were used for *in-silico* computational studies. The receptors were obtained from RCSB Protein Data Bank, the ligands were obtained from CORINA Molecular Network and docking was carried out through Patch Dock online server. On the analysis of the docked complex we were able to find potential binding affinity between the ligands of *Aloe vera* seed and the chosen receptor. Our study has demonstrated the potential binding affinity against hepatotoxicity and arthritis receptors. Among the docked complex the ligands like Heptacosane, Hexatriacontane, Tritetracontane, Tetratetracontane, Hentriacontane, Tetracosane, 11-decyl, Tetratetracontane and Tetracontane has demonstrated potential interaction. The ligands like Tritetracontane and Tetracontane has shown much hydrogen bonding. The seeds of *Aloe vera* and its potential binding active compounds can be further studied through *in-vivo* animal work to know its beneficial effect against inflammation.

Keywords: *Aloe vera*, *in-silico*, GC-MS analysis, docking, Patch dock

INTRODUCTION

Aloe vera is known to have salutary effects on health and has been extensively utilized for therapeutic purposes from time immemorial. "*Aloe, Aloe capensis, Aloe spicata, Aloe vera*, Chirukattali" are some of the familiar names by which *Aloe vera* is known. The medicinal and healing agents derived from *Aloe vera* has substantial role in the field of medicine[1]. In the field of cosmetology, *Aloe vera* is one of the natural products that is being used for skincare, sun-protection and anti-aging[2]. It also has various uses in the field of dermatology[3].

Aloe vera belongs to "Liliaceae" family and it is commonly called as "burn plant", "lily of desert", "elephant's gull" etc. It is a succulent plant with short stem and grows up to a height of 60-100 cm. The colour of the plant is green to grey green and in some varieties it may show white flecks on the surface of the stem[1]. The leaves are very thick and fleshy, marginated with spines and contain a clear viscous gel[3]. The leaf has three parts namely an inner clear gel, middle latex and an outer thick layer[4]. *Aloe vera* is a perennial plant that grows in the temperate and subtropical regions of the world, which include Africa, Asia, Europe and America. In India it is found in Rajasthan, Andhra Pradesh, Gujarat, Maharashtra and Tamil Nadu[4].

Aloe vera is acknowledged with numerous salubrious properties such as "anti-oxidant, anti-inflammatory, wound healing, cell proliferation, anti-allergic, analgesic, anti-microbial (anti-bacterial, anti-viral, anti-fungal), antiseptic, anti-cancer, anti-tumour, immunomodulatory and anti-mutagenic"[3]. The pharmacological and phytochemical properties of *Aloe vera* have already been proved and verified. In the context of the gastro protective activity of *Aloe vera*, the extract of *Aloe vera* is found to decrease the gastric acid secretion in the instance of gastric acid lesions. In mice, the blood glucose level is decreased by decreasing the insulin resistance by using processed *Aloe vera* gel[3]. Bioavailability of co-administered vitamins in humans is also known to be enhanced by *Aloe vera*. The gel of *Aloe vera* leaf improves the *in vitro* penetration of compounds through the skin on the basis of their molecular weight which is a beneficial property for transdermal drug delivery and it is also conferred with anti-diabetic property[5]. *Aloe vera* is also recognized to be one of the rare sources of organic Vitamin B12[1].

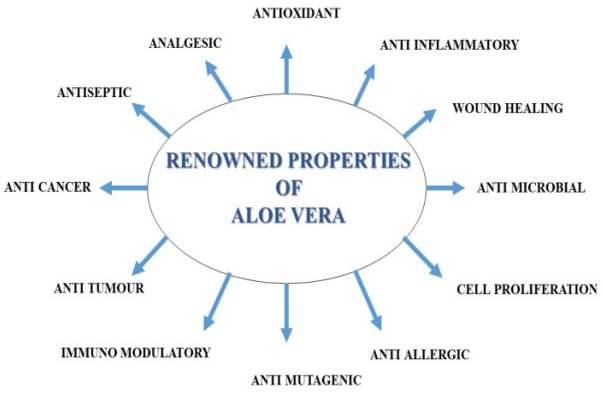

Figure 1: Properties of *Aloe vera*

GC-MS is a technique that recruits two other techniques like gas chromatography and mass spectrometry, for the analysis of bioactive compounds existing in a mixture such as the parts or

extracts of medicinal plants[6]. It is mainly used for identification and quantitation of unknown components in a sample mixture. Molecular docking nowadays has become an important and common component of drug discovery. Its relative low-cost and perceived simplicity of use has led to an ever-increasing popularity within the academic communities. Several deliberations which can markedly boost the success as well as enhancement of the true bioactive hit compound are generally discounted at initial stages of the molecular docking stud. *In-silico* work is mainly done to prognosticate the drug's interaction with the body and also with the pathogens. There is a variety of *in-silico* techniques in use, some of which arebacterial sequencing techniques, molecular modelling and whole cell stimulations. Patch Dock is an algorithm used in molecular docking. The input mainly includes two molecules which could be proteins, DNA, peptides, drugs. The output includes a list of the potential complexes which are sorted depending upon shape complementarily[7]. The aim of our research is to identify the bioactive compounds present in the seeds of *Aloe vera* using GC-MS and the effective binding site of these compounds against the toxic receptors of arthritis and hepatotoxicity.

MATERIAL AND METHODS

Seed Extraction

The seeds of *Aloe vera* were collected and shade-dried for two weeks after which it was pulverized and stored for further use. The plant was authenticated by Professor Jayaraman, Director of Plant Anatomy Research Center, Chennai and the authentication number is PARC/2019/3960.

GC-MS Analysis

The pulverized *Aloe vera* seeds were given for GC-MS analysis in order to retrieve the active compounds present in the seeds. The result of GC-MS analysis is represented as a graph as shown below.

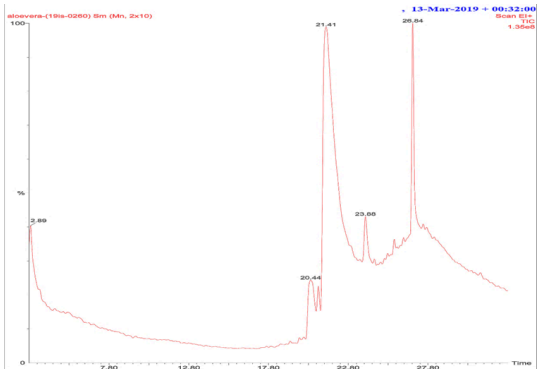

Figure 2: GC-MS analysis of *Aloe vera*

In-silico Docking

In-silico docking using Patch Dock online server was carried out to find the potential binding site, bond length, residues and atoms involved in the bond formed between the active compounds of the seed and receptors involved in gouty arthritis and hepatotoxicity.

Receptor Designing

The receptors involved in the pathological disease manifestation of Arthritis and Hepatotoxicity were identified from literature surveys. A list of the receptors was made and their PDB structures were obtained from RCSB Protein Data Bank[8]. List of receptors were represented in Table 1.

Ligand Designing

Ligands are the active compounds present in the *Aloe vera* seeds were identified via GC-MS analysis. The ligand names are listed, and their canonical smiles were obtained from Pub Chem. These canonical smiles are given as input in Corina Molecular Network to get the PDB structures of the ligands[8]. List of ligands were represented in Table 2.

In-Silico Docking

The PDB files of each receptor and ligand were given as input to Patch Dock online server to accomplish molecular docking. The results of the docking process were fetched from the user's email id.

Analysis of Docked complex

The docked complexes of each receptor with each of the ligands were analyzed to identify any bond that was formed between them. This was done with the aid of PyMOL software. In case of the presence of bonds, the bond length and the residues and atoms involved in the bonds were identified, labeled and tabulated.

RESULT

The results of interaction between the receptors and ligands showed that a few of the ligands had binding potential with the receptors. The docking results are tabulated below.

Docked complex with 1TWM

The docked complex of 1TWM receptor with Heptacosane ligand (Figure 3) showed interacting residue as ALA-1 with a bond length of 3.2. The other ligands however did not show any binding affinities with the receptor.

Docked complex with 2C4K

The docked complex of 2C4K receptor with Hexatriacontane ligand (Figure 3) shows the interacting residue as ARG-25 and the bond length is 2.4. The atom involved is oxygen. The other ligands did not show any affinity towards this receptor.

Docked complex with 2CKJ

The docked complex 2CKJ receptor with the ligands Tritetracontane (Figure 3) showed the formation of three hydrogen bonds with interacting residues and bond lengths of MET-827:- 2.9,GLU-832:- 2.5 and GLU-832:- 1.7 respectively.

Docked complex with 2NAQ

The docked complex of 2NAQ receptor with the ligands Tetratetracontane (Figure 3) showed the formation of a hydrogen bond with interacting residue LYS-84 and a bond length of 1.8 showing considerable bond strength.

Docked complex with 2Z62

The docked complex of the receptor 2Z62 with ligands Hentriacontane, Heptacosane, Tetracontane and Tetratetracontane (Figure 3) showed interacting residues and bond length SER-292:-2.1, SER-184:-3.2, LYS:-186:-3.2 and ASN-44:-2.8 respectively.

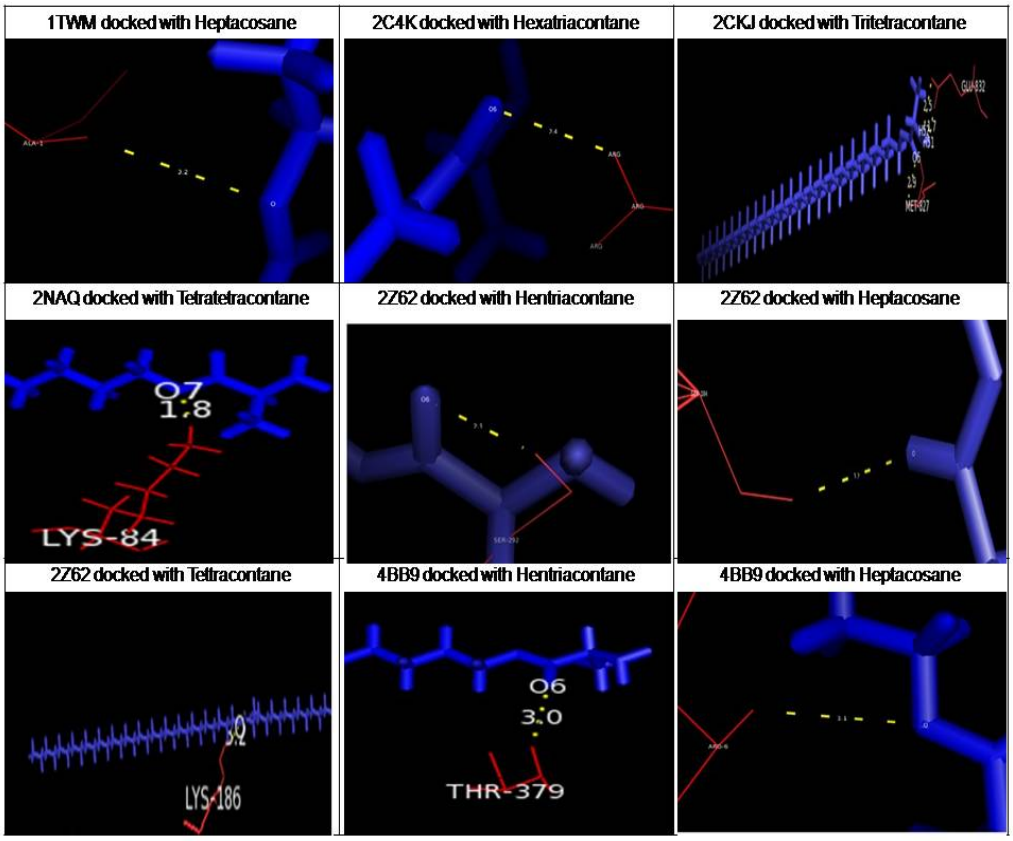

Figure 3: Docked complex with 1TWM, 2C4K, 2CKL, 2NAQ, 2Z62, 4BB9 receptor

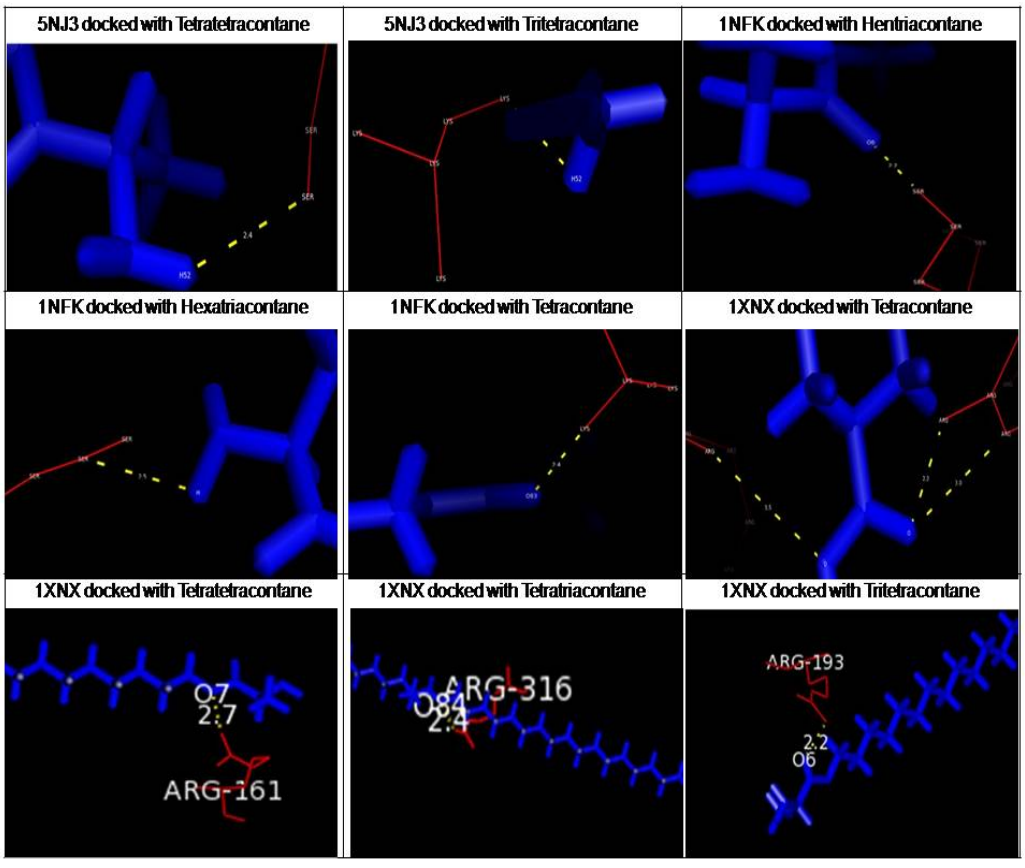

Figure 4: Docked complex with 5NJ3, 1NFK, 1XNX receptor

Table 1: Receptor

S. No.	Receptor	PDB Id.
1	IL-1B	1TWM
2	Human Phosphoribosylpyrophosphate synthetase- associated protein 1	2C4K
3	Human milk xanthine oxidoreductase	2CKJ
4	PDZ Domain Containing Protein 1	2EEI
5	NACHT, LRR and PYD domains containing protein 3	2NAQ
6	Serum and Glucocorticoid- regulated Kinase 1	2R5T
7	Toll-like receptor 4	2Z62
8	Glucokinase Regulator	4BB9
9	ATP Binding Cassette Subfamily G Member 2	5NJ3
10	Apo Human Pregnane X	1ILG
11	Nuclear Factor Kappa B	1NFK
12	Nuclear Bile Acid Receptor	1OSH
13	Constitutive Androstane Receptor	1XNX
14	LXRalpha	5AVI

Table 2: Ligands

Molecule Name	Molecule formula	Molecular weight (g/mol)	Pub Chem compound Id.
Tritetracontane	$C_{43}H_{88}$	605.177 g/mol	522398
Tetratetracontane	$C_{44}H_{90}$	619.204 g/mol	23494
Pentatriacontane	$C_{35}H_{72}$	492.961 g/mol	12413
Hexatriacontane	$C_{36}H_{74}$	506.988 g/mol	12412
Hentriacontane	$C_{31}H_{64}$	436.853 g/mol	12410
Tetratriacontane	$C_{34}H_{70}$	478.934 g/mol	26519
Heptacosane	$C_{27}H_{56}$	380.745 g/mol	11636
Tetracontane	$C_{40}H_{82}$	563.096 g/mol	20149
Nonacosane	$C_{29}H_{60}$	408.799 g/mol	12409
Hexacosane	$C_{26}H_{54}$	366.718 g/mol	12407
Triacontane, 11, 20- dodecyl-	$C_{50}H_{102}$	703.366 g/mol	293358
Octacosane	$C_{28}H_{58}$	394.772 g/mol	12408
Pentacosane	$C_{25}H_{52}$	352.691 g/mol	12406
Heptacosane, 1-chloro-	$C_{27}H_{55}Cl$	415.187 g/mol	545593
Tritriacontane	$C_{33}H_{68}$	464.907 g/mol	12411
Dotriacontane	$C_{32}H_{66}$	450.88 g/mol	11008
Tetracosane, 11-Decyl-	$C_{34}H_{70}$	478.934 g/mol	294707

Docked complex with 4BB9

The docked complex of the receptor 4BB9 with ligands Hentriacontane and Heptacosane (Figure 3) showed interacting residues and bond length THR-379:- 3.0 and ARG-6:- 3.1 respectively.

Docked complex with 5NJ3

The docked complex of 5NJ3 receptor with Tetratetracontane ligand (Figure 4) shows interaction with the residue SER-443 with the bond length 2.4. The ligand Tritetracontane also shows the interaction with this receptor with the residue LYS-326 and bond length is 2.9.

Docked complex with 1NFK

The docked complex of 1NFK shows interaction with 3 ligands (Figure 4). They are Hentriacontane, Hexatriacontane and Tetratriacontane with the respective bond lengths such as 2.2, 2.5, and 2.4. The Hentriacontane shows the interaction with residue SER-240, the Hexatriacontane shows the interaction with residue SER-72 and Tetratriacontane interacts with UNK-1.

Docked complex with 1XNX

The docked complexes of the receptor 1XNX with the ligands Tetracontane, Tetratetracontane, Tetratriacontane and Tritetreacontane (Figure 4) were observed to show bond interactions. The interacting residues and bond length of 1XNX with Tetracontane are ARG: 2.2, ARG: 3.0, ARG:- 3.5 respectively. The interacting residue and bond length of 1XNX with Tetratetracontane are ARG-161: 2.7 respectively. The interacting residue and bond length of 1XNX with Tetratriacontane are ARG-316: 2.4 respectively. The interacting residue and bond length of 1XNX with Tritetracontane are ARG-193: 2.2 respectively.

DISCUSSION

According to a study conducted by WHO, 20% of the world population depends on therapeutic products for their health issues and these therapeutic agents are known to be isolated from medicinal plants. As a result, this study was undertaken to determine the effectiveness of the active compounds of the seeds of *Aloe vera* plant in the treatment of gouty arthritis and hepatotoxicity. From the various receptors of gouty arthritis and hepatotoxicity that was taken for study, positive results were obtained for 1TWM, 2C4K, 2CKJ, 2NAQ, 2Z62, 4BB9, 5NJ3, 1NFK and 1XNX. IL-1B (1TWM) is known to be a proinflammatory cytokine secreted by activated macrophages. It is found that IL-1B instigates an elevation in the levels of NGF, which is an "important mediator of inflammation"[9] and is a critical "regulator of peripheral nociception"[10] in arthritis. The increased activity of the enzyme 2C4K results in the increased uric acid production (gout) and purine nucleotide synthesis. This leads to inflammatory arthritis[11]. 2CKJ has a role in inflammatory response as well as in defense against microbes[12]. NACHT, LRR and PYD domains containing protein 3 (2NAQ) is known to be involved in apoptosis, signaling pathways involved in induction of inflammatory responses and in signal transduction[10]. 2Z62 has a significant role mainly in triggering inflammation[13]. 5NJ3 are

apical transporters and they also secrete uric acid apically. It is known to increase the uric acid level in the urine under the influence of insulin and cause gouty arthritis[14]. 1XNX is identified as a key regulator of hepatotoxicity. Activation of 1XNX results in altered gene expression specific to its activation leading to increased proliferation of hepatocytes thereby causing the formation of transmuted hepatic loci and eventually the growth of liver tumors[15]. Since the activities of these receptors in the pathology of gouty arthritis and hepatotoxicity are known, we can come to a conclusion that the masking of the activities of these receptors can hinder their associated pathophysiology. For this reason, these receptors were docked with the active compounds of *Aloe vera* seeds to determine the extent of the interactions between them and to decide whether these active compounds can be used as potential drugs against these receptors.

CONCLUSION

The present study on the seed of *Aloe vera* has revealed its active compounds through GC-MS analysis. The *in-silico* docking analysis had predicted the potential binding affinity of the active compounds of *Aloe vera* against the gouty arthritis and hepatotoxicity receptors. Among the docked complex the ligands like Heptacosane, Hexatriacontane, Tritetracontane, Tetratetracontane, Hentriacontane, Tetracosane, 11-decyl and Tetracontane has demonstrated potential interaction with the receptors. The ligands like Tritetracontane and Tetracontane has shown much hydrogen bonding, which could be further studied to find its potential in *in-vivo* model.

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