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In-silico analysis of active compounds has potential inhibitors against diabetic

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Abstract: *Plants are naturally produced important sources of medicines. Today, a large number of drugs in use derived from plants. A Decalepis hamiltonii (Asclepiadaceae) to treat the various diseases of to human such as diabetic and cancer. GC MS Analysis was carried out to identify the compounds of the selected drug and In silico studies carried out to assess the antidiabetic potential. In silico docking exercise of different herbal based ligands with anti-diabetic properties, revealed that PBRy got docked onto diabetic protein with the lowest calculated interaction energy. The oleic acid (-14.29 kJ mol−1) was docked into active site of* ***ERRα*** *receptor. The green dotted line denoted the hydrogen bonds. The interactions of amino acid residues involved in molecular interactions with oleic acid. In this study, it is confirmed that the Decalepis hamiltonii has significant anti-diabetic activity.*

Keywords*: Methanol, root, Decalepis hamiltonii, anti-diabetic protein*

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I. Introduction

The medicinal plant species worldwide are used in traditional medicines for treating different disease. The world health organization has estimated that about 80% of the population living in the developing countries depends tremendously on traditional medicines for their primary health needs. More than half of the World's population still depends exclusively on medicinal plants. Which offer the active ingredients of most traditional medicinal products (Kumar and Navarathnam, 2013). Plants are acknowledged as a good source for medicines. In India, lots of plants are used traditionally for the management and control of diabetes mellitus as alternatives to synthetic antidiabetic drugs. (Singh et al., 2007) Further pharmacological studies are underway to identify the active constituents of the plant extracts responsible for the showed activities. *Decalepis hamiltonii* Wight & Arn an endemic, endangered, climbing shrub and native of southern peninsula. This plant has been used in Ayurveda, the ancient Indian traditional system of medicine to stimulate appetite, relieve flatulence and as a general tonic (Nayar et al., 1978) Diabetic prevented is one of the life threading diseases in India. Diabetics' mellitus is chartered by abnormally high level of glucose in the blood. Majority of diabetic people are insulin depend and depend on insulin injections. Instead of injections consumption of insulin is preferable choice. To supplement only and minimic action are to be considered one such plant that has antidiabetic activity (Kim et al., 2006). In this present study were antidiatic properties of *Decalepis hamiltonii* have been using different assay and challenge highlights a key force of natural product investigation for potent antidiabetic activity compounds can be identified from *Decalepis hamiltonii*. The Molecular docking method is use to inhibit identified effective molecule to targeted diabetic protein. More biological activities are presented in natural products since used for drug discovery. Molecular docking is a key tool in structural molecular biology and computer-assisted drug design.

II. Material And Methods

Collection of material

The Root of *Decalepis hamiltonii* has been collected from kolli hills, Namakkal district of Tamilnadu, India. The taxonomic identification of plant was done with comparing the Flora of Presidency of Madras, by Gamble J.S., 1921.

Preparation of solvent extraction

50gm of *Decalepis hamiltonii* root was packed in Soxhlet apparatus for extraction and 500 ml of methanol was used as solvent. Soxhlet was kept running for 72 hours, until the solvent colour appears in the collection tube. Methanol was removed by evaporation using rotary vapour at not more than 40°C. The residue was then placed in an oven at 40°C for about 48hours to remove the moisture. The resulting dried mass was then

powdered and used for further studies. The compounds namely were identified by GC-MS analysis were screened against the anti diabetic, protein. The compound details were retrieved from the Pubchem database and the chemical structures were generated from SMILES notation (Simplified Molecular Input Line Entry Specification) by using the Chemsketch Software (www.acdlabs.com).

Protein Data Bank

The Protein Data Bank (PDB) archive is the single worldwide repository of information about the 3D structures of large biological molecules, including proteins and nucleic acids. The Protein Data Bank (PDB) is a repository for the three-dimensional structural data of large biological molecules, such as proteins and nucleic acids. The data, typically obtained by X-ray crystallography or NMR spectroscopy and submitted by biologists and biochemists from around the world, are freely accessible on the Internet via the websites of its member organizations (PDBe, PDBj, and RCSB). The PDB is overseen by an organization called the Worldwide Protein Data Bank, WWPDB.

Preparation of protein structure

The structural information of the macromolecules determined by x-ray crystallographic and NMR methods are available in the PDB. The 3D structure protein Receptor (PDB I.D: 4IFI) was downloaded from the Protein Data Bank (PDB) (http://www.rcsb.org/pdb/) the water molecules were removed from protein file 4IFI before docking. Energy minimization by applying for CHARMM (Chemistry at Harvard Macromolecular Mechanics) force fields, It's a program for macromolecular dynamics; it can be used for energy minimization, normal modes and crystal optimizations and also incorporates free energy methods for chemical and conformational free energy calculations.

PUBCHEM

The Pubchem bioassay data (http://pubchem.ncbi.nlm.nih.gov) is a public repository for biological Activities of small molecules and small interfering RNAs (siRNAs) hosted by the US National Institutes of Health (NIH). It archives experimental descriptions of assays and biological test results and makes the information freely accessible to the public. A Pubchem Bioassay data entry includes an assay description, a summary and detailed test results. Each assay record is linked to the molecular target, whenever possible, and is cross-referenced to other National Center for Biotechnology Information (NCBI) database records. 'Related Bioassays' are identified by examining the assay target relationship and activity profile of commonly tested compounds. A key goal of PubChem Bioassay is to make the biological activity information easily accessible through the NCBI information retrieval system- Entrez, and various web-based PubChem services. An integrated suite of data analysis tools is available to optimize the utility of the chemical structure and biological activity information within PubChem, enabling researchers to aggregate, compare and analyze biological test results contributed by multiple organizations. Describe the PubChem Bioassay database, including data model, bioassay deposition and utilities that PubChem provides for searching, downloading and analyzing the biological activity information.

Preparation of Ligand structures

The identified Chemical compound namely was derived from *Decalepis hamiltonii* Wight & arn and this compound structure were retrieved from Pubchem online server both of these compounds were under investigation of Chemsketch (Chemically intelligent drawing interface free ware developed by Advance Chemistry Development, Inc., (http://www.acdlabs.com) was used to construct the structure of the ligands. The ligand molecules were generated and the three dimensional optimizations were done and then saved MOL file (a file format for holding information about the atoms, bonds, connectivity and coordinates of a molecule).

Drug likeliness prediction

Ligand property was predicted by using "Lipinski drug Filters" (http://www.scfbio-iitd.res.in/utility/LipinskiFilters.jsp). Lipinski rule of five helps in distinguishing drug-like and non-drug-like properties and predicts high probability of success or failure due to drug likeliness for molecules. The Lipinski filter helps in early preclinical assessment and thereby avoiding costly late stage preclinical and clinical failures.

Docking analysis:

The docking analysis is performed by Argus lab 4.0.1 for the anti-diabetic and cancer protein interacts with GC-MS of *Decalepis hamiltonii.* The compound or ligand selected for based on Lipinski's rule of five. Fitting points are added to hydrogen bonding groups on the protein. The interaction between the binding pockets of target protein, antidiabetic protein investigation compound to find out the accurate binding model for the active site of protein. The mechanism of ligand placement is based on binding site position. The protein ligand docking

energy values performance of this compound was based on the Scoring functions which is implemented in docking program to make various assumptions and implications to fit best complexes, which includes terms of hydrogen bonds employed by Argus lab 4.0.1 to rank the docked bases and to assess the binding site and the number of rotatable bonds present.

Ligand binding sites prediction

After docking the docked structure was saved as ".Pdb" file and further explored to predict the binding sites using "ligand explorer" software. The predicted binding sites, based on the binding energy, and amino acids make up the binding cavity. Here ligand binding site represents the site where the ligands most efficiently bind with the protein, among all the active site.

Discovery Studio Visualizer

The docking results were visualized using Accelyrs Discovery Studio 4.1 Visualizer. The discovery studio visualizer is also a free viewer that is designed to offer an interactive environment for viewing and editing molecular structures, sequences, X-ray reflection data, script and other data. DS Visualizer is handier for analyzing the docking results.

III. Results And Discussion

Natural sources are increasingly in identification of new drug agents and are using important for many clinical purposes. Molecular Docking is important methods in computerized drug designing for targeted diseases. This plant produces a diverse array of secondary metabolites that are pharmaceutically important and used as chemotherapeutic agents in the treatment of several types of aliments. In Silico technique strongly supports and helps to identify the novel and more potent inhibitors through the mechanism of Ligand-Receptor interaction. Here we used GC-MS extraction of *Decalepis hamiltonii* root for antimicrobial, antidiabetic and anti-inflammatory responsible protein. All experimental analysis was in fairly good agreement with molecular modeling findings. We enhanced the simple docking procedure by means of a sort of combined target and ligand-based drug design approach. Advantages of this combination strategy, based on a similarity parameter for the identification of weak binding chemical entities are illustrated in this work with the discovery of a new lead compound for NF-kappaB. Further biochemical analyses based on EMSA were performed and biological effects were tested on the compound exhibiting the best docking score. All experimental analysis was in fairly good agreement with molecular modeling findings (Piccagli *et al*., 2008).

S. No	Compound Name	Molecular Formula	Molecular weight	Hydrogen donor & acceptor	Docking energy kcal/mol
1.	Glycerin	$C_3H_8O_3$	92.09	3,3	-6.715
2.	4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6- methyl	$C_6H_8O_4$	144.12	2,4	-6.73
3.	Benzaldehyde, 2-hydroxy-4- methoxy	$C_8H_8O_3$	152.14	1,3	-7.702
4.	Mome inositol	$C_6H_{12}O_6$	180.2	6,6	-4.57
5.	Pentadecanoic acid, 14-methyl-, methyl ester	$C_{16}H_{32}O_2$	256.42	0,2	-13.19
6.	n- Hexadecanoic acid	$C_{16}H_{32}O_2$	256.42	1,2	ND
7.	9, 12-Octadecadienoic acid, methyl ester	$C_{19}H_{34}O_2$	297.2	0,2	-6.74
8.	11-Octadecenoic acid, methyl ester	$C_{19}H_{36}O_2$	296.48	1,3	ND
9.	Oleic acid	$C_{18}H_{34}O_2$	282.46	1,2	-14.29
10.	Thunbergol	$C_{20}H_{34}O$	290.48	1,1	ND

Table: 4 Molecular interaction amino acids for target- ligand molecule

S. No	Compound Name	Docked amino acids
1.	Glycerin	LYS426,VAL364,THR335
2.	4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl	LYS426,ARG419,ARG372,GLY368,GLU301,TYR422
3.	Benzaldehyde, 2-hydroxy-4- methoxy	CYS325,MET506,PHE495
4.	Mome inositol	GLU382,GLU302,GLU331,ARG372
5.	Pentadecanoic acid, 14-methyl-, methyl ester	CYS325
6	Oleic acid	LEU324,PHE328,LEU509,MET506,VAL504
7	9, 12-Octadecadienoic acid, methyl ester	MET506,PHE328,LEU505,PHE382,LEU398,LEU324

Amino acid – Hydrogen interaction of amino acids. Amino acid – hydrophobic interaction of amino acids.

The molecular interaction between the ligand and the protein (receptor) was investigated using the Ligand fit protocol. Showen in table.1 and 2)

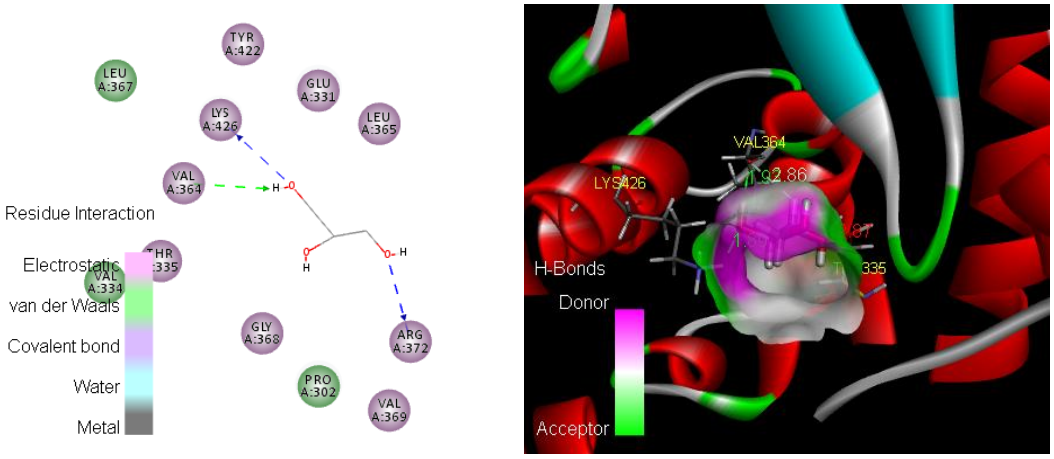

Figure.1 In silico analysis of antidiabetic activity of glycerin from root extract of *Decalepis hamiltonii*

The molecular interaction between the ligand and the protein (receptor) was investigated using the Ligand fit protocol. The glycerin was docked into active site of **ERRα** receptor. The green dotted line denoted the hydrogen bonds. The interactions of amino acid residues involved in molecular interactions with glycerin (Figure.1)

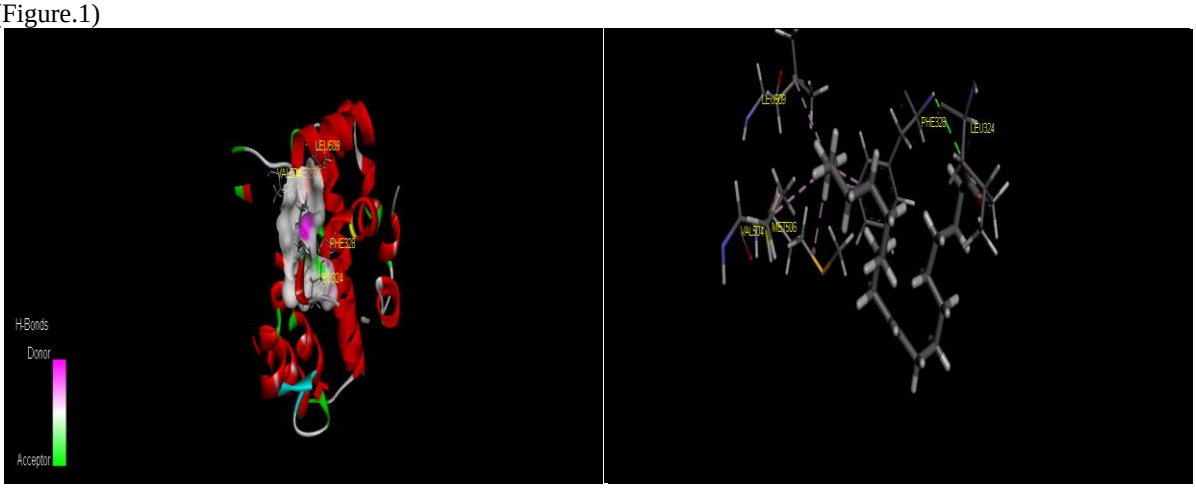

Figure.2 In silico analysis of antidiabetic activity of oleic acid from root extract of *Decalepis hamiltonii*

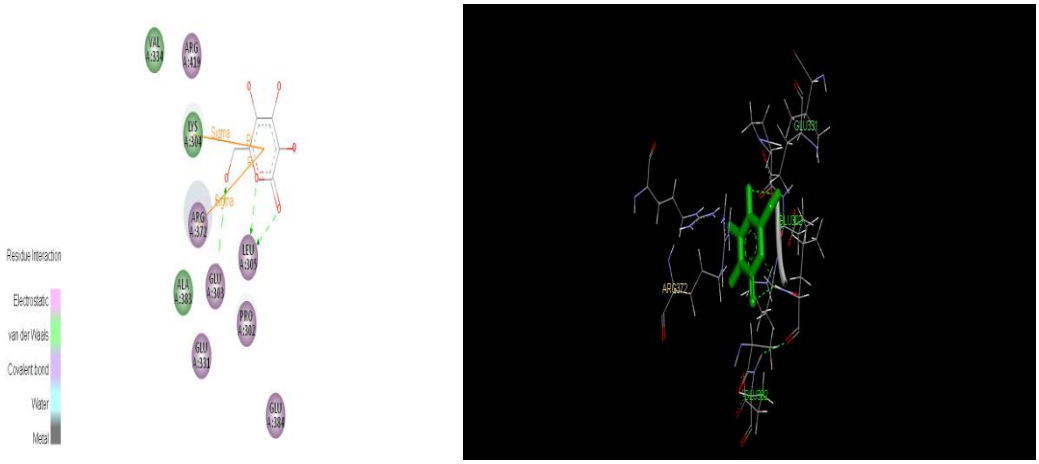

Figure.3 In silico analysis of antidiabetic activity of Mome inositol from root extract of *Decalepis hamiltonii*

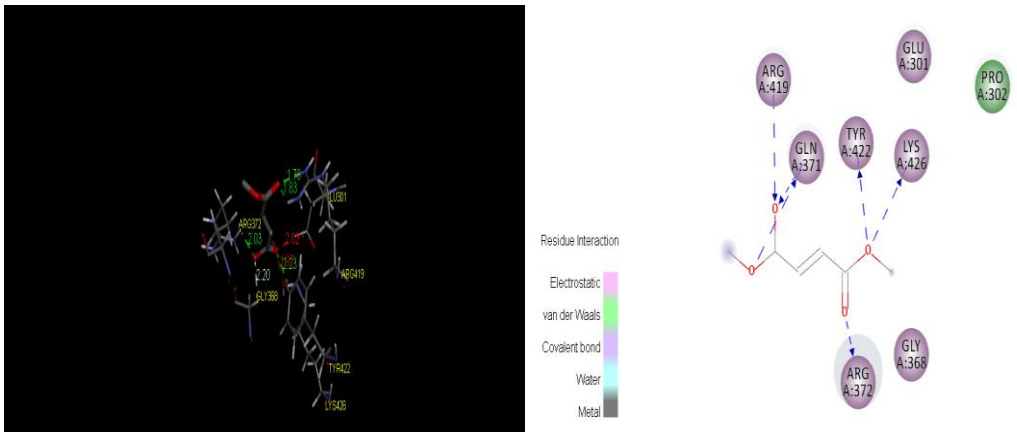

Figure.4 In silico analysis of antidiabetic activity of momeinsotial from root extract of *Decalepis hamiltonii*

The molecular interaction between the ligand and the protein (receptor) was investigated using the Ligand fit protocol. The oleic acid (-14.29 kJ mol−1) was docked into active site of **ERRα** receptor. The green dotted line denoted the hydrogen bonds. The interactions of amino acid residues involved in molecular interactions with oleic acid (Figure.2)

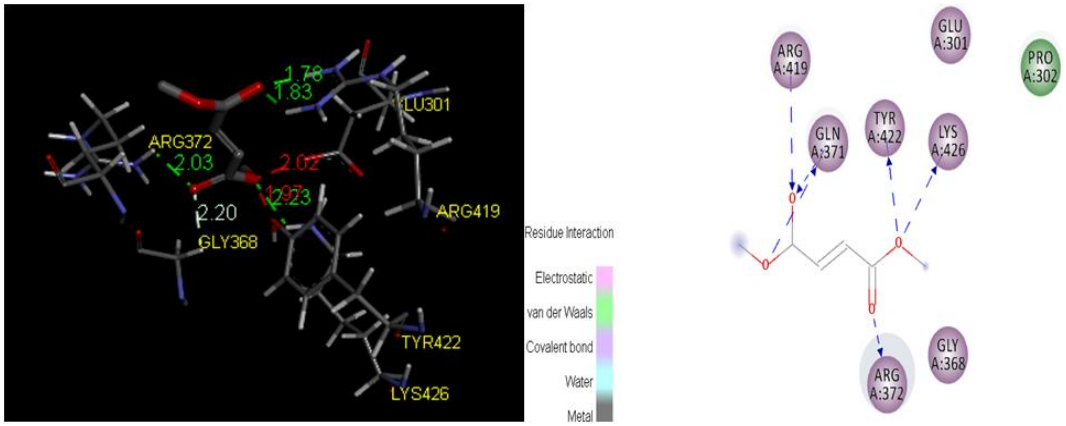

Figure. 5 3D and 2D structures for amino acid regions for Benzaldehyde, 2-hydroxy-4- Methoxy interact with Targeted protein

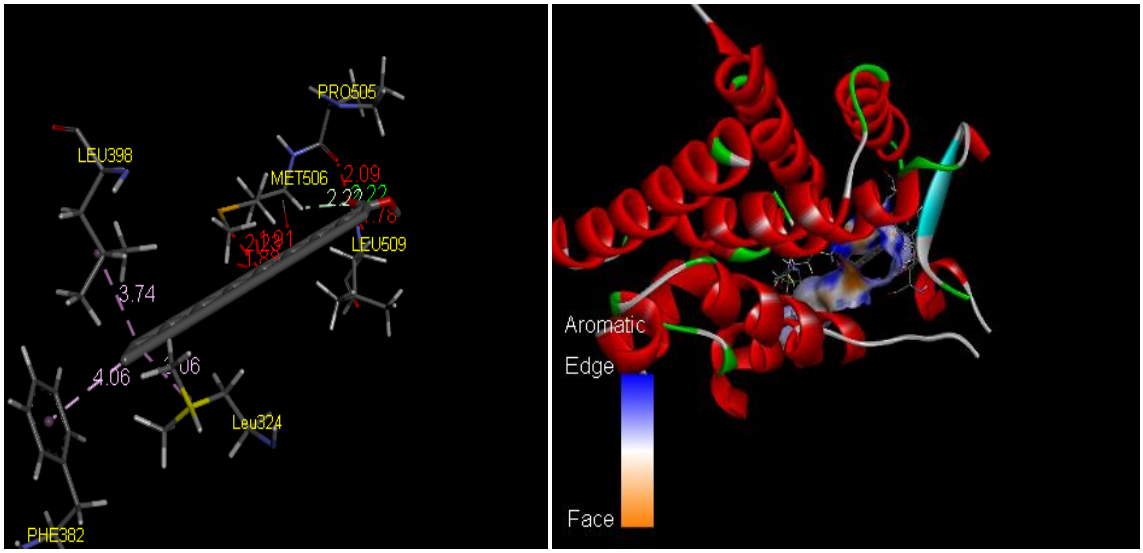

Figure.6 In silico analysis of antidiabetic activity of 9, 12-Octadecadienoic acid, methyl ester from root extract of *Decalepis hamiltonii*

Screening methods were routinely and extensively used to reduce cost and time of drug discovery. It has been clearly demonstrated that the approach utilized in this study was successful in finding novel anti-diabetic inhibitors from plant source. The plant compounds that targeted the PBRY gamma protein were screened and ranked based on their dock score. The lipinkis prediction helped in the identification of more suitable ligand towards target protein. The dock score and other scores (LEU324,PHE328,LEU509,MET506,VAL504) were observed the more the vander-walls interactions show that the ligand structure is having number of alkyl groups due to which Vander-walls interactions can be formed. If the hydrophobic interactions are more it shows that the ligand is having groups that can participate in the hydrophobic interactions. If the charge interactions are presents it helps finding more appropriate binding and so shows greater affinity to the receptor, contributing more potency. Lipinkis rule of five is used as a first step filter to perform virtual screening of compounds, in an effort to quickly eliminate lead candidates that have poor physicochemical properties for oral bio availability. However the compound having good dock scores which had similar action like standard drugs. Future perspectives understanding the interactions between proteins and ligand are crucial for the pharmaceutical and functional food industries. The compounds were screened for inhibition of glycogen synthase kinase-3 (GSK-3) protein, a wound-healing biomarker, by molecular docking and dynamic studies. Taraxerol may be a potent inhibitor of GSK-3 _ because it exhibited minimum binding (−12.59 kJ mol−1) and docking (−11.25 kJ mol−1) energy. Molecular dynamics studies revealed that taraxerol had minimum potential energy with the target protein. Wound-healing was studied in experimental rats *in vivo* (Rajanaika *et al.*, 2014). The plant compounds that targeted protein were screened and ranked based on their dock score. The lipinkis prediction helped in the identification of more suitable ligand towards target protein. Molecular Docking Compounds Identification of docking Energy -17.6025kcal/mol.

IV. Conclusion

D.hamiltonii methanol root extract. The docking studies further confirmed the antidiabetic property of the bioactive compounds revealed via GC-MS analysis of this extract and suggested that first time demonstrated a strong (diabetic) inhibitory property of this extract was maybe due to the identified bioactive compounds.

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