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A Systematic Way to Understand the Anti-obese Potentials of *Cissus quadrangularis* (Pirandai): A Nutraceutical Approach

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ABSTRACT

Background: The development of obesity involves hormones and neurotransmitters. The prevalence of obesity is measured by body mass index (BMI) raised to unacceptable levels in both men and women worldwide. Thyroid hormones are involved in multiple physiological processes, regulate basal metabolic rate, promote the adrenergic nervous system to generate heat in response to cold exposure and stimulate gluconeogenesis and lipolysis and lipogenesis. The increase in the production of thyroid hormone will increase the basal metabolic rate in the body. Thus, the increase in BMR reduces the breakdown of LDL-cholesterol, total cholesterol, and triglycer ides, which causes fat storage. The reduction in the fat level will eventually lead to a lower risk of obesity.

Methods: *Cissus quadrangularis* has been reported to reduce obesity in humans, but no scientific evidence is available to support its use. The computational approach is used to study its biological properties such as molecular docking and functional analysis was performed using BIOVIA Discovery Studio software.

Result: The molecular docking, pharmacodynamic and pharmacokinetic studies conducted on the active principles of *Cissus quadrangularis* showed good interaction with selected target proteins involved in obesity. Almost all the active principles possess anti-obesity properties. Amoyrone and ascorbic acid of *Cissus quadrangularis* has shown excellent interaction, drug likeliness, pharmacokinetic properties. This finding might help in developing an alternate, cost-effective, safe, eco-friendly anti-obese drug. However the results could be validated with *in vivo* and *in vitro* studies.

Key words: Computational biological approach, *Cissus quadrangularis*, Molecular interaction, Obesity.

INTRODUCTION

Obesity is defined as a condition of abnormal or excessive fat accumulation in adipose tissue, to the extent that health is impaired. This excess fat is distributed either around the waist and trunk or peripherally around the body. In general, obesity is associated with several diseases in mankind. Obesity also carries serious implications for psychosocial health, mainly due to societal prejudice against fatness.

Thyroid hormones are involved in multiple physiological processes, regulate basal metabolic rate, promote the adrenergic nervous system to generate heat in response to cold exposure and stimulate gluconeogenesis and lipolysis and lipogenesis. Patients with thyroid dysfunction may experience changes in body weight and body composition (Adesanya, 1999).

Pirandai, a climbing plant in a grape family whose botanical name is *Cissus quadrangularis,* also called Devil's backbone or Veldt grape in English: Hadjod or Jangliangoor in Hindi; Mangaravalli or Asthisamhaara in Kannada: Changalam and Kokkitaya-all or Nalleru in Telgu has many remarkable scientifically confirmed health benefits. It has been prescribed in ancient Ayurveda texts by Bhava Prakasha and Chakra Dutta as a general tonic, especially for patients with bone related issues. Since then, it has been used as an external application and as an internal medication by bonesetters. The plant has vitamins, minerals, triterpenoids and carotenoids, components that give it a variety of health benefits. It can be incorporated into cookies to increase their nutritional value (Bernadette Biondi, 2010).

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The objective is to perform molecular docking studies of the photo-active chemical ligands of *C. quadrangularis* and their pharmacodynamics in the human obesity pathway thereby understanding their anti-obese property (De Ruyck 2006).

MATERIALS AND METHODS

This research work was carried out at College of Food and Dairy Technology, Koduveli, Chennai-600 052 and Department of Bioinformatics, Madras Veterinary College, Chennai-600 007, Tamil Nadu, India during Jan-May 2021.

For identification and preparation of drug targets and ligands, molecular docking and functional analysis were done by using BIOVIA Discovery Studio - a commercial software for Pharmacodynamics studies of the interaction of ligands towards their drug targets. The protein targets were identified as 3D drug target molecules which were downloaded from the online Protein Database Protein Data Bank (PDB) *viz.* URL:https://www.rcsb.org/.

The ligands which were extensively studied were retrieved from the PubChem database *viz*., URL:https://pubchem.ncbi.nlm.nih.gov/.

Molecular docking of the identified drug target and collected plant active components were done using the software BIOVIA Discovery Studio. The pharmacodynamic analysis was carried out in the Prediction of Activity Spectra for Substances (PASS) Online server.

Prediction of activity spectra for substances (PASS) online is the openly available online server. This resource is intended to predict the spectrum of biological activity of organic compounds based on their structural formulas for more than 4000 types of biological activity with an average accuracy of more than 95% (Filimonov *et al*., 2014). The PASS server is opened through the URL: www.pharmaexpert.ru/passonline/ (Filimonov). The SMILES format is entered into the tool for the prediction.

The pharmacokinetic analysis is a web-based application for predicting ADME data and building drug-like libraries using the *in silico* method.

RESULTS AND DISCUSSION

Cissus quadrangularis, also known as veldt grape, adamant creeper, or devil's backbone, is a plant that belongs to the grape family. Native to certain parts of Asia, Africa and the Arabian Peninsula, Historically, it has been used to treat many conditions, including obesity, hemorrhoids, gout, asthma and allergies and recent research has found that this power-packed plant may also help promote bone health, relieve joint pain and protect against chronic conditions like heart disease, diabetes and stroke 9 (Jia *et al*., 2014). The healing properties of this plant are attributed to its high contents of vitamin C and antioxidant compounds like carotenoids, tannins and phenols. Traditionally, *Cissus quadrangularis* has been shown to reduce obesity in humans but there is no scientific evidence to support these uses. In the present study, biological activity has been proved using a computational approach (Garrow *et al*., 2006).

The fundamental goal in drug design is to predict whether a given molecule will bind to a target and if so how strongly. *In-silico* docking experimentation involved predictions from biological data with computer-based models to reduce the use of the biological system. This computational tool has the vast range to allow researchers to refine their experimental database reducing costs and time and increasing the research efficacy. *In-silico* interaction analysis between therapeutic markers and plant bioactive principles is the modern trend in the drug industry to identify drug-like molecules. *In-silico* methods can help in identifying drug targets via bioinformatics tools. Computational tools offer the advantage of delivering new drug candidates more quickly and at a lower cost (Julius, 2006).

The proteins thyroid-stimulating hormone (TSH), thyroid peroxidase (TPO) and thyroid peroxidase (TPO) and thyroglobulin which are involved in the thyroid signaling pathway were undertaken for the study. The proteins were selected based on the role they play in the thyroidsignaling pathway. The protein TSH, thyroglobulin and thyroid peroxidase have 16, 102 and 23 active sites respectively. These binding sites were predicted using the Biovia Commercial tool. Table 1 shows the selected proteins and the number of active sites present (Kim, 2015).

The phytochemicals present in the *Cissus quadrangularis* have been identified based on documentary evidence. The 3D structure of the phytochemicals has been retrieved from the PubChem database which has been listed in Table 2.

After the identification of receptors of the thyroid signaling pathway and phytochemicals of *Cissus quanragularis*, molecular interaction work was undertaken with the help of BIOVIA discovery studio 2020. The results of the interaction study have been depicted here under Table 3 and Plate 1-3.

Pharmacokinetics and pharmacodynamics result

Pharmacokinetic analysis the ADME studies carried out using Swiss ADME revealed the pharmacokinetic properties of ascorbic acid, ampyrone and. The gastrointestinal absorption is high whereas penetration of the blood-brain barrier is absent in both theligands. Skin permeability varies from -6.02 to -7.82 cm/s suggestive of topical application.

Toxicity predictions

Toxicological screening is very important for the development of new drugs and the extension of the therapeutic potential

Table 1: Target protein structure information.

Name of the target	No. of active sites	RCSBPDB ID
Thyroid-stimulating hormone (TSH)	16	3G04
Thyroglobulin	102	6SCJ
Thyroid peroxidase (TPO)	23	Modeled and validated

Table 2: Phytochemicals of *Cissus quadrangularis*.

Name of the phytochemicals	PUBCHEM ID
Calcium oxalate	33005
Coloside A	6438266
Alpha amyrin	225688
Adrenosterone	223997
Alpha amyrenone	12306155
Ampyrone	2151
Ascorbic acid	54670067
Carotene	6419725
3 Oxo 5 beta steroid	439810
Phytosterol	12303662

Table 3: Docking score of the receptor drug targets and ligands.

Name of the target	Name of the interacting ligand	Dock score	Binding energy
Thyroid-stimulating hormone (TSH)	Ampyrone	105.20	-61.00
	Ascorbic acid	87.93	-58.25
	Phytosterol	135.87	-78.62
Thyroglobulin	Ascorbic acid	120.123	-43.02
	Alpha - Amyrin	78.43	-39.21
Thyroid peroxidase (TPO)	Amoyrone	170.31	-81.67
	Ascorbic acid	81.00	-74.00

of existing molecules. The US Food and Drug Administration (FDA) states that it is essential to screen new molecules for pharmacological activity and toxicity potential in animals.

Toxicity was predicted with the help of the tool PreADMET. The results showed that the interacting phytochemicals are free from toxicity.

Pharmacodynamic study

The pharmacodynamic study was carried out with PASS online server. The results have been displayed in Plate 4- 7.

Cissus quadrangularis, also known as veldt grape, adamant creeper, or devil's backbone, is a plant that belongs to the grape family. Native to certain parts of Asia, Africa and the Arabian Peninsula, Historically, it has been used to treat many conditions, including obesity, hemorrhoids, gout, asthma and allergies and recent research has found that this power-packed plant may also help promote bone health, relieve joint pain and protect against chronic conditions like heart disease, diabetes and stroke. The healing properties of this plant are attributed to its high contents of vitamin C and antioxidant compounds like carotenoids, tannins and phenols. Traditionally, *Cissus quadrangularis* has been shown to reduce obesity in humans. but there is no scientific evidence to support these uses. In the present study, biological activity has been proved using a computational approach (Lee, 2016).

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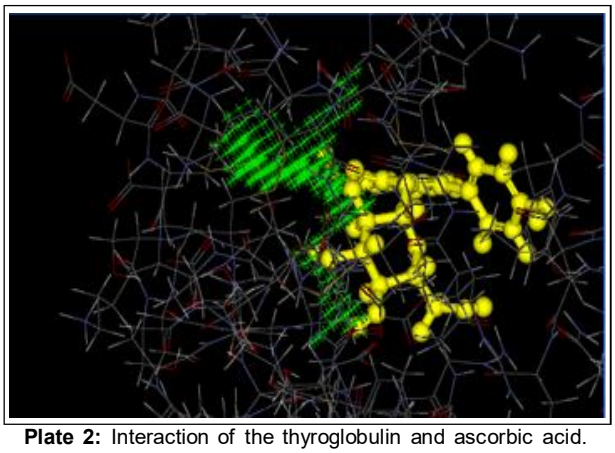


Plate 2: Interaction of the thyroglobulin and ascorbic acid.

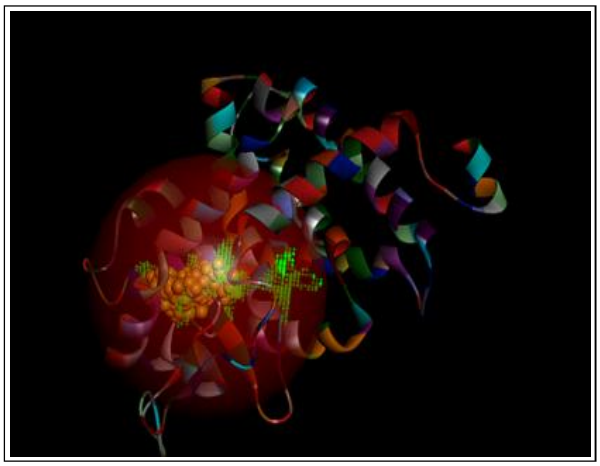


Plate 1: Interaction of the thyroid stimulating hormone and ligand (Phytochemical) Ampyrone.

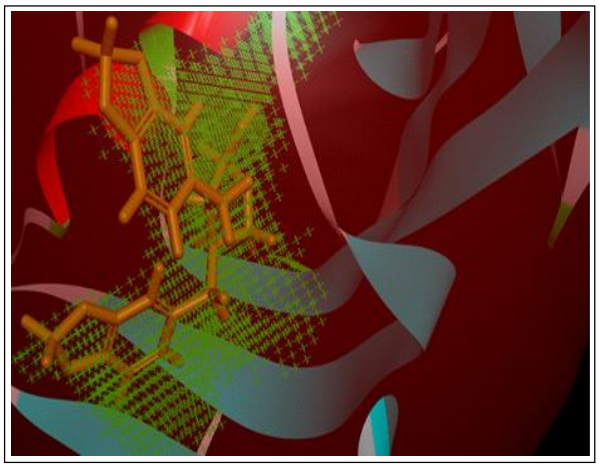


Plate 3: Interaction of receptor drug target TPO and ligand Ampyrone.

0,802	0,004	Cholestanetriol 26-monooxygenase inhibitor
0,799	0,002	Peptidoglycan glycosyltransferase inhibitor
0,801	0,006	Oxidoreductase inhibitor
0,792	0,001	Bile-salt sulfotransferase inhibitor
0,778	0,004	Alopecia treatment
0,783	0,014	Antineoplastic
0,770	0,003	Acetylcholine neuromuscular blocking agent
0,770	0,003	Antiacne
0,767	0,002	Cholestenone 5alpha-reductase inhibitor
0,769	0,005	Antisecretoric
0,765	0,003	Erythropoiesis stimulant
0,766	0,007	Glyceryl-ether monooxygenase inhibitor

Plate 4: Pharmacodynamic analysis of ampyrone.

All Pa>Pi Pa>0,3 Pa>0,7 ok

Pa	Pi	Activity
0,978	0,001	Testosterone 17beta-dehydrogenase (NADP+) inhibitor
0,973	0,001	CYP2B5 substrate
0,960	0,003	CYP2C12 substrate
0,955	0,002	CYP2J substrate
0,951	0,002	CYP2J2 substrate
0,940	0,001	CYP2A1 substrate
0,935	0,002	27-Hydroxycholesterol 7alpha-monooxygenase inhibitor
0,934	0,004	CYP2B substrate
0,922	0,001	CYP2A2 substrate
0,919	0,002	Ovulation inhibitor
0,916	0,003	CYP3A1 substrate
0,912	0,001	CYP2B11 substrate
0,911	0,004	CYP2B6 substrate
0,908	0,003	Lysase inhibitor
0,899	0,002	CYP2A11 substrate
0,900	0,003	Cholesterol antagonist
0,898	0,004	Anesthetic general
0,890	0,006	CYP3A4 substrate
0,886	0,003	CYP3A inducer
0,886	0,005	Prostaglandin-E2 9-reductase inhibitor
0,880	0,003	Male reproductive disfunction treatment
0,879	0,003	UGT1A substrate

Plate 5: Pharmacodynamic analysis of phytosterol.

The proteins thyroid-stimulating hormone (TSH), thyroid peroxidase (TPO) and thyroid peroxidase (TPO) and thyroglobulin which are involved in the thyroid pathway were undertaken for the study. The Proteins were selected based on the role they play in the thyroidsignaling pathway (Mullur, 2014). The protein TSH, thyroglobulin and thyroid peroxidase have 16, 102 and 23 active sites respectively. These binding sites were predicted using the Biovia Commercial tool (Nagani *et al.,* 2011).

The 3D structure of the 10 phytochemicals present in the *Cissus quadrangularis* was screened from the PubChem database. The phytochemicals were subjected to pharmacokinetic and pharmacodynamic studies to identify their efficacy and toxicity (Prabhavathi *et al*., 2016).

The ADME studies carried out using PreADMET revealed the pharmacokinetic properties of the interacting 3 phytochemicals. The gastrointestinal absorption is high whereas penetration of the blood-brain barrier is absent in both the ligands. Skin permeability varies from -6.02 to -7.82 cm/s suggestive of topical application.

The pharmacokinetic study showed that the compounds are free from toxicity. The pharmacodynamics activity reveals that the compounds have very good anti-obese activity. The molecular interaction study was carried out with Biovia software and the interaction was measured based on the docking score. Similar studies were performed in Zhang (2008). Although all the phytochemicals present in *Cissus quandragularis* have good interaction with all the proteins involved in the thyroid signaling pathway only the compounds with a score of 60 were taken into consideration. The compounds have very good bindingactivity against the thyroid receptors.

From the study, it is evident that the ascorbic acid had a good interactionwith all the three targets with dock scores of 87.93,120.123 and 81.00 respectively and the binding energy is also less. The phytochemical amoyrone has good interaction with TSH and TPO with dock scores of 105.20 and 170.31 respectively (Kaur and Malik, 2014).

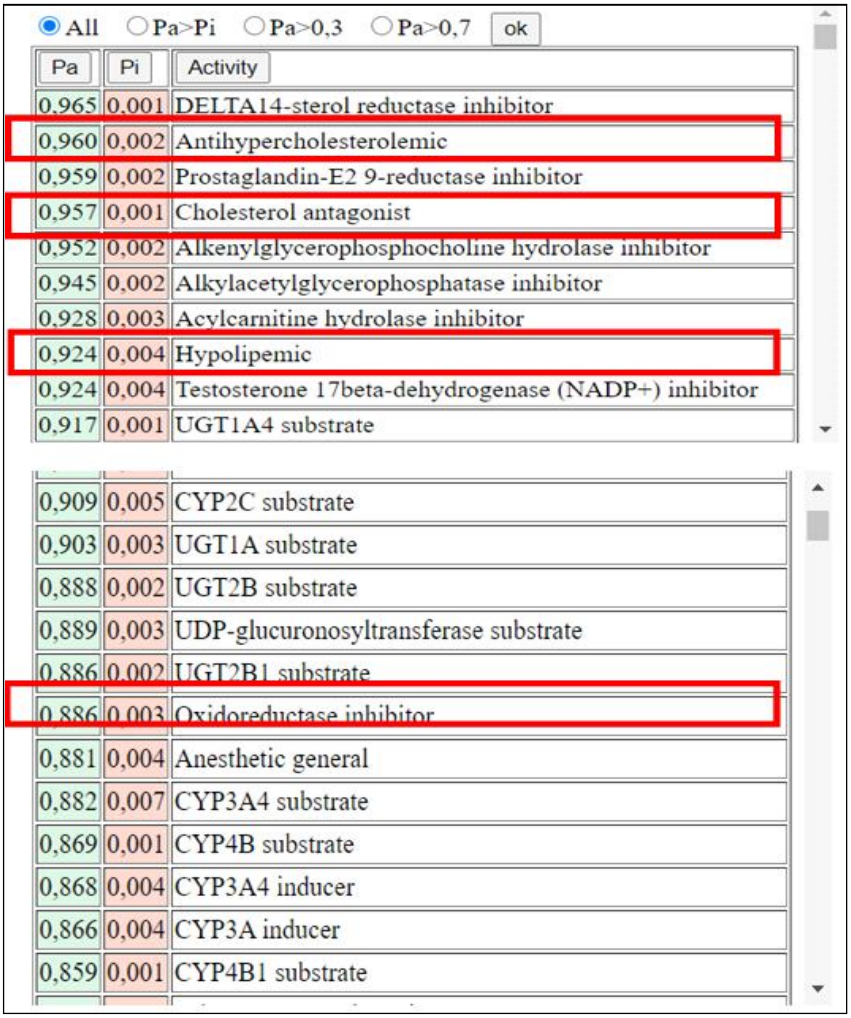
Natural remedies have been used for a long time for the treatment of obesity in our traditional healthcare practices. Our study supports the traditional practices.

Future research

A deeper understanding of the interaction of ligands Amoyrone and Ascorbic acid on proteins involved in lipid metabolism through other approaches (*in vivo* and *in vitro*) might be undertaken to produce novel drug candidates to safeguard mankind from obesity.

0,876	0,003	Hepatic disorders treatment
0,864	0,004	Caspase 3 stimulant
0,865	0,007	Mucomembranous protector
0,851	0,005	Hypolipemic
0,840	0,003	Antiulcerative
0,839	0,005	Membrane integrity antagonist
0,835	0,002	Nitric oxide antagonist
0,826	0,019	Testosterone 17beta-dehydrogenase (NADP+) inhibitor
0,808	0,003	Lipid peroxidase inhibitor
0,809	0,017	Alkenylglycerophosphocholine hydrolase inhibitor
0,793	0,003	Antiviral (Influenza)
0,789	0,002	Caspase 8 stimulant

Plate 6: Pharmacodynamic analysis of ascorbic acid.



All Pa>Pi Pa>0,3 Pa>0,7 ok

Pa	Pi	Activity
0,965	0,001	DELTA14-sterol reductase inhibitor
0,960	0,002	Antihypercholesterolemic
0,959	0,002	Prostaglandin-E2 9-reductase inhibitor
0,957	0,001	Cholesterol antagonist
0,952	0,002	Alkenylglycerophosphocholine hydrolase inhibitor
0,945	0,002	Alkylacetylglycerophosphatase inhibitor
0,928	0,003	Acylcarnitine hydrolase inhibitor
0,924	0,004	Hypolipemic
0,924	0,004	Testosterone 17beta-dehydrogenase (NADP+) inhibitor
0,917	0,001	UGT1A4 substrate
0,909	0,005	CYP2C substrate
0,903	0,003	UGT1A substrate
0,888	0,002	UGT2B substrate
0,889	0,003	UDP-glucuronosyltransferase substrate
0,886	0,002	UGT2B1 substrate
0,886	0,003	Oxidoreductase inhibitor
0,881	0,004	Anesthetic general
0,882	0,007	CYP3A4 substrate
0,869	0,001	CYP4B substrate
0,868	0,004	CYP3A4 inducer
0,866	0,004	CYP3A inducer
0,859	0,001	CYP4B1 substrate

Plate 7: Pharmacodynamic analysis of Alpha-Amyrin.

CONCLUSION

The dock scores recorded in this study show good interaction between the active principles of *Cissus quandragularis* with selected targets involved in obesity. And the ligands Amoyrone and Ascorbic acid hold excellent drug likeliness, pharmacokinetic properties. This finding may be considered as a lead to developinga cost-effective, safe, eco-friendly anti-obese drug.

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Conflict of interest

The authors have no conflict of interest.

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