

The Journal of Phytopharmacology

(Pharmacognosy and phytomedicine Research)

Research Article

ISSN 2320-480X
JPHYTO 2020; 9(2): 76-82
March- April
Received: 06-03-2020
Accepted: 31-03-2020
©2020, All rights reserved
doi: 10.31254/phyto.2020.9201

D' Silva Wilnoska W

Department of Pharmacology and Toxicology, KLE College of Pharmacy, Belagavi, KLE Academy of Higher Education and Research (KAHER), Belagavi 590010, India

PR Biradar

Department of Pharmacology and Toxicology, KLE College of Pharmacy, Belagavi, KLE Academy of Higher Education and Research (KAHER), Belagavi 590010, India

Patil Ashwini M

Department of Pharmacology and Toxicology, KLE College of Pharmacy, Belagavi, KLE Academy of Higher Education and Research (KAHER), Belagavi 590010, India

Correspondence:

D' Silva Wilnoska W

Department of Pharmacology and Toxicology, KLE College of Pharmacy, Belagavi, KLE Academy of Higher Education and Research (KAHER), Belagavi 590010, India
Email: wilnoskadsilva@gmail.com

Network pharmacology of *Luffa cylindrica* with targets related to obesity

D'silva Wilnoska W, PR Biradar, Patil Ashwini M

ABSTRACT

With obesity being one of the causing factors of Metabolic Syndrome, this study was undertaken to pinpoint the phytoconstituents from *Luffa cylindrica* that can be utilized to regulate proteins associated with obesity. With eighteen such phytoconstituents being identified in *Luffa cylindrica*, detailed investigations were carried out on each of these compounds. The parameters of these investigations were drug likeness score and ADMET score comprising distribution, absorption, excretion, metabolism and toxicity profile. Of all the compounds, Rutin proved to have the highest drug likeness score. Simultaneously, docking studies and gene set enrichment analysis were also conducted on the phytoconstituents. While the docking studies were undertaken to establish their binding affinity with obesity-related proteins, the gene set enrichment analysis was carried out to find pathways modulated by the phytoconstituents. The docking studies revealed the binding energy of luteolin-7-o-beta-o-glucuronide methyl to be the highest. The gene set enrichment analysis identified a total of twenty-five different pathways that were involved in obesity. Signal transduction and metabolism was identified to score the highest gene count.

Keywords: ADMET, *Luffa cylindrica*, Network pharmacology, Obesity.

INTRODUCTION

With the number of overweight adults worldwide being placed in excess of a billion and more than 300 million people being currently identified as medically obese, it goes without saying that obesity is becoming increasing prevalent globally, across the entire spectrum of human populations worldwide^[1]. In order for obesity to be controlled and treated, there needs to be uniformity in its measurement and diagnosis. How are normal, overweight and obese persons to be classified? Towards this end, BMI (Body Mass Index) has come to be used as a unit of measurement of obesity worldwide. It is calculated as a ratio of a patient's weight in kilograms to the square of the patient's height in meters.

WHO has proposed the classification of normal and overweight adults as follows: Adults with a BMI 18.5 to 24.9 kg/m² are classified as Normal. Adults with a BMI 25 to 29.9 kg/m² are classified as Overweight. Adults with a BMI of 30 kg/m² are classified as Obese with this category being further subdivided as Class I obese, 30 to 34.9 kg/m² Class II obese, 35 to 39.9 kg/m² and Class III obese or morbidly obese^[2] being identified as 40 or greater kg/m²^[2].

In keeping with this classification, more than 35% of men and in excess of 40% of women in the United States are obese. Obesity has been identified as going hand in hand with health problems such as type 2 diabetes, a rising risk for coronary heart disease, gallstones, as well as different types of cancer and disability^[3]. In obese adults, abnormal inflammation caused by adipose tissue dysfunction is triggered by an imbalance in adipocytokines production. This in turn is associated with the development of cardiovascular diseases termed CVDs and innumerable site-specific cancers^[4,5,6].

As a consequence of the fact that obesity is a chronic disease, a majority of the medications used to treat it are approved for long-term treatment. In this context, only two anti-obesity medications; viz., Phentermine and Orlistat, have been granted approval by The Food and Drug Administration (FDA), the drug regulatory body of the USA. Of these, Phentermine treats obesity by acting as an adrenergic agonist that suppresses appetite for food on the one hand, while increasing resting energy expenditure on the other; whereas Orlistat induces weight loss by means of slowing down the action of pancreatic and gastric lipase in the process of digestion, thus resulting in a reduction in the absorption of fat from the gastrointestinal passage. These medications cause a wide variety of side-effects of which dry mouth, irritability, insomnia,

dizziness, abdominal pain, constipation, dyspepsia, vomiting, diarrhoea, nausea are the most widely recognized and well known [7].

As a result of this, many plants such as *Camellia sinensis*, *Glycine max*, *Citrus depressa*, *Capsicum annum*, and *Coffea Arabica* that have active components culturally accepted and recognized for their efficacy, safety, ability to reduce these side-effects are being used in anti-obesity treatment [9,10,11,12]. Today, consumers are well-aware of anti-obesity products derived from the leaves of green tea (*Camellia sinensis*). The major bioactive ingredient present in green tea is polyphenols which include flavones, flavonols, and flavan-3-ols also known as catechins. Several clinical trials conducted on catechins have shown the considerable beneficial effects of catechins on reducing body weight, lowering levels of serum leptin in the digestive tract thus leading to a marked reduction in the absorption of fatty acids [13].

When taken in this context, the study of the *Luffa cylindrica* (L.) plant, also known as *Luffa aegyptiaca*, as a natural remedy for obesity gains considerable importance. The main active ingredients in *Luffa cylindrica*, which is a member of the family Cucurbitaceae, comprise flavonoids, glycosides, terpenoids, saponins, tannins, anthraquinones, alkaloids and sterols [14].

The saponins isolated from the aerial parts of the plant have been known to have anti-obesity effects [15]. However, the probable mechanism of *Luffa cylindrica* in the management of obesity has not been illuminate. Hence, the aim of the current study is to probe this mechanism by which the *Luffa cylindrica* or *Luffa aegyptiaca* aids in the management of obesity via network pharmacology approach. It will focus on identifying those phytoconstituents of *Luffa cylindrica* which can act on the proteins involved in obesity and the pathways modulated by these phytoconstituents which will target the obesity-inducing proteins and thus aid in obesity control and management

MATERIALS AND METHODS

Mining of phytoconstituents and proteins involved in obesity

Phytoconstituents present *Luffa cylindrica* were mined from the available literature, scientific journals, articles and traditional medicinal books. The database was constructed for the phytoconstituents, their types, SMILES and PubChem CID. The canonical SMILES and PubChem CID of each phytoconstituents were retrieved from the PubChem Database. SMILES were queried for the prediction of the target in swiss target prediction with known ligand molecules. The proteins involved in obesity were identified with reference to the known targets of obesity reported in Therapeutic Target Database (TTD). Gene ID of each protein molecule identified as the target of obesity was retrieved from the UniProt.

Drug likeness prediction and ADMET

Canonical SMILES was queried for the prediction of drug likeness and ADMET of individual phytoconstituent. Drug likeness score was predicted via "Lipinski's rule of five" model by using MolSoft (<http://www.molsoft.com/>). Similarly, admetSAR2.0 [16] was used to predict ADMET profile of individual phytoconstituents.

Pathway and network analysis

Set of proteins involved in obesity was queried reactome pathway for gene enrichment analysis. Cytoscape 3.7.2 [17] was used to construct the network between phytoconstituents, protein molecules, and identified pathways. The colour and node size scale were used to interpret the whole network which is based on the number of edges (edge count).

Docking studies

Three-dimensional structure of caffeic acid, apigenin, ginsenoside Rgl, lucyoside Q, 1-o-caffeoyl-beta-D-glucose, 1-o-coumaroyl-beta-D-glucose, luteolin-7-o-beta-o-glucuronide methyl ester were retrieved

from PubChem database and minimized using mmff94 force field. The target molecule 5HT2C and CDK2 receptor were retrieved from the RCSB (<https://www.rcsb.org/>) database. Discovery Studio was used to remove water molecules and heteroatoms from the protein molecule. Similarly, AutoDock4.0 [18] was used to predict the binding affinity of constituents with receptors. After docking, the pose scoring the lowest binding energy was chosen to visualize the ligand-protein interaction in Discovery studio.

RESULTS

Mining of phytoconstituents and proteins involved in obesity

Eighteen different phytoconstituents were identified in *Luffa cylindrica* from open-source records. These phytoconstituents were identified as phenolic, flavonoids, poly-phenols, triterpenoid saponins. Similarly, the majority of the targeted obesity protein molecules were surface proteins and enzymes (Fig.1.).

Pathway and network analysis

Gene set enrichment analysis identified twenty-five different pathways, out of which six pathways were involved to modulate proteins involved in the obesity. Signal transduction and metabolism was identified to score the highest count of genes. Table 1: represents Pathways and genes involved in obesity. Table 2: Details of role of pathway involved in obesity Fig 2 represents network of proteins interacting with the phytoconstituents of *Luffa cylindrica*

Drug likeness and ADMET

Drug likeness score of all the compounds was predicted, the highest was scored by Rutin 1.10 followed by Luteolin-7-o-beta-D-glucuronide methyl ester 1.09. (Table 3). ADMET profile predicted that gallic acid, caffeic acid, p-coumaric acid, myrecetin, apigenin and lucylin A to possess CaCO-2 permeability. Similarly, rutin, Apigenin-7-o-beta-D-glucose and Lucylin A to possess high BBB permeability, likewise p-coumaroyl, Apigenin and Lucylin A to possess high HIA. Further lucyoside N, ginsenoside RE and geinsenoside RGL were predicted to be P-glycoprotein inhibitors. Similarly, Lucyoside N and Lucyoside R were predicted to be interactive with renal organic cation transporter Further ADMET profile revealed the phytoconstituents to be safe for consumption and their heat map is represented in Fig. 3.

Docking studies

The binding energy of caffeic acid, apigenin, ginsenoside Rgl with 5HT2C was found to be -4.16, -4.09, -4.9 kcal/mol. Lucyoside Q, 1-o-caffeoyl-beta-D-glucose, 1-o-coumaroyl-beta-D-glucose, luteolin-7-o-beta-o-glucuronide methyl with CDK2 was found to be -5.64, -5.00, -4.38, -6.4 kcal/mol respectively Table 4.

DISCUSSION

The aim of the present study was to pinpoint the probable interaction of the targets involved in obesity with the reported phytoconstituents from *Luffa cylindrica*. A network representing the probable interaction of phytoconstituents, their potential targets and their molecular mechanism was constructed with utilization of multiple cheminformatic and bioinformatic tools for mining various phytoconstituents, their potential targets and the possible mechanisms that may be involved in the pathogenesis of obesity with minimal side effects [19,20]. The results were further enhanced with the utilization of *Insilco* study to investigate the interaction and binding affinity of multiple phytoconstituents.

The concept of "one compound-one protein interaction", which is the current trend of drug discovery for multiple pathogenic conditions, does not prove efficacious in multiple polygenic conditions such as, hypertension, obesity, diabetes mellitus type 2, and neurodegenerative diseases such as Alzheimer's and Parkinson's disease. A newer and a more effective approach to polygenic conditions would be to manage

them by targeting the multiple proteins involved in the disease with multiple phytoconstituents that will modulate the pathways involved in the pathogenesis of such conditions [21]

Quantification of lead hit hit to lead is crucial for the success of this concept, wherein drug likeness and ADMET profile play an important role. Identification of lead agents/molecules based on Lipinski's rule of five is assisted by drug likeness while the pharmacokinetic character of the respective phytoconstituents can be identified with the assistance of their ADMET profile through the utilization of the system regression model. The present study has identified the drug likeness of the phytoconstituent Rutin and its ability to act as a lead hit for further QSAR modeling.

A complex network of proteins can be formed by generating a chain-type reaction from the interactions of multiple proteins with a single protein involved in the disease pathogenesis. The present study succeeded in identifying such a protein-protein interaction for further assessment via enrichment analysis. The metabolism pathways to modulate 20 different genes with a false discovery rate as low as 0.01 were identified through the study.

Previous studies on the subject have revealed that lipids, glucose, amino acids and proteins, when abnormally broken down or metabolized, play the prime role in the pathogenesis of obesity. This study pursues the course of such metabolized protein molecules, targeted by the phytoconstituents compounds of *L. cylindrica*, recognizing that they could have an important role to play in the pathogenesis of obesity. This is being done in the hope of achieving a better understanding of how pharmacists can exploit this knowledge to formulate anti-obesity medications.

It can be gleaned from existing literature that amine ligand-binding receptors involving ADRA2A, ADRA2C, ADRB1, ADRB2, CHRM1, HTR2C and HTR6 tend to have a thermogenic effect on catecholamines and are mainly mediated via beta 2 receptors in obesity. The skeletal muscles serve as an area for the expenditure of a maximum amount of nervous system-mediated energy [21]. β_1 -, β_2 -, β_3 -(stimulatory), and α_2 -(inhibitory) adrenoceptor subtypes are the routes of action for catecholamines which are powerful regulators of lipolysis in adipose tissue. Thus, the role of β -adrenoceptors in energy expenditure and body weight control is an important one [22, 23, 24, 25, 26]. Evidence connecting (G protein) and G protein-coupled receptor (GPCR) signaling in insulin-responsive tissues and the pathogenesis of obesity and diabetes mellitus type 2 can be found in multiple published studies. These studies have suggested novel therapeutic targets for the said conditions [27]. The uniqueness of serotonin-releasing brain neurons is that the food intake normally controls the amount of neurotransmitter

they release. Thus, the key link in the feedback mechanism that aims at keeping carbohydrate and protein intakes more or less constant is the ability of the neurons to couple neuronal signalling properties to food consumption [28].

Furthermore, it has been identified that 5HT2C protein has an important role to play in the pathogenesis of obesity. In the present study, Ginsenoside Rg1 has been identified to have a high binding energy of -4.9 and hence can be a target for investigation as a lead hit for the obesity modulation potential of *Luffa cylindrica*. Likewise, CDK2 has also been identified to play an important role in obesity. The present study has also identified 7-o-beta-o-glucuronide methyl to possess a binding energy of -6.4 indicating a further need for investigation.

The probable mechanism of *Luffa cylindrica* as an anti-obesity agent has been investigated in the present study by evaluating the phytoconstituents, proteins and their pathway interaction via cheminformatic and bioinformatic tools. Although a few lead hits of *Luffa cylindrica* as an anti-obesity agent have been identified in the present study, the research team is of the opinion that individual testing of these hits could lead to catastrophic side effects and that this group of phytoconstituents should primarily be tested on a choice of testable agents rather than a single lead hit. The conclusions of the present study have been arrived at through CPU simulations and need to be validated with wet lab experiments.

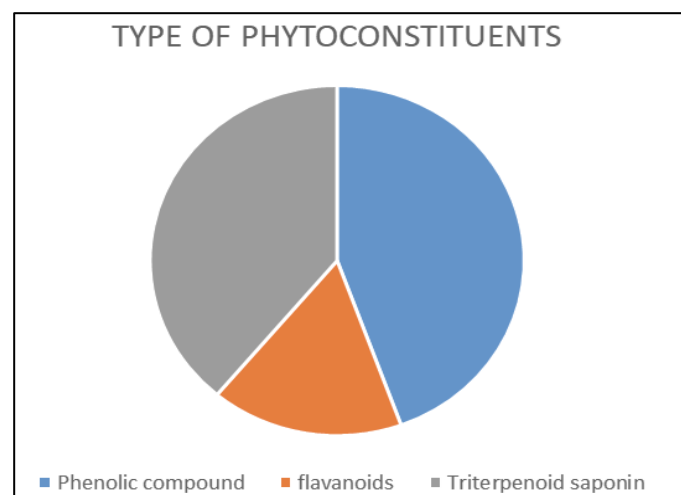


Figure 1: Types of phytoconstituents present in *Luffa cylindrica*.

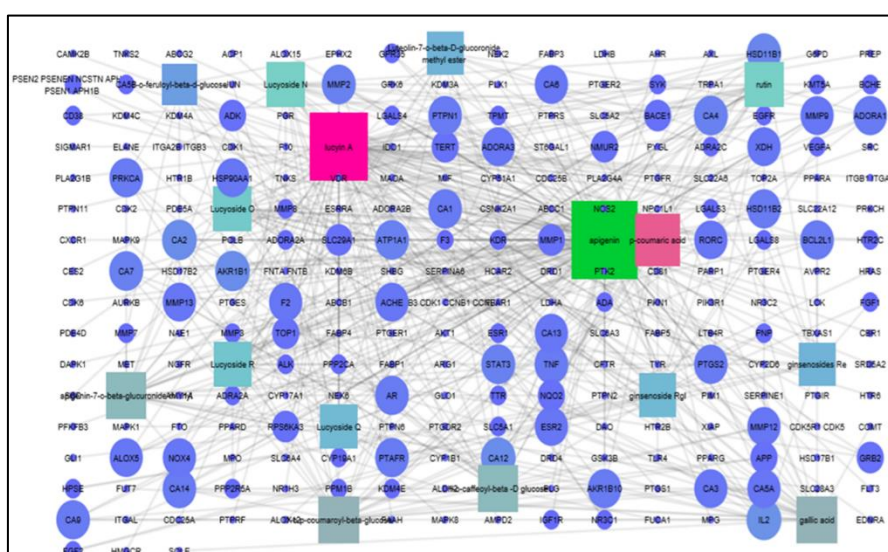


Figure 2: Network of phytoconstituents from *Luffa cylindrica* with targets related to obesity

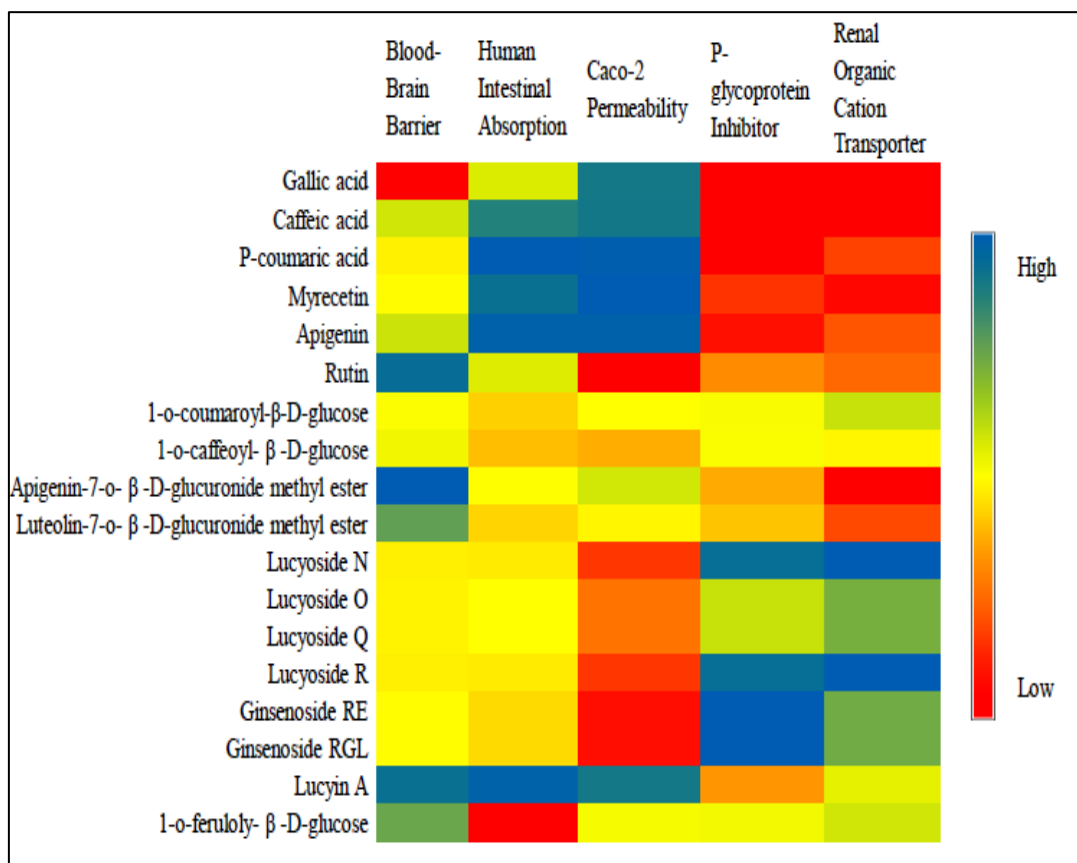


Figure 3: ADMET profile of phytoconstituents targeting protein involved in obesity.

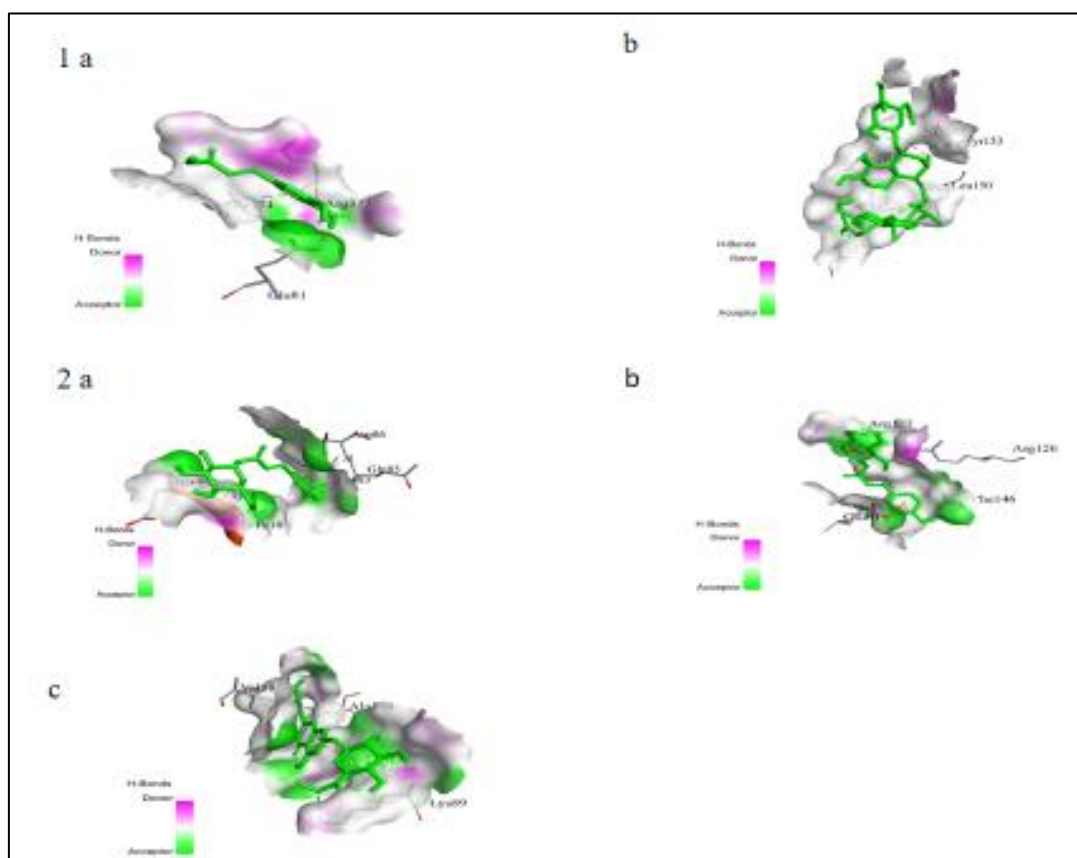


Figure 4: Interaction of (a) caffeic acid and (b) Ginsenoside RGL with (1) 5HT1A (a) 1-o-caffeoyl-beta-D-glucose (b) 1-coumaroyl-beta-D-glucose and (c) luteolin-7-o-beta-o-glucuronide methyl with (2) CDK

Table 1: Phytoconstituents modulated pathways

Pathway id	Pathway description	Count in gene set	Name of gene	P value	False discovery rate
R-HSA-1475029	Reversible hydration of carbon dioxide	12	CA1, CA12,CA13, CA14,CA2,CA3, CA4,CA5A,CA5B, CA6,CA7,CA9	1.11e-16	2.70e-14
R-HSA-373076	classA/1(Rhodopsin-like receptors	13	ADRA2A, DRA2C, ADRB1, ADRB2, BRS3, CCKAR, CCKBR, CHRM1, HTR2C, HTR6, OPRD1,OPRK1, PTAFR	6.25e-10	7.57e-08
R-HSA-500792	GPCR ligand binding	13	ADRA2A, ADRA2C, ADRB1, ADRB2, BRS3, CCKAR, CCKBR, CHRM1, HTR2C, HTR6, OPRD1, OPRK1, PTAFR	3.85e-08	2.31e-06
R-HSA-388396	GPCR downstream signalling	14	ADRA2A, ADRA2C, ADRB1, ADRB2, BRS3, CCKAR, CCKBR, CDK5, CHRM1, HTR2C, HTR6, OPRD1, OPRK1, PTAFR	2.74e-05	9.30e-04
R-HSA-372790	Signalling GPCR	14	ADRA2A, ADRA2C, ADRB1, ADRB2, BRS3, CCKAR, CCKBR, CDK5, CHRM1, HTR2C, HTR6, OPRD1,OPRK1, PTAFR	7.31e-05	0.002
R-HSA-162582	Signal transduction	20	ADRA2A, ADRA2C, ADRB1, ADRB2, BRS3, CCKAR, CCKBR, CDK1, CDK2, CDK5, CHRM1, FASN, HTR2C, HTR6, OPRD1, OPRK1, PPARG, PPARG, PTAFR, XIAP	2.09e-04	0.004
R-HSA-1430728	Metabolism	20	ADRA2A, ADRA2C, CA1, CA12, CA13, CA14, CA2,CA3, CA4, CA5A, CA5B, CA6, CA7, CA9, DGAT1, FASN, HSD11B1, MAOB, PPARG, PPARG	8.41e-04	0.01

Table 2: Details of the role of pathway involved in obesity

Pathway Description	Role in obesity
Amine ligand-binding receptors	GPCR receptors, amines bind to acetylcholine, adrenaline, noradrenaline, dopamine, serotonin, histamine.
Adrenoceptors	Heightened sympathetic nerve activity as well established observation in obesity, hypertension and type II diabetes. Fight or flight response increased heart rate, pupil dilation and energy metabolism
Signalling GPCR	Visual sense, smell, behavioural regulation, function of the autonomic nervous system and regulation of immune system inflammation, obesity and diabetes
Serotonin receptors	Appetite, metabolism, sleep, mood, sexuality, body temperature, anger aggression
Metabolism	Generate energy through oxidation, energy metabolism
NR1H2 and NR1H3 regulate gene expression linked lipogenesis	Activation results in net elimination of cholesterol from body

Table 3: Drug likeness score of phytoconstituents of *Luffa cylindrica*.

Ligand molecules	Pubchem CID	Molecular Weight (g/mol)	NHBA	NHBD	Log P	Log S (mg/l)	DLS
Gallic acid	370	170.12	5	4	0.55	27147.75	0.07
Caffeic acid	689043	180.16	4	3	1.69	847.00	-0.02
p-coumaric acid	637542	164.16	3	2	2.07	562.38	-0.74
Myrecetin	521672	318.23	8	6	1.73	164.52	-0.04
Apigenin	5280443	270.240	5	3	3.06	18.85	0.77
Rutin	5280805	610.5	16	10	-1.87	134.14	1.10
1-o-feruloyl-beta-D-glucose	13962928	356.32	9	5	-0.71	1776.29	0.05
1-o-coumaroyl-beta-D-glucose	14158117	326.3	8	5	-0.68	1542.52	-0.35
1-o-caffeoyl-beta-D-glucose	5281761	342.3	9	6	-0.16	2220.58	0.31
Apigenin-7-o-beta-D-glucuronide methyl ester	13844658	460.4	11	5	0.72	34.90	0.88
Luteolin-7-o-beta-D-glucuronide methyl ester	126962575	492.4	13	7	-0.14	184.79	1.09
Lucyoside N	78407206	650.8	10	7	3.30	1.21	0.61
Lucyoside O	85117733	634.4	9	6	4.41	0.02	0.57
Lucyoside Q	74029748	634.8	9	6	4.02	0.23	0.26
Lucyoside R	3083524	666.8	11	8	2.25	1.64	0.63
Ginsenoside Re	441921	947.2	18	12	0.62	0.13	0.32
Ginsenoside Rgl	2428657	801	14	10	1.91	0.29	0.28
Lucyin A	53463576	486.7	5	3	5.41	0.67	035

NHBA- Number of hydrogen bond acceptor, NHBD- Number of hydrogen bond donor, DLS-Drug likeness score

Table 4: Binding energy of phytoconstituents with the targets involved in obesity

Receptor	Phytoconstituents	Binding energy (kcal/mol)
5HT2C	Caffeic acid	-4.16
	Apigenin	-4.09
	Ginsenoside Rgl	-4.9
CDK2	Lucyoside Q	-5.64
	1-o-caffeoyl-beta-D-glucose	-5.00
	1-o-coumaroyl-beta-D-glucose	4.38
	luteolin-7-o-beta-o-glucuronide methyl	-6.4

CONCLUSION

The current study exhibits potential molecule of *Luffa cylindrica* to interact with majority of proteins that are implicated in the pathogenesis obesity. The results demonstrated that Lucyoside Q, 1-o-caffeoyl-beta-D-glucose with CDK2 exhibited highest binding affinity interaction via hydrogen bonding and pi-interaction. Prediction of the drug likeness character of the molecule has also helped to identify Rutin shows highest drug likeness score. The findings of current study are based only on computational predictions, which needs to be further proven by well-designed wet-lab protocols.

Conflict of interest

Nil

ACKNOWLEDGEMENT

The authors are thankful to Prof. Dr. Sunil S. Jalalpure for providing necessary facilities and Pukar Khanal for designing, interpreting and drafting this manuscript.

REFERENCES

1. Popkin BM, Adair LS, Ng SW. Global nutrition transition and the pandemic of obesity in developing countries. 2012; 70(1):3-21.
2. Stevens-Lapsley JE, Petterson SC, Mizner RL, Snyder-Mackler L. Impact of body mass index on functional performance after total knee arthroplasty. 2010; 25(7):1104-9.
3. Kopelman PG. Obesity as a medical problem. 2000; 404(6778):635-43.
4. Lavie CJ, McAuley PA, Church TS, Milani RV, Blair SN. Obesity and cardiovascular diseases: implications regarding fitness, fatness, and severity in the obesity paradox. J Am Coll Cardiol 2014; 63(14):1345-54.
5. Bhaskaran K, Douglas I, Forbes H, dos Santos-Silva I, Leon DA, Smeeth L. Bodymass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults. Lancet 2014; 384(9945):755-65.
6. Dixon JB, Egger GJ. A narrow view of optimal weight for health generates the obesity paradox. Am J Clin Nutr 2014; 99(5):969-70.
7. Saunders KH, Umashanker D, Igel LI, Kumar RB, Aronne LJ. Obesity Pharmacotherapy. Med Clin North Am. 2018; 102(1):135-148.
8. Zhi J, Melia AT, Guerciolini R, Chung J, Kinberg J, Hauptman JB et al. Retrospective population-based analysis of the dose-response (fecal fat excretion) relationship of orlistat in normal and obese volunteers. Clin Pharmacol Ther. 1994; 56(1):82-5.
9. Lee YS, Cha BY, Saito K, Choi SS, Wang XX, Choi BK, Yonezawa T et al. Effects of a Citrus depressa Hayata (shiikuwasa) extract on obesity in high-fat diet-induced obese mice. Phytomedicine. 2011; 18(8-9):648-54.

10. Ivan Torre-Villalvazo, Armando R Tovar, Victoria E Ramos-Barragán, Marco Antonio Cerbón-Cervantes, Nimbe Torres. Soy Protein Ameliorates Metabolic Abnormalities in Liver and Adipose Tissue of Rats Fed a High Fat Diet. The Journal of Nutrition, 2008; 138(3):462-468.
11. Murase T, Misawa K, Minegishi Y, Aoki M, Ominami H, Suzuki Y, Shibuya Y et al. Coffee polyphenols suppress diet-induced body fat accumulation by downregulating SREBP-1c and related molecules in C57BL/6J mice. Am J Physiol Endocrinol Metab. 2011; 300(1):E122-33.
12. Joo JI, Kim DH, Choi JW, Yun JW. Proteomic analysis for antiobesity potential of capsaicin on white adipose tissue in rats fed with a high fat diet. J Proteome Res. 2010; 9(6):2977-87.
13. Rains TM, Agarwal S, Maki KC. Antiobesity effects of green tea catechins: a mechanistic review. J Nutr Biochem. 2011; 22(1):1-7.
14. Nan-Nong Sun, Tsung-Yen Wu, Chi-Fai Chau. Natural Dietary and Herbal Products in Anti-Obesity Treatment. Molecules. 2016, 21(10):1351.
15. Khare CP. Indian Medicinal Plants. Springer-Verlag New York 2007.
16. Khanal P, Patil BM. Gene set enrichment analysis of alpha-glucosidase inhibitors from Ficus benghalensis. Asian Pacific Journal of Tropical Biomedicine. 2019; 9(6):263-270
17. Khanal P, Patil BM, Mandar BK, Dey YN, Duyu T. Network pharmacology-based assessment to elucidate the molecular mechanism of anti-diabetic action of Tinospora cordifolia. Clinical Phytoscience. 2019; 5:35.
18. Morris GM, Huey R, Lindstrom W, Sanner MF, Belew RK, Goodsell DS et al. AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. J Comput Chem 2009; 30(16):2785-2791.
19. Khanal P, Mandar BK, Magadam P, Patil BM, Hullatti KK. In silico docking study of limonoids from Azadirachta indica with pfpk5: a novel target for Plasmodium falciparum. Indian J Pharm Sci 81:326-332
20. Khanal P, Mandar BK, Patil BM, Hullatti KK. In silico antidiabetic screening of borapetoside C, cordifolioside A and magnoforine. Indian J Pharm Sci, 81:550-555
21. Khanal P, Patil BM. α -Glucosidase inhibitors from *Duranta repens* modulate p53 signaling pathway in diabetes mellitus. Advances in Traditional Medicine, 1-2.
22. Kazuko Masuo, Gavin W. Lambert. Relationships of Adrenoceptor Polymorphisms with Obesity. Journal of Obesity Article ID 609485, 2011, 10.
23. Iwashita S, Tanida M, Terui N et al., "Direct measurement of renal sympathetic nervous activity in high-fat diet-related hypertensive rats," Life Sciences, 2002; 71(5):537-546.
24. Monroe MB, Seals DR, Shapiro LF, Bell C, Johnson D, Parker-Jones P. "Direct evidence for tonic sympathetic support of resting metabolic rate in healthy adult humans," American Journal of Physiology, 2001; 280(5):E740-E744,
25. Blaak EE, van Baak MA, Kempen KPG, Saris WHM. "Role of α - and β -adrenoceptors in sympathetically mediated thermogenesis," American Journal of Physiology, 1993; 264(1, 1):E11-E17.
26. Hagström-Toft E, Enoksson S, Moberg E, Bolinder J, Arner P. " β -adrenergic regulation of lipolysis and blood flow in human skeletal muscle in vivo," American Journal of Physiology, 1998; 275(6):E909-E916,
27. Enoksson S, Talbot M, Rife F, Tamborlane WV, Sherwin RS, Caprio S. "Impaired in vivo stimulation of lipolysis in adipose tissue by selective β 2-adrenergic agonist in obese adolescent girls," Diabetes, 2000; 49(12):2149-2153,
28. Michelle E Kimple, Joshua C Neuman, Amelia K Linnemann, Patrick J Casey. Inhibitory G proteins and their receptors: emerging therapeutic targets for obesity and diabetes. Experimental & Molecular Medicine, 2014, 46.
29. Richard J Wurtman, Judith J, Wurtman. Brain Serotonin, Carbohydrate-Craving, Obesity and Depression. Obesity research 1995; 3(4)

HOW TO CITE THIS ARTICLE

D'silva Wilnoska W, PR Biradar, Patil Ashwini M. Network pharmacology of *Luffa cylindrica* with targets related to obesity. *J Phytopharmacol* 2020; 9(2):76-82.