NETWORK PHARMACOLOGY AND MOLECULAR DOCKING TECHNIQUES TO EXPLORE THE PHARMACOLOGICAL MECHANISM OF CATECHINS AND THEIR DERIVATIVES AGAINST METABOLIC SYNDROME

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ABSTRACT

Objective: Metabolic syndrome (MetS) is one of the most prevalent disorders in both industrialized and developing nations that it is characterized by a set of risk variables that encompass abdominal obesity, dyslipidemia, hypertension, and insulin resistance MetS constitutes a collective set of cardiometabolic attributes that raise the risk of type 2 diabetes mellitus and cardiovascular diseases. Catechins possess anti-inflammatory and antioxidant effects which may provide defense against many chronic diseases. The present study attempts to associate the pharmacological benefits of catechins and their derivates against MetS using *in silico* approaches.

Methods: Identification of the ligands and target proteins was done using drugbank and protein-protein interaction network stitch, respectively. The ligands and proteins were docked using pyrx and the docked complexes were visualized on BIOVIA to identify the potential ligand. ADMET analysis was done for the same ligands to study their pharmacological properties.

Results: The proteins glutathione peroxidase 1 and tumor protein P53 were identified as target proteins expressed in MetS which also showed effective docking results with the ligands hesperidin and gamma-tocopherol, respectively. The study's findings concurred with those of earlier studies indicating that the derivatives of catechins such as hesperidin and gamma-tocopherol had potential benefits in the prognosis of MetS.

Conclusion: The investigation findings concluded that the ligands hesperidin and gamma-tocopherol may be therapeutic against MetS prevention and management.

Keywords: Metabolic syndrome, Type 2 diabetes mellitus, Cardiovascular diseases, Obesity, Glutathione peroxidase 1, Tumor protein P53, Catechins.

INTRODUCTION

Metabolic syndrome (MetS), one of the most prevalent disorders in both industrialized and developing nations, is characterized by a bundle of risk factors that encompass hypertension, abdominal obesity, dyslipidemia, and insulin resistance [1]. MetS is a well-known non-communicable disease that has emerged as the major health hazard of the modern era, predominantly due to the rise in fast food intake and a sedentary lifestyle with little or no physical activity [2]. The National Cholesterol Education Program-Adult Treatment Panel III guidelines state that the diagnosis of MetS should be made if three or more of the following criteria are present: waist circumference >35 inches and >40 inches in females and males, respectively, triglyceride levels >150 mg/dL, low levels of HDL cholesterol apparently, 50 mg/dL in females and 40 mg/dL in males, blood pressure ≥130/≥85 mmHg, and fasting plasma glucose ≥110 mg/dL [3]. As a result of these predisposing risk factors, MetS is related to a higher incidence of cardiovascular diseases (CVD), type 2 diabetes mellitus (T2DM), stroke, non-alcoholic hepatic steatosis, and other metabolic disorders [4]. Although the etiology of MetS is uncertain, genetic susceptibility, environmental variables, diet quality and sedentary lifestyle, oxidative stress, inflammation, circadian rhythm disorders, and imbalance in gut flora have all been identified as potential contributors [5]. Even though MetS is of multifactorial origin, the basic pathophysiology of the disease is shown in Fig. 1.

MetS constitute a collective set of cardiometabolic attributes that raise the risk of T2DM and CVD by a five-fold and a two-fold rise during the subsequent 5–10 years, respectively [6]. One of the most defining symptoms of MetS is obesity, which was seen in 604 million adults and

108 million children, according to a 2015 global survey of obesity in 195 countries [2]. The rate of overweight and obese individuals was found to be 15.2% and 18.4%, respectively, among 4111 adolescents aged 12–19, based on the findings of the National Health and Nutrition Examination Survey 2009–10 (NHANES) [7]. According to prevalence estimates of 2% and 4% for children and teenagers, respectively, MetS may have impacted an estimated 25.8 million children and 35.5 million adolescents in 2020 [8]. The NHANES survey discovered that the frequency of MetS among US citizens was 33% from 2003 to 2012, with women being much more likely than men to have it (35.6 vs. 30.3%) [9]. Studies [10,11] conducted in India highlighted that the overall frequency of MetS was reported to be 30% in adults >18 years, compared to a 5.2% incidence in adolescents (10–19 years). Due to behavioral trends, the metropolitan population appears to be the most susceptible to acquiring MetS [12]. Contrarily, MetS were more prominent among US adults who reside in a rural setting, which may be related to the varied socioeconomic traits and lifestyles noted in rural versus urban censuses [13].

Various target proteins are expressed in MetS and with disease risk factors. In the present study, glutathione peroxidase 1 (GPX1) and the tumor protein P53 (TP53) were investigated to MetS. GPX1 is a selenoprotein that is crucial for shielding cells from oxidative damage. It is well established that oxidative stress and inflammation linked to MetS are induced by an elevation in free fatty acid levels in adipocytes [14]. TP53, on the other hand, is a tumor suppressor antigen involved in DNA damage repair mechanisms. TP53 partakes in the control of cellular metabolism, as well as the metabolism of glucose, lipids, amino acids, oxidative stress, and inflammation [15,16].
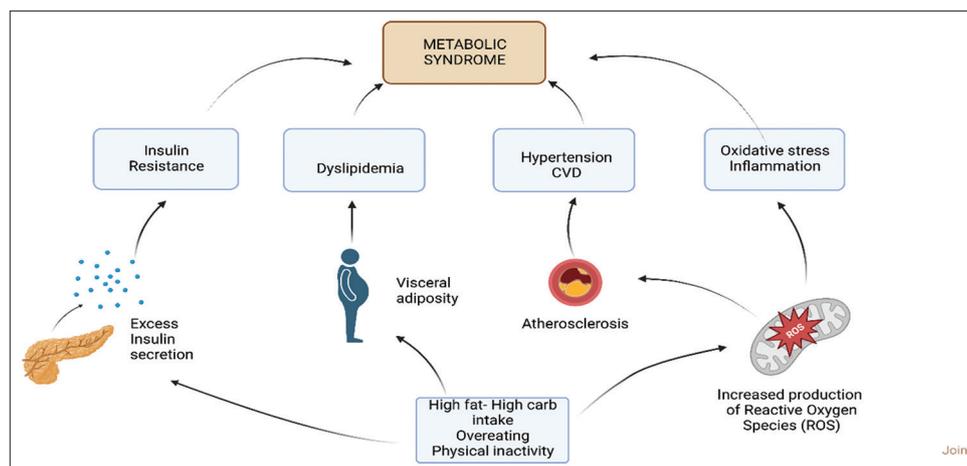
Fig. 1: Overview of the pathophysiology of MetS

Catechins are flavonols, which are naturally occurring polyphenolic substances and constituents belonging to the flavonoid family. They can be found in a variety of plants, but green tea contains most of them. Catechin is found in significant levels in fresh tea leaves, rock-rose leaves, wide beans, red wine, black grapes, strawberries, and apricots, whereas epicatechin is more commonly found in apples, blackberries, broad beans, cherries, black grapes, pears, raspberries, and chocolate. Catechins possess anti-inflammatory and antioxidant effects which may provide defense against a plethora of long-term illnesses, such as cancer, diabetes, CVD, and obesity [17]. Green tea catechins obtained from the leaves of *Camellia sinensis* (green tea) have the potential to reduce body fat through their antioxidant properties. Studies have discovered that the catechin epigallocatechin gallate has been strongly linked to improved fat oxidation and reduced fat deposition, suggesting that catechins have anti-obesity properties that could be used to mitigate MetS [18]. The present study attempts to associate the pharmacological benefits of catechins and their derivates against MetS using *in silico* approaches.

METHODS

Retrieval of ligands
The IMPPAT (Indian Medicinal Plants, Phytochemistry, and Therapeutics) and DrugBank (https://go.drugbank.com) databases were used to find the possible ligands. All of the ligands chosen for the current investigation had their canonical SMILES retrieved and the top 21 ligands were downloaded in SDF format from PubChem.

Identification of known and predicted proteins
The target proteins for MetS were identified employing the chemical database STITCH (http://stitch.embl.de/) and the canonical smiles of the top 21 ligands were used to build the ligand-protein interactions. Another database called GeneCards (https://www.genecards.org/) was used to identify the known proteins for the condition.

Protein-protein interaction (PPI) network stitch
Both the known and predicted proteins for the disease are subjected to build PPI on the STRING (https://string-db.org/) database. The clusters are generated using k-means clustering and the major clustered proteins are then identified.

Gene ontology and pathway enrichment analysis
ShinyGO 0.76.3 (http://bioinformatics.sdstate.edu/go/) is used to perform the pathway enrichment analysis for the primary clustered proteins. The target proteins are then identified by determining which dominant pathway is specifically expressed by the proteins.

Retrieval of proteins
The FASTA sequence of the target proteins GPX1 and TP53 with UniProt ID P07203 and K7PPA8, respectively, was retrieved from

the UniProt database (https://www.uniprot.org/). The protein's crystal structure was then downloaded in the PDB format following homology modeling.

Homology modeling
Contrary to all other methods, comparative homology modeling is the only technique capable of accurately constructing a 3-D model of a protein from its known amino acid composition. The 3D models of the TP53 and GPX1 were created using the Swiss Model (https://swissmodel.expasy.org/). The FASTA sequence of the proteins was used to build 3D models of the proteins.

For homology modelling 1gp1.1.A and 3q05.1 was taken as template for GPX1 and TP53 respectively. Cellular tumor antigen P53 with a sequence identity of 90.16% and 92.7%, respectively, was selected to build the model. The best model was selected based on their GMQE (Global Mean Quality Estimate) and QMEANDisCo values. The secondary structures and Ramachandran plots of the respective proteins are obtained from pdbSumgenerate. The ProSA web server (https://prosa.services.came.sbg.ac.at/prosa.php) provided the Z-plot of the proteins.

Protein purification
Using the Biovia Discovery Studio visualizer, the proteins GPX1 and TP53 were purified. Before docking, proteins are purified, and the following procedure was followed: The crystallographic structure and the free energy of the water molecule do not match. Water molecules were completely removed before docking since they have the potential to negatively impact docking scores. To hasten binding with the chosen ligands for the inquiry, the prebound ligands are removed from the crystal structures. To make the protein structures simpler, extra chains were eliminated; however, chain A was left in place for analysis. Structures that have been refined are improved by the addition of polar hydrogen atoms.

Molecular docking
The purified proteins (GPX1 AND TP53) were uploaded into PyRx (https://pyrx.sourceforge.io/) as macromolecules one at a time and the top 21 ligands were loaded into PyRx. The ligands were converted from. SDF format to PDB format using the OPENBABEL. The ligands were docked independently against GPX1 AND TP53 using the PyRx web server and energy reduction was done. Hesperidin, Naringin, Silibinin, (+)-Catechin gallate, and gamma-Tocopherol were discovered to be the most effective compounds binding with GPX1, while tocotrienol, gamma-tocopherol, hesperetin, dihydromyricetin, and 4'-methyl-epigallocatechin were found to be the most effective compounds binding with TP53. These compounds were chosen for further research based on their binding affinity with the target proteins after the docking findings were received.

Visualization

The conformations with the highest binding scores were downloaded in PDB format using Dassault Systems BIOVIA Discovery Studio Visualizer (https://discover.3ds.com/discovery-studio-visualizer-download), and 3D models were created.

Pharmacological studies

SwissADME analysis (http://www.swissadme.ch/index.php) was utilized to evaluate the pharmacological properties of the ligands. The physicochemical qualities evaluated are lipophilicity, polarity, insolubility, size, flexibility, and saturation. The best ligands are then chosen using the LIPINSKI rule of five. Toxicity was investigated using ProTox (https://tox-new.charite.de/protox II/index. php?site=compound input).

RESULTS

PPI network construction

The target proteins were identified using the PPI network analysis with the default clustering options. Using K-means clustering, three groups were found among 44 proteins. One of the largest clusters had 26 proteins, with TP53 having the most interactions with the first shell proteins The family of GPX proteins, which consists of a total of 11 proteins, was another cluster taken into consideration. Thus, the target proteins TP53 and GPX1 were identified.

Pathway enrichment analysis using ShinyGO

The top three pathways expressed by GPX1 are glutathione metabolism, thyroid hormone synthesis, and arachidonic acid metabolism, with the glutathione metabolism pathway being predominant.

Fig. 2 indicates that mismatch repair, platinum drug resistance, and homologous recombination were the top 3 pathways expressed by TP53 among which the mismatch repair pathway was predominant

Protein structure analysis of GPX1 and TP53

According to the PDBsum data, the projected secondary structure of protein GPX1 consists of two sheets, three beta hairpins, four beta bulges, eleven strands, four helices, 31 beta turns, and four gamma turns, as shown in (c). The Ramachandran plot is used to see the energetically permissible areas where amino acid torsions are angled against one another in a protein structure. The sterically permissible regions on the graph that allows for stable peptide conformation are represented by the red areas on the graph. One hundred and ninety-seven amino acid residues, that is, 88.7%, fall in the favored region, while two residues, that is, 0.9%, fall in the prohibited zone. The subregions account for the remaining 9.5%. Two hundred ad twenty-two of the 262 residues are non-proline or non-glycine, followed by glycine residues (17), proline

residues (21), and end residues (2). (Fig. 3). Z score for GPX1 was found to be −6.19, as shown in Z plot (e).

According to the PDBsum data, the predicted secondary structure of protein TP53 consists of two sheets, two beta alpha beta units, two beta hairpins, three beta bulges, seven strands, nine helices, three helix-helix contacts, 21 beta turns, and one gamma turn (c). One hundred and thirty-seven amino acid residues, or 90.1%, fall in the preferred region, while 0 residues, or 0.0%, fall in the prohibited zone. The sub-regions account for the remaining 9.9%. Out of the 184 residues, 152 are non-proline and non-glycine residues, 16 of which are glycine residues, 14 of which are proline residues, and two of which are end residues (Fig. 4). Z score for TP53 was found to be -6.1, as shown in Z plot (e).

Pharmacological studies

Lipinski filter analysis

A compound must follow at least four of the five criteria in Table 1 that constitutes the Lipinski rule.

ADME analysis

There are four essential features of an ADME analysis. The blood–brain barrier limits the amount of the substance's intracranial movement (BBB). The development of a drug necessitates this information. To maximize the drug's effectiveness, a significant amount of gastrointestinal (GI) adsorption is recommended. Furthermore, the substance must be readily soluble. Therefore, lower negative solubility thresholds are accepted.

Molecular docking results

Table 2 lists, respectively, the binding affinities of all the chosen ligands toward the GPX1 and TP53 proteins as determined by PyRx.

The docking conformation with the highest binding energy was taken into account for further analysis. The phytocompounds above −6.7 including the compounds hesperidin, naringin, silibinin, (+)-catechin gallate, gamma-tocopherol, and hematoxylin were shown to have the highest binding energy with GPX1, whereas compounds such as tocotrienol, gamma-tocopherol, hesperetin, dihydromyricetin, 4'-methyl-epigallocatechin, and 5-deoxyflavanone with binding energy <−5.5 showed a highest binding affinity with TP53 in this investigation. Therefore, these three are considered for further analysis.

Visualization

Molecular interactions of the top ligands with GPX1

As shown in Fig. 5, GPX1 showed the maximum number of interactions including amino acids such as lysine, alanine, tyrosine, histidine,
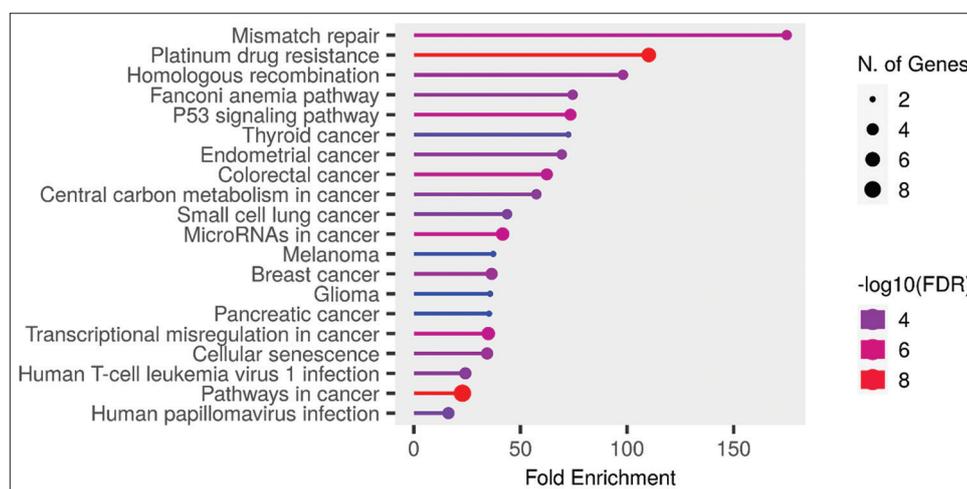

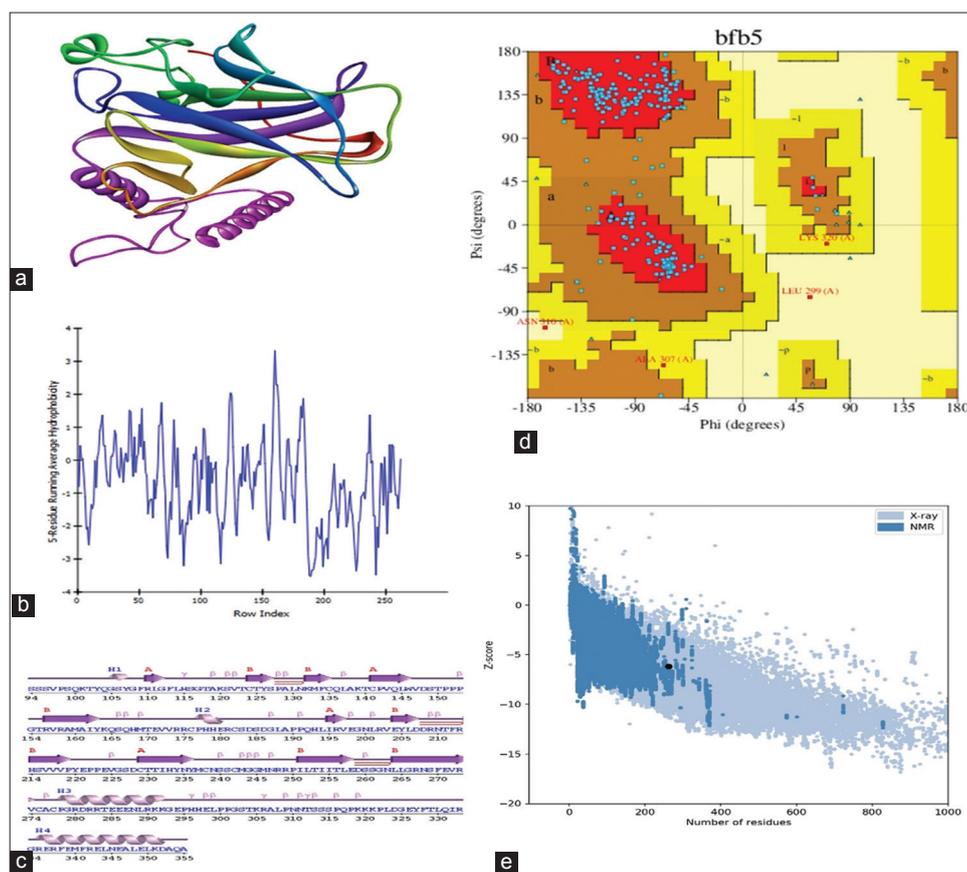**Fig. 2: Pathway analysis for the protein mediated by TP53**

Fig. 3: Structural analysis of protein GPX1. (a) 3D structure, (b) hydropathy plot, (c) secondary structure, (d) Ramachandran plot, and (e) Z plot

Table 1: Results of Lipinski rule properties obtained using SwissADME

Ligand	Mol wt	MLogP	H Donors	H acceptors	Molar refractivity
Epigallocatechin	306.27	−0.29	6	7	76.36
Epicatechin	290.27	0.24	5	6	74.33
Dihydromyricetin	320.25	−1.16	6	8	76.78
Hesperetin	302.28	0.41	3	6	78.06
Silibinin	482.44	−0.4	5	10	120.55
Naringenin	272.25	0.71	3	5	71.57
Hematoxylin	302.28	0.49	5	6	77.22
Hesperidin	610.56	−3.04	8	15	141.41
Tocotrienol	382.58	5.28	1	2	122.95
(+)-Catechin gallate	442.37	0.05	7	10	110.04
4'-Methyl-epigallocatechin	320.29	−0.04	5	7	80.83
Epigallocatechin gallate	458.37	−0.44	8	11	112.06
Gamma-tocopherol	416.68	5.94	1	2	134.31
5-deoxyflavanone	256.25	1.27	2	4	69.55
Chromanol	220.31	2.82	1	2	67.17
Naringin	580.53	−2.77	8	14	134.91

phenylalanine, asparagine, and glutamate with the ligand hesperidin with a binding energy of −8.1 (Table 3). Silibinin (c) showed the next highest interactions with amino acids arginine, tryptophan, glutamate, tyrosine, and asparagine with GPX1. GPX1 shared four interactions with both (+)-catechin gallate (d) and hematoxylin (f) involving amino acids tyrosine, two asparagine molecules, and arginine and serine, proline, and two asparagine molecules, respectively. Naringenin (b) interacted with serine, asparagine, and tyrosine. The least interactions of GPX1 were seen with gamma-tocopherol involving arginine and proline. Among all the amino acid interactions with the above ligands, asparagine was found to most commonly interact with all the ligands except gamma-tocopherol.

Molecular interactions of the top ligands with TP53

As shown in Fig. 6, TP53 showed a maximum number of interactions including amino acids such as leucine, valine, methionine, proline, glutamate, and asparagine with the ligand 4'-methyl-epigallocatechin. Hesperetin (c) showed the next highest interactions with amino acids leucine, methionine, phenylalanine, and alanine. GPX1 shared four interactions with both dihydromyricetin (d) and 5-deoxyflavanone (f) involving amino acids alanine, phenylalanine, asparagine, and methionine and alanine, methionine, and two leucine molecules, respectively. Gamma-tocopherol (b) interacted with proline and two leucine molecules. The least interactions of GPX1 were seen with tocotrienol involving leucine and lysine. Among all the amino acid
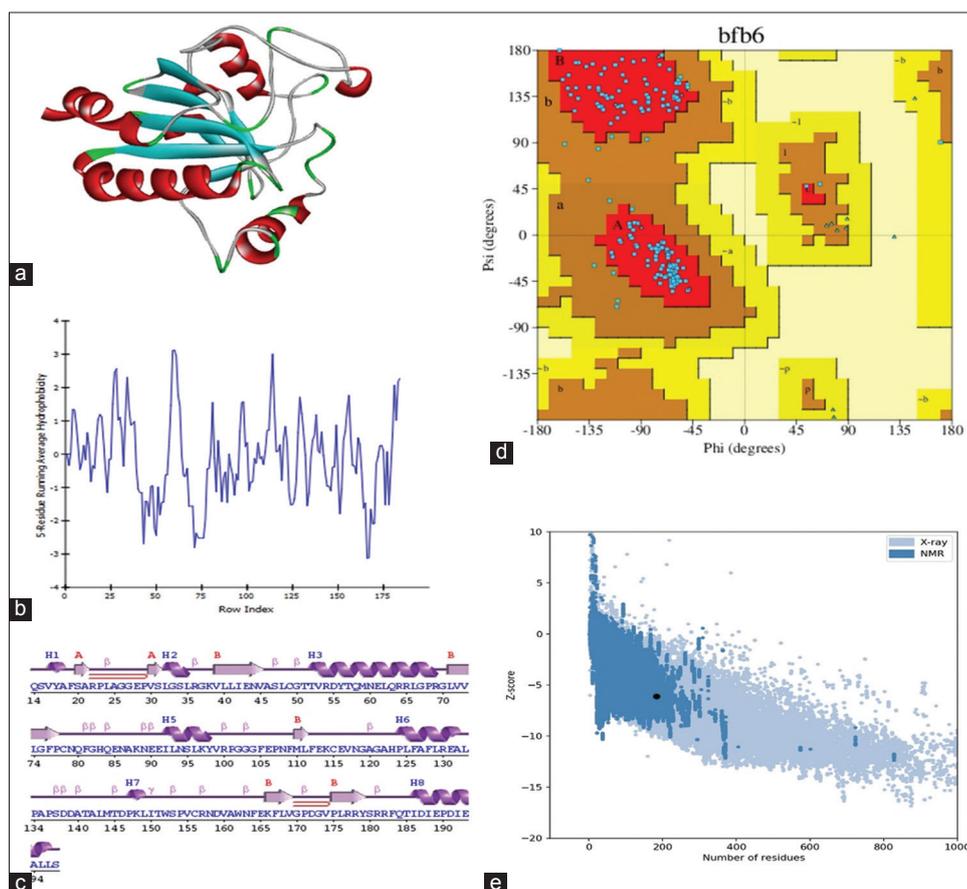
Fig. 4: Structural analysis of protein TP53. (a) 3D structure, (b) hydropathy plot, (c) secondary structure, (d) Ramachandran plot, and (e) Z plot
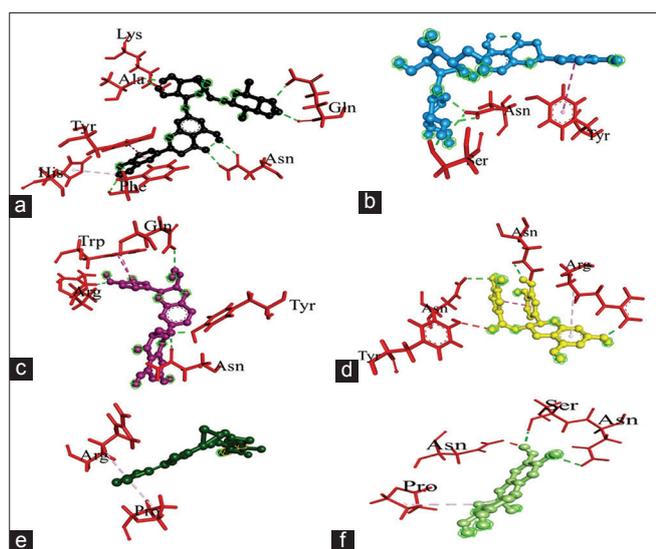

Fig. 5: Visualization of molecular interactions of GPX1 with the top 6 ligands. (a) GPX1- hesperidin, (b) GPX1-naringin, (c) GPX1-silibinin, (d) GPX1 with (+)-catechin gallate, (e) GPX1 with gamma-tocopherol, and (f) GPX1-hematoxylin

interactions with the above ligands, leucine was found to be most commonly interacting with all the ligands except dihydromyricetin.

DISCUSSION

More than 40 years ago, in the late 1980s, when the numerous clustering signs of MetS were still present, G M Reaven discovered the condition

Table 2: Docking score of proteins GPX1 and TP53 with selected ligands

Protein	Ligand	Binding affinity
GPX1	Hesperidin	−8.1
	Naringin	−7.9
	Silibinin	−7.3
	(+)-Catechin gallate	−7
	Gamma-tocopherol	−6.9
	Hematoxylin	−6.7
TP53	Tocotrienol	−6.9
	Gamma-tocopherol	−6.6
	Hesperetin	−5.8
	Dihydromyricetin	−5.7
	4'-Methyl-epigallocatechin	−5.6
	5-deoxyflavanone	−5.5

[19]. Most of the mechanisms involved in MetS are primarily triggered by visceral obesity. Insulin resistance is exacerbated by visceral fat accumulation. Adipose tissue releases proinflammatory cytokines as a result of insulin resistance, which raises the risk of CVD. The convergence of several proatherogenic pathways in MetS leads to an inflammatory mechanism that ultimately results in the medical symptoms of MetS [20]. The present study investigates the pharmacological benefits of catechins on MetS employing target proteins GPX1 and TP53 as an approach to manage and alleviate the symptoms associated with the disease. The results of present research is helpful in identifying key metabolic pathways regulated by the target clusters.
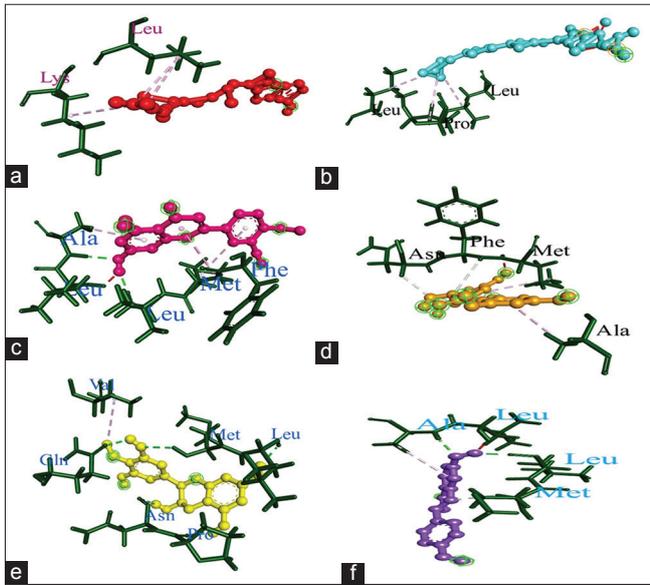
The PPI network created as depicted in Fig. 7 provided a clear understanding of the identification of the target proteins implicated in

MetS in this study, namely, GPX1 and TP53. In the previous research, GPX1 gene polymorphisms have been linked to a disproportionately higher prevalence of MetS and its symptoms in Japanese men than in Japanese women, including central obesity [21]. According to Fig. 8, GPX1 was primarily implicated in thyroid hormone synthesis and the
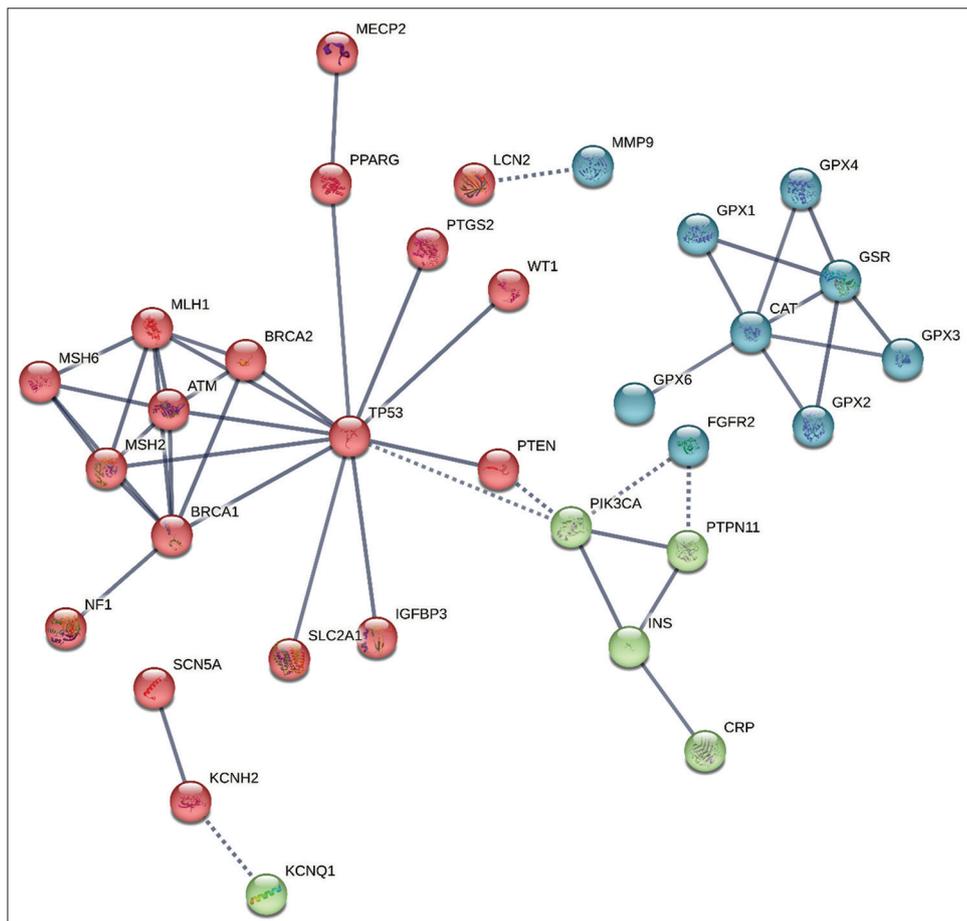
glutathione metabolism pathway. The onset of obesity, the control of associated factors such as energy metabolism, inflammation, and insulin resistance, as well as concomitant diseases such as type II diabetes and CVD, are all mediated by GSH-dependent enzymes and GSH, one of the body's most prevalent antioxidant molecules [22]. Blood pressure, cholesterol, and glucose metabolism, as well as energy homeostasis, are all impacted by thyroid hormones in a variety of ways, according to recent research, which suggests that perturbations in thyroid function may affect the features of the MetS [23]. As a result, MetS has been linked to GSH metabolism and thyroid metabolism. The role of TP53 in MetS is unclear, nevertheless. In cancer, the protein TP53 is highly expressed mostly implicated in DNA damage and repair pathways (Fig. 2). Activated p53 plays a prooxidant role when under extreme cellular stress, which increases oxidative stress and accelerates cell death [24].

Fig. 6: Visualization of molecular interactions of TP53 with top 6 ligands. (a) TP53-tocotrienol, (b) TP53 with gamma-tocopherol, (c) TP53-hesperetin, (d) TP53-dihydromyricetin, (e) TP53 with 4'-Methyl-epigallocatechin, and (f) TP53 with 5-deoxyflavanone

The present study employed 21 phytocompounds from catechins which were selected on DrugBank after adjusting the similarity threshold to 0.7. Out of the top 20 compounds based on their binding affinities to GPX1 and TP53, four of them were the same for both proteins, namely, hematoxylin, gamma-tocopherol, hesperetin, and epicatechin. Thus, each of the 16 compounds was subjected to a thorough pharmacological examination and evaluated for several factors, including toxicity, the number of hydrogen atom donors and acceptors, molecular weight, and physicochemical and ADMESAR features (Tables 1 and 3-5). It is clear from the findings of these analyses that each of the compounds that were chosen had druggable characteristics and passed the Lipinski and ADMET analysis criteria. All of the chemicals fall under drug toxicity classes 4-6, which suggests that these substances are not lethal.

The top six ligands with the best binding affinity with their respective proteins were docked and visualized. The molecular docking results

Fig. 7: Protein-protein interaction network of known and predicted proteins

Table 3: Toxicity prediction

Ligands	Toxicity class	Hepatotoxicity	Carcinogenicity	Mutagenicity	HSE	MMP
Epigallocatechin	6	0.72	0.51	0.55	0.94	0.55
Epicatechin	6	0.72	0.51	0.55	0.94	0.55
Dihydromyricetin	4	0.69	0.68	0.51	0.99	1
Hesperetin	4	0.7	0.7	0.87	0.88	0.72
Silibinin	4	0.78	0.72	0.69	0.92	0.73
Naringenin	4	0.67	0.62	0.83	0.93	0.74
Hematoxylin	4	0.8	0.58	0.8	0.8	0.85
Hesperidin	6	0.81	0.93	0.9	0.98	0.99
Tocotrienol	4	0.94	0.79	0.91	0.88	0.62
(+)-Catechin gallate	4	0.7	0.54	0.7	0.98	0.79
4'-Methyl-epigallocatechin	6	0.71	0.71	0.74	0.89	0.59
Epigallocatechin gallate	4	0.7	0.54	0.7	0.98	0.79
Gamma-tocopherol	5	0.93	0.79	0.95	0.98	0.86
5-deoxyflavanone	4	0.64	0.5	0.74	0.95	0.76
Chromanol	5	0.77	0.74	0.85	0.66	0.93
Naringin	5	0.81	0.9	0.73	0.99	0.99

Table 4: Physicochemical properties

Ligand	Molecular weight	Fraction Csp3	Rotatable bonds	TPSA	Lipophilicity
Epigallocatechin	306.27	0.2	1	131	0
Epicatechin	290.27	0.2	1	110	0.36
Dihydromyricetin	320.25	0.13	1	148	0.59
Hesperetin	302.28	0.19	2	96	2.6
Silibinin	482.44	0.24	4	155	1.9
Naringenin	272.25	0.13	1	87	2.52
Hematoxylin	302.28	0.25	0	110	1.19
Hesperidin	610.56	0.54	7	234	−0.14
Tocotrienol	382.58	0.54	9	29	8.21
(+)-Catechin gallate	442.37	0.14	4	177	1.53
4'-Methyl-epigallocatechin	320.29	0.25	2	120	0.33
Epigallocatechin gallate	458.37	0.14	4	197	1.17
Gamma-tocopherol	416.68	0.79	12	29	10.33
5-deoxyflavanone	256.25	0.13	1	67	2.3
Chromanol	220.31	0.57	0	29	3.64
Naringin	580.53	0.52	6	225	−0.44

Table 5: ADME data obtained using SwissADME

Ligands	BBB	GI Absorption	PGP substrate	Solubility (LOGSw-SILICOS IT)
Epigallocatechin	No	High	No	−1.56
Epicatechin	No	High	Yes	−2.14
Dihydromyricetin	No	Low	No	−1.44
Hesperetin	No	High	Yes	−3.53
Silibinin	No	Low	No	−4.5
Naringenin	No	High	Yes	−3.42
Hematoxylin	No	High	Yes	−2.63
Hesperidin	No	Low	Yes	−0.58
Tocotrienol	No	Low	Yes	−6.95
(+)-Catechin gallate	No	Low	No	−3.09
4'-Methyl-epigallocatechin	No	High	Yes	−2.26
Epigallocatechin gallate	No	Low	No	−2.5
Gamma-tocopherol	No	Low	Yes	−8.79
5-deoxy flavanone	Yes	High	Yes	−4
Chromanol	Yes	High	No	−4.33
Naringin	No	Low	Yes	−0.49

Where, BBB: Blood–brain barrier, GI absorption: Gastrointestinal absorption, PGP: p-glycoprotein

demonstrated that the ligand hesperidin had the best binding affinity with GPX1 and gamma-tocopherol with that of TP53. The binding of hesperidin with GPX1 was visualized that it was discovered that the ligand had made stronger connections at PHE A:113, TYR A:126, ASN A:268, LYS A:320, ALA A:129, GLN A:100, etc. Similarly, visualization of gamma-tocopherol with TP53 showed that the ligand had acquired connections with two leucine and proline, even though TP53 had the highest number of interactions with the ligand 4'-methyl epigallocatechin (Fig. 6).

In a randomized controlled trial study [25], 49 patients with MetS received a 500 mg dosing of hesperidin or a placebo 2 times daily for 12 weeks. In contrast to the placebo group, hesperidin significantly reduced serum levels of glucose, insulin, triglycerides, total cholesterol, low-density lipoprotein cholesterol, TNF-, and hs-CRP, while only glucose and insulin showed a substantial reduction in the control group, according to the data. According to a different study [26], a single oral dose of the water-soluble hesperidin derivative glucosyl hesperidin
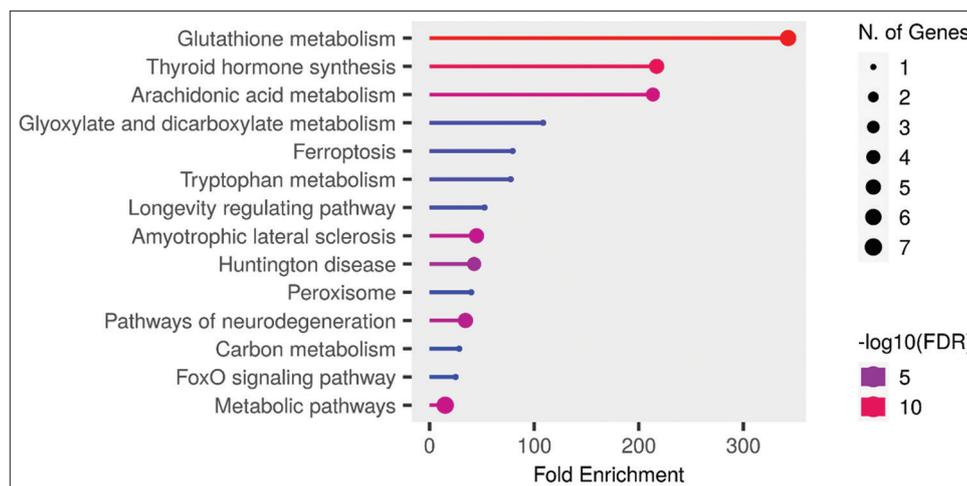
Fig. 8: Pathway analysis for the protein mediated by GPX1

(G-hesperidin) was found to improve a dose-dependent decrease in systolic blood pressure in hypertensive rats. Accordingly, the results of the aforementioned research show that hesperidin administration can reduce inflammatory state and metabolic abnormalities in MetS patients. An isoform of vitamin E, gamma-tocopherol, is an essential nutrient, lipid-soluble, and antioxidant vitamin for the body. It is found in plant foods such as nuts, seeds, and vegetable oils, as well as in animal products such as eggs and dairy [27]. According to recent studies, gamma-tocopherol may be beneficial in the treatment of MetS which is linked with a higher risk of heart disease and other chronic illnesses. Due to its powerful anti-inflammatory capabilities, gamma-tocopherol may have therapeutic effects by reducing oxidative damage and inflammatory indicators in individuals with MetS [28]. While additional investigation is required to fully comprehend gamma tocopherol's function in the management of MetS, it appears to offer considerable potential advantages. Gamma tocopherol consumption may be a helpful strategy for people with MetS to lower their risk of chronic diseases and enhance general health.

CONCLUSION

MetS is a modern-day condition that is fast-growing and necessitates considerable lifestyle and dietary adjustments to treat. The present study performed an *in silico* attempt to employ catechins and their derivatives against MetS and discovered that gamma-tocopherol and hesperidin may be used therapeutically to prevent and treat the disorder as well as its adverse effects, including T2DM and CVD, which was consistent with earlier studies.

ACKNOWLEDGMENT

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