Molecular docking Study of vanillic acid and catechin hydrate as anti-inflammatory and antioxidant agents towards PPAR-γ and Glutathione S-transferase omega-1 Complex agonists

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ABSTRACT

Objectives: The purpose of this research was to evaluate the anti-inflammatory and antioxidant properties of vanillic acid and catechin hydrate towards the PPAR-γ receptor and the Glutathione S-transferase omega-1 Complex using molecular docking. and perform the ADMET studies of these compounds.

Material and Methods: For the molecular docking analysis of the molecule, PDB ID 4xum and PDB ID 3vln were used. Using indomethacin and ascorbic acid as reference standards based on its antioxidant and anti-inflammatory properties. For the ADMET study, software including QikProp, SwissADME, and ProTox-II were employed.

Results: Catechin hydrate and vanillic acid were found to have affinity for the PPAR-γ receptor and the Glutathione S-transferase omega-1 Complex. Catechin hydrate and vanillic acid molecules' simultaneous docking studies scores for antioxidant activity and anti-inflammatory activity were -7.549 Kcal/mole and -9.795 Kcal/mole, and -4.217 Kcal/mole and -7.862 Kcal/mole, respectively. These molecules exhibited a promising results towards the in silico antioxidant and anti-inflammatory properties when compared to their references.

Conclusion: Vanillic acid and catechin hydrate have demonstrated anti-inflammatory and antioxidant properties by molecular docking. Their ADMET studies additionally underscored their potential for pharmaceutical use.

Keywords: Vanillic acid, Catechin hydrate, anti-inflammatory, antioxidant, PPAR-γ, Glutathione S-transferase omega-1 Complex,

INTRODUCTION

Anti-inflammatory, antibacterial, antioxidant, anti-cancer, and antidiabetic are a few of the important pharmacological properties that vanillic acid and catechin hydrate demonstrate (1,2). Vanillic acid, a bioactive compound, offers several benefits (3). Its functions include those of an antioxidant and an anti-inflammatory (4). By eliminating excess reactive oxygen species (ROS), directly addressing free radicals, and inhibiting the enzymes that make them, it effectively reduces inflammatory reactions and avoids oxidative damage (5). The fact that it protects kidney and cardiovascular function is remarkable (6). Catechin hydrate has anti-inflammatory and antioxidant properties that protect against free radicals (7). Numerous in-vitro and in-vivo investigations were carried out to assess the antioxidant and anti-inflammatory properties of these substances.

PPAR-γ, also known as NR1C3, is a transcription factor protein that regulates inflammation, cell differentiation, and the metabolism of genes related to fat and carbohydrates (8). This protein belongs to the class of nuclear receptors known as peroxisome proliferator-activated receptors, or PPARs (9). Three different PPARs (α, β, and γ) exist; each is encoded by a different gene (10). This protein has a strong affinity for adipose tissues across the body and is involved in the process known as adipogenesis, which results in the production of fat cells (11). PPAR-γ has an anti-inflammatory effect through multiple mechanisms, including the regulation of the inflammatory transcription factor NF-κB and the release of cytokines (12). Additionally, anti-inflammatory M2 macrophages balance shifting PPAR-γ and decrease inflammation by initiating a cascade of cellular events that may potentially impact the activity of inflammatory enzymes (13). Additionally, PPAR-γ increases the creation of certain molecules that effectively decrease inflammation and activate Interleukin-10 (14).

Free radicals are produced by regular metabolic processes and naturally occurring pollutants (15). These radicals constantly tax the body's antioxidant defences, which results in oxidative stress (16). In addition, it damages cells and results in chronic inflammation, which can trigger a series of diseases that include cellular dysfunction, premature ageing, and chronic illnesses including diabetes, cancer, and heart disease (17). The omega-1 enzyme glutathione S-transferase aids in the combination of glutathione with hazardous substances and free radicals (18). The omega-1 enzyme glutathione S-transferase aids in detoxification by removing toxins from the body (19). This enzyme is a member of the glutathione S-transferase omega-1 enzyme class, this enzyme may have a role in responses brought on by stress (20). It may also alter

disease susceptibility and the metabolism of certain toxins and carcinogens, which in turn impact chemicals that produce inflammation (21). It acts as an essential cellular antioxidant by combining glutathione with dangerous and carcinogenic substances. By neutralising toxic chemicals, the GSTO1 enzyme helps the body get rid of them. It indirectly supports the cell's antioxidant system by eliminating harmful substances from the body (22).

Edoema, pyrexia, nociception, and tissue damage are among the many adverse outcomes of dysregulated or chronic inflammation, which ultimately result in functional limitations and decreased mobility (17). Utilising medication-assisted approaches to managing such persistent inflammation and its impact on life remains a significant challenge (23). Many chronic disorders, and more importantly, those prevalent in modern medicine, including coronary artery disease, type II diabetes, and various malignancies, are influenced by chronic inflammation in their genesis and progression (24). Catechin hydrate has emerged as a potential ligand with proven PPAR-γ activation, which may explain its reported anti-inflammatory properties. PPAR-γ agonism offers a possible target for therapy for anti-inflammatory action (25). Additionally, by lowering inflammatory cascades initiated by free radicals, the antioxidant qualities of vanillic acid and catechin hydrate may contribute to explaining the mechanism of their proposed anti-inflammatory properties (26).

The aim of this research was to ascertain the role of the glutathione S-transferase omega-1 (GSTO-1) complex and the PPAR-γ activity modulating vanillic acid and catechin hydrate by comparing their reference standards. We used a computational method based on molecular docking simulation to assess potential binding interactions between these natural chemicals and the previously identified targets. In order to identify any potential risk concerns, do the ADMET evaluation of each molecule, including reference standards.

Material and Method

Software

Glide v9.1 Schrodinger software was utilised for molecular docking studies. The calculation of binding free energy was done using MM-GBSA. Toxicological prediction was performed using ProTox-II, and ADME characteristics were computed using SwissADME and QikProp v6.8.

Molecular docking study:

Protein Data Bank data (PDB ID: 4xum) and (PDB ID: 3vln) via http://www.resb.org were used to co-crystallise protein structures. Based on a carefully selected set of reference

molecules and ligands, the ensuing molecular docking studies were constructed. Using the protein preparation wizard, the imported protein underwent many processes, such as bond order arrangement and hydrogen atom restoration. An internal ligand heterostate was subsequently formed by carefully adding formal charges to co-factors in proteins. Complex molecular docking investigations were performed using the Glide module (Glide v9.1) in the Schrodinger programme. The MM-GBSA was then used to compute the binding free energy. Furthermore, SwissADME and QikProp v6.8 were used to thoroughly assess the ADMET features. ProTox-II was carefully used to forecast the toxicity of the molecular hits from the MM-GBSA investigation. Establishing a receptor grid is necessary to pinpoint the precise binding position of the drugs under study. In this attempt, the centroid of the co-crystallised crystals was meticulously positioned within a 10 Å radius, using default settings with a scale factor of 1.0. This was a complicated process that the Protein Preparation Wizard came in very handy for. After that, the ligands containing the reference molecule were carefully investigated by utilising Maestro's advanced ligand creation tool in conjunction with the OPLS2005 force field. Many possible conformers, tautomers, or stereoisomers were created as a result. These ligands' post-energy minimization, when combined with the XP mode and a Van der Waals scaling factor of 0.8, was suitable for molecular docking investigations. Additionally, all water molecules within a 5 Å radius were methodically removed in order to preserve the integrity of the computer research.

MM-GBSA :

The binding free energy between proteins and ligands (small molecules) is computed using a computer technique known as MMGB/SA (Molecular Mechanics/Generalized Bom Surface Area) in computational chemistry and structural biology. To predict the binding affinity of potential therapeutic candidates to target proteins, it is commonly employed in drug development and protein-ligand interaction investigations. The MMGBSA method combines generalised Born solvent models, surface area calculations, and molecular mechanics which characterises a system's internal energy using force fields.

ADMET Prediction:

Toxicity prediction was performed using ProTox-II. To determine ADME characteristics for the top scores from the MM-GBSA research, QikProp v6.8 and SwissADME were used. Several ADMET property predictions make up the outcome.

RESULTS

Protein preparation and receptor grid generation for anti-inflammatory activity: Using indomethacin 2-[1-(4-chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]acetic acid, the PPAR-γ ligand binding domain's crystal structure (PDB ID: 4XUM) was obtained. After processing the protein structure using the protein preparation wizard panel, a grid around the active site of the protein was created using Glide v9.1's receptor grid building panel. The protein structure is appropriate for docking and further computer investigation.

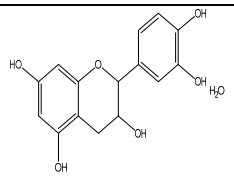
Protein preparation and receptor grid generation for anti-oxidant activity: The Protein Data Bank provided the ascorbic acid crystal structure of the glutathione S-transferase omega-1 complex (PDB ID: 3VLN). Using the Glide v9.1 receptor grid generation panel, a grid surrounding the protein's active sites was created after the protein structure was processed using the protein preparation wizard panel. The thorough processing verifies that the protein structure is appropriate for additional docking and computing research.

Ligand Preparation: The compounds were originally drawn using the 2D sketcher, and they were subsequently optimised by geometric minimization with the use of the OPLS 5 force field. LigPrep was utilised to ensure that compound structures were improved for more study. This procedure is essential for increasing the accuracy of computational research and generating a more reliable representation of the molecular properties and interactions inside the compounds.

Ligand Docking with Glide: Start the Glide programme, then choose between Standard Precision (SP) and Extra Precision (XP) for the docking strategy. XP offers more accuracy, albeit requiring more processing power. Configure the docking parameters, scoring functions, position sampling, and ligand flexibility. The molecular docking scores are shown in Tables Nos. 1 and 2.

Table No. 1: Molecules with their dock score and Binding Free Energies for (PPAR-γ)

Anti-inflammatory activity

Compound name	2D structure	Dock Score Kcal/mole	dG Binding Kcal/mole
Catechin hydrate		-9.795	-67.37

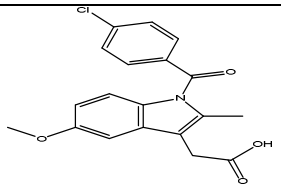
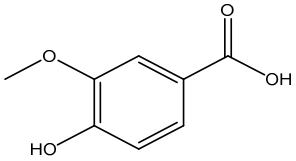
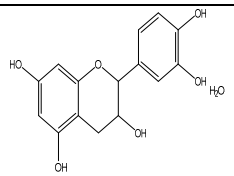
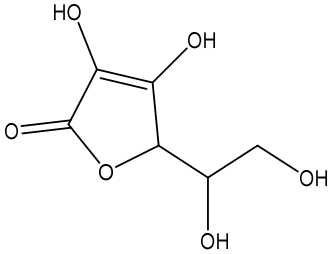
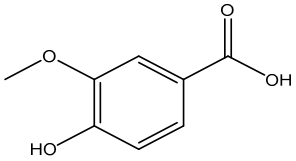
Reference Indomethacin		-13.109	-101.09
Vanillic acid		-7.862	-35.44

Table No. 2: Molecules with their dock score and Binding Free Energies (Glutathione S-transferase omega-1 Complex) for antioxidant activity

Compound name	2D Structure	Dock Score Kcal/mole	dG Binding Kcal/mole
Catechin hydrate		-7.549	-53.76
Reference Ascorbic acid		-7.164	-30.71
Vanillic acid		-4.217	-29.31

MM-GBSA: The Prime/MM-GBSA procedure was employed to determine the relative binding energy of certain ligands. The study's input for the MM-GBSA was the pv.maegz file, which was generated via XP docking. The active site of the protein was engineered to conform to the ligand within a 5 o'A range. This methodology provides a comprehensive analysis of ligand-protein interactions, taking into consideration the flexibility of the active site and providing valuable insights into the energetics of ligand binding. Compounds with lower (more

negative) total binding free energies are more likely to exhibit substantial interactions with the target protein, which makes them prime candidates for more investigation. Tables 3 and 4 display the binding interactions of all compounds with the receptors PPAR-γ and glutathione S-transferase omega-1 complex for antioxidant activity. Tables Nos. 5 and 6 provide interaction pictures of all compounds with PPAR-γ and glutathione S-transferase omega-1 complex.

Table No. 3 Binding interactions of all molecules with the receptors Glutathione S-transferase omega-1 Complex for antioxidant activity

Compound Name	2D Interactions	Distance (A^0)
Catechin hydrate	H-bond:PRO124,PRO124,TRP180	1.77,2.56,1.96
Reference Ascorbic acid	H-Bond:ASN67,GLU85,SER86,PRO73	2.04,1.81,1.83,2.05
Vanillic acid	H-bond: GLU85,SER86,VAL72 Pi-Pi Stacking:PHE34	1.60,2.10,2.19 4.07

Table No. 4 Binding interactions of all molecules with the receptors for (PPAR-γ) anti-inflammatory activity

Compound Name	2D Interactions	Distance (A^0)
Catechin hydrate	Pi-Pi Stacking: HIE449 H-bond:PHE360	4.44 1.91
Reference Indomethacin	Pi-Pi Stacking:HIE449,HIE449 H-bond: SER289,HIE323,TYR473,HIE449	4.60,4.74 1.88,1.96,1.75,1.99
Vanillic acid	H-bond:SER289,HIE323,HIE449, TYR473,PHE282	2.04,2.32,1.96, 1.51,1.64

Table No. 5 Interaction images of all molecules with Peroxisome proliferator-activated receptor gamma (PPAR-γ) for anti-inflammatory activity

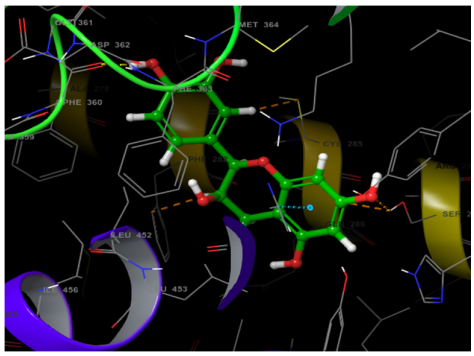
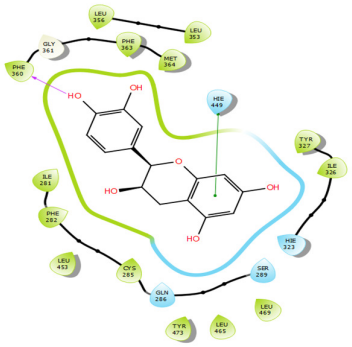
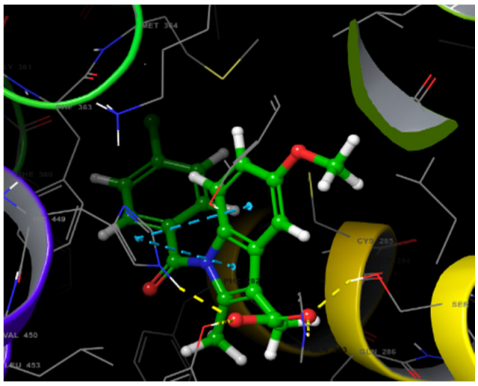
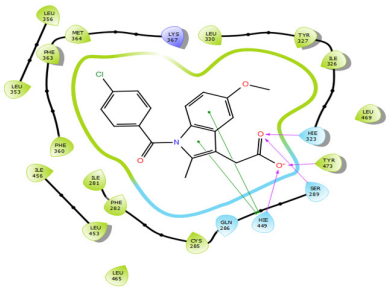
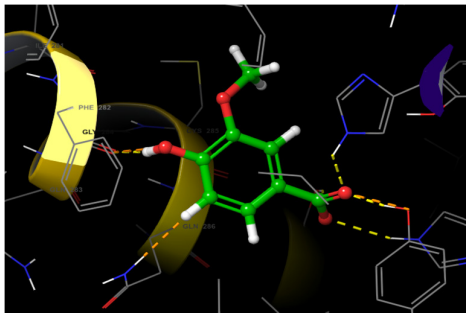
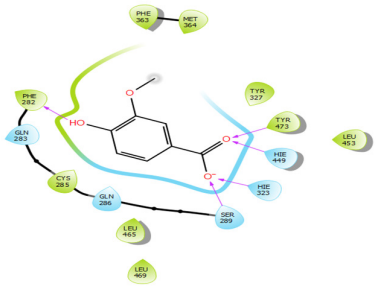
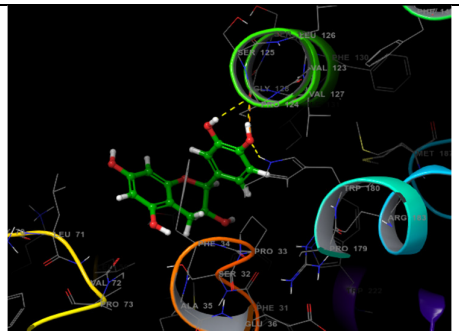
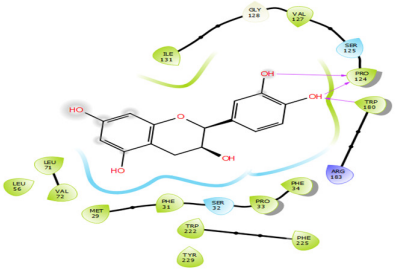
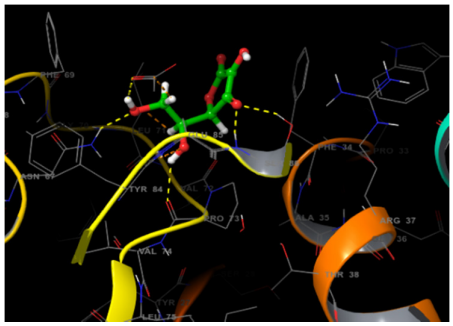
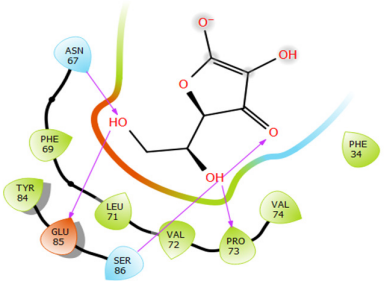
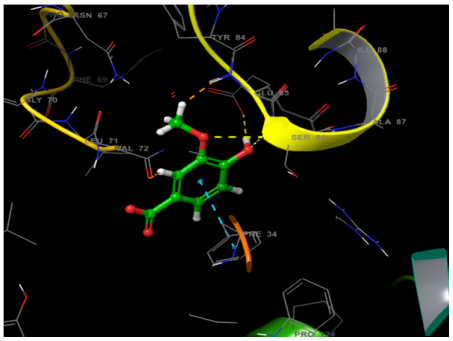
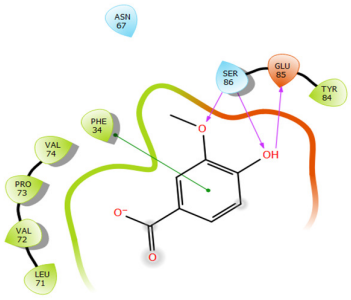
Compound Name	3D Image	2D Image
Catechin hydrate		
Reference Indomethacin		
Vanillic acid		

Table No. 6 Interaction images of all molecules with Glutathione S-transferase omega-1 Complex with Ascorbic Acid for antioxidant activity

Compound Name	3D Image	2D Image
Catechin hydrate		
Reference Ascorbic acid		
Vanillic acid		

ADMET Prediction: SwissADME and QikProp v6.8 were used to calculate ADME characteristics. The various ADME (absorption, distribution, metabolism, and excretion) characteristics of the substances were assessed using QikProp. These characteristics cover a broad spectrum of important elements and provide comprehensive knowledge of the pharmacokinetic and drug-like qualities. The evaluated features include Central Nervous System interaction, Solvent Accessible Surface Area, Polar Surface Area (PSA), Madin Darby Canine Kidney Cell Line Permeability (MDCK), Number of Nitrogen and Oxygen atoms (NandO), log hERG (Human ether-à-go-go-related gene), predicted aqueous solubility (LogS), Acceptor Hydrogen Bond (Accept HB), predicted octanol/water partition coefficient (Log

Po/w), predicted blood/brain partition coefficient (Log BB), prediction of binding to human serum albumin (Log Khsa), Donor Hydrogen Bonds (Donor HB), predicted qualitative human oral absorption (HOA, with values ranging from 1 for low, 2 for medium, and 3 for high), number of Rule of Five violations, and Caco-2 permeability (PCaco). Whether or not the compounds are suitable for drug development is determined in part by the pharmacological potential of the compounds, as revealed by these comprehensive investigations. Table No. 7 displays the results of the QikProp v6.8 ADME investigation of compounds.

Table No. 7 ADME study of molecules by QikProp v6.8

Sr. No.	Compound name	CNS	SASA	Donor HB	Accpt HB	Log Po/w	logS	Log HERG	PCaco	logBB	PMDCK	Log Khsa	HOA	PSA	NandO	Rule of Five
1	Catechin hydrate	-2	511.634	5.000	5.450	0.471	-2.618	-4.806	58.246	-1.861	22.895	-0.427	2	114.301	6	0
2	Reference indomethacin	-1	598.586	1.000	5.750	4.261	-5.130	-3.364	181.654	-0.641	245.547	0.052	3	82.301	5	0
3	Vanillic acid	-1	365.648	2.000	3.500	1.054	-1.464	-1.780	77.136	-0.912	39.450	-0.743	3	79.420	4	0

SwissADME was used to assess the substances' diverse ADME (Absorption, Distribution, Metabolism, and Excretion) properties. These properties cover a broad spectrum of important variables, providing a thorough understanding of the pharmacokinetic and drug-like properties. Among the assessed qualities are molecular weight, the quantity of Rule of Five infractions, GI absorption, bioavailability score, synthetic accessibility, and the anticipated blood/brain partition coefficient (Log BB) and octanol/water partition coefficient (Log Po/w). The pharmacological potential of the compounds is elucidated by these comprehensive investigations, which aid in determining their suitability for medication development. Table No. 8 displays the results of SwissADME's ADME analysis of compounds.

Table No. 8 ADME study of molecules by SwissADME

Sr. no.	Compound Name	MW	H-bond Acceptor	H-bond Donors	Log P	GI Absorption	BBB Permeant	Bioavailability Score	Lipinskin Violation	Synthetic Accessibility
1	Catechin hydrate	308.28 g/mol	7	6	1.17	High	No	0.55	1	3.60

2	**Reference Ascorbic acid**	176.12 g/mol	6	4	0.39	High	No	0.56	0	3.47
3	**Vanillic acid**	168.15 g/mol	4	2	1.40	High	No	0.85	0	1.42

ProTox-II was used to predict toxicity for the docking score and the ideal score obtained from the MM-GBSA investigation. The ProTox-II portal was utilised to forecast the toxicity of the compounds with regard to hepatotoxicity, carcinogenicity, mutagenicity, cytotoxicity, and immunotoxicity, as indicated in Table No. 9.

Table No. 9 Toxicity study of molecules by ProTox-II

Sr. No.	Compound Name	Hepatotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity	ProTox-II Class
1.	**Catechin hydrate**	Inactive	Inactive	Inactive	Less Active	Inactive	6
2.	**vanillic Acid**	Less Inactive	Less Inactive	Inactive	Inactive	Inactive	4
3.	**Reference Ascorbic Acid**	Inactive	Inactive	Inactive	Inactive	Less Inactive	5
4.	**Reference Indomethacin**	Active	Less Active	Less Active	Inactive	Inactive	2

DISCUSSION

Vanillic acid and catechin hydrate had higher antioxidant and anti-inflammatory properties in comparison to ascorbic acid and indomethacin, respectively, according to molecular docking study results. Docking studies revealed that catechin hydrate and vanillic acid exhibited significant binding affinity towards the well-characterised crystal structures of the glutathione S-transferase omega-1 complex and PPAR-γ. A larger negative value, as determined by the MM-GBSA binding free energies, denotes more favourable interactions between the ligands and target proteins. Indomethacin and ascorbic acid are classified in classes 2 and 5, respectively, whereas catechin hydrate and vanillic acid are classified in classes 6 and 4, respectively, according to the ADMET analysis of all components. Both molecules do not

exhibit hepatotoxicity, cytotoxicity, carcinogenicity, immunotoxicity, or mutagenicity. The absence of significant adverse effects in both compounds suggests that they are suitable for use in medicinal applications. To acquire a better understanding of these phytochemicals' efficacy, in vivo research is required.

CONCLUSION

When compared to their reference standards, the docking study indicates that catechin hydrate and vanillic acid exhibit strong binding affinities to target proteins that exhibit antioxidant and anti-inflammatory properties. Additionally, ADMET studies of these compounds demonstrated their efficacy in the production of pharmaceutical products. Nevertheless, further in vivo research is needed to completely evaluate the therapeutic potential of these phytochemicals.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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