

STRUCTURE-BASED DRUG DESIGNING STUDIES TOWARDS EXPLORING THE POTENTIAL ANTICANCER ACTIVITY OF SELECTED PHYTOCOMPOUNDS AGAINST HISTONE DEACETYLASE 10 PROTEIN

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Received: 14 June 2018, Revised and Accepted: 01 August 2018

ABSTRACT

Objective: Histone deacetylases (HDACs) are proteins which play a crucial role in cell growth, maintenance, and regulation. Abnormal HDAC proteins produced by genetic mutations are common in human cancers. HDAC10 is a class II HDAC member, and its expression in many cancers has been documented. The aim of this study was to determine the best docking of phytochemicals selected from a list of such compounds in the database of chemicals for HDAC10.

Methods: The crystal structure of HDAC10 was retrieved from Protein Data Bank and prepared for docking studies by post-translational modification (PTM) analysis. Then, we have screened 450 phytochemicals for molecular docking studies and determined their binding affinities against HDAC10 by using PatchDock server.

Results: The PTM analysis showed that myristoylation sites were more abundant in HDAC10 which might be important functional sites for the gene regulation. The results revealed the receptor/inhibitor interactions within an active domain consisting of 30 important amino acid residues. Affinity-based studies have indicated the docking energy levels by calculating hydrogen bonding, steric, and hydrophobic interactions. Among the inhibitors, we could shortlist four compounds which showed excellent binding affinity. Hence, we evaluated drug binding affinities of these four compounds and determined their atomic contact energy values. Analysis of the docking results showed holacurtine>periplogenin>3,3'-diindolylmethane>epigallocatechin as the order of binding affinities, with holacurtine having the best docking score.

Conclusion: It is proposed from these studies that the docking and scoring methods could be useful for selecting and shortlisting the promising antitumor molecules. These molecules could be further tested using *in vitro* and *in vivo* methods to confirm their role in HDAC10-associated cancers. Furthermore, myristoylation sites in HDAC10 could form an important binding site for selecting hit inhibitor compounds. The PTM studies together with the binding mode analysis facilitate the protein-protein interaction studies of HDAC10, and thioredoxin-interacting protein is considered as one of the transcriptional regulators of HDAC10.

Keywords: Histone deacetylase 10, Post-translational modifications, Phytochemicals, Docking studies, Thioredoxin-interacting protein.

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INTRODUCTION

Histones are the basic proteins, and its acetylation process is a key prerequisite for chromatin decondensation and structure [1]. Studies confirm that histones play a pivotal role in the regulation of chromatin structure, function, and dynamics [2,3]. Researches provide the information regarding known histone acetyltransferases (HAT) and histone deacetylases (HDACs) and their effects on transcription of target genes *in vivo* [4]. HDACs regulate various cellular processes through enzymatic deacetylation of both histone and non-histone protein [5]. These proteins play crucial roles in a variety of biological processes including cell cycle progression, proliferation, differentiation, and development [6]. The role of HDAC in cancer was studied for the first time in 1998 [7]. Several recent studies also have implicated that individual HDAC enzymes can form potential therapeutic targets for treatment against cancers, fibrotic disorders, immune and neurological disorders [8-10]. HDAC family consists of two major classes, namely class I and class II, based on the homologies to yeast deacetylases both share a highly conserved catalytic domain which is considered as receptor for many drugs, especially in cancer studies [11]. Hence, HDAC inhibitors (HDACi) represent a new class of targeted anticancer agents [12].

HDACi has extensively demonstrated the antitumor efficacy *in vitro* and *in vivo*. *In vitro* experiments in cancer cell cultures and *in vivo* studies using mouse xenograft model have shown that HDACi delivers potent anticancer effects [13]. Therefore, the determination of HDACi has become one of the most important research fields of the anticancer drugs. Several classes of HDACi have been found to have potential anticancer activities and undergoing preclinical studies [14]. Studies have reported that HDAC class II proteins were modeled and two known inhibitors, namely suberoylanilide hydroxamic acid (SAHA) and trichostatin A, were docked using AutoDock to identify the pharmacological properties [15]. The inhibition of HDAC activity leads to the modulation of expression of a specific set of genes which can result in growth arrest, differentiation and apoptosis [16].

HDAC10 is a member of class II HDAC which was first discovered based on sequence homology to other class II HDACs and is widely expressed in adult human tissues and cultured mammalian cells. It is a 669 residue polypeptide with a bipartite modular structure consisting of an N-terminal Hda1p-related putative deacetylase domain and a C-terminal leucine-rich domain [17]. Its mutation leads to various cancers [18-20]. Homology comparison indicates that HDAC10 is most

similar to HDAC6. Both contain a unique, putative catalytic domain which is not found in other HDACs. In HDAC10, however, this domain is not functional [21]. HDAC6 is a cytoplasmic deacetylase while HDAC10 is known to occur in both the nucleus and the cytoplasm. In the nucleus, HDAC10 contains a distinct transcriptional repressor domain. It is found that HDAC10 might uniquely play roles both in the nucleus, as a transcriptional modulator, and in the cytoplasm in an unidentified role [21]. It has been found that the knockdown of HDAC10 significantly increased the mRNA expression levels of thioredoxin-interacting protein (TXNIP) in human gastric cancer cells [22]. Real-time PCR and immunoblot analysis confirmed that inhibition of *HDAC10* induced *TXNIP* expression, more specifically which is involved in transcriptional downregulation of TXNIP. In our previous study, we identified the drug binding mechanism of TXNIP [23]. The expression levels of HDAC10 decrease in lung cancer patients class II HDACs repress critical genes and eventually cause the progression of lung cancer [24]. It has been found that HDAC10 acts as a promoter of autophagy-mediated survival in neuroblastoma cells [25] and chronic lymphocytic leukemia [26].

Only two drug compounds, namely belinostat [27] and panobinostat [28], are currently approved as inhibitors for HDAC10. This leads to increasing demands for additional therapeutics options by administering natural and phytochemicals with lesser side effects. Thus, our study is an attempt to determine the binding efficacy of a series of phytochemicals and evaluate their interaction with HDAC10. To achieve this goal, first, we have used computational algorithms to determine the different post-translational modification sites (PTMs) and binding sites. Then, docking and its simulation studies were performed. We have used several structural algorithms to identify binding sites, through analyzing surface structures. In addition, we focus mainly on the selection of compounds, and we evaluated the binding mode of selected phytochemicals for docking and scoring studies. Further, in this study, we also able to understand the drug docking mechanism of HDAC10 whether it can give a clue for non-coding regions and identify conserved sequence elements that may be involved in its gene regulation process.

METHODS

HDAC-10 sequence retrieval and its PTMs studies

The query sequence of HDAC10 was retrieved from The UniProt Knowledgebase (UniProtKB id: Q969S8). UniProtKB acts as a central hub of protein knowledge by providing a unified view of protein sequence and functional information [29]. To predict functional sites of HDAC10, the query sequence was submitted to Expasy ScanProsite online server (<https://prosite.expasy.org/scanprosite/>) which is a database used for structurally conserved motifs scanning included UniProtKB/Swiss-Prot, splice variants, and UniProtKB/TrEMBL databases. All the default settings were considered as parameters for the analysis.

HDAC10 receptor preparation

The receptor structure of HDAC10 was prepared by retrieving the three-dimensional crystal structure complex (Protein Data Bank [PDB] id:5TD7) bound with a ligand structure, namely 7-[(3-aminopropyl) amino]-1,1,1-trifluoroheptane-2,2-diol, from RCSB PDB (<http://www.rcsb.org/pdb/home/home.do>) [30]. The protein was cleaned by removing the bound molecule and the non-essential water molecules. Hydrogen atoms were added to the receptor using Biovia DS visualizer (Accelrys, BioVia, San Diego, CA, USA).

Binding pocket recognition

The probable ligand binding pockets in HDAC10 were predicted and visually identified by MetaPocket server (<http://projects.biotech.tu-dresden.de/metapocket/>), which is an online tool that locates and measures pockets in the protein structures [31].

Molecules retrieval and ligand preparation

The chemical structures of 450 phytochemicals were known to have anticancer activities which were downloaded from NCBI PubChem (<https://pubchem.ncbi.nlm.nih.gov/>) in Standard Data Format (SDF).

PubChem is an open repository for chemical structures and their biological test results [32]. The SDF files were converted to 3D structures such as mol2 and PDB using Open Babel [33] converter and visualized using Biovia DS visualizer. These molecules were further taken for molecular docking studies.

Docking studies using the selected phytochemicals

A geometry-based molecular docking algorithm, namely PatchDock server (<http://bioinfo3d.cs.tau.ac.il/PatchDock>) [34,35], was used for docking of HDAC10 with the selected phytochemicals. PatchDock is an online docking server which is designed for the purpose of the identification of the interaction sites between the receptor and ligand molecules. The molecular surface of the protein is divided into patches as per the molecular shape followed by the comparison between the patches to produce a group of transformations [36]. These transformations were further ranked based on the geometric complementarity score, and each transformation was assigned to have a score, namely PatchDock score and atomic contact energy (ACE) values.

Analysis of docking results

To optimize the observed anti-inflammatory and anticancer activities from literature studies, we evaluated the binding mode of each docked complexes. In this step, the generated poses of each docked complex were analyzed and ranked based on their predicted binding energies, termed as ACE value. These rankings were used to evaluate the binding affinity of the receptor to develop the best conformational fit with the ligands selected for analysis. Among the generated multiple conformations and associated binding energies, the pose with least energy values was considered as the best pose and reported using Biovia DS visualizer. The atomic dissolution energy of the derive complex was estimated, and the redundant solution was calculated using RMSD, clustering during the docking process [34,37]. The docking poses with interacting amino acids were graphically represented by Biovia DS 4.5. The best poses were analyzed for hydrogen bonding, steric, and hydrophobic interactions.

Drug-likeness and Lipinski's rule of five calculation and pharmacokinetics evaluation

Molecular descriptors and drug likeness properties of the selected phytochemicals were evaluated using the online tool named as Molinspiration server (<http://www.molinspiration.com>), based on Lipinski Rules of five [38]. The smiles format of each of the compound was uploaded for the analysis. As per Lipinski's rule, "drug-like" molecules must have log p_s ≤ 5, molecular weight ≤ 500, number of hydrogen bond acceptors ≤ 10, and number of hydrogen bond donors ≤ 5.

RESULTS AND DISCUSSION

PTM analysis of HDAC10

According to prediction results, there were 25 hits for PTMs which resulted as three patterns. Protein kinase C phosphorylation, Casein kinase II phosphorylation, and N-myristoylation sites were predicted as critical biochemical events required for HDAC10 regulation. Three regions were identified as protein kinase C phosphorylation sites (amino acid residues range from 51 to 53, 345 to 347, and 409 to 411). The residues occurring at 417–420 were identified as phosphothreonine, T, whereas others were phosphoserine, S. Protein kinase C appeared to react with serine or threonine residues that were located at the amino-terminal (C terminal) side close to lysine or arginine [39]. The results showed the low level score for phosphothreonine site as shown in Table 1.

Casein kinase II phosphorylation sites were relatively more abundant than protein kinase C phosphorylation sites (amino acid residues range 51–54, 56–59, 209–212, 309–312, 38–341, 397–400, 417–420, and 640–643). N-myristoylation sites were abundant more than other functional sites in HDAC10. N-myristoylation sites are involved in the amino acids residues ranging from 88 to 93, 120 to 125, 136 to 141, 217 to 222, 219 to 224, 232 to 237, 273 to 278, 294 to 299, 384 to 389, 469

Table 1: Post-translational modifications (phosphorylation sites) of HDAC10

S.no	Site	Definition	Region	Modified residue	
				Serine (S)	Threonine (T)
1.	PS00005	PKC_PHOSPHO_SITE, Protein kinase C phosphorylation site	51-53; 345-347; 409-411	51; 345; 409	
2.	PS00006	CK2_PHOSPHO_SITE, casein kinase II phosphorylation site	51-54; 56-59; 209-212; 309-312; 338-341; 397-400; 417-420; 640-643;	51; 56; 209; 309; 338; 397; 640	417

HDAC10: Histone deacetylase 10

to 474,473 to 478,498 to 503, 553 to 558, and 599 to 604. It is found that hydrophobic and steric interactions act in concert to anchor to cell membranes and proteins that are either myristoylated or farnesylated and myristoylation promotes the reversible membrane protein-protein interactions (PPIs) [40] (Table 2). These results highlight N-myristoylation, and Casein kinase II acts as a potential regulator of HDAC10 PTM and also shows that regulation of HDAC10 function may be controlled in part by post-translational phosphorylation.

Protein domain boundaries and the knowledge of its architecture are an important aspect for understanding the protein function. Detection of protein domain and architecture is a valuable tool in the areas of protein science, protein structure prediction, etc., [41]. These setups allowed us to study the behavior of residues and its role in PTMs and motif functionality. PTM studies provide an extensible clue about protein's regulation process [42]. These features include the nature of signal transduction, protein stability, etc. [43]. The mechanism of transcriptional regulation of HDAC10 with respect to drug binding with phytochemicals remains poorly understood. Therefore, multiple strategies, including motif and domain, were determined to recognize binding sites to further study the docking and its dynamics. Thus, we hypothesize that a more reliable mechanism is highly desirable to determine the binding sites, binding mode, and its role in various cancers.

Binding site determination

Eight important binding pockets were determined as catalytic sites of the HDAC-10 receptor using metaPocket server. After clustering, the top three sites from the base methods, namely PASS11 (PAS), LigsiteCS (LCS), Q SiteFinder (QSF), GHECOM (GHE), POCASA (PCS), Fpocket (FPK), SURFNET (SFN) and ConCavity (CON), were the base methods incorporated to predict all the top eight clusters. MetaPocket running report is shown in Table 3. The first MetaPocket site consists of five pocket sites with total Z score of 19.45 from SFN-1, "LCS-1," "FPK-1," "CON-2," and "GHE-2." The second MetaPocket site consists of 6 pocket sites with a total Z score of 17.42 from GHE-1, "FPK-2," "LCS-2," "SFN-2," "PAS-2," and "CON-1," and the third MetaPocket site consists of 1 pocket site with a total Z score of 2.51 from SFN-3. Eight header binding sites with potential binding site residues of the receptor are shown in Table 4. The identification of binding sites is an important step in structure-based drug design, as this helps to understand the functional sites and its mechanism of action of the protein [44]. These identified active sites were helpful to evaluate further the binding mode of docked complexes. Thus, we focused on the binding mode of the residues and evaluated its affinity to the HDAC10 receptor during the selected drug-interaction studies through docking.

HDAC10 and phytochemical binding mode analysis

To analyze the reliability of interaction mode between HDAC10 and the compounds, namely periplogenin, 3,3'-diindolylmethane and epigallocatechin, the binding energy score values were determined. Molecular docking is the standard method used to determine the binding mode of molecules with the receptors; docking was used [45,46] in many studies. In our study, holacurtine showed a lesser energy value of -300.21 compared to other three compounds. The predicted interacting residues obtained by drug interaction studies were matched with the predicted binding pocket amino acids of MetaPocket server.

Table 2: Post-translational modifications (myristoylation sites) of HDAC10

S. No	Region	Residues
1.	88-93	GQfdAI
2.	120-125	GAVqNG
3.	136-141	GQraAA
4.	217-222	GQglGF
5.	219-224	GLgfTV
6.	232-237	GMgnAD
7.	273-278	GQmqAT
8.	294-299	GGrvCA
9.	384-389	GGpvCK
10.	469-474	GMldGQ
11.	473-478	GQvnSG
12.	498-503	GLshGA
13.	553-558	GGflSC
14.	599-604	GLagGR

HDAC10: Histone deacetylase 10

Table 3: Predicted ligand binding clusters site of receptor, HDAC10, using MetaPocket server

Clusters	Z score	Number of pocket sites	Methods
1.	19.45	5	"SFN-1," "LCS-1," "FPK-1," "CON-2," "GHE-2"
2.	17.42	6	"GHE-1," "FPK-2," "LCS-2," "SFN-2," "PAS-2," "CON-1"
3.	2.51	1	"SFN-3"
4.	1.78	1	"PAS-1"
5.	0.99	1	"LCS-3"
6.	0.47	1	"PAS-3"
7.	0.44	1	"GHE-3"
8.	-0.69	2	"FPK-3," "CON-3"

HDAC10: Histone deacetylase 10

Holacurtine formed hydrogen bonds with Leu362, Ala363, Gln364, and Arg658 and steric interactions with Ser358, His361, Leu362, Ala363, Gln364, Val651, and Arg658. Holacurtine is only involving in the formation of hydrogen bond and hydrophobic bonds. Holacurtine does not form any hydrophobic bonds. In addition, inter-residue hydrogen bond interaction (Arg658-Glu655, Arg658-Met654, Arg658-Cys670, Glu652-Glu655, Glu655-Val651, and His361-Leu362) are involved in anchoring the holacurtine to the receptor HDAC10 (Fig. 1). Periplogenin forms hydrogen bond with Gln659, steric interactions with Arg658, Glu655, and Glu674, and hydrophobic interactions with His361. Arg658-Cys670, Arg658-Glu655, Arg658-Leu668, Gln659-Glu655, and Glu674-Trp676 forms inter-residue interactions with periplogenin as shown in Fig. 2. 3,3'-Diindolylmethane forms hydrogen bond interaction with Glu655, steric interactions with Arg349, Thr671, Arg658, and Glu655, and one hydrophobic bond with Cys670. Glu655-Val651, Arg349-His246, Arg658-Cys670, Arg349-Phe359, Arg658-Glu655, Arg658-Met654, and Cys670-His246 form inter-residue interactions with 3,3'-Diindolylmethane (Fig. 3). Epigallocatechin forms hydrogen bonds with Arg349, Arg658, Glu655, Arg349, and Gly567, steric interactions

could be validated to check its ADME, IC₅₀ value, and anti-inflammatory responses using both *in vitro* and *in vivo* methods. The computational observations of PTM together with the binding mode information have given information in the field of SNP and mutation studies as well as paved the way for new research approach for efficiently selecting critical regions and sites including non-coding residues for drug binding domains which may have great scope in cancer research. Furthermore, the PTM studies could form a starting point to further understand its PPI with TXNIP protein and regulation mechanisms which is still not yet determined. The docking and dynamics score studies demonstrated the selection procedure of phytochemicals toward the receptor, and these methodologies might be helpful for developing new drugs for HDAC10 protein driven cancers.

ACKNOWLEDGMENTS

The authors are grateful to JNIAS, Hyderabad, Telangana, for the facilities provided.

AUTHOR'S CONTRIBUTION

S.M. conceived the idea, participated in the study design, performed data collection and analysis, and drafted the manuscript under K.J.'s supervision. K.J. designed and supervised the study, coordinated the data collection, analysis, and its interpretation, helped in drafting the manuscript, and provided the critical revisions. A.V.N.S. coordinated the study and gave useful suggestions. All authors read and gave final approval for publication.

CONFLICTS OF INTEREST

The authors declared that there are no conflicts of interest.

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