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Colchicine as a potential HDAC inhibitor: comparative binding energies and prospects for cancer therapy repurposing

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ABSTRACT: Drug repurposing, also known as drug repositioning or drug reprofiling, is gaining momentum as a strategy to identify novel therapeutic uses for existing drugs outside their original medical indications. This approach leverages the known safety profiles and mechanisms of action of approved medications to expedite the development of treatments for various diseases. Colchicine, an ancient herbal medicine with established anti-inflammatory properties and recognized efficacy in conditions like gout and Familial Mediterranean fever, has garnered interest in its potential applications beyond traditional uses. The discovery of colchicine's binding capacity to microtubules, essential for cellular structure and mitosis, has sparked exploration into its role in cancer therapy. Histone deacetylase inhibitors (HDACs) have also shown promise in cancer research by modulating gene expression through histone and non-histone protein acetylation. While colchicine is not conventionally classified as an HDAC inhibitor, studies suggest its potential impact on HDAC activity. This study aims to investigate the similarities in enzyme binding energies between colchicine and HDAC inhibitors, exploring the potential utility of colchicine as an HDAC inhibitor and introducing a new avenue for cancer treatment. By elucidating the potential therapeutic overlap between colchicine and HDAC inhibitors, this research seeks to advance the field of drug repurposing and provide novel insights into the treatment of cancer and other diseases.

KEYWORDS: Colchicine; drug repurposing; HDAC; docking; anticancer.

1. INTRODUCTION

Drug repurposing, also known as drug repositioning or drug reprofiling, is the practice of identifying new therapeutic uses for existing drugs that are outside of their originally intended medical indications. Instead of developing new drugs from scratch, researchers and healthcare professionals explore the potential of already-approved drugs or compounds for treating different diseases or conditions. There are several reasons why drug repurposing is an attractive strategy in drug discovery and development. One of the most important reasons is cost-effectiveness. That means, repurposing existing drugs can potentially reduce the time, resources, and costs associated with developing a new drug from the ground up, as many aspects of the drug, such as safety profiles, pharmacokinetics, and formulation, are already known. The other important reason is safety. Because of these drugs have already been approved for human use for their original indications, their safety profiles have been well-established, which can speed up gaining regulatory approval for new uses. By exploring drug repurposing, researchers can uncover new therapeutic opportunities, accelerate the development timeline, and potentially bring treatments to patients more quickly. This approach has led to the discovery of novel uses for medications in a wide range of therapeutic areas, including cancer, infectious diseases, neurological disorders, and autoimmune conditions [1,2]. Colchicine, an ancient herbal medicine derived from *Colchicum autumnale*, has been utilized since 1550 BC for its potent anti-inflammatory properties in the treatment of pain and swelling (Figure 1). With advancements in technology, the active molecules of colchicine were identified in 2005, revealing its tricyclic alkaloid structure as the bioactive component responsible for its therapeutic effects. Apart from its well-known efficacy in managing the acute inflammatory phase of gout, colchicine has also been approved by the FDA in 2009 for the treatment and prevention of Familial Mediterranean fever (FMF) [3]. Besides this, prevention and curative effect of colchicine for cardiovascular diseases are also investigated [3–6]. Moreover, the

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discovery of colchicine's binding capacity to microtubules has shed light on its potential beyond its traditional uses. Microtubules serve as a crucial

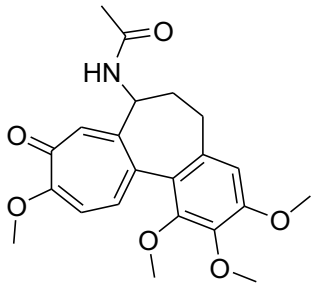

Figure 1. Molecular structure of colchicine

component of the eukaryotic cell skeleton, contributing to cell structure, intracellular transportation, and chromosomal segregation during mitosis. The unique ability of colchicine to interfere with microtubule dynamics holds promise in targeting rapidly dividing cells, which is particularly relevant in cancer therapy [7]. In parallel, histone deacetylase inhibitors (HDACs) have emerged as a promising class of compounds in cancer research due to their ability to modulate gene expression through histone and non-histone protein acetylation [1]. Histone deacetylase inhibitors (HDACis) have garnered considerable attention as potential anticancer agents due to their ability to modulate gene expression and arrest the proliferation of cancer cells. A spectrum of HDACis, including Vorinostat, Belinostat, Romidepsin, Valproic acid, Butyric acid, and Tucidinostat, exhibit substantial therapeutic efficacy in treating diverse malignancies (Figure 2). Vorinostat, a prototypical small molecule HDACi, targets both class I and II HDAC enzymes, culminating in the hyperacetylation of histone proteins and the subsequent alteration of gene expression profiles. Its clinical utility in cutaneous T-cell lymphoma underscores the promise of HDACis in oncology. Conversely, Belinostat exerts its effects via the inhibition of histone deacetylation, thereby activating gene regulatory elements involved in cell cycle arrest and apoptotic pathways, rendering it beneficial in the context of peripheral T-cell lymphoma. Romidepsin, classified as a cyclic peptide HDACi, engages HDAC active sites to foster histone acetylation, thus remodeling gene expression patterns that govern cellular proliferation. This agent's efficacy in the treatment of both cutaneous and peripheral T-cell lymphoma underscores its potential clinical utility. Meanwhile, Valproic acid, a broad-spectrum HDACi recognized primarily for its antiepileptic properties, has also evidenced oncological promise by mitigating HDAC activity and enhancing histone acetylation, suggesting a multi-faceted therapeutic repertoire. Butyric acid, an endogenous HDAC inhibitor present in dietary sources such as butter and cheese, has provoked interest owing to its regulatory influence on gene expression via the modulation of HDAC activity and histone acetylation, proposing potential application in cancer therapy and beyond. Tucidinostat, belonging to the benzamide class of HDAC is, has demonstrated efficacy against hematologic malignancies and solid tumors by precipitating hyperacetylation of histones, which leads to the disruption of gene expression patterns that are integral to the proliferation and survival of cancer cells. Collectively, the varied mechanisms of action and therapeutic applications of these HDACis signify a pivotal evolution in oncological treatment paradigms. These compounds herald a promising avenue for cancer therapeutics, poised to refine treatment outcomes and enhance patient quality of life immeasurably. Nevertheless, diligent research is imperative to elucidate the comprehensive impact of HDACis on cancer pathophysiology and to forge novel. Some studies have indicated that colchicine could potentially impact histone deacetylase (HDAC) activity, although it is not primarily classified as an HDAC inhibitor. The exact mechanisms and effects of colchicine on HDAC enzymes are still being explored, and further research is needed to elucidate the extent of its activity in this regard. By elucidating the similarities based on the enzyme binding energies of colchicine and HDAC inhibitors, the purpose of this study is to investigate whether colchicine can be used as an HDAC inhibitor, and to introduce a new drug to cancer treatment [9-12].

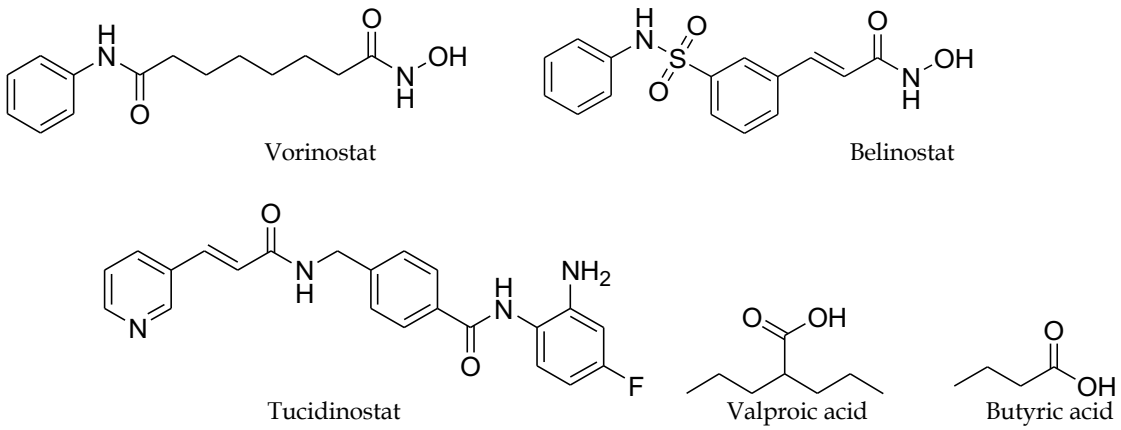

Figure 2. Molecular structures of Vorinostat, Belinostat, Tucidinostat, Valproic acid and Butyric acid.

2. RESULTS & DISCUSSION

2.1. Determining the Binding Energies

In this study, the objective was to determine the binding energies of colchicine and six HDAC inhibitors to various HDAC classes using computational modeling techniques. The calculated binding energies (in kcal/mol) of colchicine and six HDAC inhibitors (vorinostat, belinostat, romidepsin, valproic acid, butyric acid, and tucidinostat) to HDAC classes I through VII were reported. Binding energy values closer to zero represent weaker binding, while more negative values indicate stronger binding. To specifically evaluate the inhibitory potential of colchicine on histone deacetylases (HDACs), the binding energies of colchicine with HDACs I, II, III, IV, VI, and VII were calculated. The results indicated that colchicine exhibited favorable binding energies across all tested HDACs. The binding energies were between -7.6 to -9.3 kcal/mol. Notably, the most significant binding energy was observed with HDAC VI, yielding a binding energy of -9.3 kcal/mol (Table 1).

Table 1. Binding energies of Colchicine for HDACs

HDACs	Binding energy (kcal/mol)	Cavity volume	Center (x,y,z)	Docking size (x,y,z)
HDAC I	-8.6	569	-70, 25, 3	22, 22, 22
HDAC II	-8.5	3595	23, -22, -38	22, 33, 22
HDAC III	-8.6	21618	30, 63, 22	35, 35, 35
HDAC IV	-7.6	562	17, -8, 2	22, 22, 22
HDAC VI	-9.3	1474	-19, -27, 29	22, 22, 22
HDAC VII	-7.6	671	-12, 14, 24	22, 22, 22

Binding energies of the six HDAC inhibitors (vorinostat, belinostat, romidepsin, valproic acid, butyric acid, and tucidinostat) were determined for HDACs I, II, III, IV, VI, and VII. Then these energies were compared with binding energies of colchicine (Table 2). Binding energies were compared with colchicine and six HDAC inhibitors, colchicine had very high binding energy (-8.6 kcal/mol). Only 1 out of 6 inhibitors, Romidepsin (-10.1 kcal/mol) had binding energy higher than colchicine. The binding energies of the other inhibitors were lower than colchicine. The same binding energies were determined for Belinostat and Colchicine. For HDAC II, binding energy of Colchicine was -8.5 kcal/mol that was the third highest one. When the binding energies for HDAC III were compared, colchicine was found to be the molecule with the 3rd highest energy, as was the case with HDAC II.

Table 2. Binding energies of colchicine and six HDAC inhibitors (vorinostat, belinostat, romidepsin, valproic acid, butyric acid and tucidinostat)

HDACs	Colchicine	Vorinostat	Belinostat	Romidepsin	Valproic acid	Butyric acid	Tucidinostat
HDAC I	-8.6	-7.7	-8.6	-10.1	-5.6	-4.2	-8.5
HDAC II	-8.5	-7.8	-8.3	-10.8	-5.6	-4.4	-10.2
HDAC III	-8.6	-8.3	-8.6	-10.6	-5.1	-4.5	-9.4
HDAC IV	-7.6	-8.0	-9.2	-9.4	-6.0	-4.4	-9.3
HDAC VI	**-9.3**	-8.3	-9.1	**-10.5**	-5.8	-4.4	**-11.3**
HDAC VII	-7.6	-6.8	-8.6	-9.0	-4.7	-3.7	-9.7

Colchicine exhibited identical and minimal binding energies of -7.6 kcal/mol with HDAC IV and VII, respectively. While these values represent the lowest recorded within this study, they hold promise for potential drug repurposing endeavors. Moreover, upon evaluation within their respective categories, colchicine outperformed certain inhibitors such as valproic acid, butyric acid, and vorinostat. The most favorable binding energy for colchicine, -9.3 kcal/mol, was observed with HDAC VI. Although this value fell below the binding energies exhibited by romidepsin (-10.5 kcal/mol) and tucidinostat (-11.3 kcal/mol), it transcended those of the remaining inhibitors assessed in this study, as detailed in Table 2.

2.2. Docking Studies

The best binding energies were determined for HDAC VI with Tucidinostat and Colchicine. Therefore, they were submitted to the CB-Dock service to predict its binding strength and interactions with specific amino acid residues. Employing the renowned docking software AutoDock Vina, this accessible blind docking service estimates protein-ligand binding and produces docking results. This evaluation uncovered various binding affinities with the HDAC VI.

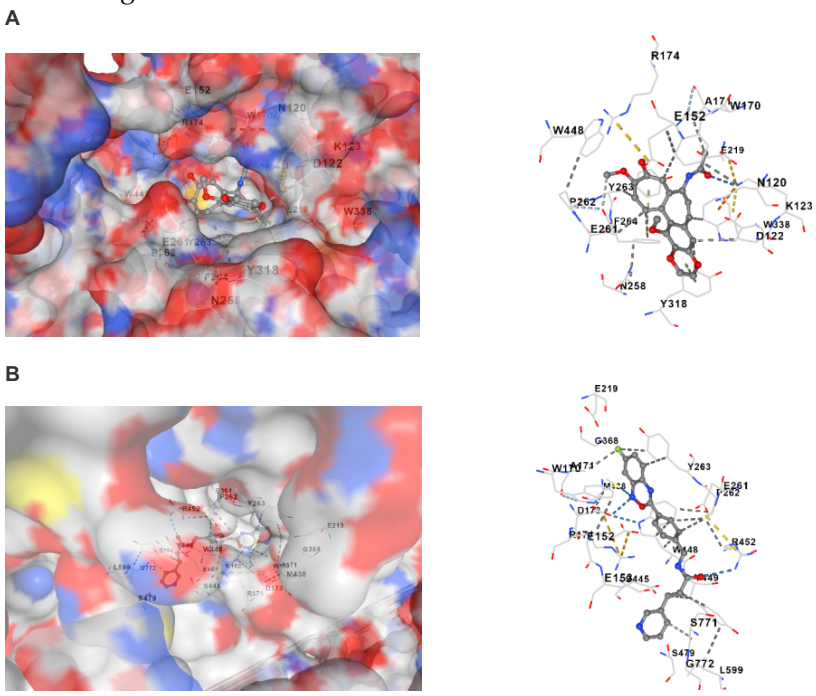

Figure 3. Molecular docking analyses of Colchicine and Tucidinostat with HDAC VI. a) Colchicine, b) Tucidinostat

As mentioned above, docking studies revealed closely related binding energies for Colchicine and Tucidinostat. The docking analysis with the HDAC6 protein has also shown that the interacting residues bear similarities. The common residues interacting with HDAC6 for tucidinostat and colchicine are as follows: ASP149, GLU152, TRP170, ALA171, ASP173, ARG174, GLU219, GLU261, PRO262, TYR263, TRP338, GLY368, MET438, TRP448 (Table 3). These interactions occur via hydrogen bonds, ionic interactions, and pi-

pi stacking. The interaction of Tucidinostat and Colchicine with many common residues of HDAC6 suggests that colchicine may be a potential HDAC6 inhibitor.

Table 3. Docking parameters and results of Colchicine and Tucidinostat.

HDAC VI	Colchicine	Tucidinostat
Binding energy (kcal/mol)	-9.3	-11.3
Cavity	1474	1344
Docking center (x,y,z)	-19, -27, 29	9, -18, 84
Dcoking size (x,y,z)	22, 22, 22	27, 27, 35
Contact residues	ASN120 GLY121 ASP122 LYS123 HIS147 PRO148 ASP149 LYS150 LEU151 GLU152 TRP170 ALA171 ASP173 ARG174 GLU219 ASN258 GLN260 GLU261 PRO262 TYR263 PHE264 ASP317 TYR318 SER319 TRP338 GLY368 MET438 TRP448	ASP149 LYS150 GLU152 GLU153 LYS154 PRO156 GLN157 VAL158 ALA160 THR161 TRP170 ALA171 ASP173 ARG174 GLU219 GLU261 PRO262 TYR263 TRP338 GLY368 MET438 SER445 ALA446 TRP448 TYR449 ARG452 SER479 LEU599 LEU724 PRO725 TYR728 ASN731 PRO732 GLU733 HIS764 LEU765 MET767 GLY768 LEU769 ALA770 SER771 GLY772

2.3. ADMET Studies

In this study, investigated drugs have already been used in clinic and their ADMET studies already were done. Therefore, it was only compared the physicochemical properties of the most active molecule, Tucidinostat, and Colchicine. ADMET study was performed with web base free tool ADMETlab 2.0 (admetmesh.scbdd.com) [13]. Drug discovery and repurposing rely on the identification of compounds with optimal pharmacokinetic and pharmacodynamic profiles. Central to this process is the assessment of molecular properties that influence bioavailability and therapeutic potential. Here, it was summarized critical physicochemical parameters employed to evaluate the 'drug-likeness' and solubility profiles of compounds, following established soft rules and guidelines. Hydrogen Bond Acceptors (nHA) and Donors (nHD), drug molecules require a balance in their ability to participate in hydrogen bonding, which is essential for biological interactions. nHA denotes the total count of oxygen (O) and nitrogen (N) atoms, with an optimal range of 0 to 12, while nHD accounts for hydroxyl (OH) and amine (NH) groups, optimally between 0 to 7. The next is rotatable Bonds (nRot) and Flexibility. Rotatable bonds signify molecular flexibility. The count excludes amide C-N bonds due to their high rotational energy barrier, with an ideal count from 0 to 11. Flexibility, calculated as nRot/nRig (number of rigid bonds), provides an insight into the molecular dynamics influencing the compound's binding affinity. The other parameter is ring structures (nRing and MaxRing). Pharmacophores often contain ring systems that contribute to molecular stability and specificity. The preferred number of ring systems is between 0 to 6, while the maximum count of atoms in the largest ring system should not exceed 18 atoms for optimal drug-like properties. The other important point is heteroatoms (nHet). Atoms other than carbon are critical for varied biological interactions. The number of heteroatoms in a drug-like molecule is optimally between 1 to 15. Formal charge (fChar) is also crucial for drug-like property that is the formal charge on a molecule ensures compatibility with biological environments, with an optimal range of -4 to +4. Topological polar surface area (TPSA) which estimates the polar region of the molecule, affecting both solubility and permeability, with an optimal range from 0 to 140 angstroms. Lastly, logarithmic values in Solubility and Distribution. The evaluation of aqueous solubility (logS), lipophilicity (logP), and the distribution coefficient at physiological pH (logD7.4) is critical for predicting a compound's oral bioavailability. Ideal logS values range between -4 to 0.5 for proper solubility, while logP values from 0 to 3 suggest a balance between membrane permeability and hydrophobic interactions necessary for therapeutic efficacy. Additionally, a logD7.4 within 1 to 3 aligns with optimal

lipophilicity and hydrophilicity, ensuring effective dissolution and biomembrane penetration, pivotal for drug absorption and action. These parameters guide the selection of candidates with favorable profiles for oral delivery in the early stages of pharmaceutical development.

Table 4. Physicochemical properties of Colchicine and Tucidinostat.

Molecules	Mwt	nHA	nHD	nRot	nRing	fChar	TPSA	logS	logP	logD
Colchicine	399.17	7	1	6	3	0	83.09	-2.68	1.094	1.485
Tucidinostat	390.15	6	4	8	3	0	97.11	-5.338	2.225	2.174

Upon examining the physicochemical parameters of colchicine and tucidinostat (Table 4), it has been observed that their molecular weights are closely aligned. While the numbers of hydrogen bond acceptors are similar for both compounds (7 and 6, respectively), a significant difference is seen in their hydrogen bond donor (nHD) properties (1 and 4). The Topological Polar Surface Area (TPSA) values for both are closely matched and fall within the optimal range. When solubility parameters were analyzed, the logS value for colchicine is within the optimum range at -2.68, whereas the value for tucidinostat at -5.338 lies outside this range. Other solubility parameters, such as logP and logD values, are within optimal limits for both molecules.

Table 5. Medicinal chemistry properties of Colchicine and Tucidinostat.

Molecules	QED	SAscore	Fsp3	MCE-18	NPscore	Lipinski rule	Pfizer rule	GSK rule	Golden triangle
Colchicine	0.833	2.924	0.364	64.0	0.755	Accepted	Accepted	Accepted	Accepted
Tucidinostat	0.444	2.132	0.045	17.0	-1.461	Accepted	Accepted	Accepted	Accepted

The Quantitative Estimate of Drug-likeness (QED) is an assessment metric that synthesizes the concept of appeal in drug candidates. This metric is operationalized by amalgamating the outcomes of multiple desirability functions, which are predicated upon a suite of eight properties indicative of drug-likeness. These properties comprise molecular weight (MW), logarithm of the octanol-water partition coefficient (log P), number of hydrogen bond acceptors (NHBA), number of hydrogen bond donors (NHBD), polar surface area (PSA), number of rotatable bonds (Nrotb), count of aromatic rings (NAr), and a tally of signals flagging potentially problematic functional groups. In determining the QED, an average value for the weights of these descriptors is employed. When decoding the results, a higher mean QED of 0.67 is observed in compounds deemed attractive, whereas this value falls to 0.49 in less appealing compounds, and further declines to 0.34 in compounds categorized as excessively complex and thus, unattractive. According to this information, Colchicine has a better QED value than Tucidinostat (Table 5). SAscore and Fsp3 values are in the optimum range for two compounds. The term MCE-18 refers to a paradigm introduced in 2018 for the advancement of medicinal chemistry, which focuses on the innovation of molecular structures through the assessment of their sp3 character complexity. This metric is poised to efficiently evaluate and assign scores to molecules, pivoting on the novelty introduced by their three-dimensional intricacy. This is derived from the increased proportion of sp3-hybridized carbon atoms, which is often associated with enhanced physical and chemical properties favorable for drug discovery. MCE-18 value of Colchine is also better than Tucidinostat (Table 5). The other parameters are accepted ranges for two molecules. Similarities may imply these two molecules may have similar HDAC inhibitory activity. Beside this, better values of Colchicine may cause higher inhibitory potential against HDAC enzymes. Indeed, while computational assessments like the MCE-18 can provide valuable insights into the potential novelty and complexity of molecular structures, the validity of such evaluations must be substantiated through empirical evidence. This involves corroborative studies conducted in vitro and in vivo. These experimental studies are critical to affirm the biological efficacy, safety, and pharmacokinetic properties of the molecules in question, ultimately ensuring that the theoretical predictions align with practical therapeutic outcomes.

3. CONCLUSION

It is evident that colchicine has similar binding energies to HDAC inhibitors, especially when comparing it to vorinostat, belinostat, and others. This is an exciting finding, as it suggests that colchicine could act as an HDAC inhibitor. This possibility could open new avenues in cancer treatment and drug repurposing. However, further research is required to validate these findings and explore the mechanism of action and the efficacy and safety of using colchicine as an HDAC inhibitor in clinical settings. Although computational models predict binding energies reliably, they cannot confirm biological activity. Thus, the next step would be to validate these findings with in vitro and in vivo studies. Results indicate that colchicine exhibits binding energies to various HDACs comparable to known HDAC inhibitors, supporting the hypothesis that it possesses HDAC inhibitory activity. This work opens a new avenue for the study of colchicine as a potential HDAC inhibitor in cancer treatment.

4. MATERIALS AND METHODS

4.1. Protein and ligand selection

The crystal structures of HDAC I, II, III, IV, VI and VII were obtained from Protein Data Bank (PDB). PDB IDs of HDAC enzymes were 4BKX, 4LXZ, 4A69, 2VQM, 5EDU and 3C10 respectively. The ligands Colchicine, Vorinostat, Belinostat, Romidepsin, Valproic acid, Butyric acid and Tucidinostat were acquired from Drugbank as SMILE format.

4.2. Preparation and molecular docking

The HDAC proteins were downloaded as pdb file format. Then they uploaded the CB-Dock web-based software [14,15] [6,7] for docking into the active site of the proteins. The binding region is successfully located using the CB-Dock protein-ligand docking approach, which also determines the size and location of the center and allows the docking zone to be customized using AutoDock Vina1.1.2. Several top cavities were automatically chosen via this approach and used for further studies.

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