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In silico-based identification of phytochemicals as novel human phosphoglycerate mutase 1 (PGAM1) inhibitors for cancer therapy

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Abstract: Targeting cancer-specific metabolic and mitochondrial remodeling has emerged as a novel and selective strategy for cancer therapy during recent years. Phosphoglycerate Mutase 1 (PGAM1) is an important glycolytic enzyme that catalyzes the conversion of 3-phosphoglycerate to 2-phosphoglycerate and plays a critical role in cancer progression by coordinating glycolysis and biosynthesis. PGAM1 has been reported to be over expressed in a variety of cancer types and its inhibition results in decreased tumor growth and metastasis. Recently, there has been a growing interest in identification and characterization of novel PGAM1 inhibitors for the treatment of cancer. In the current study, in silico tools were used to find out natural inhibitors of PGAM1. For docking studies, a database of 5006 phytochemicals were docked against PGAM1, using MOE software in order to identify the compounds which show better binding affinities than PGMI-004A. Out of 5006 compounds screened, eight compounds (1,3-cyclopentanedione, glyflavanone B, 6-demethoxytangeretin, gnaphaliin, lantalucratin A and -(-) morelensin, abyssinin II and monotesone-A) showed significant binding affinity with PGAMI active site. Further, the eight selected compounds were evaluated for different pharmacokinetics parameters using admetSAR, the obtained results demonstrated that none of these hit compounds violated Lipinski's drug rule of 5 and all the hit compounds possess favorable ADMET properties. This study has unveiled the potential of phytochemicals that could serve as probable lead candidates for the development of PGAM1 inhibitors as anti-cancer agents.

Keywords: Cancer metabolism, computational analyses, molecular operating environment, PGAM1, phytochemicals.

INTRODUCTION

Cancer, a highly complicated disease characterized by uncontrollable proliferation of cells, has been reported as second leading cause of mortalities around the globe (Sarfraz *et al*., 2018). During 2018, 18 million new cancer cases while 9.6 million deaths due to cancer have been recorded worldwide (Bray *et al*., 2018). Approximately more than 56% of the total cancer patients worldwide live in Asia which is 44% of the overall global burden of this lethal disease (Muhseen and Li, 2019). Chemotherapy integrated with radiotherapy or surgery permits curative intervention in majority of cancer patients (Arruebo *et al*., 2011), however, toxicity of chemo-drugs towards normal cells and development of drug-resistant cancer cells are major obstacles for the successful cancer treatment (Makovec, 2019). Thus, the development of drugs selectively targeting cancer cells while leaving no effect on normal cells is an emerging therapeutic intervention against cancer. In this context, targeting cancer-specific metabolic and mitochondrial remodeling has turned up as novel and selective strategy for cancer therapy (Kalyanaraman, 2017).

Metabolic reprogramming has been reported as an emerging hallmark of cancer in recent years (Pavlova and Thompson, 2016). In tumor cells unlike normal cells, energy mainly comes from aerobic glycolysis rather than oxidative phosphorylation. During increased aerobic glycolysis in cancer cells, ATP is produced inefficiently whereas building blocks (e.g., amino acids, nucleotides, and lipids) necessary for anabolic biosynthesis are formed in large amounts through various metabolic pathways branching off from glycolysis which support rapid proliferation of cancer cells (Hitosugi *et al*., 2012). Various metabolic pathways have been reported to overexpress in cancer cells based on sugar metabolism (Sarfraz *et al*., 2018). However, glycolysis has been contemplated as the main source of energy for these growing cancer cells (Sharif *et al*., 2019).

Phosphoglycerate mutase 1(PGAM1) is an essential glycolytic enzyme which catalyses the reversible transformation of 3-phosphoglycerate to 2-phosphoglycerate (Hitosugi *et al*., 2012). PGAM1 supports cancer development by coordinating glycolysis and biosynthesis, especially via pentose phosphate pathway (PPP) and serine biosynthesis (Hitosugi *et al*., 2013). PGAM1 is over expressed in numerous kinds of aggressive human cancers mainly breast, prostate, lung, colorectal, hepatocellular carcinoma and pancreatic ductal adenocarcinoma (Sharif *et al*., 2019). Previous studies have also demonstrated that PGAM1-mediated glycolysis plays critical role in tumor development, survival, and migration of cancer cells (Huang *et al*., 2019), thus, PGAM1 inhibition has potential to kill cancer cells selectively.

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The emergence of computer-aided drug designing tools has allowed the rapid assessment of chemical libraries against various drug targets in a timely and cost-effective manner (Muhseen and Li, 2019). During this study, a library of 5006 phytochemicals was screened against PGAM1 by using the in-silico approach and from these phytochemicals; eight top-ranking docking poses were selected. The selected hits were further investigated for druglikeness and ADMET profiles. Our results demonstrate that the eight selected compounds follow Lipinski drug rule of 5 and possess favourable ADMET properties. Thus, the identified inhibitors of PGAM1 could serve as template for the development of novel, safer and selective therapeutics against cancer.

MATERIALS AND METHODS

Structure retrieval and preparation

The structure of phosphoglycerate mutase 1 (PGAM1) was retrieved in 3D format from the Protein Data Bank (PDB ID: 5Y2I). The structure was then prepared by removing attached ligands and solvent, then minimizing energy (Forcefield: MMFF94x and Gradient: 0.05) with the tools available in Molecular Operating Environment (MOE 2009.10). The prepared and minimized protein structure was then saved as a receptor to perform docking analysis (Idrees, 2014).

Phytochemical library preparation

5006 phytochemicals were taken from different databases such as MAPS (Ashfaq *et al*., 2013), PubChem (https://pubchem.ncbi.nlm.nih.gov/) and MPD3 (Mumtaz *et al*., 2017) in order to prepare the ligand library. All the ligands were subjected to protonation and energy minimization to set up ready to dock ligand library.

Docking analysis

The molecular docking was accomplished via molecular operating environment (MOE) software by considering prepared protein structure as a receptor to determine the binding conformations with prepared ligand libraries (Khan *et al*., 2013). The site finder tool available in MOE software was used to select the active site residues of PGAM1 (Arg10, Arg116, Arg191, Glu13, Glu89, Asn209) (Li *et al*., 2017). The following docking parameters were utilized; placement by triangle matcher, rescoring 1 & 2 (was performed by London dG), refinement was done through force field simulation, and retain was kept at 10. The inhibitor PGMI-004A was used as a positive control. After performing the docking, the best compounds were selected based on root-mean-square deviation (RMSD) values and docking score.

ADMET and drug-likeness analysis of compounds

Compounds with the best docking scores were further subjected to drug-likeness and ADMET filters. Lipinski's rule of 5 (RO5) (Benet *et al*., 2016) was followed to calculate the physicochemical properties with the help of the Molinspiration server. After the RO5 filter, the compounds' druggability [absorption, distribution, metabolism, excretion, and toxicity (ADMET)] was assessed through the Swiss ADME web tool (Daina *et al*., 2017). It was done by simply entering the compound and run the job.

RESULTS

Docking analysis and ligands scanning

Phosphoglycerate mutase 1 structure (PDB ID: 5Y2I) with resolution of 1.92 Å was used for screening of phytochemicals. After the screening of 5006 phytochemicals against PGAM1, 16 compounds were selected presenting excellent binding affinities with PGAM1 with lower RMSD values. Compounds were graded on the basis of their docking score (blue columns), and RMSD values (red line) as shown in fig. 1.

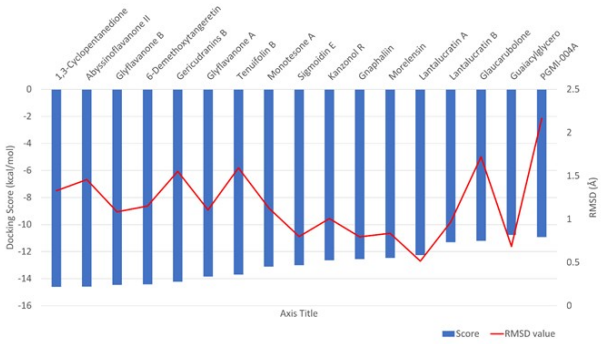

Fig. 1: The binding affinity in kcal/mol (blue columns) and the RMSD in Å of the 16 best hits and the PGM1-004A against PGAM1 active site

Among these 16 hit compounds, eight ligands with significant amino acid binding interactions with PGAM1 active site and docked PGMI-004A are shown in fig. 2. Arg10, Arg116, Arg191, Asn188 were found as common interacting amino acids in the hits like 1,3-cyclopentanedione, glyflavanone B, 6-demethoxy-tangeretin, gnaphaliin, lantalucratin A and -(-) morelensin, while additional binding interactions are also recorded with Asn17 and Asn20 in 1,3-cyclopentanedione and 6-demethoxytangeretin. PGMI-004A interacts with only one residue Arg10 and shows a higher docking score (-10.9 kcal/mol) as compared to all other selected compounds. The binding modes of the eight hits among PGMI-004A were also captured in order to provide a better understanding of residues with the PGAMI-004A docked site (fig. 2).

Lipinski RO5 drug likeness properties of hit compounds

Compounds selection was based on the lower RMSD, docking score values and excellent binding interactions with PGAM1. The selected hits were further evaluated for drug-likeness through the Molinspiration server. All the

Table 1: Results of the best compounds analyzed for Lipinski's rules

Compounds	Lipinski RO5					
	Molecular weight < 500 g/mol	Number of HBA ≤ 10	Number of HBD ≤ 5	MlogP <5	TPSA <140 Å²	Violations
PGMI-004A	463.3	10	3	4.72	120	0
Glyflavanone B	396.4	6	0	3.9	63.2	0
Gnaphaliin	314.2	6	2	2.9	89.1	0
Lantalucratin A	270.2	4	0	2.8	52.6	0
Monotesone A	356.4	6	3	3.6	96.2	0
Morelensin	368.4	6	0	3.2	63.2	0
6-Demethoxytangeretin	342.3	6	0	3.6	67.1	0
1,3-Cyclopentanedione	280.3	4	0	1.3	76.7	0
Abyssinin II	370.4	6	3	3.95	96.2	0

Table 2: ADMET properties of the PGAM1 inhibitor compounds

Admet Properties	Compound Name								
	Control	1,3-cyclo-pentanedione	Abyssinin II	Glyflavanone B	6-demethoxy -tangeretin	Monotesone A	Gnaphaliin	Lantalucratin A	-(-) Morelensin
GIT absorption	Low	High	High	High	High	High	High	High	High
BBB	−	+	−	+	+	−	−	+	+
Permeability (cm/s)	-5.81	-7.08	-5.34	-6.06	-6.21	-5.56	-5.97	-6.18	-6.31
P-gp	−	−	−	+	−	−	−	−	−
CYP1A2	+	+	+	−	+	+	+	+	−
CYP2C9	+	−	+	+	+	+	+	−	+
CYP2C19	−	+	−	+	+	−	−	+	+
CYP2D6	−	−	−	+	+	+	+	−	+
CYP3A4	+	−	+	+	+	+	+	+	+
AMES	−	−	−	−	−	−	−	−	−
Carcinogen	−	−	−	−	−	−	−	−	−

GIT absorption: the probability of compound to be absorbed by human gastrointestinal tract (presented as low and high); BBB: the probability of compound to penetrate the blood brain barrier; P-gp, the prediction of compound being P-glycoprotein substrate or its inhibitor; The probability of compound to inhibit cytochrome P450 isozymes (CYP450 1A2, 2C9, 2C19, 2D6 respectively); AMES, the prediction of a compound being a mutagen; Carcinogen, the prediction of a compound being a carcinogen; (+) presents compounds ability otherwise its inability (−) for respective properties.

selected compounds showed 0 violations to RO5 (table 1). Lipinski RO5 drug likeness properties were predicted based on the functional groups, structure as well as molecular properties of the compounds i.e. Hydrogen Bond Donors (HBD), Hydrogen Bond Acceptors, (HBA), Molecular weight of the compound, Total Polar Solvent Accessibility (TPSA) and Octane/water partition coefficient (LogP). All these parameters were found to be within an acceptable range demonstrating that these compounds possess drug like properties.

ADMET profiling of hit compounds

The eight hit compounds possessing docking score less than -13kcal/mol against PGAM1 were further investigated for ADMET profiles by the admetSAR web server (table 2). In the gastrointestinal absorption analysis, all eight hit compounds were predicted to possess high absorption by the gastrointestinal tract. Thus, all these compounds with high absorption after oral intake at gastrointestinal tract were preceded for further downstream analysis. Once in circulation, uniform distribution at every tissue ensures good treatment efficiency. During distribution property prediction, four hit compounds (1,3-Cyclopentanedione, glyflavanone B, 6-Demethoxy-tangeretinare and lantalucratin A) were predicted to possess ability to penetrate through the blood–brain barrier (BBB+), which is imperative in case of brain tumors. Furthermore, the good distribution of seven hit compounds (except glyflavanone B) at tissues is also supported as these seven compounds were anticipated as non-inhibitors or non-substrates of P glycoprotein. P glycoprotein facilitates the efflux of drugs from the cells. Compounds that are capable of bypassing P-gp efflux pump could attain sustainable levels that would ensure better target inhibition. Xenobiotic compounds are metabolized inside the cells by cytochrome P450 enzymes and this metabolism determines the concentration of respective compounds or drugs within the cells. The prediction analysis demonstrated that the two hit compounds (1,3-Cyclo-pentanedione & lantalucratin A) are non-inhibitors of CYP2C9 and CYP2D6 and five of these are predicted as CYP2C9 and CYP2D6 inhibitors. These results anticipate that these candidate molecules will be slowly metabolized which will allow them to stay long enough to inhibit PGAM1 activity. Next, to assess the adverse effects of hit compounds, the toxicity profiles were calculated from two different models. All of these compounds were predicted to be non-carcinogenic (Carc_I model). Similarly none of these compounds were predicted to be mutagens as assessed by the AMES test model.

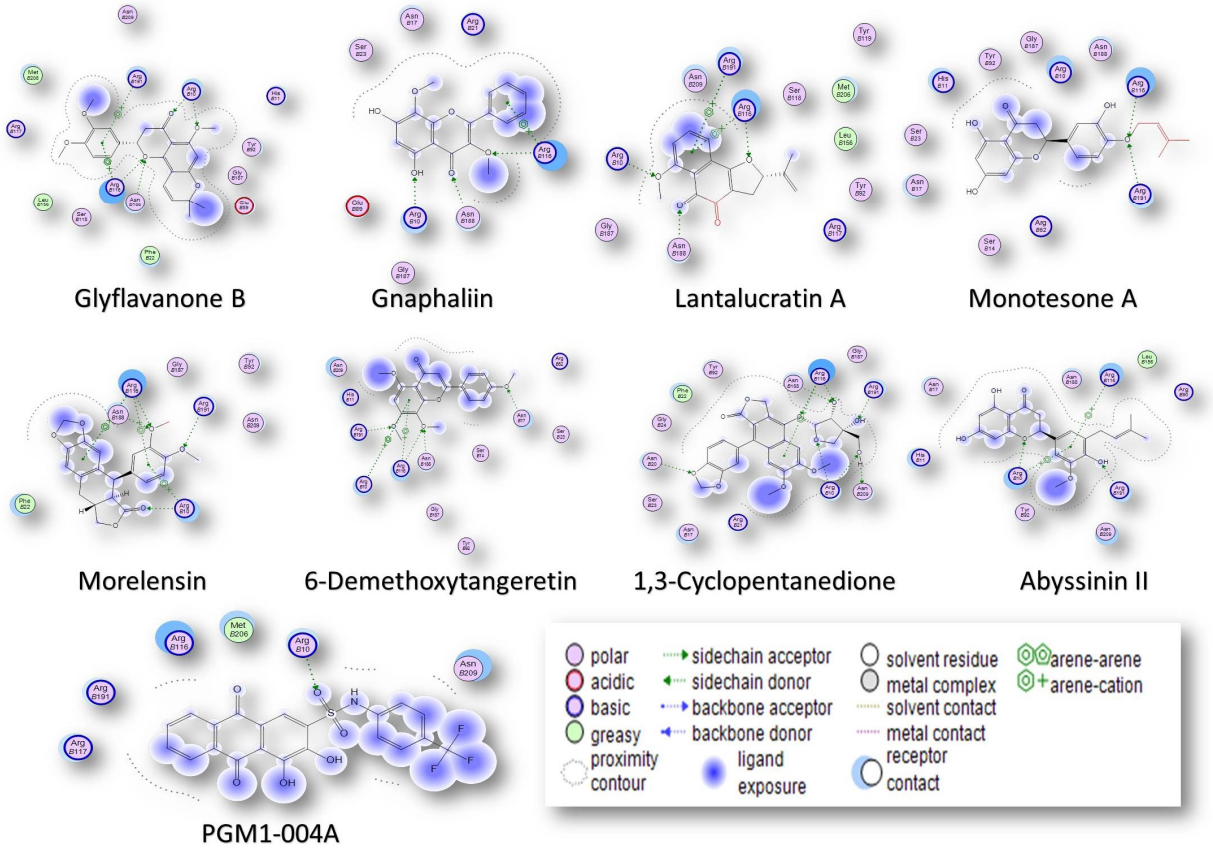

Fig. 2: Docking complexes of the best eight phyto-derived compounds and the positive control (PGM1-004A) docked into the solved structure of PGAM1. The different residues (encircled) interacting with the ligands (lines) are shown in the fig. legend.

DISCUSSION

Targeting tumor glycolysis has opened exciting avenues for the selective inhibition of cancer cell proliferation during recent years. From glycolytic enzymes, PGAM1 has received growing attention due to its unique position as coordinator of both glycolytic pathway and anabolic biosynthesis (Li *et al*., 2017). To explore new natural scaffolds and provide further opportunities for anti-cancer drug discovery, we have screened natural products library against PGAM1 by molecular docking.

Our results showed that 8 chemical compounds (1, 3-cyclopentanedione, glyflavanone B, 6-demethoxytangeretin, gnaphaliin, lantalucratin A, -(-) morelensin, monotesone A and abyssinin II) out of 5006 docked compounds demonstrate excellent PGAM1 inhibitory activity as compared to PGM1-004A (fig. 2). These identified inhibitors have diverse scaffolds, thus, providing hits for optimization and development of potential anti-cancer agents. From chemical point of view, the binding affinity of hit compounds with PGAM1 can be largely associated with the presence of -OH groups. Hydroxyl group have tendency to form hydrogen bonding and possess strong interactions with the amino acid residues of proteins.

As PGAM1 is an emerging therapeutic drug target for the selective inhibition of tumor growth (Sharif *et al*., 2019), various researchers have identified inhibitors of PGAM1. MJE3 was identified as the first inhibitor of PGAM1 by using in situ proteome-reactivity-profiling and has been reported to possess moderate anti-proliferative properties by inhibiting PGAM1 activity in breast cancer cells (Evans *et al*., 2005). In agreement with this study, the interactions of MJE3 with PGAM1 were determined by molecular docking. Docking studies showed that MJE3 form interactions with the binding pocket as a covalent adduct with K100 and also interact with various arginine residues (R10, R116, R117 and R191) of PGAM1 which further support our results (Evans *et al*., 2007), as R10, R116 and R191 were also found as common interacting amino acids of the identified hits from this study.

In addition, epigallocatechin gallate (EGCG) has also been reported as inhibitor of PGAM1 and molecular

docking has identified that EGCG form H-bonds with residues including R10, R116, R191, E13, E89, and N209 in the binding pocket of PGAM1 which is also found to be consistent with our results (Li *et al*., 2017). Thus, data from previous studies and our study demonstrate that arginine residues in the binding pocket of PGAM1 are the most common interacting residues for PGAM1 modulators. Although, EGCG inhibits PGAM1 activity at 1μM concentration, however its polyphenol ring and multiple-targets restricts its further applications (Wang *et al*., 2018).

Lantalucratin A, one of the hit compounds identified through this study, is a naphthoquinone isolated from *Lantana involucrata* which is proven to inhibit growth of various cancer cells (lung, ovarian, breast, brain, bone) with IC_{50} values of 1.0-4.9 μM (Hayashi *et al*., 2004). Thus, cross linking our results with existing literature support and justify the potential of lantalucratin A as anti-cancer agent which might be due to PGAM1 inhibition.

1,3-cyclopentanedione, another identified PGAM1 inhibitor, is a cyclic diketone isolated from *Solena amplexicaulis* (Krishnamoorthy and Subramaniam, 2014). *S. amplexicaulis* is a traditional Chinese medicine used to treat various gastrointestinal disorders. Methanolic extract of this plant is a potent inhibitor of cancer cell proliferation which induce cell cycle arrest and apoptosis via activation of intrinsic pathway in liver cancer cells (Ren *et al*., 2014). This data suggests that 1,3-cyclopentanedione might be responsible for anti-cancer activity via PGAM1 inhibition, however, further researches should be conducted in order to validate this hypothesis.

Further, to exclude the phytochemicals with adverse ADMET properties, which could make experimental animals suffer during downstream confirmatory studies or lead to termination of further experimental studies due to unfavorable properties, the eight hit compounds possessing docking score less than -13 kcal/mol against PGAM1 were further investigated for druglikeness. An ideal drug candidate follows guidelines of Lipinski's rule of 5 which are associated with drug flexibility and permeability. Interestingly, clinically approved anti-cancer drug, doxorubicin, violates three of the Lipinski's RO5 (Oyinloye *et al*., 2019). However, in agreement with this set of rules, our hit compounds could act as orally-active drug candidates on the desired target.

In order to further refine the docking and druglikeness results, ADMET profiles of hit compounds were investigated. All the hit compounds possess good absorption and distribution with non-mutagenic and non-cariogenic properties which further attests the compounds to be followed for further evaluation as anti-cancer agents in *in vitro* and *in vivo* studies.

CONCLUSION

In-silico based investigations have revolutionized the process of drug discovery during recent years by efficiently minimizing the cost and time demanded by the conventional method of drug discovery. This study has provided scientific basis for the possible utilization of phytochemicals as PGAM1 inhibitors for cancer therapy using various in silico tools. Based upon the results of this study, it can be stated that 1,3-cyclopentanedione and lantalucratin A could serve as promising lead compounds for the development of anticancer agents with inhibitory activities against PGAM1. Development of such metabolic inhibitors could specifically treat cancer patients with over expression of PGAM1 such as colorectal, breast and prostate cancers. Thus, there is an urgent need to further evaluate the efficacy of these hit compounds in vitro and in vivo in order to validate their potential for cancer therapy.

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