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Original article

Identification of medicinal compounds as potential inhibitors for mutated isocitrate dehydrogenases against chondrosarcoma

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ABSTRACT

Chondrosarcoma is the third most common cartilaginous bone tumour that is insusceptible to radio- and chemotherapy and it is inclined to metastasis. These resistant qualities are facilitated by mutant variants of isocitrate dehydrogenases (IDH) 1–2 enzyme. These mutant enzymes promote oncogenesis of chondrocytes by changing their epigenetic wardrobe leading to tumour formation. Presently, there are lack of drugs available to be exploited as a remedy for this disease. On the other hand, majority of chemotherapeutic drugs induce cytotoxicity in the cancer cells at the cost of harming surrounding healthy cells, jeopardizing human life. The current study is focused on screening various medicinal compounds against IDH1 and IDH2 combined with insilico gene expression, cancer cells cytotoxicity and ADMET (absorption, distribution, metabolism, excretion and toxicity) studies to elucidate the molecular mechanism against chondrosarcoma and also to uncover pharmacokinetic profile of these compounds. Screening of 5000 + compounds filtered two efficacious compounds (Artocarpetin and 5-Galloylquinic acid) capable of establishing hydrogen bond connections with both IDH variants. Other studies showed that these compounds downregulate *ITGAV*, *CARPIN1*, *CCL5* and *COG5* and *TNFRSF10B* gene that reduces chondrogenesis and inflammation, Artocarpetin and 5-galloylquinic acid are TP53 expression enhancer and inhibit MM9 expression that promote immunomodulation and apoptosis in these cancers. These compounds are both active against CHSA8926 and CHSA011 cell line of chondrosarcoma. However, the ADME profile of 5-galloylquinic acid is slightly unsatisfactory based on druglikness and bioavailability score criteria as compared to artocarpetin. Both of these compounds are class-5 chemicals and require high doses to elicit adverse response. Our results suggest that artocarpetin and 5-galloylquinic acid are efficacious drug candidates and could be further exploited to validate these findings *in vitro*.

1. Introduction

Chondrosarcoma (CH) is a debilitating malignant bone cancer that impairs the normal growth. The behavior of chondrocytes implicated in manufacture and replacement of worn-out cartilages in the body (Whelan and Davis, 2018). In this disease, both cellular proteins and genetic aberrations, incite uncontrollable growth of cartilaginous cells that soften the internal framework of bones, hence disrupting bone function to provide support and protection to the body. This type of cancer is third most commonly reported in almost 20% of case in adults having age ranging from 30 to 70 years (Evola et al., 2017; Limaiem and Sticco, 2019). There are two types of CHs; primary conventional and secondary CHs. De novo development of chondrosarcoma is referred to as primary CHs, and the development of preexisting cartilage tumors is called secondary CHs (Kim et al., 2011). These cancers are heterogeneous groups of tumors classified by anatomical location as central or peripheral CHs (Limaiem and Sticco, 2019). Central CHs are located and developed inside the medullary canal and peripheral CHs are found outside the bone whose connections are within the bone but may appear as exostosis. Tumour aggressiveness and disease prognosis are determined through histopathological grading criteria which is based on nuclear alteration, mitosis pattern, cellularity and presence of matrix proteins (Stevenson et al., 2018). World Health organization classified chondrosarcoma in grade I-III by keeping histopathological findings under consideration. Grade I is less aggressive and has good treatment prognosis whereas Grade II-III are life threatening often results in metastasis (Jeong and Kim,

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2018). Currently there are insufficient resources available to eradicate such tumours and other interventions are ineffective due to drug resistance, inoperable tumour location and high tumour recurrence (Nazeri et al., 2018; Stevenson et al., 2018).

New drug candidates and effective molecular targets are constantly being discovered for chondrosarcoma to devise more efficacious therapies and to further elucidate the complex tumour biology of these cancers. The current conventional therapies which include surgical resection and radio-and chemotherapy is becoming challenging against these tumours. Such challenges are imposed by cellular proteins and endogenous molecules that in turn cause drug resistance and helps the tumour cells to evade from chemotherapy influence whereas surgical intervention unable to remove grade II-III chondrosarcoma surgically because of inoperable anatomical location and risk of metastasis (Nazeri et al., 2018; Stevenson et al., 2018). Random and aggressive drug regiments can inhibit single molecular target, giving enough time for another target to proliferate to develop resistance for these drugs. On the other hand, these regiments are also another cause of death reported in these individuals due to lack of information about drug pharmacokinetics and toxicity (Livshits et al., 2014).

Cellular metabolism is under the control of Nicotinamide adenine dinucleotide (NAD) dependent enzymes known as isocitrate dehydrogenases. These enzymes facilitate oxidative decarboxylation and reductive carboxylation of isocitrate to α-ketoglutarate (KG) and the vice versa. These enzymes are divided into two distinct classes based on NADP or NAD $^{+}$ utilization as electron acceptor. IDH1 and IDH2 are Nicotinamide adenine dinucleotide phosphate ($NADP^{+}$) dependent enzymes localized in cytoplasm and mitochondria involved in krebs cycle and prevent cells from oxidative damage whereas IDH3 is NAD^{+} dependent enzyme and it is focused primarily on energy production in krebs cycle and located in mitochondrial matrix. Mutation in IDH1 and IDH2 induce neomorphic behaviour in these enzymes that are implicated in the development of chondrosarcoma (Cojocaru et al., 2020). These types of mutations are reported in more than 80% of cases which makes it an attractive target for drug screening.

There have been advancements made in therapeutics sector to acquire highly effective chemicals in order to therapeutically deal with such tumours. Medicinal compounds, on the other hand, offer brilliant solution to this appalling issue. Majority anticancer drugs are derived from medicinal plants and possess low toxicity and high effectivity against all types of cancers. Therefore, exploiting such medicinal compounds will be a breakthrough in the treatment of chondrosarcoma. In this research article, different medicinal compounds are screened insilico to procure good inhibitors for mutant isocitrate dehydrogenases in the treatment of chondrosarcoma.

2. Materials and methods

2.1. Protein targets retrieval

The two mutated versions of IDH enzyme (IDH1-IDH2) were downloaded from RCSB protein databank under the PDB ID code (5LGE and 6ADI) respectively. These receptors were prepared, refined and energy minimized through Modrefiner (Xu and Zhang, 2011) for drug screening analysis.

2.2. Ligands procurement and refinement

5000+ medicinal compounds comprised of phenolic acids, flavonoids, terpenoids, stilbenes as ligands were taken from IMMPAT database based on limited literature regarding their biological activity (Mohanraj et al., 2018). The selected compound structures were then subsequently procured from PubChem database and refined with the PRODRG server (Van Aalten et al., 1996).

2.3. In silico compound libraries screening

Both refined and minimized structures of receptors (IDH1 and IDH2) and ligands (Medicinal Compounds) were added to PyRx 0.9 system (Dallakyan and Olson, 2015). Autodock algorithm was selected for molecular docking and the ligands were at defined interface on these receptors (IDH1: Center X: −24.407, Y: −80.606, Z: 38.8415, Dimensions Å X: 30.1592, Y: 25.000, Z: 26.4113) and (IDH2: Center X: −9.7965, Y: 10.0980, Z: −10.0423, Dimensions Å X: 21.7259, Y: 23.522 and Z: 25.000). After parameters optimization, the screening system was validated by re-docking the co-existing ligands (2-[(4-Propan-2-Ylphenyl) amino]-1-[(1~{s},5~{s})-3,3,5-Trimethylcyclohexyl] benzimidazole-5-Carboxylic Acid and Vorasidenib) with the native binding position within IDH1 and IDH2 protein. Then virtual screening was carried out and obtained results and subjected to pharmacophoric mapping and LigRMSD analysis (Dallakyan and Olson, 2015) to evaluate receptor-ligand interactions and docked complex stability.

2.4. Compound's lethality prediction

The canonical SMILES of screened compounds were retrieved from PubChem database which was further exploited to predict the acute toxicity (Lethal Dose-50 value), adverse effects and organ damaged in rodent models through GUSAR (Lagunin et al., 2011), ADVER-PRED (Ivanov et al., 2018) and ROSC-Pred Web Server (Lagunin et al., 2018).

2.5. Anticancer sensitivity prediction

Different cell lines of chondrosarcoma were exploited by Pacc-Mann's database (Cadow et al., 2020) to predict anti-cancer activity of screened compounds using canonical SMILES of these compounds.

2.6. In silico gene expression and prediction of activity spectra for substances (PASS)

These analyses were performed by submitting the canonical SMILES of screened compounds in DIGEP-Pred (Lagunin et al., 2013) and PASS database (Poroikov et al., 2003) to predict drug induced gene expression and other important biological activities.

2.7. ADME and drug likeness analysis

To determine the ADME and drug likeness properties of screened compounds, pKCSM (Pires et al., 2015) and SwissADME database (Daina et al., 2017) were used.

3. Results

3.1. Virtual screening results

Virtual screening method employs different docking algorithms to evaluate high affinity compounds from library of chemical candidates deposited for drug discovery studies. The screening system was successfully reproduced binding pattern of co-existing ligands in IDH1 and IDH2 which paved our screening study to continue further. In this study, Autodock 4.2 algorithm was exploited to screen 5000+ medicinal compounds through PyRx 0.9 virtual screening platform. Among these candidates 347 compounds showed interaction with IDH1 and IDH2 receptors. These com-

pounds were further filtered based on molecular interaction between ligand and receptor followed by binding energy, inhibition constant, ligand efficiency and LigRMSD. Only two compounds 5-galloylquinic acid and artocarpetin showed favorable interaction with the active binding cleft of both IDH1 and IDH2 protein while other ligand interactions were ignored due to non-specific interaction with amino acid residues other than reported ones. Further pharmacophoric mapping of these compounds revealed that 5-galloylquinic acid established four hydrogen bonds with both of the targets using carboxylate and hydroxy group of their structure and benzene ring contributed in the formation of single hydrophobic pi-sigma bond with VAL107 in IDH1 protein (Fig. 1). Artocarpetin through hydroxyl groups formed two hydrogen bonds with GLU306 and SER293 of IDH1 receptor and 3 hydrogen bonds with GLY349, THR350, and THR352 of IDH2 protein and using oxy-group of chromene whereas both benzene and chromene rings participated in pi-sigma and pi-alkyl interaction with HIS348, VAL351 and LEU327 of target receptors (Fig. S1-S3). Another interesting finding observed in the screening analysis was both artocarpetin and 5-galloylquinic acid had similar affinity for SER293 and GLU306 in IDH1 and THR350 in IDH2 binding residues that also reflect similar therapeutic mechanism. Most of the interaction established by these compounds were amassed in the active binding cleft that provides valuable justification for protein inhibition as proven from these studies (Salman et al., 2020; Shah et al., 2020). But further studies are underway to validate these assertions. Other docking proponents such as binding energy (−5.7–6.7 Kcal/mol), ligand efficiency (−0.25–0.30 kcal/mol), inhibition constant (1.65 μM- 907.12 nM) and LigRMSD value (0.87–3.88 Å) of docked complexes were near the standards (Table 1) (Salman et al., 2020; Shah et al., 2020).

4. Cell lining studies

PaccMann database exploits structure activity relationship algorithm to predict anticancer activity based on compound's chemical structure (Cadow et al., 2020). These compounds were tested to highlight their broad-spectrum anti-cancer capability against various cell lines of chondrosarcoma harboring different mutations. The results showed that 5-galloylquinic acid hydroxyl and benzene rings are mainly responsible for anti-cancerous activity against chondrosarcoma (Fig. 2). The cell line for 5-5-galloylquinic acid to show maximum effectivity are CHSA8926 (IC50 = 0.65), CHSA0011 (IC50 = 0.64), followed by H-EMC-SS (IC50 = 0.63), CAL-78 (IC50 = 0.62) and CHSA0108 (IC50 = 0.60). Artocarpetin, on the other hand, exploited hydroxyl and two benzene rings to perform anti-cancerous activity (Fig. 2) against CHSA8926 (IC50 = 0.66), CHSA0011 (IC50 = 0.65) followed by H-EMC-SS (IC50 = 0.64) and CHSA0108 (IC50 = 0.61) cell lines as summarized in Table 2.

5. Toxicity studies

Acute toxicity involves evaluation of compound's lethality following exposure to test organism. It also determines the rare adverse effects and organ specific damage incited by compounds at particular dose. GUSAR database predicted the acute toxicity of these compounds in rats and it was found that 5-galloylquinic acid confers toxic response at 1,200,000 mg/kg when injected intraperitoneally, 800,000 for subcutaneous route, 4,000,000 orally and 200,000 intravenously. In comparison to 5-galloylquinic acid, Artocarpetin possess high acute toxicity values such as 600,000 mg/kg intraperitoneally, 2000,000 subcutaneous routes, 2,000,000 orally and intravenously as depicted in Table 3. Both of these compounds are classified as non-toxic and placed in class 5 chemicals. Unusual adverse of these compounds are hepatoxicity and nephrotoxicity whereas organ affected by these urinary bladder, liver, stomach, vascular system and intestine as predicted by Adver-Pred and ROSC-Pred database (Ivanov et al., 2018; Lagunin et al., 2018).

6. Gene expression and PASS studies

Gene expression studies quantify the expression of gene products from the coding gene counterpart and it also provides essential information about differential gene regulation in response to drugs. Insilico gene expression studies revealed that 5-galloylquinic acid downregulate the activity of *ITGAV* (Mamuya and Duncan, 2012), *CAPRIN-1* (Sabile et al., 2013), *CCL5* genes (Wang et al., 2016). These genes are involved in providing chondrosarcoma with a favorable environment to proliferate and metastasize inside the body. This compound also upregulates *CASP2* gene (de Jong et al., 2016) which is responsible for removing excessive chondrocytes by inducing apoptosis in them. Artocarpetin has a similar action as compared to 5-galloylquinic acid, by downregulating *ITGAV* along with *COG5* (Cailotto et al., 2012) and *TNFRSF10B* gene (Hou et al., 2011) that reduces chondrogenesis and inflammation as depicted in Table 4.

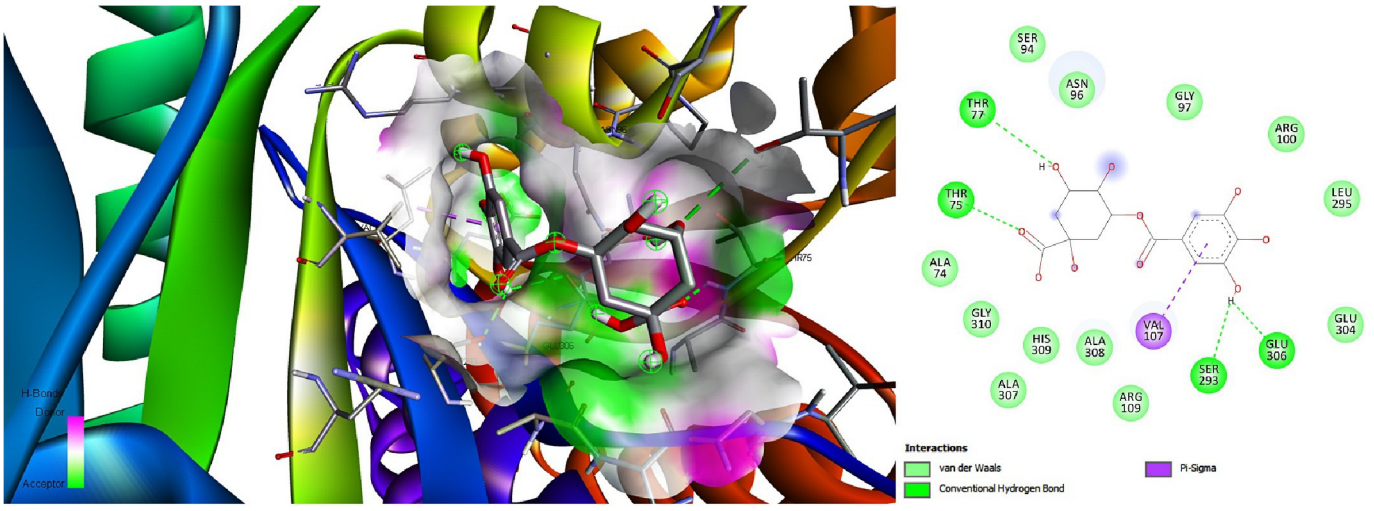

Fig. 1. 5-galloylquinic acid binding interaction with IDH1 receptor.

Table 1
Binding interaction of medicinal compounds with mutated isocitrate dehydrogenase enzymes.

No	Receptors	Ligands	Reported Active Site Residues from X-ray crystallographic structure	Hydrogen Interaction between Receptors and Ligands	Binding Energy (Kcal/mol)	Ligand Efficiency (Kcal/mol)	LigRMSD Calculation (Å)	Inhibition Constant
1	Isocitrate dehydrogenase-1 (5LGE)	Compound CID: 14,520,970 (5-Galloylquinic Acid)	LYS72, ALA74, THR75, ILE76, THR77, ARG82, ASN96, ILE130, VAL255, VAL276, GLN277, SER280, LEU288, GLY289, GLU306, ALA307, HIS309, GLY310, THR311, VAL312, THR313, ARG314, HIS315, THR327, ASN328, ASP375	THR55, THR77, SER293, GLU306	−5.7	−0.25	0.87	799.33 nM
		Compound CID: 12,308,618 (Artocarpetin)		SER293, GLU306	−6.3	−0.26	3.79	13.89 μM
2	Isocitrate dehydrogenase-2 (6ADI)	Compound CID: 14,520,970 (5-Galloylquinic Acid)	LYS112, ALA114, THR115, ILE116, THR117, ASN136, VAL315, GLN316, LEU327, GLY328, GLU345, ALA347, HIS348, GLY349, THR350, VAL351, THR352, ARG353, HIS354, THR366, ASN367, ASP414	THR117, ALA347, HIS348, THR350	−6.6	−0.27	3.88	907.12 nM
		Compound CID: 12,308,618 (Artocarpetin)		GLY349, THR350, THR352	−6.7	−0.30	1.44	1.65 μM

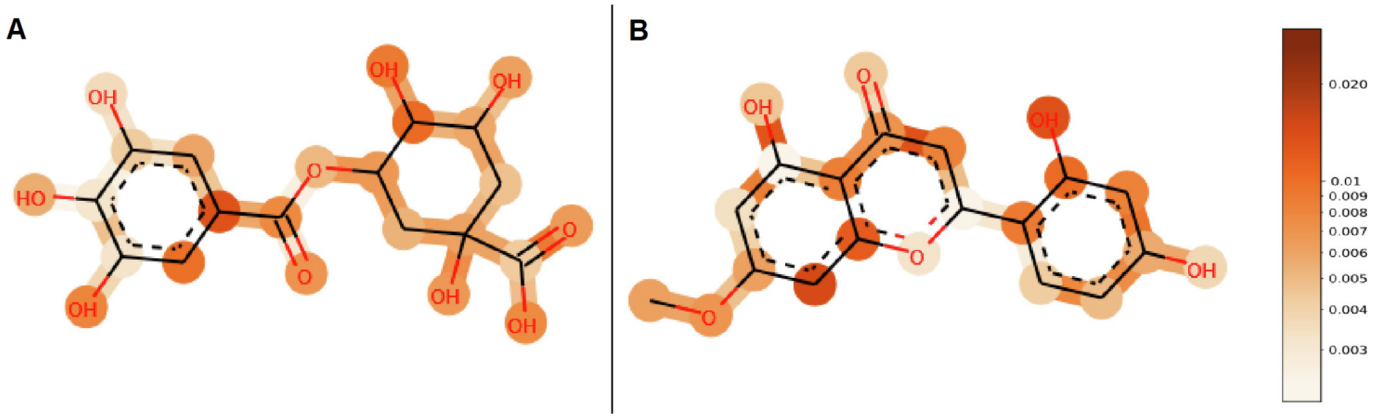

Fig. 2. Structural activity relationship of screened medicinal compounds participating in anticancer activity against Chondrosarcoma cell lines. (A) 5-Galloylquinic Acid (B) Artocarpetin.

Table 2
Anticancer activity of screened medicinal compounds against Chondrosarcoma cell lines.

No	Compounds	Histology	Site	Cosmic ID	Cell Line No.	Dataset	Cell line name	IC50 (min/max scaled)	IC50 (log(umol))
1	5-Galloylquinic acid	chondrosarcoma	bone	1303912	1303912	GDSC	CHSA8926	0.6513	3.8668
				1290767	1290767		CHSA0011	0.6474	3.7709
				1290765	1290765		H-EMC-SS	0.6351	3.4716
				907290	907290		CAL-78	0.6239	3.1987
				1290768	1290768		CHSA0108	0.6086	2.8273
2	Artocarpetin			1303912	1303912		CHSA8926	0.6640	4.1761
				1290767	1290767		CHSA0011	0.6595	4.0662
				1290765	1290765		CAL-78	0.6325	3.4102
				907290	907290		H-EMC-SS	0.6320	3.3957
				1290768	1290768		CHSA0108	0.6118	2.9056

PASS prediction of these compounds was also performed and the results showed that 5-galloylquinic acid is a tumor protein p53 (TP53 expression enhancer) that act as a tumour suppressor, and other activities include antioxidant, chemo preventive, free radical scavenger and chemoprotective agent. Artocarpetin possess comparatively more biological activities such as TP53 expression enhancer, MAP kinase stimulant (regulate cell division and apoptosis) (Guo et al., 2020), MM9 expression inhibitor (responsible for extracellular matrix degradation for cancer progression) (Gweon and Kim, 2014), anti-neoplastic and free radical scavenger. These properties allow these compounds to suppress the proliferation

Table 3
Toxicity evaluation of screened medicinal compounds.

No	Compounds	LD50 Value for Intraperitoneal Route (mg/kg)	LD50 Value for Intravenous Route (mg/kg)	LD50 Value for Oral Route (mg/kg)	LD50 Value for Subcutaneous Route (mg/kg)	Chemical Classification by OECD Project	Adverse Effects	Organ Specific Damage
1	5-Galloylquinic acid	659,800	2,105,000	2,199,000	2,619,000	Class 5	Hepatotoxicity	urinary bladder, kidney, Stomach, Vascular System, Intestine
2	Artocarpetin	1232,000	261,700	4,177,000	860,600	Class 5	Nephrotoxicity	Kidney, hematopoietic system, Stomach

Table 4
Effect of medicinal compounds on expression of target chondrosarcoma genes. *Down: Downregulation, Up: Upregulation

No	Compound	Pa	Pi	Gene Regulation	Gene Function	Reference
1	5-Galloylquinic acid	0.847	0.022	*ITGAV* down	Facilitate migration of chondrosarcoma cells	[23]
		0.784	0.028	*CAPRIN1* down	Promote osteosarcoma and extracellular matrix growth and provides them with metastatic and resistance properties	[24]
		0.666	0.024	*CCL5* down	Angiogenesis, Migration, Metastatic properties to chondrosarcoma cells.	[25]
		0.655	0.051	*CASP2* (up)	Apoptosis ability	[26]
2	Artocarpetin	0.852	0.027	*COG5* (down)	Reduces chondrogenesis	[27]
		0.805	0.021	*TNFRSF10B* (down)	Inflammatory action	[28]
		0.797	0.032	*ITGAV* (down)	Facilitate migration of chondrosarcoma cells	[23]

Table 5
Prediction of activity spectra of screened medicinal compounds.

No	Compounds	Pi	Pa	Properties
1	5-Galloylquinic acid	0,791	0,003	Antioxidant
		0,778	0,003	Free radical scavenger
		0,766	0,016	Antineoplastic
		0,747	0,005	Chemo preventive
		0,729	0,020	TP53 expression enhancer
2	Artocarpetin	0,903	0,005	TP53 expression enhancer
		0,874	0,002	MAP kinase stimulant
		0,812	0,003	MMP9 expression inhibitor
		0,812	0,007	JAK2 expression inhibitor
		0,762	0,017	Antineoplastic
		0,746	0,003	Free radical scavenger

of chondrosarcoma, expedite apoptosis and immunomodulation against growing chondrocytes population (Table 5).

7. ADME studies

These studies were performed to determine compound's chemical nature by observing its adsorption, distribution, metabolism, excretion and toxicity attributes to ensure safety and maximum effectivity in animal and clinical trials. 5-Galloylquinic acid has low intestinal absorption with moderate water solubility and skin permeability (−9.26 cm/s) and artocarpetin has high intestinal absorption with comparatively better water solubility and skin permeability (−6.01 cm/s). Both of these compounds are p-glycoprotein substrate and do not inhibit p-glycoprotein I-II. CNS and BBB permeability of 5-galloylquinic acid is high and possess no affinity for CYP enzymes. Artocarpetin has low CNS and BBB permeability profile and act as inhibitor for CYP enzymes such CYP1A2, CYP2C9 and CYP2D6 and CYP3A4 which increases drug half-life and bioavailability. 5-Galloylquinic acid and artocarpetin are non-toxic and has identical total clearance value of 0.59 and lack compatibility for renal OCT2 substrate. 5-Galloylquinic acid nearly qualify Lipinski criteria for druglikness with single violation but unfortunately low bioavailability score as compared artocarpetin that has high bioavailability and druglikness (Table 6).

8. Discussion

Isocitrate dehydrogenase 1 and 2 are important component of krebs cycle involved in conversion of isocitrate to α-ketoglutarate with the investment of NADH which is eventually reduced to NADPH and CO_2 is released. The cellular epigenetic status is regulated by alpha-ketoglutarate-dependent dioxygenase under the controlled surveillance of α-ketoglutarate which in turn disrupt the activity of 2-oxoglutrate (OG) dependent chromatin modifying enzyme responsible for chromatin remodeling for gene expression (Cojocaru et al., 2020). But mutated versions of IDH 1 and 2 enzymes promote genetic neomorphosis by upregulating the conversion of 2-ketoglutaric acid (2-KG) to D-2-hydroxyglutarate (D-2-HG) that disrupts CpG sites, and histone methylation of retinoic acid receptor-α, platelets derived growth factor subunit A and B-cell lymphoma 6 co-repressor gene (BCOR) (Lu et al., 2013). Hypermethylation of these areas instigate various types of malignant cancers including chondrosarcoma and results in tumour formation.

Thus, making IDH mutants an ideal target for drug discovery and development. These targets were exploited by Agios pharmaceuticals to develop Ivosidenib (Popovici-Muller et al., 2018) and Enasidenib (Yen et al., 2017) which are IDH1 and IDH2 inhibitors. Both Ivosidenib and Enasidenib have good pharmacokinetic profile and successfully qualified Phase-I clinical trial with flying colors.

Table 6
ADME and Druglikness Profile of Screened Medicinal Compounds.

ADME Elements	Compounds	
	5-Galloylquinic Acid	Artocarpetin
ABSORPTION		
Human Intestinal Absorption	Low	High
Water solubility (log mol/L)	−1.13 (Soluble)	−3.99 (Highly Soluble)
Skin Permeability (Log Kp)	−9.26 cm/s	−6.01 cm/s
DISTRIBUTION		
P-glycoprotein substrate	Yes	Yes
P-glycoprotein I inhibitor	No	No
P-glycoprotein II inhibitor	No	No
BBB permeability (log BB)	−1.679 (Moderate)	−1.258 (Low)
CNS permeability (log PS)	−4.166 (Moderate)	−2.338 (Low)
METABOLISM		
CYP2D6 substrate	No	No
CYP3A4 substrate	No	No
CYP1A2 inhibitor	No	Yes
CYP2C19 inhibitor	No	No
CYP2C9 inhibitor	No	Yes
CYP2D6 inhibitor	No	Yes
CYP3A4 inhibitor	No	Yes
EXCRETION		
Total Clearance (log ml/min/kg)	0.59	0.59
Renal OCT2 substrate	No	No
TOXICITY		
AMES toxicity	No	No
Hepatotoxicity	No	No
hERG Inhibition	No	No
Eye irritation	No	No
Carcinogenicity	No	No
DRUGLIKNESS AND BIOAVAILABILITY SCORE		
Lipinski	Yes; 1 Violation	Yes; 0 Violations
Bioavailability Score	0.11 (Low)	0.55 (High)

These drugs are either specific IDH1 or IDH2 mutants and possess recurring adverse effects that include QT prolongation, pyrexia, anemia, fatigue, nausea, febrile neutropenia, leukocytosis and diarrhea (Fan et al., 2020). These side effects and specific therapeutic target specificity for two different drugs hinder their usage and bear further expense to detect specific mutation of IDH in chondrosarcoma in order to begin with therapeutic intervention.

Therefore, our study was based on obtaining good inhibitors using medicinal compounds to be effective for both IDH1 and IDH2 and should possess efficient pharmacokinetic and toxicity profile. Screening analysis of 5000+ medicinal compounds whose activity was explored in chondrosarcoma revealed that 5-galloylquinic acid and artocarpetin are effective for IDH1 and IDH2. Both of these medicinal compounds established hydrogen interaction with the active binding cleft of IDH1 and IDH2 in stable conformation as evident from LigRMSD values. The activity of these compounds was further tested on different chondrosarcoma cell line. The compounds were active against CHSA8926 and CHSA0011. Also, gene expression and PASS studies showed that these compounds downregulate the expression of genes and proteins that promote chondrocytes proliferation and metastasis.

Apart from their good acute toxicity results, 5-galloylquinic acid has low intestinal absorption and bioavailability score and also does not fully qualify Lipinski criteria of druglikness as compared to artocarpetin that has efficient pharmacokinetic properties and high toxicity values. The absorption of 5-galloylquinic acid can be improved by exploiting nanodrug delivery systems (Dima et al., 2020) or compound derivatization techniques (Bajpai et al., 2016) combined with bioenhancers to increase bioavailability (Oladimeji et al., 2018).

9. Conclusion

This study, with the best of our knowledge, obtained and identified the role of two newly exploited medicinal compounds (5-Galloylquinic acid and Artocarpetin) from screening of extensive library of medicinal compounds in chondrosarcoma therapeutics. These compounds are capable of inhibiting IDH1 and IDH2 mutated variants implicated in this cancer and has effective ADMET qualities that can be further enhanced with drug delivery methods. 5-Galloylquinic acid and artocarpetin are active against chondrosarcoma cell lines and effective in downregulating the expression of some genes and proteins that progress chondrocytes proliferation and metastasis. The results obtained from this study revealed that both of these compounds are good lead compounds and findings of this research underway to be validated in animal and clinical trials for possible drug discovery and development.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' contributions

All authors contributed equally in this study.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sjbs.2021.08.077.

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