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Screening of Phytochemicals Against Cancer Biomarker: An In Silico Approach

Annapurna Sahoo and Kunja Bihari Satapathy*
School of Applied Sciences, Centurion University of Technology and Management, Odisha, India

ABSTRACT

Heparan sulphate proteoglycans (HSPGs) including Glypicans are primarily involved in critical cellular pathways. Essentially, these groups of proteins are located on the cell membrane and modulate signalling pathways resulting in the cell growth process. Strikingly, the protein level of Glypican-1 (GPC-1) rises primarily during pancreatic cancer thus can be considered as a potential clinical biomarker. GPC-1 may also activate further downstream events, supporting the cancerous phase. To restrict the activity of GPC-1, several bio molecules can be deployed, of which the phytochemicals can be the best alternative. Molecular docking-based screening of a few phytochemicals revealed that the organosulfide class of phytochemicals effectively associate with the active site of the GPC-1 and hence harbours diagnostic and therapeutic potentials against pancreatic cancer.

KEY WORDS: GLYPICAN-1, HEPARAN SULPHATE PROTEOGLYCAN, ORGANOSULFIDES, PANCREATIC CANCER, PHYTOCHEMICALS.

INTRODUCTION

Cancer still being considered as a global health problem owing to failure in restricting the casualty it causes (Ferlay et al., 2019). Though the key oncogenic signaling mechanisms are revealed as of now, being intracellular in nature, they are inaccessible to the antibodies (Bailey et al., 2018; Sanchez-Vega et al., 2018). HSPGs reside at the cell surface and in the extracellular matrix (ECM) are essentially the proteins of interest (Knelson et al., 2014; Nagarajan et al., 2018; Christianson et al., 2013). Glypicans belong to the HSPG family. Mostly, glypicans are involved in enhancing the extracellular growth, enabling overgrowth of human cells ultimately leading to cancer (Sarrazin et al., 2011). Even, glypicans are highly expressed in few cancers, regulate angiogenesis thus facilitate the tumourigenesis as apparent from several genetic evidences (Filmus et al., 2008; Fico et al., 2011; Li et al., 2018). GPC-1 is highly expressed in cancerous cells and found in the peripheral blood, thus can be a key biomarker (Lu et al., 2017; Matsuda et al., 2001; Davies et al., 2004; Suhovskih et al., 2013; Hara et al., 2016; Lewis et al., 2018).

GPC-1 knockdown inhibits the response of mitosis to fibroblast growth factor-2, thus pointing out the molecular mechanism of GPC-1 in promoting cancer (Matsuda et al., 2001). GPC-1 also plays a significant role in modulating the VEGF-A and TGF-β signalling pathways (Olsson et al., 2006; Aikawa et al., 2018; Liu et al., 2018, Sahoo et al., 2020a,b,c,d,e,f). Owing to the cleavable nature of the GPC-1 and a secreted soluble component, it is noticeable in the peripheral blood, thus acting as a potential marker (Wang et al., 2019). In order to develop a prospective diagnostic tool or therapeutic agent against GPC-1, several approaches can be considered. Using phytochemicals can also be one of the best alternatives.

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*Corresponding Author: kunjabihari.satapathy@cutm.ac.in
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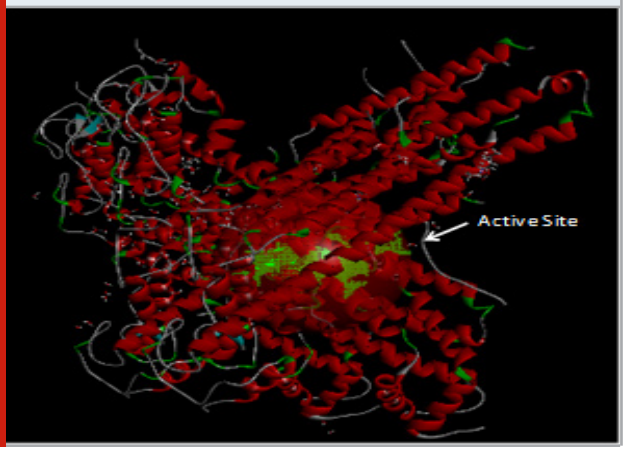
Several categories of phytochemicals are found in the plant parts like fruit, leaf, stem, root, flower and bark which contain immense pharmaceutical functionalities (Jakubowski et al., 1997). Plants possesses sophisticated defense response mechanism(s) which still needs to be elucidated clearly (Panda et al., 2016, Panigrahi et al., 2016, Panigrahi and Sahoo 2016, Panigrahi et al., 2021, Panigrahi and Satapathy 2020a,b,c). For treating diseases like cancer, phytochemical compounds like tocopherols, carotenoids, anthocyanins, phenolics etc. are effective (Altemini et al., 2017; Naczk and Shahidi2006). Several phytochemicals act as natural antioxidants, which supplements the need of the human body (Boots et al., 2008). Across the globe, it is recommended for consumption of fruits and vegetables, primarily to improve the state of health (Vivekananthan et al., 2003). We primarily screened a few phytochemicals, which are not yet globally recognized for being used against GPC-1, using a molecular docking method (BIOVIA).

Figure 1: The 3-D structure along with the active site of the GPC-1



METHODS

Viral Protein Structure and Phytochemicals dataset collection. From the Protein Data Bank (accession: 4AD7), the 3D structure of Glypican-1 protein was accessed (Fig. 1). For docking with the target protein, Glypican-1, ten numbers of phytochemicals were considered and structure data files were used for the purpose.

Molecular docking: *In silico* molecular docking was done by using the BIOVIA's Discovery Studio docking method (Behera et al., 2020, Das et al., 2020, Jena et al., 2020, Ray et al., 2020). The catalytic pocket of the GPC-1 protein was generated and subsequently targeted for ligand interaction.

RESULTS AND DISCUSSION

The positive values of the CDOCKER Energy and CDOCKER INTERACTION ENERGY represent the affinity of the ligands with the receptor proteins. Ten numbers of phytochemicals (Table 1) against the GPC-1 protein revealed that phenyl isothiocyanate, benzyl isothiocyanate and resveratrolare potential binding ligands as evident from their higher CDOCKER ENERGY and CDOCKER INTERACTION ENERGY (Table 1).

Figure 2: Chemical structure of the Phenyl isothiocyanate, Benzyl isothiocyanate and Resveratrol.

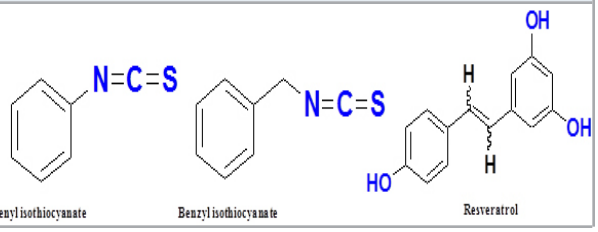
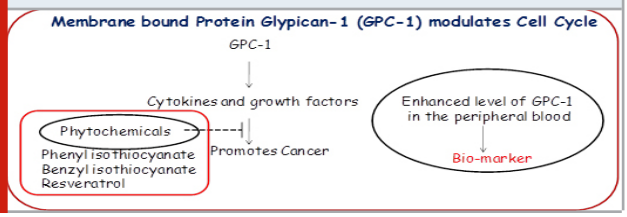


Table 1. List of phytochemicals tested for their binding affinity with the GPC-1.

Ligand			Receptor		Interaction Status		
Class	SDF accession	Phytochemical	Protein	PDB accession	Docking Result	CDOCKER Energy	CDOCKER Interaction Energy
Flavonoids	CHEBI:28775	Hesperidin	Glypican-1	4AD7	Negative	Not applicable	Not applicable
	CHEBI:23053	Epicatechin			Negative	Not applicable	Not applicable
	CHEBI:9400	Tangeretin			Negative	Not applicable	Not applicable
Organosulfides	CHEBI:85103	Phenyl isothiocyanate			Positive	11.78	14.17
	CHEBI:17484	Benzylisothiocyanate			Positive	15.02	17.41
	CHEBI:28411	Allicin			Negative	Not applicable	Not applicable
	CHEBI:47807	Sulforaphane			Negative	Not applicable	Not applicable
Anthocyanin	CHEBI:71682	Cyanidin			Negative	Not applicable	Not applicable
	CHEBI:6674	Malvidin			Negative	Not applicable	Not applicable
Stylbenes	CHEBI:45713	Resveratrol			Positive	21.23	33.55

Figure 3: Phytochemicals can be effectively used for blocking the activity of the GPC-1.



These are very common and easily available. Phytochemicals including Hesperidin, Epicatechin, Tangeretin, Allicin, Sulforaphane, Cyanidin and Malvidin did not show affinity for the active site of the GPC-1 as the docking results were failed. The chemical structure of ligand molecules (Fig. 2) showing positive affinity for the GPC-1 can be studied extensively and related synthetic molecules can be developed for wide range applications in the cancer therapeutics.

CONCLUSION AND FUTURE PERSPECTIVES

In silico molecular docking based study reveals several novel candidate molecules which can target the Glypican-1 protein. It would be highly significant being confirmed in vivo. Specific phytochemical targeting GPC-1 can be employed in two ways. Firstly, these phytomolecules may act as drug by blocking the specific sites of GPC-1, ultimately inhibiting the downstream pathways. Secondly, cost effective medical device can be developed to diagnose early stages of cancer by targeting marker proteins like GPC-1. Phytochemicals including phenyl isothiocyanate, benzyl isothiocyanate, resveratrolmay be effective. Since, glypicans are highly significant in modulating the growth factor signaling and promote cancerous activity; they should be restricted being over activated by blocking their active site (Fig. 3). Early diagnosis being a critical issue in several cancers, appropriate ligands can be developed to be used as a diagnostic tool.

CRediT authorship contribution statement
Annapurna Sahoo: conceived the idea, performed the experiments, analyzed the results, wrote the manuscript, have read and approved the final manuscript before submission. Kunja Bihari Satapathy: conceived the idea, analyzed the results, have read and approved the final manuscript before submission.

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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