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Unravelling the potential of *Diospyros* species in the treatment of pancreatic adenocarcinoma using an *in-silico* approach

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Abstract

Pancreatic cancer remains one of the fatal malignancies with limited treatment options and a high rate of drug resistance. Y-box binding protein 1 (YBX1) plays an essential role in pancreatic cancer by upregulating the low-density lipoprotein receptor-related protein-1 (LRP1), which promotes tumour growth through the Wnt/β- catenin pathway. *Diospyros* genus exhibits anticancer properties and could be used to overcome drug resistance and inhibit pancreatic ductal adenocarcinoma (PDAC). The Cancer Genome Atlas (TCGA) data and TNMplot were analyzed to perform bioinformatics analyses to investigate LRP1 gene alterations and their correlation with YBX1 in PDAC. *Diospyros* phytochemicals with high binding affinities for YBX1 (PDB ID: 6KTC) were screened through molecular docking. Further, these phytochemicals' pharmacokinetics, drug likeness and toxicity were evaluated using ADMETlab 2.0 and ProTox 3.0. According to bioinformatics analysis, the expression of YBX1 and LRP1 in PDAC samples were significantly correlated. Molecular docking identified 13 phytochemicals with high binding affinities (≤ -7.5 kcal/mol) for YBX1.Diospyrin (-9.1 kcal/mol), Kaempferol (-7.5 kcal/mol), Mamegakinone (-9.1 kcal/mol) and Neodiospyrin (-8.6 kcal/mol) showed favourable interactions. ADMET analysis confirmed that these four compounds exhibited drug-like properties. Diosprin and Kaempferol have established anticancer effects by inducing apoptosis and inhibiting carcinogenic pathways; however, Mamegakinone and Neodiospyrins' roles need further investigation using experimental studies. The promising binding affinities of these compounds suggest potential therapeutic applications in PDAC. This study highlights the potential of phytochemicals in the genus *Diospyros* as potential therapeutic molecules against YBX1 in PDAC.

Keywords

Diospyros; LRP1; molecular docking; pharmacokinetics; phytochemicals; YBX1

Introduction

Pancreatic cancer is the seventh leading cause of cancer-related mortality globally and is a fatal gastrointestinal cancer that typically remains asymptomatic until it progresses or reaches an advanced stage (1). Pancreatic ductal adenocarcinomas (PDAC) account for about 95 % of all pancreatic malignancies (2). Despite advancements in the therapeutics landscape in the last thirty years, the 5-year survival rate is still about 8%, emphasizing the necessity of mechanistic

insights into Pancreatic Ductal Adenocarcinoma (PDAC) to improve treatments (3). The absence of early detection methods, late clinical presentation, complex biological features and restricted treatment options are the key factors contributing to poor outcomes of PDACs (4). The extensive stroma enveloping pancreatic cancer cells plays a critical role in tumour invasion and growth as it limits the delivery of chemotherapeutic medications to tumour cells (5). The efficacy of treatment for pancreatic cancer is severely compromised by the high rate of drug resistance to chemotherapy. Therefore, identifying the key factors contributing to this drug resistance is critical for enhancing patient outcomes and improving prognosis. Studies have demonstrated that Y-box binding protein 1 (YBX1) is linked to various intrinsic cancer characteristics, including proliferation, invasion, metastasis and the stemness of cancer cells (6). The protein-coding gene YBX1 is a highly conserved transcription factor that functions as a versatile DNA/RNA binding protein, controlling transcription and translation (7).

The low-density lipoprotein receptor (LDLR) family consists of 14 single-transmembrane receptors with similar structures and repeat sequences. These receptors selectively identify and internalize various extracellular ligands, independently or in combination with membrane-bound co-receptors. Low-density lipoprotein receptor-related protein-1 (LRP1), Low-density lipoprotein receptor-related protein-2 (LRP2), Low-density lipoprotein receptor-related protein-3 (LRP3), Low-density lipoprotein receptor-related protein-4 (LRP4), Low-density lipoprotein receptor-related protein-8 (LRP8), Low-density lipoprotein receptor-related protein-10 (LRP10), Low-density lipoprotein receptor-related protein-11 (LRP11), Low-density lipoprotein receptor-related protein-12 (LRP12) and Low-density lipoprotein receptor class A domain containing 3 (LRAD3) are some of the 14 members (8). The most multifunctional member of this family is LRP1. It affects the two primary physiological processes: signalling pathway modulation and endocytosis (9). YBX1 upregulates the expression of LRP1. Patients with higher YBX1 expression exhibited reduced overall survival (OS) compared to those with lower expression. It stimulates the growth of pancreatic cancer, both *in vivo* and *in vitro* and its inhibition suppresses the growth of cancer cells. When overexpressed, the membrane receptor LRP1, a crucial component of the Wnt/β-catenin pathway, can impact the downstream signalling, particularly influencing the distribution and levels of β-catenin. By binding to the promoter region of LRP1, YBX1 enhances the transcription, leading to reduced degradation of β-catenin and increased nuclear accumulation. Elevated levels of β- catenin inside the nucleus act as a coactivator for the TCF/LEF family (10). Thus making YBX1 a potential therapeutic target.

Phytochemicals serve as potent lead molecules for developing new medications (11). Natural phytochemicals are valuable sources for developing novel therapies for various diseases. These substances are regarded safe for human consumption with minimal harmful side effects and have been shown to have anticancer effects by influencing the cellular signalling pathways (12, 13).

Ebenaceae is a family of tropical fruits that includes fleshy and fibrous tropical fruits such as Persimmons. Its antioxidant qualities can be harnessed to address various conditions, such as degenerative diseases, uneven skin tone and cancer. This genus is a valuable source of pharmacologically active compounds and speeds up drug discovery. This species has proven to be beneficial in the context of different cancers (14). Among the most potent naturally occurring antioxidants are carotenoids and flavonoids, which can efficiently scavenge free radicals, causing DNA damage and leading to cancer (15). Studies have shown that the genus *Diospyros* of the Ebenaceae family exhibits strong antimicrobial, antidiabetic, antioxidant, thermogenic and enzyme-inhibiting qualities (16). The fruits of this genus have been used in Chinese medicine to cure hematemesis, cough, persistent leg pain and ulcers below the knee (17). The phytochemical analysis of ethyl acetate (EtOAc) of Diospyros fleuryna leaves isolated an anticancer agent 8'-hydroxyisodiopsyrin (18). The diterpenoid diosmarioside D, obtained from the methanolic extracts of *Diospyros maritima* leaves, exhibited potent cytotoxic effects against the A549 lung adenocarcinoma cell line (19). By inhibiting the proliferation of cancer cells through the PDGFR-Rac-cJun N-terminal kinase pathway *Diospyros kaki* triggers apoptosis in cancer cells (20). This species contains Kaempferol, a pharmacologically active component that activates the antioxidant system, causing apoptosis of non-small cell carcinoma cells (21). Diospyrin and 8-hydroxyisodiospyrin from *Diospyros lotus* demonstrated significant anticancer properties (22). *D. kaki* has been shown to inhibit the proliferation through the induction of oxidative stress and apoptosis of human colorectal, liver and breast cancer *in vitro* (23). The methanolic bark extract of *Diospyros montana* was used to synthesize silver oxide nanoparticles (Ag2O NPs), demonstrating a potent effect against HepG2 cells. These effects are linked to enhanced autophagy, DNA damage and decreased mitochondrial membrane potential (24). Molecular docking experiments were used to assess the impact of potential phytochemicals from the genus *Diospyros* in pancreatic cancer.

Materials and Methods

The approach used in this study to identify potential lead compounds, combining molecular docking and the ADMET studies, is illustrated in Fig. 1

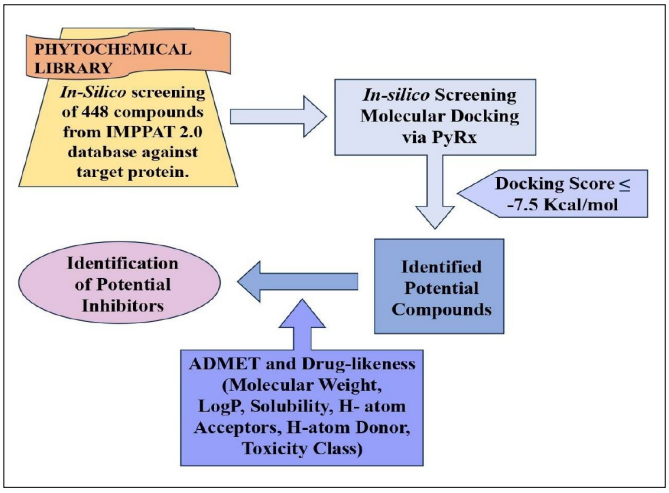

Fig. 1. Workflow for virtual screening and lead compound identification from a phytochemical library.

The cancer genome atlas (TCGA) and bioinformatics analysis

The cBioPortal for Cancer Genomics provides a web resource for exploring, visualizing and analyzing multidimensional genomics data. It is designed to access complex molecular profiling data sets into readily understandable genetic, epigenetic, gene expression and proteomic events (25). This application was used to investigate gene alterations in LRP1. Further, the TNM plot tool was used to check the expression value of the LRP1 gene and analyze the correlation between the YBX1 and LRP1 genes in Pancreatic Ductal Adenocarcinoma. TNMplot is an analytical tool that utilizes the data of gene arrays from Gene Expression Omnibus of the National Center for Biotechnology Information (NCBI-GEO) or RNA-seq data from TCGA, Genotype-Tissue Expression (GTEx) and Therapeutically Applicable Research to Generate Effective Treatments (TARGET) repositories. It compares the gene expression in tumour, metastasis and normal tissues (26).

Protein selection and preparation

The Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB) database was used to obtain the protein structure of the YBX1. The protein structure was selected from RCSB with an X-ray crystallography resolution of 2.01Å (27). The crystal structure of YBX1 CSD in complex with m5C RNA (PDB ID: 6KTC; Organism: Homo sapiens) was retrieved. The protein was further processed in BIOVIA Discovery Studio by removing the hetero atoms and water molecules and adding the polar Hydrogen atoms (Fig.2).

Phytochemicals' library generation

Indian Medicinal Plants, Phytochemistry And Therapeutics (IMPPAT 2.0), a manually created database, was used to construct the genus Diospyros' phytochemical library for virtual screening. IMPPAT 2.0 is the largest database on phytochemicals of Indian medicinal plants, capturing 4010 Indian medicinal plants, 17967 phytochemicals and 1095 therapeutic uses. It is an integrated platform for applying cheminformatic approaches to accelerate natural product-based discovery (28). Phytochemicals following Lipinskis' rule of 5 with zero violations were downloaded (Table 1). PubChem was used to retrieve the 3D structures of phytochemicals in SDF format, which were used for further analyses. PubChem is an open chemistry database containing information on small and large molecules. It depicts information on various parameters and descriptors of small chemical molecules, including their chemical structures, chemical and physical properties, biological activities, patents, safety, toxicity data and many others (29).

Virtual screening by molecular docking of selected phytochemicals

Molecular docking was conducted using the PyRx Virtual Screening Tool to investigate the binding of the various phytochemicals with 6KTC (30). The ligands were energy minimized and converted to Protein Data Bank, Partial Charge and Atom Type (PDBQT) format. Molecular docking was done, considering the following dimensions of the cavity: X: 41.2163, Y: 33.9127 and Z: 32.7282. Docking was done in triplet to confirm the proposed ligands' binding affinities after they were chosen due to their higher binding affinity than the source ligand. BIOVIA Discovery studio was used to visualize the non-bonding interactions between the docked protein and ligand complexes. This tool is widely used for molecular docking, simulation, drug discovery and development (31).

Absorption, distribution, metabolism, excretion, toxicity analysis of selected phytochemicals

Searching for compounds with desirable physiochemical and pharmacokinetic properties is essential to discovering novel and potential therapeutics. A comprehensive screening approach utilizing cutting-edge tools such as SwissADME, ADMETlab 2.0 and ProTox 3.0 was performed to identify compounds with the required attributes for drug candidacy. Compounds selected based on binding affinity were further evaluated using SwissADME based on their physicochemical properties. This included an analysis of key parameters such as Molecular Weight (MW), lipophilicity, Hydrogen bond donor (HBD), Hydrogen Bond Acceptor (HBA) and partition coefficient (LogP), among others. Compounds with a molecular weight lower than 500 Daltons, less than 10 hydrogen bond acceptors, less than five hydrogen bond donors and a LogP lower than 5 were considered fit for molecular docking. Canonical SMILES of the phytochemicals were obtained from the PubChem database and used in SwissADME to produce predictions regarding the drug-likeness and medical chemistry suitability of the selected phytochemicals (32). ADMETlab 2.0 and ProTox 3.0 are online tools to evaluate compounds' toxicity (33, 34). Phytochemicals fulfilling the SwissADME parameter requirements were later checked on ADMETlab 2.0 and ProTox 3.0 for their toxicity levels.

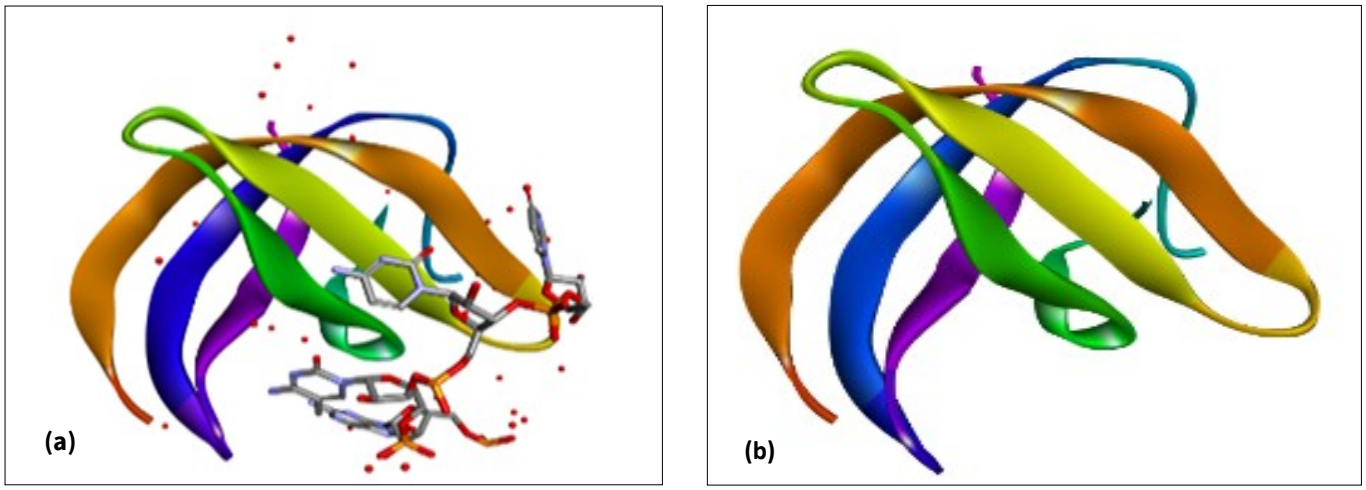

Fig. 2. Visuals of unprocessed (a) and Processed (b) protein in BIOVIA Discovery Studio.

Table 1. Phytochemicals of genus *Diospyros* passing Lipisnkis' rule of 5

Compounds	CID	Lipinskis' rule of 5	Number of Lipinskis' rule of 5 violations	BBB Permeation	Gastrointestinal absorption
(-)-Epicatechin	72276	Pass	0	No	high
(2,2'-Binaphthalene)-1,1',4,4'-tetrone, 5,5'-dihydroxy-7,7'-dimethyl-	633060	Pass	0	No	high
11-Methylgerberinol	101690823	Pass	0	No	high
2-Methoxy-4-vinylphenol	332	Pass	0	Yes	high
2-Methylanthraquinone	6773	Pass	0	Yes	high
4-Guanidinobutyric acid	500	Pass	0	No	high
5-Hydroxy-8-(4-hydroxy-7-methyl-5,8-dioxonaphthalen-1-yl)-2-methylnaphthalene-1,4-dione	633024	Pass	0	No	high
6-Hydroxy-5-methoxy-2-methyl-1,4-naphthoquinone	13468236	Pass	0	Yes	high
7-Methyljuglone	26905	Pass	0	Yes	high
8-Hydroxy-2-(8-hydroxy-6-methyl-1,4-dioxonaphthalen-2-yl)-6-methylnaphthalene-1,4-dione-Mamegakinone	167673	Pass	0	No	high
8-Methoxy-3-methylnaphthalen-1-ol	11355930	Pass	0	Yes	high
Actinidiolide, dihydro-	6432173	Pass	0	Yes	high
Ascorbic acid	54670067	Pass	0	No	high
Caffeic acid	689043	Pass	0	No	high
Citric acid	311	Pass	0	No	low
Cyanidin	128861	Pass	0	No	high
Decanoic acid	2969	Pass	0	Yes	high
Diospyrin	308140	Pass	0	No	high
Ellagic acid	5281855	Pass	0	No	high
Eugenol	3314	Pass	0	Yes	high
Flavonol 3-O-D-glucoside	11953828	Pass	0	No	high
Flavylium	145858	Pass	0	Yes	high
Gallic acid	370	Pass	0	No	high
Gerberinol	54714260	Pass	0	No	high
Glycocyamine	763	Pass	0	No	high
Guanidinosuccinic acid	439918	Pass	0	No	low
Isodiospyrin	99298	Pass	0	No	high
Kaempferol	5280863	Pass	0	No	high
Karanjachromene	14033983	Pass	0	Yes	high
Lauric acid	3893	Pass	0	Yes	high
Methyl 3,4-dihydroxybenzoate	287064	Pass	0	No	high
Methylguanidine	10111	Pass	0	No	high
Microphyllone	9928360	Pass	0	Yes	high
Myristic acid	11005	Pass	0	Yes	high
Neodiospyrin	16072922	Pass	0	No	high
Peregrinol	7092583	Pass	0	Yes	high
Plumbagin	10205	Pass	0	Yes	high
Quercetin	5280343	Pass	0	No	high
Triterpenoids	71597391	Pass	0	No	high
Yerrinquinone	618938	Pass	0	No	high

Results

Bioinformatics analysis

The LRP1 gene regulated by the YBX1 gene showed a 17.4 % mutation frequency in pancreatic cancer samples in the cBioPortal application. Pearson correlation analysis conducted through TNMplot showed a significant positive association (R = 0.18, p = 0.01) between expression levels of LRP1 and YBX1 in pancreatic adenocarcinoma tissue samples. The results suggest a potential co-regulation or functional relationship between these two genes in pancreatic cancer, indicating their involvement in a common signalling pathway or cellular process contributing to pancreatic cancer progression (Fig. 3a). Further, TNMplot was employed for expression analysis of the LRP1 gene in normal and tumour samples using RNA-seq data. A violin plot was constructed to compare Pancreatic Adenocarcinomas' tumour and normal tissues. The plot demonstrated a statistically significant upregulation of LRP1 gene expression in tumour tissue compared to normal tissue (p= 4.02e-57). In the normal tissue, the median was 1997.5, while in tumour tissue, it was 11950. The distribution of LRP1 expression in tumour samples was significantly broader, with a higher proportion of samples showing very high expression levels (Fig. 3b).

Molecular docking

Virtual screening has emerged as a powerful tool in modern drug design, enabling the rapid identification of potential drug candidates with a high affinity for target proteins or nucleic acids. It was performed to identify potential ligands that could interact with 6KTC protein and induce the desired therapeutic effects of anticancer activity. The molecular docking approach was mainly used to predict the binding orientation of the ligands to the 6KTC protein. PyRx was used to screen a library of 40 compounds. A -7.5 kcal/mol threshold was set based on the most notable negative docking results. Based on the binding energy score, 13 phytochemicals were shortlisted, out of which (2,2'-Binaphthalene)-1,1',4,4'-tetrone , 5,5'-dihydroxy-7, 7'-dimethyl-, 11-Methylgerberinol, 2-Methylanthraquinone, 6-(1,8-Dihydroxy-6-methylnaphthalen-2-yl)-5-hydroxy-2-methylnaphthalene -1,4-dione, Mamegakinone, Diospyrin, Ellagic acid, Gerberinol, Isodiospyrin, Kaempferol, Karanjachromene, Neodiospyrin and Quercetin were the candidates showing high binding affinities of -8.7, -8, -8.1, -8.9, -9.1, -9.0, -8.1, -7.5, -7.8, -7.5, -8.1, -8.6 and -7.6 kcal/mol respectively.

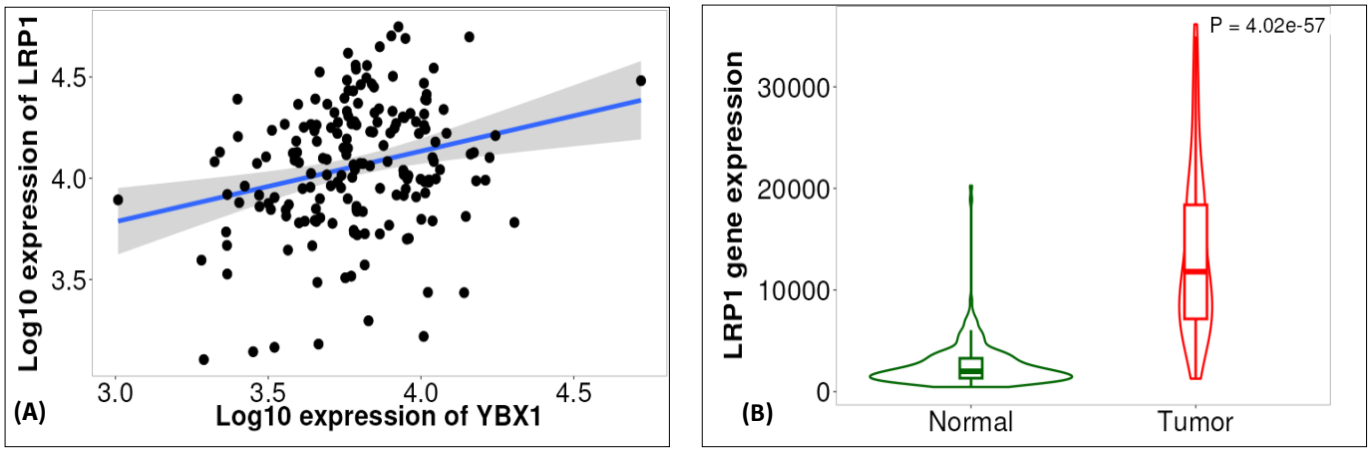

Fig. 3 (A). Scatter plot illustrating a positive correlation between log10 expression levels of LRP1 and YBX1 in pancreatic adenocarcinoma. The shaded area represents 95 % confidence interval for the regression line**;** (B). Violin plot comparing LRP1 gene expression in pancreatic tumour tissue and adjacent normal tissue. Mann-Whitney U test revealed a statistically significant difference (P = 4.02e-57).

ADME and toxicity analysis

The top 13 phytochemicals based on their binding affinity towards the 6KTC protein were identified using molecular docking. These compounds were undergone *in silico* ADME analysis to assess their pharmacokinetic properties. The molecular weight of the compounds ranged from 222.24 to 378.37 g/mol and the lipophilicity (LogP) ranged from 1.31 to 4.54. In general, for small-drug-like molecules, LogP values can range from about -0.4 to 5, with most falling within the range of 2 to 4. Further, the toxicity of these compounds was examined on ADMETlab 2.0 and ProTox 3.0. The phytochemicals with toxicity levels of 4 and 5 were selected (Table 2). Parameters such as hepatotoxicity, cytotoxicity, carcinogenicity and mutagenicity were taken into consideration to predict the toxicity probability of the selected compounds (Fig. 4). The drug-likeness analysis indicates that the 4 phytochemicals Kaempferol, Mamegakinone, Diospyrin and Neodiospyrin show favourable pharmacokinetic properties making them potential hits. Kaempferol demonstrated the highest predicted inactivity for toxicity, followed by Diospyrin, Mamegakione and Neodiospyrin.

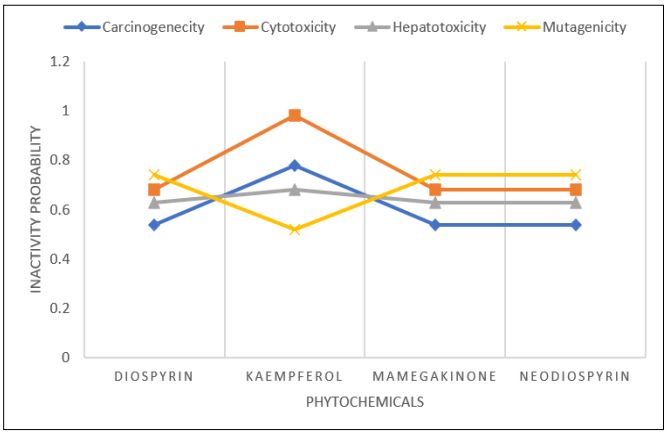

Fig. 4. This graph represents the predicted probabilities of Diospyrin, Kaempferol, Mamegakinone and Neodiospyrin being inactive (non-toxic) concerning carcinogenicity, cytotoxicity, hepatotoxicity and mutagenicity, as predicted by ProTox 3.0. Probability scores range from 0 (high probability of toxicity) to 1.2 (low probability of toxicity).

Table 3 summarizes the molecular interactions between the 6KTC protein and four selected phytochemicals. Molecular interactions were visualized using Discovery Studio, a tool for generating 2D and 3D plots. 3D plots depict bonded interactions, while 2D plots provide a comprehensive overview of bonded and non-bonded interactions, including Van der Waals forces. Fig. 5 presents representative 2D and 3D interaction plots for high-affinity ligands.

Discussion

Molecular docking is a fundamental component of computer-aided drug design (CADD). It identifies the potential drug candidates by calculating their binding positions and affinity to target proteins (35). In this study, the *Diospyros* genus was investigated for studying the effects of its phytochemicals on genes involved in the progression of pancreatic cancer.

Diospyrin is a naturally occurring compound in *D. kaki*, *Diospyros Chloroxylon* and *Diospyros sylvatica* species. It has shown promising results in cancer treatment due to its ability to induce apoptosis in cancer cells and animal models by triggering oxidative stress. It has anti-cancer properties and has been used as a lead molecule for treating several cancers. Studies evaluating diospyrin and its derivatives across various human cancer cell lines such as HeLa (cervical cancer), K- 562 (chronic myelogenous leukaemia), HL- 60 (promyelocytic leukaemia) and MCF-7 (breast cancer) demonstrated higher cytotoxicity compared to normal cells, with a potency 17 to 1441 times greater. The potent effect is likely mediated by disrupting key signalling pathways involved in cell growth and survival, particularly the NF-κB, MAPK/ERK and PI3K/Akt/mTOR pathways leading to apoptosis and tumour growth inhibition (36). Kaempferol is found in *D. kaki*. It has shown cancer-fighting abilities and is used in treat of various cancers, including breast, ovarian, lung and prostate cancers. It triggers apoptosis by activating the Bax Protein and deactivating protein kinase B. It also reduces ERK, JNK and p38 protein levels involved in cell growth and survival. Additionally, Kaempferol disrupts cancer-fuelling pathways such as the MAPK and the PI3K/Akt pathway, thereby inhibiting NF-κB and AP-1 activities (37).

The current study demonstrated the anticancer potential of neodiospyrin, isolated from *D. kaki, D. lotus* and mamegakione, found in *D. kaki*, *D. lotus* and *D. montana* through interaction with the YBX1 gene, a key regulator in pancreatic adenocarcinoma progression. However, further investigation is required to characterize these relatively studied phytochemicals' inhibitory mechanisms fully.

Table 2. Properties and predicted toxicity class of phytochemicals identified through virtual screening and molecular docking

Protein	Phytochemicals	Binding affinity (Kcal/mol)	Molecular weight	LogP	H-Bond acceptors	H-Bond donor	Toxicity Class (as per ProTox 3.0)	Drug likeness	Medicinal Chemistry (PAINS-Pan Assay Interference Structure)
6KTC	(2,2'-Binaphthalene)-1,1',4,4'-tetrone, 5,5'-dihydroxy-7,7'-dimethyl-	-8.7	374.34	3.03	6	2	3	Yes	PAINS- ene_one_D, quinone_A Brenk- 0 alert
	11-Methylgerberinol	-8	378.37	4.08	6	2	4	Yes	PAINS- 0 alert Brenk- cumarine
	2-Methylanthraquinone	-8.1	222.24	2.77	2	0	5	Yes	PAINS- quinone_A Brenk- 0 alert
	6-(1,8-Dihydroxy-6-methyl naphthalene-2-yl)-5-hydroxy-2-methylnaphthalene-1,4-dione	-8.9	360.36	4.26	5	3	2	Yes	PAINS- ene_one_D, quinone_A Brenk- 0 alert
	Mamegakinone	-9.1	374.34	3.03	6	2	4	Yes	Pain-quinone_A Brenk-0
	Diospyrin	-8.9	374.34	3.11	6	2	4	Yes	PAINS- ene_one_D, quinone_A Brenk- 0 alert
	Ellagic acid	-8.1	302.19	1.31	8	4	4	Yes	PAIN-catechol_A Brenk-catechol, cumarine, polycyclic_aromatic_hydrocarbon_3
	Gerberinol	-7.5	364.35	3.52	6	2	4	Yes	PAINS-0 alert Brenk- cumarine
	Isodiospyrin	-7.8	374.34	3.25	6	2	2	Yes	PAINS-quinone_A
	Kaempferol	-7.5	286.24	2.28	6	4	5	Yes	PAINS-0 alert Brenk -0 alert
	Karanjachromene	-8.1	334.37	4.54	4	0	5	Yes	PAINS-0 alert Brenk -0 alert
	Neodiospyrin	-8.6	374.34	3.11	6	2	4	Yes	PAIN- quinone_A
	Quercetin	-7.6	302.24	1.99	7	5	3	Yes	PAIN- catechol_A Brenk- catechol

Table 3. Overview of binding interactions between selected phytochemicals and protein residues

Phytochemicals	Hydrogen bond	Pi-anion	Pi-Akyl	Pi-Pi stacked	Van der Waals
Mamegakinone	ALA70 GLU67	GLU71	LYS68	PHE35	GLY69, GLY66, LYS2, PHE24, HIS37, THR39
Diospyrin	PHE35, LYS68, ALA70	GLU71	-	-	PHE24, VAL34, ASP33, GLU67, GLY66, GLY69
Kaempferol	THR39, HIS37, GLU67, LYS2	GLU71	LYS68	PHE35	PHE24, GLY69, GLY66
Neodiospyrin	PHE35	-	LYS68	-	PHE24, VAL34, ASP33, ALA70, GLY69, GLU71, GLY66, GLU67

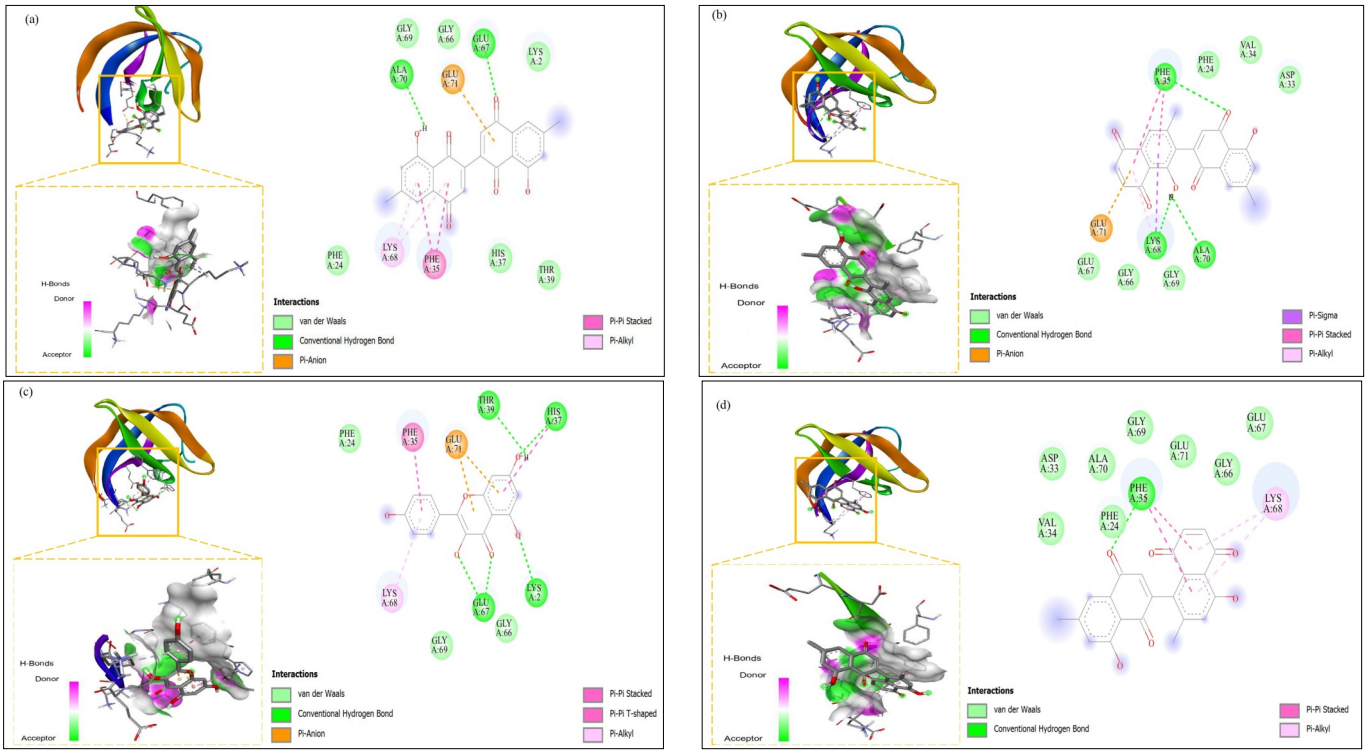

Fig. 5. 2D and 3D representation of protein-ligand complexes: (A): 6KTC and Mamegakinone complex; (B): 6KTC and Diospyrin complex; (C): 6KTC and Kaempferol complex (D) 6KTC and Neodiospyrin complex.

Conclusion

According to the current *in silico* study, modulation of the function of the Wnt/β-catenin pathway and downregulation of the LRP1 gene involved in the progression of pancreatic cancer can be done by targeting the YBX1 gene (6KTC protein). This study highlights the therapeutic potential of phytochemicals derived from the genus *Diospyros* against the YBX1 gene, suggesting their potential role in PDAC treatment. The results can be further validated by performing an MD simulation. Future studies should focus on *in vitro* and *in vivo* validation of the identified lead compounds to assess their efficacy, bioavailability and toxicity profiles.

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Authors' contributions

BY conducted initial research, data collection, manuscript drafting and primary bioinformatics analysis. MEP contributed to data analysis and data interpretation. VJU contributed to manuscript editing. SPK contributed to the critical review of the manuscript. AD assisted in manuscript formatting and referencing. PS conceptualised the study, oversaw the research process and contributed to the critical review of the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of Interest: The authors declare that they have no competing interests.

Ethical Issues: None.

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