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Molecular docking and ADME evaluation of plant-based bioactive molecules targeting nonsense-mediated mRNA decay pathway factors to modulate tumorigenesis

Sanjoy Majumder[1] & Gagan Kumar Panigrahi[2]*

[1]Department of Biotechnology, School of Biotechnology, Centurion University of Technology and Management, Odisha, India
[2]Department of Zoology, School of Applied Sciences, Centurion University of Technology and Management, Odisha, India

*Email: gagan.panigrahi@cutm.ac.in; gagan.rie@gmail.com

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Abstract

Cancer is a global health challenge that requires continuous efforts to discover effective anticancer drugs. Phytochemicals are compounds found in plants that often have medicinal properties. They possess a wide range of bioactive properties, including anticancer activity. Their multiple mechanisms of action in different physiological processes in humans make them promising candidates in the anticancer therapeutics development. The presence of these compounds makes plants valuable resources for traditional medicine and modern pharmaceutical research as well. Natural products from plants and marine sources are being used to find new anticancer agents. In humans, different cellular pathways are involved in the tumorigenesis process. Many studies have shown the role of the nonsense-mediated mRNA decay (NMD) pathway in the process of tumorigenesis. This NMD pathway is controlled by multiple proteins. In this study, we conducted a molecular docking analysis of 50 phytochemicals against the human NMD factor up-frameshit2 (UPF2) protein. The results of the molecular docking experiment and ADME properties indicate that 4 of these molecules (Genistein, Trihydroxyflavone, Baicalein and Epigallocatechin) have the potential to modulate the NMD pathway. Furthermore, these molecules comply with Lipinski's rule of five. The effects of these 4 phytochemicals may be further evaluated using *in vitro* and *in vivo* methods for novel anticancer therapeutic development.

Keywords

phytochemicals; tumorigenesis; anticancer therapeutics; nonsense-mediated mRNA decay; molecular docking

Introduction

Cancer is a complex disease caused by uncontrolled cell growth and is considered one of the most dangerous threats to human life worldwide (1). Unfortunately, treatment options for cancer are currently quite limited and many advanced anticancer drugs are not affordable for patients in poor and developing countries (2). Therefore, it is crucial to discover cost-effective, novel anti-cancer therapeutics. Fortunately, researchers are actively working to find anti-cancer agents that are both effective and affordable. Several phytochemicals have shown promise as anticancer treatments in experimental studies (3). Many studies by different researchers suggested that combinatorial use of phytochemical and conventional chemotherapeutic agents can potentially intensify the therapeutic effects while minimizing

adverse side effects (4). Continued advancements in this field are essential for overcoming the challenges encountered in the development of anticancer therapeutics from natural sources. Nowadays, other than conventional anticancer treatment, many phytocompounds are also already being used to treat cancer or as supportive care for cancer (5).

Phytochemicals are natural compounds found in plant materials that possess biological activity, having disease prevention and protection properties. Knowledge of ethnomedicines or traditional medicines has been passed down from one generation to another, forming the basis for current research on drug discovery from natural resources. Medicinal plants have been reported to have chemopreventive and anticancer therapeutic properties (6, 7). Many studies, including *in vitro* experiments, animal model studies and clinical trials, have shown that numerous phytochemicals possess pro-apoptotic, antiproliferative and anti-metastatic effects. Additionally, phytochemicals have been found to have anti-inflammatory, antibacterial, antiviral and free radical scavenging properties that help fight cancer (8, 9). Phytochemicals can modulate different signaling pathways regulating the replication and death of different types of tumor cells through various mechanisms (10). Phytomedicines are considered to be less toxic to normal cells than conventional therapies and can also be an option for cancer prevention and treatment, with or without conventional drugs. Phytomedicines offer a comparatively safe and cost-effective alternative and can be considered as an alternative to conventional cancer therapies for patients not getting any benefits or suffering from serious side effects of conventional cancer therapies (11, 12). To use the full potential of phytochemicals, they could be tested against human target proteins that have not been explored much to discover and develop new anticancer therapeutics. Numerous studies have demonstrated that core NMD proteins play a significant role in regulating the process of tumorigenesis in human beings. NMD is a post-transcriptional mRNA quality control mechanism that is present in all eukaryotes and is highly conserved throughout evolution (13). By removing or degrading aberrant mRNAs that contain premature termination codons (PTCs), NMD prevents the production and accumulation of truncated proteins, thus safeguarding cells from any harmful effects (14).

Nonsense mediated decay (NMD)

Nonsense-mediated mRNA decay (NMD) is a post-transcriptional mRNA quality control mechanism that is found to be highly evolutionary conserved among all eukaryotes (15). NMD acts by preventing the production and accumulation of truncated proteins and protects the cell from its deleterious effects. PTCs may arise due to DNA mutation, rearrangement in DNA sequence, alternative splicing, which may cause frameshift, the inclusion of PTC containing introns due to splicing error, etc. (16). Many protein factors, including up-frameshift (UPF) proteins, which are found in all eukaryotes, including humans are involved in the NMD process. Each NMD factor plays a different role in this mRNA decay pathway. The role of NMD is not only limited to aberrant transcripts, numerous studies show that NMD is a fine tuner of the expression level of normal physiological mRNAs, which otherwise gives full-length proteins (17). In this way, NMD modulates significant cellular processes and helps to maintain cellular homeostasis. By regulating endogenous mRNA levels, NMD can control many biological processes including neurological development and embryonic development (18). The core NMD machinery is formed mainly by up-frameshift factors (UPFs) which include UPF1, UPF2 and UPF3.

Role of UPF2 in NMD pathway

UPF2 plays a significant role in nonsense-mediated decay (NMD) of mRNAs that contain premature stop codons. Human UPF2 (hUPF2) is a protein that has molecular weights of 148 kDa and consists of 3 MIF4G (middle domain of translation initiation factor 4G) domains (19). These domains are named MIF4gI, MIF4GII and MIF4GIII respectively. The UPF2 MIF4G domains 1 and 2 have been studied to demonstrate their function in the structural arrangement of the exon junction complex (EJC) and UPF complex (20). UPF2 interacts with UPF3B and suppressor of morphogenesis in genetalia-1 (SMG1) and it is proposed to associate with SURF as part of the UPF3b-EJC complex. However, it can also form a complex with UPF1 and SMG1 independently of UPF3b. This suggests that UPF2 could be directly recruited to SURF by multiple protein interactions, including UPF1, SMG1 and others. It associates with the nuclear exon junction complex (EJC) and is recruited by UPF3B (21). Together, they form a UPF1-UPF2-UPF3 surveillance complex, which activates NMD. It also stimulates UPF1's ATPase and RNA helicase activities in cooperation with UPF3B. Due to the significant role of UPF2 in the normal functioning of the NMD pathway, this protein can be a potential drug target to modulate the function of the NMD pathway.

Materials and Methods

A flowchart diagram of this current study of screening of phytochemicals against the MIF4GII domain of human UPF2 protein is presented in (Fig. 1).

Selection and preparation of ligands library

Based on the literature survey, we have selected and prepared a library of 50 bioactive phytochemicals with medicinal properties. The chemical structures of these 50 phytochemicals were obtained from the PubChem database in SDF format (Table 1 and Supplementary Table 1).

Processing of ligands

Before proceeding further to the molecular docking step, energy minimization and optimization of these phytochemicals were done using Openbabel (32) in a Linux environment. Then these compounds were converted and saved in pdbqt format.

Preparation of receptor protein (UPF2)

The 3-dimensional (3D) structure of the MIF4GII domain of human UPF2 protein was downloaded from the RCSB Pro-

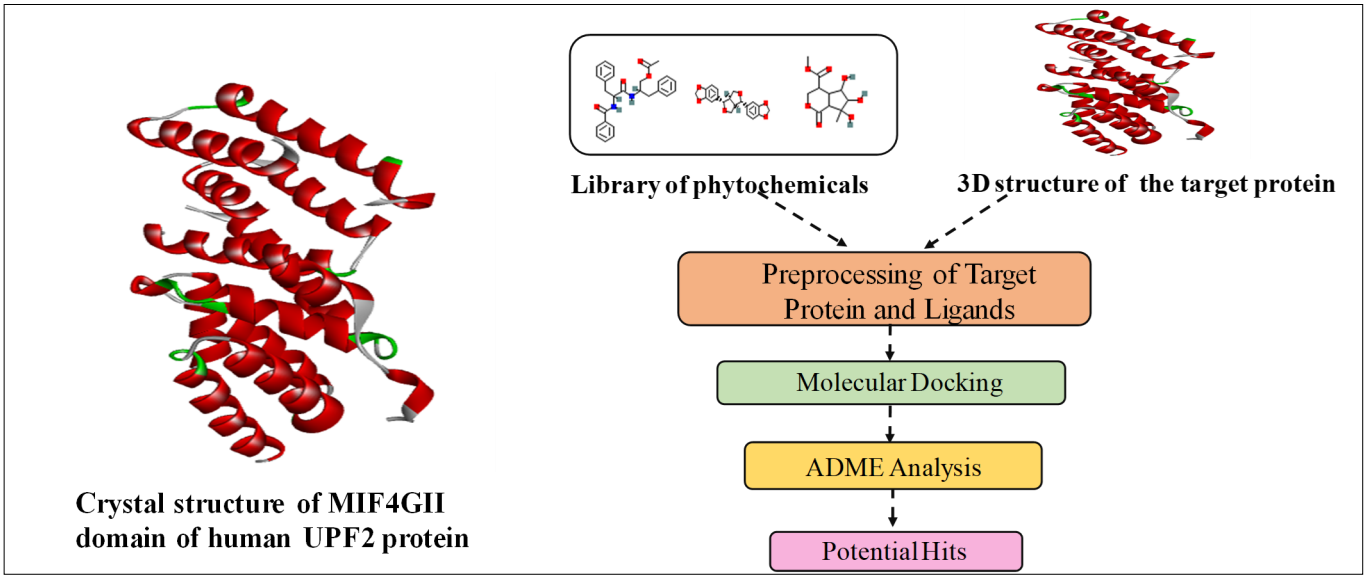

Fig. 1. Representing flow chart of the study of identifying the potential inhibitors of hUPF2 using molecular docking approach and *in silico* ADME analysis.

Table 1. List of the phytochemicals and their plant sources.

Sl. No.	Name of phytochemicals	Name of plants	Reference
1	Alisol_B	*Alisma lanceolatum*	(22)
2	Allicin	*Allium ursinum*	(23)
		Allium ampeloprasum	
3	Alpha-PINENE	*Camellia sinensis*	(24)
		Callistemon citrinus	
4	Apigenin	*Camellia sinensis*	(25)
5	Aspalathin	*Aspalathus linearis*	(26)
6	Baicalein	*Lepisorus ussuriensis*	(27)
		Scutellaria prostrata	
7	Bauerenol	*Cichorium spinosum*	(23)
8	Berberine	*Berberis vulgaris* L.	(25)
9	Capsaicin	*Capsicum pubescens*	(28)
		Capsicum annuum	
10	Celastrol	*Celastrus paniculatus*	(22)
		Tripterygium wilfordii	
11	Curcumin	*Curcuma longa*	(24)
12	Delphinidin	*Punica granatum*	(29)
13	Deserpidine	*Rauvolfia serpentine*	(25)
14	Diosgenin	*Allium cernuum*	(23)
		Dioscorea hispida	
15	Diosquinone	*Diospyros batocana,*	(25)
		Diospyros verrucosa	
16	Epigallocatechin	*Camellia sinensis*	(22)
		Eschweilera coriacea	
17	Epigallocatechin gallate	*Camellia sinensis*	(22)
		Eschweilera coriacea	
18	Eriocalyxin B	*Isodon eriocalyx*	(28)
19	Eugenol	*Ocimum tenuiflorum*	(26)
		Cinnamomum verum	
20	Evodiamine	*Tetradium ruticarpum*	(30)
		Spiranthera odoratissima	
21	Falcarindiol	*Angelica japonica*	(25)
22	Fisetin	*Fragaria ananassa*	(31)
23	Flavylium	*Tradescantia pallida*	(23)
		Callistephus chinensis	
24	Genistein	*Salvia hispanica*	(29)
		Glycine soja	
25	Gingerol	*Cuminum cyminum*	(30)
		Aframomum melegueta	
26	Hesperetin	*Camellia sinensis*	(28)
		Salvia officinalis	
27	Honokiol	*Magnolia officinalis*	(30)
		Illicium simonsii	
28	Isophytol	*Basella alba*	(27)
		Hordeum vulgare	
29	Isorhamnetin	*Caragana frutex*	(26)
		Camellia sinensis	
30	Kaempferol	*Hydrangea serrata*	(28)
		Caragana frutex	
31	Lauric_acid	*Ipomoea leptophylla*	(25)
		Arisaema tortuosum	
32	Limonene	*Camellia sinensis*	(24)
		Hypericum foliosum	
33	Luteolin	*Camellia sinensis*	(31)
		Codonopsis lanceolata	
34	Magnolol	*Magnolia henryi*	(27)
		Magnolia officinalis	
35	Maslinic_acid	*Salvia miltiorrhiza*	(22)
		Sideritis candicans	

tein Data Bank (PDB ID: 4CEK) for docking purposes.

36	Myricetin	*Caragana frutex* *Camellia sinensis*	(30)
37	Myrtenol	*Artemisia thuscula* *Alpinia latilabris*	(26)
38	Oridonin	*Isodon japonicus* *Isodon macrocalyx*	(24)
39	Papaverine	*Papaver rhoeas* *Papaver armeniacum*	(23)
40	Quercetin	*Persicaria muricata* *Camellia sinensis*	(31)
41	Resveratrol	*Humulus lupulus*	(25)
42	Rottlerin	*Mallotus philippensis*	(24)
43	Silibinin	*Silybum eburneum*	(25)
44	Tangeretin	*Camellia sinensis* *Citrus leiocarpa*	(22)
45	Tetrandrine	*Stephania tetrandra* *Cyclea barbata*	(23)
46	Trihydroxyisoflavone	*Dalbergia spruceana* *Hibiscus syriacus*	(29)
47	Tripchlorolide	*Tripterygium wilfordii*	(25)
48	OblongifolinC	*Garcinia yunnanensis* Hu.	(29)
49	Albine	*Lupinus pilosus* *Lupinus albus*	(31)
50	Capilin	*Santolina rosmarinifolia* *Glebionis segetum*	(23)

Before molecular docking, we processed the 3D structure of this human UPF2 protein using AutoDockTools 1.5.7. (33). In this pre-processing step, the removal of water molecules and other heteroatoms was done, along with adding polar hydrogens and Kollman charges. Then generated a grid box with the dimension of 126 Å × 126 Å × 126 Å and kept other parameters as default.

Molecular Docking based screening of potential inhibitor of UPF2

For this molecular docking study, we have used AutoDock Vina version 1.2.3. (34-36). To screen for potential inhibitors of human UPF2, performed a blind docking of the library of 50 bioactive phytocompounds against the MIF4GII domain of the human UPF2 protein.

Drug-likeness and ADME profiling

Phytocompounds screened through molecular docking studies have undergone *in silico* ADME analysis using the Swiss ADME server (35, 37-41). In this analysis we have checked for any violations of both Lipinski's rule and Veber's rule along with other parameters (42-47).

Results and Discussion

Molecular docking

In computational drug design molecular docking is a widely used method that helps to identify potential drug candidates against various disease targets. This advanced computational method can save a significant amount of energy, time and costs in the drug discovery process by screening large libraries of potential drug compounds in a very short time. In our study, we screened a library of 50 bioactive phytocompounds against human UPF2 using Autodock Vina 1.2.3. Based on the binding energy score, we have shortlisted the best 10 bioactive phytochemicals, namely, bauerenol, rottlerin, tetrandrine, epigallocatechin gallate, evodiamine, genistein, trihydroxy isoflavone, baicalein, maslinic acid and epigallocatechin, which show binding energy of -9.379, -9.328, -9.052, -8.972, -8.501, -8.351, -8.16, -7.983, -7.929 and -7.83 kcal/mol respectively.

Evaluation of drug likeness

A molecular docking study has identified the top 10 phytocompounds based on their binding affinity towards the UPF2 MIF4G domain. These compounds have undergone *in silico* ADME analysis to assess their pharmacokinetic properties. Four of these 10 phytocompounds show zero violations of Lipinski's and Veber's rules, making them promising hits in the process of finding novel therapeutics against cancer. The overall analysis of the drug-likeness indicates that the 4 phytochemicals genistein, trihydroxyflavone, baicalein and epigallocatechin show positive pharmacokinetic properties, which makes them potential hits. The results of the *in silico* ADME analysis of the best 10 phytochemicals using the Swiss ADME server are shown in Table 2.

Several phytocompounds possess anti-cancer properties. This docking outcome indicates that many phytocompounds might interact with amino acid residues of human UPF2 protein effectively. In the present study, we explored the potential of 50 phytochemicals against the human UPF2 (MIF4GII domain) and based on the molecular docking results and *in silico* analysis of ADME properties 4 natural compounds were selected, namely, genistein, trihydroxyflavone, baicalein and epigallocatechin for further evaluation. The binding affinity and details of various molecular interactions of the selected four phytocompounds with the MIF4GII domain of human UPF2 are displayed (Table 3).

In this study, we have used the Biovia Discovery studio visualizer to generate 2D and 3D plots of molecular interactions between proteins and ligands. The 3D plot mainly shows the different bonded interactions. To show the various bonded as well as non-bonded (e.g., Van der Waals) molecular interactions between human UPF2 and phytocompounds, we have generated a 2D plot. Here we have shown both 3D and 2D plots of molecular interactions between protein and the selected ligands with high binding affinity [Fig. 2 and 3 (A to C)].

Conclusion

Modulation of the function of the NMD pathway by targeted binding of potential phytochemicals against human UPF2 protein can be an effective strategy for anticancer therapeutics development. The molecular docking and *in silico* ADME analysis results confirmed the potential of genistein, trihydroxyflavone, baicalein and epigallocate-

Table 2. ADME properties of selected best ten phytochemicals.

Sl. No	Phytochemical	MW (g/mol)	Consenus Log Po/w	No. of H bond acceptors	No. of H bond donors	Molar refractivity	Lipinski	Vebe r	Synthetic accessibility	Bioavailability Score	TPSA	No.of rotatable bonds	Solubility (mg/ml)
1.	Epigallocatechin_Gallate	458.37	1.01	11	8	112.06	2	1	4.2	0.17	197.37	4	1.27E-01
2.	Epigallocatechin	306.27	0.42	7	6	76.36	1	0	3.53	0.55	130.61	1	2.57E+00
3.	Baicalein	270.24	2.24	5	3	73.99	0	0	3.02	0.55	90.9	1	2.51E-02
4.	Evodiamine	303.36	2.7	1	1	97.67	0	0	3.19	0.55	39.34	0	2.12E-02
5.	Maslinic_Acid	472.7	5.24	4	3	137.82	1	0	6.22	0.56	77.76	1	7.39E-05
6.	Bauerenol	426.72	7.04	1	1	135.14	1	0	6.25	0.55	20.23	0	2.94E-06
7.	Genistein	270.24	2.04	5	3	73.99	0	0	2.87	0.55	90.9	1	5.11E-02
8.	Rottlerin	516.54	4.37	8	5	145.1	1	1	4.57	0.55	144.52	6	9.83E-05
9.	Tetrandrine	622.75	5.41	8	0	186.07	1	0	7.01	0.55	61.86	4	5.96E-06
10.	Trihydroxyisoflavone	270.24	1.96	5	3	73.99	0	0	2.92	0.55	90.9	1	1.15E-01

Table 3. Results of molecular docking showing binding affinity and various molecular interactions between hUPF2 and the selected hits.

Sl. No.	Phytochemical	Binding affinity (kcal/mol)	Number of hydrogen bond	Residues involved in different types of molecular interactions
1	Genistein	-8.351	1	Hydrogen bond: GLY711 Pi–sigma: ALA464 Pi-Akyl: ARG712 Amide-Pi Stacked: THR709 Van der Waals Interaction: ASP463, ASP461, TRP459, PHE713, CYS710, LEU707, TYR754, CYS755, GLU708, TYR768
2	Trihydroxyfavone	-8.16	3	Hydrogen bond: GLU708, LEU707, ARG712 Carbon–hydrogen bond: GLY497 Pi–sigma: ALA464 Amide-Pi Stacked: THR709 Van der Waals Interaction: ASP461, ASP463, PHE467, TYR468, TRP459, PHE713, CYS710, GLY711
3	Baicalein	-7.983	3	Hydrogen bond: GLU708, TYR754, THR709 Carbon–hydrogen bond: GLY495 Pi–sigma: ALA464 Pi-Alkyl: ARG712 Amide-Pi Stacked:ASP463 Van der Waals Interaction:
4	Epigallocatechin	-7.83	4	Hydrogen bond: GLU708, TYR754, THR709, PHE713 Carbon–hydrogen bond: TYR468 Pi-Alkyl: ALA464, ARG712 Van der Waals Interaction: ASP461, ASP463, PRO620, GLU672, ARG668, GLY711, ILE458

chin as modulators of the NMD pathway. The effectiveness of these phytochemicals may be further validated through *in vitro* and *in vivo* experiments. In this study, we conclude that these 4 compounds may be used as potential modulators of the NMD pathway in the process of discovering novel anticancer therapeutics. In the coming decades, there is a possibility that phytomedicines could become a preferred treatment option for numerous diseases, including cancer and over conventional drugs. The utilization of advanced scientific technologies and knowledge of traditional medicines can greatly assist in the development of innovative anticancer phytotherapies. Integrating phytomedicines into modern healthcare systems and promoting sustainable practices can be the key to successfully achieving

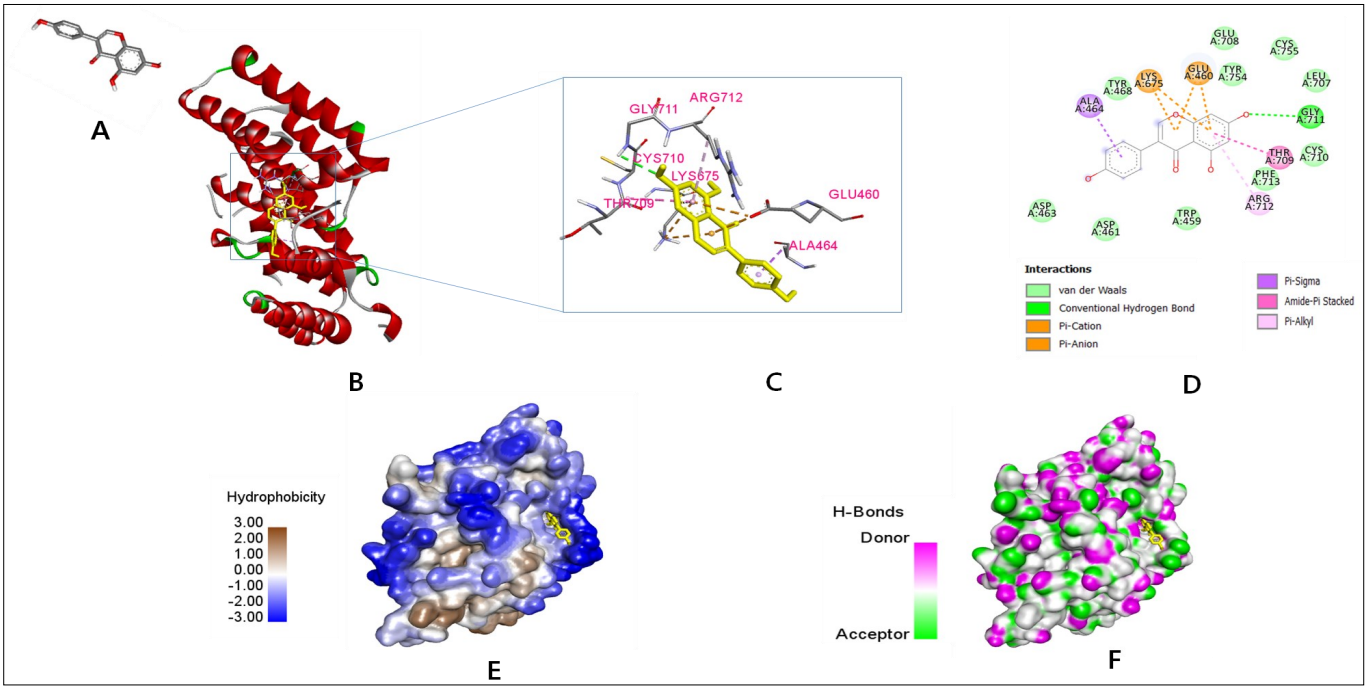

Fig. 2. 2D and 3D representation of molecular interaction between the hUPF2 (PDB ID: 4CEK) and genistein (CID_5280961): (**A**) 3D structure representation of genistein; (**B**) best binding mode of hUPF2 and Genistein; (**C**) close-up view of interactions between genistein (yellow surface) and amino acid residues of hUPF2; (**D**) 2D representation of different types of interactions between hUPF2 and genistein including van der Waals, conventional hydrogen bond, Pi–sigma and Pi-alkyl; (**E**) hydrophobicity surface representation of the structure of MIF4GII domain of hUPF2 in complex with genistein and (**F**) Surface representation of the complex showing residues as hydrogen bond donor and acceptor.

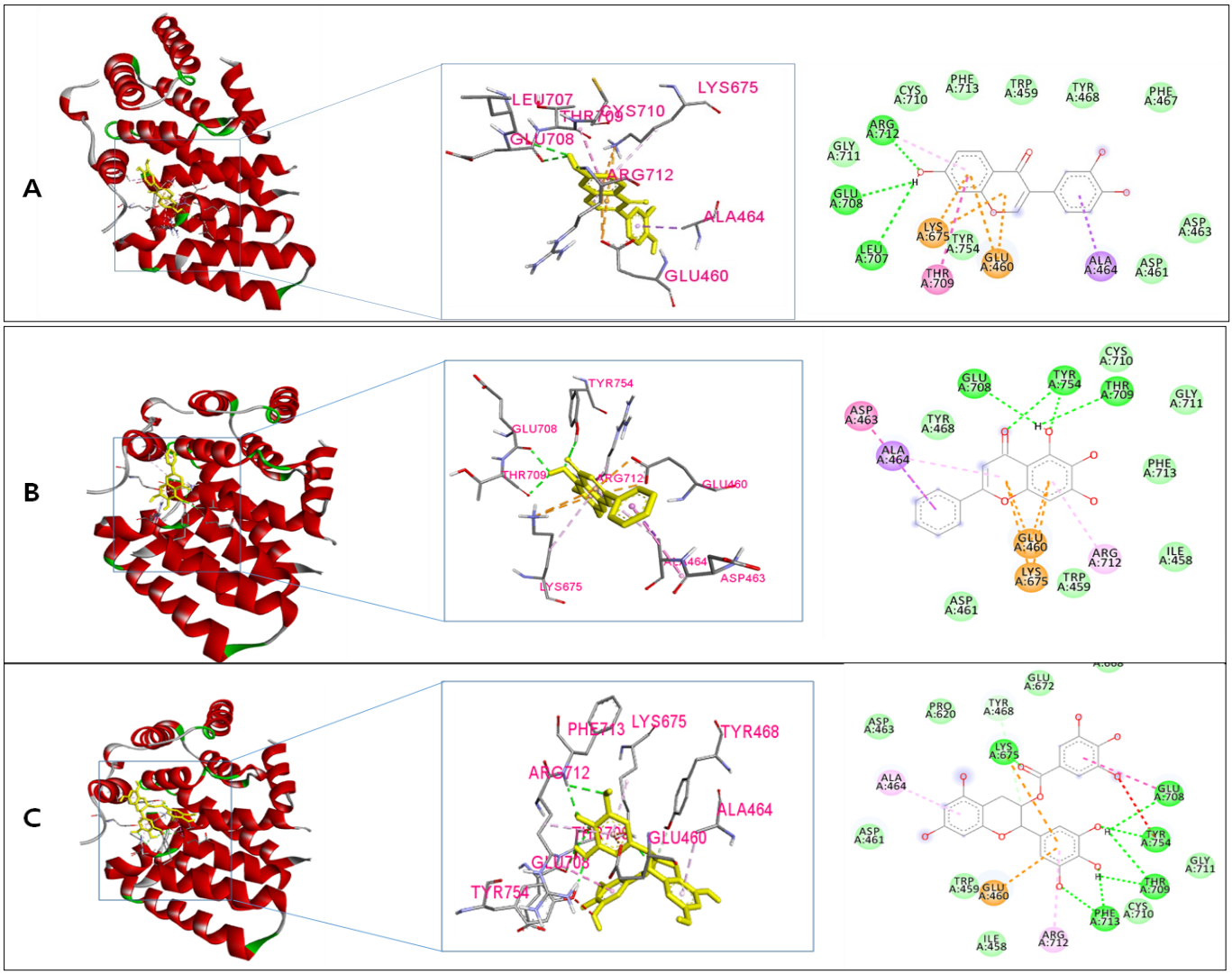

Fig. 3 . 2D and 3D representation of protein-ligand complexes: (**A**): hUPF2 and trihydroxyflavone complex; (**B**): hUPF2 and baicalein complex; (**C**): hUPF2 and epigallocatechin complex.

the United Nations' sustainable development goals (SDG 3).

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Authors' contributions

All the authors have substantial contribution for the preparation of the manuscript. GKP: conceptualized and conceived the idea. SM and GKP: data curation and writing. All the authors have read and approved the final manuscript before submission.

Compliance with ethical standards

Conflict of interest: The authors declare that they have no conflict of interest.

Ethical issues: None.

Supplementary data

Supplementary Table 1. List of phytochemicals used in preparing the ligand library.

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