https://doi.org/10.33472/AFJBS.6.5.2024. 7651-7668

AfricanJournalofBiological Sciences

In Silico Analysis of Small Molecules Targeting the Human UPF3B Protein to Identify Potential Modulators of Nonsense-mediated mRNA Decay Pathway: Novel Avenues for Anticancer Therapeutics Development

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Article History
Volume 6, Issue 5, 2024
Received: 15 May 2024
Accepted: 22 May 2024
doi:*10.33472/AFJBS.6.5.2024. 7651-7668*

Abstract

Cancer remains a significant global health challenge, necessitating ongoing efforts to develop effective anticancer medications. However, conventional drug discovery methods are costly, time-consuming, and have a negative impact on the environment. To address these issues, sustainable drug discovery approaches are being developed to minimize waste and promote eco-friendly practices. Furthermore, natural products from plant sources continue to be explored for their potential as anticancer agents. Numerous studies have highlighted the involvement of the nonsense-mediated decay (NMD) pathway, in the tumorigenesis process in humans. This study aims to explore the potential of small molecules of plant origin, known as phytomolecules, in modulating the NMD pathway's function through a molecular docking approach, followed by in silico ADME analysis. We conducted molecular docking studies of fifty phytomolecules against the human NMD factor Up-frameshift3B (UPF3B) protein. Based on the binding energy score, ten molecules with lowest score were selected for further ADME analysis. Docking results and in silico ADME analysis shows that three compounds Eriocalyxin B, Oridonin and Diosquinone could act as potential inhibitors of the human UPF3B protein and also modulate NMD pathway. The potential impact of these three compounds can be evaluated more thoroughly by employing both in vitro and in vivo methods in the development of innovative cancer treatments.

Keywords: Phytomolecules, tumorigenesis, molecular docking, anticancer therapeutics, nonsense-mediated decay

Introduction

Cancer is a multifaceted and life-threatening illness characterized by the uncontrolled proliferation of cells, posing a significant danger to human life on a global scale (Marie-Ange Majérus, 2022). Unfortunately, cancer treatment options are currently limited, and many advanced anticancer drugs are unaffordable for patients in poor and developing countries (Ocran et al., 2021). 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. In fact, several phytomolecules have shown promise as anticancer treatments in experimental studies (Choudhari et al., 2020). Many studies by different researchers suggested combinatorial use of phytocompounds and conventional chemotherapeutic agents can potentially intensify the therapeutic effects while minimizing adverse side effects (Rizeq et al., 2020; Majumder and Panigrahi, 2024). The ongoing progress in this area is crucial for addressing the obstacles faced in creating anticancer treatments derived from natural sources. Currently, aside from traditional cancer treatments, numerous plant compounds are already employed in cancer therapy or as part of supportive care for cancer (Mazurakova et al., 2022).

Phytomolecules are natural compounds present in plant materials that exhibit biological activity and possess properties for disease prevention and protection. The understanding of ethnomedicines or traditional medicines has been transmitted across generations, laying the groundwork for ongoing research into drug discovery from natural sources. Medicinal plants have been reported to have chemo preventive and anticancer therapeutic properties (Prasathkumar et al., 2021; Panigrahi et al., 2023; Sahoo et al. 2023). Many studies, including invitro experiments, animal model studies, and clinical trials, have shown that numerous phytomolecules possess pro-apoptotic, anti-proliferative and anti-metastatic effects. Additionally, phytocompounds have been found to have anti-inflammatory, anti-bacterial, antiviral, and free radical scavenging properties that help fight cancer (George et al., 2021; Majrashi et al., 2023). Phytomolecules can modulate different signaling pathways regulating the replication and death of different types of tumor cells through various mechanisms (Chirumbolo et al., 2018). Phytomedicines are considered to be less toxic to normal cells than the conventional therapies and also can 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 Chaudhary et al., 2015; Jorge et al., 2011). To use the full potential of phytocompounds they could be tested against human target proteins that have not been explored much in order to discover and develop new anticancer therapeutics. Numerous studies have demonstrated that core NMD proteins play significant role in regulating the process of tumorigenesis in human beings. NMD is a post-transcriptional mRNA quality control mechanism, which is present in all eukaryotes and is highly conserved throughout evolution (Das and Panigrahi (2024); Panigrahi et al., 2020). By removing or degrading aberrant mRNAs that contain PTC, NMD prevents the production and accumulation of truncated proteins, thus safeguarding cells from any harmful effects. NMD regulates important cellular processes and helps to maintain cellular homeostasis (Patro et al., 2023; Panigrahi et al., 2024).

Nonsense mediated decay (NMD)

Nonsense-mediated mRNA decay (NMD) is a post-transcriptional mRNA quality control mechanism found to be highly evolutionarily conserved among all eukaryotes (Panigrahi and Satapathy 2020; Sahoo et al., 2023a). 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 causes frameshift, inclusion of PTC containing introns due to splicing error etc (Panigrahi et al., 2021; Sahoo et al., 2024). Many protein factors including up-frameshift (UPF) proteins which are found in all eukaryotes including humans are involved in the NMD process. Each NMD factors play a different role in this mRNA decay pathway. Role of NMD is not only limited to aberrant transcripts, numerous studies shows that NMD is a fine tuner of expression level of normal physiological mRNAs, which otherwise gives full length proteins (Das and Panigrahi, 2024; Marija and Rickie, 2023; Sahoo et al., 2023b). In this way NMD modulates significant cellular processes and helps to maintain cellular homeostasis. By regulating endogenous mRNA level, NMD can control many biological processes including neurological development and embryonic development (Karousis et al., 2016; Jung et al. 2020; Panigrahi and Satapathy2020). The core NMD machinery is formed mainly by up-frameshift factors (UPFs) which include UPF1, UPF2 and UPF3.

Role of UPF3B in NMD pathway

The gene of UPF3 is an interesting gene involved in nonsense-mediated mRNA decay (NMD) and consists of two paralogs in mammals: UPF3A and UPF3B (Shum et al., 2016; Sahoo and Satapathy 2021). While UPF3B, located on the X-chromosome in humans, is a well-established NMD factor, the role of UPF3A located in chromosome13 is not fully understood. UPF3B plays a significant role in the decay of mRNAs containing premature stop codons. The ribonucleoprotein (RNP) domain of UPF3B is important for its functional interactions with the exon junction complex (EJC) complex. UPF3B interacts with UPF2 and is proposed to associate with SURF as part of the UPF3b-EJC complex (Chan et al., 2009; Panigrahi and Satapathy 2021; Panigrahi et al., 2021a). Together, they form a surveillance complex consisting of UPF1, UPF2, and UPF3, which activates NMD. Therefore, targeting UPF3B could be beneficial in modulating the function of the NMD pathway (Hong et al., 2024).

Materials and Methods

A flowchart diagram of this current study of screening of phytocompounds against the RNP domain of human UPF3B protein is presented in Figure 1.

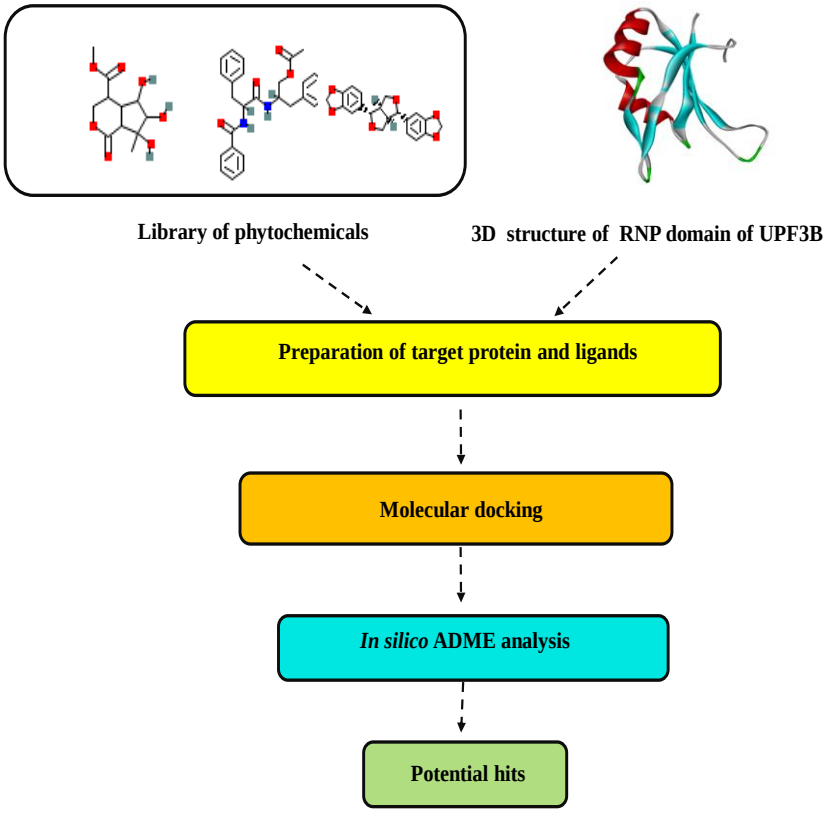

Figure 1: Representing flow chart of the study of identifying the potential inhibitors of human UPF3B using molecular docking approach and *in silico* ADME analysis.

Selection and preparation of ligands

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

Table 1: List of phytocompounds used in preparing ligand library

Sl. No.	Phytocompounds	PubChem CID	Molecular Formula
1.	Alisol B	15558620	$C_{30}H_{48}O_4$
2.	Apigenin	5280443	$C_{15}H_{10}O_5$
3.	Allicin	65036	$C_6H_{10}OS_2$
4.	Aspalathin	11282394	$C_{21}H_{24}O_{11}$
5.	Alpha-pinene	6654	$C_{10}H_{16}$
6.	Berberine	2353	$C_{20}H_{18}NO_4^+$
7.	Bauerenol	111220	$C_{30}H_{50}O$
8.	Baicalein	5281605	$C_{15}H_{10}O_5$
9.	Capsaicin	1548943	$C_{18}H_{27}NO_3$
10.	Celastrol	122724	$C_{29}H_{38}O_4$
11.	Cordycepin	6303	$C_{10}H_{13}N_5O_3$
12.	Curcumin	969516	$C_{21}H_{20}O_6$
13.	Diosgenin	99474	$C_{27}H_{42}O_3$
14.	Delphinidin	68245	$C_{15}H_{11}ClO_7$
15.	Diosquinone	122720	$C_{22}H_{14}O_7$
16.	Deserpidine	8550	$C_{32}H_{38}N_2O_8$
17.	Eugenol	3314	$C_{10}H_{12}O_2$
18.	Epigallocatechin gallate	65064	$C_{22}H_{18}O_{11}$
19.	Evodiamine	442088	$C_{19}H_{17}N_3O$
20.	Epigallocatechin	72277	$C_{15}H_{14}O_7$
21.	Eriocalyxin B	16202215	$C_{20}H_{24}O_5$
22.	Flavylium	145858	$C_{15}H_{11}O^+$
23.	Fisetin	5281614	$C_{15}H_{10}O_6$
24.	Falcarindiol	5281148	$C_{17}H_{24}O_2$
25.	Genistein	5280961	$C_{15}H_{10}O_5$
26.	Gingerol	442793	$C_{17}H_{26}O_4$
27.	Honokiol	72303	$C_{18}H_{18}O_2$
28.	Hesperetin	72281	$C_{16}H_{14}O_6$
29.	Hispolon	10082188	$C_{12}H_{12}O_4$

30.	Isorhamnetin	5281654	$C_{16}H_{12}O_7$
31.	Kaempferol	5280863	$C_{15}H_{10}O_6$
32.	Myricetin	5281672	$C_{15}H_{10}O_8$
33.	Resveratrol	445154	$C_{14}H_{12}O_3$
34.	Tangeritin	68077	$C_{20}H_{20}O_7$
35.	Oblongifolin C	10100985	$C_{43}H_{58}O_6$
36.	Oridonin	5321010	$C_{20}H_{28}O_6$
37.	Quercetin	5280343	$C_{15}H_{10}O_7$
38.	Tripchlorolide	159588	$C_{20}H_{25}ClO_6$
39.	Maslinic acid	73659	$C_{30}H_{48}O_4$
40.	Luteolin	5280445	$C_{15}H_{10}O_6$
41.	Oleanolic acid	10494	$C_{30}H_{48}O_3$
42.	Rottlerin	5281847	$C_{30}H_{28}O_8$
43.	Silibinin	31553	$C_{25}H_{22}O_{10}$
44.	Tetrandrine	73078	$C_{38}H_{42}N_2O_6$
45.	Isophytol	10453	$C_{20}H_{40}O$
46.	Lauric acid	3893	$C_{12}H_{24}O_2$
47.	Limonene	22311	$C_{10}H_{16}$
48.	Myrtenol	10582	$C_{10}H_{16}O$
49.	Papaverine	4680	$C_{20}H_{21}NO_4$
50.	Trihyroxyisoflavone	5284648	$C_{15}H_{10}O_5$

Before proceed further to molecular docking step, energy minimization and optimization of these phytocompounds were done using Openbabel (Boyle et al., 2011) in linux environment. Then these compounds were converted and saved in pdbqt format.

Preparation of receptor protein (UPF3B)

The three dimensional (3D) structure of the RNP domain of human UPF3B protein was downloaded from the RCSB Protein Data Bank (PDB ID: 1UW4) for docking purpose. Prior to molecular docking we have processed the 3D structure of this human UPF3B protein RNP domain using AutoDockTools 1.5.7. (Morris et al., 2009). In this preprocessing step removal

of water molecule and other hetero atoms were done, added polar hydrogens and Kollman charges. Then generated grid box with the X, Y and Z dimension of 66Å × 88 Å × 72 Å respectively and kept other parameters as default.

Molecular Docking based screening of potential inhibitor of UPF3B

For this molecular docking study, we have used AutoDock Vina version 1.2.3. (Trott et al., 2010). To screen for potential inhibitors of human UPF3B, performed a blind docking of the library of fifty bioactive phytocompounds against the RNP domain of the human UPF3B protein.

Drug-likeness and ADME profiling

Phytocompounds screened through molecular docking study has undergone *in silico* ADME analysis using Swiss ADME server (Daina et al., 2017). In this analysis we have checked for any violations of both Lipinski's rule and Veber's rule along with other parameters (C.A. Lipinski ,2004; Veber et al., 2002).

Results and Discussion

Molecular docking

In computational drug designing 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 span of time. In our study, we have screened a library of 50 bioactive phytocompounds against human UPF3B using Autodock Vina 1.2.3. Based on the binding energy score, we have shortlisted top ten bioactive phytocompounds (binding energy score less than 6.85). These compounds are namely Rottlerin, Eriocalyxin B, Silibinin, Diosgenin, Bauerenol, Epigallocatechin, Celastrol, Oridonin, Diosquinone, and Tetrandrine which are found to have a lower binding energy of -7.639, -7.394, -7.329, -7.244, -7.21, -7.203, -7.03, -6.956, -6.866 and -6.865 Kcal/mol, respectively.

Evaluation of drug likeness

Molecular docking study has identified the top ten phytocompounds based on their binding affinity towards UPF3B RNP domain. These compounds have undergone insilico ADME analysis to assess their pharmacokinetic properties. Three of these ten phytocompounds show zero violations

of Lipinski's and Veber's rule, making them promising hits in the process of finding novel therapeutics against cancer. Overall analysis of the drug-likeness indicates that, these phytocompounds namely Eriocalyxin B, Oridonin and Diosquinone shows positive pharmacokinetic properties which makes them potential hits. The results of the insilico ADME analysis of the top ten phytocompounds using Swiss ADME server are shown in Table 2.

Table 2: ADME properties of the top ten selected phytocompounds

Sl. No	phytochemicals	MW (g/mol)	Consenus Log Po/w	No. of H bond acceptors	No. of H bond donors	Molar refractivity	Lipinski	Veber	Synthetic accessibility	Bioavailability Score	TPSA	No.of rotatable bonds	Solubility (mg/ml)
1.	Rottlerin	516.54	4.37	8	5	145.1	1	1	4.57	0.55	144.52	6	9.87E-07
2.	Eriocalyxin B	344.4	1.68	5	2	89.8	0	0	6.36	0.55	83.83	0	1.18E+00
3.	Silibinin	482.44	1.59	10	5	120.55	0	1	4.92	0.55	155.14	4	7.99E-03
4.	Diosgenin	414.62	5.01	3	1	121.59	1	0	6.94	0.55	38.69	0	2.35E-04
5.	Bauerenol	426.72	7.04	1	1	135.14	1	0	6.25	0.55	20.23	0	2.02E-07
6.	Epigallocatechin	306.27	0.42	7	6	76.36	1	0	3.53	0.55	130.61	1	1.56E+00
7.	Celastrol	450.61	5.16	4	2	131.29	1	0	6.28	0.85	74.6	1	2.36E-05
8.	Oridonin	364.43	0.91	6	4	92.4	0	0	6.68	0.55	107.22	0	4.74E+00
9.	Diosquinone	390.34	2.37	7	2	100.75	0	0	4.47	0.55	121.27	1	1.20E-03
10.	Tetrandrine	622.75	5.41	8	0	186.07	1	0	7.01	0.55	61.86	4	1.08E-05

Several phytocompounds possess the anti-cancer properties. This docking outcome indicates that many phytocompounds might interact with amino acid residues of human UPF3B protein effectively. In the present study, we explored the potential of fifty phytocompounds against the human UPF3B (RNP domain) and based on the molecular docking results and *in silico* analysis of ADME properties three phytomolecules were selected, namely Eriocalyxin B, Oridonin, and Diosquinone for further evaluation. The binding affinity and details of various molecular interactions of these three molecules with RNP domain of human UPF3B are displayed in Table 3**.**

Table 3: Results of molecular docking showing binding energy scores and various molecular interactions between RNP domain of human UPF3B and top screened phytomolecules

Sl. No	Phytomolecule	Binding Affinity (kcal/mol)	Number of hydrogen bond	Residues involved in different types of molecular interactions
1	Eriocalyxin B	-7.394	1	Hydrogen bond: ARG56 Van der Waals Interactions: ARG57, THR87, LEU89, HIS92, MET93, TYR94, ALA95 and ARG96
2	Oridonin	-6.956	2	Hydrogen bond: ARG56 , ARG96 Van der Waals Interactions: ARG57, ASP86, THR87, LEU89, HIS92, MET93, TYR94 and ALA95
3	Diosquinone	-6.866	1	Hydrogen bond: LYS52, ARG96 Pi-alkyl: TYR79 Pi-pi stacked: PHE83, TYR89

In this study we have used Biovia Discovery visualizer to generate 2D and 3D plots of molecular interactions between protein and ligands. The 3D plot mainly shows the different bonded interactions. To show the various bonded as well as non-bonded (eg. Van der Waals) molecular interactions between RNP domain of human UPF3B and phytocompounds we have generated 2D plot. Here we have shown both 3D and 2D plots of of molecular interactions between protein and the selected ligands with high binding affinity (Figure: 2 to 4).

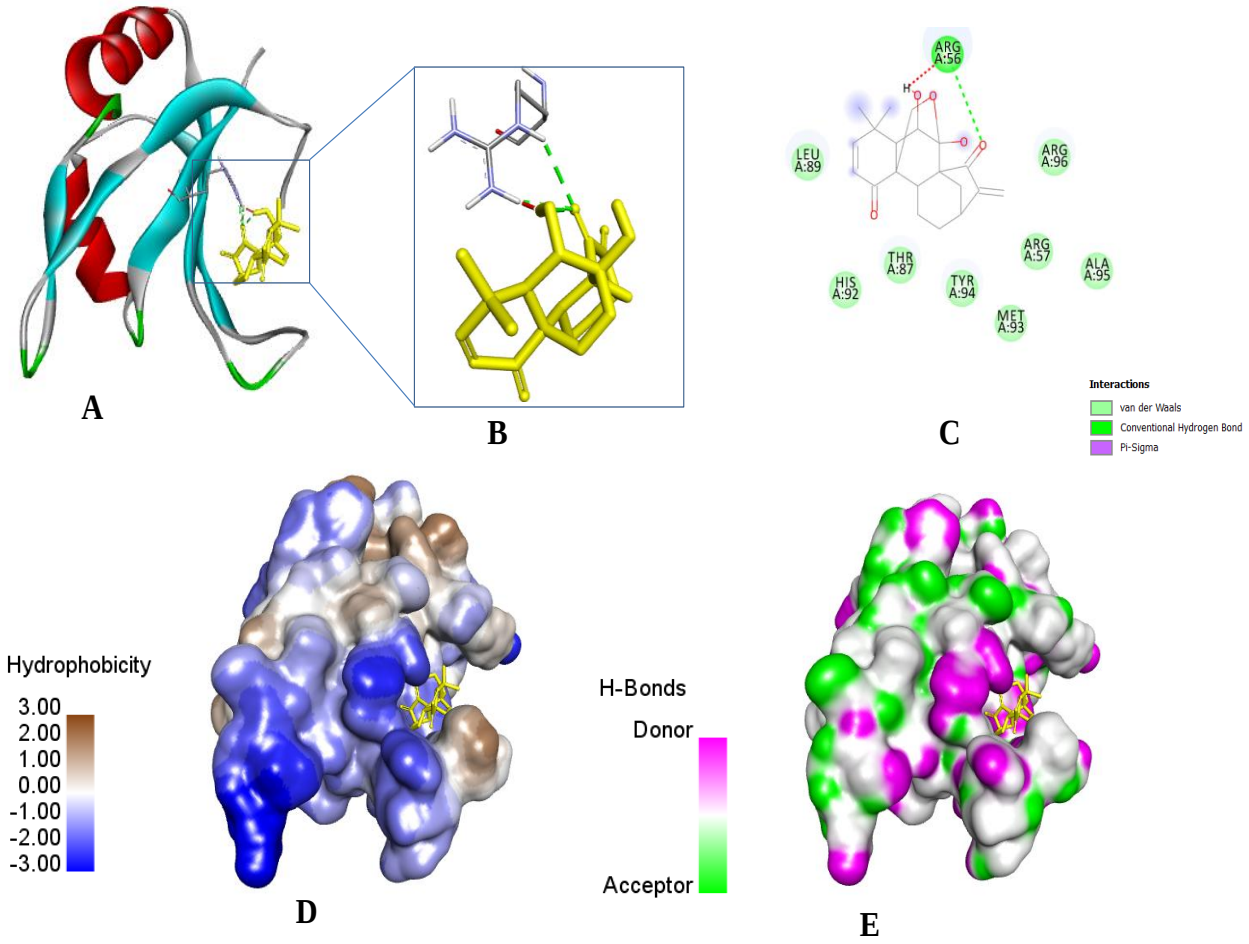

Figure 2: 2D and 3D representation of molecular interaction between the human UPF3B (PDB ID: 1UW4) and Eriocalyxin B: (A) Molecular docking complex of RNP domain of UPF3B with Eriocalyxin B; (B) close view of pocket with Eriocalyxin B (in yellow colour); (C) 2D representation of different types of interactions with Eriocalyxin B including conventional hydrogen bond (D) hydrophobicity surface representation of the RNP domain of the UPF3B in complex with Eriocalyxin B ; and (E) Hydrogen bond donor and acceptor surface representation of the complex .

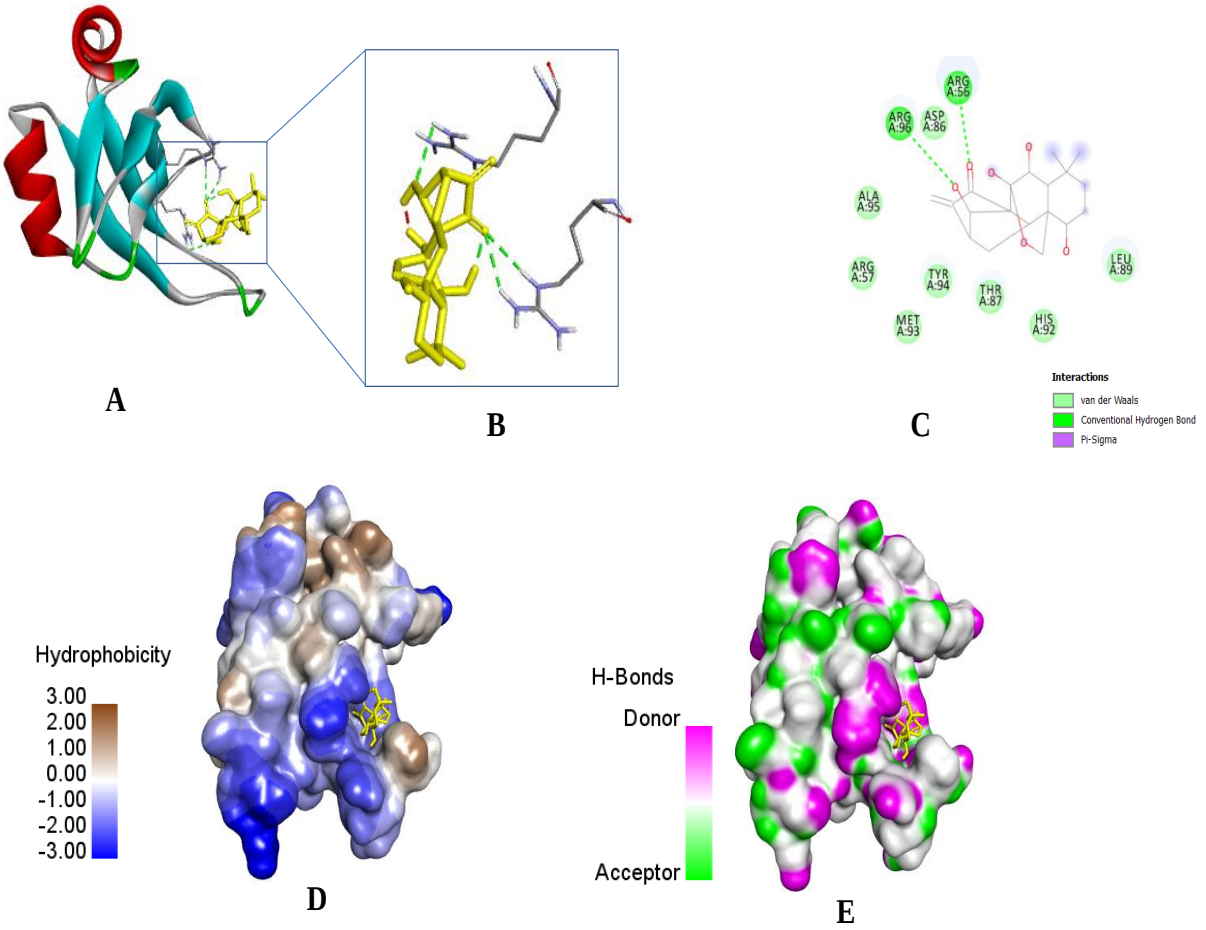

Figure 3: 2D and 3D representation of molecular interaction between the human UPF3B (PDB ID: 1UW4) and Oridonin: (A) Molecular docking complex of RNP domain of UPF3B with Oridonin; (B) close view of pocket with Oridonin (in yellow colour); (C) 2D representation of different types of interactions with Oridonin including conventional hydrogen bond (D) hydrophobicity surface representation of the RNP domain of the UPF3B in complex with Oridonin and (E) Hydrogen bond donor and acceptor surface representation of the complex .

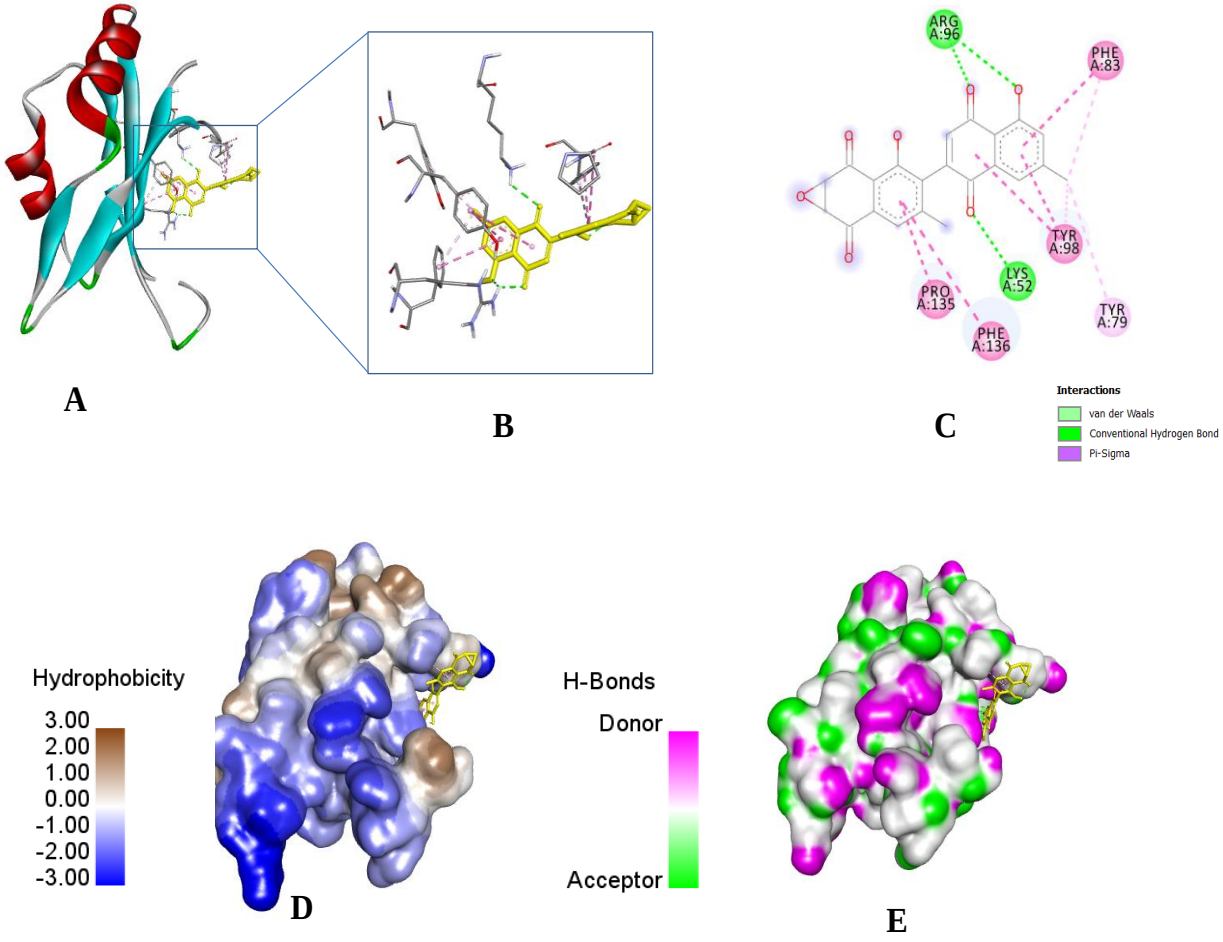

Figure 4: 2D and 3D representation of molecular interaction between the human UPF3B (PDB ID: 1UW4) and Diosquinone: (A) Molecular docking complex of RNP domain of UPF3B with Diosquinone; (B) close view of pocket with Diosquinone (in yellow colour); (C) 2D representation of different types of interactions with Diosquinone including conventional hydrogen bond (D) hydrophobicity surface representation of the RNP domain of the UPF3B in complex with Diosquinone and (E) Hydrogen bond donor and acceptor surface representation of the complex .

Conclusion

The targeted binding of potential plant-based small molecules to human UPF3B protein can effectively modulate the NMD pathway, offering a promising approach for developing novel anticancer therapeutics. The molecular docking and in silico ADME analysis results confirmed the potential of Eriocalyxin B, Oridonin, and Diosquinone as modulators of the NMD pathway. The effectiveness of these molecules may be further validated through *in vitro* and *in vivo* experiment. In this study we conclude that these three phytomolecules may be used as potential modulators of NMD pathway in the 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, over conventional drugs. The utilization of advanced scientific technologies and knowledge of traditional medicines can greatly assist in the development of innovative anticancer therapies.

Statements and Declarations

Funding
The authors would like to thank the Vice Chancellor, Centurion University of Technology and Management, Odisha for providing financial support to GKP (grant approval letter no: CUTM/VC Office/45 to GKP).

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

Human and animal rights
No animals were used in the study.

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

Acknowledgements
Authors thank the administration and management of Centurion University of Technology and Management, Odisha, India for their heartfelt support. We apologize to all colleagues whose work could not be included owing to space limitations.

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