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# Computational evaluation of bioactive compounds from *Vitis vinifera* as a novel $\beta$ -catenin inhibitor for cancer treatment

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## Abstract

**Background:**  $\beta$ -catenin is an important unit of the Wnt/ $\beta$ -catenin signaling pathway, a conserved process involving several physiological activities, encompassing differentiation and cell proliferation, etc. The dysfunction or mutation in  $\beta$ -catenin causing the initiation and advancement of various neoplasm types, including colorectal cancer, breast cancer, etc., has been reported. Therefore,  $\beta$ -catenin is a therapeutic target. Hence, designing new inhibitors targeted against  $\beta$ -catenin will prevent cancerous cells' involvement and eliminate the diseases. Studies showed that *Vitis vinifera*, a well-known grape species, contains different phytochemical substances, including aromatic acids, flavonoids, phenolic compounds, proanthocyanins, etc. *V. vinifera* exerts different anticancer properties such as apoptosis, cell proliferation, cell cycle arrest, and inhibition in cancerous cells. Structural bioinformatics methods, including molecular docking, molecular mechanics generalized Born surface area (MM/GBSA), absorption, distribution, metabolism, excretion studies (ADMET), and pharmacophore modeling approach, were used to determine the potential  $\beta$ -catenin inhibitors from *V. vinifera* bioactive compounds.

**Result:** Cis-astringin, rutin, caftaric acid, trans-caftaric acid, procyanidin B3, cis-Miyabenol C, and ampelopsin H are shown to be suitable inhibitors against  $\beta$ -catenin due to their binding affinity and interaction with the amino acids residues at the binding sites of  $\beta$ -catenin compared to Food and Drug Administration (FDA) approved drugs leucovorin Calcium and Xeloda prescribed to cure colorectal cancer.

**Conclusions:** This study suggests that *V. vinifera* could be a good plant source for compounds that might treat cancer by inhibiting the Wnt/ $\beta$ -catenin signaling pathway.

**Keywords:** Wnt/ $\beta$ -catenin signaling pathway, *Vitis vinifera*, Molecular docking, ADMET, MM/GBSA, Pharmacophore modeling

## Background

The Wnt/ $\beta$ -catenin pathway, otherwise named the canonical Wnt pathway, is a preserved mechanism that participates in different physiological activities, including apoptosis, cell proliferation, tissue homeostasis, and

differentiation (Choi et al. 2020; Salik et al. 2020; Soleas et al. 2020). The dysfunction of  $\beta$ -catenin, a significant part of the Wnt signaling pathway, has been connected with tumors' initiation and progression. High level of  $\beta$ -catenin occurs when there is overexpression of the canonical WNT pathway. Hence, mutations in the Wnt/ $\beta$ -catenin signaling pathway have been involved in different cancer types, particularly colorectal cancer, osteoporosis, and other human diseases (Clevers & Nusse, 2012; Moon et al. 2002, 2004; Nusse, 2005). The

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high mortality rate due to cancer can be prevented if this pathway is inhibited.

The Wnt signaling pathway can activate both the  $\beta$ -catenin-independent non-canonical pathway and the  $\beta$ -catenin-dependent canonical pathway. When Wnt signaling is absent, the degradation complex, comprising Axin scaffolding protein, tumor suppressor adenomatous polyposis coli (APC), and the (Glycogen synthase kinase 3) GSK 3 $\beta$ , degrades  $\beta$ -catenin, and this prevents the buildup of  $\beta$ -catenin. When Wnt signaling is present, the WNT receptor combines with low-density lipoprotein-receptor related protein 5/6 (LRP5/6) and Frizzled (FZD). This causes the interruption of the degrading complex, which induces the buildup of  $\beta$ -catenin and then moves to the nucleus and combines with the T cell factor/lymphoid enhancer-binding factor (TCF/LEF). Thus, promoting different  $\beta$ -catenin gene activation as shown in Fig 1. Mutations and dysfunction in Wnt/ $\beta$ -catenin signaling component genes such as tumor suppressor gene,  $\beta$ -catenin genes, and adenomatous polyposis coli (APC) are implicated in the constitutive activation of Wnt

signaling in more than 90% of colorectal cancer cases (Novellasedemunt et al. 20152015). Hence, there is a need to introduce therapy targeted against the Wnt/ $\beta$ -catenin signaling pathway, which prevents cancerous cell involvement and gets rid of the diseases. Therefore, careful study of the genes involved or unregulated in colorectal cancer will give a clue for the generation of new sustainable therapeutic interventions. Phytochemicals from natural sources possess promising chemoprotective properties, which might serve as reliable and alternative cancer treatments. This study used bioactive compounds from *Vitis vinifera* to design new inhibitors targeted against  $\beta$ -catenin.

*Vitis vinifera* is a well-known grape species of the family Vitaceae. The different parts of *Vitis vinifera* contain phytochemical substances, including aromatic acids, flavonoids, phenolic compounds, proanthocyanins, stilbenoids, etc. (Filocamo et al. 2015; Goufo et al. 2020; Radulescu et al. 2020). Research showed that *Vitis vinifera's* bioactive constituents have anticancer, antioxidant, antidiabetic, antiviral, and anti-inflammatory potentials

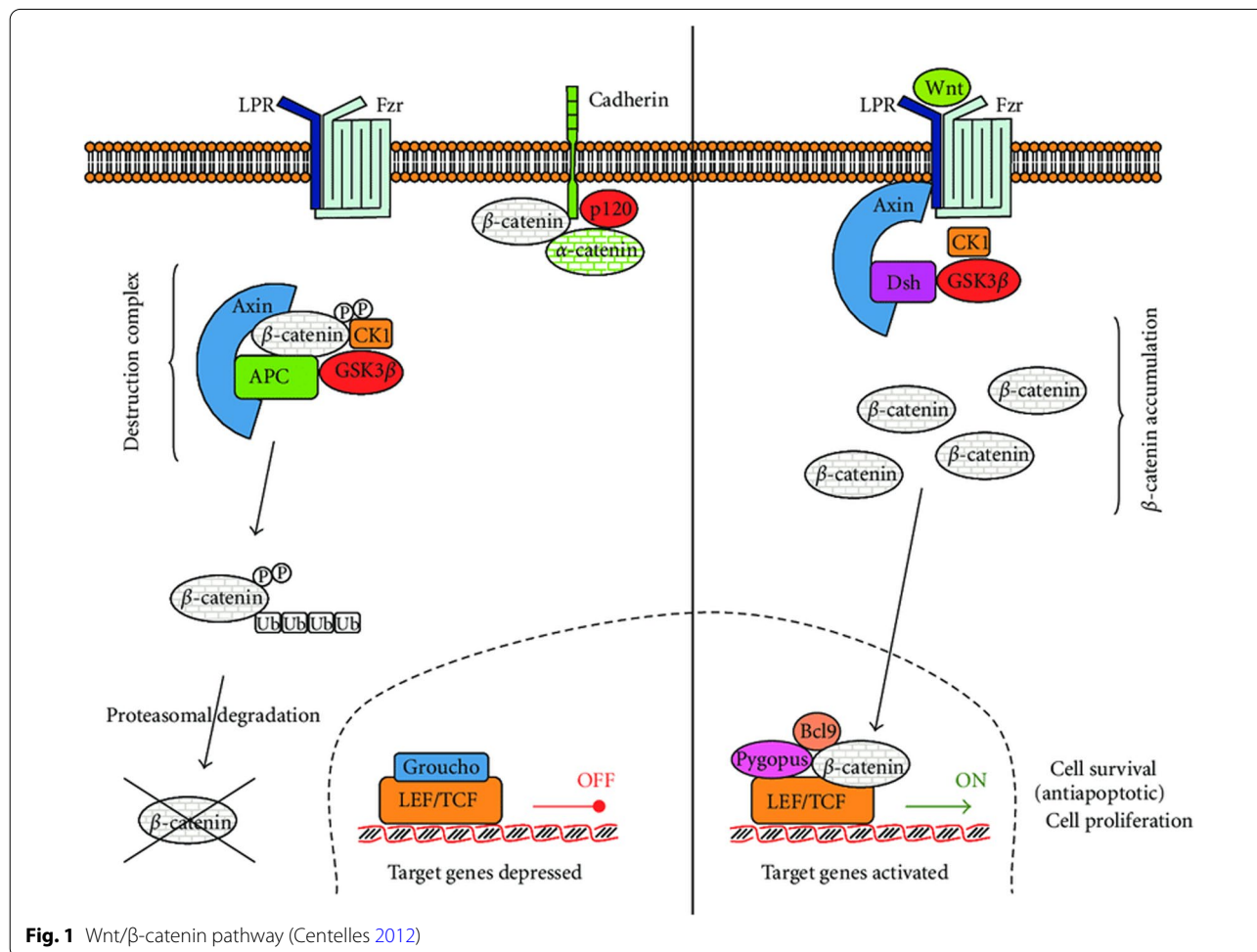


Fig. 1 Wnt/ $\beta$ -catenin pathway (Centelles 2012)

(Chaudhary et al. 2021). *Vitis vinifera* exerts different anticancer properties such as inhibition, apoptosis, cell proliferation, and cell cycle arrest in cancerous cells (Nandakumar et al. 2008).

This study employed a comprehensive computational approach to determine the therapeutic properties of different bioactive compounds from *Vitis vinifera*. The bioactive compounds were used to impede the Wnt/ $\beta$ -catenin pathway. The study includes molecular docking, ADMET screening, pharmacokinetics, and 3D pharmacophore modeling.

## Methods

### Ligand library generation and preparation

Secondary metabolites from *V. vinifera* that have been described were extracted in standard format (SDF) from the online database, Pubchem (Kim et al. 2016). Using the ligPrep tool (Release Schrödinger, 2017), the mined structures were converted into a three-dimensional structure by ionizing at pH ( $7.2 \pm 0.2$ ) and removing salt with Epik (Shelley et al. 2007; Schrodinger, 2021). The OPLS3 force field (Harder et al. 2016) was used for ionization and tautomeric state creation.

### Preparation of target

X-ray crystalline structure of  $\beta$ -catenin coupled with an inhibitor (PDB ID: 1JDH) (Asthana et al. 2014) was recovered from Protein Data Bank. The protein was processed with the protein preparation wizard tool of Maestro, Schrodinger Suite. The protein was refined by optimizing the H-bond assignment and minimized using the OPLS3 force field.

### Receptor grid generation

The receptor grid depicts the sector where the ligand and protein interact. The Receptor Grid Generation tool was used to create the processed protein grid on the binding site (Glide Grid). Selecting the co-crystallized ligand at the active site of 1JDH revealed the binding location. The ligand on the protein's crystal structure revealed information about the active site. A cubic grid box including all amino acid residues at the active site was automatically generated with the coordinate  $X = -0.360$ ,  $Y = 14.401$ , and  $Z = 47.310$ , respectively.

### Docking

Docking was done on maestro 11.1 (Schrödinger Release 2017) with the Glide tool. Using extra precision (XP) and standard precision (SP) docking algorithm, the crystal structure of  $\beta$ -catenin was utilized to virtually screen the prepared compounds to predict compounds with the lowest docking score. The docking research was carried

out with the protein expressed as a rigid body and the ligand's rotatable bonds set to be free.

To create comparison research, known cancer standards were docked using the same approach.

### ADMET/Tox screening

To establish the pharmacokinetic profile, drug-likeness, and toxicity of the hit compounds, the swissADME (<http://www.swissadme.ch>) and Pro-Tox II online servers (<https://tox-new.charite.de/prottox> II) online servers were used.

### MM/GBSA

The molecular mechanics/generalized Born surface area (MM/GBSA) continuum solvent model was employed to discover the docked protein–ligand complex binding free energy.

Rotamer search techniques from prime were used with the VSGB solvent approach and OPLS3 force field to complete this project.

### Pharmacophore modeling

The lead compounds' receptor–ligand complexes were examined. A hypothesis (E-pharmacophore) was generated using the Schrodinger suite's phase interface to highlight the significant properties that actively contribute to the lead ligands' characteristic binding to the active sites of the target proteins.

## Results

This study features a computational approach to screen phytochemicals of *V. vinifera* against  $\beta$ -catenin, a therapeutic target protein that takes part in carcinogenesis through the wnt pathway by employing molecular docking, pharmacokinetics screening, MM/GBSA, and pharmacophore modeling approach.

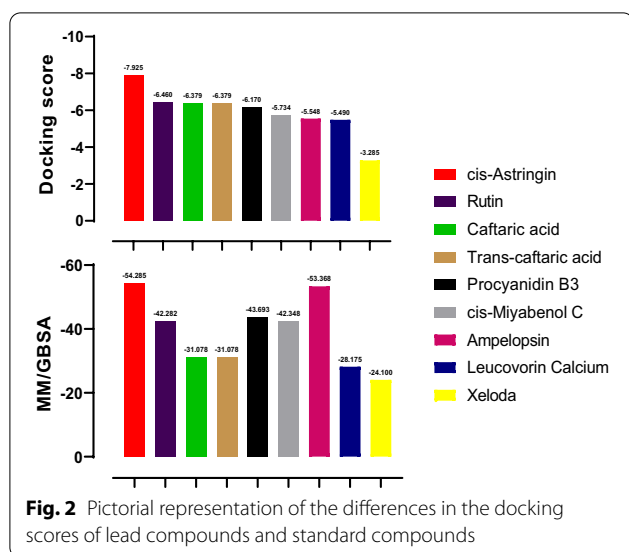
The molecular docking and binding energy study (Figs. 2 and 3) predicted seven compounds as lead compounds that show a better inhibitory potential when compared with the standard compounds, leucovorin Calcium and Xeloda.

A pharmacophore hypothesis which analyzes the characteristic binding of the top-scoring ligands to the target was analyzed and represented in Fig. 4

The lead compounds were subjected to ADME/Tox screening to study their physicochemical properties, pharmacokinetics profile, drug-likeness and toxicity. The results are recorded in Tables 1, 2 and 3.

## Discussion

The molecular docking result identified seven compounds from *V. vinifera* that showed better inhibitory potential against the target enzyme by having better



docking scores when compared with the standard compounds such as leucovorin Calcium and Xeloda currently used to manage cancer. A more negative docking score indicates more inhibitory potential. The docking scores, as represented in Fig. 2, show that cis-astringin, rutin, caftaric acid, trans-caftaric acid, procyanidin B3, cis-Miyabenol C, and ampelopsin H show better inhibitory potential by having docking scores of  $-7.925$ ,  $-6.460$ ,  $-6.379$ ,  $-6.379$ ,  $-6.170$ ,  $-5.734$  and  $-5.548$  kcal/mol, respectively, compared to leucovorin Calcium and Xeloda which are standard compounds used to treat cancer with the docking score of  $-5.490$  and  $-3.285$  kcal/mol, respectively.

The differences in the lead compounds and standards docking scores are pictorially represented in Fig. 2.

Structural-based drug design is predominantly based on the interaction of protein–ligand, as significant inhibition is primarily determined by the interaction of the ligand with the combination of amino acid residues at the active site of the target enzyme. The interaction which contributes significantly to the inhibition of  $\beta$ -catenin in this study is shown in Fig. 3.

The 2D interaction, as shown in Fig. 3, shows that cis-astringin has hydrogen bonds with GLN 24, GLN 28,

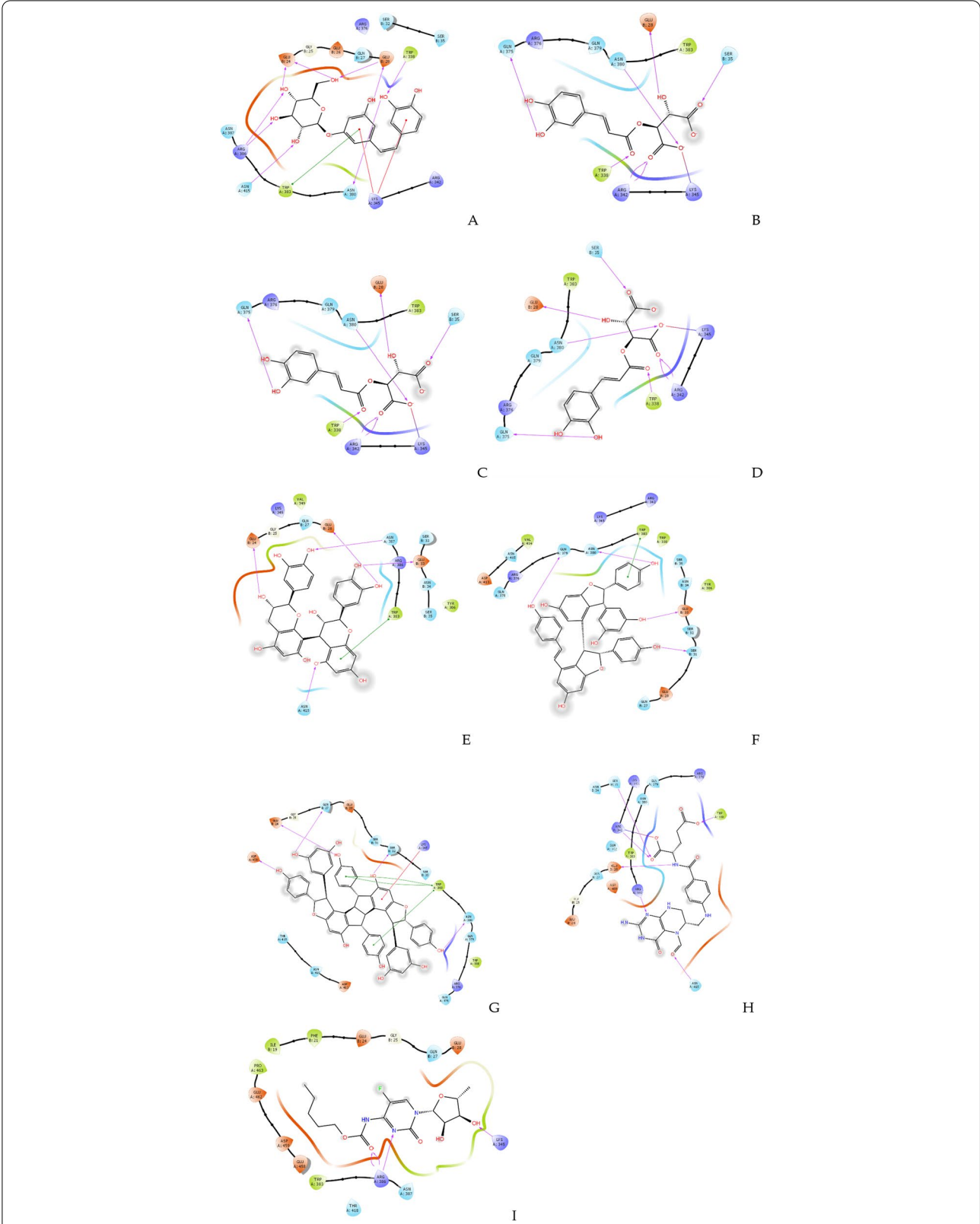
TRP 338, ARG 386, ASN 415, and ASN 380, pi-cation with LYS 345, and pi-pi stacking with TRP 383. Rutin forms hydrogen bonds with GLN 24, GLN 28, ARG 386, ASP 459, and ASN 415. Caftaric acid has hydrogen bonds with GLN 375, ASN 380, GLU 28, SER 35, TRP 338, ARG 342, and a salt bridge with LYS 345. Trans-caftaric acid has hydrogen bonds with GLN 375, ASN 380, GLU 28, SER 35, TRP 338, ARG 342, and a salt bridge with LYS 345. Procyanidin B3 shows a hydrogen bond with GLN 24, GLN 28, ASN 387, GLU 33, and ASN 415. It also has pi-pi stacking TRP 383. Cis-Miyabenol C has hydrogen bonds with ASN 380, GLN 379, GLU 33, and SER 31. It also has pi-pi stacking with TRP 383. Ampelopsin H shows hydrogen bonds with GLN 24, GLN 27, ASP 459, SER 32, and ASN 380. It also has pi cation with LYS 345 and pi-pi stacking with TRP 383. Leucovorin Calcium, a standard compound compared with the lead compounds, has hydrogen bonds with SER 35, ARG 342, GLN 28, ARG 386, TRP 338, and ASN 415. It also has a salt bridge with ARG 342, while Xeloda, a standard compound, has hydrogen bonds with ARG 386 and LYS 345.

The MM-GBSA technique is a significantly more accurate way of estimating protein–ligand complexes' binding free energies (dG) (Bandyopadhyay et al. 2021). It is one of the promising approaches used to increase virtual screening results. A negative dG value suggests that the complexes generated were stable in the target's binding pocket (Bathula et al. 2021). All lead compounds show a negative dG value, as shown in Fig. 2. The binding free energy of the docked complexes was  $-54.285$ ,  $-42.282$ ,  $-31.078$ ,  $-31.078$ ,  $-43.693$ ,  $-42.348$ , and  $-53.368$  kcal/mol for cis-astringin, rutin, caftaric acid, trans-caftaric acid, procyanidin B3, cis-Miyabenol C, and ampelopsin H, respectively. This implies that all the hit compounds are more stable in the target's binding pocket than the standard compounds leucovorin Calcium and Xeloda, which have  $-28.175$ , and  $-24.100$  kcal/mol as their free binding energy.

A pharmacophore hypothesis founded on the complex formed was developed to analyze the characteristic binding of the top-scoring ligands to the target. PHASE graphical user interface in Schrodinger's suite puts forward essential information on the molecular orientation

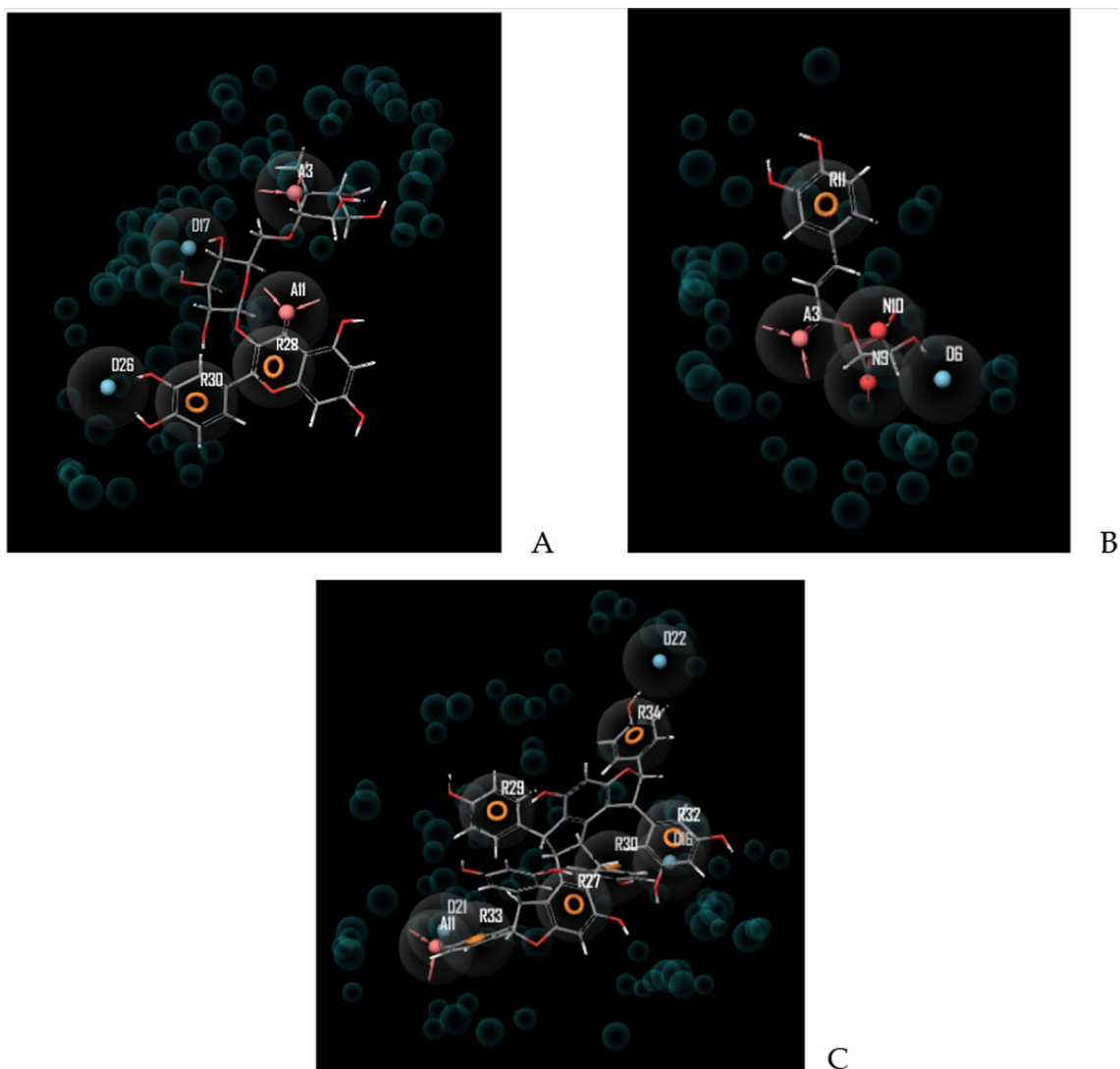
(See figure on next page.)

**Fig. 3** Interaction between the lead compounds and the amino acid residues at the active site of the target compared with standards. **A**—2D interaction between cis-astringin and the amino acid residues at the active site of the target. **B**—2D interaction between Rutin and the amino acid residues at the active site of the target. **C**—2D interaction between caftaric acid and the amino acid residues at the active site of the target. **D**—2D interaction between trans-caftaric acid and the amino acid residues at the active site of the target. **E**—2D interaction between procyanidin B3 and the amino acid residues at the active site of the target. **F**—2D interaction between cis-Miyabenol C and the amino acid residues at the active site of the target. **G**—2D interaction between ampelopsin H and the amino acid residues at the active site of the target. **H**—2D interaction between leucovorin Calcium and the amino acid residues at the active site of the target. **I**—2D interaction between Xeloda and the amino acid residues at the active site of the target



**Fig. 3** (See legend on previous page.)





**Fig. 4** Pharmacophore model of compounds picked randomly from lead compounds. **A:** Rutin/ $\beta$ -catenin complex. **B:** Trans-caftaric acid/ $\beta$ -catenin complex. **C:** Ampelopsin H/ $\beta$ -catenin complex

**Table 1** Physicochemical properties of the lead and standard compounds

Compound	Mol MW (g/mol)	Consensus log P	ESOL log S	ESOL class	Bioavailability score	Rule of five
Cis-astringin	406.38	0.28	-2.80	Soluble	0.55	1
Rutin	610.52	-1.51	-3.30	Soluble	0.17	3
Caftaric acid	312.23	-0.29	-1.55	Soluble	0.11	0
Trans-caftaric acid	312.23	-0.29	-1.55	Soluble	0.11	0
Procyanidin B3	578.52	1.53	-5.14	Moderately soluble	0.17	3
Cis-Miyabenol C	680.70	5.51	-9.03	Poorly soluble	0.17	2
Ampelopsin H	906.93	6.56	-11.33	Insoluble	0.17	3
Leucovorin	511.50	-10.81	-1.76	Very soluble	0.17	2
Calcium xeloda	359.35	0.83	-2.07	Soluble	0.55	0

**Table 2** SwissADME pharmacokinetic profile of the lead and standard compounds

Compound	GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
Cis-astringin	Low	No	No	No	No	No	No	No
Rutin	Low	No	Yes	No	No	No	No	No
Caftaric acid	Low	No	No	No	No	No	No	No
Trans-caftaric acid	Low	No	No	No	No	No	No	No
Procyanidin B3	Low	No	No	No	No	No	No	Yes
Cis-miyabenol C	Low	No	No	No	No	No	No	No
Ampelopsin H	Low	No	Yes	No	No	No	No	No
Leucovorin calcium	Low	No	Yes	No	No	No	No	No
Xeloda	High	No	Yes	No	No	No	No	No

**Table 3** ProToxII server toxicology profile of the lead and standard compounds

Compound	Predicted LD50 (mg/kg)	Predicted toxicity class	Carcinogenicity	Hepatotoxicity
Cis-astringin	1380	4	–	–
Rutin	5000	5	–	–
Caftaric acid	3800	5	–	–
Trans-caftaric acid	3800	5	–	–
Procyanidin B3	2500	5	–	–
Cis-Miyabenol C	500	4	–	–
Ampelopsin H	500	4	–	–
Leucovorin	135	3	–	–
Calcium xeloda	1000	4	–	+

of vital functional groups predominantly involved in the characteristic binding of high-affinity ligands to the protein target (Dixon et al. 2006).

The generated E-pharmacophore hypothesis (Fig. 4) contains H-bond donor, H-bond acceptor interactions, and aromatic rings. This hypothesis can be used to form the basic structural foundation that will be general to all potential inhibitors of the protein target and can also be employed to create a basic skeleton of compounds with a specific angular distance that will bond firmly to the ligand-binding site of the targets.

The absorption, distribution, metabolism, and excretion (ADME) analysis has proven to be an essential component of the drug discovery process. It is a highly economical method for *in silico* prediction of drug action within a biological system (Kenakin et al. 2016). In this study, we use the SwissADME and Protox-II servers to predict the drug-like and toxicity profile of the selected lead and standard compounds.

The physicochemical properties are established on the Lipinski rule, which considers the five (5) main criteria to determine if a drug is orally active (Lipinski et al. 1997). The results are shown in Table 1. Cis-astringin showed very good physicochemical properties, low molecular

weight, and a favorable bioavailability score and solubility. This makes it the top drug-like compound among the test compounds based on physicochemical profiling. While Calcium Xeloda showed a good physicochemical profile with no violation of the Lipinski's rule, leucovorin has a very poor physicochemical profile, and the molecular weight exceeds the Lipinski's standard (500 g/mol), the bioavailability score is low, and compared to Cis-astringin, it is a poor compound.

The pharmacokinetic profile of the compounds is shown in Table 2. Ampelopsin H, rutin, and the standard compounds were P-glycoprotein substrates. P-glycoprotein is one of the ATP binding cassette (ABC) proteins involved in discharging molecules from the cell and preventing compounds from bioaccumulating and eliciting their response. (Lin et al. 2003) The low gastrointestinal absorption rate of the test compounds and leucovorin indicates their poor lipophilic nature. However, Calcium Xeloda showed a high rate of gastrointestinal absorption. The test and standard compounds do not permeate the blood–brain barrier. Cytochrome P450 (CYP) is a family of enzymes that catalyze the phase 1 metabolism of xenobiotics at large. Any compound that inhibits selected isoforms would induce a drug–drug interaction. (Esteves

et al. 2021). Except for procyanidin B3, which was predicted to inhibit the isoform CYP34A, all of the other test compounds and the standard compounds were expected to be non-inhibitors of these enzymes and these cannot induce a drug–drug interaction.

The Pro-tox II online server estimated the toxicity profile of compounds, and it is shown in Table 3. The least toxic compound is rutin. It has the highest predicted LD50 value of 5000 mg/kg and ranks 5 in the toxicity class. (It ranges from 1 to 6, i.e., most toxic to least toxic.) It is predicted to have no carcinogenic or hepatotoxic effect. Leucovorin has an expected LD50 value of 135 mg/kg and ranks 3 in toxicity, making it the most toxic compound. Although Calcium Xeloda is not predicted to be as toxic as leucovorin, it is a hepatotoxic compound.

## Conclusions

This work used *in silico* analysis to predict seven compounds from *V. vinifera* phytoconstituents: cis-astringin, rutin, caftaric acid, trans-caftaric acid, procyanidin B3, cis-Miyabenol C, and ampelopsin H as lead compounds that can bind to  $\beta$ -catenin more robustly than the conventional compounds. When these lead compounds are subjected to ADME/Tox screening, it is discovered that they are somewhat drug-like, with cis-astringin being the most drug-like compound compared to the co-crystallized compound.

This shows that these compounds could be better drug-like molecules, and *V. vinifera* could be a good plant source for a drug-like compound that could cure tumors by suppressing the Wnt/ $\beta$ -catenin pathway's target enzyme,  $\beta$ -catenin.

Lead compound optimization and additional *in vitro* and *in vitro* analyses are recommended to validate this experiment.

## Abbreviations

ADMETox: Absorption, distribution, metabolism, excretion, and toxicity; APC: Adenomatous polyposis coli; MMGBSA: The molecular mechanics/generalized Born surface area; TCF/LEF: T cell factor/Lymphoid enhancer-binding factor; LRP5/6: Low-density lipoprotein-related protein 5/6; FZD: Frizzled; CYP: Cytochrome p450; ABC: ATP binding cassette; GSK3: Glycogen synthase kinase 3; FDA: Food and Drug Administration; XP: Extra precision; SP: Standard precision.

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## Author contributions

AOA was involved in conceptualization and manuscript writing. AOA contributed to result analysis and manuscript writing. OO was involved in manuscript editing and result analysis. PAA and SOO contributed to experimentations and manuscript editing. All authors have read and approved the manuscript.

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## Availability of data and materials

All data and materials are available on request.

## Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interest.

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