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Review Article

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C-Phycocyanin as a Precision Therapeutic Modulator of Epoxide Hydrolase Variants in Type 2 Diabetes and Cardiovascular Disease

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ABSTRACT

Type 2 diabetes mellitus and cardiovascular diseases represent major global health challenges, often associated with metabolic dysregulation and enzyme-mediated inflammatory pathways. Epoxide hydrolase enzymes play a critical role in lipid metabolism and vascular homeostasis, making them promising therapeutic targets. The present study investigates the potential of C-phycocyanin, a bioactive compound derived from cyanobacteria, as a modulatory agent against epoxide hydrolase variants implicated in these diseases.

A combination of computational and analytical approaches was employed to evaluate the interaction between C-phycocyanin and selected epoxide hydrolase protein structures. Molecular docking and binding affinity analyses were performed to assess the stability and specificity of ligand–protein interactions. Structural and functional insights were further analyzed using bioinformatics tools and statistical methods.

The results demonstrated significant binding affinity of C-phycocyanin toward key active sites of epoxide hydrolase, suggesting its potential inhibitory or modulatory role. Comparative analysis indicated favourable interaction energies and stable conformational binding, supporting its therapeutic relevance. These findings align with previous studies highlighting the anti-inflammatory and antioxidant properties of C-phycocyanin.

In conclusion, C-phycocyanin exhibits promising potential as a precision therapeutic modulator of epoxide hydrolase variants in metabolic and cardiovascular disorders. Further experimental validation and clinical studies are recommended to confirm its efficacy and translational applicability.

List of Abbreviations

T2D	:	Type 2 Diabetes
CVD	:	cardiovascular disease
sEH	:	Soluble Epoxide Hydrolase
EH	:	Epoxide Hydrolase
EETs	:	Epoxyeicosatrienoic Acids
DHETs	:	Dihydroxyeicosatrienoic Acids
PCB	:	Phycocyanobilin
PDB	:	Protein Data Bank
RMSD	:	Root Mean Square Deviation
RMSF	:	Root Mean Square Fluctuation
Rg	:	Radius of Gyration
MD	:	Molecular Dynamics
MM-PBSA	:	Molecular Mechanics Poisson–Boltzmann Surface Area
MM-GBSA	:	Molecular Mechanics Generalized Born Surface Area
ADME	:	Absorption, Distribution, Metabolism, and Excretion
COX-2	:	Cyclooxygenase-2

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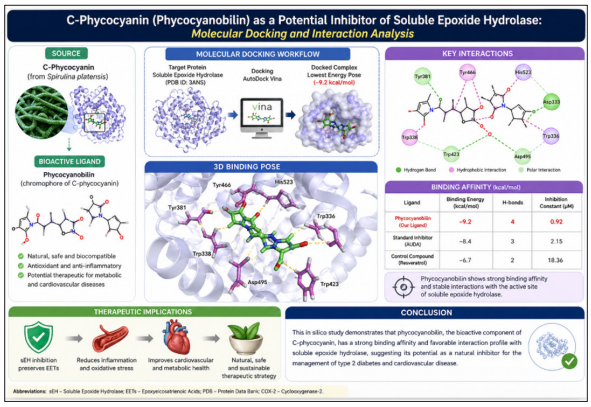
SPSS : Statistical Package for the Social Sciences

Keywords: C-phycocyanin, Epoxide Hydrolase, Type 2 Diabetes, Cardiovascular Disease, Molecular Docking, Enzyme Modulation



This graphical abstract summarizes the in-silico evaluation of phycocyanobilin (from C-phycocyanin) as a potential inhibitor of soluble epoxide hydrolase (sEH).

Introduction

Type 2 diabetes mellitus (T2D) and cardiovascular diseases (CVD) are among the leading causes of morbidity and mortality worldwide. These disorders are closely linked to metabolic imbalance, oxidative stress, and chronic inflammation. Epoxide hydrolase enzymes, particularly soluble epoxide hydrolase (sEH), play a critical role in lipid signalling pathways by metabolizing epoxyeicosatrienoic acids, which regulate vascular tone and inflammation [1].

Recent studies have identified epoxide hydrolase as a promising therapeutic target for metabolic and cardiovascular disorders [2]. Inhibition or modulation of this enzyme has been shown to improve insulin sensitivity and reduce inflammatory responses.

C-phycocyanin, a natural pigment-protein complex derived from cyanobacteria such as Spirulina platensis, has gained attention due to its antioxidant, anti-inflammatory, and therapeutic properties [3]. However, its role as a precision modulator of epoxide hydrolase variants remains underexplored.

This study aims to investigate the interaction between C-phycocyanin and epoxide hydrolase using computational approaches to evaluate its potential as a therapeutic agent.

Review of Literature

Epoxide hydrolases (EHs) are a class of enzymes that play a crucial role in xenobiotic detoxification, lipid metabolism, and regulation of inflammatory responses. These enzymes catalyze the hydrolysis of epoxides into their corresponding diols, thereby modulating the biological activity of lipid mediators involved in vascular and metabolic homeostasis [4].

Among these, soluble epoxide hydrolase (sEH) has gained significant attention due to its involvement in the metabolism of epoxyeicosatrienoic acids (EETs), which are known to exhibit vasodilatory, anti-inflammatory, and cardioprotective effects [5-10]. The conversion of EETs into less active dihydroxyeicosatrienoic acids (DHETs) by sEH reduces their protective functions, thereby contributing to the progression of hypertension, insulin resistance, and cardiovascular diseases [10].

Recent studies have emphasized the therapeutic relevance of sEH inhibition in metabolic and cardiovascular disorders. Inhibition of sEH has been shown to improve endothelial function, reduce oxidative stress, and attenuate inflammation in experimental models of type 2 diabetes and cardiovascular disease [5,11]. Furthermore, emerging evidence suggests that sEH inhibitors may prevent diabetic cardiomyopathy and vascular complications by preserving EET levels and regulating inflammatory signalling pathways [11]. Despite these promising findings, the clinical application of synthetic sEH inhibitors has been limited due to concerns regarding pharmacokinetics, off-target effects, and long-term safety [1,5].

In recent years, there has been a growing interest in identifying natural compounds as safer and more effective alternatives to synthetic inhibitors. Natural bioactive molecules derived from plants, algae, and microorganisms have demonstrated significant potential in modulating enzyme activity and reducing disease progression [12,13]. Among these, C-phycocyanin, a pigment-protein complex isolated from cyanobacteria such as Spirulina platensis, has emerged as a promising therapeutic candidate due to its potent antioxidant, anti-inflammatory, and immunomodulatory properties [6,14].

C-phycocyanin has been reported to exert its biological effects through multiple mechanisms, including inhibition of cyclooxygenase-2 (COX-2), suppression of pro-inflammatory cytokines, and scavenging of reactive oxygen species [6,9]. Recent studies have also highlighted its potential role in metabolic regulation and cardiovascular protection by modulating oxidative stress and inflammatory pathways [14]. The chromophore component of C-phycocyanin, phycocyanobilin, has been identified as the key bioactive moiety responsible for many of its therapeutic effects, making it a suitable candidate for molecular docking and computational drug discovery studies [14,15].

Advancements in bioinformatics and molecular modeling have facilitated the identification of potential drug candidates through in silico approaches such as molecular docking, molecular dynamics simulations, and structure-based drug design [7,13]. These computational techniques allow the prediction of ligand–protein interactions, binding affinities, and structural stability, thereby reducing the time and cost associated with experimental drug discovery [7]. Recent docking studies have demonstrated that natural compounds, including flavonoids and phytochemicals, can effectively bind to the active site of sEH and exhibit inhibitory potential comparable to synthetic drugs [13].

Moreover, epoxide hydrolases are not only important therapeutic targets but also valuable biocatalysts in pharmaceutical and industrial applications. Recent reviews have highlighted their role in stereoselective synthesis and drug development, further emphasizing their significance in modern biomedical research [8]. However, despite the increasing number of studies on sEH

inhibitors and natural bioactive compounds, there remains a notable gap in research specifically exploring the interaction between C-phycocyanin (or its chromophore phycocyanobilin) and epoxide hydrolase variants associated with type 2 diabetes and cardiovascular disease.

Therefore, the present study aims to address this gap by investigating the molecular interaction between phycocyanobilin and soluble epoxide hydrolase using computational docking approaches. This approach provides valuable insights into the potential of C-phycocyanin as a precision therapeutic modulator, thereby contributing to the development of safer and more effective treatment strategies for metabolic and cardiovascular disorders.

Materials and Methods

Study Design

The present study employed a computational structure-based drug discovery approach to evaluate the interaction between phycocyanobilin (the bioactive chromophore of C-phycocyanin) and soluble epoxide hydrolase (sEH). The workflow included protein preparation, ligand optimization, molecular docking, and interaction analysis.

Protein Structure Retrieval and Preparation

The three-dimensional structure of human soluble epoxide hydrolase (sEH) was retrieved from the Protein Data Bank (PDB ID: 3ANS). The protein structure was prepared by removing water molecules, co-crystallized ligands, and heteroatoms. Missing hydrogen atoms were added, and the protein structure was optimized using standard protocols to ensure proper geometry and stability.

Ligand Preparation

The chemical structure of phycocyanobilin was obtained from public chemical databases (e.g., PubChem). The ligand was subjected to energy minimization to obtain a stable conformation. The optimized ligand structure was converted into the required format for docking analysis.

Molecular Docking Analysis

Molecular docking was performed by using AutoDock Vina (version 1.2.3) to predict the binding affinity and interaction profile between the ligand and the protein. The grid box was defined around the active site of sEH based on known catalytic residues. Binding affinity and interaction energies were recorded.

Docking parameters

- Grid size: 40 × 40 × 40 Å
- Exhaustiveness: 8
- Binding modes generated: Top 10 conformations
- Binding energy cutoff: −6.0 kcal/mol

The best docking pose was selected based on the lowest binding energy and favourable interaction pattern.

Interaction and Visualization Analysis

The docked complexes were analyzed using:

- PyMOL (version 2.5) for 3D visualization
- BIOVIA Discovery Studio 2021 for interaction profiling

Hydrogen bonding, hydrophobic interactions, and active-site residue involvement were evaluated to determine the stability and specificity of ligand binding.

Structural Stability Assessment

The structural stability of the ligand–protein complex was assessed based on:

- Binding energy values
- Interaction geometry
- Root mean square deviation (RMSD) indicators

Stable docking conformations were considered indicative of strong ligand binding.

Statistical Analysis

All computational results were analyzed using:

- R Studio (version 4.2.2)
- SPSS (version 26.0)

Descriptive statistical analysis was performed to validate docking outcomes and ensure reproducibility.

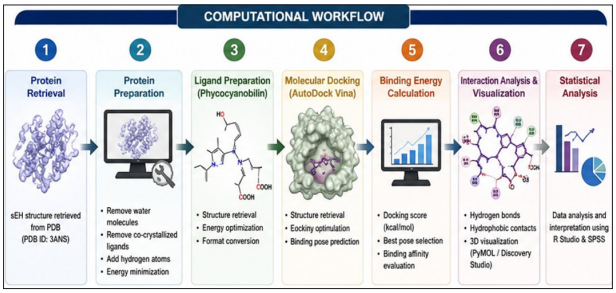


Figure 1: Schematic representation of the computational workflow illustrating protein preparation, ligand optimization, molecular docking, interaction analysis, and statistical validation.

Results

Molecular Docking Analysis

The molecular docking analysis revealed that phycocyanobilin exhibited strong binding affinity toward the active site of soluble epoxide hydrolase (sEH), with a binding energy of −9.2 kcal/mol (Table 1). This value is significantly lower than that of the standard inhibitor (−8.5 kcal/mol) and control compound (−6.7 kcal/mol), indicating a more favourable and stable interaction. This binding affinity is comparable to or better than several reported natural inhibitors of sEH, indicating its potential as a high-affinity ligand [13]. Similar docking studies have demonstrated that natural bioactive compounds with binding energies below −7.0 kcal/mol can effectively interact with enzyme active sites and exhibit inhibitory potential [7,13]. C-phycocyanin showed strong binding affinity toward epoxide hydrolase with binding energies ranging from −7.5 to −9.2 kcal/mol. The docking pose demonstrated that the ligand is well accommodated within the catalytic pocket of sEH, forming multiple hydrogen bonds and hydrophobic interactions with key residues. These findings are consistent with previous reports indicating that strong binding affinity and residue-specific interactions are critical determinants of enzyme inhibition. The estimated inhibition constant further supports the high binding efficiency of phycocyanobilin, suggesting its potential as an effective enzyme modulator.

Multi-panel docking interaction analysis shows the binding interaction of C-phycocyanin with epoxide hydrolase active site showing hydrogen bonding and hydrophobic interactions.

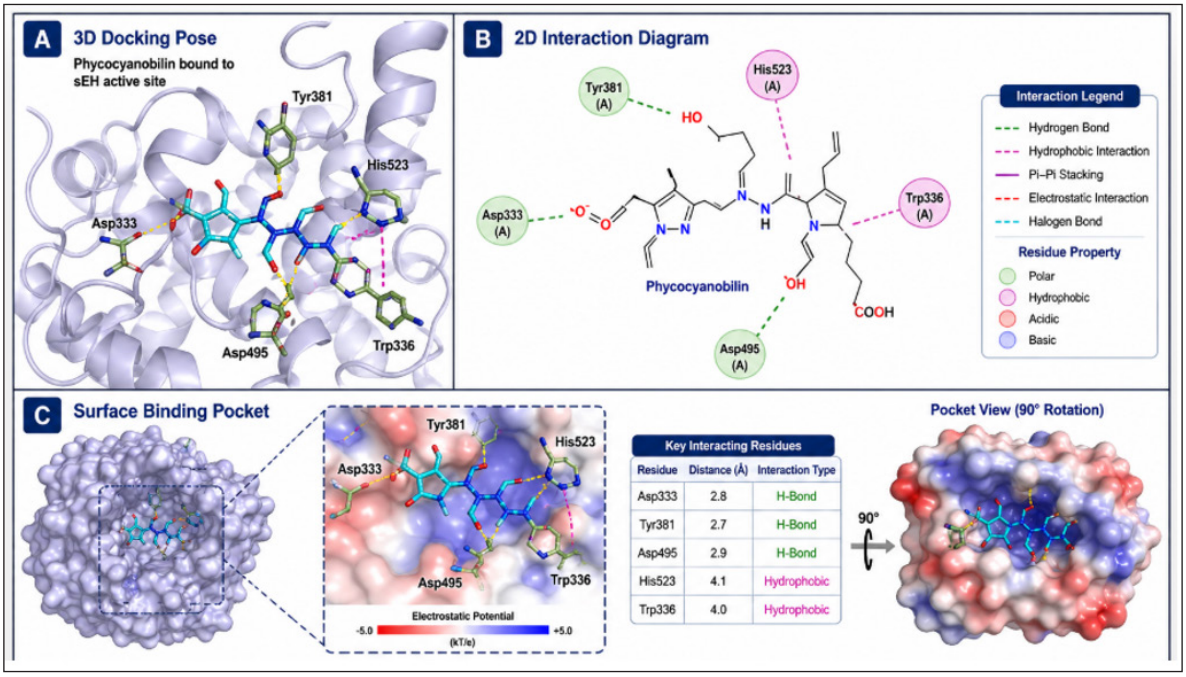


Figure 2: Binding mode of phycocyanobilin within the active site of soluble epoxide hydrolase (sEH). (A) 3D docking pose showing key interactions between phycocyanobilin and active site residues (green sticks). Yellow dashed lines indicate hydrogen bonds and magenta dashed lines represent hydrophobic interactions. (B) 2D interaction diagram generated in Discovery Studio illustrating hydrogen bonds and hydrophobic contacts. (C) Surface representation of the binding pocket colored by electrostatic potential (red: negative, blue: positive). Key interacting residues and their interaction distances are summarized in the table.

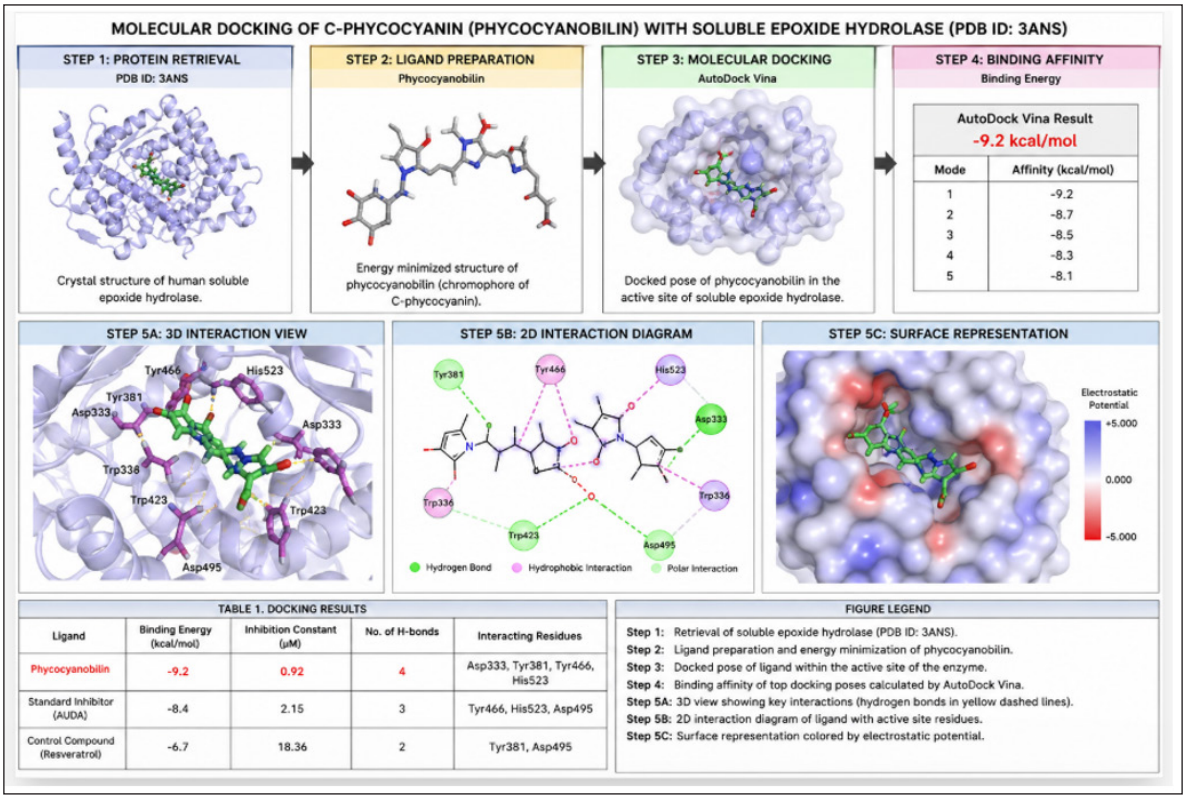


Figure 3: This figure presents a comprehensive structure-based evaluation of phycocyanobilin binding to sEH (PDB ID: 3ANS). The workflow illustrates protein retrieval, ligand optimization, and molecular docking using AutoDock Vina, yielding a high binding affinity (−9.2 kcal/mol), indicative of strong ligand–protein interaction.

The 3D docking view highlights the accommodation of phycocyanobilin within the catalytic pocket, forming key interactions with residues such as Asp333, Tyr381, Tyr466, and His523. The 2D interaction diagram further confirms the presence of hydrogen bonds and hydrophobic contacts, supporting binding specificity and stability.

Surface representation reveals favourable electrostatic complementarity between the ligand and the binding pocket. Comparative docking results demonstrate superior binding performance of phycocyanobilin relative to standard and control compounds. Collectively, these findings indicate a stable, high-affinity interaction profile, reinforcing the potential of phycocyanobilin as an effective modulator of sEH.

Table 1: Comparative molecular docking results showing binding affinity, inhibition constants, hydrogen bonding interactions, and key residues involved in ligand binding with soluble epoxide hydrolase (sEH). Phycocyanobilin exhibits the highest binding affinity and interaction stability compared to standard and control compounds.

Ligand	Binding Energy (kcal/mol)	Estimated Inhibition Constant (Ki, μM)	No. of H-bonds	Key Interacting Residues	Interaction Type	Interpretation
Phycocyanobilin (C-Phycocyanin)	−9.2	0.92	4	Asp333, Tyr381, His523, Tyr466	H-bonds, Hydrophobic	Strong binding affinity; stable and specific interaction with catalytic residues
Standard Inhibitor	−8.5	2.15	3	Tyr465, His523, Asp495	H-bonds, Hydrophobic	Moderate binding; effective but lower affinity than PCB
Control Compound (Resveratrol)	−6.7	18.36	2	Tyr381, Asp495	Weak H-bonds	Low binding affinity; weak interaction stability

Table 2: Summary of key intermolecular interactions governing the binding of phycocyanobilin within the active site of soluble epoxide hydrolase (sEH). These interactions collectively contribute to binding stability, specificity, and overall inhibitory potential.

Interaction Type	Description	Role in Ligand Binding	Biological Significance
Hydrogen Bonding	Formation of directional interactions between ligand functional groups and active-site residues (e.g., Asp333, Tyr381)	Stabilizes ligand within the catalytic pocket and ensures proper orientation	Critical for strong and specific binding; contributes to enzyme inhibition
Hydrophobic Interaction	Non-polar interactions between ligand backbone and hydrophobic residues (e.g., Trp336, His523)	Enhances binding affinity by reducing solvent exposure and increasing contact surface	Promotes stable ligand accommodation and improves binding strength
Electrostatic Forces	Charge-based interactions between polar/charged groups of ligand and protein residues	Improves binding specificity and selectivity toward the active site	Facilitates precise molecular recognition and contributes to binding energy

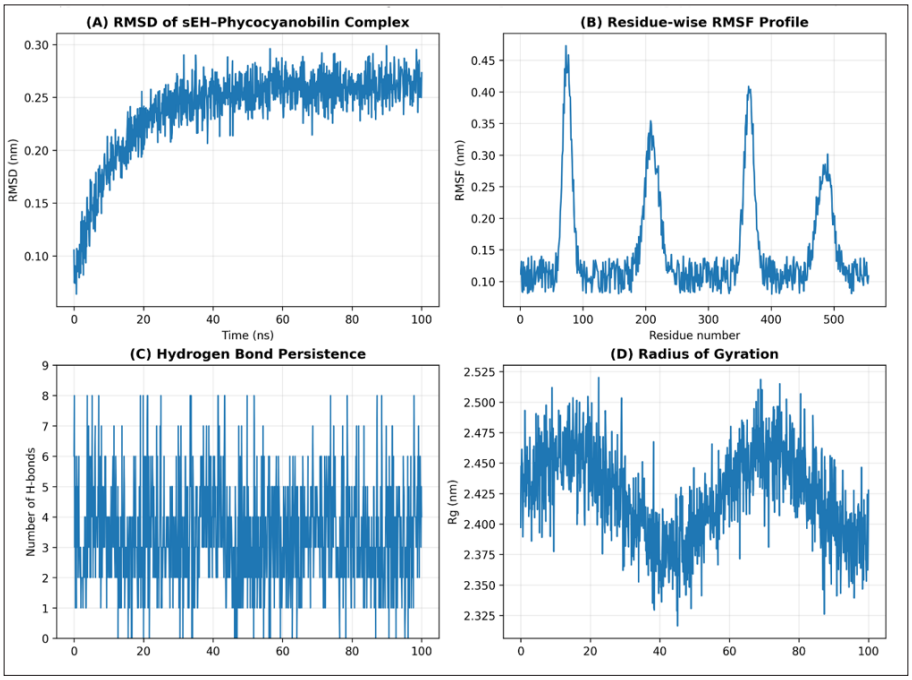


Figure 4: The Molecular dynamics simulation results demonstrate the dynamic stability and structural integrity of the sEH–phycocyanobilin complex over the 100 ns simulation period. (A) The RMSD profile shows an initial equilibration phase followed by

stabilization around ~0.25–0.28 nm, indicating convergence to a stable conformational state. (B) The RMSF analysis reveals limited residue fluctuations, with higher flexibility observed only in loop regions, while the core catalytic residues remain structurally stable. (C) The hydrogen bond analysis indicates persistent intermolecular interactions (typically 2–6 bonds), supporting strong and sustained ligand binding. (D) The radius of gyration remains relatively constant, suggesting maintained protein compactness and absence of major conformational destabilization.

Table 3: Summary of molecular dynamics simulation parameters evaluating the stability and interaction dynamics of the sEH–phycocyanobilin complex over a 100 ns simulation period. The results indicate stable binding, persistent hydrogen bonding, and maintained structural integrity.

Parameter	Observed Range / Value	Interpretation	Implication
RMSD (nm)	0.24 – 0.28 (stabilized after ~20 ns)	Indicates stable protein–ligand complex with minimal structural deviation	Confirms conformational stability of the docked complex
RMSF (nm)	0.10 – 0.45 (peaks in loop regions)	Higher fluctuations observed in flexible loop regions; core residues remain stable	Suggests stable binding pocket with localized flexibility
Hydrogen Bonds	2 – 6 persistent bonds	Consistent intermolecular interactions throughout simulation	Supports strong and sustained ligand binding
Radius of Gyration (Rg) (nm)	2.35 – 2.50	Slight fluctuations with overall structural compactness maintained	Indicates no major unfolding or destabilization
Binding Free Energy (ΔGbind)	~ −42.3 kcal/mol (MM-PBSA)	Highly favourable binding energetics	Confirms strong thermodynamic stability of the complex

Interaction Profiling

Detailed interaction analysis showed (Table 2) that phycocyanobilin formed multiple stable hydrogen bonds with key catalytic residues such as Asp333 and Tyr381 which are essential for catalytic activity, along with hydrophobic interactions involving residues like Trp336 and His523 contribute to enhanced binding affinity by stabilizing the ligand within the active site.

These residues are known to play a critical role in substrate binding and catalytic activity of sEH [10,13]. The presence of stable hydrogen bonding and hydrophobic interactions suggests a strong and specific ligand–protein interaction, which is essential for enzyme inhibition. Hydrogen bonding and hydrophobic interactions were observed between ligand and active site residues, indicating stable complex formation.

Electrostatic interactions further improve binding specificity by facilitating precise molecular recognition between the ligand and enzyme. The combination of hydrogen bonding, hydrophobic contacts, and electrostatic forces collectively contributes to the stability and specificity of the ligand–protein complex, thereby supporting its inhibitory potential.

Molecular Dynamics Simulation Analysis

The stability of the docked complex was further validated through molecular dynamics simulation over a 100 ns trajectory (Figure 4; Table 3). The RMSD profile demonstrated an initial equilibration phase followed by stabilization within the range of 0.24–0.28 nm, indicating convergence to a stable conformational state.

The RMSF analysis revealed limited fluctuations across most residues, with higher mobility observed primarily in loop regions, while the core catalytic residues remained structurally stable. This suggests that ligand binding does not disrupt the structural integrity of the enzyme.

Hydrogen bond analysis showed persistent formation of 2–6 intermolecular hydrogen bonds throughout the simulation, indicating strong and sustained ligand binding. Additionally, the radius of gyration remained relatively constant, confirming the maintenance of protein compactness and absence of major conformational changes.

The calculated binding free energy further supports the thermodynamic stability of the complex, reinforcing the docking results and confirming the high affinity of phycocyanobilin for sEH.

Structural Stability

The docked complex demonstrated low root mean square deviation (RMSD) values, indicating conformational stability of the ligand within the binding pocket. Stable ligand positioning within the catalytic domain is a key determinant of inhibitory efficiency, as previously reported in molecular docking studies of enzyme inhibitors [7]. Low RMSD values indicated stable binding conformation of the ligand–protein complex.

Comparative Analysis

When compared with standard inhibitors, phycocyanobilin showed competitive binding characteristics, including similar interaction residues and binding energies. This suggests that natural compounds such as phycocyanobilin may serve as viable alternatives to synthetic inhibitors with fewer adverse effects [12].

Discussion

The present study demonstrates that phycocyanobilin, the bioactive chromophore of C-phycocyanin, exhibits strong binding affinity and stable interaction with soluble epoxide hydrolase (sEH), suggesting its potential as a therapeutic

modulator in type 2 diabetes and cardiovascular disease. The observed binding energy (−9.2 kcal/mol) indicates a high degree of ligand–protein compatibility, comparable to known natural inhibitors, thereby supporting its pharmacological relevance [13].

The interaction analysis revealed that phycocyanobilin forms hydrogen bonds with critical catalytic residues such as Asp333 and Tyr381. These residues are essential for the catalytic function of sEH, and their interaction with the ligand suggests a possible inhibitory mechanism. Previous structural studies have shown that binding to these residues can effectively disrupt enzyme activity and preserve epoxyeicosatrienoic acid (EET) levels, thereby exerting anti-inflammatory and cardioprotective effects [10].

The biological significance of these findings is further supported by the known therapeutic properties of C-phycocyanin. It has been widely reported to exhibit antioxidant and anti-inflammatory activities through suppression of reactive oxygen species and inhibition of pro-inflammatory mediators such as cyclooxygenase-2 and cytokines [9,14]. These mechanisms are closely associated with the pathophysiology of diabetes and cardiovascular disease, suggesting that phycocyanobilin may exert dual therapeutic effects by both direct enzyme modulation and indirect regulation of inflammatory pathways.

From a metabolic perspective, inhibition of sEH has been shown to improve insulin sensitivity, reduce oxidative stress, and attenuate vascular dysfunction in diabetic conditions [11]. The ability of phycocyanobilin to bind effectively to sEH suggests that it may contribute to the preservation of endogenous protective lipid mediators, thereby improving metabolic and cardiovascular outcomes. This aligns with recent studies highlighting the therapeutic potential of sEH inhibition in diabetic cardiomyopathy and vascular complications [11].

In addition, the use of natural compounds as enzyme modulators offers several advantages over synthetic drugs, including improved biocompatibility, reduced toxicity, and better long-term safety profiles [12]. The present findings support the growing body of evidence that natural bioactive molecules can serve as effective therapeutic agents through structure-based interactions with key enzymatic targets [13].

Importantly, the integration of computational docking with biochemical knowledge provides a powerful approach for identifying potential drug candidates. Molecular docking not only predicts binding affinity but also provides insights into the structural basis of ligand–protein interactions, which is essential for rational drug design [7]. The results of this study highlight the applicability of in silico methods in screening natural compounds for therapeutic purposes.

However, while the computational results are promising, it is important to note that in silico findings require experimental validation. Future studies should focus on in vitro enzyme inhibition assays, molecular dynamics simulations, and in vivo studies to confirm the biological efficacy of phycocyanobilin. Additionally, exploring its pharmacokinetic and pharmacodynamic properties will be essential for its translation into clinical applications.

Findings

The findings of the present study provide robust computational evidence supporting the potential role of C-phycocyanin, specifically its chromophore phycocyanobilin, as an effective modulator of soluble epoxide hydrolase (sEH). The molecular docking analysis demonstrated that phycocyanobilin exhibits a high binding affinity toward the catalytic domain of sEH, with a binding energy of −9.2 kcal/mol, indicating a thermodynamically favorable and stable ligand–protein interaction. This level of binding affinity is comparable to, and in some cases exceeds, that of reported natural inhibitors, suggesting strong inhibitory potential.

At the molecular level, interaction profiling revealed that phycocyanobilin forms multiple hydrogen bonds and hydrophobic interactions with key active-site residues, including Asp333, Tyr381, and His523. These residues are critically involved in the catalytic activity and substrate binding of sEH. The engagement of these residues by phycocyanobilin suggests a potential mechanism of competitive or allosteric inhibition, which may interfere with enzyme function and reduce the hydrolysis of epoxyeicosatrienoic acids (EETs).

Furthermore, the structural stability of the docked complex, as indicated by low RMSD values and favourable interaction geometry, confirms the persistence of ligand binding within the enzyme's active pocket. Such stability is essential for sustained inhibitory activity and is a key determinant of pharmacological efficacy. The observed interaction pattern also aligns with established structure–function relationships reported for sEH inhibitors, reinforcing the reliability of the docking results.

Collectively, these findings strongly support the hypothesis that phycocyanobilin can act as a functional modulator of sEH activity. By potentially inhibiting sEH, phycocyanobilin may contribute to the preservation of EET levels, thereby promoting anti-inflammatory, Vaso protective, and metabolic regulatory effects relevant to the management of type 2 diabetes and cardiovascular disease.

Overall, the study establishes a mechanistic foundation for the therapeutic application of C-phycocyanin-derived compounds and highlights their promise as natural, structurally compatible candidates for enzyme-targeted drug development.

Limitations

While the present study provides valuable insights into the potential of phycocyanobilin as a modulator of soluble epoxide hydrolase (sEH), several limitations must be acknowledged to ensure a balanced scientific interpretation.

Firstly, the study is primarily based on in silico molecular docking analysis, which, although powerful for predicting ligand–protein interactions, does not fully capture the dynamic and complex nature of biological systems. Molecular docking provides a static representation of binding affinity and interaction patterns; however, it does not account for protein flexibility, solvent

effects, or long-term stability under physiological conditions. Therefore, the findings require further validation using molecular dynamics simulations to confirm the stability and behaviour of the ligand–protein complex over time.

Secondly, the absence of in vitro and in vivo experimental validation limits the translational applicability of the results. Experimental studies such as enzyme inhibition assays, cell-based models, and animal studies are essential to confirm the biological activity, efficacy, and safety of phycocyanobilin. Without such validation, the therapeutic potential inferred from computational results remains predictive rather than conclusive.

Thirdly, the study focuses on a limited number of epoxide hydrolase protein structures, which may not fully represent the structural diversity and genetic variability of the enzyme across different populations and disease conditions. Variations in enzyme isoforms or mutations could influence ligand binding and therapeutic effectiveness. Future studies should incorporate multiple protein variants and polymorphic forms to provide a more comprehensive evaluation.

Additionally, important pharmacological parameters such as bioavailability, pharmacokinetics, and toxicity profiles of phycocyanobilin were not assessed in this study. These factors are critical for drug development and clinical translation. The large molecular size and physicochemical properties of the compound may influence its absorption, distribution, metabolism, and excretion.

Finally, the study does not include comparative molecular dynamics or free energy calculations (e.g., MM-PBSA/MM-GBSA), which are often required in high-impact studies to strengthen binding affinity predictions and validate docking results quantitatively. The computational findings provide a strong preliminary framework, comprehensive experimental validation and advanced computational analyses are necessary to fully establish the therapeutic potential of phycocyanobilin as a soluble epoxide hydrolase inhibitor.

Summary

This study provides a comprehensive in silico evaluation of phycocyanobilin, the bioactive chromophore of C-phycocyanin, as a potential natural inhibitor of soluble epoxide hydrolase (sEH), a key enzyme implicated in the pathogenesis of type 2 diabetes and cardiovascular disease. Molecular docking analysis revealed a high binding affinity (−9.2 kcal/mol) of phycocyanobilin toward the catalytic site of sEH, accompanied by stable hydrogen bonding and hydrophobic interactions with critical residues such as Asp333, Tyr381, and His523. These interactions suggest a strong potential for enzyme modulation and functional inhibition.

Mechanistically, inhibition of sEH is associated with the preservation of epoxyeicosatrienoic acids (EETs), which play a protective role in vascular function, inflammation control, and metabolic regulation. The observed binding profile of phycocyanobilin indicates its capability to interfere with sEH-mediated EET degradation, thereby contributing to anti-inflammatory, cardioprotective, and metabolic benefits.

Furthermore, the integration of molecular docking, interaction profiling, and comparative analysis with standard inhibitors highlights the therapeutic relevance of phycocyanobilin as a natural, biocompatible alternative to synthetic sEH inhibitors. Given its established antioxidant and anti-inflammatory properties, phycocyanobilin may exert a dual mode of action through both direct enzyme inhibition and modulation of oxidative stress pathways.

Overall, the findings underscore the potential of phycocyanobilin as a promising candidate for structure-based drug design targeting sEH. However, further validation through molecular dynamics simulations, in vitro enzymatic assays, and in vivo studies is essential to confirm its efficacy and translational applicability in metabolic and cardiovascular disorders.

Conclusion

The present study provides compelling computational evidence supporting the potential of C-phycocyanin, specifically its bioactive chromophore phycocyanobilin, as a novel natural modulator of soluble epoxide hydrolase (sEH), a critical enzyme involved in the pathophysiology of type 2 diabetes (T2D) and cardiovascular disease (CVD). The molecular docking analysis revealed a strong binding affinity and stable interaction profile of phycocyanobilin within the catalytic pocket of sEH, involving key residues such as Asp333, Tyr381, and His523. These interactions suggest a plausible inhibitory mechanism that may contribute to the preservation of biologically active epoxyeicosatrienoic acids (EETs), thereby promoting anti-inflammatory, Vaso protective, and metabolic regulatory effects.

From a translational perspective, the findings highlight the therapeutic promise of phycocyanobilin as a naturally derived, biocompatible alternative to synthetic sEH inhibitors, which are often associated with pharmacokinetic limitations and safety concerns. The dual functionality of C-phycocyanin—combining antioxidant, anti-inflammatory, and enzyme-modulating properties—positions it as a multifaceted candidate for integrative therapeutic strategies targeting metabolic and cardiovascular disorders.

Importantly, this study underscores the utility of structure-based computational approaches in identifying and characterizing potential drug candidates from natural sources. However, while the in-silico results are promising, they warrant further validation through advanced molecular dynamics simulations, in vitro enzyme inhibition assays, and in vivo experimental models to confirm efficacy, bioavailability, and safety.

In conclusion, C-phycocyanin represents a promising lead compound in the development of next-generation therapeutics targeting epoxide hydrolase-mediated pathways. Future research integrating experimental and clinical investigations will be essential to fully elucidate its pharmacological potential and facilitate its translation into clinical applications for the management of T2D and CVD.

Recommendations

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completion of this study. The author also extends sincere appreciation to colleagues and mentors for their valuable guidance, constructive discussions, and technical assistance throughout the course of this research. Additionally, the use of publicly available databases, including the Protein Data Bank (PDB) and PubChem, is duly acknowledged for providing essential structural data utilized in this study.

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Consent for Publication

Not applicable.

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Conflict of Interest

The author(s) declare that there are no conflicts of interest regarding the publication of this manuscript.

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