Research Article

Cissus quadrangularis Phytosomes' Bioactivity Assessment: Cytotoxic, Anti-Inflammatory and Antioxidant Properties

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ABSTRACT

Aim: *Cissus quadrangularis* is a widely used medicinal plant known for its therapeutic properties, including bone repair and anti-inflammatory effects. Phytosomes, a novel drug delivery system, can enhance the bioavailability of herbal compounds. This study investigates the antioxidant, anti-inflammatory and cytotoxic activities of *Cissus quadrangularis* phytosomes and explores their molecular binding interactions. **Materials and Methods:** Molecular docking was conducted to evaluate the binding affinity of cholesterin with target 1CVU using the Schrödinger software. Antioxidant activity was assessed by DPPH and nitric oxide scavenging assays. The anti-inflammatory potential was evaluated using protein denaturation and proteinase inhibitory assays. Cytotoxicity was determined by MTT assay on RAW 264.7 cells. **Results:** Molecular docking revealed a strong binding affinity of cholesterin to the 1CVU target (ΔGcf-8.4 kcal/mol). Phytosomes demonstrated significant antioxidant activity, with DPPH inhibition reaching 95.50% at 1000 µg/mL and nitric oxide scavenging achieving 98.59% inhibition. Anti-inflammatory assays showed a dose-dependent inhibition of protein denaturation (up to 96.3%) and proteinase inhibition (96.3%) at 1000 µg/mL. The cytotoxicity assay indicated a concentration-dependent decrease in cell viability, suggesting potential therapeutic applications. **Conclusion:** The results highlight *Cissus quadrangularis* phytosomes as effective antioxidant and anti-inflammatory agents with significant cytotoxic potential. These findings support their potential therapeutic application in managing oxidative stress and inflammation. Further *in vivo* studies are warranted to confirm these results.

Keywords: Anti- inflammatory activity, Antioxidant, Beta sitosterol, *Cissus quadrangularis Cissus quadrangularis* Phytosomes, Inflammation, RAW 26.7 cells.

INTRODUCTION

Across the tropical world, *Cissus quadrangularis* is a perennial herb with therapeutic qualities. In India, it is one of the most widely utilized medicinal plants. The plant is said to be indigenous to West Africa, Java, Malaysia, Sri Lanka and India. The phytochemical composition, pharmacological actions and toxicological assessment of this plant are investigated. Bone repair is one of its uses.[1] This plant is recommended by Ayurveda for a number of medical conditions. Synonym for *Cissus quadrangularis* is *Cissus succulent*, commonly referred to as pirandai in Tamil and horjora in Hindi, is a member of the Vitaceae family. In tropical forest regions of Asia and Africa, the plant is commonly observed.[2] Our earlier studies[3] have laid the groundwork for comprehending the advantages of *Cissus* by highlighting its initial biological activity and phytochemical makeup. This follow-up research aims

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to produce phytosome formulation and better elucidate the efficacy of Cissus quadrangularis.

Recently, dosage formulations called phytosomes (phytophospholipid complex) have been developed to improve the stability and therapeutic impact of herbal medication. At the moment, phytochemicals found in bioactive herbs are thought to be the greatest treatments for long-term illnesses. Enhancing the stability and bioavailability of the bioactive components of plant-based medicines is a viable strategy to boost their effectiveness. Phospholipids are the active element in phytosomes, which exploit their amphiphilic qualities to preserve and solubilize plant extracts. Phospholipids' special qualities in drug delivery and their application in herbal remedies to increase bioavailability lead to noticeably greater health advantages. The current condition of drug delivery can be changed and revolutionized with the advent of phytosome nanotechnology.[4] This research articles covers a comprehensive analysis of the molecular docking, *In vitro* anti-inflammatory, In vitro antioxidant and MTT assay of *Cissus quadrangularis* on the suppression of pro-inflammatory mediators in RAW 264.7 cells for the phytosomes synthesized before.

MATERIALS AND METHODS

Chemicals required

The chemicals required included Beta-sitosterol (Merck Pvt, India), Ascorbic acid, sodium nitroprusside, bovine albumin, phosphate buffered saline, trypsin, tris-HCL buffer, methanol, casein, sodium borate buffer, lipoxygenase, linoleic acid, MTT reagent, DMSO were purchased from (SRL Pvt, India0).

Molecular docking

Molecular dynamics (MD) simulation

Molecular Dynamics (MD) simulations were performed using Desmond 2020.1 from Schrödinger, LLC, focusing on the 1CVU protein and its complex with Cholesterin. Simulations were conducted at 27°C with the OPLS-2005 force field and an explicit solvent model utilizing SPC water molecules within a periodic boundary solvation box of dimensions 10 Å x 10 Å x 10 Å.[5] To mimic physiological conditions, Na+ ions were added to neutralize the system's charge and a 0.15 M NaCl solution was included. The system was initially equilibrated using an NVT ensemble for 10 ns to stabilize the protein-ligand complexes. This was followed by further equilibration and minimization using an NPT ensemble for 12 ns. The Nose-Hoover chain coupling scheme was employed for the NPT ensemble with a relaxation time of 1.0 ps, maintaining the temperature and a pressure of 1 bar across all simulations. The time step for these simulations was set to 2 fs. Pressure control was managed using the Martyna-Tobias-Klein method; incorporating a relaxation time of 2 ps. Long-range electrostatic interactions were calculated using the particle mesh Ewald method with a 9 Å cutoff for Coulomb interactions. The RESPA integrator was employed with a 2 fs time step to handle bonded forces. The final production run extended to 100 ns. Stability of the MD simulations was monitored by calculating the Root Mean Square Deviation (RMSD), Root Mean Square Fluctuation (RMSF), Radius of gyration (Rg) and Solvent-Accessible Surface Area (SASA).

Binding Free Energy Analysis

Binding free energies of the ligand-protein complexes were analyzed using the Molecular Mechanics Generalized Born Surface Area (MM-GBSA) method. The Python script thermal_mmgbsa.py was utilized to compute the Prime MM-GBSA binding free energy over the last 50 frames of the simulation trajectory, with a 1-step sampling size. The additivity principle was employed to estimate the binding free energy of Prime MM-GBSA (kcal/mol). This involved summing individual energy components, including Coulombic interactions, hydrogen bonds, van der Waals forces, covalent interactions, self-contact, protein solvation, lipophilic interactions and ligand solvation.[6,7] The equation used to calculate ΔG_{bind} is as follows:

$$\Delta G_{bind} = \Delta G_{MM} + \Delta G_{solv} - \Delta G_{SA}$$

Where,

ΔG_{bind} represents the binding free energy,

ΔG_{MM} denotes the difference between the free energies of ligand-protein complexes and total energies of protein and ligand in their isolated form.

Characterization of standard Beta-sitosterol (Merck Pvt, India)

UV-Vis spectroscopy scanning

A beta-sitosterol solution (1 mg in 10 mL ethanol) was scanned from 200–800 nm using a UV-Vis spectrophotometer to identify the characteristic peak around 200-300 nm.[8]

Calibration curve for the standard Beta-sitosterol

A calibration curve for beta-sitosterol at 220 nm was created by measuring the absorbance of standard ethanol solutions (0-12 µg/mL) using a UV-Vis spectrophotometer. The unknown concentration of

Cissus quadrangularis phytosomes was then determined by comparing its absorbance to the calibration curve.

In vitro Antioxidant activity for the synthesised CQ phytosomes

DPPH Assay

Standard ascorbic acid and *Cissus quadrangularis* phytosome were made at different concentrations separately. DPPH were combined and after 30 min of dark incubation at room temperature, the samples were examined in a UV spectrophotometer at 517 nm. A graph was developed once the scavenging activity was estimated.

Nitric Oxide Scavenging

The standard ascorbic acid and phytosome concentrations (100, 200, 400, 800and 1000 µg/mL) were made separately and mixed with sodium nitroprusside (10 mM in phosphate-buffered saline) and incubated for 4 hr at 37ºC. After the incubation period, 0.5 mL of Griess reagent was added and the absorbance at 546 nm was determined. The graph was drawn.[9]

Anti-inflammatory activity for the synthesised CQ phytosomes

Protein Denaturation Assay

Using the adjustments outlined by Gunathilake *et al*.,[10] the protein denaturation assay was carried out. 0.02 mL of *Cissus quadrangularis* extract, 4.78 mL of phosphate buffered saline (PBS, pH 6.4) and 0.2 mL of 1% bovine albumin made up the reaction mixture (5 mL). After 15 min of incubation at 37ºC in a water bath, the mixture was heated to 70ºC for five min. Using a UV/VIS spectrometer, turbidity was measured at 660 nm after cooling.[11] Using the following formula, the percentage inhibition of protein denaturation was determined:

$$\%\ Inhibition\ of\ denatureation = 100\ X\ (1-\frac{A2}{A1})$$

A1 is Absorption of control, A2 is the absorption of the test.

Proteinase Inhibitory Activity

With few modifications, Sakat *et al*.'s[12] technique was used to measure proteinase inhibitory activity. 1 mL of 20 mL of Tris-HCl buffer (pH 7.4), 1 mL of the test sample (0.02 mL of *Cissus quadrangularis* extract in 0.980 mL of methanol) made up the reaction solution (2 mL). After 5 min of incubation at 37ºC, 1 mL of 0.8% (w/v) casein was added and the mixture was left to incubate for an additional 20 min. The addition of 2 mL of 70% perchloric acid stopped the process. The supernatant's absorbance was measured at 210 nm following centrifugation. Using the following formula, the percentage inhibition of protein denaturation was determined:

$$\%\ Inhibition\ of\ denatureation = 100\ X\ (1-\frac{A2}{A1})$$

A1 is Absorption of control; A2 is the absorption of the test.

Lipoxygenase Inhibition Assay

After making several adjustments, the lipoxygenase inhibition activity was determined using Wu's technique. For 5 min at room temperature (30±2ºC), a mixture of lipoxygenase (10 µL, 8000 U/mL) and sodium borate buffer (1 mL, 0.1 M, pH 8.8) was incubated with 10 mL of *Cissus quadrangularis* extract in a 1 mL cuvette. Ten microliters of linoleic acid substrate (10 mmol) were added to start the reaction. At 234 nm, absorbance was observed. Calculating the % inhibition required the use of.[10]

$$\%\ Inhibition = \frac{(Absorbance\ of\ the\ control - absorbance\ of\ the\ sample)}{(absorbance\ of\ the\ control)} = 100\ X$$

MTT assay for the synthesised CQ phytosomes

In triplicate, RAW264.7 cells (2×105/well) were seeded onto 96-well plates. Following a 24 hr incubation period in the presence of *Cissus quadrangularis* phytosomes (0, 10, 20, 40, 60, 80 and 100) were introduced. After the treatment, 4 hr were spent incubating 20 µL of MTT reagent (5 mg/mL). Formazan crystals were dissolved in 150 µL of DMSO. At 570 nm, absorbance was measured and cell viability was estimated with control cells.[13,14]

RESULTS

Docking studies

The molecular docking study between cholesterin and the 1CVU protein revealed a significant binding interaction, with a binding free energy of ΔG = –8.4 kcal/mol (Table 1). The docking poses and the interactions are illustrated in Figure 1, showing the molecular surface and the interaction of cholesterin with key residues such as Val291, Phe210 and Leu391.

Molecular Dynamics Simulation

To further evaluate the stability and convergence of the 1CVU protein complexed with cholesterin, Molecular Dynamics (MD) simulations were conducted. As depicted in Figure 2A, the Root Mean Square Deviation (RMSD) of the Cα-backbone stabilized at approximately 2.4 Å, indicating a stable protein conformation. The

ligand, cholesterin, demonstrated an RMSD value of approximately 8 Å, signifying adequate convergence. Furthermore, the Radius of gyration (Rg) indicated a decrease in protein compactness, from 24.0 Å to 24.2 Å, upon ligand binding (Figure 2C). This reduction in compactness further supports the formation of a highly compact protein-ligand complex. A stable hydrogen bond between the protein and cholesterin was also observed throughout the simulation (Figure 2D), reinforcing the stability of the complex.

Molecular Mechanics Generalized Born Surface Area (MM-GBSA) calculations

To quantify the binding free energy and additional energetic contributions, the Molecular Mechanics Generalized Born Surface Area (MM-GBSA) method was utilized. The results indicated that the stability of the 1CVU-cholesterin complex was primarily driven by favorable Coulombic interactions (ΔGbindCoulomb), van der Waals interactions (ΔGbindvdW) and lipophilic interactions (ΔGbindLipo). In contrast, ΔGbindCovalent and ΔGbindSolvGB contributed to destabilizing the complex. Table 2 summarizes these findings, demonstrating that the binding free energy. The 1CVU-cholesterin complex was notably high, signifying a strong binding affinity and stability of the complex. This suggests that cholesterin is a highly effective ligand for 1CVU, potentially facilitating stable molecular interactions critical for its biological function.

Table 1: *Cissus quadrangularis Binding Affinity.*

Ligand	Binding Affinity (kcal/mol)
6RMJ-M_BetaAmyrone	–6.5
6RMJ-M_BetaSitosterolacetate	–5.9
6RMJ-M_Cholesterin	–6.1
6RMJ-M_Prednisolone	–6.1
1CVU-M_BetaAmyrone	–8.2
1CVU-M_BetaSitosterolacetate	–7.4
1CVU-M_Cholesterin	–8.4
1CVU-M_Prednisolone	–8.3

Characterization of standard Beta-sitosterol

UV-Vis spectroscopy scanning

The UV-Vis spectrophotometric analysis of the beta-sitosterol standard was carried out within the wavelength range of 200-800 nm to assess its optical properties. A distinct absorption peak was detected at approximately 220 nm, correlating with the characteristic peak of beta-sitosterol as identified by previous studies (Wei *et al*., 2010).[8] Shah *et al*. (2010)[15] also reported the absorption peak of beta-sitosterol to be around 202 nm in ethanol, which serves as a reference for this analysis. These results confirm the presence of beta-sitosterol in the sample through the observed spectral peaks (Figure 3). The absorbance data were used for subsequent calibration curve development.

Calibration Curve for the standard Beta-sitosterol

A calibration curve for beta-sitosterol at 220 nm was established by preparing a series of standard solutions

Table 2: Binding free energy components for the 1CVU+Cholesterin calculated from MM-GBSA.

Energies (kcal/mol)	1CVU+Cholesterin
ΔG_{bind}	–45.31
ΔG_{bind}Lipo	–25.60
ΔG_{bind}vdW	–46.69
ΔG_{bind}Coulomb	–0.39
ΔG_{bind}SolvGB	25.66
ΔG_{bind}Covalent	1.71

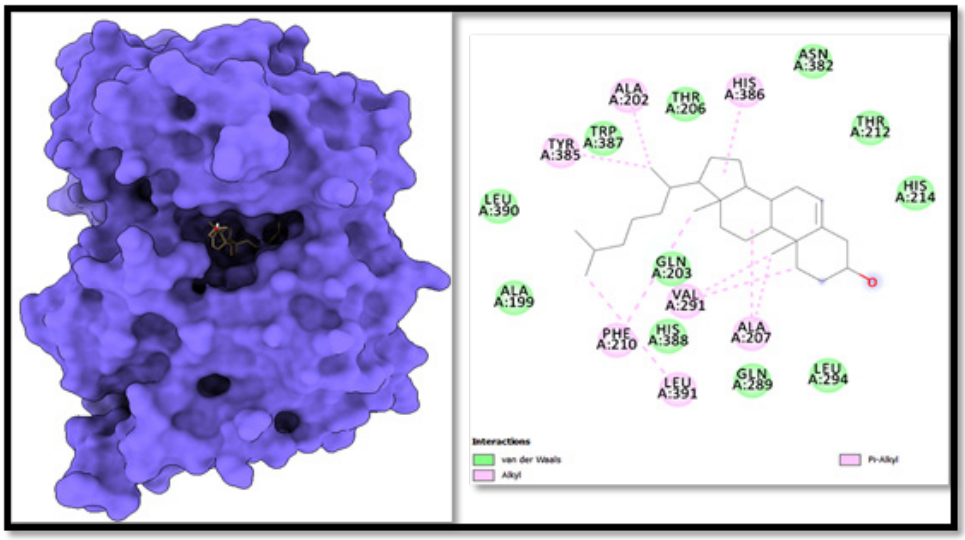

Figure 1: Surface view of the best pose of 1CVU with Cholesterin complex is displaying the surface view on the left panel and 2D interaction profile of the ligand with binding cavity residues.

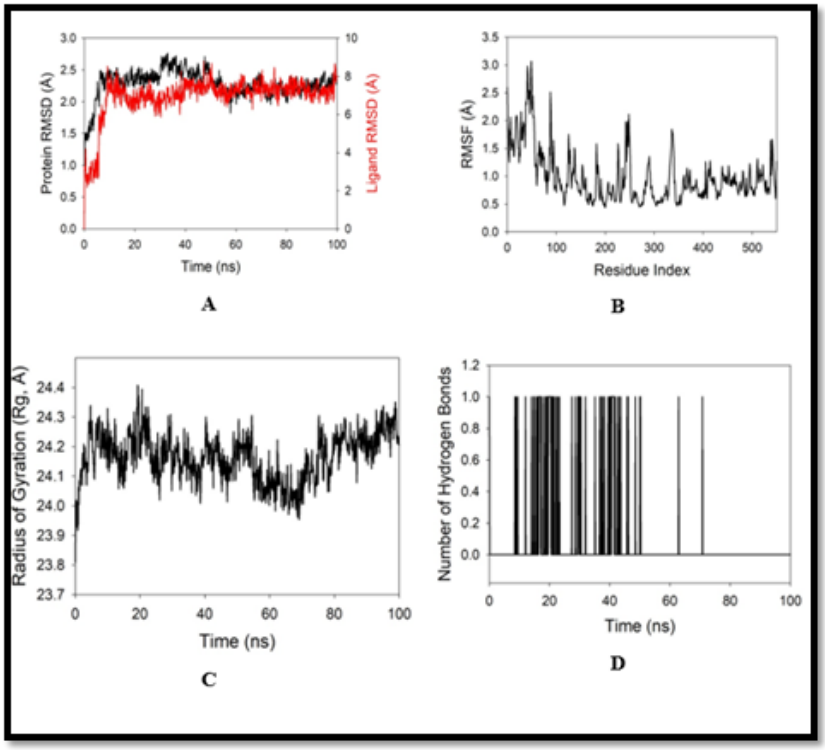

Figure 2: ***MD simulation analysis of 100 ns trajectories of (A) Cα backbone RMSD of 1CVU+Cholesterin, (B) RMSF of Cα backbone of 1CVU+Cholesterin (C) Cα backbone radius of gyration (Rg) of 1CVU+Cholesterin. (D) Number of hydrogen bonds formed between 1CVU and Cholesterin.***

at concentrations of 0, 2, 4, 6, 8, 10 and 12 µg/mL. The absorbance for each solution was measured using a UV-Vis spectrophotometer and the linear regression analysis provided a highly correlated curve with an R^2 value of 0.999 (Figure 4). This curve was subsequently used to calculate the unknown concentrations of beta-sitosterol in the *Cissus quadrangularis* phytosome samples. The absorbance values of the phytosome samples were measured at 220 nm and the corresponding concentrations were extrapolated using the linear regression equation derived from the standard calibration curve.

In vitro antioxidant for the synthesised CQ phytosomes

DPPH Antioxidant Activity

The antioxidant activity of the synthesized *Cissus quadrangularis* (CQ) phytosomes was evaluated using the DPPH radical scavenging assay. The results demonstrated a dose-dependent increase in free radical scavenging activity, with inhibition rates ranging from 82.27% at 200 µg/mL to 95.50% at 1000 µg/mL (Figure 5). This significant antioxidant activity, comparable to the standard antioxidant, highlights the potential of CQ phytosomes in mitigating oxidative stress and their therapeutic implications for managing oxidative stress-related diseases.

Nitric oxide scavenging- *Cissus quadrangularis* phytosomes

The nitric oxide scavenging activity of *Cissus quadrangularis* phytosomes was assessed, revealing a dose-dependent inhibition, with activity increasing from 70.89% at 100 µg/mL to 98.59% at 1000 µg/mL (Figure 6). This potent nitric oxide scavenging effect, closely mirroring the standard antioxidant, underscores the effectiveness of CQ phytosomes in neutralizing reactive nitrogen species and their potential use in treating conditions related to oxidative stress and inflammation.

Anti-inflammatory activity for the synthesised phytosomes

Protein denaturation

The anti-inflammatory potential of *Cissus quadrangularis* phytosomes was assessed through a protein denaturation inhibition assay. The results exhibited a dose-dependent inhibition of protein denaturation, with inhibition increasing from 72.5% at 100 µg/mL to 96.3% at 1000 µg/mL (Figure 7). These findings suggest that *Cissus quadrangularis* phytosomes have substantial anti-

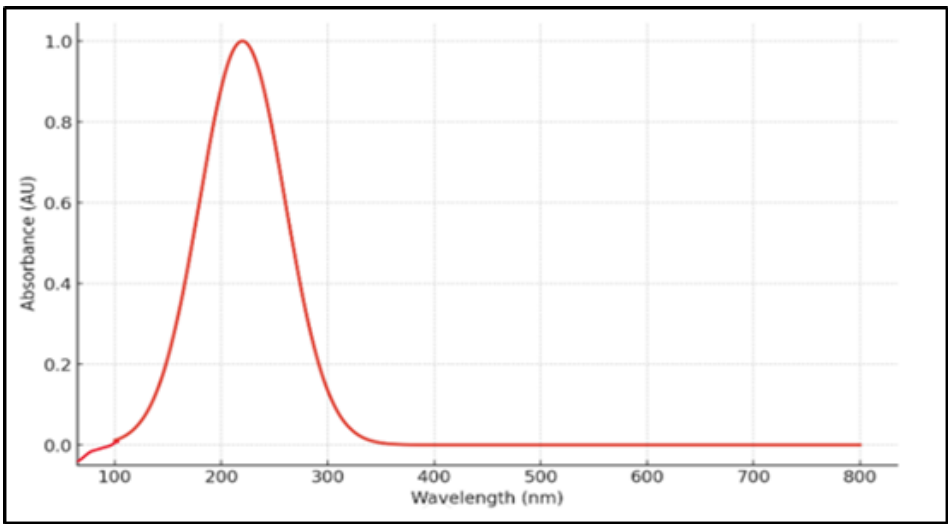

Figure 3: UV- Vis Spectra of Standard Beta-sitosterol at 220 nm.

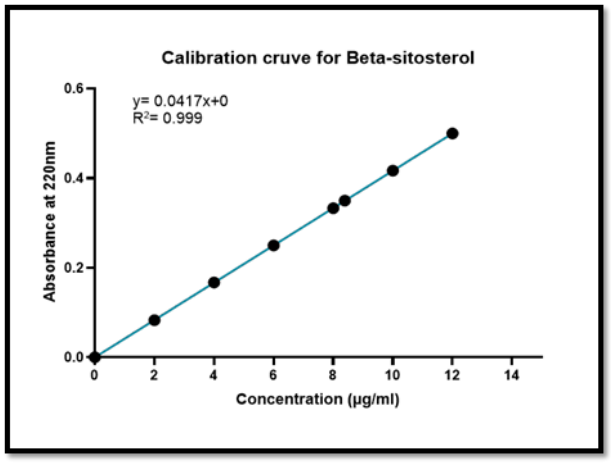

Figure 4: Calibration Curve for the standard Beta-sitosterol at 220 nm.

inflammatory properties, making them promising candidates for therapeutic applications where protein denaturation plays a key role in disease pathology, such as rheumatoid arthritis.

Proteinase Inhibitory Activity

The proteinase inhibitory activity of *Cissus quadrangularis* phytosomes was evaluated, showing a similar dose-dependent effect. The inhibition of proteinase activity ranged from 72.5% at 100 µg/mL to 96.3% at 1000 µg/mL (Figure 8). These results demonstrate that CQ phytosomes are effective in inhibiting proteinase enzymes, which are involved in the inflammatory response, further supporting their potential as anti-inflammatory agents.

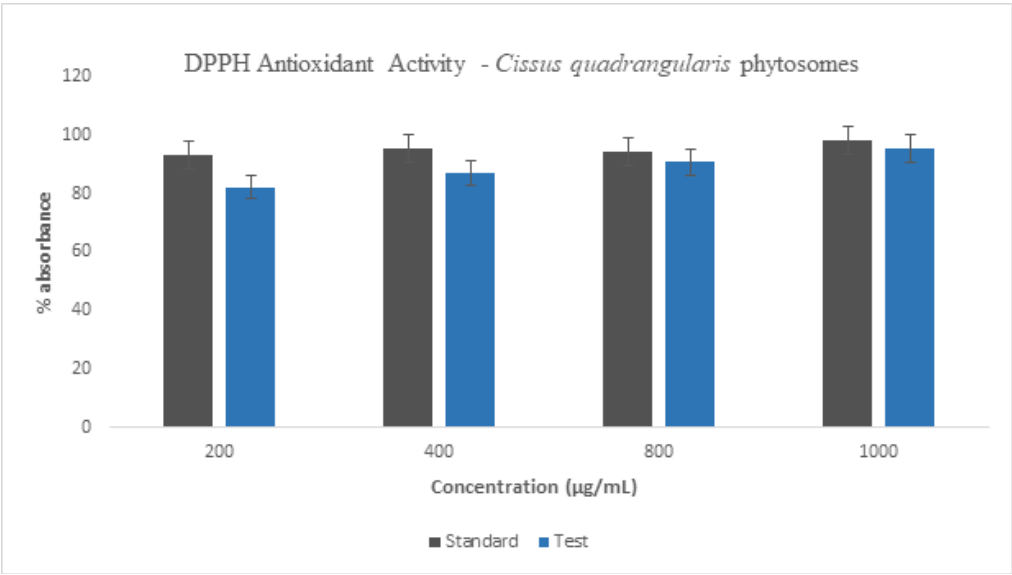

Figure 5: DPPH Antioxidant Activity - Cissus quadrangularis phytosomes.

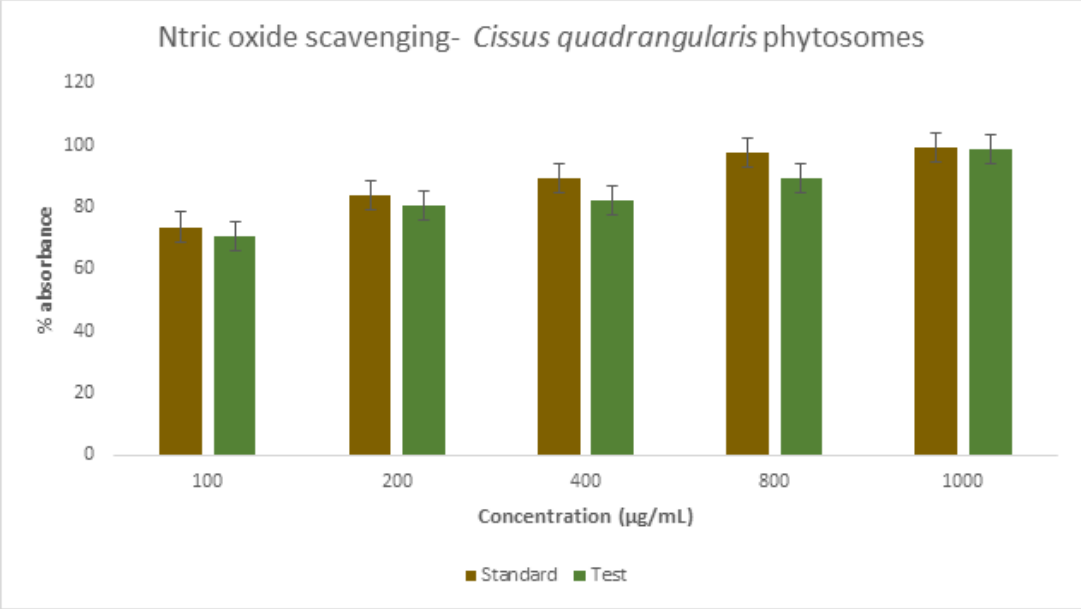

Figure 6: Nitric oxide scavenging-Cissus quadrangularis phytosomes.

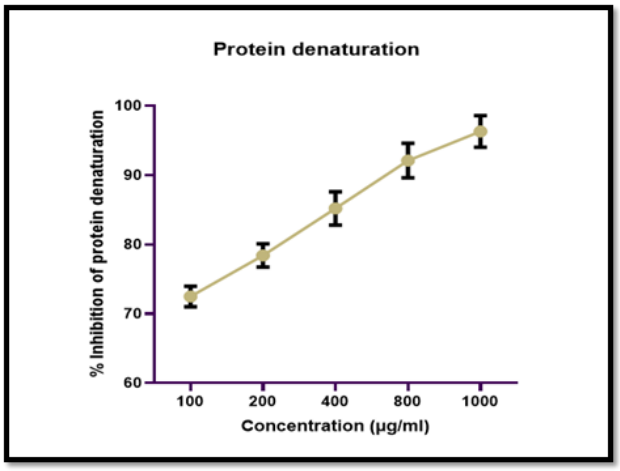

Figure 7: Protein denaturation of Synthesized *Cissus quadrangularis* Phytosome.

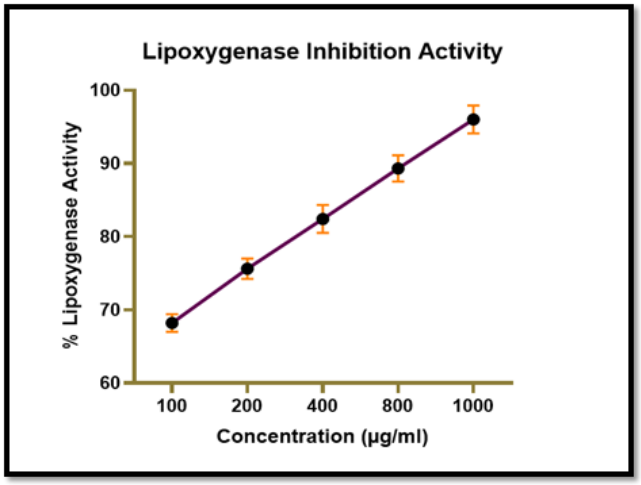

Figure 9: Lipoxygenase inhibition of Synthesized *Cissus quadrangularis* Phytosome.

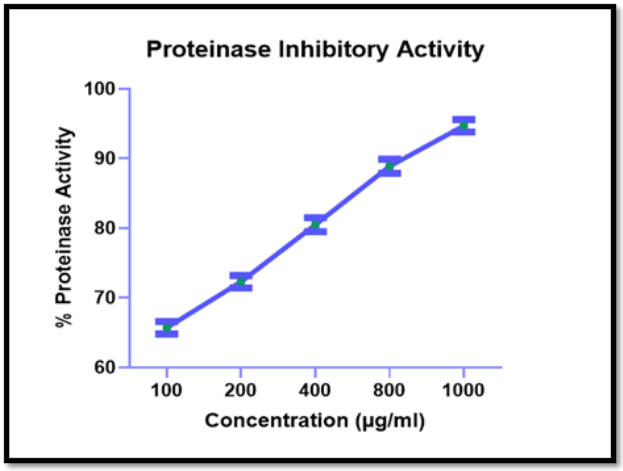

Figure 8: Proteinase inhibition of Synthesized *Cissus quadrangularis* Phytosome.

Lipoxygenase Inhibition Assay

The lipoxygenase inhibitory assay revealed that *Cissus quadrangularis* phytosomes exhibited inhibition in a concentration-dependent manner, with inhibition rates increasing from 68.2% at 100 µg/mL to 96.0% at 1000 µg/mL (Figure 9). This indicates that CQ phytosomes can significantly inhibit the lipoxygenase pathway, a key mediator of inflammation. Therefore, CQ phytosomes may have potential applications in managing inflammatory conditions, including those affecting bone health.

MTT assay for the synthesised CQ phytosomes

The cytotoxicity results from the MTT assay showed a concentration-dependent decrease in RAW 264.7 cell

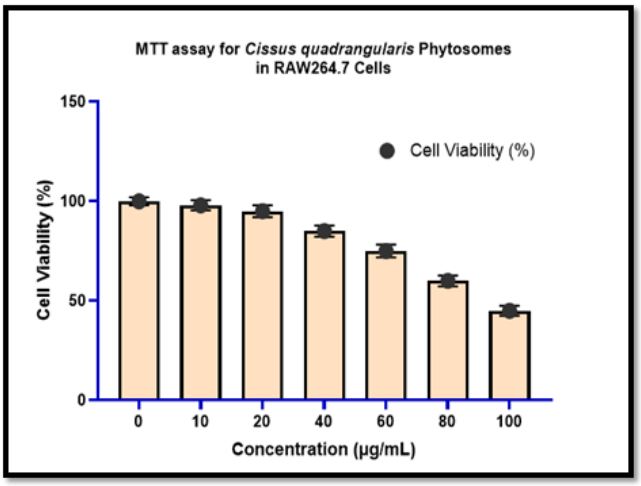

Figure 10: MTT assay of Cissus quandrangularis Phytosomes in RAW 264.7 cells.

viability (Figure 10). At 100 µg/mL, cell viability was reduced to 58.7%, suggesting the potential cytotoxic effect of the phytosomes at higher concentrations This reduction in cell viability suggests the potential cytotoxicity of CQ phytosomes, which could be advantageous for therapeutic applications requiring selective cytotoxic effects, such as cancer treatment.

DISCUSSION

The present study aimed to evaluate the therapeutic potential of Cissus quadrangularis through the development of a phytosome formulation and its examination using molecular interactions, antioxidant and anti-inflammatory assays. The findings contribute to the growing evidence supporting the medicinal properties of Cissus quadrangularis, particularly in its potential applications for treating oxidative stress, inflammation and cellular damage. The molecular docking results showed a significant binding affinity of cholesterin to the 1CVU target, with a binding energy of ΔG -8.4 kcal/mol. This suggests strong interactions, consistent with previous studies, where plant-derived compounds exhibited notable molecular binding to inflammation-related proteins. These results support the hypothesis that *Cissus quadrangularis* can modulate inflammatory responses through its binding capacity, similar to findings by Gupta *et al.* (2020),[5] which highlight the molecular interaction of plant compounds with inflammatory mediators.

Molecular dynamics simulations reinforced the stability of the protein-ligand complex, with the Cα-backbone RMSD stabilizing at 2.4 Å, further indicating a stable conformation. Such findings are consistent with prior research that emphasizes the importance of stable molecular interactions for effective therapeutic outcomes. This stability suggests that *Cissus quadrangularis* phytosome formulations could provide sustained therapeutic effects by maintaining consistent interactions with protein targets involved in inflammation.

The antioxidant activity of *Cissus quadrangularis* phytosomes, evaluated through the DPPH and nitric oxide scavenging assays, demonstrated significant dose-dependent free radical scavenging activity. The DPPH assay results revealed that the phytosome formulation exhibited inhibition rates that increased from 82.27% at 200 µg/mL to 95.50% at 1000 µg/mL, comparable to standard antioxidants. These findings align with those reported by Shah *et al.* (2010),[15] who identified similar antioxidant activity in plant-derived compounds, reinforcing the therapeutic potential of *Cissus quadrangularis* in combating oxidative stress. The nitric oxide scavenging activity further supports this, with inhibition levels reaching 98.59% at 1000 µg/mL, indicating strong antioxidant properties. These results confirm the role of *Cissus quadrangularis* as an effective natural source of antioxidants, capable of mitigating oxidative stress, which is a significant factor in many chronic conditions.

In terms of anti-inflammatory activity, the phytosome formulation showed promising results in inhibiting protein denaturation, a key marker of inflammation. The protein denaturation assay revealed that inhibition increased from 72.5% at 100 µg/mL to 96.3% at 1000 µg/mL, suggesting that *Cissus quadrangularis* may serve as a valuable anti-denaturation agent. Similarly, the proteinase inhibitory activity demonstrated dose-dependent inhibition, further highlighting the anti-inflammatory potential of the phytosome formulation. These results are in line with other studies that have shown the anti-inflammatory effects of plant-based formulations, such as the work by Wei *et al.* (2010),[8] which reported significant inhibition of inflammatory mediators through plant phytochemicals.

The MTT assay results provided additional insight into the cytotoxicity and potential therapeutic applications of the phytosome formulation. The concentration-dependent decrease in RAW 264.7 cell viability indicates that the *Cissus quadrangularis* phytosome formulation may exert cytotoxic effects on inflammatory cells, suggesting its potential as a therapeutic agent for conditions associated with chronic inflammation. These results are consistent with earlier studies that have reported similar cytotoxic effects of plant extracts on inflammatory cell lines, supporting the potential use of *Cissus quadrangularis* in managing inflammation-related disease

SUMMARY

This study investigated the therapeutic potential of *Cissus quadrangularis* phytosome formulations, focusing on their antioxidant and anti-inflammatory properties. The molecular docking analysis indicated a strong binding affinity of cholesterin to the 1CVU target, suggesting potential anti-inflammatory action. *In vitro* assays revealed that the *Cissus quadrangularis* phytosomes exhibited significant antioxidant activity, with the DPPH and nitric oxide scavenging assays showing dose-dependent increases in free radical scavenging. Additionally, the anti-inflammatory assays demonstrated effective inhibition of protein denaturation and proteinase activity, confirming the potential of the phytosome formulation in reducing inflammation.

The strengths of this study include its multi-faceted approach, combining molecular docking with a variety of *in vitro* assays to comprehensively assess the pharmacological properties of *Cissus quadrangularis*. However, the study is limited by the absence of *in vivo* validation, which is critical for confirming the therapeutic potential of the formulation in biological systems. Furthermore, the investigation focused on a limited range of concentrations and cell types, potentially restricting the broader applicability of the results.

These findings have significant implications for clinical practice, suggesting that *Cissus quadrangularis* phytosomes may serve as effective natural remedies for managing oxidative stress and inflammation-related conditions. From a policy perspective, this research supports the inclusion of *Cissus quadrangularis* in traditional medicine guidelines. Future studies, particularly *in vivo* experiments and clinical trials, are warranted to validate these findings and explore the broader applicability of *Cissus quadrangularis* phytosome formulations in therapeutic settings. This study lays the groundwork for further research into enhancing the efficacy and safety of this medicinal plant, potentially contributing to advancements in herbal medicine and integrative healthcare

CONCLUSION

The phytosomes of *Cissus quadrangularis* exhibit cytotoxic, anti-inflammatory and antioxidant characteristics, rendering them promising candidates for therapeutic use. Their improved effectiveness and bioavailability point to potential therapeutic uses. Subsequent research must to concentrate on comprehensive mechanistic analyses and *In vivo* assessments.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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