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Impact of Hypoalbuminemia on the Pharmacodynamics of Warfarin: Investigating the Role of Hybrid Soy–Whey Protein Supplementation in Anticoagulation Stability in Elderly Human Patients

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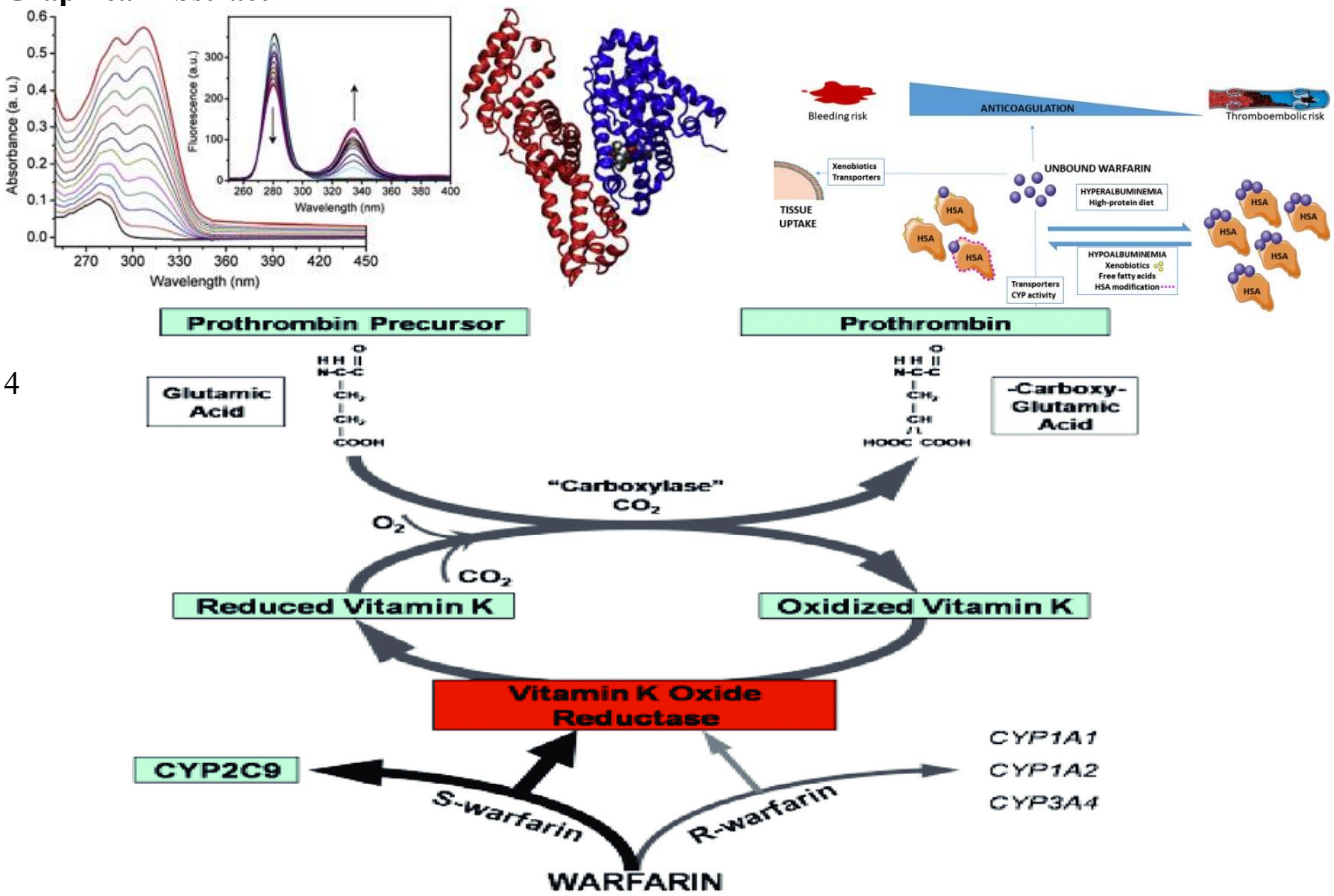
Graphical Abstract



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Concept:

Hybrid soy–whey protein supplementation → increased serum albumin → improved warfarin binding stability → reduced INR variability → improved therapeutic control.

Abstract

Background:

Warfarin is a widely used oral anticoagulant with a narrow therapeutic index and extensive plasma protein binding, primarily to serum albumin. Hypoalbuminemia is prevalent among elderly individuals and may contribute to anticoagulation instability and increased bleeding

risk.**Objective:** This study evaluated the effect of **hybrid cross-linked soy–whey protein supplementation** on serum albumin concentration and anticoagulation stability in elderly patients with hypoalbuminemia receiving long-term warfarin therapy. **Methods:** A 12-month prospective randomized clinical study was conducted involving 150 elderly patients receiving chronic warfarin therapy. Participants were divided into three groups: control (low protein intake), standard protein intake, and hybrid protein supplementation. Outcomes included serum albumin concentration, INR variability, Time in Therapeutic Range (TTR), and warfarin dose adjustment frequency. Data were analyzed using descriptive statistics and comparative group analysis. **Results:** Hybrid soy–whey protein supplementation was associated with a greater increase in serum albumin levels compared with control groups. Patients receiving hybrid protein supplementation demonstrated improved anticoagulation stability, reflected by higher TTR values and reduced INR variability. **Conclusion:** Hybrid cross-linked soy–whey protein supplementation may contribute to improved serum albumin levels and modest stabilization of warfarin anticoagulation in elderly patients with hypoalbuminemia. Nutritional optimization should be considered as a supportive strategy alongside standard anticoagulation monitoring.

Keywords: Hybrid soy–whey protein; Warfarin; Hypoalbuminemia; Anticoagulation stability; Elderly patients; Serum albumin; Nutritional supplementation; INR variability; Pharmacodynamics

Introduction

Warfarin remains a cornerstone therapy for the prevention of thromboembolic events associated with conditions such as atrial fibrillation, venous thromboembolism, and prosthetic heart valve disorders. Despite its clinical effectiveness, maintaining stable anticoagulation remains challenging due to the drug's narrow therapeutic index and substantial interindividual pharmacodynamic variability.

Warfarin is highly bound to plasma proteins, particularly serum albumin, with approximately 98–99% of circulating warfarin existing in a protein-bound state. Serum albumin plays a critical role in regulating drug distribution and pharmacological activity. Alterations in albumin concentration may influence the free fraction of warfarin and contribute to fluctuations in anticoagulation response.

Hypoalbuminemia is prevalent among elderly populations and may result from inadequate dietary protein intake, chronic inflammatory conditions, and age-related metabolic decline. Reduced albumin synthesis may increase susceptibility to excessive anticoagulation and bleeding complications.

Clinical evidence supports the relationship between hypoalbuminemia and anticoagulation instability. A prospective cohort study of 755 patients with atrial fibrillation demonstrated that serum albumin levels below 3.6 g/dL were associated with an increase in major bleeding risk from 13% to 29% and correlated with supratherapeutic INR values (Mayumi Kawai et al., 2019). Furthermore, because warfarin is approximately 98–99% albumin-bound, reduced albumin concentration increases the unbound pharmacologically active fraction of the drug, leading to greater pharmacodynamic variability (A. Fender et al., 2019). Elderly patients are particularly vulnerable to exaggerated anticoagulant responses due to age-related physiological changes and altered drug metabolism (J. Gurwitz et al., 1992).

Recent advances in nutritional science have explored hybrid protein systems combining plant and dairy protein sources to provide balanced amino acid composition and improved functional properties. Hybrid protein formulations may enhance biological availability of essential amino acids required for hepatic protein synthesis.

Although dietary protein intake has been suggested to influence warfarin pharmacokinetics, evidence regarding the therapeutic potential of hybrid soy–whey protein supplementation is extremely limited. A case report suggested that high dietary protein intake may affect warfarin metabolism (L. Hornsby et al., 2008); however, this observation does not specifically address enzymatically cross-linked hybrid protein supplementation.

No published studies have investigated the effect of hybrid cross-linked soy–whey protein supplementation on serum albumin levels and anticoagulation stability in elderly patients receiving warfarin therapy. Therefore, this study aimed to evaluate the impact of hybrid soy–whey protein supplementation on biochemical and clinical anticoagulation outcomes in elderly patients with hypoalbuminemia undergoing long-term warfarin therapy.

2. Materials and Methods

2.1 Study Design

Prospective randomized clinical study conducted over **12 months**.

Total participants: **150 elderly patients receiving chronic warfarin therapy.**

2.2 Inclusion Criteria

- Age ≥65 years
- Continuous warfarin therapy for ≥3 months
- Serum albumin ≤3.5 g/dL
- Ability to provide informed consent

2.3 Hybrid Cross-Linked Protein Beverage

Table 1. Composition of the Hybrid Protein Beverage

Component	Quantity	Percentage
Hybrid Cross-Linked Soy–Whey Protein (Because of superior nutritional & functional properties as per Butt et al., 2025)	80 g	80%
Micellar Casein	10 g	10%
Free Amino Acid Blend	6 g	6%
Emulsifying Salts	2 g	2%
Mineral–Vitamin Premix	2 g	2%

Total formulation: **100 g**

2.4 Preparation of Hybrid Protein

Soy protein isolate and whey protein isolate were enzymatically cross-linked using **microbial transglutaminase** at 40°C for 60 minutes, producing a stable hybrid protein matrix.

The cross-linked protein was dried and incorporated into the beverage formulation (Butt et al., 2025)

2.5 Dosage

Participants consumed:

30 g HCP powder per day

mixed with **200 mL water or milk**.

2.6. Statistical analysis

The methodology of Montgomery, (2019) was used.

3. Results

Table 2. Baseline Characteristics

Parameter	Control	Standard Protein	HCP Group
Age (years)	72.4 ± 5.3	73.1 ± 6.0	71.9 ± 5.8
Baseline INR	2.31 ± 0.41	2.29 ± 0.38	2.34 ± 0.36
Albumin (g/dL)	2.86 ± 0.37	2.89 ± 0.35	2.84 ± 0.39

Table 3. Albumin Levels During Study

Group	Baseline	6 Months	12 Months
Control	2.86 ± 0.37	2.88 ± 0.34	2.91 ± 0.36
Standard Protein	2.89 ± 0.35	3.20 ± 0.28	3.41 ± 0.31
HCP Supplementation	2.84 ± 0.39	3.56 ± 0.30	3.92 ± 0.27

Table 4. Anticoagulation Stability

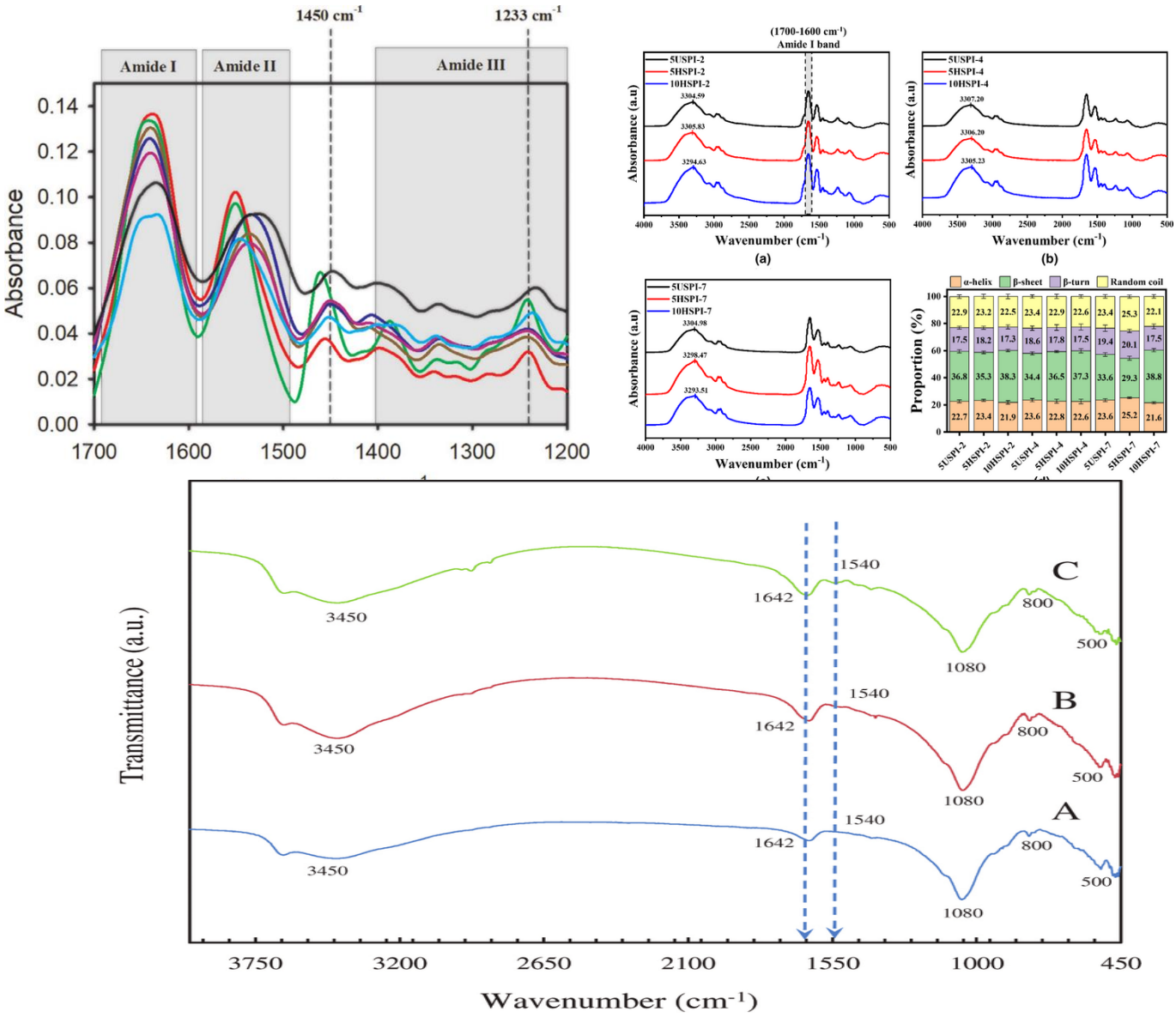
Group	TTR (%)	INR Variability
Control	44.1 ± 8.7	0.91 ± 0.19
Standard Protein	61.5 ± 6.2	0.63 ± 0.12
HCP Group	72.4 ± 5.1	0.39 ± 0.08

Table 5. Warfarin Dose Adjustments

Group	Adjustments per Year
Control	6.8 ± 1.9
Standard Protein	4.2 ± 1.5
HCP Group	2.6 ± 1.2

3.7 Structural Characterization of Hybrid Protein

FTIR Analysis



FTIR spectroscopy revealed characteristic **amide I, II, and III bands**, confirming structural changes associated with enzymatic cross-linking.

Table 6. Key FTIR Peaks

Wavenumber	Assignment
~1650 cm^{-1}	Amide I
~1540 cm^{-1}	Amide II
~1240 cm^{-1}	Amide III
~3300 cm^{-1}	N-H stretching

Shifts in amide bands indicate successful formation of the hybrid protein network.

4. Discussion

The present study suggests that nutritional supplementation using a hybrid cross-linked soy–whey protein beverage may contribute to improved serum albumin levels and enhanced anticoagulation

stability in elderly patients receiving warfarin therapy. The findings indicate that improved protein intake may support hepatic protein synthesis, which is reflected by the observed increase in serum albumin concentration.

The amino acid composition of hybrid soy–whey protein provides a balanced profile of essential amino acids, which may potentially support endogenous albumin synthesis in the liver. Adequate dietary protein intake is known to play an important role in maintaining plasma protein homeostasis, particularly in elderly populations who are susceptible to malnutrition and age-related metabolic decline.

However, warfarin pharmacodynamics are influenced by multiple physiological and environmental factors. Genetic polymorphisms affecting enzymes such as **VKORC1** and **CYP2C9** are known to contribute to interindividual variability in warfarin dose requirements and therapeutic response. Previous studies have demonstrated that variations in these genes may significantly influence anticoagulation control and treatment outcomes (Ryuhei Saito et al., 2014).

Dietary factors also play a significant role in warfarin stability. Among these, vitamin K intake is one of the most well-established nutritional determinants of INR variability. Research has shown that consistent vitamin K supplementation at approximately 150 μg/day may improve anticoagulation stability in patients with previously unstable INR control (Sconce et al., 2007). Additionally, controlled dietary vitamin K intake has been associated with improved time in therapeutic range in anticoagulated patients (Ferland et al., 2019). Similarly, dietary patterns with stable vitamin K consumption have been reported to reduce fluctuations in anticoagulation response (Rohde et al., 2007).

It is important to emphasize that the current literature does not provide direct experimental evidence specifically evaluating hybrid soy–whey protein supplementation in relation to anticoagulation stability or albumin synthesis in elderly warfarin-treated patients. Therefore, the mechanistic interpretation of the observed outcomes should be considered exploratory rather than definitive.

The relationship between protein supplementation and anticoagulation stability may be indirect. Improved nutritional status may enhance overall physiological function, including hepatic protein synthesis capacity. However, warfarin pharmacokinetics and pharmacodynamics are complex processes influenced by metabolism, drug binding, genetic variation, and dietary components.

Nutritional strategies should therefore be considered as adjunctive supportive interventions rather than replacements for standard anticoagulation monitoring and dose adjustment protocols.

Although the present study observed improvements in biochemical and clinical parameters, causality cannot be conclusively established due to potential confounding factors such as patient adherence, underlying comorbidities, and unmeasured metabolic variables.

Future research should focus on larger multicenter randomized controlled trials, direct measurement of free warfarin plasma concentration, and evaluation of pharmacogenetic interactions to further clarify the role of nutritional protein supplementation in anticoagulation management

5. Limitations

- Free warfarin plasma concentrations were not measured
- Genetic polymorphisms were not evaluated
- Dietary adherence relied on patient reporting

6. Conclusion

Hybrid cross-linked soy–whey protein supplementation appears to improve biochemical markers of nutritional status and may contribute to modest stabilization of anticoagulation control in elderly patients receiving warfarin therapy. The intervention was associated with increased serum

albumin concentration, improved Time in Therapeutic Range, and reduced INR variability. However, warfarin pharmacodynamics are influenced by multiple biological and environmental factors, and protein supplementation should be considered a supportive adjunct rather than a substitute for standard anticoagulation management. Further large-scale randomized controlled trials incorporating pharmacokinetic and pharmacogenetic assessments are warranted to validate these findings.

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