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Network Pharmacology-based Prediction and In Vivo Validation of Red Ginger and Turmeric Extract Combinations against Hypercoagulability in Isoproterenol-Induced Rats

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ABSTRACT

Background: Myocardial infarction is a critical cardiovascular condition often preceded by a hypercoagulable state. Red ginger (*Zingiber officinale* var. *rubrum*, ZOR) and turmeric (*Curcuma longa* L., CL) are recognized for their anticoagulant properties, yet their multi-target pharmacological interactions remain poorly understood. This study aimed to evaluate the anticoagulant potential of ZOR and CL combinations using an integrated network pharmacology and *in vivo* approach. **Methods:** Network pharmacology analysis was employed to predict potential molecular targets of ZOR and CL bioactive compounds. For *in vivo* validation, rats were treated with single extracts (300 mg/kg bw) or combinations (ratios 1:1, 1:3, 3:1), followed by isoproterenol-induced hypercoagulability. Anticoagulant activity was assessed by measuring Prothrombin Time (PT) and activated Partial Thromboplastin Time (aPTT). **Results:** Network pharmacology identified 10 key hub proteins, including STAT3, AKT1, and MTOR, indicating a multi-target mechanism. *In vivo*, isoproterenol effectively induced hypercoagulability. While ZOR (300 mg/kg BW) showed the highest individual potency, all combinations significantly prolonged PT and aPTT ($p < 0.05$). Based on Chou-Talalay analysis, the interaction was dose-dependent; PT showed nearly additive to synergistic effects (CI: 0.86–1.07), whereas aPTT exhibited antagonistic trends (CI: 1.06–1.50) at higher ZOR ratios. Consequently, combination effects remained stable without exceeding the most potent single dose. **Conclusion:** The ZOR and CL combination provides a consistent anticoagulant response through additive interactions, likely mediated by the modulation of the AKT/mTOR signaling axis and coagulation factors. This integration offers a promising, safer multi-target strategy for preventing thrombotic events in myocardial infarction.

Keywords: Anticoagulant, *Curcuma longa*, Coagulation, Isoproterenol, Network Pharmacology, *Zingiber officinale* rubrum.

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INTRODUCTION

Myocardial Infarction (MI) is defined as sudden myocardial tissue death resulting from ischemia or thrombotic occlusion in the coronary arteries, often triggered by blood thickening and thrombus formation[1,2]. As a leading cause of mortality worldwide, the pathogenesis of MI involves a complex interplay between atherosclerosis and hypercoagulation, where a ruptured plaque triggers a cascade of clotting factors leading to total arterial occlusion[1]. The management of this condition requires therapeutic agents capable of thinning the blood to restore coronary perfusion and prevent recurrent thrombotic events. While synthetic anticoagulants and antiplatelet drugs such as heparin and aspirin are standard treatments, their long-term use is frequently associated with serious side effects, including gastric ulceration[3] and an increased risk of spontaneous hemorrhage[4].

Consequently, there is a growing interest in exploring natural alternatives that offer comparable efficacy with improved safety profiles. Traditional Indonesian rhizomes, specifically Red Ginger (*Zingiber officinale* var. *rubrum*, ZOR) and Turmeric (*Curcuma longa* L., CL), have long been utilized in ethnomedicine for cardiovascular health[5]. Previous studies have established that red ginger possesses potent antioxidant[6] and anti-inflammatory[7] activities that protect cardiac tissue from oxidative stress. Furthermore, Ginger has been reported to inhibit platelet aggregation by interfering with the cyclooxygenase pathway[8], similar to the mechanism of aspirin. Turmeric, on the other hand, contains curcuminoids which are recognized for their anti-cholesterol properties[9] and their ability to modulate the coagulation cascade[10].

Recent pharmacological evaluations have demonstrated that curcumin, the primary bioactive compound in Turmeric, can act as a specific inhibitor of Factor Xa and thrombin, thereby prolonging blood clotting time[11]. Additionally, research by Ahmad et al. (2022) and Rani et al. (2024) highlighted that Indonesian medicinal plants, including ZOR and CL, exhibit significant anticoagulant activity by extending both Prothrombin Time (PT) and activated Partial Thromboplastin Time (aPTT)[12,13]. Furthermore, the multi-compound and multi-target nature of these herbal extracts makes it challenging to pinpoint the exact molecular pathways involved in their combined effect using traditional *in vivo* methods alone[14,15]. However, most existing studies have focused on these extracts in isolation, leaving a significant gap in understanding their combined interaction and efficacy across various formulation ratios, particularly in reversing hypercoagulability induced by myocardial infarction.

To address this complexity, network pharmacology has emerged as a powerful tool to systematically explore the synergistic or additive mechanisms of herbal medicines[15]. By integrating bioinformatics

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and network analysis, it is possible to predict how bioactive compounds from ZOR and CL interact with key proteins in the coagulation cascade, such as Coagulation Factor X (F10) and Tissue Factor (F3). This approach provides a theoretical foundation that complements experimental data, offering a more comprehensive understanding of how these extracts modulate the extrinsic and intrinsic pathways at the molecular level[16].

The novelty of this research lies in its integrated approach, combining network pharmacology predictions with a systematic *in vivo* evaluation of various ZOR and CL ratios to identify an optimal balance between efficacy and dosage reduction, assessed through PT and aPTT prolongation percentages. By aligning bioinformatic target predictions with PT and aPTT prolongation percentages, this study investigates the potential for a stable additive interaction that can maintain significant anticoagulant activity while minimizing the individual dose of each extract. This dual-method strategy aims to provide a scientific basis for an integrated herbal strategy that offers a broader pharmacological shield for the prevention and long-term management of myocardial infarction, potentially reducing the dose-dependent side effects associated with high-dose monotherapy or synthetic agents.

MATERIALS AND METHODS

Network Pharmacology Analysis

Identification of Bioactive Compounds

Bioactive constituents of *Zingiber officinale* var. rubrum and *Curcuma longa* L. were identified through comprehensive literature mining and specialized phytochemical databases, including Dr. Duke's Phytochemical and Ethnobotanical Databases and the KNApSAcK Family database. Chemical structures for these compounds were sourced from PubChem and converted into canonical SMILES strings for downstream analysis. To ensure drug-likeness and biological relevance, the compounds were further filtered using SwissADME for Lipinski's Rule of Five compliance and PASS Online to predict potential blood coagulation-related activities.

Prediction of Potential Targets

Potential protein targets for the identified compounds were predicted using the Swiss Target Prediction database (http://www.swisstargetprediction.ch/). To ensure the reliability of the predicted interactions, a probability threshold of ≥ 0.5 was applied. Furthermore, the search was strictly limited to *Homo sapiens* to focus on human-specific molecular pathways.

Identification of Anticoagulation-Related Targets

Anticoagulation and coagulation disorder-related genes were sourced from the GeneCards database (https://www.genecards.org/) using the keyword 'anticoagulation.' To identify potential therapeutic targets, the predicted phytochemical targets were intersected with these anticoagulation-related genes. Furthermore, we integrated the phytochemical targets of Red Ginger and Turmeric using Venny 2.1 (https://bioinfogp.cnb.csic.es/tools/venny/) to pinpoint shared targets between the two plants. Overlapping targets were ultimately defined as the specific genes through which Red Ginger and Turmeric exert their anticoagulation effects.

Construction of Protein–Protein Interaction (PPI) Network

The identified overlapping targets were uploaded to the STRING database (https://string-db.org/) to develop a protein–protein interaction (PPI) network. To ensure data robustness, the analysis was restricted to *Homo sapiens* with a high-confidence score threshold of 0.7. The resulting interactome was subsequently exported and visualized using Cytoscape software (version 3.10.4) for further network analysis.

Network Topology Analysis

Topological features of the Protein–Protein Interaction (PPI) network were evaluated using the CytoHubba plugin within Cytoscape (version 3.10.4). Key hub proteins were identified based on several centrality metrics, including degree, betweenness, closeness, and stress. These high-ranking hub genes were subsequently selected as the primary targets likely responsible for the synergistic anticoagulant properties of the studied plant combination.

Functional Enrichment Analysis

To elucidate the biological pathways involved, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis was conducted using the STRING-DB database (https://string-db.org/). This analysis allowed for the identification of significantly enriched signaling pathways associated with the identified target genes.

In Vivo Validation

Materials and reagents

The primary botanical materials consisted of Red Ginger (*Zingiber officinale* var. *rubrum*) and Turmeric (*Curcuma longa* L.), which were processed into ethanolic extracts using 96% ethanol. Myocardial infarction was induced using Isoproterenol powder (Tokyo Chemical Industry Co., Ltd., Japan). For the coagulation and antiplatelet assays, the study employed Prothrombin Time (PT) assay kits (AKL 20207022681), activated Partial Thromboplastin Time (aPTT) assay kits (AKL 20207020497), and $CaCl_2$. Standard pharmacological agents included Heparin (Inviclot®), Ketamine HCl (Dexa Medica, Indonesia), and *Sodium Carboxymethyl Cellulose* (Na-CMC) as a suspending agent. Blood samples were collected using 3 mL sodium citrate vacuum tubes to prevent premature coagulation.

Instrumentation

Extraction and solvent recovery were performed using a macerator and a rotary evaporator (Heidolph®, Germany). Analytical weighing was conducted on a Shimadzu analytical balance (BL 2200H, Japan). Animal treatments were administered via rat oral gavage needles (sonde). For sample preparation and biochemical analysis, the study used a dry bath (ONilab®) and a centrifuge (Boeco S8). Precision liquid handling was managed using micropipettes (Thermo Fisher Scientific, USA) with corresponding tips, while samples were processed in Eppendorf tubes.

Sample Collection and Identification

The rhizomes of red ginger (*Zingiber officinale* var. rubrum) and turmeric (*Curcuma longa* L.) were collected in February 2025 from Dago, West Java, Indonesia (Coordinates: -6.8462, 107.6559). The turmeric and red ginger were harvested at 8 and 10 months of age, respectively. Botanical identification and authentication were performed at the Jatinangor Herbarium, Plant Taxonomy Laboratory, Universitas Padjadjaran. The specimens were officially registered under certificate numbers 106/HB/02/2025 (for ginger) and 105/HB/02/2025 (for turmeric).

Preparation and Extraction

The fresh rhizomes were washed under running water, sliced, and dried in a hot-air oven at 55 °C for 24 hours. The moisture content of the dried ZOR and CL rhizomes was determined to be 10% (w/w) using the azeotropic distillation method with a Stahl apparatus (Merck, Germany). The dried material was subsequently ground into a fine powder. Extraction was conducted via maceration using 96% re-distilled ethanol at a ratio of 1:10 (w/v). The resulting filtrates were concentrated using a rotary evaporator (Heidolph, Germany) at 40 °C to obtain the crude extracts. The yields were recorded, and the extracts were stored at 4 °C for further experimental analysis[17].

Ethical Approval

The experimental protocols in this study were strictly conducted following the ethical guidelines for animal research. Approval was granted by the Research Ethics Committee of the Faculty of Pharmacy, Universitas Jenderal Achmad Yani (No: 11003/KEP-UNJANI/III/2025). All procedures adhered to the 3Rs (Reduction, Refinement, Replacement) principles and the 5 Freedoms to ensure the highest standards of animal welfare.

Animals

Male *Wistar* rats (*Rattus norvegicus*; 190–250 g; 8–12 weeks old) were obtained from the Faculty of Medicine, Universitas Padjadjaran (Jl. Ir. Soekarno Km 21, Sumedang, West Java 45363, Indonesia). The animals were acclimatized for 7 days under laboratory conditions prior to the study. Animals were housed in groups of 8-10 per cage (60 x 45 x 10 cm) at 22–24 °C with a 12 h light/dark cycle, receiving standard diet and water *ad libitum*. Inclusion was restricted to healthy, active rats, while those showing illness, aggressive behavior, or mortality before study completion were excluded[18].

Sample Size

The sample size was determined using the Federer formula (t-1)(n-1) ≥ 15. With t = 8 experimental groups, a minimum of n = 3.14 rats per group was required. A total of 32 rats were used in this study (n=4 per group). Data from 3 representative rats per group that strictly met the inclusion criteria and showed no technical pre-analytical errors (e.g., hemolysis or insufficient blood volume) were included in the final statistical analysis to satisfy the Federer formula requirements[19].

Experimental Design and MI Induction

Following a 7-day acclimatization, rats were randomly assigned to eight groups (n=4) and received daily oral treatments for 20 days: G1 (Normal Control: 0.5% Na-CMC); G2 (Negative Control: 0.5% Na-CMC); G3 (Positive Control: Heparin 60 IU/kg); G4 (ZOR 300 mg/kg); G5 (CL 300 mg/kg); and G6–G8 (ZOR+CL combinations at ratios of 150:150, 75:225, and 225:75 mg/kg, respectively). On days 21 and 22, myocardial infarction was induced in all groups except G1 via intraperitoneal injection of Isoproterenol (85 mg/kg) at 24-hour intervals. Twenty-four hours after the final induction (Day 23), blood was collected via cardiac puncture under anesthesia. On day 24, the blood samples were processed for anticoagulant and thrombolytic activity assays[20].

Prothrombin Time (PT) Assay

The PT assay was performed by pre-incubating the PT reagent in a water bath at 37°C for 10 minutes. A 25 µL plasma sample was pipetted into a serological tube and incubated at 37°C for 1–2 minutes. Subsequently, 50 µL of the pre-warmed PT reagent was added to the sample[21]. The coagulation time was monitored using a stopwatch, which was stopped immediately upon the formation of fibrin threads detected via a sterile applicator or inoculating loop. The recorded duration (seconds) represented the PT value. To evaluate the potency of the extracts, the percentage of anticoagulant activity (%PT) was calculated using the following formula:

$$\%PT = \frac{PT\ \{treatment\} - PT\ \{negative\ control\}}{PT\ \{negative\ control\}}\ x\ 100\%$$

Activated Partial Thromboplastin Time (aPTT) Assay

The aPTT assay was conducted by pre-warming the aPTT reagent and 0.025 M Calcium Chloride ($CaCl_2$) at 37°C in a water bath. A 25 µL plasma sample was mixed with 25 µL of the aPTT reagent in a serological tube and incubated at 37°C for 5 minutes to activate the intrinsic pathway. Coagulation was initiated by adding 25 µL of the pre-warmed $CaCl_2$ solution[22]. The time interval from the addition of $CaCl_2$ until the first appearance of fibrin threads, detected using a sterile applicator or inoculating loop, was recorded as the aPTT value in seconds. The percentage of anticoagulant activity for aPTT was determined using the formula:

$$\%aPTT = \frac{aPTT\ \{treatment\} - aPTT\ \{negative\ control\}}{aPTT\ \{negative\ control\}}\ x\ 100\%$$

The pharmacological interaction between ZOR and CL extracts was quantitatively evaluated using the Combination Index (CI) method, which is based on the Loewe additivity principle. This analysis compares the doses of the extracts used in combination with the doses of each extract required to produce the same biological effect when administered individually. The CI values were calculated according to the median-effect equation as described by Chou[23]:

$$CI = \frac{(D)1}{(Dx)1} + \frac{(D)2}{(Dx)2}$$

Where: (D)1 and (D)2 represent the doses of ZOR and CL in the combination, respectively; (Dx)1 and (Dx)2 represent the doses of ZOR and CL alone required to achieve an equivalent prolongation of Prothrombin Time (PT). The nature of the interaction was categorized based on the calculated CI values: synergism was defined as CI < 1, additivity as CI=1, and antagonism as CI > 1[24].

Statistical Analysis

All data were expressed as mean ± standard deviation (SD). Statistical significance was analyzed using GraphPad Prism 10 (GraphPad Software, Inc., USA). Normality and homogeneity of variance were assessed prior to comparative analysis. Differences between experimental groups were evaluated using one-way analysis of variance (ANOVA), followed by Tukey's post hoc test for multiple comparisons. A p-value of less than 0.05 ($p < 0.05$) was considered statistically significant.

RESULTS

Network Pharmacology Analysis

Bioactive constituents from *Zingiber officinale* var. rubrum (ZOR) and *Curcuma longa* (CL) were prioritized based on their documented anticoagulant potential. Following a pharmacokinetic evaluation via the SwissADME platform, eight compounds were found to adhere to Lipinski's Rule of Five. These include 6-gingerol, 6-shogaol, 10-shogaol, and gingerdione from ZOR, alongside curcumin, demethoxycurcumin, bisdemethoxycurcumin, and α-turmerone from CL. These selected compounds were subsequently utilized for target protein prediction to explore their involvement in anticoagulation mechanisms.

Data retrieval from the GeneCards database yielded 1,773 targets associated with anticoagulation. Intersection analysis identified 59 overlapping targets for *Z. officinale* var. rubrum (ZOR) and 70 for *C. longa* (CL) that correlate with anticoagulation processes. These intersections, visualized in Figure 1, represent the potential molecular targets for each plant. After merging the target sets and removing redundancies, a total of 107 unique proteins were finalized for subsequent computational analysis (Table 1).

Table 1. List of protein codes resulting from Venny intersection between proteins predicted to interact with secondary metabolites ZOR and CL with proteins related to anticoagulation.

Sample	Protein Code
Z.O.rubrum dan *C. longa*	BACE1, APP, TLR9, F3, SRC, PLCG1, ALOX5, CDK1, MTOR, SERPINE1, GSK3B, EGFR, MMP13, CTSL, MMP8, BMP1, NFE2L2, PTGS1, MET, RPS6KB1, TOP1, RAF1, BRAF, PDGFRB, FLT3, AGTR1, ALPL, HSP90AA1, MCL1, DPP4, AKR1B1, STAT6, ESR1, STAT3, AKT1, CA2, MMP14, NOX4, ADAM17, PREP, CXCR2, CFD, BCL2, THRA, CSF1R, ALOX5AP, CYP19A1, EPHX1, EPHX2, ADRA2A, HRH2, DRD1, HRH1, CHRM3, P2RX7, AKR1C3, CYP17A1, CACNA1B, NQO2,, ABCG2, S1PR3, ALOX12, NR1I2, SHBG, FABP1, PLA2G7, CYP2C9, CYP2C19, MPI, HTR3A, MAP2K1, ERN1, MMP9, PCNA, KDR, CDK4, MMP3, MMP7, ANPEP, MIF, NOX1, PDE5A, PDE3B, PIK3CG, PIK3CA, ELANE, MMP12, FGFR1, PARP1, MAPK14, ALK, GSTP1, TTR, CYP3A4, EIF2AK2, PTK2, VDR, ADORA1, LDLR, FPR2, IGF1R, NPC1L1,CALCA, F10, ACP1, ALOX15, NR3C1

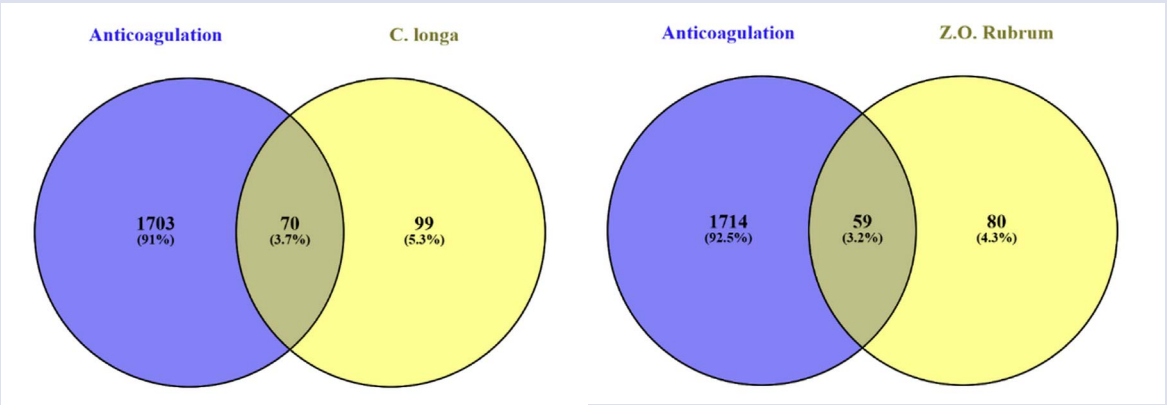

Figure 1. Venn diagrams depicting the number of proteins correlated with coagulation (purple) and proteins predicted to interact with compounds in specific extracts (light yellow). The intersection (dark yellow) represents anticoagulation-related proteins predicted to interact with compounds in: (a) ZOR and (b) CL.

Figure 2. Protein-protein interactions of 107 intersection proteins between anticoagulation proteins and target proteins ZOR and CL obtained from String-DB analysis.

Protein–protein interaction (PPI) analysis was conducted to evaluate the functional relationships between the identified target proteins. The results revealed a PPI network comprising 107 nodes and 880 edges, significantly exceeding the expected number of 337 edges. This high interaction density, relative to random expectation, is further supported by an extremely low PPI enrichment p-value (nearly zero), confirming that the network architecture is not the result of a chance occurrence. These findings indicate that the proteins within the network possess significant biological associations and are likely co-functional in the same signaling pathways or biological processes (Figure 2).

A cluster analysis was performed to identify protein groups with high levels of interaction within the protein–protein interaction (PPI) network. This analysis aimed to determine the most significant primary clusters within the network (Figure 3a). Based on the results of this analysis, the clusters with the highest levels of connectivity were selected for further analysis. Next, hub genes were identified, namely central genes that play a crucial role in maintaining the stability and regulation of the complex PPI network. The analysis revealed ten key proteins acting as hub proteins: STAT3, SRC, HSP90AA1, BCL2, AKT1, ESR1, MCL1, MTOR, PARP1, and EGFR, which are thought to play a crucial role in biological mechanisms associated with anticoagulation activity (Figure 3b).

To further elucidate the biological mechanisms, functional enrichment analysis was conducted. The KEGG pathway analysis explicitly identified the coagulation signaling pathway as a primary targeted mechanism (Figure 4). The integration of these findings underscores the multi-target synergistic potential of ZOR and CL compounds. The identified hub genes, such as STAT3 and AKT1, act as central nodes that converge on the coagulation pathway, likely through the regulation of Tissue Factor-mediated processes and vascular homeostasis. This confirms that the anticoagulation activity of the extracts is achieved through a systemic modulation of the signaling network rather than a single targeted pathway.

In Vivo Validation

Prothrombin Time (PT) Analysis

The Prothrombin Time (PT) assay revealed that Isoproterenol induction in the negative control group significantly shortened coagulation time compared to the normal control, indicating a marked hypercoagulable state. In contrast, pretreatment with *Zingiber officinale* var. rubrum (ZOR) and *Curcuma longa* (CL) extracts, both as monotherapy and in combination, significantly prolonged PT durations relative to the negative control ($p < 0.05$). While ZOR at 300 mg/kg BW exhibited a slightly higher anticoagulant effect than CL at the same dose, the most pronounced extension of PT among treatment groups was observed in the Heparin-treated positive control (60 IU/kg BW), which maintained values closest to the normal baseline.

Interestingly, the three combination ratios (ZOR150/CL150, ZOR75/CL225, and ZOR225/CL75) all effectively delayed fibrin formation, showing significant anticoagulant activity compared to the negative control ($p < 0.05$). However, statistical analysis indicated no significant difference (*ns*) between these combination groups, suggesting that varying the proportions of ZOR and CL within the tested ranges resulted in comparable efficacy in modulating the extrinsic and common coagulation pathways. These findings suggest that the integration of both extracts provides a stable inhibitory effect on the coagulation cascade in the context of induced myocardial infarction. The effects of red ginger and turmeric extracts on Prothrombin Time (PT) are illustrated in Figure 5.

Based on these results, the CI values varied across the tested dose ratios. The combination of ZOR75/CL225 exhibited a synergistic effect with a CI value of 0.86. In contrast, the ZOR150/CL150 ratio yielded a CI value of 0.94, indicating a nearly additive interaction. Furthermore, the ZOR225/CL75 ratio resulted in a CI value of 1.07, which remains within the nearly additive range according to the established criteria.

Percentage of Prothrombin Time Prolongation (%PT)

The anticoagulant potency of the treatments was further evaluated by calculating the percentage of PT prolongation relative to the negative control group (Figure 6). The normal control and Heparin groups (60 IU/kg BW) exhibited the highest prolongation percentages, reaching (358.59±0.39%) and (282.34±0.44%), respectively ($p < 0.05$). Among the herbal treatments, *Zingiber officinale* var. *rubrum* (ZOR) at 300 mg/kg BW showed a significantly higher prolongation effect (101.07±0.25%) compared to *Curcuma longa* (CL) at the same dose (42.41±0.12%).

All combination groups (ZOR150/CL150, ZOR75/CL225, and ZOR225/CL75) demonstrated significant anticoagulant activity with

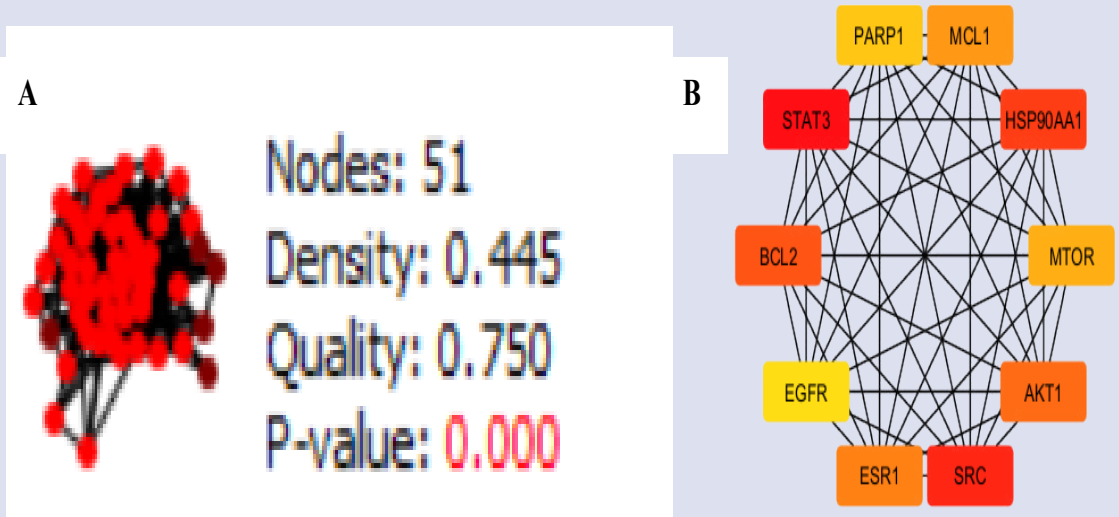

Figure 3. Identification of key clusters and central proteins within the PPI network. (a) Major clusters representing highly interconnected protein groups within the network. (b) The ten most central hub proteins—identified through MCC-CytoHubba analysis in Cytoscape—associated with anticoagulation activity and targeted by ZOR and CL compounds.

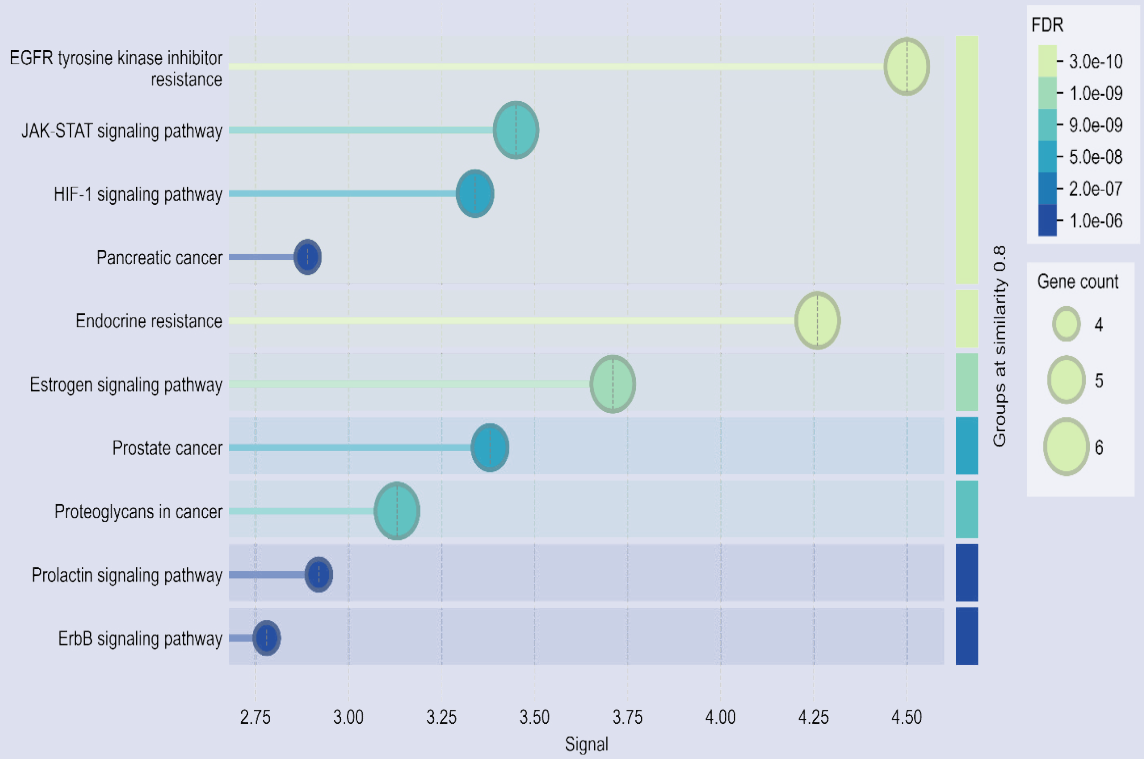

Figure 4. Functional enrichment analysis using the KEGG database. The diagram highlights the significant involvement of the target proteins in the coagulation signaling pathway, confirming the biological mechanism through which ZOR and CL compounds exert their anticoagulation effects.

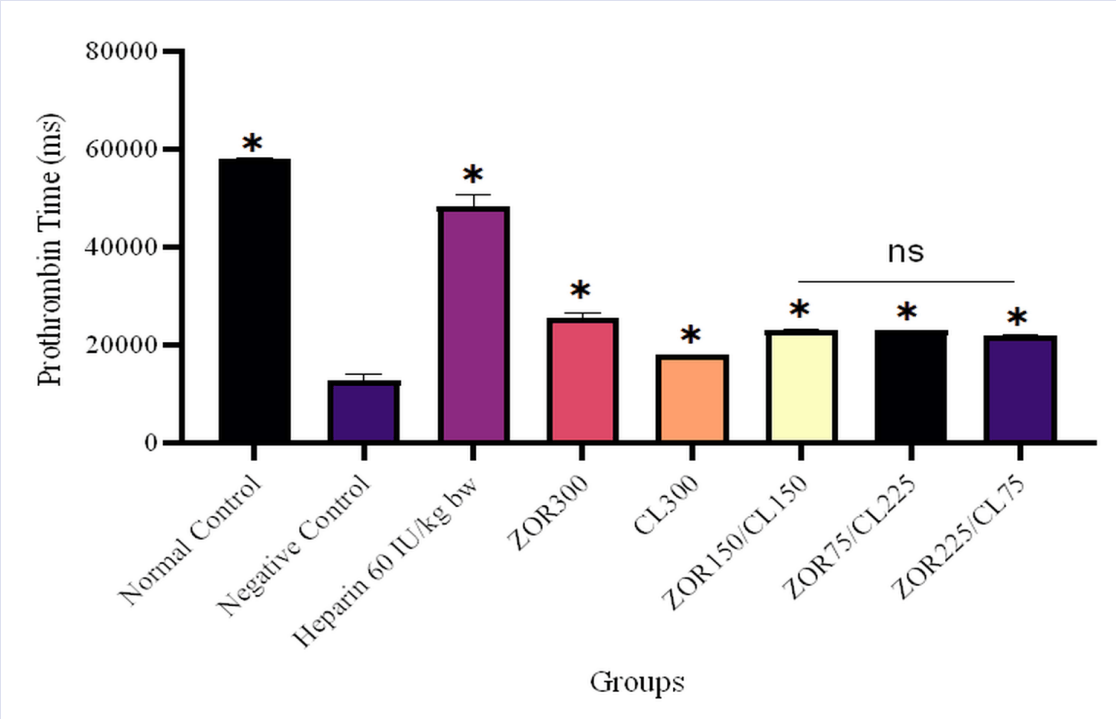

Figure 5. Effect of Red Ginger (ZOR) and Turmeric (CL) extracts on Prothrombin Time (PT) in Isoproterenol-induced rats. Values are expressed as Mean ± SD (n=4). Statistical significance was analyzed via One-Way ANOVA followed by Tukey's post hoc test; (*) $p < 0.05$ vs. negative control; (ns) non-significant between indicated groups.

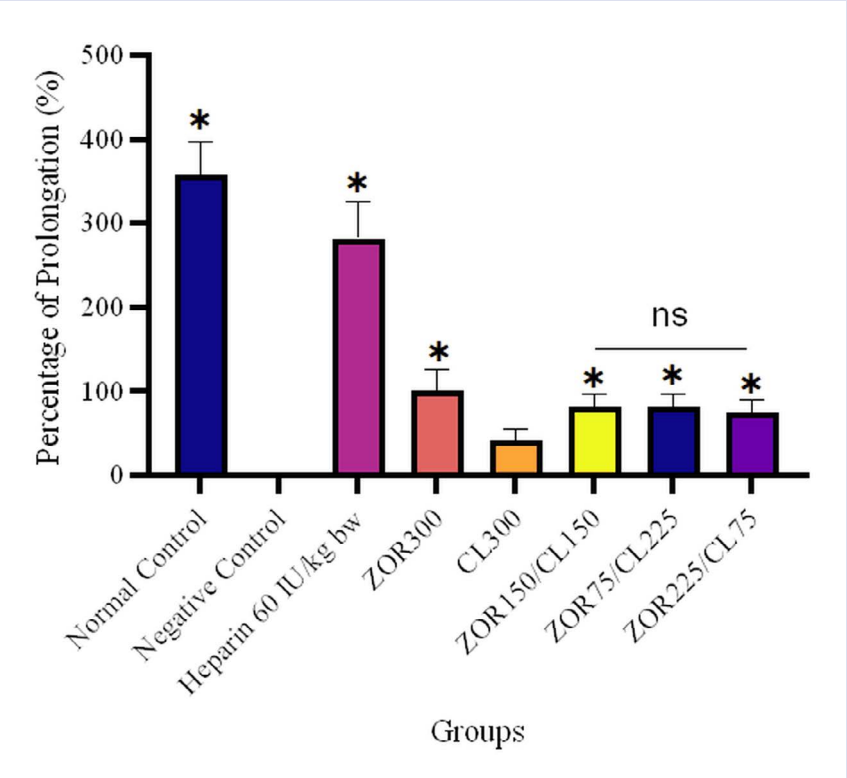

Figure 6. Effect of Red Ginger (ZOR) and Turmeric (CL) extracts on Percentage of Prothrombin Time Prolongation (%PT) in Isoproterenol-induced rats. Values are expressed as Mean ± SD (n=4). Statistical significance was analyzed via One-Way ANOVA followed by Tukey's post hoc test; (*) $p < 0.05$ vs. negative control; (ns) non-significant between indicated groups.

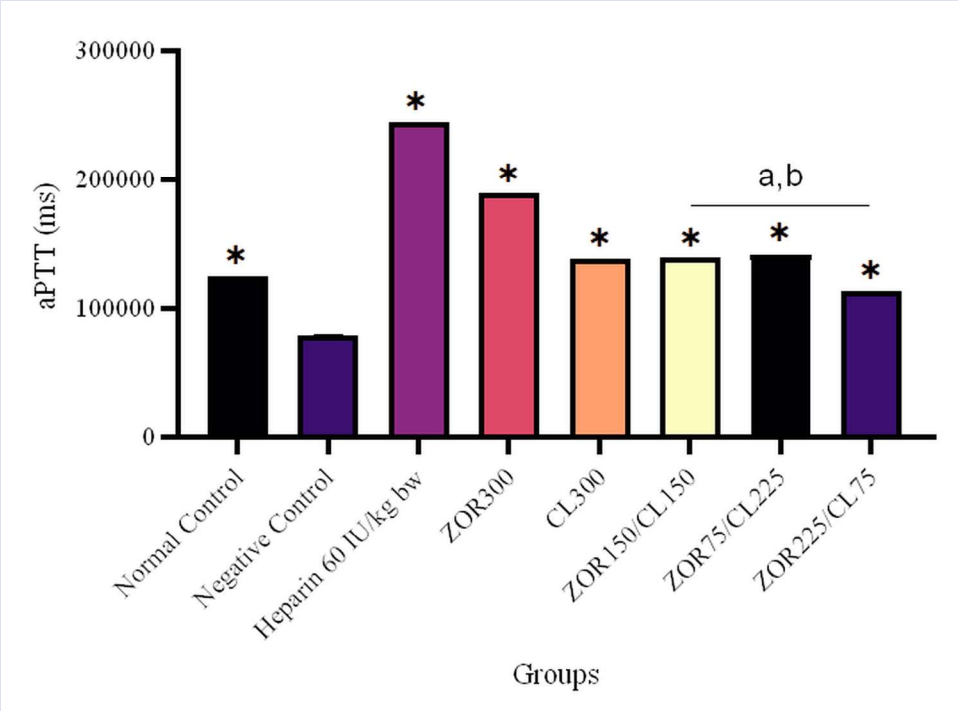

Figure 7. Effect of red ginger and turmeric extracts on activated Partial Thromboplastin Time (aPTT). Data are shown as Mean ± SD (n=4). (*) denotes a significant difference compared to the negative control ($p < 0.05$). The notation (a) represents a significant difference compared to the ZOR 300 mg/kg group, while (b) indicates a significant difference compared to the CL 300 mg/kg group.

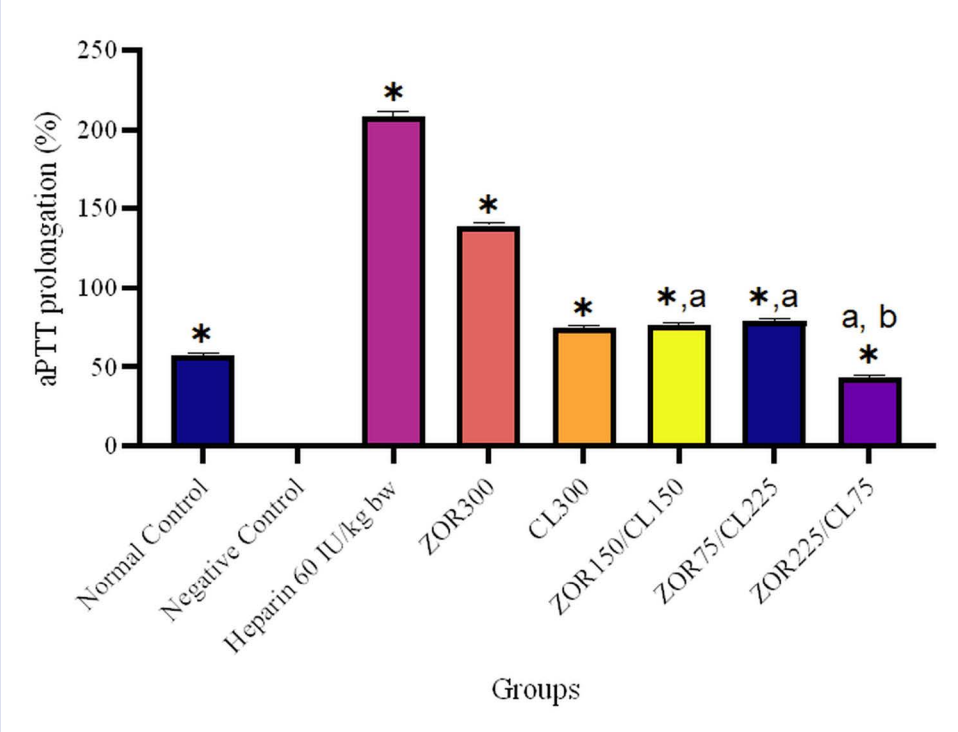

Figure 8. Percentage of activated Partial Thromboplastin Time (aPTT) prolongation. Data are presented as Mean ± SD (n=4). Asterisks (*) indicate a significant difference compared to the negative control group ($p < 0.05$). The notation (a) represents a significant difference compared to the ZOR 300 mg/kg bw group, while (b) represents a significant difference compared to the CL 300 mg/kg bw group.

prolongation percentages ranging between 70% and 80% compared to the negative control ($p < 0.05$). Statistical analysis revealed no significant difference (*ns*) among the three combination ratios, suggesting that the interaction between ZOR and CL produces a stable and consistent enhancement of the extrinsic coagulation pathway regardless of the specific proportion used.

Activated Partial Thromboplastin Time (aPTT) Analysis

The aPTT assay was employed to evaluate the inhibition of the intrinsic and common coagulation pathways. As shown in Figure 7, isoproterenol induction in the negative control group significantly shortened the aPTT (79,388±600.23 ms) compared to the normal control (125,024±9.23 ms), indicating a hypercoagulable state. All treatment groups, including single extracts and combinations, demonstrated a significant prolongation of aPTT compared to the negative control ($p < 0.05$, denoted by *). ZOR at 300 mg/kg BW showed the highest activity among herbal groups (190,073±8 ms), which was notably higher than CL at 300 mg/kg BW (139,020±4.36 ms).

Interestingly, the combination groups (ZOR150/CL150 and ZOR75/CL225) exhibited aPTT values (approx. 140,000 ms) that were significantly different from the ZOR 300 mg/kg group (denoted by a) and the CL 300 mg/kg group (denoted by b). However, the combination ZOR225/CL75 showed a slightly lower prolongation (114,084±9.45 ms). While all combinations successfully mitigated the effects of isoproterenol, the recorded aPTT values for the combinations remained lower than the potency of the single ZOR 300 mg/kg extract.

The combination of ZOR75/CL225 yielded a CI value of 1.06, which is categorized as a nearly additive effect (0.90 – 1.10). In contrast, the ZOR150/CL150 and ZOR225/CL75 ratios resulted in CI values of 1.20 and 1.50, respectively. According to the established criteria (CI > 1.10), these results indicate a clear antagonistic interaction between the two extracts in terms of aPTT prolongation.

Percentage of aPTT Prolongation

The analysis of aPTT prolongation percentage further characterizes the inhibitory effect of the extracts on the intrinsic and common coagulation pathways (Figure 8). The negative control group, representing the isoproterenol-induced hypercoagulable state, showed no prolongation, while the Heparin-treated group (60 IU/kg bw) exhibited the highest prolongation at 208.70±0.02%. Among the single herbal treatments, ZOR 300 mg/kg bw demonstrated a substantial prolongation effect of 139.43±0.02%, which was significantly higher than the 75% prolongation observed in the CL 300 mg/kg bw group ($p < 0.05$).

The combination treatments showed varying degrees of efficacy in prolonging aPTT. The ZOR150/CL150 and ZOR75/CL225 groups yielded prolongation percentages of approximately 75–80%, which were statistically comparable to the single CL 300 mg/kg bw treatment but significantly lower than the ZOR 300 mg/kg bw group (denoted by a). Meanwhile, the ZOR225/CL75 combination exhibited the lowest prolongation among the treatment groups at 43.71±0.01%, showing a significant difference compared to both the ZOR 300 and CL 300 single treatments (denoted by a, b). These results indicate that while the combinations effectively prolong aPTT compared to the negative control, they do not produce a synergistic enhancement over the most potent single extract (ZOR 300 mg/kg bw).

DISCUSSION

The Network Pharmacology (NP) analysis demonstrates that the synergistic anticoagulant effects of *Zingiber officinale* var. *rubrum* (ZOR) and *Curcuma longa* (CL) are mediated through a robust regulatory network centered on ten hub proteins, most notably STAT3, AKT1, MTOR, and SRC[25–27]. These proteins converge at the JAK-STAT and HIF-1 signaling axes, which function as critical molecular intersections between systemic inflammation and hemostatic activation[28,29]. In

the context of isoproterenol-induced hypercoagulability—a state characterized by myocardial oxidative stress and the systemic release of pro-inflammatory cytokines—the modulation of these pathways is pivotal. By targeting this signaling axis, the bioactive constituents of ZOR and CL likely inhibit the phosphorylation and subsequent nuclear translocation of dimerized STAT proteins[28]. This suppression downregulates the expression of pro-inflammatory genes, effectively disrupting the detrimental crosstalk between 'cytokine storms' and the coagulation cascade, thereby mitigating thrombus formation[30].

Furthermore, the involvement of the HIF-1 signaling pathway provides a mechanistic explanation for the extracts' efficacy under stressful physiological conditions. Isoproterenol-induced cardiac stress often leads to localized hypoxia and the generation of reactive oxygen species (ROS), which in turn activate the HIF-1α/HIF-1β complex. Our findings suggest that ZOR and CL modulate this pathway to regulate the expression of target genes such as VEGF and PAI-1, which are pivotal in maintaining blood vessel integrity and thrombus stability[29]. This multi-target interaction demonstrates that the extracts do not merely inhibit a single clotting factor but rather stabilize the entire vascular microenvironment, preventing the transition from oxidative stress to a systemic hypercoagulable state.

These *in silico* predictions were partially corroborated by *in vivo* observations, specifically in the modulation of the extrinsic pathway. The combination of ZOR75/CL225 at a synergistic ratio (CI < 0.9) significantly prolonged Prothrombin Time (PT), reflecting a potent synergy in inhibiting the extrinsic and common coagulation pathways. Interestingly, while the same dose demonstrated a prolongation of activated Partial Thromboplastin Time (aPTT), the interaction was found to be nearly additive, suggesting that the combined extracts exert a more pronounced synergistic effect on the extrinsic cascade than on the intrinsic system. This distinction aligns with the network pharmacology findings where hub genes may preferentially modulate specific coagulation factors. The ability of these natural compounds to bridge inflammation, oxidative stress, and fibrinolysis through the JAK-STAT and HIF-1 axes explains the enhanced efficacy of the combination[28,29]. This targeted yet holistic modulation effectively mitigates isoproterenol-induced hypercoagulability, validating the utility of network pharmacology in distinguishing between synergistic and additive potentials of polyherbal formulations for cardiovascular homeostasis.

To validate these *in silico* predictions, the *in vivo* anticoagulant activity was evaluated through the measurement of PT and aPTT. The results demonstrate that the administration of red ginger (*Zingiber officinale* var. *rubrum*, ZOR) and turmeric (*Curcuma longa* L., CL) rhizome extracts significantly modulates the extrinsic and common pathways of the coagulation cascade. In this study, the induction of Isoproterenol in the negative control group successfully established a hypercoagulable state, characterized by a significant shortening of both PT (12,728 ± 1.13 ms) and aPTT (79,388 ± 600.23 ms) compared to the normal baseline. All treatment groups, including single and combination extracts, significantly prolonged these values ($p < 0.05$), demonstrating potent anticoagulant properties that corroborate the hub protein modulation identified in the network analysis.

The evaluation of Prothrombin Time (PT) and activated Partial Thromboplastin Time (aPTT) is crucial for identifying the inhibitory effects of natural products on the extrinsic and intrinsic pathways, respectively[31]. In this study, single extract administration revealed that *Zingiber officinale* var. rubrum (ZOR) at 300 mg/kg bw outperformed *Curcuma longa* L. (CL) 300 mg/kg bw in both parameters, achieving approximately 100% prolongation in PT and 140% in aPTT. This superiority is largely attributed to the presence of [6]-gingerol, shogaols and paradol in red ginger, which act as potent inhibitors of thrombin and platelet aggregation[32,33]. [6]-gingerol specifically suppresses the cyclooxygenase-1 (COX-1) pathway and reduces thromboxane A2 (TXA2) formation, thereby collectively slowing fibrin thread formation[33]. Conversely, the anticoagulant activity of CL is primarily driven by curcuminoids, which are known to inhibit Factor Xa and thrombin (Factor IIa)[34–36]. Although effective, the slightly lower efficacy of CL compared to ZOR in this model may be due to differences in bioavailability and ligand-binding affinity toward coagulation factors during the extreme hypercoagulable state induced by isoproterenol.

Based on the statistical analysis and the calculated Combination Index (CI), the interaction between *Zingiber officinale* var. rubrum (ZOR) and *Curcuma longa* L. (CL) in this study is characterized as dose-dependent additive to antagonistic, rather than purely synergistic.In the PT assay, the combination groups (G6, G7, and G8) exhibited stable prolongation percentages (70–80%). This stability is quantitatively supported by the CI values of ZOR150/CL150 (CI = 0.94) and ZOR75/CL225 (CI = 0.86), which fall within the nearly additive to synergistic range according to the Chou-Talalay criteria[24]. These results suggest that at specific ratios, the bioactive compounds—likely gingerols from ZOR and curcuminoids from CL—work harmoniously to inhibit the extrinsic pathway and the common pathway of coagulation, specifically targeting Factor VII[37,38]. Conversely, the aPTT assay revealed a different interaction profile. While the combinations showed significant differences compared to single doses, the CI values for ZOR150/CL150 (CI = 1.20) and ZOR225/CL75 (CI = 1.50) indicate a clear antagonistic interaction. Based on these results, it is evident that increasing the proportion of ZOR interferes with the anticoagulant activity in the intrinsic pathway. This is demonstrated by the fact that the total prolongation remained below the level achieved by the single ZOR 300 mg/kg BW dose. Such antagonism may arise from competitive binding or counteractive effects on intrinsic factors (Factors VIII, IX, XI, or XII). Previous studies have noted that while individual plant extracts may exhibit anticoagulant properties, their combination can lead to "counter-active synergism" where compounds compete for the same enzymatic sites in the coagulation cascade[39]

The absence of a synergistic "jump" suggests that gingerols and curcuminoids may compete for the same binding sites or enzymatic targets within the coagulation cascade, such as Factor X or prothrombin. Literature suggests that when two compounds target the same step in a pathway, their combined effect often follows an additive model where the total response is the sum of their individual potencies at reduced concentrations, rather than a multiplicative enhancement[40,41].

Despite the lack of statistical synergy, the combination of *Zingiber officinale* var. *rubrum* and *Curcuma longa* L. holds significant therapeutic promise for preventing myocardial infarction. Myocardial infarction is often preceded by thrombosis triggered by hypercoagulability[42]. The ability of these combinations to consistently prolong PT and aPTT indicates a multi-target inhibition of the coagulation cascade.

The primary advantage of the combination therapy over single-extract administration lies in its balanced and synergistic phytochemical profile. By integrating *Zingiber officinale* var. *rubrum* and *Curcuma longa* L., a significant anticoagulant effect is achieved while utilizing lower individual doses of each extract, such as 150 mg/kg bw instead of 300 mg/kg bw. This dose reduction is clinically crucial for minimizing potential adverse effects, specifically the gastrointestinal irritation and dyspepsia frequently associated with the chronic consumption of high-dose gingerols[43].

Furthermore, the combination provides a broader pharmacological shield by targeting multiple steps in the pathophysiology of myocardial infarction. While gingerols and shogaols strongly target platelet-related pathways and thrombin activity—as evidenced by the significant PT and aPTT prolongation—curcuminoids offer profound anti-

inflammatory benefits that further stabilize the vascular endothelium. This multi-target approach is essential, as the thrombotic events leading to myocardial infarction are driven not only by coagulation factors but also by underlying vascular inflammation[44].

Consequently, the stable anticoagulant response observed across the combination groups (G6, G7, and G8) suggests that this herbal integration provides a more holistic and safer preventative strategy compared to high-dose monotherapy. By extending the coagulation time through both intrinsic and extrinsic pathways, this combination therapy potentially prevents the formation of occlusive thrombi, thereby reducing the risk of acute ischemic events in a hypercoagulable state.

CONCLUSION

The combination of *Zingiber officinale* var. rubrum and *Curcuma longa* L. effectively mitigates isoproterenol-induced hypercoagulability by significantly prolonging both PT and aPTT. Based on the Chou-Talalay analysis, the interaction is characterized as dose-dependent, ranging from nearly additive to synergistic in the extrinsic pathway (PT), while showing antagonism in the intrinsic pathway (aPTT) at higher ratios. Despite the lack of pure synergism across all parameters, the combination provides a stable anticoagulant response and a balanced phytochemical profile at reduced individual doses. These findings suggest that this herbal integration represents a promising and safer holistic strategy for the prevention of thrombotic events in myocardial infarction, though optimal dose-weighting is crucial to avoid antagonistic interference in the intrinsic coagulation cascade.

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