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HYPOCHOLESTEROLEMIC AND ANTI-ATHEROSCLEROTIC POTENTIAL OF CURCUMA RANGJUED RHIZOME EXTRACT VIA INHIBITION OF HMG-COA REDUCTASE

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ABSTRACT

HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase) is the key enzyme in the mevalonate pathway that governs cholesterol biosynthesis. Inhibition of HMG-CoA reductase effectively reduces hepatic cholesterol production. While synthetic statins are widely prescribed for hypercholesterolemia, their adverse effects highlight the need for natural, plant-derived HMG-CoA reductase inhibitors. Certain natural anti-inflammatory compounds, including polyphenols, flavonoids, and plant extracts, have been reported to inhibit HMG-CoA reductase, thereby suppressing cholesterol biosynthesis (Chaudhary et al., 2023).

Curcuma rangjued, commonly known as Scorpion Turmeric (Hue et al., 2024), is traditionally recognized for its potent anti-inflammatory properties, yet it remains underexplored scientifically. Building on prior evidence that the n-hexane fraction of C. rangjued rhizomes exhibits significant anti-inflammatory activity (Hue et al., 2024), we applied a green extraction method to isolate bioactive constituents from fresh rhizomes, designated as GERC7. The inhibitory potential of GERC7 against HMG-CoA reductase was evaluated following the protocol described by Cho et al. (2024).

Gas chromatography–mass spectrometry (GC–MS) analysis revealed that GERC7 primarily contains curcumenol, germacrone, and isocurcumenol, all recognized as potent anti-inflammatory sesquiterpenes (Gushiken et al., 2022). GERC7 demonstrated significant inhibition of HMG-CoA reductase activity, with an IC_{50} value of 58.12 ± 2.14 µg/mL, showing a statistically significant difference compared to the inhibitor-free control ($p < 0.05$). These results suggest that C. rangjued represents a promising medicinal resource with potential to reduce endogenous cholesterol synthesis and, consequently, the risk of atherosclerosis. Further in vivo studies are warranted to confirm its therapeutic potential as an alternative approach for managing hypercholesterolemia and related cardiovascular diseases.

Keywords: HMG-CoA reductase, GERC7, Curcuma rangjued, Nghe Bo Cap, Atherosclerosis.

1. INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of mortality worldwide. An estimated 17.9 million people died from CVDs in 2019, accounting for approximately 32% of all global deaths (WHO, 2019). Atherosclerosis develops as low-density lipoprotein (LDL) accumulates within the arterial endothelium as a consequence of elevated blood cholesterol or hypercholesterolemia. Hypercholesterolemia is influenced by the intake of

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cholesterol-rich foods and by endogenously synthesized cholesterol in the liver (Linton et al., 2019). The enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase plays a pivotal role in regulating the cholesterol biosynthetic pathway (Baskaran et al., 2015). Inhibition of HMG-CoA reductase activity reduces cholesterol synthesis and consequently enhances hepatic LDL uptake through the regulation of LDL receptors (Marahatha et al., 2021).

Turmeric is a major genus within the Zingiberaceae family and is widely cultivated in the Central Highlands of Vietnam. Traditional medicinal preparations derived from Curcuma longa, which contain the bioactive compound curcumin, have long been investigated and used for treating respiratory infections, bronchitis, asthma, gastric disorders, and various inflammatory skin conditions. However, Curcuma rangjued (Hue et al., 2024), locally known as Nghe Bo Cap, although sharing several general characteristics with other turmeric species, differs markedly from all Curcuma species documented in China, Laos, Cambodia, and Vietnam. Distinguishing traits include inflorescences emerging from among the leaf sheaths; a green inflorescence axis often marked by reddish streaks along the midrib; pale-green bracts; light-red coma bracts with a whitish base; and particularly, the pronounced bitterness of the rhizomes. Its unique phytochemical composition further contributes to pharmacological properties of potential relevance to human health. In traditional medicine, Nghe Bo Cap is recognized for its potent anti-inflammatory activity, with curcumenol, germacrone, and related constituents—rather than curcumin—identified as its principal bioactive compounds (Hue et al., 2024), which have demonstrated anti-inflammatory and antioxidant effects (Gushiken et al., 2022). Therefore, leveraging the anti-inflammatory properties of Nghe Bo Cap represents a promising research direction, particularly for supporting therapeutic strategies targeting atherosclerosis.

2. MATERIALS AND METHODS

2.1. Research Materials

Fresh rhizomes of Nghe Bo Cap (Curcuma rangjued) were collected in Gia Lai Province, Vietnam. Atorvastatin 10 mg tablets were obtained from STADA–Vietnam. The HMG-CoA reductase activity assay kit was purchased from Sigma-Aldrich (St. Louis, MO, USA).

2.2. Research Methods

2.2.1. Procedure for Preparing GERC7 from Nghe Bo Cap Rhizomes

Preparation of Nghe Bo Cap Extract

The extraction of fresh Nghe Bo Cap rhizome powder was carried out according to the method of Abubakar et al. (2020) with minor modifications. Two kilograms of dried rhizome powder were placed in an extraction flask with 6 liters of n-hexane and stirred continuously overnight (16 hours). The mixture was filtered to obtain 6 liters of n-hexane extract. The residue was subsequently re-extracted twice with n-hexane and twice with ethanol. All extracts were combined, and the solvents were removed by distillation, yielding a yellow liquid designated as sample Nb. The extraction procedure was repeated three times to determine the extraction efficiency.

GC-MS Analysis of Bioactive Compounds

The chemical composition of sample Nb was analyzed using gas chromatography–mass spectrometry (GC-MS) with a TG-5MS column (30 m × 0.25 mm × 0.25 µm). The injection port temperature was set at 260°C, and the detector temperature at 240°C. Retention indices (RI) were calculated and compared with reference data from the NIST 14 and Wiley 8 libraries (Adam, 2017). Compounds were identified based on their mass spectra and retention indices.

a. Nghe Bo Cap rhizomes collected from cultivated gardens

b. Nghe Bo Cap rhizomes before grinding

Figure 1. Image of Scorpion Turmeric raw material used to prepare the GERC7 test sample

Preparation of GERC7 Extract

Steam distillation was performed following the method of Marcac et al. (2023). The system was heated at 80°C for the first 2 hours to stabilize, then gradually increased to 90–100°C and maintained continuously. After half of the distillation time, the essential oil fraction was collected, and the remaining water extract was returned to the distillation flask. Heating continued until the end of the process, after which the entire fraction of essential oil and condensate was recovered. The collected distillate was emulsified with "Rung Sesan" honey to obtain the test sample, GERC7.

The chemical composition and bioactive constituents of GERC7 were analyzed using gas chromatography–mass spectrometry (GC-MS) as described by Baskaran et al. (2015).

2.2.2. HMG-CoA Reductase Inhibition Assay

The inhibitory activity of GERC7 on HMG-CoA reductase was determined using a commercially available assay kit according to the manufacturer's instructions (Sigma-Aldrich, St. Louis, MO, USA). Appropriate concentrations of GERC7 and the positive control atorvastatin were incubated with HMG-CoA reductase in the provided assay buffer. Enzyme activity was measured spectrophotometrically at the specified wavelength. The percentage of inhibition was calculated relative to the control.

The concentration of the purified enzyme solution (Sigma) ranged from 0.52 to 0.85 mg protein/mL. Pravastatin (Sigma) was used as the positive control. The rate of NADPH consumption was monitored every 20 seconds for up to 15 minutes using a spectrophotometric method. The percentage (%) of enzyme activity inhibition was calculated using the following formula:

$$\%\text{inhibition} = \frac{\Delta\text{Absorbance}_{control} - \Delta\text{Absorbance}_{test}}{\Delta\text{Absorbance}_{control}} \times 100$$

In there:

+ $\Delta\text{Absorbance}_{control}$: the change in absorbance in the absence of the test sample

+ $\Delta\text{Absorbance}_{test}$: the change in absorbance in the presence of the test sample

The final results are expressed as IC_{50} values, representing the concentration of the test sample that causes 50% inhibition of HMG-CoA reductase activity. Data are presented as mean ± SD. Statistical analysis was performed using Student's t-test in Microsoft Excel 2020. Differences were considered statistically significant at $p < 0.05$.

2.2.3. Data Analysis

All experiments, including extraction, GC-MS analysis, and enzyme inhibition assays, were performed in triplicate. Data were expressed as mean ± standard deviation (SD) and analyzed using appropriate statistical methods.

3. RESULTS

3.1. Analysis of Major Components in the n-Hexane Fraction of Curcuma rangjued rhizome

To investigate the major constituents of C. rangjued rhizome collected in Gia Lai, non-polar bioactive compounds were extracted for analysis.

Table 1. Bioactive compound quantities by peak order from GC-MS chromatogram of Curcuma rangjued extract

Peak Order	Compound	Content
1	Alpha-pinene	3.25%
2	β-pinene	10.89%
3	D-limonene	1.23%
4	Eucalyptol	16.11%
6	Beta elemene	3.82%
12	Curcumenoid	6.49%
14	Germacrone	25.59%
15	Curcumenol	20.65%

Note: Mass spectrometric analysis was performed using a TG-5MS 30m column (30 m × 0.25 µm × 0.25 mm). Injector temperature was maintained at 260°C, detector temperature at 240°C. Compound identification was based on retention indices (RI) and compared with NIST 14 and Wiley 8 libraries (Adam, 2017).

Extraction of C. rangjued rhizomes with n-hexane yielded a viscous yellow liquid (denoted as Nb) after three repetitions, with a yield of 9.86% ± 2.27% relative to fresh rhizome powder. Unlike common turmeric (Curcuma longa), GC-MS analysis of fresh Nb sample identified major valuable constituents (Table 1), including germacrone (25.59%), curcumenol (20.65%), and eucalyptol (16.11%).

Several studies have demonstrated that germacrone modulates T-lymphocyte balance to attenuate inflammatory progression (Tan et al., 2022) and exhibits anti-inflammatory and antioxidant effects (Fang et al., 2023). Curcumenol reduces inflammatory conditions (Yang et al., 2021), and eucalyptol possesses anti-inflammatory activity (Kim et al., 2020). Meanwhile, Ajoolabady argued that there is a close relationship between inflammation and atherosclerosis (Ajoolabady et al., 2024). This evidence suggests that sample Nb, containing anti-inflammatory compounds, demonstrates potential against atherosclerosis. However, due to the low yield of the n-hexane fraction and the objective of avoiding harmful organic solvents, steam distillation was employed as a safer alternative for bioactive compound recovery.

3.2. Formulation Process of Nghe bo cap Rhizomes for Producing the GERC7

Steam distillation extraction represents an environmentally clean methodology, utilizing water vapor as the solvent. This approach minimizes

environmental impact compared with organic solvents that generate waste, require air treatment, and demand explosion-proof equipment (Souza et al., 2020). This method often yields low efficiency, with essential oils showing poor solubility and stability in aqueous media, which limits pharmaceutical applications and leads to activity loss through volatilization. To enhance bioactive compound recovery efficiency, the process was optimized by reusing extraction water after the first half-cycle and emulsifying the final product with natural honey, achieving higher yields and improved quality. Recovery efficiency reached 50% relative to fresh material.

GC-MS analysis of sample GERC7 identified 16 bioactive compounds, including valuable constituents: germacrone (9.68%), curcumenol (17.66%), and isocurcumenol (36.5%). Several studies have confirmed that germacrone reduces oxidative stress (Fang et al., 2023), while curcumenol attenuates inflammatory conditions (Yang et al., 2021).

3.3. Evaluation of HMG-CoA Reductase Inhibitory Activity

Inhibition of HMG-CoA reductase reduces hepatic cholesterol biosynthesis. The in vitro inhibitory effect of GERC7 on HMG-CoA reductase is presented in Table 2.

Table 2. IC_{50} values of GERC7 against HMG-CoA reductase activity

Samples	IC50 (µg/mL)
GERC7 (µg/mL)	58.12 ± 2.14*
Pravastatin (nM)	68.95 ± 1.13**

*Values expressed as mean ± SD (n = 3). *p < 0.05; **: p < 0.001 compared to reactions without inhibitor*

Data in Table 2 demonstrate that GERC7 significantly inhibited HMG-CoA reductase activity with an IC_{50} of 58.12 ± 2.14 µg/mL, showing statistically significant difference compared to inhibitor-free control ($p < 0.05$).

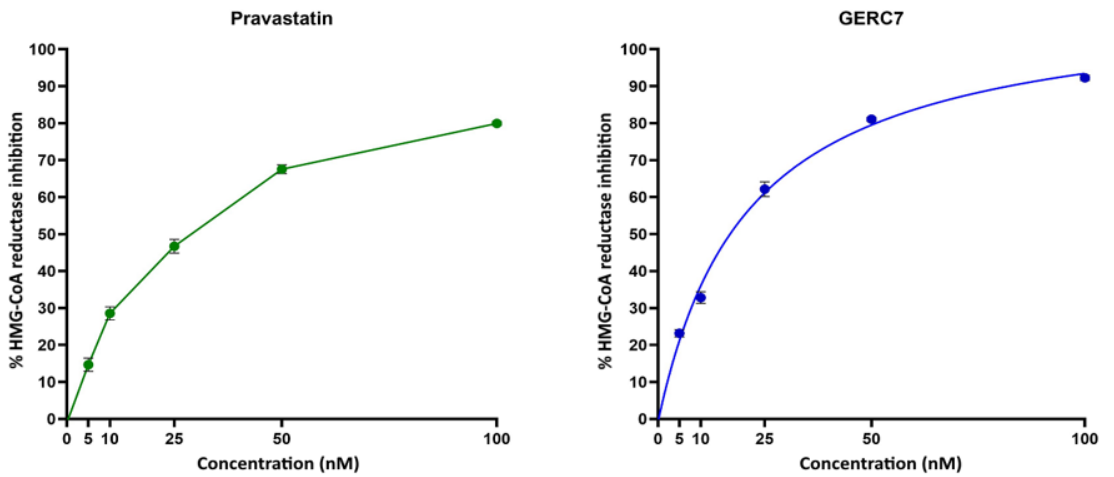

Figure 3. Inhibition curve of HMG-CoA reductase (%) for the test sample

Figure 3 illustrates concentration-dependent inhibition of HMG-CoA reductase activity by GERC7. Time-course spectral scans showed stronger inhibitory activity at increasing concentrations, suggesting direct interaction between the test sample and the enzyme.

4. DISCUSSION

The experimental results demonstrate that GERC7, a green extract from Curcuma rangjued rhizomes, inhibits HMG-CoA reductase with an IC_{50} of 58.12 ± 2.14 µg/mL, statistically different from negative controls ($p < 0.05$). This finding indicates that this extract holds potential for cholesterol biosynthesis inhibition at the in vitro level. Although HMG-CoA reductase inhibitory acvitity is lower compared to pure statins (pravastatin), GERC7 represents a complex extract containing multiple components (curcumenol, germacrone, isocurcumenol, and auxiliary compounds), reflecting synergistic effects rather than single purified compound efficacy. Studies indicate statins are commonly used to treat hypercholesterolemia. Due to statin side effects such as myalgia, elevated liver enzymes, or intolerance in some patients, natural plant-derived HMG-CoA reductase inhibitors are needed. Given its non-toxic nature (Hue et al., 2025) and content of curcumenol, germacrone, and isocurcumenol with strong anti-inflammatory properties (Yang et al., 2021; Fang et al., 2023), C. rangjued presents high potential for hypercholesterolemia treatment. Therefore, GERC7 offers scientific and applicative value, particularly for statin-intolerant patient populations, though further studies on pharmacokinetics, toxicity, and practical efficacy are required.

5. CONCLUSION

This study demonstrated that Curcuma rangjued rhizome extract, rich in curcumenol, germacrone, and isocurcumenol, exhibited HMG-CoA reductase inhibitory activity with an IC_{50} of 58.12 ± 2.14 µg/mL ($p < 0.05$ compared to negative controls), indicating biological potential for cholesterol synthesis modulation. Although inhibitory potency is lower than statins, these in vitro results provide first evidence that GERC7 directly affects the key enzyme in cholesterol biosynthesis.

Consequently, GERC7 may be considered a promising natural compound source for developing next-generation lipid-modulating products or supplements for statin-intolerant patients. Future research should focus on fraction separation, determination of IC_{50} values of purified compounds, cellular toxicity assessment, in vivo model efficacy, and particularly bioavailability evaluation of organic bioactive compounds to establish practical application potential.

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