



Research Article

In Silico Evaluation of Feasible Flavonoid-Based MURF-1 Inhibition for Sarcopenia Treatment

Ahn Ji Myung¹, Lee Sangmoon^{1,2}, Park Ho Je^{2,3}, Sanghyun Ahn²

¹Seolmyung Keoran Medicine Clinic, Gumi, Gyeongbuk 39312, Republic of Korea

²Department of Anatomy, College of Korean Medicine, Semyung University, Jecheon, Chungbuk 27136, Republic of Korea

³Goesan County Public Health Center, Goesan-gun, Chungbuk 28384, Republic of Korea

Abstracts



OPEN ACCESS

Received: 20 June 2025

Revised: 15 July 2025

Accepted: 10 August 2025

Published: 31 August 2025

Corresponding Author:

Sanghyun Ahn, Department of Anatomy, College of Korean Medicine, Semyung University, Jecheon, Chungbuk 27136, Republic of Korea
Tel: 82-043-649-1684
Fax: 82-043-649-1702
Email: smkmana@semyung.ac.kr

Copyright: © This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Background/Objectives: Sarcopenia is an age-related syndrome characterized by progressive loss of skeletal muscle mass and strength. Muscle RING Finger-1 (MURF-1), an E3 ubiquitin ligase, plays a pivotal role in muscle protein degradation and is considered a major driver of sarcopenia-associated muscle atrophy. This study aimed to investigate the therapeutic potential of flavonoid-based compounds as inhibitors of MURF-1 activity.

Methods: A variety of flavonoid subclasses—including flavanol, flavanone, flavone, isoflavone, flavonol, and anthocyanidin—were selected and their 3D structures were generated using ChemDraw, followed by energy minimization. Molecular docking simulations were performed using AutoDock to assess binding interactions and affinity with MURF-1. Flavonoid compounds were ranked based on predicted inhibitory potential. A comprehensive literature review was also conducted through PubMed and Google Scholar to evaluate the relevance of flavonoid–MURF-1 interactions in sarcopenia.

Results: Docking analysis revealed that several flavonoid compounds exhibited strong binding affinity to the active site of MURF-1, suggesting potential inhibitory effects. Among them, flavonols and isoflavones showed particularly favorable interaction energies. These results, combined with literature data, highlight the possibility that flavonoids may downregulate MURF-1 expression or activity, contributing to preservation of muscle mass and function

Conclusion: Flavonoid-based compounds show promise as candidate therapeutic agents for suppressing MURF-1-mediated muscle atrophy. These findings provide a foundation for developing novel strategies targeting sarcopenia through nutraceutical or pharmacological interventions.

Keywords: Sarcopenia; MURF-1; Flavonoids; Molecular docking; In silico analysis



Acknowledgy

This research was supported by Research Foundation of Seolmyung Keoran Medicine

Conflict of Interest

The authors have no conflicts of interest to declare and agreed to the published version of the manuscript.

Author Contributions

Lee Sagmoon and Park Ho Ge performed molecular docking analysis using AutoDock Vina. Ahn Ji Myung and Sanghyun Ahn participated in the study design and contributed to writing of the manuscript.

Introduction

Sarcopenia is an age-related condition characterized by a progressive decline in muscle mass and function, and is a major contributor to reduced quality of life, falls, and fractures in the elderly population [1]. This condition arises from an imbalance between muscle protein synthesis and degradation. Muscle RING Finger-1 (MURF-1) has been identified as a key factor promoting muscle atrophy [2]. As an E3 ubiquitin ligase, MURF-1 ubiquitinates contractile proteins such as myosin heavy chain (MHC), targeting them for proteasomal degradation [3]. This mechanism accelerates muscle protein breakdown, ultimately leading to muscle wasting.

Current treatments for sarcopenia—such as protein synthesis stimulators, hormone therapy, and exercise interventions—remain limited in their efficacy [4]. Consequently, there is growing interest in developing novel, natural compound-based therapeutic strategies to prevent or treat this condition [5, 6]. Flavonoids, a class of naturally occurring compounds with antioxidant, anti-inflammatory, and antimicrobial properties, have attracted attention for their potential to improve muscle health [7]. Recent studies suggest that certain flavonoids may suppress MURF-1 expression and mitigate muscle atrophy.

In silico approaches have emerged as powerful tools to complement experimental methods and enable efficient screening of drug candidates [8]. Structure-based drug design and molecular docking simulations enable the prediction of novel compounds, significantly reducing the time and cost required for experimental validation. While natural product research often faces challenges due to the structural complexity and lengthy evaluation processes, in silico methods can rapidly predict target binding potential and identify promising candidates for further study. Such approaches offer notable advantages in the investigation of complex, multifactorial diseases such as sarcopenia.

This study evaluates the potential of flavonoid compounds as MURF-1 inhibitors using in silico analysis and establishes a framework for identifying new therapeutic strategies for sarcopenia.

Materials & Methods

Three-dimensional modeling of flavonoid compounds

A set of flavonoid compounds—including flavanol, flavanone, flavone, isoflavone, flavonol, and anthocyanidin—was selected, and optimized three-dimensional (3D) structures were generated for each. Chemical structures were initially drawn in two dimensions (2D) using ChemDraw software. These structures were then converted into



3D models using Avogadro or Chem3D software, followed by energy minimization to ensure accurate representation of molecular geometry and charge distribution. The resulting optimized 3D structures were saved in Protein Data Bank (PDB) format for subsequent analysis.

Preparation of MURF-1 protein structure

The 3D structure of Muscle RING Finger-1 (MURF-1) was predicted using AlphaFold2. The protein structure was prepared for docking using AutoDockTools, which included the addition of hydrogen atoms and charge assignment. Potential ligand-binding sites were identified, and the predicted active site region was defined as the docking target.

Molecular docking analysis using AutoDock Vina

Molecular docking simulations were performed using AutoDock Vina to predict the binding affinity of each flavonoid compound to MURF-1. The docking procedure consisted of the following steps:

First, grid box setup: The docking grid was positioned around the predicted active site of MURF-1 to encompass the potential binding pocket.

Second, docking execution: AutoDock Vina was used to simulate the possible orientations and conformations of each flavonoid within the defined grid, allowing for translational, rotational, and conformational flexibility.

Third, binding energy calculation: Binding affinities were expressed as docking scores (kcal/mol), with lower values indicating stronger predicted interactions between the ligand and MURF-1.

Last, result visualization and analysis: Docking results were visualized using AutoDockTools to assess the binding poses and interaction patterns for each compound. Compounds with higher predicted binding affinity were considered potential candidates for further investigation as MURF-1 inhibitors in sarcopenia therapy.

Results

2D and 3D structure modeling of flavonoid compounds

A total of eight representative flavonoid compounds were designed in both two-dimensional (2D) and three-dimensional (3D) formats using ChemDraw and Chem3D software (Figure 1). The selected compounds represent major subclasses of flavonoids, including flavone, flavanone, flavanol, isoflavone, flavonol, and anthocyanidin. Figure 1 illustrates the 2D chemical structures, while Figure 2 presents the corresponding energy-minimized 3D structures generated for subsequent molecular docking analysis.

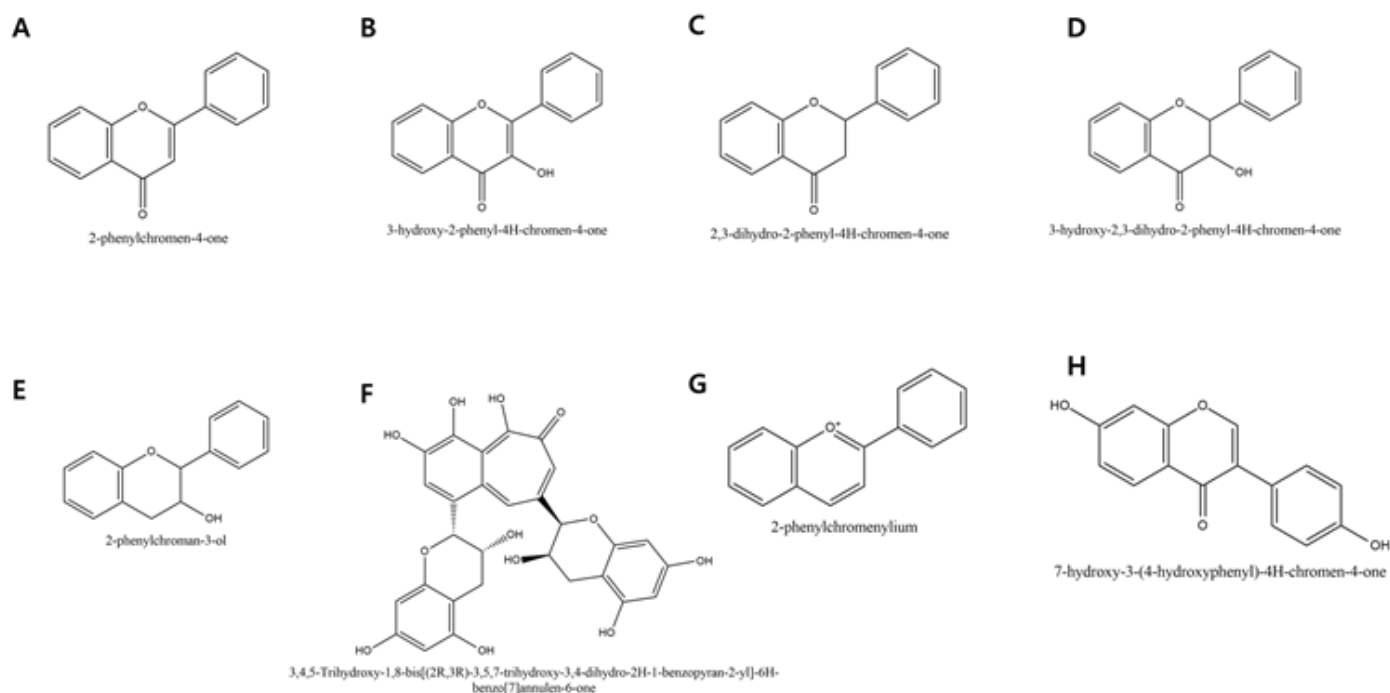


Figure 1. Chemical structures of representative flavonoid compounds drawn using ChemDraw. Structures include: (A) 2-Phenylchromen-4-one (Flavone), (B) 3-Hydroxy-2-phenyl-4H-chromen-4-one (Flavonol), (C) 2,3-Dihydro-2-phenyl-4H-chromen-4-one (Flavanone), (D) 3-Hydroxy-2-(3-hydroxyphenyl)-4H-chromen-4-one (Flavanonol), (E) 2-Phenylchroman-3-ol (Flavanol), (F) 3,4,5-Trihydroxy-1,8-bis[(2R,3R)-3,5,7-trihydroxy-3,4-dihydro-2H-1-benzopyran-2-yl]-6H-benzo[7]annulen-6-one (Theaflavin), (G) 2-phenyl-3,4-dihydro-2H-chromene (Anthocyanidin derivative), (H) 7-Hydroxy-3-(4-hydroxyphenyl)-4H-chromen-4-one (Isoflavone derivative).

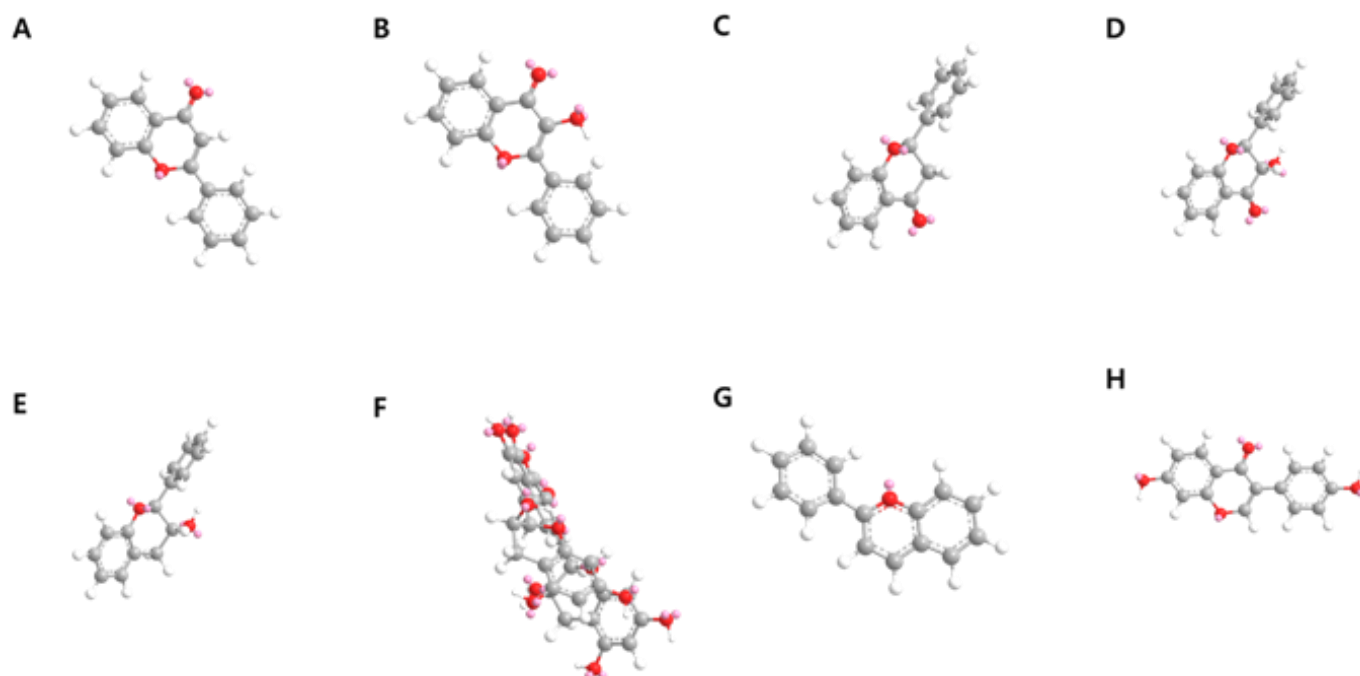


Figure 2. Three-dimensional (3D) molecular structures of representative flavonoid compounds were generated for molecular docking analysis. Structures were constructed using ChemDraw and energy-minimized using Chem3D/Avogadro software prior to docking simulations with the MURF-1 protein. Displayed compounds include: flavanol, flavanone, flavone, isoflavone, flavonol, and anthocyanidin derivatives, visualized in ball-and-stick representation to highlight atomic composition (carbon: grey, oxygen: red, hydrogen: white).

In silico prediction of binding affinity between MURF-1 and flavonoids

The predicted binding affinities of each flavonoid compound to the MURF-1 protein are as follows: plibon, -6.796 kcal/mol; flavonol, -6.923 kcal/mol; flavanone, -7.193 kcal/mol; flavadonol, -7.228 kcal/mol; flavanol, -6.943 kcal/mol; theaflavin, -8.039 kcal/mol; anthocyanin, -6.787 kcal/mol; and isoflavone, -7.070 kcal/mol.

Theaflavin exhibited the strongest predicted binding affinity (-8.039 kcal/mol), indicating superior interaction with MURF-1 compared to the other flavonoids. Anthocyanin showed the weakest binding affinity (-6.787 kcal/mol), reflecting lower binding stability. All compounds demonstrated negative binding energy values, which indicates the potential to form stable complexes with MURF-1.

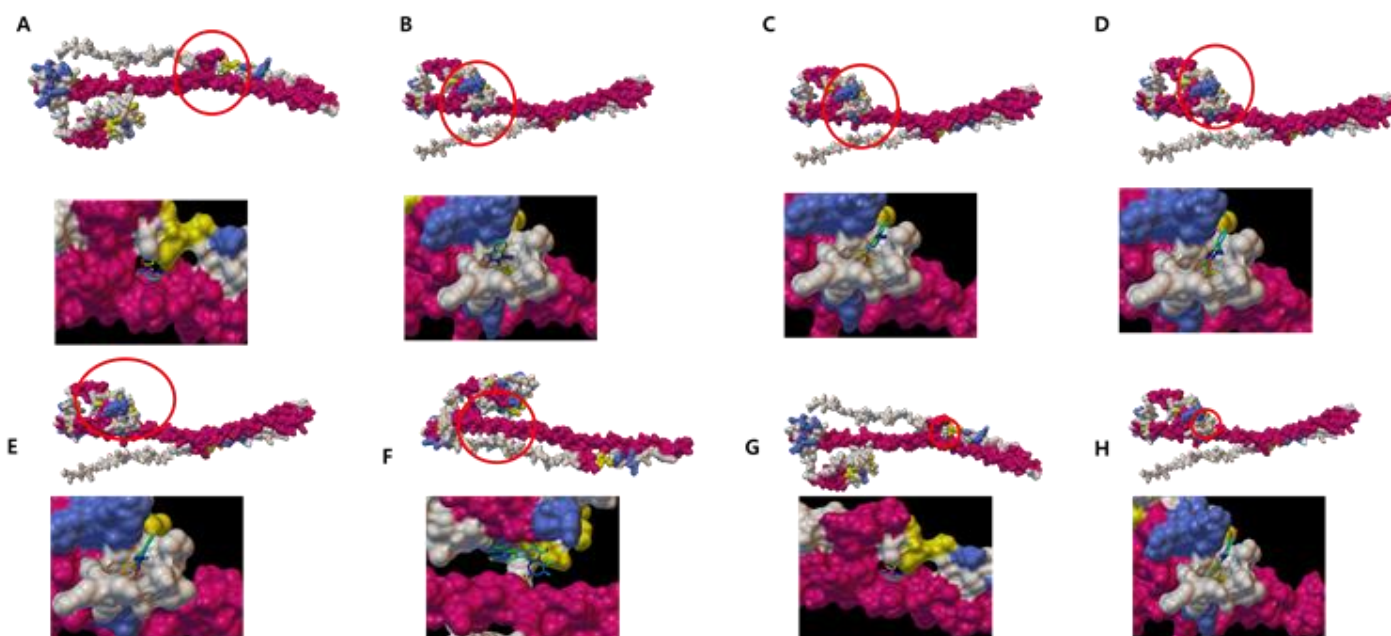


Figure 3. Binding affinity prediction of energy-minimized flavonoid structures with MURF-1 protein using AutoDock Vina. Red circles indicate the binding sites of each flavonoid ligand on the MURF-1 surface.

Discussions

This study evaluated the binding potential of various flavonoid compounds to the MURF-1 protein using in silico molecular docking analysis. All tested compounds exhibited negative binding affinity values, indicating potential to form stable complexes with



MURF-1. Theaflavin showed the strongest predicted binding affinity (-8.039 kcal/mol), identifying it as a lead candidate for MURF-1 inhibition. Anthocyanin displayed the weakest binding affinity (-6.787 kcal/mol), which may necessitate structural modification or the development of derivatives.

Flavonoids can vary considerably in their interaction with protein binding sites due to structural diversity [9]. The trends observed in this study are consistent with previous reports, highlighting the influence of the number and position of hydroxyl groups, aromatic ring planarity, and glycosidic substitutions on binding affinity [10]. In particular, theaflavin, with its extended aromatic framework and multiple hydroxyl substitutions, may achieve high affinity for MURF-1 by forming strong hydrogen bonds and π - π stacking interactions within the active site.

MURF-1, an E3 ubiquitin ligase, plays a central role in muscle protein degradation and is a key pathological factor in sarcopenia and other muscle-wasting disorders [11]. Previous studies have demonstrated that certain flavonoids modulate the ubiquitin-proteasome system to attenuate muscle atrophy [12]. For example, quercetin has been shown to suppress the expression of MuRF-1 and Atrogin-1 in both high-fat diet-induced obesity models and tail suspension models, thereby alleviating muscle mass loss. Similarly, (-)-epicatechin has been reported to inhibit FoxO1A and MuRF-1, leading to improvements in muscle atrophy. Other flavonoids, such as baicalin and genkwanin, have been reported to suppress MuRF-1-related proteolytic pathways while promoting muscle protein synthesis pathways [13,14].

Meta-analyses have further demonstrated that flavonoid intake improves musculoskeletal health markers in middle-aged and older adults, with increases in muscle mass and improvements in functional performance measures, such as the Timed-Up and Go test, in patients with sarcopenia [15,16,17]. These findings suggest that flavonoids not only suppress muscle atrophy but may also help preserve or enhance muscle function [18,19,20].

This study is limited to *in silico* analysis. Further evaluation of absorption, distribution, metabolism, and excretion (ADME) profiles, as well as cytotoxicity, is required. High binding affinity does not always correlate with biological activity; therefore, validation using *in vitro* cell models and *in vivo* animal studies is necessary to ensure accurate interpretation. Future research should include structure-based optimization based on docking results to enhance the inhibitory potential of flavonoid derivatives against MURF-1.



Conclusion

In conclusion, this study demonstrates a close relationship between flavonoid structural characteristics and binding affinity for MURF-1, highlighting theaflavin as a particularly promising candidate for sarcopenia therapy. Given their multi-target regulatory properties, low toxicity, and high safety profile, flavonoid-based natural compounds offer considerable potential for the development of preventive and therapeutic strategies not only for sarcopenia but also for a range of other muscle disorders.

References

1. Larsson L, Degens H, Li M, Salviati L, Lee YI, Thompson W, Kirkland JL, Sandri M. Sarcopenia: Aging-Related Loss of Muscle Mass and Function. *Physiol Rev.* 2019;99(1):427–511.
2. Gumucio JP, Mendias CL. Atrogin-1, MuRF-1, and sarcopenia. *Endocrine.* 2013;43(1):12–21.
3. Clarke BA, Drujan D, Willis MS, Murphy LO, Corpina RA, Burova E, Rakhilin SV, Stitt TN, Patterson C, Latres E, Glass DJ. The E3 Ligase MuRF1 degrades myosin heavy chain protein in dexamethasone-treated skeletal muscle. *Cell Metab.* 2007;6(5):376–385.
4. Huang LT, Wang JH. The Therapeutic Intervention of Sex Steroid Hormones for Sarcopenia. *Front Med (Lausanne).* 2021;8:739251.
5. Bagherniya M, Mahdavi A, Shokri-Mashhadi N, Banach M, Von Haehling S, Johnston TP, Sahebkar A. The beneficial therapeutic effects of plant-derived natural products for the treatment of sarcopenia. *J Cachexia Sarcopenia Muscle.* 2022;13(6):2772–2790.
6. Yadav A, Yadav SS, Singh S, Dabur R. Natural products: Potential therapeutic agents to prevent skeletal muscle atrophy. *Eur J Pharmacol.* 2022;925:174995.
7. Kim C, Hwang JK. Flavonoids: nutraceutical potential for counteracting muscle atrophy. *Food Sci Biotechnol.* 2020;29(12):1619–1640.
8. Agamah FE, Mazandu GK, Hassan R, Bope CD, Thomford NE, Ghansah A, Chimusa ER. Computational/in silico methods in drug target and lead prediction. *Brief Bioinform.* 2020;21(5):1663–1675.
9. Liu EH, Qi LW, Li P. Structural relationship and binding mechanisms of five flavonoids with bovine serum albumin. *Molecules.* 2010;15(12):9092–9103.
10. Ćorković I, Gašo-Sokač D, Pichler A, Šimunović J, Kopjar M. Dietary Polyphenols as Natural Inhibitors of α -Amylase and α -Glucosidase. *Life.* 2022;12(11):1692.
11. Sartori R, Romanello V, Sandri M. Mechanisms of muscle atrophy and hypertrophy: implications in health and disease. *Nat Commun.* 2021;12(1):330.
12. Huang Z, Fang Q, Ma W, Zhang Q, Qiu J, Gu X, Yang H, Sun H. Skeletal Muscle Atrophy Was Alleviated by Salidroside Through Suppressing Oxidative Stress and Inflammation During Denervation. *Front Pharmacol.* 2019;10:997.
13. Le NH, Kim CS, Park T, Park JH, Sung MK, Lee DG, Hong SM, Choe SY, Goto T, Kawada T, Yu R. Quercetin protects against obesity-induced skeletal muscle inflammation and atrophy. *Mediators Inflamm.* 2014;2014:834294.
14. Ramirez-Sanchez I, Navarrete-Yañez V, Ramirez L, Galera L, Mendez-Bolaina E, Najera V, Ceballos G, Villarreal F. Restorative effects of (+)-epicatechin in a rodent model of aging induced muscle atrophy: underlying mechanisms. *Food Funct.* 2024;15(7):3669–3679.
15. Li Y, Liu Y, Tan R, Liu Y. Effect of flavonoids on skeletal muscle mass, strength and physical performance in middle-aged and older adults with or without Sarcopenia: A meta-analysis of randomized controlled trials. *Front Nutr.* 2022;9:1013449.
16. Nikawa T, Ulla A, Sakakibara I. Polyphenols and Their Effects on Muscle Atrophy and Muscle Health. *Molecules.* 2021;26(16):4887.
17. Draganidis D, Karagounis LG, Athanailidis I, Chatzinikolaou A, Jamurtas AZ, Fatouros IG. Inflammaging and Skeletal Muscle: Can Protein Intake Make a Difference? *J Nutr.* 2016;146(10):1940–1952.

18. Wu C, Suzuki K. The Effects of Flavonoids on Skeletal Muscle Mass, Muscle Function, and Physical Performance in Individuals with Sarcopenia: A Systematic Review of Randomized Controlled Trials. *Nutrients*. 2023;15(18):3897.
19. Munguía L, Ortiz M, González C, Portilla A, Meaney E, Villarreal F, Nájera N, Ceballos G. Beneficial Effects of Flavonoids on Skeletal Muscle Health: A Systematic Review and Meta-Analysis. *J Med Food*. 2022;25(5):465–486.
20. Wang Y, Tian Z, Li Z, Kim JC. Effects of Flavonoid Supplementation on Athletic Performance in Healthy Adults: A Systematic Review and Meta-Analysis. *Nutrients*. 2023;15(21):4547.