

Novel HP2MGL resin-based enrichment of flavonoids from *Dendrobium catenatum* flower and their antiaging efficacy

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ABSTRACT

This study aimed to enrich flavonoids from *Dendrobium catenatum* Wall ex Lindl flowers using macroporous resins and investigate their bioactivity. The optimal enrichment process with HP2MGL resin was established with a total flavonoid concentration of 0.50 mg/mL, a sample flow rate of 1 BV/h, and a sample volume of 25.5 BV. Desorption was performed using 80% ethanol at a flow rate of 3 BV/h and an eluent volume of 5 BV. The purified extract showed a 7.3-fold increase in purity compared to the crude extract. A total of 33 major compounds in the purified flavonoids were identified and quantified, including flavonols and flavonoid C-glycosides, with hyperoside being the most abundant. In vivo tests demonstrated that the enriched extract extended the lifespan of *Caenorhabditis elegans*, enhanced locomotion, and increased superoxide dismutase activity while significantly reducing oxidative stress markers such as lipofuscin, reactive oxygen species, and malondialdehyde. The findings provide a practical method for large-scale extraction of flavonoids from *D. catenatum* flowers and suggest that *Dendrobium catenatum* flower extract (DCFE-E) exhibits strong antiaging properties, indicating potential applications in functional foods and cosmetics. This research contributes to the scientific understanding of *D. catenatum* resource utilization and enhances the value of its products.

KEYWORDS

antiaging; *Caenorhabditis elegans*; *Dendrobium catenatum* flowers; flavonoids, enrichment

1 | INTRODUCTION

Dendrobium catenatum Wall ex Lindl is a perennial epiphytic herb of the genus *Dendrobium* in the Orchidaceae family. This plant's fresh or dried stems are commonly utilized for its therapeutic properties, which include nourishing yin, eliminating heat, nourishing the stomach, moistening the lungs, alleviating cough, and enhancing eyesight. Therefore, it is believed that they strengthen the

body and improve health (Wei et al., 2016; Yan et al., 2015). Recently, because of advancements in tissue culture and cultivation techniques, *D. catenatum* has been extensively grown, leading to an increase in its leaf and flower resources. However, although *D. catenatum* has been increasingly applied in the food industry, its aboveground parts (leaves and flowers) are primarily regarded as by-products and, scientifically, have not been fully developed. Our previous research indicated the

Abbreviations: *C. elegans*, *Caenorhabditis elegans*; DCFE, *Dendrobium catenatum* flower extract; DCFE-E, the enriched product of *Dendrobium catenatum* flower extract; DCFH-DA, 2,7-dichlorodihydrofluorescein diacetate; LB, Luria-Bertani; MDA, malondialdehyde; NGM, nematode growth medium; ROS, reactive oxygen species; SOD, superoxide dismutase; TFC, total flavonoid content; UPLC-QTRAP-MS/MS, ultrahigh performance liquid chromatography-triple quadrupole/linear ion trap mass spectrometry.

Yuntao Guo and Danni Lai contributed equally to this study.

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presence of various bioactive compounds, such as phenylpropanoids, C-glycosyl flavones, and O-glycosyl flavones in the flowers of *D. catenatum*. These compounds provide stronger antioxidant activity for *D. catenatum* flowers, especially their phenolic components, such as flavonoids (Zhang et al., 2019). Therefore, determining the biological activity of these natural chemicals in the by-products may help the utilization of these resources more effectively.

As the population ages, the risk of tissue damage increases, as does the likelihood of developing cancer, neurodegenerative, or cardiovascular diseases (Calcinotto et al., 2019). Many studies have indicated that flavonoids' positive impact on chronic diseases mostly comes from their antioxidant qualities, which allow them to counteract free radicals and effectively bind redox metal ions (Butterfield & Halliwell, 2019). Additionally, flavonoids have been shown to promote the synthesis of antioxidant enzymes (Jomova et al., 2023). Traditional Chinese medicines, rich in flavonoids with diverse chemical structures, targeting multiple molecules, and exhibiting low toxicity, hold significant potential in preventing aging and age-related diseases (Wu et al., 2021). Furthermore, flavonoids have garnered attention for their various biological activities, including antioxidant (de Lima et al., 2024), anti-inflammatory (Kaushal et al., 2022), antidiabetic (Rajan et al., 2022), and skin-protective activities (Estrella-Parra et al., 2019).

Despite the richness of flavonoids in *D. catenatum* flowers, further research is warranted to verify their bioactivity. In vitro cell models serve as valuable tools for evaluating the biological activity of ingredients. While some toxic ingredients may induce multi-system disorders in vivo, such as alterations in behavior and metabolism, organoid models can only approximate organ responses in vitro and may capture only partial phenotypes of specific models, such as oxidative stress or inflammation models (Hofer & Lutolf, 2021). Rodent models provide insights into in vivo phenotypes but necessitate higher doses, longer experimental periods, more complex techniques, and stricter controls. *Caenorhabditis elegans* models offer a unique advantage, as they combine the sensitivity of in vitro models with the partial in vivo phenotypes observed in rodent models, enabling the elicitation of toxicity with the same dose in both cellular and *C. elegans* models (Li et al., 2023). *C. elegans* models could provide quicker and more effective results in food science research. The lifespan test is a specific scientific method used to evaluate the antiaging effects of drugs (Navarro-Hortal et al., 2022; Wang, Wang, et al., 2022). Given the lack of verification regarding the antiaging activity of flavonoids in *D. catenatum* flowers, this study marks the first employment of *C. elegans* models to assess such activity.

Traditional extraction methods frequently rely on alcohol solvents known for their robust solubility;

nevertheless, this practice often yields extracts where flavonoids coexist with various other components, consequently diminishing their purity. Hence, it becomes imperative to devise an efficient flavonoid enrichment technique, enabling a more thorough investigation into the biological activities inherent within the flavonoid components extracted from *D. catenatum* flowers. Macroporous resin chromatography is a commonly used separation and enrichment technology for purifying natural product active components (Chen et al., 2022), such as flavonoids in jujube peel (Shen et al., 2022) and polyphenols in leaves (Hou et al., 2020). This technology offers benefits such as easy operation, cost-effectiveness, substantial purifying efficiency, little solvent usage, and convenient regeneration. Many macroporous resins use ethanol-water solutions for adsorbing and desorbing target components, which promotes environmentally friendly product purification and treatment operations. Furthermore, the adsorption capacity of the macroporous resin for different polarity components is determined by its physical properties, including polarity, particle size, surface area, van der Waals force, and hydrogen bonding interaction (Chen et al., 2022; Guo et al., 2021). Therefore, using macroporous resin to enrich flavonoids from *D. catenatum* flowers is a feasible strategy.

The aim of this study was to develop an efficient method to enrich flavonoids from *D. catenatum* flowers and to study their biological effects using the *C. elegans* model. First, seven resins are screened to determine the optimal resin for total flavonoid enrichment. Second, the ideal enrichment settings are determined through studying the impact of adsorption kinetics, sample pH, and eluent concentration on adsorption-desorption capacity. Third, the ideal dynamic enrichment settings are identified by assessing dynamic adsorption and desorption. Fourth, the products of *D. catenatum* flower extract (DCFE-E) after enrichment are detected via UPLC-QTRAP-MS/MS. Subsequently, using *C. elegans* as a model organism, the antiaging properties of DCFE-E are studied in vivo. By comprehensively understanding flavonoids and their biological activities in *D. catenatum* flowers, more health benefits and potential applications delaying aging could be discovered. This would encourage the efficient use of this rich resource and provide a scientific foundation for creating novel antiaging treatments and dietary supplements.

2 | MATERIALS AND METHODS

2.1 | Plant materials

The flowers were collected in the Lin'an area of Hangzhou, Zhejiang Province. After harvesting, the samples were rapidly stabilized at 90°C by hot air for 8 min. The samples were subsequently dehydrated in a 60°C oven

until a stable weight was achieved and then coarsely pulverized and filtered through a 60-mesh screen. The resulting material was subsequently stored in a temperature-stabilized, light-protected desiccator.

2.2 | Chemicals and strains

Macroporous resins (D-101-IHP-20\AB-8\HP2MGL\NKA-9\HPD-500/ADS-9) were obtained from HeCheng New Material Technology Co., Ltd. (Zhengzhou, China). The specific physicochemical parameters of these resins are mentioned in Supporting Information S1: Table S1. Aladdin Biotechnology Co., Ltd. supplied levamisole, dimethyl sulfoxide (DMSO), and 2,7-dichlorodihydrofluorescein diacetate (DCFH-DA). All other chemical reagents for this investigation were of analytical grade.

2.3 | Preparation of crude *D. catenatum* flower extract

The *D. catenatum* flowers were ground into powder and then extracted using an 80% ethanol solution at 50°C for 30 min with a solid–liquid ratio of 30:1. The extraction was repeated thrice and the supernatants were collected. After overnight sedimentation, the supernatants were filtered and concentrated using rotary evaporation at 55°C. The concentrations obtained were freeze-dried and kept at −20°C for further examination.

2.4 | The total flavonoid content (TFC) assay

A 2 mL aliquot of the sample extract was accurately pipetted into a 25 mL volumetric flask preloaded with 1 mL of a 5% NaNO₂ solution. The mixture was incubated at room temperature for 6 min to allow the system to reach equilibrium. Following this, 1 mL of a 10% Al(NO₃)₃ solution was added, and the reaction was allowed to proceed for an additional 6 min. Subsequently, 10 mL of a 4% sodium NaOH solution was introduced into the flask. The final volume was adjusted to 25 mL with 80% ethanol. After a 15-min incubation period, the absorbance of the resulting solution was measured at 510 nm using a spectrophotometer.

2.5 | Optimization of *D. catenatum* flowers extract enrichment processes

2.5.1 | Resin screening

Pretreated macroporous resin (1 g) and DCFE solution (10 mL) are prefilled into 50 mL centrifuge tubes and placed on a constant temperature shaker at 25°C and 180 rpm for 12 h. The TFC in the supernatant was

determined. Formula (1) was used to evaluate the adsorption capacity. The macroporous resin was agitated with 15 mL of 80% ethanol at 25°C and 180 rpm for 12 h until the adsorption equilibrium was reached. We then measured the TFC in the supernatant to ascertain the desorption capacity. The following Formulas (1)–(3) were used to determine the desorption capacity and desorption rate.

$$q_e = \frac{(C_0 - C_e)V_i}{W}, \quad (1)$$

$$q_d = \frac{C_d V_d}{W}, \quad (2)$$

$$D(\%) = \frac{C_d V_d}{(C_0 - C_e)V_i} \times 100. \quad (3)$$

The following symbols were used to represent the relevant parameters: C_0 is the initial TFC concentration (mg/mL) in the solution; C_e is the TFC concentration (mg/mL) in the solution at adsorption equilibrium; C_d is the TFC concentration (mg/mL) in the desorption solution; V_i is the volume (mL) of the DCFE solution; V_d is the volume (mL) of the desorption solution; W represents the dry weight (mg) of the resin, while D represents the desorption (%).

2.5.2 | Adsorption kinetics

In a 250 mL conical flask, transfer 1 g of the pretreated resin and add 100 mL of the flavonoid-containing DCFE solution (0.50 mg/mL). The residual flavonoid concentration was estimated at certain intervals while the conical flask was shaken for 12 h at 25°C and 180 rpm (30, 60, 90, 120, 180, 240, and 360 min). To clarify the adsorption process of flavonoids and rationally design an adsorption system in accordance with it, the adsorption kinetics of flavonoids on HP2MGL resin were assessed using three standard kinetic models:

The pseudo-first-order model had the following linear form:

$$\lg(q_e - q_t) = -\frac{k_1 t}{2.303} + \lg q_e. \quad (4)$$

The pseudo-second-order model had the following linear form:

$$\frac{t}{q_t} = \frac{1}{k_2 q_e^2} + \frac{t}{q_e}. \quad (5)$$

The intraparticle diffusion model had the following linear form:

$$q_t = k_i t^{1/2} + C. \quad (6)$$

The quantity of flavonoids adsorbed at a certain time t (min) is represented by the variable q_t . The pseudo-first order, pseudo-second order, and intraparticle diffusion models' rate constants are represented by the symbols k_1 , k_2 , and k_i , respectively. In the Weber–Morris model, C stands for the thickness of the boundary layer.

2.5.3 | Influence of pH on the process of adsorption and desorption

A centrifuge tube (50 mL capacity) containing 1 g of pretreated resin was filled with 10 mL of DCFE solution. The pH of the solutions was modified from 1 to 8 by using a 4% (v/v) solution of HCl or a 4% (w/v) solution of NaOH, as needed. The following Equations (7), (3), and (8) calculated the adsorption capacity, desorption capacity, and recovery.

$$A \quad (\%) = \frac{C_0 - C_e}{C_0} \times 100, \quad (7)$$

$$R \quad (\%) = \frac{C_d V_d}{C_0 V_i} \times 100. \quad (8)$$

Here, A and R denote the rate of adsorption and recovery.

2.5.4 | Influence of eluent concentration on the desorption capacity

Flavonoid adsorption experiments were performed on HP2MGL resin, as described in Section 2.5.1. The HP2MGL resin containing the sample was first cleaned with deionized water after the absorption equilibrium was achieved. Next, various ethanol concentrations in water (20%, 40%, 60%, 80%, and 95%) were employed as the eluent to desorb the flavonoids for 12 h at 25°C and 180 rpm, 25 mL.

2.5.5 | Dynamic adsorption/desorption process

The wet loading method was utilized for the dynamic adsorption and desorption experiments that followed. The HP2MGL resin underwent pretreatment before being introduced into a glass column of 15 mm in outer diameter, 200 mm in height, and weighing a total of 12.0 g.

(1) Dynamic adsorption experiments

The column received the DCFE solution (0.50 mg/mL) at flow rates of 1, 3, and 5 BV/h. Afterward, 6 mL effluent samples were prepared for each flow rate, and the TFC was calculated at every flow rate.

(2) Dynamic desorption experiments

The column reached adsorption equilibrium with the DCFE solution, and then the adsorbed HP2MGL resin was rinsed with distilled water until the water running out of the column was transparent. One hundred milliliters of 80% ethanol was used to elute the flavonoids from the resin by passing it through the column at flow rates of 1, 3, and 5 BV/h, determined from the optimum ethanol concentration identified in the static desorption experiment. The TFC in the 6 mL effluent sample was determined at each flow rate.

2.6 | HPLC-DAD analysis

The methods used in the HPLC-DAD assay were following those employed in our previous studies (Zhang et al., 2019).

2.7 | UPLC-QTRAP-MS/MS analysis

The DCFE-E was analyzed utilizing a UPLC-ESI-MS/MS system. UPLC conditions included a Waters ACQUITY UPLC HSS T3 C18 column (100 mm × 2.1 mm i.d., 1.8 μm) with a solvent system comprising 0.05% formic acid in water (A) and acetonitrile (B). Gradient elution was carried out as follows: 0–1 min, 10%–20% B; 1–9 min, 20%–70% B; 9–12.5 min, 70%–95% B; 12.5–13.5 min, 95% B; 13.5–13.6 min, 95%–10% B; 13.6–15 min, 10% B; with a flow rate of 0.35 mL/min, temperature set at 40°C, and injection volume of 2 μL.

Flavonoids underwent analysis using scheduled MRM on a QTRAP[®] 6500+ LC-MS/MS System equipped with an electrospray ionization (ESI) Turbo Ion-Spray interface, operating in both positive and negative ion modes. ESI source parameters were configured as follows: ion source ESI+/-, source temperature of 550°C, IS of 5500 V (positive) and -4500 V (negative), and CUR of 35 psi. Data acquisition was performed utilizing Analyst 1.6.3 software (Sciex), and metabolite quantification was conducted using Multiquant 3.0.3 software (Sciex).

2.8 | Detection of lifespan-related parameters in *C. elegans*

2.8.1 | Strain preparation and *C. elegans* treatment

Escherichia coli (*E. coli*) OP50 was grown in LB medium, and N2 worms were grown in nematode growth media (NGM) plates at 20°C with *E. coli* OP50 as their meal. To obtain synchronized eggs, adult worms were lysed using a bleach solution (20:25:55 of sterile water, 100% sodium hypochlorite, and 2 mol/L NaOH). The eggs were washed using M9 buffer and then moved to NGM

plates. Following a 48-h incubation at 20°C, L4 worms of the same age were gathered for further testing.

2.8.2 | Lifespan assay

The DCFE-E solution was diluted to the working concentration using sterile water and added to NGM plates for subsequent analyses. Three concentration gradients were designed for this experiment, namely the blank control group (final concentration of 0.1% DMSO), the low dose group (25 µg/mL drug), the medium dose group (50 µg/mL drug), and the high dose group (100 µg/mL drug). Worms at the synchronized L4 stage were moved to NGM/OP50 plates following the outlined procedure. The NGM plates were changed every 2 days until all worms were dead. Worms were deemed dead if they showed no reaction after being touched by the picker. Deaths of missing worms and eggs hatching in adult worms were not recorded.

2.8.3 | Body length

The synchronized L4 nematodes were placed on NGM plates with varying levels of DCFE-E, and then kept at 20°C for 5 days. Images were taken using a stereo fluorescence microscope (Olympus, SZX-16), and worm dimensions were assessed using the accompanying software.

2.8.4 | Locomotion ability

Each group included one plate with 30 worms. The *C. elegans* were moved to fresh plates every day to avoid overcrowding or contamination by other worms at their different developmental stages. On day 5 of treatment, the *C. elegans* were collected in M9 droplets, and the number of body bends in 10 s was recorded.

2.8.5 | Reproductive assay

The synchronized L4 worms were moved to NGM plates with different doses of the medication, each plate containing just one worm. The worms were moved to fresh NGM plates every day for 5 days, while keeping the old plates. After 3 days, the number of hatched worms on the old plates was documented, and the total larval count was recorded as fecundity.

2.8.6 | Determination of lipofuscin level

Following a cultivation period of 5 days, the worms were rendered unconscious using a solution of levamisole hydrochloride (10 mM) and immobilized on slides coated with 2% agarose. The spontaneous blue fluorescence of

lipofuscin in the body of the worms was observed and photographed under a stereofluorescence microscope. The worms from various treatment groups were subjected to fluorescence intensity measurements using ImageJ software.

2.8.7 | Relative changes in reactive oxygen species (ROS)

To two individual 1.5 mL microfuge tubes, 30 *C. elegans* cultured on both the blank and experimental group medium were added and kept for 5 days. Each *C. elegans* specimen was washed thrice thoroughly with M9 buffer solution to remove any residual bacteria from the surface, and the supernatant was aspirated carefully after each washing step. Then, 990 µL of M9 buffer solution and 10 µL of DCFH-DA were mixed, and 1 mL of this mixture was added to each microfuge tube of *C. elegans*. The tubes were incubated in darkness at 37°C for 1 h and then rinsed twice with M9 buffer solution. Next, 10 mM levamisole was used to anesthetize the *C. elegans* and they were suspended at the bottom of the microfuge tubes. Then, a coverslip was placed on a 2% agarose slide with 20 µL of *C. elegans* suspension on it and observed within 1 h. Fluorescence pictures were taken using a fluorescence microscope that offered a full-body view. The relative intensity of fluorescence in worms was estimated using the Image J software.

2.8.8 | Measurement of malondialdehyde accumulation and superoxide dismutase activities

Following a 10-day culture period, worms were rinsed thrice with M9 buffer and then moved to 1.5 mL centrifuge tubes. The worms were homogenized on ice using a handheld homogenizer, and the supernatant was centrifuged. The SOD and MDA levels were measured following the instructions of the commercial kits.

2.9 | Statistical analysis

The ggplot2 R package was used for compositional analysis and mapping. The experimental data were analyzed using SPSS 25 software. For one-way analysis of variance of multiple comparisons, Duncan's test was used. Unless otherwise stated, all experiments were initiated from the L4 stage.

3 | RESULT AND DISCUSSION

3.1 | Resin screening

The composition of flavonoids in *D. catenatum* flowers included various subclasses, including flavones and

O- and C-glycosides. The adsorption and desorption performances of different macroporous resins varied due to differences in polarity, pore size, and surface area, rendering resin selection crucial for the efficient enrichment of DCFE (Li et al., 2022). Comparative analysis of seven resins revealed superior adsorption and desorption capacities of HP2MGL resin compared to other resins (Figure 1). This observation indicates that DCFE may predominantly comprise polar components rich in polar hydroxyl groups and glycosidic bonds (Chen et al., 2022), which are well-matched by the polarity of HP2MGL resin. The adsorption and desorption performances of D-101-I, HP-20, and AB-8 were similar, possibly influenced by their surface areas and similar polarities. The surface areas followed the order D-101-I > HP-20 > AB-8; their adsorption capacities displayed a similar trend. Despite moderate polarity resembled that of HP2MGL, NKA-9 resin exhibited significantly lower adsorption capacity attributed to its considerably smaller surface area, highlighting the significance of a larger surface area in enhancing the adsorption capacity of the resin. HPD-500 and ADS-7 exhibited adsorption capacities like HP2MGL, but their desorption capacities differed significantly, possibly due to their strong polarities. Thus, appropriate polarity and surface area are critical for effective purification. Given that HP2MGL resin has strong adsorption capability and easy elution of adsorbed flavonoids, it was chosen for the subsequent purification of DCFE based on these factors.

3.2 | Adsorption kinetics

The kinetics of flavonoid adsorption at 25°C on HP2MGL resin were investigated. There was a rapid increase in adsorption capacity during the adsorption process of flavonoids onto the HP2MGL resin within the initial 90 min, followed by a gradual and slight increase

until equilibrium was attained at 420 min, reaching a maximum value of 22.01 mg/g (Figure 2A). During the initial stage of adsorption, the resin featured abundant adsorption sites, and there was a significant concentration gradient of flavonoids between the DCFE solution and the resin. These factors facilitated the transfer of DCFE flavonoids into the HP2MGL resin. As the adsorption process continued, the resin's adsorption sites were saturated, leading to a drop in the concentration difference of flavonoids and a subsequent fall in the adsorption rate until reaching equilibrium.

DCFЕ adsorption on HP2MGL resin was examined by applying three recognized kinetic models (Figure 2B–D). After fitting the models to the experimental data, the matching equations and parameters were computed and are shown in Table 1. Depending on the R_2 values, the pseudo-second-order model was determined to be the most appropriate. Relative to the pseudo-first-order model (12.55 mg/g), the projected q_e value (22.63 mg/g) of this model closely matched the experimental value (22.01 mg/g). The adsorption process of DCFE on HP2MGL resin occurred in three stages: film diffusion (or boundary layer diffusion), intraparticle diffusion, and final adsorption. The intraparticle diffusion model could significantly determine the rate-limiting phase but was not suitable for assessing the complete adsorption process (Figure 2D). The assessment of the intraparticle diffusion model made it possible to assess whether intraparticle diffusion occurred during the adsorption kinetics. In this model, an increase in C value indicated a greater impact of film diffusion on adsorption (Hou & Zhang, 2021; Li et al., 2022). In addition to intraparticle diffusion, this process also involved additional adsorption processes, including film diffusion, which influenced the pace at which DCFE was adsorbed on HP2MGL resin.

3.3 | Effect of pH on adsorption and desorption

The presence of weakly acidic phenolic hydroxyl groups may affect the flavonoid adsorption ability of macroporous resins. This investigation investigated how sample pH affected the HP2MGL microporous resin, and its ability to adsorb. The abilities of HP2MGL for flavonoid adsorption and desorption were assessed at various pH levels. The adsorption capability of HP2MGL was steady between pH 1.0 and 3.0 but decreased between pH 4.0 and 8.0. On the other hand, at pH values below 3.0, there was no discernible difference in the desorption and recovery of flavonoids (Figure 3A). As a result, the flavonoid solution's pH value may have an impact on the degree of ionization, which in turn may have an impact on the absorbable capacity of the microporous resin. Under weakly alkaline conditions, flavonoids in *D. catenatum* flowers may undergo ionization, leading to their decreased absorption. In contrast, weakly acidic conditions may stabilize flavonoids in *D. catenatum* flowers, resulting in

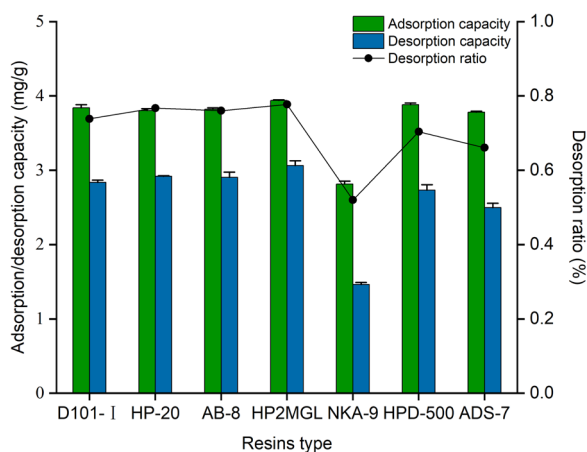


FIGURE 1 Adsorption/desorption capacity and the desorption ratio of total flavonoids of seven resins.

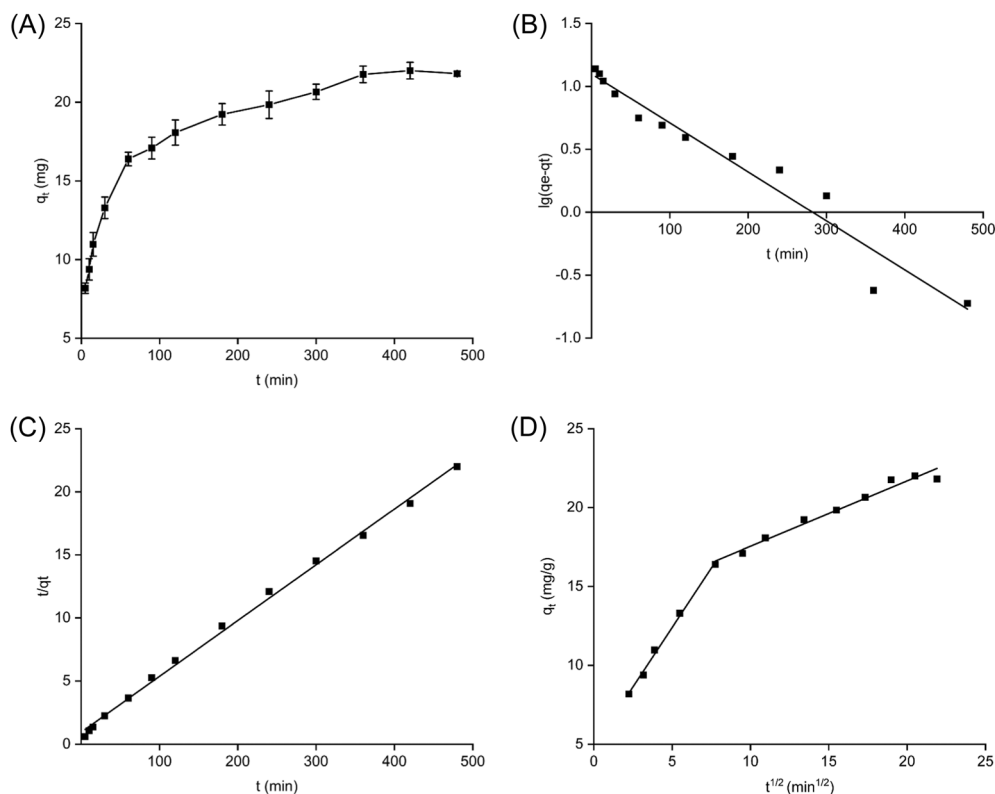


FIGURE 2 (A) The adsorption kinetics curve, (B) linear correlations based on pseudo-first-order, (C) pseudo-second-order, and (D) intraparticle diffusion models for total flavonoids on HP2MGL resin at 25°C. q_e is the equilibrium adsorption capacity, and q_t is the adsorption capacity at time t .

TABLE 1 Kinetics equations and parameters for the adsorption of *D. catenatum* flower extract (DCFE) on HP2MGL resin.

Models	Equations	Parameters
Pseudo-first-order	$\lg(q_e - q_t) = -0.00389t + 1.09872$	$k_1 = 0.0089$ $q_e = 12.55$ $R^2 = 0.9533$
Pseudo-second-order	$t/q_t = 0.04418t + 0.95435$	$k_2 = 2.046 \times 10^{-3}$ $q_e = 22.63$ $R^2 = 0.9975$
Intraparticle diffusion (first stage) (second stage)	$q_t = 1.506t^{1/2} + 4.86847$ $q_t = 0.41553t^{1/2} + 13.38368$	$k_i = 1.506$ $C = 4.86847$ $R^2 = 0.9956$ $k_i = 0.41553$ $C = 13.38368$ $R^2 = 0.9747$

their enhanced absorbability (Chen et al., 2022). Therefore, the DCFE solution with a pH of 3.5 was selected to ensure favorable adsorption conditions.

3.4 | Effects of various concentrations of ethanol on desorption rates

The concentration of ethanol is an essential factor affecting the flavonoids desorption capacity of macroporous resins. The solubility of flavonoids was influenced by the polarity of

ethanol, which decreased as the ethanol concentration increased. Lower ethanol concentrations decreased polyphenol dissolution due to increased polarity, while higher ethanol concentrations facilitated the dissolution of alcohol-soluble contaminants through lower polarity. (Hou & Zhang, 2021). The desorption of *D. catenatum* flower flavonoids rapidly increased as the ethanol concentration ranged from 20% to 60% (Figure 3B). As the concentration of ethanol increased, the rate at which the desorption capacity increased slowed down progressively and peaked at 80%. The desorption of *D. catenatum* flower flavonoids,

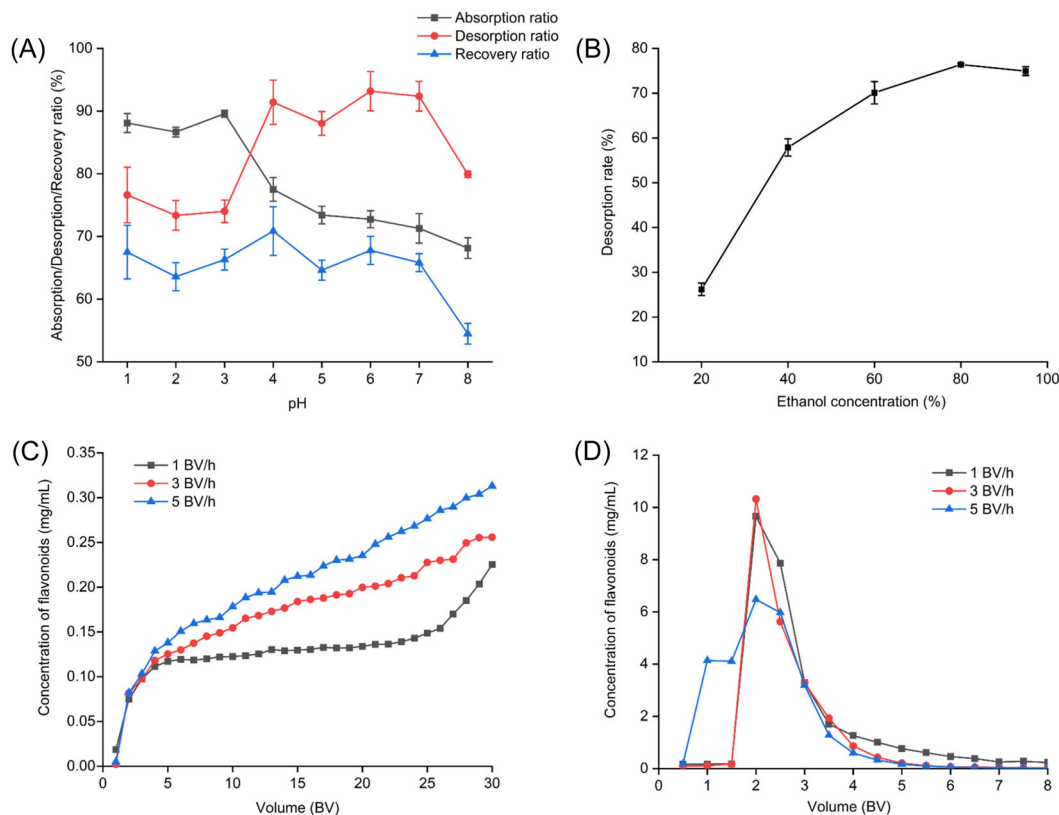


FIGURE 3 (A) Effect of the sample pH on the adsorption capacity of HP2MGL resin, (B) the effect of ethanol concentration on the desorption capacity of the HP2MGL resin, (C) dynamic breakthrough curves, and (D) desorption curves.

however, decreased at 95% ethanol concentration. This phenomenon can be explained by the hydrogen bonding and van der Waals forces between the resin and the flavonoids, which increase in strength as their polarities approach each other. The dielectric constant of the medium in the adsorption system changed as the volume percent of the eluent was increased. This broke the contact forces between the flavonoids and the resin and facilitated their desorption (Sun et al., 2022). However, an excessively high volume of the eluent fraction resulted in the leaching out of more alcohol-soluble impurities from the resin. These impurities compete with polyphenols to bind with ethanol–water molecules, thereby impeding the desorption process. Based on the results, a dynamic adsorption and desorption investigation was conducted using an 80% ethanol concentration. This concentration was chosen as it provided the best desorption efficiency while reducing the negative impact of competing contaminants.

3.5 | Determination of dynamic adsorption and desorption conditions

3.5.1 | Dynamic adsorption curves

The ideal loading volume and flow rate were established based on the analysis of leached flavonoids concentrations

at different flow rates. The leakage rate increased gradually with the flow rate at 1, 3, and 5 BV/h (Figure 3C). This may be because of the short residence time of flavonoids in the column at high flow rates, which prevented them from diffusing adequately and coming in contact with the resin, leading to poor adsorption (Li et al., 2022). We found that at lower flow rates, the flavonoids were more in contact with the resin and were absorbed better. The flavonoids in the DCFE solution were sufficiently exposed to the resin to be adsorbed at a flow rate of 1 BV/h and a loading of 25.5 BV. Therefore, the HP2MGL resin column was loaded with 25.5 BV of DCFE for dynamic adsorption at a flow rate of 1 BV/h.

3.5.2 | Dynamic desorption curves

The optimal desorption conditions are crucial to achieve efficient recovery of flavonoids from the resin column. In this study, ethanol at 80% concentration at flow rates of 1, 3, and 5 BV/h eluted the flavonoids from the resin column in static desorption experiments. Differences were seen in the desorption curves at various flow rates (Figure 3D). The desorption curves exhibited distinct and concentrated peaks when the flow rates were set at 1 and 2 BV/h, indicating optimal elution conditions. However, the desorption curves were broader, at the flow

rate of 5 BV/h, accompanied with a tailing phenomenon. This tailing phenomenon may be due to the higher flow rate, which caused incomplete desorption of flavonoids from the resin. Moreover, the desorption capacity of *D. catenatum* flower flavonoids was higher at flow rates of 1 and 3 BV/h compared to that at 5 BV/h. These findings imply that lower flow rates enable more efficient desorption of flavonoids from the resin. The flow rate of 3 BV/h and an appropriate eluent volume of 5 BV were selected for future experiments based on the elution efficiency and desorption capacity of HP2MGL resin for flavonoids in *D. catenatum* flowers.

3.6 | Analysis of enrichment result

Our research team had previously identified 21 phenolic plant markers from 11 different strains of *D. catenatum* flowers that serve as quantitative indicators of flower quality and authenticity (Zhang et al., 2019). The polyphenol profiles of DCFE were analyzed by HPLC-DAD before and after purification (Figure 4A). The enrichment of DCFE was achieved using the HPMGL resin, followed by elution with 80% ethanol. The resulting eluate was concentrated and lyophilized, and yielded a flavonoid-rich product (DCF-E). By comparing the UV absorption spectra and retention times of the standards, eight major components of DCFE were revealed, including six flavonoids and two phenolic acids, that could be efficiently enriched using HP2MGL resin, consistent with our previous results (Supporting Information S1: Table S2). The purity of DCF-E was determined to be 25.49%, representing a significant increase of 7.26-fold compared to the initial increase of 3.5% in the case of DCFE. The results indicated that the

HP2MGL resin is both practical and efficient for the enrichment of flavonoids from *D. catenatum* flowers.

We used UPLC-QTRAP-MS/MS to analyze the DCFE-E flavonoid components above the high detection limit of HPLC-DAD for both qualitative and quantitative purposes. This analysis revealed the presence of 25 additional flavonoids, with flavonol compounds being the main components (Table 2). Among these, the content of flavonoid compounds, hyperoside, rutin, hydroxysafflor yellow A, vitexin, astragalin, and others was high, with antioxidant properties and wide distribution in nature. Among these, the content of hyperoside was the highest, with multiple biological activities, including anti-inflammatory, antibacterial, antiviral, antidepressant, cardioprotective, neuroprotective, and organ-protective effects, and maybe a candidate for the development of new drugs (Wang, Wei, et al., 2022). Hydroxysafflor yellow A can resist oxidative stress by increasing SOD activity and reducing ROS levels, and protecting mitochondrial function by inhibiting the opening of mitochondrial permeability transition pores. In addition, hydroxysafflor yellow A can also prevent iron-dependent cell death and parthanatos, and protect cells from

TABLE 2 Effects of enriched *D. catenatum* flower extract (DCF-E) on the lifespan of *C. elegans*.

Group	Mean lifespan (days)	Maximum lifespan (days)	Change in mean lifespan (%)
Control	14.84 ± 1.04 ^a	24	–
25 µg/mL	14.88 ± 1.09 ^a	25	0.27
50 µg/mL	17.22 ± 1.16 ^b	27	16.04
100 µg/mL	17.85 ± 1.13 ^b	28	20.28

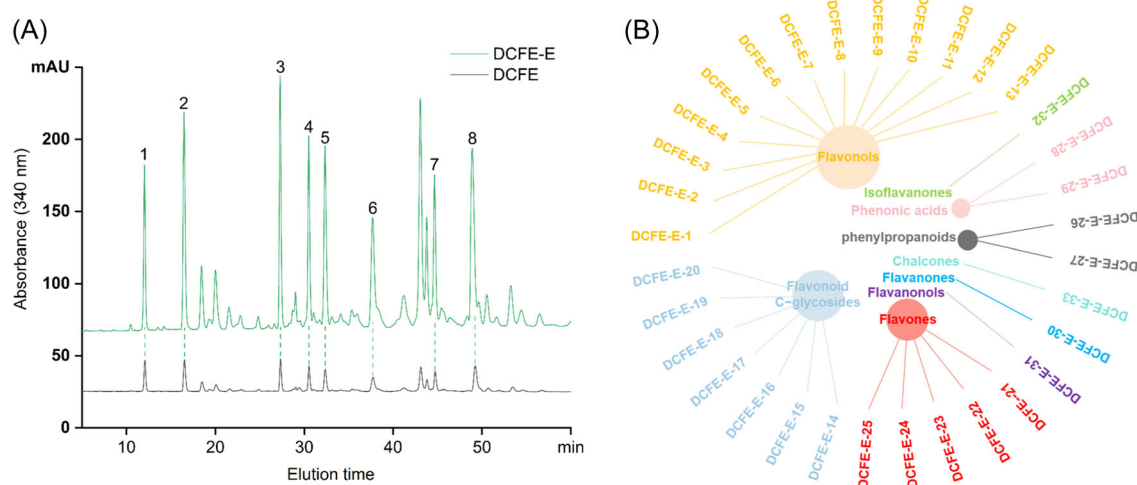


FIGURE 4 (A) HPLC chromatograms of *Dendrobium catenatum* flower extract (DCF-E) and DCFE-E. The composition of major flavonoid components in DCFE-E; (B) flavonoid composition in DCFE-E. Refer to Supporting Information S1: Table S3 for the compounds corresponding to a given number.

oxidative damage (Xue et al., 2021). Vitexin is a natural C-glycosylated flavonoid that exists in many medicinal plants, and it shows strong free radical scavenging and antioxidative stress abilities in vivo and in vitro, which is attributed to its O-dihydroxy structure on the A ring (Peng et al., 2021). In summary, after detection, the flavonoid composition of DCFE-E revealed mainly flavonoid C-glycosides and flavonols (Figure 4B). Many of these compounds have potent pharmacological activities, indicating that DCFE-E, as a natural product, is worthy of further studies to determine its biological activities.

3.7 | The enriched *D. catenatum* flower extract could prolong the lifespan of *C. elegans*

The lifespan of *C. elegans* is approximately two to 3 weeks. The lifetime regulatory circuits of *C. elegans* are extremely conserved, and its gene sequence shows a significant resemblance to the human genome (Li et al., 2023). *C. elegans* models are commonly utilized in research to evaluate medication candidates for age-related metabolic illnesses and to assess the credibility of their molecular mechanisms. This can serve as a great reference for antiaging experiments (Zhang et al., 2023). *C. elegans* treated to DCFE-E at concentrations of 50 and 100 µg/mL showed enhanced average lifespan and improved locomotion ability compared to the control group. lifespan was extended by 16.04% and 20.28%, respectively, while locomotion ability improved by 16.37% and 29.24%, respectively (Figure 5A,B and Table 3). Prior research has demonstrated that the longevity of *C. elegans* may be increased by reducing body size and reproductive ability. The investigation found that various quantities of the extract had no impact on the reproduction and body size of the worms, as

illustrated in Figure 5B–E. Overall, DCFE-E had a substantial impact on extending the lifespan of *C. elegans* without any adverse impacts on its growth and reproductive capabilities.

3.8 | The DCFE-E markedly decreased the buildup of age-related lipofuscin

Lipofuscin, a pigment associated with aging, accumulates in worms as they age. The level of lipofuscin accumulation increases with age. To investigate the impact of DCFE-E on extending the lifetime of *C. elegans*, variations in lipofuscin were analyzed. (Guerrero-Rubio et al., 2023). The fluorescence microscope images in Figure 6A,E demonstrate a significant reduction in lipofuscin content in the DCFE-E experimental group compared to the blank group. The worms exposed to 100 µg/mL of DCFE-E exhibited a 55.25% decrease in lipofuscin content, indicating a direct effect of DCFE-E on delaying aging.

3.9 | The enriched *D. catenatum* flower extract resisted oxidative stress damage

ROS are generated due to normal aging or environmental stress. Excessive ROS levels, surpassing the capacity of antioxidant enzymes, lead to oxidative stress-induced damage to proteins and DNA structures, thereby accelerating the aging process and triggering apoptosis (Peng et al., 2021). The measurement of ROS levels serves as a practical and innovative method to assess antioxidant activity in vivo in *C. elegans* (Dong et al., 2021; Sun et al., 2022). Some plant-derived flavonoids have demonstrated the ability to scavenge ROS in *C. elegans* and reduce the level of oxidative stress it

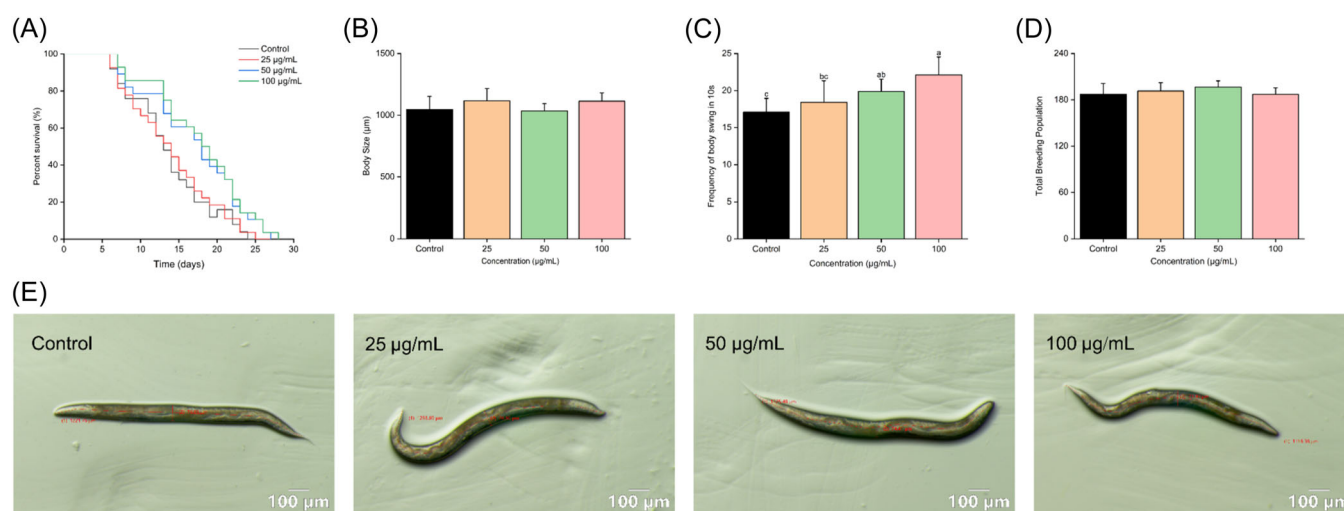


FIGURE 5 Effects of DCFE-E on life phenotypic of *C. elegans*. (A) Life curve, (B, E) body size, (C) locomotion ability, and (D) reproductive capacity. DCFE-E, enriched *D. catenatum* flower extract.

TABLE 3 Characterization of flavonoid fractions in enriched *D. catenatum* flower extract (DCFE-E) by UPLC-QTRAP-MS/MS.

No.	RT (min)	Identity	Molecular formula	Molecular weight	A (nmol/g)	(m/z) [M-H] ^{+/−}
1	2.09	Hydroxysafflor yellow A	C ₂₇ H ₃₂ O ₁₆	612.1690	341.2565	611.2[M-H] [−]
2	2.46	Baimaside	C ₂₇ H ₃₀ O ₁₇	626.1483	24.5420	625.1[M-H] [−]
3	2.63	Spinosin	C ₂₈ H ₃₂ O ₁₅	608.1741	13.9435	607.2[M-H] [−]
4	2.63	Taxifolin 7-O-rhamnoside	C ₂₁ H ₂₂ O ₁₁	450.1162	1.3992	449.1[M-H] [−]
5	2.68	Rutin	C ₂₇ H ₃₀ O ₁₆	610.1534	1045.1675	609.1[M-H] [−]
6	2.7	7-Hydroxy-4H-chromen-4-one	C ₉ H ₆ O ₃	162.0317	1.8134	161[M-H] [−]
7	2.74	Vitexin	C ₂₁ H ₂₀ O ₁₀	432.1056	154.3029	431.1[M-H] [−]
8	2.76	Quercimeritrin	C ₂₁ H ₂₀ O ₁₂	464.0955	53.3469	463.09[M-H] [−]
9	2.77	Hyperoside	C ₂₁ H ₂₀ O ₁₂	464.0959	3377.9581	465.1[M-H] ⁺
10	2.8	Miquelianin	C ₂₁ H ₁₈ O ₁₃	478.0747	1.1860	477.1[M-H] [−]
11	2.85	Nicotiflorin	C ₂₇ H ₃₀ O ₁₅	594.1585	285.4633	593.2[M-H] [−]
12	2.88	Narcissin	C ₂₈ H ₃₂ O ₁₆	624.1690	75.6374	623.2[M-H] [−]
13	3.02	Astragalin	C ₂₁ H ₂₀ O ₁₁	448.1006	143.1220	447.1[M-H] [−]
14	3.03	Avicularin	C ₂₀ H ₁₈ O ₁₁	434.0849	16.7166	433.1[M-H] [−]
15	3.07	Isorhamnetin 3-O-glucoside	C ₂₂ H ₂₂ O ₁₂	478.1111	123.5466	477.1[M-H] [−]
16	3.14	Syringaldehyde	C ₉ H ₁₀ O ₄	182.0579	11.8716	181.1[M-H] [−]
17	3.95	Tiliroside	C ₃₀ H ₂₆ O ₁₃	594.1373	2.1219	593.1[M-H] [−]
18	4.15	Eriodictyol	C ₁₅ H ₁₂ O ₆	288.0634	5.9635	287.1[M-H] [−]
19	4.19	Luteolin	C ₁₅ H ₁₀ O ₆	286.0477	1.2299	285[M-H] [−]
20	4.24	Quercetin	C ₁₅ H ₁₀ O ₇	302.0426	116.2243	301.1[M-H] [−]
21	4.96	Naringenin chalcone	C ₁₅ H ₁₂ O ₅	272.0685	15.3576	271.1[M-H] [−]
22	5.12	Kaempferol	C ₁₅ H ₁₀ O ₆	286.0477	22.7545	285[M-H] [−]
23	5.21	Diosmetin	C ₁₆ H ₁₂ O ₆	300.0634	1.7083	299.1[M-H] [−]
24	5.29	Isorhamnetin	C ₁₆ H ₁₂ O ₇	316.0583	44.7874	315.1[M-H] [−]
25	8.34	Corylin	C ₂₀ H ₁₆ O ₄	320.1049	2.6923	319.1[M-H] ⁺

experiences (Lu et al., 2017; Yang et al., 2020). However, research on the efficacy of flavonoid components in *D. catenatum* flowers is scarce.

C. elegans labeled with a fluorescent probe were examined under a fluorescence microscope after being exposed to different concentrations of DCFE-E for 5 days starting at the L4 stage. ROS levels in nematodes reduced in a dose-dependent way with increasing doses of DCFE-E as compared to the control group without DCFE-E (Figure 6B,F). The reduction in ROS levels induced by DCFE-E was quantified in terms of fluorescence percentage, with the blank control group set as 100%. Notably, administration of DCFE-E at a dose of 100 µg/mL led to a 20.85% decrease in fluorescence intensity in *C. elegans*, suggesting the potential of DCFE-E treatment to mitigate ROS accumulation in live cells during aging. The presence of enhanced flavonoids in DCFE-E may

contribute to its ability to contain phenolic compounds that can eliminate free radicals and regulate signaling pathways related to stress response and longevity (Hu et al., 2021; Sun et al., 2023). These findings imply that DCFE-E may be absorbed by *C. elegans*, thereby reducing ROS production in cells during aging and safeguarding the internal antioxidant defense system. Furthermore, maintaining an optimal intracellular ROS balance is crucial for regulating cellular adaptive stress responses and facilitating the elimination of foreign substances by the body's immune system. Thus, the ability of DCFE-E to effectively scavenge ROS may contribute to sustaining an optimal equilibrium of intracellular ROS levels.

SOD, an endogenous antioxidant enzyme, directly scavenges free radicals and serves as the primary defense against ROS-mediated damage (Zhang et al., 2023). SOD

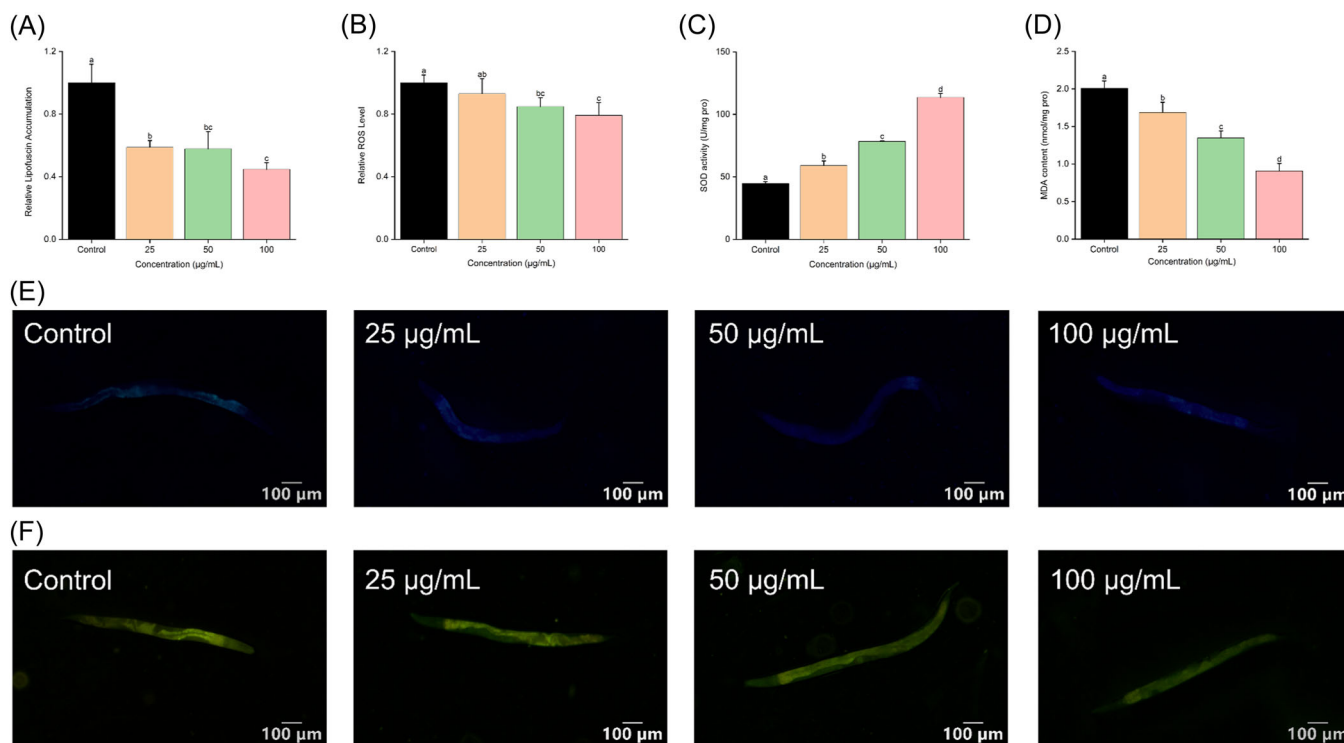


FIGURE 6 (A) Lipofuscin quantification, (B) relative change in ROS levels, (C, D) relative content of SOD and MDA, (E) fluorescence microscopy photos of *C. elegans* of different treatment groups at 15 days, and (F) fluorescence microscopy photos of *C. elegans* treated with fluorescent probes (H2DCF-DA), different treatment groups were incubated for 5 days before the test.

activity was increased by 31.72%, 74.59%, and 153.15% compared to the blank control when exposed to 25, 50, and 100 $\mu\text{g/mL}$ DCFE-E, respectively (Figure 6C). The results indicate that DCFE-E efficiently removes ROS in worm cells and boosts their antioxidant capability. MDA is the final product of polyunsaturated fatty acid peroxidation in cells. Excessive MDA production, due to an increase in free radicals, can cause oxidative damage to the body (Yang et al., 2023). Treatment with DCFE-E decreased lipid peroxidation levels in the worm body by 16.05%, 20.14%, and 32.62% (Figure 6D), indicating that DCFE-E may alleviate cell damage caused by MDA.

Our data confirmed that treatment with 100 $\mu\text{g/mL}$ DCFE-E was the most effective in a dose-dependent manner. DCFE-E has the potential to enhance antioxidant enzyme activity, including SOD, and reduce the buildup of MDA and ROS during nematode senescence. Thus, DCFE-E improves *C. elegans*' ability to handle oxidative stress, which helps sustain the health of the *C. elegans*. However, the mechanism underlying the antiaging effect of DCFE-E remains unclear. Future investigations will focus on elucidating the molecular mechanism of DCFE-E biological activity in nematodes by detecting nematode gene expression, fluorescently labeling genes or proteins, and constructing specific nematode models and related mutants. Finally, there are some challenges to applying the experimental results based on the *C. elegans* model to humans. First and foremost is the

issue of dose conversion. Due to the dose-dependent nature of effects, there is a lack of standardized conversions for translating effective doses from *C. elegans* to humans. Dose conversion criteria for animals and humans have been established and standardized according to body surface area and metabolic rate, but guidelines for *C. elegans* have not yet been established. In addition, the high sensitivity of the model may result in toxicity being observed at lower doses that may not manifest as noticeable phenotypes in humans due to the processes of food digestion involving degradation, denaturation, and metabolism. To address this challenge, integrating the advantages and disadvantages of different model organisms into the experimental design can facilitate the refinement of experimental protocols. This approach allows to maximize the strengths of each model, ultimately facilitating a systematic, accurate, and efficient understanding of natural bioactive compounds.

4 | CONCLUSION

In this study, we established an effective protocol for enriching flavonoids extracted from *D. catenatum* flowers using HP2MGL microporous resin. The DCFE solution was loaded onto the resin column with an initial TFC of 0.50 mg/mL, a loading volume of 25.5 BV, and a flow rate of 1 BV/h, optimizing the enrichment process. Subsequent

elution with 5 BV of 80% ethanol at a flow rate of 3 BV/h yielded DCFE-E with a TFC of 25.49%, representing a significant 7.3-fold increase in purity compared to DCFE alone. Through HPLC-DAD, we identified and quantified eight major components within DCFE-E, which was further analyzed using UPLC-QTRAP-MS/MS to reveal its composition predominantly consisting of flavonols and flavonoid C-glycosides. DCFEE exhibited notable biological effects, including lifespan extension, improved movement, and reduced lipofuscin accumulation in *C. elegans*. Additionally, it enhanced antistress capacity as indicated by increased SOD activity, decreased MDA levels, and reduced ROS buildup. These findings underscore DCFE-E's potential as an antiaging component warranting further investigation.

AUTHOR CONTRIBUTIONS

Yuntao Guo: Conceptualization; methodology; investigation; data curation; visualization; writing—original draft. **Danni Lai:** Data curation; visualization; writing—review and editing. **Fupeng Pan:** Data curation; visualization. **Maidinai Sabier:** Methodology; investigation. **Jingjing Liu:** Methodology; investigation. **Qiaoxian Yu:** Funding acquisition; supervision; project administration. **Pan Wang:** Supervision; project administration. **Jinping Si:** Funding acquisition; supervision; project administration. **Xinfeng Zhang:** Conceptualization; resources; writing—review and editing; supervision; project administration.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ETHICS STATEMENT

None declared.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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