



THE RADICAL-SCAVENGING POTENTIAL AND OXIDATIVE STRESS MODULATION OF *Rosa Alba* L. ABSOLUTE AGAINST GENTAMICIN-INDUCED RENAL TOXICITY

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ABSTRACT:

Purpose: This study aimed to evaluate the radical scavenging capacity and potential modulation of oxidative stress exerted by *Rosa alba* L. absolute in a model of gentamicin-induced nephrotoxicity.

Material/Methods: The antioxidant activity of *R. alba* L. absolute was examined using electron paramagnetic resonance (EPR) spectroscopy. In vivo EPR measurements were performed to assess scavenging activity against hydroxyl ($\bullet\text{OH}$) and superoxide ($\bullet\text{O}_2^-$) radicals, as well as the DPPH radical scavenging capacity (DPPH \bullet). Tissue homogenates were prepared from renal samples and serum obtained from Balb/c mice. Animals were randomly allocated into four experimental groups (n = 6): (a) the control group, receiving an intraperitoneal injection (i.p.) of 1 mL isotonic NaCl solution (0.9%) daily along with a standard diet; (b) the *R. alba* group, administered *R. alba* absolute orally at 80 mg·kg⁻¹ body weight·day⁻¹; (c) the gentamicin (GM) group, injected i.p. with GM at 200 mg·kg⁻¹ body weight·day⁻¹ to induce acute nephrotoxicity; and (d) the combination group, receiving GM (200 mg·kg⁻¹) followed 2 hours later by *R. alba* absolute (80 mg·kg⁻¹·day⁻¹) administered orally. EPR spectroscopy was further employed to analyze oxidative alterations and conformational modifications in renal proteins, with a particular focus on sulfhydryl (-SH) group integrity in albumin. Protein carbonylation (PC) levels were quantified using an enzyme-linked immunosorbent assay (ELISA).

Results: The findings demonstrated that *R. alba* L. absolute exhibited pronounced antioxidant activity, effectively scavenging hydroxyl and superoxide radicals and displaying notable DPPH radical neutralization capacity.

Conclusions: Moreover, oral administration of *R. alba* significantly attenuated protein oxidation and carbonylation, thereby mitigating oxidative damage to renal proteins (p < 0.05).

Keywords: *Rosa alba* L., radical-scavenging potential, oxidative stress, gentamicin nephrotoxicity,

INTRODUCTION

Essential oils obtained from white oil-bearing roses (*Rosa damascena* Mill., *Rosa alba* L., *Rosa gallica* L., and *Rosa centifolia* L.) - including their oils, absolutes, and related extracts—have attracted considerable scientific interest due to their diverse bioactive constituents [1]. More than 214 chemical compounds have been identified in the essential oil of *Rosa alba* L. (RA, family Rosaceae). The predominant phytoconstituents include terpene alcohols (citronellol, geraniol, and nerol), phenethyl alcohol, eugenol, methyleugenol, tannins, and both saturated and unsaturated aliphatic hydrocarbons such as nonadecane, geranyl acetate, and squalene [2, 3].

In traditional medicine, RA has been employed for the treatment of various ailments, including palpitations, headache, stomatitis, gallstones, bronchitis, rheumatism, diabetes, microbial and uterine infections, and acute inflammatory conditions [4]. Experimental studies have demonstrated that *R. alba* possesses substantial antioxidant activity in vitro [5]. Moreover, *R. alba* wastewater has been reported to display redox-modulating and antineoplastic properties, suggesting effective chelation of transition metals such as iron (II/III) and copper (II), along with stable anticytotoxic potential [3, 4, 5]. Collectively, these findings indicate that *R. alba* exerts detoxifying effects under oxidative stress conditions.

The strong antioxidant capacity of *R. alba* is attributed to its elevated total polyphenol content (7.6 mg·mL⁻¹, relative to quercetin) [3]. Its antioxidant properties exhibit dose dependence, with notable scavenging activity against DPPH \bullet and superoxide ($\bullet\text{O}_2^-$) radicals, as well as reduction of ABTS \bullet^+ concentrations, thereby confirming its protective and detoxifying role under acute oxidative stress [3]. The essential oil of *R. alba* (250–1000 $\mu\text{g}\cdot\text{mL}^{-1}$) dem-

onstrated only weak cytotoxic and genotoxic effects in *Hordeum vulgare* plant cell assays [6]. Furthermore, Naikwade et al. (2009) reported potential neuroprotective effects of *R. alba*, indicating its possible utility in memory restoration and the management of cognitive disorders, including Alzheimer's disease [7]. Interestingly, *R. alba* wastewater exhibited lower clastogenic potential than *Rosa damascena* L., although it predominantly induced chromatid breaks, with relatively few isochromatid breaks in normal lymphocyte cells [8].

Acyclic monoterpene alcohols, sesquiterpene hydrocarbons, and their oxygenated derivatives are well recognized for their ability to neutralize short-lived radical species, chelate transition metals, and elicit antioxidant and anti-inflammatory responses [9,10].

Gentamicin (GM), an aminoglycoside antibiotic effective against Gram-negative bacteria, remains widely used in the clinical management of urinary tract infections [11]. However, prolonged GM administration (typically over seven days) is associated with cumulative toxicity, metabolic disturbances, and progressive renal impairment [12]. GM-induced nephrotoxicity is characterized by structural damage to the proximal tubular cells, mitochondrial dysfunction, and increased renal inflammation [11, 12, 13]. Intracellular accumulation of GM promotes the overproduction of reactive oxygen and nitrogen species (ROS/RNS), resulting in oxidative stress, inflammation, and fibrotic remodeling [13]. These processes are accompanied by lipid peroxidation and protein oxidation, driven by excess generation of $\bullet\text{O}_2^-$, H_2O_2 , $\bullet\text{NO}$, and ONOO^- radicals, which are key mediators of redox homeostasis and adaptive responses to xenobiotic stress [14, 15].

The regulation of intracellular redox balance is maintained through endogenous enzymatic and non-enzymatic systems, as well as exogenous antioxidants such as vitamin E and plant-derived polyphenols [16–18]. GM therapy disrupts these mechanisms, impairs lipid peroxidation control, and precipitates renal injury [19].

To the best of our knowledge, no studies have yet addressed the antioxidant and nephroprotective effects of *RA absolute* against GM-induced nephrotoxicity in a 10-day *in vivo* Balb/c mouse model. Therefore, the present investigation was designed to evaluate the intracellular radical-scavenging potential of *RA absolute* in GM-induced renal injury, focusing on the modulation of transmembrane protein oxidation/carbonilation and ROS-mediated oxidative stress.

MATERIALS AND METHODS

Plant material and absolute preparation

Fresh pink flowers of *Rosa alba* L. (500 g) were collected in the early morning (between 05:00 and 09:00) on May 25, 2020, under conditions of 80% relative humidity and ambient temperature ranging from 13 to 14.5°C at the Institute of Roses and Essential Oil Crops (IREMC), Kazanlak, Bulgaria. The plant material was subjected to triple extraction (3×) with *n*-hexane by maceration. The resulting extracts were pooled, filtered, and concentrated under reduced pressure at 40°C to yield a yellow-orange,

waxy, paraffin-like semi-solid product—*Rosa alba* concret.

An ethanolic (96%) solution of *Rosa alba* concret was subsequently cooled to 24°C and stored at -20°C for 24 h. After cooling, the solution was filtered three times, dehydrated with anhydrous sodium sulphate (Na_2SO_4), and vacuum-evaporated to obtain *RA absolute*, a yellow-orange viscous liquid characterized by its distinctive rose fragrance.

The *RA absolute* used in this study was supplied by the Institute of Roses and Essential Oil Crops (Kazanlak, Bulgaria). Botanical authentication of the plant material was performed at the Technical University (Stara Zagora, Bulgaria). Voucher specimens were deposited at the Institute of Biodiversity and Ecosystem Research, Bulgarian Academy of Sciences (IBER-BAS), under accession number *R. alba* – 178 484 SOM. Chemical characterization of the *RA absolute* confirmed the presence of major monoterpene alcohols, including phenethyl alcohol (16.2%), geraniol (9.89%), and citronellol/nerol (6.17%) [20].

Antiradical potential of R. alba absolute

Hydroxyl ($\bullet\text{OH}$) radicals ability : Non-specific $\bullet\text{OH}$ detection of *RA absolute* (0.1 – 25 $\mu\text{g ml}^{-1}$) was performed by thermal incubation (55°C) for 15 minutes in the dark, until the degradation of the pink reactive chromogen-deoxyribose by $\bullet\text{OH}$, at 532 nm [21]; as follows: % *Inhibition* = $(A_{\text{control}} - A_{\text{test}}) / A_{\text{control}} \times 100$

Superoxide ($\bullet\text{O}_2^-$) radical ability: The $\bullet\text{O}_2^-$ Inhibition of *RA absolute* (0.1 – 2.5 $\mu\text{g ml}^{-1}$) was determined by using the nitroblue-tetrazolium (NBT) reduction to form blue-colored formazan, at 560 nm [22]. Incubation for 10 min at 24°C resulted in separation by centrifugation (1000 x g) of the *n*-butanol layer to the extent that the intensity of the chromogen could be measured. A decrease in absorbance indicated maximal $\bullet\text{O}_2^-$ Inhibition of *RA absolute*.

The antiradical 2,2-diphenyl-1-picrylhydrazyl (DPPH \bullet) scavenging assay: The DPPH \bullet capacity was performed by the EPR method [23,24]. *RA absolute* (50 $\mu\text{g ml}^{-1}$) was incubated with 250 μL , 80 mM DPPH/ ethanol solution, and after 10 min incubation in the dark (23°C), the DPPH \bullet scavenging ability was calculated:

$$\text{Scavenged DPPH}\bullet (\%) = [(I_0 - I)/I_0] \times 100,$$

where I_0 is the integral intensity of the DPPH-H/R signal of the control sample and I is the integral intensity of the DPPH signal after addition of the tested sample to the control sample; in settings as follows: center field 3516.00 G, sweep width 200.00 G, modulation amplitude 5.00 G, 1 scan per sample.

Animal experimental design and ethical approval

A total of 24 male Balb/c mice (body weight: 35–37.8 g; age: 9 weeks) were obtained from the Neurobiology Institute (Slivnitsa, Bulgaria) and housed in the accredited animal care facility, Trakia University (TrU), Bulgaria. All experimental procedures were conducted in compliance with the ethical standards of the Bioethics Committee at Trakia University (license No. 317/6000-

0333/09.12.2021) and were in accordance with Directive 2010/63/EU on the protection of animals used for scientific purposes. Animals were maintained under controlled environmental conditions: six mice per cage, temperature $24 \pm 5^\circ\text{C}$, humidity 55%, and a 12 h light/dark photoperiod. Standard laboratory chow and filtered water (pH 5.7) were available ad libitum.

The murine model of GM-induced nephrotoxicity was established by intraperitoneal (IP) administration of GM at a dose of $200 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ for 10 consecutive days, a protocol known to induce direct impairment of renal homeostasis [25,26]. For oral administration, *RA absolute* was prepared as an isotonic suspension by homogenizing the compound with 0.9% NaCl solution, 15 min before dosing. The *RA absolute* was administered at $80 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ body weight. The animals were randomly divided into four experimental groups (n = 6):

- Control group – received 1 mL NaCl (0.9%) via IP injection daily while maintained on a standard diet;
- RA* group – administered *RA absolute* orally (per os, PO) at $80 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$;
- GM group – injected intraperitoneally with GM ($200 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$) to induce acute nephrotoxicity;
- GM + *RA* group – received GM ($200 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$, IP), followed 2 hours later by *RA absolute* ($80 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$, PO).

Twenty-four hours after the final treatment, all animals were weighed and anesthetized by intraperitoneal injection of Nembutal ($50 \text{ mg}\cdot\text{kg}^{-1}$). The kidneys were immediately excised, cooled, and processed for biochemical analysis. The right kidney was placed in ice-cold phosphate-buffered saline (PBS; 0.05 M, pH 7.5, 4°C), homogenized, and used for subsequent experimental assays.

Renal hydroxyproline (Hyp) measurement

The development of fibrotic changes in renal tissue was assessed by quantitative analysis of Hyp content (drying at 110°C for 24 h, hydrolysis with 6N HCl, and incubation at 110°C). For this purpose, renal Hyp was determined spectrophotometrically at absorbance 550 nm [27], and expressed as $\mu\text{g}/\text{Hyp}$ per gram of renal tissue.

Protein oxidation (PO) measurement

Spin conjugation with 3-maleimido propyl (5-MSL) was used to analyze the oxidation and the degree of conformational (-SH) changes in the protein/albumin structure in the kidneys. For this purpose, an *in vivo* EPR method was used [28]. Right kidney tissue (10 mg) was mixed with 20 mM 5-MSL dissolved in 900 μL dimethyl sulfoxide (DMSO); centrifuged at 1000 rpm for 15 min at 4°C . Protein/albumin conformational changes were measured in triplicate, with parameters: 3505 G, power 6.42 MW, amplitude 5 G, 12 modulations, in arbitrary units.

Protein carbonyl (PCC) measurement

Oxidative carbonylation of proteins was assessed with an ELISA Kit (OxiSelect Total Carbonyl Protein Cell Biolabs). PCC was determined after reaction with dinitrophenylhydrazine (DNPH) to DNP hydrazone, for 2

hrs at 37°C . Carbonyl derivatives were expressed as $\text{nmol}\cdot\text{mg}^{-1}$, relative to oxidized or reduced BSA standards, at absorbance 370 nm.

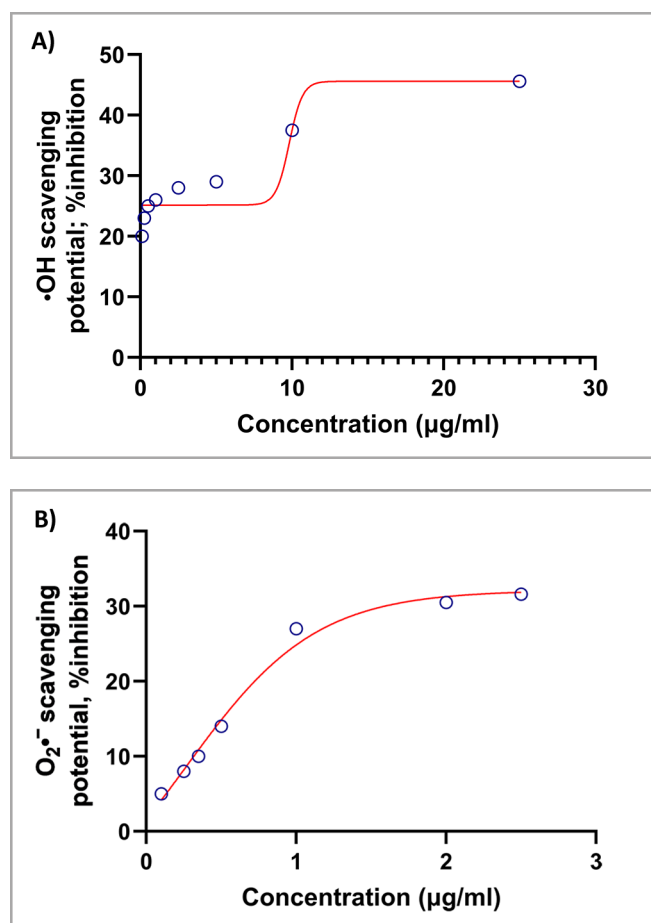
Statistical Analysis

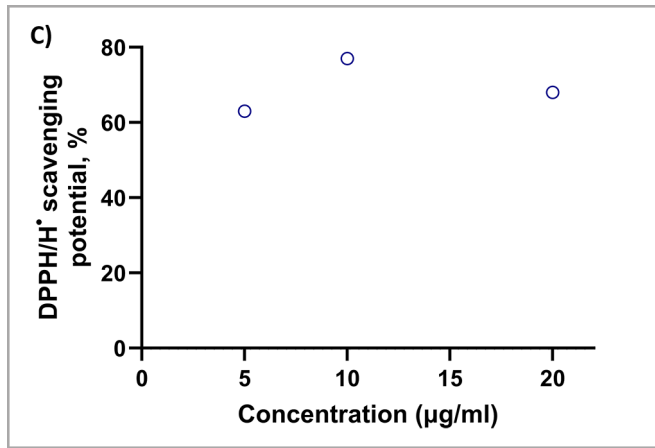
Spectral EPR analyses were performed with fivefold measurement in recorded EPR spectra, and the results are presented in arbitrary units (a.u.). Spectral processing was performed using Bruker WIN-EPR *SimFonia* 1.2/6130860 software. Statistical analysis was performed with Statistica 8, StaSoft, Inc. (Madrid, Spain), and the results were expressed as means \pm S.E. All data were expressed as means \pm S.E. and obtained by one-way ANOVA, and in the LSD post hoc test, $p > 0.05$ was considered statistically significant. LSD post hoc tests were used to define which groups were different from each other.

RESULTS

The radical scavenging activity of *RA absolute* is presented in Figure 1. The results show that *RA absolute* has significant radical neutralization capabilities. Specifically, at a concentration of $26 \mu\text{g}/\text{ml}$, *RA absolute* inhibits 45% of $\cdot\text{OH}$ radicals, while at $2 \mu\text{g}/\text{ml}$, it inhibits 30% of $\cdot\text{O}_2^-$ radicals. *In vitro*, the maximum, 70% DPPH \cdot antiradical activity, was recorded at a $10 \mu\text{g}/\text{ml}$ concentration.

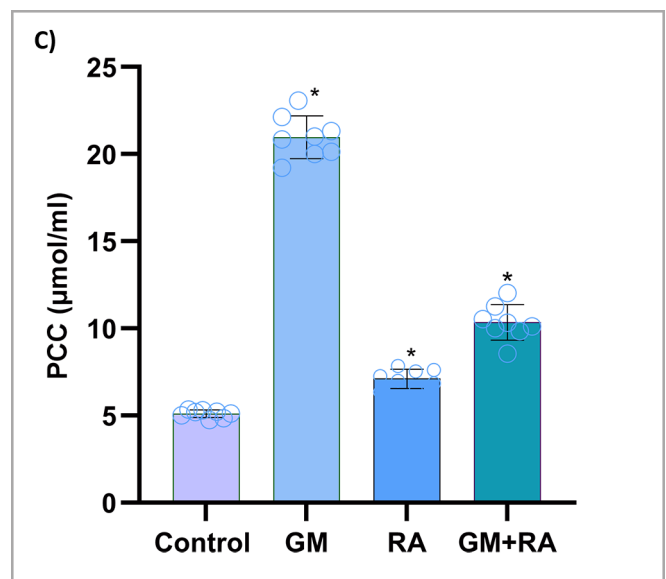
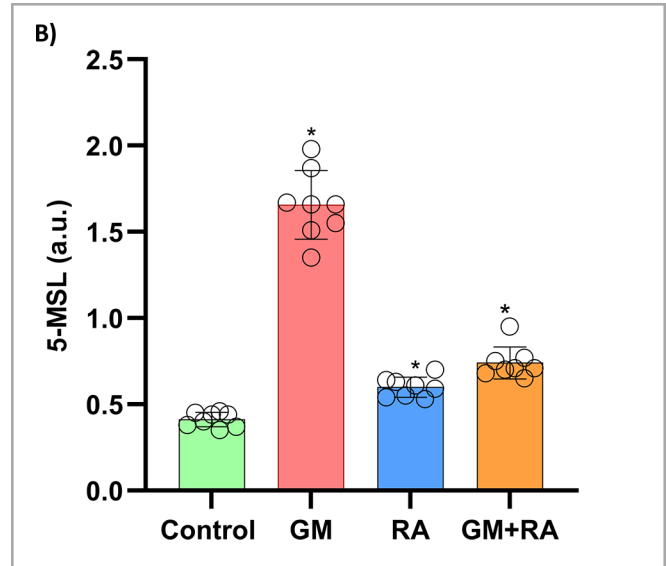
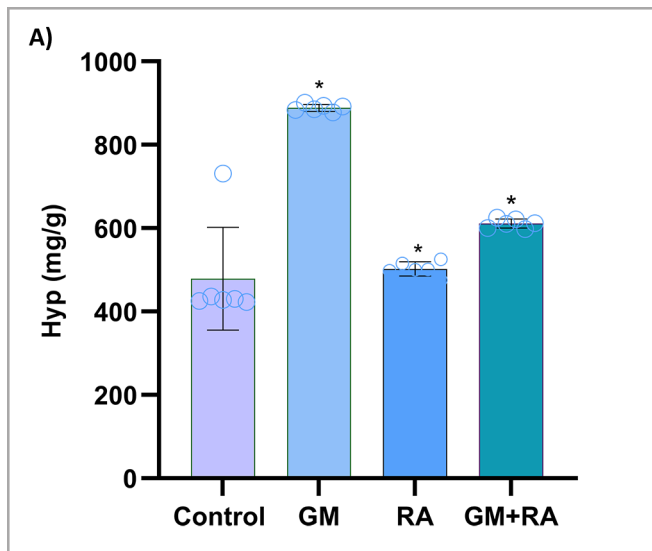
Fig. 1. Hydroxyl ($\cdot\text{OH}$) (A), superoxide ($\cdot\text{O}_2^-$) (B) and antiradical DPPH \cdot (C) radical-scavenging ability





Acute GM administration (Fig. 2A) resulted in a significant elevation of Hyp content in renal tissue compared with the controls ($p < 0.05$), indicating enhanced collagen deposition. In contrast, treatment with *RA absolute*, either alone or in combination with GM, markedly attenuated collagen accumulation in kidney tissue relative to both the control and GM-groups ($p < 0.05$ and $p < 0.005$, respectively).

Fig. 2. Protein oxidation and protein carbonilation measurement. The Hyp content (A), 5-MSL levels (B), PCC (C) in control, GM treatment group, the *RA absolute*, *RA absolute* + GM group. LSD post hoc test, * $p < 0.05$ vs. control; ** $p < 0.005$ vs. GM.



In vivo protein oxidation was evaluated using 5-MSL–albumin/protein conjugation (Fig. 2B). Following GM administration, the level of oxidized renal proteins increased by approximately 2.3-fold compared with the controls ($p < 0.05$). Oral administration of *RA absolute* ($80 \text{ mg}\cdot\text{kg}^{-1}$) alone or in combination with GM significantly reduced protein oxidation, restoring values close to those observed in the controls ($p < 0.05$).

GM exposure also produced a statistically significant increase in renal PCC compared with controls ($p < 0.05$) (Fig. 2C). Treatment with *RA absolute* ($80 \text{ mg}\cdot\text{kg}^{-1}$) significantly suppressed GM-induced PC formation relative to the GM-treated group ($p < 0.005$).

Correlation analysis revealed a strong positive relationship between PC and PO ($r = 0.85$, $p = 0.001$), as well as a significant correlation between Hyp and PCC content ($r = 0.76$, $p < 0.05$), suggesting a coordinated oxidative remodelling of renal proteins and extracellular matrix components under GM-induced stress.

DISCUSSION

The present study investigated the relationship between the radical-scavenging capacity of *RA absolute* and its potential modulatory effects on acute oxidative processes in a model of GM-induced nephrotoxicity. Essential oils and their derivatives are well known for their rich phytochemical composition and reactive oxygen species (ROS) scavenging capacity, which collectively enhance antioxidant defense, promote protein and DNA repair mechanisms, and mitigate the toxic consequences of oxidative stress [2, 3, 7]. The chemical profile of *RA absolute* includes major monoterpene alcohols such as phenethyl alcohol (16.2%), geraniol (9.89%), and citronellol/nerol (6.17%), compounds previously implicated in antioxidant protection [3, 29]. It has been proposed that the antioxidant efficacy of *R. alba* L. largely stems from the presence of geraniol and citronellol [3, 29]. Mileva et al. demonstrated that Bulgarian *R. alba* essential oil exhibits superior DPPH• radical scavenging activity compared to either monoterpene alcohol alone [29]. Presented *in vitro* results confirmed the strong antioxidant potential of *RA absolute*, which showed 70% DPPH radical scavenging activity at concentrations as low as 10 $\mu\text{g}\cdot\text{mL}^{-1}$. Moreover, *RA absolute* demonstrated a stable capacity to neutralize not only DPPH• radicals but also superoxide ($\bullet\text{O}_2^-$) and hydroxyl ($\bullet\text{OH}$) radicals across a concentration range of 2–26 $\mu\text{g}\cdot\text{mL}^{-1}$ (Fig.1). Considering that under physiological conditions $\bullet\text{O}_2^-$ radicals serve as precursors for highly reactive $\bullet\text{OH}$ radicals, these findings suggest that *RA absolute* acts as a potent ROS modulator, likely through the synergistic activation of its monoterpene alcohol components (geraniol, citronellol/nerol). Consequently, *RA absolute* may function as a detoxifying agent under conditions of acute oxidative stress [30, 31]. Prolonged GM administration is known to trigger acute renal inflammation, structural damage to glomeruli and renal tubules, and disruption of redox homeostasis, leading to enhanced protein oxidation and denaturation due to ROS accumulation [32–34]. In the present study, treatment with *RA absolute* at 80 $\text{mg}\cdot\text{kg}^{-1}$ body weight effectively attenuated these effects, likely by reducing the overproduction of $\bullet\text{O}_2^-$, $\bullet\text{OH}$, H_2O_2 , and alkoxyl radicals. Mileva et al. previously reported that *R. alba* essential oil protects against Fe^{2+} /ascorbic acid-induced lipid peroxidation in liposomal membranes, confirming its strong antioxidative potential [35].

Our findings based on 5-MSL conjugation further indicate that *RA absolute* stabilizes albumin conformation by protecting sulfhydryl (-SH) groups and reducing protein oxidation in renal tissue. Gentamicin administration typically promotes collagen deposition and renal fibrosis through activation of myofibroblasts and epithelial-to-myofibroblast transdifferentiation [36, 37, 38]; however, *RA absolute* treatment directly suppressed early fibrotic and inflammatory responses, most likely via regulation of collagen synthesis. Geraniol has previously been shown to inhibit CCl_4 -induced nephrotoxicity and to restore normal renal histoarchitecture, including corpuscles, glomeruli, and tubular structures [27]. Similarly, citro-

nellol and nerol have been reported to mitigate oxidative damage by scavenging $\bullet\text{O}_2^-$, H_2O_2 , and $\bullet\text{OH}$ radicals in models of GM-induced renal toxicity [28, 29, 30]. The present data suggest that *RA absolute* functions as a redox modulator that promotes physiological protein re-oxidation and terminates excessive extracellular matrix deposition. Furthermore, Scandiffio et al. highlighted the pharmacological role of (E)- β -caryophyllene, a sesquiterpene hydrocarbon also present in *RA absolute*, as an antioxidant and anti-inflammatory compound capable of mitigating renal fibrosis and oxidative injury [31]. Carbonyl stress represents a critical pathological process that compromises protein function through oxidative modification and accumulation of reactive dicarbonyl intermediates [32]. GM penetrates renal cells via oxygen-dependent transport mechanisms [33], leading to increased protein carbonyl content (PCC), collagen deposition, and PO - hallmarks of oxidative renal injury. Treatment with *RA absolute* (80 $\text{mg}\cdot\text{kg}^{-1}$) markedly reduced GM-induced ROS accumulation by decreasing $\bullet\text{O}_2^-$ and $\bullet\text{OH}$ radical levels and restoring cytosolic and mitochondrial enzyme activity.

The combined administration of GM and *RA absolute* for 10 days appeared to enhance the enzymatic conversion of $\bullet\text{O}_2^-$ and $\bullet\text{NO}$ radicals into less reactive peroxynitrite (ONOO^-), thereby alleviating renal oxidative burden. This redox modulation may facilitate an antigen-specific immune response that promotes restoration of protein redox balance, decreases carbonylation, and attenuates GM-induced oxidative stress and fibrosis. Collectively, these findings support the hypothesis that *RA absolute* exerts protective effects against GM-induced nephrotoxicity through multifactorial mechanisms involving radical scavenging, inhibition of protein oxidation, suppression of collagen deposition, and modulation of redox homeostasis.

CONCLUSIONS

The present study demonstrates the pronounced radical-scavenging potential and oxidative stress-modulating properties of *RA absolute* in a model of GM-induced nephrotoxicity. The findings indicate that white *RA absolute* effectively mitigates renal oxidative damage by preventing protein oxidation/carbonylation and reducing the ROS accumulation. Its capacity to neutralize highly reactive $\bullet\text{O}$, γ $\bullet\text{OH}$ radicals, which play a central role in oxidative injury, underscores its potential as a natural antioxidant and protective agent against drug-induced renal toxicity.

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