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Research Article

Comparison of the antioxidant and anti-inflammatory activities of leaf extracts from grain amaranths (*Amaranthus* spp.)

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Abstract This study assessed the antioxidant and anti-inflammatory activities of leaf extracts from grain amaranths (*Amaranthus spp*.). Among all the extracts, the ethanol extract of *Amaranthus cruentus* leaves (Ar) exhibited the highest antioxidant activity, including the DPPH free radical scavenging activity and ORAC. In addition, Ar strongly inhibited nitric oxide production by suppressing the MEK/ERK signaling pathway in lipopolysaccharide-stimulated RAW264 murine macrophages. HPLC analysis revealed 13 polyphenolic compounds in the leaf extracts of grain amaranth and indicated that Ar contained more rutin than the other extracts. Taken together, these results show the impact of species diversity on the phytochemical contents and bioactivities of plant extracts and suggest that the nonedible parts, such as leaves, of *A. cruentus* should be considered for use as crude drugs and dietary health supplements.

Keywords Grain amaranth, antioxidant activity, anti-inflammatory activity, rutin

Introduction

Phytochemicals, such as sterols, polyphenols, alkaloids, and sulfur-containing compounds obtained from plants, have been extensively studied in terms of their pharmaceutical value or therapeutic potential by the cosmetic and pharmaceutical industries. The biosynthesis of specific phytochemicals is greatly affected by environmental and agronomic factors (Moniodis et al. 2018). Recent studies have revealed that the phytochemical levels of various plants significantly depend on their genetic background (Friedrich et al. 2017; Ju et al. 2021; Li et al. 2012), indicating that genetic factors are the primary factors that affect the production of phytochemicals.

Amaranth is regarded as one of the ancient crops worldwide. The genus *Amaranthus* includes around 60 species; most of these species are cultivated as grains, leafy vegetables, ornamental plants, and weeds (Manyelo et al. 2020a). Since amaranth has garnered increasing interest worldwide because of the excellent nutritional value in its grains and leaves (Písaříková et al. 2006), numerous chemical constituents, such as phytopigments (betacyanins, betaxanthins, chlorophylls, and carotenoids) and polyphenolic compounds (hydroxycinnamic acid, benzoic acid, and rutin), have been isolated from it (Karamać et al. 2019; Manyelo et al. 2020b; Sarker and Oba 2020). Thus, amaranth may be useful as a functional source in the cosmetic, functional food, and pharmaceutical industries. In fact, weedy amaranth (*A. spinosus* and *A. viridis*) has been used as an astringent, diaphoretic, diuretic, emollient, febrifuge, and galactagogue (Sarker and Oba 2019). Recent pharmaceutical studies have revealed additional pharmaceutical properties of weedy amaranth, such as antioxidant, antimicrobial, hepatoprotective, anti-inflammatory, and antidiabetic activities (Reyad-Ui-Ferdous et al. 2015).

The leaves of grain amaranth (*A. hypochondriacus*, *A. caudatus*, and *A. cruentus*) have been found to contain hydroxycinnamic acid derivatives and rutin and to exhibit higher levels of antioxidant activities than the seeds (Karamać et al. 2019). This finding indicates the potential of the nonedible parts (e.g., leaves) of grain amaranth to be used as crude drugs and dietary health supplements. However, significant attention has been focused only on the pharmacological properties of weedy amaranth.

In the present study, we assessed the antioxidant and anti-inflammatory effects of ethanol extracts obtained from nine different varieties of grain amaranth (six varieties of *A.*

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Table 1 Description of the samples used in this study

Sample	IT number	Species
Ah1	IT197078	*Amaranthus hypochondriacus*
Ah2	IT235715	*Amaranthus hypochondriacus*
Ah3	IT238342	*Amaranthus hypochondriacus*
Ah4	IT262653	*Amaranthus hypochondriacus*
Ah5	IT262681	*Amaranthus hypochondriacus*
Ah6	IT288964	*Amaranthus hypochondriacus*
Ar	IT199951	*Amaranthus cruentus*
Ac1	IT197098	*Amaranthus caudatus*
Ac2	IT218869	*Amaranthus caudatus*

hypochondriacus, one variety of *A. cruentus*, and two varieties of *A. caudatus*). Our findings suggested genetic variability in their biological activities. In addition, HPLC analysis revealed 13 polyphenolic compounds and indicated that the variation in biological activities between different species was driven by the different levels and compositions of polyphenolic compounds.

Materials and Methods

Plant materials and extraction

Grain amaranth varieties (Table 1) were obtained from the National Agrobiodiversity Center of the Rural Development Administration, Republic of Korea, and were cultivated in the experimental field managed by Chungbuk National University to avoid environmental and agronomic effects on the composition and level of phytochemicals. Leaf materials were harvested 90 days after planting and lyophilized using a freeze dryer (FreeZone Freeze Dry System, Labconco, Kansas City, MO, USA). The ground materials were soaked in ethanol for 24 h and subjected to ultrasonication (15 min × thrice). Filtered ethanol extracts were evaporated and stored at -20°C until further use.

Analysis of antioxidant activities

The free radical scavenging activity and oxygen radical antioxidant capacity (ORAC) of each extract were determined using 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals and fluorescein, respectively, as described by Ju et al. (2021). The DPPH free radical scavenging activity was expressed as the concentration required to reduce half of the DPPH free radicals (RC50), and ORAC was expressed as µM of Trolox equivalents (µM TE).

Determination of cell viability and nitrite oxide (NO) level

RAW 264.7 murine macrophage cells were cultured in Dulbecco's modified Eagle's medium (DMEM; GIBCO, Grand Island, NY, USA) supplemented with 100 U/mL of penicillin–streptomycin and 10% fetal bovine serum. The cells were plated at a density of 1.5 × 104 cells/mL in 96-well plates and incubated at 37°C for 24 h in a humidified incubator containing 5% CO_2. Following this, the cells were treated with each concentration of extract and stimulated with lipopolysaccharide (LPS, 1 µg/mL). After incubation for 24 h, cell viability was determined using MTT solution, as described by Yoo et al. (2021). Moreover, NO production was assessed using the Griess reagent system (Promega Co., Ltd., Madison, USA), according to the manufacturer's instructions. The results are representative of five independent experiments.

Western blot analysis

Proteins were extracted using RIPA lysis buffer (50 mM Tris-HCl pH 7.5, 150 mM NaCl, 1% Triton X-100, 0.1% sodium dodecyl sulfate, 0.5% sodium deoxycholate, 1 mM ethylenediaminetetraacetic acid, and 10 mM NaF) and quantified using the Pierce™ BCA Protein Assay Kit (Thermo Fisher Scientific, Waltham, MA, USA), according to the manufacturer's protocol. Following this, 20 µg of protein was separated by SDS–PAGE and transferred to a PVDF membrane (Millipore, Billerica, MA, USA). The membrane was then blocked with 5% nonfat dried milk and incubated with antibodies. The signal was detected and visualized with the ECL reagent using an Azure c280 imaging system (Azure Biosystems, Inc., Dublin, CA, USA). The results are representative of three independent experiments.

Table 2 Sequences of the primers used in qRT-PCR analyses

Gene	Primer sequences (5′-3′)	Accession number
COX-2	F-CCTCTGCGATGCTCTTCC R-TCACACTTATACTGGTCAAA	AF233596.1
iNOS	F-TCCTACACCACACCAAAC R-CTCCAATCTCTGCCTATCC	AF427516.1
TNF-α	F-AGCACAGAAGCATGATCCG R-CTGATGAGAGGGAGGCCATT	AY423855.1
IL-6	F-CCACTTCACAAGGTCGGAGGCTTA R-GTGCATCATCGCTGTTCATACAATC	DQ788722.1
b-actin	F-CCCATCTCCTAAGAGGAGGATG R-AGGGAGACCAAAGCCTTCAT	NM_007393.5

F, forward; R, reverse.

Quantitative real-time RT-PCR (qRT-PCR)

Total RNA was extracted using TRI Reagent (Invitrogen, Carlsbad, CA, USA), and cDNA was synthesized using the ReverTra Ace® qPCR RT Master Mix with gDNA Remover (TOYOBO, Co., Ltd., Osaka, Japan). qRT-PCR was performed using the SYBR® Green Real-Time PCR Master Mix (TOYOBO, Co., Ltd, Osaka, Japan) on the CFX96^{TM} Real-Time System (Bio-Rad, Hercules, CA, USA). The expression level of each gene was normalized to that of *β-actin.* Table 2 summarizes the specific primer pairs used for qRT-PCR.

HPLC analysis

HPLC analysis was conducted using an Agilent Technologies 1260 series HPLC unit equipped with a diode array detector (Agilent Technologies, Waldbronn, Germany). Chromatographic separation was performed on a Poroshell 120 EC-c18 column (4.6 × 150 mm, 4 μm) using a mixture of solvent A (water) and solvent B (acetonitrile containing 0.1% formic acid) at a flow rate of 1.0 mL/min, as described by Ju et al. (2021). Polyphenolic compounds in the extracts were identified by comparing their retention times and UV spectral data with those of the standards.

Statistical analysis

All the experiments were conducted in three independent replicates. The data are expressed as the means ± standard errors (SEs). One-way analysis of variance (ANOVA) and Duncan's test were performed using IBM SPSS software (version 25) in order to determine the significance of the data (p value < 0.05).

Results and Discussion

Comparison of antioxidant activities of nine different varieties of grain amaranth

Reactive oxygen species (ROS) act as intracellular signaling molecules in the regulation of various biological processes; however, excessive ROS formation resulting from an imbalance between cellular production and antioxidative mechanisms causes oxidative damage to cellular components, such as DNA, membranes, and lipids, and various diseases, including vascular disorders, autoimmune diseases, neurodegenerative diseases, and respiratory diseases (Checa and Aran 2020). In the present study, to assess the antioxidant activities of different varieties of grain amaranth, ethanol extracts were prepared and their DPPH free radical scavenging activities were analyzed. As shown in Fig. 1A, Ar showed the highest radical scavenging activity (IC_{50} = 907.9 ± 60.3 μg/mL) among all the tested varieties of grain amaranth. In addition, compared with the other genotypes, Ar exhibited the highest ORAC (80.9 ± 16.8 μM TE) (Fig. 1B). DPPH free radical scavenging and ORAC assays indicated that genotypic variation within a species did not influence the antioxidant activity.

Anti-inflammatory potential of grain amaranth varieties

Various plant extracts have been found to potentially function as natural therapeutic agents against inflammation, which is characterized by the overproduction of inflammatory mediators, such as ROS and pro-inflammatory cytokines (Rodríguez-Yoldi 2021). Therefore, the anti-inflammatory effect of amaranth has previously been studied using the leaf extract of weedy amaranth (*A. spinosus*) (Olajide et al. 2004). The

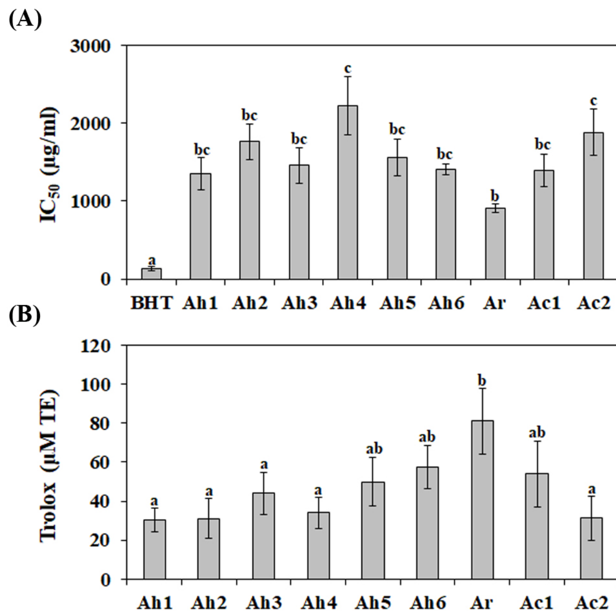

Fig. 1 Comparison of antioxidant activities among nine different varieties of grain amaranth. The antioxidant activities were based on the DPPH free radical scavenging (A) and ORAC (B) assays. Mean separation within columns according to Duncan's multiple range test at a 0.1% level

findings have indicated the potential application of amaranth leaf extract as a natural anti-inflammatory agent; however, the leaves of grain amaranth have been considered a useless by-product. To assess the anti-inflammatory activities of and variations among nine different varieties of grain amaranth, the inhibitory effect of each extract on LPS-induced NO production in RAW264.7 cells was assessed. As shown in Fig. 2A, treatment with 100 μg/mL Ar markedly inhibited NO production in LPS-stimulated RAW264.7 cells; however, treatment with the other extracts had a low inhibitory effect on LPS-induced NO accumulation. To assess whether the inhibitory effect of Ar on NO production was mediated by cell viability, the cytotoxic effect of each extract on LPS-treated RAW264.7 cells was determined by the MTT assay. No significant cytotoxic effect was observed for any of the tested extracts (Fig. 2B and 2D), indicating that the anti-inflammatory effect of Ar was not resulting from cytotoxicity. In addition, Ar inhibited LPS-induced NO production in a dose-dependent manner (Fig. 2C). Similar to antioxidant activity, a major factor influencing the anti-inflammatory activity of grain amaranth should be the genetic diversity between species.

In RAW 264.7 cells, LPS can induce an inflammatory response, at least in part, through its ability to increase the levels of pro-inflammatory mediators, including NO and prostaglandin E2 (Aldridge et al. 2008), which are mainly synthesized by inducible NOS (*iNOS*) and cyclooxygenase-2 (COX-2), respectively (Zhang et al. 2015). In addition, LPS is well known to be a strong inducer of pro-inflammatory cytokines, such as tumor necrosis factor alpha (*TNF-α*) and

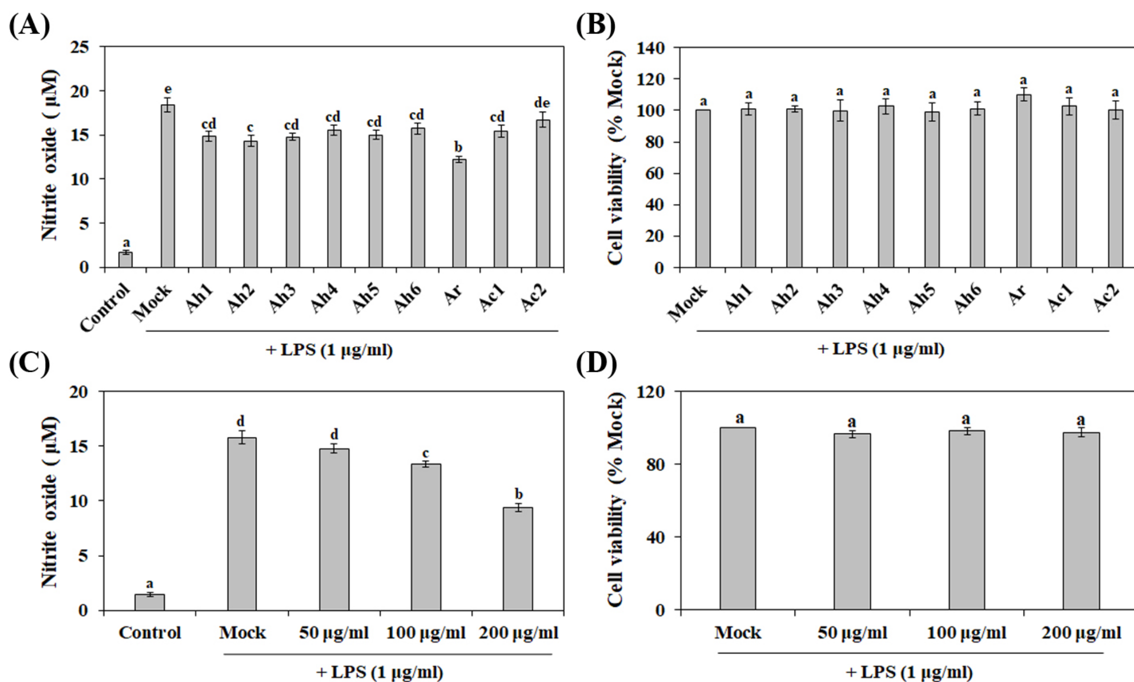

Fig. 2 Comparison of anti-inflammatory effects among nine different varieties of grain amaranth. Effect of each extract on nitric oxide (NO) production (A) and cell viability (B) in lipopolysaccharide (LPS)-treated RAW 264.7 cells. Dose-dependent effect of *Amaranthus cruentus* leaf extract (Ar) on LPS-induced NO production (C) and cytotoxicity (D) in RAW264.7 cells. Data are presented as the mean ± SE from three independent experiments. Letters indicate significant differences ($p < 0.05$)

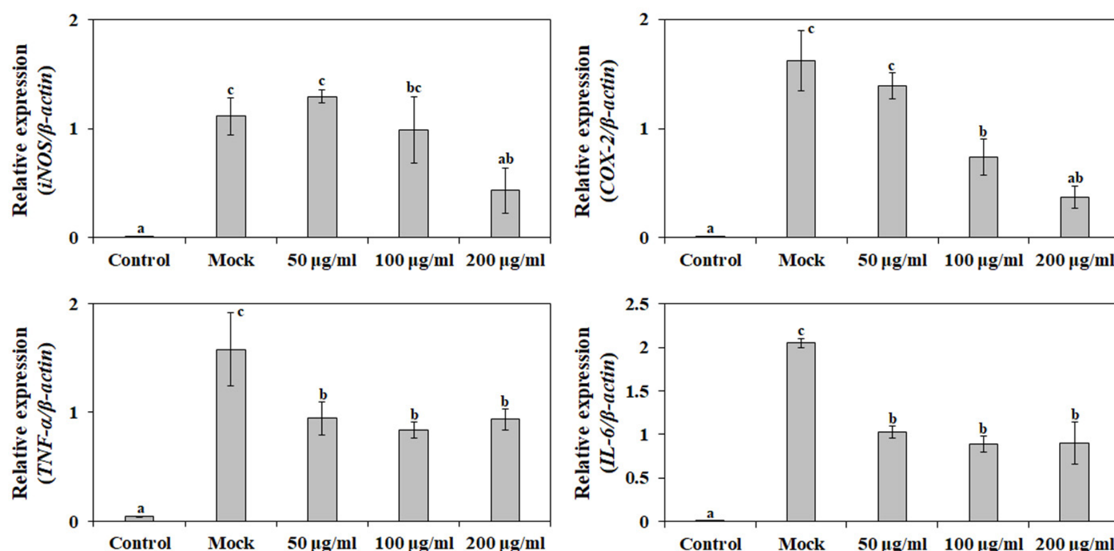

Fig. 3 Effect of *Amaranthus cruentus* leaf extract (Ar) on *iNOS, COX-2, TNF-α,* and *IL-6* expression in lipopolysaccharide-stimulated RAW264.7 cells. The expression level of each gene was normalized to that of *β-actin*. All the values are expressed as the mean ± SE from three independent experiments. Letters indicate significant differences between groups ($p < 0.05$)

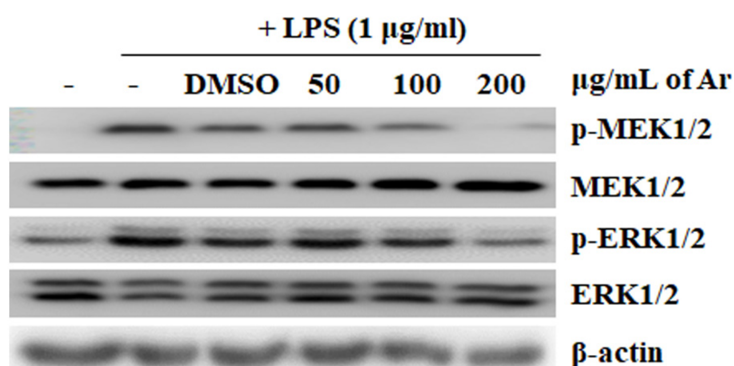

Fig. 4 Effect of *Amaranthus cruentus* leaf extract (Ar) on the lipopolysaccharide-induced activation of the MEK/ERK cascade. The activation of MEK1/2 and ERK 1/2 was assessed via western blot analysis using antibodies against phospho-MEK1/2 (p-MEK1/2), MEK1/2, p-ERK1/2, and ERK1/2

interleukin-6 (*IL-6*), which play a key role in inflammatory reactions (Frost et al. 2002). To further assess the anti-inflammatory effect of Ar, the transcription levels of pro-inflammatory genes under the stimulation of LPS with Ar were analyzed by qRT-PCR. Significantly increased levels of *iNOS*, *COX-2*, *TNF-α*, and *IL-6* were observed in LPS-stimulated RAW 264.7 cells; these increases were reduced by treatment with Ar (Fig. 3), indicating that Ar inhibited the inflammatory response by downregulating pro-inflammatory mediators and cytokines.

The LPS-induced activation of mitogen-activated protein kinase (MAPK) cascades plays critical regulatory roles in the production of pro-inflammatory mediators and cytokines (Manzoor and Koh 2012). Therefore, the MAPK cascade is an important target for anti-inflammatory therapy. As shown in Fig. 4, LPS-induced MEK/ERK activation was inhibited by Ar. This indicates that the Ar-mediated anti-inflammatory effect can be attributed to the inactivation of the MEK/ERK cascade, resulting in the suppression of LPS-induced transcriptions of pro-inflammatory mediators.

Polyphenolic compounds in leaf extracts of grain amaranth

Polyphenolic compounds are receiving increasing attention because of their health-promoting properties in many chronic disorders and diseases, including diabetes, cardiovascular diseases, inflammation, cancer, rheumatoid arthritis, and neurodegenerative diseases (Shakoor et al. 2021). In higher plants, genetic factors are considered to explain the intraspecific variability of phytochemicals, including polyphenolic compounds (Asensio et al. 2020). To further analyze the variations in phytochemicals among nine different varieties of grain

Table 3 Polyphenolic compounds in the leaf extracts from nine different varieties of grain amaranth

Compound number	Compound	μg/g of extract								
		Ah1	Ah2	Ah3	Ah4	Ah5	Ah6	Ar	Ac1	Ac2
1	Gallic acid	ND[a]	0.45 ± 0.00[a]	ND[a]	0.25 ± 0.00[a]	0.37 ± 0.00[a]	ND[a]	0.19 ± 0.00[a]	ND[a]	ND[a]
2	3,4-Dihydroxybenzoic acid	116 ± 1.53[c]	ND[a]	ND[a]	ND[a]	51.6 ± 12.0[b]	198 ± 39.3[d]	26.5 ± 6.41[ab]	ND[a]	ND[a]
3	4-Hydroxybenzoic acid	1.01 ± 0.11[b]	1.34 ± 0.09[b]	2.52 ± 0.08[c]	0.31 ± 0.00[a]	0.18 ± 0.01[a]	0.08 ± 0.00[a]	0.21 ± 0.00[a]	0.08 ± 0.00[a]	0.27 ± 0.00[a]
4	2, 4-Dihydroxybenzoic acid	0.3 ± 0.05[a]	ND[a]	0.42 ± 0.02[a]	0.25 ± 0.06[a]	ND[a]	ND[a]	0.58 ± 0.00[a]	0.13 ± 0.00[a]	ND[a]
5	Caffeic acid	ND[a]	ND[a]	ND[a]	ND[a]	0.7 ± 0.00[a]	ND[a]	1.85 ± 0.02[b]	ND[a]	ND[a]
6	Syringic acid	256 ± 49.4[bc]	318 ± 15.7[c]	467 ± 18.4[d]	84.7 ± 34.8[a]	70 ± 20.4[a]	48.1 ± 0.00[a]	47.7 ± 0.00[a]	84 ± 14.0[a]	150 ± 42.6[ab]
7	p-Coumaric acid	ND[a]	ND[a]	ND[a]	ND[a]	0.29 ± 0.09[ab]	0.63 ± 0.40[b]	0.15 ± 0.02[a]	0.36 ± 0.01[ab]	0.09 ± 0.00[a]
8	Ferulic acid	ND[a]	ND[a]	ND[a]	ND[a]	ND[a]	1.51 ± 0.50[b]	ND[a]	ND[a]	ND[a]
9	Sinapinic acid	ND[a]	ND[a]	ND[a]	ND[a]	ND[a]	5.14 ± 0.00[a]	ND[a]	ND[a]	ND[a]
10	Rutin	ND[a]	ND[a]	ND[a]	ND[a]	2.51 ± 0.08[a]	ND[a]	46.8 ± 1.51[c]	5.88 ± 0.57[b]	1.44 ± 0.25[a]
11	Quercetin 3-β-D-glucoside	ND[a]	ND[a]	ND[a]	ND[a]	ND[a]	ND[a]	2.49 ± 0.17[b]	ND[a]	ND[a]
12	Benzoic acid	ND[a]	ND[a]	ND[a]	ND[a]	0.46 ± 0.00[a]	0.18 ± 0.00[a]	1.84 ± 0.23[b]	0.71 ± 0.00[a]	ND[a]
13	Kaempferol 3-O-β-rutinoside	6.67 ± 0.03[e]	9.5 ± 0.04[f]	24.1 ± 0.01[f]	5.33 ± 0.01[d]	0.68 ± 0.04[bc]	1.01 ± 0.21[c]	0.23 ± 0.00[a]	0.76 ± 0.02[bc]	0.64 ± 0.04[b]

Superscript letters indicate significant differences between groups ($p < 0.05$).

amaranth, their polyphenolic compounds were determined using HPLC. All the tested samples were found to contain 4-hydroxybenzoic acid, syringic acid, and kaempferol 3-O-β-rutinoside; however, quercetin 3-β-D-glucoside was specific to Ar (Table 3). In *A. hypochondriacus*, variations between genotypes were observed in the polyphenolic compounds, suggesting that the genotype is an important factor affecting the phytochemical contents. Furthermore, Ar contained the highest content of rutin (46.8 ± 1.51 μg/g of extract), which plays a role in the prevention of various diseases, including cancer, cardiovascular diseases, neurodegenerative diseases, and diabetes (Gullón et al. 2017). Similar to our finding, rutin was found to be the dominant phenolic compound in the vegetative part of *A. cruentus* in a previous study (Manyelo et al. 2020b). Thus, the high antioxidant and anti-inflammatory activities of Ar could be mediated by the presence of active polyphenolic compounds, such as rutin.

Conclusion

The present results clearly indicate the variations in antioxidant and anti-inflammatory activities among nine different varieties of grain amaranth and suggest that species diversity plays an essential role in determining the polyphenol contents and biological activities. In addition, Ar was found to possess the highest antioxidant and anti-inflammatory activities among all the tested extracts, suggesting that Ar is a promising source as a crude drug and dietary health supplement.

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