Growing Korean Angelica (*A. gigas* Nakai) in Central Pennsylvania - Root Pyranocoumarin Profile at Different Harvesting Time

Junxuan Lü[1, 2*,Ψ], Dongxiao Sun[1,3Ψ], Tongyao Fan[1], Sangyub Kim[1], Eugene J. Lengerich[2,4] and Cheng Jiang[1]

[1]Department of Pharmacology, Pennsylvania State University College of Medicine, Hershey, PA.
[2]PennState Cancer Institute, Pennsylvania State University College of Medicine, Hershey, PA.
[3]Mass Spectrometry Core Facility, Pennsylvania State University College of Medicine, Hershey, PA.
[4]Department of Public Health Sciences, Pennsylvania State University College of Medicine, Hershey, PA.

***Corresponding Author:** junxuanlu@pennstatehealth.psu.edu

[Ψ]Equal first authors

Manuscript received: November 28, 2023

Keywords: decursin, decursinol angelate, herbal quality control, medicinal herbal cultivation, phytochemical profiling

ABSTRACT

The dried roots of *Angelica gigas* Nakai (AGN) plants (also known as Korean Angelica or Cham Dang Gui) are a popular medicinal herbal ingredient in Korea. Herbal dietary supplements made of imported AGN root extracts from Korea have been marketed in the United States for cognitive memory health and pain relief. Although AGN plants are sold by plant nurseries in the US for ornamental purposes, their cultivation for potential herbal medicinal use has not been reported in the academic literature. Here we describe the signature chemical profile of AGN plants cultivated in Hershey, and State College, in the State of Pennsylvania (PA) from 2017 to 2023. Stem rot was a disease that led to the premature death of some growing and flowering plants. We analyzed dried roots harvested in 2018 (N = 5) and in 2019 (N = 3) for AGN plants grown in Hershey and those harvested in October 2023 from the initial 2017 planting in the State College site (N = 5) for their pyranocoumarins, decursin (D) and decursinol angelate (DA). Both D and DA were detected in all root samples, with a majority (10/13) meeting and exceeding the Korean Pharmacopeia specification. The DA/D ratios in individual plants were consistent with those grown in Korea (<0.8) except one 3-year plant which yielded a ratio of 1.03. Therefore, AGN could be cultivated as a medicinal herbal crop upon horticultural optimization in PA and similar northern US states.

INTRODUCTION

The dried roots of *Angelica gigas* Nakai (AGN) plants (also known as Korean Angelica or Cham Dang Gui) have been used in traditional Korean herbal medicine for centuries for many ailments (Lu et al., 2022). More than a dozen beneficial bioactivities have been attributed to the alcoholic or water extracts of AGN roots, including anti-cancer, pain-killing, neurological health, etc. (Lu et al., 2022). Herbal supplements made with imported AGN root alcoholic extract powders (trade-named INM-176) have been marketed in the United States to boost memory (e.g., Cogni.Q by Quality of Life Labs, Inc.) and aid in pain management (e.g., Decursinol-50 by SunBio Corp.) (Zhang et al., 2012; Lu et al., 2022). Clinical trials are being carried out in the PennState Health/College of Medicine system to evaluate the immune enhancement (Lu, 2018) and pharmacokinetics dose response to Cogni.Q in prostate cancer patients (Joshi, 2022).

The pyranocoumarin compound decursin (D), and its isomer decursinol angelate (DA), and their phytochemical precursor decursinol (DOH) are signature compounds unique to AGN that chemically distinguish it from other common Oriental medicinal Angelica species such as Chinese (*A. sinensis;* Dang Gui) or Japanese (*A. acutiloba*) counterparts (Zhang et al., 2012; Lu et al., 2022). DA is approximately 50-80% as abundant as D. DOH constitutes less than 1% of D+DA in the AGN alcoholic extract. Being hydrophobic compounds, the pyranocoumarins are extractable only when the alcohol solvent exceeds a critical concentration (Zhang et al., 2012). Together, D and DA may constitute 3.0-8.2% of dried AGN root or as high as 60% of the dried ethanol extract, depending on the extraction protocols and sourcing of AGN roots (Zhang et al., 2012; Tang et al., 2015; Lu et al., 2022). A recent paper has reported varying D and DA contents of AGN plants grown in different production regions of South Korea (harvested October 2017) (Pyeongchang 37.5567° N, 128.4826° E; Jecheon 37.0597° N, 128.1410° E; Bonghwa 36.9341° N, 128.9129° E) (Park et al., 2020), implicating the gravel content in soil samples as a positive correlate for D and DA content. The contents of D and DA as well their ratio are important parameters for the quality control (QC) of AGN roots, their extracts and supplement products as well as authentication of the species.

The AGN species is usually regarded as a biennial. Although AGN plants are sold by plant nurseries in the US for ornamental purposes, their cultivation for potential herbal medicinal use has not been reported in the academic literature. Here we report contents of D and DA in the dried roots of AGN plants grown in Hershey and State College, PA, from 2017 to 2023.

MATERIALS AND METHODS

Chemicals. For analytical standards, decursin (item No. 25214) and DA (item No. 25212) were purchased from Cayman Chemical Co., USA. Their authenticity was confirmed by mass spectrometry (MS) and nuclear magnetic resonance (NMR) in-house at Penn State College of Medicine core facilities. High performance liquid chromatography (HPLC)-grade methanol, acetonitrile and dimethyl sulfoxide (DMSO) used for HPLC-tandem mass spectrometry (HPLC-MS-MS) analyses were purchased from Fisher Scientific, USA.

Positive and negative control extract preparations. As a positive control, an AGN root ethanolic extract powder trade-named INM-176 was used. It was generously donated by Scigenic, Inc. Anyang, Korea. The powder was formulated as a 5x concentrate equivalent of the dried roots and was used for production of the commercially marketed AGN-containing products Cogni.Q and Decursinol-50. As a negative control, store-bought Chinese Angelica roots (*A. sinensis*) were cut and ground and extracted per the same protocol as described below for the AGN roots grown in Hershey.

Commercial source of plants and cultivation locations. Seedlings of AGN plants were purchased from Digging Dog Nursery, Albion, CA 95410 (elevation 174 ft or 53 m; latitude 39.208008 and longitude -123.680006) in Spring of 2017. Ten seedlings were planted on April 17, 2017 by JL in Hershey, PA 17033 (Elevation 411 ft or 125 m; latitude 40.285519, and longitude -76.650589) in the front yard (full sun) (Fig. 1) and backyard (shaded in morning). Ten seedlings were planted by co-author EJL near State College, PA (elevation 1,200 ft or 370 m, latitude 40.7933949 and longitude -77.8600012) in late April 2017.

Root harvest and processing. In Hershey site, the roots of 2-year plants were harvested in fall of 2018 and were soaked and washed in a plastic tub until visibly dirt-free (Fig. 3). The roots of 3-year plants were similarly unearthed in the fall of 2019 and processed by the same washing and air-drying procedures. The air-dried roots were sampled as # 1-5 for the 2018 harvest and # 6-8 for the 2019 harvest (3-year plants).

For those planted at the State College site in 2017, overgrowth of other plants and shrubs severely limited their vegetative size. The roots from 5 plants that had blossomed during the summer of 2023 were harvested on October 13, 2023, and processed by the same procedures as above (designated as # 9-13), with the addition of 12h drying in a 50^{o}C oven.

Phytochemical extraction with 80% methanol.

The root extraction method was adapted from Choi et al. (Choi et al., 2003) with modifications. Air-dried AGN roots were cut into smaller pieces with scissors before being crushed using a Ninja Blender and then with a heavy-duty Robot Coupe Blixer 3 Series blender or manually with pestle and mortar if the quantity was limited. The resulting root powder samples were weighed (up to 1 g per tube) and suspended in 20 mL of 80% methanol in a polypropylene plastic tube. The tubes were incubated in a 60°C oven and vortexed occasionally. Following the incubation for 2-3 days, the mixture was cooled to room temperature and centrifuged at 4,000 g for 10 minutes. The supernatant was collected into a new tube and the root pellet was subjected to another round of extraction using 20 ml of 80% methanol for 5-6 h at 60ºC. The resulting supernatants from the first and second extractions were pooled together (40 ml total volume) and stored at -20°C in the dark. Samples were submitted to Penn State College of Medicine Mass Spectrometry Core for D and DA analysis.

A sample of Chinese Dang-gui roots (*Radix Angelica Sinensis*) was analyzed as a negative control. The AGN root extract powder INM-176, as a positive control (~200 mg per tube), was analyzed June 2023 along with the Hershey roots and November 2023 along with State College roots.

HPLC-MS-MS method. Based on our earlier 2-column HPLC-MS-MS method (Li et al., 2013; Zhang et al., 2015) with modifications, D and DA were separated and quantified using Sciex 6500 Q Trap mass spectrometry coupled with an ExionLC separation system (Sciex, USA) in Mass Spectrometry Core Facilities in Penn State College of Medicine. A Kinetex XB-C18 column (2.6 µm, 100 x 2.1 mm, Phenomenex, USA) and a Poroshell 120 EC-C18 column (2.7 µm, 50 x 3 mm, Agilent, USA) were combined in serial arrangement to separate D and DA. An isocratic elution was conducted using a flow rate of 0.4 mL/min, at 50 % mobile phase A (water) and 50 % mobile phase B (acetonitrile).

The Sciex 6500 Q Trap mass spectrometer was equipped with an electrospray ionization probe operated in positive mode. The decluster potential (DP) was 100 V; the entrance potential (EP) was 10 V, the collision energy (CE) was 27 V and the collision cell exit potential (CXP) was 15 V, while the curtain gas (CUR) was 35 L/h, the collision gas (CAD) was set at low. The ion-spray voltage was 5500 V, the temperature was 500 °C. The Gas 1 was 35 L/h and gas 2 was 35 L/h. The multiple reaction monitoring mode (MRM) was used to analyze and quantify D and DA, with the transitions of *m/z* 329 (D or DA molecular ion) > 229 (DOH minus an oxygen atom). For standard compounds, the identity and purity of D and DA purchased from Cayman Chemical were confirmed upon receipt at Penn State College of Medicine by HPLC-MS-MS and by NMR. The D and DA stock solutions were prepared in DMSO and diluted in 80% methanol into the working range of 1-250 ng/ml for the standard curves. Analytical method performance parameters are shown in Figure 4.

Statistical analyses. Two-tail Student t-test was used to compare the mean root D or DA level by their harvest year (2018 vs. 2019) for Hershey site and for the Hershey samples combined vs. the Stage College samples. Alpha = 0.05 for statistical significance.

RESULTS

Growing conditions 2017-2019 for Hershey, PA plants. After planting on April 17, 2017 in Hershey, PA (Fig. 1A), 8 out of 10 seedlings survived the first year. They grew to about 1 foot tall and did not flower the first year. The next year, young leaves appeared in early March. By late April 2018, the plants grew to about 1 foot tall (Fig. 1B). Five of the 8 grew to 3-5 feet tall from June to early July. By middle July, purple blossoms with umbrella arrangement on the major stem were in full bloom (Fig. 1C). The blossoms persisted on branched stalks 5-6 feet tall and lasted through early August (Fig. 1D). By end of August and early September, 2018, seeds were visible (Fig. 1E). Toward the end of October, 2018, the stalks of these typical biennials had withered (Fig. 1F).

Plant disease. Two plants were diseased with black stem rot (Fig. 2, A-C). The first plant withered in later June and died by July 1, 2018 (Fig. 2A). By July 14, 2018, the dried-up plant showed black stem

and rotting roots (Fig. 2B). In early August 2018, another blooming plant withered with evident signs of black stem rot (Fig. 2C).

Figure 1. The life-cycle of AGN plants grown in Hershey, PA. A. Seedlings planted in April 17, 2017. B. Spring growth in second year, photographed on April 24, 2018. C. Early blossom on the main stem, photographed on July 21, 2018. D. Full blossoms on branches, photographed on August 3, 2018. E. Seeds by late August-early September, photographed on September 1, 2018. F. Stalks drying up in the fall, photographed on October 21, 2018.

3-Year AGN plants. Unlike the typical biennial life cycle above, three plants did not thrive and flower the second year. In the spring and summer of 2019, these 3-year plants grew and blossomed (Fig. 2D). By the end of August 2019, they were 5-6 feet tall with purple umbrella flowers. These plants did not suffer visibly from the stem rot disease.

Figure 2. Plant disease (A-C). A and B. Stem rot in a plant before flowering, photographed on July 1 and 14, 2018. C. Stem rot in a flowering plant, photographed on August 8, 2018. D. 3-year plants, photographed on August 30, 2019 with a yard stick.

Root harvest and processing. In the summer and fall of 2018, the roots of the flowered plants were harvested (Fig. 3A), soaked and washed in tap water until visibly free of dirt (Fig. 3B) and hung on a cloth line to air dry (Fig. 3C). The patio on the northwest corner of the house had afternoon sun only. Due to the extreme wet fall in 2018, mold was visible on most of the roots. After a couple of months, the roots appeared darkened (Fig. 3D) and were stored inside the house. Both the fresh and the dried roots gave off a strong and distinctly herbal medicinal aroma. The dried roots were sampled for chemical profiling as #1-5 (Fig. 3D). The roots of the 3-year plants were harvested in 2019, washed and air dried as described above and sampled as # 6-8 for the chemical profiling (Fig. 3E).

Growing conditions and harvesting for AGN plants at State College, PA, site, 2017-2023. In 2017, 10 seedlings were planted in the yard of co-author EJL, a slightly more northern latitude and higher

elevation than Hershey, PA. They had similar survival and growing patterns, except delayed in blooming a few days to a week. The roots were not harvested in 2018 or subsequent years until 2023. Plants had continued to emerge and grow from either surviving roots or from fertile seeds at the site of original planting. The soil was shallow and rather poor, and overgrown with shrubs and other plants to compete with the AGN plants. Five AGN plants blossomed in mid-August, 2023. When harvested on October 13, 2023, their roots were diminutive and less odorous in comparison to those grown in Hershey.

Pyranocoumarins D and DA were detected in all AGN roots. The HPLC-MS-MS analyses (sample elution profiles in Fig. 4) of the positive control INM-176 powder (analyzed in June 2023 along with the Hershey root samples and in November 2023 along with the State College root samples) showed 14.45-15.08% D and 11.23-11.26% DA, and DA/D ratio of 0.74-0.78 (Table 1A, B). As expected of the *Angelica* species differences in phytochemical compositions, the Chinese Angelica root sample showed D and DA content (0.0014% D, 0.0005% DA), ~4 orders of magnitude less than in AGN samples (Table 1A).

The root extracts of Hershey and State College AGN plants yielded detectable and variable % of D and DA (Table 1). For the Hershey roots (Table 1A), the 2018 harvest (2-year plants plus diseased plants) as a group contained mean D of 5.58% (median 5.31%, range 2.90% - 8.98%) and mean DA of 3.50% (median DA 3.64%, range 1.71% - 4.55%). Their mean DA/D ratio was 0.64. The 2019 harvest (3-year plants) contained group mean D of 3.18% (median 3.69%, range 2.02 % - 3.82%) and mean DA of 2.17% (median 2.09%; range 2.06% - 2.36%). It is noteworthy that one of the 3-year plants had a DA/D ratio of 1.03 ($\pm$ 0.06, 5 replicate samples), in contrast to the other two plants with the typically expected values of below 0.8 (0.57 and 0.62). Statistically, t-tests (2-tail) indicated D and DA levels in 2018 harvest as a group did not differ ($p > 0.05$) from the 2019 harvest 3-year plants.

In spite of the diminutive size of the roots of the State College AGN plants, their mean D (5.06%) and DA (3.10%) (Table 1B) were not statistically different from the Hershey roots combined (D 4.68%; DA 3.00%). Nor was there a difference for the D+DA and DA/D ratios between the two cultivation sites.

Figure 3. Harvesting and processing of AGN roots. A. Digging up the roots. B. Soaking and washing. C. Air drying on a cloth line. D. Air-dried roots from 2-year plants, 2018 harvest. E. Air-dried roots from 3-year plants, 2019 harvest.

DISCUSSION

Our results show the growth of a cultivar of AGN purchased from the Digging Dog Nursery in the Central PA locals of Hershey and State College with a general compatibility of climate and soil for AGN cultivation. Stem rot disease negatively affected the health of some growing and flowering plants, leading to their premature demise. Expecting a biennial life

cycle, we found a sizable fraction of them grew as 3-year plants. Our HPLC-MS-MS analyses detected D and DA in all the AGN roots harvested in 2018 (2-year plants plus diseased plants) and 3-year plants (harvested 2019) grown in Hershey, PA (Table 1A) and in the State College root samples harvested in 2023 (Table 1B). Overall, the Hershey roots and the Stage College roots did not differ significantly in their mean D, DA, D+DA and their DA/D ratios.

The Korean Pharmacopeia stipulates that dried AGN roots should contain or exceed 6% "total active compounds" which were defined as the sum of D + DA + nodakenin (Park et al., 2020). Based on the reported nodakenin contents in AGN roots from the 3 sampled production regions of South Korea and their respective proportionality to "D + DA" (Park et al., 2020), the D + DA sum should have cut-off values in the following range 4.86% - 5.71% to meet the 6% "total active compound" specification. By this cut-off criterion, 6 out of 8 AGN roots grown in Hershey and 4 out of 5 State College AGN roots (i.e., 10/13 total = 77%) exceeded the Korean Pharmacopeia specification. In comparison, 11 out of the 18 (= 61%) Korean AGN root samples met Korean Pharmacopeia specification (Park et al., 2020).

The DA/D ratios in roots of individual AGN plants grown in Hershey (=< 0.75) (Table 1A) and in the State College root samples (=<0.79) (Table 1B) were consistent with those grown in Korea, except one 3-year plant from Hershey 2019 harvest which had a ratio of 1.03 ($\pm$ 0.06, 5 replicates). As a reference value, the DA/D ratio of AGN INM-176 powder was 0.74-0.78 (Table 1). Because of the commercial scale production of INM-176 AGN powder, its DA/D ratio reflected likely the average of pooled AGN roots in kilogram or tonnage quantities. In the Korean study of the 3 different production regions, the DA/D ratios ranged from 0.60 to 0.87 (Park et al., 2020).

Although the AGN roots harvested in 2018 (2-year plants and diseased plants) vs. those harvested in 2019 (the 3-year plants) did not differ statistically for their D and DA levels (Table 1A), the 2018 roots had a wider range (min-max) for each compound. Many factors could have contributed to the greater variability between 2018 and 2019, including rainfall and temperature patterns, harvesting timing, plant disease and post-harvest processing.

The Korean study of the 3 AGN production regions had identified gravel content in the soils to have a strong positive correlation with D and DA content in the roots, whereas weather conditions did not seem to correlate (Park et al., 2020). More research is warranted to address issues affecting the growth and health of the AGN plants and the quality and yield of their roots in the US.

CONCLUSIONS

This preliminary study demonstrated the feasibility of growing the particular AGN cultivar (Digging Dog Nursery) in Central PA and its rich production of decursin and decursinol angelate comparable or even superior to AGN cultivars grown in their native habitats of South Korea. More research on agronomic practices such as root harvest timing and post-harvest processing to optimize root yield and pyranocoumarin content should be conducted to ensure the medicinal herbal quality. These will be essential to establish an economically viable US production base of medicinally active AGN in Central PA and similar northern US states. In conclusion, AGN could be cultivated as a medicinal herbal crop upon horticultural optimization in PA and similar northern US states.

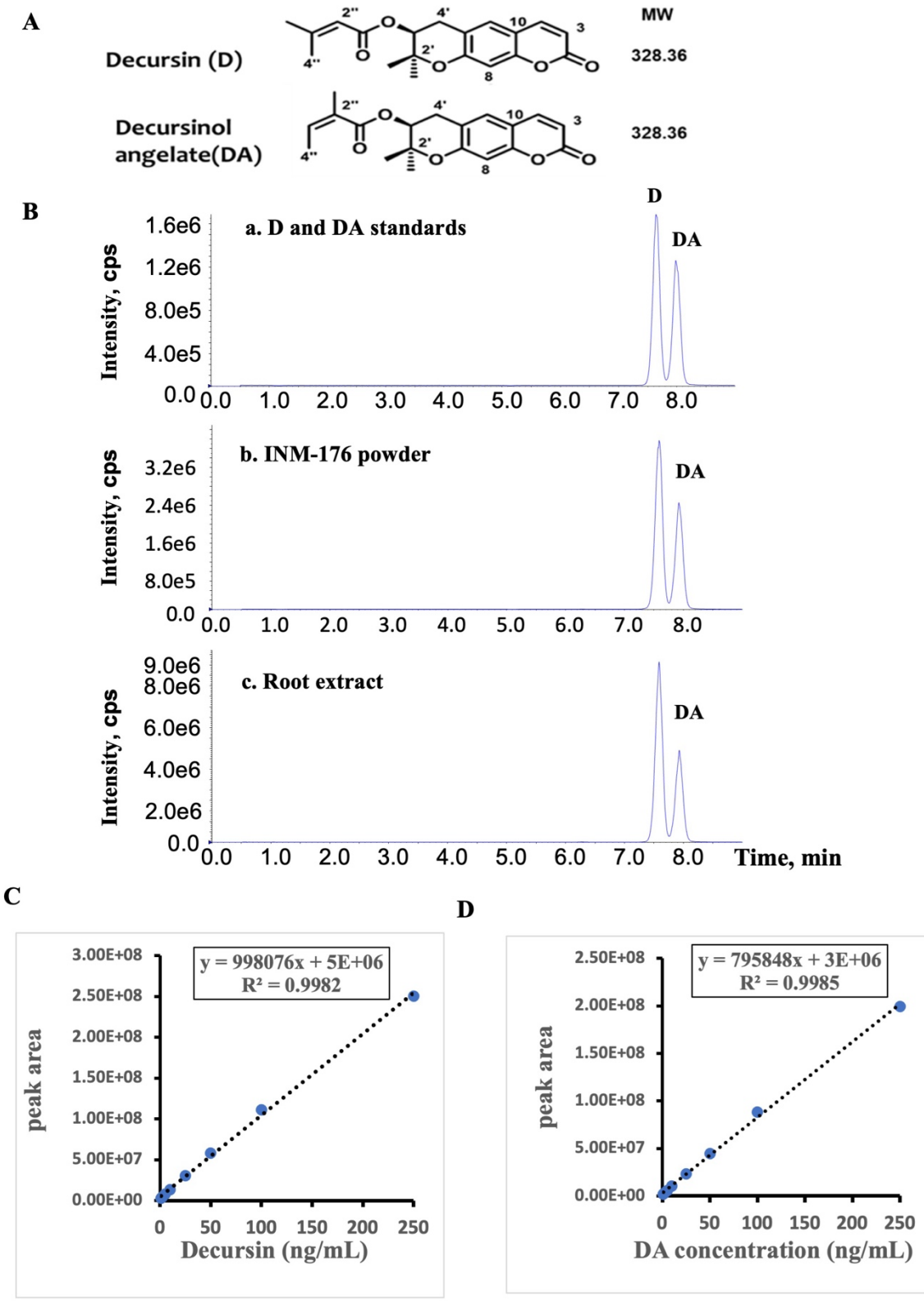

Figure 4. Quantifying decursin (D) and decursinol angelate (DA) content. A. Chemical structures. B. HPLC-MS/MS MRM elution profiles of (a) D and DA standard mix, (b) INM-176 powder, and (c) a root extract sample. C and D. standard curves of MRM peak area vs. D and DA concentration in the range of 1-250 ng/ml.

Table 1. Pyranocoumarin contents measured in air-dried roots of AGN plants grown (A) in Hershey, PA, harvested in 2018 and in 2019 and (B) in State College, PA, harvested in October 2023.

Sample ID	Metrics	Decursin (D) % w/w	Decursinol angelate (DA) % w/w	D + DA, % w/w	DA/D ratio
A. Hershey roots					
INM-176 AGN powder (Positive control, analyzed June 2023)	Average (CV; n[1])	15.08% (3.6; 3)	11.23% (5.8; 3)	26.31% (4.6; 3)	0.74 (2.2; 3)
Chinese Angelica root (Negative control)	Average (CV; n[1])	0.0014% (71.4; 3)	0.0005% (60; 3)	0.0020% (65; 3)	0.40 (10.5; 3)
AGN Root 1; 2018 harvest	Average (CV; n[1])	5.31% (8.7; 6)	3.64% (8.8; 6)	8.94% (8.6; 6)	0.69 (2.2; 6)
AGN Root 2; 2018 harvest	Average (CV; n[1])	2.90% (4.5; 6)	1.71% (4.7; 6)	4.61% (4.6; 6)	0.59 (0.5; 6)
AGN Root 3; 2018 harvest	Average (CV; n[1])	4.71% (17.0; 3)	3.11% (13.5; 3)	7.82% (15.7; 3)	0.66 (4.2; 3)
AGN Root 4; 2018 harvest	Average (CV; n[1])	5.99% (9.0; 6)	4.50% (7.6; 6)	10.49% (8.2; 6)	0.75 (3.5; 6)
AGN Root 5; 2018 harvest	Average (CV; n[1])	8.98% (7.5; 6)	4.55% (7.5; 6)	13.52% (7.5; 6)	0.51 (1.0; 6)
2018 Harvest as a group (N=5)	**Mean ± SD**	**5.58% ± 2.22%**	**3.50% ± 1.17%**	**9.08% ± 3.29%**	**0.64 ± 0.094**
AGN Root 6; 2019 harvest	Average (CV; n[1])	3.82% (3.7; 4)	2.36% (3.0; 4)	6.19% (3.2; 4)	0.62 (3.1; 4)
AGN Root 7; 2019 harvest	Average (CV; n[1])	3.69% (12.2; 4)	2.09% (12.0; 4)	5.77% (12.1; 4)	0.57 (1.6; 4)
AGN Root 8; 2019 harvest	Average (CV; n[1])	2.02% (15.3; 5)	2.06% (12.1; 5)	4.08% (13.5; 5)	1.03 (5.3; 5)
2019 Harvest as a group (N=3)	**Mean ± SD**	**3.18% ± 1.00%**	**2.17% ± 0.17%**	**5.35% ± 1.11%**	**0.74 ± 0.25**
t-test, 2018 vs. 2019 harvests	P value	0.084	0.054	0.064	0.576
All Hershey roots combined (N=8)	**Mean ± SD**	**4.68% ± 2.16%**	**3.00% ± 1.12%**	**7.68% ± 3.21%**	**0.67 ± 0.16**
B. State College roots					
INM-176 AGN powder (Positive control, analyzed November 2023)	Average (CV; n[1])	14.45% (4.5; 3)	11.26% (3.9; 3)	25.72% (4.2; 3)	0.78 (0.6; 3)
AGN Root 9; 2023 harvest	Average (CV; n[1])	7.23% (6.5; 3)	4.62% (7.4; 3)	11.85% (6.9; 3)	0.64 (0.9; 3)
AGN Root 10; 2023 harvest	Average (CV; n[1])	3.39% (1.8; 3)	1.73% (1.7; 3)	5.12% (1.8; 3)	0.51 (0.8; 3)
AGN Root 11; 2023 harvest	Average (CV; n[1])	5.13% (8.2; 3)	2.43% (7.8; 3)	7.56% (8.1; 3)	0.47 (1.3; 3)
AGN Root 12; 2023 harvest	Average (CV; n[1])	4.77% (2.3; 3)	3.77% (1.6; 3)	8.54% (2.0; 3)	0.79 (0.6; 3)
AGN Root 13; 2023 harvest	Average (CV; n[1])	4.82% (3.1; 3)	2.95% (1.7; 3)	7.77% (2.6; 3)	0.61 (1.6; 3)
State College roots as a group (N=5)	**Mean ± SD**	**5.07% ± 1.38%**	**3.10% ± 1.13%**	**8.17% ± 2.42%**	**0.60 ± 0.125**
t-test, State College vs. Hershey roots	P value	0.728	0.880	0.776	0.426

[1]Coefficient of variation, as % of root average; number of replicate samples for each root.

ACKNOWLEDGEMENTS

The analytical work for pyranocoumarins was supported, in part, by the National Cancer Institute (NCI) grant R01CA260901. The authors thank Mr. Hee-Sul Lee (President and CEO) and Scigenic Co. Ltd of Anyang, Republic of Korea for the generous donation of INM-176 powder for research.

The analytical method development and sample analyses were carried out at the Mass Spectrometry Core Facilities at The Pennsylvania State University College of Medicine. The Mass Spectrometry Core (RRID:SCR_017831) services and instruments used in this project were funded, in part, by the Pennsylvania State University College of Medicine via the Office of the Vice Dean of Research and Graduate Students and the Pennsylvania Department of Health using Tobacco Settlement Funds (CURE). The content is solely the responsibility of the authors and does not necessarily represent the official views of the University or College of Medicine. The Pennsylvania Department of Health specifically

disclaims responsibility for any analyses, interpretations or conclusions.

The authors thank Ms. Gaelyn C. Lyons from the Penn State College of Medicine Biomedical Science Graduate Program for contributing to AGN root extraction during her rotation as a first-year graduate student and Professor Jason Liao of Department of Public Health for consultation for statistical analyses.

REFERENCES

Choi, S.S., Han, K.J., Lee, H.K., Han, E.J. and H.W. Suh, H.W. 2003. Antinociceptive profiles of crude extract from roots of *Angelica gigas* Nakai in various pain models. Biol. Pharm. Bull. 26: 1283-1288.

Joshi, M. 2022. NCT05375539. https://www.clinicaltrials.gov/study/NCT05375539?term=cogni.q&rank=1)

Li, L., Zhang, J., Xing, C., Kim, S.H., Jiang, C. and Lu, J. 2013. In vitro metabolism of pyranocoumarin isomers decursin and decursinol angelate by liver microsomes from man and rodents. Planta Med. 79: 1536-1544.

Lu, J. 2018. NCT03630328 (https://www.clinicaltrials.gov/study/NCT03630328?term=cogni.q&rank=2)

Lu, J., Jiang, C., Schell, T.D., Joshi, M., Raman, J.D. and C. Xing. 2022. *Angelica gigas*: Signature Compounds, In Vivo Anticancer, Analgesic, Neuroprotective and Other Activities, and the Clinical Translation Challenges. Am J Chin Med 50: 1475-1527.

Park, Y., Park, P.S., Jeong, D.H., Sim, S., Kim, N., Park, H., Jeon, K.S., Um, Y., and Kim. M.J. 2020. The Characteristics of the Growth and the Active Compounds of *Angelica gigas* Nakai in Cultivation Sites. 2020. Plants (Basel) 9,823.

Tang, S.N., Zhang, J., Wu, W., Jiang, P., Puppala, M., Zhang, Y., Xing, C., Kim, S.H., Jiang, C. and Lu, J. 2015. Chemopreventive effects of Korean Angelica versus its major pyranocoumarins on two lineages of transgenic adenocarcinoma of mouse prostate carcinogenesis. Cancer Prev. Res. (Phila) 8: 835-844.

Zhang, J., Li, L., Hale, T.W., Chee, W., Xing, C., Jiang, C. and Lu, J. 2015. Single oral dose pharmacokinetics of decursin and decursinol angelate in healthy adult men and women. PLoS One 10: e0114992.

Zhang, J., Li, L., Jiang, C., Xing, C., Kim, S.H. and Lu, J. 2012. Anti-cancer and other bioactivities of Korean *Angelica gigas* Nakai (AGN) and its major pyranocoumarin compounds. Anticancer Agents Med. Chem. 12: 1239-1254.