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Comparative Phytochemical Analysis of Chinese and Bay Starvine (*Schisandra* spp.): Potential for Development as a New Dietary Supplement Ingredient

James T. Lyles, PhD[a,b], Paula Tyler, BS[a], E. Jane Bradbury, PhD[c,d], Kate Nelson, BS[e], Carl F. Brown, MS[f], Stefanie T. Pierce, BA[f], and Cassandra L. Quave, PhD [a,c,e]

[a]Center for the Study of Human Health, Emory College of Arts and Sciences, Atlanta, GA, USA; [b]The Bent Creek Institute, Asheville, NC, USA; [c]Emory Herbarium, Emory College of Arts and Sciences, Atlanta, GA, USA; [d]Herbal Anthropology Project, San Francisco, CA, USA; [e]Department of Dermatology, Emory University School of Medicine, Atlanta, GA, USA; [f]Department of Environmental Sciences, Emory College of Arts and Sciences, Atlanta, GA, USA

ABSTRACT

Schisandra chinensis (Chinese starvine) is a popular dietary supplement with a rich history of use in traditional Chinese medicine. *Schisandra glabra* (bay starvine) is the only North American representative of the genus, and little is known about its history of traditional use, chemistry, and potential biological activity. In this study, we conducted comparative high-performance liquid chromatography-diode array detector (HPLC-DAD) analysis on *S. glabra* and *S. chinensis* fruits. Additional characterization of *S. glabra* was performed by liquid chromatography-Fourier transform mass spectrometry (LC-FTMS). Quantitative analysis of four bioactive marker compounds revealed that *S. glabra* does not have statistically higher levels of schisandrin A or schisandrol B than *S. chinensis*. *S. glabra* has lower levels of schisandrol A and γ-schisandrin. Total phenolic contents of the two species' fruits were not statistically different. *S. glabra* had higher total tannin content than *S. chinensis*. We discuss the relevance of this analytical analysis to the study of *S. glabra* as a potential dietary supplement ingredient and give specific consideration to the conservation challenges involved in commercially developing a regionally threatened species, even in semicultivated conditions.

KEYWORDS

conservation; dietary supplements; *Schisandra chinensis*; *Schisandra glabra*; schisandrin A; γ-schisandrin; schisandrol A; schisandrol B

Introduction

Schisandra glabra (Brickell) Rehder, Schisandraceae, a deciduous liana with stems up to 1.25 cm in diameter, is the only known North American representative of the genus *Schisandra*, which is common throughout eastern Asia (Panero & Aranda, 1998). The glabrous, elliptically shaped leaves are dark green above and paler beneath, with acuminate tips and entire, occasionally sparsely toothed, leaf margins. Leaves are alternately arranged (Radford, Ahles, & Bell, 1968), though may appear whorled due to short internode lengths on foliar stems (E. J. Bradbury, personal observation, October 2014). While *S. glabra* is monoecious, the flowers, approximately 0.05 cm diameter, are imperfect, either staminate or pistillate. The floral perianth contains equivalently sized sepals (white) and petals (rose

CONTACT Cassandra L. Quave cquave@emory.edu The Center for The Study of Human Health, Emory University, 550 Asbury Circle, Candler Library 107, Atlanta, GA 30322, USA.

to red). The red, round or oval berries contain 1–2 seeds, are 6–10 mm long, and dangle in small, loose bunches on an elongate spike 4–7 cm long (Radford, Ahles, & Bell, 1968).

The range of *S. glabra* is limited to the Southeastern United States (Georgia, Florida, Alabama, Mississippi, Louisiana, Arkansas, Kentucky, Tennessee, South Carolina, North Carolina) and an isolated population in the cloud forests of Hidalgo, along the Sierra Madre of Mexico (USDA, 2014; Panero & Aranda, 1998). In the United States, *S. glabra* is classified as threatened or endangered throughout 50% of its range (USDA, 2014). *S. glabra* is known by several common names, including "American starvine," "bay starvine," "scarlet woodbine," "climbing-magnolia," "magnolia vine," and "wild sarsaparilla." Originally, *S. glabra* was classified in the genus *Stellandria* by John Brickell in 1803 (Brickell, 1803). Nearly simultaneously, the same species was named *Schisandra coccinea* by André Michaux (Michaux, 1803). However, in 1944, Alfred Rehder moved *Stellandria glabra* into the genus *Schisandra*, correctly classifying the species as a member of the Schisandraceae (Rehder, 1944). Occasionally, *S. glabra* is still referred to in the literature by the incorrect taxonomic synonym, *Schisandra coccinea*.

Schisandra chinensis (Turczaninow) Baillon, commonly known as "Chinese starvine" in English and "Wu Wei Zi" in Mandarin, is a liana native to the forests of Eastern Asia, including Russia, China, Japan, and Korea. It has alternate, elliptic leaves and waxy, unisexual, white or cream flowers growing in clusters of 2 to 5. It produces bright red fruits that contain 1–2 yellow seeds (Hancke, Burgos, & Ahumada, 1999). *S. chinensis* is primarily known for its use in traditional Chinese medicine (TCM) to treat disorders of the reproductive, respiratory, nervous, and digestive systems (Panossian & Wikman, 2008). Historically, *S. chinensis* has been used for varying maladies, including impotence, gonorrhea, diarrhea, dysentery, impairment of body fluids, spontaneous sweating, cough, asthma, jaundice, urinary tract disorders, and diabetes (Panossian & Wikman, 2008). In Russia, Chinese starvine fruits are considered a stimulant and adaptogen. The Nanai hunters consumed berries and seeds to improve night vision and to reduce hunger, thirst, and exhaustion (Panossian & Wikman, 2008). *S. chinensis* was used by the Soviet military during the Second World War for these benefits and in 1968 was included in the USSR National Pharmacopeia (Panossian & Wikman, 2008).

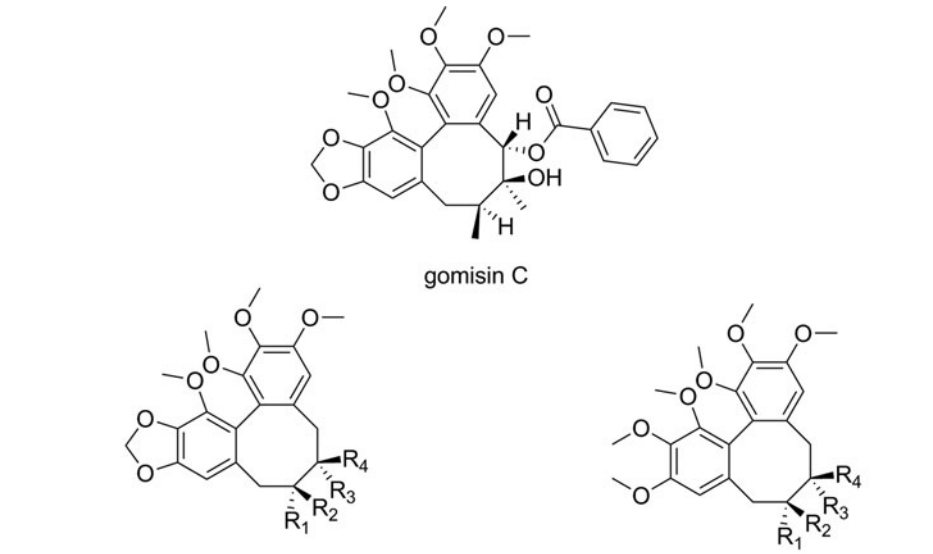
In addition to its use in TCM, *S. chinensis* fruits are sold as a dietary supplement and in various multi-ingredient products sold in the United States. The domestic herbal and botanical dietary supplements market in 2014 was over $6.4 billion (Smith et al., 2015). Since data on *Schisandra* sales were not available (it was not in the top-selling herbal supplements), a survey of health food stores and pharmacies in Atlanta, Georgia, was conducted. It yielded 35 different products and aided in understanding *Schisandra*'s market relevance.

Research on the use of *S. chinensis* fruits in Western medical applications has found it to decrease circulating monocyte levels in Chinese hepatitis B patients, suppress lung inflammation, and attenuate human colorectal cancer cell proliferation (Bae et al., 2012; Gnabre et al., 2010; Yip, Loo, & Chow, 2007). Two commercial products containing *S. chinensis* exhibit stress-protective effects in pneumonia and cancer patients (Kormosh, Laktionov, & Antoshechkina, 2006; Narimanian et al., 2005). *S. chinensis* has also been used to improve attention and cognitive accuracy, as a central nervous system (CNS) stimulant for psychosomatic depression, and has been shown to prevent chemotherapy-induced immunosuppression in ovarian cancer patients (Aslanyan et al., 2010; Kormosh et al., 2006; Leman, 1952; Panossian & Wikman, 2008;).

The chemistry of the genus and *S. chinensis* has been well reviewed (Shi et al., 2015; Xiao et al., 2008). The focus of this work is on several dibenzo[*a,c*]cyclooctadiene lignans, schisandrol A, schisandrol B, schisandrin A, and γ-schisandrin, often cited as being

responsible for *S. chinensis*'s medicinal benefits including the anti-inflammatory, hepatoprotective, and stimulant activities (Hancke et al., 1999; Panossian & Wikman, 2008). Schisandrol A reverses P-glycoprotein (P-gp) mediated multidrug resistance in cancer cells by interfering with the efflux pump functions of P-gp-substrate complexes and increasing cellular retention of the substrates (Fong et al., 2007). Schisandrol B (syn. gomisin A) is considered the most potent hepatoprotective compound in *S. chinensis*, with physiological effects ranging from several mechanisms inhibiting or reversing cancer progression in liver and leukemia cells (Hwang et al., 2013; Teraoka, Shimada, & Aburada, 2012; Wan et al., 2010) to down-regulating pro-inflammatory mediators (Teraoka, Shimada, & Aburada, 2012) and inducing endothelial vasorelaxation (Park et al., 2009). Schisandrin A inhibits P-gp-mediated efflux of Tacrolimus (FK506), thus increasing bioavailability of this immunosuppressive (Qin et al., 2014), exhibits anticarcinogenic activity by inhibiting cytochrome P450 3A activity (Li, Xin, & Su, 2012), and acts as an anti-inflammatory via acting as a platelet-activating factor receptor antagonist (Panossian & Wikman, 2008). Hypoxia inhibition and cardioprotective activity due to reoxygenation-induced apoptosis are attributed to γ-schisandrin (Chiu et al., 2008).

Due to their consistent presence in *S. chinensis* fruits and their demonstrated physiological effects, schisandrol A, schisandrol B, schisandrin A, γ-schisandrin, and gomisin C (Figure 1) are used as marker compounds in many *S. chinensis* botanical identity tests (Upton, 1999). By comparison, there is little existing data on the phytochemical profile *S. glabra*. The aims of this study were (1) to establish the phytochemical profile of *S. glabra* by high-performance liquid chromatography coupled with a diode array detector (HPLC-DAD); (2) to quantify schisandrol A, schisandrol B, schisandrin A, and γ-schisandrin in *S. glabra* and *S. chinensis* using HPLC-DAD; (3) to compare total phenolic and tannin content in both species; and



	R_1	R_2	R_3	R_4
γ-schisandrin	CH_3	H	CH_3	H
schisandrol B	H	CH_3	OH	CH_3

	R_1	R_2	R_3	R_4
schisandrin A	CH_3	H	CH_3	H
schisandrol A	CH_3	OH	CH_3	H

Figure 1. Structures of compounds used as phytochemical markers of *S. chinensis* in botanical identity tests.

(4) to evaluate the potential medical utility of *S. glabra*, considering both phytochemical and ecological perspectives.

Materials and methods

Market survey

A small-scale survey of six area botanical and dietary supplement retailors in four categories (local or national chain natural grocers and local or national chain pharmacy and supplement stores) in Atlanta, Georgia, was undertaken. All products containing *S. chinensis* were recorded and categorized by type (juice, tea, bulk, tincture, extract, or capsule).

Plant material, extraction, and sample preparation

Schisandra glabra fruits were identified and collected from the Lullwater forest research preserve by C. Brown and S. Pierce on the Emory University campus in October 2013. Voucher specimens from this population are deposited at the Emory University Herbarium (GEO). Fruits from *S. chinensis* (certificate of analysis number 973) were purchased from the American Herbal Pharmacopoeia (Scotts Valley, CA, USA) and provided by Health, Education and Research in Botanical Medicines (Ashland, OR).

Prior to extraction, the dry fruits were pulverized into a fine powder using a Waring blender. For HPLC analysis, samples were subjected to ultrasonic extraction for 20 minutes at room temperature with 1 g sample in 30 mL HPLC-grade methanol (Fisher Scientific; Pittsburgh, PA). Extracts were filtered sequentially with 20–25 μm pore filter paper, then <1 μm pore filter paper. The marc was re-extracted and filtered as before for a total of three extractions. The three filtrates were combined and concentrated in vacuo at temperatures <40°C. The residues were transferred to separate vials and dried under forced air. The dried residues were massed and samples were dissolved to 20 mg/mL in HPLC-grade dimethyl sulfoxide (DMSO) (Fisher Scientific) for analysis. The samples were stored at -20°C until analyzed.

Standard solutions

Standards of schisandrol A, schisandrol B, schisandrin A, and γ-schisandrin (>96% purity) were purchased from ChromaDex (Irvine, CA). For HPLC analysis, stock solutions of schisandrol A were prepared at 0.01 mg/mL and 0.20 mg/mL in DMSO, of schisandrol B at 0.25 mg/mL in methanol, and of schisandrin A and γ-schisandrin at 0.625 mg/ml in methanol. Standards were stored at -20°C until analysis.

HPLC

The quantification of the four dibenzo[*a,c*]cyclooctadiene ligands was performed by HPLC-DAD detection following a chromatographic method adapted from Hu et al. (2013) by incorporating 0.1% acetic acid into the mobile phases. The analysis was performed on an Agilent 1260 Infinity system running OpenLab CDS ChemStation (Agilent Technologies, Santa Clara, CA, USA). An Agilent ZORBAX Eclipse XDB-C18 (250 mm $\times$ 4.6 mm, 5 µm) column with compatible guard column at a column temperature of 30°C was used for the analysis. Mobile phase reagents were HPLC-grade and purchased from

Fisher Scientific, except for the Type 1 water, which was obtained from an EMD Millipore MILLI-Q water system (Billerica, MA). Mobile phase consisted of a linear gradient elution 0.1% acetic acid in acetonitrile (A) and 0.1% acetic acid in water (B) at a flow rate of 1 mL/min. Initial conditions were 50:50 (A:B) for 17 minutes, then to 55:45 (A:B) at 25 minutes, to 75:25 (A:B) at 30 minutes until 35 minutes, to 65:35 (A:B) at 40 minutes, and to 50:50 (A:B) at 45 minutes until 52 minutes Triplicate 10 µL sample injections were made, and varying volumes of the standard stock solutions were injected to produce a calibration curve with concentrations that bracketed the samples. Samples were monitored at 217 nm and 254 nm; compounds were identified by comparing retention times and UV profiles to external standards. Quantification of each compound was calculated by applying linear least squares regression to the peak area of the standard injections to produce a standard curve for each of the four lignans. The peak area for the corresponding compound in the plant sample was then compared to the standard curve and the concentration determined. The limits of detection (LOD) and quantification (LOQ) were calculated from the standard curves at 3.3σ and 10σ, respectively (ICH, 2005).

Mass spectrometry

Liquid chromatography-Fourier transform mass spectrometry (LC-FTMS) was performed on *S. glabra* extracts using the same chromatographic conditions described previously, with 20 µL injected for analysis. The data were acquired in MS^1 mode scanning from a *m/z* of 100–1,000 on a Thermo Scientific LTQ-FTMS in positive atmospheric pressure chemical ionization (APCI) and positive electrospray ionization (ESI) modes and processed with Thermo Scientific Xcalibur 2.2 SP1.48 software (San Jose, CA). For APCI acquisition, the capillary temperature and APCI vaporizer temperature were 275.0°C and 450.0°C, sheath gas of 50, source voltage and current 6.0 kV and 5.0 µA, and the capillary voltage 60.0 V. In ESI mode the capillary temperature was 275.0°C, sheath gas of 40, source voltage and current 5.0 kV and 100.0 μA, and the capillary voltage +35.0 V.

Total tannin content

Tannin content was quantified by adapting the Folin-Denis assay for 96-well plate methodology (Oliveira et al., 2009). All mixtures were prepared in triplicate. Tannic acid stock solution was prepared at 20 µg/mL (w/v) in DMSO and serially diluted to final well concentrations from 0.016 to 2.00 µg/mL in Folin-Denis reagent (FDR; Sigma-Aldrich; St. Louis, MO). Samples and DMSO controls were incubated at a 1:20 ratio in FDR for 3 minutes before 100 µL of 8% (w/v) $Na_2CO_{3(aq)}$ was added to each well. Absorbance at 725 nm was measured with the Biotek Instruments Cytation3 Cell Imaging Multi-Mode Reader (Winooski, VT) after 120 minutes at room temperature. Tannic acid equivalents in mg/mL per g of dry fruit were determined from a linear least squares regression analysis of the standard solutions.

Total phenolic content

Phenolic content was quantified with a modified microscale Folin-Ciocolteu assay (Reynertson et al., 2008). Mixtures were prepared in three to five replicates. Gallic acid stock solution was prepared at 0.5 mg/mL (w/v) in DMSO and serially diluted to give a final well concentration from 0.625 to 10.00 µg/mL in 10% (v/v) Folin-Ciocolteu reagent (FCR; Sigma-Aldrich; St. Louis, MO). Samples and DMSO controls were incubated at a 1:10 ratio in FCR

for 5 minutes before 100 µL of 10% (w/v) $Na_2CO_{3(aq)}$ was added to each well. Absorbance at 765 nm was measured with a Cytation3 reader after 60 minutes at room temperature. Gallic acid equivalents in mg/mL per g of dry fruit were determined from the linear least squares regression analysis of the standard solutions.

Statistical analysis

All continuous variables are reported as sample mean and 95% confidence interval of the mean response. The confidence interval was calculated from the estimated uncertainty of the linear least squares regression analysis of the standards using a two-tailed t value with n-2 degrees of freedom. Pairwise comparisons between the two species were performed by using a two-tailed, homoscedastic t test and considered statistically significant if $p < .05$. All data analysis was performed in Microsoft Excel.

Results

Overall extraction yield was lower in *S. glabra* than in *S. chinensis*, at 20% versus 37%, respectively (dry extract/dry fruit). All four target compounds (schisandrol A, schisandrol B, schisandrin A, and γ-schisandrin) were detected in both *S. glabra* and S. *chinensis* (Table 1) with an additional 10 peaks present from 10 to 35 minutes in the *S. glabra* chromatogram (Figure 2; Table 2). All quantifications were above the limits of detection (LOD) and limits of quantification (LOQ), and thus the values reported were determined with an acceptable level of precision and accuracy for further statistical comparisons to be made (Table 1). Levels of schisandrin A and schisandrol B in *S. glabra* are not statistically different from those in *S. chinensis*. *S. glabra* has lower levels of the other target compounds, schisandrol A and γ-schisandrin, which was recently shown to reduce the carditoxicity of the antineoplastic drug doxorubicin (Thandavarayan et al., 2015). The quantities of schisandrol A and γ-schisandrin were determined to be statistically different between the two species with $p < .05$.

To the authors' knowledge, this is the first quantitative analysis of these compounds in *S. glabra* by HPLC-DAD or MS. This HPLC-DAD method may prove useful in fingerprint analysis as the quantities of two marker compounds were found to be statistically different in the species. Since the levels of schisandrin A and schisandrol B are not significantly different they cannot be used as a marker compound to differentiate the species.

The total tannin content of *S. glabra* was 32% higher than that of *S. chinensis* (Table 3). Although the total phenolic content of *S. glabra* and *S. chinensis* fruits are not statistically different at $p < .05$ (Table 3), when the dry fruit extracts are considered, instead of the dry

Table 1. Quantitative analysis of compounds in the fruits of *S. glabra* and *S. chinensis*.

	Analyte concentration (mg/g)			
	S. glabra	*S. chinensis*	LOD (μg/mL)	LOQ (μg/mL)
schisandrol A	0.0811 ± 0.001*	1.49 ± 0.03*	0.1	0.3
schisandrol B	3.58 ± 0.03	3.01 ± 0.05	0.06	0.2
schisandrin A	16.2 ± 0.1	16.8 ± 0.1	0.2	0.4
γ-schisandrin	13.2 ± 0.1*	57.8 ± 0.1*	0.07	0.2

The analyte concentration is shown as mean ± 95% confidence deviation in mg compound per gram of dried plant material. The limit of detection (LOD) and limit of quantification (LOQ) for each compound was calculated as 3.3σ and 10σ respectively both are expressed as mg/mL.

*Compounds were found to be statistically different between the two species by a pairwise, 2-tailed, homoscedastic t test at $p < .05$.

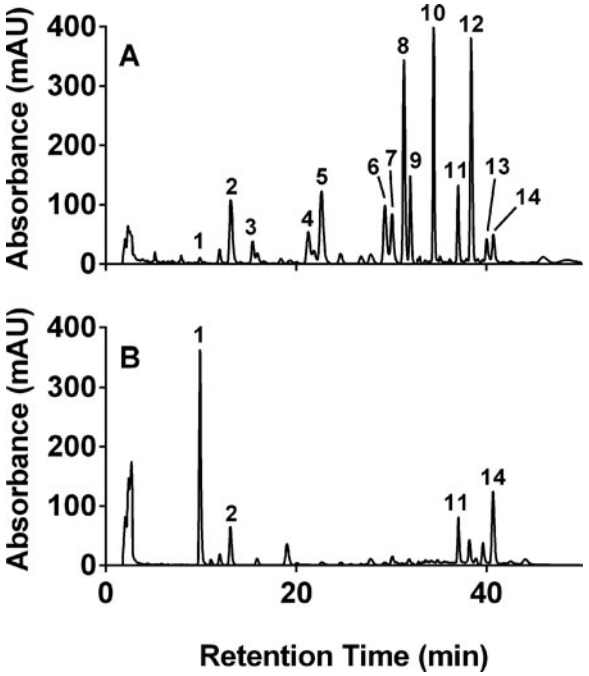


Figure 2. (A) The HPLC chromatograms at 254 nm of *S. glabra* fruits; (B) *S. chinensis* fruits showing (1) schisandrol A, (2) schisandrol B, (9) gomisin C, (11) schisandrin A, and (14) γ-schisandrin. The *S. chinensis* chromatogram (B) is shown at twice the normal scale for better peak visualization. Peak numbers correspond with LC-FTMS data shown in Table 2.

Table 2. LC-FTMS data for *S. glabra* fruit extract.

Peak	Retention time (min)	Compound	Predicted formula (Δ ppm)	m/z [M+H]+
1	10.14	schisandrol A	$C_{24}H_{33}O_7$ (−5.6)	433.2207[†]
2	13.84	schisandrol B	$C_{23}H_{29}O_7$ (−1.7)	417.1901
3	16.12		$C_{24}H_{31}O_6$ (1.1)	415.2120
4	22.56		$C_{24}H_{31}O_7$ (1.5)	431.2071
5	23.27		$C_{24}H_{31}O_7$ (1.5)	431.2071
7	30.30		$C_{23}H_{27}O_7$ (1.6)	415.1758
8	31.22		$C_{24}H_{31}O_6$ (1.5)	415.2121
9	31.62	gomisin C*	$C_{30}H_{33}O_9$ (−4.1)	537.2103
10	33.91		$C_{23}H_{27}O_6$ (0.3)	399.1809
11	36.63	schisandrin A	$C_{24}H_{33}O_6$ (0.0)	417.2277
12	38.36		$C_{14}H_{28}O_4$ (8.6)	260.2005[†]
13	40.09		$C_{24}H_{31}O_6$ (0.6)	415.2123
14	41.10	γ-schisandrin	$C_{23}H_{29}O_6$ (0.9)	401.1961

All data presented in Table 2 were acquired in positive APCI, except for peak 1 (schisandrol A) and peak 12, which required positive ESI mode to yield acceptable ionization. Peak numbers correspond to the chromatogram shown in Figure 3. Compounds were identified by comparison of retention times and mass spectra to authentic standards, except for gomisin C, which was identified only by comparison of mass spectral data to published values.

[†]Ions reported from positive ESI mode.

fruit material, extracts of *S. glabra* have significantly higher total phenolic content than do extracts of *S. chinensis*, 71 ± 1 and 38 ± 1 GAE/g dry extract, respectively ($p < .001$).

The market survey yielded 35 different products containing *S. chinensis* (Figure 3). The local vitamin and dietary supplement store sold the most *S. chinensis* products; the national

Table 3. Total tannic content and total phenolic content for *S. glabra* and *S. chinensis* fruits.

	Total tannin content	Total phenolic content
S. glabra	1.29 ± 0.15*	14.0 ± 0.5
S. chinensis	0.88 ± 0.25*	14.3 ± 0.3

The total tannin content is reported as mg/mL tannic acid equivalents (TAE) per g dry fruit, and the total phenolic content is reported as mg/mL gallic acid equivalents (GAE) per g dry fruit. The results are shown as mean ± 95% confidence deviation.
*A pairwise comparison of the means for the species was performed with a 2-tailed, homoscedastic *t* test at $p < .001$.

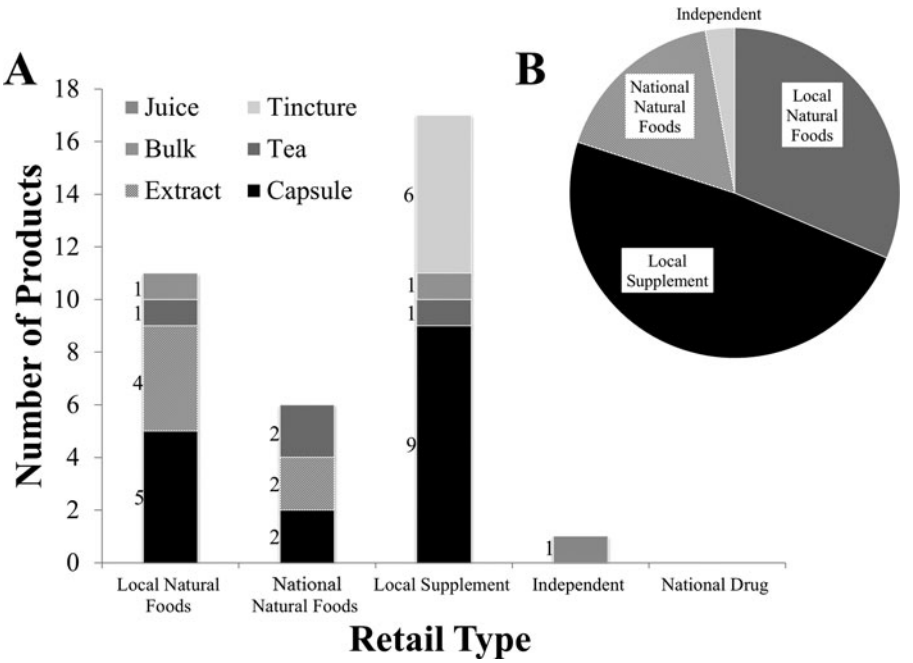


Figure 3. (A) The amount and type of products containing *S. chinensis* available in Atlanta, Georgia, metro area stores; (B) the percentage of the products available at each type of retailor. Numbers in the chart represent the number of each type of product in that category. Retailors were classified as a local or national chain natural foods grocer, a local supplement store, or national chain drug store. Products were categorized as juice, tincture, bulk (whole, dry berries), tea, extract, or capsules.

chain pharmacy did not sell any. Of the products being sold, 71% were multiherb mixtures, with capsules or pills the most prevalent type (43%).

Discussion

The market survey data demonstrate the relative popularity and diversity of *Schisandra*-containing products and indicate the growing need for phytochemical studies of *Schisandra* species, such as *S. glabra*, for comparison to *S. chinensis*. The nature of this local market survey was very small scale; broader conclusions would require a larger national survey. Although HPLC-DAD quantification showed that *S. glabra* has lower levels of schisandrol A and γ-schisandrin than *S. chinensis*, the presence of additional peaks in the HPLC-DAD and MS chromatograms, as well as the higher tannin content of *S. glabra*, suggest that its chemistry is more complex than that of *S. chinensis* and may provide new medicinally active compounds. Notably, *S. glabra* produces as much schisandrol B as *S. chinensis*, and this compound

is reported to have a wide range of physiological effects, including being the most potent hepatoprotective compound in *S. chinensis* (Hwang et al., 2013; Park et al., 2009; Teraoka et al., 2012; Wan et al., 2010). In addition, although the dry fruits of *S. glabra* and *S. chinensis* do not differ in total phenolic content, extraction of *S. glabra* yields an extract with a higher phenolic concentration. Therefore, a smaller amount of *S. glabra* fruit would be required to produce the same extracted total phenolic values as *S. chinensis*. This analysis of *S. glabra* is based on collections from a single population, and additional variability may be seen across its range. Furthermore, the comparisons of *S. glabra* were made to a single authentic *S. chinensis* botanical sample, which cannot fully represent all the variability seen across the *S. chinensis* range and varied growth conditions (i.e., wild vs. cultivated). Whereas these results establish an exciting potential for an additional plant source of the bioactive compounds prized in *S. chinensis*, unfortunately, currently, the amount of wild-growing *S. glabra* is too low to meet even the most modest economic demand. Therefore, any potential medicinal development of *S. glabra* is impossible until supply limitations and conservation concerns are addressed. Over-harvesting of economically valuable wild medicinal plant species is a leading cause of wild medicinal species endangerment (Bae et al., 2015; Cech, 2002; Ghasemi Pirbalouti et al., 2014; Turner, 2001; Westfall & Glickman, 2004). Examples of threatened wild medicinal plants in the United States due to over-harvesting include American ginseng (*Panax quinquefolius* L., Araliaceae), bloodroot (*Sanguinaria canadensis* L., Papaveraceae), and goldenseal (*Hydrastis canadensis* L., Ranunculaceae), all of which experienced significant population decline, resulting in threatened or endangered status (Chitty, 2014; Graf et al., 2007; Lim, Mudge, & Vermeylen, 2005; Robbins, 2000; Van der Voort & McGraw, 2006). While over-harvesting of *S. glabra* would quickly deplete the wild-grown populations, the current threatened status of *S. glabra* is likely due to anthropogenic habitat destruction, such as land use practices that allow invasion of the remnant *S. glabra* populations by other plant species, and not currently over-harvesting (Valente, 2007).

Four categories of solutions have been proposed to address over-harvesting of medicinal and aromatic plants (MAPs): (1) international regulations to prevent the sale of wild-harvested MAPs (Robbins, 2000; Westfall & Glickman, 2004); (2) regulations establishing sustainable wild-harvest levels of specific MAPs (Chitty, 2014; Robbins, 2000; Turner, 2001; Van der Voort & McGraw, 2006); (3) strategies aimed at conserving entire biomes of MAP habitat (Ghasemi Pirbalouti et al., 2014), and (4) cultivation of MAP species (Canter, Thomas, & Ernst, 2005; Graf et al., 2007; Lim et al., 2005). Of these options, cultivation is the only solution that has the potential to provide the large volume of plant material required while simultaneously protecting wild MAP populations (Ghasemi Pirbalouti et al., 2014). However, cultivation of MAPs does present some significant challenges, specifically, those associated with the cost of successfully cultivating wild species in an agricultural system as well as documented changes in biochemistry of wild versus cultivated MAPs. Both bloodroot and American ginseng produce statistically significantly lower quantities of target secondary compounds under cultivation than in wild populations (Graf et al., 2007; Lim et al., 2005). Several other MAP species, including *S. chinensis*, produce highly variable quantities of target secondary compounds depending on cultivation conditions (Canter, Thomas, & Ernst, 2005; Lee et al., 2011). In addition, as the majority of MAPs worldwide are non-timber forest products, including *S. glabra*, successful cultivation of MAPs often requires costly manipulation of the agricultural system to mimic natural forested habitat (Ghasemi Pirbalouti et al., 2014). Two solutions that address both of these concerns are (1) intercropping of MAPs with cultivated timber stands and (2) use of MAPs as ground cover in riparian buffer zones (Ghasemi Pirbalouti et al., 2014).

Schisandra glabra is well suited to both of these cultivation schemes due to its natural growth habit as shade-tolerant, creeping ground cover along riverbanks and creeksides throughout the Southeastern United States (SEUS). Moreover, both cultivation options for *S. glabra* are particularly viable given other economic activities and ecological concerns in the SEUS, which would allow cultivation of *S. glabra* to remain within its native range. Riverbank erosion remains a significant ecological and economic threat in the SEUS (Pezeshki, Schaff, & Shields, 2000), and the well-established cultivation of paper lumber in the region provides ample forest plantations for intercropped plantings. Indeed, the USA remains the top global contributor to the paper industry (FAO, 2016), with production levels from the SEUS alone far outstripping the entire domestic production of pulpwood in any other country (Wear & Greis, 2012). However, to ensure the success of either riparian buffer zone plantings or forest plantation intercropping of *S. glabra*, future research must address both viability of specific cultivation methods and biochemical effects of cultivation on target compounds. Presently, no research has been conducted that addresses either of these concerns, though research on *S. chinensis* suggests that seed cultivation of *Schisandra* may be difficult due to entrenched seed dormancy and temporally inconsistent germination of *S. chinensis* seeds, both extremely common characteristics of wild plants (Khallouki et al., 2011; de Wet & Harlan, 1975). For this reason, the viability of clonal propagation of *S. glabra* through plant cuttings should be explored in addition to confirmation of the trends in seed biology observed in *S. chinensis*.

Conclusions

Although phytochemical analysis of *S. glabra* suggests that it could be a viable domestic alternative to *S. chinensis*, as well as a source of novel, potentially medicinal, compounds not found in *S. chinensis*, progress toward development of *S. glabra* as a source of medicinal lignans is significantly hampered by economic and ecological concerns. Future research on *S. glabra* should incorporate not only phytochemical studies of the compounds reported here but also assessment of the viability of different cultivation schemes of the taxon as well as the effects of cultivation on target compounds.

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Declaration of interest

The authors declare no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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About the authors

James T. Lyles, PhD, is a Postdoctoral Fellow in Emory University's Center for the Study of Human Health. He works to isolate and identify Staphylococcal quorum quenching compounds and biofilm inhibitors from ethnobotanically identified plant sources. Previously, Dr. Lyles worked with The Bent Creek Institute developing botanical authentication methodology.

Paula Tyler, BS, graduated from Emory University in 2015 with a BS in Chemistry and Anthropology & Human Biology. Her research interests include phytochemistry, medicinal natural products, and molecular mechanisms of infectious disease.

E. Jane Bradbury, PhD, is Director of Research at Herbal Anthropology Project, a 501(c)3 for-purpose organization dedicated to supporting indigenous groups in community-led projects to preserve and protect traditional knowledge. She pursues an interdisciplinary combination of research, teaching, and outreach activities that explore the complex relationships among plants and human societies and the emergent biocultural landscapes.

Kate Nelson, BS, is a Research Specialist in Dermatology at Emory University School of Medicine. Her research interests include anti-infective natural products and pharmacology of natural products.

Carl F. Brown, MS, is Adjunct Faculty in Environmental Sciences at Emory University. His interests include the role of Schisandra glabra in the conservation of forests and indigenous culture.

Stefanie T. Pierce, BA, is affiliated researcher with Environmental Sciences, Emory University. Her primary focus is the endangered Mvskoke (Creek) language and its relationship to Southeastern historical landscapes.

Cassandra L. Quave, PhD, is an Assistant Professor of Dermatology and Human Health at Emory University. Her research interests include medical ethnobotany, medicinal plants, and anti-infective natural products.

ORCID

Cassandra L. Quave http://orcid.org/0000-0001-9615-7886

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