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Phytochemistry of Wild Populations of *Panax quinquefolius* L. (North American Ginseng)

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A survey of the phytochemistry of *Panax quinquefolius* L. (North American ginseng) collected from wild populations in Ontario, Quebec, Maine, Vermont, and Wisconsin was undertaken. Reverse-phase HPLC was used to determine the natural variation of levels of ginsenosides Rg1, Re, Rf, Rb1, Rc, Rb2, and Rd and their total in leaf, stem, and root of authentic wild-grown material. The totals in roots varied from 1 to 16%, with the greatest number of individual samples having 4−5% total ginsenosides. The lack of ginsenoside Rf in roots of authentic wild populations confirmed its status as a phytochemical marker differentiating American and Asian ginseng. Ten geographically isolated wild populations were collected, and several showed significant variation in the levels of major ginsenosides. There was no statistical difference in mean ginsenoside content between wild and cultivated *P. quinquefolius* roots at 4 years of age, suggesting there is no phytochemical justification for wild crafting. Baseline data on total ginsenoside levels for authentic wild *P. quinquefolius* reported here provide reference levels for quality assurance programs.

KEYWORDS: ***Panax quinquefolius*; North American ginseng; ginsenosides; phytochemical variation; principal component analysis**

INTRODUCTION

Panax quinquefolius L. (North American ginseng, Araliaceae) is one of the top 10 selling natural health products in the United States (*1*). *P. quinquefolius* is indicated for fatigue and as an immunostimulant in times of stress. Experimental studies have shown this herb to have estrogenic (*2*), antimutagenic (*2*−*4*), and hypoglycemic effects (*5*−*7*) and also to improve impaired memory and learning (*8*−*10*). Although polysaccharides and polyacetylenes are implicated in some of these physiological effects, much of the bioactivity is associated with ginsenosides.

Ginsenoside (**Figure 1**) content has been used to characterize the different wild populations of the Asian *Panax* spp. (*11*) and cultivated *P. quinquefolius* (*12*). Most ginseng products in the botanical market are now standardized to their ginsenoside content.

The natural range of *P. quinquefolius* is throughout the eastern temperate forest region of North America, from southern Quebec to Minnesota, and south from Oklahoma to Georgia (*13*). The populations occur in mature deciduous forests dominated by *Acer saccharum* Marsh. (sugar maple) and other hardwoods. The fragmentation of the mature hardwood forests by human activity, the continued overharvest of the *P. quinquefolius* roots, and the autogamous nature of the species have contributed to its patchy distribution and the poor gene flow between populations (*14*, *15*).

Little information is available on ginsenoside variation in the wild populations. Establishing the nature of phytochemical variation would be of interest for several reasons. Information on ginsenoside levels in wild ginseng is important for quality assurance programs such as the American Botanical Council's Ginseng Evaluation Project (*16*, *17*) so that claims of pure root products in commercial material can be compared to authentic ginseng. Establishing the variation in wild populations provides information to growers about the best seed sources and their conservation. Establishment of superior genotypes would provide an economic incentive for the rehabilitation of forest ginseng, and cultivation of North American ginseng genotypes with the appropriate ginsenoside levels in agricultural lands would conserve wild *P. quinquefolius* populations.

The objective of this study was to determine the phytochemical variation in wild *P. quinquefolius* populations. Because ginseng occurs in widely separated and highly patchy forest habitats, we hypothesized that genetic isolation of populations may be reflected in distinct chemotypes of *P. quinquefolius*.

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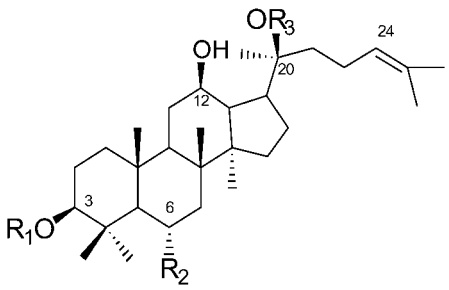

	R_1	R_2	R_3
Rb1	Glc-^{2}Glc-	H	Glc-^{6}Glc-
Rb2	Glc-^{2}Glc-	H	Ara(p)-^{6}Glc-
Rc	Glc-^{2}Glc-	H	Ara(f)-^{6}Glc-
Rd	Glc-^{2}Glc-	H	Glc-
Re	H	Rha-^{2}Glc-O-	Glc-
Rf	H	Glc-^{2}Glc-O-	H
Rg1	H	Glc-O-	Glc-

Figure 1. Structures of major ginsenosides in *Panax* spp. from Tanaka and Kasai (*11*).

MATERIALS AND METHODS

Plant Material. Nineteen whole plants (leaves, stem, and root) and an additional 19 roots were collected by the authors under the supervision of conservation authorities or obtained from donors from sites in Ontario, Quebec, Maine, Vermont, and Wisconsin. Exact locations are not provided to protect those remaining plants found in their natural range. *P. quinquefolius* is endangered in most of its natural range in Canada and the United States (*13*). Voucher specimens of *P. quinquefolius* (no. 19501−19510) have been deposited in the herbarium at the University of Ottawa.

Extraction of Ginsenosides. The plants were dried on the laboratory bench at 20−22 °C for 4−6 weeks. The different plant parts (leaves, stem, and root) were then milled to no. 40 mesh particle size with a Thomas-Wiley laboratory mill (Philadelphia, PA). An accurately weighed sample (1 g) of the ground plant material was extracted twice with 20% aqueous methanol (30 mL) under reflux in a water bath at ~55 °C for 30 min each time. The combined extract was evaporated (~40 °C) to dryness in vacuo, and the residue was redissolved in 10 mL of HPLC grade methanol. This was filtered using a 0.2 μm nylon filter (Chromatographic Specialties Inc., Brockville, ON), and 5 μL was injected into the HPLC system.

Ginsenoside Analysis. A Beckman high-pressure liquid chromatography (HPLC) system (Beckman Coulter Canada Inc., Mississauga, ON) was used for ginsenoside analyses. The system consists of a module 168 diode array detector, a module 126 solvent delivery system, a module 502 autosampler, and a computer equipped with System Gold software. The ginsenosides Rg1, Re, Rf, Rb1, Rc, Rb2, and Rd (from Dr. H. Fong, University of Illinois at Chicago, and Indofine Chemical Co., Somerville, NJ) were weighed accurately and mixed together as pure standards at concentrations of 0.01−0.1 mg/mL in HPLC grade methanol. Analyses based on peak area (AU) were performed, and the response factors (mg/mL/AU) calculated and built into the method. Separation of the ginsenosides was achieved with a 250 × 4.6 mm, 5 μm, reverse-phase Ultrasphere C-18, octadecylsilane column (Beckman Coulter Canada Inc.) connected to a 4 × 4 mm, 5 μm, LiChroCart LiChrospher 100 RP-18 guard column (EM Science, Cherry Hill, NJ). The mobile phase was water (A) and acetonitrile (B) at a constant composition of 21% B from 0 to 20 min followed by a linear gradient to 42% B from 20 to 60 min. The flow rate was 1.3 mL/min, and the detector was set at 203 nm.

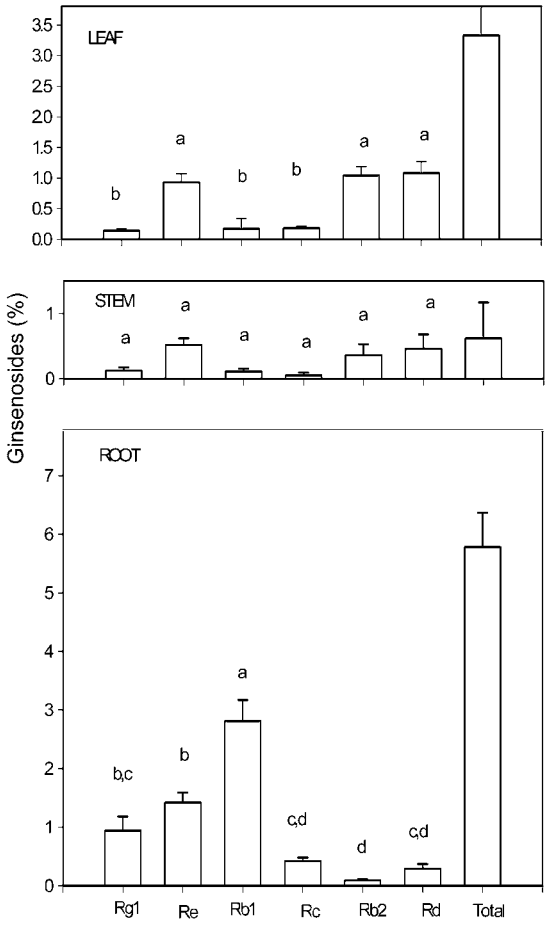

Figure 2. Profiles of the major ginsenosides in authentic wild *P. quinquefolius*. Ginsenoside content, measured using reverse-phase HPLC, was the mean ± SEM of 19 leaves, 19 stems, and 38 roots. Mean contents in each plant part accompanied by the same letter (a–d) are not significantly different in Tukey's multiple-comparison tests.

Principal component analysis (PCA) on both the covariance and the correlation matrices (only the correlation matrix is shown here) was used to reduce in a few dimensions the dispersion matrices of the ginsenoside variables. Individuals were scored onto the PCA axes as well as the resulting variables' vectors. The latter portray the relative weight and direction of each onto the PCA space. All statistical analyses were performed using SAS procedures (*18*).

Other Statistical Analyses. One-way or two-way analyses of variance (ANOVA) of the data were carried out using General Linear Models procedures of SYSTAT (*18*). Tukey's multiple-comparison tests provided further tests when significant P statistics resulted from an initial ANOVA. All results were expressed as mean ± SEM and considered to be statistically significant if $P < 0.05$.

RESULTS AND DISCUSSION

The mean results of the ginsenoside (Rg1, Re, Rb1, Rc, Rb2, and Rd) analyses for the different plant parts showed a distinct ginsenoside profile for leaf, stem, and root (**Figure 2**). Leaf and root profiles were strikingly different, whereas stems showed a relatively even profile across all ginsenosides. Leaves had high contents of Re, Rb2, and Rd (all ~1%), and other ginsenosides were significantly lower. There were no significant differences in individual ginsenosides in the stem. In contrast, there was more variation in ginsenoside content in the roots: Rb1 (2.81 ± 0.36%) was significantly higher than any other ginsenoside. Re was present in half the amount of Rb1 and was statistically similar to Rg1 but was statistically more abundant than Rc, Rb2,

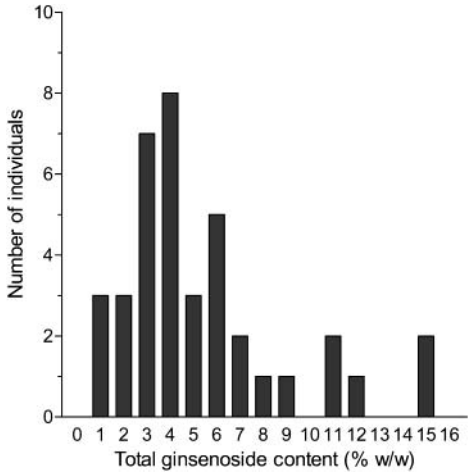

Figure 3. Frequency distribution of total ginsenoside content within 38 *P. quinquefolius* roots.

and Rd. Rb2 (0.09 ± 0.02%) was statistically the lowest amount of all the ginsenosides.

None of the root analyses show detectable amounts of ginsenoside Rf. This confirms that this ginsenoside found in *Panax ginseng* CA Meyer (Asian ginseng) is a reliable marker separating the two species (*16*).

Roots had significantly more total ginsenosides (5.78%) than the leaves (3.33, $P < 0.05$) and the stems (0.67, $P < 0.001$). In a separate ANOVA (not shown), the higher ginsenoside content in the roots was attributed to significantly higher contents of Rb1, Rc, and Rg1.

Researchers who previously studied cultivated ginseng also reported the difference in ginsenoside profile and content within the parts of a plant. The decreasing order of ginsenoside content in these studies was bud-flower > leaf > root > rhizome > seed (*19*, *20*). Li et al. (*21*) reported that *P. quinquefolius* leaves contain mainly Re and Rd, whereas the roots contain mainly Rb1 and Re. They suggested that the leaves mature and accumulate these compounds, as there is a corresponding decrease in the roots. Although our root results are similar to those in the literature (*21*, *22*), our leaf results add Rb2 as a saponin present in substantial amounts. In addition, although the major ginsenosides have been identified in the stem (*23*), their quantification and variation is reported here for the first time. Although leaf concentrations are only 50% of roots, the levels (3.33%) are appreciable and represent a source of ginsenosides that could be harvested renewably if leaves are collected in the late fall.

The frequency at which a wild root was sampled with a specific ginsenoside content is plotted against the ranges of total ginsenoside content in **Figure 3**. This frequency distribution shows that no wild roots below 1% or above 16% content were sampled. Roots of between 4 and 4.9% content were most frequently sampled in our study, and 60% of the roots had total ginsenoside contents between 3 and 6.9%. Because of the small number of leaf and stem samples, a frequency distribution of ginsenoside content was not determined for leaves and stem. However, the ranges (lowest and highest amounts) of total ginsenosides were 0.03−10.15% for stem and 0.18−6.57% for leaves. There was not enough statistical power to examine age as a factor in the ginsenoside content of our wild collections, but generally ginsenoside content was highest in older roots.

There were a large number of 4-year-old wild roots and leaves available for a comparative study with cultivated ginseng that is normally harvested at this age. The 4-year-old wild roots were compared to 4-year-old cultivated ginseng roots harvested in the same year and region (**Table 1**). The results are also compared to previous studies for cultivated ginseng of the same age (**Table 1**). An important conclusion is that there appears to be no difference between total ginsenoside contents of wild and cultivated North American ginseng of the 4-year-old age class. Wild populations do, however, include a few roots of exceptional ginsenoside content as noted in **Figure 3**. This may have led to the misconception that "woods-grown" or wild ginseng is medicinally more "potent". Foster (*24*) noted in a review that wild *P. quinquefolius* root has higher levels of ginsenosides than the cultivated root, contrary to this study. However, in a finding similar to our study with North American ginseng, Tanaka (*25*) reported no significant difference in saponin composition between wild and cultivated Asian ginseng.

Table 1. Comparison of Mean Ginsenoside Contents of Cultivated and Wild 4-Year-Old *P. quinquefolius* Leaves and Roots

		ginsenoside content[a] (% w/w)						
		Rg1	Re	Rb1	Rc	Rb2	Rd	total
		Leaves						
cultivated	Li et al. (*21*)	0.28	1.56	0.23	0.32	0.62	1.74	4.18
wild	this study[b]	0.14	0.93	0.17	0.18	1.04	1.08	3.33
		Roots						
cultivated	Court et al. (*28*)	0.16	1.53	1.93	0.25	0.04	0.41	4.32
cultivated	Li et al. (*21*)	0.18	1.10	1.22	0.18	0.02	0.29	3.00
cultivated	this study[c]	0.25	1.75	1.88	0.36	0.13	0.48	4.85
wild	this study[b]	0.94	1.42	2.81	0.42	0.09	0.29	5.78

[a] Percentages were calculated based on the weighed ground plant material; [b] Refer to **Figure 2**. [c] Average of 12 cultivated *P. quinquefolius* roots collected in late September 1998 from Northern Lights Ginseng Farm, Quyon, PQ, Canada.

Some variation in ginsenoside concentrations may result from differences in collection times and in the tissues used for the ginsenoside quantifications. Kim et al. (*26*) reported seasonal variation in saponin and carbohydrate content in *P. ginseng* roots: whereas saponin content peaked in the summer, carbohydrate content, which was mainly due to the increase of sucrose, peaked in the winter. Furthermore, if lateral roots and root hairs are removed from the main root, as they are in most commercial products, then the ginsenoside content is different. Soldati and Sticher (*27*) reported that *P. ginseng* root hairs have twice as much ginsenoside content as lateral roots, which, in turn, have 3 times as much ginsenoside content as the main root. These authors also reported variation in the kind of ginsenoside present: Re was the prominent ginsenoside in root hairs, whereas Rb1 was prominent in lateral roots, and Rg1 was the prominent ginsenoside in the main root. We have also observed these differences in our investigations with cultivated *P. quinquefolius* (not shown).

An ANOVA followed by Tukey's multiple-range test revealed that there was significant variation in total ginsenoside content by population (**Figure 4**). Between the highest and lowest populations the content ranged from 10.93 ± 1.56 to 2.73 ± 0.63%. Two pairs of populations were significantly different ($P < 0.01$) from each other: populations 3 and 9 and populations 9 and 10.

The PCA yielded two axes that explained a total of 54% of the variability in ginsenoside content (**Figure 5**). A third axis explained an additional 15% of variability in the data set but yielded no improvement in separation of the populations. Rb1 and Rc contents heavily influenced the first axis, explaining 35% of the variability. Re, Rb2, and Rd had intermediate effects. All loadings were positive, indicating that increases in the scores of axis 1 corresponded to increases in all ginsenosides.

There was no single variable that heavily influenced axis 2; however, Rg1 and Rb2 both had intermediate and positive

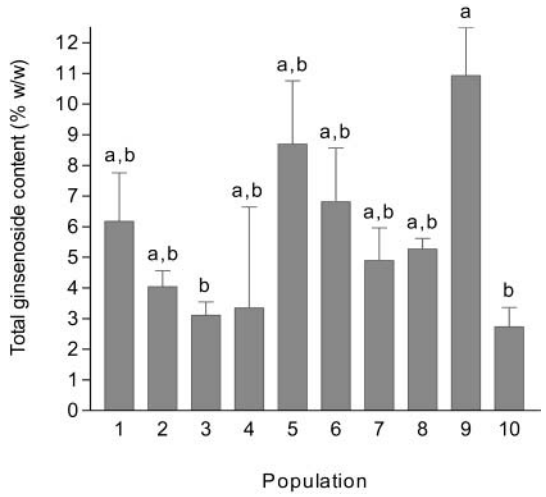

Figure 4. Total ginsenoside content in the roots of 10 wild populations of *P. quinquefolius*. Ginsenosides Rg1, Re, Rb1, Rc, Rb2, and Rd were measured using reverse-phase HPLC. Total ginsenoside content is the mean ± SEM for two to five roots per population. Means followed by the same letter (a, b) are not significantly different in Tukey's multiple-comparison test ($P < 0.05$) between the populations.

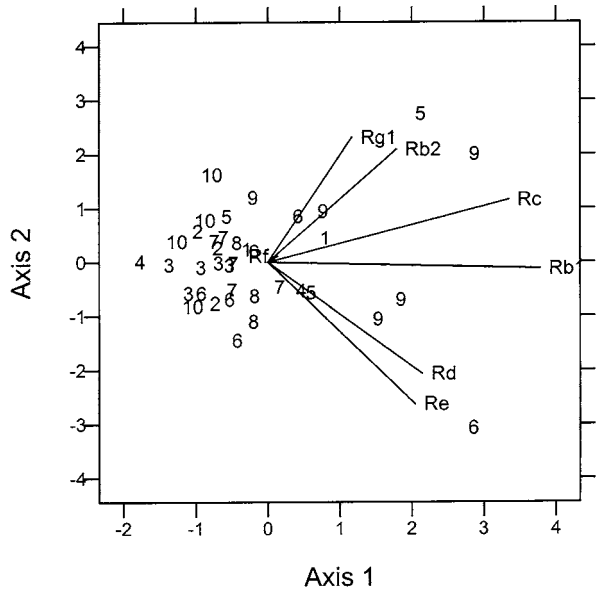

Figure 5. Principal component analysis plot of six major ginsenosides from the roots of *P. quinquefolius*. Lines indicate relative loadings of these variables on axes 1 and 2. Scores for individuals within populations are indicated with numbers corresponding to the individual's population (1–10). PCA was run on a correlation matrix for standardized ginseng variables.

loadings, and Re and Rd both had intermediate and negative loadings. The other variables had small to negligible influence. Orthogonal rotations did not improve the separation of ginsenosides on the axes.

Visual examination of the spread of populations along the first two axes showed some separation of populations, primarily along axis 1, with populations 9 and 5 seeming to have the highest scores (**Figure 5**). This was confirmed by an ANOVA, which showed a significant difference among populations. There was no significant difference in axis 2 scores among populations, despite sufficient power (85%) to detect differences. Tukey's post-hoc comparison of means test yielded two homogeneous groups for axis 1: one group consisted of populations 3, 10, 2, 4, 7, 8, 6, 1, and 5, and the other consisted of populations 2, 4, 7, 8, 9, 1, 5, and 9 (populations are listed in order of increasing mean axis 2 scores). Populations 3 and 10 had the lowest scores for axis 1, but these were not different from populations 2, 4, 7, 8, 6, 1, and 5, whereas population 9 had the highest mean scores for axis 1, but these also were not different from populations 2, 4, 7, 8, 6, 1, and 5.

The PCA revealed some separation among populations along axis 1 that was most influenced by the concentrations of Rb1 and Rc. In **Figure 5**, population 9 can be characterized by relatively high concentrations of Rb1 and Rc, whereas populations 3 and 10 tend to have low concentrations of Rb1 and Rc. Given the ambiguous separation of variables along axis 2, it is not surprising there were no significant differences among populations for this axis. Due to the number of populations, where the populations came from, and the small sample size within populations, the PCA results are only a tentative first step in determining population variation in North American ginseng.

In previous studies the age of the plant also affected ginsenoside concentrations. Court et al. (*28*) showed that ginsenoside concentrations increase with root age: changes were specifically attributable to Rb1 and Re. They recommended a harvest of the ginseng crop at age 4 year of age rather than 3 to obtain a higher amount of ginsenosides. Soldati and Tanaka (*29*) showed similar results for cultivated *P. ginseng*; moreover, their study determined that there is no marked increase in ginsenoside concentration after the fifth summer. Our results from the ANOVA and the PCA, using age as a variable, did not demonstrate a markedly different result from the analyses without the age variable. This was likely a result of the low number of samples. Our samples also had considerable age variation in some populations (population 2 had roots with age ranges of 8−25, population 7 had age ranges from 14 to 28, and population 8 had age ranges of 13−37) and no variation in others (populations 1, 4, and 6, which were all 4-year-old roots).

Phytochemical variation between populations was supported by both the ANOVA of total ginsenosides (**Figure 4**) and the PCA of six ginsenosides (**Figure 5**) that showed several examples of statistically different levels between certain populations. Population 9, which represented a population in Iberville County in Quebec, was established as the most different from the other populations. Populations 3, 7, and 8, which were all from Frontenac County in Ontario and geographically close together, showed that they were still distinct populations.

The variation observed in ginsenoside concentration in the different accessions may be of both environmental and genetic origin (*30*, *31*). Influences from the environment, such as soil nutrients and texture, humidity of soil and air, and light conditions, can affect the chemical profile of populations. In the published literature Rb1, Rc, and Rd have been shown to be most susceptible to varying environmental conditions (*21*). The influences of soil, nutrient, and water are best evaluated in highly replicated and uniform conditions of cultivation. Therefore, in this study we did not attempt to measure soil or other environmental parameters, because it was unlikely that firm conclusions could be drawn on the basis of such a small sample size. Genetic variation also plays a role in ginsenoside concentration. Preliminary data in a study on genetic variation in wild populations of *P. quinquefolius*, including some of the populations studied here, suggest genetic differences between populations that may reflect a history of fragmentation (isolation) and size reduction through past harvesting (personal communication from A. Nault and D. Gagnon).

An important feature of the study was to provide baseline data on authentic *P. quinquefolius*. One of the challenges of the Ginseng Evaluation Project's (GEP) evaluation of 414

commercial products (*16*, *17*) was the lack of detailed information on authentic material. In our study of wild roots, no root had <1%, and 13% had surprisingly high total ginsenoside content (>10%). The large number (20%) of commercial products tested in the GEP claiming ginseng root content and with <1% ginsenosides suggests adulteration in commercial products. Wild-crafters and forest ginseng producers can compare their product with authentic levels described in **Figure 3**.

This is the first report of phytochemical variation in naturally occurring ginsenoside levels in a significant survey of wild ginseng populations. A limitation of the study was the low sample size per population, which was a result of the endangered status of *P. quinquefolius* and the collection limits set by conservation authorities. We believe that if more samples could be taken, the SEM would have been smaller and even greater differences identified.

Conservation implications of the study are clear. Because there is no significant difference between wild-grown and cultivated ginseng at 4 years of age, destructive root harvests should be discontinued until the status of the species improves. Ginseng growers should consider growing older or high ginsenoside content roots to satisfy demand for this product.

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