Variations in Ginsenosides of Raw Ginseng According to Heating Temperature and Time

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Abstract

Objectives: Ginsenosides found in ginseng, and the hydrolysates derived from their conversion, exhibit diverse pharmacological characteristics [1]. These have been shown to include anti-cancer, anti-angiogenic, and anti-metastatic effects, as well as being able to provide hepatic and neuroprotective effects, immunomodulation, vasodilation, promotion of insulin secretion, and antioxidant activity. Therefore, the purpose of this study was to examine how quickly the ginsenosides decompose and what kinds of degradation products are created under physicochemical processing conditions that don’t involve toxic chemicals or other treatments that may be harmful.

Methods: The formation of ginsenoside-Rg2 and ginsenoside-Rg3 was examined. These demonstrated diverse pharmacological effects.

Results: We also investigated physicochemical factors affecting their conversion. The heating temperatures and times yielding the highest concentration of ginsenosides (-Rb1, -Rb2, -Re, -Rd, -Rf, -Rg1, and –Re) were examined. Additionally, the heating temperatures and rates of conversion of these ginsenosides into new ‘ginseng saponins,’ were examined.

Conclusion: In conclusion, obtained provide us with effective technology to control the concentration of both ginsenosides and the downstream converted saponins (ginsenoside-Rg2, Rg3, Rg5, and Rk1 etc.), as well as identifying the processing conditions which enable an enrichment in concentration of these compounds.

1. Introduction

The efficacy of ginseng has long been recognized in the field of Asian traditional medicine, and the pharmacological potency of ginseng has been verified scientifically. The root of ginseng comprises approximately 70% carbohydrates, of which approximately 5% are ginsenosides, which are known to be responsible for its major pharmacological effects. Saponin can be found in diverse kinds of plants. The saponin, found in ginseng, is a ginsenoside of the dammarane type existing only in plants of the genus of panax. Approximately 100 ginseng saponin structures have been identified to date [2].

At the end of the era of the ’Han dynasty’ (around B.C. 40) in China, there was a term, ‘ginseng,’ among...
2.1. Materials

The fresh ginseng (Panax ginseng C. A. Meyer), thermally treated at 105°C in these experiments, was a six-year-old root of medium size harvested in 2018 from Poong-gi. The fresh ginseng, treated at temperatures of 120°C, 94°C, and 80°C were six-year-old medium sized roots harvested in 2014 from Geum-san. Soils attached to the roots of fresh ginseng were removed by spraying with highly pressurized water, and remaining impurities were cleaned by brushing of the roots in flowing water. The washed and cleaned specimens were homogenised to a standard consistency and then 300 g of respective specimens were collected into containers with a lid for processing under varied temperatures and times.

2.2. Heat Treatment of Ginseng

Upon completion of processing of fresh ginseng at different temperatures and times, the specimens were lyophilized to prevent additional changes in the ginsenosides (GS). The preparation of the specimens for heat treatment comprised three times repetition of the specimens of condition 1.

2.3. GS Extraction and Component Analysis

Samples of ginseng, were extracted for analysis by HPLC according to the analytical method for detecting saponins of Kim et al. Samples were disintegrated and passed through 100 mesh of standard sieves for the analysis [3]. One gram of each specimen, prepared for the analysis, was put into a 50 mL conical tube and then 50 mL of 70% MeOH was applied, followed by ultrasonic extraction three times for one hour (shaking the tube in between for the residuals to be well mixed).

The three extracted liquids were mixed and then 3 mL of the extract was centrifuged at 15,000 rpm for 15 minutes. The supernatant thereof was filtered through a membrane filter (0.25 μL) to obtain test solutions.

An ‘ACQUITY HPLC H-Class’ (Waters Corporation) was used with an ACQUITY UPLC BEH C18 1.7 μm 50 mm column for GS analysis. Peaks were detected by UV detector (203 nm).

GS standards were purchased from Ambo Institute (Korea). HPLC grade water and acetonitrile (J.T. Baker), were used as a gradient elution system under analytic conditions specified below. The column temperature was set at 40°C, and the injection volume and flow rate were set at 2 μl and 0.6 mL/min., respectively (Table 1).

2.4. Analysis of LC/MS to Identify GS-Rg5 and Rk1

GS-Rg5, and Rk1 were analyzed by a UPLC I-class/TQ-S MSMS System.

Rk1 and Rg5 have the same molecular weight of 766 g/mol. Therefore, it was separated by C18 reverse phase column chromatography and analyzed using a mass spectrometer. (Figs. 1 - 3)
### HPLC Conditions

LC system: Waters ACQUITY UPLC I-Class, Software: MassLynx  
Column: ACQUITY UPLC BEH C18 1.7um, 2.1 X 100 mm  
Mobile Phase A: 0.01% formic acid in DW,  
Mobile Phase B: 0.01% formic acid in acetonitrile  
Pump mode: Gradient, Flow Rate: 0.4 mL/min,  
Column Temp: 35℃, Sample Temp: 15℃  
Total Run Time: 43 min, Injection Volume: 5 μl

### MS Conditions (Waters Xevo TQ-S MSMS)

Ionization Mode ESI negative, Capillary 2.50 kV,  
Source Temp. 120 °C, Desolvation Temp. 800  
Desolvation Gas Flow 500 L/hr, Cone Gas Flow 150 L/hr, Collision Gas flow 0.15 mL/min.

### 2.5. MRM transitions

The ionization mode of the GS-Rg5 and GS-Rk1 was negative; MRM was 765.46 → 603.32 and cone voltage was 40; and the collision energy was set at 30.  
When using the MRM method under these conditions, even if the protons of the analyte having the same mass and the interfering substance pass through the Q1 mass filter, the generated ions appear differently through the collision induction reaction of the collision tube. In addition, only the generated ions for the analyte were transferred from the Q2 mass filter to the detection unit, so that only the complete target component information could be detected and analyzed with excellent selectivity and sensitivity.

### Table 1 Gradient elution system of HPLC

| No. | Time   | Flow (mL/min) | %A  | %B  |
|-----|--------|---------------|-----|-----|
| 1   | Initial| 0.600         | 85.0| 15.0|
| 2   | 0.50   | 0.600         | 85.0| 15.0|
| 3   | 14.50  | 0.600         | 70.0| 30.0|
| 4   | 15.50  | 0.600         | 68.0| 32.0|
| 5   | 18.50  | 0.600         | 62.0| 38.0|
| 6   | 24.00  | 0.600         | 57.0| 43.0|
| 7   | 27.00  | 0.600         | 45.0| 55.0|
| 8   | 31.00  | 0.600         | 45.0| 55.0|
| 9   | 32.00  | 0.600         | 10.0| 90.0|
| 10  | 38.00  | 0.600         | 10.0| 90.0|
| 11  | 38.50  | 0.600         | 85.0| 15.0|
| 12  | 43.00  | 0.600         | 85.0| 15.0|

### 2.6. Preparation of Specimens

#### 2.6.1. Preparation of Standard Solutions

GS-Rk1 and GS-Rg5 standard solutions at a concentration of 4 μg/ml, were diluted 10-fold by applying 10% acetonitrile, and analyzed by injecting 5 μl into the instrument.

#### 2.6.2. Preparation of Specimen Samples

Extracts of raw ginseng heated at a temperature of 105℃ for 48 hours were filtered through a 0.2 μm syringe filter and then analyzed by injecting 5 μl into the instrument.

### 3. Results and Discussion

Changes over time in the saponin constituents of fresh ginseng powder thermally treated at 105℃ were examined. Specimens of fresh ginseng thermally treated for different times revealed continuous increases in protopanaxadiol (PPD) type ginsenosides of GS-Rb1, Rb2, Rc and Rd, among the major saponins for up to three hours. However, their concentrations diminished after three hours and the Rb1, Rb2, and Rd became undetectable after 30 hours, while Rc was not detected after 27 hours. Rg3, a degradation product of PPD type ginsenosides, reached its peak values after 30 hours of complete decomposition of GS-Rb1, Rb2, Rc, and Rd, and remained without significant variation in concentration for some time, but after about 40 hours, it began to decrease (Table 2 and Fig. 1).
Table 2  Content change of diol-type ginsenosides with heating time of raw ginseng at 105°C (mg/g)

| hr | Rb1  | Rc   | Rb2  | Rd   | Rg3S | Rg3R |
|----|------|------|------|------|------|------|
| 0  | 1.775| 1.381| 0.767| 0.51 | N/D  | N/D  |
| 0.5| 1.436| 2.031| 0.967| 0.401| N/D  | N/D  |
| 1  | 2.06 | 2.363| 1.247| 0.508| 0.294| 0.3  |
| 1.5| 2.723| 2.729| 1.513| 0.514| 0.346| 0.62 |
| 2  | 3.148| 3.031| 1.661| 0.572| 0.429| 0.658|
| 2.5| 3.682| 3.291| 1.92 | 0.628| 0.504| 0.394|
| 3  | 4.189| 4.029| 2.056| 0.957| 0.951| 0.521|
| 6  | 3.942| 3.818| 1.954| 1.001| 1.724| 0.817|
| 9  | 3.166| 3.02 | 1.59 | 0.867| 2.655| 1.201|
| 12 | 2.39 | 2.22 | 1.233| 0.789| 3.375| 1.521|
| 16 | 1.516| 1.301| 0.786| 0.722| 4.421| 1.949|
| 24 | 0.547| 0.121| 0.214| 0.506| 5.492| 1.964|
| 27 | 0.487| N/D  | 0.161| 0.472| 5.559| 2.183|
| 30 | N/D | N/D  | N/D  | N/D  | 5.665| 2.09 |
| 33 | N/D | N/D  | N/D  | N/D  | 5.634| 1.94 |
| 36 | N/D | N/D  | N/D  | N/D  | 5.648| 1.822|
| 39 | N/D | N/D  | N/D  | N/D  | 5.706| 1.924|
| 42 | N/D | N/D  | N/D  | N/D  | 5.672| 1.907|
| 48 | N/D | N/D  | N/D  | N/D  | 5.052| 1.735|

Figure 1  Comparison of Changes in Peak Patterns of Ginsenosides Before (a) / After (b) Heat Applications at 105°C for 30 Hours to Raw Ginseng.
Conversely, the GS-Rg1 and Re, the major saponins of the protopanaxatriol (PPT) type ginsenosides, exhibited a slight increase for up to two hours of heating, and then decreased after 2.5 hours; Re, Rg1, and Rf were not detected after 16 hours, 24 hours, and 33 hours, respectively. Rg2, known as a degradation product of GS-Re, showed maximum concentration after 12 hours, and then decreased gradually. The degradation product of GS-Rg1, the GS-Rh1, increased inversely with the degradation of GS-Rg1. The degradation product of GS-Re, the GS-Rg2, also exhibited inverse proportional increase concomitant with degradation of GS-Re (Table 3 and Fig 1). The creation of GS-Rg5 and Rk1 from the dehydration reaction of carbon at position C-20 of GS-Rg3 was identified from examining the content before and after heating fresh ginseng at 105°C.

The creation of GS-Rg5 and Rk1 were also identified from the mass analysis of LC/mass (Table 4 and Figs 2 - 4). Following heat treatment of specimens of fresh ginseng at 94°C, the increase in content of GS-Rb1 and the decrease in content of GS-Rg3, were examined. In the graph illustrating the results, the concentration of GS-Rb1 reached its peak after six hours, but then became undetectable by 30 hours at 105°C and 48 hours at 94°C (Table 5).

Changes in the major GS's at a temperature of 80°C, were examined. As presented in Table 6, the concentration of GS-Rb1 reached its peak after 48 hours (2 days), while the content of GS-Rg3 reached its peak after 12 days from heat treatment, and then it started to decrease after 500 hours. Upon completion of heat application with steam at 120°C to red ginseng of moisture content 30%, the rise and fall in content of GS-Rg3 reached its peak after 12 days from heat treatment, and then it started to decrease after 500 hours. Upon completion of heat application with steam at 120°C to red ginseng of moisture content 30%, the rise and fall in content of GS-Rg3 reached its peak after 12 days from heat treatment, and then it started to decrease after 500 hours. Upon completion of heat application with steam at 120°C to red ginseng of moisture content 30%, the rise and fall in content of GS-Rg3 reached its peak after 12 days from heat treatment, and then it started to decrease after 500 hours. Upon completion of heat application with steam at 120°C to red ginseng of moisture content 30%, the rise and fall in content of GS-Rg3 reached its peak after 12 days from heat treatment, and then it started to decrease after 500 hours. Upon completion of heat application with steam at 120°C to red ginseng of moisture content 30%, the rise and fall in content of GS-Rg3 reached its peak after 12 days from heat treatment, and then it started to decrease after 500 hours.

The major GS's of fresh ginseng, GS-Rb1, Rb2, Rc, and Rd, appeared to initially increase following heat treatment and our analysis identified the conditions, under which

Table 3 Content change of triol-type ginsenosides with heating time of raw ginseng at 105°C (mg/g)

| heating time | Rg1 | Re  | Rf  | Rh1 | Rg2s | Rg2r |
|--------------|-----|-----|-----|-----|------|------|
| 0            | 3.347 | 2.963 | 0.889 | N/D | N/D  | N/D  |
| 0.5          | 3.26  | 2.918 | 0.771 | 0.097 | 0.352 | 0.079 |
| 1            | 3.226 | 2.743 | 0.817 | 0.113 | 0.344 | 0.09  |
| 1.5          | 3.534 | 3.178 | 0.76  | 0.124 | 0.348 | 0.09  |
| 2            | 3.573 | 3.073 | 0.759 | 0.164 | 0.346 | 0.103 |
| 2.5          | 3.594 | 3.091 | 0.765 | 0.253 | 0.472 | 0.108 |
| 3            | 3.448 | 2.719 | 0.937 | 0.177 | 0.559 | 0.209 |
| 6            | 2.821 | 1.723 | 0.916 | 0.651 | 0.85  | 0.282 |
| 9            | 2.122 | 0.727 | 0.9   | 0.861 | 1.058 | 0.348 |
| 12           | 1.701 | 0.181 | 0.854 | 0.948 | 1.229 | 0.378 |
| 16           | 1.5   | N/D  | 0.812 | 0.989 | 1.143 | 0.402 |
| 24           | N/D   | N/D  | 0.65  | 0.908 | 1.031 | 0.399 |
| 27           | N/D   | N/D  | 0.575 | 0.855 | 0.977 | 0.408 |
| 30           | N/D   | N/D  | 0.57  | 0.807 | 0.889 | 0.387 |
| 33           | N/D   | N/D  | N/D   | 0.784 | 0.826 | 0.394 |
| 36           | N/D   | N/D  | N/D   | 0.746 | 0.789 | 0.377 |
| 39           | N/D   | N/D  | N/D   | 0.672 | 0.673 | 0.367 |
| 42           | N/D   | N/D  | N/D   | 0.631 | 0.639 | 0.36  |
| 48           | N/D   | N/D  | N/D   | 0.408 | 0.423 | 0.33  |

Table 4 Change in Ginsenosides content before and after 30-hour heating of raw ginseng at 105°C (mg/g)

| Peak Name | Before Heat Application Content of Ginsenosides | After Heat Application Content of Ginsenosides |
|-----------|-----------------------------------------------|-----------------------------------------------|
| Rk1       | N/D                                           | 2.075                                         |
| Rg5       | N/D                                           | 3.756                                         |
Table 5  Content change of ginsenosides with heating time of raw ginseng at 94°C (mg/g)

| Time (h) | Rb1  | Rg3 (s+r) |
|---------|------|-----------|
| 0       | 3.94 | N/D       |
| 3       | 7.76 | N/D       |
| 6       | 8.8  | 0.43      |
| 9       | 8.65 | 1.08      |
| 12      | 8.14 | 1.6       |
| 16      | 7.07 | 2.21      |
| 24      | 6.23 | 4.71      |
| 36      | 0.92 | 6.71      |
| 48      | N/D  | 7.42      |

Figure 2  Mass Chromatogram of LC / mass of Ginsenoside Rk1 Standard.

Figure 3  Mass Chromatogram of LC / mass of Ginsenoside Rg6 Standard.
The time to peak concentration of Rb1 at 94℃ was found that a large amount of GS of red ginseng, the conditions, satisfying degradation under which all the major GSs (Rg1, Rb1, Rb2, Rc, and Rd), appear to initially maximum concentration and our analysis identified time at lower temperature or shorter heating time at higher temperature are necessary to obtain.

| Table 6 | Content change of ginsenosides with heating time of raw ginseng at 80℃ (mg/g) |
|---------|---------------------------------------------------------------|
| day    | hr | Rg1 | Re | Rb1 | Rg3s | Rg3r |
| 0      | 0  | 3.347 | 3.218 | 3.465 | N/D | N/D |
| 2      | 48 | 2.024 | 1.84 | 8.734 | 1.025 | 0.552 |
| 4      | 96 | 0.617 | 0.555 | 6.517 | 2.252 | 1.143 |
| 6      | 144 | N/D | N/D | 3.808 | 3.762 | 1.799 |
| 8      | 192 | N/D | N/D | 2.853 | 4.526 | 1.933 |
| 10     | 240 | N/D | N/D | 0.908 | 5.857 | 2.314 |
| 12     | 288 | N/D | N/D | 6.011 | 2.014 |
| 14     | 336 | N/D | N/D | 6.118 | 2.451 |
| 16     | 284 | N/D | N/D | 6.055 | 2.431 |
| 18     | 432 | N/D | N/D | 5.9 | 2.511 |
| 21     | 504 | N/D | N/D | 5.678 | 2.35 |

| Table 7 | Content change of ginsenosides with heating time of red ginseng at 120℃ (mg/g) |
|---------|---------------------------------------------------------------|
| Moisture Content (%) | Red Ginseng | 30%-1hr | 30%-2hr | 30%-3hr | 30%-4hr |
| GS      |                  |        |        |        |        |
| Rg3     | 0.07             | 0.33   | 0.72   | 1.76   | 2.18   |
| Rb1     | 1.80             | 2.44   | 1.20   | 0.49   | N/D    |
peak levels of all the major GS were created. Furthermore, we were able to define the degradation kinetics of GS-Rg3, Rg2, and Rh1 in fresh ginseng. It was found that a large amount of GS-Rk1 and Rg5 etc. was created in accordance with the increasing time of heat treatment [6-8].

For the manufacturing of red ginseng, the conditions, satisfying maximum concentrations of major GS of the fresh ginseng (GS-Rb1, Rb2, Rc, and Rd), were less than one hour at 120°C and 2.5 - 3 hours at 105°C. The time to peak concentration of Rb1 at 94°C and 80°C took longer at lower temperatures. Thus, for the manufacturing of the red ginseng, it is predicted that the longer heating time at lower temperature or shorter heating time at higher temperature are necessary to obtain maximum concentrations of the seven kinds of major GS.

The reductions in GS-Rd with time is less than was seen for GS-Rb1, Rb2, and Rc. This is because the decomposition of PPDs GS-Rb1, Rb2, and Rc, results in GS-Rg3 via conversion into GS-Rd [8-10].

The increase in PPD type GSs upon initial heating resulted from the release of the malonyl group from malonyl-PPDs. Under identical conditions, the rate of decomposition of the GS of the PPTs was faster than the GS of the PPD-type except for the GS Rf. The conversion ratio of GS-Rh1 resulting from GS-Rg1 and of GS-Rg2 resulting from GS-Re, appeared lower than that of Rg3, which is known to be a degradation product of GS-Rb1, Rb2, Rc, and Rd of the PPD-type.

This implies the presence of relatively lower content of the malonyl-PPT than the malonyl-PPD [11]. The lower rate of decomposition of GS-Rf can be attributed to the bonding of the OH-group such as carbon at C-20 position of GS-Rg2, the degradation product of GS-Re [12]. Yang et al. [13] reported the major GS in fresh ginseng decreased significantly in accordance with the increasing number of steaming treatments, while the (content of) GS-Rg3 appeared increased. However, in the study by Yang et al., the initial increase or decrease in concentration of GS was unavailable due to the lack of detailed measurements during initial steaming. In another study by Kim et al. [14], factors, inducing concentration changes, were not clarified because of the use of specimens for which drying temperature information was not provided.

Go et al. [15] reported results on ingredients of GS included in the extracted concentrates of commercially available white ginseng and red ginseng, wherein the extracted concentrate of white ginseng appeared to have higher GS content than red ginseng. The differences in content of GS-Rb1, Rb2, Rc, and Rd were attributed to differences in the heat treatment used in respective manufacturing processes, wherein red ginseng used a longer duration of heat application for the processes of extraction and concentration, whereas white ginseng had heat applied for a shorter length of time.

Nam et al. [10] used six-year-old roots of the fresh ginseng and repeated the treatment of steaming for three hours at 96°C and drying at 50°C. The method resulted in red ginseng of moisture content below 15% - 20% after drying, therefore the samples may exhibit less or uneven moisture content, that may cause differences in the rate of hydrolysis of GS compared to fresh ginseng, with moisture content of approximately 75% - 80%. In this study, the factors, that caused changes in GS content according to treatment of steaming, were identified as the time and temperature of steaming.

In all of the GS-Aglycon of ginseng, the Glc-Glc, bonded with C3 or C6 and was dropped-off from the position at C20, suggesting the decomposition reaction is induced by acid. At the C20 position, the results of hydrolysis, caused by hydrolytic enzyme, were not reported because of the presence of steric hindrance. The difference in electron density based on theoretical calculation could be a factor behind the increasing reaction at C20 [12].

The weight of hydrolysate decreased compared to the concentration of GS's of PPD types. This resulted from the decomposition of Glc(2-1)Glc bonded with GS-Aglycon thereby converted into GS-Rg3 of molecular weight of 785 g/mol compared to the weight of 1,109 g/mol of GS-Rb1. Such properties can be observed from similar reactions of GS Rg1 and Re [16]. The ingredients of GS-Rg3, Rg5, and Rk1 of PPD saponins, are unique components of red ginseng resulting from processing via heat treatment, and have been reported to exhibit diverse pharmacological activities. However, the corresponding components contained in red ginseng are rare. The efficacy of ginseng can be augmented by increasing the concentration of such ingredients. Thus, it is predicted that the conditions by which boiling water is used for the decoction of ingredients of red ginseng as in the traditional way, would result in increased levels of GS-Rg3, Rg2, Rg5, and Rk1 in red ginseng [17-21].

4. Conclusion

In this study, changes in GS content, which are the major components behind the efficacy of ginseng, were examined for their dependence on times and temperatures of heat treatment, when applied to fresh ginseng. To secure the uniformity of specimens, samples of the fresh ginseng were comminuted. To identify and analyze the increase or decrease in GS content, the intervals of GS measurement were subdivided according to the varied times of heat treatment. Saponins of the PPD type comprising GS-Rb1, -Rb2, -Rc, and -Rd all exhibited common increases with time of initial heat treatment up to a point, thereafter which they started decreasing. With these reductions, the content of GS-Rg2, Rg3, Rh1, Rg5, and Rk1 simultaneously began increasing. The heat treatment times to reach peak level of GS-Rg3 content appeared as 250 hours at 80°C, 50 hours at 94°C, and 30 hours at 105°C, corresponding to the timepoints at which PPD-type GSs became undetectable. However, the GS-Re and Rg1 saponins, exhibited no definite increase in the initial heat treatment. The decomposition of sugar, bonded with C20 carbon of GS Aglycon, the GS-Re and Rg1 of PPT GSs, proceeded faster than the saponins of the PPD-type. The sugar, which was bonded with the C20 carbon of GS Aglycon commonly from the PPT and the PPD saponins, was dropped out; therefore the lower rate of decomposition of GS-Rf can be attributed to the absence of the sugar bond with the C20 carbon of the GS Aglycon.
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