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The Trends in Chemical Studies of Ginseng

Koo Dong Han

Professor Emeritus, Natural Products Research Institute, Seoul National University
Seoul 110, Korea

Ginseng has been worshiped for centuries in Asian countries as a remedy for prolonging life expectancy. The unique tonic activities of ginseng have been recognized for more than two thousand years and ginseng has been known as "the Best Medicine".

The chemical investigation on ginseng was started aiming the separation of biologically active principles. However, the traditional pharmacological method failed to clarify the specific effects of ginseng so that the chemical work in the early stage was focused on the chemical components which are specifically present in ginseng, rather than on the chemical components with specific pharmacological activities.

Recently, a variety of pharmacological activities of dammarane triterpene glycosides, the unique chemical components of ginseng, has been recognized and related to the prolonging activities of longevity by ginseng. These pharmacological activities include adaptogenetic activity, stimulation or depression of central nervous system and stimulation on the biosyntheses of proetins and nucleic acids.

These have been two main trends on the research related to ginseng. The details will be discussed on the following.

The first paper on the chemistry of ginseng appeared in 1854. Garriques[1] reported the separation of saponin named panaquillon from American ginseng. This was the beginning of the research on dammarane saponins and the research on the chemical components on ginseng was focused on saponins until the end of 1930's. However, the chemical technique of those days merely permitted the separation of fractions with constant physical properties and any conclusive evidence was not obtained regarding to the chemical structures of them. The pharmacological activities of these saponins reported during this period were only nonspecific activities of general saponins such as hemolytic, expectorative activities, etc. Therefore no significant result was considered to be obtained until the end of 1930's despite the enormous effort devoted to the investigation of ginseng saponins by Asahina, Kondo, Godake and others.

As the result, attention was given to the non-saponin fractions of ginseng. And the pharmacological research was carried out with ginseng powder or extract rather than with each separated chemical components. In the following, the chemical components so far reported to be present in addition to saponins, are summerized.

1. Fatty Acids

Sakai[2] reported the separation of an unsaturated fatty acid fraction from the ether extract and named it "panaxsäure". The presence of linoleic, stearic and palmitic acids was revealed by Kondo[3].

Panaxsäure was reported to have hypertensive activity at low dose level and hypotensive action at high dose level.

2. Panacene

Sakai[2] reported the separation of an essential oil with the unique fragrance of ginseng. It was named "panacene" and assumed to be C_5H_8. Panacene was reported to stimulate circulatory and respiratory centers at low dose and to paralyze them at high dose. This was the beginning of the research on the essential oils of ginseng. In 1961, Takahashi *et al.*[4] conducted fractional distillation of ether extract of ginseng and recognized the presence of unique fragrance of ginseng in the low-boiling fraction. Compounds A_1, A_2, B, and C were isolated on the furthur fractionation of the low boiling fraction with the aid of gas chromatography or column chromatography filled with active alumina. Compound A was identified as a sesquiterpene, β-elemene ($C_{15}H_{24}$).

There were only few who showed interest in the fragrant components of ginseng. As the result, most of the chemistry of this fraction remains to be solved.

3. Panaxynol

Takahashi *et al.*[5] isolated a yellow viscous liquid from a neutral fraction of the ether extract of ginseng and named it "panaxynol". The chemical structure was elucidated by the total synthesis as 1,9-(*cis*)-hepta-decadiene-4,6-diyn-3-ol, $CH_2=CH-CH(OH)-C\equiv C-C\equiv C-CH_2-CH=H-(CH_2)_6-CH_3$. Recently, Wrobel *et al.*[6] reported the separation of three new polyyne compounds from ginseng. The

chemical structures of two of them were determined as $CH_2=CH-CH(OH)-C\equiv C-C\equiv C-CH(OH)-CH_2-CH(OH)-(CH_2)_6-CH_3$ and $CH_2=CH-CH(OH)-C\equiv C-C\equiv C-CH(OH)-(CH_2)_6-CH_3$. The isolation of 3-hydroxy-5-methyl-*r*-pyrene was also reported.

The polyyne compounds were once considered as unique components of ginseng. However, the biological activities were unclear and they seemed rather widely distributed in natural products. Panaxynol was also isolated from carrot[7] and was proved not to be a unique component of ginseng.

However, the possibilities of polyyne compounds to be the active components of ginseng could still not be excluded since the biological activities have not been fully understood.

4. Steroids and Fats

Takahashi *et al.*[8] confirmed the presence of β-sistosterol and β-sitosterol glycoside in ginseng. The presence of campesterol and stigmasterol was also recognized in ginseng. This class of compounds is widely distributed in the plant kingdom and clearly no unique components of ginseng.

Most phytosterols consist of various sterols. However, the steroid chemistry of ginseng should be re-examined since Ahn[9] reported that β-sitosterol was the only steroid component in ginseng and that campesterol and stigmasterol, which had already been reported to exist in ginesng, were not present in it.

5. Saccharides and Organic Acids

Lee and Lee[10] recognized the presence of carbohydrates such as sucrose(8.5%), fructose(0.5%), and glucose(0.97%). Various organic acids were detected in ginseng. They include fumaric, succinic, malic, citric, and tartaric acids. Pectin[11] was isolated which is composed of D-galacturonic acid, D-galactose, etc. A trisaccharide[12] which is composed of two moles of glucose and one mole of fructose was also isolated.

6. Nitrogen-containing Compounds

Vogt *et al.*[13] obtained four homogeneous fractions of peptides from the aqueous methanol extract of ginseng on two-dimensional high voltage electrophoresis. The

amino acid compositions of the four oligopeptide fractions were reported as the following. The following six amino acids were contained in all four fractions: aspartic acid, serine, glutamic acid, glycine, alanine and arginine. In addition to these six amino acids, each fraction contains the following amino acids.

Fraction 1 : threonine, proline, leucine, isoleucine, lysine and histidine

Fraction 2 : threonine, valine, β-aminobutyric acid, β-aminoisobutyric acid, lysine, histidine, hydroxyproline and two unknown amino acids.

Fraction 3 : threonine, proline, methionine, leucine, alloisoleucine, isoleucine, phenylalanine, β-aminobutyric acid, tyrosine, lysine and histidine.

Fraction 4 : one unidentified amino acid.

The sequence of amino acids in each fractions, however, is not determined yet.

The biological activities of these peptide fractions should be evaluated since various oligopeptides are known to show significant bioactivities.

7. Flavonoids and Vitamins

Komatsu *et al.*[14] reported the isolation of panesenoside, a flavonoid glycoside, and kaempferol, a flavonoid.

The presence of vitamins in ginseng was recognized by An[15] and niacin and pantothenic acid by Goto.[16] Kim *et al.*[17] confirmed the presence of vitamin B groups such as pantothenic acid, biotin, nicotinic acid, folic acid and vitamin B_{12}.

8. Basic Components and Trace Elements

The presence of alkaloids in ginseng has been known since the beginning of research on its chemistry. The alcohol or aqueous extract of ginseng showed positive reaction to Dragendorff reagent. Kondo[18] prepared picrate from the alkaloid fraction and Takadori *et al.*[19] isolated the Dragendorff-positive component and confirmed it as choline.

Recently, Woo[20] separated the alkaloid fraction from ginseng and found that it increased the survival time of animals bearing ascites tumor induced by HeLa cell. Wrobel[21] also separated nitrogen-containing components from the chloroform extract.

Pijck *et al.*[22] analyzed trace elements contained in ginseng and reported the presence of Mn(19.0ppm), V (0.023ppm), Cu(7.1ppm), Co(0.44ppm), and As(0.25 ppm). Pijck reported the presence of germanium in high quantity comparing to other

plants. He also explained the tonic effects of ginseng with the cytotoxicity of germanium: germanium was assumed to stimulate the replacement of aged cells with new cells. However, this concept has not been generally accepted.

These components are not unique components of ginseng and are distributed in various plants. Therefore, the research on these compononts was considered to be of little help in the search for active principles of ginseng.

Later in 1960's, Shibata[23] utilized various chromatographic and spectroscopic methods for isolation, purification and structural determination and studied the chemical structures of ginseng saponins in both aglycone and glycoside levels.

As already mentioned, the separation of panaquilon, $C_{32}H_{56}O_{14}$, was the beginning of the research on dammarane glycosides of ginseng saponins. Panaquilon was isolated in 1856 from Canadian ginseng, *Panax quinquefolium* L. by Garriques and assumed to be a mixture of dammarane glycosides and oleanolic acid.

Asahina[24] reported the isolation of another saponin with the molecular formula of $C_{23}H_{38}O_{10}$. Kondo[25] isolated a compound, $C_{27}H_{48}O_3$, and named it panax sapogenol and it was later identified as panaxadiol. Godake[26] isolated a saponin from Korean ginseng and named it panaxin, the structure of which has been utilized as a model for the structural studies of dammarane aglycone.

Later the pharmacological work by Breckman(1957) and Petkov(1961) who recognized its tonic effects and antifatigue effects on central nervous system by ginseng saponins led Shibata of Japan and Elyakov of Soviet Union to give enormous efforts on phytochemical investigations of ginseng. As the results, the problems related to the chemistry of ginseng saponins can be now considered to be almost thoroughly solved.

Summarization of the chemical investigations regarding ginseng in the past has been roughly attempted. The present view is generally that saponins are the active principles of ginseng. However, the biological activities so far investigated are not sufficient to explain the prolonging effect of life expectancy of man by ginseng. The pharmacological and biological activities of ginseng have been reexamined on every aspect on the level of extracts, but not on that of pure compounds.

The understanding of the distribution and metabolism of ginseng saponins in animal body is considered essential for a thorough explanation of the pharmacological or biological activities on molecular level.

While Shibata achieved enormous progress in the field of phytochemistry of ginseng, little work was done in Korea with the most of her research facilities destroyed

during the Korean War. Recently, Han *et al.* attempted to explain the relationships the chemical structures of ginseng saponins and the biological activities of ginseng. between Woo *et al.*[27] have established radio-labeling synthetic methods of ginseng saponins and succeeded in preparing the radioactive ginseng saponins. These labeled saponins provided important means to trace the fate of saponins *in vivo*. The distribution patterns of these saponins in various animal organs were examined. And furthur investigations are expected to achieve conclusive evidence regarding the distribution, metabolism and mechanism of actions of ginseng saponins. The research in this aspect of ginseng is regarded far ahead in Korea than in other countries.

There are still many problems to be solved with other chemical components in ginseng such as polyacetylenes, peptides, basic components and other unknown components. Chang *et al.* attempted to identify the active principles by the examination of the effects of fractions of ginseng extracts on various enzyme preparations. This approach may open new aspects in the study of ginseng.

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