

特別講演

## Some Recent Studies on the Oriental Plant Drugs. The Biologically Active Principles of Paeony and Ginseng Roots.

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One of the characteristic features of Chinese Medicine is recognized as the practical use of combinations of crude drugs in the forms of various prescriptions according to the symptoms of illness. Such crude drugs are mostly dried plant roots, rhizomes, leaves, fruits and seeds, sometimes dried animal organ preparations even fossils or minerals. In the oldest book of Chinese Medicine, Sang Han Ron,\*\* 113 prescriptions were described in which about 80 crude drugs were included, and in other old literature, Shin Nong Bon Tcho Keun,\*\*\* 365 crude drugs were recorded. Such drugs, in particular, those included in Sang Han Ron are generally low toxic, and the prescriptions are acting mild with less side effects, but it does not exclude at all the possibility of quick symptomatic effect in some cases. It is obviously not so easy task to determine the effect of the individual drug from the total effects of various prescriptions which are generally consisted of many kinds of crude drugs. About 200 years ago, in the middle of Edo era, a Japanese medical doctor, Yoshimasu Todo\*\*\* wrote a series of books named "Yakucho",\*\*\*\* in which he described the essential effect of some important crude drugs mainly based on his own clinical experiences on the various prescriptions in which the certain drug plays the main role. This book is very suggestive to evaluate the effects of some Chinese drugs. The actual effects of Chinese medicine and drugs have widely been recognized by the East Asian peoples during their long age experiences, but still it has not been studied sufficiently by modern scientific methods to give generally acceptable evidences. During past some years, my collaborators and I have been engaged to study some well-known Chinese drugs chemically to find out the active principles in determining their chemical structures under the collaboration of pharmacologists, Prof. K. Takagi and his coworkers.

In the present lecture, I would like to present two topics from our recent investigations: The studies on the principles of Paeony and Ginseng roots.

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### Paeoniflorin, a Monoterpene Glucoside in Paeony Root

Zakyak (Shakuyaku\*) is the root of *Paeonia albiflora* PALLAS (Ranunculaceae) is a very popular and an important drug in Chinese medicine, which is used to relax muscle contraction ceasing pain in abdomen. A prescription consisting of Paeony root and Licorice is employed to cure pain chiefly caused by muscle contraction in abdomen and legs or by bile and kidney stone.

Mutanpi, the bark of *Paeonia suffruticosa* is also a well-known Chinese drug which is said to be effective for uterine diseases, disorder of menses, and curing pain. According to old Chinese medical sense, it is a blood-purifier.

The roots of *Paeonia officinalis* in Europe and *Paeonia emodi* in India are also employed to cure similar diseases involving epilepsy.

In 1907 Asahina and Okuno<sup>1)</sup> isolated benzoic acid from the extract of Shaoyao, and any other special principle was not known until Shibata and Nakahara<sup>2)</sup> reported a new glucoside, paeoniflorin. Paeoniflorin is also found as a minor principle in Mutanpi,<sup>3)</sup> the principal principle of which was known to be paeonol.

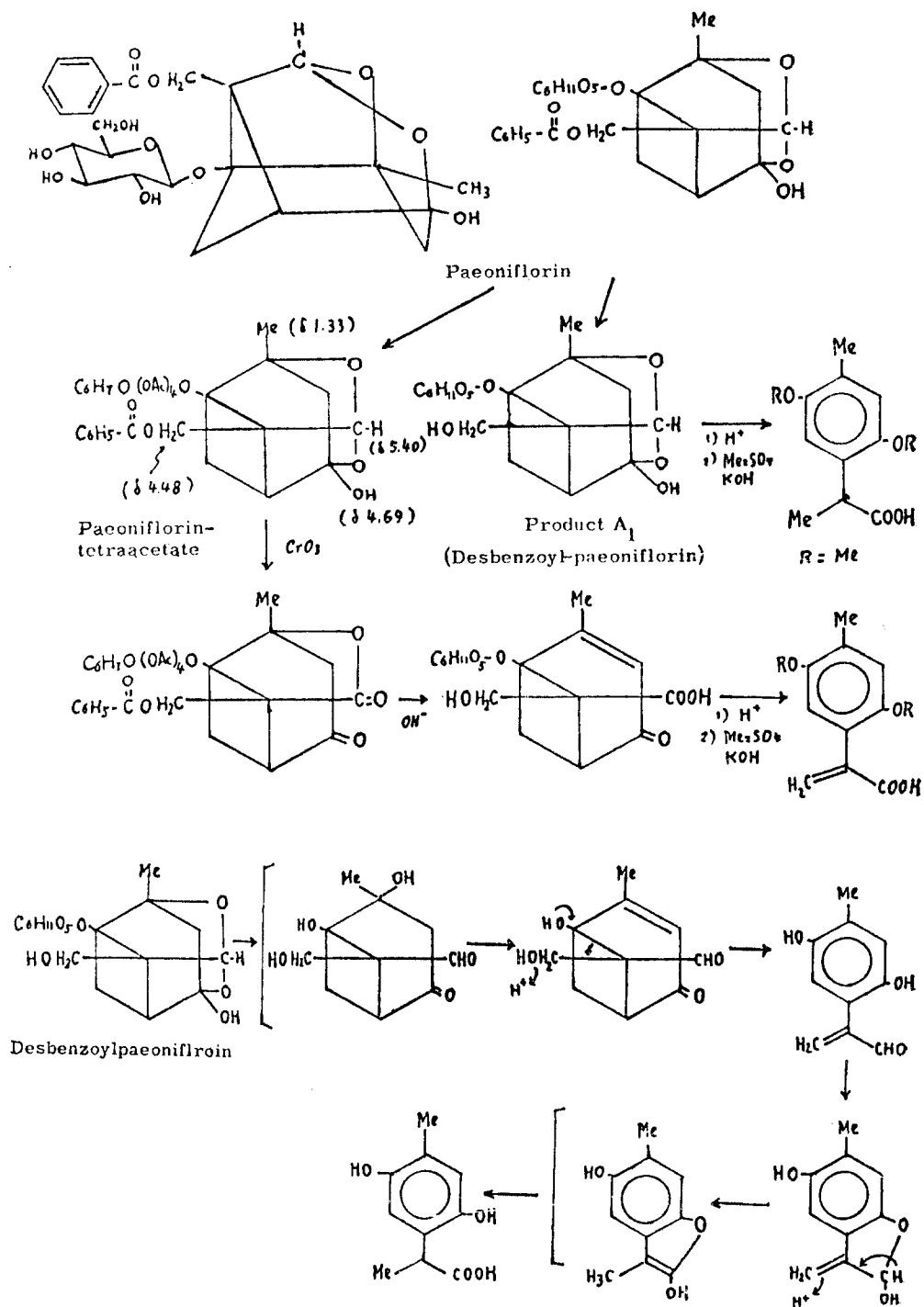
The pharmacological actions of paeoniflorin has extensively been studied by Takagi and Harada<sup>4)</sup> to show sedative, analgetic antiinflammatory actions. A synergetic action with FM 100, a fraction of Licorice extracts, has been demonstrated to agree the classical indication of "Shaoyao-Gancao-Tao".

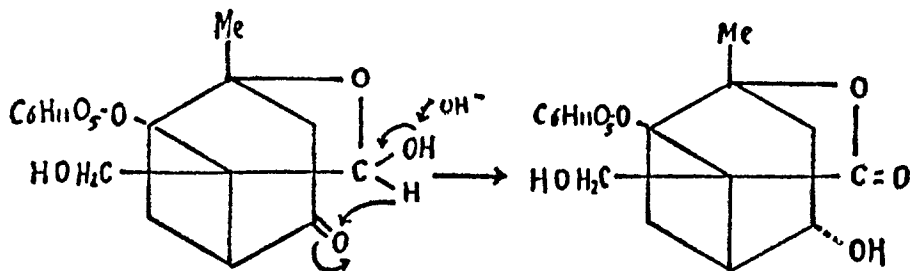
The structure of paeoniflorin has been studied by Aimi, Inaba, Watanabe(née Nakahara) and Shibata<sup>5)</sup> to establish an unique cage-like stereochemical structure belonged to monoterpene glucoside. Benzoic acid was found to be separated from paeoniflorin on alkaline hydrolysis. Paeoniflorin is very unstable against mineral acids to give a resinous substance and D-glucose. Desbenzoylpaeoniflorin (product A<sub>1</sub>) afforded an aglycone which was proved to be a hydroquinone derivative having a methyl and a  $\beta$ -propionic acid groupings at the 1,4-positions. However, neither aromatic ring nor carboxylic group exist in the original glucoside. Although all the ten carbon atoms of the originally assumed aglycone part of paeoniflorin are retained in the aromatic aglycone, a complex rearrangement should occur during the process of the acid hydrolysis.

On the basis of these results, the original compound, paeoniflorin, has been formulated as a monoterpene glucoside. The n.m.r. spectral evidence also agreed a hemiketal-hemiacetal ring system, a tertiary hydroxyl linked with D-glucosyl moiety, a benzoyl grouping linked with a primary alcoholic hydroxyl which is located at a quarternary carbon atom(AB type doublet of  $-\text{CH}_2-$ ).

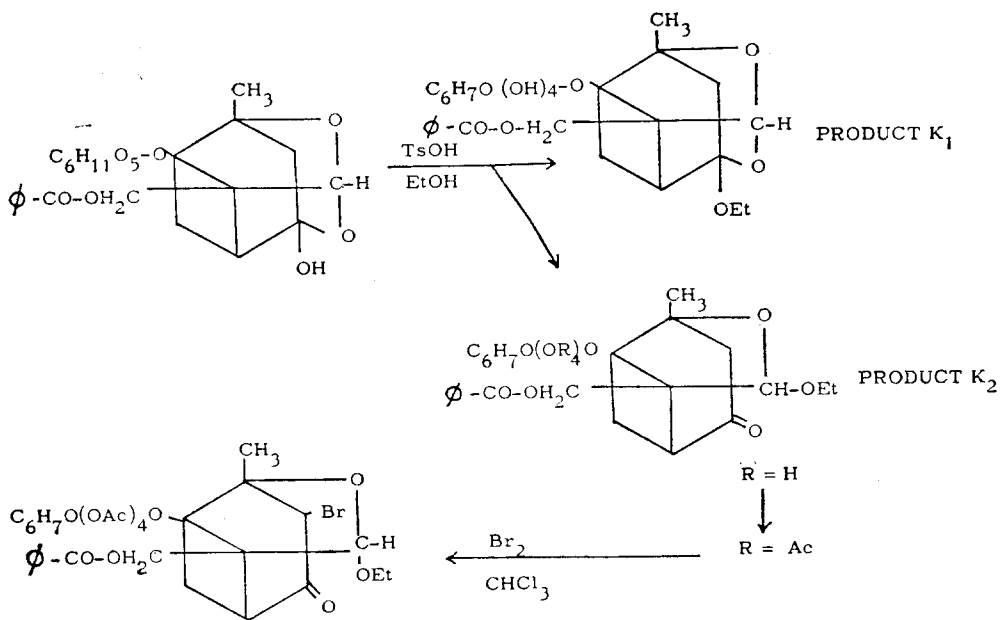
The formation of *dl*-2(2,5-dihydroxy-4-methyl) phenylpropionic acid from desbenzoylpaeoniflorin by the action of mineral acid can be explained by the following mechanism:

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## X-RAY CRYSTALLOGRAPHY OF PAEONIFLORIN DERIVATIVE



Orthorhombic (Recrystallized from MeOH)

Lattice Constant:  $a = 13.59 \text{ \AA}$ ,  $b = 21.74 \text{ \AA}$ ,  $c = 12.61 \text{ \AA}$ Space group:  $P_{2_1}2_12_1$   $D_m$   $1.354 \text{ g. cm}^{-3}$   $D_x$   $1.352 \text{ g. cm}^{-3}$   
(in  $\text{CCl}_4 + n\text{-Hexane}$ )CuK $\alpha$ 

R value: 0.11

The benzoyl grouping of paeoniflorin is removed by heating paeoniflorin in  $2N$   $Na_2CO_3$  leaving a product  $C_{16}H_{24}O_{10}$ . Their spectrum of this compound shows a  $\gamma$ -lactone absorption at  $1750\text{ cm}^{-1}$ . The following mechanism was postulated to the transformation.

The absolute configuration of paeoniflorin has finally been established by the X-ray crystallographical determination of the structure of a bromo derivative of the product  $K_2$  acetate, which was derived from paeoniflorin by the treatment with *p*-toluenesulphonic acid in ethanol.

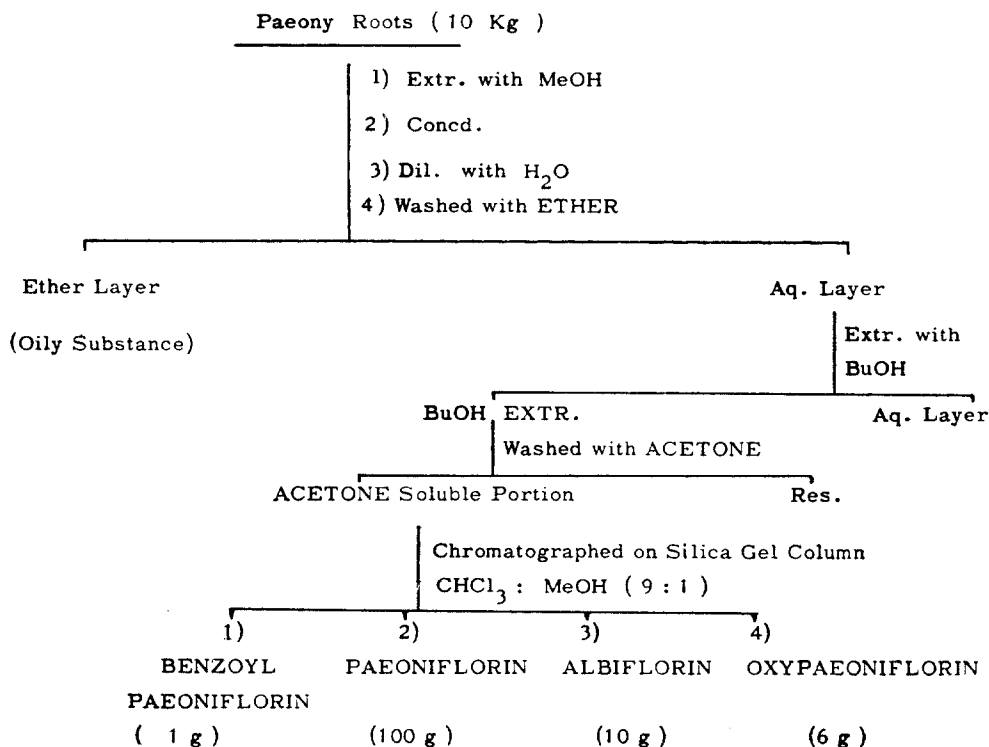
By the chromatographical treatment of the paeony root extracts, some minor components have been isolated. The structures of albiflorin, oxypaeoniflorin, and benzoylpaeoniflorin have been deduced on the basis of the established structure of paeoniflorin.<sup>6)7)</sup>

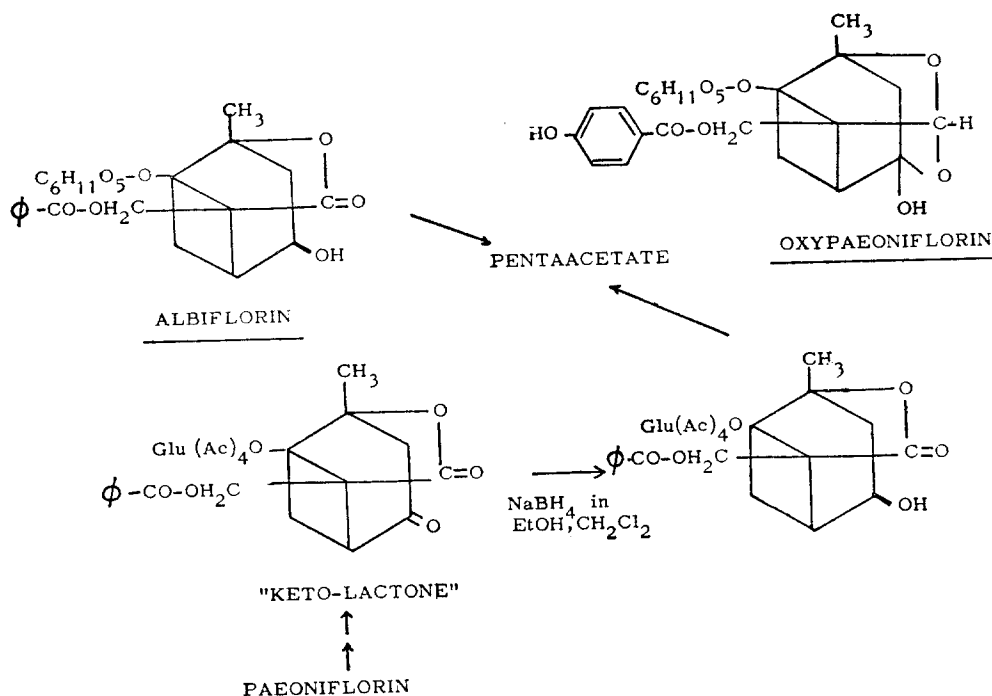
### Dammarane-type Triterpene Saponins and Sapogenins in Ginseng.

Ginseng (Rensun [Ninjin]) is a very famous and precious Chinese drug which is believed by East Asian people as a tonic drug, but the effective principle has long been obscure.

The first scientific study on Ginseng was reported by Garrique(1854)<sup>8)</sup> who obtained a saponin named panaquilon from American Ginseng (root of *Panax quinquefolium* C.A MEYER).

#### EXTRACTION OF PAEONY ROOTS





PANAX GINSENG C.A.MEYER (ROOT) (ARALIACEAE)

人參(麗參) 補肺陰以益五臟之津液, 安精神, 定魂魄止驚悸, 開心益智 明目 除邪氣  
(本草求原)

(Korean Ginseng) 主治心下痞堅痞鞭支結也, 旁治不食嘔吐喜唾心痛腹痛煩悸(藥徵), 吉益東洞  
PANAX QUINQUEFOLIUM L. (ROOT)

(花旗參) 補肺降火生津液除煩倦 虛而有火相宜(本草綱目拾遺)

(American Ginseng)

PANAX SANCHI HOO (PANAX QUINQUEFOLIUM var. NOTOGINSENG) (ROOT)

三七 散瘀定痛 治吐血衄血 血痢血崩爲金瘡杖瘡要藥(本草新義)

(San-Chi Ginseng) in South China

PANAX JAPONICUS C.A. MEYER (RHIZOME) (PANAX PSEUDO-GINSENG subsp.

竹節人參(土參 東洋參) in Japan JAPONICUS (MEYER) HARA)

PANAX PSEUDO-GINSENG (WALLICH)

In East Himalaya (Nepal to Bhutan)

Subsp. Pseudo-Ginseng

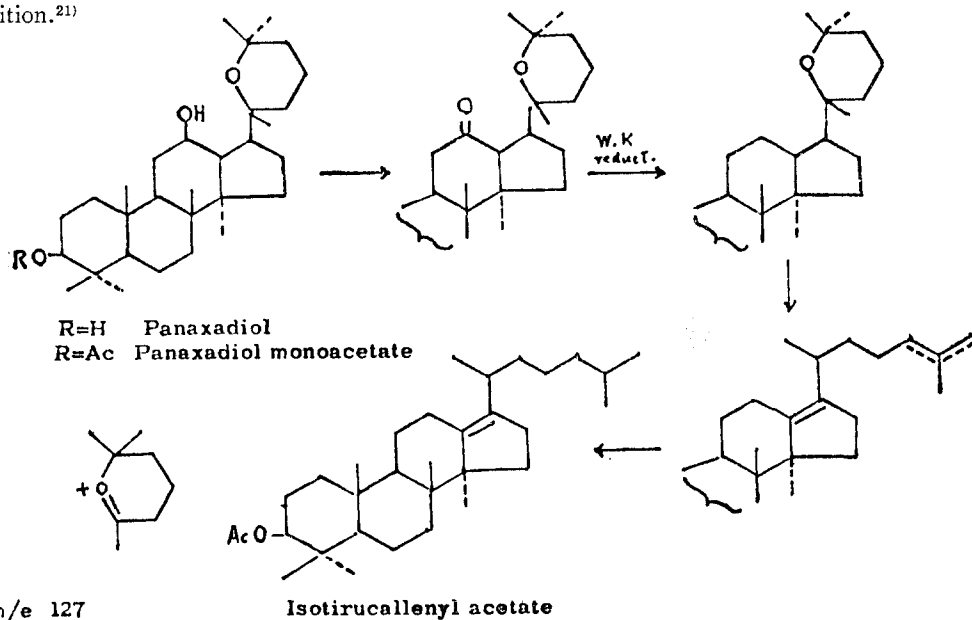
Subsp. Himalaicus

var. Angustifolius

var. Bipinnatifidus

Some Japanese organic chemists such as Asahina (1906)<sup>9)</sup>, Kondo (1915)<sup>10)</sup> and Kotake (1930)<sup>11)</sup> and their co-workers reported the isolation of saponins, prosapogenins, and sapogenins, but the chemical natures of these principles were not fully investigated.

Recently, Ginseng has attracted general interest of scientists in Europe, Russia and Far East. Hörhammer *et al.* (1961)<sup>12)</sup>, Wagner-Jauregg *et al.* (1962)<sup>13)</sup>, Elyakov, Kochetkov and their co-workers (1962)<sup>14)</sup> isolated saponins and sapogenins, while Lin (1961)<sup>15)</sup> reported ginsengenin as the sapogenin of ginseng. The pharmacological and clinical investigations were also reported by Esdorn (1958)<sup>16)</sup>, Schultz (1958, 1959)<sup>17)</sup>, and Brekhman (1957)<sup>18)</sup>. According to the extensive work of Brekhman<sup>19)</sup> ginseng extracts show a stimulation action. In 1962, Fujita, Itokawa and Shibata<sup>20)</sup> reported the isolation of a sapogenin, named panaxadiol,  $C_{30}H_{50}O_3$ , m.p. 250°,  $[\alpha]_D +1.0$ , by the acid hydrolysis of saponin fraction of ginseng, the roots of cultivated *Panax ginseng* C.A. MEYER. Panaxadiol was proved under a correlation with isotirucallenol and by the mass spectrum indicating a parent peak at  $m/e$  127 to be a tetracyclic triterpene having a trimethyltetrahydropyane ring at the 17-position.<sup>21)</sup>



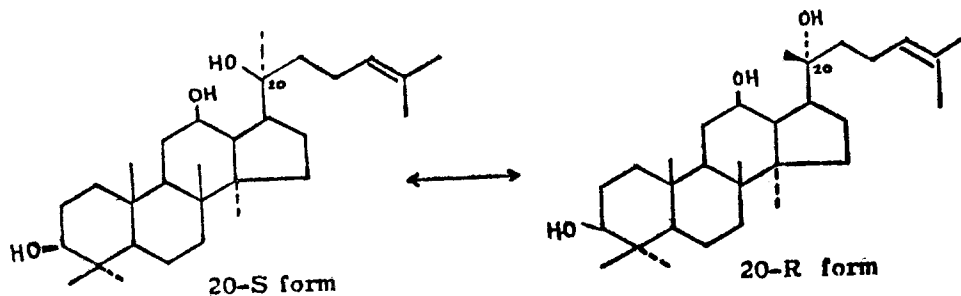
Thereafter it was proved that panaxadiol is an artifact which is formed by the cyclisation of side chain during the process of acid hydrolysis of saponins (ginsenosides  $Rx^*$  ( $x = a, b_1, b_2, c, d, e, f$ )). A chlor-containing sapogenin which was obtained by acid hydrolysis of ginsenoside  $Rb_1, b_2, c$  fraction using conc. HCl at room temperature was treated with tertiary butoxide to yield protopanaxadiol having an open side chain.<sup>22)</sup> The stereochemical correlation of dihydroprotopanaxadiol with dammaradiol I was established by elimination

\* Kochetkov, Elyakov and their coworkers reported the isolation of six saponins, named panaxosides A, B,<sup>14)</sup> C, D, E, and F, from Ginseng.

12 $\beta$ -hydroxyl via 12-keto compound which was reduced by Wolff-Kishner reduction.<sup>23)</sup>

The chirality at C<sub>(20)</sub> of protopanaxadiol was finally established to be S, which was obtained by careful treatment of ginsenosides *Rb*<sub>1</sub>, *Rb*<sub>2</sub> and *Rc* with sodium metaperiodate followed by sodium borohydride and 2*N* H<sub>2</sub>SO<sub>4</sub> at room temperature.

Thus the sapogenin named S-protopanaxadiol was formulated 3-epi-betulafolienetriol (= 12 $\beta$ -hydroxydammarenediol- II). The S-configuration at C<sub>(20)</sub> is very readily epimerized into R to form an equilibrium mixture of epimers.<sup>24,25)</sup>



The R-configuration at C<sub>(20)</sub> of R-protopanaxadiol was established by the degradation of panaxadiol into (-)methyl cinate which was identified with (-) R-methyl cinate prepared from (-) R-linalool by a few step reactions retaining the original chirality.<sup>26)</sup> By this experiment, the absolute configuration of C<sub>(20)</sub> dammarenediol I<sup>27)</sup> was established to be R, while that of dammarenediol II<sup>26)</sup> and betulafolienetriol<sup>28)</sup> is S. Ginsenoside *Rg*<sub>1</sub>, m.p. 194-196°, [ $\alpha$ ]<sub>D</sub><sup>19-50</sup> +32° (pyridine), was purified through its crystalline acetate, C<sub>42</sub>H<sub>72</sub>O<sub>12</sub> (C<sub>2</sub>H<sub>2</sub>O)<sub>10</sub>, m.p. 242-243°, [ $\alpha$ ]<sub>D</sub><sup>24-50</sup> +7.0° (chloroform).

On acid hydrolysis, it afforded D-glucose and panaxatriol, C<sub>30</sub>H<sub>52</sub>O<sub>4</sub>, m.p. 238°, [ $\alpha$ ]<sub>D</sub><sup>22</sup> +14.2° (chloroform), whose structure was established to be 6 $\alpha$ -hydroxy-20R-panaxatriol.<sup>29)</sup> On the analogy of the genuine sapogenin of ginsenosides *Rb*<sub>1</sub>, *b*<sub>2</sub>, *c*, the genuine sapogenin of ginsenoside *Rg*<sub>1</sub> should be named S-protopanaxatriol being formulated 6 $\alpha$ -12 $\beta$ -dihydroxydammarenediol II. This was confirmed by the following reactions: On oxidation panaxatriol yielded a diketonic compound ( $\nu$  C=O 1720cm<sup>-1</sup>: Six-membered ring C=O) which gave only a monosemicarbazone indicating that one of the carbonyls is hindered. The Wolff-Kishner reduction of the diketonic compound afforded a monoketonic compound, C<sub>30</sub>H<sub>50</sub>O<sub>3</sub>, m.p. 199° ( $\nu$  C=O 1714cm<sup>-1</sup>) by the reduction of a less hindered ketone. The n.m.r. spectrum of this compound revealed, AB-type doublet at  $\delta$ 2.60 and 1.80 (1H each) and a singlet at  $\delta$ 2.19 (1H). These signals disappeared when the monoketonic compound was deuterized indicating that three active protons would exist at the  $\alpha, \alpha'$ -positions of the carbonyl to

form a system of  $\begin{array}{cccc} & & \text{H} & \\ & & | & \\ - & \text{C} & - & \text{C} & - & \text{C} & - & \text{C} & - \\ & | & & | & & | & & | & \\ & \text{H} & & \text{O} & & \text{H} & & & \end{array}$ , which can only be represented by the carbonyl at

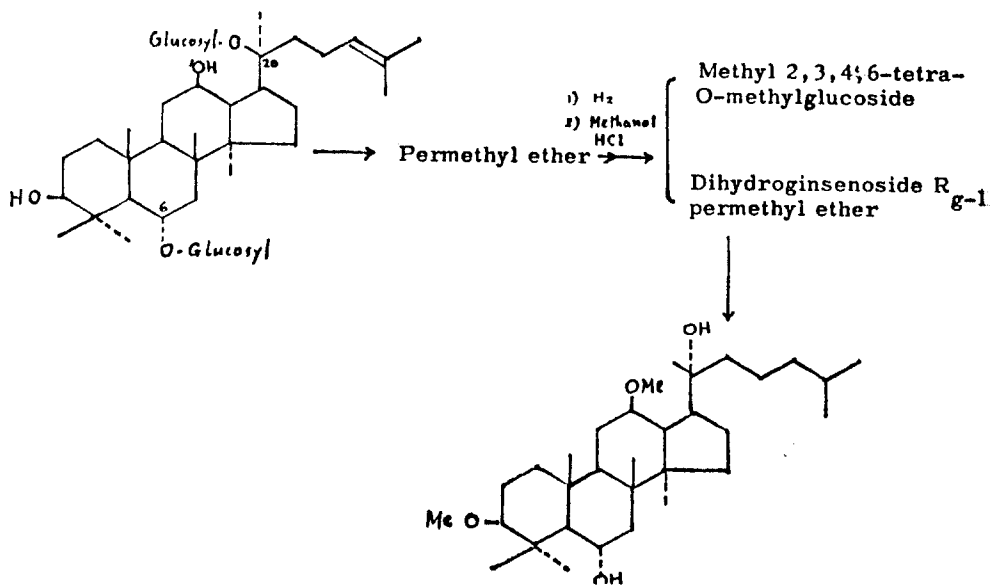
the 6-position of the ring B.

The hydroxyl at the 6-position of panaxatriol shows a resistance for acetylation to indi-

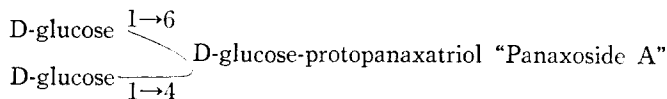


cate the  $\alpha$ -(equatorial) conformation in comparison with the similar nature of the 6- $\alpha$  hydroxyl of zeorin.

Ginsenoside Rg<sub>1</sub> contains two glucosyl moieties and, on methylation with sodium hydride in dimethylsulfoxide and methyl iodide afforded a permethyl ether whose dihydro derivative yielded on methanolysis methyl 2, 3, 4, 6-tetra-O-methylglucoside and 3, 12-O-dimethyl-protopanaxatriol. Therefore, two glucosyl moieties are attached to 6 $\alpha$  and 20-hydroxyls.<sup>30)</sup>



Ginsenoside Rg<sub>1</sub> was proved to be identical with panaxoside A by the comparison of authentic samples for which we are grateful to Prof. Elyakov, Institute of Biologically Active Substances, USSR Academy of Science. However Elyakov, Strigina and Kochetkov<sup>31)</sup> proposed the structure of panaxoside A which is inconsistent with our result obtained in the study of ginsenoside Rg<sub>1</sub>.



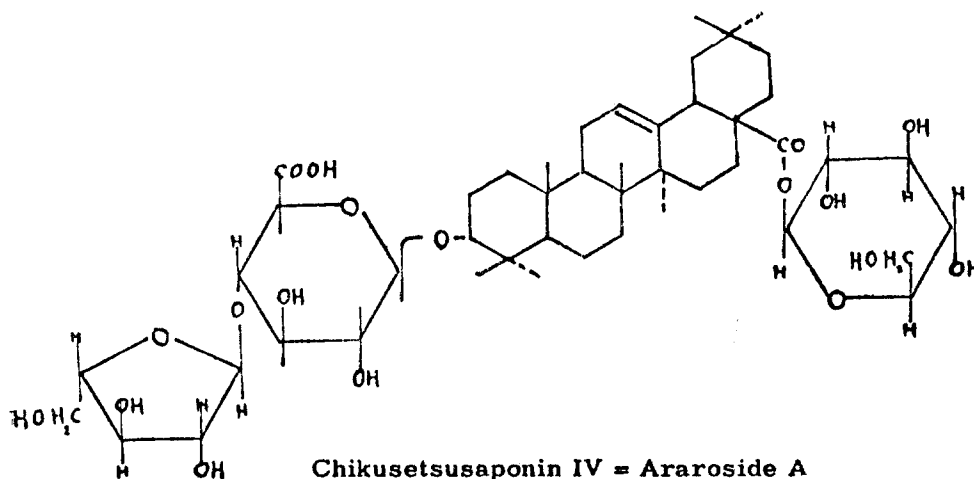
The saponins of Ginseng show no haemolytic action, and the toxicity is very low. Takagi et al.<sup>32)</sup> studied the pharmacological action of our sample of Ginsengsaponins and found that ginsenoside Rb-rich fraction revealed a sedative action to the animal, which was demonstrated by decreasing of avoiding movement for the conditioned reaction using Schuttle box, and pole climbing test. On the other hand, the ginsenoside Rg-rich fraction showed increasing of locomotive action of mice suggesting a stimulative effect to the central nervous system. Russian workers<sup>17, 33)</sup> reported also the stimulative and antifatigue action of Ginseng extracts. They recognized Ginseng saponins as a drug increasing nonspecific

resistance.<sup>34)</sup> It is worthwhile to note that the pharmacological actions of ginsenosides or panaxosides agree in some extent the old indications about Ginseng.

The roots or rhizomes of some other *PANAX* species are also used as Chinese drugs. The root of *Panax quinquefolium* C.A. MEYER which is exported from U.S.A. known as American Ginseng in Chinese drug market is employed for almost the same purpose with Korean Ginseng. San-Chi Ginseng, the root of *Panax san-chi* Hoo (or *Panax quinquefolium* var. *notoginseng*) which is produced in South China is employed by Chinese people for haemorrhagic diseases.

The rhizome of *Panax pseudo-ginseng* subsp. *japonicus* (= *Panax japonicus*) widely growing in Japan is used as a substitute for Korean Ginseng. The saponin fractions of these drugs gave different patterns of thin layer chromatograms.<sup>35)</sup> It was known by the earlier investigations that the rhizome of *Panax pseudo-ginseng* subsp. *japonicus* contains saponins whose genin is oleanolic acid. Fujita, Itokawa and Shibata isolated panaxadiol from the hydrolysate of saponins of this drug, and Shibata, Ando *et al.*<sup>36)</sup> obtained panaxadiol from the saponin of ground part of this plant. Shoji and his collaborators<sup>37,38)</sup> isolated three crystalline saponins of rhizome of *Panax pseudo-ginseng* subsp. *japonicus* and named Chikusetsu saponins III, IV and V. The compositions of these saponins were as follows: Chikusetsusaponin III = protopanaxadiol, glucose and xylose; chikusetsusaponin IV = oleanolic acid, arabinose, glucose, and glucuronic acid; chikusetsusaponin V = oleanolic acid, glucose, and glucuronic acid.

Chikusetsusaponin IV,  $C_{47}H_{74}O_{18} \cdot 4H_2O$ , m.p.  $235^\circ$  (decompl),  $[\alpha]_D^{19} -9.7^\circ$  (pyridine), was studied to formulate the same structure proposed by Kochetkov *et al.*<sup>39)</sup> for araloside A, a saponin of *Aralia manschurica* Rupr. et Max. (Araliaceae), a tonic in Chinese medicine. The direct comparison of both samples has not been made.



In closing this lecture, I would like to emphasize that the new compounds isolated from

Paeony and Ginseng roots exhibit pronounced pharmacological activities in animal experiments, which reveal a good agreement with the symptomatic actions of those drugs described in the old literatures of traditional Chinese Medicine.

Similar results have also been obtained in our studies on some other Chinese drugs, such as the roots of *Bupleurum*, *Platycodon*, *Aralia*, *Pueraria* and *Periploca*. I believe that this kind of work could provide not only the scientific evidences for the old medicine but also could be developed to the preparation of new remedies which might be effective for some diseases without the fear of unfavourable side effects.

**Acknowledgements:** The original works which have been elucidated in this lecture were carried out under the collaboration of my coworkers whose names are listed below. I wish to express my warm thanks to them.

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