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Biochemistry of Ginseng Constituents and Plant Triterpenes

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人蔘成分과 植物 Triterpene의 生化學

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Introduction

Korean ginseng (高麗人蔘) roots are products of the perennial herb, *Panax ginseng* C. A. MEYER, the economically important member of the family *Araliaceae*, which is native to Korea and Manchuria, and is cultivated for commercial purposes in Korea, Japan, Manchuria and Russia. The ginseng root is fleshy, light yellow brown, spindle-shaped and often divided so that it may resemble a human form. It has a unique odor, and a bitter then sweetish taste. The stem is single, straight and approximately 60 cm in height with 3~5 long-stalked leaflets. The flower is small, yellowish green, and on a single terminal umbel. The fruit is bright red, with normally two seeds laterally compressed. Ginseng is normally collected after 5~7 years cultivation.

American ginseng (*Panax quinquefolium* L., 洋蔘, 花旗人蔘 or 廣東人蔘) is indigenous and cultivated in North America; *P. pseudo-ginseng* WALL. in the Southern part of China; *chikusetsu-ninjin* (*P. japonicus* C. A. MEYER, 竹節人蔘) is indigenous in Japan. They have been substituted for Korean ginseng for a long time. Commercial ginseng-*sanchi* or *sanchi* (人蔘三七) is most often considered to be *P. pseudo-ginseng* or *Gynura segetum* (LOUR.) MERR., but the actual species is precisely unknown[1,2].

For at least two thousand years ginseng is reported to have contributed considerably to the health of the body and mind of the Oriental. Its therapeutic virtue is quite general. This is apparent even in its genus name, *Panax*, which is derived from the Greek *panakos* meaning a cure-all. The first recorded pharmacological actions of ginseng appeared in *"Shen-Nüng*'s

Materia Medica" (神農本草經) in about 196 A.D. and is, "A tonic to the five viscera, quieting the spirits, establishing the soul, allaying fear, expelling evil effluvia, brightening the eye, opening up the heart, benefiting the understanding, and if taken for some time it will invigorate the body and prolong life" (補五臟 安精神 安魂魄 止驚悸 除邪氣 明目 開心 益智 久服輕身延年)[3]. The Oriental people traditionally use large quantities of ginseng roots and extracts for either geriatrics, tonic, stomachic, or aphrodisiac effects. The Russian BREKHMAN and DARDYMOV[4,5] reported the plant to possess anabolic, adaptogenic, anti-stress, hypothermic, central nervous system stimulation, radio-protective, antibiotic, minor hyperglycemic and anticancer activity. The Korean OH *et al.*[6], HONG *et al.*[7] and SUH and KIM[8] have reported the saponin fractions in mice to potentiate nembutal hypnosis, to retard the onset-time of cocaine induced convulsions, to reduce body temperature, and to enhance the process of sexual behavior. The Japanese TAKAGI *et al.*[9,10] essentially confirmed in mice and rats the results of Korean pharmacologists, and also observed the crude ginseng saponin fraction to have an over-all tranquilizing effect. A purified ginseng saponin produced histamine-like, cholinergic, and papaverine-like effects. Ginseng saponin has been considered an active principle for ginseng's most therapeutic properties. Other than saponins, ginseng plants contained many substances phytosterols, steroids, oils, acids, carbohydrates, flavonoids, nitrogen-containing compounds, vitamins and inorganics. Some chemical studies[11~38] during 1854~1949 have also been summarized in Table I. A few of them are valuable, but most of them unvalued. From chemical points of view, a brief plant triterpene chemistry as well as the biosynthesis of plant triterpenes is reviewed so that one can understand the ginseng saponin chemistry. The review on the biosynthesis of plant triterpenes may be quite helpful for future biosynthetic studies when a chemist or a pharmacologist needs labeled compounds from ginseng plants.

Plant Triterpenes

a. Definition

Triterpenes represent an extremely diversified family of plant constituents. The triterpenes are C_{30} compounds. Very often triterpenes occur as glycosides, which are called saponins. Saponins exhibit a persistent froth when shaken with water and, in addition, will hemolyze a suspension of red blood cells. The sugar and acid portion of the saponin molecule is principally responsible for the hemolytic properties[39], and non-hemolytic sapogenins exist[40]. Saponins usually exist in plants in the form of glycosides, and the removal of its attached sugars by hydrolysis yields the genin (aglycone).

Reviews have been published on the chemistry of triterpenoid saponins[41~44], cardenolides[45,46] and bufadienolides[46].

b. Chemical Classes

Triterpenoid sapogenins and related compounds may be classified according to the mode of squalene cyclization (Fig. 1): A. Dammarane type[47,48], B. Cycloar-

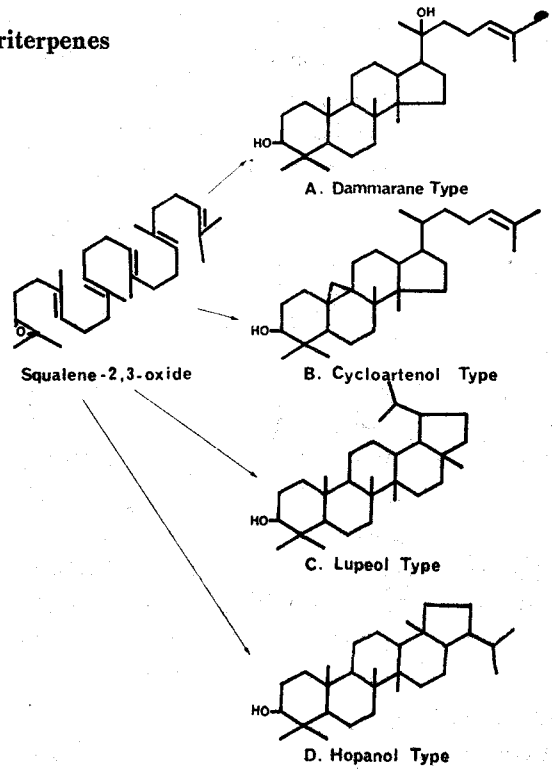


Fig. 1. Cyclization of Squalene: Types of Plant Triterpenes.

Table I. Chemical Investigations during 1850~1949.

A. *Panax ginseng*

Date	Substances Investigated	References
1890	Panaquilon	11)
1905	Panaquilon ($C_{32}H_{56}O_4$)	12)
1908	Panaxapogenin, ($C_{23}H_{38}O_{10}$, m.p. 190° C)	12)
1915	Al, Fe, Mn, K, P_2O_5, SiO_2, panacen, phytosterol (m.p. 133° C), saponin (m.p. 220° C) and prosapogenin (sapogenin+D-glucose)	13)
1917	Oil (b.p. 105~110° C/15 mmHg)	14)
1918	Stearic, palmitic and linoleic acid, phytosterol (m.p. 133~4° C) and volatile oil ($(C_5H_8)_x$, b.p. 247° C)	15)
1920	Panaquilon	12)
1920	Saponin (mol. wt. 876, glucose+pentose), panaxsapogenol ($C_{27}H_{48}O_3$, 3 OH, one ethylene, m.p. 242.5° C) and its isomer (m.p. 130° C)	16)
1921	Amylase	17)
1926	Ginsenin (saponin)	18)
1927	Panaxasapogenin (m.p. 303~4° C)	19)
1928	Amylase and phenolase	20)
1930	Panacen, panaxic acid, phytosterin and saponin	21,22)
1931	Saponin ($C_{38}H_{66}O_{12}$, m.p. 208~210° C), and $C_{20}H_{53}O_3Cl$ (m.p. 209° C)	23)
1931	S, P, Fe, Al, Ca, Mg, Si and Mn	24)
1932	Panaxigenin chloride ($C_{30}H_{53}O_3Cl$), anhydropanaxigenin ($C_{30}H_{52}O_3$, m.p. 256~8° C), and acetyl panaxigenin (m.p. 111~2° C)	25)
1933	S and Vitamin B	26)
1937	Saponin	27)
1940	Phytosterol (m.p. 134~146° C)	28)
	B. *Panax quinquefolium*	
1854	Panaquilon ($C_{24}H_{25}O_{18}$) and panacon ($C_{22}H_{19}O_8$)	29)
1921	Phytosterol (m.p. 132~4° C), saponin ($(C_8H_{12}O_5)_x$, m.p. 170~2° C) and sapogenin ($(C_{21}H_{32}O_5)_x$, m.p. 188~191° C)	30)
1930	Panacen, panaxic acid, phytosterin and saponin	21,22)
1939	Oil	31)
	C. *Panax japonicus*	
1904	Saponin (m.p. 150° C)	12)
1923	Saponin and sapogenin	32)
1929	Saponin, prosapogenin ($C_{48}H_{76}O_{15}$, m.p. 222~4° C), sapogenin+glucose+glucuronic acid	33)
1930	Sapogenin I (mol. wt. 451~475, m.p. 304° C)	34)
1930	Sapogenin ($C_{35}H_{55}(OH)_2COOH$)	35)
1932	Panax sapogenin (oleanolic acid, $C_{31}H_{50}O_3$, m.p. 305° C)	36)
	D. *Panax bipinnatifidum*	
1937	Arasaponin A ($C_{30}H_{52}O_{10}$, m.p. 195~210° C), arasapogenin A (m.p. 244° C and 252° C)+glucose, arasaponin B ($C_{23}H_{38}O_{10}$, m.p. 190~200° C) and arasapogenin B+glucose	37)
1941	Arasapogenin B ($(C_{29}H_{52})_3$, m.p. 247° C)+glucose	38)

tenol type[49,50], C. Lupeol type[51~53], and D. Hopanol type[54].

Among the sugar and acid hydrolyzed components [41,43] from saponins reported are glucose, arabinose, galactose, fructose, fucose, xylose, rhamnose, glucuronic acid, galacturonic acid, 6-deoxy sugars, formic acid, acetic acid, *n*-butyric acid, *iso*-butyric acid, *iso*-valeric acid, methyl butyric acid, angelic acid, tiglic acid, ethyl machaerinate, benzoic acid, *o*-monomethylaminobenzoic acid, echinocystic acid, tenuifolic acid, glucuronolactone, 1,3-dimethyl acrylic acid, cinnamic acid and ferulic acid. The linkage of sugars[45] to genins in the cardiac glycosides follows the general pattern: genin-(rare sugar)$_m$-(glucose)$_n$.

c. Plant Distribution

Over 6,000 plants representing 208 families and 1,397 genera were screened for steroidal saponins by the U.S. Department of Agriculture. They observed that steroidal saponins were present often in monocots belonging to the *Liliaceae*, *Amaryllidaceae*, and *Dioscoreaceae* families; and in the *Scrophulariaceae* and *Solanaceae* families[55,56]. The triterpenoid saponins are present in a very large number of species and often characterize whole families (*e.g.* in *Primulaceae*) or intrafamiliar entities (*e.g.* in *Berberidaceae* and *Ranunculaceae*)[50].

In many plants, triterpenes such as friedelin, friedelinol, oleanolic acid and ursolic acid were isolated in high concentrations from the cork and cuticular waxes. Triterpenes have not yet been found in the waxes of *Magnoliales* and *Ranunculales*. All triterpenes from the ferns and lycopenes can arise from squalene without rearrangements (hopane, serratane and dammarane). Morphologically and anatomically primitive plants contain simpler triterpenes, and an evolutionally pattern for triterpenes has become recognizable[57].

The distribution of dammarane-type triterpenes such as ginseng panaxadiol and panaxatriol appears restricted to the genera *Panax* in the *Araliaceae* family. However, many other dammarane-type triterpenoid sapogenins are present in the genera *Bacopa*[58,59], *Alnus*[60], *Betula*[61], *Colletia*[62], *Dipteryx*[63], *Pouteria*[64], and *Mammillaria* (a cactus)[65]. The oleanane-type triterpenes (*e.g.* oleanolic acid and hederagenin) are found principally in the genera *Aralia*[66], *Eleutherococcus*[67], *Hedera*[68], *Kalopanax*[69], and to some extent in *Panax*[70,71].

d. Plant Physiology

Application of saponin solutions stimulated the development of shoots and roots in *Begonia*[72], induced tumors in *Hedera helix*[73], and influenced chlorophyll synthesis in *Euonymus japonicus*[74]. KELLER[75] has found that digitonin and solanine effect the leaf movements of *Phaseolus multiflorus*. Saponins have also been found to inhibit root growth in tomato[76], garden cress, and barley[77].

Germination is promoted by saponins in peas[78], corn[79], tomato[76], and other seeds[80]. Saponins increase the growth rate of excised wheat embryos[81,82]. Digitonin and tomatine as well as some other genins have growth-regulating activity in the *Avena* coleoptile[83].

Ginseng Triterpenes

a. Phytosterols and Oils

Ether-soluble extracts have been reported for American ginseng roots (0.60 %), the above-ground parts (1.42 %), callus tissues (0.92 %) and Korean ginseng roots (0.82 %)[84].

GSTIRNER *et al.*[85] and WROBEL *et al.*[86] isolated β-sitosterol (0.50 %) from *P. ginseng* roots. LIN[87] isolated stigmasterol (0.05 %) from Manchurian *P. ginseng* fiber-roots.

KIM and STABA[88] reported a sterol fraction which was proved to be β-sitosterol and stigmasterol present in the American ginseng root ether extracts. TAKAHASHI *et al.*[89~91] extracted stearic acid from the acid fraction and daucosterin (0.03 %), β-sitosterol (0.01 %), β-elemene and panaxynol (0.04 %) from the neutral fractions of *P. ginseng* root ether extracts. ANGUELAKOVA *et al.*[92~94] identified estriol and estrone by thin-layer chromatography in the fat-soluble extracts of

P. ginseng roots. MANKI and TOMIMORI[95] isolated nanocosane, 1-octacosanol and β-sitosterol from the non-volatile fraction of the ether extracts of *P. ginseng* leaves, stems, and flowers parts. TAKAHASHI and YOSHIKURA[96~98] proved the structure of panaxynol to be 1,9-*cis*-heptadecadiene-4,6-diyn-3-ol. WROBEL *et al.*[86] isolated 1-heptadecaene-4,6-diyn-3,8-diol in the petroleum ether extract, and 1-heptadecaene-4,6-diyn-3,8,10-triol and 3-hydroxy-5-methyl-γ-pyrone from *P. ginseng* ether extracts.

YOSHIKURA and HIROSE[99] identified by gas-liquid chromatography and mass spectrometry germacrene-D, β-santalene and β-farnesene in the volatile oil (0.16 %) of *P. japonicus* rhizomes.

b. Saponins

Ginseng roots contain 8.6 % ethanolic and 2 % aqueous extracts[85]. LIN[87] obtained 3.8 % crude saponins from methanolic extracts of Manchurian *P. ginseng* fiber-roots. FUJITA *et al.*[100] reported *P. ginseng* methanolic extracts to contain 4 % crude saponins. MANKI and TOMIMORI[95] isolated 8~10 % crude saponins from *P. ginseng* leaves and stems, and 6~7 % from its flowers. ANDO *et al.*[71] reported crude saponin content of *P. ginseng* roots (2~4 %), fiber-roots (8~13 %), 1~2 year-old roots (3~4 %), American ginseng roots (6~7 %), ginseng-*sanchi* (12 %) and *P. japonicus* rhizomes (8 %). KIM and STABA[88] reported that the average concentration (% plant dry weight) of semi-purified saponins present in American ginseng plants was 13.8 % (leaves), 9.0 % (fruits), 7.9 % (stems) and 6.3 % (roots), and of purified saponins 3.1 % (roots).

The Japanese SHIBATA *et al.*[101~103] demonstrated that thin-layer chromatograms of methanolic ginseng extracts contained many saponins which they designated as ginsenosides Ro, Ra, Rb_1 (0.47 %), Rb_2 (0.21 %), Rc (0.26 %), Rd (0.15 %), Re (0.15 %), Rf (0.05 %), Rg_1 (0.17 %), Rg_2 (0.01 %), Rg_3, Rh_1 and Rh_2. In contrast with this result, the Russian ELYAKOV *et al.*[104~106]

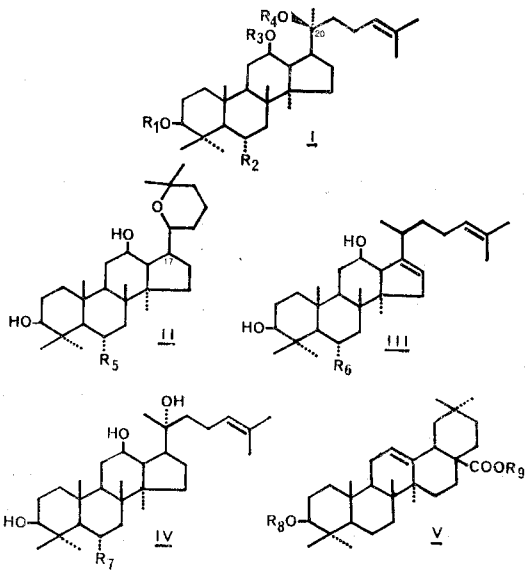


Fig. 2. Ginseng Saponins and Sapogenins.

Ia: **Ginsenoside Rb_1;** R_1=−β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside, R_2=R_3=H, R_4=−β-D-glucopyranosyl-(1→6)-β-D-glucopyranoside. *Ib:* **Ginsenoside Rb_2;** R_1=−β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside, R_2=R_3=H, R_4=−α-L-arabinopyranosyl-(1→6)-β-D-glucopyranoside. *Ic:* **Ginsenoside Rc;** R_1=−β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside, R_2=R_3=H, R_4=−α-L-arabinofuranosyl-(1→6)-β-D-glucopyranoside. *Id:* **Ginsenoside Rd;** R_1=−β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside, R_2=R_3=H, R_4=−β-D-glucopyranoside. *Ie:* **Ginsenoside Re;** R_1=H, R_2=O-β-D-rhamnopyranosyl-(1→2)-β-D-glucopyranoside, R_3=H, R_4=-β-D-glucopyranoside. *If:* **Ginsenoside Rf;** R_1=R_3=R_4=H, R_2=-β-D glucopyranosyl-(1→2)-β-D-glucopyranoside. *Ig:* **Ginsenoside Rg_1;** R_1=R_3=H, R_2=-O-β-D-glucopyranoside, R_4=-β-D-glucopyranoside. *Ih:* **Ginsenoside Rg_2;** R_1=R_3=R_4=H, R_2=O-β-D-rhamopyranosyl-(1→2)-β-D-glucopyranoside. *Ii:* **Prosapogenin;** R_1=-β-D-glucopyranosyl-β-D-glucopyranoside, R_2=R_3=R_4=H. *Ij:* **Chikusetsu-saponin III;** R_1=[β-D-glucopyranosyl-(1→2)]-[β-D-xylopyranosyl-(1→6)]-D-glucopyranoside, R_2=R_3=R_4=H. *Ik:* **20S-Protopanaxadiol;** R_1=R_2=R_3=R_4=H. *Il:* **20S-Protopanaxatriol;** R_1=R_3=R_4=H, R_2=OH. *Im:* **Panaxapogenol;** R_1=R_2=R_3=H, R_4=-β-D-glucopyranoside. *IIa:* **Panaxadiol;** R_5=H. *IIb:* **Panaxatriol;** R_5=OH. *IIIa:* R_6=H or OH. *IVa:* **20R-Protopanaxadiol;** R_7=H. *IVb:* **20R-Protopanaxatriol;** R_7=OH. *Va:* **Chikusetsu-saponin VI;** R_8=-β-D-arabinofuranosyl-(1→2)-β-D-glucopyranoside, R_8=-1β-D-glucpyranoside. *Vb:* **Ginsenoside Ro (Chikusetsu-saponin V);** R_8=-β-D-glucopyranosyl-(1→2)-β-D-glucuronate, R_9=-1β-D-glucopyranoside. *Vc:* **Compound O;** R_8=H, R_9=-β-D-glucopyranoside. *Vd:* **Oleanolic acid;** R_8=R_9=H.

isolated six saponins designated as panaxosides A, B, C, D, E and F according to their increasing polarity. The Japanese and Russian results are not fully comparable by one-dimensional thin-layer chromatography. However, the physical and chemical properties of ginsenosides Rg_1 (Fig. 2, *Ig*) and its decaacetate were found to be identical with those of panaxoside A[106~108]. The structures of ginsenosides R_0 (Fig. 2, *Vb*), Rb_1 (Fig. 2, *Ia*), Rb_2 (Fig. 2, *Ib*), Rc (Fig. 2, *Ic*), Rd (Fig. 2, *Id*), *Re* (Fig. 2, *Ie*), Rg_1 (Fig. 2, *Ig*) and *Rg_2* (Fig. 2, *Ih*) have been identified[106~107,109].

The Russian results[104,110~112] are summarized as follows: panaxosides A (m.p. 176~8° C, 3 glucose), B (m.p. 182~5° C, 2 glucose and 1 rhamnose), B′ (m.p. 175~7° C, 3 glucose), C (m.p. 185~7° C, 2 glucose and 1 rhamnose), D (m.p. 157~60° C, 5 glucose), E (m.p. 185~7° C, 4 glucose and 1 rhamnose) and F (m.p. 185~7° C, 6 glucose). These ginseng saponins were isolated by gradient column chromatography from Sephadex A-25, G-25, G-50[113,114], Bio-gel[115], cellulose[116], silica gel and/or alumina[109,117,118].

Table II. Suggested Similarity of Panaquilins, Ginsenosides and Panaxosides Isolated from American and Korean Ginseng Roots.

American Roots	Korean Roots		
Panaquilin*	Ginsenoside*	Ginsenoside**	Panaxoside***
—	—	Ro	—
—	Ra	Ra	F
B	Rb_1, Rb_2	Rb_1, Rb_2	E
C	Rc	Rc	D
D	Rd	Rd	—
E-1	—	—	—
E-2	Re_2	Rd	C
E-3	Re_3	Re	B
—	Rf	Rf	—
G-1	Rg_1	Rg_1	A
G-2	—	Rg_2	—
—	—	Rg_3	—
—	—	Rh_1	—
—	—	Rh_2	—

* By Kim and Staba[88]. American and Korean ginseng root saponins examined by two-dimensional thin-layer chromatography.

** By Shibata *et al.*[103]. Korean ginseng root saponins identified by one-dimensional thin-layer chromatography.

*** By Elyakov *et al.*[112]. Korean ginseng root saponins identified by one-dimensional thin-layer chromatography.

Kim and Staba[88] reported that American ginseng contained panaquilins A, B (1.71 %), C (0.30 %), D (0.20 %), E-1, E-2, E-3 (0.99 %), G-1 (0.09 %), G-2 (0.05 %), (c) and (d) identified by two-dimensional thin-layer chromatography established. Their two-dimensional thin-layer chromatography may be used for the identification of ginseng saponins as well as for the comparative chemical studies (Table II).

Kondo *et al.*[70,110,120] isolated *chikusetsu*-saponin III (1.17 %) (Fig. 2, *Ij*), *chikusetsu*-saponin IV (0.43 %) (Fig. 2, *Va*) and *chikusetsu*-saponin V (5.35 %) (Fig. 2, *Vb*) from methanolic extracts of *P. japonicus* rhizomes (total crude saponins; 23.6 %). *Chikusetsu*-saponin V contains oleanolic acid (Fig. 2, *Vd*), glucose, glucuronic acid and ashes. The chemical structure of *chikusetsu*-saponin is identical with araloside A present in *Aralia manchurica*[121~124] and of *chikusetsu*-saponin V (Fig. 2, *Vb*) identical with ginsenoside Ro[109].

c. Sapogenins

Shibata *et al.*[72,102] examined the saponins and sapogenins from various ginseng plants by one-dimensional thin-layer chromatography. Ginseng-*sanchi* (commercial) contains all the main saponins of Korean ginseng roots with ginsenosides Rb and Rg_1 predominating, whereas American ginseng contains principally ginsenosides Rb and Rg_3. The hydrolyzed saponin products of Korean, American and ginseng-*sanchi* contain dammarane-type triterpenes, while those from *P. pseudo-ginseng* and *P. japonicus* contain oleanane-type triterpenes. Fujita *et al.*[108] isolated panaxadiol (0.1 %) (Fig. 2, *IIa*) from the hydrolysis of *P. ginseng* root saponins, and by partial hydrolysis prosapogenin (Fig. 2, *Im*) and glucose. Kim and Staba[88] reported that American ginseng contained panaxadiol (panaquilins B, C and E), panaxatriol (panaquilins E and G-2), and oleanolic acid (panaquilin D). They did not identify panaquilins A, G-2, (c) and (d) genins.

Lin[87] obtained oleanolic acid, ginsengenin (identical with panaxadiol), glucose and arabinose from the

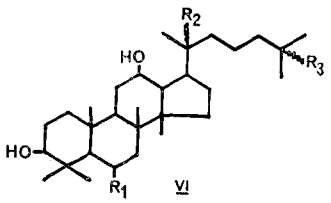
hydrolysates of *P. ginseng* fiber-roots. WAGNER-JAUREGG and ROTH[125,126] isolated a sapogenin named panaxol from *P. ginseng* roots which was identical with panaxadiol. HÖRHAMMER *et al.*[127] isolated oleanolic acid and β-sitosterol from *P. ginseng* saponin hydrolysates. Dilute mineral acid hydrolysis of ginsenosides Ro, Rb and Rc, and Rg formed the sapogenins oleanolic acid, panaxadiol and panaxatriol (Fig. 2, *IIb*), respectively[102,107,128,129].

SHIBATA *et al.*[108,109] reported that the acid hydrolysis of ginsenosides Rb, Rc, and Rd gives panaxadiol, and of ginsenosides Re, Rf, Rg_1 and Rg_2 gives panaxatriol. Panaxadiol and panaxatriol are tetracyclic terpenes of the dammarane series which contain a trimethyltetrahydropyrane ring at C_{17}. Mild hydrolysis (Smith's degradation or oxidation with periodate followed by alkaline treatment) of the saponins resulted in 20-*epi*-protopanaxadiol (20S-protopanaxadiol) (Fgi. 2, *Ik*) which is considered to be the genuine sapogenin of the ginsenosides Rb∼Rd[101,130,131]. Partial hydrolysis of ginsenosides Rb and Rc results in the prosapogenin and ultimately protopanaxadiol (Fig. 2, *IIIb*) and its isomer, *iso*-protopanaxadiol (Fig. 2, *IIIb*, double bond located at C_{25})[131]. YOSIOKA *et al.*[132] reported that panaxapogenol (Fig. 2, *Im*) was isolated from the bacterial hydrolysates of ginsenosides Rb and Rc. Mild hydrolysis of ginsenoside Rg gives 20S-protopanaxatriol (Fig. 2, *Il*)[107].

JHANG *et al.*[84] identified panaxadiol, panaxatriol and oleanolic acid from both American and Koean ginseng callus and suspension tissue cultures. FURUYA *et al.*[133] isolated panaxadiol, panaxatriol, oleanolic acid, and daucosterin from *P. ginseng* petiole callus tissue cultures.

FUJITA *et al.*[100] reported that the hydrolysis of *P. japonicus* rhizome saponins resulted in large amounts of oleanolic acid and small amounts of panaxadiol. YOSIOKA *et al.*[134] reported that the bacterial hydrolysis of *P. japonicus* saponins resulted in oleanolic acid and compound O (Fig. 2, *Vc*).

ELYAKOV *et al.*[104,105] reported that hydrolysis of panaxosides A, B and C gave an equilibrium mixture containing genins A_1∼A_6 in which genin A_6 (panaxatriol) is the main hydrolyzed product. Hydrolysis of panaxosides D, E and F gave an analogous mixture containing genins F_1∼F_5 (F_5, panaxadiol). Geninis A_1∼A_6 and genins F_1∼F_5 (Fig. 3) are considered to be artifacts resulting from the hydrolysis of panaxosides with methanolic acid solution. Genins A_1∼A_5 and F_1∼F_4 resulted from the addition of methanol/water to the double bond or hydroxyl group of the side chain in the genuine aglycone structure (Fig. 2, *IIIa*, *IVa* and *IVb*)[135∼137].



VI

Fig. 3. Hydorlyzed Products of Panaxosides A∼F.
A_1 : R_1=R_2=R_3=OH
A_2 : R_1=R_2=OH, R_3=OCH_3
A_5 : R_1=OH, R_2=R_2=R_3=OCH_3
F_1 : R_1=H, R_2=R_3=OH
F_2 : R_1=H, R_2=OH, R_3=OCH_3
F_4 : R_1=H, R_2=R_3=OCH_3

Other Ginseng Constituents

a. Organic Acids and Carbohydrates

PARK[138], and LEE and LEE[139] identified citric, fumaric, *iso*-citric, ketoglutaric, linoleic, oleic, maleic, malic, pyruvic, succinic, tartaric and several unidentified acids in ethanolic Korean ginseng root extracts using column and paper-partition chromatography.

LEE and LEE[139] reported that ginseng roots contained fructose (0.5 %), glucose (1.0 %) and sucrose (8.5 %). TAKIURA and NAKAGAWA[140] examined Japanese grown *P. ginseng* roots and found approximately 1.5 % of glucose and sucrose and approximately 3.3 % of sucrose and maltose. PARK[138] identified by paper chromatography fructose, glucose, glucuronic acid, maltose, raffinose and sucrose in ginseng root ethanolic extracts.

GSTIRNER *et al.*[85,141] identified dextrose, fructose and sucrose in *P. ginseng* roots and *P. japonicus* rhizomes, and sucrose in *P. quinquefolium* roots.

TAKIURA and NAKAGAWA[142,143] separated four trisac-

charides from aqueous *P. ginseng* root extracts: trisaccharide A (0.08 %, 1-fructosyl sucrose; O-α-D-glucopyranosyl-(1→2)-O-β-D-fructofuranosyl-(1→2)-β-D-fructofuranoside); trisaccharide B (panose; O-α-D-glucopyranosyl-(1→6)-O-α-D-glucopyranosyl-(1→4)-O-α-D-glucopyranoside); trisaccharide C (0.2 %, α-maltosyl-β-D-fructofuranoside).

JHANG *et al.*[84] reported crude fiber present in Korean ginseng roots (5.9 %), American ginseng roots (6.5 %), above-ground parts (24.5 %), and callus tissues (6.7 %).

OVODOV and SOLOV'EVA[144] obtained crude polysaccharides (40 %) from hot water *P. ginseng* root extracts. The polysaccharides consisted of a pectin. The pectin was prepared by DEAE cellulose column chromatography into acidic polysaccharide fraction having the same qualitative monosaccharide compositions[145]. SOROCHAN *et al.*[146] reported ginseng pectin (panaxan) to contain 60 % uronic acid (methoxyl group, 5.0 % and mol. wt., 25,000~29,000) and the purified galacturonan to contain 100 % uronic acid (methoxyl group, 5.9 % and mol. wt., 15,000~20,000). GSTIRNER *et al.*[141] reported that Korean, American ginseng and *P. japonicus* roots contained calcium polyuronide compounds and arabinose.

b. Flavonoids

KOMATSU *et al.*[147] obtained 0.2 % flavonoids from *P. ginseng* stem and leaf, and 0.1 % from the flower. Ethanolic extracts of the above-ground portions contained panasenoside (kaempferol-3-O-glucogalactoside), trifolin (kaempferol-3-O-galactoside), and kaempferol.

c. Nitrogen-Containing Compounds

Korean ginseng roots are reported to contain about 2 % nitrogen and other ginseng roots about 1.5~1.9 % nitrogen as determined by the Kjeldahl method[85,141]. JHANG *et al.*[84] reported crude protein present in Korean ginseng roots (9 %) and American ginseng roots (8.7 %), above-ground parts (10.3 %), and callus tissues (32.5 %). Alcoholic extracts of ginseng roots are reported to contain 0.1~0.2 % choline[148] and pyrrolidone[149]. A growth factor, the ester of an α-hydroxy betaine and hydroxy choline (4.8 mg/4 kg of ginseng roots or 0.00012 %) isolated from *P. quinquefolium* roots[150].

By high resolution paper electrophoresis, GSTIRNER and VOGT[141] reported 5 peptide bands in white Korean ginseng roots and *P. japonicus* rhizomes, but only 4 bands in American ginseng roots. Glycopeptides were present in white Korean ginseng roots, sulfur-containing peptides in *P. quinquefolium* roots, and free glutamic acid in *P. ginseng* and *P. japonicus* roots. GSTIRNER and BROWN[85] also identified cysteine, glutamic acid, tyrosine, α-aminobutyric acid from Korean ginseng root aqueous extracts by means of paper chromatography. Two-dimensional high voltage electrophoresis on Sephadex G-25 separated four homogenous low molecular weight peptide fractions. Hydrolysis of the isolated oligopeptides resulted in the formation of aspartic acid, alanine, arginine, glycine, glutamic acid and serine.

d. Vitamins

GSTIRNER and VOGT[141] reported the ascorbic acid content of white Korean ginseng roots (3.9 mg%), *P. japonicus* rhizomes (12.0 mg%), and *P. quinquefolium* roots (23.1 mg%). GOTO[151,152] reported *P. ginseng* root aqueous extracts to contain 60 γ/g of niacin and 10 γ/g of pantothenic acid, and *P. japonicus* 20 γ/g of niacin and 11 γ/g of pantothenic acid. By means of microbial assays, KIM and HER[153] estimated 6.6 γ/g pantothenic acid and 9.2 γ/g of biotin in *P. ginseng* roots. KIM *et al.*[154] showed a variation of some vitamins based on the age of *P. ginseng* roots (Table III).

However, ginseng plant, itself, could not biosynthesize vitamin B_{12}. It is assumed that microorganisms may produce vitamin B_{12} that plants absorb easily from soils[155].

Table III. Variation of Ginseng Vitamin Contents.

Age (years)	Vitamin B_{12} (mγ/g)	Nicotinic acid (γ/g)	Folic acid (mγ/g)
2	0.40	13.7	50.6
3	0.37	16.0	51.6
4	0.50	15.0	67.9
5	0.57	15.4	63.8
6	0.60	15.5	40.0

Table IV. Inorganic Constituents of Ginseng Plants and Callus.

Inorganics	American Ginseng			Korean Ginseng
	Roots	Above-ground Parts	Callus	Roots
Ash, %	4.64	8.46	12.52	5.59
P, %	0.27	0.33	0.52	0.31
K, %	0.86	1.72	3.38	0.97
Ca, %	0.25	1.08	0.36	0.32
Na, %	0.05	0.06	0.48	0.05
Mg, %	0.12	0.17	0.22	0.13
Al, ppm	285.0	43.3	24.0	231.0
Fe, ppm	366.0	108.0	306.0	407.0
Zn, ppm	57.2	49.8	114.3	36.5
Cu, ppm	10.4	10.7	7.1	12.6
Mo, ppm	10.6	9.8	14.0	11.2
Mn, ppm	55.4	156.1	127.6	87.3
B, ppm	23.6	45.8	96.0	28.4

e. Inorganics

GSTIRNER and BROWN[85] reported that *P. ginseng* roots contained 5.9 % of ash, 0.12 % of total sulfur and traces of phosphorous. The sulfur found in the petroleum ether extracts may have been an artifact from the processing of the root. By means of radioactivation analysis, PIJCK *et al.*[156~158] reported present in dried *P. ginseng* Mn (19~26 ppm), V (0.02 ppm), Cu (7~8 ppm), Co (0.06 ppm) and As (0.25~0.44 ppm). More recently JHANG *et al.*[84] reported the inorganic constituents present in American ginseng plants, callus, and Korean ginseng roots as shown in Table IV.

Biosynthesis of Plant Saponins and Sapogenins

a. Biosynthesis of the Isoprenoid Structure from Acetate

Mevalonic acid (MVA), a six carbon-atom compound derived by the condensation of three molecules of acetic acid, is the essential and universal progenitor of terpenoid compounds. The biologically active isomer has the 3R configuration, and will form the "isoprene unit" by simultaneously losing water and carbon dioxide (Fig. 4).

The condensation of two molecules of acetyl coenzyme-A to yield acetoacetyl coenzyme-A appears to be identical with the first stage in the pathway leading to acetate derived poly-β-keto compounds, to cyclization of the polyketide, or to fatty acids. Terpenoid biosynthesis, however, departs from this pathway at an early stage, and, by an aldol-like condensation of one molecule of acetyl coenzyme-A with one acetoacetic acid molecule forms β-hydroxy-β-methylglutaryl coenzyme-A. Reduction of the latter compound results in MVA. Phosphorylation of MVA by adenosine triphosphate (ATP) yields MVA-5-phosphate which is converted into the basic biogenetic isoprene unit, isopentenyl pyrophosphate (IPP). MVA-5-phosphate participation in isoprenoid biosynthesis is dependent upon an enzyme-catalyzed conversion into an equilibrium mixture of the isopentenyl and the dimethylallyl esters.

b. Biosynthesis of Sesquiterpenes

Sesquiterpenes (C_{15} units) are very common in higher plants. Their biosynthesis may occur from one or more isomers of farnesyl pyrophosphate (FPP). The double bonds between C_2 and C_3, and between C_6 and C_7 of farnesol permit four possible geometric isomers (Fig. 5). The enzyme FPP synthetase has been isolated from cotton roots and is capable of catalyzing the formation of all four FPP geometric isomers[159]. The predominant 2,6-*trans,trans*-isomer can be formed from MVA and is a well-established steroid precursor.

Water-soluble enzyme obtained from *Pinus radiata* seedlings can transform 2-C^{14} MVA into two sesquiterpene alcohols, 2,6-*trans,trans*-farnesol and 2-*cis*, 6-*trans*-farnesol. These sesquiterpene alcohols and *trans*-FPP are formed from a union of IPP and geranyl pyrophosphate (GPP). However, neryl pyrophosphate (NPP) is completely inactive as a farnesol precursor, but may be a precursor of cyclic monoterpenes[160]. Cell-free extracts of orange flavedo convert 2-C^{14} MVA

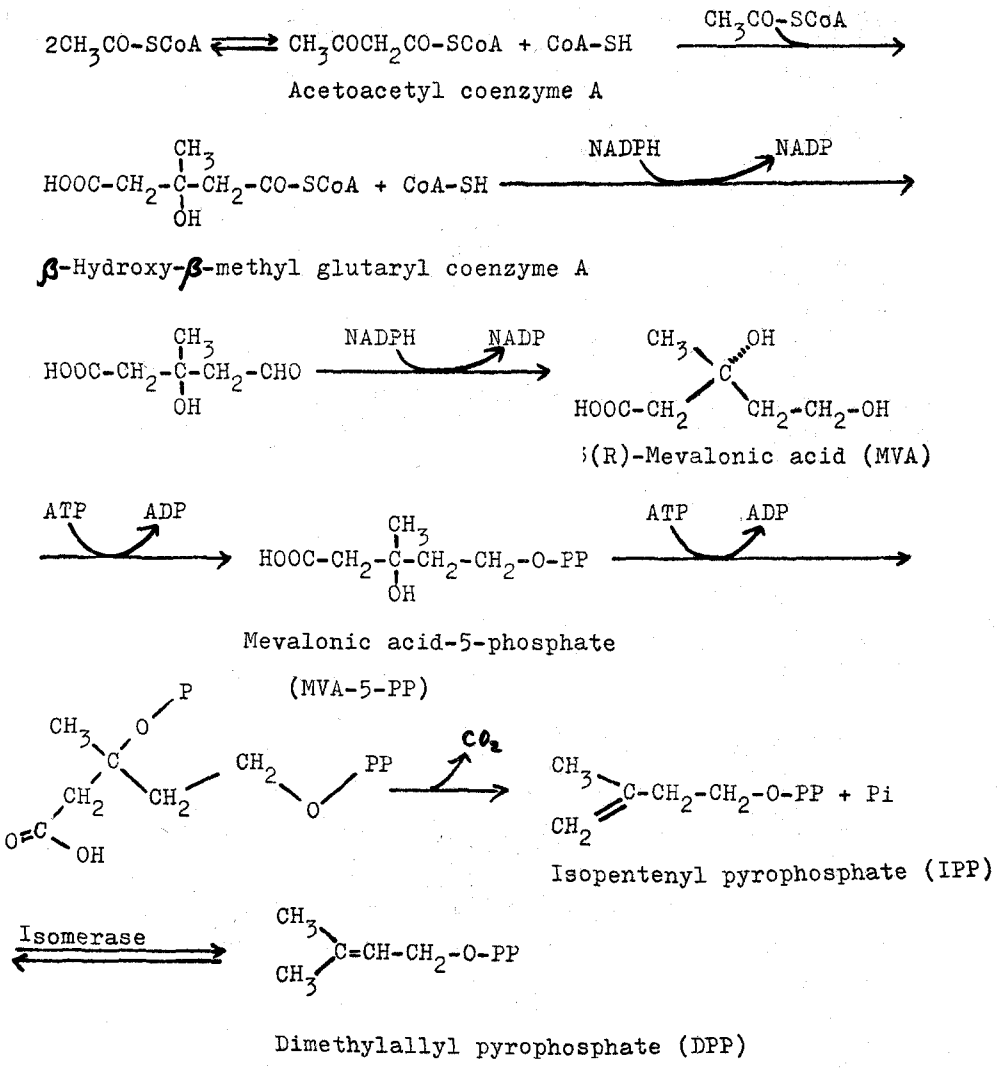


Fig. 4. Biosynthesis of Mevalonic Acid.

into phosphorylated derivatives of isopentenol, dimethylallyl alcohol and farnesol, and 4-C^{14} IPP into phosphorylated derivatives of dimethylallyl alcohol, nerol and geraniol. No interconversion of NPP and FPP was observed[161].

c. Biosynthesis of Squalene

Squalene is present in a number of plants in low concentration[162], and consists of two farnesyl residues combined tail to tail (Fig. 5). The labeling pattern of squalene from 2-C^{14} MVA in peas is identical to that from animals, although plants and animals may differ in the manner in which squalene is cyclized[163]. The incorporation of 2-C^{14} MVA into squalene and farnesol has been demonstrated in tobacco tissue culture systems consisted of a soluble fraction involved in FPP synthesis, and a microsomal fraction to convert the FPP to squalene. The cell system for squalene biosynthesis requires the cofactors ATP, NADPH, Mn^{++} and thiols[164]. Heintz *et al.*[166] reported that bramble (*Rubus fruticosus*) tissue culture cell free system in the presence of NADPH incorporated labeled MVA into squalene, but accumulated presqualene alcohol in the presence of NADPH,

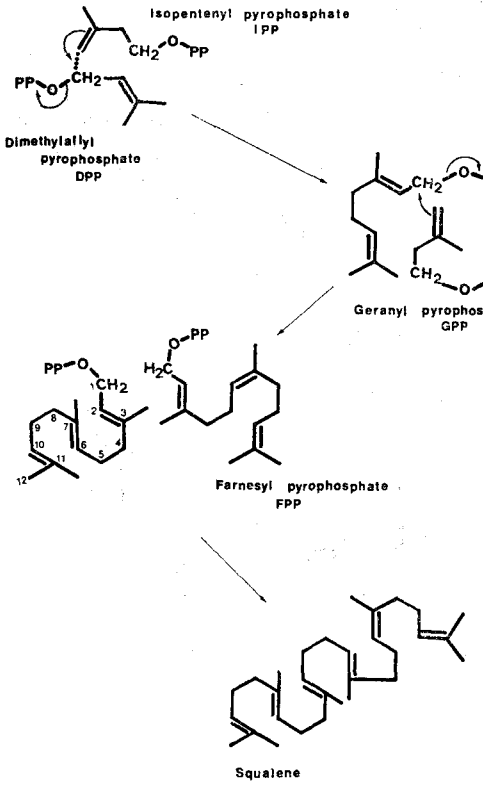


Fig. 5. Biosynthesis of Squalene.

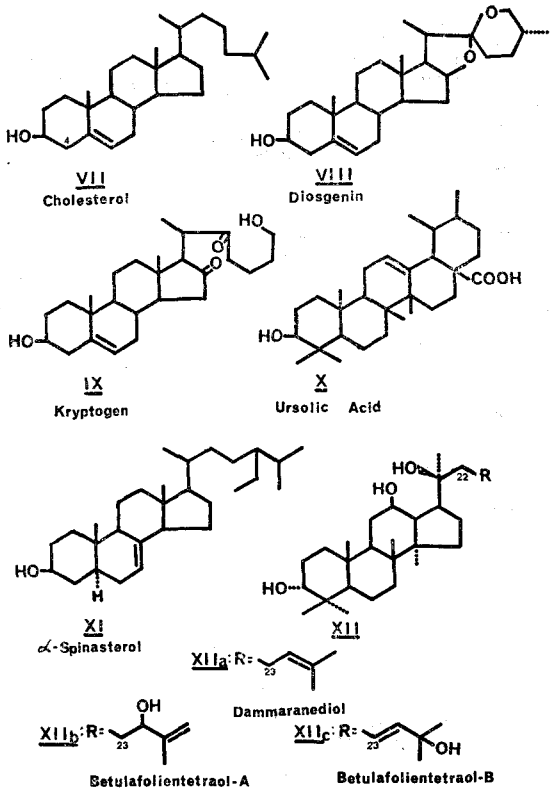


Fig. 6. Structure of Some Triterpenes.

d. Biosynthesis of Triterpenes

KARNICK [167] observed that saponin concentration of *Dioscorea deltoidea* and *D. prozeri* increased with the age of the tuber. The optimum sapogenin content was found when the plants were just shedding their leaves and the tubers were becoming dormant. HARDMAN and SOFOWORA[168] observed that the total sapogenin content of *Balanites* seedlings rose to a maximum in 5 days. BENNETT and HEFTMAN[160] demonstrated that cholesterol -4-C^{14} (Fig. 6, *VII*) was converted to the sapogenin diosgenin (Fig. 6, *VIII*) and kryptogenin (Fig. 6, *IX*) by *Dioscorea spiculiflora* seedlings.

The leaf, stem, or flower tissues of *Salvia officinalis* incorporate 2-C^{14}-acetate into sterols, and into triterpenes such as oleanolic acid (Fig. 2, *Vc*) and ursolic acid (Fig. 6, *X*)[170]. With further growth of the germinated bud of *S. officinalis* the quantity of ursolic acid became higher, whereas that of oleanolic acid became lower[171]. However, after some time both triterpene acids attained an equilibrium. Labeled acetate was incorporated into oleanolic acid glycosides in variable quantities depending upon the ages and organs of *Calendula officinalis*[172].

Although squalene is thought to be the biosynthetic precursor of the pentacyclic triterpenoids, its biosynthesis has not been thoroughly demonstrated in higher plants known to contain pentacyclic compounds. It is known that in germinating pea seeds both squalene and pentacyclic β-amyrin (Fig. 7C, *XVIII*) are obtained from labeled mevalonate, and that the proportion of squalene decreases as the amount of β-amyrin increases[173]. KNAPP and NICHOLAS[174] administered 2-C^{14} MVA to banana peel slices for time periods varying from 30 minutes to 6 days. They observed that cycloartenol (Fig. 7A, *XIV*) and 24-methylene sterols were labeled after 8 hours. *Spinacea oleracea* and *Medicago sativa* leaves are known to incorporate 2-C^{14}, (4R) -4-H^3 MVA into cycloartenol, 4-desmethyl sterols and α-spinasterol (Fig. 6, *XI*)[175].

In animals the first cyclic precursors of cholesterol

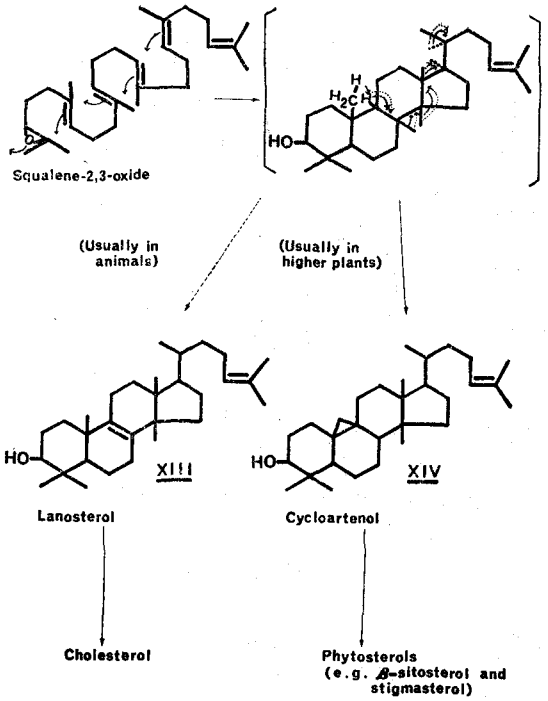


Fig. 7A. Biosynthesis of Lanosterol and Cycloartenol.

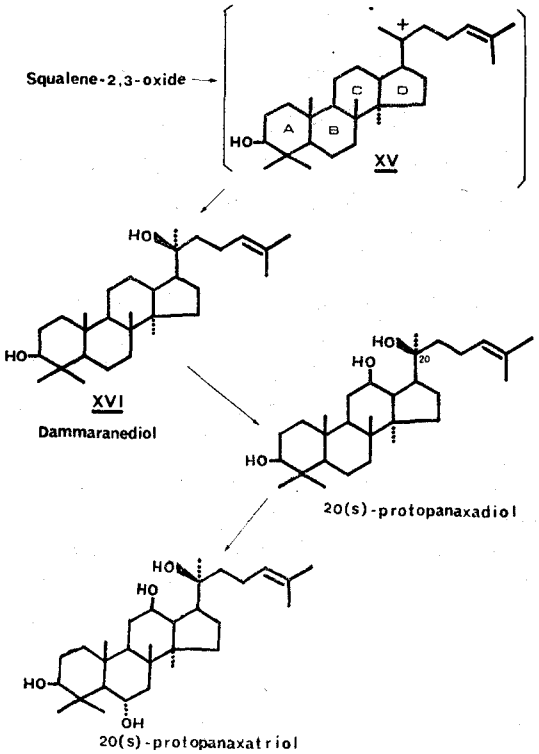


Fig. 7B. Schematic Biosynthetic Pathway of Dammarane-Type Triterpenes.

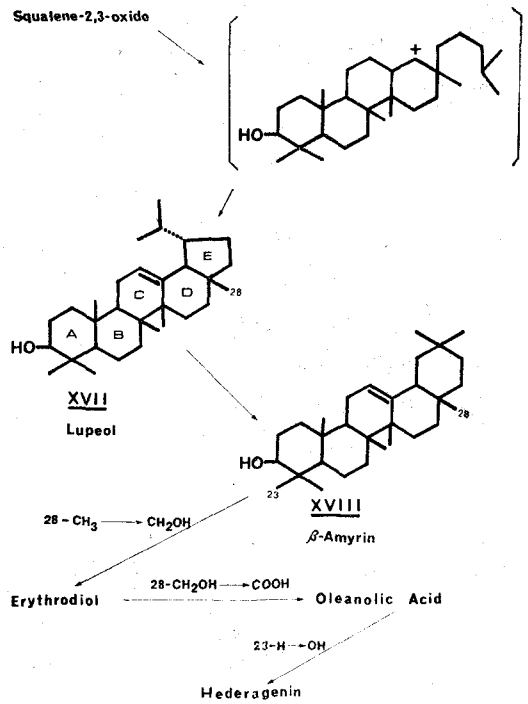


Fig. 7C. Biosynthesis of Oleanolic Acid.

in lanosterol (Fig. 7A, *XIII*) but the existence of lanosterol in higher plants is extremely restricted and probably it is present only in the latex of the *Euphorbiaceae*[176]. In plants, the role of lanosterol appears to be taken by cycloartenol (Fig. 7A). The labeled acetate[177] and MVA[178] are quickly incorporated into cycloartenol but not lanosterol. The compound cycloartenol, a product of direct cyclization of squalene-2, 3-oxide, is not produced by isomerization of lanosterol[179].

Dammaranediol (Fig. 7B, *XVI*) could arise from direct reaction of the precursor (Fig. 7B, *XV*) with water at C_{20} has a relatively stable chair conformation in rings A, B and C. It is assumed that protopanaxatriol (Fig, 2. *II*) and betulafolientetraol-A or B (Fig. 6, *XIIb* or *XIIc*) form through dammaranediol and betulafoliendiol (Fig. 6, *XIIa*), respectively, and differ from each other at the oxidation position (Fig. 7B). The presence of dammaranediol has not been reported in ginseng plants, but its existence might be found as an intermediate of ginseng sapogenins. Kim

and STABA[180,181] have studied that sodium acetate-U-C^{14} was a good precursor, but tritiated squalene was not for American ginseng sapogenins.

Oleanolic acid biosynthesis (Fig. 7C) may occur from the parent substance lupeol (Fig. 7C, *XVII*) by modifications of ring E and C_{28}.

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