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REVIEW

Physiological functions of solanaceous and tomato steroidal glycosides

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Abstract Solanaceous plants are widely distributed. They are used as food and in folk medicine. Our studies focused on these plants, starting with *Solanum lyratum* and *S. nigrum*, which are used as anti-cancer and anti-herpes agents. Extensive investigations in 45 *Solanum* plant species revealed that a considerable amount of glycosides such as spirosolane, solanidane, spirostane and furostane is in these plants, and some of the isolated glycosides showed strong anti-proliferative activity against various cancer cell lines and anti-herpes activity. Furthermore, we have discovered a few new hypothetical biosynthetic routes in which the pathways for the biosynthesis of 16-acyl-pregnane and pregnane glycosides were the most interesting. The occurrence of these pregnane compounds indicates that they might be internally biosynthesized in the plant from furostanol glycosides by a reaction that is similar to Marker degradation. Furthermore, this may imply that the administration of steroidal glycosides may result in their metabolization into pregnane derivatives possessing various activities. In order to perform metabolic experiments using the steroidal glycosides, we recently isolated tomato glycosides from ripe tomato fruits for the first time. For this experiment, we examined the metabolites in urine obtained from persons that consumed tomatoes. We obtained androstane derivatives that were probably metabolized via pregnane derivatives from tomato glycoside. Hence, when a steroidal glycoside is administered, it may be metabolized into a type of steroidal hormone with various physiological activities.

Keywords Steroidal glycoside · Pregnane glycoside · Tomato glycoside · *Lycopersicon esculentum* · Spirosolane-type · Solanocapsine-type · Saponin metabolism · Seasonal variation · Cytotoxicity · Anti-herpes activity · Anti-arteriosclerosis

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Introduction

Marker chemically converted a natural steroidal glycoside to a steroidal hormone, thereby consolidating the status of steroidal glycosides in the plant kingdom [1]. Subsequently, numerous searches that aimed to discover alternative raw materials for hormone synthesis were performed, especially in various species of plants belonging to Dioscoreacea and Liliaceae. We did not attempt to isolate steroidal raw material since our aim was to identify the exact substance possessing the biological activity. Hence, we decided to experiment with plants containing steroidal glycosides that can be used as anti-cancer agents. We were strongly interested in *Solanum nigrum* and *S. lyratum* as they are used as crude anti-cancer drugs. They are weeds that grow everywhere, and their western counterpart, *S. dulcamala*, has been used for treatment of various

cancers since ancient Greek times [2]. These plants were extensively used for cancer treatment in Shanghai around 1980. Additionally, they have been used as anti-viral herbs in the Tohoku district. Plants belonging to the Solanaceae family have 90 known genera, comprising 2,000 species, and have important uses in folk medicine and as food. Initially, we undertook the chemical analysis of the steroidal glycosides included in the *Solanum* species. Other *Solanum* species and the tomato have now been included in these studies.

Solanum steroidal glycosides

Initially, we were interested in *S. lyratum* and *S. nigrum*, which have been used as anti-cancer agents since ancient times in various countries. They are typical *Solanum* specimens and are grasses that are found to grow wild. We isolated novel solanidane oligoglycosides and spirostanol glycosides [3, 4] from these palnts. These compounds exhibited anti-proliferative activity against uterine cancer cell lines [4].

Thus far, we have investigated more than 45 solanaceous plant species (Table 1). We cultivated sollanaceous plants annually in the University Botanical Garden, in cooperation with the Ministry of Agriculture, Forestry and Fisheries. We sowed the seeds in spring and harvested the plants in autumn. We isolated over 300 pure glycosides of spirosolane, solanidane, spirostane (**1**), and furostane glycosides (**2**) from plants belonging to the *Solanum* genera and elucidated their chemical structures [5].

Table 1 *Solanum* species so far examined in our laboratory

Solanum abutiloides	*S. maximowiezii*
S. achrolcucum	*S. melongena*
S. aculeatissimum	*S. mummosum*
S. aethiopicum	*S. muricatum*
S. anguivi	*S. myriacantum*
S. biflorum	*S. nigrum*
S. chacoense	*S. nodiflorum*
S. cilistum	*S. paniculatum*
S. cynathem	*S. reflexum*
S. demissum	*S. sanitwongsei*
S. depilatum	*S. sisymbriifolium*
S. dulcamara	*S. spinosissimum*
S. ferox	*S. sodomaeum*
S. gilo	*S. stramonifolium*
S. indicum	*S. surattense*
S. integrifolium	*S. torvum*
S. japonense	*S. toxicarium*
S. jurpeva	*S. ruberosum*
S. khasianum	*S. vanhuerchii*
S. lycocarpum	*S. vervascifolium*
S. lyratum	*S. viarum*
S. macrocarpon	*S. xanthocarpum*

The biogenesis of furostanol and spirostanol glycosides from cholesterol has already been established. In addition, we found a few new hypothetical biogenetic routes (Fig. 1). That is to say, we have discovered a precursor of furostanol, polyhydroxy-cholestane glycoside (**3**) [6], the conjugated cholesterol glycoside with acetyl Co-A or maronyl Co-A that forms an aromatic E-ring (**4**) [7], 16,22-dicarbonyl-cholesterol glycosides (**5**) [6, 8], lactone glycosides (**6**) at the E-ring and pregnane and 16-acyl-pregnane glycosides (**7**, **8**) [8]. The most attractive compounds for us are pregnane [9] and 16-acyl-pregnane [6, 8] glycosides.

This is because the occurrence of the pregnane compounds suggests that they might be biosynthesized in the plant internally from furostanol glycosides by a reaction similar to Marker degradation. Furthermore, this indicates that administered steroidal glycosides may be metabolized into pregnane derivatives possessing various activities. We would like to describe this feature later.

Bioactivities of *Solanum* steroidal glycosides

First, we measured the anti-proliferative activities of *S. nigrum* and *S. lyratum* against various cell lines. However, this experiment might be irrelevant in the study of glycosides since the sugar linkages in them would be broken during digestion with foods. The results showed that spirostanol oligoglycosides (**9**: dioscin, **10**: SL-4) possessing tigogenin and diosgenin as sapogenol moieties and β-chacotriosyl or β-lycotetraosyl moieties as a sugar component were the most inhibitorily effective against the proliferation of cancer cell lines [10, 11] (Fig. 2).

Traditionally, *S. lyratum* and *S. nigrum* have been used against herpes. We also attempted to treat the herpes patients infected by the Varicella zoster virus with a topical cream containing a 0.5% extract of *S. nigrum*. We treated ten volunteers under the supervision of a medical doctor. Of these patients, eight showed significantly good recovery similar to that observed on treatment with acyclovil. A series of steroidal glycosides were evaluated. Among them, diosgenin β-chacotrioside and tigogenin β-lycotetraoside are the most effective against herpes [12] (Fig. 3).

Pregnane glycosides

For the first time, we isolated a pregnane glycoside, Pd (**11**), which was the focus of our studies, together with a

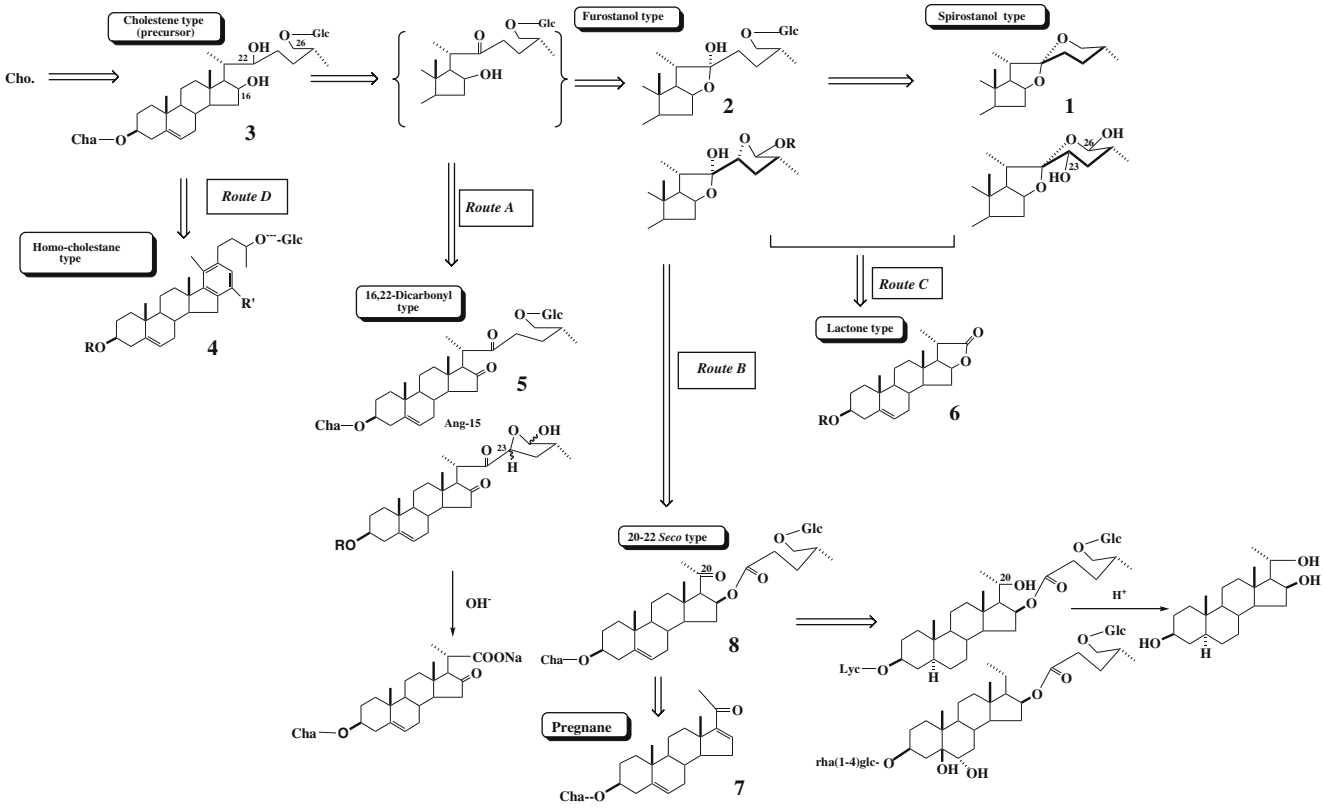

Fig. 1 Proposed biosynthetic pathway

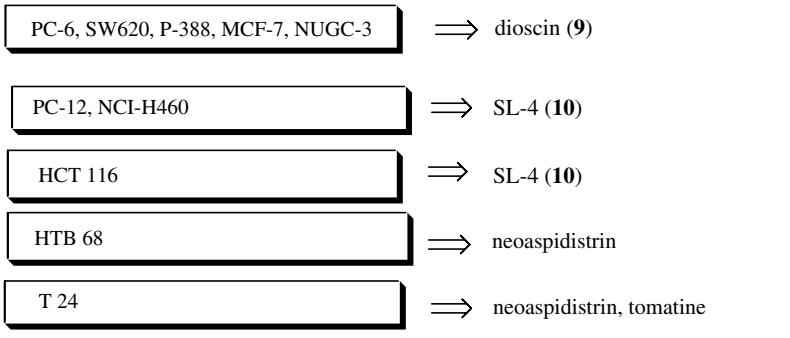

Fig. 2 Antiproliferation activities against various cancer cell lines

significant quantity of diosgenin glycosides: Pa, Pb and Pc, from *Paris polyphilla* [9] (Fig. 4), which has been extensively used in Chinese medicine. In recent years, many pregnane glycosides have been obtained mainly from the *Dioscorea* [13–16], *Allium* [8], *Tacca* [17], *Solanum* [6], and *Cestrum* [18] genera (Fig. 5). Based on this fact, the above-mentioned theories regarding the biogenesis of pregnane from furostanol and spirostanol glycosides are plausible.

Here, we suggest the mechanism responsible for the efficacy of steroidal glycosides. After being orally administered, they are partly metabolized to pregnane derivatives in the liver by the action of P-450 and show various bio-activities, one of which is an anti-cancer activity. However, they do not kill the cancer cells; instead, they control proliferation of cancer cells by acting as an antagonist for the proliferation stimulant hormone. On the other hand, when they are used externally as anti-herpes and anti-skin cancer agents, steroidal glycosides enter cells via endogenous lectins that have receptors specific for the sugar moiety of the glycoside. The receptors bind the steroidal glycoside and thereby initiate a chain of events that culminate in the internalization of steroidal glycoside with concomitant delivery of sapogenol to the cell. Once inside the cell, sapogenol affects the lysosomes and mitochondria, causing the rupture of the cytoplasmic membranes. Initially, the nucleus contracts, then enlarges, and finally the nuclear membrane ruptures [19] (Fig. 6).

Tomato glycosides

For the metabolic analysis of steroidal glycosides, we decided the tomato would be appropriate since we were convinced that it had steroidal glycosides because its aerial parts and immature fruits are rich sources of tomatine. Hence, we carried out the isolation of steroidal glycosides from the ripe fruit. Tomato, the fruit of *Lycopersicon esculentum*, is widely used as a fresh vegetable and for cooking. The species of tomato in the market are roughly classified into two groups—the first is the pink color-type and the second is the red-color type. The pink color-type tomato is used mainly as a fresh vegetable, and the red color-type tomato is used in pasta sauces and cooking.

The tomato has attracted considerable attention since it contains lycopene, which is a strong anti-oxidant. Recent studies have reported the following con-

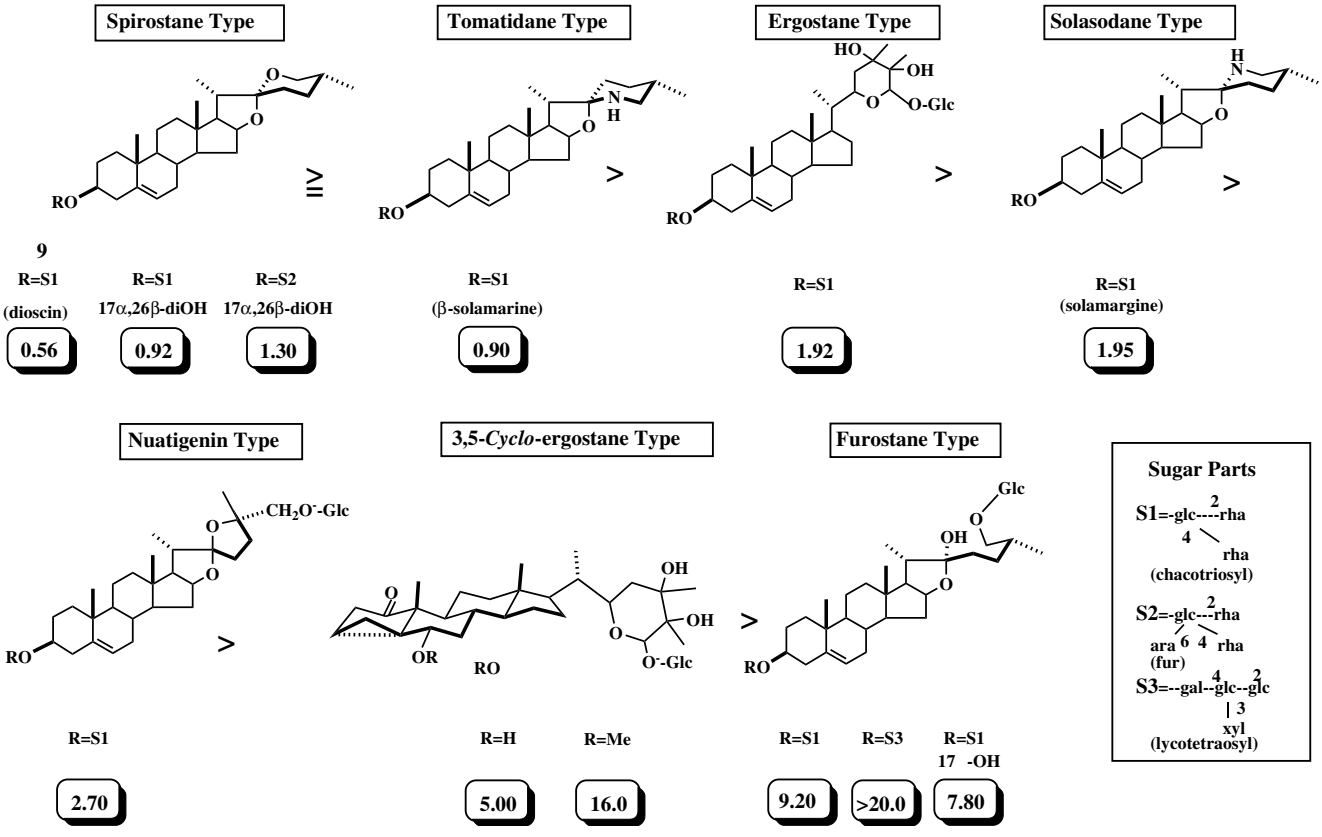

Fig. 3 Anti HSV-1 activities (EC_{50}: μg/ml)

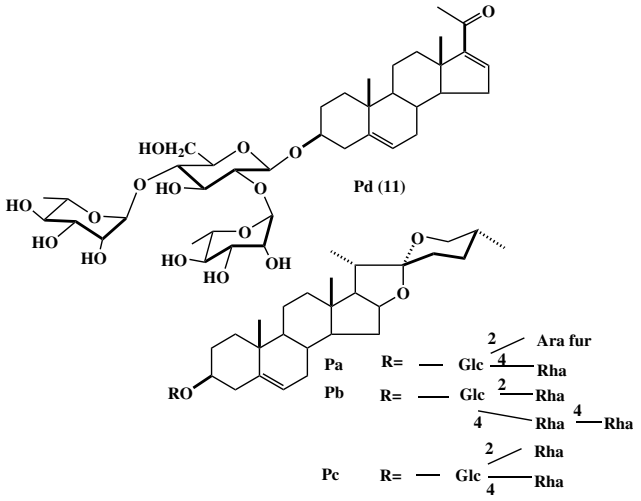

Fig. 4 Steroidal glycosides isolated from *Paris polyphylla*

stituents of tomato: a bitter component named TFI [20], was isolated from tomato seeds; steroidal alkaloid glycosides, tomatine (**12**), and several spirosolane glycosides were obtained from the stems and leaves [21]; lactone [22], pregnane [23] and several spirosolane derivatives [24] from the roots of the tomato stock were reported. However, the steroidal alkaloid is thought to be absent in the ripe fruit.

A simple procedure, namely, smashing the tomato by hand in water, followed by filtration, gave the filtrate. The filtrate was then subjected to polystyrene column chromatography. It was first eluted with water, followed by methanol (MeOH). The methanolic eluate was subsequently subjected to reversed silica gel column chromatography to yield a major tomato saponin, esculeoside A (**13**) as colorless needles. Crystals weighing 440 mg were obtained from 1.78 kg of the commercial ripe cherry tomato. From 7.53 kg of the pink color-type, 331 mg of the same compound was also obtained [25, 26] (Fig. 7).

The molecular formula of esculeoside A (**13**) was estimated by the HR-FABMS. The ^{1}H-NMR spectrum showed the presence of two angular methyl signals-a secondary methyl signal and an acetyl methyl signal together with five anomeric proton signals. These signals indicate that esculeoside A (**13**) may be a steroidal glycoside. On acid hydrolysis, esculeoside A yielded colorless needles of a sole sapogenol, designated esculeogenin A (**14**). The EI-MS showed a molecular ion peak at *m/z* 447 as the base peak together with

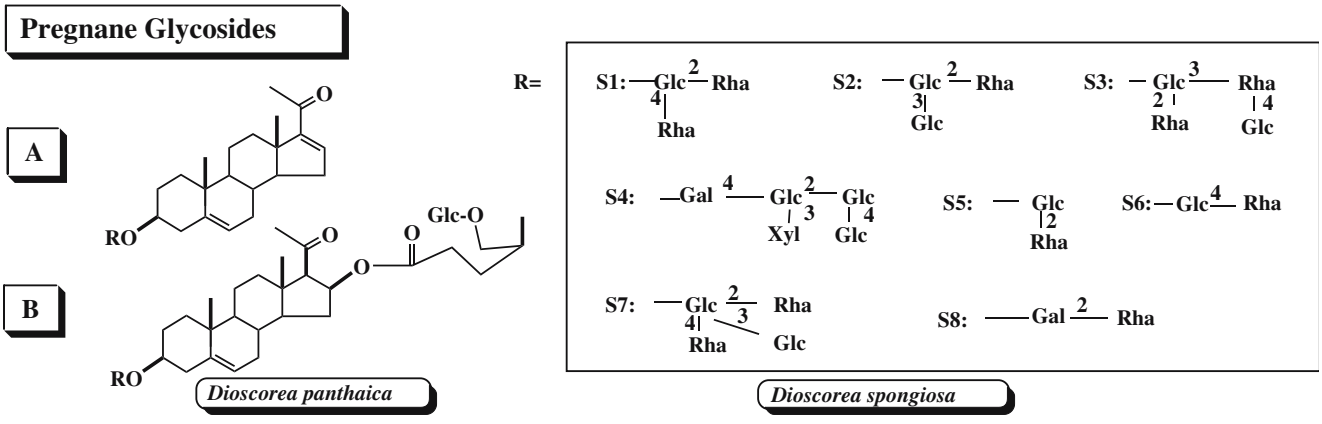

Fig. 5 Pregnane and 16-acylpregnane glycosides

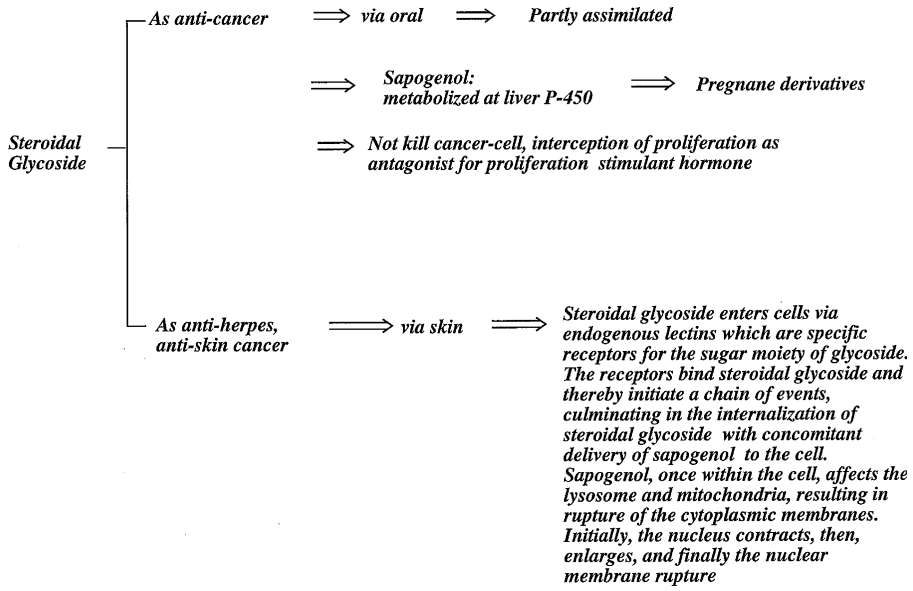

Fig. 6 Hypothetical metabolism of steroidal glycosides

characteristic peaks at *m/z* 170 and *m/z* 146 that originated from α-cleavages between C-16-oxygen and C-22, and between C-20 and C-22, respectively, indicating that esculeogenin A is a spirosolane-type derivative with two hydroxy groups present at the F-ring. On the other hand, the ^{13}C-NMR spectrum showed a total of 27 signals, including 4 oxygen-bearing carbons, 1 spirosolane center carbon at δ 101.7, and 1 nitrogen-bearing carbon at δ 40.3. 2D-NMR measurements using FG-COSY, HMQC, and HMBC revealed the locations of each function: (1) A sequence of correlation from methyl proton at C-21 through C-20, H-20, C-22 into H_2-26 suggested esculeogenin A to be a spirosolane derivative; (2) a correlation from H-20 to C-23 indicated the presence of a hydroxyl group at C-23; (3) H_2-26 to C-27 revealed the presence of a hydroxyl group at C-27. Next, we discuss the configurations at C-22, C-23, and C-25. The proton signal at C-23 appeared at δ 4.04 as a signal of dd, *J*=6.1, 10.4 Hz; therefore, C-23-OH may be oriented in the equatorial plane. The configuration at C-25 was determined to be *S* by the *J* values of H_2-26. The C-22 configuration was deduced by comparison of the carbon chemical shift at C-20 to those of several steroidal alkaloids obtained from the aerial and underground parts of the tomato. In other words, in the case of 22α*N*-spirosolane, the signal due to C-20 appeared around δ 35.0, while in the 22β*N*-isomer, it resonated around δ 43.0, despite the substitution of C-23 with an oxygen-bearing moiety. The signal due to C-20 in esculeogenin A occurred at δ 35.0, thus indicating its configuration to be 22α*N*(22*S*)-spirosolane. Therefore, the structure of esculeogenin A (**14**) was represented as (5α,22*S*,23*S*,25*S*)-3β,23,27-trihydroxyspirosolane. Meanwhile, the absolute configurations of the corresponding trimethylsilyl ethers of methyl 2-(polyhydroxyalkyl)-thiazolidine-4(*R*)-carboxylates, derived from the sugar mixture of the hydrolysate, were determined by GLC [27]. Of all the signals, the carbon signals originating from the sugar were deduced to have originated from sapogenol. One of these signals was due to the β-D-glucopyranosyl moiety and the other due to the β-D-xylopyranosyl-(1 → 3)-[β-D-glucopyranosyl-(1 → 2)]-β-d-glucopyranosyl-(1 → 4)-β-D-galactopyranosyl moiety, that is, the β-lycotetraosyl moiety [28]. Moreover, HMBC between hydroxymethyl protons at C-27 and terminal glucosyl C-1 suggested that the terminal β-D-glucopyranosyl moiety combined with C-27-OH, and the β-lycotetraosyl moiety combined with C-3-OH. Next, esculeoside A (**13**) was subjected to enzymatic hydrolysis. β-Glucosidase breaks down esculeoside A (**13**) to

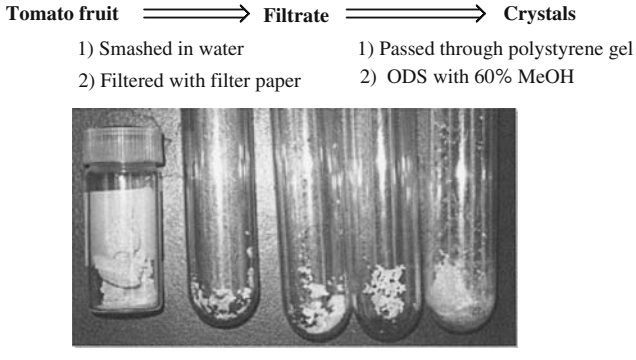

Fig. 7 Crystals of esculeoside A

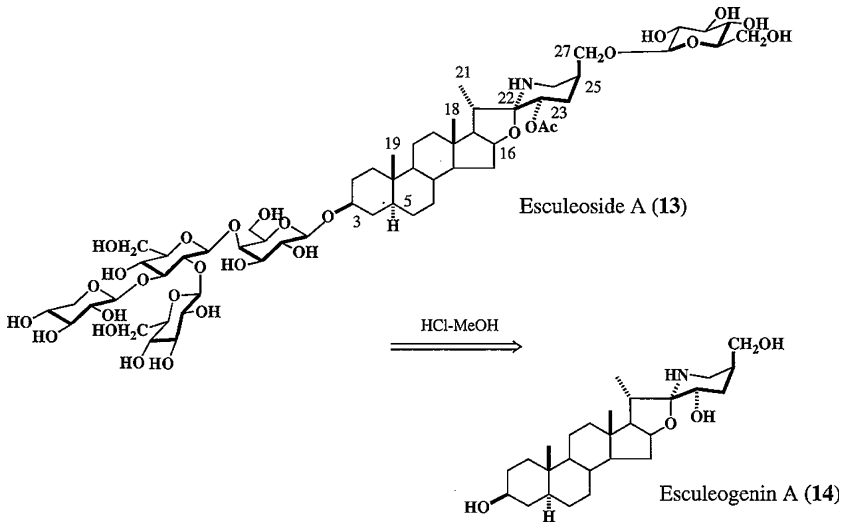

Fig. 8 Esculeoside A (**13**) and esculeogenin A (**14**)

prosapogenin A in which the carbon signal due to C-27 shifts to δ 63.3 in a higher field, suggesting that the β-D-glucopyranosyl moiety at C-27-OH has been eliminated. Therefore, prosapogenin A was elucidated as 3-*O*-β-lycotetraosyl esculeogenin A (**13**). On the other hand, esculeoside A was treated with tomatinase to yield prosapogenin B in which the carbon signal at C-3 appeared at δ 70.7 without a glycosylation shift, indicating prosapogenin B to be 27-*O*-β-D-glucopyranosyl esculeogenin A (**14**). Further, in the ^{1}H-NMR spectrum of esculeoside A (**13**), one acetyl group appeared to be attached to C-23-OH by the HMBC between H-23 and the acetyl carbonyl group. A methine proton signal at C-23 displayed at δ 5.38 as dd with J=5.5, and 11.0 Hz, indicated an α-configuration of the acetoxyl group. Consequently, the structure of esculeoside A (**13**) was determined as 3-*O*-β-lycotetraosyl (5α,22*S*,23*S*,25*S*)-23-acetoxy-3β,27-dihydroxyspirosolane 27-*O*-β-D-glucopyranoside [26] (Fig. 8).

On the other hand, a major steroidal alkaloid glycoside, esculeoside B (**15**), has been obtained from the red color-type tomato. The cultivated red color-type tomato (6.5 kg) named Italian San Marzano was treated in a manner similar to the one used to obtain esculeoside A (**13**) from the pink-type tomato to provide 1,290 mg of esculeoside B (**15**) as an amorphous powder. The HR-FABMS of esculeoside B (**15**) showed a molecular formula. The ^{1}H-NMR spectrum showed two tertiary methyl signals and one secondary methyl signal together with five anomeric proton signals. In the ^{13}C-NMR spectrum, just as in the case of esculeoside A, signals due to a β-lycotetraosyl moiety and the β-D-glucopyranosyl moiety were first assigned, and the remaining 27 carbon signals were observed to be made up of 3 methyls, 1 hydroxymethyl, 1 hemiketal carbon, 1 nitrogen-bearing methine carbon, 1 nitrogen-bearing methylene carbon and 2 oxygen-bearing methine carbons. By using FG-COSY, HMQC, and HMBC, all the carbon signals of esculeoside B could be assigned, including, the HMBC between the methyl protons at C-21 and the nitrogen-bearing methine carbon at C-22. The occurrence of the hemiketal carbon function at δ 93.4 conclusively characterized a novel sapogenol, with a solanocapsine-type framework, which is a rare natural product [29]. Next, NOESY between H-20 and H-22 revealed that the configurations of both H-20 and H-22 were in *cis*-correlation. The configuration at C-25 was also deduced to be *S* since the axial proton at C-26 signal appeared at δ 3.44 as t-like, J=12.5 Hz. The configuration of the hydroxyl group at C-23 was estimated as α-axial since that C-21 methyl group shifted toward a lower field at δ 1.62 in a 1, 3-diaxial correlation with the C-23-OH group. Acid hydrolysis gave inseparable complicated sapogenols that were different from those obtained from esculeoside A (**13**). Therefore, esculeoside B (**15**) was subjected to enzymatic hydrolysis by tomatinase [30]. Esculeoside B obtained prosapogenin C, which was then treated with β-glucosidase to obtain esculeogenin B (**16**) [31]. Hence, the structure of esculeoside B (**15**) may be represented as 3-*O*-β-lycotetraosyl (5α,22*S*,23*R*,25*S*)-22,26-epimino-16β,23-epoxy-3β,23,27-trihydroxy-cholestane 27-*O*-β-D-glucopyranoside [26] (Fig. 9).

Tomato pregnane glycoside

We have isolated (5α)-pregna-16-en-3β-ol-20-one 3-*O*-β-lycotetraoside (**17**) as a minor component from the

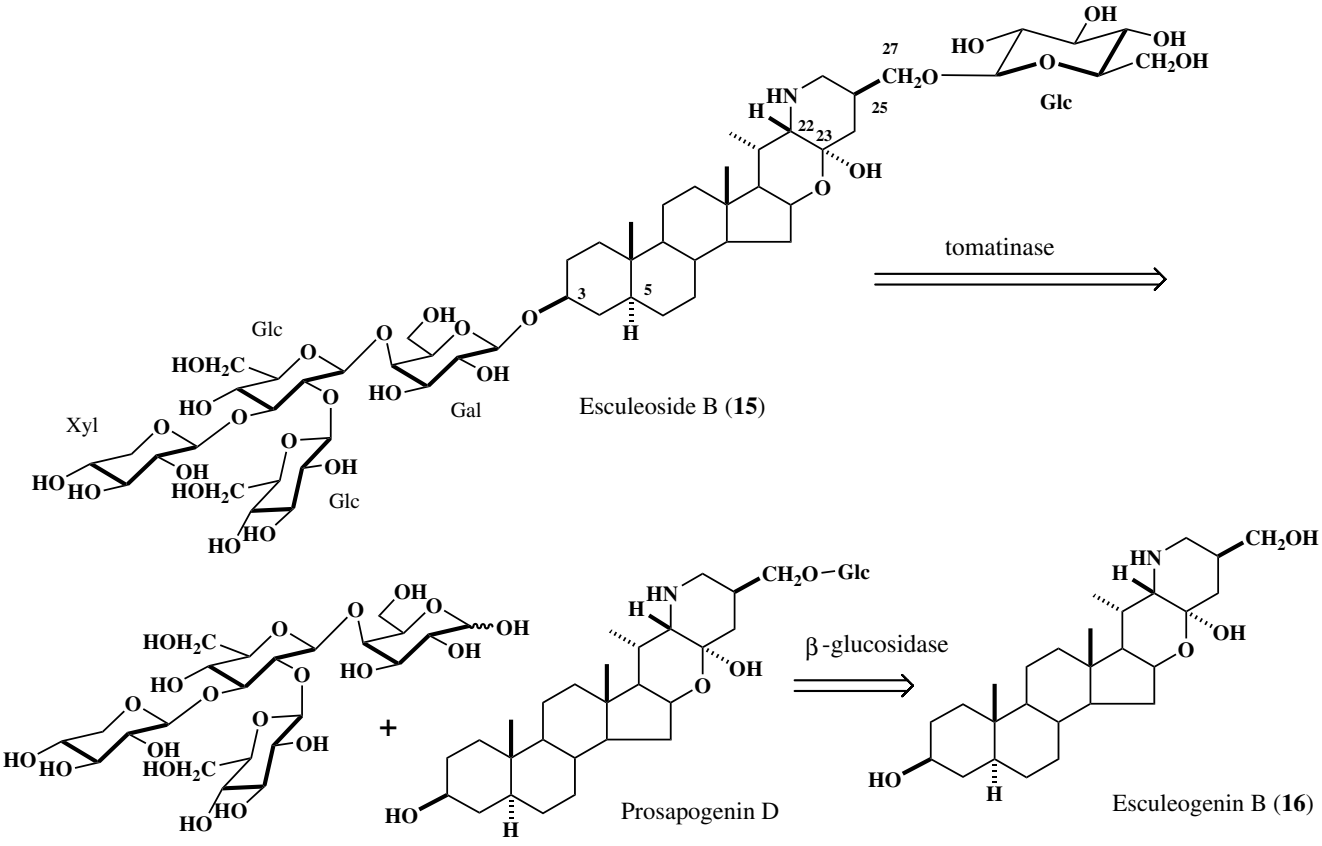

Fig. 9 Esculeoside B (**15**) and esculeogenin B (**16**)

over-ripe tomato fruit [32] (Fig. 10). This indicates that the type of steroidal glycoside varies as the tomato matures, that is, tomatine in the green immature fruit is oxidized at C-23 and at C-27 in the ripe fruit to give esculeoside A. Further, esculeoside A (**13**) is converted into the pregnane glycoside in the over-ripe fruit. This seasonal variation also suggests variations in the internal metabolism in the human body (Fig. 11).

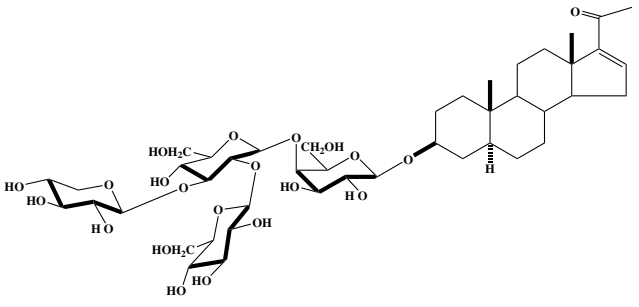

Fig. 10 Pregnane glycoside (**17**) isolated from overripe tomato

Chemical conversions of tomato sapogenols

Chemical correlation between esculeosides A (**13**) and B (**15**) was attained by refluxing the minor component isoesculeogenin A (**18**) with pyridine and water [31] (Fig. 12). In this reaction, the hydroxyl group at C-23 was converted to an enol by E-ring fission, followed by the attack of a C-16-oxygen on C-23 to afford esculeogenin B (**16**) [31].

Next, esculeogenin A (**14**) was converted into a pregnane derivative by refluxing with pyridine (Fig. 13). This reaction is unexpected as it suggests the presence of a hydroxyl group at C-23 that makes the E, F-ring very fragile, thereby leading to bond fission between C-20 and C-22 to afford a pregnane derivative (**19**) [33]. The mechanism for this reaction is tentatively speculated to be as follows: the acquisition of H-20 by pyridine caused a double-bond formation between C-20 and C-22 and the opening of an E-ring, followed by dehydration of C-23-OH to form a 22(*N*)-ene derivative, of which nitrogen was then protonated, and the transfer of the 22(*N*)-ene to the nitrogen raised the bond fission between C-20 and C-22.

In the case of spirosolane, particularly tomatidine (**20**), normal acetylation with pyridine and acetic anhydride at room temperature yielded δ 20(22)-pseudo acetate, which could then easily give rise to a

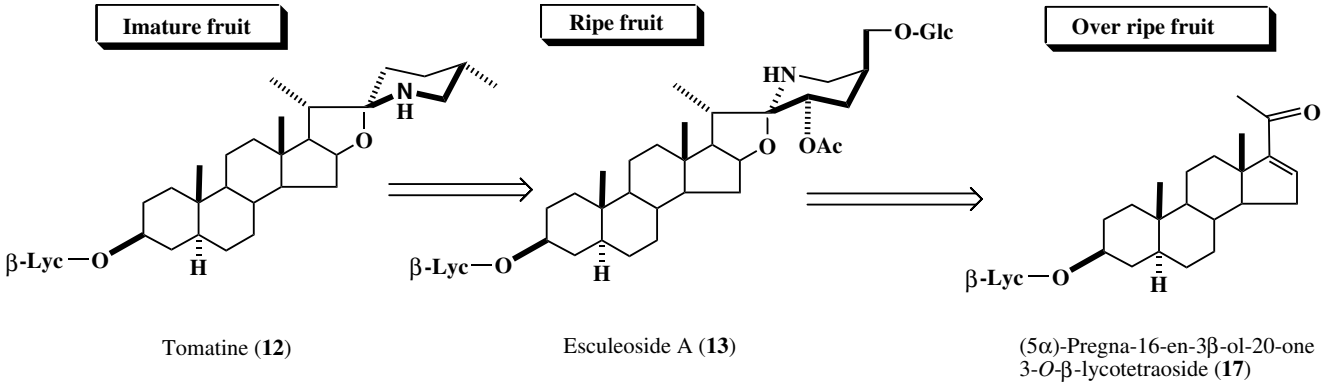

Fig. 11 Seasonal variation of tomato glycosides

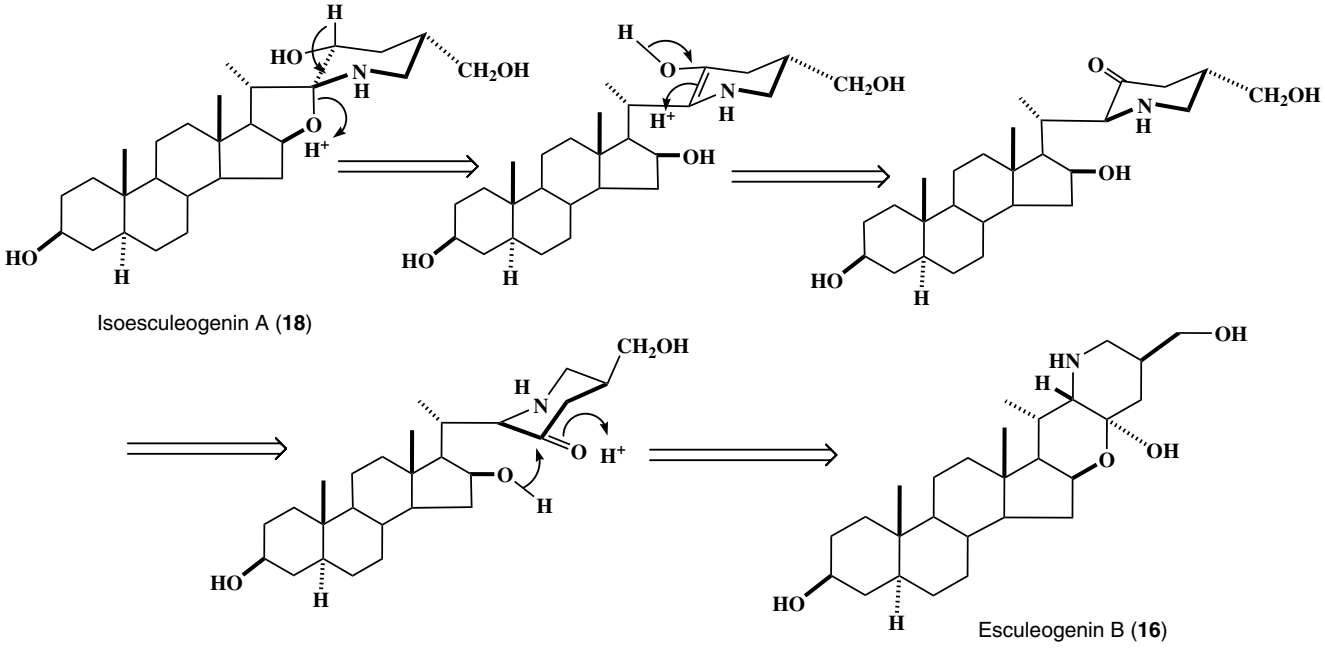

Fig. 12 Isomerization of isoesculeogenin A (**18**) into esculeogenin B (**16**)

pregnane compound (**21**). Therefore, this reaction is a new method to obtain pregnane compounds without the use of diosgenin (Fig. 14).

Bioactivities of tomato glycosides

Here, we examined the bio-activities of the tomato. Taking into account that steroidal alkaloid glycosides possess anti-proliferative activity against various tumor cell lines, these tomato steroidal alkaloid glycosides, esculeosides A (**13**) and B (**15**), could also be expected to possess potent anti-cancer activity. The anti-proliferative activity of esculeoside A (**13**) against MCF7, a human breast cancer cell, and B16F2F, a mouse melanoma cell line, has been examined. The GI_{50} values of esculeoside A (**13**) against MCF7 and B16F2F were 13.3 and 7.9 μM, respectively. Next we checked the suffocating activity of saturation for the ground membrane of cancer cells. Esculeogenin A (**14**) (1 mg/ml) showed a better anti-proliferative effect on the cell lines than doxorubicin. Furthermore, the anti-herpes (anti-HSV-1) activity of esculeogenin A (**14**) was also evaluated. It showed an EC_{50} of 42 μg/ml. Next, we investigated the anti-foam cell formation effect. In the early stage of atherosclerotic lesion formation, low density lipoprotein (LDL) accumulates along the vascular wall in endothelial cells and is converted to oxidized LDL. On the other hand, monocytes migrate to the inside of the arterial wall where they differentiate into macrophages and express scavenger receptors. Macrophages use these receptors for oxidized LDL

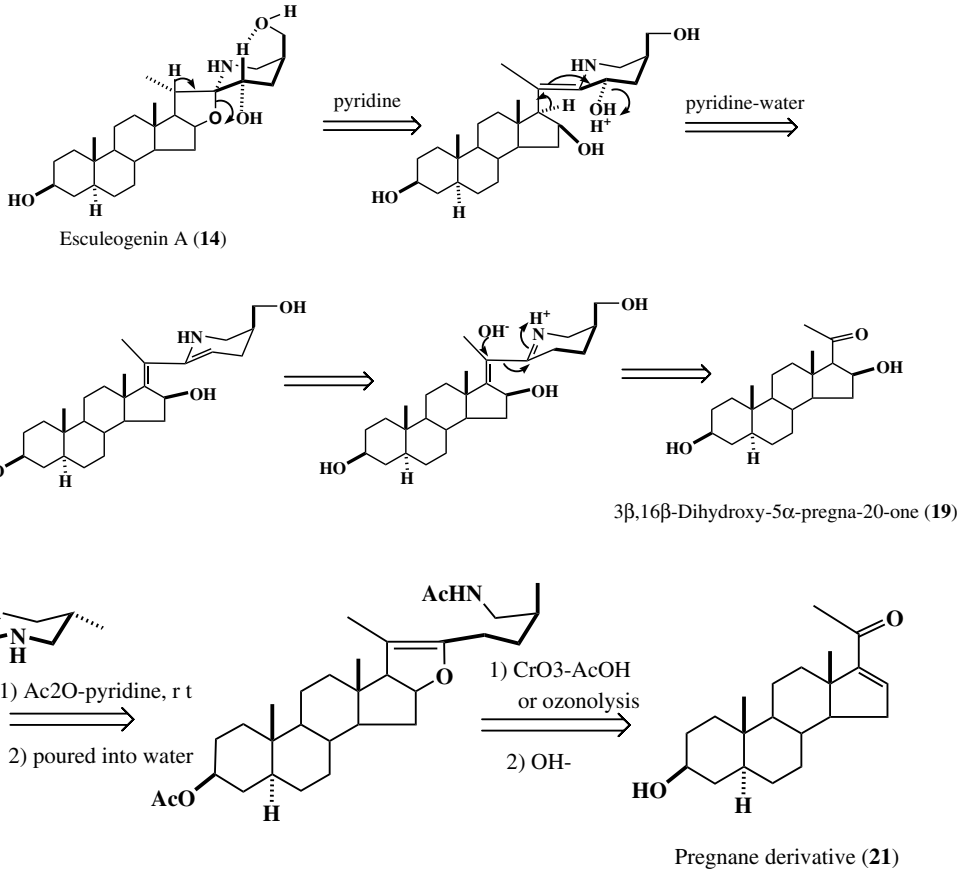

Fig. 13 Facile conversion of esculeogenin A (**14**) into preganane derivative (**19**)

Fig. 14 Chemical conversion of tomatidine (**20**) into pregnane derivative (**21**)

intake. These macrophages then change into foam cells (FC) filled with cholesterol ester (CE). In the experiment to check for the accumulation of CE by acetyl LDL (AcLDL), an esculeosides A (**13**) and B (**15**) and esculeogenin A (**14**) anti-foam cell (FC) formation effect was observed in a dose-dependent manner. During cholesterol metabolism in macrophages, oxidized LDL is internalized by the scavenger receptors. This oxidized LDL is stored in lysosomes that are formed as FC, which is converted into CE by the action of acyl CoA cholesteryl acetyltransferase (ACAT). CE accumulates and macrophages are changed into foam cells. It has become apparent that esculeosides A and B are involved in the control of expression of scavenger receptors and esculeogenin A, which impedes the ACAT reaction.

Investigation of other biological functions is currently in progress.

Metabolic experiment on tomato glycosides

Based on the above-mentioned evidence, we can make the following observations. First, the fact that pregnane glycosides are obtained along with normal spirostanol and furostanol glycosides (**1**, **2**); second, tomato steroidal glycoside, esculeogenin A (**14**), is easily converted into a pregnane derivative (**19**) by refluxing with aquous pyridine, and third, a pregnane glycoside was obtained from the over-ripe tomato fruit (Fig. 15). The above facts strongly suggest that the steroidal glycosides administered orally could be metabolized into a pregnane derivative, which is a type of steroidal hormone.

For the next experiment, eight males consumed tomatoes—2 kg per adult over a period of 2 days. Their urine was collected for 48 h and passed through a polystyrene gel (Diaion HP-20). The first eluate with water was discarded, and the second eluate with MeOH was collected. The methanolic residue (7.42 g) was subjected to Sephadex LH-20, silica gel, and ODS column chromatographies to afford three androstane derivatives (**22**–**24**) [34, 35]. These androsterone analogues are usually excreted in normal persons; however, since none of these excretions was detected in the control sample, the occurrence of androsterone analogues indicates that they would be excreted via the production of progesterone by those that consumed tomatoes, that is, the tomato steroidal glycoside might

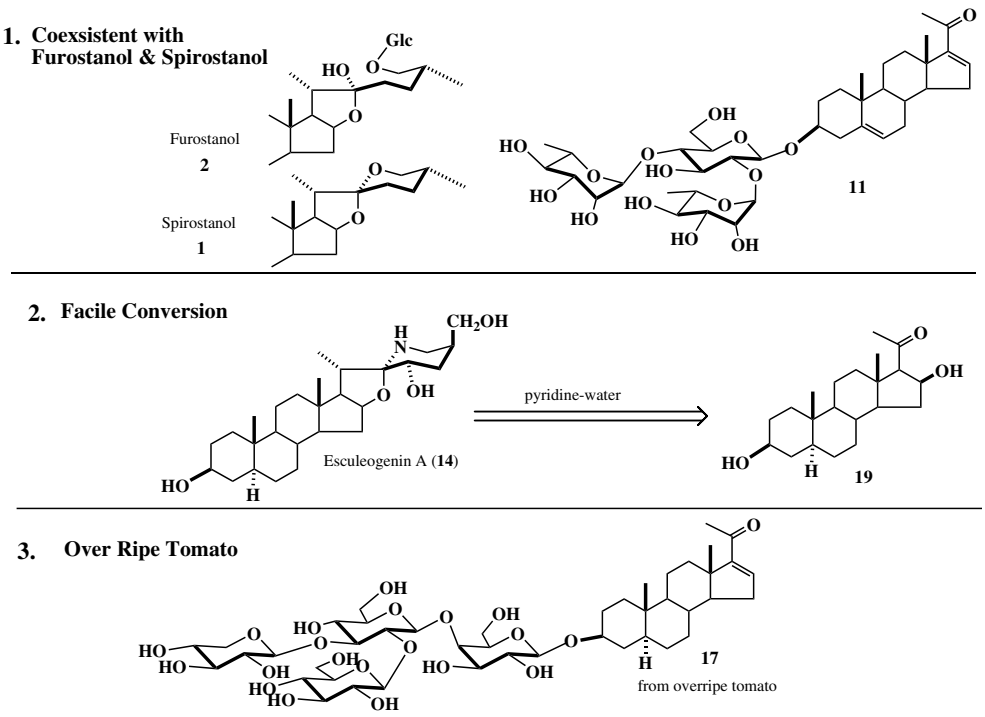

Fig. 15 Reasons of metabolism for steroidal glycosides into pregnane

stimulate the hormone secretor or would itself be metabolized into the pregnane. Generally, it is possible that when steroidal glycosides such as spirostanol and furostanol glycosides are administered orally, they could be metabolized, leading to the introduction of a hydroxyl group at C-23, and these intermediates would next be metabolized into pregnane derivatives that show various pharmacological bio-activities. The final metabolites are excreted as androsterone analogues in urine. When a steroidal glycoside is administered, it partially stays on the surface of the small intestine and affects the receptor or acts as a mediator of the nervous system that controls the rise in blood sugar levels, that was proposed by Yoshikawa [36]. On the other hand, the remainder that is assimilated is metabolized to a type of pregnane hormone that influences various physiological reactions such as osteoporosis and has the same effect as the female hormone. Also, the steroidal glycoside is absorbed via the skin and acts against the herpes virus and skin tumors (Fig. 16).

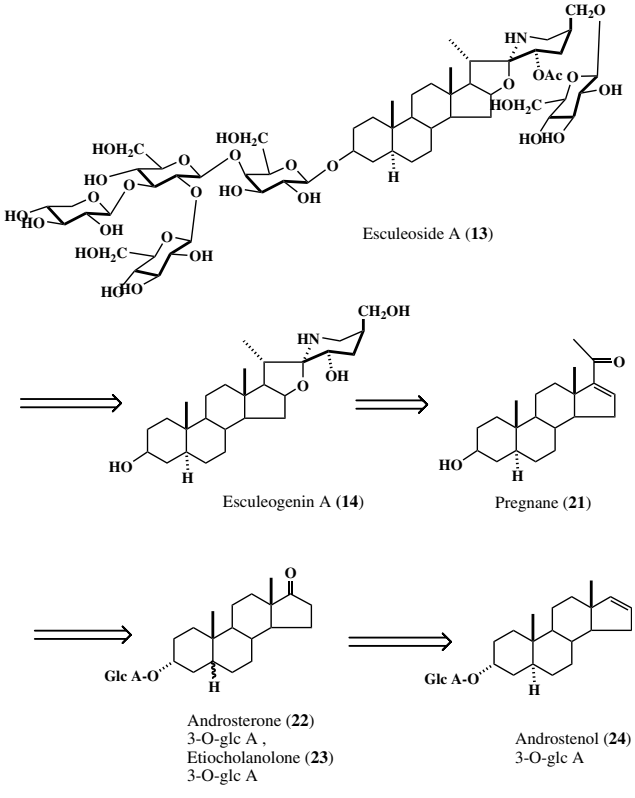

Fig. 16 Hypothetical metabolism of steroidal glycoside

Health foods and medicines derived from diosgenin

Here, we would like to introduce the actual benefits of health food and cosmetics containing steroidal glycosides. Firstly, in the USA, there is a health food named Wild Mexican Yam, whose description explains that it is beneficial to women. Yam contains diosgenin, which is changed into progesterone by the internal metabolism and transports Ca^{+2} into the cell. Osteoporosis and menstruation syndromes are not alleviated by the daily intake of the diosgenin in yams. Wild yam has been

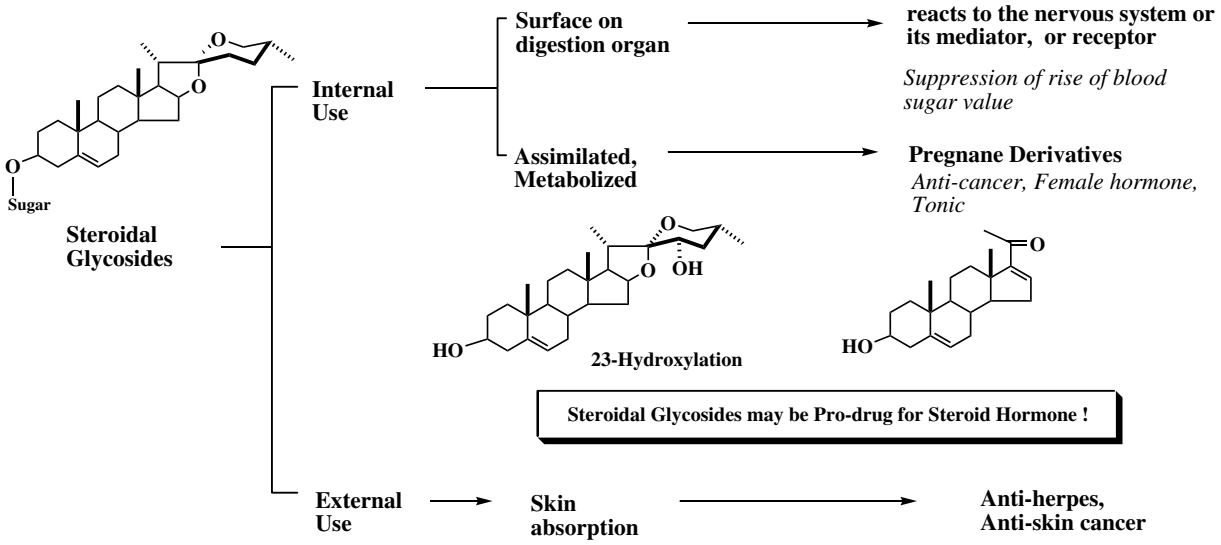

Fig. 17 Effectiveness of steroidal glycosides

used as a medicinal treatment for several centuries. This document clearly shows the metabolism of steroidal glycoside into progesterone.

The root of *Trillium erectum*, Beth root, has been used by women to ease childbirth as a root preparation named Rydea-Pincas that assists in the process of childbirth preparation and to treat irregular menstruation, uterus hemorrhage, and various female diseases. This plant also contains a large amount of diosgenin. Diosgenin could be metabolized into compounds similar to female hormones. Beth root is a synonym for birth root.

In Thailand and India, *Solanum* fruit is sometimes used as a vegetable in soups.

The daily consumption of *Solanum* fruit, from which we isolated new 22-β-*O*-spirostanol glycosides, in daily life is also considered useful for the prevention of cancer.

In China, a popular medicine named *Yunnan Baiyao* is used to improve blood circulation, to dissipate stagnation, to reduce swelling and to relieve pain. This medicine is composed of two crude drugs. This plant also contains a large amount of diosgenin.

Recently, a mix of ecdysterone has been used for a French cosmetic for skin beauty care. Ecdysterone may also be metabolized into a type of pregane, thus operating as a female hormone.

Effectiveness of steroidal glycosides

In summation, the use of steroidal glycosides is classified into internal and external uses. Regarding the former, there are two cases: one is action on the surface of the digestive tract, and the other is action after assimilation and metabolism. Unassimilated steroidal glycoside acts on the nervous system or its mediator or receptors to suppress the rise in blood sugar levels. On the other hand, the assimilated glycoside is first metabolized into C-23-hydroxylated spirostane or furostane, and further into pregnane derivatives, which demonstrate various bio-activities. In external use, steroidal glycoside is absorbed via the skin and demonstrates anti-herpes and anti-skin-cancer activities as mentioned before (Fig. 17). Steroidal glycosides are regarded as natural pro-drugs of steroidal hormone.

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