CHAPTER II

HISTORICAL REVIEW

The Genus *Smilax*

Smilax, a large genus of climbers of the family Liliaceae, (Smilacaceae-sensu stricto) are about 210 species throughout the tropics and in the northern warm temperate regions (15).

The rhizomes or tuburous roots of several species of genus *Smilax* furnish the drug Sarsaparilla (16). Sarsaparilla (U.S.P. 1920 to 1955 , N.F. 1955 to 1965) is the dried root of the following *Smilax* spp. (13)(17).

Smilax aristolochiaefolia Miller, known in commerce as Mexican, Vera Cruz, Tampico or Gray Sarsaparilla.

S. regelii Killip et Morton (*S. oranta* Hooker) known in commerce as Honduras or Brown Sarsaparilla.

S. febrifuga Kunth known in commerce as Ecuadorian Sarsaparilla.

A form of *S. regelii* Killip et Morton (*S. ornata* Hook. f.) probably yields the commercial variety known as Jamaica, Costa Rica, Central American or Red Sarsaparilla.

The rhizome of *Smilax china* Linn., a native of China and Japan has been employed under the name of China root for similar purposes with the official Sarsaparilla.

Smilax glabra Roxb. has been official in Japanese Pharmacopoeia (18), Chinese Materia Medica (8) and Chinese Pharmacopoeia (19).

Part used of the drug Sarsaparilla is root because of it's length. The roots are very long, roughly furrowed and quite uniform in thickness seldom exceeding 6 mm in diameter. In the past it was employed in the treatment of syphilis and skin diseases (16).

The chief constituents are sarsasapogenin (the sapogenin of sarsasaponin), smilagenin (isosarsasapogenin) and other phytosterols (β-sitosterol, stigmasterol), parillin and smilacin, previously reported as glycosides, are impure forms of sarsasaponin . It also contains resin, volatile oil, starch and calcium oxalate, Sarsaparilla is classed as a flavoring agent (13).

Owing to being composed of saponins, it was reported that *Smilax* sp. extract has been used for excess sludge treatment (20). The saponins are useful as bulking prevention agent for treatment of organic wastewater by activated sludge process (21).

Medicinal Properties of *Smilax* species

The species of *Smilax* are used medicinally in the various geographical area (see Table 1, page 13-15) and also used in the following countries ; Portugal, Belgium, United States, France, Italy, Germany, Turkey, Brazil, China, Japan, Peru, Australia, Mexico and Columbia.

Table 1 Medicinal Properties of *Smilax* species

Geographical Area	Botanical Origin	Part Used	Indication	References
Sumatra and Malay Peninsula	*Smilax calophylla*	rhizomes leaves	for aphrodisiac and tonic, to treat gonorrhea, application to swellings.	(22), (23)
Malay Peninsula	*S. china*	root	for syphilis and gonorrhcea tonic	(15)
India		root	some extent like sarsaparilla, as a depurative, diaphoretic, stimulant, alterative, antisyphilitic aphrodisiac, sudorific, demulcent	(24)
Eastern Asia		rhizome	for chronic skin affections, an antidote against mercurial poisoning,	(25)
			for aphrodisiac	(23)
Sumatra and Malay Peninsula	*S. helferi*	rhizome	for aphrodisiac, poulticing boils on the head	(23)
		root	for skin diseases, syphilis and chronic rheumatism	(22)
Malay Peninsula Philippines	*S. leucophylla*	leaves & root	for syphilitic ulceration of the nose	(22), (23)
Malay Peninsula	*S. myosotiflora*	rhizomes leaves, fruit	for aphrodisiac, remedy for syphilis	(22), (23)
India	*S.ovalifolia*	rhizomes	as a substitute for sarsaparilla	(25)
Indo-China, Malay Peninsula			for treating venereal disease	(25)

Table 1 continued

Geographical area	Botanical Origin	Part Used	Indication	References
China	*Smilax nipponica*	underground parts	for people with pains in the joints or weak back	(25)
Omei-Shan	*S. riparia* var. angusta		for refrigerant	(25)
Shensi	*S. sieboldii*		use as *Clematis chinensis*	(25)
Taiwan	*S. stenopetala*		a dressing on wounds and swellings	(25)
Thailand	*S. myrtillus*	leaves & roots	being used medicinally by the natives	(25)
Indo-China	*S. macrophylla*	roots	for galactogogue and childbirth	(25)
	S. megacarpa (*S. extensa*)	roots	for galactogogue and childbirth	(25)
Phillipines	All species of *Smilax*	roots & rhizome	to be depurative, anti-syphilitic, antirheumatic rendeial for irregular menses	(25)
Phillipines	*S. bracteata*	roots	to be drunk at childbirth, immediately afterward to treat post partum haemorrhage as a depurative, an emmenagogue, antisyphilitic, and uterine tonic	(25)
		rhizomes	for emmenagogue as a depurative	(25)

Table 1 continued

Geographical Area	Botanical Origin	Part Used	Indication	References
Assam & Manipur	*Smilax lanceifolia*	roots	for rheumatic pains, as poultice over the affect part	(16)
	S. perfoliata		to be used for the same purposes as *S. ovalifolia* in indigenous medicine.	(16)
India	*S. aspera*	roots	to be used as a substitute for Indian sarsaparilla.	(16)
Himalayas	*S. glaucophylla*	all parts	to have shown positive antispasmodic action in isolated guinea-pig ileum.	(16)
Bihar	*S. ocreata*	roots	to be used against dysentery	(16)
Himalaya to Kerala	*S.zeylanica*	roots	to be used as a substitute for sarsaparilla in the treatment of venereal diseases and skin troubles.	(15), (16)
			to be applied for rheumatism and pains in lower extremities	(15)
		bulbous root	for sores, swellings and abscesses.	(16)
Nepal		roots	for gonorrhoea, other discharges from mucous membranes	(15)
Tropical America	*S. medica*	roots	for venereal diseases	(23)
Tropical America	*S. ornata*	roots	for venereal diseases	(23)

Smilax species in Some Tropical and Sub-tropical Regions

In some tropical and sub-tropical Asiatic regions *Smilax* spp. were surveyed as the following :

Geographical regions	No. of *Smilax* spp.	No. of *Heterosmilax* spp.	References
Indo-China	31	5	(26)
Malay Peninsula	13	1	(27)
India	33	1	(28)
Taiwan	21	4	(29)
China Mainland	18	5	(30)

Smilax species of Thailand

Smilacaceae of Thailand surveyed by Tetsuo Koyama (31) includes the genus *Smilax* with 5 sections, 24 species and 8 subspecies, and 3 species of *Heterosmilax*. The recorded Thai vernacular names are as follows :

Section 1 Macranthae

1. *Smilax ovalifolia* Roxb.
   - thaowan yang (เถาวัลย์ยั้ง) (Central)
   - khrua dao (เครือเดา), dao luang (เดาหลวง) (Northern)
   - nampao (หนามเปา) (Northern/Shan)
2. *S. bracteata* Presl
   2.1 *S. bracteata* Presl ssp. *bracteata* (*S. stenopetala* A. Gray)
   2.2 *S. bracteata* Presl ssp. *verruculosa* (Merr.) T. Koyama
   - khuang thon (เขืองโทน)
3. *S. megacarpa* A. DC.

4. *Smilax zeylanica* Linn.

4.1 *S. zeylanica* Linn. ssp. *zeylanica* Linn.

4.2 *S. zeylanica* Linn. ssp. *hemsleyana* (Craib) T. Koyama

5. *S.inversa* T. Koyama

6. *S. luzonensis* Presl.

- khuang (เขือง) (Eastern)

- yan that (ย่านทาด), falaep (ฟ้าแลบ) (Peninsular)

7. *S. verticalis* Gagnep.

- khrua dao (เครือด่าว) (Northern)

8. *S. extensa* Wall. ex A. DC.

9. *S. lanceifolia* Roxb.

- dao (เดา), nam dao (หนามเดา) (Northern)

- thao yang dong (เถายั้งดง) (South-easthern)

10. *S. griffithi* A. DC.

11. *S. siamensis* T. Koyama

12. *S. perfoliata* Lour.

- khrua dao (เครือเดา), kamkung (ก้ามกุ้ง), sadao (สะเดา) daonam (เดาน้ำ) (Northern)

- khuang plongsan (เขืองปล้องสั้น) (Northren)

- kamlang khwai thuk (กำลังควายถึก) (Peninsular)

13. *S. blumei* A. DC.

Section 2 China

14. *Smilax davidiana* A. DC.

- khuang thon (เขืองโทน), khuang soi (เขืองสร้อย)

15. *S. china* Linn.

16. *S. microchina* T. Koyama

- huaya khaaoyen (หัวยาข้าวเย็น)

Section 3 Vaginatae

17. *Smilax biumbellata* T. Koyama

18. *S. microphylla* C.H. Wright

18.1 *S. microphylla* C.H. Wright ssp. *microphylla*

18.2 *S. microphylla* C.H. Wright ssp. *elongata* (Warb.) T. Koyama

19. *S. rigida* Kunth

19.1 *S. rigida* Kunth ssp. *rigida*

19.2 *S. rigida* Kunth ssp. *myrtillus* (A. DC.) T. Koyama

Section 4 Coilanthus

20. *Smilax calophylla* A. DC.

21. *S. glabra* Roxb.

- yahua (ยาหัว) (North-eastern)

22. *S. corbularia* Kunth

22.1 *S. corbularia* Kunth ssp. *corbularia*

- hua khaao-yen-nuea (หัวข้าวเย็นเหนือ)
- hua khaao-yen-wok (หัวข้าวเย็นวอก)

22.2 *S. corbularia* ssp. *synandra* (Gagnep.) T. Koyama

23. *S. myosotiflora* A. DC.

Section 5 Coprosmanthus

24. *Smilax pottingeri* Prain

Heterosmilax polyandra Gagnep.

H. indica A. DC.

H. pertenuis T. Koyama

- hua khaao-yen-nuea (หัวข้าวเย็นเหนือ) (Northern)

Chemical Investigation of *Smilax* species

The investigated chemical constitutents of *Smilax* species are shown in Table 2, page 19-20

Table 2 Chemical Investigation of *Smilax* species

Botanical Origin	Plant Part	Chemical Constituents	References
Smilax aristolochiaefolia	roots	sarsasapogenin, parillin, smilagenin, sitosterol, stigmasterol	(32), (33)
S. aspera	roots	yamogenin	(32)
	roots	sarsasapogenin, asperagenin, high tannin content, 31-norcyclo-artanol β-sitosterol	(16)
	stem & root	heteroside parillin, potassium nitrate	(34)
	leaf	asperoside (bisdesmosine 22-hydroxy furostanol saponin)	(35), (36)
S. china	tuberous root	tannin, resin, cinchonin, smilacin sarsasaponin, diosgenin	(16), (37)
	tubers	isoseryl s-methylcysteamine sulfoxide	(38)
	seeds	fatty oil 11.1 %	(16)
	leaves	rutin	(16)
		flavonoids	(39)
	leaves & stems	13-hentriacontanone	(40)
	rhizome	five diosgenin glycosides characterized as prosapogenin A of dioscin, gracillin, methyl protogracillin, methyl protodioscin and 22-hydroxy analog	(41)
S. excelsa		diosgenin	(32)
		diosgenin, tigogenin	(42)
S. glabra	rhizome	β-sitosterol, stigmasterol	(16), (43)

Table 2 continued

Botanical Origin	Plant Part	Chemical Constituents	References
Smilax glabra	rhizome	β-sitosterol, stigmasterol glucoside and colouring matter	(16), (43)
	rhizome	diosgenin, tigogenin	(8)
	rhizome	astibin, engeletin, 0-(3)-caffeoyl shikimic acid, shikimic acid, ferulic acid β-sitosterol	(44)
Smilax glabra	leaf	quercetin, kaempferol	(44)
S. glycyphylla	leaf	phloretin 2-rhamnoside	(45)
		glycyphyllin	(46)
S. medica		sarsasapogenin	(47)
	leaf	flavonoids	(39)
		pollinastanol	(48)
S. officinalis		sarsasapogenin	(47)
S. ornata		sarsasapogenin, smilacin(smilasaponin) phytosterolin (sitosterol)	(47), (49)
S. parvifolia	roots	diosgenin, diosgenin-3-O-B-D-glucopyranoside	(50)
S. pseudochina	roots	essential oil, hexose, tannins, alkaloids, phytosterol, and β-linolic and oleic acid	(51)
S. sieboldi		tigogenin, neotigogenin, laxogenin	(52)
Smilax sp. (Sarsaparilla)	leaves	β-carotene, neo-β-carotene, cryptoxanthin, lestein, and lutein epoxide (source of provitamin A)	(53)

Saponins and Sapogenins

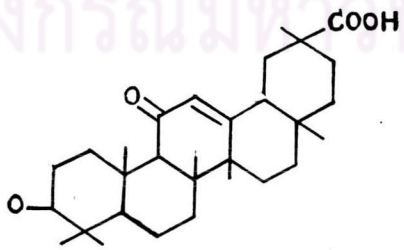
A group of plant glycosides known as saponins share in varying degrees, three common characteristics : (a) foaming in aqueous solution (b) they cause haemolysis of red blood cells when injected into the blood-stream of animals and therefore highly toxic intravenously, but comparative harmless when ingested. (c) the formation of molecular compounds with cholesterol and other 3β-hydroxy steroids (54) (46). Upon hydrolysis they yield an aglycone known as a " sapogenin " (13)

There are two types of saponins :

1. Triterpene saponins

The structure of these saponins are mostly pentacyclic possess the oleanane ring system, or more rarely ursane or dammarane systems. Many are acidic, due to the presence of one or two carboxyl groups in the aglycone and or sugar moiety other oxygen containing groups may also be present in the sapogenin, i.e. -OH, $-CH_2OH$ or -CHO.

All triterpene saponins possess haemolytic activity, which varies from strong to weak, depending on the type of substitution. The example of this saponin is glycyrrhizin (A).

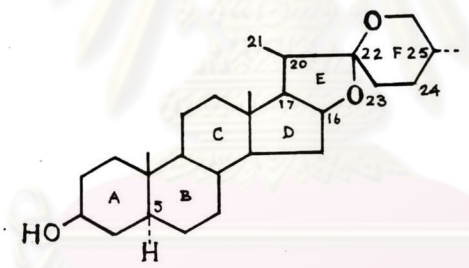


(A)

2. Steroid saponins

The sapogenins of the steroid saponins are mostly spirostanols. Furostanol derivatives are usually converted into spirostanols during isolation procedures : these sapogenins do not carry carboxyl groups. Steroid saponins posssess few sugar units than the triterpene saponins (55).

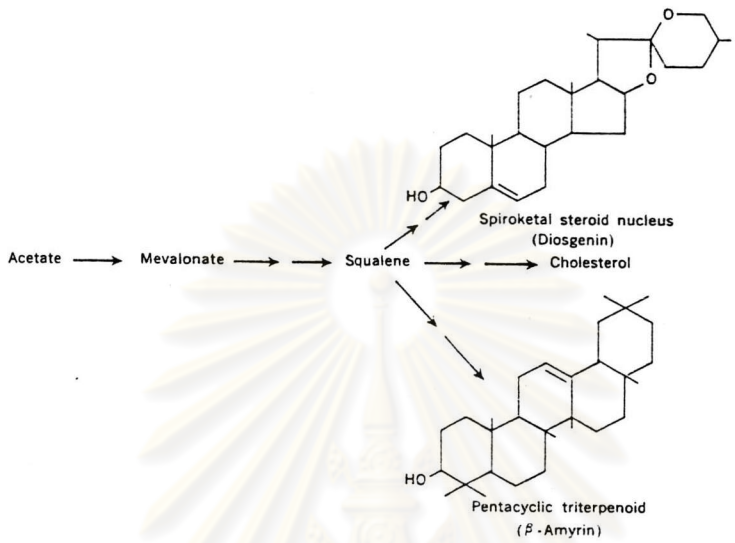
The basic structure of steroid sapogenins is shown as the tigogenin skeleton (B). They are internal ketal of 16,27-dihydroxy-22-ketosteroids with 27 carbon atoms and contain two heterocyclic rings. Ring E is a five-membered (furan) and ring F is a six-membered (pyran) oxyene heterocyclic ring. The rings are joined at C-22 in spiroketal. The C-3 hydroxyl group is almost invariably β-oriented (56).



(B)

Saponins have been detected in over seventy families of plants (57). The steroidal saponins are rather widely distributed among plants. They occur in the Liliaceae family in *Yucca, Trillium, Chlorogalum, Smilax, Nolina,* and *Agapanthus* in the Amaryllidaceae family in *Agave* and *Manfreda* ; in the Dioscoreaceae family in *Dioscorea* ; in the Scrophulariaceae family in *Digitalis.* Previous work indicated that the distribution of saponins was probably even wider. The haemolysis test which was used in the survey, fails if tannins are also present in the plant extracts (58).

The main biosynthetic pathway leading to both types of sapogenins is similar and involves the head-to-tail coupling of acetate units (13). (see Scheme 1)

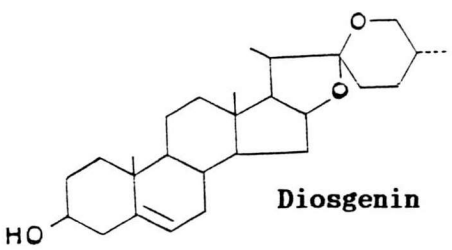


Scheme 1 Biosynthesis of sapogenins (13)

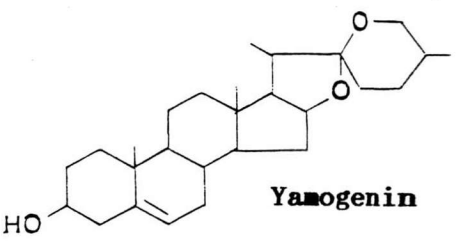
Information on the biological activities of saponins are action on metabolism, cardio-vascular system, antimicrobial activity, reproductive system, anti-inflammatory, and antisclerotic agent (32).

A number of steroidal sapogenins of certain structural types, while they are in themselves not used as therapentic agents, serve as useful starting materials for the chemical synthesis and the practical production of a number of steroidal hormone substances which are medically important agents (54).

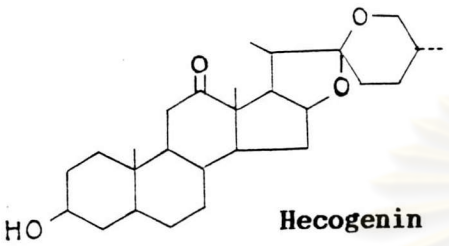
Among the sapogenins which have been found to be the most useful starting materials for chemical conversion to medicinal hormone substances are diosgenin, hecogenin, sarsasapogenin and their respective stereoisomers yamogenin, sisalagenin and smilagenin (54).



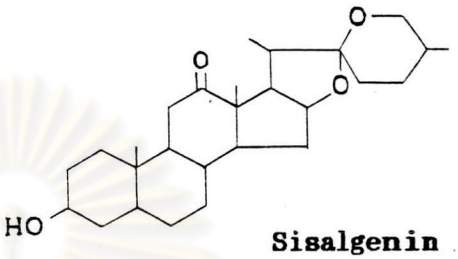
Diosgenin



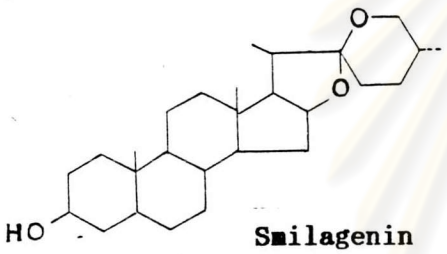
Yamogenin



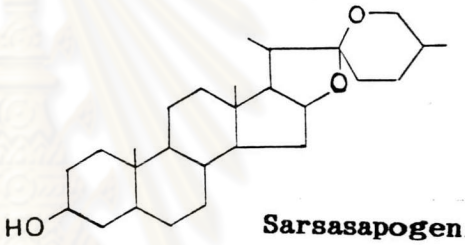
Hecogenin



Sisalgenin



Smilagenin



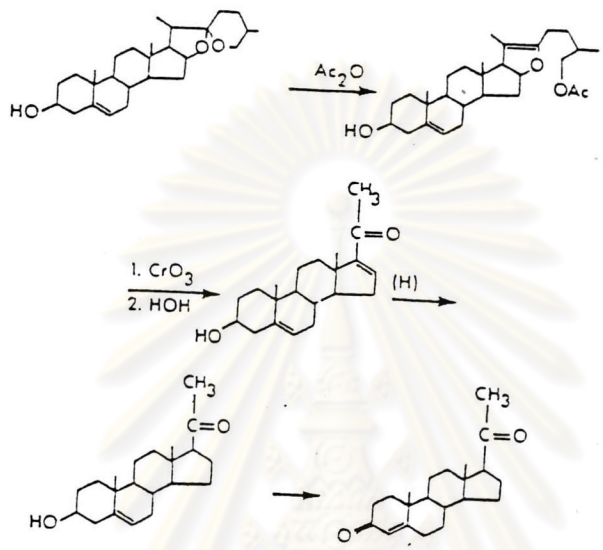
Sarsasapogenin

Major Plant Starting Materials for Hormone Synthesis (23)

Source	Compound
Dioscorea spp.	diosgenin, botogenin
Agave spp.	hecogenin, manogenin, gitogenin
Solanum spp.	solasodine
Strophanthus spp.	sarmentogenin
Smilax spp.	sarsasapogenin, smilagenin

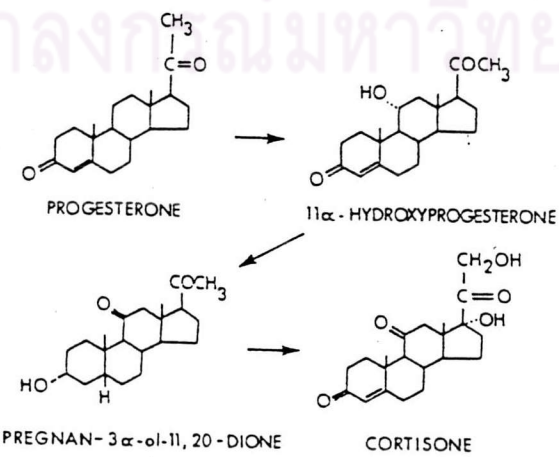
Most hormones obtained in a pure state and on a large scale must be synthesized by combined chemical and microbiological processes. However partial synthesis (ie., starting with a performed steroidal nucleus) is far more practical than total synthesis. Progesterone, for example can be synthesized from diosgenin in only four steps. Diosgenin is treated with acetic

anhydride (AC_2O) and yields an ester of the pseudosapogenin. this when oxidized with chromium trioxide (CrO_3) following by hydrolysis, yields two intermediates compound and finally progesterone (22). (see Scheme 2)



Scheme 2 Synthesis of progesterone from diosgenin (23)

By chemical means, together with techniques of enzyme hydroxylation (especially at the 11 position) with the use of appropriate micro-organisms (the fungus Rhizopus (23)), these sapogenins are converted to a number of other adrenocortical steroids e.g. cortisone and sex hormones of medicinal importance (54). (see Scheme 3)



Scheme 3 Conversion of progesterone to cortisone by combining chemical and microbiological (using Rhizopus) synthesis (23)