Chemistry and Physiological Properties of Gymnemic Acid, the Antisaccharine Principle of the Leaves of *Gymnema sylvestre*

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After chewing a few leaves of *Gymnema sylvestre*, the ability to taste sweet substances—e.g., sucrose, sodium saccharin, and sodium cyclamate—is suppressed for a few hours. Earlier investigations detected the acidic and glycosidic nature of the active principle which was called gymnemic acid. More recently some components of this material, which appeared to be a mixture, were isolated. The major component, gymnemic acid A_1, which still possesses the antisweet property, has been shown to be a D-glucuronide of a new hexahydroxytriterpene (esterified with different acids). On the basis of physical and chemical data the structure of the new triterpene could nearly be established.

The leaves of the tropical plant *Gymnema sylvestre* R.Br. possess a strange property. After chewing one or two leaves one is unable to detect the sweet taste, and the bitter taste is also suppressed to some extent. Drinking sweet tea one can fully appreciate the aroma of the tea but not the taste of the sugar (*Pharm. J.*, 1847-8). Sugar itself is like sand which dissolves slowly in the mouth (*Pharm. J.*, 1847-8). In a sweet orange only the taste of citric acid can be detected (Hooper, 1886/87, 1887). The taste sensitivity for other sweet substances like glycerol (Shore, 1892), saccharin (Warren and Pfaffmann, 1959; Yackzan, 1964), and sodium cyclamate (Yackzan, 1964) is also suppressed. Quinine sulfate taken as a solid after a dose of leaves tastes like chalk (Hooper, 1886/87, 1887). Even picric acid in saturated solution is said to excite no taste sensation after chewing a few leaves (Shore, 1892). The roots show the same properties (Stöcklin *et al.*, 1967) but these strange effects last for only a few hours (Hooper, 1886/87, 1887).

Gymnema sylvestre belongs to the asclepiadaceae, a family whose plants usually have an acrid taste due to the presence of the very toxic cardiac glycosides. But the leaves of *Gymnema sylvestre* have only a slightly bitter taste and are not toxic to humans in gram quantities. The plant, a large woody much branched climber running over the tops of high trees, grows in Central and Western India (Hooker, 1885; Mhaskar and Caius, 1930), in tropical Africa, and in Australia (Simes *et al.*, 1959; Webb, 1952).

BACKGROUND INVESTIGATIONS

Physiological and Medicinal Properties. The above-mentioned property of this plant was first reported in the western literature in 1847 (*Pharm. J.*, 1847-8; *Proc. Linnean Soc.*, 1847), but seems to have been known long before in India. The Hindustani name Gur-mar (Chopra *et al.*, 1928, 1929), meaning sugar-destroying, is characteristic.

Because of this property the leaves of *Gymnema sylvestre* have been investigated. Other physiological and medicinal properties have been known among the natives of India (Chopra *et al.*, 1958; Mhaskar and Caius, 1930) and have been found during later investigations (Gharpurey, 1926; Sinsheimer *et al.*, 1968; Yackzan, 1964, 1966). In India the leaves have been used as a stomachic, diuretic, and remover of cough, throat trouble, and pain in the eyes. Wonderful results against diabetes mellitus have been claimed (Gharpurey, 1926). The powdered roots have been used by Hindu physicians as a remedy for snake bite (Mhaskar and Caius, 1930). None of these uses among the natives of India has been proved definitively to be of value, but the leaves have at least some effect on blood sugar. A wide literature covers the effect of *Gymnema sylvestre* on blood sugar in animals and in men (Chatterjee, 1958; Chopra *et al.*, 1928, 1929, 1958; Gharpurey, 1926; Gupta, 1961, 1962, 1963a, b; Gupta *et al.*, 1961, 1962; Gupta and Seth, 1962; Gupta and Variyar, 1959, 1961, 1964; Jain and Sharma, 1967).

As early as 1887 Hooper noted that the antisweet principle was of an acidic nature and called it gymnemic acid. Though his material was a dark colored mass, the name gymnemic acid has been retained by all later authors. Its effect on the four taste qualities, sweet, bitter, sour, and salty, was first investigated extensively by Shore (1892). His characterization of the action of the leaves has on the whole been accepted by all later investigators and proved by electrophysiological techniques and is therefore worth mentioning. He summarizes his results in the following manner:

> From a large number of experiments with these four substances I find that the action of gymnema on the taste they excite may be stated briefly as follows:
>
> Glycerine. The sweet taste is very readily prevented in all regions.
>
> Quinine. The bitter taste is easily prevented, but not so readily as that of glycerine, especially at the back of the tongue.
>
> H_2SO_4. Acid taste in dilute solutions not affected at all. Very dilute solutions still with ease detected. After prolonged action of gymnema 0.05% H_2SO_4 still detected at the tip.
>
> NaCl. Salt taste very slightly, if at all, influenced. After prolonged action 0.5% still detected at the tip.

The same results were reported completely independently 2 years later by Kiesow (1894). Both inves-

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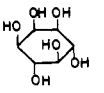
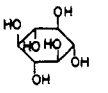
Table I. Components Isolated from *Gymnema sylvestre*

Tartaric acid
Phytol, $C_{20}H_{40}O$
Nonacosane, n-$C_{29}H_{60}$
Hentriacontane, n-$C_{31}H_{64}$
Tritriacontane, n-$C_{33}H_{68}$
Pentatriacontane, n-$C_{35}H_{72}$

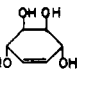
(−)-Viburnitol



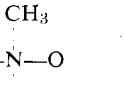
Myoinositol ?



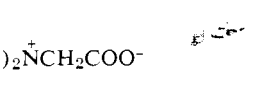
Scyllitol ?



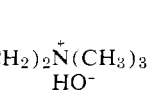
Conduritol A



Trimethylamine oxide

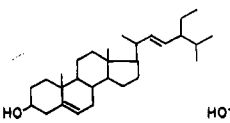


Betaine

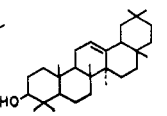


Choline

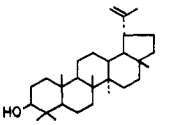
Adenine



Stigmasterol



β-Amyrin



Lupeol

tigators found a slight effect on the taste sensations of NaCl solutions, which perhaps may be due to the known sweet taste of very dilute salt solutions (Pfaffmann, 1959).

Chemical Investigations. During the chemical investigations a number of pure compounds were isolated and identified (Table I). None shows antisweet activity. Tartaric acid had been identified by Hooper (1886/87, 1887) and confirmed by Mhaskar and Caius (1930). Phytol was obtained after degradation of chlorophyll (Mhaskar and Caius, 1930). Different hydrocarbons (all with an odd C-number) (Manni, 1963; Manni and Sinsheimer, 1965; Mhaskar and Caius, 1930; Power and Tutin, 1904b) and different cyclitols (Manni, 1963; Manni and Sinsheimer, 1965; Mhaskar and Caius, 1930; Posternak and Schopfer, 1950; Power and Tutin, 1904a, b, c) could be obtained in crystalline form. The two inositols isolated by Mhaskar and Caius (1930) have been characterized only by their melting points, but these lead to the suggestion that they were myoinositol and scyllitol. Several nitrogen-containing substances have been isolated in small yield after toilsome work (McIlhenny, 1966; Sinsheimer and McIlhenny, 1967) and stigmasterol, β-amyrin, and lupeol (Khastgir *et al.*, 1958) are the only polycyclic components isolated from the plant. Later investigators could not always confirm the earlier results and it seems probable that either the plant had not always been identified properly or that the species *Gymnema sylvestre* exists in different chemical variants.

Before 1950 very little was known about the chemical nature of gymnemic acid. In 1889 Hooper reported that it occurs as a potassium salt in the plant. From the analyses of the acid and of different salts and from titration results he even gave a formula, which later could not be confirmed. After boiling gymnemic acid with dilute hydrochloric acid the antisaccharine property was destroyed and the reaction liquid obtained reduced Fehling's solution. Therefore, Hooper (1889) concluded that gymnemic acid is a glycoside. Power and Tutin (1904b) could not detect any sugar after treatment with dilute hydrochloric or sulfuric acid, but the antisaccharine property had been destroyed by this treatment as well as by treatment with potassium hydroxide.

RECENT INVESTIGATIONS OF ACTIVE PRINCIPLE

Physiological Investigations. Physiological investigations during the last 20 years show some interesting features. Andersson *et al.* (1950) proved by electrophysiological methods that the response to sucrose in dogs was almost completely abolished and the response to strychnine was greatly reduced. Neural and psychophysical results of Diamant *et al.* (1965) indicated that in men only the taste of sweet-tasting chemicals (sucrose, fructose, sodium saccharin, and sodium cyclamate) is affected by aqueous extracts of *Gymnema sylvestre;* there was no effect on the taste response to other solutions such as NaCl, citric acid, quinine hydrochloride, and quinine sulfate. On the contrary, other workers (Hooper, 1886/87, 1887, 1889; Kiesow, 1894; Quirini, 1891; Shore, 1892) reported an effect on bitter-tasting substances.

In 1959 Warren and Pfaffmann reported the isolation of microcrystalline gymnemic acid. They showed that its potassium salt, potassium gymnemate, contains about the same activity as the aqueous extract of the leaves. The threshold sensitivity for sucrose and sodium saccharin is changed to the same degree. The inhibition effect of potassium gymnemate is not proportional to its concentration, but levels off at the higher concentrations. In 1964 Yackzan confirmed that the water-soluble material of the leaves depresses the taste sensitivity in human beings to sucrose, saccharin, and sodium cyclamate, and demonstrated by electrophysiological techniques the suppression of taste sensitivity to sucrose in hamsters. He also showed that *Gymnema sylvestre* suppressive effect in the hamster extended to other taste substances—quinine hydrochloride, NaCl, and HCl solutions. This suggested that the effect of the plant

leaves extract on the taste receptor is general and not specific for sugars or sweet substances. Yackzan suggested anatomical and biochemical changes in the taste receptor. The mechanism of suppressing taste sensitivity has not yet been explained. But it is evident that taste suppression involves direct interaction with the taste buds and it is different from that obtained by cocaine, which shows a local anesthetic effect.

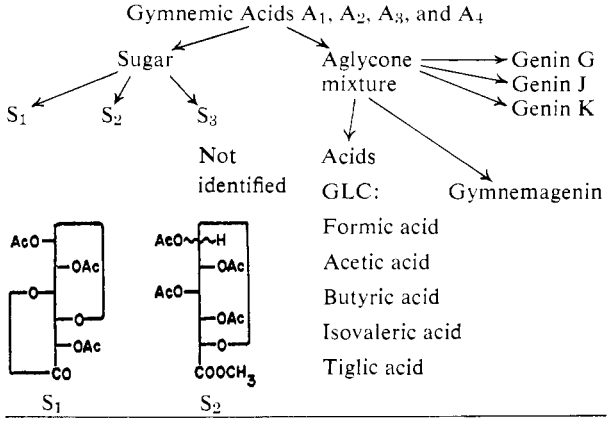
Chemistry of Active Principle. Warren and Pfaffmann's gymnemic acid (1959) appeared to be a glycoside which yielded glucose, arabinose, and a small quantity of glucuronolactone upon hydrolysis (Pfaffmann, 1959). They confirmed the results of earlier workers (Hooper, 1889; Power and Tutin, 1904b) that the hydrolyzate had no effect on taste. Some years later Yackzan (1966) reported the isolation of gymnemic acid with about the same melting point as Warren and Pfaffmann, and suggested that gymnemic acid could be a saponin because of its glycosidic nature, its foaming in aqueous solution, and its ability to hemolize erythrocytes in a weak solution.

Crude gymnemic acid is best obtained by mineral acid precipitation from the aqueous extract of the leaves (Hooper, 1886/87, 1887). After the residue has been dried, representing about 5 to 10% of the leaves, it can be extracted with chloroform to withdraw some inactive material. With acetone all physiologically active material (about 50%) can be extracted. Power and Tutin mentioned (1904b) that gymnemic acid is soluble in acetone, and in 1964 Yackzan used acetone for separation. The remaining acetone-insoluble brownish powder showed no antisaccharine activity (Stöcklin, 1965), had a relatively high nitrogen content (about 2.7%) (Stöcklin, 1967b), and was at least partly of glycosidic nature (Stöcklin, 1965). The acetone-soluble material can be chromatographed on silica gel using ethyl acetate with increasing proportions of acetone (Sinsheimer *et al.*, 1968). It is especially important to avoid acids and bases as far as possible. Warren and Pfaffmann (1959) crystallized the crude mineral acid precipitate twice from ethyl carbonate and once from a large amount of ether and obtained good separation.

When we started our investigation on gymnemic acid little was known about its chemical nature. Therefore neither loss of material by degradation nor production of artificial products could be eliminated. First we isolated a material which showed one spot in four different TLC systems but was separated in a fifth system into four spots, A_1, A_2, A_3, and A_4, based upon increasing polarity. The gymnemic acid isolated by Warren and Pfaffmann (1959) showed only the spots A_1 (about 70%) and A_2. A_1 was by far the major component and could be isolated in pure form. Since we used acidic and basic solvents for this separation, the loss was very large. Therefore we used the mixture of A_1, A_2, A_3, and A_4 for degradation experiments.

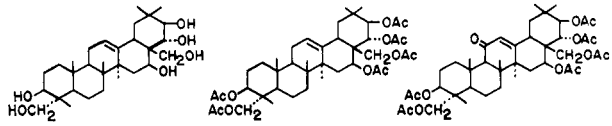
After acidic hydrolysis of this material we obtained material containing a water-soluble sugar and another containing a chloroform-alcohol-soluble aglycone. Both showed several spots on TLC and PC. Better results were obtained by dissolving the gymnemic acid A_1, A_2, A_3, and A_4 mixture in 10^{-2} N $KHCO_3$ solution and adding a β-D-glucosidase isolated from snails. After extraction of the reaction mixture with chloroform-alcohol, the remaining water-soluble material showed only one spot in PC and paper electrophoresis and had the same R_f value as glucuronic acid. TLC of the aglycone mixture showed four spots; at least some of them arose from hydrolysis of ester groups in the slightly alkaline solution or from enzymatic degradation. After chromatography of this material, three substances (G, J, and K) were obtained in pure form. After mild saponification each gave the same crystalline deacylgenin, which was called gymnemagenin, and which was also obtained as the only neutral component after alkaline hydrolysis of the crude aglycone mixture. The acids obtained by this procedure were investigated only by gas and paper chromatography and contained formic acid, acetic acid, butyric acid, isovaleric acid, and tiglic acid (Table II).

Table II. Degradation of Gymnemic Acids A_1, A_2, A_3, and A_4



The sugar solution was neutralized, concentrated, acidified, treated with diazomethane, and acetylated. After chromatography of the obtained material, three crystalline substances were isolated: the main product, S_1, a by-product, S_2, and a trace of a third product, S_3. S_1 could be identified as tri-*O*-acetyl-β-D-glucofururonolactone. S_2 showed two different crystal forms and melting points and was identified as a mixture of the two anomers of the methyl ester of tera-*O*-acetyl-D-glucuronic acid. S_3, from which only 2 mg. were obtained, could not be identified (Stöcklin *et al.*, 1967).

The structure of gymnemagenin has not yet been established completely but a formula has been proposed mainly from data obtained by physical methods (Stöcklin, 1967a, 1968, 1969). The molecular formula $C_{30}H_{50}O_6$ led to the suggestion that gymnemagenin could



Gymnemagenin	Hexa-*O*-acetyl-gymnemagenin	11-Oxo-hexa-*O*-acetyl-gymnemagenin
$C_{30}H_{50}O_6$ (506) m.p. 328–35°	$C_{42}H_{62}O_{12}$ (758) m.p. 290–91°	$C_{42}H_{60}O_{13}$ (772) m.p. 315.5–16°

be a pentacyclic triterpene. The ultraviolet spectrum showed only end absorption, indicating one double bond, probably trisubstituted. The infrared spectrum showed a broad HO-band but no absorption in the car-

Table III. Gymnemic Acids Isolated in Pure or Nearly Pure Form

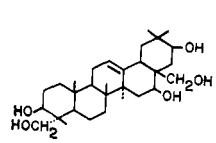
Warren and Pfaffmann (1959)	70%	30%	—	—	—	—
Yackzan (1964, 1966)	+	+	?	?	—	—
Stöcklin (1965)						
Stöcklin *et al.* (1967)	A_1	A_2	A_3	A_4	—	—
Sinsheimer *et al.* (1968)	A	B	—	—	C	D

bonyl region. The positive reaction toward periodate indicated the presence of at least one 1,2-diol group. Acetylation under mild conditions led to the hexaacetate. Its positive reaction with tetranitromethane confirmed the presence of a double bond. But this double bond could not be hydrogenated with Pt in acetic acid, which is characteristic for the hindered double bond in the oleanene skeleton. Oxidation of the hexaacetate with chromic acid in acetic acid gave the 11-oxo derivative, also typical of this skeleton. Mass spectra and NMR spectra of different derivatives including several isopropylidene derivatives (Stöcklin, 1967a, 1969) are consistent with the proposed structure without proving it.

Gymnemic acids A_1, A_2, A_3, and A_4 are therefore probably β-D-glucuronides of different acylated gymnemagenins. It has not yet been shown if the sugar part contains one or more molecules of glucuronic acid and if the glucuronic acid is partly esterified. The mass spectrum of gymnemic acid A_1 is not very informative but contains some indications that the glucuronic acid might be linked in furanoid form (Bauer, 1967; Stöcklin, 1967b).

The different gymnemic acids are reported in Table III. Warren and Pfaffmann's gymnemic acid contains about 70% A_1 and 30% A_2. Judging from the melting points obtained in different portions of gymnemic acid by Yackzan (1964, 1966), his material contains A_1 and A_2 and probably also traces of A_3 and A_4. From our mixture of gymnemic acids A_1, A_2, A_3, and A_4 (Stöcklin *et al.*, 1967), A_1 could be isolated in pure and A_2 in nearly pure form. At least two of these components show very strong antisaccharine activity. Sinsheimer *et al.* (1968) could isolate the four gymnemic acids, A, B, C, and D. A and B were identical with A_1 and A_2, respectively, by direct comparison on TLC in five systems (Sinsheimer *et al.*, 1968). It is uncertain if their acids C and D, which contain glucose in addition to glucuronic acid, show the antisaccharine property and if gymnemagenin is also the aglycone of these two acids. Sinsheimer *et al.* (1968) tested their four acids against influenza virus in vitro. Gymnemic acid A showed good inhibition, B a moderate one, and C and D none.

After enzymatic degradation of more polar fractions which did not contain gymnemic acids A_1 and A_2, we were able to isolate unacylated gymnemagenin and a new pentahydroxytriterpene. The latter was called gymnestrogenin and a formula has been proposed based on physical data and biosynthetic considerations. Gymnestrogenin probably differs from gymnemagenin by the absence of the 22α-hydroxy group (Stöcklin, 1968). The sugars obtained by enzymatic degradation were identified by chromatographic methods as glucuronic acid and glucose. It is possible that gymnemic acids C and D of Sinsheimer's group (1968) may contain gymnestrogenin as aglycone.



GYMNEMIC ACIDS IN FOOD CHEMISTRY, AN OUTLOOK

Acidic saponins—i.e., esterified triterpene glycosides containing glucuronic acid or galacturonic acid—are very common in plants. But the suppression of sweet sensitivity has been reported only for *Gymnema sylvestre*, a few other less known species of the same genus (Hooper, 1889), and *Eriodictyon californicum* (H. & A.) Greene (fam. Hydrophyllaceae), a shrub growing in Northern California, also known as yerba santa (Pfaffmann, 1959; Yackzan, 1964, 1966). Two other plants seem to modify taste sensations. The Sudanese plant *Bumelia dulcifica* is said to change sweet and bitter to sour (Pfaffmann, 1959) and the berry (miracle fruit) of the Nigerian plant *Synsepalum dulcificum* (Schum.) Daniell (fam. Sapotaceae) changes the sour taste to sweet (Inglett *et al.*, 1965). Though the physiological properties of the last two plants are reported to be different, Hutchinson and Dalziel (1963) classify them as synonyms. Recently Kurihara and Beidler (1968) showed that the active principle of *Synsepalum dulcificum* is a basic glycoprotein and is therefore completely different from the gymnemic acids.

It seems reasonable to expect other saponins to have an effect similar to the gymnemic acids but we should not forget that the taste sensations are very sensitive to changes in the geometry of the molecules (Beidler, 1966; Solms, 1967). Like the flavor potentiators, different flavor modifiers and inhibitors probably will be found in the future, but only by chance unless somebody starts a systematic investigation of the effect on taste sensations of a large number of compounds.

An investigation, testing the suppression or modifying of taste sensations by known saponins and different simple furanoid and pyranoid glucuronides, could perhaps help find other physiologically active components and show which part of the molecule is responsible for taste suppression. It would be particularly interesting to check the action of completely deacylated gymnemic acid on the taste suppression of sweet substances. The gymnemic acids are active as acids (Kiesow, 1894) and as potassium or sodium salts (Shore, 1892; Warren and Pfaffmann, 1959). But there still exists no quantitative comparison of the taste suppression of these forms and no comparison of the relative strength of the active principle on sweet and bitter tasting substances.

It would further be interesting to test the action of gymnemic acid on other sweet compounds like inorganic salts—e.g., salts of Pb and Be or NaCl and KCl in very dilute solutions—and the large number of sweet organic substances not yet examined (Pfaffmann, 1959). These investigations could lead to better knowledge of the mechanism of taste sensations.

If readily available substances which selectively suppress or modify taste sensations are found, they will receive their place in food chemistry, as flavor potentiators (Solms, 1967) already have.

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