Resin Glycosides from the Morning Glory Family

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Contents
1. Introduction ......................................................... 79
2. Ethnobotanical Background and Discovery .......................... 79
3. Structural Diversity .................................................. 82
  3.1. Chemical Composition ........................................ 82
  3.2. Resin Glycosides .............................................. 83
4. Isolation Techniques ................................................ 123
5. Structure Elucidation of Resin Glycosides .......................... 123
  5.1. Degradative Chemical Methods ................................ 123
  5.2. Spectroscopic Methods ....................................... 124
  5.3. Crystallographic Methods .................................... 128
  5.4. Molecular Modeling .......................................... 130
6. Strategies for Synthesis ............................................ 131
  6.1. Tricolorin A ................................................... 131
  6.2. Ipomoeassin E .................................................. 135
  6.3. Woodrosin I ................................................... 138
7. Significance ........................................................ 138
  7.1. Traditional Medicine and Morning Glories ..................... 140
  7.2. Biological Activities ......................................... 142
  7.3. Pharmacology and Toxicology ................................ 145
  7.4. Chemical Ecology ............................................. 146
References ............................................................. 147

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Plate 1. Ethnobotany and Background. Convolvulaceae, the botanical name for the morning glory family, derives from the Latin *convolvo*, referring to its growth of intertwining vines (A: Heavenly blue, *Ipomoea tricolor*). The purgative properties of the Mexican roots were readily accepted in Europe when introduced in the sixteenth century, since pre-Christian folk tradition had already proclaimed the virtues of *skammonia* as found in Dioscorides’ work *De Materia Medica*, ca. 50–68 A.D.
1. Introduction

Resin glycosides are part of a very extensive family of secondary metabolites known as glycolipids or lipo-oligosaccharides and are constituents of complex resins (glycoresins) (1) unique to the morning glory family, Convolvulaceae (2). These active principles are responsible for the drastic purgative action of all the important Convolvulaceous species used in traditional medicine throughout the world since ancient times. Several commercial purgative crude drugs can be prepared from the roots of different species of Mexican morning glories. Their incorporation as therapeutic agents in Europe is an outstanding example of the assimilation of botanical drugs from the Americas as substitutes for traditional Old World remedies (3). Even though phytochemical investigations on the constituents of these drugs were initiated during the second half of the nineteenth century, the structure of their active ingredients still remains poorly known for some examples of these purgative roots. During the last two decades, the higher resolution capabilities of modern analytical isolation techniques used in conjunction with powerful spectroscopic methods have facilitated the elucidation of the active principles of these relevant herbal products.

This chapter describes the ethnobotanical information associated with the purgative morning glory species and how traditional usages were instrumental in plant selection for chemical studies. The advantages and limitations of available analytical techniques for the isolation, purification, and structure characterization of the individual constituents of these complex glycoconjugates are also discussed. Structure elucidation has been conducted on resin glycoside mixtures of 34 convolvulaceous species pertaining to the subfamily Convolvuloideae, with the exception of Cuscuta (two species), and include five genera: Ipomoea (23 spp.), Merremia (three spp.), Convolvulus (three spp.), Operculina (two spp.), and Calystegia (one sp.). A reliable compilation of the structures of the individual resin glycosides and their glycosidic acid derivatives known to date is provided.

2. Ethnobotanical Background and Discovery

The botanical name Convolvulaceae for the morning glory family derives from the Latin convolvo, meaning interlaced, and describes a growth pattern of intertwining vines wrapping around a support, and is characteristic of the majority of the species
Plate 2. Jalap (“Rhizoma Jalapae”), the root of Ipomoea purga. The root of this evergreen vine (A: Traditional production system in Central Veracruz, Mexico) is one of several distantly related tuberous New World Ipomoea species, including I. orizabensis, I. stans, I. jalapa, and I. simulans, which are the source of a group of valued purgative remedies known as “jalaps”. The therapeutic benefits were recognized early as illustrated by this eighteenth century illustration (B: Juan Navarro’s Natural History. Historia Natural o Jardín Americano, a manuscript of 1801 fol. 211, with permission of UNAM). Fresh and darker smoke-dried roots of “Rhizoma Jalapae” (C) of which the drug consists. Examples of the fragmented roots into which they are offered commercially (D).
The most noticeable anatomical characteristics of this family are the presence of cells in foliar and floral tissues, seeds, and the periderm of tuberous roots, which secrete glycoresins. The ethnopharmacological knowledge of plant containing-resin glycosides strongly influenced early phytochemical investigation and the discovery of these bioactive principles. In Mesoamerica, purgative remedies, known to the pre-Hispanic Aztecs as “cacamotli tlanoquiloni”, consisted of diverse kinds of tuber-shaped roots, which varied in morphological characteristics, habitat, and potency of effects. Contemporary investigations have identified these roots as belonging to the genus *Ipomoea*, currently recognized as *I. purga*, *I. orizabensis*, *I. stans*, and *I. jalapa*, together with a few others less often used. The Spanish colonists took notice of these perennial, herbaceous bindweeds with cathartic, acrid-tasting, and resin-producing roots because their purgative properties were important to sixteenth century European galenic medicine. These Mexican purgative roots were readily accepted as a New World succedaneum of scammony (*Convolvulus scammonia*), an Eastern Mediterranean herb, known in English as Syrian or purging bindweed, which had been used since pre-Christian times. In addition, several field (*Convolvulus arvensis*), hedge (*C. sepium*), and sea (*Calystegia soldanella*) bindweed types were likewise extensively documented in European herbals for their purgative properties.

In fact, a major commercial enterprise was launched between the Americas and Europe that continues to this day from the introduction to the Old World of the so-called “root of Michoacan”, named after the Western province of New Spain where it was thought to have been originally found and known in English herbals as “rhubarb of the Indies”. The mild effects of this new drug gained a rapid and widespread acceptance in Europe, as well as being subsequently viewed and known as a panacea. The precise identification of this root is still much disputed, although it is now generally agreed that it is *I. purga* (Plate 2). In recognition of its important benefits, the colonists bestowed the vernacular name “Jalapa” on this signature species ("officinal jalap" or “Rhzoma Jalapa”), for they found it in abundance in the tropical region of Xalapa, in the state of Veracruz. A second purgative root likewise restricted to the tropical areas in the Gulf of Mexico, “Orizaba jalap”, identified as *I. orizabensis*, often has been used as a substitute or adulterant for the true jalap, producing a moderately strong cathartic. Even today, this root is referred to as false jalap or Mexican scammony. The jalap medicinal plant complex included “jalapa hembra” or “oficinal” (*I. purga*), “jalapa macho” (*I. orizabensis*) and “jalapa de Tampico” (*I. simulans*), although in the ethnobotany of the neotropical and Indomalayan ecozones, several morning glories belonging to the genera *Ipomoea*, *Merremia*, and *Operculina* are also employed.

The cathartic crude drugs are derived from the roots, which are rich in glycore-sins (10–18% dry weight), and provoke peristaltic movements in the small intestine. Pharmaceutical products come in the form of liquid alcoholic extracts, root or resins powders that are consumed singly or in combination with other ingredients to modify the therapeutic effect. Once the demand for these roots declined due to various reasons, German and Italian herbalists introduced to the world market other plants such as Brazilian-grown jalap, *I. operculata* (syn. *Operculina macrocarpa*),
and “Indian jalap”, the roots of Ipomoea turpethum (syn. O. turpethum), which are available as milder but still very effective laxatives.

Phytochemical reports for jalap root were published as early as the second half of the nineteenth century (2), although most of the botanical and chemical descriptions found in the literature up to even recently are confusing and not scientifically reliable. The structural complexity of the resin glycosides seriously hampered the isolation of individual analogues limiting these chemical studies to the characterization of only their products of chemical degradation (11). Resin glycosides were seen as very large, high molecular weight polymers of oligosaccharides glycosidically linked to a hydroxylated fatty acid (12). In the 1980s, the application of high-performance liquid chromatography (HPLC) led to the isolation of four pure natural constituents from a resin glycoside mixture for the first time. They were collectively called orizabins from the Mexican scammony (I. orizabensis), their supposed source (13). The use of contemporary techniques such as high-field nuclear magnetic resonance (NMR) and high-resolution mass spectrometry (MS) allowed for the structure characterization of the above-mentioned compounds as individual macrolactones of a distinctive glycosidic acid and forced the rethinking of the long sustained hypothesis of a polymeric structure for this class of compounds.

3. Structural Diversity

3.1. Chemical Composition

Resin glycosides are glycosyl derivatives of monohydroxy and dihydroxy C_{14} and C_{16} fatty acids. Their structures are unusual for they are amphipatic metabolites, meaning that their structure contains hydrophobic (fatty acid aglycones) as well as hydrophilic (sugar or glycone) moieties. The latter are composed by a heteropolysaccharide of only a few residues (up to six), which are of no more than four different monosaccharides. Sugar units found in these metabolites are d-glucose and epimers of pentoses (L-rhamnose, d-fucose, d-quinovose, and d-xylose) in their pyranose forms. The O-glycosidic linkage is the only type connecting the monosaccharide residues between each other and with the aglycone. L-Rha-(1→2)-d-Fuc, L-Rha-(1→4)-L-Rha, and D-Glc-(1→2)-D-Fuc moieties represent highly conserved disaccharide subunits. The structural complexity arises from the variable linkage positions as (1→2), (1→3), (1→4), and (1→6). Short-chain aliphatic acids, e.g., acetic (ac), propionic (pa), n-butyric (ba), isobutyric (iba), (2S)-methylbutyric (mba), 3-methylbutyric (3-mba), (−)-(2R,3R)-3-hydroxy-2-methylbutyric (nilic acid, nla), and tiglic (tga) acids, arylalkyl acids such as (E)-cinnamic acid (ca), and
saturated fatty acids with different chain lengths, e.g., \( n \)-hexanoic (hexa) or caproic, \( n \)-octanoic (octa) or caprylic, \( n \)-decanoic (deca) or capric, \( n \)-dodecanoic (dodeca) or lauric, \( n \)-hexadecanoic (hexadeca) or palmitic, \( n \)-octadecanoic (octadeca) or stearic, and \( n \)-eicosanoic (eicosa) or arachidic acids, are among the most frequently found ester substituents linked to the oligosaccharide cores. Most of them contain jalapinolic acid, \((11S)\)-hydroxyhexadecanoic acid, as the aglycone, which is always arranged to form a macrolactone ring spanning two or more units of their saccharide backbones. The chemical diversity of these oligosaccharides is further increased by the diverging possibilities of cyclization of the glycosidic acid cores into corresponding macrolactones. In addition, the multiple variations caused by acylation considerably increase their structural variety. In fact, on the whole, a large number of resin glycoside congeners occur in the Convolvulaceae family as well as a remarkable number in each species.

### 3.2. Resin Glycosides

The presence of resin glycosides in Convolvulaceous plants has been established through two approaches. The first one was by means of an ethnomedical rationale associated with the laxative properties of the herbal drugs (3). The second one was the isolation of the crude resins and the identification of their hydrolysis products (2), mainly through isolation of the glycosidic acid produced under saponification (10). Resin glycosides were classified into two groups based on their solubility in ether: jalapin (soluble) and convolvulin (insoluble). The jalapin group shares the common structure of a macrolactone composed by one acylated glycosidic acid. Members of the convolvulin group possess larger molecular weights, which could be a result of being oligomers of glycosidic acids (12).

Up to now, Convolvulaceae resin glycosides have not been reviewed per se but have been included in two reviews (2, 11). The latest is not comprehensive, dealing only with the structural composition of resin glycosides through their products of hydrolysis (2). Since 239 of these compounds are presently known, a comprehensive review is presented in this chapter. The chemical diversity of these resin glycosides has been divided into groups based on the size of their oligosaccharide cores, thus imposing a logical sequence of structural complexity among congeners and listed in alphabetical order. To date, 53 different glycosidic acids have been identified, of which a large number have been accorded trivial names based on their plant source. In the present review, individual glycosidic acids are named according to the rules established by the Chemical Abstracts Service and only the structures for intact resin glycosides are presented. They are not IUPAC names but clearly describe the fragments of which each oligosaccharide is composed. For example, the correct IUPAC name for compound 1 would be \((2R,3R)-(3S,4S,4aR,16S,17aR)-2\text{-methyl-6-oxo-16-propyl-4-}((2S,3R,4S,5R)-3,
4,5-trihydroxy-6-methyltetrahydro-2H-pyran-2-yloxy)hexadecahydropyrano-[3,2-b][1,4]dioxacyclopentadecin-3-yl)-3-hydroxy-2-methylbutanoate.

3.2.1. Disaccharides

Cuscutic Resinoside A

Cuscutic resinoside A (1; tetradecanoic acid, (11S)-[6-deoxy-3-O-(6-deoxy-\(\alpha\)-L-mannopyranosyl)-4-O-[(2R,3R)-3-hydroxy-2-methyl-1-oxobutyl]-\(\alpha\)-L-manno-pyranosyl]oxy]-intramol. 1,2'-ester) was obtained from the ethyl acetate-soluble fraction of a methanol extract prepared from the seeds of *Cuscuta chinensis* Lam. The purification of this compound employed a combination of column and preparative-scale HPLC. The structure was deduced from spectroscopic evidence and acid hydrolysis (14). The degradative process gave convolvulinolic acid, nilic acid, and L-rhamnose. The sugar components were identified by GC analysis after being converted to their thiazolidine derivatives. This disaccharide has a unique macrocyclic lactone, which is placed between C-1 and C-2 of the first rhamnose moiety.

Ipomoeassins A–F

Six individual disaccharides have been isolated from the glycoresin of the leaves of *Ipomoea squamosa* Choisy collected in the Suriname rainforest, ipomoeassins A–F (2–7). The ethyl acetate-soluble extract was subjected to flash column chromatography over C\(_18\) silica gel and the fraction successively purified by HPLC on C\(_18\) and phenyl columns. The structures for the ipomoeassin series were elucidated by spectroscopic data and chemical degradation. The alkaline hydrolysis of ipomoeassin A gave two acids, cinnamic and tiglic acids, identified by GC-CIMS. Acid hydrolysis also gave the 11-hydroxy-4-oxo-tetradecanoic acid as the aglycone and two sugars, D-glucose and D-fucose. The absolute configurations of the aglycone stereogenic centers at C-5 (ipomoeassins C–E) and C-11 (ipomoeassins A and B) were determined by Mosher’s ester formation (15, 16).
Muricatins

Misra and Tewari studied the alcoholic extract from seeds of *Ipomoea turbinata* Lag., sub nom. *Ipomoea muricata* (L.) Jacq., and isolated a resin glycoside named muricatin A (17, 18). The structures of muricatin A and of its alkaline hydrolysis product, muricatin B, were not elucidated. Later, Khanna and Gupta found that muricatin A was actually a resin glycoside mixture, which by alkaline hydrolysis liberated n-caproic, palmitic and stearic acids, and muricatin B (hexadecanoic acid, 11-[[6-deoxy-4-O-(6-deoxy-α-L-mannopyranosyl)-α-L-mannopyranosyl]-oxy]) as the glycosidic acid. Acid hydrolysis of this derivative gave l-rhamnose as the only sugar component and jalapinolic acid as the aglycone (19).

### 3.2.2. Trisaccharides

#### Cus-1 and Cus-2

The acylated trisaccharides cus 1 and cus 2 were isolated from the CHCl3-soluble extract of the seeds of *Cuscuta chinensis*. The extract was fractionated over Sephadex LH-20 and the fractions rich in resin glycosides were chromatographed by column chromatography using normal and reversed phases, followed by preparative HPLC. The oligosaccharide cores of both cus-1 (8) and cus-2 (9) are composed of two l-rhamnoses and one d-glucose. Cus-1 (d-glucose, O-6-deoxy-α-L-mannopyranosyl-(1→3)-O-[2(S), 4(2R,3R)]-6-deoxy-4-O-(3-hydroxy-2-methyl-1-oxobutyl)-2-O-(11-hydroxy-1-oxotetradecyl)-α-L-mannopyranosyl-(1→2)-6-acetate) has convolvulinolic acid as the aglycone,
which is linked at the C-2 of the first rhamnose unit, while cus-2 (D-glucose, \(O\)-6-deoxy-\(\alpha\)-L-mannopyranosyl-(1→3)-\(O\)-[2(S),4(2R,3R)]-6-deoxy-4-\(O\)-(3-hydroxy-2-methyl-1-oxobutyl)-2-\(O\)-(11-hydroxy-1-oxohexadecyl)-\(\alpha\)-L-mannopyranosyl-(1→2)-6-acetate) has jalapinolic acid. Acylation is found at C-4 of the first rhamnose by nilic acid and at C-6 of glucose by acetic acid. These compounds were characterized as a new group of resin glycosides since their aglycone hydroxy group at C-11 is not linked to the oligosaccharide chain (20).

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Cuscutic Acids A₁–A₃

An ether-insoluble resin glycoside fraction was obtained from the seeds of *Cuscuta australis* R. Br. Identification and characterization of the alkaline hydrolysis products revealed the material to be composed of three glycosidic acids, cuscutic acids A₁–A₃. In acid A₁ (hexadecanoic acid, (11S)-[(O-6-deoxy-\(\alpha\)-L-mannopyranosyl-(1→2)-O-\(\beta\)-D-glucopyranosyl-(1→2)-6-deoxy-\(\beta\)-D-galactopyranosyl)oxy]) the aglycone is jalapinolic acid. Two triglycosides with convolvulinolic acid were also identified: cuscutic acids A₂ (tetradecanoic acid, (11S)-[(O-6-deoxy-\(\alpha\)-L-mannopyranosyl-(1→2)-O-\(\beta\)-D-glucopyranosyl-(1→2)-6-deoxy-\(\beta\)-D-galactopyranosyl)oxy]) and A₃ (tetradecanoic acid, (11S)-[(O-6-deoxy-\(\alpha\)-L-mannopyranosyl-(1→2)-O-\(\beta\)-D-glucopyranosyl-(1→2)-\(\beta\)-D-glucopyranosyl)oxy]). So far, no intact resin glycosides have been isolated containing these glycosidic acids. It is possible that the glycosidic resin found in *C. australis* is a complex mixture of glycosidic ester-type oligomers (up to heptamers). Their core consists of the above-mentioned cuscutic acids acylated at various positions (21).

Tricoloric Acid C

Two trisaccharide macrolactones have been characterized from the aerial parts of *Ipomoea tricolor* Cav. (syn. *Ipomoea violacea* L.) (heavenly blue), namely, tricolorins