

Therapeutic Potential of Biologically Active Resin Glycoside Natural Products

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Abstract: Resin glycosides are naturally occurring oligosaccharides, primarily found in the morning glory plants (*convolvulaceous* family). The unique structural feature of this class of natural products is the presence of a macrolactone ring. The hydrophobic side-chain of the macrolactone maintains a fine balance on the highly polar polysaccharide backbone, making them amphiphilic. Various parts of the morning glory plant have been used as folk medicines for centuries throughout the world. The commentary bellow emphasizes on the potential application of resin glycosides in the development of new therapies. **Key words:** Resin glycosides, macrolactone, folk-medicine, total synthesis, SAR

Comments:

Carbohydrates forms the essential constituents in all living organism, which are involved in various biochemical and physiological processes. Resin glycosides belongs to a subset of natural products within the broader field of carbohydrate. Resin glycosides are plant glycolipids, which are primarily isolated from plants within the morning glory family (*convolvulaceous*). These are complex mixture of secondary metabolites known as glycolipids or oligosaccharides and represent unique metabolites in plant kingdom. The chemical composition of resin glycosides includes a sugar backbone, which is decorated with diverse acylation pattern and a hydroxy-fatty acid chain (Figure 1). The sugar building blocks are D-glucose and four methyl pentose: D-fucose, L-rhamnose, D-quinovose and D-xylose. On the other hand, fatty acids are of different lengths (jalapinic acid being the most common), which esterify the oligosaccharide core at variable positions. The most significant feature of these resin glycosides is the macrocyclic structure formed by the intramolecular lactonization of the fatty acid with the hydroxy group of second or third sugar moiety.

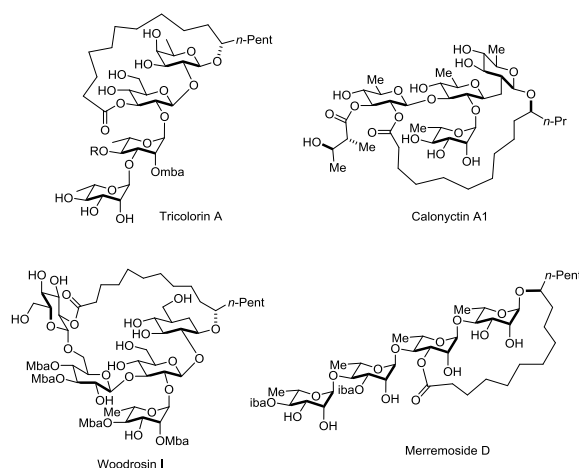


Figure 1: Representative examples of resin glycosides

About 650 species of morning glories (*Convolvulaceae* family) are found across world's tropical and sub-tropical regions, and more than 300 species come from the Americas alone. From the ethnomedical point of view, two prominent examples of the use of plants belonging to *Convolvulaceae* family are *I.purga* (aka jalap root) and *I. orizabensis* (Mexican scammony or false jalap), which are the New World succedanea that had been used since pre-Christian era in Europe.^[1] Similarly, crude extract and powder of various parts of morning glory plant have been used for centuries across the globe in folk medicine for the treatment of various maladies (e.g., pharyngitis, typhus, swollen veins, appendicitis, scorpion-bites and cancer etc.).^[2] After the advent of the modern

analytical tools (e.g., NMR spectroscopy, high-resolution mass-spectrometry and X-Ray crystallography), and modern chromatographic technique such as HPLC, structure of many resin glycosides has been illustrated.^{[2],[3]} These developments have sparked interest in the synthetic and biology community to investigate detail structure activity relationship (SAR) study on resin glycoside natural products. However, a detail SAR study has been frequently hindered by synthetic inaccessibility and/or limited availability from natural in pure form. Thus, development of resin glycosides to a modern medicine remains largely scarce.

Recent development in the synthetic methods has enabled complex oligosaccharide synthesis forging the gap between the material availability and SAR study. Many successful strategies have been reported for the total synthesis of complex resin glycosides.^{[3],[2b]} However, these approaches can be broadly divided in to two categories (i) construction of the macrolactone and (ii) synthesis of the sugar backbone and their possible stereoisomers for SAR study. Macrolactonization of the fatty acid chain on the sugar back bone presents a challenge in regioselectivity resulting in a smaller or bigger macrolactone. Since the size of the macrolactone could greatly influence the conformation as well as other physiochemical properties, total control of regioselectivity in lactone formation is desirable. It has been observed that the outcome of the macrolactonization could be largely dictated by the type of sugar unit on the oligosaccharide backbone. Thus, a diverse range of macrolactonization methods have been developed to meet the demand manifested by those unique system. The most popular methods include: Yamaguchi protocol (2,4,6-trichlorobenzoyl chloride, Et₃N, DMAP),^[4] Corey-Nicolaou conditions (2,2'-pyridyl disulfide, PPh₃),^[5] Template-directed macrodimerization mediated by DMC (2-chloro-

1,3-dimethylimidazolium chloride),^[6] and Keck macrolactonization (DCC, DMAP).^[7] To overcome the issue of regioselectivity, alternative methods have been developed. These include intramolecular glycosylation^[8] and Ring-closing metathesis (RCM).^[9] For the synthesis of the glycosidic linkage of the sugar back bone, the C-2 hydroxyl group of each sugar unit has been largely utilized as a directing group in controlling the anomeric stereochemistry. Thus, most glycosylation involves activation of anomeric hydroxyl group to obtain an oxonium ion, which is stabilized by a C-2 acetyl group (the directing group). Schmidt's glycosylation (trichloroacetimidates) has been most successfully utilized in resin glycoside synthesis.^[10] Some of the lesser known yet successful method involve use of thioglycosides^[11] and silver mediated glycosylation using anomeric bromides,^[12] and Pd-catalyzed glycosylation.^[13] The later offers an additional advantage in SAR studies. In the Pd-catalyzed *de-novo* approach, all of the stereocenters on a monosaccharide building block are derived from an achiral starting material.^[14] Thus, this method can be used to synthesize a plethora of natural and unnatural analogs in a stereocontrolled manner, which is ideal for a systematic SAR analysis.^[15]

Conclusion:

Resin glycosides, which are carbohydrate-derived structures, offers many advantages: First, they are readily accessible from natural sources and has exhibited medicinal value in traditional medicine around the world. The natural source is limited to only specific enantiomers and diastereomers for any given natural product. For example, D-sugars are abundant in nature whereas the enantiomer L-sugars are rarely found in nature. But, the recent advances in the synthetic methodologies has rendered access to both natural and unnatural enantiomers and diastereomers,

which positioned us to carry out systematic SAR of many resin glycosides.^{[16],[3a]} The multifunctionality of carbohydrate provides possibility of structural modifications through different positions of the sugar ring. Also by appending various groups on the sugar ring and by varying the number of sugar units, the physiochemical properties (like solubility, polarity and bioavailability) could be modulated. The number of novel structures that can be constructed using carbohydrate building blocks increases exponentially by the fact that a large number of enantiomeric and diastereomeric analogs can be synthesized for a single building block. Thus, the interesting biological and physiochemical properties of the resin glycosides coupled with the opportunity for a systematic and modular SAR demonstrate potential applications of resin glycosides in medicine.

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