Steroidal (Glyco)Alkaloids: Classification

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Steroidal (glycol)alkaloids S(G)As are secondary metabolites made of a nitrogen-containing steroidal skeleton linked to a (poly)saccharide, naturally occurring in the members of the Solanaceae and Liliaceae plant families. The genus *Solanum* is familiar to all of us as a food source (tomato, potato, eggplant), but a few populations have also made it part of their ethnobotany for their medicinal properties. The recent development of the isolation, purification and analysis techniques have shed light on the structural diversity among the SGAs family, thus attracting scientists to investigate their various pharmacological properties.

Solanum steroid glycoalkaloid

1. Introduction

Nutrition is a vital act of communion with nature. Plants use the sun's energy to transform minerals and gases into a cornucopia of organic molecules such as carbohydrates, lipids, terpenes, steroids, etc. Directly or indirectly, they supply all the energy and building blocks needed for the growth and maintenance of the human body. History shows that plants have been used for their medicinal properties in all civilizations and they continue today to be a source of bioactive molecules. The *Solanum* genus is comparatively a large one, encompassing over 1500 species and it is of particular importance in most of the world, as it includes popular food crops such as tomato (*Solanum lycopersicum*), potato (*Solanum tuberosum*) and eggplant (*Solanum melongena*). Two etymologies have been proposed: *sol* + *anum* ("of the Sun") or *solor* + *nus* ("soothing"). Fittingly, it also contains various nightshade species used as folk medicine [1], such as the yellow-fruit nightshade (*Solanum virginianum*) used in Ayurveda medicine and the black nightshade (*Solanum nigrum*) used in both Western and Eastern traditional medicine. The genus *Solanum* is part of the Solanaceae family, which also includes the genera *Capsicum* (bell and chili peppers), *Nicotiana* (tobacco) as well as *Datura*, *Mandragora* and *Atropa* among others. It can thus be seen that many plants of this family are cultivated for their secondary metabolites like capsaicin and nicotine or are poisonous such as the deadly nightshade (*Atropa belladonna*).

At the interface between food, medicine, and poison, Steroidal Alkaloids (SAs) and their glycosidic versions are secondary metabolites that are especially prominent in the *Solanum* genus. Steroidal GlycoAlkaloids (SGAs) consist of a (poly)saccharide linked to a hydrophobic steroidal skeleton containing a nitrogen atom. They accumulate in different organs of the plants (leaves, roots, fruits, tubers, etc.) [2][3][4] and play a key role in the plant-environment interactions, in particular against bacterial and fungal attacks [5][6]. Their anti-nutrient properties and human toxicity are well-documented [3][7][8][9][10][11], while they more recently have attracted the attention of

researchers for their wide range of pharmacological properties (anticancer, antibiotic, anti-inflammatory, etc.) [12][13][14][15]. For instance, Coramsine (SBP002) was an experimental chemotherapeutic drug composed of two steroidal glycoalkaloids (solamargine and solasonine) isolated from the species *Solanum linneanum* (devil's apple) [16].

2. Steroidal (Glyco)Alkaloids: Classification

Steroidal alkaloids are nitrogenous derivatives of steroids and have been isolated and characterized from many organisms including animals (amphibians, sea sponges, etc.) and plants (Solanaceae, Liliaceae, etc.). They are important secondary metabolites with a wide range of potential therapeutic applications [17]. For instance, the steroidal alkaloid drug marketed Zytiga®, was approved in 2011 by the FDA for the treatment of metastatic castration-resistant prostate cancer [18]. The nitrogen atom is incorporated to the steroidal backbone either as heterocyclic ring, basic side chain or as a substituent at the C-3 position. Monomeric steroidal alkaloids are commonly classified into four groups based on their carbon heterocyclic skeleton: (1) Pregnane (C_{21}); (2) Cyclopregnane (C_{24}); (3) Cholestane (C_{27}); (4) Others (**Figure 1**).

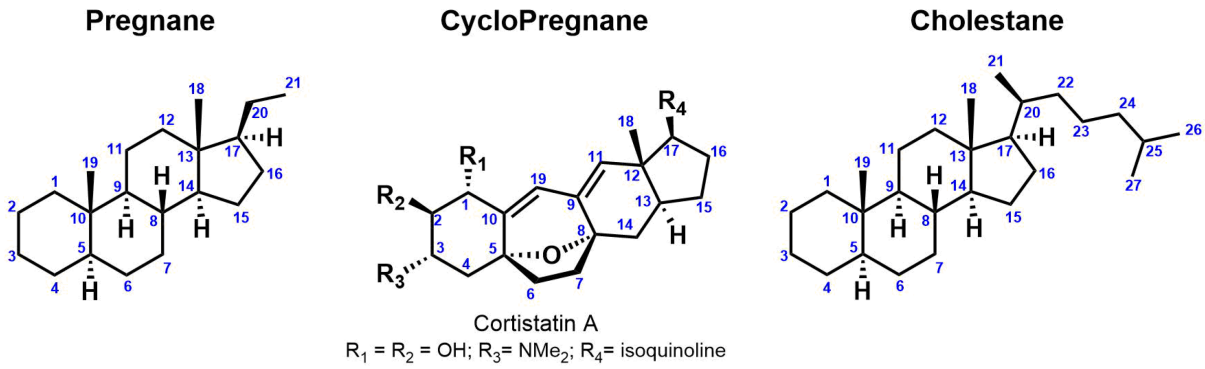

Figure 1. Steroid categories according to their carbon framework.

The occurrence of the *Solanum* steroidal alkaloid is well-documented and they mainly belong to C_{27}-cholestane family [18][19]. These metabolites are characterized by the common ABCD steroid skeleton, and they are conventionally subdivided into three main types: **spirosolane**; **solanidane** (aka. Solanidine); and **verazine** (aka. 22/23,26-epiminocholestane) types (**Figure 2**).

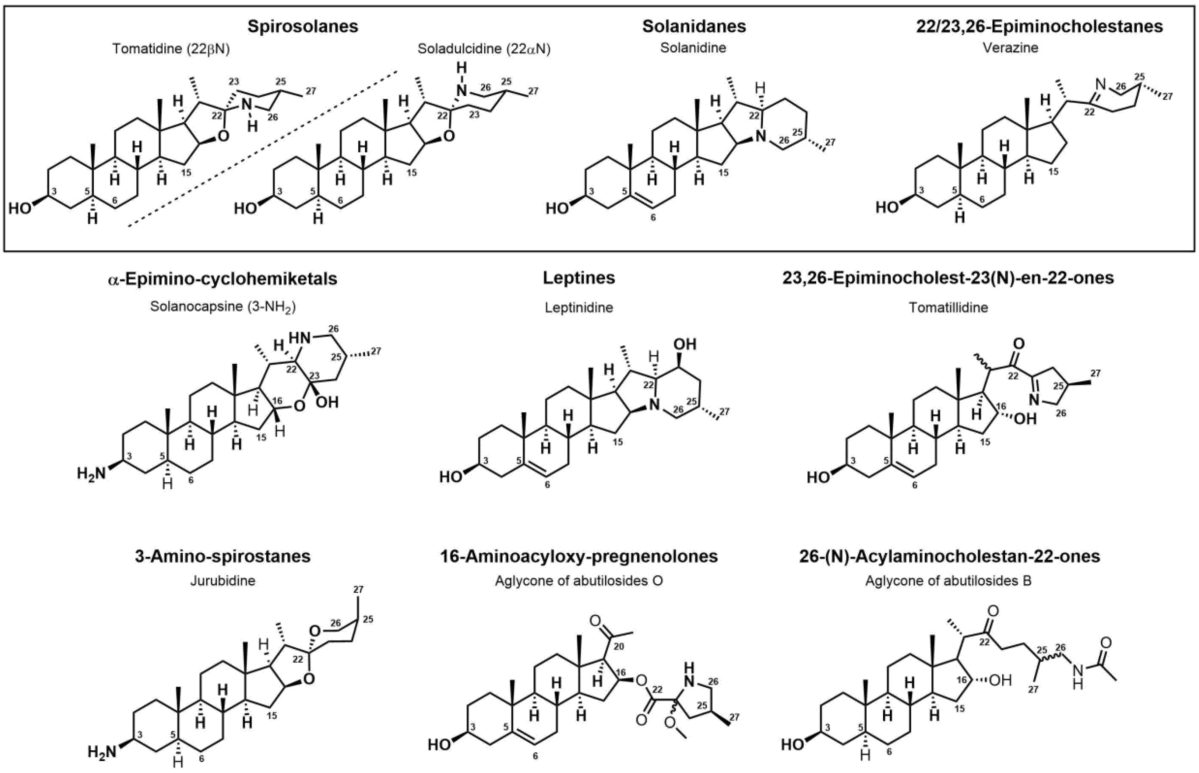

Figure 2. Classification of steroidal alkaloids.

The **Spirosolane** type is characterized by a 1-oxa-6-azapiro [4][5] decane ring system (E and F rings) and can be divided into two stereoisomeric subgroups: 22αN- and 22βN-spirosolanes (**Figure 2**). The C_{27} methyl group always take place in equatorial position within the Spirosolane family. The **Solanidane** family possess a fused indolizidine pattern with the 22R,25S configuration (**Figure 2**). Solanidine and its 5a,6-dihydro analog, demissidine, are the most common SAs of this structural entity. The **Verazine** group has a 22/23,26-epiminocholestane skeleton and differs by the non-conjugated N-containing F-ring and the absence of ring E (**Figure 2**). For analogs with a saturated piperidine F-ring, 22αN and 22βN-diastereoisomers also exist. Noteworthy, the C_{16} position can be saturated or substituted (e.g., -OH).

Over the last few decades, purification and extraction techniques of natural compounds have considerably progressed along with the abilities of researchers to elucidate complex chemical structures. Therefore, further phytochemical investigations resulted in the discovery of new metabolites with unique structural features thus leading to the creation of six additional (sub)types: **α-Epiminocyclohemiketal**; **Leptine**; **23,26-Epiminocholest-23(N)-en-22one**; **3-Aminospirostane**; **26-(N)-Acylaminocholestan-22-one**; and **16-Aminocycloxy-pregnenolone** (**Figure 2**) [18][19].

The most prevalent metabolite of the **α-Epiminocyclohemiketal** family is solanocapsine, which contains two nitrogen atoms and is characterized by its α-epiminocyclohemiketal functionality. Its worth mentioning that 3-hydroxy analogues were discovered later. **Leptines** are solanidane equivalents with a 23-hydroxy/acetyl group. For instance, leptinidine is the 23β-hydroxy analog of solanidine (**Figure 2**). The **23,26-Epiminocholest-23(N)-en-22-one** type is defined by the C_{22} exocyclic carbonyl function and the unsaturated bond between the C_{23} and the

nitrogen of the five-membered ring. The **3-Aminospirostane** group (aka jurubidine type) is constituted of 3-amino analogues of spirostane steroids that contrast from previous metabolites by the oxygen replacing the basic nitrogen N_{22}. Another family characterized by the lack of N_{22} basic nitrogen is the **26-(N)-Acylaminocholestan-22-one**. These metabolites exhibit an almost identical side chain to the cholestane framework, likely because the N-acetyl group prevents the cyclization. The **16-Aminoacyloxy-pregnenolone** type is unique with its C_{21} pregnane skeleton instead of the usual C_{27} cholestane framework. It is a recent category with only two SGAs isolated to date [20][21].

It is to be noted that steroidal alkaloids often exist in nature as glycosides named Steroidal GlycoAlkaloids (SGAs) [22]. The biosynthesis of *Solanum* SGAs has been partially elucidated and it relies on the cytosolic mevalonate pathway with cholesterol as a key precursor [23][24]. It can be separate into two main operations: the aglycone construction and glycosylation. A significant number of glycoalkaloid metabolism (GAME) genes are involved in the initial regulation of the structural modification of the cholesterol backbone by hydroxylation, transamination, oxidation, etc., followed by glycosylation reactions [25].

The polar entity in SGAs includes one to several monosaccharides in various combinations (branched, linked or linear). The most common units are D-galactose, D-glucose, D-xylose, L-arabinose and L-rhamnose which interconnected offer a variety of disaccharides, trisaccharides and tetrasaccharides [19]. The predominant glycosidic chains of the solanum SGAs are solatriose, chacotriose, lycotetraose and commertetraose (**Figure 3**). The glycosidic linkage mostly occurs at the C_3 position of the steroidal backbone (monodesmosidic) by contrast to bisdesmodic metabolites that own an additional sugar at another location of the steroidal skeleton (e.g., Esculeoside A) [26]. The α/β anomeric configuration of the glycosidic bond at the C-3 hydroxy position of the aglycone is driven by the D/L-configuration of the monosaccharide. The oligosaccharide chain plays a pivotal role in directing biological applications as observed for the SGA Tomatine and its non-glycosidic analog Tomatidine that display different therapeutical properties.

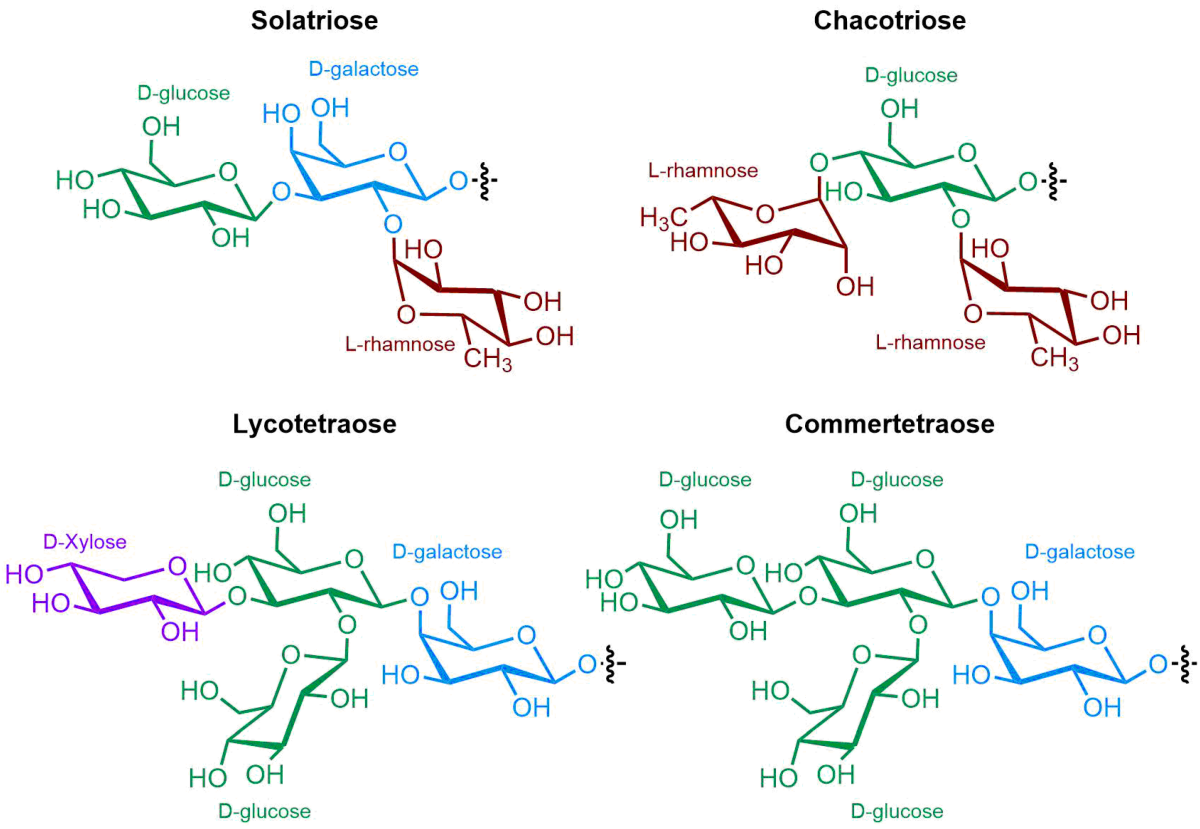

Figure 3. Chemical structures of the main oligosaccharide units of Solanum SGAs.

The popularity of SGAs arises from the structural diversity offered by the aglycone structure, the nature of the side chain and the combination of carbohydrates. The aglycone unit often shares the tetracyclic 5α-androstane of the C_{27} cholestane skeleton while divergence mostly occurs by substitutions; rearrangement of the side chain (C_{20}–C_{27}); and the position of substituents. Interestingly, 5α-saturated and 5-unsaturaded analogs have been detected for almost all categories of *Solanum* SGAs.

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