Therapeutic properties and structural characterization of steroidal saponins: a review

https://doi.org/10.32712/2446-4775.2021.1101

Pereira, Gabriela Moysés1*; Cruz, Maria de Fátima Simão Jucá1.

1Universidade Federal do Rio de Janeiro (UFRJ), Instituto de Pesquisas de Produtos Naturais, Centro de Ciências da Saúde, Cidade Universitária, CEP 21941-902, Rio de Janeiro, RJ, Brasil.

*Correspondência: gabrielamoyses@ufrj.br.

Abstract

Medicinal plants are sources of bioactive substances that can act to maintain human health. Among the compounds widely distributed in medicinal plants, there are steroidal saponins, an important class of secondary metabolites that are characterized as the active principle of these natural products. The structure of steroidal saponins is composed of a steroidal aglycone covalently linked to portions of carbohydrates and due to the complexity of its structure, the structural characterization processes are laborious. Steroidal saponins have been investigated over the years, due to their potent therapeutic properties such as antimicrobial, anti-inflammatory and cytotoxic. In this work were summarized the studies found in the scientific literature in the last two decades, about the investigation of the therapeutic properties and structural characterization of the steroidal saponins. Furthermore, recent studies have suggested that some saponins like candidates for the treatment of patients with Coronavirus disease (COVID-19). Studies on steroidal saponins are of great importance, as they can be potent therapeutic agents.

Keywords: Steroidal saponins. Active principles. Structural characterization. Therapeutic properties.

Introduction

Saponins are a group of bioactive glycosides, widely distributed in the plants. They can be classified into two groups based on the nature of their aglycone skeleton: steroidal saponins which are present mainly in the monocotyledonous angiosperms and triterpenoid saponins which occur mainly in the dicotyledonous angiosperms 1).

Steroidal saponins are a group of natural compounds that consist of a steroidal aglycone, designated sapogenin, covalently linked to sugar moieties 1). Because of its amphipathic nature, these substances have the capacity to form a foam when in contact with water and they possess pharmacological and medicinal properties2), such as antifungal, anti-inflammatory, anticancer and antiulcerogenic activities3). There are distributed in various plant species and are found in abundance in the families Agavaceae, Alliaceae, Asparagaceae, Dioscoreaceae, Liliaceae, Melanthiaceae, Solanaceae, Trilliaceae and Zygophyllaceae. Many industrial and commercial applications are reports to saponins, they are found in beverages, cosmetics and pharmaceutical products. Furthermore, they are used as raw materials for the production of sterol
hormones, as food additives and due its therapeutic properties, have been investigated over the years, toward the development of new natural medicines[3].

Steroidal saponins possess 27 carbon atoms in the aglycone and can be divided into spirostane and furostane based on the nature of their aglycone skeleton. The type spirostane possess a skeleton hexacycle ABCDEF-ring system and sugar moieties commonly linked at C-3. Already, the furostane type presents a pentacyclic ABCDE-ring system with the sixth open F ring and sugar moieties commonly linked at C-3 and C-26 (FIGURE 1)[1,3].

FIGURE 1: Aglycone moiety of saponins: (A) Steroidal spirostane (B) Steroidal furostane. R =H or CH3. The image was adapted of reference [1].

Steroidal saponins can also have functional groups in the aglycone where the most common are -OH and -OCH3. Furthermore, can also contain insaturations in ring. The sugars usually found are glucose, galactose, arabinose, xylose and rhamnose[5]. According to the literature, the furostane steroidal saponin isolated from Yucca gloriosa L. rhizomes (Agavaceae) showed the functional group OCH3 linked at C-22 and sugar moieties of galactose and glucose (FIGURE 2A)[6]. Already, the furostane steroidal saponin from Allium sativum L. var. Voghiera (Alliaceae) showed the group OH linked at C-5 and at C-22 (FIGURE 2B). It’s also reported that the spirostane steroidal saponin from Asparagus filicinus (Asparagaceae) presented the group OH linked at C-17 and showed moieties of the glucose, arabinose and xylose[7] (FIGURE 2C) and the spirostane steroidal saponin from Smilacina japonica (Liliaceae) showed an insaturation on C-ring, the functional group OH linked at the C-17 and C-24 and presented the sugars galactose, glucose and xylose[8] (FIGURE 2D). This large structural diversity is responsible for the various biologic activities of saponins and because they are complex substances become labor intensive the processes of structural characterization.
FIGURE 2: Examples of saponins. (A) Furostane steroidal saponin from *Yucca gloriosa* L. rhizomes[6], (B) Furostane steroidal saponin from *Allium sativum* L. var. Voghiera[7], (C) Spirostane steroidal saponin from *Asparagus filicinus*[8] (D) Spirostane steroidal saponin from *Smilacina japonica*[9].
Material and Methods

In this review are summarized the studies found in the scientific literature about structural characterization and main biological activities reported for steroidal saponins in the last two decades. Thus, this review has been prepared by collecting information about biosynthesis, techniques of structural elucidation and therapeutic properties of steroidal saponins. The main scientific bases used for the development of this work were Science Direct, Capes periodicals portal and Google academic.

Results and Discussion

The search in Science Direct, Capes periodicals portal and Google academic using the terms “steroidal saponins” resulted in 11,922; 5,514 and 34,900 articles respectively. This large amount of articles show that research on steroidal saponins is of great relevance arousing the interest primarily of researchers in the field of chemistry and health.

The following topics will address the two biosynthetic pathways described in the literature (FIGURE 3 and FIGURE 4), the techniques by structural characterization and main signals attributed at $^1$H and $^{13}$C NMR (FIGURE 6). Finally, will be discussed the therapeutic properties of the steroidal saponins that was summarized in the TABLE 1.
Biosynthesis

Steroidal saponins are derived of the C5 isoprene units, dimethylallyl diphosphate (DMAPP) and isopentenyl diphosphate (IPP) and is described that such isoprene units can be formed by two biosynthetic pathways, the mevalonate pathway and an alternative pathway known as deoxyxylulose phosphate[10].

In the mevalonate pathway occurs the formation of the mevalonic acid as precursor of the reaction. Initially, two molecules of acetyl-coenzyme A are connected for Claisen condensation to give acetoacetyl-CoA. Subsequently, another molecule of acetyl coenzyme A is incorporated via a stereospecific aldol addition giving the ester $\beta$-hydroxy-$\beta$-methylglutaryl-CoA (HMG-CoA). Subsequently occurs a hydrolysis and enzymatic reduction giving the mevalonic acid. Then, the mevalonic acid is transformed in the isoprene unit isopentenyl diphosphate (IPP), through the successive phosphorylation of the hydroxyl groups, followed by decarboxylation and elimination of a group pyrophosphate. Subsequently, an isomerase removes a proton at C-2 of IPP giving the dimethylallyl diphosphate (DMAPP) (FIGURE 3)[10].

Deoxyxylulose phosphate pathway was posteriorly discovered and probably is more widely utilized in nature than is the mevalonate pathway. The compound 1-Deoxy-D-xylulose 5-phosphate is the precursor of the reaction and is formed from two products of glycolysis, pyruvic acid and D-glyceraldehyde 3-phosphate. In this biosynthetic pathway, initially the pyruvic acid reacts with the thiamine diphosphate (TPP) that mediates the decarboxylation of pyruvate producing an acetaldehyde equivalent bound in the form of an enamine. This, reacts as a nucleophile, in an addition reaction with the D-glyceraldehyde 3-phosphate. Subsequent release from the TPP carrier generates 1-Deoxy-D-xylulose 5-phosphate (DXP), that through of a rearrangement type pinacol-pinacolone, followed by reduction, the DXP is converted to 2-methyl-D-erythritol-4-phosphate, resulting in the isoprene unit isopentenyl pyrophosphate (IPP) in a sequence that not fully elucidated yet (FIGURE 4)[10].
Saponins have as precursor the oxidosqualene, that is formed from the isoprene units IPP and DMAPP. Initially a unit C5 of the IPP is condensed with a unit C5 of DMAPP resulting in the molecule C10 of the geranyl diphosphate (GPP). This is linked with a unit of IPP resulting in a unit C15 of farnesyl diphosphate (FPP). The union of two molecules of FPP originates the squalene, that by action of squalene monoxygenase form oxidosqualene. In sequently, occur a series of reactions of the cyclization, rearrangement, migration of hydride, methyl, formation of carbocation, forming a great diversity of steroid skeletons (FIGURE 5)\textsuperscript{[10,11]}.

It is reported that oxidosqualene cyclization can proceed via the "chair-chair-chair" or via the 'chair-boat-chair' conformation. Triterpenes saponins originate from the "chair-chair-chair" conformation, while steroids saponins arise from the 'chair-boat-chair conformation'.

FIGURE 5: The cyclization of oxidosqualene to the various steroids skeletons\textsuperscript{[10,11]}, Isopentenyl diphosphate (IPP); Dimethylallyl diphosphate (DMAPP); Geranil diphosphate (GPP); Farnesil diphosphate (FPP).
Spirostane saponins are formed by enzymatic hydrolysis of furostane saponins, such hydrolysis occurs by action of the enzyme $\beta$-glucosidase, that is an enzyme specific to cleave the glucose unit linked to C-26 allowing that the oxygen to be free and make an intramolecular bond with the carbon in C-22, leading to the closure of the F ring, but this mechanism isn’t fully elucidated\[12].

The biogenetic relationship between the furostane and spirostane derivatives also is still contestable\[3]. It’s reported that furostanolic saponins to be usually contained in fresh plants and it are gradually converted into spirostanol saponins during the drying process. Moreover, there are reports that usually furostane saponins showed low toxicity, while spirostanes are highly toxic\[3].

**Structural characterization**

Steroidal saponins are complex substances, so the structural characterization process takes a lot of work, requiring to comparisons with the literature data and a big numbers techniques, being the most common: the indispensable ¹D and ²D Nuclear Magnetic Resonance (NMR), Mass Spectrometry to determine mass molecular, acid hydrolysis and chromatographic techniques for identification the sugars.

In the ¹H NMR spectrum of steroidal saponins, extensive interproton couplings are observed and, consequently, only a few signals can be attributed. Some examples are the singlets of the angular methyl groups (H₃-18, H₃-19) and doublets for the methyl groups (H₃-21, H₃-27) (FIGURE 6).

**FIGURE 6:** Main groups of aglycone identified by NMR.: (A) Methyl groups (CH₃-18, CH₃-19, CH₃-21) and spirostanic carbon (C-22) by Steroidal spirostane (B) Methyl groups (CH₃-18, CH₃-19, CH₃-21, CH₃-27), furostane carbon (C-22), methyl group (CH-25) and methylene group (CH₂-26) by Steroidal furostane. The image was adapted of reference\[1].

(A)

(B)
A steroidal saponin from Dioscorea althaeoides R. Knuth showed the typical signals for singlets of H3-18 at δ 0.83 ppm; H3-19 at δ 1.02 ppm and doublets H3-21 at δ 1.15 ppm and H3-27 at δ 0.7 ppm[14]. The signal of spirostane carbon (C-22) (FIGURE 6) is observed generally in the region at δ 109.0-110.0 ppm. The furostane carbon from Dioscorea althaeoides R. Knuth showed the C22 at δ 109.2 ppm[13] and the spirostane saponin from Smilax officinalis (Liliaceae) showed the C22 at δ 110.0 ppm[14]. The furostane carbon (FIGURE 6) commonly is observed at the δ 112-112.5 ppm. Five furostanes saponin from Dioscorea althaeoides R. Knuth showed the C22 at δ 111.8 (two saponins), δ 111.9 (one saponin) and δ 112 ppm (two saponins)[7].

According to the literature, through the difference of the chemical shift between the diastereotopic hydrogens H26a and H26b, it is possible to identify the configuration at the C-25. The stereochemistry is defined S if ≠a,b ≥ 0.57 ppm and defined R if ≠a,b≤ 0.48 ppm[6,18]. Furostane steroidal saponin from Yucca gloriosa L. rhizomes showed C-25 configuration was deduced to be R based on the difference of chemical shifts (FIGURE 2A)[6].

The complete assignments of the overall structure of the aglycone skeleton are achieved by a combination of 1H, 13C, DEPT and 2D NMR methods, such HSQC, 1H–1H COSY and HMBC experiments.

In aglycone steroidal saponin from Smilacina japonica (FIGURE 2D) were found HMBC correlations for methyls hydrogens for Hs-18, Hs-19, Hs-21 and Hs-27. The Hs-18 showed correlations with C-12 (δC 41.1), C-13 (δC 38.3), C-14 (δC 53.2) and C-17 (δC 61.3), Hs-19 with C-1 (δC 35.1), C-5 (δC 42.5), C-9 (δC 146.8), C-10 (δC 37.7), Hs-21 with δC C-17, C-20 (δC 42.1), C-22 (δC 108.9) and spirostane Hs-27 with C-24 (δC 25.4), C-25 (δC 26.4), C-26 (δC 64.3)[9]. In addition, were found HMBC correlations of the olefinic hydrogen H-11 with C-10, C-12, C-13 and C-14[8].

Some aglycones also have a hydroxyl group at C-17 (FIGURE 2C; 2D). The presence the OH at C-17 in the saponin from Asparagus filicinus (FIGURE 2C) was also supported by the HMBC correlations between OH-17 ((δH 5.06) and the C-13 (δC 45.4); C-16 (δC 90.0); C-17 (δC 90.0) and C-20 (δC 44.8)[9].

Acid hydrolysis is generally used to identity the sugars portion. The literature commonly reports acid hydrolysis or HCl[9-13] or H2SO4[8-16].

The acid hydrolysis with HCl 2M of the sugars of the saponin from Smilacina japonica (FIGURE 2D) generated glucose, galactose and xylose, which were identified by thin layer chromatography[9]. The anomeric carbons were determined by the analysis of the 1D and 2D NMR spectra showed xylose anomer (δH 4.49; δC 103.3); galactose anomer (δH 4.20; δC 101.1) and two glucose anomerics [(δH 4.71; δC 102.4), (δH 4.41; δC 103.3)][9]. To determine the sequence of the oligosaccharide chain and the correlation between sugars and aglycone are use analysis of the 2D NMR spectra.
Therapeutic properties

Steroidal saponins are bioactive compounds and over the years have been reported in many studies about their biological properties, where is widely described the antifungal, antibacterial, anti-inflammatory, cytotoxicity and gastroprotective activities\[19-44\]. Others therapeutic properties, such as, antianoxia, anti-hyperlipidemia, anti-thrombotic, molluscicidal, anthelmintic and anti-tumor also are related\[43-50\]. TABLE 1 shows a summary of the main biological activities.

Antifungal activity

The antifungal activity is very reported in the Alliaceae\[7,19,20\] and Dioscoreaceae\[21,22\] families. The aginoside, a spirostane steroidal saponin from Allium nigrum L. was evaluated against phytopathogens showed a significant antifungal activity\[20\]. Furostane and spirostane steroidal saponins from Persian leek were evaluated against various fungal pathogens (Penicillium italicum, Aspergillus niger, Trichoderma harzianum and Botrytis cinerea) and Persicosides A and B, two spirostane steroidal saponins showed the highest activity on the tested fungi than the other tested saponins based on furostanol\[20\]. A spirostane saponins from Dioscorea villosa (discoreae) presented antifungal activity against Candida albicans, Candida glabrata and Candida tropicalis\[21\]. These results show the relationship of the spirostane skeleton on the activity, indicating that a spirostane aglycon is a structural feature increasing the antifungal activity of saponin compounds\[20\].

Antibacterial activity

Antibacterial activity is also reported for spirostane saponins. Seven spirosanol saponins from P. polyphylla var. yunnanensis showed significant antimicrobial activity against P. acnes\[23\]. One spirosanol saponin from Cordyline fruticosa (L.) A. Chev. also showed a moderate antibacterial activity against the Gram-positive Enterococcus faecalis\[24\]. The authors point out that saponins deserve more attention as antibacterials, since this property is often assumed as less important over the antifungal activity. They believe that saponins might represent new and effective antibacterial agents\[24\].

Anti-inflammatory activity

Saponins with anti-inflammatory activity are reported in various families of plants, such as Liliaceae, Asparagaceae, Alliaceae, Agavaceae, Orchidaceae and others\[25-30\]. Steroidal saponins from Smilax china (Liliaceae) showed anti-inflammatory properties, inhibited the effects on cyclooxygenase-2 enzyme (COX-2)\[25\]. Sun et al.\[26\] isolated four steroidal furostanol saponins from the rhizomes of Aspidistra elatior Blume (Asparagaceae), their structures were determined based on chemical methods and spectral data and the isolated compounds, named aspidsaponins E-H were tested in vitro assay for inhibitory activities against LPS-induced nitric oxide production in RAW264.7 macrophages. Among them, compounds aspidsaponins G and aspidsaponins H showed excellent anti-inflammatory activities with IC50 values 82.1 and 65.9 μM, respectively\[26\].

Cytotoxic activity

Cytotoxic activity is one of the most common reported for saponins, there are reported of this activity in families Agavaceae, Taccaceae, Orchidaceae, Dracaenaceae, Liliaceae, Amaryllidaceae, Asparagaceae, Solanaceae and others\[31-42\].
Three steroidal saponin from *Allium flavum* (Amaryllidaceae) exhibited moderate cytotoxicity against human colorectal cancer cell line (SW480)[31]. Five steroidal saponins from *Ophiopogon japonicus* (Liliaceae) showed cytotoxicity activity against five human cancer cell lines (HepG2, HLE, BEL7402, BEL7403 and Hela)[32]. A phytochemical study on *T. Tschonoskii* rhizomes, result in the isolated of twenty-four steroidal saponins. The citotoxic activity was analyzed against HepG2 cells and the results showed that two compounds that possess aglycone of pennogenin exhibited a remarkable cytotoxic activity, which presumed that the aglycone of pennogenin is critical for the cytotoxic activity. The authors believe that the structural changes on pennogenin due to substituents or the configuration difference could result in the activity disappeared[33]. Seven steroidal saponins from *Dioscorea zingiberensis* Wright (Dioscoreaceae) inhibited the proliferation of a panel of established human and murine cancer cell lines in vitro, where the zingiberensis saponin had more cytotoxic effect than the other saponins, demonstrated that this saponin is an effective natural agent for cancer therapy[34].

**Gastroprotective activity**

It is reported that four steroid saponins from *Paris polyphylla var. yunnanensis* (Liliaceae) strongly inhibited gastric lesions induced by ethanol and indomethacin[43]. Preliminary biological investigations made with a furostane saponin isolated from *Agave angustifolia var. marginata*, indicated a significant protective effect against induced gastric ulcers using in vivo experimental models and demonstrated negligible toxicity on membrane integrity in the in vitro assays[44].

**TABLE 1:** Main biological activities of steroidal saponins in families and plant species.

| Active biologic | Family       | Species                                | References |
|-----------------|--------------|----------------------------------------|------------|
| **Antifungal**  | Alliaceae    | *Allium sativum* L. var. *Voghiera*     |            |
|                 | Alliaceae    | *Allium cepa* L.                       |            |
|                 | Alliaceae    | *Allium nigrum* L.                     |            |
|                 | Alliaceae    | *Persian leek*                         |            |
|                 | Dioscoreaceae| *Dioscorea villosa*                    |            |
|                 | Dioscoreaceae| *Dioscorea nipponica*                  |            |
| **Antibacterial**| Melanthiaceae| *Paris polyphylla var. yunnanensis*    |            |
|                 | Agavaceae    | *Cordyline fruticosa* (L.) A. Chev.    |            |
| **Antiinflammatory** | Liliaceae    | *Smilax china*                         |            |
|                 | Asparagaceae | *Aspidistra elatior* Blume             |            |
|                 | Alliaceae    | *Allium ampeloprasum* var. *porrum*    |            |
|                 | Agavaceae    | *Agave attenuata*                      |            |
|                 | Agavaceae    | *Agave brittoniana*                    |            |
|                 | Orchidaceae  | *Bletilla striata*                     |            |
| **Cytotoxic**   | Amaryllidaceae| *Allium flavum*                        |            |
|                 | Liliaceae    | *Ophiopogon japonicus*                 |            |
Therapeutic properties and structural characterization of steroidal saponins: a review

Pereira, Cruz

The emergence of Corona Virus Disease 2019 (COVID-19) has been declared as a pandemic by the World Health Organization. Scientists around the world aim to find an effective treatment for COVID-19. Some hypotheses are found in the literature that saponins can help in the treatment of symptoms caused by the disease.

He et al.[51] investigated therapeutic potentials of Chinese Herbal Medicine (CHM) to combat renal injury in COVID-19 patients. In this study, were selected active ingredients from CHM, contends mainly flavonoids and saponins which generally have the effects of anti-inflammation and anti-tumor. The diosgenin, a sapogenin that can reduce apoptosis by regulating PI3K/Akt, ERK and JNK signaling pathways was a the top listed one[51,52]. Furthermore, the authors believe that the stigmasterol and sitogluside sapogenins may play the role of preventing renal injury by acting on multiple targets in oxidativestress, inflammation, or apoptotic pathways. The authors suggest that CHM are promising to protect the kidney through the mechanisms of anti-oxidation, inhibition of inflammation and apoptosis pathways[51].

| Plant Family | Species Name | Properties |
|--------------|--------------|------------|
| Liliaceae | Trillium tschonoskii | Gastroprotective |
| Dioscoreaceae | Dioscorea zingiberensis Wright | Anti-hyperlipidemia |
| Agavaceae | Cordyline fruticosa (L.) A. Chev. | Anti-tumor |
| Agavaceae | Agave utahensis | Anti-anoxia |
| Taccaceae | Tacca chantrieri | Anti-thrombotic |
| Orchidaceae | Bletilla striata | Molluscicidal |
| Amaryllidaceae | Allium schoenoprasum | Anti-thrombotic |
| Amaryllidaceae | Allium flavum | Anti-tumor |
| Dracaenaceae | Dracaena draco | Anti-tumor |
| Liliaceae | Smilax aspera L. | Anti-tumor |
| Asparagaceae | Anemarrhena asphodeloides | Anti-anoxia |
| Solanaceae | Cestrum parqui | Anti-thrombotic |
| Asparagaceae | Sansevieria cylindrica Bojer | Anti-thrombotic |
| Liliaceae | Paris polyphylla var. yunnanensis | Gastroprotective |
| Agavaceae | Agave angustifolia var. marginata | Anti-anoxia |
| Alliaceae | Allium ampeloprasum var. porrum | Anti-anoxia |
| Liliaceae | Selaginella uncinata | Anti-anoxia |
| Dioscoreaceae | Dioscorea nipponica | Anti-thrombotic |
| Dioscoreaceae | Dioscorea zingiberensis C.H. Wright | Anti-thrombotic |
| Agavaceae | Yucca desmettiana | Anti-thrombotic |
| Melanthiaceae | Paris polyphylla | Anthelmintic |
| Asparagaceae | Liriope graminifolia | Anthelmintic |

Saponins and COVID-19

The emergence of Corona Virus Disease 2019 (COVID-19) has been declared as a pandemic by the World Health Organization. Scientists around the world aim to find an effective treatment for COVID-19. Some hypotheses are found in the literature that saponins can help in the treatment of symptoms caused by the disease.

He et al.[51] investigated therapeutic potentials of Chinese Herbal Medicine (CHM) to combat renal injury in COVID-19 patients. In this study, were selected active ingredients from CHM, contends mainly flavonoids and saponins which generally have the effects of anti-inflammation and anti-tumor. The diosgenin, a sapogenin that can reduce apoptosis by regulating PI3K/Akt, ERK and JNK signaling pathways was a the top listed one[51,52]. Furthermore, the authors believe that the stigmasterol and sitogluside sapogenins may play the role of preventing renal injury by acting on multiple targets in oxidativestress, inflammation, or apoptotic pathways. The authors suggest that CHM are promising to protect the kidney through the mechanisms of anti-oxidation, inhibition of inflammation and apoptosis pathways[51].
Bailly et al. [53] believe that triterpenoid saponins Saikosaponin A, Saikosaponin B, and Saikosaponin D from Bupleurum falcatum L. are candidate treatment for COVID-19 owing to their anti-inflammatory, immunomodulatory, and antiviral activities. The authors recommend future well-designed randomized controlled trials to evaluate the safety and efficacy of Saikosaponins in patients with COVID-19 [53]. Bailly et al. [53] analyzed the anti-coronavirus potential of the glycyrrhizic acid (GLR), a triterpene saponin non-hemolytic, potent immuno-active anti-inflammatory agent. It is used to treat liver diseases and specific cutaneous inflammation. GLR has shown activities against different viruses, including SARS-associated Human and animal corona viruses. Bailly et al. [53] conclude that glycyrrhizic acid should be further considered and rapidly evaluated for the treatment of patients with COVID-19.

Conclusion

Steroidal saponins are macromolecules distributed in various plant species. The studies about this compounds class is greatly important, because they are very bioactive, can be potent therapeutic agents. Some results have been showing the relationship of the skeleton on the activity, so lots of chemical groups in skeleton saponin have influence directly in higher or lower biological activity. The largest records of bioactive saponins are found in the Agavaceae, Alliaceae, Dioscoreaceae and Liliaceae families and the main biological activities registered are antifungal, antibacterial, anti-inflammatory, cytotoxic and gastroprotective. Besides that, in this review was showed the importance of chemical and physical methods for the complete assignments of the overall structure of steroidal saponins. Some hypotheses are found in the literature that saponins can help in the symptoms caused by COVID-19, being appointed with candidates the treatment of patients with by this disease. Further clinical studies are needed regarding the action of these saponins on Sars-CoV-2.

References

1. Sparg SG, Light ME, Staden JV. Biological activities and distribution of plant saponins. J Ethnopharmacol. 2004; 94: 219-243. ISSN 0378-874. [CrossRef].
2. Vincken JP, Heng L, Groot A, Gruppen H. Saponins, classification and occurrence in the plant kingdom. Phytochemistry. 2007; 68: 275-297. ISSN 0031-9422. [CrossRef].
3. Wang Y, Gao W, Li X, Wei J, Jing S, Xiao P. Chemotaxonomic study of the genus Paris based on steroidal saponins. Biochem System Ecol. 2013; 48: 163-173. ISSN 0305-1978. [CrossRef].
4. Oleszek WA. Chromatographic determination of plant saponins. J Chromatogr A. 2002; 967: 147-162. ISSN 0021-9673. [CrossRef].
5. Francis G, Kerem Z, Makkar HPS, Becker K. The biological action of saponins in animal systems: a review. British J Nutr. 2002; 88: 587-605. ISSN 1475-2662 [PubMed].
6. Skhirtladze A, Plaza A, Montoro P, Benidze M, Kemertelidze E, Pizza C et al. Furostanol saponins from Yucca gloriosa L. rhizomes. Biochem System Ecol. 2006; 34: 809-814. ISSN 0305-1978. [CrossRef].
7. Lanzotti V, Barile E, Antignani V, Bonanomi G, Scala F. Antifungal saponins from bulbs of garlic, Allium sativum L. var. Voghiera. Phytochemistry. 2012; 78: 126-134. ISSN 0031-9422. [CrossRef].
8. Zhou LB, Chen DF. Steroidal saponins from the roots of Asparagus filicinus. Steroids. 2008; 73: 83-87. ISSN 0039-128X. [CrossRef].
9. Liu X, Zhang H, Niu XF, Xin W, Qi L. Steroidal saponins from *Smilacina japonica*. *Fitoterapia*. 2012; 83: 812-816. ISSN 0367-326X. [CrossRef]

10. Dewick PM. *Medicinal natural products: a biosynthetic approach*. 2nd Ed. West Sussex: Wiley; 2002. ISBN 9780470741672.

11. Geyter E, Lambert E, Geelen D, Smagghe G. Novel Advances with Plant Saponins as Natural Insecticides to Control Pest Insects. *Pest Technol*. 2007; 1(2): 96-105. [Link]

12. Arthan D, Kittakoop P, Esen A, Svasti J. Furostanol glycoside 26-O-b-glucosidase from the leaves of *Solanum torvum*. *Phytochemistry* 2006; 67: 27-33. ISSN 0031-9422. [CrossRef]

13. Li X, Jing S, Man S, Li X, Zhao C, Wang Y et al. A new acetylated spirostanol saponin and other constituents from the rhizomes of *Dioscorea altithoeides* R. Knuth (Dioscoreaceae). *Biochem Syst Ecol*. 2016; 65: 17-22. ISSN 0305-1978. [CrossRef]

14. Bernardo RR, Pinto AV, Parente JP. Steroidal saponins from *smilax officinalis*. *Phytochemistry* 1996; 43(2): 465-469. ISSN 0031-9422. [CrossRef]

15. Antunes AS, Silva BP, Parente JP, Valente AP. A New Bioactive Steroidal Saponin from *Sansevieria cylindrica*. *Phytot Res*. 2003; 17: 179-182. ISSN 1099-1573. [PubMed]

16. Ohtsuki T, Sato M, Koyano T, Kowithayakorn T, Kawahara N, Yukihiro G et al. Steroidal saponins from *Calamus insignis* and their cell growth and cell cycle inhibitory activities. *Bioorg Med Chem*. 2006; 14: 659-665. ISSN 0968-0896. [CrossRef]

17. Carotenuto A, Fattorusso E, Lanzotti V, Magno S, De Feo V, Carnuccio R et al. Porrigenins A and B, novel cytotoxic and Antiproliferative Sapogenins Isolated from *Allium porrum*. *J Nat Prod*. 1997; 60(10): 1003-1007. ISSN 1520-6025. [CrossRef]

18. Agrawal PK. Dependence of 1H NMR chemical shifts of geminal protons of glycosyloxy methylene (H2-26) on the orientation of the 27-methyl group of furostane-type steroidal saponins. *Magn Resonan Chem*. 2004; 42: 990-993. ISSN 1097-458X. [CrossRef]

19. Mostafa A, Sudisha J, El-Sayed M, Tsuyoshi IT, Yamauchi N et al. Aginoside saponin, a potent antifungal compound, and secondary metabolite analyses from *Allium nigrum*. *Phytochem Letters*. 2013; 6: 274–280. ISSN 1874-3900. [CrossRef]

20. Sadeghi M, Zolfaghari B, Senatore M, Lanzotti V. Spirostan, furostan and cholestan saponins from *Persian leek* with antifungal activity. *Food Chem*. 2013; 141: 1512-1521. ISSN 0308-8146. [CrossRef]

21. Sautour M, Miyamoto T, Lacaille-Dubois MA. Steroidal saponins and flavan-3-ol glycosides from *Dioscorea villosa*. *Biochem System Ecology*. 2006; 34(1). ISSN 0305-1978. [CrossRef]

22. Cho J, Choi H, Lee J, Kim M-S, Sohn H-Y, Lee DG. The antifungal activity and membrane-disruptive action of disoin extracted from *Dioscorea nipponica*. *Biochim Biophy Acta*. 2013; 1828: 1153-1158. ISSN 0005-2736. [CrossRef]

23. Qin X-J, Sun D-J, Chen C-X, Sun H-Y, He L et al. Steroidal saponins with antimicrobial activity from stems and leaves of *Paris polyphylla* var. *yunnanensis*. *Steroids*. 2012; 77: 1242-1248. ISSN 0039-128X. [CrossRef]

24. Fouedjou RT, Teponno RB, Quassinti L, Bramucci M, Petrelli D, Vitali LA et al. Steroidal saponins from the leaves of *Cordyline fruticosa* (L.) A. Chev. and their cytocidal and antimicrobial activity. *Phytochem Letters*. 2014; 7: 62-68. ISSN 1874-3900. [CrossRef]
25. Shao B, Guo H, Cui Y, Ye M, Jian HU, Guo D. Steroidal saponins from *Smilax china* and their anti-inflammatory activities. *Phytochemistry*. 2007; 68: 623-630. ISSN 0031-9422. [CrossRef].

26. Sun Z-Y, Zuo S-Q, Yang X, Lan J-H, Liu C-X, Guo Z-Y et al. Aspidosaponins E-H, Four new steroidal saponins from the rhizomes of *Aspidistra elatior* Blume and their anti-inflammatory activity. *Phytochem Letters*. 2019; 34: 68-73. ISSN 1874-3900. [CrossRef].

27. Adão CR, Silva BP, Parente JP. A new steroidal saponin from *Allium ampeloprasum var. porrum* with anti-inflammatory and gastroprotective effects. *Phytochem Letters*. 2011; 4: 306-310. ISSN 1874-3900. [CrossRef].

28. Silva BP, Sousa AC, Silva GM, Mendes TP, Parente JP. A New Bioactive Steroidal Saponin from *Agave attenuata*. *Zeitschrift für Naturforschung* 2002; 57c: 423-428. ISSN 0939-507. [CrossRef].

29. Silva BP, Parente JP. A New Bioactive Steroidal Saponin from *Agave brittoniana*. *Zeitschrift für Naturforschung*. 2007; 62b: 1193-1198. ISSN 0939-507. [Link].

30. Wang W, Imeng H. Cytotoxic, anti-inflammatory and hemostatic spirostane-steroidal saponins from the ethanol extract of the roots of *Bletilla striata*. *Fitoterapia*. 2015; 101: 2-18. ISSN 0367-326X. [CrossRef].

31. Rezgui A, Mitaine-Offer A-C, Paululat T, Delemasure S, Patrick Dutartre P, Lacaille-Dubois M-A. Cytotoxic steroidal glycosides from *Allium flavum*. *Fitoterapia*. 2014; 93: 121-125. ISSN 0367-326X. [CrossRef].

32. Li N, Zhang L, Zeng K-W, Zhou Y, Zhang J-Y, Che Y-Y et al. Cytotoxic steroidal saponins from *Ophiopogon japonicus*. *Steroids*. 2013; 78: 1-7. ISSN 0039-128X. [CrossRef].

33. Yang Y-J, Pang X, Wang B, Yang J, Chen X-J, Sun X-G et al. Steroidal saponins from *Trillium tschonoskii* rhizomes and their cytotoxicity against HepG2 cells. *Steroids*. 2015; 106: 1-7. ISSN 0039-128X. [CrossRef].

34. Tong Q-Y, He Y, Zhao Q-B, Qing Y, Huang W, Wu X-H. Cytotoxicity and apoptosis-inducing effect of steroidal saponins from *Dioscorea zingiberensis* Wright against cancer cells. *Steroids*. 2012; 77: 1219-1227. ISSN 0039-128X. [CrossRef].

35. Yokosuka A, Mimaki Y. Steroidal saponins from the whole plants of *Agave utahensis* and their cytotoxic activity. *Phytochemistry*. 2009; 70: 807-815. ISSN 0031-9422. [CrossRef].

36. Yokosuka A, Mimaki Y, Sashida Y. Spirostanol saponins from the rhizomes of *Tacca chantrieri* and their cytotoxic activity. *Phytochemistry*. 2002; 61: 73-78. ISSN 0031-9422. [CrossRef].

37. Timité G, Mitaine-Offer A-C, Miyamoto T, Tanaka C, Mirjolet J-F, Duchamp O et al. Structure and cytotoxicity of steroidal glycosides from *Allium schoenoprasum*. *Phytochemistry*. 2013; 88: 61-66. ISSN 0031-9422. [CrossRef].

38. Hernández JC, León F, Quintana J, Estévez F. Bermejo J. Icogenin, a new cytotoxic steroidal saponin isolated from *Dracaena draco*. *Bioorg Med Chem*. 2004; 12: 4423-4429. ISSN 0968-0896. [CrossRef].

39. Ivanova A, Mikhova B, Batsalova T, Dzhambazov B, Kostova I. New furostanol saponins from *Smilax aspera* L. and their in vitro cytotoxicity. *Fitoterapia*. 2011; 82: 282-287. ISSN 0367-326X. [CrossRef].

40. Zhao Y-F, Zhou J, Zhang M-J, Zhang M, Huang X-F. Cytotoxic steroidal saponins from the rhizome of *Anemarrhena asphodeloides*. *Steroids*. 2020; 155: 1-5. ISSN 0039-128X. [CrossRef].

41. Mosad RR, Ali MH, Ibrahim MT, Shaaban H, Emara M, Wahba AE. New cytotoxic steroidal saponins from *Cestrum parqui*. *Phytochem Letters*. 2017; 22: 167-173. ISSN 1874-3900. [CrossRef].
42. Raslan MA, Melek FR, Said AA, Elshamy AI, Umeyama A, Mounier MM. New cytotoxic dihydrochalcone and steroidal saponins from the aerial parts of Sansevieria cylindrica Bojer ex Hook. *Phytochem Letters*. 2017; 39-43. ISSN 1874-3900. [CrossRef].

43. Matsuda H, Pongpiriyadacha Y, Morikawa T, Kishi A, Kataoka S, Yoshikawa M. Protective effects of steroidal saponins from *Paris polyphylla* var. *yunnanensis* on ethanol- and indomethacin-induced gastric mucosal lesions in rats: structural requirement for activity and mode of action. *Bioorg Med Chem Let*. 2003; 13: 1101-1106. ISSN 0960-894X. [PubMed].

44. Pereira GM, Ribeiro MG, Silva BP, Parente JP. Structural characterization of a new steroidal saponin from *Agave angustifolia* var. *Marginata* and a preliminary investigation of its in vivo antilucreogenic activity and in vitro membrane permeability property. *Bioorg Med Chem Let*. 2017; 27: 4345-4349. ISSN 0960-894X. [CrossRef].

45. Zheng J, Zheng Y, Zhi H, Dai Y, Wang N, Wu L et al. Two new steroidal saponins from *Selaginella uncinata* (Desv.) Spring and their protective effect against anoxia. *Fitoterapia*. 2013; 88: 25-30. ISSN 0367-326X. [CrossRef].

46. Wang T, Choi RCY, Li J, Bi CWC, Ran W, Chen X et al. Trillinin, a steroidal saponin isolated from the rhizomes of *Dioscorea nipponica*, exerts protective effects against hyperlipidemia and oxidative stress. *J Ethnopharmacol*. 2012; 139: 214-220. ISSN 0378-874. [CrossRef].

47. Li H, Huang W, Wen Y, Gong G, Zhao Q, Yu G. Anti-thrombotic activity and chemical characterization of steroidal saponins from *Dioscorea zingiberensis* C.H. Wright. *Fitoterapia*. 2010; 81: 1147-1156. ISSN 0367-326X. [CrossRef].

48. Diab Y, Ioannou E, Emam A, Vagias C, Roussis V. Desmettianosides A and B, bisdesmosidic furostanol saponins with molluscicidal activity from *Yucca desmettiana*. *Steroids*. 2012; 77: 686-690. ISSN 0039-128X. [CrossRef].

49. Wang G-X, Han J, Zhao L-W, Jiang D-X, Liu Y-T, Liu X-L. Anthelmintic activity of steroidal saponins from *Paris polyphylla*. *Phytomed*. 2010; 17: 1102-1105. ISSN 0944-7113. [CrossRef].

50. Wang K-W, Zhang H, Shen L-Q, Wang W. Novel steroidal saponins from *Liriope graminifolia* (Linn.) Baker with anti-tumor activities. *Carbohyd Res*. 2011; 346: 246-258. ISSN 0008-6215. [CrossRef].

51. He T, Qu R, Qin C, Wang Z, Zhang Y, Shao X et al. Potential mechanisms of Chinese Herbal Medicine that implicated in the treatment of COVID-19 related renal injury. *Saudi Pharm J*. 2020; 28: 1138-1148. ISSN 1319-0164. [CrossRef].

52. Hsieh MJ, Tsai TL, Hsieh YS, Wang CJ, Chiou HL. Dioscin-induced autophagy mitigates cell apoptosis through modulation of PI3K/Akt and ERK and JNK signaling pathways in human lung cancer cell lines. *Arch Toxicol*. 2017; 91: 2495-2496. ISSN 1432-0738. [PubMed].

53. Bailly C, Vergote G. Glycyrrhizin: An alternative drug for the treatment of COVID-19 infection and the associated respiratory syndrome. *Pharmacol Therap*. 2020; 214: 107618. ISSN 0163-7258. [CrossRef].