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Biological Activity and Isolated Compounds in *Sapindus saponaria* L. and other Plants of the Genus *Sapindus*

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SUMMARY. Species of *Sapindus* (Sapindaceae) are widespread throughout the tropics (*e.g.,* Brazil, China and India). The present report is based on available data and references on species of this genus. The main substances found in plants of the genus Sapindus are acetylated triterpenic saponin and acyclic sesquiterpene oligoglycosides. These plants have antimicrobial, spermicidal, antiulcer, hepatoprotective, molluscicidal, fungicidal and anti-inflammatory activity. In Brazil, the fruit of *Sapindus saponaria* L. is employed in folk medicine in the treatment of ulcers and external wounds.

INTRODUCTION

The family Sapindaceae Juss includes 140 to 150 genera and approximately 2000 species. Twenty-two genera, with approximately 380 species, most of them from the Amazon region, have been recorded in the Brazilian flora [1].

A tropical tree of this family, which occurs in Brazil from the Amazon region to the states of Goiás and Mato Grosso, *Sapindus saponaria* L. is popularly known as "sabão-de-macaco", "saboeiro", "saboneteiro", "fruta de sabão" and "sabão-de-soldado" [2]. The fruit of *S. saponaria,* is used by local population as soap for washing clothes, and for curing ulcers, external wounds and inflammations [3]. The etymology of the term Sapindus is from Greek *sapo* = soap and *indicus* = from India 1.

The saponins are naturally occurring surface-active glycosides. Saponin consists of a sugar moiety usually containing glucose, galactose, glucuronic acid, xylose, rhamnose or methylpentose, glycosidically linked to a hydrophobic aglycone (sapogenin), which may be a triterpenoid or steroid in nature. Experiments demonstrating the physiological, immunological and pharmacological properties of saponins have stimulated considerable clinical interest in these substances [4]. In water, saponins produce abundant and persistent suds that are stable to diluted mineral acids [5].

The acyclic sesquiterpene oligoglycosides are glycosylated terpenoids. The terpernoids are derived from C_5 isoprene units joined in a head-to-tail fashion. The sesquiterpenes are derived from three C_5 isoprene units (C_{15}) and contain 15 carbon atoms. Processes for attaching sugar units to a suitable atom of the aglycone give glycoside derivatives such as acyclic sesquiterpene oligoglycosides [6].

Species of *Sapindus* have been investigated as sources of saponins for cosmetics, because of their astringent characteristics and also their pharmacological uses. Compounds derived from some species, classified as triterpenics, have anti-ulcerogenic and anti-neoplasic actions [1].

Isolated Compounds and Biological Activity in Species of the Genus Sapindus

Sapindus mukorossi GAERTN is the best-known species of the genus Sapindus, and is traditionally used in oriental medicine as a spermicide.

KEY WORDS: Acyclic sesquiterpene oligoglycosides, *Sapindus,* Saponin.

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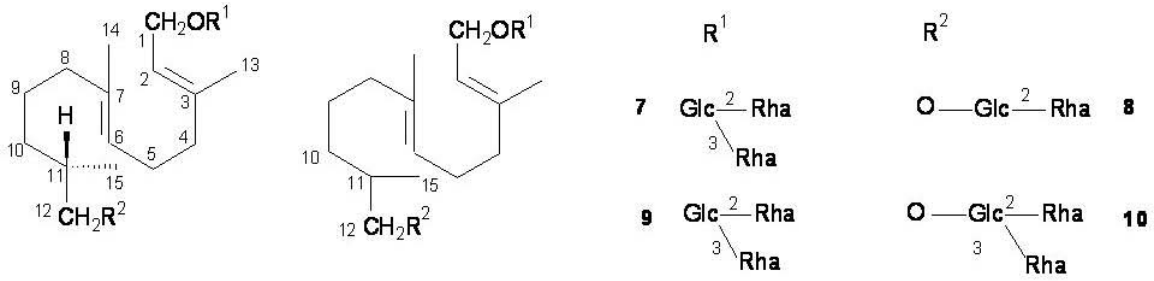

Figure 1. Mukoroziosides Ia (7), Ib (8), IIa (9) and IIb (10). Glc: β-glucopyranosyl; Rha: α-rhamnopyranosyl.

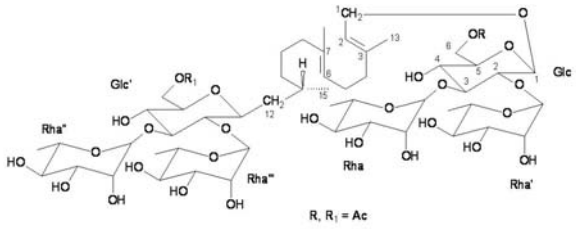

Figure 2. Structure of mukurozioside **A** [10].

Takagi *et al.* [7] investigated the anti-inflammatory activities of hederagenin and crude saponin isolated from *S. mukorossi,* using carrageenin-induced edema, granuloma pouch and adjuvant arthritis in rats. The effects of these agents on vascular permeability and acetic-acid-induced writhing in mice were also examined. Anti-inflammatory activity on carrageenin edema was observed after intraperitoneal and oral administration of crude saponin, whereas hederagenin and the other agents showed activity only when administered intraperitoneally. Takagi *et al.* [7] observed that crude saponin showed a significant inhibitory effect on granuloma and exudate formations in rats, inhibited the increase in vascular permeability and the number of writhings induced by acetic acid in mice, and significantly inhibited the development of hind-paw edema associated with adjuvant arthritis in rats after oral administration. They concluded that the results suggested that crude saponin shows some degree of anti-inflammatory activity.

Kasai *et al.* [8] isolated four acyclic sesquiterpene oligoglycosides (ASOGs), named mukoroziosides Ia, Ib, IIa and IIb, from fruit pericarps of *S. mukorossi* (Fig. 1).

Raghuvanshi *et al.* [9] developed a spermicide compound, called Praneem polyherbal, featuring anti-microbial traits, from the pericarp of fruit of *S. mukorossi,* leaves of *Azadirachta indica,* and oil of *Mentha citrata*. The association of these three plants produced a highly powerful spermicide, which was tested on rabbits and

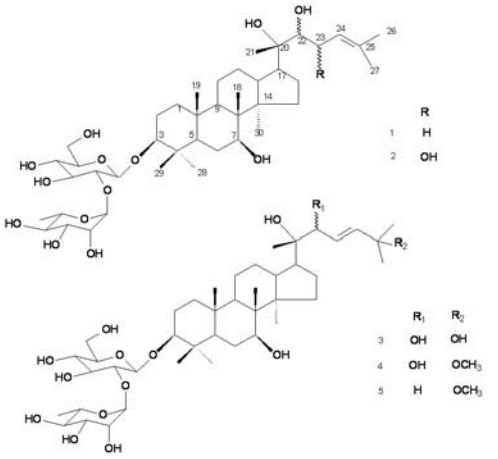

Figure 3. Structures of damaran-type saponins (**1**, **2**, **3**, **4**, **5**) [13].

on human sperm through *in vitro* and *in vivo* studies. When this spermicide was applied to the vagina of female rabbits, pregnancy failed to occur.

Sun *et al.* [10] isolated mukurozioside A (Fig. 2), a new acyclic sesquiterpene oligoglycoside, from pericarps of *S. mukorossi,* and determined its structure by NMR spectroscopy and mass spectrometry (ESI-MS).

Maikhuri *et al.* [11] compared the effects of synthetic spermicides and of *S. mukorossi*-isolated saponins by means of the mobility, structural and physiological integrity of the plasma membrane, lipid peroxidation and the defense mechanism against oxidative radicals of human spermatozoids, to study the mechanism of their activity. Ojha *et al.* [12] reported less toxicity in saponins from *S. mukorossi* for *Lactobacillus acidophilus* when compared to Nonoxynil–9, and therefore suggested that these saponins would have advantages as a spermicide. Kuo *et al.* [13] identified three known phenylpropanoid glycosides and five new *S. mukorossi*–isolated saponins (Fig. 3), by spectroscopic analyses and chemical methods. They reported cytotoxic activity of saponins in human tumor cells.

Ibrahim *et al.* [14] reported that an extract from the pericarp of fruit of *S. mukorossi* inhibited the growth of *Helicobacter pylori,* and assessed the extract's antimicrobial activity through *in vitro* and *in vivo* assays. Ni *et al.* [15] identified six new tirucallane-type triterpenic saponins, sapimukosides E–J (**1-6**) (Fig. 4), isolated from roots of *S. mukorossi*. They established their structures through hydrolytic cleavages, mass spectrometry (MS) and ^{1}H NMR, ^{13}C NMR and NMR 2D spectroscopy.

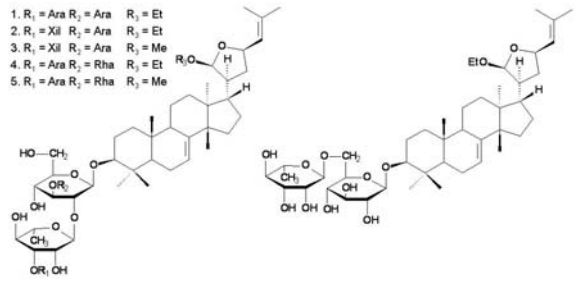

Figure 4. *Sapimukosides* E–J (1–6) [15].

Huang *et al.* [16] isolated five new tirucallane-type saponins, sapinmusaponins F-J (**1-5**) (Fig. 5) from the galls of *S. mukorossi*. They elucidated the structures on the basis of spectroscopic analysis including 1D and 2D NMR techniques (^{1}H-^{1}H COSY, HMQC, HMBC, TOCSY, and NOESY). Compounds **1-5** showed anti-platelet-aggregation effects, but no obvious cytotoxic activity for platelets as assayed by lactate dehydrogenase (LDH) leakage. Compounds **1-5** also showed moderate activity in a 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced Epstein-Barr virus early antigen (EBV-EA) activation assay.

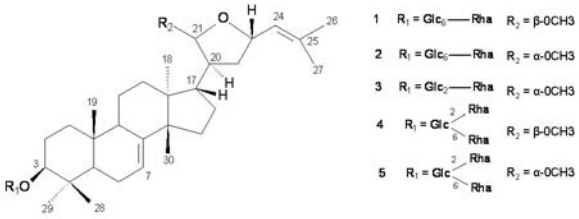

Figure 5. Sapimukosides E–J (1–6) [16].

Ibrahim *et al.* [17] studied the hepatoprotective capacity of *S. mukorossi* and *Rheum emodi* extracts in CCl_4 treated male rats. For *in vitro* studies, they used primary rat hepatocyte monolayer cultures. To evaluate the effects *in vivo,* the hepatoprotective capacity of the extract of the fruit pericarp of *S. mukorossi* and the rhizomes of *R. emodi* was analyzed in liver-injured CCl_4 treated male rats. They observed that the extracts of *S. mukorossi* and *R. emodi* have a protective capacity both *in vitro* in primary hepatocyte cultures, and *in vivo* in a rat model of CCl_4-mediated liver injury.

Sapindus delavayi (Franch) Radlk was studied by Wong *et al.* [18]. They isolated five new acyclic sesquiterpene oligoglycosides (pyishiausosides Ib, IIb, IVb, IIIa and IVa). They produced an extract from the pericarp of *S. delavayi* fruits in methanol (MeOH) under heating. From the above-mentioned extract, a non-glycoside fraction was separated in CC silica gel (EtAc–MeOH–H_2O, 12:2:1 – 6:2:1), resulting in the isolation of ten compounds: mukoroziosides Ia, Ib, IIa and IIb; proagenin from IIb, and pyishiausides Ib, IIb, IVb, IIIa and IVa (Fig. 6).

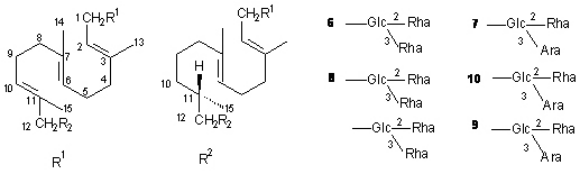

Figure 6. Pyishiauside Ib (**6**), IIb (**7**), IVb (**8**), IIIa (**9**) and IVa (**10**) [18].

Sapindus emarginatus was investigated by Kanchanapoom *et al.* [19]. They isolated three new acetylated triterpenic saponins from the pericarp of fruits, traditionally used in Thai medicine as an anti-pruritis compound (Fig. 7): hederagenin 3-O-(2-O-acetyl-β-D-xylopiranosyl)-(1→3)-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranoside; 23-O-acetyl-hederagenin 3-O-(4-O-acetyl-β-D-xylopyranosyl)-(1→3)-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranoside and oleanoic acid 3-O-(4-O-acetyl-beta-D-xylopyranosyl)-(1→3)-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranoside), in addition to hederagenin, five previously known triterpenic saponins and mukorozioside IIb.

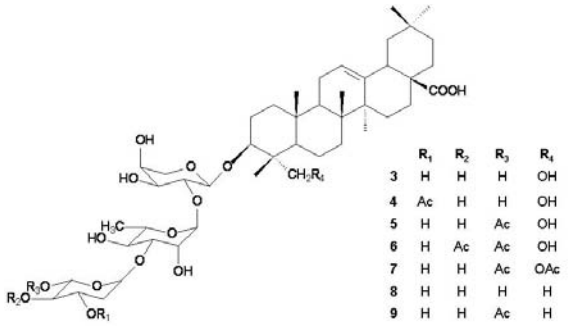

Figure 7. New acetylated triterpenic saponins (**4**, 7 and **9**) [19].

Sapindus trifoliatus L. was studied by Kasai *et al.* [20]. They isolated two known saponins and a new acyclic sesquiterpenic oligoglycoside, called trifolioside II (Fig. 8) from the methanol extract of *S. trifoliatus*. Its structure was elucidated by enzyme hydrolysis of the cellulase-isolated compound, incubated in acetate for 7 days at 37 °C, by ^{13}C NMR analyses of compounds.

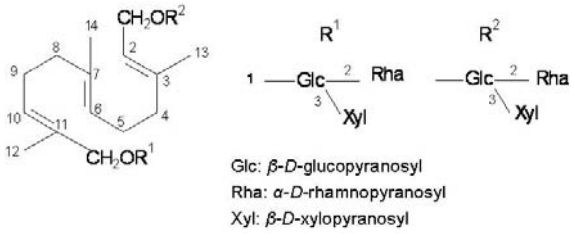

Figure 8. Trifolioside II [20].

Arul *et al.* [21] studied the anti-inflammatory action of an ethanol extract of *S. trifoliatus* seeds by paw-edema induction and pleurisy methods caused by carrageenin and granuloma formation. The extract produced decreases in paw edema and in pleural sweating volume, and had an inhibitory effect on leucocyte migration. A decrease in granuloma weight was also reported. Arulmozhi *et al.* [22] conducted a pharmacological study with the aqueous pericarp extract of fruits of *S. trifoliatus*. The effect of this extract on the central nervous system was investigated for possible anti-migraine characteristics. The results suggested that plant has potential neuroleptic properties. In addition, Arulmozhi *et al.* [23] studied the effect of the aqueous pericarp extract of fruits of *S. trifoliatus* in an *in vivo* migraine hyperalgesic model. The results showed that antagonism to dopamine D_2 might underlie the mechanism involved in the anti-hyperalgesic activity of the plant extract. These researchers [24] also investigated the effect of the aqueous lyophilized extract of the pericarp of *S. trifoliatus* fruits through *in vivo* and *in vitro* experimental models of inflammation. The *in vitro* evaluation showed the extract's inhibitory activity against the inflammatory agents 5-lipoxygenase, cyclooxygenase, leukotriene B4 and nitric-oxide synthase. The extract significantly inhibited inflammation of paw edema caused by carrageenin, histamine, serotonin and zymosan in rats and mice. Moreover, topical application significantly inhibited ear edema caused by inflammatory agents such as 13-acetate-O-tetradecanoil-phorbol (TPA), capsaicin or arachidonic acid. The authors concluded that the extract has an anti-inflammatory activity, probably mediated by the 5-lipoxygenase and cyclo-oxygenase pathways.

Isolated Compounds and Reported Biological Activities in Sapindus saponaria L.

In a phytochemical analysis, Wahab and Selim [25] identified flavonids, lipids and steroids in apolar extracts from seeds of *S. saponaria*.

Lemos *et al.* [26] isolated a new saponin 3-β-*O*-[α-L-rhamnopyranosyl-(1→3)-β-D-glycopyranosyl]-hederagenin (Fig. 9) from the ethyl-acetate fraction of fruits of *S. saponaria,* and reported anti-microbial activity.

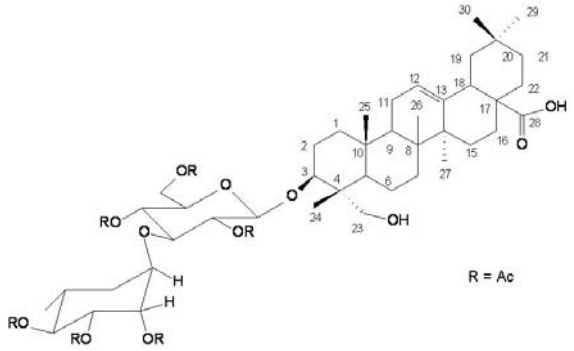

Figure 9. 3-b-*O*-[α-L-rhamnopyranosyl-(1→3)-β-D-glycopyranosyl]-hederagenin [26].

Ribeiro *et al.* [27] analyzed *S. saponaria* and collected 12 fractions from n-butanol fraction of the plant extract, developed with a $CHCl_3$-MeOH-H_2O (85:10:1) and $CHCl_3$-MeOH (1:1) system. Two of the 12 fractions were separated in a low-pressure silica-gel column ($CHCl_3$-MeOH-H_2O, 70:12:1) or RP-18 (MeOH-H_2O, 75:25). They obtained three saponins (Fig. 10) with molluscicidal activity.

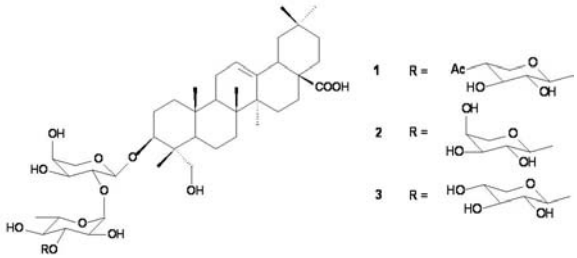

Figure 10. Molluscicidal saponins [27].

Albiero *et al.* [28] investigated the inhibitory effect of a hydro-alcoholic extract of leaves and fruits of *S. saponaria* on stress-induced gastric lesions. Their results showed that both extracts caused a decrease in gastric secretion. However, the saponin- and tannin-rich fruit extract was more effective in anti-ulcerogenic activity.

Murgu & Rodrigues Filho [29] studied compounds in *S. saponaria* fruits by liquid chromatography with UV and MS detection (LC/UV/ESI-MS) and MS/MS fragmentation methods. They reported that the main glycosides in these fruits were saponins (SAP) derived from triterpenes hederagenin and oleanolic acid and oligoglycosides from acyclic sesquiterpene oligoglycosides (ASOGs) (Fig. 11). The above analytical methods aided in the detection of up to 30 SAPs and 63 ASOGs, which the plant produces as a complex mixture of naturally acetylated glycosides. Quantitative analysis of saponified glycosides showed that the amount of SAPs accumulated during fruit maturation remained constant, while the amount of ASOGs sharply increased after three months.

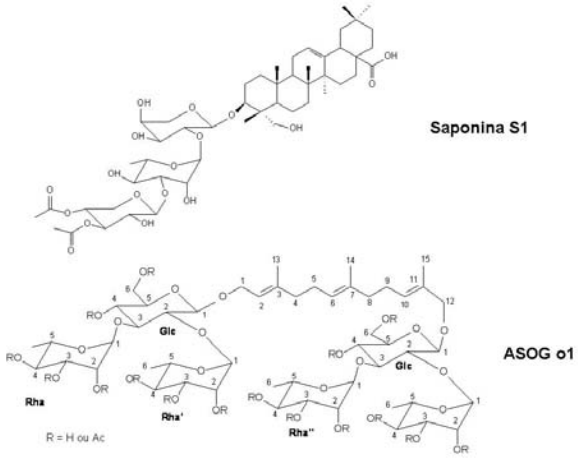

Figure 11. Saponin S1 and ASOG O1 [29].

In a phytochemical study of *S. saponaria* extract, Tsuzuki *et al.* [30] isolated two saponins (Fig. 12) from extracts of the dried pericarp of *S. saponaria,* and investigated it for antifungal activity against clinical isolates of the yeasts *Candida albicans* and C. non-*albicans* from vaginal secretions of women with vulvovaginal candidiasis. The hydroalcoholic extract was bioactivity-directed against a clinical isolate of *C. parapsilosis,* and showed strong activity. The butanolic extract and one fraction showed strong activity against all microorganisms tested. They identified the saponin structures using spectroscopy NMR data and mass spectrometry (MS), based on literature data. These compounds showed strong activity against *C. parapsilosis*.

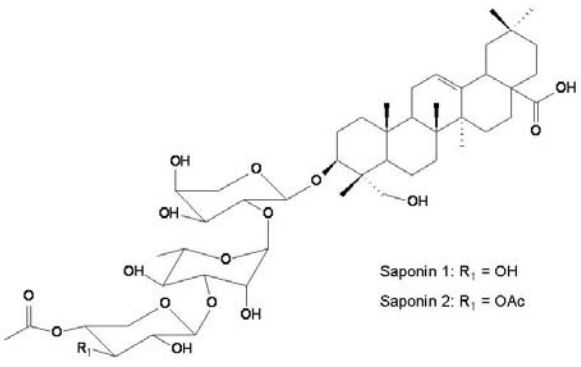

Figura 12. Saponin 1 and Saponin 2 [30].

CONCLUSION

The main objective of this review was to present the research carried out with species of the genus *Sapindus,* in order to organize the data produced. The use of species of *Sapindus* in folk medicine worldwide is validated by scientific studies that have demonstrated the efficacy of the extracts in various experimental models. This review allowed finding many biological and pharmacological studies with fractions of crude extracts and isolated substances that show antimicrobial, spermicidal, antiulcer, molluscicidal, antifungal and anti-inflammatory activities, with good results. The main bioactive substances found in the genus *Sapindus* are saponins and acyclic sesquiterpene oligoglycosides.

These species produce a complex mixture of glycosidic compounds with diverse biological effects. It is difficult to establish clear functionality and structure-activity relationships regarding the effects of saponins and OGSAs, because there are many saponins with similar chemical structures, and also because of the complexity of cellular physiological reactions, which are often differently influenced by differences in stereo-structures of effector ligands.

The Brazilian species of *Sapindus* have wide and long-term traditional uses in the local folk medicine. All the pharmacological studies carried out with *S. saponaria* extracts suggest its potential as an appropriate material to be used in the development of a topical medicine product, as a good phytotherapeutic agent.

In spite of the several existing chemical and pharmacological studies with different *Sapindus* extracts, and although the properties of several isolated substances suggest their potential as suitable natural resources for developing new compounds for the pharmaceutical industry, studies that associate these compounds with biological activity are few. Many of the substances responsible for some promising activity of the extract remain obscure. Further investigation will be necessary to elucidate the mechanisms involved in the pharmacological activity of species of *Sapindus*.

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