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REVIEW ARTICLE

MEDICINAL PLANTS OF THE GENUS SAPINDUS (SAPINDACEAE) - A REVIEW OF THEIR BOTANY, PHYTOCHEMISTRY, BIOLOGICAL ACTIVITY AND TRADITIONAL USES

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ABSTRACT

Objective: Sapindus is a genus of Sapindaceae family comprises three major species: The American spices, *Sapindus saponaria* and two Asian species, *Sapindus mukorossi* and *Sapindus trifoliatus* and are well known for their folk medicinal values. Several important studies have been published in the intervening years, which have prompted us to reassess Sapindus. In the current review, we provide a comprehensive over view on the botany, traditional uses, phytochemistry and biological activities of the species of Sapindus.
Methods: A literature survey was performed by searching the scientific data bases Pubmed, Google Scholar, SciFinder, Scopus and Web of Science, in addition to traditional Indian medicine and Ayurvedic texts for information on Sapindus.
Results: Plants of the genus Sapindus have been used in traditional medicine for the treatment of ulcers, external wounds, inflammation, epilepsy, dental caries, arthritis, joint pain, gout and rheumatism. Phytochemical studies of this genus have identified more than 103 compounds. Of these compounds, triterpenoidal saponins of oleanane, dammarane and tirucullane are regarded as the active group that is most likely to be responsible for the observed biological activities. The crude extracts, as well as the isolated compounds, from the genus possess antimicrobial, anticancer, spermicidal, hepatoprotective, antioxidant, anti-inflammatory, anti-platelet aggregation, anti-hyperlipidemic, anti-migraine, anti-diabetic, anti-ulcerogenic and analgesic properties.
Conclusion: It is evident from the available literature that Sapindus species possess potential for use as a beneficial therapeutic remedy. Nevertheless, there is clearly a need for further studies focusing on in-vivo with emphasis on molecular mechanisms and eventually clinical trials.
Keywords: Biological activities, Botany, Phytochemistry, Sapindus, Saponins

INTRODUCTION

Sapindus is a genus of shrubs and small trees in the Sapindaceae family [1, 2]. The genus comprises three major species: The American spices, *Sapindus saponaria* and two Asian species, *Sapindus mukorossi* and *Sapindus trifoliatus*. The American species *Sapindus saponaria* is popularly known as western soapberry, cherrioni, jaboncillo, sabao-de-macaco, saboeiro, saboneteiro, fruta de sabao, sabao-de-soldado and grows on clay soils and on dry limestone uplands from southwestern Missouri to Louisiana, and westward through Oklahoma and Texas to southern Colorado, New Mexico, southern Arizona, northern Mexico and Brazilian Amazon region [3]. Asian species, *Sapindus mukorossi* and *Sapindus trifoliatus* are known as soapnut, soapberry, washnut, reetha, aritha, dodan, doadni and flourishes well in deep clay loamy soil with an annual rainfall of 150-200 mm. *Sapindus mukorossi* is widely distributed in upper reaches of Indo-Gangetic plains, Shivaliks and sub Himalayan tracts at altitudes from 200 m to 1500 m, while *Sapindus trifoliatus* is commonly found in the Western Ghats and plains of South India [4, 5].

The members of genus Sapindus are well known for their folk medicinal values. The fruit of *S. saponaria* is used by loacal population for curing ulcers, external wounds and inflammation [6]. *S. mukorossi* is well known for its detergent and insecticidal properties and it is traditionally used for removing lice from the scalp. The fruits are of considerable importance for their medicinal value for treating a number of diseases like excessive salivation, pimples, epilepsy, chlorosis, migranes, eczema and psoriasis. In Japan its pericarp is called “enmei-hi”, which means “life prolonging pericarp” and in China “wu-huan-zi”, the “non-illness fruit”. The powdered seeds are employed in the treatment of dental caries, arthritis, common colds, constipation and nausea. The leaves are used in baths to relieve joint pain and the roots are used in the treatment of gout and rheumatism [7-11].

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Fruits of *S. trifoliatus* have been considered as a tonic, stomachic, alexipharmic, astringent and sedative to the uterus and also useful in chronic dysentery, diarrhea, cholera, hamicrania, paralysis and epileptic fits of children. The roots used as a collyrium in sore eyes and opthalmia. The seeds are employed to stimulate the uterus in childbirth and to increase mensuration [5, 7, 12-14].

Recently, a number of studies have been conducted on the phytochemical and biological activities aspects of Sapindus. Phytochemical studies of Sapindus plants have identified more than 103 compounds, including flavonoids, triterpenoids, glycosides, carbohydrates, fatty acids, phenols, fixed oil, and saponins. Of these compounds, saponins are regarded as the active group that is most likely to be responsible for the observed biological effects [4, 7, 15-17]. Moreover, both in-vivo and in-vitro experiments have demonstrated that Sapindus exhibits a diverse set of antimicrobial, anticancer, spermicidal, hepatoprotective, anxiolytic, antioxidant, Anti-inflammatory, anti-platelet aggregation, anti-fertility, anti-hyperlipidemic, anti-migraine, anti-diabetic, anti-pruritis, anti-ulcerogenic and analgesic biological effects [4, 7, 12, 16-18.] These studies will be evaluated in detail in this review.

Several important studies have been published in the intervening years, which have prompted us to reassess Sapindus. In the current review, we provide a comprehensive over view on the ethnopharmacology, phytochemistry and biological activities of the species of Sapindus.

BOTANICAL DESCRIPTIONS

The genus Sapindus is classified in the division Magnoliophyta, class Magnoliopsida, subclass Rosidae, order Sapindales and family Sapindaceae [13, 16, 17].

The three species of the genus are the American *Sapindus saponaria* and two Asian species, *Sapindus mukorossi* and *Sapindus trifoliatus.* Sapindus species are deciduous trees that thrive in tropical climates. *Sapindus saponaria* is a well known plant in American region, and has been used as traditional medicine by local population since ancient times. *Sapindus saponaria* is widely distributed with populations reported in southwestern Missouri to Louisiana, and westward through Oklahoma and Texas to southern Colorado, New Mexico, southern Arizona, northern Mexico and Brazilian Amazon region [3, 6].

Sapindus saponaria is a small to medium deciduous tree, 7.7 to 15.4 m tall. The heavy, strong, close grained wood splits into thin strips. It contains long, pinnate leaves. This plant is described as polygamo-dioecious. That is, individual trees in a population may be truly dioecious (having only male or female flowers) or they may contain flowers with both male and female functions. The small, white flowers, borne in rather large clusters of terminal or axillary panicles, open during May to July. The fruit, a yellow, translucent, globular drupe measuring 10 to 14 mm in diameter, usually contains a single, dark brown, hard-coated seed, but occasionally 2 or 3 seeds are present. The fruits ripen during September to October and persist on the tree until late winter or spring [19, 20].

Sapindus mukorossi is a tree of tropical and sub-tropical region of Asia. It is a deciduous tree widely grown in upper reaches of Indo-Gangetic plains, Shivaliks and sub Himalayan tracts at altitudes from 200 m to 1500 m. The Sapindus mukorossi is a fairly large tree with a straight trunk up to 12 meters in height, sometimes attaining a height of 20 m and a girth of 1.8 m, with a globose crown and rather fine leathery foliage. Bark is dark to pale yellow, fairly smooth, with many vertical lines of lenticels and fine fissures exfoliating in irregular wood scales. The blaze is 0.8-1.3 cm, hard, not fibrous, pale orange brown, brittle and granular. Leaves are 30-50 cm long, alternate, paripinnate; common petiole very narrowly bordered, glabrous; leaflets 5-10 pairs, opposite or alternate, 5-18 by 2.5-5 cm, lanceolate, acuminate, entire, glabrous, often slightly falcate or oblique; petioles 2-5 m long. Inflorescence is a compound terminal panicle, 30 cm or more in length, with pubescent branches. Flowers are about 5 mm across, small, terminal, polygamous, greenish white, subsessile, numerous, mostly bisexual. Sepals 5, each with a woolly scale on either side above the claw. Fruits are globose, fleshy, 1-seeded drupe, sometimes two drupels together, about 1.8-2.5 cm across. Seeds are 0.8-1.3 cm in diameter, globose, smooth, black and loosely placed in dry fruit [4, 16].

The third species, *Sapindus trifoliatus*, occurs in the Western Ghats and plains of South India. This is a deciduous tree and flourishes well in deep clay loamy soil with an annual rain fall of 200 mm. It can reach a height of 25 m. Leaves are alternate, 15-40 cm long, pinnate, with 14 - 30 leaflets and the terminal leaflet often absent. The leaflets are elliptic-lance shaped, smooth with tipped points and slightly oblique based. They are often found in pairs of 2 or 3 and are 8 to 18 cm long and 5 to 7.5 cm wide. The flowers form in large panicles. The flowers are small greenish white in color and open during November to January. The fruit is a small leathery-skinned drupe 1-2 cm in diameter. The fruits are solitary globose appears in the month of July-August. The fruit is velvety when young and turns hard and smooth on maturing. The fruits and seeds are slightly smaller than the north Indian species [5, 13, 21].

TRADITIONAL USES

Sapindus species have a long history as traditional remedies (Table 1) [5-14]. All these species have been used in the areas where they are naturally distributed. *Sapindus saponaria* is mainly used in American region, while *Sapindus mukorossi* and *Sapindus trifoliatus* are mainly used in Asian countries as a traditional remedy. Interestingly, all these species have been used as detergent.

Sapindus saponaria

The fruit of *S. saponaria*, is used by local population for curing ulcers, external wounds and inflammations [6].

Sapindus mukorossi

Sapindus mukorossi is well known for its folk medicinal values. Pericarps of *Sapindus mukorossi* have been traditionally used as an expectorant as well as a source of natural surfactant [9]. Due to the presence of saponins,

soapnut is well known for its detergent and insecticidal properties and it is traditionally used for removing lice from the scalp. The fruits are of considerable importance for their medicinal value for treating a number of diseases like excessive salivation, pimples, epilepsy, chlorosis, migranes, eczema and psoriasis. In Japan its pericarp is called "enmei-hi", which means "life prolonging pericarp" and in China "wu-huan-zi", the "non-illness fruit". The powdered seeds are employed in the treatment of dental caries, arthritis, common colds, constipation and nausea. The seeds of are used in Ayurvedic medicine to remove tan and freckles from the skin. It cleanses the skin of oily secretion and is even used as a cleanser for washing hair as it forms a rich, natural lather. The leaves are used in baths to relieve joint pain and the roots are used in the treatment of gout and rheumatism [7-11]. Since ancient times, *Sapindus mukorossi* has been used as a detergent for shawls and silks. The fruit was utilized by Indian jewelers for restoring the brightness of tarnished ornaments made of gold, silver and other precious metals [10].

Sapindus trifoliatus

The plant is very commonly used in Indian Ayurvedic healing system. It is also used in Unani and Tibetan indigenous medicine [13]. In folklore practice, some of the tribes of Orissa (India) use the aerial parts of this plant for the treatment of diabetes mellitus. Fruits of *Sapindus trifoliatus* have been considered as a tonic, stomachic, alexipharmic, astringent and sedative to the uterus and also useful in chronic dysentery, diarrhea, cholera, hamicrania, paralysis and epileptic fits of children. The roots used as a collyrium in sore eyes and opthalmia. The seeds are employed to stimulate the uterus in childbirth and to increase mensuration [5, 7, 12-14].

Table 1: Species of Sapindus and its traditional uses

Species	Common names	Traditional uses	Ref
Sapindus saponaria L (Hook. & Arn.) Benson	Western soapberry, Cherrioni, Jaboncillo, Sabao-de-macaco, Saboeiro, Saboneteiro	Curing ulcer External wounds Inflammation	3, 6
Sapindus mukorossi L.Gaertn.	Soapnut, Soapberry, Washnut, Reetha, Aritha, Dodan, Doadni	As expectorant, Source of natural surfactant Insecticidal, treating excessive- salivation, pimples, epilepsy, chlorosis, migrane, eczema, psoriasis, dental caries, arthritis common cold, constipation, nausea, joint pain, gout and rheumatism	4, 9, 7-11
Sapindus trifoliatus L.	Soapnut, Soapberry, Washnut, Reetha, Aritha, Dodan, Doadni	considered tonic, stomachic, alexipharmic, astringent and sedative to uterus; treating diabetes, chronic dysentery, diarrhea, cholera, paralysis and epileptic- fits of children's; used as collyrium in sore eyes, opthalmia, to induce labour pain and normal contraction of uterus after child birth	5,7,12-14,22

PHYTOCHEMISTRY

Phytochemical studies of Sapindus plants have identified more than 103 compounds, including flavonoids, triterpenoids, glycosides, carbohydrates, fatty acids, phenols, fixed oil, and saponins. Of these compounds, saponins are regarded as the active group that is most likely to be responsible for the observed pharmacological effects. These saponins are found throughout the plant but are especially concentrated in the fruit [4, 7, 15-17]. Saponins are secondary plant metabolites with divergent biological activities [23]. Sapindus saponins are a mixture of six sapindosides (sapindosides A, B, C, D and mukorozi saponins (E1 and Y1), with sapindoside B as one of the major constituents, and identified by liquid chromatography and mass spectroscopy [24]. Saponins are a large family of structurally-related compounds of steroid or triterpenoid aglycone (sapogenin) linked to one or more oligosaccharide moieties by glycosidic linkage. The aglycone, or sapogenin, may contain one or more unsaturated C-C bonds. The oligosaccharide chain is normally attached at the C3 position (monodesmosidic), but many saponins have an additional sugar moiety at the $C_{2,6}$ or $C_{2,8}$ position (bidesmosidic). The great complexity of the saponin structure arises from the variability of the aglycone structure, the nature of the side chains and the position of attachment of these moieties on the aglycone [23]. The carbohydrate moiety consists of pentoses, hexoses or uronic acids. Due to this complexity, saponins are difficult to classify. Because it is no longer customary to classify compounds based on their physicochemical or biological properties, a state of the art classification based on the biosynthesis of the saponin carbon skeletons was proposed by Vincken et al [25].

Different types of triterpene, saponins of oleanane, dammarane and tirucullane type were isolated from the galls, fruits and roots of Sapindus species. Oleanane type triterpenoid saponins named Sapindoside A & B (Fig. 34 & 35) were reported from the fruits [26]. Sapindoside C (Fig. 36) [27], Sapindoside D (Fig. 37) [28], which is a hexaoside of hederagenin, and Sapindoside E (Fig. 38) [29], a nonaoside of hederagenin, was isolated and identified from the methanolic extract of the fruits of Sapindus species.

Dammarane-type saponins, named Sapinmusaponins A & B (Fig. 11 & 12), C-E (Fig. 15, 16, 17), together with three known phenylpropanoid glycosides, were isolated from the galls of *Sapindus mukorossi* [30]. Tirucallane-type saponins, sapinmusaponins F-J (Fig. 18-22), were isolated from the galls as reported by Huang et al [31]. The structures of these saponins were elucidated on the basis of spectroscopic analysis including 1D and 2D NMR techniques.

Triterpene saponins of oleanane type like, Sapinmusaponin K-N (Fig. 25-28), Mukorozisaponin G & E1 (Fig. 29-30), Sapindoside A & B along with dammarane types like Sapinmusaponin O and P (Fig. 13 & 14) were isolated from fruits and the galls of *Sapindus mukorossi* as per Huang et al [32]. In another study by Nakayama et al., Mukorozisaponin Y1 (Fig. 31), Y2 (Fig. 32), X (Fig. 33) were isolated from the pericarp [33].

Fractionation of an ethanolic extract of the galls of *Sapindus mukorossi* has resulted in the isolation of two tirucallane type triterpenoid saponins, sapinmusaponin Q and R (Fig. 23-24), along with three known oleanane type triterpenoid saponins: sapindoside A, sapindoside B, and hederagenin-3-O-[β-D-xylopyranosyl-(1→3)]-α-L-rhamnopyranosyl-(1→2)+-α-L arabinopyranoside [34]. The roots of *Sapindus mukorossi* contain tirucallane-type triterpenoid saponins like Sapimukoside A & B [35] and Sapimukoside C & D [36]. Further investigation of the roots of *Sapindus mukorossi* by Ni et al., reported the presence of Sapimukosides E-J [37]. The structures of Sapimukosides A-J are shown in Fig. 1-10 respectively. Table 2 shows whole view of all the saponins isolated from genus Sapindus.

Table 2: List of saponins isolated from genus Sapindus

Saponins	Chemical name	Oleanane/Tirucullane/ Dammarane type	Structure	Ref
Sapindoside				
A	Hederagenin-3-O-α-L-arabinosyl-(2→1)-α-L-rhamnopyranoside	Oleanane	34	26
B	Hederagenin-3-O-α-L-arabinosyl-(2→1)-O-α-L-rhamnopyranosyl-(3→1)-β-D-xylanopyranoside	Oleanane	35	26
C	Hederagenin-3-O-β-D-glucosyl(1→4)-β-D-xylosyl (1→3)-α-Lrhamnosyl(1→2)-α-L-arabinoside	Oleanane	36	27
Sapinmusaponin				
A	3,7,20(S),22-tetrahydroxydammar-24-ene-3-O-a-L-rhamnopyranosyl-(1→2)-D- glucopyranoside	Dammarane	11	30
B	3,7,20(S),22,23-pentahydroxydammar-24-ene-3-O-a-L-rhamnopyranosyl-(1→2)-D glucopyranoside	Dammarane	12	30
C	3,7,20(S),22,25-pentahydroxydammar-23-ene-3-O-a-L-rhamnopyranosyl-(1→2)-D-glucopyranoside	Dammarane	15	30
D	25-methoxy-3,7,20(S),22-tetrahydroxydammar-23-ene-3-O-a-L-rhamnopyranosyl-(1→2)-D-glucopyranoside	Dammarane	16	30
E	25-methoxy-3,7,20(R)-trihydroxydammar-23-ene-3-O-a-L-rhamnopyranosyl-(1→2)-D-glucopyranoside	Dammarane	17	30
F	21 β-methoxy-3-β-21(S), 23I-epoxy tirucall-7,24-diene-3-O-α-L-rhamnopyranosyl-(1→6)-β-D- glucopyranosyl	Tirucullane	18	31
G	21α-methoxy-3-β-21(S), 23I-epoxy tirucall-7,24-diene-3-O-α-L-rhamnopyranosyl-(1→6)-β-D- glucopyranosyl	Tirucullane	19	31
H	21α-methoxy-3-β-21(S), 23I-epoxy tirucall-7,24-diene-3-O-α-L-rhamnopyranosyl-(1→2)-β-D- glucopyranosyl	Tirucullane	20	31
I	21β-methoxy-3-β-21(S), 23I-epoxy tirucall-7,24-diene-3-O-α-L-dirhamnopyranosyl-(1→2,6)-β-D- glucopyranosyl	Tirucullane	21	31
J	21α-methoxy-3-β-21(S), 23I-epoxy tirucall-7,24-diene-3-O-α-L- dirhamnopyranosyl-(1→2,6)-β-D-glucopyranosyl	Tirucullane	22	31
K	hederagenin-3-O-(3-O-acetyl-alpha-L-	Oleanane	25	32

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	arabinopyranosyl)-(1→3)-alpha-L-rhamnopyranosyl-(1→2)-alpha-L-arabinopyranoside			
L	hederagenin-3-O-(4-O-acetyl-alpha-L-arabinopyranosyl)-(1→3)-alpha-L-rhamnopyranosyl-(1→2)-alpha-L-arabino-pyranoside	Oleanane	26	32
M	hederagenin-3-O-(2,3-O-diacetyl-beta-D-xylopyranosyl)-(1→3)-alpha-L-rhamnopyranosyl-(1→2)-alpha-L-arabinopyranoside	Oleanane	27	32
N	hederagenin-3-O-(2,4-O-diacetyl-beta-D-xylopyranosyl)-(1→3)-alpha-L-rhamnopyranosyl-(1→2)-alpha-L-arabinopyranoside	Oleanane	28	32
O	3,7,20(S)-trihydroxydammar-24-ene-3-O-alpha-L-rhamnopyranosyl-(1→2)-beta-D-glucopyranoside	Dammarane	13	32
P	3,7,20(R)-trihydroxydammar-24-ene-3-O-alpha-L-rhamnopyranosyl-(1→2)-beta-D-glucopyranoside	Dammarane	14	32
Q	21α-methoxy-3β, 21I, 23(S)-epoxytirucall-7,24-diene-3-O-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside	Tirucullane	23	34
R	21α-methoxy-3β, 21I, 23(S)-epoxytirucall-7,24-diene-3-O-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranosyl-(1→2)-β-D- glucopyranoside	Tirucullane	24	34
Sapinmukoside				
A	3-O-α-L-rhamnopyranosyl-(1→2)-*α-L-arabinopyranosyl-(1→3)+ – β-D-glucopyranosyl-21, 23R-epoxyl tirucall-7, 24R-diene-3 β, 2-diol	Tirucullane	1	35
B	3-O-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranosyl-21, 23R-epoxyl tirucall-7, 24R-diene-3 β, 21-diol	Tirucullane	2	35
C	3-O-α-L-rhamnopyranosyl-(1→2)-[α-L-arabinopyranosyl-(1→3)]-β-D-glucopyranosyl (21,23R)-epoxyl tirucalla-7, 24-diene-(21S)-ethoxyl-3β-ol	Tirucullane	3	36
D	3-O-α-L-rhamnopyranosyl-(1→2)-[α-L-arabinopyranosyl-(1→3)]-β-D-glucopyranosyl (21,23R)-epoxyl tirucall-7, 24-diene-(21S)-methoxyl-3β-ol	Tirucullane	4	36
E	3-O-α-L-arabinopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→2)-[α-L-arabinopyranosyl-(1→3)]-β-D-glucopyranosyl (21,23R)-epoxyl tirucalla-7,24-diene-21β-ethoxyl-3β-ol	Tirucullane	5	37
F	{3-O-β-D-xylanopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→2)-[β-L-arabinopyranosyl-(1→3)]-β-D-glucopyranosyl 21,23R-epoxyl tirucalla-7, 24-diene-21β-ethoxyl-3β-ol}	Tirucullane	6	37
G	{3-O-β-D-xylanopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→2)-[α-L-arabinopyranosyl-(1→3)]-β-D-glucopyranosyl (21,23R)-epoxyl tirucalla-7,24-diene-21β-methoxy-3β-ol}	Tirucullane	7	37
H	{3-O-α-L-arabinopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→2)-[α-L-rhamnopyranosyl-(1→3)]-β-D-glucopyranosyl 21,23R-epoxyl tirucalla-7,24-diene-21β-ethoxy-3β-ol}	Tirucullane	8	37
I	{3-O-α-L-arabinopyranosyl-(1→3)-α-L-	Tirucullane	9	37

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J	rhamnopyranosyl-(1→2)-[α-L-rhamnopyranosyl-(1→3)]-β-D-glucopyranosyl 21,23R-epoxyl tirucalla-7,24-diene-21β-methoxy-3β-ol} {3-O-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranosyl 21,23R-epoxyl tirucalla-7,24-diene-21β-ethoxyl-3β-ol}	Tirucullane	10	37
Mukorozisaponin				
G	Hederagenin-3-O-(2-O-acetyl-β-D-xylanopyranosyl)-(1→3)-α-L-rhamnopyranosyl-(1→2)-α-L- arabinoside	Oleanane	29	32
E1	Hederagenin-3-O-α-L-arabinosyl-(1→3)-α-L-rhamnopyranosyl-(1→2)-α-L-arabinoside	Oleanane	30	32

Figure 1: Structure of sapimukosides A-J

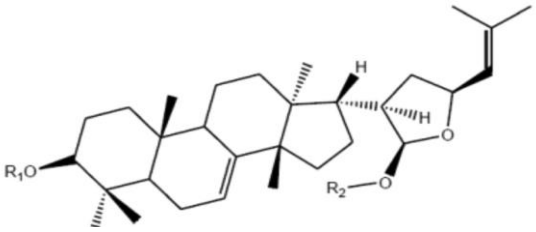

Fig	R1	R2
1	**Glc (3-Ara, 2-Rha)**	**H**
2	**Glc6-Rha**	**H**
3	**Glc (3-Ara, 2-Rha)**	**Et**
4	**Glc (3-Ara, 2-Rha)**	**Me**
5	**Glc (3-Ara, 2-Rha3-Ara)**	**Et**
6	**Glc (3-Ara, 2-Rha3-Xyl)**	**Et**
7	**Glc (3-Ara, 2-Rha3-Xyl)**	**Me**
8	**Glc (3-Rha, 2-Rha3-Ara)**	**Et**
9	**Glc (3-Rha, 2-Rha3-Ara)**	**Me**
10	**Glc6-Rha**	**Et**

Abbreviations: Glc: β-D-Glucopyranosyl Rha: α-L-hamnopyranosyl Ara: α-L-rabinopyranosyl Xyl: β-D-Xylopyranosyl

Figure 2: Structure of sapimusaponins A-B and O-P

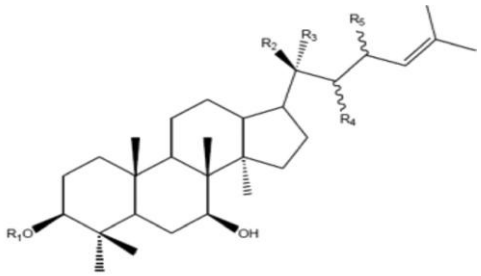

Fig	R1	R2	R3	R4	R5
1	Glc_2-Rha	H	OH	OH	H
12	Glc_2-Rha	H	OH	OH	OH
13	Glc_2-Rha	OH	CH_3	H	H
14	Glc_2-Rha	CH_3	OH	H	H

Figure 3: Structure of sapimusaponins C-E

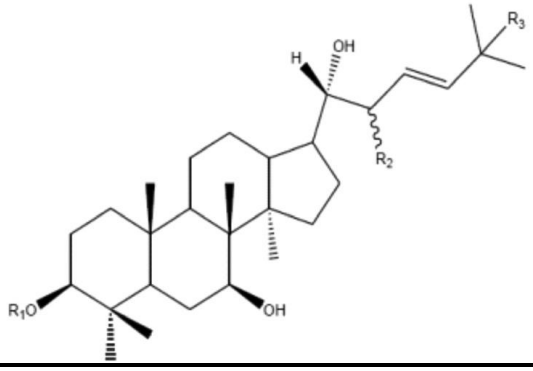

Fig	R1	R2	R3
15	Glc_2-Rha	OH	OH
16	Glc_2-Rha	OH	OCH_3
17	Glc_2-Rha	H	OCH_3

Figure 4: Structure of sapimusaponins F-J and Q-R

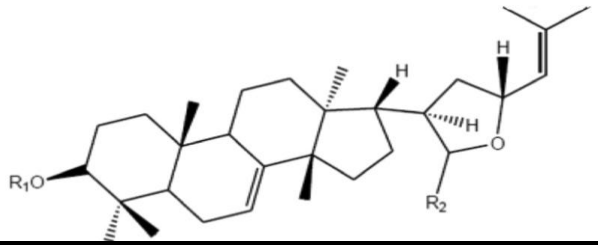

Fig	R1	R2
18	Glc_6-Rha	β-OCH_3
19	Glc_6-Rha	α-OCH_3
20	Glc_2-Rha 2-Rha	α-OCH_3
21	Glc 6-Rha 2-Rha	β-OCH_3
22	Glc 6-Rha	α-OCH_3
23	Glc_2-Glc 2-Glc	α-OCH_3
24	Glc 6-Rha	α-OCH_3

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Figure 5: Structure of sapimusaponins K-N, sapindosides A-E, mukorozi saponin E1, G, Y1, Y2 and X

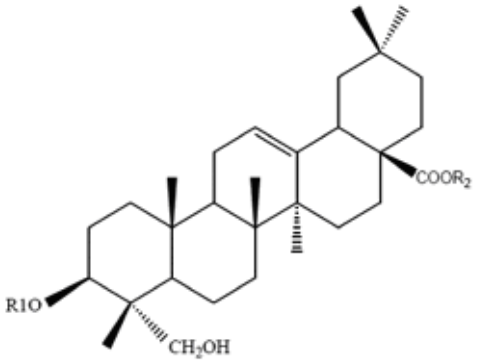

Fig	R1	R2
25	**Ara_2-Rha_3-Ara_3-OAC**	**H**
26	**Ara_2-Rha_3-Rha_4-OAC**	**H**
	2-OAC	
27	**Ara_2-Rha_3-Xyl**	**H**
	3-OAC	
	2-OAC	
28	**Ara_2-Rha_3-Xyl**	**H**
	4-OAC	
	3-OAC	
29	**Ara_2-Rha_3-Xy**	**H**
	4-OAC	
30	**Ara_2-Rha_3-Xyl_4-OAC**	**H**
31	**Ara_2-Rha_3-Xyl**	**Glc_2-Glc**
32	**Ara_2-Rha_3-Xyl**	**Glc_2-Glc**
33	**Ara_2-Rha**	**Glc_2-Glc**
34	**Ara_2-Rha**	**H**
35	**Ara_2-Rha_3-Xyl**	**H**
36	**Ara_2-Rha_3-Xyl_4-Glc**	**H**
	2-Rha	
37	**Ara_2-Rha_3-Xyl_4-Glc**	**H**
	3-Glc	
		6-Rha
38	**Ara_2-Rha_3-Xyl**	**Ara_2-Rha_3-Xyl_4-Glc**
		2-Glc

BIOLOGICAL ACTIVITIES

The traditional medicinal applications of Sapindus species have inspired many biological investigations. Several extracts of Sapindus species and isolated compounds have been evaluated for their anti-microbial, insecticidal, spermicidal, anti-cancer, hepatoprotective, anxiolytic, tyrosinase inhibition and free radical scavenging property, anti-inflammatory, anti-platelet aggregation, anti-hyperlipidemic, anti-migraine, CNS activity, anti-diabetic, anti-ulcerogenic, analgesic, anti-asthmatic, anti-trichomonas, molluscicidal and piscicidal activities [4, 7, 12, 16-18].

Anti-microbial activity

Several studies have demonstrated that Sapindus species possess anti-microbial effects in-vivo and in-vitro. Leaf extracts of Sapindus species were reported anti-microbial activity against bacteria. Both methanolic and aqueous extract showed varying degree of inhibitory potential against *Escherichia coli* and *Psuedomonas aeruginosa*. Methanolic extract of leaves also showed the antifungal activity against the tested fungus *Aspergillus niger*. Sapindua showed strong antibacterial activity against *M. flavus*, *S. epidermidis* and *P. morganii* [15]. Another investigation was also reported on the leaf extract against six bacterial strains, *Pseudomonas testosteroni*, *Staphylococcus epidermis*, *Klebsiella pneumonia*, *Bacillus subtilis* and *Proteus morganii* and showed most potent antibacterial activity [38]. The crude extract of *Sapindus mukorossi* exhibits a strong growth inhibition against the pathogenic yeast *Candida albicans*, which causes cutaneous candidiasis. Extracts from the dried pericarp of Sapindus fruits were investigated for their antifungal activity against clinical isolates of yeasts *Candida albicans* and *Candida non-albicans* from vaginal secretions of women with Vulvovaginal Candidiasis. Four clinical isolates of *C. albicans*, a single clinical isolate of each of the species *C. parapsilosis*, *C. glabrata*, *C. tropicalis*, and the strain of *C. albicans* ATCC 90028 were used. The hydroalcoholic extract was bioactivity-directed against a clinical isolate of *C. parapsilosis*, and showed strong activity. The n-BuOH extract and one fraction showed strong activity against

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all isolates tested [39]. The saponin fraction inhibited the dermatophytic fungi *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Sabouraudites canis* and *Epidermophyton floccosum* [11]. Ibrahim et al. evaluated that ethanolic and chloroform extracts of *Sapindus mukorossi* inhibited the growth of *Helicobacter pylori* (both sensitive and resistant), at very low concentrations, when given orally for seven days to male wister rats. In the in-vitro study, the isolates show a considerable zone of inhibition at very low concentration (10µg/mL) and in the in-vivo study the *Helicobacter pylori* infection was cleared with minimal dose extracts of 2.5 mg/mL [40]. Lemos and co-workers reported the anti-microbial activity of saponin from the ethyl-acetate fraction of fruits of *S. saponaria* [18].

Table 3: Biological effects of genus Sapindus

Biological Effect	Details	Extracts / compounds	Ref
Anti-microbial activity	Antibacterial potential against E. coli, P. aeruginosa, M. flavus, P. morganii, P. testosterone, K. pneumonia, B. subtilis	Methanolic and aqueous leaf extract of *S. mukorossi*	15, 38
	Anti-fungal effect against A. niger	Methanolic leaf extract of *S. mukorossi*	15, 38
	Growth inhibition against the pathogenic yeast C. albicans and C. non-albicans	Alcoholic dried pericarp extract of *S. mukorossi*	39
	Inhibit growth of H. Pylori M	Ethanolic and chloroform extract of *S. mukorossi*	40
Insecticidal activity	Significant mortality on insects Sitophilus oryzae and Pediculus humanus	Ethanolic extract of *S. mukorossi*	43
Spermicidal activity	Pregnancy failed to occur	Fruit pericarp extract of *S. mukorossi*	44,45,46
Anti-cancer activity	Cytotoxic effect on human tumor cell lines (Hepa59T/VGH, NCL, HeLa and Med)	Saponins from galls extract of *S. mukorossi*	47,48,49
	Inhibit proliferation of human breast Cancer cell lines (SKBR3 and MDA- MB435)	Fruit extract of *S. trifoliatus*	13
Hepatoprotective activity	Protective capacity on primary hepatocytes culture and rat model of CCl_4 mediated liver injury	Fruit pericarp extract of *S. mukorossi*	50
Anxiolytic Activity	Significant anxiolytic activity	Methanolic extract of *S. mukorossi*	51
Tyrosinase inhibition and free radical scavenging activity	Inhibit proliferation of human melanoma and lung cell lines	Methanolic extract of seeds of *S. mukorossi*	52
Anti-inflammatory activity	Inhibitory effect on granuloma and exudates formation	Crude saponins and hedeagenin isolated from *S. mukorossi*	53
	Inhibit increase in vascular Permeability	_____do_____	53
	Reduce number of writhing induced- By acetic acid	_____do_____	53
	Inhibit the hind paw edema-associated with adjuvant arthritis	_____do_____	53
	Inhibit effect on leucocyte migration	Ethanolic extract of Seeds of *S. trifoliatus*	54
	Inhibitory activity against Inflammatory agents 5-lipoxygenase, cyclooxygenase, Leukotriene B_4 and nitric oxide- Synthase	Aqueous extract of fruit pericarp of *S. trifoliatus*	55

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Anti-platelet Aggregation activity	More potent anti-platelet aggregation activity that aspirin	Sapinmusaponins Q&R and F-J isolated from ethanolic extract of galls of *S. mukorossi*	34
Anti-hyperlipidemic activity	Lower plasma glycerides and cholesterol level	Methanolic fruit extract	56
Anti-migraine activity	Anti-migraine hyperalgesic potential	Aqueous extract of pericarp of *S. trifoliatus*	57
CNS activity	Reduction in spontaneous activity	Methanolic extract of fruit pericarp	58
	Reduction in exploratory behavioral pattern	_____do_____	58
	Muscles relaxant activity	_____do_____	58
	Inhibition of cocaine induced Hyperactivity	_____do_____	58
	Potentiate phenobarbitone sodium- induced sleeping time	_____do_____	58
	CNS depressant action	_____do_____	59
Anti-diabetic activity	Significant hypoglycemic effect	Alcoholic extract of leaves	60
Anti-ulcerogenic activity	Reduce gastric secretion	Hydro-alcoholic extract of leaves and fruits of S. saponaria	61
	Reduction in pylorus ligation induced ulcers	Methanolic and aqueous extract of leaves of *S. trifoliatus*	12
Analgesic activity	Reduce diabetic neuropathic pain	Ethanolic extract of *S. trifoliatus*	62
Anti-trichomonas activity	Inhibit ability of parasites to adhere to HeLa cells	Saponin mixture	63, 44
	Decrease proteolytic activity of the parasites cystein proteinases	Saponin mixture	63, 44
Molluscicidal activity	Against golden apple snail, Pomacea-canaliculata and Lymnaea acuminate	extract of fruit pericarp of *S. mukorossi*	65, 66
Piscicidal activity	High potential for fish eradication	extract of fruit pericarp of *S. mukorossi*	67
Anti-asthmatic activity	Inhibit acetylcholine induced bronchoconstriction	Aqueous extract of fruit of *S. mukorossi*	68

Insecticidal activity

Saponins possess insecticidal activity, causing mortality and/or growth inhibition in the insects tested the cotton leafworm *Spodoptera littoralis* caterpillars and the pea aphid *Acyrthosiphon pisum*. In the experiments with *Acyrthosiphon pisum*, 0.1% saponin killed all aphids, whereas with Spodoptera some caterpillars were still able to develop into apparently normal adults on food containing 7% saponins [41]. Saponins can be employed as novel natural tactics in integrated pest management (IPM) to control pest insects, which fit in modern agriculture and horticulture [42]. Ethanolic extract of *Sapindus mukorossi* was investigated for repellency and insecticidal activity against *Sitophilus oryzae* and *Pediculus humanus*. Average mortality percentage indicated that the extracts caused significant mortality and repellency on the target insects and bioassays indicated that toxic and repellent effect was proportional to the concentration [43].

Spermicidal activity

Saponins from *Sapindus mukorossi* are known to be spermicidal [44]. Morphological changes in human ejaculated spermatozoa after exposure to this saponin were evaluated under scanning electron microscopy. The minimum effective concentration (0.05% in spot test) did not affect the surface topography after exposure for one minute. However, incubation of spermatozoa for 10 minutes resulted in extensive vesiculation and a disruption of the plasma membrane in the head region. Higher concentrations (0.1%, 1.25%, 2.5% and 5.0%) caused more or less similar changes which included vesiculation, vacuolation, disruption or erosion of membranes in the head region. These findings suggest that the morphological changes observed are due to

alterations in the glycoproteins associated with the lipid bilayer of the plasma membrane of spermatozoa [8]. This spermicidal property has been used in contraceptive cream [45]. A contraceptive cream developed by the CDRI (Lucknow) is going to hit the Indian markets. It is advocated to be totally safe and easy to use. It is intended for post-coital use [46]. Raghuvanshi et al. 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 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 [18].

Anti-cancer activity

Due to the great variability in saponin structure, saponins always display anti-tumorigenic effect through varieties of anti-tumor pathways [47]. Kuo and co-workers tested the cytotoxic effect of saponins isolated from the galls of *S. mukorossi*. The preliminary bioassay data revealed that saponins showed moderate cytotoxic activity (ED_{50} ~ 9–18 µg/mL) against human tumor cell lines (Hepa59T/VGH, NCL, HeLa and Med) [48]. Strychnopentamine was the reference compound used in the study. All saponins were reported to be at least five times less active than the reference compound [49]. Pradhan and co-workers reported that fruit extract of *S. trifoliatus* inhibit the proliferation of human breast cancer cell lines SKBR3 and MDA-MB435 [13].

Hepatoprotective activity

Ibrahim and co-workers reported that the extracts of fruit pericarp of *Sapindus mukorossi* (2.5 mg/L) and rhizomes of *Rheum emodi* (3.0 mg/L) have a protective capacity both in-vitro on primary hepatocytes cultures and in-vivo in a rat model of carbon tetrachloride (CCl_4) mediated liver injury as judged from serum marker enzyme activities [50]. Thus, it was concluded that the extracts of *Sapindus mukorossi* and *Rheum emodi* do have a protective capacity both in-vitro on primary hepatocytes cultures and in in-vivo in a rat model of CCl_4 mediated liver injury.

Anxiolytic activity

Methanolic extracts of *S. mukorossi* (200 and 40 mg/L) show significant anxiolytic activity as compared to standard anxiolytics Diazepam (2 mg/Kg) and Fluoxetine (10 mg/Kg) [51].

Tyrosinase inhibition and free radical scavenging activity

Chen et al. first evaluated that the extracts of *S. mukorossi* seeds using methanol (MeOH), ethyl acetate (EA) or hexane as solvents show tyrosinase inhibition and free radical scavenging properties. *S. mukorossi* extracts showed strong specific inhibition activities on the proliferation of human melanoma and lung cell lines. The data exhibited the high potential of applying *S. mukorossi* extracts in medical cosmetology, food supplementation, antibiotics and chemotherapy [52].

Anti-inflammatory activity

Takagi and co-workers 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. They 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 crude saponin shows some degree of anti-inflammatory activity [53]. Arul and co-workers reported 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 [54]. Arulmozhi and co-workers 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 inhibitory activity against the inflammatory agents 5-lipoxygenase, cyclooxygenase, leukotriene B4 and nitricoxide 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. They concluded that the extract has an anti-inflammatory activity, probably mediated by the 5-lipoxygenase and cyclo-oxygenase pathways [55].

Anti-platelet aggregation activity

Biological evaluation of ethanolic extract of the galls of *S. mukorossi* showed that two saponins isolated sapinmusaponins Q and R demonstrated more potent anti-platelet aggregation activity than aspirin [34]. Sapinmusaponins F-J isolated from the galls of *S. mukorossi* showed anti-platelet-aggregation effects, but no obvious cytotoxic activity for platelets as assayed by lactate dehydrogenase (LDH) leakage was reported [31].

Anti-hyperlipidemic activity

The saponins from Sapindus species fruit extract found to have significant anti-hyperlipidemic activity. Methanolic extract at a dose of 100 and 200 mg/kg significantly lowered both plasma glycerides and cholesterol levels. The cholesterol lowering activity of the fruit extract result from the breakdown of LDL cholesterol by enhancing enzymatic action [56].

Anti-migraine activity

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Arulmozhi and co-workers 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 D2 might underlie the mechanism involved in the anti-hyperalgesic activity of the plant extract [57].

CNS activity

Methanolic extract of fruit of Sapindus species found to produce CNS depressant activity. The methanolic extract of Pericarps at 100 and 200 mg/kg caused a significant reduction in the spontaneous activity, exploratory behavioral pattern, muscle relaxant activity, inhibition of cocaine induced hyperactivity and also extensively potentiated phenobarbitone sodium–induced sleeping time. This extract produced a considerable increase in the hypnotic effect induced by the phenobarbitone in a dose dependent manner, suggesting a profile sedative activity [58]. Various scientific research reports showed that presence of triterpenoids in the methanolic extract may be responsible for the CNS depressant activity [59].

Anti-diabetic activity

Jeyabalan and co-workers studied the anti-hyperglycemic effect of alcoholic extract of leaves of Sapindus species in the glucose overloaded hyperglycemic rats. The extract at different doses exhibited a significant hypoglycemic activity in dose dependent manner. The study also revealed that level of total hemoglobin, glycosylated hemoglobin, serum creatinine, serum urea and lipid profiles measured showed the anti-diabetic activity [60].

Anti-ulcerogenic activity

Albiero and co-workers 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 [61]. In another study, Kishore and co-workers reported that methanolic and aqueous extracts of leaves of *S. trifoliatus* showed significant reduction in the pylorus ligation induced ulcers in rats [12].

Analgesic activity

Sahoo and co-workers investigated the ethanolic extract of *Sapindus trifoliatus* in in-vivo model of diabetic neuropathic pain. They concluded that extract showed significant effectiveness in diabetic neuropathic pain and protection produced by stimulation of adenosine A1-receptors [62].

Anti-trichomonas activity

Tiwari and co-workers demonstrated that the Sapindus saponin mixture shows anti-Trichomonas activity at a 10-fold lower concentration (0.005%) than its minimal effective spermicidal concentration against human spermatozoa (0.05%) [63]. Saponin concentration dependently inhibited the ability of parasites to adhere to HeLa cells and decreased the proteolytic activity of the parasite's cysteine proteinases. This was associated with the decreased expression of adhesin AP65 and membrane-expressed cysteine proteinase TvCP2 genes. Saponins produced no adverse effect on host cells in mitochondrial reduction potential measurement assay. Saponins also reversed the inhibitory mechanisms exerted by Trichomonas for evading host immunity. Early response of saponins to disrupt actin cytoskeleton in comparison with their effect on the nucleus suggests a membrane-mediated mode of action rather than via induction of apoptosis [44, 63].

Molluscicidal activity

Extracts of *Sapindus mukorossi* showed molluscicidal effect against the golden apple snail and *Pomacea canaliculata* Lamarck. (Ampullariidae) with LC_{50} values of 85, 22 and 17 ppm at 24, 48 and 72 h exposure period, respectively [64]. Upadhyay and Singh, reported that *S. mukorossi* fruit pericarp is a potential source of botanical molluscicides against *Lymnaea acuminate* [65]. These snails are the intermediate host of liver fluke *Fasciola gigantica*, which causes 94% fascioliasis in the buffalo population of northern India [66]. Ribeiro and co-workers reported molluscicidal activity of alcoholic extract of *Sapindus saponaria* [18].

Piscicidal activity

Effects of *Sapindus mukorossi* have been studied on fish. Pericarp of *S. mukorossi* is the most toxic parts yielding 100% mortality rate within 12 hours and mean survival time was found to be 1.18 hours. LD_{10}, LD_{50}, LD_{100} ranging between 3.5 ppm and 10 ppm at 48 hrs and possess high potential for fish eradication. *S. mukorossi* fruit pericarp can be used as a selective eradicant for horny fish like *Heteropneustes fossils* and *Channa punctuate* [67].

Anti-asthmatic activity

Parganiha and co-workers evaluated the in-vitro anti-asthmatic activity of *Sapindus mukorossi* on acetylcholine induced contraction of goat tracheal chain preparation. They reported that the aqueous extract of *S. mukorossi* fruits at the doses of 380 mcg/ml and 640 mcg/ml significantly inhibited acetylcholine induced bronchoconstriction of isolated goat trachea and concluded that the aqueous extract of fruit of *S. mukorossi* has significant anti-asthmatic potential [68].

CONCLUSIONS

In this review, we documented the existing traditional uses of the species of the genus Sapindus and summarized recent research in to the phytochemistry and biological properties of the genus. Previous studies have documented that Sapindus species have traditionally been used to treat ulcers, external wounds, inflammation, excessive salivation, pimples, epilepsy, chlorosis, migraines, eczema, psoriasis, dental caries, arthritis, common colds, constipation, nausea, joint pain, gout and rheumatism. Some of these traditional uses have been validated by phytochemical and modern pharmacological studies. The extracts and single compounds derived from the genus have been found to possess various biological activities, especially in the areas of anti-microbial, insecticidal, spermicidal, anti-cancer, hepatoprotective, anxiolytic, tyrosinase inhibition and free radical scavenging property, anti-inflammatory, anti-platelet aggregation, anti-hyperlipidemic, anti-migraine, CNS

activity, anti-diabetic, anti-ulcerogenic, analgesic, anti-asthmatic, anti-trichomonas, molluscicidal and piscicidal activities. Triterpenoidal saponins of oleanane, dammarane and tirucullane types are regarded as the active group that is most likely to be responsible for the observed biological properties.

Although increased interest has prompted more studies on the phytochemistry and biological activities of the genus Sapindus, there are still many areas where our current knowledge could be improved. (i) Several traditional uses of the genus have been validated in recent biological studies; however, some of these biological activities were only tested in-vitro. Thus, the effectiveness of these compounds in-vivo needs to be further investigated. (ii) The genus Sapindus is a rich source of triterpenoidal saponins of oleanane, dammarane and tirucullane, many with the same skeletal structure. Therefore, it would be interesting to investigate the structure-activity relationships of these saponins. We would expect to find high efficiency compounds from these saponins. (iii) It is evident from the available literature that Sapindus species possess potential for use as a beneficial therapeutic remedy. However, the analysis of previous biological research suggests that a clear assignment of active molecules and mechanisms of action is remain lacking. Taken together, the importance of genus Sapindus has been highlighted based on their wide usage in traditional medicine as well as potential in beneficial therapeutic remedy. Nevertheless, there is clearly a need for further studies focusing on in-vivo with emphasis on molecular mechanisms and eventually clinical trials.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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