Symphonia globulifera, a Widespread Source of Complex Metabolites with Potent Biological Activities

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- ethnomedicine
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Abstract

Symphonia globulifera has been widely used in traditional medicine and has therefore been subjected to several phytochemical studies in the American and African continents. Interestingly, some disparities have been observed concerning its metabolic profile. Several phytochemical studies of *S. globulifera* have led to the identification of more than 40 compounds, including several polycyclic polyprenylated acylphloroglucinols. Biological evaluations have pointed out the promising biological activities of these secondary metabolites, mostly as antiparasitic or antimicrobial, confirming the traditional use of this plant. The purpose of this review is to describe the natural occurrence, botanical aspects, ethnomedicinal use, structure, and biogenesis, as well as biological activities of compounds isolated from this species according to their provenance.

Introduction

Higher plants are known to be a rich source of various bioactive compounds [1], some of which have found practical applications in traditional medicine [2]. *Symphonia globulifera* L. f. has been widely used in traditional medicine to fight against various disorders such as parasitic disease [3,4] or body pain [5]. Extracts of this plant have shown very good biological activities against several pathologies, opening a vast field of research towards the identification of complex metabolites. Since the first publication in 1992 [6] describing some polycyclic polyprenylated acylphloroglucinols (PPAPs) from *S. globulifera* as HIV inhibitors, the interest for this plant and its bioactive compounds has been ever growing. Like the plants of the *Garcinia* genus, which also contain PPAPs [7], the plants of the species *S. globulifera* have emerged on both American and African continents, and show some morphological diversity through sites [8]. This morphological differentiation and the existence of some subfamilies and differences in country soil and climate have probably induced a variation in the metabolome and generated a pool of chemodiversity. The purpose of this review is to describe the botanical aspects, the ethnomedical uses, metabolites, and biogenesis, as well as the biological activities of all compounds from this species depending on their provenance.

Classification and Botanical Characteristics of *Symphonia globulifera*

The family Clusiaceae (Guttiferae) comprises about 40 genera and more than a thousand species. The genus *Symphonia* includes 17 species [9]. *S. globulifera* is broadly distributed across the Neotropics and equatorial Africa. It is the only *Symphonia* species found outside Madagascar [10].

Some of the vernacular names of this plant are “manil marécage”, “palétuvier jaune” (French Guiana), “barillo” (Guatemala, Honduras), “cerillo” (Costa Rica, Panama), “machare” (Colombia), “mani”, “paraman” (Venezuela), “mataki” (Surinam), “manni” (Guiana), “anany” (Brazil), and “brea-caspi” (Peru). *S. globulifera* plants are generally tall trees (in general more than 15 m high) with opposite leaves exhibiting characteristic aerial roots and producing a bright yellow latex. The flowers are red with a red staminal column and black anthers and organized as a sympodium. Fruits are drupes (4–5 cm), ovoid, or globular. Seeds are intensively red inside [10–12].

This species is also characterized by important morphological variations, which seem to be de-

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Table 1 Traditional use of *S. globulifera* in Africa and South America.

Localization	Part of plant	Preparation method	Therapeutic use
Africa			
Gabon	Bark	Decoction	Scabies [15]
South Uganda	Bark	Decoction	Coughs, intestinal worms, prehepatic jaundice, fever [4]
South Uganda	Sap	Sap burned like incense	Chasing away evil spirits [4]
Cameroon	Leaves	Decoction	Antiparasitic [17]
Nigeria	Leaves	Decoction	Skin disease, malaria, diabetes [16]
South America			
Panama	Leaves	Cataplasm	Body pain, skin ailments [5]
Brazil	Latex	Plaster	To get pregnant, pulled muscles, fractures [18]
Brazil	Bark	Infusion or with soda	Vaginal discharge [18]
Colombia	Bark	Decoction	Cutaneous leishmaniasis [3]

pendent of its ecological distribution [8]. Indeed, at least three varieties exist, var. *angustifolia* Maguire, var. *macoubea* Vesque, and var. *major* Diels [8, 13], and a small number of supposed subspecies such as *Symphonia* sp1. However, none of these differences have been yet considered sufficient to merit splitting into more than one species.

Phylogenetic analyses have demonstrated that marine dispersal played a primary role in the migration and establishment of *S. globulifera* in the Neotropics. The regional populations were genetically isolated through the Pleistocene and earlier [9]. In Central Africa, *S. globulifera* survived the Pleistocene glacial periods in a few major shelters, essentially centered on mountainous regions close to the Atlantic Ocean [14]. The capacity for adaptation in different geographical and climate conditions contributed to the survival and to the genetic and morphological diversity of the species.

Ethnomedicine

Medicinal plants have been playing an important role in providing health care to a large section of the population, especially in developing countries. *S. globulifera* has been used for the treatment of several disorders, mainly in Africa and South America.

Africa

The African traditional medicine proposes an accurate use of local plants though poorly scientifically studied. Concerning *S. globulifera*, preparations are mainly decoctions, with applications ranging from serious disorders, such as scabies, to spiritual remedies (**Table 1**).

Ethnopharmaceutical studies presented in **Table 1** were performed on a large panel of medicinal plants (around 120 plants). The establishment of this panel was based on several criteria such as the use defined by an ethnic group, an area of the country, or the country in general. For instance, the Gabonese studies focused on the use of medicinal plants relating to the single Masango ethnic group [15], chosen because it is one of the few ethnic groups in Gabon that have kept medical practices as part of its cultural heritage. Therefore, among the plants used by the Masango, decoctions of *S. globulifera* bark are produced to cure the serious problem of scabies.

More recently, studies from Nigeria [16] and Uganda [4] describe the use of *S. globulifera* not only in terms of ethnicity but also depending on the region of occurrence: Akwa Ibom State (Nigeria) and the Sango bay area (Uganda). In Nigeria, leaves of *S. globulifera* are used as a decoction and are applied on the body to treat skin disease, which is the largest application followed by malaria and diabetes. Other traditional uses in Nigeria are described in the literature to treat erective problems, venereal diseases, or wounds using the fruits and leaves of *S. globulifera* [19]. However, information regarding the type of preparation was not described; the data has been discarded from **Table 1**.

The Ssegawa's study [4] highlights the medicinal plants used by 13 villages in three subcounties surrounding the Sango bay ecosystem in the Rakai district, Central Uganda. A questionnaire has been distributed to collect data on local plant names, uses, parts used, and modes of preparation and administration. From this study, it appears that the *S. globulifera* biological activities are dependent on the vegetal parts. Thus, the bark extract presents broad applications ranging from treating coughs and prehepatic jaundice to fever and intestinal worms. A different application has been observed for the sap extract, which is used for spiritual application to chase away evil spirits. While this traditional use of *S. globulifera* has been proven to exist, the obvious lack of scientific meaning makes its difficult to understand.

Leishmaniasis and others protozoal diseases are a plague without a sustainable cure, which dramatically affects the African continent. Considering the great potential of Cameroon in terms of biodiversity, traditional knowledge, and practice, Lenta et al. [17] undertook an ethnopharmacological survey on medicinal plants used against protozoal diseases in this country. Data were collected by contact and interviews with local traditional healers in the Ndé and Mifi divisions of the West Province of Cameroon. The selected plants, including *S. globulifera*, were collected and further evaluated for their *in vitro* antiprotozoal activity and cytotoxicity (**Table 2**).

Overall, mainly decoctions of bark or leaves of *S. globulifera* are used in the African traditional medicine, indicating the presence of polar metabolites as the main source of activity. The results of the study presented in **Table 2** may participate in understanding the traditional use and strengthen the presence of active metabolites in polar extracts. Remarkably, South American traditional remedies are slightly different and present other panels of applications.

South America

The traditional use of *S. globulifera* in South America is not as widespread as in the African continent. Literature resources highlight its use principally in Panama, Brazil, and Colombia (**Table 1**). Similar to Africa, the bark, which is the most used part of the plant, is prepared as a decoction or infusion.

S. globulifera from Cameroon			
Local name: Kebanti	Place of collection: Bangangté	Voucher No. 32192/HNC	Part used: leaves
Methanolic extract		IC_{50} (µg/ml)	SI
Plasmodium falciparum		4.1 ± 0.5	12.75*
Trypanosoma cruzi		> 30	1.5*
Trypanosoma brucei rhodesiense		11.5 ± 0.5	4.5*
Leishmania donovani		2.1 ± 0.8	24.9*
Cytotoxicity		52.3 ± 5.6	

* SI (selectivity index): ratio of cytotoxic activity on L-6 cells to antiparasitic activity

Table 2 *In vitro* activity of *S. globulifera* leaf methanolic extract.

In Panama, the need to explore the ethnobotanical resources in order to develop appropriate programs for their agricultural, medical, pharmaceutical, silvicultural, and commercial use is increasing [5]. Moreover, since massive deforestation has been accelerated, there is a high emergency to collect information and try to save the renewable botanical resources in order to develop appropriate programs in silviculture and agriculture. For this purpose, a study was performed on the local plants. *S. globulifera* was part of the study, and its fresh latex was shown to be used and applied as a cataplasm against skin ailments and body pain.

The Brazilian Amazon region has a considerable coastline [18]. In Pará State, for example, more than 1500 km of coastline extends from the Amazon River's estuary to the state of Maranhão, covered by mangroves and swamps, defined by abundant natural resources and great scenic beauty. As secondary vegetation, *S. globulifera* has been described in this mangrove area. It has been shown that the use of its latex favors pregnancy and is active against pulled muscles and fractures. The latex is thus used under a plaster form and is therefore easy to apply on bone fractures. Regarding the barks, they are prepared as an infusion or with soda against vaginal discharge.

In Colombia [3], the plants were collected in four different areas guided by local knowledgeable healers. *S. globulifera* was harvested on the Bajo Calima site. The decoction of the bark is traditionally rubbed on the skin for the treatment of cutaneous leishmaniasis.

In summary, the traditional uses of *S. globulifera* on both the African and American continents are specific but present some similarities. The application of cataplasm directly on the body to treat skin diseases or cutaneous leishmaniasis revealed the presence of polar molecules, which are attractive for cosmetic, dermatologic, and antiparasitic applications. Comparing the practices in both continents, the bark seems to contain the main active metabolites, while the leaves and fruits are poorly used. Finally, from all these surveys, a potent and promising antiparasitic activity of *S. globulifera* metabolites emerges.

Secondary Metabolites

Secondary metabolites of *S. globulifera* are mainly PPAPs. Up to now, a total of 15 of them have been isolated from this species in addition to the xanthone derivatives of PPAPs: two oxy-PPAPs (**Table 3** and **Fig. 1**). In **Table 3**, each compound is described (name, plant part, and country of collection). It is worth noticing that most PPAPs and oxy-PPAPs described in the literature are numbered as a bicyclo[3.3.1]nonane-1,3,9-trione, although Ciochina et al. [20] numbered PPAPs as a bicyclo[3.3.1]nonane-2,4,9-trione. The first numbering is the one that will be followed here. All the compounds are detailed in **Table 3** and described in subsections.

Polycyclic polyprenylated acylphloroglucinols

Even if three types of PPAPs are described (A, B, and C) [38], all the PPAPs characterized from *S. globulifera* belong to the type B family (**Fig. 1**). All of them have been isolated from roots; however, guttiferone A (**1**) has also been isolated from leaves and seeds. To date and with the exception of the guttiferones A (**1**) and B (**2**), all isolated PPAPs have not been described in any other plant. Guttiferone B (**2**) has also been isolated from *Garcinia oblongifolia* and *Garcinia cowa* [32–34] and guttiferone A (**1**) from about ten other plant species like *Garcinia livingstonei* [35], *Rheedia edulis* [36], *Garcinia macrophylla* [37], *Garcinia virgate* [38], *Garcinia brasiliensis* [39]. As for many type B PPAPs, secondary cyclization has been observed, as illustrated with the presence of a dimethylpyran (**5, 6, 7, 8, 9, 10, 11, 17**) or furan moiety (**12, 13**) obtained from the epoxydation of a prenyl followed by a ring closure. Compounds **14** and **15** belong to the oxy-PPAPs category, cyclized PPAPs into xanthones. To date, 14 natural type B oxy-PPAPs have been reported, three have been obtained via chemical reactions or biotransformation from garcinol (**47**) [40] and guttiferone A (**1**) [41]. The biogenesis of oxy-PPAPs is discussed later in this review.

Polyhydroxylated polyprenylated xanthones and maclurin

Besides these PPAPs, maclurin (**36**), 21 polyhydroxylated polyprenylated xanthones, and benzophenone have been isolated from *S. globulifera* (**Fig. 2** and **Table 3**). Prenylated xanthones, such as the well-known gambogic acid, are extensively represented in the Clusiaceae and Hypericaceae families [42,43]. These molecules have been isolated from several plant parts of *S. globulifera*, such as heartwood, twigs, roots, seeds and leaves. Most of the compounds show side decoration-like prenylated moieties, which can later be involved in the formation of a dimethyldihydropyran core (**18, 20, 21, 23, 26**, and **27**). Only one dimer (**20**) resulting from the phenolic coupling has been isolated.

Biflavonoids

Another interesting group of natural products has been isolated and described from *S. globulifera* (**Fig. 3**). The latter is a small number of biflavonoids comprising three members that could be depicted as the heterodimerization of apigenin (**39, 40**) or a luteolin (**41**) moiety on one hand, with a luteolin (**39**) or dehydroquercetin moiety (**40, 41**) on the other hand. They all present a junction between C-3 and C-8. To date, three biflavonoids have been isolated from the leaves and twigs of this plant. Biflavonoids are restricted to a few groups of plants and are commonly isolated from species of the Clusiaceae family. Morelloflavone (**39**)

Table 3 Secondary metabolites isolated from *S. globulifera*.

No.	Name	Plant part	Country	Molecular weight*	Ref.
Polycyclic polyprenylated acylphloroglucinols and oxy-PPAPs					
1	Guttiferone A	seeds	Cameroon	602.36	[21]
		roots	Central African Republic		[6]
		leaves	Cameroon		[17]
2	Guttiferone B	roots	Central African Republic	670.42	[6]
3	Guttiferone C	roots	Central African Republic	670.42	[6]
4	guttiferone D	roots	Central African Republic	670.42	[6]
5	14-Deoxy-7-*epi*-isogarcinol	root barks	French Guyana	586.37	[22]
6	Symphonone A	root barks	French Guyana	600.35	[22]
7	Symphonone B	root barks	French Guyana	670.42	[22]
8	Symphonone C	root barks	French Guyana	618.36	[22]
9	7-*epi*-Coccinone B	root barks	French Guyana	618.36	[22]
10	Symphonone D	root barks	French Guyana	636.37	[22]
11	Symphonone E	root barks	French Guyana	636.37	[22]
12	Symphonone F	root barks	French Guyana	618.36	[22]
13	Symphonone G	root barks	French Guyana	618.36	[22]
14	Symphonone H	root barks	French Guyana	600.35	[22]
15	Symphonone I	root barks	French Guyana	600.35	[22]
16	7-*epi*-Garcinol	root barks	French Guyana	602.36	[22]
17	7-*epi*-Isogarcinol	root barks	French Guyana	602.36	[22]
Polyhydroxylated polyprenylated xanthones and benzophenones					
18	Globulixanthone C	root barks	Cameroon	326.08	[23]
19	Globulixanthone D	root barks	Cameroon	326.12	[23]
20	Globulixanthone E	root barks	Cameroon	618.19	[23]
21	Gaboxanthone	seeds	Cameroon	438.17	[21]
22	Globuliferin	seeds	Cameroon	440.18	[21]
23	Symphonin	seeds	Cameroon	438.17	[21]
24	Globulixanthone A	root barks	Cameroon	324.10	[24]
25	Globulixanthone B	root barks	Cameroon	380.16	[24]
26	Xanthone V1	leaves	Cameroun	394.14	[17]
27	Ananixanthone	bark	Brazil	378.15	[25]
28	1,7-Dihydroxyxanthone	heartwood	Uganda	228.04	[26]
29	1,5,6-Trihydroxyxanthone	heartwood	Uganda	244.04	[26]
30	1,3,5,6-Tetrahydroxyxanthone	heartwood	Uganda	260.03	[26]
		twigs	Cameroon	260.03	[27]
31	Norathyriol	heartwood	Uganda		[26]
		twigs	Cameroon		[27]
32	Symphoxanthone	heartwood	Uganda	328.09	[28]
33	Globuxanthone	heartwood	Uganda	312.10	[28]
34	Ugaxanthone	heartwood	Uganda	328.09	[29]
35	Mbarraxanthone	heartwood	Uganda	312.10	[29]
36	Maclurin	heartwood	Uganda	262.05	[30]
37	Gentisein	twigs	Cameroon	244.04	[27]
38	Globulixanthone E	twigs	Cameroon	342.11	[27]
Biflavonoids					
39	Morelloflavone	leaves	–	556.10	[31]
40	GB-2	leaves	–	574.11	[31]
		twigs	Cameroon		[27]
41	GB3	twigs	Cameroon	590.11	[27]

* Molecular weights are calculated

was also isolated from other species belonging to the Clusiaceae, such as *G. livingstonei* [35] or *Garcinia xanthochymus* [44].

Methyl nervonate

A last metabolite has been recently isolated and named methyl nervonate (**42**) by the authors [45]. It has been characterized in the anther oil of *S. globulifera* from Brazil (▶ **Fig. 4**). This fatty acid may have an important functional role in the pollination process. Harvesting location plays a role in the metabolic profile, especially for PPAPs present in the root bark extract. Indeed, Marti et al. [22] did not identify guttiferones A–D (**1**–**4**) described by Gustafson et al. [6], highlighting notable disparities in the metabolome of the species between those two continents (harvested in May 2006 and March 1988, respectively). The collection of different subspecies could eventually be considered the origin of the metabolic disparities. Moreover, such differences in the nature of major metabolites are uncommon, even for a single species growing in two different locations. As we pointed out, *S. globulifera* has a high rate of acclimatization and might adapt its defensive metabolites according to, for example, the microbial environment. However, there is a need to clearly report the phenomena, which requires further investigations.

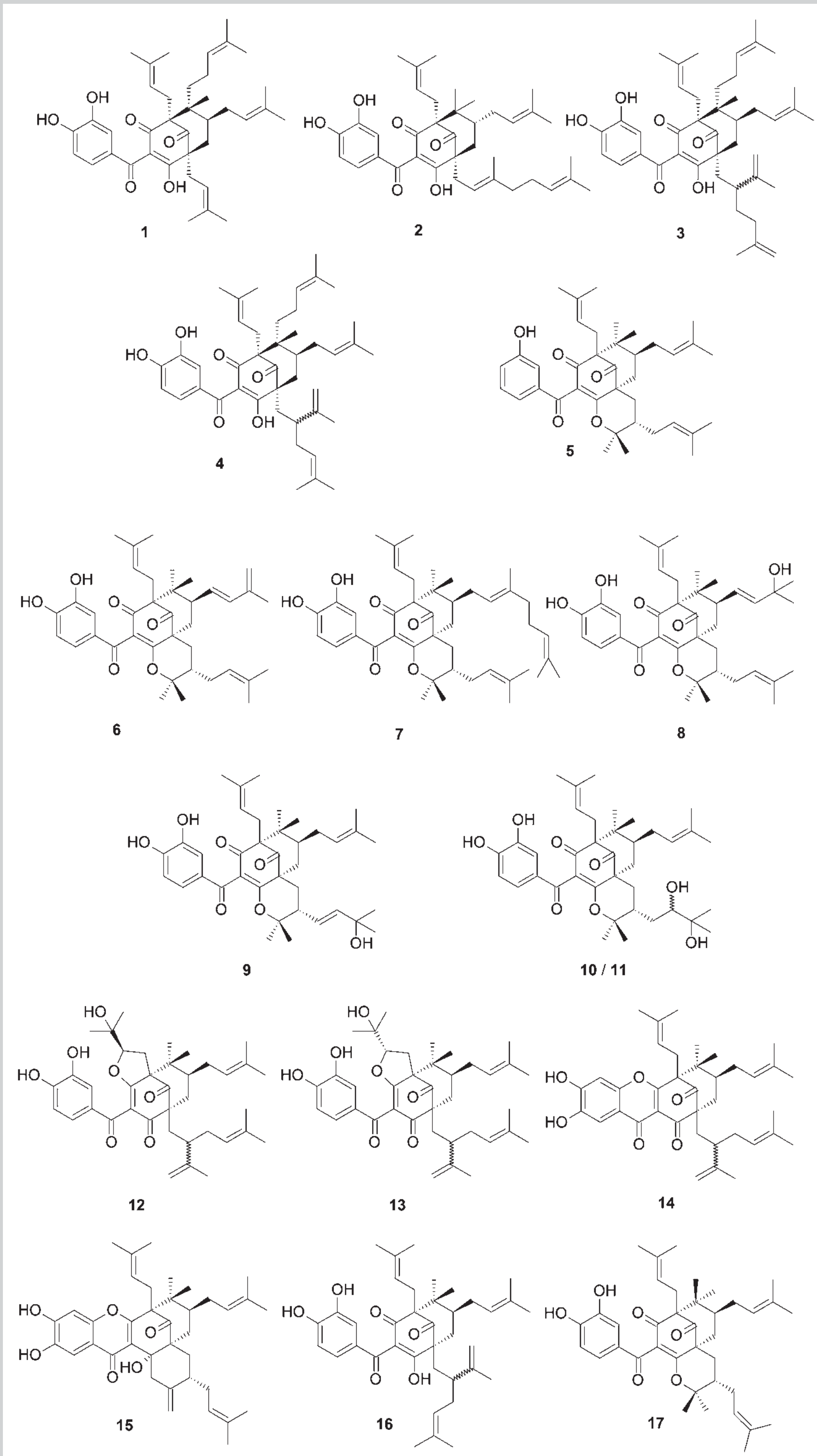

Fig. 1 Chemical structures of polycyclic polyprenylated acylphloroglucinols and oxy-polycyclic polyprenylated acylphloroglucinols of *S. globulifera*.

Biosynthesis

All the secondary metabolites isolated from *S. globulifera* have the same biosynthetic origin (**Fig. 5**). The biosynthesis starts from shikimic acid to generate amino acids such as tyrosine or phenylalanine [46].

Phenylalanine is converted into cinnamic acid, by phenylalanine ammonia lyase (PAL) [47]. Cinnamic acid can then follow two different pathways to generate either biflavonoids or prenylated xanthones and PPAPs. Concerning biflavonoids, there is an early enzymatic hydroxylation to convert cinnamic acid into 4-hydroxy-coumaric acid [48,49]. A polyketide synthase generates then the phloroglucinol moiety of the chalcone [50]. A chalcone isomerase is responsible for the cyclization of the chalcone into the corresponding flavones [51,52]. Two hypotheses can be cited for the biflavonoids biosynthesis, the chalcone, or the flavonoid dimerization. Yamaguchi et al. [53] have highlighted the participation of some peroxidase enzymes to accomplish the dimerization of flavones into biflavonoids. Some biomimetic syntheses of

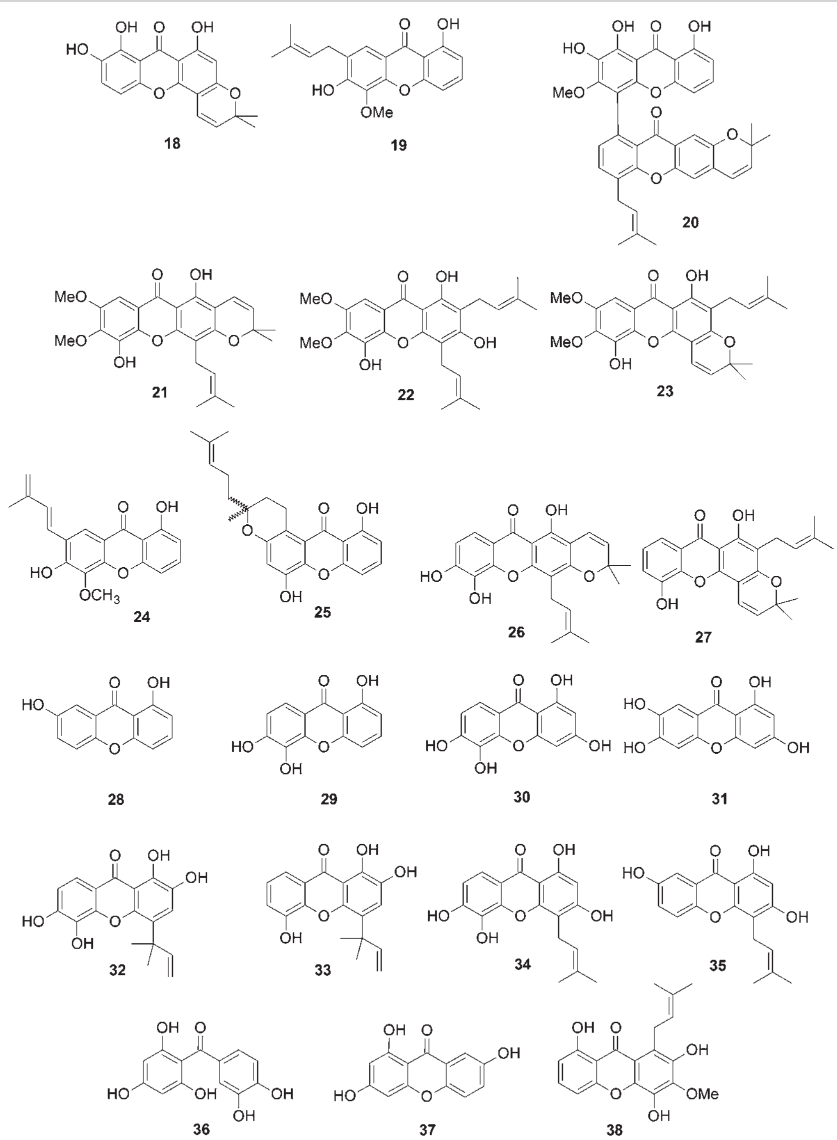

Fig. 2 Chemical structure of xanthones and maclurin from *S. globulifera.*

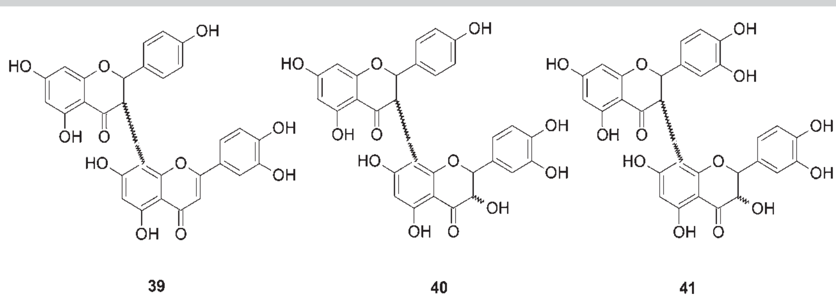

Fig. 3 Chemical structure of biflavonoides from *S. globulifera*.

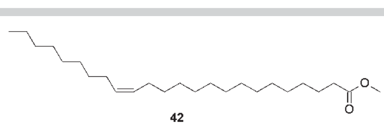

Fig. 4 Chemical structure of methyl nervonate (**42**).

biflavonoids validate this hypothesis [54]. Dimers are generated from monomers in the presence of an oxidant (potassium ferricyanide), which is well known to be able to generate phenolic oxidative coupling.

The biosynthesis of xanthones and PPAPs also starts from phenylalanine being converted into a phenyl-CoA moiety, which is reduced into protocatechuic acid. It has been shown that coumaric acid, cinnamic acid, and phenylalanine were well incorporated

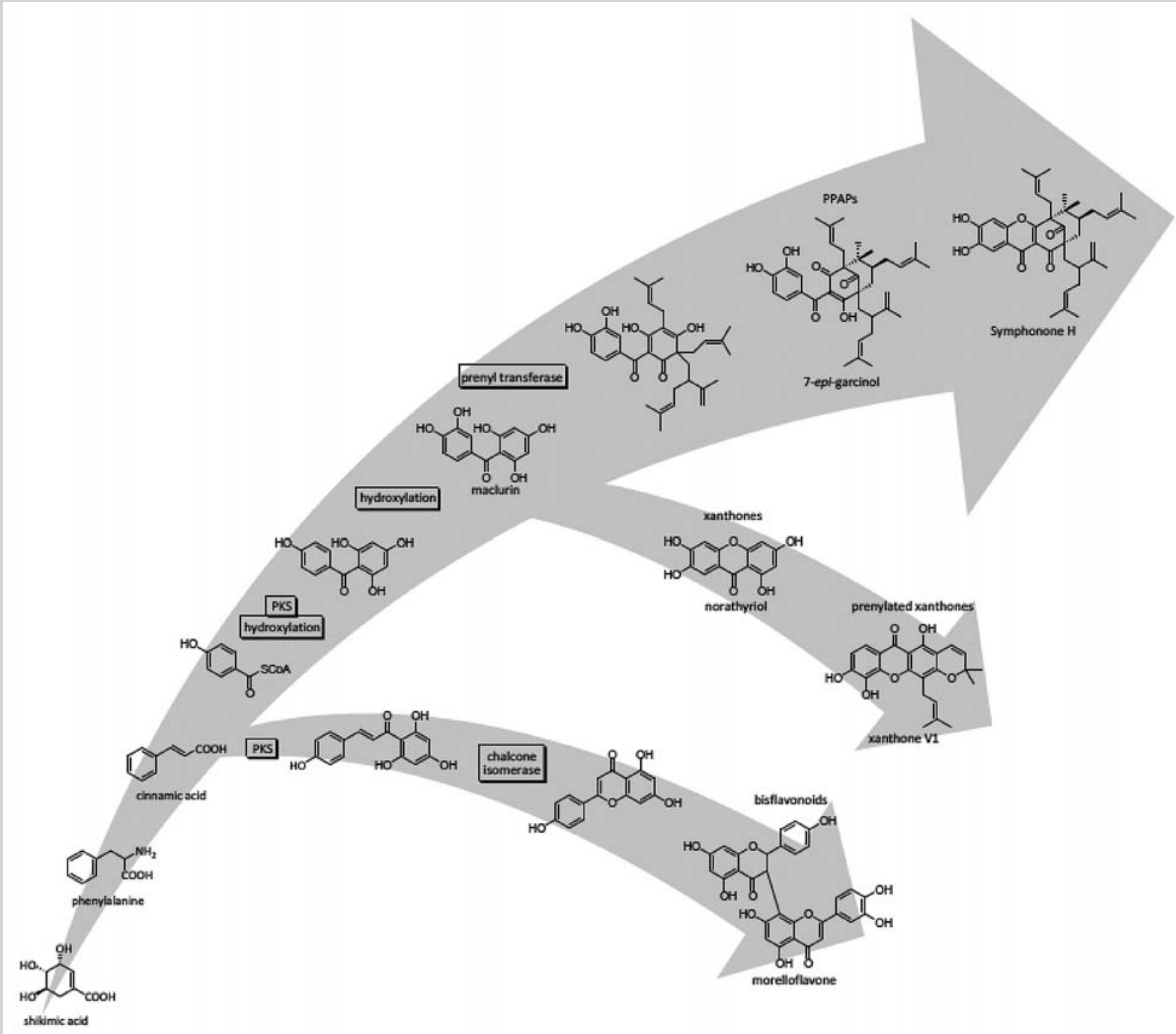

Fig. 5 Biosynthesis pathway of *S. globulifera* secondary metabolites.

during xanthone-labeled biosynthesis experiments. As for the flavonoids, this moiety is subjected to an enzyme-assisted hydroxylation to afford the catechol acyl-CoA, which is then taken in charge by a PKS to generate the phloroglucinol part. The latter is finally transformed in the polyhydroxylated benzophenone [55–58]. This polyhydroxylated benzophenone is the starting point of both prenylated xanthones and PPAPs.

This pathway is a major divergence between plants and bacteria/fungi. Indeed, xanthones of the microorganism world are generally synthesized from full polyketides [59,60]. Peters et al. pointed out evidence of enzymatic participation in the xanthone synthesis from the polyhydroxylated benzophenone. The ring closure to generate the xanthone core is mediated via a P450 cytochrome and a xanthone synthase, and occurs through an oxidative coupling [61]. Atkinson and coworkers predicted the implication of a hydroxylated benzophenone for the xanthone biosynthesis through a phenol oxidative coupling [62]. As for the biflavonoids dimers, these compounds can be obtained using potassium ferricyanide as an oxidant. Further functionalization (hydroxylation, methoxylation, prenylation) occurs once this xanthone core (synthesis) is obtained.

The hypothetic PPAPs biosynthesis has already been described by Kumar et al. [7] in their review on *Garcinia* species (**Fig. 6**). All compounds of this family (**1** to **17**) seem to be derived from maclurin (**36**), after being taken in charge by prenyl transferases. Several studies have been done on hyperforin [63–65] to elucidate the mechanism and the sequence of crucial steps. Prenylation occurs first on position 6, then on position 4, and finally one more on position 6. The nine-membered ring is formed by a concerted mechanism where the next prenyl transfer involves an intramolecular activation and cyclization leading to the unique backbone. This reactivity was confirmed by some biomimetic syntheses [66]. In the presence of an oxidant, the prenylated acylphloroglucinol moiety can itself be cyclized to generate the bicyclo[3.3.1]nonane-9-one skeleton.

Further modifications can also be performed by the plant, such as additional prenylation, hydroxylation, condensation into tetrahydropyran, or condensation in a more complex cycle. Consider-

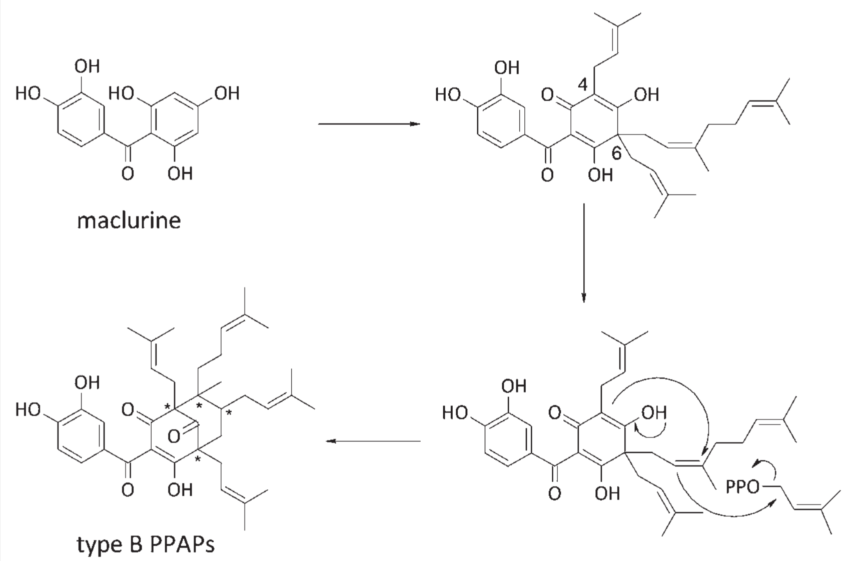

Fig. 6 Biosynthesis of type B polycyclic polyprenylated acylphloroglucinols.

ing those side modifications and the different stereochemistry possibilities, *S. globulifera* is able to produce a number of different analogs.

Symphonone H (**14**) belongs to the oxy-PPAPs family present in the *Garcinia* genus. The biosynthesis of such compounds has been discussed by several authors. In 2008, Xu et al. identified two compounds structurally related, guttiferone L (**43**) and garciyunnanin B (**44**), in their study of *G. yunnanensi* and in the same organ (pericarp) [34]. As represented in ▶ **Fig. 7**, the authors proposed a biosynthetic pathway for the conversion of guttiferone L (**43**) into garciyunnanin B (**44**). Their hypothesis involves the unique 3,4,6-trihydroxyphenyl skeleton converting into an intramolecular cyclization. The activation of the carbonyl in C-3 in enolate leads to the subsequent condensation on the C-16 position with the loss of water and formation of the xanthone. Even if this cyclization mechanism is possible, guttiferone L (**43**) (▶ **Fig. 7**) is, to date, the only tri-hydroxylated type B PPAP isolated, while several other type of oxy-PPAPs (including trihydroxylated xanthones) have been found, suggesting another mechanism and thus a poor probability of this pathway.

In their recent study of thorelione A (**45**), N'guyen et al. [67] provided a mechanism involving a *pseudo*-Michael addition (▶ **Fig. 7**). Their hypothesis is based on the attack of the free doublet of the enol C-3 in the C-16 position of the aromatic ring. The delocalization of the negative charge on the ketone followed by a return to aromaticity leads to the loss of a proton and the formation of the oxy-thorelione A (**46**).

The third mechanism (▶ **Fig. 7**) proposed by the Sang [40, 68] and Huang groups [33] involves a radical intermediate. The oxidation of the enolate to the enolate radical results in the formation of a C_{ar}-O bond. These fully conjugated compounds allow for the delocalization to the mono ketone form. The keto-enol equilibrium allows for the return on the most stable tautomer. The free rotation of the acyl then allows the formation of the angular (C1–C16) and linear xanthones (C3-C16) found in some other species such as *G. indica* [34].

This mechanism is supported by the Huang group, who used the oxidants 2,2-diphenyl-1-picrylhydrazyl (DPPH) or azo-bis-(isobutyronitril) (AIBN) (▶ **Fig. 8**) that generate radical species and transformed garcinol (**47**) into the two corresponding xanthones **48** and **49**.

In 1969, Atkinson et al. already reported this mechanism as a classical biomimetic oxidative coupling leading to xanthones [62]. They managed to perform this oxidative coupling using potassium ferricyanide (known as a radical donating reagent) with 2,3′-dihydroxybenzophenone, which is structurally close to maclurin (**37**).

Recently, our group has selectively converted guttiferone A (**1**) into the corresponding oxy-PPAP, 3,16-oxy-guttiferone, and maclurin (**36**) into norathyriol (**31**) using yeast [41] (▶ **Fig. 9**). This work involves an enzymatic reaction whose mechanism has not yet been defined. Enzymes might also be responsible for the biosynthesis of these derivatives in plants. In *S. globulifera*, symphonone H (**14**) is strongly related to 7-*epi*-garcinol (**16**), which is probably the biosynthetic precursor of this oxy-PPAP.

Biological Activities

Phytochemical studies performed on the isolated metabolites of *S. globulifera* were extended to the study of their biological activities. Remarkably, a number of them were performed on protozoal or microbial diseases. The potent biological activities of these isolated molecules would confirm the traditional use of the plants (▶ **Table 4**).

Antimalarial activity

Among the exhaustive list of NPs possessing such activity, polyhydroxyxanthones, oxygenated, and prenylated xanthones, bixanthones and xantholignoids have been reported to potentially be a novel class of antimalarial agents with enhanced efficacy on multidrug resistant *Plasmodium* parasites. Seed shell extracts of *S. globulifera* contain three novel prenylated xanthones [gaboxanthone (**21**), globuliferin (**22**), symphonin (**23**)] and guttiferone A (**1**) (▶ **Fig. 1**). Compound **1** possesses interesting antiplasmodial activities on *P. falciparum* W2 strains [21] (▶ **Table 4**). This first study on the potential of *S. globulifera* part extracts led to the exploration of the bark roots and the identification of 12 new PPAPs. The new PPAPs were evaluated for their antima-

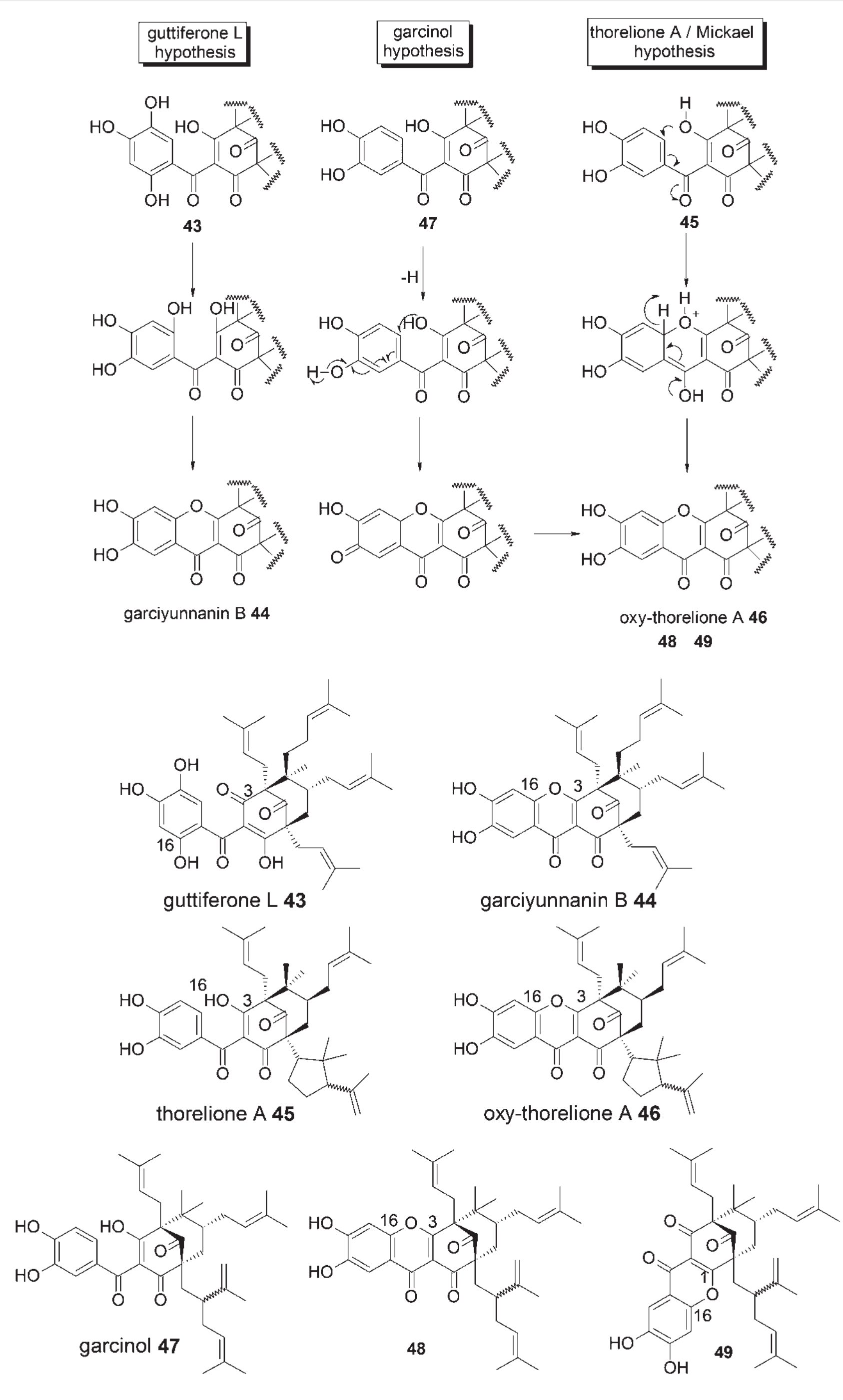

Fig. 7 Proposed pathways for the biosynthesis of oxy-polycyclic polyprenylated acylphloroglucinols.

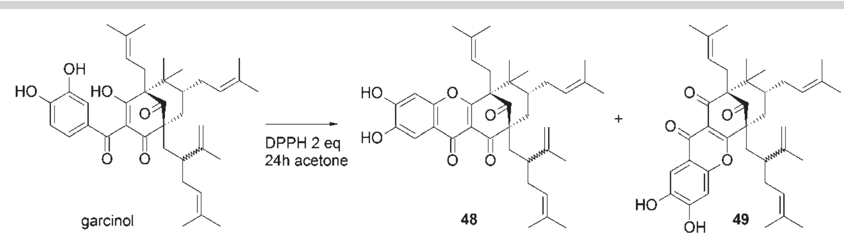

Fig. 8 Synthesis of xanthones **48** and **49** using 2,2-diphenyl-1-picrylhydrazyl (DPPH) and azo-bis-(isobutyronitril) (AIBN).

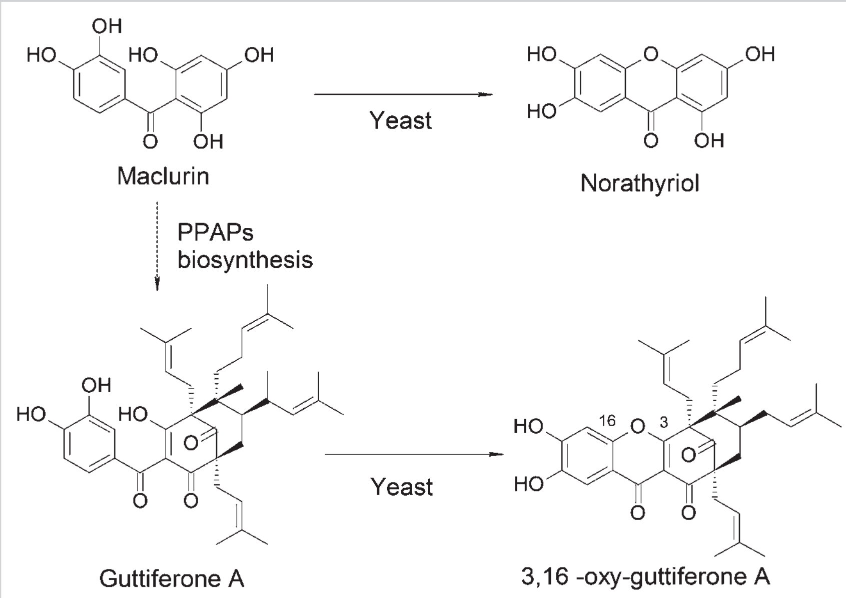

Fig. 9 Intramolecular cyclization of maclurin and guttiferone A.

Table 4 Biological activities of *S. globulifera* secondary metabolites.

Antiplasmodial activity				
		IC_{50} (µM)		**IC_{50} (µM)**
No.	**Name**	***P. falciparum* W2**		***P. falciparum* FcB1**
1	Guttiferone A	3.17		–
5	14-Deoxy7-*epi*-isogarcinol	–		2.5
6	Symphonone A	–		2.8
7	Symphonone B	–		3.3
8	Symphonone C	–		2.6
9	7-*epi*-Coccinone B	–		3.3
10	Symphonone D	–		2.1
11	Symphonone E	–		2.7
12	Symphonone F	–		3.2
13	Symphonone G	–		2.1
14	Symphonone H	–		3
15	Symphonone I	–		6.7
16	7-*epi*-Garcinol	–		10.1
17	7-*epi*-Isogarcinol	–		3.2
21	Gaboxanthone	3.53		–
22	Globuliferin	1.29		–
23	Symphonin	3.86		–
Antioxidant activity				
% Inhibition DPPH free radical				
21	Gaboxanthone	28		
22	Globuliferin	23		
23	Symphonin	54		
1	Guttiferone A	89		
Antiparasitic activity				
IC_{50} (µM) *L. donovani*				
1	Guttiferone A	0.16		
26	Xanthone V1	1.4		
Antimicrobial activity (minimum inhibitory concentration µg/mL)				
		Gram-positive bacteria		**Gram-negative bacteria**
		S. aureus	*B. subtilis*	*E. coli*
18	Globulixanthone C	14.05	8.24	Inactive
19	Globulixanthone D	8	12.5	Inactive
20	Globulixanthone E	4.51	3.12	Inactive
–	Streptomycin	6.25	0.85	Inactive
Cytotoxic activity (IC_{50} KB cells µg/mL)				
24	Globulixanthone A	2.15		
25	Globulixanthone B	1.78		

larial activity [22] (*P. falciparum* FcB1) and presented good to moderate IC_{50} values ranging from 2.1 to 10.1 µM (▶ **Table 4**).

Antioxidant activity

It has been proven that the *Plasmodium* infected red blood cells are under constant oxidative stress caused by exogenous reactive oxidant species and reactive nitrogen species produced by the immune system of the host and by the endogenous production of reactive oxidant species. Therefore, compounds able to exhibit both antiplasmodial and antioxidant activities are promising candidates as antimalarial agents. Thus, compounds **1, 21, 22**, and **23** have been engaged in the free radical scavenging DPPH assay (▶ **Table 4**). The xanthones (**21, 22**, and **23**) possess a limited antioxidant activity, while guttiferone A (**1**) has shown the best activity with 89% of inhibition of the DPPH radical.

Antileishmanial activity

The antiplasmodial activities of PPAPs and xanthones from *S. globulifera* mentioned before were confirmed, as they also possess interesting antileishmanial properties. Guttiferone A (**1**) is the lead compound of the series [69] (▶ **Table 4**). Furthermore, xanthone V1 (**26**) extracted from the leaves of *S. globulifera* also exhibits an interesting antiparasitic activity (▶ **Table 4**). One of the major drawbacks of antileishmanial agents actually used in therapeutics is their substantial cytotoxicity towards the host cells due to an evident lack of selectivity. The relative cytotoxicity of compounds **1** and **26** was then evaluated towards normal rat skeletal muscles cells (L-6 cells). Interestingly, the aforementioned compounds have demonstrated a low cytotoxicity (IC_{50} = 7.3 and 18 µM, respectively, ▶ **Table 4**) allowing consideration for future development against the *Leishmania donovani* parasite.

Antimicrobial activity

The bioguided isolation from *S. globulifera* extracts that exerted antimicrobial activity led to the identification of globulixanthones C, D, and E (**18**–**20**). Compounds **18**–**20** were then tested for their antimicrobial effect on gram-positive (*Staphylococcus aureus, Bacillus subtilis, Vibrio anguillarium*) and gram-negative (*E. coli*) bacteria in an agar well diffusion assay [23]. As depicted in ▶ **Table 4**, compounds **18**–**20** possess activities in the same range as streptomycin on gram-positive bacteria. However, they possess no activity on gram-negative bacteria, suggesting a selective killing. Biflavonoids **40** and **41** and xanthones **30** and **31** extracted from the stems of *S. globulifera* [27] have also shown good antimicrobial activity.

Anticancer activity

Natural products have played a consequent role in this course as it is estimated that 20% of anticancer drugs actually sold are derived from natural products. Root bark extracts of *S. globulifera* have been shown to possess interesting cytotoxic activity and the bioguided extraction led to the identification of globulixanthone A (**24**) and B (**25**) [24]. These two compounds were evaluated for their cytotoxic activity towards human epidermoid carcinoma of the nasopharynx (KB cell line, ▶ **Table 4**). Compounds **24** and **25** possess good properties, but no mechanistic studies have been run to date.

Anti-HIV activity

PPAPs from *Clusia torresii* (clusianone, 7-epi-clusianone, 18,19-dihydroxyclusianone) have been proven to be potent anti-HIV agents that act by inhibiting gp120-sCD4 interaction. This mechanism of action denotes a probable interference with the viral attachment to the CD4 membrane receptor implying an effect on infection. The MeOH extracts of *S. globulifera* have shown an activity *in vitro* toward HIV infected human cells (CEM-SS cells) [6]. The bioguided extraction has led to the identification of guttiferones A, B, C, and D (compounds **1**–**4**) as the active ingredients with an EC_{50} comprised between 1–10 µg/mL, but no indications of a corresponding decrease of viral replication has been observed [6]. However, further mechanistic studies should be pursued.

Anti-FAS activity

Lipid biosynthesis is essential for the cell viability of all cellular living organisms and is notably ruled by FAS (fatty acid synthase) activity. As differences exist between the FAS of different organisms, FAS became an emerging target for diseases caused by microorganisms such as fungi or bacteria [70, 71]. Two major types of FAS prevailed: type I exists in animal and fungi, and consists in a single multifunctional polypeptide [73], while type II exists in bacteria and plants, and comprises several enzymes, each of them assuring a step of the carbon chain elongation [72]. In a study aiming to identify new types of FAS inhibitors [31], ethanolic extracts of *S. globulifera* leaves were evaluated. The structural elucidation of the active compounds has led to the first identification of morelloflavone (**39**) and GB-2 (**40**), two original biflavonoids. Compounds **26** and **27** were active against FAS prepared from *Saccharomyces cerevisiae* with IC_{50} values of 30 and 23 µg/mL, respectively.

Anticholinesterase activity

Acetylcholinesterase is a hydrolase responsible for the hydrolysis of acetylcholine to acetate and choline. It is found mainly in neuromuscular junctions and synapses, and plays a critical role in the transmission of nervous information. Its inhibition, leading to an accumulation of acetylcholine and the blockade of neurotransmission, is of importance notably for drug detoxification [74] or Alzheimer's disease treatment (improvement of cognitive function) [75]. Compound **1** isolated from *S. globulifera* is a potent inhibitor of acetylcholinesterase and butyrylcholinesterase [IC_{50} = AChE 0.88 µM (galanthamine = 0.5) and BChE = 2.77 µM (galanthamine = 8.5)] (▶ **Table 4**).

Conclusion

Interest in *S. globulifera* has been growing for several years for two reasons: the bioactivity of its secondary metabolites and a curious morphological diversification through times and sites. These differentiations have probably induced variations in the metabolome in order for the plant to adapt to the different African and American environments. A species able to rapidly acclimate to its environment by adapting its metabolome is an obvious rich source of new compounds and deserves to be studied in more detail. *S. globulifera* thus encloses various and complex secondary metabolites, such as PPAPs or flavonoid dimers. Moreover, the possible biogenesis of complex xanthones through oxidative ring closure from phloroglucinol derivatives is unprecedented. The traditional use by African or South American populations was then confirmed by biological assays, highlighting the impressive knowledge of nature gathered in those parts of the world, though still understudied. All the secondary metabolites isolated from *S. globulifera* have shown moderate to good antimicrobial activities. Especially, guttiferone A, a major metabolite and lead compound, presents an impressive panel of diverse biological activities, and hemisynthetic derivatives have been proven to be potent antiparasitic agents [76]. Finally, *S. globulifera* could be illustrated as the perfect example of the paradigm of modern phytochemistry: a widespread source of complex metabolites with potent biological activities.

Conflict of Interest

The authors report no conflicts of interest.

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