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Phytochemical review of the lichen genus *Stereocaulon* (Fam. Stereocaulaceae) and related  
pharmacological activities highlighted by a focus on nine species

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## **Abstract**

The *Stereocaulon* genus is one of the fruticose lichen groups distributed worldwide from tropical zones to polar zones. However, the scientific study of this tricky genus is still limited, making it a challenge to study the group further. Detailed morphological studies are essential to discriminate closely shaped species which is illustrated through personal data focused on phyllocladia, apothecia and spores of nine species. Secondary metabolites isolated from *Stereocaulon* species are mostly some depsides, depsidones, diphenylethers and dibenzofurans which can have a taxonomic value. The use of *Stereocaulon* lichens as a traditional medicine in several regions of the world and pharmacological studies of extracts and isolated compounds have been compiled. Biological activities as cytotoxic, anti-inflammatory, antibacterial, antifungal or antioxidant are reported.

## **Keywords**

Biogenetic, bioactivities, folk medicines, lichens, secondary metabolites, *Stereocaulon*

## Introduction

Among the symbiotic organism called lichen formed between two major different partners that are fungi (mycobiont) and/ or algae/ cyanobacteria as photobiont without excluding the lichen-associated microbiome, one of an interesting genus is *Stereocaulon*. The genus *Stereocaulon* Hoffm. (Stereocaulaceae, Lecanorales, Ascomycota) includes about 130 species of wide distribution (Kirk et al. 2001) and all possess a dimorphic thallus, being crustose (called primary thallus) and shrubby (called secondary thallus or pseudopodetium) (Figure 1). According to Lamb, the pseudopodetia may develop holostelidially through elongation of the medullary tissue only (Lamb 1951), and this genus is clearly differentiated from the *Cladonia/Cladina* genera having a hollow pseudopodetium.

Most of these species are growing on rocks, metal-rich spoil heaps, on shingle, soil and amongst terricolous mosses generally as pioneer species (Purvis et al. 1992; Singh et al. 2013). They are found from the Arctic and Antarctic to the tropics in both hemispheres (Lamb 1951). As said Riddle in 1910 (Riddle 1910):

“Anyone who has attempted to determine material of *Stereocaulon* or has studied the material in our herbaria must have realized the confusion which exists in regard to the distinctive of the species characters of the species. This confusion arises in part from the great variability and their tendency to intergrade”

Fortunately, thanks to his work and many other works of famous lichenologists as Nylander in his Synopsis Lichenum (Nylander 1860), Magnusson (Magnusson 1926), Dodge (Dodge 1929), Johnson (Johnson 1938), Duvigneaud (Duvigneaud 1942, 1944, 1955) and more recently to Lamb compendium (Lamb 1951, 1977, 1978), complemented by Boekhout for the Columbian *Stereocaulon* species (Boekhout 1982) and McCarthy for the Australasian lichens (McCarthy 2012), the lack of monographies and papers has disappeared and keys of classification for the *Stereocaulon* species are now available. Nevertheless, although there

have been numerous taxonomic studies of *Stereocaulon*, it remains a tricky genus for lichenologists and the systematic arrangement of the species within the genus is not an easy task. The extreme polymorphic, the high plasticity and adaptability of some *Stereocaulon* species (sometimes not supported by any variation in chemistry) is a source of confusion and as a result many superfluous names were established. 34 taxa corresponding to the common name “snow lichen” are recognized in the plants database of US while 813 species and varieties are listed in Index Fungorum website (Index Fungorum 2018; Natural Resources Conservation Service 2018). As usual in lichenology, chemotaxonomy is often addressed and useful but their determination has to be based on both morphological and chemical data. New trends are the use of barcoding based on ITS molecular analysis resulting in revised classifications (Högnabba 2006; Hognabba et al. 2014).

Proper identification of the material to be phytochemically studied is required as a first step before isolation and biological valorization of its metabolites. *Stereocaulon* lichens are a source of a number of lichen compounds, some being very common such as the depside atranorin encountered in many lichens but others are unusual such as diphenylethers. For all these compounds but also for crude extracts, few biological studies have been conducted. We propose to report in this paper the chemical composition described for *Stereocaulon* species along with their traditional use and the reported pharmacological activities.

### **Morphology and classification of genus *Stereocaulon***

Morphologically, *Stereocaulon* genus consists of crustose-type primary thallus and fruticose-type secondary thallus. As for the *Cladonia* genus, the primary thallus is composed of basal granules called phylloclades, which usually disappear quickly but in some cases can be found and which are of major importance for classification and identification. The secondary thallus is often presented in branched, shaped and erect forms and is known as pseudopodetium (Fig.2). This pseudopodetium has a cartilaginous compact axis formed by

parallel hyphae surrounded by a loose medulla that becomes an essential difference compared to *Cladonia* whose axis is hollow with a cortex containing phyllocladia or not. Phyllocladia contain green algae photobionts belonging to the *Trebouxia* genus and shapes of these phyllocladia play an important role in taxonomy, for delimitation of *Stereocaulon* species and were well described by Duvigneaud (Duvigneaud 1955). As an example to illustrate the importance of this character, we describe here the diversity observed in nine *Stereocaulon* species which were selected in a previous study (Ismed 2012): one is undoubtedly boreal circumpolar (*S. grande*), two are western atlantic (*S. evolutum*, *S. dactylophyllum*), *S. vesuvianum* is widely distributed in both hemispheres in volcanic regions, three were of southeast Asia (*S. graminosum*, *S. halei*, *S. montaganeanum*) and two belongs to south-east Africa (*S. scutelligerum*, *S. vulcani*). Looking at the morphology of their phyllocladia, they can be variable and range from granular even peltate (*S. graminosum*, *S. vesuvianum*, *S. vulcani*), digitate even coralloid (*S. dactylophyllum*, *S. evolutum*, *S. grande*), papillose (*S. dactylophyllum*, *S. evolutum*), with phyllocladioid branchlets (*S. halei*, *S. montaganeanum*, *S. scutelligerum*) (Fig.3). Secondary thallus contains several important organs (Fig.1); one of them is apothecia as a reproductive organ which contains spores. The apothecia position is located at the terminal or lateral and has a convex or almost spherical disc shape with light brown to dark color. In studied species described above, the height of the hymenium and hypothecium were checked on slices of apothecia without forgetting to note the pigmentation of the hypothecium. For example, *S. graminosum* exhibited a colored hypothecium (Fig.4). Features of the spores like their size and the number of septa were also crucial for the identification and helped us to distinguish *S. halei*, which is fusiform shape with 1 to 3 septa, from *S. montaganeanum* with a vermiform shape (Fig.5). The last organ is cephalodium containing a secondary photobiont belonging to cyanobacteria (*Nostoc*, *Rhizonema* or *Stigonema*). Three types of cephalodia are described by Johnson (Johnson 1938): spherical,

botryose and scrobiculate based on the feature, the size and the internal organization between cephalodial hyphae and cyanobacteria. Lamb divided the scrobiculate type into two subtypes based on the medullary constitution: sacculate and protosacculate (Lamb 1976). We observed that cephalodia of *S. halei* and *S. montagneanum* were of scrobiculate type. Using Scanning Electron Microscopy (SEM) and light microscopy after paraffin inclusion then HES (Hematoxylin Eosin Saffron) coloration, cephalodia of *S. montagneanum* were of sacculate type with arachnoid hyphae and a well-defined cortex (Fig.6) while those of *S. halei* were protosacculate with compacted hyphae and not well-defined cortex (Fig.7).

Among the several lichenologists who described *Stereocaulon* species, Lamb remains the most famous. In 1951, he proposed a classification based on morphological form and anatomy, thus dividing *Stereocaulon* genus into three subgenera namely *Enteropodium*, *Pilophoris* and *Holostelidium* including also sections and subsections (Lamb 1951). However, the identification process does not depend solely on *Stereocaulon* morphology. The main compounds observed with microchemistry or Thin Layer Chromatography (TLC) in *Stereocaulon* also play an important role in the lichen identification, as used by Duvigneaud (Duvigneaud 1955) and Lamb in The Conspectus about The Lichen Genus *Stereocaulon* (Lamb 1977, 1978). Another way to confirm the identity of the species is the use of molecular biology analysis. Three recent papers are based on molecular data: Myllys studied the phylogenetic relationships of all members of the Stereocaulaceae (Myllys et al. 2005) and Högnabba (Högnabba 2006; Högnabba et al. 2014) attempted to clarify phylogenetic relationships of several taxa within this genus. Through ITS1-5.8S-ITS2 and partial  $\beta$ -tubulin analysis, 49 different *Stereocaulon* species were organized by Högnabba in 2006 and compared to the classification by Lamb (Lamb 1977).

## **Biogenetic pathways of lichen compounds and secondary metabolites of the genus *Stereocaulon***

The number of secondary metabolites isolated from lichens was around 800 compounds in 1996 (Huneck and Yoshimura 1996) and has now increased beyond 1050 compounds (Stocker-Wörgötter 2008; Elix 2014). However, the phytochemical studies of the *Stereocaulon* genus are still limited and most of the compounds were only major ones and were usually detected by TLC. As an example, the major compounds were easily TLC-visualized from the nine previous species collected in several places in the world, The composition of their methanolic extracts revealed until 17 spots using HPTLC-UV (Fig.S2, SD M1) ; *S. halei* was the less rich extract (4 spots) compared to *S. dactylophyllum*, *S. montagneanum*, *S. graminosum*, *S. vulcani* exhibiting 7 spots. Among these compounds, only the major compounds revealed in all *Stereocaulon* extracts with ( $R_f = 0.80$ ;  $\lambda_{\max} = 280,310$  nm), ( $R_f = 0.64$ ;  $\lambda_{\max} = 220,250,280$  nm), ( $R_f = 0.51$ ;  $\lambda_{\max} = 280,310$  nm), ( $R_f = 0.33$ ;  $\lambda_{\max} = 280,310,340$  nm) were unambiguously identified as atranorin, methyl orcinol carboxylate, lobaric acid and stictic acid (Fig.S2). These preliminary data were in agreement with the compounds reported by Lamb from 123 species in its *Conspectus about Stereocaulon* genus (Fig.S3) (Lamb 1977).

Phytochemical studies were thoroughly only performed on 40 species and subspecies and structural diversity from *Stereocaulon* genus was restricted to depsides, depsidones, diphenylethers, dibenzofuranes, monoaromatic phenols, terpenoids and steroids and polyols. Depsides, depsidones, monoaromatic phenols, diphenylethers, dibenzofurans and anthraquinones are derivatives synthesised from acetate-polymalonate pathways. The biosynthesis of depsides and depsidones begin with the condensation of monoaromatic compounds such as orsellinate and orcinol. These latter may also be regarded as the precursor of depside biogenesis (Seshadri 1944; Yamazaki et al. 1965; Stocker-Wörgötter

2008) or from the decomposition or degradation of a depside (Hylands and Ingolfsson 1985; Huneck et al. 1989) Diphenylethers are a combination of two phenolics with ether bonds. This group of compounds is formed from the opening of the ester bond from the depsidone ring by hydrolysis reaction followed by nucleophilic attack and prototropic regulation, but without decarboxylation or O-methylation as described for the biosynthesis of loxodin and norlobaridone respectively (Foo and Galloway 1979; Chooi 2008) (Fig.S1). Others suggested that some diphenylethers have been formed during extraction (Gonzalez et al. 1995; Millot et al. 2008) or by treatment of depsidones using hot alkali as described for lobariol carboxylic acid or lobarin from lobaric acid (Asahina and Nonomura 1935; Han et al. 2012). One of the most common and widely known depside is atranorin, and almost all species of *Stereocaulon* genus contain it (Lamb 1977). Furthermore, several other depsides have been also discovered. Among depsides without aliphatic chain (such as atranorin), lecanoric acid was isolated from *S. curtatum* and *S. corticulatum* (Huneck and Follman 1965; Hamada and Ueno 1990), while from *S. evolutum* were reported for the first time methyl-3-methyllecanorate and cladonioidesin, along with a new depside (Vu et al. 2015). Some depsides with aliphatic side chains have been reported such as miriquidic acid from *S. curtatum* (Hamada and Ueno 1990), perlatolic acid from *S. ramulosum* (Vila et al. 2008), and *S. meyeri* (Fox and Huneck 1970), and anziaic acid from *S. ramulosum* (Vila et al. 2008) (Fig.8).

In addition to the ester bond described for depsides, the depsidones have an ether bridge. So far, there are two types of depsidone commonly discovered in *Stereocaulon*, the furano-type depsidone such as the stictic acid group and the prenyl-type depsidone such as lobaric acid (Fig. 9). Stictic acid and its derivatives are very common in the *Stereocaulon* genus and we confirmed it in our unpublished results given that it was identified by HPTLC-UV in six out of the nine species (*S. dactylophyllum*, *S. graminosum*, *S. montagneanum*, *S.*

*vesuvianum*, *S. vulcani*, *S. scutelligerum*), (Ismed 2012) (Fig.S2, SD M1). Elix reported that stictic acid compounds isolated from lichen experienced a chemosyndrome phenomenon (Elix 1996; Elix and Wardlaw 2000). This phenomenon also have been reported to occur on stictic acid derivatives from *S. montagneanum* collected in Indonesia, through a variation in the degree of oxidation of functional groups such as CHO, COOH, CH<sub>2</sub>OH or OH and methylation of phenolic groups such as OCH<sub>3</sub>, OH (Ismed et al. 2017). From this species, some depsidones were isolated and reported for the first time in the *Stereocaulon* genus such as peristictic acid and menegazziaic acid (Ismed et al. 2017). Others like cryptostictic acid, constictic acid, vesuvianic acid and norstictic acid have been isolated previously from *S. azureum* (González et al.1992), *S. vesuvianum* var. *pulvinatum*, *S. alpinum* (Solberg 1977; Ingolfsdottir et al. 1986) and from *S. mayeri*, *S. argus*, *S. spathuliferum* f. *pygmaeum* (Huneck 1972, 1974; Ramaut et al. 1978) respectively.

Meanwhile, three depsidones of prenyl-type have been recorded. The first one is lobaric acid which represents the most third common compound in *Stereocaulon* genus. Methanolic extracts of *S. evolutum*, *S. grande*, *S. halei* contained lobaric acid as major compound (Ismed 2012). Other close structural compounds are colensoic acid which was isolated from *S. colensoi* (Fox et al. 1970) and norlobaric acid from *S. paschale* (Carpentier et al. 2017) (Fig 9).

The diphenylether group (synonym, pseudodepsidones) is less common among lichen metabolites compared to the depsides and depsidones groups. Several pseudodepsidones compounds were reported such as sakisacaulon isolated from *S. sasakii* (Morita et al. 2009), lobarin from *S. halei* (Ismed et al. 2012), methyl sakisacaulon, methyl lobarin, anhydrosakisacaulon A, esterified lobarin, esterified sakisacaulon from *S. alpinum*, and *S. paschale* (Seo et al. 2009; Bhattarai et al. 2013; Carpentier et al. 2017) (Fig. 10).

Few compounds belonging to the dibenzofurane group have been found in the *Stereocaulon* genus. Some of them are strepsilin from *S.azoreum* and *S. evolutum* (González et al. 1992; Vu et al. 2015), porphyrilic acid from *S.strictum*, *S. strictum var compressum* (Huneck 1974), and hypostrepsilalic acid which was isolated from spore-derived mycobiont culture of *S. japonicum* (Miyagawa et al. 1997). Recently, Carpentier isolated three dibenzofuranes from *S. paschale* (Carpentier et al. 2017) (Fig. 11).

Monoaromatic phenolic compounds are a group of compounds that often appear in lichen metabolites and also in *Stereocaulon*. Some of them have been isolated such as ethyl haematommate from *S. pomiferum* and *S. paschale* (Li et al. 1991; Cai et al. 2009), methyl  $\beta$ -orsellinate from *S. ramulosum* and *S. alpinum* (González et al. 1992; Seo et al. 2009), atranol from *S. vesuvianum* (Caccamese et al. 1986), 4,6-dihydroxy,2-methoxy, 3-methylacetophenone from *S. vesuvianum* and *S. alpinum* (Bolognese et al. 1974; Hylands and Ingolfssdottir 1985), methyl orcinol carboxylate from *S. curtatum* and *S. ramulosum* (Hamada and Ueno 1990; Vila et al. 2008) and methyl haematommate from *S. alpinum* (Seo et al. 2009) (Fig. 12).

Terpenoids and steroids are derivatives from mevalonate pathways and come from the assembly of isoprenic units, which are formed from acetylCoA. Isopentenylpyrophosphate (unit C5) and geranylgeranylpyrophosphate (unit C20) become precursors of diterpenes and carotenoids, respectively while squalene is a precursor for steroids and triterpenes. They are less often isolated. There are several steroids compounds that have been found, such as ergosterol peroxide, cerevisterol and brassicasterol from *S. azoreum* and *S.tomentosum* (Bruun 1976; González et al. 1992). Then, some other steroids such as lichesterol, dihydroergosterol, stigmasterol and ergosterol have been also isolated from *S. tomentosum* (Solberg 1987). Meanwhile, there are only a few triterpenoids that have been reported:  $\alpha$ -amyryn, lupeol and taraxerol from *S.azoreum* (González et al. 1992) (Fig. 13).

Some other secondary metabolites of the genus *Stereocaulon* have ever been reported such as the anthraquinone isolated from *S. graminosum* (Aghoramurthy et al. 1961), 9-cis-octa decenamamide from *S. alpinum* (Ingólfssdóttir et al. 1997), some fatty acid derivatives (such as dicarboxylic acid and bourgeanic acid) from *S. vesuvianum* and *S. tomentosum* (Bruun 1973; Solberg 1977), ventosic acid from *S. myriocarpum* (Aghoramurthy et al. 1961) but also 1,3,7-trimethylguanidine from *S. ramulosum* (Vila et al. 2008) (Fig. 14). So far there have been no reports of derivatives from shikimic acid pathway such as pulvinic acids.

Polyols have also been reported from this genus like D-arabitol from *S. colensoi*, *S. myriocarpum* and *S. piluliferum* (Aghoramurthy et al. 1961; Fox et al. 1970; Malik et al. 1972), galactitol from *S. ramulosum* (Vila et al. 2008) and mannitol from *S. colensoi* (Fox et al. 1970) (Fig. 15). Furthermore, some polysaccharides known for their chemotaxonomic value that have been isolated belong to linear  $\alpha$ -D-glucanes such as isolichenane from *S. japonicum* (Yokota and Shibata 1978; Yokota et al. 1979) and *S. ramulosum* (Baron et al. 1988, 1989) but also from linear  $\beta$ -D-glucanes of laminaran type (from *S. ramulosum* (Baron et al. 1988, 1989)) and heteropolysaccharides such as galactomannanes from *S. ramulosum* (Baron et al. 1988, 1989) and *S. paschale* (Hauan and Kjolberg 1971; Gorin and Iacomini 1985).

Finally, it is interesting to note that the chemical composition is not fully supported by the molecular data or the classification of Lamb. In our preliminary studies on the nine species, the multivariate analysis on the data resulted from analytical composition studies showed that the chemical composition of *S. dactylophyllum* (subgenus *Stereocaulon* section *Stereocaulon*) is closer to *S. vesuvianum* (*Stereocaulon* section *denudata* subsection *denudata*) than to *S. evolutum* (subgenus *Stereocaulon* section *Stereocaulon*). (Fig. 16, SD M2)

## Folk medicine and Pharmacological studies

The utilization of *Stereocaulon* genus in traditional medicine is quite rare. However, some ethnopharmacological reports mention *Stereocaulon* to be used in treatments of ailments. Lavergne reported that *S.vulcani* with its called name "fleur de roche" was used by Reunion Islanders as a treatment against syphilis, ulcers and wound healers (Lavergne 1989). The people of Indo-Tibetan Himalayas call *S. himalayense* under the name "chanchal" which they use for the treatment of urinary infection (Sharma 1997). *S. paschale* is used as symptomatic treatment for type 2 diabetes in Cree community in Quebec, Canada (Fraser et al. 2007).

Some usual cytotoxic, antioxidant or antimicrobial assays have been carried out on extracts from this genus. For instance, a methanolic extract of *S. paschale* showed a weak free radical scavenging activity  $IC_{50}$  0.88 mg/mL, a MIC (Minimum Inhibitory Concentration) ranging from 0.625 to 10 mg/mL against the growth of *Bacillus subtilis* and *B.cereus* and a very moderate cytotoxic effect against FemX (human melanoma) and LS174 (human colon carcinoma) cell line with  $IC_{50}$  46.67 and 71.71  $\mu$ g/mL respectively (Rankovic et al. 2014).

The crude acetone extract of four lichen species collected in the Philippines was reported active against the growth of *S. aureus* and *B. subtilis*. One of them, *S. massartianum*, was the most powerful against both bacteria with a diameter of inhibition > 19 mm. (Santiago et al. 2010). An ethanolic extract from *S. foliolosum* inhibits the growth of *M. tuberculosis* H37Rv with MIC 500  $\mu$ g/mL which is compared to rifampicin and isoniazid (MIC value 0.25 and 0.1  $\mu$ g/mL, respectively) (Gupta et al. 2007). The *n*-hexane extract of *S. himalayense* is highly active against the soil pathogenic fungi *Rhizoctonia bataticola* with an  $ED_{50}$  value 51.36  $\mu$ g/ml (Goel et al. 2011). Unfortunately, no further phytochemical studies led to isolation of the compounds involved in the antimicrobial activities.

Moreover, some isolated lichen substances from the *Stereocaulon* genus are reported to be pharmacologically active. Lobaric acid has been tested as an anti-inflammatory, cytotoxic and antimicrobial agent. Suggesting a possible anti-inflammatory activity, lobaric acid inhibits selectively four times higher the 5-lipoxygenase enzyme ( $IC_{50}$  7.3  $\mu$ M) than cyclooxygenase (Ingolfsdottir et al. 1996). Moreover, it inhibits the growth of *S. aureus*-1199B, a type of multidrug resistant bacteria to certain fluoroquinolones, with a MIC value of 17.52  $\mu$ M compared to norfloxacin (MIC 100  $\mu$ M) (Kokubun et al. 2007). This compound was not very cytotoxic as a moderate cytotoxic activity was shown on three malignant cell lines (T-47D and ZR-75-1 from breast carcinomas and K-562 from erythro-leukemia), with  $ED_{50}$  31.76, 97.92 and 53.67  $\mu$ M, respectively (Ogmundsdóttir et al. 1998).

Furthermore, lobaric acid and its derivatives, two pseudodepsidones, isolated from *S. alpinum* potentially inhibit protein tyrosine phosphatase1B (PTP1B), a negative regulator of insulin considered to be a promising target for treatment of type 2 diabetes mellitus and breast cancer. The  $IC_{50}$  values for lobaric acid (0.87  $\mu$ M), methyl sakisacaulon (2.48  $\mu$ M) and methyl lobarin (6.86  $\mu$ M) were better than those of the positive control, ursolic acid (3.08  $\mu$ M) (Seo et al. 2009). Another pseudodepsidone from this species, lobastin, was evaluated as antibacterial against gram-positive bacteria (*B. subtilis* and *S. aureus*) with MIC values 44 and 35.2  $\mu$ M compared to ampicillin 2.7  $\mu$ M (Bhattarai et al. 2013). Lobastin has also been reported active as anti-inflammatory in atherosclerotic conditions inhibiting protein expression of VCAM 1 (Vascular Cell Adhesion Molecules 1) induced by TNF- $\alpha$  at concentrations of 0.22-21.9  $\mu$ M (Lee et al. 2016).

Recently, atranorin and its derivatives were reported as antiviral agents against hepatitis C virus with  $IC_{50}$  10-70  $\mu$ M (Vu et al. 2015). Atranorin was found to inhibit virus penetration in cells like the positive control erlotinib while two hemisynthetic compounds inhibits the viral replication like telaprevir (Vu et al. 2015). Among monoaromatic phenols,

methyl  $\beta$ -orsellinate from *S. alpinum* was reported 5 to 40 times more active as preservative (MIC 0.16-2.74 mM) than *p*-hydroxybenzoate (MIC 2.92-14.58 mM) and chlorocresol (MIC 0.70-2.80 mM) against *Pseudomonas aeruginosa* (Ingólfssdóttir et al. 1985). Methyl haematommate was active as an antifungal (Hickey et al. 1990), 9-cis-octadecenamide from the group of alkamides as anti-inflammatory agent with IC<sub>50</sub> 64.3  $\mu$ M (Ingólfssdóttir et al. 1997).

## **Conclusion**

*Stereocaulon* is a tricky genus to be identified but largely distributed and quite easy to collect as sometimes covering large parts of lands or rocks, particularly in volcanic places. Although partially investigated for phytochemistry, a variety of compounds have been isolated. Some compounds are frequently found and abundant in many species of this genus like atranorin, stictic acid or lobaric acid. Some of them have shown interesting activities but uses in traditional medicines are not fully supported as bioassays are only carried with *in vitro* tests. However, abundance of *Stereocaulon* species in some places combined with high amount of specific compounds offers a unique opportunity to go further in finding and optimizing new drug candidates.

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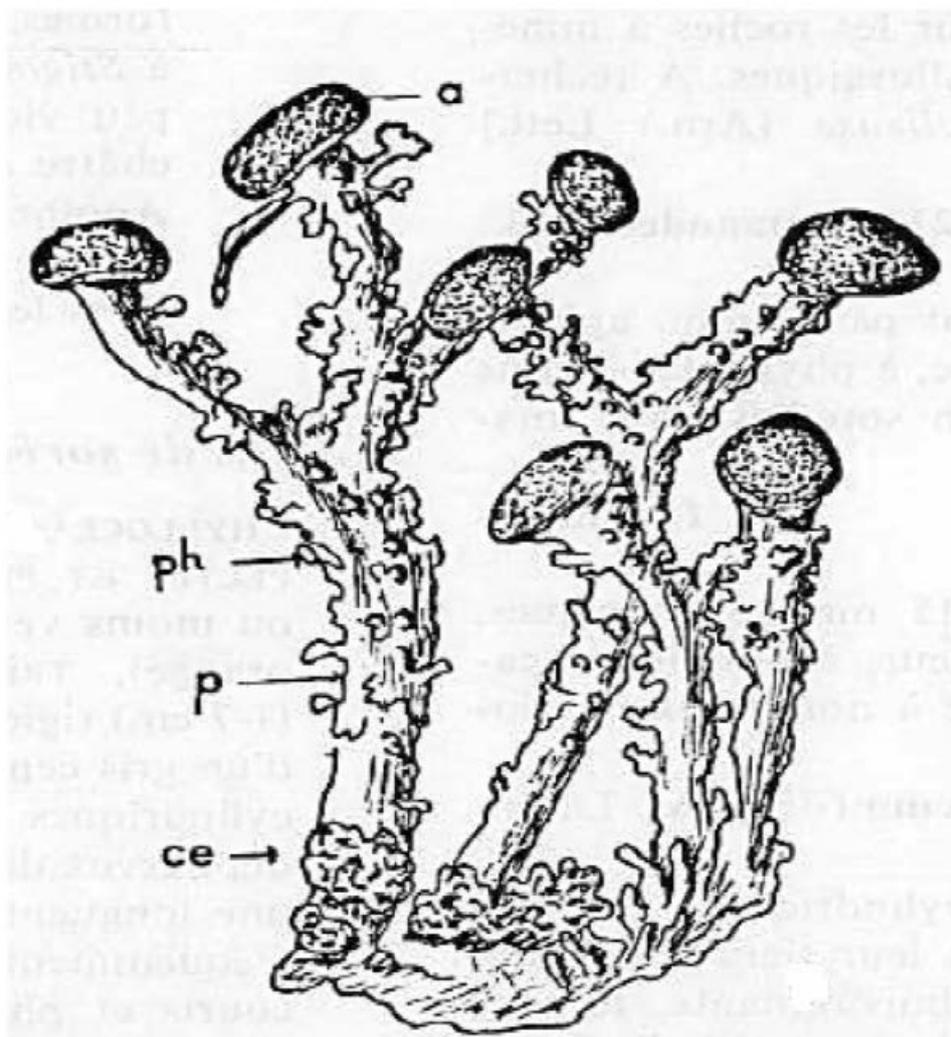
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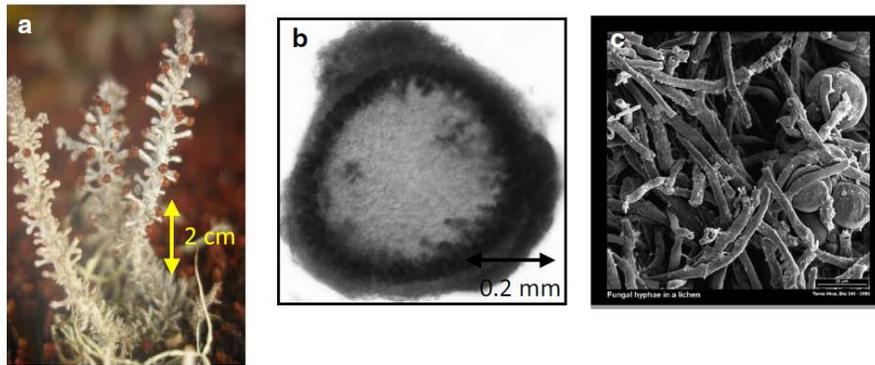
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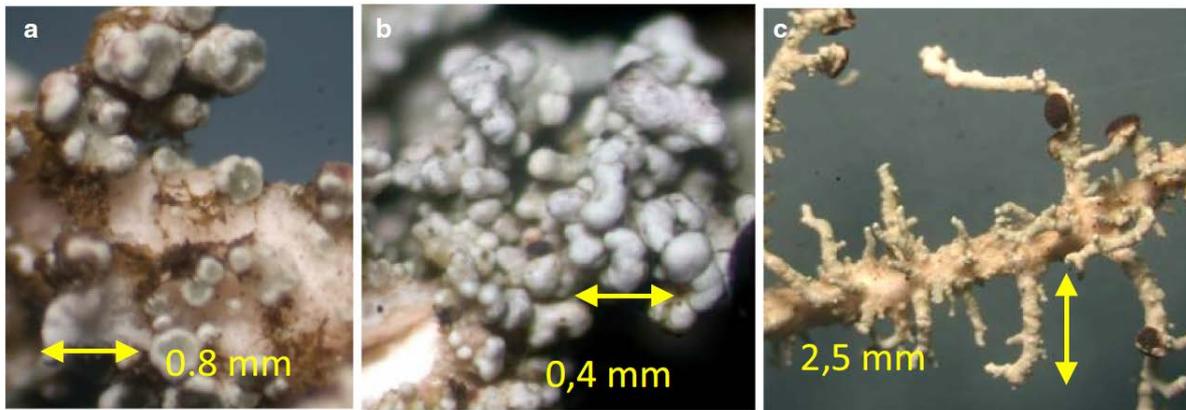
## Figures



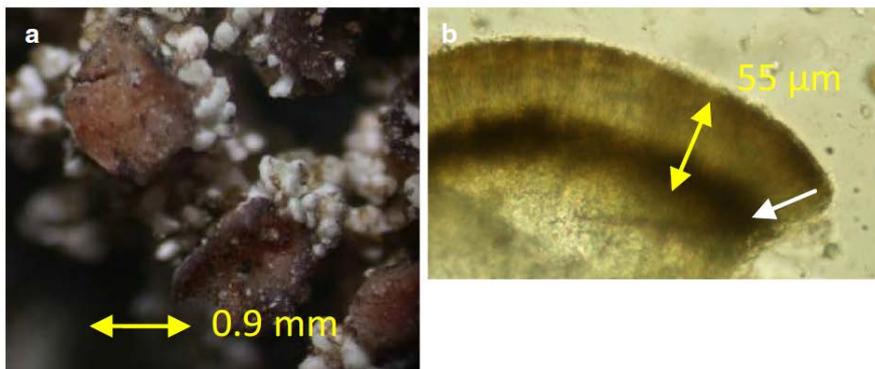
**Fig. 1** General morphology of a *Stereocaulon* (J. Asta). a: apothecia; ph: phyllocladia; p: pseudopodetium; ce: cephalodia



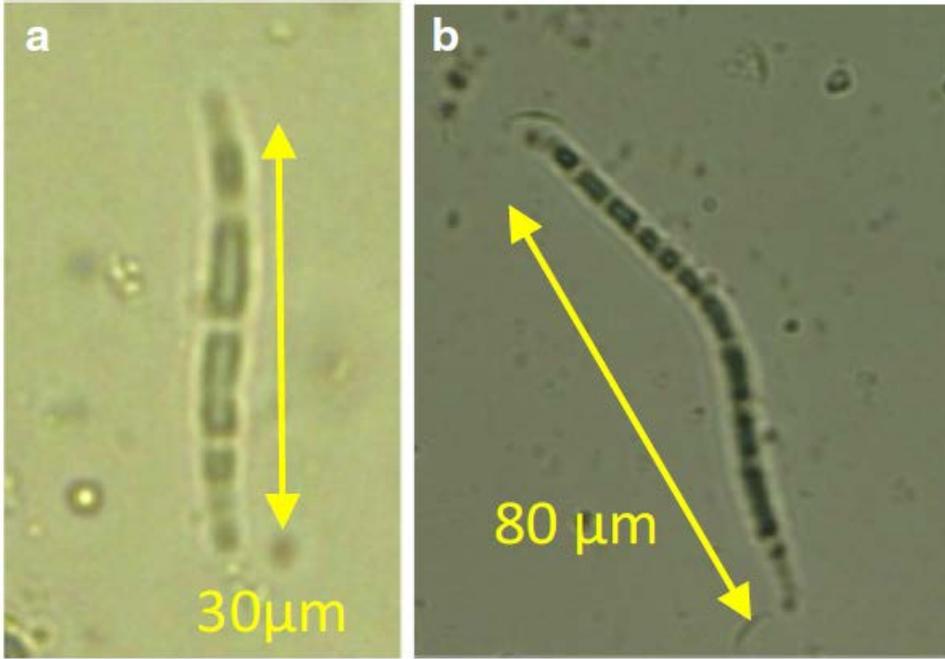
**Fig. 2** Morphology of the pseudopodetium of *Stereocaulon* genus. **a** General morphology, **b** transversal section of the internal structure, **c** internal structure (SEM, X25\_ see supplementary data M1)



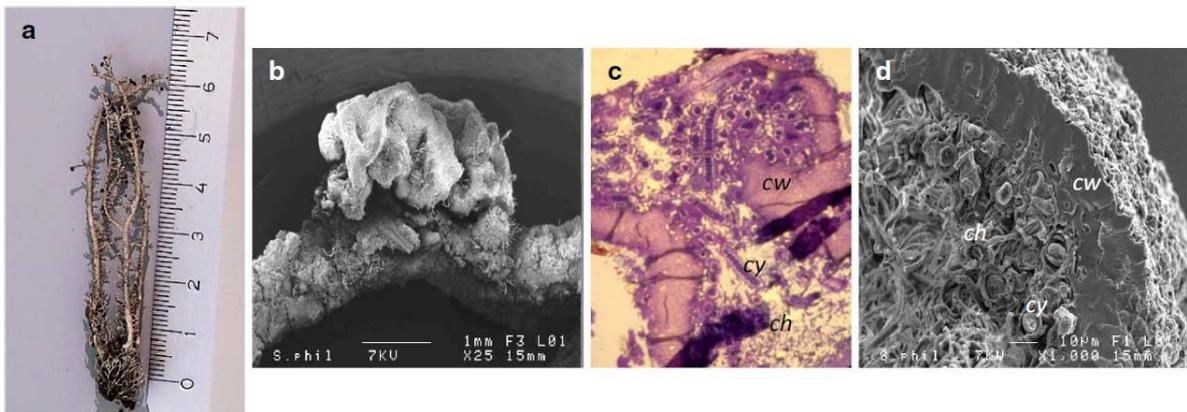
**Fig. 3** Morphology of phyllocladia. **a** Peltate, granuliform, verruciform for *S. vulcani*, **b** corralloid, digitate, papilliform for *S. evolutum*, **c** phyllocladioid branchlets for *S. scutelligerum* (see supplementary data M1)



**Fig. 4** Morphology of apothecia for *S. graminosum*. **a** General aspect, **b** colored hypothecium resulting from a transversal slice of the apothecium underlined by the white arrow (see supplementary data M1)

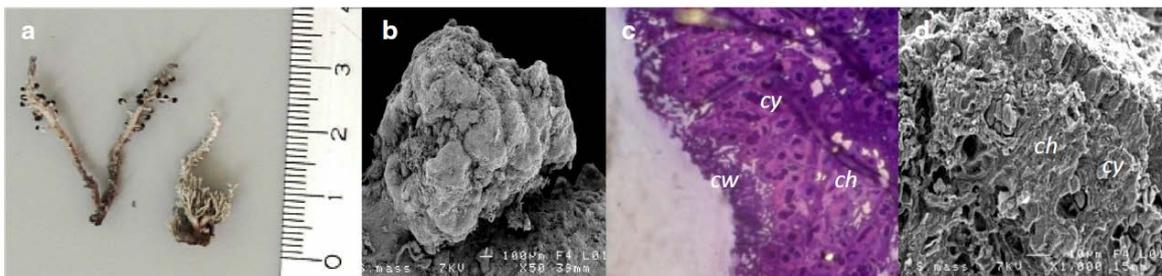


**Fig. 5** Morphology of spores. **a** Fusiform for *S. halei*, **b** vermiform for *S. montagneanum* (see supplementary data M1)



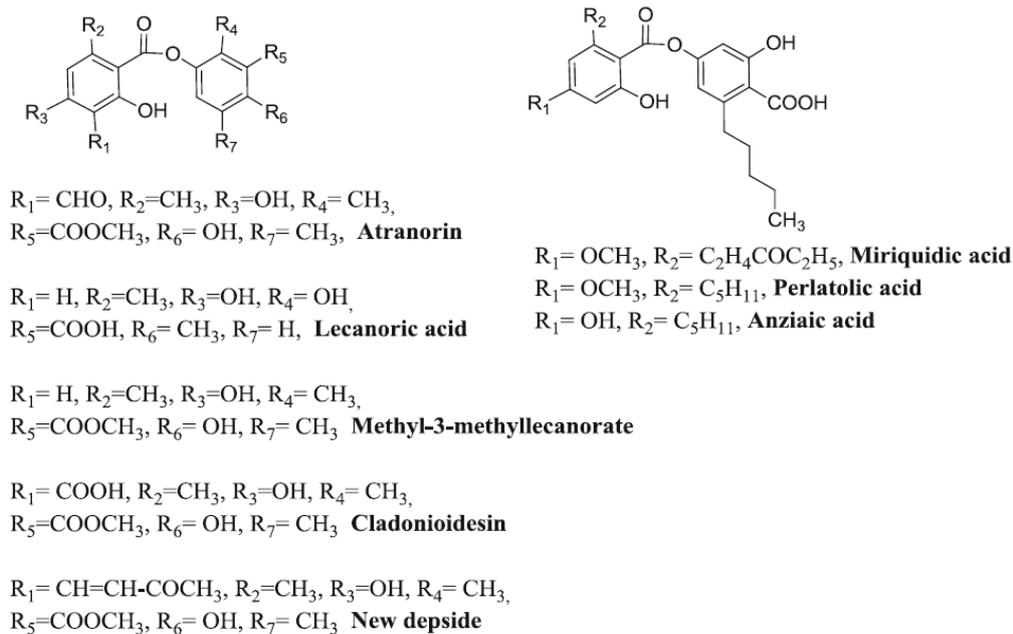
**Fig. 6** *S. montagneanum*. **a** General morphology, **b** detail of an external cephalodium (SEM,  $\times 25$ ) **cd** transversal section of a sacculate cephalodium (light microscopy,  $\times 400$ , HES

coloration and SEM,  $\times 400$ , respectively)—*ch* cephalodial hyphae, *cw* cephalodial wall (cortex), *cy* cyanobacteria (see supplementary data M1)

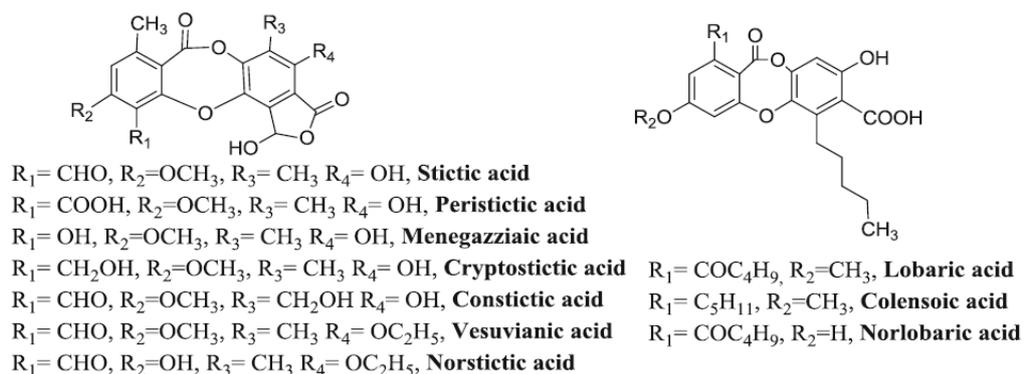


**Fig. 7** *S. halei*. **a** General morphology, **b** detail of an external cephalodium (SEM,  $\times 25$ ) **cd** transversal section of a protosacculate cephalodium (light microscopy,  $\times 400$ , HES coloration

and SEM,  $\times 400$ , respectively)—*ch* cephalodial hyphae, *cw* cephalodial wall (cortex), *cy* cyanobacteria (see supplementary data M1)

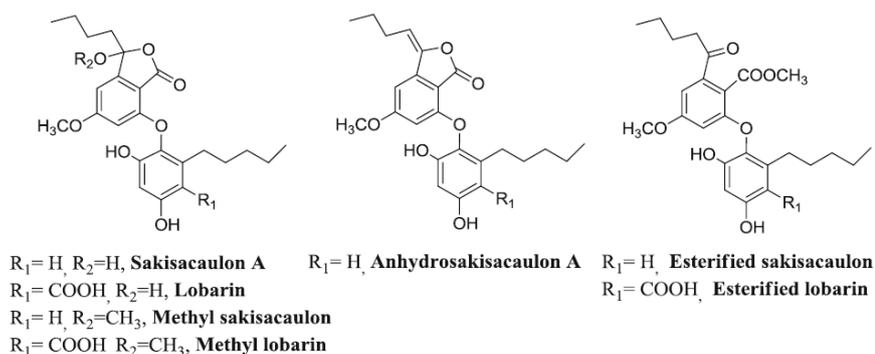


**Fig. 8** Structure of depsides isolated from *Stereocaulon* species

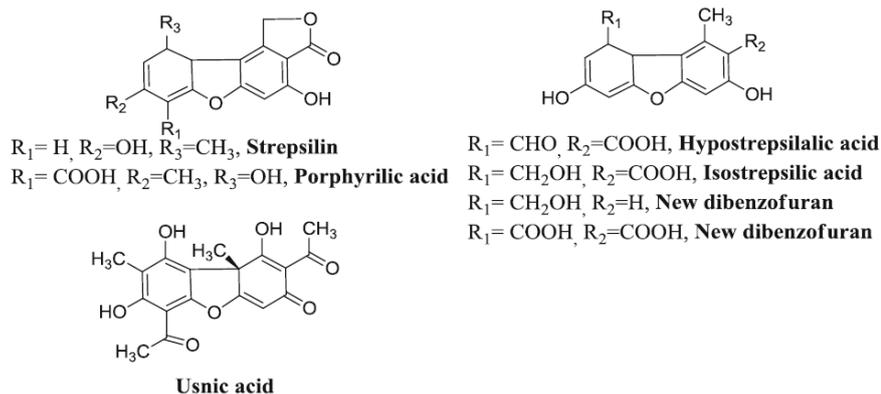


**Fig. 9** Structure of depsidones isolated from *Stereocaulon* species

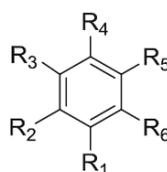
**Fig. 10** Structure of diphenylethers isolated from *Stereocaulon* species



**Fig. 11** Structure of dibenzofurans isolated from *Stereocaulon* species and the related usnic acid

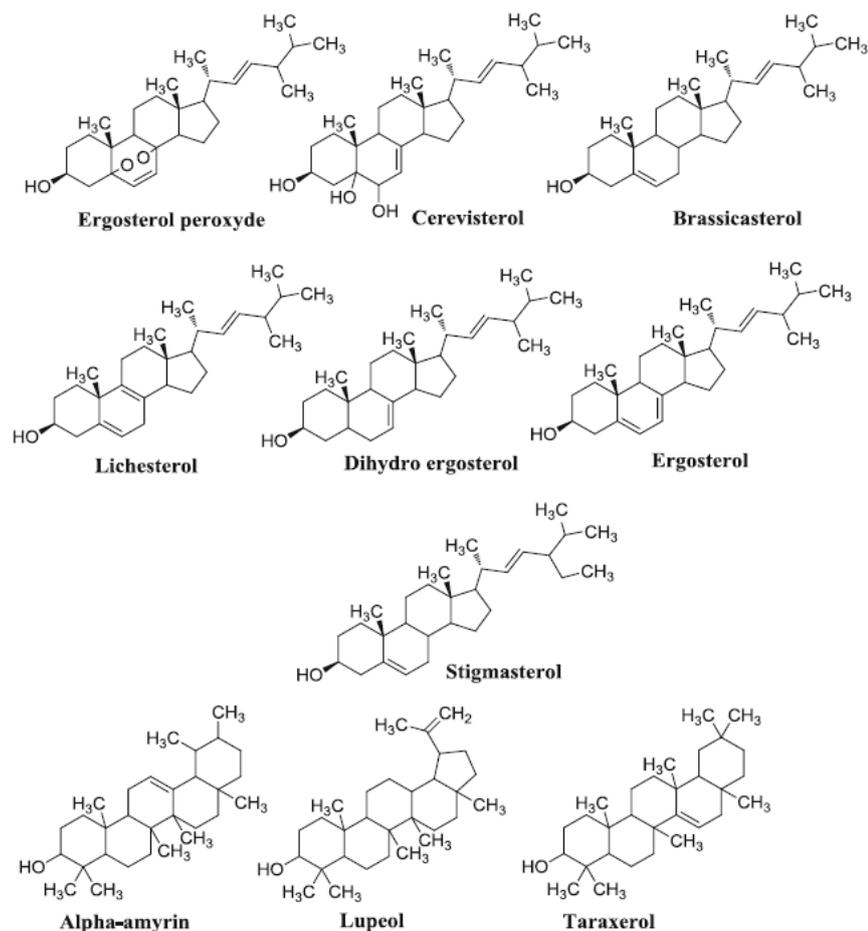


**Fig. 12** Structure of monoaromatic phenols isolated from *Stereocaulon* species

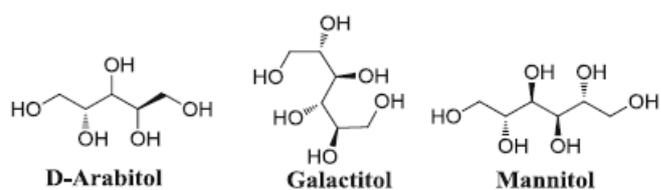
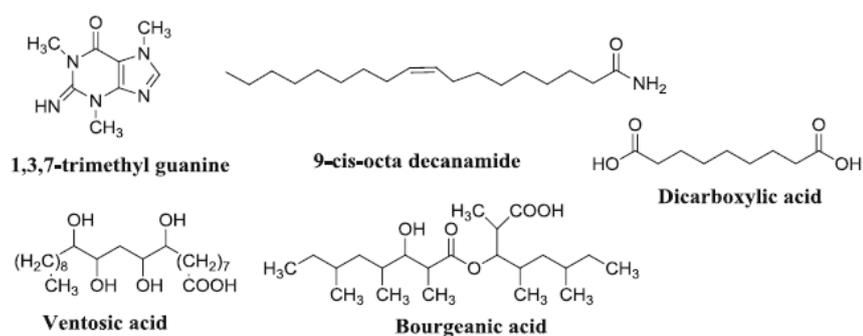


- $R_1 = CHO, R_2 = OH, R_3 = H, R_4 = CH_3, R_5 = COOC_2H_5, R_6 = OH$ , **Ethyl haematommate**  
 $R_1 = COOCH_3, R_2 = OH, R_3 = H, R_4 = OH, R_5 = H, R_6 = CH_3$ , **Methyl Beta-orsellinate**  
 $R_1 = CHO, R_2 = OH, R_3 = OH, R_4 = CH_3, R_5 = H, R_6 = OH$ , **Atranol**  
 $R_1 = COCH_3, R_2 = OCH_3, R_3 = CH_3, R_4 = OH, R_5 = H, R_6 = OH$ , **4,6-dihydroxy,2-methoxy-3-methylacetophenone**  
 $R_1 = COOCH_3, R_2 = OH, R_3 = CH_3, R_4 = OH, R_5 = H, R_6 = CH_3$ , **Methyl Beta-orcinol carboxylate**  
 $R_1 = CHO, R_2 = OH, R_3 = H, R_4 = CH_3, R_5 = COOCH_3, R_6 = OH$ , **Methyl haematommate**

**Fig. 13** Structure of steroids and terpenoids isolated from *Stereocaulon* species



**Fig. 14** Structure of miscellaneous compounds isolated from *Stereocaulon* species



**Fig. 15** Structure of polyols isolated from *Stereocaulon* species

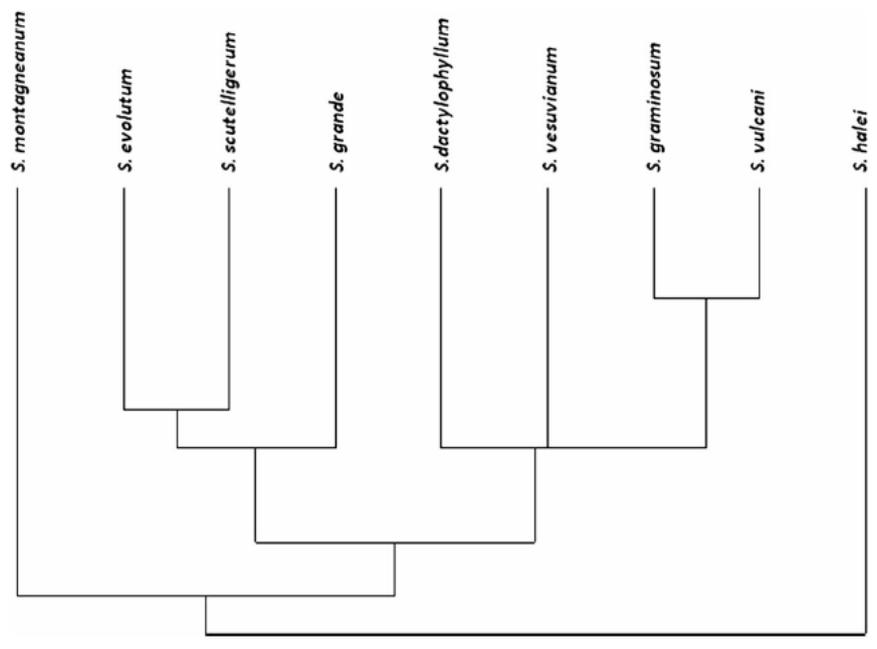


Fig. 16 Dendrogram constructed for the nine methanolic extracts of *Stereocaulon* species obtained from the HPTLC-UV analytical data (Rf) based on Dice similarity, Simple linkage