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Phytochemistry and Pharmacology of the Genus *Tovomita*

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The genus *Tovomita* (Fam. Clusiaceae) comprises 45 species mainly found in tropical regions of Central and South America. Most of the species of the title genus have been used for centuries as natural remedies. Phytochemicals isolated from *Tovomita* spp. include prenylated and unprenylated benzophenones and xanthones. The aim of this review is to examine in detail from a phytochemical and pharmacological point of view what is reported in the past and current literature about the properties of phytopreparations and individual active principles obtained from plants belonging to the *Tovomita* genus.

Keywords: Benzophenones, Clusiaceae, Oxyprenylated secondary metabolites, *Tovomita* spp., Xanthones.

The genus *Tovomita* (order Malpighiales, family Clusiaceae) comprises 45 species, most of which are represented by trees from 2 m to 10 m in height and having a geographical distribution covering the tropical areas of central and south America. Plants belonging to the title genus have leaves usually grouped in branching sympodial clusters, terminal inflorescences bearing few little flowers, fruits represented by succulent pyriform capsules, about 3 cm long, having a green or brown-green exocarp and purple shells inside bearing one or two green seeds with an orange aryl. Most *Tovomita* species have been used for a long time in the ethnomedical folk traditions of indigenous South American populations as hallucinogenic and anti-diarrheal agents [1]. The secondary metabolites isolated from *Tovomita* species include triterpenoids, steroids, xanthones, and benzophenones, the two last two representing the main chemotaxonomic markers of this genus. The aim of this review is to examine from phytochemical and pharmacological perspectives the different *Tovomita* species for which the extraction, isolation, structural characterization, and description of the biological activity of individual compounds and/or phytopreparations are reported in the literature. A substructure search, performed using the SciFinder Scholar database, and searches by keywords in PubMed, Medline, and Scopus, indicated that to date 9 species have been cited in this perspective. For each plant, listed in alphabetical order, a discussion on its phytochemistry and pharmacognosy is provided.

T. brasiliensis (Mart.) Walp. is endemic of the Amazonian rainforest where it is also known by the common names "manguarana" and "taxiubarana". The aqueous extract obtained by infusion of flowers is used to cure diarrhea, and the oil of fruits to treat rheumatism [2]. The first phytochemical study of this plant appeared in the literature in 1982 when Braz Filho and coworkers isolated and structurally characterized from trunk wood extracts 1,5-dihydroxy-6,7-dimethoxyxanthone (**1**), betulinic acid (**2**) and β-sitosterol (**3**) [3].

Eighteen years later Marques and coworkers obtained from root and stem extracts of *T. brasiliensis* two novel dichromeno-xanthones, [1,6-dihydroxy-6',6'-dimethylpyrano(2',3':3,4)-6",6"-dimethylpyrano(2",3":7,8)]xanthone (**4**), and [1,6-dihydroxy-6',6'-dimethylpyrano(2',3':2,3)-6",6"-dimethylpyrano(2",3":7,8)]xanthone (**5**), named respectively brasilixanthone A and brasilixanthone B, along with the already reported betulinic acid (**2**), sitosterol (**3**), friedelin (**6**), stigmasterol (**7**), lupeol (**8**), α- and β-amyrin (**9** and **10**), and lanosta-7,24-dien-3β-ol (**11**) [4]. A further reinvestigation by the same research group of the hexane extract of stems afforded cycloarta-24-en-3β-ol (**12**) as an additional triterpenoid [2].

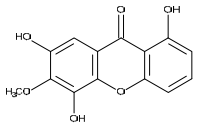
T. brevistaminea Engl. is a tree widely distributed in Brazil, French Guyana, Guyana, Venezuela, and Colombia. The first and up to now only phytochemical and pharmacological report about this plant was reported in 1999 by Seo and coworkers. These authors isolated from the methanol extract of roots two *C*-prenyl chromenoxanthones, namely trapezifolixanthone (**13**) and manglexanthone (**14**), and three *C*-prenyl benzophenones named tovophenones A (**15**), B (**16**), and C (**17**) [5].

These authors evaluated also the *in vitro* cytotoxicity of each isolated compound using the KB (oral epidermoid carcinoma) cell line. In this respect it is interesting to note that all three benzophenones (**15-17**) were found to be only marginally active, recording EC_{50} values ranging from 8.2 to 10 μg/mL, while trapezifolixanthone (**13**) and manglexanthone (**14**) exhibited significant cytotoxic activity, providing EC_{50} values of 4.1 and 1.9 μg/mL respectively.

T. choisyana Planch. & Triana is a small tree mainly growing in Brazil, French Guyana, Guyana, Surinam, Colombia, Peru, and Ecuador. Only two brief reports on this plant appeared in the literature at the beginning of the 1970s when Gabriel and Gottlieb described the isolation from wood extracts and structural characterization of tovoxanthone (**18**), along with betulinic acid (**2**), sitosterol (**3**), and stigmasterol (**7**) [6,7].

T. excelsa Andrade-Lima & G. Mariz is a small tree endemic in Brazil. Only one study has been reported in the literature about this plant in 1984 when De Oliveira and coworkers described the isolation and characterization from trunk wood extracts of betulinic acid (**2**) and 4,8-dihydroxy-7-methoxyxanthone (**19**).

Some years later the exact structure of xanthone **19** was revised by Patnaik and coworkers and corrected to 4,5-dihydroxy-3-methoxy-



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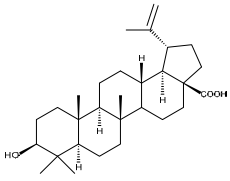

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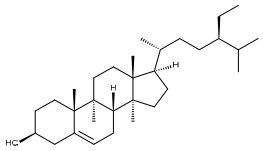

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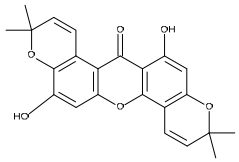

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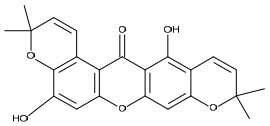

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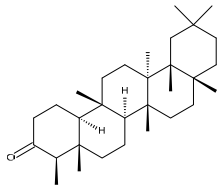

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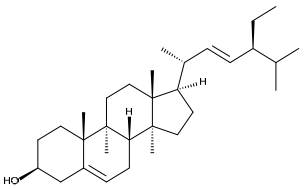

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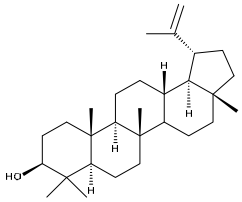

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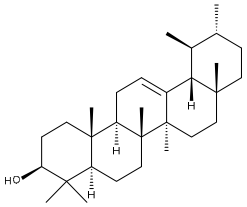

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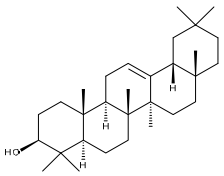

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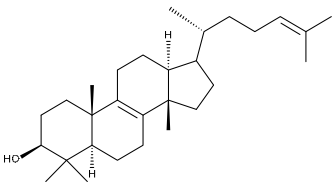

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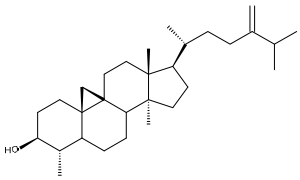

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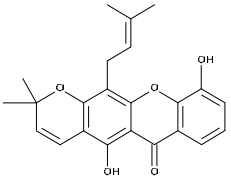

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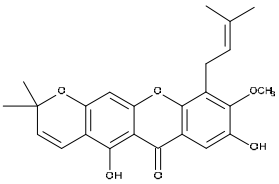

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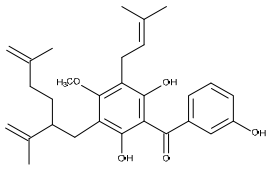

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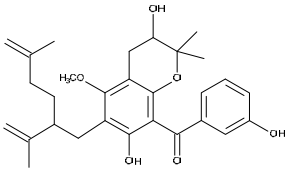

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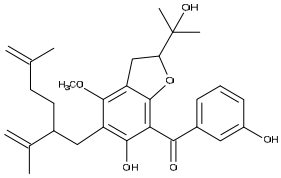

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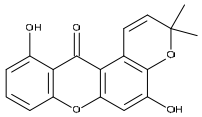

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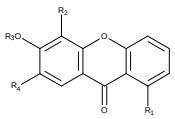

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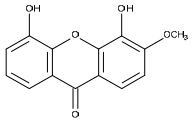
20 $R_1 = OH, R_2 = OCH_3, R_3 = R_4 = H$
21 $R_1 = OCH_3, R_2 = OH, R_3 = R_4 = H$
22 $R_1 = OH, R_2 = H, R_3 = H, R_4 = OH$



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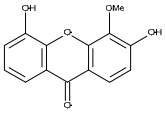

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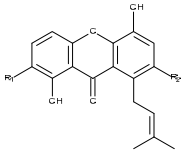
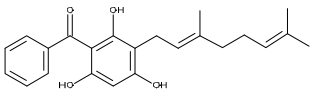


25 $R_1 = R_2 = OH$
26 $R_1 = OH, R_2 = H$
27 $R_1 = H, R_2 = OH$



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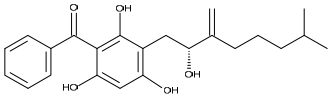

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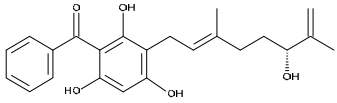

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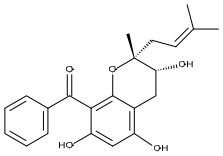

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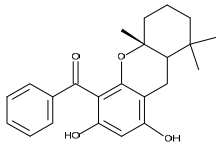

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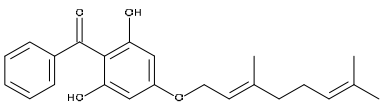

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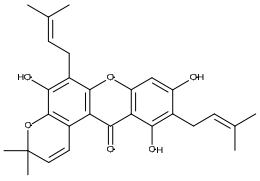

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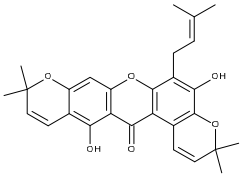

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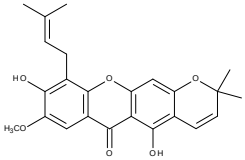

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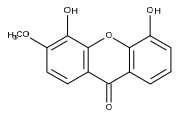

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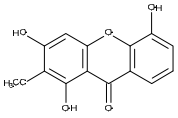

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xanthone (**23**). These authors compared the structure of an authentic sample obtained by chemical synthesis with that of the natural product isolated from trunk wood extracts of *T. excelsa* following the same procedure reported by De Oliveira and coworkers in 1984 [9].

T. krukovii A.C. Smith is a tree widely distributed in Peru, Colombia, and Brazil. The only literature report refers to the isolation from the ethanol extract of the whole plant, structural characterization and anti-*Candida albicans* activity of four xanthones, namely 3,5-dihydroxy-4-methoxyxanthone (**24**), 1,3,5,7-tetrahydroxy-8-isopentenylxanthone (**25**), 1,3,5-trihydroxy-8-isopentenylxanthone (**26**), 1,5,7-trihydroxy-8-isopentenylxanthone (**27**), and 3-geranyl-2,4,6-trihydroxybenzophenone (**28**), along with betulinic acid (**2**)[10]. Some of the isolates were found to have appreciable inhibitory effects against *Candida albicans* secreted aspartic proteases. In particular compounds **25**, **26**, **28**, and **2** recorded IC_{50} values in this respect of 15 µg/mL, 25 µg/mL, 40 µg/mL, and 6.5 µg/mL respectively. Moreover, compound **28** showed an inhibitory activity on the growth of *C. albicans*, *C. neoformans*, *Staphylococcus aureus*, and methicillin resistant *S. aureus*.

T. longifolia (L.C. Rich) Hochr. is a tree typically growing in moist forests of Panama, Guyana, and Brazil. Only one report has been cited in the literature about this plant when in 2006 Pecchio and coworkers provided insights into the isolation from leaf extracts and structural characterization of six benzophenones, namely 3-(2-hydroxy-7-methyl-3-methyleneoct-6-enyl)-2,4,6-trihydroxybenzophenone (**29**), (E)-3-(6-hydroxy-3,7-dimethylocta-2,7-dienyl)-2,4,6-trihydroxybenzophenone (**30**), 8-benzoyl-2-(4-methylpenten-3-yl)chromane-3,5,7-triol (**31**), 5-benzoyl-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene-6,8-diol (**32**), 4-geranyloxy-2,6-dihydroxybenzophenone (**33**), and 3-geranyl-2,4,6-trihydroxybenzophenone (**28**) [11].

By means of bioassay guided fractionation, these authors showed also that compound **32** was the most active one in terms of cytotoxic activity *in vitro* against MCF-7 (human breast cancer) (EC_{50} = 1.8 µg/mL), H-460 (human lung cancer) (EC_{50} = 2.1 µg/mL), and SF-268 (human central nervous system cancer) (EC_{50} = 1.7 µg/mL) cell lines. Good values in terms of growth inhibitory activities were also recorded for compound **31** (MCF-7 EC_{50} = 6.7 µg/mL, H-460 EC_{50} = 7.8 µg/mL, SF-268 EC_{50} = 6.5 µg/mL) and compound **32** (MCF-7 EC_{50} = 4.8 µg/mL, H-460 EC_{50} = 4.4 µg/mL, SF-268 EC_{50} = 2.0 µg/mL). Appreciable antimicrobial effects *in vitro* were shown by compound **31** against *Mycobacterium smegmatis* (MIC = 6.25 µg/mL), *Klebsiella pneumonia* (MIC = 6.25 µg/mL), *Salmonella gallinarum* (MIC = 12.5 µg/mL), and *Pseudomonas aeruginosa* (MIC = 12.5 µg/mL), compound **32** against *M. smegmatis* (MIC = 25.0 µg/mL) and *K. pneumonia* (MIC = 25.0µg/mL), compound **33** against *S. aureus* (MIC = 12.5 µg/mL) and *M. smegmatis* (MIC = 12.5 µg/mL), and finally compound **28**, which was seen to be marginally active only against *M. smegmatis* (MIC = 50.0 µg/mL) [11].

T. macrophylla (Pl. & Tr.) Walp. is a tree growing in Guyana, Brazil, Peru, Colombia, Ecuador, and Panama. Examination of the wood extracts led to the isolation of two prenylated chromenoxanthone named tovophyllin A (**34**) and tovophyllin B (**35**), along with betulinic acid **(2**), sitosterol (**3**), and β-amyrin (**9**) [12].

T. mangle G. Mariz is a tree typically growing in Brazilian rainforests. Root extracts of this plant provided one xanthone, namely mangleanxanthone (**14**), betulinic acid (**2**), and two benzophenones, tovophenone A (**15**) and tovophenone B (**16**) [12, 13].

T. pyrifolium Planch & Triana is a plant widely distributed in the Amazonian regions of Ecuador and Brazil, as well as in Guyana. The only report about this plant appeared in the literature in 1975 when Mesquita and coworkers investigated the chemical composition of wood extracts; they recording the presence of tovophyllin A (**34**) and tovophyllin B (**35**), and of three xanthones named tovopyrifolin A (**36**), B (**37**), and C (**38**) [14].

In Table 1 we have summarized the list of *Tovomita* spp. so far investigated with their main isolated and structurally characterized class of compounds.

Table 1: Summary of the phytochemical composition of *Tovomita* spp.

Spp.	Phytochemicals
T. brasiliensis	Xanthones, Steroids, Triterpenes
T. brevistaminea	Xanthones, Benzophenones
T. choisyana	Xanthones, Steroids, Triterpenes
T. excelsa	Xanthones, Triterpenes
T. krukovii	Xanthones, Benzophenones
T. longifolia	Xanthones, Benzophenones
T. macrophylla	Xanthones, Steroids, Triterpenes
T. mangle	Xanthones, Benzophenones, Triterpenes
T. pyrifolium	Xanthones, Benzophenones

In this review we summarized the natural products isolated from selected plants belonging to the genus *Tovomita* and analysed claims of their pharmacological properties. In most cases a single compound was seen to be the effective pharmacological active agent. It is clear that further phytochemical studies need to be carried out in the near future to provide a more detailed pattern of the natural constituents and of the biologically active principles in extracts and/or phytopreparations. From data collected in this review, it is evident that the genus *Tovomita* comprises therapeutically promising, interesting, and valuable plants, some of which are already used in the ethnomedical traditions of indigenous populations. Considering that only about 20% of the *Tovomita* species have been investigated so far for the isolation and structural characterization of secondary metabolites, and that there are only few studies describing their pharmacological properties, this genus merits more attention in the on-going search for new bioactive principles and lead compounds.

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