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Campomanesia genus – a literature review of nonvolatile secondary metabolites, phytochemistry, popular use, biological activities, and toxicology

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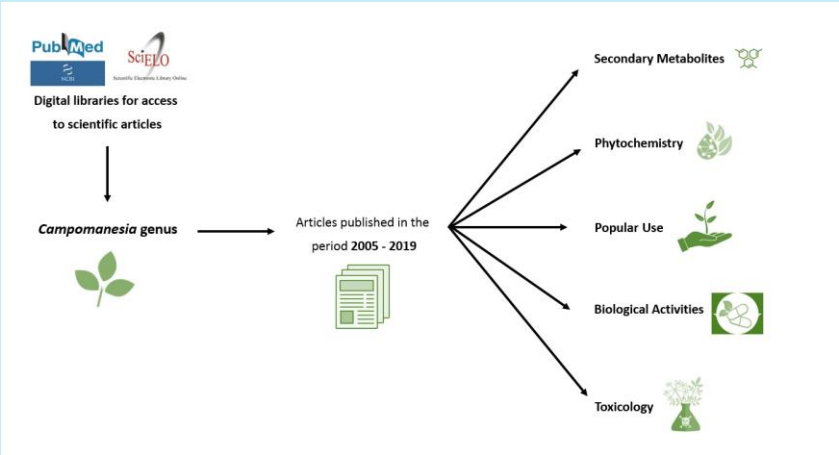
ABSTRACT: The genus *Campomanesia* belongs to the Myrtaceae family and has about 30 species. It is characterized by citrus-flavored fruits. Several articles describe the extensive use of its fruit, such as in the food industry, however, other parts of the plants are also used for food or pharmacological purposes such as the leaves, flowers, seeds, and roots. Analyzing works published on the genus in the period 2005-2019, we observed that the classes of main flavonoid compounds present are anthocyanins, chalcones, coumarins, tannins, and saponins. Species of this genus are also used as a medicine in the treatment of wounds, toothaches, fractures, and bruises. Therapeutic activities have also been detected for *Campomanesia*, such as antimicrobial, antiulcerogenic, antiprotozoal, anti-inflammatory, and antidiarrheal activity, antiproliferative and antioxidant potential, antiplatelet, antithrombotic, and fibrinolytic activities, as well as hypotensive effects. There are a small number of works demonstrating the low toxic potential of plant extracts. Thus, the *Campomanesia* genus presents pharmacological potential to be explored.



CONTENTS

1. Introduction

Plants can be used as sources of alternative substances, including therapeutic resources for human medicines[1]. Mesopotamian documents, dated 2600 BC, show the use of more than 1,000 production plants, including those that are now untreated, colds, parasitic, and inflammation[2]. When we analyze the medicines released between 1981 and 2014, 4% are produced from natural

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products, and 27% are synthetic compounds. However, considering the origin of the other products, 59.1% are semi-synthetic molecules, synthetic drugs with pharmacophoric groups, based on natural product structures, mimicking natural or botanical products[3].

The use of medicinal plants as an alternative or additional therapeutic resources has increased significantly[4]. Although synthetic drugs are usually the first choice of treatment for many diseases, these chemical drugs sometimes have undesirable effects and, consequently, the acceptance of alternative medicines has increased substantially[5]. Also, in some pathologies, resistance is developing to the drugs already used in treatment. These data demonstrate the importance of natural products in drug research, and the development of new medicines, justifying work in this area. The Scielo and PubMed databases were searched, during the period 2005-2019, and the keywords used were: *Campomanesia*, Myrtaceae, "*Campomanesia* and biological activities," "*Campomanesia* and popular use," "*Campomanesia* and toxicology."

The Myrtaceae family comprises 175 genera and 5,970 species, native to all continents of the southern hemisphere[6]. They are divided into shrubs and trees with sebaceous glands in the leaves, lower or semi-inferior ovaries, flowers, usually, with numerous stamens, internal phloem, and traces of xylem vessels[7,8]. The genus *Campomanesia* belongs to the Myrtaceae family and has about 30 species[9]. This genus is characterized by its citrus-flavored fruits[10]. However, although several articles describe the extensive use of the fruit, such as in the food industry, other parts of the plants are also used for food or pharmacological purposes, such as leaves, flowers, seeds, and roots.

The species include: *C. xanthocarpa*, *C. adamantium*, *C. corimbosa*, *C. cambessedean*, *C. pubescens*, *C. guazumifolia*, *C. reitziana*, and *C. lineatifolia*, among others.

2. Secondary metabolites and phytochemistry

A striking feature of the genus *Campomanesia* is the presence of the high content of phenolic compounds, mainly in *Campomanesia adamantium*. Analyzing works published in the period 2005-2019 for the genus, we observed that the main classes of flavonoid compounds present are anthocyanins, chalcones, coumarins, tannins, and saponins. These compounds have in common the biosynthetic pathway derived from phenylpropanoids that contribute to all aspects of plant responses to biotic and abiotic stimuli[11].

However, changes occur in the formation, concentration, and type of secondary metabolites in the various species, which may be influenced by the environmental stress, climate, and soil of each region. For example, fruits of *Campomanesia xanthocarpa* contain a high concentration of phenolic compounds, including chlorogenic acid and ascorbic acid[12] and the leaves contain a large number of saponins, tannins, and terpenes, besides the consistent presence of flavonoids and phenolic compounds, such as gallic acid, quercetin, and chlorogenic acid[13,14].

Campomanesia adamantium is one of the most commonly studied species. It has shown significant therapeutic potential, in addition to the presence of phenolic compounds such as gallic acid, catechins, ellagic acid, and flavonoids[15,16].

Fruits of *Campomanesia pubescens*, when ripe, have a high content of vitamin C and phenolic compounds[17], among them, flavanones and chalcones[18,19].

Few studies describe both the biological activities and compounds of *Campomanesia guazumifolia*. However, a survey by Catelan et al.[20] identified the presence of glycosylated flavonoids: quercetin pentose, quercetin deoxyhexoside, myricetin deoxyhexoside, and quinic acid. The fruits of the *C. reitziana* species contain dimethyl cardamonine as their main active compound[21].

Phytochemical studies with the *C. lineatifolia* species revealed the presence of flavonoids, tannins, catechin, quercitrin, and champanones A, B, and C[22]. A survey by Osorio et al. showed that the beta-tricetones compound contributes to the fruity odor[23].

Campomanesia leaves are rich in volatile oils, which were reviewed by Stefanello *et al.* in 2011, who described geraniol, α-pinene, limonene, linalool, spathulenol, and caryophyllene[24]. The essential oil from *C. guaviroba* was analyzed, and sixteen compounds were identified, of which the largest constituent was myrtenal[25].

3. Popular use

The Myrtaceae family presents a wide variety of fruits, which are consumed throughout the

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Brazilian territory and present characteristics of a considerable amount of acidity through ascorbic acid, minerals, fibers, and monoterpene hydrocarbons. Fruits are used to make liqueurs, juices, and sweets. However, the population uses other parts such as the leaves, seeds, and roots in the form of powders, gums, teas, juices, oils, or different types associated with medicinal use[10,26]. Native species from the Midwest region, such as *Campomanesia*, are used by indigenous peoples as food since they represent a source of vitamins and minerals[27]. However, species of this genus are also used as a medicine in the treatment of wounds, toothaches, fractures, and bruises[28].

From the advances in research directed to natural products, the use of medicinal plants has significantly increased, to provide alternative or additional forms of treatments used in the daily life of the population. *C. xanthocarpa* is an example of this species which is associated with popular and traditional use, as it demonstrates extensive medicinal use: fruit peel infusions for the treatment of productive cough and dysentery, leaf tea for reducing cholesterol and fighting urinary and uterine infections, and the peel can be used to treat cystitis, diarrhea, and hemorrhoids[13,28]. *C. pubescens* is used by the population of Mato Grosso (Brazilian State) as food (jelly, juices, and liqueurs) and also as a medicinal plant due to its purifying, antidiarrheal, and cholesterol-lowering action[29,30]. Infusions of *C. velutina* leaves and branches are popularly used to treat diarrhea and intestinal cramps[31].

4. Biological activities

One of the most commonly studied activities is *in vitro* antioxidant activity. DPPH is the most widely used method, probably because these are quick and cheap chemical tests[32]. This activity is related to the concentration of phenolic compounds present in samples. Antimicrobial activities against anti-inf, fungi, and protozoa are also widely studied[22,33,34].

The biological activities described are listed in Tab. 1, including anti-inflammatory, cytotoxic, antinociceptive, and protective activities of the gastric mucosa. These activities, in most cases, are related to flavonoid activities, which are effective in some cases[35].

C. xanthocarpa has been studied to confirm its popular use in treatment for hypercholesterolemic patients; this species was able to reduce blood levels of TC and LDL[13]. In addition to this effect, it has been shown that this species has important therapeutic activities such as antimicrobial[36], antiulcerogenic[37], antiprotozoal[34], anti-inflammatory[38], and antidiarrheal[39] as well as antioxidant potential[40], antiplatelet, antithrombotic, and fibrinolytic activities[41,42], and, more recently, hypotensive effects[14].

Campomanesia adamantium has the characteristic of being a small tree that produces edible fruits with beneficial effects on health, presenting activities such as antimicrobial[18,27,33,43], antidiarrheal[44], and antiproliferative[45,46]. In addition, its leaves and roots have anti-inflammatory and antinociceptive activities[47].

In the studies conducted with *C. guazumifolia*, the antioxidant activity, antimicrobial activity, and anti-inflammatory potential with low toxicity of leaf infusions of this species were evidenced[20]. Few biological activities are described for *C. reitziana* and *C. lineatifolia*. *C. reitziana* showed antinociceptive and gastroprotective potential, and *C. lineatifolia* demonstrated anti-inflammatory and gastroprotective effects[21,48,49].

5. Toxicology

Currently, plants are used as food, nutraceuticals, phytonutrients, medicinal plants, and herbal medicines, thus representing alternative therapies to existing treatments for various pathologies[28,50]. Despite the widespread use of plants as medicine and functional food, there is often no scientific evidence to support their pharmacological properties and toxic potential[51,52]. It is estimated that only three-quarters of the currently marketed natural products of plant origin have the safety information that enables their proper use[53]. Regarding *Campomanesia*, this scenario is no different. Although these species are widely used as food and medicine in folk medicine, studies on the toxicology of many species are still scarce[54].

A study on the acute and subacute toxicity of ethanolic extract of *C. guazumifolia* leaves, where adult and female rats received the extract orally at different concentrations for 14 and 28 days respectively, showed that the doses used did not produce significant physiological or pathological changes, or mortality, indicating that the LD50 is greater than 2000 mg kg-^{1} [54]. Leaf infusion of the same species was shown to have low toxicity in *in vivo* models of acute and subacute toxicity, with

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no observed clinical signs or changes in hematological, biochemical, or histological parameters, suggesting that the LD50 is above 5000 mg kg^{-1} [20].

A similar study of acute and sub-chronic toxicity using the aqueous extract of *C. velutina* leaves and branches demonstrated different changes in male and female Swiss mice. The extracts at doses of 600 and 1200 mg kg^{-1} showed signs of toxicity such as diarrhea, anemia, changes in the kidneys, brain, and heart, suggesting that the safest dose of the extracts is 300 mg kg^{-1} [31]. The ethanolic extract of *C. pubescens* leaves demonstrated cytotoxic and genotoxic effects through *Allium* strain bioassay, toxic effects were observed in the dividing cell and increased chromosomal alterations[20]. *In vivo* studies with *Wistar* and *Drosophila* melanogaster rats showed that the ethanolic extract obtained from fruits of *C. pubescens* under the experimental conditions used did not demonstrate significant genotoxic or clastogenic effects, indicating that fruit consumption is safe[54].

The aqueous extract and essential oil of *C. xanthocarpa* leaves were also evaluated using the *Allium* strain test, allowing the observation of a genotoxic effect of the samples: mitotic index reduction and chromosomal mutations[55]. The extract of the leaves of this same species, when submitted to acute toxicity test in vivo, showed no signs of toxicity[38]. Hydroalcoholic extract from *C. adamantium* fruits, when subjected to acute and subacute toxicity tests in *Wistar* rats, proved to be safe, as no clinical signs of toxicity were observed[56].

Preclinical toxicity studies of herbal medicines are recommended by international regulatory agencies. In Brazil, the National Health Surveillance Agency (ANVISA) is the body responsible for regulating these products and includes, among its various resolutions, a specific one for toxicity tests, aiming to ensure and evaluate the safety and quality of herbal medicines before they are used by the population[57]. However, toxicity tests with species of the genus *Campomanesia* are still scarce, requiring further studies in this area.

6. Conclusion and future perspectives

Several articles published in recent years demonstrate the importance of the genus *Campomanesia*, not only as food but also, mainly, for its pharmacological potential. In this sense, studies claim that different parts of the plants of this genus present promising results for various biological activities, ranging from antioxidant activity to antiproliferative activity, for example. The secondary metabolism of plants is responsible for the production of compounds that have these biological activities. In the case of the *Campomanesia* genus, phenolic acids and other groups of compounds such as flavonoids, anthocyanins, and tannins stand out. Through these studies, the potential of these species to treat different diseases becomes evident. However, for this genus to be used commercially, a lot of work is needed to produce a finished product. For herbal medicine, studies of the major compounds present, markers, and quantifications of these compounds should be performed. Besides, for the development of allopathic medications, active compounds must be isolated, and the structure identified, as well as analysis of the biological activities. Toxicity tests and possible mechanisms of action are also required. Given this, there is a vast territory to be explored, represented by the genus *Campomanesia*.

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Table 1. Description of the studied species, parts, biological activity found, and identified compounds from the *Campomanesia* genus.

Genus	Part of the plant and extract	Biological Activities	Compounds	Reference
C. adamantium	The ethanolic crude extract of leaves and ethyl acetate and butanol fractions	Antioxidant activity	Isoquercitrin and quercetin	[58]
C. adamantium	Ethyl acetate and aqueous extracts of leaves	Antinociceptive and anti-inflammatory activities	Myricitrin, myricetin, and quercetin	[47]
C. adamantium	Fruit and leaf extracts	Antiproliferative activity in the PC-3 cells	Cardamonin	[45]
C. adamantium	Hydroalcoholic extract of fruit peels	Anti-inflammatory, antihyperalgesic and antidepressant activities	Quercetin, myricetin, 5,7-dihydroxy-6 methylflavanone, 5,7 dihydroxy-8 methylflavanone and 2 '4′-dihydroxy6′-methoxycalcon and in the ethyl acetate fraction of 7-hydroxy-5-methoxy-6 -methylflavanone, 5,7-dihydroxy-6,8-dimethylflavanone, and 2 ', 4'-dihydroxy 3',5'-dimethyl-6'-methoxyicalcone	[56]
C. adamantium	Hydroalcoholic fruit extract	Hepatoprotective activity *in vitro*	Presence of flavonoids	[48]
C. adamantium	Ethanolic extracts of leaves, bark, and seeds	Antifungal Potential	-	[59]
C. adamantium	Aqueous root extract	Antioxidant and antihyperlipidemic	Gallic acid and ellagic acid	[60]
C. adamantium	Peel Extract	Antidiarrheal, cytotoxic, and anti-inflammatory activities	Phenolic compounds	[44]
C. adamantium	Aqueous extract of leaves and roots	Antileukemic activity	di-hexoside/quinic acid, ellagic acid O-pentoside, ellagic acid, O-methyl ellagic acid O-hexoside, ellagic acid O-deoxyhexoside, and O-methyl ellagic acid sulfate, gallic acid, ellagic acid O-hexoside, O-methyl ellagic acid O-deoxyhexoside, and O-dimethyl ellagic acid sulfate	[61]
C. adamantium	Dichloromethane extracts from pulp and fruit peel	Antiproliferative activity	7-hydroxy-5-methoxy6-C-methylflavanone, 5,7-dihydroxy6-C-methylflavanone, 5,7-dimethoxy6-C-methylflavanone, 5,7-dihydroxy-6, 8-C-methylflavanone, 4’,6’-dihydroxy-30-methyl20-methoxy-chalcone, Champanone C, 4’,6’-dihydroxy-30, 5’-dimethyl-2’ -methoxy -chalcone and Champanone D	[46]
C. adamantium	Methanolic bark extract	Potential antiplatelet effect	Phenolic Compounds, Total Flavonoids, Condensed Tannins	[62]
C. guazumifolia	Aqueous extract of the leaves	Anti-inflammatory potential with low toxicity	Quercetin pentose, quercetin deoxyhexoside, myricetin deoxyhexoside, and quinic acid.	[20]
C. lineatifolia	Methanolic seed extract	Antimicrobian activity	Champanone A, Champanone B, and Champanone C.	[22]
C. pubescens	Ethanolic Fruit Extract	Anxiolytic and antidepressant effects	1,2-hydroxy3′-methyl-4′, 6′-dimethoxychalcon and 2, 7-hydroxy5-methoxy-6-methylflavanone, 3, 5-hydroxy-7-methoxy-8-methylflavanone; 4, 2′, 4′-dihydroxy-3′, 5′-dimethyl6′-methoxychalcone; and 5, 2′, 4′-dihydroxy-5′-methyl-6′-methoxychalcona	[63]

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continuation of **Table 1.**				
C. pubescens	Fresh fruit ethanolic extract	Low acute and subchronic toxicity	2-hydroxy3′-methyl-4′, 6′-dimethoxychalcon; 7-hydroxy-5-methoxy-6-methylflavanone; 5-hydroxy-7-ethoxy-8-methylflavanone; 2′, 4′-dihydroxy3′, 5′-dimethyl-6′-methoxychalcone and 2′, 4′-dihydroxy-5′-methyl-6′-methoxychalcone.	[54]
C. pubescens	Ethanolic leaf extract	Antioxidant activity and suggested cytotoxic and genotoxic effects	7-hydroxy-6-methyl-5-methoxyflavanone, 5,7-dihydroxy-6-methylflavanone, 5,7-dihydroxy-8-methylflavanone, 2´,4´-dihydroxy-6´-methoxychalcone, 5,7-dihydroxy-6,8- dimethylflavanone, 2´,4´-dihydroxy-5´-methyl-6´-methoxychalcone and 2´,4´-dihydroxy-3´,5´-dimethyl-6´-methoxychalcone	[64]
C. pubescens	Ethanol extract of fruit pulp	Low toxicity without genotoxic or clastogenic effects.	High levels of flavonoids	[65]
C. velutina	Aqueous extract of leaves and branches	Acute and subchronic toxicity.	Presence of phenolic compounds including flavonoids and tannins	[31]
C. xanthocarpa	Aqueous extract of the leaves	Reduction in weight gain and blood glucose in animals	-	[66]
C. xanthocarpa	Hydroalcoholic extract of the leaves	Antiulcerogenic action and showed no acute toxic effects	Presence of flavonoids, saponins, and tannins	[37]
C. xanthocarpa	Aqueous extract of the leaves	Antiplatelet, antithrombotic, and fibrinolytic activity in mice and also in human blood and mice obtained antithrombotic activity.	Presence of saponins, tannins, and terpenes and a small presence of flavonoids	[41]
C. xanthocarpa	Fruits	Antioxidant activities	Phenolic compounds and ascorbic acid.	[40]
C. xanthocarpa	Aqueous extract	Anti-*Trichomonas vaginalis* activity	-	[34]
C. xanthocarpa	Extract of the leaves	Protective effect on the endothelium	-	[67]
C. xanthocarpa	Aqueous extract of fresh plant	Inhibit biofilm formation and bacterial growth.	-	[68]
C. xanthocarpa	Hydroalcoholic leaf extract	Anti-Inflammatory Activity without toxicity	2 ', 6'-dihydroxy-3'-methyl-4'-methoxychalcone and 2', 4'-dihydroxy-3 ', 5'-dimethyl-6'-methoxychalcone	[38]
C. xanthocarpa	Leaf extract	Antiplatelet Activity	-	[42]
C. xanthocarpa	Aqueous extract of the leaves	Hypotensive effect	Presence of gallic acid, chlorogenic aci, and quercetin, theobromine	[14]
C. xanthocarpa	Fruits	Antioxidant activity	Lutein, Zeaxanthin, β-cryptoxanthin, α-carotene, β-carotene, Lycopene, Thiamine, Riboflavin, Pantothenic Acid, Pyridoxine, Biotin, Vitamin C, Vitamin A	[69]
C. xanthocarpa	Aqueous extract of the leaves	Antioxidant activity, protective effect against DNA in blood cells and reduced LPO levels and increased SOD activity in kidney	Presence of quercetin, rutin, and ellagic, rosmarinic, caffeic, gallic, and chlorogenic acids in the extract.	[70]

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