**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.

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**1. Introduction**

Plants can be used as sources of alternative substances, including therapeutic resources for human medicines¹. Mesopotamian documents, dated 2600 BC, show the use of more than 1,000 production plants, including those that are now untreated, colds, parasitic, and inflammation². When we analyze the medicines released between 1981 and 2014, 4% are produced from natural
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.

The use of medicinal plants as an alternative or additional therapeutic resources has increased significantly. 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. 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. 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. The genus Campomanesia belongs to the Myrtaceae family and has about 30 species. This genus is characterized by its citrus-flavored fruits. 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.

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 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.

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.

Fruits of Campomanesia pubescens, when ripe, have a high content of vitamin C and phenolic compounds, among them, flavanones and chalcones.

Few studies describe both the biological activities and compounds of Campomanesia guazumifolia. However, a survey by Catelan et al. 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.

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

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. The essential oil from C. guaziroba was analyzed, and sixteen compounds were identified, of which the largest constituent was myrtenal.

3. Popular use

The Myrtaceae family presents a wide variety of fruits, which are consumed throughout the
Brazilian territory and present characteristics of a considerable amount of acidity through ascorbic acid, minerals, fibers, and monoterpenic 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. 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. However, species of this genus are also used as a medicine in the treatment of wounds, toothaches, fractures, and bruises.

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. 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. Infusions of C. velutina leaves and branches are popularly used to treat diarrhea and intestinal cramps.

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. 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.

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.

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. In addition to this effect, it has been shown that this species has important therapeutic activities such as antimicrobial, antilucregenic, anti-inflammatory, and antidiarrheal, as well as antioxidant potential, antiplatelet, antithrombotic, and fibrinolytic activities, and, more recently, hypotensive effects.

Campomanesia adamantium has the characteristic of being a small tree that produces edible fruits with beneficial effects on health, presenting activities such as antimicrobial and antioxidant potential, antidiarrheal, and antiproliferative. In addition, its leaves and roots have anti-inflammatory and antinociceptive activities.

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. 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.

5. Toxicology

Currently, plants are used as food, nutraceuticals, phytoneutrients, medicinal plants, and herbal medicines, thus representing alternative therapies to existing treatments for various pathologies. 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. 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.

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. 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. Leaf infusion of the same species was shown to have low toxicity in in vivo models of acute and subacute toxicity, with
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 \textit{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 \textit{C. pubescens} leaves demonstrated cytotoxic and genotoxic effects through \textit{Allium} strain bioassay, toxic effects were observed in the dividing cell and increased chromosomal alterations\(^{30}\). \textit{In vivo} studies with \textit{Wistar} and \textit{Drosophila} melanogaster rats showed that the ethanolic extract obtained from fruits of \textit{C. pubescens} under the experimental conditions used did not demonstrate significant genotoxic or clastogenic effects, indicating that fruit consumption is safe\(^{53}\).

The aqueous extract and essential oil of \textit{C. xanthocarpa} leaves were also evaluated using the \textit{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 \textit{C. adamantium} fruits, when subjected to acute and subacute toxicity tests in \textit{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 \textit{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 \textit{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 \textit{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 \textit{Campomanesia}.
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-methylflavonone, 5,7-dihydroxy-8-methylflavonone and 2′,4′-dihydroxy-6′-methoxychalcon and in the ethyl acetate fraction of 7-hydroxy-5-methoxy-6-methylflavonone, 5,7-dihydroxy-6,8-dimethylflavanone, and 2′,4′-dihydroxy-3′,5′-dimethyl-6-methoxychalcone | [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-hexose, ellagic acid O-deoxyhexose, and O-methyl ellagic acid sulfate, gallic acid, ellagic acid O-hexose, O-methyl ellagic acid O-deoxyhexose, and O-dimethyl ellagic acid sulfate | [61]      |
| *C. adamantium* | Dichloromethane extracts from pulp and fruit peel | Antiproliferative activity                              | 7-hydroxy-5-methoxy-6-C-methylflavanone, 5,7-dihydroxy-6-C-methylflavonone, 5,7-dimethoxy-6-C-methylflavonone, 5,7-dihydroxy-6-C-methylflavonone, 4′,6′-dihydroxy-30-methyl20-methoxy-chalcone, 7-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 deoxyhexose, myricetin deoxyhexose, and quinic acid. | [20]      |
| *C. lineatifolia* | Methanolic seed extract      | Antimicrobial activity                                   | Champanone A, Champanone B, and Champanone C.                             | [22]      |
| *C. pubescens* | Ethanolic Fruit Extract      | Anxiolytic and antidepressant effects                   | 1,2-dihydroxy3′-methyl-4′, 6′-dimethoxychalcon and 2, 7-hydroxy-5-methoxy-6-methylflavonone, 3, 5-hydroxy-7-methoxy-8-methylflavanone, 4, 2′, 4′-dihydroxy-3′, 5′-dimethyl-6′-methoxychalcone; and 5, 2′, 4′-dihydroxy-5′-methyl-6′-methoxychalcona | [63]      |
### 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. |
|------------------|----------------------------------|---------------------------------------|---------------------------------------------------------------------|
| **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-dimethyllflavanone, 2', 4'-dihydroxy-5'-methyl-6'-methoxychalcone and 2', 4'-dihydroxy-3', 5'-dimethyl-6'-methoxychalcone |
| **C. pubescens** | **Ethanol extract of fruit pulp** | **Low toxicity without genotoxic or clastogenic effects.** | High levels of flavonoids |
| **C. velutina** | **Aqueous extract of leaves and branches** | **Acute and subchronic toxicity.** | Presence of phenolic compounds including flavonoids and tannins |
| **C. xanthocarpa** | **Aqueous extract of the leaves** | **Reduction in weight gain and blood glucose in animals** | - |
| **C. xanthocarpa** | **Hydroalcoholic extract of the leaves** | **Antiulcerogenic action and showed no acute toxic effects** | Presence of flavonoids, saponins, and tannins |
| **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 |
| **C. xanthocarpa** | **Fruits** | **Antioxidant activities** | Phenolic compounds and ascorbic acid. |
| **C. xanthocarpa** | **Aqueous extract** | **Anti-Trichomonas vaginalis activity** | - |
| **C. xanthocarpa** | **Extract of the leaves** | **Protective effect on the endothelium** | - |
| **C. xanthocarpa** | **Aqueous extract of fresh plant** | **Inhibit biofilm formation and bacterial growth.** | - |
| **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 |
| **C. xanthocarpa** | **Leaf extract** | **Antiplatelet Activity** | - |
| **C. xanthocarpa** | **Aqueous extract of the leaves** | **Hypotensive effect** | Presence of gallic acid, chlorogenic aci, and quercetin, theobromine |
| **C. xanthocarpa** | **Fruits** | **Antioxidant activity** | Lutein, Zeaxanthin, β-cryptoxanthin, α-carotene, β-carotene, Lycopene, Thiamine, Riboflavin, Pantothenic Acid, Pyridoxine, Biotin, Vitamin C, Vitamin A |
| **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. |
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