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Chemical Constituents and Biological Activities of *Araucaria angustifolia* (Bertol.) O. Kuntze: A Review

Cátia S Branco[1], Tiago S Rodrigues[1], Émilin D Lima[1], Caroline Calloni[1], Gustavo Scola[2] and Mirian Salvador[1]

1 Laboratory of Oxidative Stress and Antioxidants, Biotechnology Institute, University of Caxias do Sul, RS 95070560, Brazil
2 Medical Science Building, Room 4204, 1 King's College Circle, University of Toronto, Toronto, ON M5S 1A8, Canada

Corresponding author: Mirian Salvador

msalvado@ucs.br

Laboratory of Oxidative Stress and Antioxidants, Biotechnology Institute, University of Caxias do Sul, RS 95070560, Brazil.

Tel: +55542182105
Fax: +55542182664

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Abstract

Araucaria angustifolia is a tree that belongs to Araucariaceae family and it is mainly found in Southern Brazil. This plant has a notable therapeutical history in folk medicine holding great socioeconomic and environmental importance. Until now, some studies were conducted to assess its chemical composition, biological and pharmacological properties. The studies have shown that the bark, knot, needles (leaves), seeds and bracts (sterile seeds) contain high concentrations of active compounds and exhibit different biological effects. In the folk medicine the different parts of this plant are used to treat various types of illnesses, such as shingles, respiratory tract infections, sexually transmitted diseases and some types of wounds. Bearing this in mind, this review focuses on all currently chemical and biological effects already reported for *A. angustifolia* and provide a novel perspective and useful information for future research.

Keywords: *Araucaria angustifolia*; Medicinal plant; Chemical compounds; Biological effects

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Introduction

Araucaria is one among three genera that belong to the family Araucariaceae, occupying an isolated position amidst the conifers [1]. The genus Araucaria includes nineteen species and presents the largest geographical range in this family, widespread from South America to Australia and Pacific islands [2]. Although the family Araucariaceae is now restricted to the southern hemisphere [3], fossil evidence shows that it previously occurred also in the northern part of the globe [4]. *Araucaria angustifolia* (Bertol.) O. Kuntze is a subtropical species known popularly as Araucaria or Brazilian pine. Native species can be found in mountain climate throughout southern Brazil, northeastern Argentina and eastern Paraguay [1]. Nowadays, *A. angustifolia* is critically endangered [5] due to long periods of logging for wood and agriculture purposes [1]. The *araucaria* seed, named *pinhão,* is a seasonal product and has great nutritional value being a source of dietary fiber, carbohydrates, proteins and minor nutrients [6-8]. More importantly, they contain higher content of phenolic compounds [9]. In addition to the powerful chemical characterization of the seeds, other parts of the tree are equally important. Studies have reported that the resin (found in the wood and knots), the dead bark (which is naturally discarded by the tree) and the leaves (needles) retain an intriguing chemical composition with dynamic biological activity [10-16]. Our group has importantly contributions regarding *A. angustifolia* biological effects. We reported that bracts (sterile seeds) contain high levels of chemical compounds with important pharmacological actions in several models of study [17-20]. Despite the different extraction conditions employed in distinct studies, phenolic compounds can be regarded as the major constituents in this particular plant. Even though few pharmacological studies have been performed on this plant, there is a notable history of medicinal use by native populations. Infusions of leaves, bark and knots are used to treat anemia, muscle strains, varices, renal and sexually transmitted diseases [21-23]. Moreover, the syrup produced from resin is used

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to treat respiratory tract infections [24], indicating a therapeutic versatility in the empiric uses of *A. angustifolia*. Although the scientific literature about this plant is scarce, the majority of the studies have attempted to identify their chemical constituents and left aside their role in biological systems. Given this, the purpose of this review is to provide an overview of the main chemical compounds found in *A. angustifolia* and its biological activities, bringing evidences as basis for further research.

Botanical characterization

A. angustifolia is a subtropical gymnosperm pertaining to the family Araucariaceae, order Coniferales. This species was described for the first time by Bertoloni in 1820 as *Columbea angustifolia* Bert. After, it was redescribed by Richard Rich as *Araucaria brasiliana* and rectified by Otto Kuntze as *Araucaria angustifolia* (Bert.) Ktze [1]. It occurs as a major species within the Araucaria moist forests favored by altitudes ranging from 500 to 1,500 m [25]. The tree is tolerant to low temperatures [24] and has physiological adaptability to light and shade shifting conditions of the environment [1]. *A. angustifolia* stands out among other arboreal species due to its large and umbelliform canopy **(Figure 1)**. It features a rectilinear, cylindrical trunk that can reach 25 to 50 m height and may range between 1 to 2 m in diameter [26]. The trunk presents a purplish-brown colored, rough outer shell and an inner shell which is resinous and whitish [24]. As time goes by, the outer shell (dead bark) is naturally discarded by the tree, which may live 200 years on average [25]. The young tree is symmetrical, cone shaped, covered with alternate and grouped branches from base to apex, containing dark-green acicular (needle-shaped) leaves that remain attached to the tree for many years and can reach up to 6 cm long and 1 cm wide [1]. *A. angustifolia* is predominantly dioecious [27], *i.e.,* it features male and female specimens that have their own distinct strobili. The female strobili, known as cone, are globular or ovoid, having closely overlapping scales [28] and bracts inserted on a conic central axis **(Figure 2A)**. The male catkins are elongated, cylindrical, dense and covered by scales **(Figure 2B)**, which arrange themselves in a spiral [28]. The scales from the base open to allow the release of pollen and dissemination occurs through wind. Both strobili develop during summer [29].

Figure 1 Photograph of pine *Araucaria angustifolia*. The tree exhibit canopy umbelliform in peculiar shape and large with a rectilinear and cylindrical trunk (photographed by Cátia S. Branco).

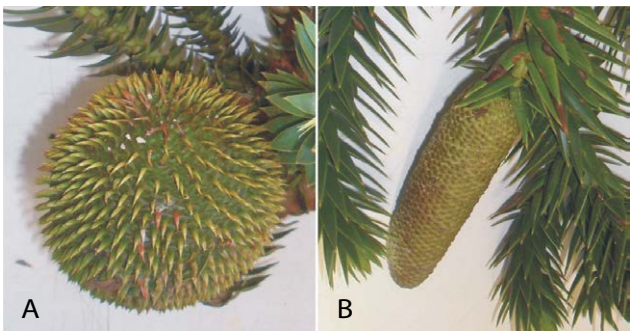

Figure 2 *Araucaria angustifolia* strobili female (A) and male (B) specimens (photographed by Cátia S. Branco).

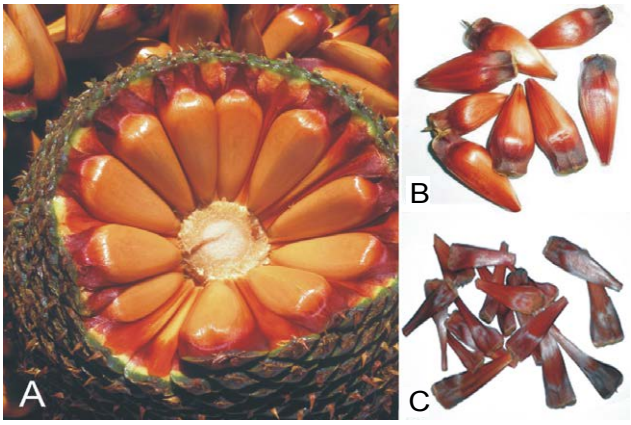

Figure 3 Mature female reproductive structure showing a conic central axis (A), seeds (B), and bracts (C). Photographed by Cátia S. Branco and adapted from Embrapa, Brazil (https://www.embrapa.br/busca-de-imagens/-/midia/685001/pinhas-e-pinhoes).

The fecundated cone **(Figure 3A)** may measure 10 to 25 cm in diameter and weigh up to 4.7 kg, containing more than 1,000 elements [17], including seeds **(Figure 3B)** and bracts **(Figure 3C).** Bracts occurrence is about five times higher than fertile seeds [17]. The reproductive process of species is long. Pollination occurs during September and October and, once fertilized, the cones mature in 2 to 3 years [1,29]. It usually takes 12 to 15 years for a young plant to start producing seeds. These seeds, popularly known as *pinhão,* are dispersed mainly from May to August [1,25]. They exhibit yellowish-brown coloration, encased in a very resistant dark-brown coat along with an internal adherent membrane **(Figure 4)**. Araucaria seeds are fleshy and have ovate-oblong format, ranging from 3 to 8 cm in length and 1 to 2.5 cm in width, weighing approximately 8 g [6,9].

Ethnopharmacology

The medicinal potential of *A. angustifolia* has been initially explored by indigenous populations. Posteriorly, it began to be widely used in different parts of South America for treatment of several illnesses. Different parts of the tree (bark, resin, knots leaves and seeds) are employed in folk medicine, prepared mainly as infusions or tinctures. In respect to the empirical use of *A. angustifolia* bark, there are some reports about the use of

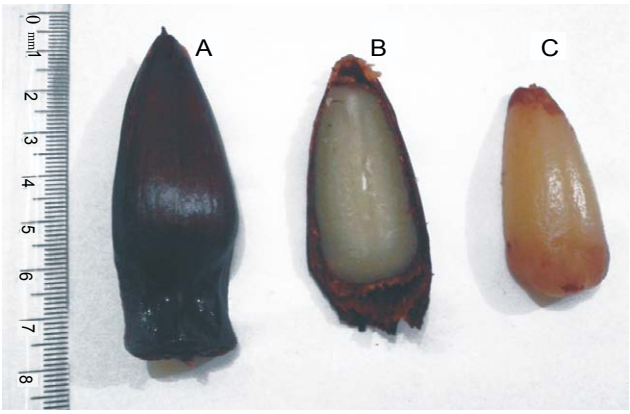

Figure 4 *Araucaria angustifolia* cooked seeds (*pinhão*) showing external coat (A), longitudinal section exhibiting embryo (B) and internal edible portion (C) (Photographed by Cátia S. Branco).

infusions in order to treat topically muscle strains and varices [21]. Besides bark, the knots extracted from old trunk are used orally as infusion for treatment of renal and sexually transmitted diseases [21,22]. Moreover, a syrup produced from bark resin is used to treat respiratory tract infections, mainly bronchitis [24]. *A. angustifolia* leaves are also employed in ethnomedicine. Infusion of leaves (young or senescent) is orally used for the treatment of scrofula, fatigue and anemia, whereas tinctures from them are topically used on dermatological conditions such as dryness skin and wounds [21,22,24]. The leaves are also used to treat herpes disease, since they exhibit important antiviral activity [15]. Araucaria seeds are medically employed in treatment of heartburn, anemia and tumors [22,23].

Nutritional aspects

Apart from the empiric uses of the seeds, they are considered an excellent source of energy and nutrients, due to its constitution of complex carbohydrates [30] especially starch which displays low glycemic index when compared to white bread [6]. Furthermore, it presents low contents of lipids and proteins, being a source of dietary fiber, magnesium and copper **(Table 1)**. Proteins from *araucaria* seeds has nutritional value comparable to legume seeds that contain lysine and histidine as limiting amino acids [31], and may be used also as a complementary source of protein in food formulations [8]. Cooked seeds are reported as food of low glycemic index. This is mainly due to the high content of amylose in the starch that probably contributes to the formation of resistant starch in the seeds after cooking, generating a slow absorption of glucose by the organism [6]. Consumption of foods that present low glycemic response might play an important role in the prevention and treatment of metabolic chronic diseases and their cardiovascular complications, such as dyslipidemia, obesity and diabetes [32].

Chemical Characterization of *A. angustifolia*

Besides carbohydrates and proteins of nutritional interest, *A. angustifolia* is reported to contain important secondary metabolites. The plant is a rich source of polyphenols, besides steroids and terpenoids. A complete overview of the main chemical compounds described in different parts of *A. angustifolia* is shown in **Table 2** and a description of these constituents is given below.

Polyphenols

Polyphenols are structurally characterized by the presence of a benzene ring bound to one or more hydroxyl (-OH) groups [33]. Among the antioxidant compounds that integrate human diet, polyphenols are majority and great quantities of them are found in fruits, vegetables, nuts, cereals, chocolate and beverages including tea, coffee and wine (for review, see Ref. [34]). Regular consumption of polyphenols brings benefits for health specially reducing the risk of developing age-related degenerative diseases. These beneficial effects are associated to their capacity to scavenge oxidatively generated free radicals, such as those derived from lipids and nucleic acids [35,36]. There are a variety of classification systems for polyphenols, though they are generally divided into two major distinguishable classes regarding their basic chemical structure: flavonoids and nonflavonoids [34].

Flavonoids: Flavonoids may be divided into six subclasses: flavonols, flavones, isoflavones, flavanones, anthocyanidins, and flavan-3-ols [34]. The most common flavonoids found in *A. angustifolia* have their chemical structure presented in **(Figure 5).** Catechin **(Figure 5A)** and epicatechin **(Figure 5B)** are flavan-3-ols, the most complex subclass of flavonoids. This subclass ranges from simple monomers to oligomeric and polymeric proanthocyanidins, which are also known as condensed tannins [34,37]. Quercetin **(Figure 5C)** is a flavonol, whereas apigenin **(Figure 5D)** is a flavone. Seccon *et al.* [12] showed that the hydroalcoholic extract from Araucaria dead bark presents a total phenolic content of 64 mg/g of gallic acid equivalents (including 1.85 mg/g of anthocyanin content and 12 mg/g of proanthocyanidin

Table 1 Proximate composition of cooked *Araucaria angustifolia* seeds (*pinhão*).

Composition		Value
Moisture (g/100 g)		50.35 ± 0.71
Starch (g/100 g)		34.48 ± 0.72
Protein (g/100 g)		3.31 ± 0.05
Lipid (g/100 g)		1.26 ± 0.09
Ash (g/100 g)		1.41 ± 0.02
Dietary Fiber (g/100 g)	Soluble	0.55 ± 0.18
	Insoluble	5.17 ± 0.25
Calcium (mg/100 g)		16.0
Potassium (mg/100 g)		727.0
Magnesium (mg/100 g)		53.0
Iron (mg/100 g)		0.80
Zinc (mg/100 g)		0.80
Copper (mg/100 g)		0.18

Adapted from Cordenunsi et al. [6] and Brazilian Food Composition Table [30]

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Table 2 Overview on the chemical constituents identified in different parts of *Araucaria angustifolia.*

Plant Material	Solvent Used	Analysis Method	Compounds Identified	Reference
Bark	Benzene	Chromatography	(+)-pinoresinol dimethyl ether (eudesmine)[P], sitosterol[S] and sugiol[T]	[50]
Bark	Ethanol/water	LC/UV spectrophotometry/ NMR	Benzoic acid[P], *p*-hydroxybenzoic acid[P], protocatechuic acid[P], quercetin[P], (-)-epiafzelechin protocatechuate[P], (-)-epiafzelechin *p*-hydroxybenzoate[P] and (-)-epicatechin[P]	[12]
Bracts	Water	HPLC/UV spectrophotometry	Catechin[P], epicatechin[P] and rutin[P]	[17]
Bracts	Water	HPLC/UV spectrophotometry	Catechin[P], epicatechin[P], quercetin[P] and apigenin[P]	[18]
Bracts	Water	HRMS (MS, MS/MS mode)	Quinic acid, 4'-methoxytectorigenin[P], 3-glucoside-dihydroquercetin[P] and amentoflavone 4',4'',7,7''-tetramethyl ether[P]	[19]
Knot	Benzene	Chromatography/^{13}C NMR	Secoisolariciresinol monomethyl ether[P] and lariciresinol-4-methyl ether[P]	[48]
Knot	Benzene	Chromatography/^{13}C NMR	Pinoresinol[P], secoisolariciresinol[P], lariciresinol[P], isolariciresinol[P] and isolariciresinol-4'-methyl ether[P]	[49]
Leaves	Methanol	HPLC/MS/NMR	Amentoflavone[P], mono-, di-, tri- and tetra-*O*-methylamentoflavone[P] and ginkgetin[P]	[13,14]
Leaves	Ethanol / water	HPLC/TLC/UV spectrophotometry/NMR	Bilobetin[P], II-7-*O*-methyl-robustaflavone[P] and cupressuflavone[P]	[15]
Leaves	Ethanol	GC/MS	B-sitosterol[S], ent-kaurene[T] and phyllocladene[T]	[16]
Leaves (exudate)	Acetone	TLC/CG-MS	*p*-coumaric acid[P], *E* and *Z* communic diterpenic acids[T]	[43]
Propolis	Ethanol	TLC/CG/CG-MS	5,6,7-trihydroxy-3,4'-dimethoxyflavone[P], kaempferid[P], aromadendrine-4'-methyl ether[P], *E* and *Z* 2,2-dymethyl-6-carboxyethenyl-8-prenyl-2H-benzopyranes[P], dihydrocinnamic acid[P], *p*-coumaric acid[P], ferulic acid[P], caffeic acid[P] and di- and triterpenes[T]	[38]
Propolis	Ethanol/water	HPLC/UV spectrophotometry/NMR	Quercetin[P], rutin[P], gallic acid[P], protocatechuic acid[P], chlorogenic acid[P] and its esther derivates, *p*-coumaric acid[P], syringic acid[P], vanillic acid[P], caffeic acid[P] and ferulic acids[P]	[39]
Resin (knot)	Chloroform/methanol	TLC/^{1}H and ^{13}C NMR	Hinokiresinol[P], cryptoresinol[P], secoisolariciresinol[P], isolariciresinol[P], pinoresinol monomethyl ether[P], 2,3-bis-(*p*-hydroxyphenyl)-2-cyclopentene-1-one[P] and 4,4'-dihydroxychalcone[P]	[11]
Resin (wood)	Dichloromethane/ methanol	GC/MS	Lignans[P], 4-hydroxybenzaldehyde[P], hydroquinone[P], *p*-coumaric acid[P], ferruginol diterpene[T]	[10]
Seedling stages	Ethanol	TLC/MS/NMR	*E* and *Z* octadecyl ferulate[P], biflavones[P], benzaldehydes[P] and its derivates, vanillin[P], pinoresinol[P], eudesmin[P], lariciresinol[P], cabreuvine[P], irisolidone[P] and diterpenes[T]	[41]
Seeds	Phosphate-HCl buffer	HPLC	Lectins	[61,62]
Seeds	Methanol	HPLC	Catechin[P] and quercetin[P]	[6]
Seeds	*N*-hexane/water	Chromatography	*N*-acetyl-D-glucosamine-specif lectin	[59]
Seeds	Glycine-HCl buffer	Chromatography	Lectins	[60]
Seeds	ND	Chromatography	Lectins	[65]
Seeds	Ethanol / water	HPLC	Catechin[P], quercetin[P] and gallic acid[P]	[9]
Seeds	Methanol	HPTLC	Flavonoids[P] and proanthocyanidins[P]	[40]
Seeds (coat)	Ethanol / water	Chromatography	Proanthocyanidins[P]	[64]

Analysis Methods: gas chromatography (GC); liquid chromatography (LC); thin layer chromatography (TLC); high performance liquid chromatography (HPLC); high performance thin layer chromatography (HPTLC); high resolution mass spectrometry (HRMS); multiple reaction monitoring mode (MRM); mass spectrometry (MS); nuclear magnetic resonance (NMR); not described (ND).
Compounds Classes: polyphenols[P]; steroids[S]; terpens[T].

content) along with the presence of flavonols, mainly quercetin, besides the flavan-3-ols catechin and epicatechin. Biflavonoids (dimeric flavonoids) were identified in *A. angustifolia* leaves [13-15], besides high amounts of proanthocyanidins [15]. Flavonoids are also found in *A. angustifolia* propolis, which is the resinous substance collected from the tree and processed by bees [38,39], and also in the seeds. Cordenunsi *et al.* [6] described that, in the seed, phenolic compounds can migrate

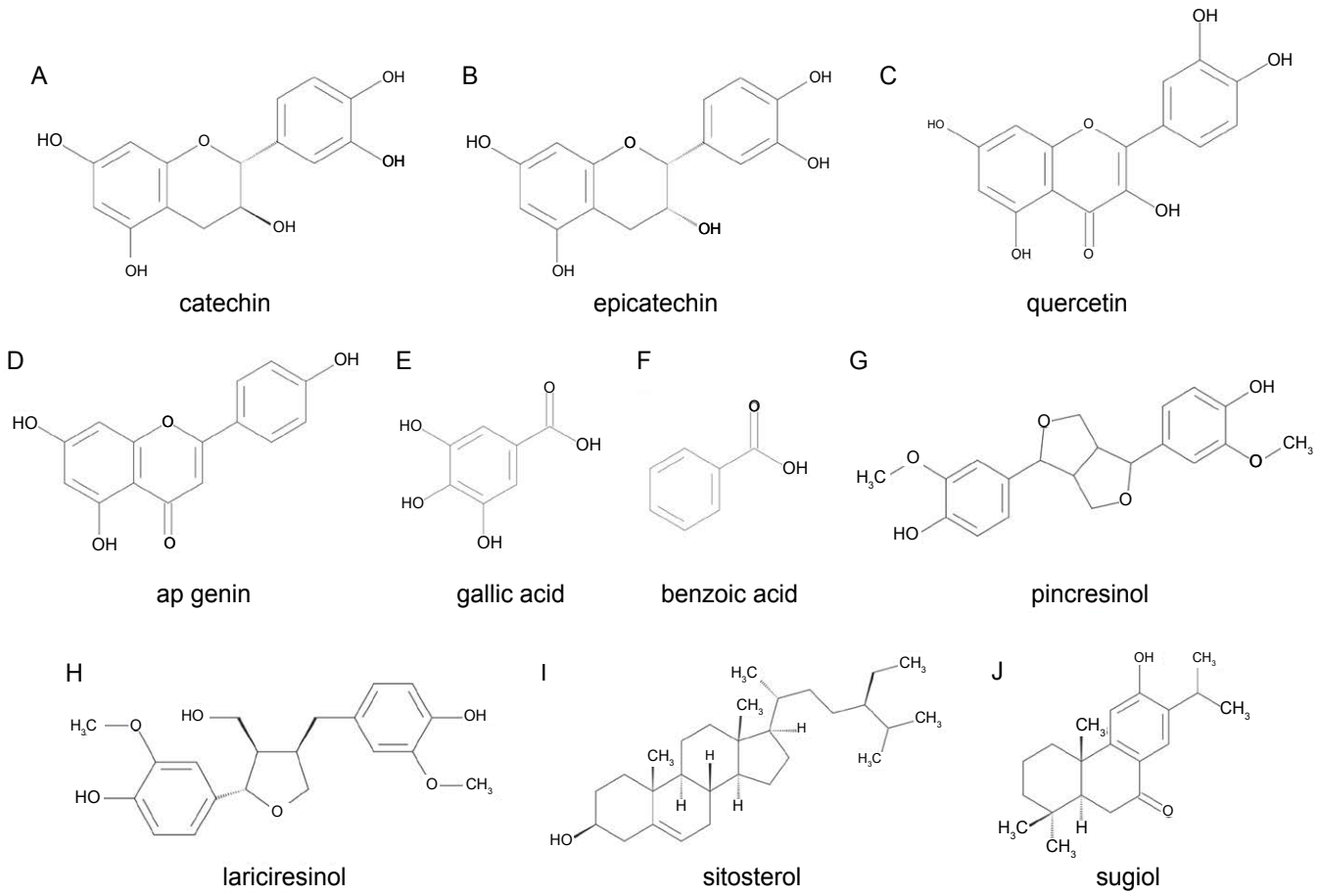

Figure 5 Main chemical compounds found in *Araucaria angustifolia* tree. Images obtained using Symyx Draw 4.0.0 software (Symyx Technologies Inc., Santa Clara, California, USA).

from the internal coat to the pulp during heating process, and therefore significant amounts of catechin and quercetin may be found in cooked seed. Similar results were reported in another study [9], showing differences between extracts obtained from cooked and raw seeds regarding flavonoids (11.89 ± 0.26 µg/mg in cooked seeds and 1.16 ± 0.02 µg/mg in raw seeds extract) and proanthocyanidins (40.70 ± 0.59 µg/mg in cooked seeds and 0.45 ± 0.02 µg/mg in raw seeds extracts) contents. Recently, Mota *et al.* [40] investigated two extracts, one from the external coat and other from the inner seed pulp (endosperm and embryo). Both of them presented proanthocyanidins in its constitution, but the coat extract exhibited around tenfold the concentration of proanthocyanidins compared to inner seed extract (148 versus 10 mg cyanidine chlorohydrate/g extract). Taking into account the high levels of flavonoids found in *araucaria* seeds, our research group has focused on the bracts (sterile seeds), demonstrating that this material is rich in flavan-3-ols, flavonols [17], flavones [18] and biflavonoids [19]. Biflavonoids were also reported by Fonseca *et al.* [41] in tissues samples from *A. angustifolia* at different stages of differentiation and development, showing that seedlings stems, which are source of explants, display a variety of apigenin dimers.

Phenolic acids and their derivatives: Phenolic acids, other important class of polyphenols, can be classified as derivatives of either benzoic acid or cinnamic acid. Benzoic acid derivatives include gallic (3,4,5-trihydroxy-), vanillic (4-hydroxy-3-methoxy-) and protocatechuic (3,4-dihydroxy-) acids, whereas *p*-coumaric (4-hydroxy-), caffeic (3,4-dihydroxy-), and ferulic (4-hydroxy-3-methoxy-) acids are cinnamic acid derivatives. In addition, phenolic acids may originate from hydroxycinnamic acid, such as chlorogenic acid (3-caffeoylquinic acid) [42]. It has been shown that *A. angustifolia* species contain phenolic acids **(Table 2)**, being gallic acid **(Figure 5E)** the most common one. This compound was already detected in the seeds [9] and in the propolis [39], whereas benzoic acid **(Figure 5F)** was identified in the bark [12], and also in the propolis [39]. Exudate from leaves presents *p*-coumaric acid [43], which was also found in the propolis [10] along with dihydrocinnamic, ferulic and caffeic acids [38]. Some other phenolic acids, including protocatechuic acid (9.1 µg/mL) and ester derivatives of chlorogenic acid (7.9 µg/mL), were quantified in *A. angustifolia* propolis along with minor amounts (<1.8 µg/mL) of *p*-coumaric, syringic, vanillic, caffeic and ferulic acids [39].

Lignans: Plant secondary metabolites also include lignans, compounds that present carbon skeletons constructed by the

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oxidative coupling of two or three phenyl propane units and are biosynthesized through the shikimic acid pathway [10,44]. They are classified in five main types: lignans, neolignans, norlignans, hybrid lignans, and oligomeric lignans [45]. These compounds are important components of foods since they occur either freely or in its glycosylated form in plants, mainly wood and resin [46,47]. Some lignans extracted from plants of the genus *Araucaria* have been analyzed, specifically in the species *A. angustifolia* [10,11,41,48-50] and *A. araucana* [51]. Regarding *A. angustifolia*, lignans have been reported mainly in the wood, knots and resin, and the chemical structures of the most representative compounds are shown in **(Figures 5G-5H).** Fonseca *et al.* [48,49] identified different lignans, such as pinoresinol dimethyl ether, secoisolariciresinol, lariciresinol, isolariciresinol, isolariciresinol-4'-methyl ether, secoisolariciresinol monomethyl ether and lariciresinol-4-methyl ether in the knots of *A. angustifolia* dead trees. Presence of lignans including secoisolariciresinols, lariciresinols and pinoresinols were also detected from the knot [11] and wood [10] resins. Other parts of *A. angustifolia*, including seedling stems [41] and trunk bark [50] also contain lignans (pinoresinols, lariciresinols and eudesmin) in its composition.

Steroids and terpenes

Steroids and terpenes are isoprenoids synthesized *via* the mevalonate pathway. They constitute an important group of small secondary metabolites associate with plant signaling. Terpenic compounds, including di- and triterpenes usually accumulate as conjugates with carbohydrates and other macromolecules, mainly as triterpene glycosides [52]. Bankova *et al.* [43] reported the presence of terpenes, specifically diterpenic acids in the exudate from *A. angustifolia* leaves. Diterpenes were also identified in the wood resin [10]. Besides resin, propolis contain terpenic compounds mostly di- and triterpenes [38]. Steroids and terpenoids were also identified in *A. angustifolia* leaves [16] and bark, mainly the steroid sitosterol **(Figure 5I)** and the diterpene sugiol **(Figure 5J)** [50]. Isoprenoids are synthesized during different stages of plant development. Fonseca *et al.* [41] detected diterpenes from the seedling to roots of *A. angustifolia.*

Biological Activities

Despite its traditional uses as medicinal product, there are few studies aiming to elucidate the pharmacological potential of the different parts *A. angustifolia* tree. Major studies regarding the diverse biological activities are summarized in **Table 3.**

Antioxidant activity

Antioxidant activity is the most reported biological action for *A. angustifolia*. The antioxidant defense system controls the levels of reactive oxygen species (ROS) promoting useful molecular functions minimizing oxidative damage [35]. Taking into account that the misbalance of the antioxidant system lead to the generation of oxidative stress and this disturbance exerts a critical role in aging chronic degenerative diseases and cancer, natural products rich in antioxidants may be considered as health-promoting bioactive agents [53-55]. Corroborating with this evidence, several reports showed that *A. angustifolia* exerts antioxidant effects in different study models **(Table 3)**. An extract from araucaria dead bark demonstrated cytoprotective effects in mouse L929 fibroblasts against oxidative stress induced by hydrogen peroxide (H_2O_2). In a dose-responsive manner, the highest concentration of 1 mg/mL was able to increase cellular protection by 131% [12]. The compound catechin isolated from the bark was able to protect against lipid peroxidation induced by UV radiation (IC_{50} 18 ± 4 µM) and ascorbyl radical (IC_{50} 6 ± 0.25 µM) exposure in rat liver treated microsomes [12]. In a similar way, our group previously reported that an extract obtained from *A. angustifolia* bracts displayed antioxidant effects against ROS-induced oxidative stress in *Saccharomyces cerevisiae.* The concentration of 0.15% avoided cytotoxic effects induced by H_2O_2 and, the concentrations of 0.05, 0.10 and 0.15% exhibited non-mutagenic and antimutagenic activities in the same model. These effects were attributed to the antioxidant capacity of phenolic compounds, which could be responsible for neutralizing H_2O_2 avoiding hydroxyl radical formation, therefore preventing DNA damage [17]. Our group also reported that the bracts extract presented antioxidant and antigenotoxic activities in MRC5 human lung fibroblast cells. In this study, the aqueous extract from araucaria bracts (25 and 50 µg/mL) significantly protected MRC5 cells against H_2O_2-induced cytotoxicity and oxidative damage to lipids, proteins and DNA [18]. Additionally, the bracts extract was able to avoid depletion of superoxide dismutase and catalase activities [18]. Yamaguchi *et al.* [13] reported that a biflavonoid fraction obtained from extract of *A. angustifolia* leaves was effective to protect plasmid DNA against single strand break induced by either singlet oxygen or Fenton reaction at concentrations of 20 to 100 µM. The antioxidant effect of this extract was also evaluated in calf thymus DNA and the biflavonoid fraction was capable of preventing formation of cyclobutane thymine dimer (at concentrations of 0.5 to 2.0 mg) and 8-oxo-7,8-dihydro-2'-deoxyguanosine (at concentrations of 100 and 500 µM), avoiding oxidation of nucleotides [14].

Antiproliferative and cytotoxic activities

There are few studies in the scientific literature regarding the potential anticancer effects of *A. angustifolia*. Búfalo *et al.* [38] reported cytotoxic effects of araucaria propolis on human laryngeal epidermoid carcinoma (HEp-2) cells. In this study, it was observed cytotoxic effects induced by propolis in a dose (5, 10, 25, 50 and 100 µg/well) and time (6, 24, 48 and 72 h) dependent manner against HEp-2 cells *in vitro*. Moreover, changes in cell morphology were observed, including lysis and disorganization of the cellular monolayer. In another study, Meneghelli *et al.* [39] reported the effects of *A. angustifolia* propolis on viability, proliferation, cell migration, capillary tube formation, and angiogenesis using *in vitro* and *in vivo* models. Hydroalcoholic extract of propolis was able to decrease viability in 24 (IC_{50} 297 µg/mL) and 72 (IC_{50} 130 µg/mL) hours, proliferation (at doses of 130 to 180 µg/mL for 72 h) and tubulogenesis (at doses of 150 to 200 µg/mL for 24 h) on human endothelial cells. Furthermore, the angiogenesis and vasculogenesis processes, also evaluated in this study, were inhibited using chorioallantoic and yolk-sac membranes from chick embryos (450 mg propolis.kg^{-1}), indicating that *A. angustifolia* propolis is a potential therapeutic agent for angiogenic diseases, such as cancer. Recently, our group

Table 3 Overview on the biological effects of *Araucaria angustifolia*.

Plant Material	Study Model	Biological Effects	Reference
Bark	*In vivo* (L929 mouse fibroblasts and rat liver microsomes)	Antioxidant activity against H_2O_2-induced oxidative stress; prevention of microsome lipid peroxidation	[12]
Bracts	*In vivo* (cells of *Saccharomyces cerevisae*)	Antioxidant and antimutagenic activities against H_2O_2	[17]
Bracts	*In vitro* (MRC5 human lung fibroblast cells)	Antioxidant and antigenotoxic activities against H_2O_2	[18]
Bracts	*In vivo* (velvetbean caterpillar *Anticarsia gemmatalis*)	Entomotoxic; pro-oxidant and genotoxic activities	[20]
Bracts	*In vitro* (human larynx Hep-2 cancer cells)	Antitumor and pro-apoptotic activities; induction of mitochondrial dysfunction; genotoxicity	[19]
Leaves	*In vitro* (*Escherichia coli* HB 101 / plasmid pBluescript PUC19	Effective to quench singlet oxygen ($^1O_2$); DNA protection against single strand break	[13]
Leaves	*In vitro* (Calf thymus DNA)	Protection against UV-induced thymine dimmers formation	[14]
Leaves	*In vitro* (Herpes Simplex Virus type 1)	Antiviral activity	[15]
Leaves	*In vitro* (*Lactuca sativa* seeds)	Allelopathic activity	[16]
Leaves (exudate)	*In vitro* (*Staphylococcus aureus* and *Candida albicans*)	Antibacterial action but no antifungal effect	[43]
Propolis	*In vitro* (human larynx Hep-2 cancer cells)	Cytotoxicity	[38]
Propolis	*In vitro* and *in vivo* (human endothelial cells and chick embryos)	Antiproliferative, antitubulogenic and antiangiogenic activities	[39]
Seeds	*In vivo* (human volunteers)	Low glycemic response	[6]
Seeds	*In vitro* and *in vivo* (*X. axonopodis* pv. *passiflorae*, *C. michiganensis* subsp. *Michiganensis*, rats and rabbits)	Antibacterial activity against Gram-positive and –negative; anti-inflammatory and hemagglutinating activities	[59]
Seeds	*In vivo* (Swiss and Wistar rats)	Anti- and pro-edematogenic actions	[60]
Seeds	*In vivo* (Swiss rats)	Depressant activity in the central nervous system	[65]
Seeds (coat)	*In vitro* and *in vivo* (human and porcine α-amylase and rats)	Inhibition of human salivary and porcine pancreatic α-amylase; reduction in post-prandial glycemic levels in rats	[64]

demonstrated that the aqueous extract from *A. angustifolia* bracts present selective antiproliferative effects (IC_{50} 250 µg/mL for 24 h) mediated by mitochondrial dysfunction and apoptosis activation on human larynx HEp-2 cancer cells. The inhibition of cell proliferation was accompanied by pro-oxidant effects, including oxidative damage to lipids and proteins, nitric oxide production, along with depletion of superoxide dismutase and catalase antioxidant activities at concentrations (100, 250 and 500 µg/mL). The bracts extract also generated genotoxic and apoptotic effects, as well as inhibition on complex I of the mitochondrial electron transport chain and reduction on ATP production, indicating the potential of bioactive compounds from *A. angustifolia* bracts on the modulation of mitochondrial function on cancer cells [19,56].

Allelopathic and entomotoxic activities

Plants produce and store high levels of secondary metabolites that are subsequently released into the environment, which may affect other plants or animals [57]. Plants also present entomotoxic actions against insect-pests, showing an important potential to be explored mainly due to the emergence of insects resistant to chemical insecticides and to the rise of organic agriculture [58]. There are only two studies in the scientific literature exploring the allelopathic and entomotoxic potentials of araucaria. In a study conducted by Braine *et al.* [16], it was showed that the extract from *A. angustifolia* leaves (187.5 and 250 mg) presents allelopathic potential on germination and growth of *Lactuca sativa* seeds, and the main allelochemical compounds identified in the ethanolic extract were *ent*-kaurene and phyllocladene. This allelopathic potential seems to serve *A. angustifolia* on the successional dynamics of Araucaria Moist Forests. Our group has investigated the entomotoxic effect of an aqueous extract obtained from bracts of *A. angustifolia* on the velvetbean caterpillar *Anticarsia gemmatalis* (Lepidoptera: Erebidae) [20]. This extract, rich in phenolic compounds, was able to increase the number of malformed pupae (0.15, 1.5 and 7.5 mg), along with a decrease in the emergence of the insects (1.5 and 7.5 mg), and these effects were related with the lipid, protein and DNA damage detected in the larvae *via* oxidative stress.

Antiviral and antibacterial activities

In traditional medicine *A. angustifolia* has been used for treatment of infectious diseases caused by pathogenic agents. The antiviral activity of araucaria was showed in a study conducted by Freitas *et al.* [15] with Herpes simplex virus type 1 (HSV-1) model. HSV is a double-stranded DNA enveloped virus, extremely widespread in human populations and responsible for a broad range of human infectious diseases, such as gingivo-stomatitis, genital diseases and encephalitis. The crude hydroethanolic extract (HE) obtained from *A. angustifolia* leaves and some different fractions of this extract were able to induce virucidal activity against HSV-1, exhibiting antiherpetic potential (IC_{50} 32.10 ± 3.65 µg/mL for HE). This effect was associated with the content of biflavonoids and proanthocyanidins present in the leaves.

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Antibacterial potential of *A. angustifolia* was investigated in a few studies. Santi-Gadelha *et al.* [59] prepared an aqueous extract from *araucaria* seeds and then purified and characterized a lectin (N-acetyl-D-glucosamine-specific lectin) with antibacterial activity (150 µg/mL) against Gram-negative (*Xanthomonas axonopodis pv. passiflorae*) and Gram-positive (*Clavibacter michiganensis* subsp. Michiganensis) strains at doses of 150 µg/mL. Bankova *et al.* [43] also reported the antibacterial action of leaves exudate (0.4 mg of extract) against strains of the pathogen *Staphylococcus aureus*, which is a major causing agent of nosocomial and community-acquired infections.

5.5 Anti-inflammatory and antiedematogenic activities

Chemical compounds from plants are able to exhibit anti-inflammatory and antiedematogenic activities. It has been shown that *A. angustifolia* seeds may modulate acute inflammation process *in vivo*. Santi-Gadelha *et al.* [59] elucidate the mechanism involved in the anti-inflammatory effect of a lectin (N-acetyl-D-glucosamine-specific lectin) from aqueous extract of *A. angustifolia* seeds in rats. The inflammation was induced in a paw edema model by subcutaneous injection of carrageenan, which is able to release several inflammatory mediators, including biogenic amines, prostaglandins, and nitric oxide. Intravenous injection of lectin (0.01, 0.1 and 1 mg/kg) prior carrageenan reduced paw edema inhibiting the cellular event of acute inflammation *via* carbohydrate site interaction [59]. In another study, Mota *et al.* [60] have described the effects of a lectin (N-acetyl-glucosamine-ligant) from *A. angustifolia* seeds in the same model of paw edema in rats, and the anti-inflammatory and pro-edematogenic actions were evaluated. Intravenous injection of lectin (0.1 and 1 mg/kg) inhibited the dextran-induced edema and vascular permeability, which were prevented by association of the lectin with its binding sugar N-acetyl-glucosamine. Lectin also inhibited edema induced by serotonin. The mechanism associated with anti-inflammatory and pro-edematogenic actions appears to be involved in a common pathway to activation or inhibition of inflammatory mediators from resident mast cells [60].

Actions on metabolism and central nervous system

Amongst the different parts of *A. angustifolia*, the seed has been reported as having effects on modulation of energetic metabolism and central nervous system. Araucaria seeds are rich in lectins [61,62], an important group of glycoproteins widely studied. Lectins are able to induce different actions in various biological systems, including cell agglutination and glycoconjugate precipitation, once they recognize and bind to carbohydrates or other substances derived from sugars [63]. The effect of *A. angustifolia* seeds consumption on the glycemic metabolism was studied for the first time by Cordenunsi *et al.* [6]. The analysis of the carbohydrate availability evaluated in a short-term assay (two weeks) in humans showed that the glycemic responses produced by seeds cooked with the coat were 23% lower when compared to white bread. This result is important because foods that present a low glycemic index are linked to the beneficial effects on preventing and controling chronic non-infectious diseases. In a recent study, Silva *et al.* [64] also investigated the effects of a seed coat extract on glycemic levels of rats and activity of α-amylases (human salivary and porcine pancreatic). The seeds coat extract (250 mg/kg), rich in proanthocyanidins, was effective in diminishing the post-prandial glycemic levels in rats after starch administration. Moreover, the extract was able to inhibit both human salivary (range up to 80 µg/mL) and porcine pancreatic (range up to 50 µg/mL) α-amylases, indicating that araucaria seeds present potential to be used in therapeutic interventions aiming to suppress postprandial hyperglycemia in diabetic patients. The effects of araucaria lectins on central nervous system were investigated in an animal model of epilepsy [65]. Lectin was isolated and purified from *A. angustifolia* seeds, and then dissolved in saline before administration to rats. Seizures were induced with pentylenetetrazol, pilocarpine and strychnine and were monitored during 1 hour. The behavioral profile (locomotor activity) was also evaluated. Lectin (10 mg/kg) increased latency to convulsions and latency to death in both the pentylenetetrazol- and strychnine-induced seizures; however it was not able to protect in the pilocarpine model. In addition, lectin (0.1, 1 and 10 mg/kg) was able to reduce locomotor activity, showing depressant effect similar to the drug diazepam. These effects were attributed to the capacity of lectin from *araucaria* seeds to modulate GABAergic and glycinergic systems.

Conclusions and Future Prospects

This is the first work that has summarized the relevant literature concerning the chemical constituents, biological activities and ethnobotanical aspects of the conifer *A. angustifolia*, an important plant with a long tradition of medicinal and nutritional uses in South America. This review provides many contributions for the natural products research area, since they show the beneficial effects performed by the chemical compounds existent in this plant for prevention and treatment of some human pathologies. Considering the social and ecological importance of *A. angustifolia*, it is essential that conservation programs must be performed and constantly updated. Moreover, it is also important to improve researches involving the development of pharmaceutical products using residual parts of the plant, since the use of bracts, dead barks and needles would not compromise *A. angustifolia* reminiscent populations nor human and animal feed.

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