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Chemicaland Pharmacological Contributions of *Platymiscium* ("Jacarandá") Species

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Abstract
The present work had as objective the identification which species belonging to the genus *Platymiscium* were studied chemical and pharmacologically until now. The collection of these data was obtained using "*Platymiscium*" as keyword on the scifinder database. After data analyses showed the chemical study only of four species. It was to observed, the incisive presence of flavonoids. Coumarins have also been shown to be the second important class of natural products in this genus. Different biological assays were described in the literature involving extracts or compounds isolated from this genus. According to the data collected in this study, it is suggested the necessity of a careful chemical study involving extracts of *Platymiscium floribundum* varieties, to confirm the current botanical classification proposed. Therefore, this review will present a detailed description of studies performed with species of *Platymiscium* from the chemical and pharmacological points of view, aiming to help further researches in this area.

Keywords: *Platymiscium*, flavonoids, coumarins, biological activities

1. Introduction
Fabaceae family is considered one of the largest botanical families in the world, consisting of about 727 genera, 19,325 species and 36 tribes. It is distributed in three subfamilies: Papilionoideae (Faboideae), *Caesalpinioideae* and Mimosoideae [1]. Species belonging to the genus *Platymiscium* (Fabaceae) are mainly found in Neotropical region, covering all of Central America, southern Mexico, South Florida, all islands of the Caribbean and South America. It is composed of nineteen species: *Platymiscium speciosum*, *P. stipulare*, *P. floribundum*, *P. trinitatis*, *P. filipes*, *P. hebestachyum*, *P. trifoliolatum*, *P. pinnatum*, *P. pinnatum* var. *diadelphum*, *P. dimorphandrum*, *P. lasiocarpum*, *P. albertinae*, *P. parviflorum*, *P. calyptratum*, *P. yucatanum*, *P. curuense* and *P. pubescens*, *P. gracile* and *P. jejunum* [2]. Among these species, *Platymiscium floribundum* stands out, which is easily recognized by the straight, angulated and unarmed branches. According to klitgaard (2005) recent taxonomic revision of the genus, there are four varieties based on geographical distribution, habitat and size of the flowers, being *Platymiscium floribundum* var. *floribundum*, var. *latifolium* (Benth.) Benth. var. *nitens* (Vogel) Klitgaard and var. *obtusifolium* (Harms) Klitgaard [2]. The species *P. praecox* Benth. And *P. blanchetii* Benth. Were renamed as *P. floribundum* Vogel var. *floribundum* [2].
The plants produce an enormous structural and chemical variety of natural compounds which are responsible for their biological functions and/or as phytoalexins to defend against predators [3]. Until now, natural products remain the best source of new drugs [4]. The family Fabaceae is known by the presence of flavonoids. This class is found throughout the plant kingdom, whereas isoflavonoids are more restricted in the Papilionoideae subfamily. The literature reports a variety of biological activities of isoflavones such as estrogenic, antiangiogenic, antioxidant, chemoprevention of osteoporosis, prevention of other postmenopausal disorders, cardiovascular disease, anti-gastritis, anticancer, antidiabetic and anti-HIV activities [5, 9]. In this sense, the chemical and pharmacological studies are important strategies to the search of new drugs to the world health. The present work aims to carry out a bibliographical review using Scifinder as database. The keyword utilized was *Platymiscium* and the selection of works was based on the chemical and pharmacological studies.

2. Photochemistry
From the chemical point of view, the most studied species to date are: *P. yucatanum* [10], *P. praecox*, currently recognized as *P. floribundum* Vogel var. *floribundum -P. trinitatis* [12, 13], *P. floribundum* [14, 15] and *Platymiscium floribundum* var. *latifolium* (Benth.) Benth. [16]. The studies of the most different plant organs showed the incisive presence of flavonoids and coumarins in the extracts.

Ten different classes of flavonoids were observed, being chalcone, hydroxychalcone, flavone, flavanone, flavanonol, isoflavone, isoflavanone, flavonol, pterocarpan and biflavonoid. It was observed the predominant occurrence of pterocarpans and isoflavonoids. According to the number of metabolites present in each species, *P. floribundum* is the most studied from the chemical point of view. *P. floribundum*, besides being the most studied species until the present moment, shows a great variety of classes of natural products. In addition to the different classes of flavonoids, it also has rare classes such as biflavonoid and isoflavonequinone. Another important class of natural products representative in the genus is coumarins. Next, some details of the main results found in the literature for each *Platymiscium* species will be presented.

2.1 *Platymiscium floribundum* Vogel

The phytochemical study of ethanolic, hexanic, dichloromethane and petroleum ether extracts from leaves, stem (sapwood and bark), seeds and roots of *P. floribundum* performed by Falcão *et al*. (2005); Feitosa (1999); Militão *et al*. (2005); Militão *et al*. (2006); Pereira-Junior *et al*. (2012); Veloso *et al*. (2012) and Vila-Nova *et al*. (2013) showed the isolation showed the isolation of 6*H*-benzofuro[3,2-*c*][1] benzopyran,6a,11a-dihydro-2,3,9-trimethoxy, (6a*R*,11a*R*), (-)-homopterocarpin (3,9-dimethoxypterocarpan), (-)-3-hydroxy-9-methoxypterocarpan, (6a*R*,11a*R*)-vesticarpan, 6*H*-benzofuro [3,2- *c*] [1] benzopyran-1,2-diol,6a,11a-dihydro-9-methoxy-, (6a*R*,11a*R*)-, 6*H*-benzofuro[3,2- *c*] [1]benzopyran-3,4,10-triol,6a, 11a-dihydro-9-methoxy-, (6a*S*,11a*S*)-, (+)- homopterocarpin, (+)-medicarpin, (+)-2,3,9-trimethoxypterocarpan, 6*H*-benzofuro [3,2-*c*][1]benzopyran-3,4-diol,6a,11a-dihydro-9-methoxy-,(6a*S*,11a*S*)-,(+)-3,10-dihydro-9- methoxy pterocarpan, 4-hydroxymedicarpin, (6a*R*,11a*R*)-3,8-dihydroxy-9- methoxy pterocarpan, 2,3,9-trimethoxypterocarpan, 3,4-dihydroxy-9-methxypterocarpan (vesticarpan); chalcone 2',4',4-trihydroxychalcone; hydroxychalcone 1-propanone, 1-(2,4- dihydroxyfenil)-3-hydroxy-3-(4-methoxyphenyl)-, (-)-, 7,3',5'-trihydroxyflavanone, (±) - liquiritigenin,4*H*-1-benzopyran-4-one,2,3-dihydro-7-hydroxy-3-(3-hydroxy-5- methoxyphenil) -8-methoxy-, calicosine, 3- (2-hydroxy-4-methoxyphenyl) -6-methoxy-7- [6-methoxy-3-(4-methoxyphenyl) -4-oxo-4*H*-1-benzopyran-7-il]oxy]-4*H*-1-benzopyran-4-one,7-hydroxy-6,4'-dimethoxy isoflavonaquinone, coumarin (1,2-benzopyrone), scoparone, 8-hydroxy-6,7-dimethoxy-2*H*-1-benzopyran-2-one (fraxidin), 6,7,8- trimethoxycoumarin, 7,8-dimethoxy-6-hydroxycoumarin, 2*H*-1-Benzopyran-2-one,8- hydroxy-5,6,7-trimethoxy-, annonacinone, corossolone, β-sitosterol, stigmasterol, 3-*O*- acetyl eritrodiol, 5-alyl-1,2,3-trimethoxy-benzene (elemicin), 3,4-dimethoxycinnamaldehyde, D-manose, acetylglucosamine, diphenyl blue (6CI) [14, 20]. The pterocarpan (+)-medicarpin showed the antituberculosis activity against *Mycobacterium tuberculosis* H37Rv with MIC values of 50 µg/mL [23]. This compound showed phytotoxic effect on the *Medicago sativa* seed germination [24]. According to [24] the coumarin 8-hydroxy-6,7-dimethoxy-2*H*-1-benzopyran-2-one (fraxidin) showed antitumoral and antioxidant activities [25].

2.1.2 *Platymiscium floribundum* var. *latifolium*

According to the chemical study of the hexanic and dichloromethane extracts of *P. floribundum* var. *latifolium* performed by Sannomiya (2001), the following substances were isolated: afrormosin, 7-*O*-methylafrormosin, 6,7,8,4'-tetramethoxy-isoflavone, 7,8,4'-trimethoxy-isoflavone, 7,4'-di-*O*-methyldaidzein, formononetin, odoratin, scoparone, tomentin, 5,6,7-trimethoxycoumarin, isoscopoletin, β-amyrin, lupeol, methyl olean-12-en-3β-acethoxy-28-oate, mixtures of fatty acid methyl esters, triglyceride, methyl *trans*-3,4-dimethoxycinnamate, methyl *cis*-3,4-dimethoxycinnamate and methyl *trans*- ferulate [16].

2.1.3 *Platymiscium floribundum* var. *floribundum* previously recognized as *Platymiscium praecox* Mart.

According to Ahluwalia & Kumar (1977) and Braga de Oliveira (1970; 1972), the following compounds were isolated from the ethanolic extracts of *P. praecox*: coumarins 1,2-benzopyrone, scoparone, 7-hydroxy-4,8-dimethoxy-5-methylcoumarin, 4-O- demethyl-8-methoxycoumarin, 2-H-1-benzopyran-2-one, 4,7,8-trihydroxy-5-methyl-, 4,7,8-trimethoxy-5-methylcoumarin, 4,7-dihydroxy-8-methoxy-5-methylcoumarin, 7- hydroxy-4-methoxy-5-methylcoumarin, 7-*O*-glucosyloxy-4-methoxy-5-methylcoumarin), 7-hydroxy-4-methoxy-5-methylcoumarin acetate, 7-*O*-glucosyloxy-4-methoxy-5- methylcoumarin tetraacetate, 2-H-1-benzopyran-2-one, 4-(acetyloxy) -5-methyl-7 - [(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl) oxy] -, 7-hydroxy-4-methoxy-5-methylcoumarin and 7-*O*-glucosyloxy-4-methoxy-5-methylcoumarin; the chalcones 2',4',4-trihydroxychalcone and isoliquiritigenin; flavanones (±) -liquiritigenin, (+)-7- hydroxy flavanone, (2S, 3S)-3,7-dihydroxyflavanone diacetate and (-)-7- hydroxy flavanone; flavonols 7-hydroxyflavonol and 4',7-dihydroxyflavonol; isoflavone 6,7-dihydroxy-4'-methoxy-isoflavone; (2S-trans) - (9CI), (+) - 3,7-dihydroxy-2-phenyl-dihydroxyflavanone, 1- (2-hydroxy-3,4-dimethoxy-6-methylphenyl) ethanone, 3,4- dihydroxyflavone triacetate and other compounds, such as diatol, 1-(2-hydroxy-3,4-dimethoxy-6-methylphenyl) ethanone, 4,5-trihydroxytoluene, dicarboximethane, methyl 3,5-diacetoxy-4-methoxybenzoate, 3,5-dihydroxy-4-methoxytoluene, 1,3-benzenediol, 5-hydroxymethyl) -2-methoxy-, benzene, 2-methoxy-5-methyl-1,3-bis (phenylmethoxy) and chlorophenylmethane [11, 26, 27].

Some of these compounds isolated from *Platymiscium floribundum* var. *floribundum* showed important biological activities such as scoparone, which showed an important gastroprotective effect on gastric lesion induced by HCl/ethanol in rats [28]. This coumarin shows action against *Leishmania infantum* chagasi promastigote and amastigote forms and inhibits AchE [29]. The liquiritigenin has recognized action on the treatment of menopausal symptoms, and estrogen-dependent disorders [30]. The useful action in the prevention and treatment of liver diseases of liquiritigenin was registered by Kim *et al*. (2008) [31]. The isoliquiritigenin is a potential chemopreventive tumor treatment in China [32].

2.2 *Platymiscium yucatanum* Standley

According to Reyes-Chilpa *et al*. (1998) from hexane, methanolic, methylene chloride and acetone extracts from the *P. yucatanum* nucleus pterocarpans (-) - homopterocarpin (3,9-dimethoxypyrocarpan), (+)-medicarpin, (+)-3-hydroxy-9-methoxy- pterocarpan [(+)-medicarpan] and (+)-3,9-dimethoxy-pterocarpan [(+)- homopterocarpan]); flavanone (±)-liquiritigenin; chalcones 1-(2,5-dihydroxyphenyl)-3-(4-hydroxyphenyl)-2-propen-1-one and 4,2',5'-trihydroxychalcone described and coumarin scoparone [10]. Meyer *et al*. (2011) patented the use of homopterocarpin and other pterocarpans in the formulation of cosmetics or pharmaceutical formulation to treat the cellulite [33]. The homopterocarpin and *Pterocarpus erinaceus* extract showed the gastro protection effect against indomethacin-induced ulcer by antioxidative mechanism and modulation of gastric homeostasis [34].

2.3 *Platymiscium trinitatis* Benth.

The phytochemical study of ethanolic extracts of *P. trinitatis* wood, performed by Hakamata *et al*. (1998) and Craveiro & Gottlieb (1974) resulted in the isolation of 9 compounds. Among them are the coumarin scoparone; pterocarpans (+)-medicarpin, (+)- 3,10-dihydroxy-9-methoxy-pterocarpan (vesticarpan), 9-methoxy-6*H*-benzofuro[3,2- c][1]benzopyran-1,3-diol, 6*H*-benzofuro[3,2-c][1]benzopyran-3,10-diol,6a,11a-dihydro- 9-methxy-,diacetate,(6a*S*-*cis*)-(9Cl), (+)-3-hydroxy-9-methoxy-pterocarpan (+)- medicarpan e (+)-3,9-dimethoxy-pterocarpan [(+)-homopterocarpin] (homopterocarpin); isoflavone (-)-5,7-dihydroxy-4'-methoxy-isoflavone (biochanin A) and isoflavanone dihydrobiochanin [12-13].

2.4 *Platymiscium gracine* Benth.

The wood of *P. gracine* showed the presence of homopterocarpin, calycosin and scoparone [35].

Nineteen pterocarpans were isolated from leaf extracts, bark, heartwood and roots of *P. floribundum*, the core of *P. yucatanum*, *P. trinitatis* wood and *P. gracine* [11, 13, 15, 22, 17- 18, 35].

From the core and bark of the *P. floribundum* trunk, the wood and heartwood of *P. floribundum* var. *floribundum* and the core of *P. yucatanum*, four chalcones were isolated [10, 11, 16, 20, 27]. A hydroxylchalcone as well as six flavanones were isolated from the root extracts, heartwood and bark of *P. floribundum* Vogel and from the trunk, wood and heartwood of *P. floribundum* var. *floribundum* and the heartwood of *P. yucatanum* [10, 11, 20, 22, 27].

The extracts of roots, heartwood and bark of *P. floribundum* trunk, *P. trinitatis*, *P. gracine* and wood and heartwood of *P. floribundum* var. *floribundum* produced fourteen isoflavonoids, which were isolated, as well as one isoflavanone [11, 13, 14, 16, 20, 27]. According to Falcão *et al*. (2005), extracts of roots and core of *P. floribundum* showed the presence of a biflavonoid and an isoflavonaquinone [15, 22].

The studies with *P. floribundum*, *P. yucatanum*, *P. trinitatis* and *P. gracine* showed the isolation of twenty-five coumarins from stem (heartwood and sapwood), bark and roots extracts [10, 11] [Craveiro *et al*. 1974] [16, 20, 21, 26, 27, 35].

According to the studies carried out by Vila-Nova *et al*. (2013), two furanones were obtained from stem extracts (heartwood and sapwood) of *P. floribundum* [21].

From the extracts of *P. floribundum* species, twenty-six compounds belonging to the most diverse classes of secondary metabolites were isolated and / or identified. Among them two steroids, four triterpenes, triglycerides, methyl esters of fatty acids, and seventeen other compounds [16] [18-20] [26].

The review from the literature carried out in this work showed that four species of *Platymiscium* and two varieties of *P. floribundum* are well described, which produce isoflavonoid biomarkers of the Fabaceae family. In addition to this class of flavonoids, the concomitant occurrence of coumarins was observed, fact previously observed only in the genera *Millettia*, *Ononis*, *Sophora*, *Medicargo*, *Cyclopia* and *Astragalus* [36-41].

3. Pharmacological activities

The flavonoid class has many pharmacological activities, including antioxidant, anticancer, cancer chemopreventive, antiviral, antimicrobial and effect as enzymatic inhibition [42, 44].

Table 1 shows the main pharmacological activities presented by the compounds and/ or extracts from species of the genus *Platymiscium*. *P. yucatanum* species has a popular use in the treatment of stomach pains and snake bites [10]. Until now three species were pharmacologically studied. The extracts and metabolites of *P. floribundum* presented the most varied pharmacological activities among them, such as cytomodulatory agents in the treatment of tumors/cancer, leishmanicidal, cytotoxic, anti-inflammatory, antianginal, immunosuppressive and vasodilator properties [21]. Scoparone isolated from the trunk heartwood from *P. floribundum* showed *in vitro* anti-Leishmania-activity presenting an EC_{50} = 9.11 27.51 µg/mL, depending on Leishmania species. The better results were observed against *L. mexicana* (EC_{50} = 9.11 ± 0.25 µg/mL). The extracts of *P. yucatanum* and *P. trinitatis* show phytoalexin and antifungal activities, highly resistant to the fungi *Lenzites trabea* and *Coriolus versicolor* [10, 12].

According to Reyes-Chilpa *et al*. (1998), the *in vitro* antifungal action of *P. yucatanum* extracts is associated with the presence of the flavonoids 4,2',5'-trihydroxy- chalcone, isoliquiritigenin, (+)-liquiritigenin, medicarpin and homopterocarpin and the coumarin dimethyl ether from aesculetin [10]. The antifungal activity was measured at 0, 25 mg/mL. The pterocarpan (+)-medicarpin inhibited the growth of *Lenzites trabea* and *Coriolus versicolor* [10]. On the other hand, the coumarin aesculetin dimethyl ether and (+) - liquiritigenin were active only against *C. versicolor*. Among all evaluated compounds, the (+)-medicarpin presented a higher fungicidal action.

Table 1: Pharmacological activities involving extract or substances isolated from *Platymiscium*

Specie	Compound	Pharmacologic/ Biological Activity	Reference
P. floribundum	(+)-3,9-dimethoxy-pterocarpan [(+)-	Cytotoxic to tumor cells	[22]
	homopterocarpin]; (+)-liquiritigenin;		
	2,3,9-trimethoxypterocarpan;		
	vesticarpan; isoliquiritigenin		
	6*H*-benzofuro[3,2-*c*][1]benzopyran,6a,11a-dihydro-	Induction of apoptosis in leukemia cells	[18]
	2,3,9-trimethoxy-,(6a*R*,11a*R*); (-)-		
	homopterocarpin (3,9-		
	dimethoxypterocarpan); (6a*R*,11a*R*)-		
	vesticarpan; (+)-medicarpin		
P. floribundum var. latifolium	tomentin	Fungicidal activity against *Fusarium oxysporium*	[16]
P. yucatanum	(+)-medicarpin	Fungicidal activity against *Coriolus versicolor*	[10]
No mentionated	2,3,9-trimethoxypterocarpan	Cytomodulatory agents in the treatment of tumors	[15]

The extracts of *P. floribundum* var. *floribundum* and *P. trinitatis* are used in the formulation of sunscreens because they exhibit excellent absorption in UVB (290 nm) and UVA (332 nm) regions [45]. The kojic acid and extracts from *Platymiscium trinitatis*, *Coptis japonica* Makino, *Polygala tenuifolia* Willd, *Puerariae lobata* Willd, *Saponaria officinalis*, *Salvia officinalis* L., *Narcissus tazetta* L. var. chinensis, *Aesculus hippocastanum* L., *Thea sinensis* L., *Tulipa gesneriana* L., *Althaea officinalis* L., *Raphanus sativus*, *Beta vulgaris* L., *Lycoris radiata* Herbert, *Lawsonia*

alba and *L. spinosa* L. are employed in the preparation of a formulation for the prevention of erythema [46].

According to Sannomiya (2001), the dichloromethane extract (2 mg/mL) of the root of *P. floribundum* var. *latifolium* showed *in vitro* bactericidal activity against *Staphylococcus aureus* and the methanolic extract showed *in vitro* fungicidal activity against *Aspergillus fumigatus* [16]. Scoparone, tomentin and 5,6,7-trimethoxycoumarin (2mg/mL) isolated from the dichloromethane extract, was submitted to the bioautography assay. Only tomentin showed fungicidal activity against *Fusarium oxysporium*. The structural comparison of tomentin, scoparone and 5,6,7-trimethoxycoumarin allowed to infer that the presence of the hydroxyl group at C-5 is important for the observed fungicidal activity [16]. Another activity evaluated was the anti-insecticidal activity of dichlorometane extract from *P. floribundum* var. *latifolium* against house fly, *Musca domestica* L. based on LC 50 value= 433µg/mL obtained by antifeedant larvae assay [16].

According to Trevisan and Macedo (2003), *Platymiscium floribundum*, *Amburana cearensis*, *Lippia sidoides*, *Solanum asperum* and *Paullinia cupana* showed results against *in vitro* acetylcholinesterase inhibition [47].

(+)-2,3,9-trimethoxypterocarpan was isolated from a species belonging to the genus

Platymiscium; it has a cytomodulatory action and can act in the cancer treatment [48].

The pterocarpans 2, 3, 9-trimethoxypterocarpan, homopterocarpin, (6a*R*,11a*R*)- vesticarpan and (+)-medicarpin isolated from the *P. floribundum* extract showed the induction of apoptosis in HL-60 human leukemic cells [17].

The flavonoids homopterocarpin, vesticarpan and liquiritigenin isolated from the heartwood of *Platymiscium floribundum* showed cytotoxic activity against human cancer cell lines *in vitro* assays [22].

4. Conclusions

The genus *Platymiscium* consists of nineteen species, of which four were studied from a chemical and pharmacological point of view. It was isolated one hundred five secondary metabolites. Among them it is possible to find fifty-two flavonoids, twenty-five coumarins, two furanones, six triterpenes/steroids and twenty other compounds. This literature review showed that species belonging to the genus *Platymiscium* of the family Fabaceae produce isoflavonoids as markers. In addition to this specific class of flavonoids, there is the concomitant occurrence of coumarins, which were only observed before in genera *Millettia*, *Ononis*, *Sophora*, *Medicargo*, *Cyclopia* and *Astragalus*. According to this study, a larger number of works involving extracts of *P. floribundum* was observed. Extracts from this species produced a wide diversity of secondary metabolites including flavonoids, coumarins, triterpenes/steroids and furanones. The highest number of *in vitro* pharmacological activities evaluated is associated with the extracts and / or compounds of

P. floribundum, being the most varied possible such as leishmanicidal, cytotoxic, cytomodulating in the treatment of tumors, antianginal, immunosuppressive and others.

The species belonging to this genus are widely recognized for their high commercial value due to the quality of their wood, especially with respect to *P. floribundum* and *P. yucatanum*. Only *P. yucatanum* has popular use in the treatment of stomach pains and snake bites. In this genus, it is also evident the high commercial value that their wood represents. An important characteristic attributed to its wood is the high resistance to fungi, making it advantageous for the carpentry, in the construction of furniture, musical instruments, crafts, among others. This action is associated with the presence of flavonoids and coumarins in their extracts.

An important fact observed in this work is that of the three-species studied, the *P. praecox* (*P. floribundum* var. *floribundum*) and *P. floribundum* var. *latifolium* extracts did not show the presence of pterocarpans. According to the current taxonomic classification established by Klitgaard (2005), *P. praecox* is recognized as *P. floribundum* Vogel var. *floribundum*, and according to this literature review, extracts of *P. floribundum* present a high content of pterocarpans. Thus, our analyses suggest the necessity of a careful chemical investigation involving the extracts of *P. praecox* and *P. floribundum* var. *latifolium* to confirm the botanical classification of the specimen studied and the necessity of the different variations for *P. floribundum*.

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6. Author contributions

N. Lee and M. Sannomiya performed the analysis of data. All authors wrote, read, revised and approved the manuscript.

7. Conflict of interest: The authors declare no conflict of interest.

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