Pharmacognosy Reviews
Vol 1, Issue 1, Jan- May, 2007

PHCOG REV.
An official Publication of Phcog.Net

PHCOG REV.: Plant Review

The Chemistry and Pharmacology of the South America genus *Protium* Burm. f. (Burseraceae)

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ABSTRACT
The family Burseraceae is considered to contain about 700 species comprised in 18 genera. Their resiniferous trees and shrubs usually figures prominently in the ethnobotany of the regions where it occurs, given that such a property has led to the use of species of this family since ancient times for their aromatic properties and many medicinal applications. Although the family is distributed throughout tropical and subtropical regions of the world, the majority of the scientific available information is limited to Asiatic and African genera, such as *Commiphora* (myrrh), *Canarium* (elemi incense) and *Boswellia* (frankincense), or the genus *Bursera* (linaloe), occurring in Mexico. In the Neotropics, the Burseraceae family is largely represented by the genus *Protium*, which comprises about 135 species. The present review compiles the published chemical and pharmacological information on the South American genus *Protium* and updates important data since the last review reported in the scientific literature on Burseraceae species.
KEYWORDS - *Protium*, Burseraceae, Pharmacology, Phytochemistry, Review.

INTRODUCTION

The family Burseraceae was probably originated in the Eocen period, in North America. Migration passed trough the tropical and subtropical regions around the world, resulting in about 18 known genera and 700 species distributed throughout the South of the American continent and Europe, later reaching Africa, Asia and Oceania (1). Until recently considered as belonging to the Order Rutales (2,3,4), the cumulative statistical DNA sequence-based data has actually re-classified the family Burseraceae in the Order Sapindales, class Dicotiledoneae and subclass Rosidae (5,6). In Neotropics, Burseraceae is represented by 228 species comprised into 8 genera (7), that may be classified according three tribes: Bursereae (*Beiselia* Forman, *Bursera* Jacq. ca. and *Commiphora* Jacq. ca.), Canarieae (*Dacryodes* Vahl and *Trattinnickia* Willd.) and Protieae (*Crepidospermum* Hook f., *Protium* Burn. f. and *Tetragastris* Gaertn) (1,8). *Protium* is the most heterogeneous genus in the family. It is the main genus in South America, being split in 135 known species (7). Identification of trees from *Protium* species is not an easy task during the non-flowering periods, and they are frequently confounded with other species of the Burseraceae family. Moreover, due to the presence of trunk resins, *sapopemas* (sort of tabular roots) and composed leaves, such a misleading may include some other species of Anacardiaceae (Sapindales) (7). On the other hand, some specific plant-insect interaction may produce characteristic alterations in leaf of *Protium* species that may be an useful tool to their identification (7,9).

Traditional uses of *Protium* species

Like the well-known Asiatic and African Burseraceae species (myrrh, frankincense, etc.) the great importance of the *Protium* species is solely and undoubted imparted to their capacity to produce abundant aromatic oleoresins. Trees belonging to this genus are denominated by a series of popular names that bring to mind this prominent property, such as: *anine, caraño, animecillo, copal, copalillo, almécega, almíscar, galbano, breu, breu branco, breu vermelho, jauaricica, goma-limão* or *Brasilian-elemi* (10,11,12,13). After releasing their volatile compounds, the exudates turn to a malleable yellowish material that turns to a hard gray resin on standing on the wounded trunks. This material is used in the manufacture of varnishes and dyes or to fix and make any kind of wooden boat impermeable. The resin is also often burned to illuminate the houses in the forest and repel undesirable insects. Its burning produces aromatic smokes for many religious rituals (7,13,14,15,16,17). Fruits of *Protium* species are very aromatic. *P. icicariba* produces edible fruits containing more than 10% in sugar; their seeds produce 25% of clear pleasant tasting fatty oil, sometimes suggested as a substitute for olive oil (12). The resin has been widely used for diverse purposes by the native tribes in their traditional medicine, e.g. as an external agent (cosmetics), to heal wounds (bandages), to avoid worsening of broken limbs and teeth, or as emollient, rubifaciente and antiseptic. The smoke is inhaled as an analgesic. The root bark is astringent and claimed to have renal clearance and anti-syphilitic properties (12,15,16,17).

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Genus Protium

Taxonomical classification

Kingdom	*Plantae, Plants*
Subkingdom	*Tracheobionta, Vascular plants*
Superdivision	*Spermatophyta, Seed plants*
Division	*Magnoliophyta, Flowering plants*
Class	*Magnoliopsida, Dicotyledons*
Subclass	*Rosidae*
Order	*Sapindales*
Family	*Burseraceae*
Tribe	*Protieae*
Genus	*Protium*

Botanical description

Petiolules apically flexed and 'pulvinate' on terminal leaflet, typically long and slender; leaflets sometimes rather thin (as uniquely in the short-petioluled genus Bursera). Inflorescence always axillary, usually reduced, and more or less fasciculate, when open usually reduced with very slender axis and branches. White, yellow, beige or greenish unisexual flowers, up to 5 mm long; three to five petals. Usually 8-10 stamens. Oblique or capsular drupaceous fruits, usually reddish, either asymmetric and laterally dehiscent with one or two seeds or symmetrically 5-carpellate with woodier valves; the inner surface of valves conspicuously red, the seeds partly covered by whitish succulent aril. Trees sometimes with silt roots or silt buttresses, these often rather dense and with a kneelike curve; eventually tabular trunk basis (sapopemas) (7,10).

Other properties are describe for different parts of the plants, such as being a tonic and stimulant (12,17), analgesic, wound-healing or contraceptive (14,17,18), laxative (19), hemostatic, anti-rheumatic, and for the treatment of gonorrhea, stomach and pulmonary diseases, and in dentistry applications (12,20), among others.

Phytochemistry

Fresh oleoresins from Burseraceae species may contain up to 30% of essential oils; this content being reduced to around 8% or less on solidifying (17). Essential oil from the resin is predominantly constituted of monoterpenes, mostly represented by the menthane-type skeleton with variable levels of unsaturation. On this hand, phellandrenes, terpinolene and limonene, and moreover the fully aromatized p-cymene and respective alcohols, are the most abundant compounds found in a study of the resins from *P. heptaphyllum* (21,22) and *P. icicariba* (23), as well as six other species of *Protium* exudates (24). α-Pinene was also significant in the fresh oleoresins of most reported species, and the highly oxidized p-ment-3-en-1,2,8-triol was reported in *P. heptaphyllum* (25). Aged resins of this latter species; as well as commercial (blended) samples, usually show large amounts of phenylpropanoids (e.g. up to 25% dillapiole) in their composition (21). Sesquiterpenes are usually detected in traces in most of the resin oils reported (20), but this proportion was described as inverse for *P. decandrum* (26). Sesquiterpenes represent the main feature in the chemical profile of the leaf oil, ranging from 78-94% for essential oils of *P. strumosum*, *P. grandifolium*, *P. llewelynii* and *P. hebetatum*. Nevertheless some species are reported as possessing higher content in monoterpenes in the leaves; as in the cases of *P. icicariba* (23), *P. decandrum* (26), *P. llewelynii and P. heptaphyllum* (limonene) (27,28,29).

Caryophyllene is usually ubiquitous and the most predominant sesquiterpene among those present in *Protium* leaf essential oils. This compound may be accompanied by a significant presence of α-humulene (20,27), aromadendrene (30), bergamotene isomers (26) or other selinenes-type sesquiterpenes (29). Sesquiterpene alcohols are mostly represented by cadinane and eudesmane-types (29). Oils from stems and tiny branches also showed similar chemical profiles with the leaf oil (31,26). Terpinolene, followed by other p-menthene isomers constitute approximately 75-90% of the essential oil of *P. icicariba* fruits (23); whereas α-pinene predominates (20%) in *P. baianus* (30,32). The chemical compounds reported in the essential oils of *Protium* species are shown in Table 1.

Besides the essential oils, the non-volatile compounds in *Protium* exudates are mostly constituted of triterpenes from the oleanane and ursane series, and at a less extent, from lupane, taraxane and friedelane series. The pentacyclic triterpenes α-myrin and β-amyrin are by far the most frequent constituents. The isolation or characterization of these two secondary alcohols, together with lupeol, are frequently mentioned in chemical studies reporting on resin from *Protium* species, as well as their corresponding ketones α–amyrone, β-amyrone and lupenone (33,20,34,18,35). Brein (3ß,16ß-dihydroxy-olean-12-ene) and maniladiol (3ß,16ß-dihydroxy-urs-12-ene) were isolated from the resins of *P. kleinii* and *P. heptaphyllum* (14,36,37). Other more rare dihydroxy- or 3-oxo-hydroxy-triterpenes were isolated (low-

Table 1 – Chemical composition and pharmacological activities of Protium species

Species	*Isolated or characterized constituent*	*Pharmacologic Action*
Protium altsonii	**Resin (essential oil):** α–thujene, α–pinene, canphene, sabinene, β–pinene, *p*-menth-3-ene, α–phellandrene, α–terpinene, *p*-menth-1-ene, *p*–cymene, β–phellandrene, menth-1(8)-ene, 1,8-cineole, γ–terpinene, dihidroterpineol, menth-1-en-8-ol, terpinen-4-ol, α–terpineol (24).	
P. apiculatum	**Resin (essential oil):** 4-methyl-1-(1-methylethyl)-ciclohexane, limonene, *p*–cymene, n-heptadecane, γ–gurjunene (35). **Resin:** α-amyrone (35)	
P. aracouchini	**Roots, wood and leaf** (methanolic extract).	Citotoxic to brine shrimp larvae (19,61)
P. baianus	**Leaf (essential oil):** epi-α-muurolol, α-cadinene, valencene, 7-epi-α-selinene, *cis*-isolongifolanone, aromadendrene (30,32). **Fruit:** α-pinene (30). **Resin (essential oil):** *p*-cymene, α-phellandrene, tricyclene, β-phellandrene, β-(E)-santalol acetate (66). **Resin:** α–amyrin, β–amyrin, mangiferolic acid (32).	Acaricidal (*Tetranychus urticae*) (66).
P. decandrum	**Leaf (essential oil):** α-elemene, β-caryophyllene, terpin-4-ol (26). **Branches (essential oil):** α-*t*-bergamotene, terpin-4-ol, caryophyllene oxide (26). **Resin (essential oil):** , α-*trans*-bergamotene, α-cis-bergamotene (26).	
P. glabrenses	Bark	Antimalarial (*Plasmodium berguei*) (46).
P. grandifolium	**Leaf (essential oil):** *p*-cymene, limonene, *p*-cymenene, 4,8-dimethyl-1,3,7-nonatriene, α–terpineol, methyl salicilate, δ–elemene, α–cubebene, α–copaene, β–elemene, β–caryophyllene, γ–elemene, α–guaiene, α–humulene, alloaromadendrene, γ–muurolene, germacrene D, β–selinene, valencene, zingiberene, α–muurolene, β–bisabolene, γ–cadinene, δ–cadinene, cadin-1,4-diene, γ–selinene, selin-3,7(11)-diene, germacrene B, (E)-nerolidol, α–caryophyllene, globulol, viridiflorol, 10-epi–γ–eudesmol, 1-epi-cubenol, epi–α–cadinol, δ–cadinol, epi–α–muurolol, juniper camphor (29). **Resin (essential oil):** α–pinene, *p*-cymene, camphor, α–cubebene (35).	Anti-inflammatory and inhibition of nitric oxide production; *in vitro* antitumor (29).
P. hebetatum	**Stem:** α–amyrin, β–amyrin, campesterol, stigmasterol, scopoletin (42). **Leaf (essential oil):** n-hexenol, *p*-cymene, limonene, *p*-cymenene, linalool, *p*-cymen-8-ol, α–terpineol, α–copaene, β–caryophyllene, aromandrene, α–humulene, alloromandrene, γ–muurolene, germancrene D, β–bisabolene, γ–cadinene, δ–cadinene, cadin-1,4-diene, γ–selinene, calacorene, (E)-nerolidol, ledol, spatulenol, globulol, viridiflorol, 10-epi-cubenol, isopatulenol, epi–α–cadinol, d-cadinol, epi–α–muurulol, cadalene (29). **Resin (essential oil):** α–pinene, β–pinene, *p*-cymene, α–phellandrene, α–terpinene, β–phellandrene, camphene, sabinene, α–cubebene, δ–cadinene (24,35). **Resin:** α-amyrone, β–amyrin, friedelan-3-one (35).	Anti-inflammatory and inhibition of nitric oxide production; *in vitro* antitumor (29).
P. heptaphyllum	**Stem:** *p*-coumaric acid ethyl ester, scopoletin, fraxetin, propacin, cleomiscosin A, 3-*O*-β-D-glycopyranosyl-β-sitosterol, quercetin (3,5,7,3',4'-OH-flavonol) (25,40,41) **Leaf:** quercetin-3-*O*-ramnosyl,6-methoxy-7-hydroxycoumarin (25,41) **Fruit:** (-)catequin (25). **Resin (essential oil):** α–pinene, 1,3-pentadiene, myrcene, α–phellandrene, *O*-methylanisol, α–terpinene, *p*-cymene,	Cercaricidal (48). Anti-colinesterase (25,48). Anti-inflammatory and inhibition of nitric

	limonene, 1,8-cineole, γ–terpinene, α–terpinolene, linalool, *p*–menth-1,5,8-triene, camphor, carvacrol, terpinen-4-ol, *p*–cymen-8-ol, α–terpineol, 2,5-dimethoxy-benzene, 3,5-dimethoxybenzene, δ–elemene, α–ylangene, α–cubebene, α–copaene, β–bourbunene, β–elemene, methyl eugenol, α–gurjunene, 2,3,5-trimethoxytoluene, β–caryophyllene, γ–elemene, α–humulene, alloromadendrene, germacrene D, β-selinene, α–selinene, viridiflorene, α–muurolene, β–bisabolene, δ–cadinene, γ–cadinene, myristicin, α–calacorene, elemicin, caryophyllene oxide, 1,2,3,4-tetramethoxy-5(2)-propenylbenzene, humulene epoxide, tetradecanal, dilapiol, δ-cadinol, selin-11-en-4α-ol, apiol, *p*–menth-3-en-1,2,8-triol. (20,25,29,35).	oxide production; *in vitro* antitumor (29). Citotoxic to brine shrimp larvae (62).
	Resina (Óleo Fixo): α–amyrin, β–amyrin, brein, maniladiol, α–amyrone, β–amyrone, lupenone, 3β,24-dihydroxy-urs-12-ene, 3β–hydroxi-urs-9(11),12-diene, 3β–hydroxi-olean-9(11)-12-diene, 3α–hydroxitirucala-8-24-dien-21-oic acid, 3α–hydroxitirucala-7,24-dien-21-oic acid, 3–oxo-20S-hydroxy-taraxastano, 3β,20S-dihydroxy-taraxastane, friedelin, epi-Ψ-taraxastanonol, epi-Ψ-taraxastanodiol, 3β-dihydroxy-urs-12-ene (14,18,20,25,35,36).	Treatment of pruritus (53,54); hepatoprotective (53,54); antinociceptive (53,55,56); gastroprotective (49,53); anti-inflammatory (49,53,51); analgesic (20)
P. icicariba	**Epiticular wax and essential oil:** α–copaene, n-tetradecane, β–caryophyllene, γ–elemene, germacrene D, n-pentadecane, biclogermacrene, δ–cadinene, β–copaen-4α-ol, n-hexadecane, guaiol, n–heptadecane, n-octadecane, 1-methyl-pentadecanoic methyl ester, n-heptacosane, n-triacontane, n–hentriacontane, n-dotriacontane, β–amyrin, α–amyrin, lupen-3-one, friedelan-1-one, friedelin (23). **Leaf (essential oil):** α–pinene, sabinene, β–pinene, β–myrcene, α–terpinene, *p*-cymene, limonene, β–phellandrene, α–phellandrene, trans–β–ocymene, γ–terpinene, α–terpinolene, α–terpineol, terpinen-4-ol, *p*-cymen-8-ol, dehydro-*p*-cymene, bicloelemene, δ–elemene, α–cubebene, α–copaene, β–elemene, trans-caryophyllene, γ–elemene, α–amorphene, aromadendrene, germecrene D, ledene, biclogermacrene, δ–cadinene, cis-calamene, terpinolene epoxy, cadin-1,4-diene, selin-3,7(11)-diene, germacrene B, ledol, spatulenol, globulol, viridiflorol, 10-epi–γ–eudesmol, *epi*-cubenol, 1,10-epoxigermacrene D, t-muurolol, t-cadinol, juniper camphor (23). **Fruit (essential oil):** α–thujene, α–pinene, sabinene, β–pinene, β–myrcene, α–phellandrene, α–terpinene, *p*-cymene, limonene, β–phellandrene, trans–β–ocymene, γ–terpinene, α–terpinolene, dehydro-*p*-cymene, epoxiterpinolene, 4-terpinenol, *p*-cymen-4-ol, p-cymen-8-ol, α–terpineol, trans-caryophyllene, cis-2,3-pinanediol, α–cubebene, γ–elemene, α–copaene, germacrene D, biclogermacrene, δ–cadinene, cis-calamene, cadina-1,4-diene, germacrene B, spatulenol (23). **Resin (essential oil):** α–pinene, sabinene, β–pinene, β–myrcene, α–phellandrene, γ–3-carene, α–terpinene, *p*-cymene, limonene, 1,8-cineoleo, γ–terpinene, α–terpinolene, dihydro-*p*-cymene, 1,3,8-*p*-mentha-triene, epoxyterpinolene, 1,8-menthedienol, terpinen-4-ol, *p*-cymen-8-ol, α–terpineol, ylangene, β–bourbonene, cyperene, α–santalene, germacrene D, myristicin (23).	
P. kleinii	**Resin:** α-amyrin, β-amyrin, brein, 3-oxo-11β,16β-dihydroxy-urs-12-ene, 3-oxo-11β- hydroxy-ursa-12-ene, 3-oxo-11β- hydroxy-olea-12-ene, 3-oxo-11α- hydroxy-olea-12-ene, 3-oxo-11α-hydroxy-urs-12-ene (37).	Antinociceptive (57,58); anti-inflammatory (50).
P.l llewelynii	**Leaf (essential oil):** 3-hexen-1-ol, (E)-2-hexanal, α–pinene, limonene, terpinolene, 4,8-dimethyl-1,3,7-nonatriene, n-hexyl butyrate, methyl salicilate, δ–elemene, α–cubebene, α–ylangene, α–copaene, β–elemene, α–gurjunene, β–caryophyllene, α–trans-bergamotene, α–guaiene, α–humulene, γ–muurolene, germacrene D, β–selinene, valencene, α–selinene, α–muurolene, β–bisabolene, γ–cadinene, δ–cadinene, cadin-1,4-diene, α–calacoreno, germacrene B, (E)-nerolidol, caryophyllene oxyde, humulene epoxide, 1-epi-cubenol, api–α–cadinol, δ–cadinol, epi–α–muurolol 29).	Anti-inflammatory and inhibition of nitric oxide production; *in vitro* antitumor (29).

	Resin (essential oil): α–pinene, *p*-cymene, α–cubebene, caryophyllene, δ–cadinene (35). **Resin:** α-amyrone, β–amyrin (35).	
P. nitidifolium	**Resin (essential oil):** α–pinene, camphene, sabinene, *p*-menth-1-ene, *p*–cymene, β–phellandrene, γ–terpinene, terpinen-4-ol (24).	
P. opacum	**Stem:** propacin (43).	
P. paniculatum var. "nova"	**Resin (essential oil):** α–pinene, camphene, α–phellandrene, limonene, α–terpinene, *p*–cymene, β–phellandrene, 1,8-cineole, α–terpineol, α–cubebene, α–muurolene, α–ylangene, β–elemene, cyperene, α–gurjunene, caryophyllene, α–bergamotene, α–humulene, β–cubebene, γ–cadinene, δ–cadinene (24,35). **Resin:** α-amyrone, β–amyrin (35).	
P. paniculatum var. *riedelianum*	**Resin (essential oil):** α–thujene, α–pinene, β–pinene, *p*–menth-3-ene, α–phellandrene, α–terpinene, *p*-menth-1-ene, *p*-cymene, β–phellandrene, 1,8-cineole, dihydroterpineol, menth-1-en-8-ol (24).	
P. spruceanum	**Leaf:** sabinene, α–terpinene, *p*-cymene, β–phellandrene, limonene, γ–terpinene, terpinen-4-ol, β–caryophyllene, germacrene B (28). **Branches:** sabinene, α-terpinene, *p*-cymene, β-phellandrene, limonene, γ-terpinene, terpinen-4-ol (28). **Resin (esential oil):** α-thujene, α-pinene, sabinene, *p*-menth-2-ene, *p*–menth-3-ene, β–phellandrene, limonene, α-phellandrene, α-terpinene, sabinene, α-terpinene, *p*-cymene, γ-terpinene, *cis*-sabinene hidrate, *p*-menth-1-eno, *p*-cymene, β-phellandrene, canfor, 4-terpinenol, dihydroterpineol, α-terpineol (24,28).	
P. strumosum	**Leaf (essencial oil):** *p*-cymene, limonene, terpinolene, linalool, 1-terpinen-4-ol, timol, δ-elemene, α-cubebene, α-ylangene, α-copaene, β-bourbunene, β-elemene, β-caryophyllene, γ-elemene, α-humulene, alloaromadendreno, γ-muurolene, germacrene D, β-selinene, α-selinene, β-bisabolene, γ-cadinene, δ-cadinene, cadina-1,4-diene, α-calacorene, germacrene B, β-calacorene, spatulenol, globulol, 10-epi-γ-eudesmol, 1-epi-cubenol, epi-α-cadinol, epi-α-muurolol, α-cyperone, α-eudesmol acetate (29). **Resin (essential oil):** α-pinene, limonene, *o*-cymene, *p*-cymene, β-phellandrene, α-cubene, caryophyllene, terpinolene, *p*-cymenene, camphor, *p*-cymen-8-ol, α-terpineol, 1,2,3,4,4a,5,6,8a-octahydro-7-methylnaphtalene (24,35). **Resin:** α-amyrin, β–amyrin, friedelan-3-one (35).	Anti-inflammatory and inhibition of nitric oxide production; *in vitro* antitumor (29).
P. tenuifolium	**Wood:** (+)-(2S,3S)-2-(3",4"-methylenedioxybenzil)-3-(3',4'-methylenedioxyacetophenone)-butyrolactone, (-)-cubebin epimers (33). **Resin:** α-cubebene, α-bergamotene, n-pentadecane, 1,2,3,4-tetrahydro-1,6-dimethyl-4-(1-methylethyl)-naphtalene, n-hexadecane, n-heptadecane, n-octadecane, α-amyrin, β-amyrin (35).	
P. unifoliolatum	**Wood:** 5-methoxyjusticidin A, 9-(1,3-benzodioxol-5-yl)-4,5,6,7-tetramethoxynaphto-(2,3-C)-furan-1-(3H)-one (45). **Bark:** 5-methoxypropacin (44). **Leaf (essential oil):** α-pinene, β-pinene, limonene, α-terpinolene, benzoic acid, 2-hydroxymethyl ester, α-copaene, *trans*-caryophyllene, α-humulene, β-cubebene, eremophilene, β-bisabolene, δ–cadinene (27).	

yield) from the resin more polar fractions. Thus 3-oxo-11β,16β-ihydroxy-urs-12-ene, 3-oxo-11β-hydroxy-urs-12-ene and 3-oxo-11β,dihydroxy-olean-12-ene in *P. kleinii* (37) and ψ-taraxastanodiol, ψ-taraxastanonol, 3β,24-dihydroxy-urs-12-ene, 3-oxo-20*S*-hydroxytaraxastane and 3β,20*S*-dihydroxytaraxastane were found in *P. heptaphyllum* (20,36). 3α-Hydroxy-tirucalla-8,24-dien-21-oic and 3α-hydroxy-tirucalla-7,24-dien-21-oic acids together with ursa-9(11),12-dien-3β-ol and oelana-9(11):12-dien-3β-ol were also isolated from this latter (14). Mangiferolic acid and an unspecified tetracyclic cycloartane triterpene were found in *P. baianus* (30). The friedelane-type skeleton was represented by the small amounts of friedelin in the constitution of the resin of *P. heptaphyllum* and *P. hebetatum* (20,35) and in the epicuticular leaf wax of *P. icicariba* (23). Leaves of this latter species have also been reported as containing the usual mixture of amyrins and lupeol plus α-tocopherol (38). A large amount of 3-epifriedelanol, accompanied by friedelin, lupeol, lupenone, α- and β-anyrin and 3-*O*-β-glycopyranosyl-sitosterol, were isolated or characterized from the ethanolic extracts of the leaves of *P. strumosum* (39). Sitosterol and stigmasterol were also isolated in the leaves of *P. heptaphylum* (40).

Chemical investigation on the stem of *Protium* species has led to the identification of steroids, triterpenes, cumarins, lignans and other derivatives. Quercetin-3-*O*-ramnosil and 6-methoxy-7-hydroxycumarin were found in leaves of *P. heptaphyllum* (41). Scopoletin and steroids were isolated from *P. hebetatum* stems (42) and fraxetin was isolated from stems and barks of *P. opacum*, together with the *p*-coumaric ethyl ester (40). In both cases these compounds were followed by the presence of the *Protium* usual triterpenes and steroids. The infrequent occurrence of coumarinolignoid metabolites was exemplified by the isolation of propacin from the trunk wood of *P. opacum* (43), cleomiscosin A from *Protium hebetatum* stems (42), and 5-methoxypropacin from the same part of *P. unifoliolatum* (44). The wood of *Protium* species has also furnished other lignan classes; e.g. the oxo-parabenzlactone [dibenzyl-butyrolactone type] together with a mixture of (-)-cubebin epimers [dibenzyl-tetrahydrofurane type] in *P. tenuifolium* (32) and 5-methoxyjusticidine A [arylnaphtalene type] (45). See Table 1 and Figure 1.

Pharmacology

Species of the genus *Protium* comprise a very attractive commercial botanical source of aromatic compounds. In folk medicine, gum and oleoresins from species of *Protium* are used for many purposes, e.g. tonic and stimulant (17), healing of ulcers and as antiinflammatory agent (12); to treat headaches, and skin and eyelid inflammation and rheumatic pains (46), amongst other medicinal applications. In spite of the numerous and widely spread species, few studies are available on Neotropical Burseraceae species (47), in contrast with the traditional African and Asiatic species. Most of the detailed pharmacological investigation on *Protium* species have only become available during the two past decades and are highly concentrated in the oleoresin and its either volatile or non-volatile fraction. The essential oil from leaves and fruits of *P. heptaphyllum* possesses cercaricidal activity (48), and the essential oils from *P. strumossum*, *P. grandifolium and P. llewellynii* leaves show an inhibitory effect on the growth of *Escherichia coli* at doses from 1.25 to 0.50 mg/mL (39). The essential oils from *P. strumossum*, *P. grandifolium*, *P. hebetatum* and *P. llewellynii* leaves and *P. hepataphyllum* resin were screened for anti-inflammatory activity by the use of a mouse pleurisy model induced by zymosan (500 μg/cavity) or lipopolysacharide (LPS) (250 ng/cavity). Most of the samples were able to inhibit the accumulation of neutrophils to different degrees. In general, oils constituted of a high content of sesquiterpenes were able to inhibit protein extravasation without changing the leukocytes counts. Samples presenting phenylpropanoids (e.g. resin) or high content in monoterpenes were effective to inhibit the LPS-induced eosinophil accumulation in the mouse pleural cavity. Except for *P. llewellynii* [which elicited the nitric oxide (NO) production by 50%], the *in vitro* treatment oils inhibited the NO production from stimulated mouse macrophages in the range 46-74% (100 μg/well). The oil from *P. heptaphyllum* resin also inhibited the LPS-induced NO production. On the other hand, antinociceptive effect was not observed in the writhing test induced by acetic acid, when animals received oral administration of the essential oils (100 mg/Kg) (29).

Gastric inflammation and ulcer induced by pure or HCl-acidified ethanol are significantly attenuated by treating mice with *P. heptaphyllum* resin (200 to 400 mg/kg), by reducing the total acidity without much change in gastric secretory volume. Moreover, the gastro-protective property was compatible with the complete absence of toxicity shown by the resin up to the oral dose of 5 g/Kg in rats (49). Similar p.o doses of the oleoresin were able to inhibit the formation of cotton pellet-induced granuloma in rats; but had no efficacy on acute edema induced by carrageenan in the hind-paw model. On the same hand, both the ethereal extract and α-amyrin from *P. kleinii* (the most abundant pentacyclic triterpene of the resin) produced a dose-related inhibition of both ear edema (ID_{50} = 0.55 and 0.31 mg/ear, respectively) and the influx of polymorphonuclear cells (ID_{50} = 0.72 and 0.45 mg/ear, respectively) in response to induction by 12-*O*-tetradecanoylphorbol acetate (TPA) induction. Likewise, both samples given topically prevented an increase of the pro-inflammatory cytokine interleukin-1ß levels, comparable to the response to dexamethasone, and in a dose-related manner (50). Anti-inflammatory and platelet antiagregant effect of β-amyrin from *P. hepatphyllum* was also assayed (51). An investigation of the mechanism involved in the inhibition of TPA-induced skin inflammation in mice by α-amyrin showed a dose-dependent inhibition of prostaglandin E_2 levels, with similar inhibition of COX-2 expression in the mouse skin tissue. Surprisingly, any alteration of either COX-1 or COX-2 activities *in vitro* was not observed. Topical treatment with α-amyrin was able to prevent I-κB degradation and consequent NF-κB activation. Taken together, these studies indicate that α-amyrin and derivatives could be potentially relevant for the development of a topical agent in aid of treating the inflammatory diseases (52).

The mixture of α e β-amyrins from *P. heptaphyllum* was also demonstrated to suppress the Dextran T40® and compound 48/80-induced scratching behavior in the mouse. The efficacy of the mixture (100 and 200 mg/Kg p.o.) suggested a potential anti-pruritic effect of the pentacyclic triterpenoids for use in the treatment of itches and pruritus derived from allergy, dermatitis or eczema (34). Administering 50 and 100 mg/Kg of the same mixture in mice attenuated the acetaminophen-induced acute increase in serum alanine aminotransferase and aspartate aminotransferase activities, suppressing the mortality completely, with further evidences of the suppression of liver cytochrome-P450. These results strongly suggest the triterpenes hepatoprotective potential by decreasing oxidative stress and the formation of toxic metabolites (53,54).

Attenuation of the visceral nociception effect in mice was observed by administering a mixture of α- and β-amyrin (100 mg/Kg) in the cyclophosphamide-induced bladder pain; and intracolonic mustard oil-induced nociceptive behaviors were completely inhibited by 10 mg/Kg of the same mixture, in a naxolone-reversible manner. The putative mechanism was investigated as shown to involve the opioid and vaniloid receptors (55,56). The ethereal fraction from the resin of *P. kleinii* (30 to 300 mg/Kg p.o. or 5 to 60 mg/kg i.p.) indirectly confirmed these results in a dose-related manner, when assessed against acetic acid-induced writhing (57). Part of such effects was putatively related to the presence of the triterpene brein, isolated from the extract, which produced a significant dose-related antinociception in both phases of formalin induced-licking (ID50 15.3 and 20.6 for early and late phases, respectively) (57).

All these results agree with the preliminary analgesic effects reported in mice for the crude ethereal extract of the oleoresin from *P. heptaphyllum*, by the writhing test (50 mg/Kg) or the formalin-induced test (25 mg/Kg). In these assays, the mixture of ψ-taraxastanonol and epi-ψ-taraxastanodiol was shown to be five times more potent than the crude extract or its neutral fraction. Moreover the mixture of α- and β-amyrin showed no efficacy at the doses assayed in those two specific pain-inducing models (20). This failure was later also observed for ethereal fraction of *P. kleinii* resin in the thermal model of pain, the tail flick and the hot plate tests. The involvement of opioid and vaniloid receptors without the participation of α-adrenoceptor in the analgesic effect was reinforced by the hypertermic response blocking in mice induced by sub-plantar or intra-colonic application of capsaicin, when orally administered with the mixture of α- and β-amyrin (3 to 100 mg/Kg). These results are in accordance with the inhibition of neurogenic nociception caused by topical injection of capsaicin (mean ID_{50} values of 6.2 and 16.0 mg/k for i.p. and p.o. routes, respectively) from the ethereal fraction of *Protium kleinii* oleoresin (57). The involvement of the protein kinase A and protein kinase C in the anti-nociceptive mechanism was also suggested from reductive effect exerted by α- and β-amyrin on these protein-sensitive pathways, such as the hyperalgesia produced by the i.p injection of carrageenan, capsaicin, bradykinin, substance P, prostaglandin E2, 8-bromo-cAMP and by TPA (58).

Essential oil, the hexane soluble fraction of the oleoresin, several extracts and some isolated compounds from different parts of *P. heptaphyllum*, were screened as acetylcholinesterase (AchE) inhibitors, using the Ellmann's microplate assay and/or silica gel thin-layer chromatography. The best results were found for the oleoresin (0.5 mg/Kg) and (-)-cathequin (1.0 mg/Kg) (25,59). Bark extracts from *P. glabrescens* showed a strong anti-plasmodium activity, reaching 61% of inhibition at the dose of 100 mg/Kg, when screened (IC_{50} = 4 μg/mL; Peters-Robinson test) against *Plasmodium berghei* NK65 strain, in infected mice. The *in vivo* efficacy was suggested to be due to a probable NO production; although no isolated compound has been correlated to the bioactivity in this case, and moreover no effectiveness was observed *in vitro* (46). On the same hand, the chloroform extracts of *P. heptaphyllum* bark and stem (250 mg/Kg) led to 58% reduction of the parasitaemia. In this experiment, phenylpropanoid compounds were characterized in the crude samples (60). Volatile compounds from *Protium* species demonstrated to be highly effective on inhibiting the growth of JJ74 (mouse monocytic cell), SP2/0 (mouse plasmocytoma) and Neuro-2A (mouse neuroblastoma) neoplasic cell lines; an effect mostly attributed to the monoterpene present in the essential oils (29). Investigations on the toxicity of essential oils of *P. heptaphyllum* and extracts from roots of *P. araconchini* included the brine shrimp toxicity assay using *Artemia* sp. and indicated to the anti-cancer potential of these substrates (61,19,62,63).

CONCLUSION

Although the South American Burseraceae species have wide and long-term traditional uses in the local ethnomedicine, the majority of the available scientific information about the Burseraceae species is limited to genera occurring in Asia and Africa, e.g. *Commiphora* (myrrh), *Canarium* (elemi incense) and *Boswellia* (frankincense) (16); or the genus *Bursera* (linaloe; copal), the latter mostly occurring in Mexico (64). Such a contrast may be extended to the aromatic potential of those species, whose correct commercial exploitation could lead to an immediate and highly feasible resource for the auto-sustainability of the rain forest communities, which has not been duly explored (13). The volatile compounds of the *Protium* oleoresins confer them a strong turpentine-like or mangolike odor (10) due to the substantial presence of unsaturated menthane-related derivatives together α-pinene (24).

On the other hand, important features of the traditional medicine based on the *Protium* species (as other Neotropical Burseraceae) could easily be correlated to ayurvedic therapeutics, which use botanically or chemically standardized Burseraceae species as crude drugs for a plethora of medicinal treatments (65), as part of the effort for developing new pharmaceuticals. All the chemical and pharmacological work carried out so far with different *Protium* oleoresins points to their potential as a very appropriate triterpene-based material to be used in the development of dermal products, either medicinal bandages,

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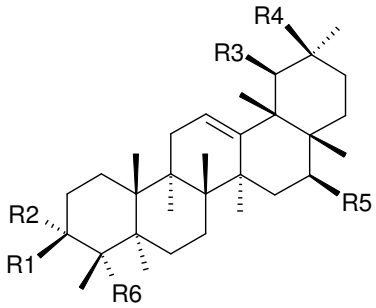
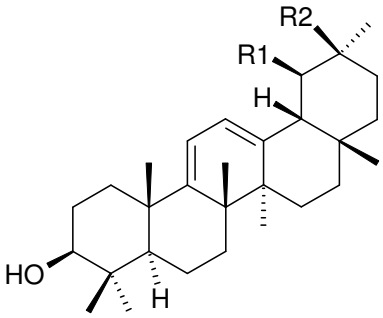
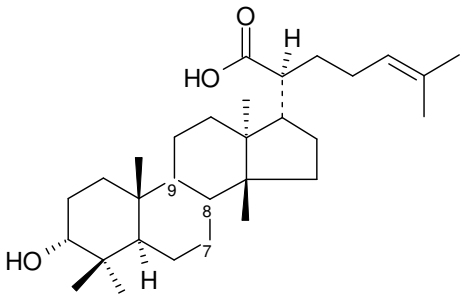
Figure 1 - Compounds isolated from Burseraceae species

I. Triterpenes and Sterorols



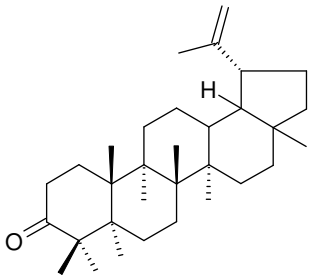
	R1	R2	R3	R4	R5	R6
α-amyrin	OH	H	CH_3	H	H	CH_3
β-amyrin	OH	H	H	CH_3	H	CH_3
brein	OH	H	CH_3	H	OH	CH_3
maniladiol	OH	H	H	CH_3	OH	CH_3
α-amyrinone	=O		CH_3	H	H	CH_3
β-amyrinone	=O		H	CH_3	H	CH_3
3β,24-dihydroxy-urs-12-ene	OH	H	CH_3	H	H	CH_2OH



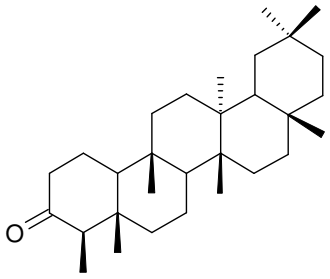


	R1	R2
3-β-hydroxi-urs-9(11),12-dienol	CH_3	H
3-β-dihydroxy-olean-9(11),12-dienol	H	CH_3

	C=C
3α-hydroxy-tirucal-7,24-dien-21-oic acid	Δ^7
3α-hydroxy-tirucal-8,24-dien-21-oic acid	Δ^8



lupenone



friedelin

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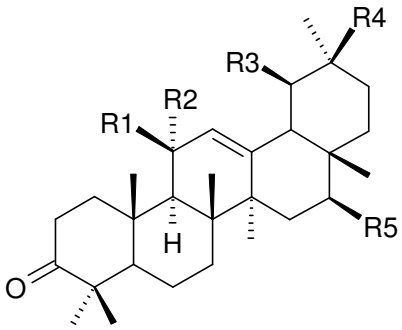
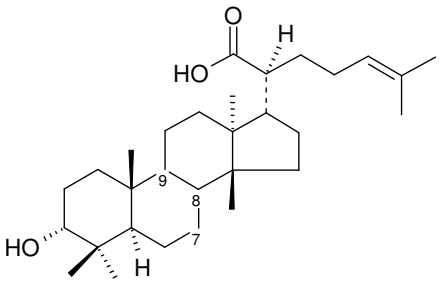
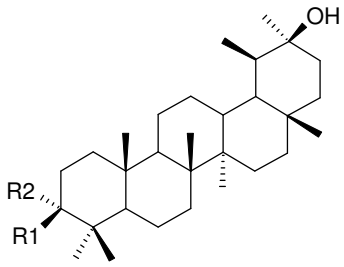


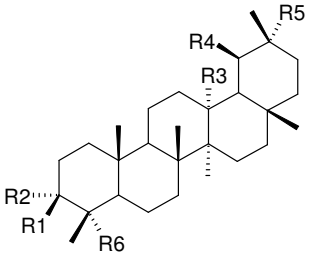
	R1	R2	R3	R4	R5
3-oxo-11β,16β-dihydroxy-urs-12-ene	OH	H	CH_3	H	OH
3-oxo-11β-hydroxy-urs-12-ene	OH	H	CH_3	H	H
3-oxo-11β-hydroxy-olean-12-ene	OH	H	H	CH_3	H
3-oxo-11α-hydroxy-olean-12-ene	H	OH	CH_3	H	H
3-oxo-11α-hydroxy-urs-12-ene	H	OH	H	CH_3	H



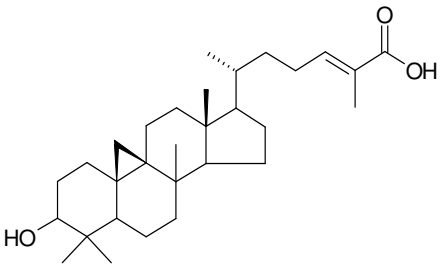


	C=C
3α-hydroxy-tirucal-7,24-dien-21-oic acid	Δ^7
3α-hydroxy-tirucal-8,24-dien-21-oic acid	Δ^8

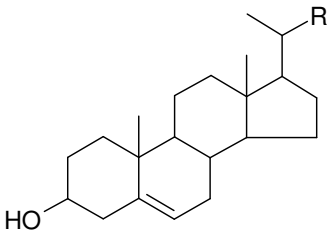
	R1	R2
epi-Ψ-taraxastanonol	=O	
epi-Ψ-taraxastanodiol	OH	H



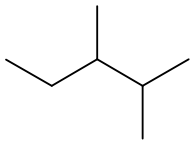
	R1	R2	R3	R4	R5	R6
3-oxo-20*S*-hydroxytaraxtane	OH	H	H	CH_3	OH	CH_3
3β,20*S*-dihydroxytaraxtane	=O		H	CH_3	OH	CH_3
friedelan-3-one	=O		CH_3	H	CH_3	H

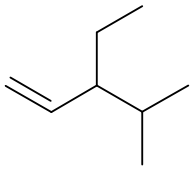


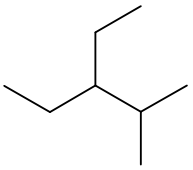
mangiferolic acid



R -

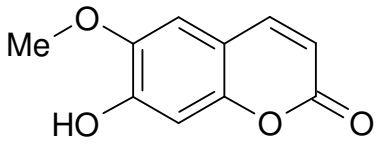




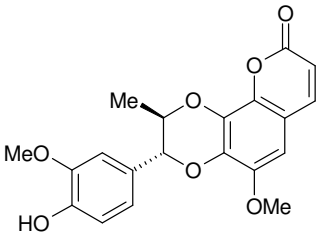


campesterol stigmasterol sitosterol

II. Coumarins

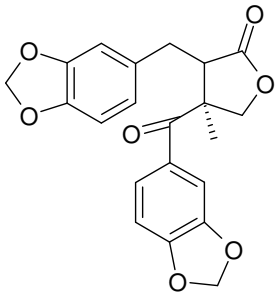


scopoletin

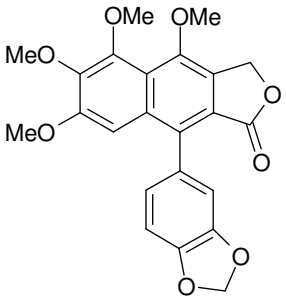


propacin

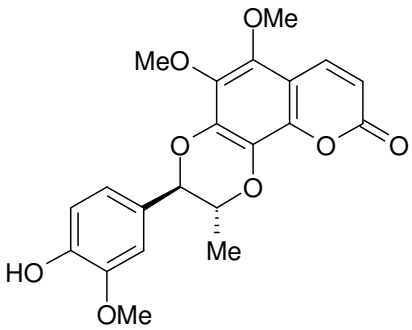
III. Lignans



oxo-parabenzlactone



5-methoxyjusticidin A



5-methoxypropacin

cosmetics and cosmeceutics (34,52,66) or odontological materials (67). Skin diseases also could be a focus for the medicinal application of *Protium* essential oils, given that they possess antiseptic properties (16) and acaricidal activity (68). The inherent cytotoxicity of lignans and coumarinolignoids present in the wood and roots of *Protium* species must be better explored in a search for new anti-neoplasic agents (as the similarity between some reported lignans and the well-established etoposide and podophyllotoxin derivatives) (69).

The properties of lowering the water permeability and protecting against oxidative processes also indicate the

Protium resins as suitable natural resources for developing general packing material for the pharmaceutical and food industry, aiming to improve the shelf life of their products (70). From the ecological point-of-view, the sustainability of any large-scale resin production would require either an organized scheme for extracting the forestry resource as well as developing or adapting its tapping by chemical means (71). The main goal of the present comprehensive review was to present the research carried out with species of the *Protium* genus, widely spread is South America, in order to organize the data produced since the previous effort in surveying the botanical family Burseraceae (72).

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