Phenolic compounds from fruits of *Protium tovarense* Pittier and their potential pharmacological actions

Compuestos fenólicos de los frutos de *Protium tovarense* Pittier y su potencial actividad farmacológica

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Abstract

From the methanolic extract of the fruit peels of the species *Protium tovarense* Pittier, a series of compounds of phenolic nature were isolated by chromatographic techniques and characterized using Nuclear Magnetic Resonance Spectroscopy (NMR) in one and two dimensions and mass spectrometry (MS). Scoparone (**I**), trans-tiliroside (**II**), quercetin-3-O-rutinoside (**III**), kaempferol-3-O-rutinoside (**IV**) and (+) catechin (**V**) were identified; all these compounds have recognized pharmacological actions, which are pointed out in this publication, and were isolated from this plant for the first time.

Key words: *Protium tovarense*, phenolics, pharmacological actions.

Resumen

A partir del extracto metanólico de las cáscaras de los frutos de la especie *Protium tovarense* Pittier, se aisló mediante el uso de técnicas cromatográficas, una serie de compuestos de naturaleza fenólica los cuales se caracterizaron a través de espectroscopia de Resonancia Magnética Nuclear (RMN) en una y dos dimensiones y espectrometría de masas (EM). Se identificó a: escoparona (**I**), trans-tilirósido (**II**), quercetina-3-O-rutinosido (**III**), kamferol-3-O-rutinosido (**IV**) y (+) catequina (**V**); todos estos compuestos, aislados por primera vez de esta especie, cuentan con reconocidas acciones farmacológicas, las cuales son señaladas en esta publicación.

Palabras clave: *Protium tovarense*, fenólicos, acciones farmacológicas.

Introduction

Plants belonging to Burseraceae family include 19 genera and more of 700 species according to Daly *et al.* (2011), however, until these days the found data related to genera and species are inconsistent, some authors mention 20, 18, and 16 genera, and also a different number of species (Weeks *et al.*, 2005; Rüdiger *et al.*, 2007). This family is recognized with medicinal properties in diverse countries of the tropical and subtropical regions around the world (Daly and Fine, 2011; Daly *et al.*, 2011). Many species belonging to it produce aromatic resins and exudates widely used in folklore medicine and perfumery (Siddiqui, 2011). The medical use of these exudates includes analgesic, anti-inflammatory, to treat skin diseases and healing ulcers (Duwiejua *et al.*, 1993). The essential oils of many species of Burseraceae are also recognized with pharmacological activities, anticancer, antifungal, anti-inflammatory, and larvicide (Murthy *et al.*, 2016).

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Protium genus is one of the bigger under Burseraceae, species of *Protium* produce oleoresins as other genus in the family; different parts of these plants are frequently used in traditional medicine as antiseptics, stimulating tonics, pain relievers, contraceptives, laxatives, hemostats, anti-rheumatics and for treatment of gonorrhea, stomach and lung diseases, among others (Rüdiger *et al.*, 2007; Marques *et al.*, 2010). Some species had been the object of intensive research especially in Brazil, where they are considered, really important by their medical properties and how industrial resources (Rüdiger *et al.*, 2007; Daly and Fine 2011; Daly *et al.*, 2012).

Protium heptaphyllum (Aubl.) Marchand, is one of the more studied species, in Brazil is considered an important therapeutic agent, being used as an anti-inflammatory, analgesic, expectorant, and healing agent. The antinociceptive activity and the chemical composition of the essential oil from the resin of this species had been reported (Rao *et al.*, 2007; Marques *et al.*, 2010). Pharmacological studies demonstrated antinociceptive, cytotoxic, and anti-inflammatory activities of this resin (Siani *et al.*, 1999). The presence of compounds, *p*-menth-3-ene-1,2,8-triol, α, and β amyrin, quercetin, brein, quercetin-3-O-rhamnosyl, (-) catechin, and scopoletin were reported from phytochemical investigations (Bandeira *et al.*, 2002). Taraxanes and ursanes triterpenes were also reported in other research of the oleoresin (Susunaga *et al.*, 2001).

Protium kleinii Cuatrec., an endemic tree from Brazil southern was investigated by their anti-inflammatory and antinociceptive activity, and a series of triterpenes were isolated from the resinous bark (Siani *et al.*, 1999; Lima *et al.*, 2005).

The chemical constituents and antifeedant activity of *Protium javanicum* Burm. f., a plant from India, showed that coumarins, flavonoids, lignans, and terpenes are the main constituents (Adfa *et al.*, 2013).

From *Protium hebetatum* Daly, the chemical composition and antibacterial activity were investigated; the main compounds include monoterpenes and coumarins (Costa *et al.*, 2012; Conrado *et al.*, 2015).

Protium neglectum Swart, locally called as "currucay", has been used in Venezuela as a traditional remedy for inflammations, as an inhalant to clear the respiratory and bronchial passages, and for hound healing. The antibacterial activity and the chemical composition of the essential oil from this medicinal plant had been recorded, as well the presence of triterpenes from the resinous exudates and the antioxidant activity of the phenolics present in it (Suárez *et al.*, 2007; Padilla *et al.*, 2008).

The species *Protium tovarense* Pittier is a tree commonly known in Venezuela by the name of "tacamahaca". The oleoresin of this tree "caraña", is used as a healing agent. In view of the recognized medicinal uses of plants from this genus, the peels of the fruits of *Protium tovarense* Pittier were considered to be the initial part in the first phytochemical and pharmacological study of this species, the chemical isolated metabolites are described here as well the potential pharmacology of each one of these compounds.

Experimental

General experimental procedure

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. NMR spectra were recorded with a Varian 400 MHz for ^{1}H and 100 MHz for ^{13}C. Chemical shifts were reported in δ (ppm), relative to the signal of tetramethylsilane (TMS), and coupling constants (J) are given in Hz. Low-resolution mass spectra were measured in a VARIAN Saturn 2000. Optical rotations were measured in a Lynos Photonies Typ SR6, Spannung. TLC analyses were carried out on precoated silica gel G254 (Merck) plates. For column chromatography, silica gel 60 (Merk 100–200 mesh) was used, and RP-18 (Merck, KGaA, Darmstadt, Germany, 40–63 μm) was used as stationary phases. Normal phase Thin Layer Chromatography (TLC), with fluorescence indicator at 254 nm, was purchased by Sigma-Aldrich. After exposure to UV light (254 and 366 nm), the plates were revealed with a mixture of sulphuric acid and p-anisaldehyde. All solvents used are PA grade.

Plant Material

The fruits of the species *Protium tovarense* Pittier used to carry out this work, were collected by Belandria, Castillo, and Meier, at the National Park El Ávila, El Tigre sector at 1900 masl, in November 2011, and were identified by Meier W. A voucher specimen VEN 3301 has been deposited in the Herbarium Nacional de Venezuela, Universidad Central de Venezuela.

Extraction and isolation

The air-dried fruits of *P. tovarense* (400 g), were separated from the pulp, and the ground peels (150 g) were extracted by maceration with MeOH. The evaporated crude extract dissolved in MeOH/H_2O (1:1) and was partitioned with hexane, CH_2Cl_2 and EtOAc successively, to obtain 4 fractions, including the aqueous-methanolic one. After TLC analyses of the different fractions, the CH_2Cl_2 and EtOAc fractions were considered the richer and interesting to separate.

The CH_2Cl_2 soluble fraction (1.5 g) was subjected to column chromatography using silica gel eluted with hexane/CH_2Cl_2 gradient mixtures, CH_2Cl_2, EtOAc, leading to 1% MeOH in EtOAc obtaining 30 fractions of 50 mL. The eluates were pooled based on TLC. Combined fractions eluted with 100% CH_2Cl_2 gave pure (**I**) (32 mg) (Ma *et al.*, 2006; Rumzhum *et al.*, 2012) and a series of mixtures of fatty acids, revealed by analysis of GC.

The EtOAc fraction (2 g) was submitted to normal phase CC (200 g of silica) and was eluted with a mixture of CH_2Cl_2/EtOAc (70 fractions of 50 mL each), according to increasing polarity gradient (from 90:10 to 0:100). Finally, the column was washed down with a mixture of EtOAc/MeOH (90:10). The fractions were combined according to their TLC patterns (normal phase TLC, eluted according to metabolite polarity), to obtain the pure compounds *trans*-tiliroside (**II**) (30 mg) (Luhata *et al.*, 2016, Devi and Kumar, 2018), and rutin (**III**) (17 mg) (Ganbaatar *et al.*, 2015). A subsequent gradient fractionation of a 35 mg fraction, performed with RP-18 and MeOH/EtOAc in isocratic elution with polarity (90:10), afforded the two main fractions; one of these afforded the flavonoid kampferol-3-O-rutinoside (**IV**)

(15 mg) (Ning *et al.*, 2008), and (+) catequine (**V**)(10 mg) (El-Razek, 2007).

Scoparone (**I**): Yellow powder, mp 145-147 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (1H, d, *J* = 9.4 Hz, H-4), 6.89 (1H, s, H-5), 6.82 (1H, s, H-8), 6.26 (1H, d, *J* = 9.4 Hz, H-3), 3.83 (3H, s, 6-OMe), 3.80 (3H, s, 7-OMe); ^{13}C NMR (100 MHz, $CDCl_3$): 160.1 (C-2), 149.7 (C-6), 144.7 (C-4), 140.1 (C-7), 138.5 (C-8), 138.3 (C-9), 114.6 (C-3), 114.4 (C-10), 100.2 (C-5), 60.5 (OMe-7), 56.0 (OMe-6). MS, m/z: 207 $[M + H]^+$.

Trans-tiliroside (**II**): Pale yellow powder; mp 268-270 °C; ^{1}H-NMR (400 MHz, DMSO) δ: 7.98 (2H, d, *J* = 9.0 Hz, H-2′, H-6′), 7.36 (1H, d, *J* = 8.5 Hz, H-2‴, H-6‴), 7.33 (1H, d, *J* = 16.0 Hz, H-8‴), 6.84 (2H, d, *J* = 9.0 Hz, H-3′, H-5′), 6.78 (1H, d. *J* = 8.5 Hz, H-3‴, H-5‴), 6.38 (1H, d, *J* = 2.0 Hz, H-8), 6.15 (1H, d, *J* = 2.0 Hz, H-6), 6.09 (1H, d, *J* = 16.0 Hz, H-7‴), 5.42 (1H, d, *J* = 7.5 Hz, H-1″), 4.25 (1H, m, H-6″a), 4.02 (1H, m, H-6″b), 3.38 (1H, m, H-5″), 3.28-3.22 (2H, m, H-2″, H-3″). ^{13}C-NMR (100 MHz, DMSO) δ: 177.9 (C-4), 166.7 (C-9‴), 165.0 (C-7), 161.4 (C-5), 160.6 (C-5), 160.4 (C-4‴), 159.0 (C-4′), 156.3 (C-9), 156.2 (C-2), 144.5 (C-7‴), 133.1 (C-3), 130.6 (C-2′, C-6′), 130.2 (C-2‴, C-6‴), 124.8 (C-1″), 120.6 (C-1′), 115.6 (C-3‴, C-5″), 115.0 (C-3′, C-5′), 113.5 (C-8‴), 103.7 (C-10), 101,0 (C-1″), 98.6 (C-6), 93,6 (C-8), 76.3 (C-2″), 74.0 (C-2″), 69.8 (C-4″), 62.8 (C-6″). MS m/z: 595.3 $[M+ H]^+$.

Rutin (quercetin-3-O-rutinoside) (**III**). Yellow poder. ^{1}H-NMR (400 MHz, CD_3OD): δ: 7.71 (1H, d, *J* = 2.2 Hz, H-2′), 7.67(1H, dd, *J* = 8.5, 2.2 Hz, H-6′), 6.90 (1H, d, *J* = 8.4 Hz, H-5'), 6.44 (1H, d, *J* = 2.1 Hz, H-8), 6.23 (1H, d, *J* = 2.1 Hz, H-6), 5.16 (1H, d, *J* = 7.8 Hz, H-1″), 4.57 (1H, d, *J* = 1.6 Hz, H-1‴), 3.85 (1H, *J* = 11.0, 1.6 Hz, H-6″a), 3.65 (1H, dd, *J* = 3.5, 1.6 Hz, H-2‴), 3.56 (1H, dd, *J* = 9.4, 3.4 Hz, H-3‴), 3.53 (1H, m, 5‴), 3.52 (1H, m, H-6″b), 3.43 (1H, m, H-3″), 3.42 (1H, m, H-2″), 3.40 (1H, m, H-2″), 3.34 (1H, m, H-5″), 3.29 (1H, m, H-4‴), 1.16 (3H, d, *J* = 6.2 Hz, H-6‴); ^{13}C-NMR (100 MHz, CD_3OD): 179.5 (C-4), 166.5 (C-7), 163.7 (C-5), 160.5 (C-2), 157.2 (C-4′), 150.1 (C-4′), 146.0 (C-3′), 145.9 (C-3′), 135.4 (C-3), 123.5 (C-6′), 123.4 (C-1′), 117.7 (C-2′), 116.0 (C-5′), 106.1 (C-10), 104.6 (C- 1″), 102.4 (C-1‴), 99.9 (C-6), 95.2 (C-8), 78.2 (C-3″), 77.3 (C-5″), 75.5(C-2″), 73.6 (C-4‴), 72.4 (C-3‴), 72.1 (C-2‴), 71.4 (C-4″), 69.8 (C-5‴), 68.5 (C-6″), 17.9 (C-6‴). MS, m/z: 611 $[M+ H]^+$.

Kaempferol-3-O-rutinoside (**IV**). Yellow amorphous solid. ^{1}H-NMR (400 MHz, CD_3OD) δ: 8.10 (2H, d, *J* = 8.8 Hz, H-2′, H-6′), 6.91 (2H, d, *J* = 8.8 Hz, H-3′, H-5′), 6.41 (1H, d, *J* = 2.1 Hz, H-8), 6.20 (1H, d, *J* = 2.1 Hz, H-6), 5.10 (1H, d, *J* = 7.5 Hz, H-1″), 4.50 (d, 1H, *J* = 1.5 Hz, H-1‴), 3.80 (1H, dd, *J* = 1.0, 12.5 Hz, H-6″a), 3.62 (1H, dd, *J* = 1.5, 3.0 Hz, H-2‴), 3.61 (1H, dd, *J* = 1.5, 3.0 Hz, H-2‴), 3.50 (1H, dd, *J* = 3.0, 9.5 Hz, H-3‴), 3.43 (1H, dq, *J* = 6.0, 9.5 Hz, H-5‴), 3.41 (1H, dd, *J* = 7.5, 9.0 Hz, H-2″), 3.40 (1H, t, *J* = 9.0 Hz, H-3″), 3.37 (1H, dd, *J* = 6.0, 12.5 Hz, H-6″b), 3.30 (1H, ddd, *J* = 1.0, 6.0, 9.0 Hz, H-5″), 3.26 (1H, t, *J* = 9.5 Hz, H-4‴), 3.22 (1H, t, *J* = 9.0 Hz, H-4″), 1.10 (1H, d, *J* = 6.1 Hz, H-6‴). ^{13}C NMR (100 MHz, CD_3OD) δ: 178.4 (C-4), 164.5 (C-7), 162.9 (C-5), 161.5 (C-2), 159.2 (C-4′), 158.3 (C-9), 135.2 (C-3), 132.5 (C-2′, C-6′), 122.6 (C-1′), 116.0 (C-3′, C-5′), 105.5 (C-10), 104.3 (C- 1″), 102.4 (C-1‴), 99.8 (C-6), 95.2 (C-8), 78.2 (C-3″), 77.4 (C-5″), 75.6 (C-2″), 73.6 (C-

4‴), 72.4 (C-3‴),72.1 (C-2‴), 71.5 (C-4″), 69.7 (C-5‴), 68.5 (C-6″), 17.5 (C-6‴). MS, m/z: 595.1 $[M+H]^+$.

(+) Catechine (**V**): α $[CH_3OH]^{24}$ = 58.25. ^{1}H-NMR (400 MHz, CD_3OD) δ: 6.85 (1H, d, *J* = 1.9 Hz, H-2′), 6.78 (1H, d, *J* = 8.1 Hz, H-5′), 6.75 (1H, dd, *J* = 1.8, 8.1 Hz, H-6′), 5.92 (1H, d, *J* =2.3 Hz, H-6), 5.87 (1H, *J* = 2.3 Hz, H-8), 4.21 (1H, d, *J* = 7.5 Hz, H-2), 3.98 (1H, m, H-3), 2.86 (1H, dd, *J* = 5.5, 16.1 Hz, H-4b), 2.52 (1H, dd,*J* = 8,2, 16.1 Hz, H-4a). ^{13}C NMR (100 MHz, CD_3OD) δ: 156.5 (C-7), 156.2 (C-5), 155.5 (C-9), 99.4 (C-10), 94.9 (C-6), 94.1 (C-8), 81.5 (C-2), 67.4 (C-3), 27.1 (C-4), MS m/z: 260.1 $[M+H]^+$.

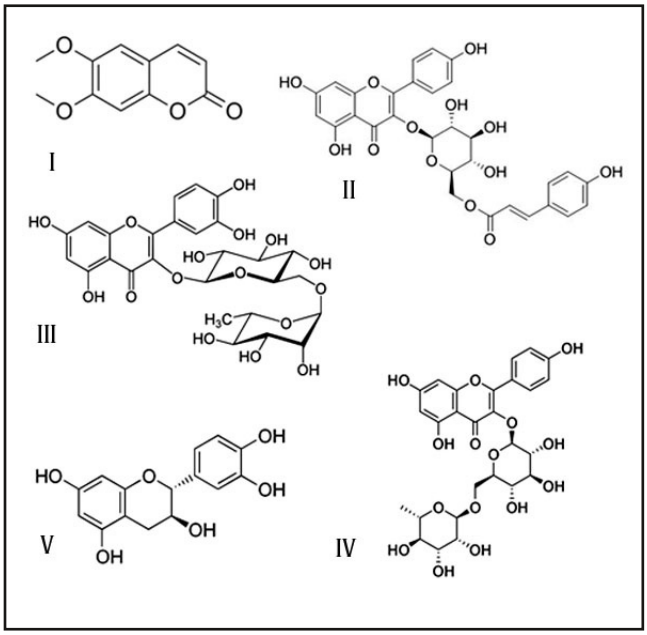

Figure 1. Chemical structures of isolated phenolics

Results and discussion

All the compounds isolated in this first phytochemical research of *Protium tovarense* may be included in the classification of phenolic compounds (**Figure 1**), these are those metabolites which contain aromatic rings substituted by hydroxyl groups, being examples phenolic acids as ferulic, coumaric, rosmarinic; flavonoids is a varied family of compounds belonging to the phenolic ones; coumarins as well phenolic glycosides are contained within this wide grouping. The simple phenolic, are well studied, and from a long time ago is well known their pharmacological activities including anti-inflammatory, hepatoprotector, antitumoral among others (Fraga, 2009; Mahdi *et al.*, 2013; Saha *et al.*, 2019). The literature regarding at this point that includes the flavonoids is also rich, from antioxidants to antivirals, the diverse biological activities mentioned for these compounds are wide (Ahmad *et al.*, 2015; Panche *et al.*, 2016; Xiao *et al.*, 2016; Karak, 2019; Khalid *et al.*, 2019; Rana and Gulliya, 2019). The coumarins are recognized with properties like immunostimulant, anti-coagulant, anti-depressant, antibacterial, and anti-cancer (Jain and Joshi, 2012; Srikrishna *et al.*, 2018; Hussain *et al.*, 2019).

The results of this phytochemical study showed that the fruits of *Protium tovarense*, has between the major compounds scoparone (**I**), this is a common coumarin which had been investigated for the diverse pharmacological activities that this small molecule presents, anti-allergy (Choi and Yan, 2009), antitumor (Kim *et al.*, 2013), anti-inflammatory (Srikrishna *et al.*, 2018); regarding this effect, an interesting work revealed that scoparone has anti-neuroinflammatory properties for which could be used how promising compound to be investigated to develop novel drugs for the prevention and treatment of neuroinflammatory diseases (Cho *et al.*, 2016). The effect of

scoparone in vasorelaxation is well known for a long date (Huang *et al.*, 1991, 1992), and recent research pointed out that scoparone has a strong antiplatelet activity for which it has been considered a lead compound to prevent platelet-derived vascular disease (Lee, 2019), and specifically to prevent cardiac fibrosis (Fu *et al.*, 2018).

Trans-tiliroside (**II**) is an interesting flavonoid with a p-coumaroyl moiety, which has been the objective of a series of pharmacological studies, antioxidant, anti-microbial, antifungal, antidiabetic and antihyperlipidemic, antiviral and cytotoxic, anti-inflammatory, anti-rheumatism, inhibition of neuroinflammation and acute inflammation and hepatoprotective activities are included (Luhata and Luhata, 2017, Devi and Kumar, 2018, Grochowski *et al.*, 2018). The antiprotozoal activity was demonstrated (Calzada *et al.*, 2017), as well antihypertensive (Silva *et al.*, 2013) antiproliferative effect in cancer cells (Da'I *et al.*, 2016), neuroprotector (Velagapudi *et al.*, 2018), and recently as a potential drug, to treat osteoporosis (Li *et al.*, 2019).

One of the more ubiquitous flavonoids in nature is rutin (3,3',4',5,7-pentahydroxyflavone-3-O-rhamnoglucoside) (**III**), its common name is precisely due to this abundance, and is the reason for which has been submitted to a large series of pharmacological assays and endorsed with several therapeutic properties, the list is long, and some authors had reviewed this potential (Chua, 2013; Sharma *et al.*, 2013; Hosseinzadeh and Nassiri-Asl, 2014; Al-Dhabi *et al.*, 2015; Ganeshpukar and Saluja, 2017; Gullón *et al.*, 2017). Rutin has demonstrated an interesting cardioprotective effect, proving to be an interesting leader compound to works in heart failure (Siti *et al.*, 2020); its anti-inflammatory and antinociceptive effects are indeed for this glycosylated flavonoid (Mascaraque *et al.*, 2014, Selvaraj *et al.*, 2014).

In this research, was also isolated kamferol-3-O-rutinoside (IV), this metabolite included under the glycosylated flavonoids, shared some pharmacological properties with rutin such as antidiabetic (Habtemariam and Lentini, 2015) anti-inflammatory (Hwang *et al.*, 2019), hepatoprotective (Wang *et al.*, 2015); antinociceptive (Toker *et al.*, 2004) as well antiangiogenic activity (Kumazawa *et al.*, 2013).

Finally between the isolates from *Protium tovarense* fruits was found catechin (V), an old known flavonoid, which had been the goal of many pharmacological types of research, some properties like as antispasmodic, bronchodilator (Ghayur *et al.*, 2007), anti-infective agent (Schimamura *et al.*, 2007), antiviral (Mantani *et al.*, 2001), anticancer (Manikandan *et al.*, 2012; Delgado *et al.*, 2014), as well the antioxidant effect claimed for the flavonoids (Li *et al.*, 2019).

Conclusion

The results of this first phytochemical analysis of *Protium tovarense*, showed that the fruits contain phenolic compounds as major constituents, all these isolated compounds are recognized with diverse pharmacological actions. From the point of view of the chemotaxonomy, the compounds here are described agreeing with other

compounds isolated from the genus. The developing investigation of the leaves and stem barks of this plant allows characterizing all the metabolites present in this plant used indistinctly like other species of the genus, in the folkloric medicine of Venezuela. The pharmacological actions of the metabolites found in this species make it a good candidate to assay in vitro and in vivo therapeutic activities.

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