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Brickellia paniculata (Mill.) B.L. Rob: A Review of Medicinal Uses and Chemo-Biological Potential

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Abstract

Medicinal plants (MP) are a reservoir of chemical structures and have great economic importance due to their diverse biological activities. These are used by more than 80% of the world population, for this reason these are overexploited because they are a source of main drug (taxol, morphine, vincristine, vinblastine, artemisinin, galegin, etc.), and also have high nutritional, timber, cosmetic, and/or agricultural value. At present, China exports 120,000 tons of MP, India about 32,000 tons while Europe imports 400,000 tons; this overexploitation has caused many of these plants to be in danger of extinction. Also, MP are raw material for the development of phytodrugs such as Ginseng, Hyperikan, EchinaceA, Kava-kava, Vitango, Plantival, Prostasan among others, whose therapeutic efficacy and safety has been scientifically assayed. *Brickellia paniculata* is widely used in Mexico in traditional medicine, and has been poorly investigated from the chemical and biological point of view; so in this paper we describe the biological and chemical reports for this medicinal plant.

Keywords: Xantomicrol; Diterpenes; Brickellia paniculata; Cytotoxic Compounds

Introduction

Medicinal Plants as a Source of Bioactive Compounds and Phytodrugs

Plants make up an enormous reservoir of chemical structures, their medicinal use being of major economic importance due to various biological activities described, that over the years have improved man's survival thanks to their use in Traditional Medicine (TM) and to being a source of many of the drugs of current therapy [1,2].

TM is widely used, and is for some developing countries a widely used health system that is growing rapidly and is of great economic importance due to its affordability, coupled with the high cost of health systems. In Africa, up to 80% of the population used TM to help satisfy its health needs. In Asia and Latin America, populations continue to use TM as a result of historic circumstances and cultural beliefs. In China, TM is highly transcendent, due to the high percentage (over 60%) of the population that uses it. Meanwhile, in many developed countries, the percentage of the population that uses TM at least once is 48% in Australia, 70% in Canada, 42% in the U.S., 38% in Belgium and 75% in France [3].

Today, medicinal plants (MP) are used by around 80% of the world population; making them overexploited, not only as a source of main income, but also for their nutritional, lumber, cosmetic, agricultural and/or medicinal value. For example, it is estimated that China exports 120,000 tons of MP, India 32,000 tons, while Europe imports 400,000 tons of MP. All the above leads to overexploitation of the species, and many of them are in danger of extinction [4,5].

The International Union for the Conservation of Nature

and the World Widelife Fund note that there are between 350,000 and 550,000 species of MP globally, of which around 20% have documented research on their biological potential, around 15,000 species are in danger of extinction due to overexploitation and destruction of habitat [5,6].

Today, scientific interest in MP has increased, due to the elevated costs and side effects of allopath drugs, added to the ever more frequent appearance of microorganisms (parasites, bacteria or virus) strain resistant to current treatments [3,7]. It should be mentioned that about 25% of the main agents of allopath drugs currently in use were isolated and/or semi-synthesized from plants [4].

In the literature, numerous bioactive compound obtained from MP are broadly described, with current therapeutic importance, among which we can mention taxol, morphine, vincristine, vinblastin, artemisinin, galegin, among others [8,9]. Other examples are digoxin, used as a cardiotonic and isolated from *Digitalis purpurea* (common name purpura); aescin, used as an anti-inflammatory and venotonic, it was isolated from *Aesculus hippocastanum* (common name Indi knut); another compound used for circulatory disorders is ajmalicin, isolated from *Rauwolfia sepentina*; paclitaxel (anticancerigen) has been semi-synthesized by Bristol-MyersSquibb since 2002, this is obtained from the compound 10-desacetylbacatin III isolated from the plant *Taxus baccata*; diosgenin, a steroid sapogenin obtained from the tubers of several *Dioscorea* species, it is a raw material to semi-synthesis of the progesterone [10]. Guanidin is another natural product with good hypoglucemic activity, isolated from *Galega officinalis* (L); however, this compound is toxic for human consumption, and is semi-synthesized into compounds with less toxicity and with similar pharmacological effect; one of these molecules was metformin (dimethylbiguanide), which is actually used in the treatment of diabetes mellitus type 2. It is worth mentioning that, due to the high demand for metformin in the market, companies have a need to discover new sources of raw material from MP [11].

On the other hand, the development of phytodrugs from MP is also important; these are make-up from vegetal material or some derivative from them, where the main ingredient is the aerial or underground part of a plant; this includes duly standardized extracts, tinctures, juices, resins, fatty acids and essential oils presented in some pharmacological form, whose therapeutic efficacy and safety has been scientifically confirmed [12].

Some phytodrugs examples are ginseng, which is obtained from plants of the genus *Panax* (*P. ginseng* and *P. quinquefolium*), that come from Asia and America, respectively. The main biological effect of ginseng is a "tonic" drug, since it has the ability to increase the capacity to tolerate tensions, which increases physical and mental output. Another phytodrug from St. John's wort (*Hypericum perfotarum*) is hyperikan, which is standardized based on its content hypericin; its main pharmacological use is against depression; *Ginkgo biloba* (Ginkgo) belongs to the family of Ginkgoaceae, active components present in the leaf extract are gingolides (gingolide A-C, J and M), which are a mixture of sesquiterpenic and diterpenic lactones and flavonoids; the majority of the commercial preparations of ginkgo are standardized leaf extracts with approximately 5 to 7% terpenic lactons and 22 to 27% flavonoids, and is used mainly for the treatment of cognitive decline associated with cerebral blood circulation disorders such as dementia.

The phytodrug made from *Echinacea purpurea*, has the commercial name Echinace-A, which is standardized from its content of echinocosides (derived from cafeic acid), whose main biological effect is immunostimulant activity [13]. In Oceania, the Kava-kava is the extract of the root and rhyzome obtained from *Piper methysticum*, this product is standardized with 30% kava lactones, which are used for their neurotransmitting activity [14]. Another phytodrug is Vitango, obtained from *Rhodiola rosea;* the extract is standardized with 3 to 5% rosavins and 1% salidrosides, and this product reduces the stress associated with physical and mental work [15]. Plantival is a mixture of extract from *Valeriana officinalis* (160 mg) and *Melissa officinalis* (80 mg), and is used as an anxiolytic and antidepressive in children [16]. Another phytodrug is known as Prostasan, it is the extract of *Serenoa repens* standardized to 25% fatty acids, the dosage used is 160 mg, the main effect is antiandrogenic and against benign prostate hyperplasia [17]. Recently, a phytodrug (Acheflan) has been developed with anti-inflammatory effect from *Cordia verbenaceous*, which is standardized with its content of α-humelen [18], this medicinal plant is widely used in Brazil for treatment inflammatory processes.

Other products that are under registration with the Food and Drug Administration (FDA) are Verengen, it contain polyphenols (catechins) from green tea (*Camelia sinensis*) to treat genital and perianal warts; Mytesi or Fulyzaq, is made with extract standardized from *Croton lechleri,* and contain an oligomeric mixture of proantocianidin (catechin, galocatechin, epicatechin and epigalocatechin) and is used to treat diarrhea in HIV patients; other phytodrugs is Sativex, that contains derivatives of canavinol useful in treating multiple sclerosis. Other two products are Marinol and Cesamet (obtained from the marijuana, *Cannabis sativa*), useful in treating vomit in cases of chemotherapy [18]. It is estimated that around 50% of the drugs approved by the FDA are products that come from some natural source or are derivate coming from plants, or from land and aquatic microorganisms [3,9]. Given the importance of medicinal

plants as a source of bioactive compounds, the object of this work is to describe the chemical and biological information described in the scientific literature on the medicinal species *Brickellia paniculata.*

Material and Methods

An exhaustive search was made (from 1960 to 2019) in the main scientific portals: Scopus, PubMed and WorldWideScience.org. The key words used were: medicinal plants, *Brickellia paniculata*, polyphenols, and bioactive compounds.

Results

Ethnobotanic Information from *Brickellia paniculata* (Mill.) B.L. Rob

This medicinal species (Figure 1) belongs to the family Asteraceae, the genus is originated in the new world and includes around 100 species that grown wild from the south of Canada to South America, and are reported in the biosphere reserve Tehuacán-Cuicatlán (Flora del Valle of Tehuacán-Cuicatlán). In Mexico, a great number of the species have been located, and some possess medicinal properties, mainly to treat gastrointestinal problems [19]. They are commonly known as *prodigiosa o ch´ail pox* (Tzetzal and Tzotzil languages, Chiapas). In the Atlas of Medicinal Plants of Mexico, two species of the same genus are registered with the same common name (prodigious) that correspond to *B. cavanillesii* and *B. squirrosa* [19].

Figure 1: Greenhouse sample of the medicinal species *Brickellia paniculata.*

Commonly, in the southeast of the country, the aerial parts and stems of this plant are used to treat stomachaches, watery diarrhea and gastrointestinal problems, so it is an important herbal resource for the residents of this area [20-22].

Chemical Investigation of *Brickellia paniculata* (Mill.) B.L. Rob

From Methanol (MeOH) extract of the aerial parts of *B. paniculata,* a diterpene 3α-angeloiloxy-2α-hydroxy-13,14Z-di-dehydrocativic acid (**1**) was isolated; this compound was also isolated from petroleum ether extract of *B. eupatoriedes* aerial parts [23-27]. From MeOH extract of *B. paniculata,* other diterpene and an one flavonoid were also isolated, these were identified as 3α-angeloiloxy-2α-hydroxicativic acid (**2**) [28] and a 5,4´-dihydroxy-6,7,8-trimethoxyflavone (also known as Xantomicrol, **3**). This last metabolite was the main constituent in this extract [26,27] and also was also isolated from *Ocimum gratissimum* and was proposed as a biomarker to identify chemotaxonomy of the species [29,30]. Xantomicrol was also isolated from ethyl acetate and diethyl ether extracts of the *Dracocephalum kotschyii* leaves [31-33], and from some species of the *Sideritis* genus [34] such as *S. angustifolia* and *S. jahandiezii* [35], and from *Baccharis pentlandii, B. nitida* [36,37].

Compound **3** was isolated from acetonic extract of *Thymus vulgaris* [38], and from *Varthemia iphionoides* (ethanolic extract) [39]; in addition, from the MeOH and MeOH 70% extracts from *Stachys chrysantha, S. schtschegleevii* and of *S. candida* aerial parts [40,41], and in the MeOH extract from propolis collected in the state of Sonora was also isolated [42]. Some species (*Varthemia, Bacharis, Ambrosia, Bracteantha, Olearia* and *Brickellia*) from Asteraceae family are source of this compound, and only in two species of the family Fabaceae and one species of the family Rutaceae and Scrophulariaceae has been reported [35].

Biological Investigation of *Brickellia paniculata* (Mill.) B.L. Rob

MeOH extract from leaves of *B. paniculata* showed antimicrobial activity against *Escherichia coli* and *Candida albicans* [43] with a minimum inhibitory concentration (MIC) = 23 mg/mL; this extract showed a moderate anti-inflammatory effect (64% inhibition of edema at 20 min and the 7th h the inhibition was 37%) in the *in vivo* model of subplantar edema induced with carrageenan, the extract was administered by intraperitoneal via at dose of 400 mg/kg [44]. This extract also inhibited the contraction of the guinea pig ileum induced by electric stimulation; resulting in spasmolitic activity [45]. Through bio-guided chemical fractionation from this extract, the active compounds were

isolated and was chemically identified as **1** and **3**. Both compounds have been isolated from several species of *Brickellia* genus [23-25,46,47]. These compounds were responsible for antispasmodic activity, by relaxing the smooth musculature of the guinea pig ileum *in vitro* through the antagonist effect of Ca (2 mM), the effect was similar to that of papaverine, positive control [26,27]. Xantomicrol was more potent that the 3α-angeloiloxy,2α-hydroxy,13,14Z-di-deshydrocativic acid, since this compound (**3**) inhibited the contraction induced with KCl 60 mM. On the other hand, 3α-angeloiloxy-2α-hydroxy-13,14Z-di-deshydrocativic acid (**1**) proved to be more potent than xantomicrol in inhibiting the contraction induced with oxytocin 10 mUI/mL [27,48].

Xantomicrol is a compound with significative *in vitro* cytotoxic activity, it inhibited the cellular proliferation of some cell lines (Table 1) using MTT colorimetric assay [bromide of 3-(4,5-dimethyltiazol-2-yl) -2,5-diphenyltetrazolium bromide] [32], this activity was determined in six human cellular lines (K562: human chronic myeloid leukemia; HL60: human promyelocitic leukemia; Saos-2: human osteogenic sarcoma; A2780-cp: human ovarian carcinoma resistant to cisplatin; A2780-s: human ovarian carcinoma sensitive to cisplatin; HFFF-P16: human fetal foreskin fibroblast). The mean inhibitory concentration (IC_{50}) was < 1.69 µg/mL against 5 of the six cellular lines tested, excepting line HFFF-P16, with IC_{50} = 13.8 µg/mL, and regarding the cytotoxic index it showed poor activity respect to positive control (doxorubicin) (Table 1).

Regarding Xantomicrol activity, Moghaddam, et al. [49] reported that it compound was evaluated against the following cell lines: human gastric adenocarcinoma -AGS- (IC_{50} = 4.5 µg/mL), human colon carcinoma -HT-29- (IC_{50} = 42.6 µg/mL), HL-60 (IC_{50} = 38.5 µg/mL), human osteosarcoma -SaOs-2- (IC_{50} = 40.6 µg/mL), murine fibrosarcoma -WEHI-164- (IC_{50} = 32.8 µg/mL), and HFFF-P16 (IC_{50} = 55.9 µg/mL). The complete trial was MTT, and the results showed that the compound was more active against the AGS line and scarcely active against the other cell lines. Xantomicrol also showed a significative antiplatelet activity [39]. Another researchers group described the antiproliferative effect of Xantomicrol (isolated from pollen collected in the state of Sonora, México) against six cell lines [normal subcutaneous connective tissue (L-929), murine B cell lymphoma (M12.C3.F6), murine macrophage cell line (RAW 264.7), virus transformed from Abelson murine leukemia (A-MuLV), human lung carcinoma (A-549), human cervical carcinoma (HeLa), human colon adenocarcinoma (Ls 180)], the results obtained showed scare activity against M12.C3.F6 (IC_{50} = 38.5 µM) and RAW 264.7 (IC_{50} = 48.7 µM), and against the other cell lines it was inactive (IC_{50} > 80.45 µM) [42]. On the other hand, the fraction rich in polyphenols obtained from *Ambrosia artemisiifolia* that contains Xantomicrol showed hepatoprotector and hypolipemic activity in *in vivo* model [50]. Also, compound **3** has antioxidant activity [38].

Cell line	IC_{50} (µg/mL)		Cytotoxic index	
	Xantomicrol	Doxorubicin	Xantomicrol	Doxorubicin
K562	1.69	0.11	8.2	0.18
HL60	0.88	0.04	15.76	0.42
Saos-2	0.75	0.02	18.5	1.1
A2780-cp	1.56	0.06	8.9	0.32
A2780-s	0.89	0.06	15.5	0.32
HFFF-P16	13.8	0.018	-	-

Table 1: Cytotoxic activity of Xantomicrol (3) against several cell lines [32].
K562: human chronic myeloid leukemia; HL60: human promyelocitic leukemia; Saos-2: human osteogenic sarcoma; A2780-cp: human ovarian carcinoma resistant to cisplatin; A2780-s: human ovarian carcinoma sensitive to cisplatin; HFFF-P16: human fetal foreskin fibroblast.

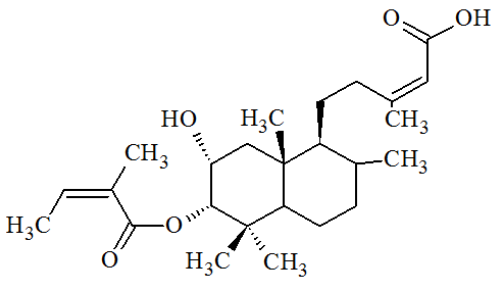
In an *in vitro* study performed on macrophages, was found that Xantomicrol inhibited on the release of prostaglandins, leukotriens and tromboxans at a concentration of 100 µM [41]. Anti-inflammatory activity has been described for the ethyl acetate extract from *Stachys schtscheglevii*, which contains compound **3**; in this case the model used was of carrageenan, and it was reported that the extract at 100 mg/kg showed good anti-inflammatory activity at 2 hr, and doses of 200 and 400 mg/kg exhibited a good percentage of inhibition at 2, 3 and 4 hr; however, in this study no described the reference drug [40].

Other biological activities that have been described for Xantomicrol (obtained from *Varthemia iphionoides*) is antifungal activity against *Fusarium solani, Aspergillus niger* and *Candida tropicalis*), and was inactive with *Staphylococcus aureus, Bacillus cereus* and *Salmonella typhimurium* [35,39,51], antispasmodic (determined in rat uterus, stimulated with KCl 60 mM and oxytocin 10 mUI/mL), also reduced the spasms induced with acetylcholine, histamine

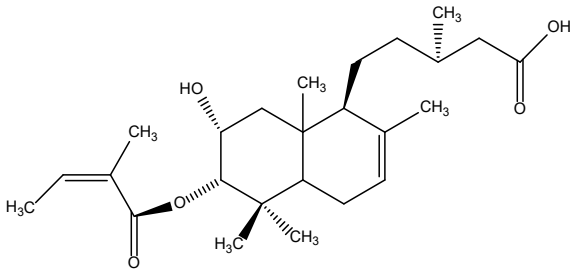
and barium chloride [26,27,48].

Conclusion

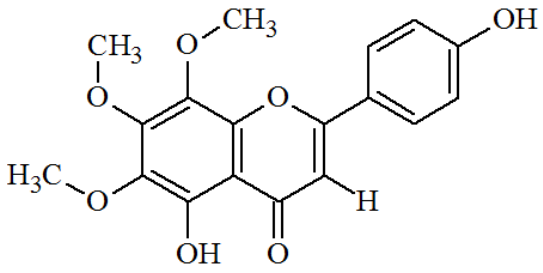
Brickellia paniculata is a plant widely used in traditional medicine in our country; to date there is scarce research performed on the biological potential and chemical importance. Of the few studies carried out, only one flavone has been isolated, it was chemical identified as Xhantomicrol, and two diterpenes identified as 3α-angeloiloxy-2α-hydroxy-13,14Z-di-dehydrocativic acid and 3α-angeloiloxy-2α-hydroxicativic acid. Xantomicrol is the main compound in MeOH extract from *B. paniculata* aerial parts. It has been reported that this secondary metabolite exhibited a significative cytotoxic activity, and that the species *Brickellia paniculata* may constitute a potential source of anti-inflammatory and cytotoxic compound.



3α-angeloiloxy,2α-hydroxy-13,14 Z dehydrocativic acid (1)



3α-angeloiloxy-2α-hydroxicativic acid (2)



Xantomicrol (**3**)

Disclosure

All authors have read and approved the final version of the manuscript and declare that they have no conflicts of interest.

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