

Physalis angulata L. (Bolsa Mullaca): A Review of its Traditional Uses, Chemistry and Pharmacology

[*Physalis angulata* L. (Bolsa Mullaca): Revisión de Usos Tradicionales, Química y Farmacología]

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Abstract

Physalis angulata is a specie of the Solanaceae family, which edible fruit is used in several countries of tropical and subtropical regions of the world as medicinal and fruit-tree. This review shows research over the last 30 years, about traditional uses, chemical constituents and pharmacology of this specie. The studies related to traditional uses show that *P. angulata* is known for its antimalarial, anti-inflammatory and post-partum treating properties. It presents the different pharmacological experiments *in vitro* and *in vivo* models that have been made, also the identification of phytochemical constituents with medicinal importance, the main being physalins and withanolides. Pharmacological studies have shown antiparasitic, anti-inflammatory, antimicrobial, antinociceptive, antimalarial, antileishmanial, immunosuppressive, antiasthmatic diuretic, and antitumor activities, thus validating its traditional uses and demonstrating the great potential of this specie for further development within the pharmaceutical industry.

Keywords: *Physalis angulata*, Solanaceae, traditional medicine, phytochemistry, pharmacological activities.

Resumen

Physalis angulata, es una especie de la familia Solanaceae, de frutos comestibles, que en diferentes países de regiones tropicales y subtropicales del mundo utilizan como medicinal y frutal. La presente revisión muestra las investigaciones realizadas durante los últimos 30 años, sobre los usos tradicionales, componentes químicos y farmacología de esta especie. Los estudios referidos a los usos tradicionales, muestran que la especie es conocida por propiedades antimaláricas, antiinflamatorias y en el tratamiento de postparto. Se muestran los diferentes experimentos farmacológicos de ensayos *in vitro* y modelos *in vivo* que se han realizado, asimismo la identificación de sus constituyentes fitoquímicos con importancia medicinal, siendo los principales las fisalinas y los witanólidos. Los estudios farmacológicos revelan que tiene actividad antiparasitaria, antiinflamatoria, antimicrobiana, antinociceptiva, antimalárica, antileishmania, inmunosupresor, antiastmático, diurético y antitumoral, validando de esta manera sus usos tradicionales y demostrando el gran potencial que tiene esta especie para un mayor desarrollo dentro de la industria farmacéutica.

Palabras Clave: *Physalis angulata*, Solanaceae, medicina tradicional, fitoquímica, actividad farmacológica.

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INTRODUCTION

Physalis is an important genus of the Solanaceae family. Most of the species are herbaceous annuals or perennials, native tropical North and South America. Some species have edible fruits and tea made from its roots is considered within popular medicine. The medicinal uses of *Physalis* are numerous: a wide variety of species are used for asthma, urinary problems, rheumatism, and tumors. Their anti-inflammatory and anti-spasmodic properties are also known (Silva *et al.*, 2005). Also some species of *Physalis* are used in local crafts, ornamental and food, the most common and most important use is in the preparation of sauces (Sánchez *et al.*, 2008).

Physalis angulata L., known in the Peruvian Amazon as bolsa mucalla or mullaca, is a much branched annual shrub, perennial in subtropical zones, and can grow until it reaches 1.0 m. The flowers are bell-shaped, but the most distinctive feature is the fruiting calyx which enlarges to cover the fruit and hangs downwards like a lantern. Each fruit is like a yellow pearl in to a small lantern shape pod and very delicious to eat. In Peru it is widely distributed within following departments: Amazonas, Cajamarca, Huánuco, Junín, La Libertad, Loreto, Madre de Dios, Pasco, San Martín and Ucayali (Mejía and Rengifo, 2000).

This review evidences the great interest about this plant. Therefore, the objective of this review was to get updated comprehensive information about *P. angulata* including their traditional uses in traditional medicine, phytochemistry and pharmacology. It performed an articles selection of last thirty years with the purpose of finding the best information about this species, by systematic review in following bibliographic databases: Science Direct, EBSCO, WILEY, PubMed, Open Access Journals DOAJ, Scientific Electronic Library Online (SCIELO), Springer Link and RSC Journals.

Use in Traditional Medicine

Recent ethnopharmacological studies show that *Physalis angulata* is used in many parts of the world to treat several diseases, as anticancer, antibacterial, for diabetes, treatment of malaria, anemia and reducing fever. In Peru, it has been documented that native groups in the Peruvian Amazon, use the decoction of leaves and fruit for "Tertian" due to postpartum infections (Jovel *et al.*, 1996) and maceration of aerial part for the treatment of malaria (Ruiz *et al.*, 2011).

Also, mestizo populations use it for treatment of diabetes, by taking a glass of macerated root combined with honey, twice daily for 60 days. The root infusion is taken for hepatitis; the leaf infusion is used as a diuretic, for asthma, malaria, inflammation and as a disinfectant, the unripe fruit is used to treat scabies (Mejía and Rengifo, 2000).

In Brazil, the sap is used for earache, the roots boiled with the genus *Bixa* and *Euterpe* for jaundice (Duke and Vásquez, 1994). In the state of Paraíba, people use the leaves infusion as a sedative and against inflammations of bladder, spleen and kidney; in the case of inflammations a tea is taken until symptoms disappear and as sedative it is drunk at night (Agra *et al.*, 2007). In Marudá community, state of Pará, root is taken as a tea for hepatitis symptoms, anemia, urine infection, stomachache, prostate and kidney stones (Coelho-Ferreira, 2009). In Bolivia, the indigenous community of Tacana, the root decoction is used to treat fever (Bourdy *et al.*, 2000).

In Nigeria the traditional use reported is broad, wherein all parts of the plant have been used for medicinal purposes; entire plant is for childbirth, diuretic, fever, gonorrhoea, jaundice, liver diseases, malaria, nephritis, postpartum hemorrhage, rashes, skin sores, sleeping sickness, to prevent abortion, tumors. The fruits are recommended for infection, infertility, inflammation, postpartum infection, skin diseases. The leaves are also used for asthma, dermatitis, diuretic, earache, fever, gonorrhoea, hemorrhage, hepatitis, infections, inflammation, liver disorders, malaria, postpartum infection, rheumatism, skin diseases, to prevent abortion, worms (schistosomiasis). The root is used for diabetes, earache, fever, hepatitis, jaundice, liver disorders, malaria and rheumatism (Lawal *et al.*, 2010). In Kenya the infusion of the whole plant is used for worms and stomach pain (Geissler *et al.*, 2002).

In Samoa, the leaves are used as antibacterial (Cox, 1993). In the Kingdom of Tonga, the crushed leaves are topically applied for skin inflammation (Whistler, 1991). In Indonesia use the root decoction as a remedy for postpartum, muscle aches and hepatitis (Roosita *et al.*, 2008). In India, leaf paste is used as an external application for wounds (Sudhakar *et al.*, 2009).

Besides medicinal uses, in Mexico the fruits are used to make sauces commonly accompanied by other plants species such as onion (*Allium cepa* L.) and

peppers (*Capsicum sp.*) of various kinds (Santiaguillo and Blas, 2009).

Summary of use *P. angulata* in traditional medicine is presented in Table 1.

Table 1
Use in traditional medicine of *Physalis angulata*

| Country | Part(s) used | Ethno medicinal uses | Preparation(s) | Reference(s) |
|--|-----------------------|--|---|---|
| Peru Loreto, Ucayali, San Martin, Madre de Dios | Leaves, fruits, roots | Postpartum infections, diuretic, asthma, malaria, inflammations, scabies | Maceration, infusion, decoction, direct application | Jovel <i>et al.</i> , 1996; Pérez, 2002; Ruiz <i>et al.</i> , 2011; Mejía and Rengifo, 2000. |
| Bolivia | Roots | Fever | Decoction | Bourdy <i>et al.</i> , 2000. |
| Brazil | Roots | Inflammations, hepatitis, anemia, urine infection, diabetes, prostate, earache | Infusion, tea, sap | Agra <i>et al.</i> , 2007; Coelho-Ferreira, 2009; Duke and Vásquez, 1994. |
| Indonesia | Roots | Remedy for postpartum, muscle aches, hepatitis | Decoction | Roosita <i>et al.</i> , 2008. |
| India | Leaf | Wounds | Paste used as a external application | Sudhakar <i>et al.</i> , 2009. |
| Nigeria | Whole plant | Childbirth, diuretic, fever, gonorrhea, jaundice, liver diseases, malaria, nephritis, postpartum hemorrhage, rashes, tumours, diabetes | Infusion, decoction | Lawal <i>et al.</i> , 2010. |
| Ivory Coast | Whole plant | Malaria | Decoction | Guédé <i>et al.</i> , 2010. |
| Kingdom of Tonga | Leaves | Skin inflammation | Applied topically | Whistler, 1991. |
| Kenya | Whole plant | Worms, stomach ache | Infusion | Geissler <i>et al.</i> , 2002. |
| Equatorial Guinea | Leaf | Anti-dermatitis | Enema | Akendengué, 1992. |

CHEMICAL CONSTITUENTS

Phytochemical studies on *P. angulata* revealed that it contained flavonoids, alkaloids and many different types of plant steroids. The main components are commented below.

Physalins

Physalins are the steroidal lactone constituents from *Physalis* and other closely related genera, belonging to the family Solanaceae. The physalins are biogenetically related to the withanolides (Chen *et al.*, 2011). From the stems and leaves of *P. angulata*, the

isolation of five new physalins E, F, H, I and K, along with physalins B, G and D is reported by Row *et al.* (1978, 1980). Two new physalins, physalins U and V, together with seven known ergostane-type steroidal compounds were isolated from methanol extract of *P. angulata* (Kuo *et al.*, 2006). Damu *et al.* (2007) reported the isolation of a new minor physalin, physalin W.

Withanolides

The withanolides are a group of naturally occurring steroids built on an ergostane skeleton, in which C-22

and C-26 are appropriately oxidized in order to form a δ -lactone ring. These compounds are specific for the Solanaceae family, and, in particular, for the genera *Withania*, *Acnistus*, *Dunalia*, *Physalis*, *Datura*, *Lycium* and *Jaborosa*. So far, notable activities were reported for withanolides, including anticancer, anticonvulsive, immunosuppressive, and antioxidant properties (Glotter, 1991).

Four new withanolides, physagulin A, B, C and D, were obtained from the methanolic extract of the fresh leaves and stems of *P. angulata* (Shingu *et al.*, 1991; 1992).

Trypanocidal activity-guided fractionation of MeOH extract from aerial parts of *P. angulata* resulted in isolation of ten withanolides, physagulins A, B, C, and F, withangulatin A, whitaminimin and four new physagulins H, I, J and K (Nagafuji *et al.*, 2004).

A study of the methanol extract from aerial part of *P. angulata* resulted in isolation of new withanolides, designated physalin L, M and N (Abe *et al.*, 2006).

Also He *et al.* (2007) reported isolation and structure elucidation of eleven withanolides of MeOH extract from aerial parts of *P. angulata*, four new compounds, physagulins L, M, N and O; and seven known withanolides identified as withangulatin A, physagulin K, whitaminimin, physagulin J, physagulin B, pubesenolide and physagulin D. Although repeat names for physagulins L, N and M, they have different chemical structures.

The cytotoxic assay guided fractionation of methanol extract *P. angulata* resulted in isolation a

novel withaniloide, physanolide A, with an unprecedented skeleton (Kuo *et al.*, 2006).

Fractionation of CHCl_3 and *n*-BuOH soluble of MeOH extract from the whole plant was guided by *in vitro* cytotoxic activity assay using cultured HONE-1 and NUGC cells led to isolation of seven new withanolides, withangulatin B, C, D, E, F, G and H (Damu *et al.*, 2007). Lee *et al.* (2008) reported isolation and structural elucidation of minor withanolides, withangulatin I from *P. angulata*.

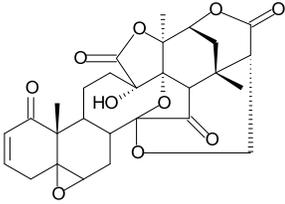
Jin *et al.* (2012) reported the discovery of three antiproliferative withanolides with an unusual carbon framework, namely, physangulidines A, B and C, isolates from *P. angulata* L. using bioassay-directed isolation technique.

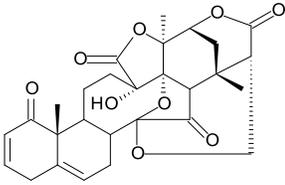
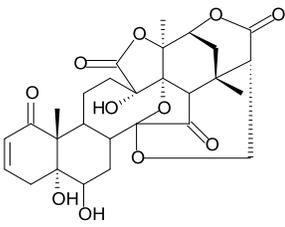
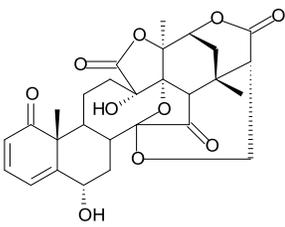
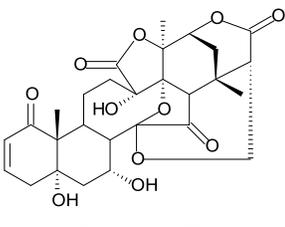
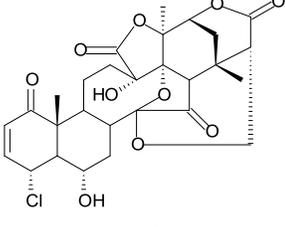
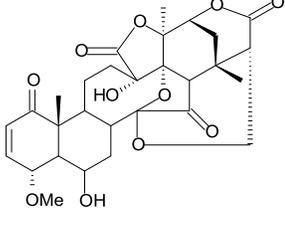
Carotenoids

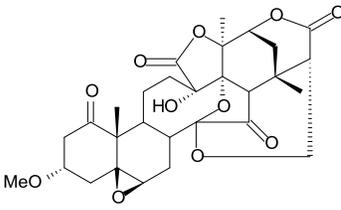
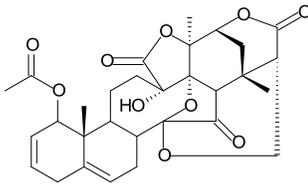
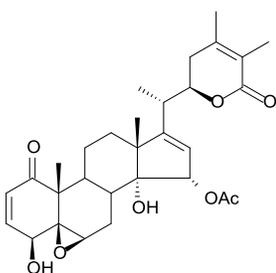
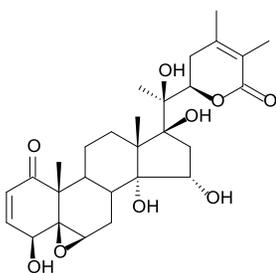
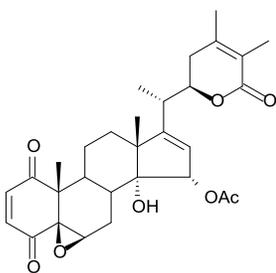
A positive correlation has been observed between ingestion of vegetables and fruits containing carotenoids and prevention of several chronic-degenerative diseases, such as cancer, inflammation, cardiovascular disease, cataract and age-related macular degeneration. Carotenoids from fruit of *P. angulata* were determined by HPLC-PDA-MS/MS and 22 compounds have been identified. all-trans- β -carotene was major carotenoid, contributing 62.2% to total carotenoid, followed by 9-cis- β -carotene and all-trans- α -cryptoxanthin, contributing around 2.9 and 2.7%, respectively (De Rosso and Mercadante, 2007).

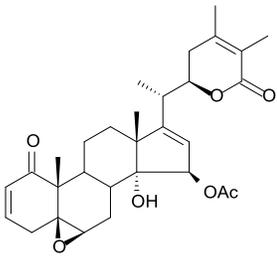
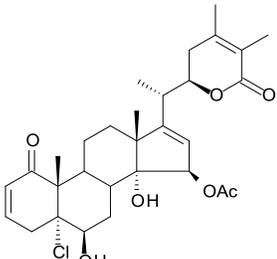
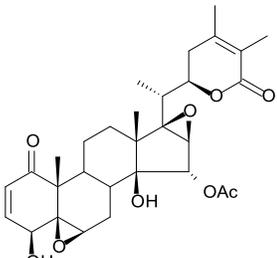
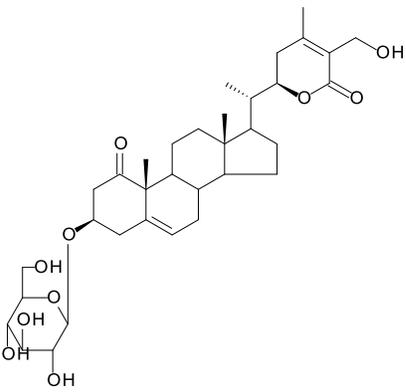
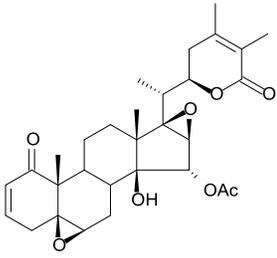
The chemical structures, pharmacological activities and bibliographic references are show in Table 2.

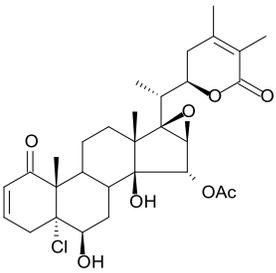
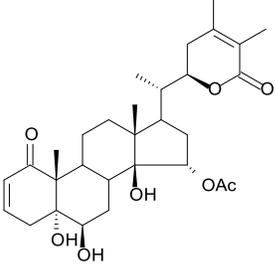
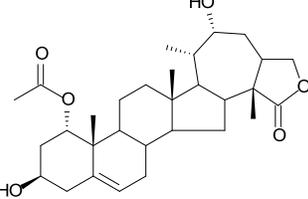
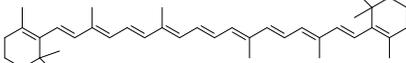
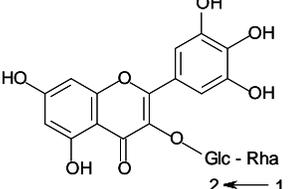
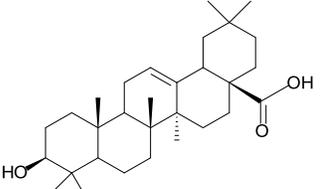
Table 2
Chemical structure of the main constituents of *Physalis angulata*

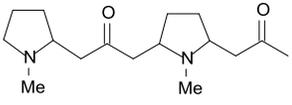
| Structure | Plant part (Bibliographic reference) | Activities |
|--|---|--|
| Physalins | | |
|  <p>Physalin F</p> | Leaves (Row <i>et al.</i> , 1978) | Antitumour effect <i>in vivo</i> against P388 lymphocytic leukemia in mice (Chiang <i>et al.</i> , 1992), antimalarial activity (Sá <i>et al.</i> , 2011), immunosuppressive activity (Brustolim <i>et al.</i> , 2010; Soares <i>et al.</i> , 2006), antileishmanial activity against <i>L. amazonensis</i> (Guimarães <i>et al.</i> , 2010), cytotoxicity against human renal cancer cells (Wu <i>et al.</i> , 2012). |

| | | |
|--|-----------------------------------|---|
|  <p>Physalin B</p> | Leaves (Row <i>et al.</i> , 1978) | Anti-melanoma effect (Hsu <i>et al.</i> , 2012), antileishmanial activity against <i>L. amazonensis</i> (Guimarães <i>et al.</i> , 2010), antitumour activity (Ferreira <i>et al.</i> , 2006), antimalarial activity (Sá <i>et al.</i> , 2011), anti-inflammatory effect (Vieira <i>et al.</i> , 2005). |
|  <p>Physalin D</p> | Leaves (Row <i>et al.</i> , 1980) | Antitumour activity (Ferreira <i>et al.</i> , 2006), antimicrobial activity against Gram-positive bacteria (Helvacı <i>et al.</i> , 2010). |
|  <p>Physalin G</p> | Leaves (Row <i>et al.</i> , 1980) | Antimalarial activity (Sá <i>et al.</i> , 2011), antileishmanial activity against <i>L. amazonensis</i> (Guimarães <i>et al.</i> , 2010). |
|  <p>Physalin E</p> | Leaves (Row <i>et al.</i> , 1978) | Anti-inflammatory effect (Pinto <i>et al.</i> , 2010). |
|  <p>Physalin H</p> | Leaves (Row <i>et al.</i> , 1978) | Immunosuppressive activity on T cells activation and proliferation both <i>in vitro</i> and <i>in vivo</i> (Yu <i>et al.</i> , 2010). |
|  <p>Physalin I</p> | Leaves (Row <i>et al.</i> , 1980) | |

| | | |
|---|---|---|
|  <p>Physalin U</p> | Whole plant (Kuo <i>et al.</i> , 2006) | Weak cytotoxicity against different cell lines (Damu <i>et al.</i> , 2007). |
|  <p>Physalin W</p> | Whole plant (Kuo <i>et al.</i> , 2006) | |
| Whithanolides | | |
|  <p>Withangulatin A</p> | Whole herb (Chen <i>et al.</i> , 1990) | Anticancer against the HCT-116 cell line (He <i>et al.</i> , 2007), trypanocidal activity against epimastigotes and trypomastigotes of <i>T. cruzi</i> <i>in vitro</i> (Nagafuji <i>et al.</i> , 2004), inhibitory activities against COLO 205 and AGS cancer cells (Lee <i>et al.</i> , 2008). |
|  <p>Withangulatin B</p> | Whole plant (Damu <i>et al.</i> , 2007) | Strong cytotoxic against multiple tumour cell lines (Damu <i>et al.</i> , 2007). |
|  <p>Withangulatin I</p> | Whole plant (Lee <i>et al.</i> , 2008) | Inhibitory activities against COLO 205 and AGS cancer cells (Lee <i>et al.</i> , 2008). |

| | | |
|--|--|---|
|  <p>Physagulin A</p> | Leaves and stems (Shingu <i>et al.</i> , 1992) | Trypanocidal activity against epimastigotes and trypomastigotes of <i>T. cruzi</i> <i>in vitro</i> (Nagafuji <i>et al.</i> , 2004). |
|  <p>Physagulin B</p> | Leaves and stems (Shingu <i>et al.</i> , 1992) | |
|  <p>Physagulin C</p> | Leaves and stems (Shingu <i>et al.</i> , 1991) | Trypanocidal activity against epimastigotes and trypomastigotes of <i>T. cruzi</i> <i>in vitro</i> (Nagafuji <i>et al.</i> , 2004). |
|  <p>Physagulin D</p> | Leaves and stems (Shingu <i>et al.</i> , 1992) | Either weak or no activity against different human tumour cell lines (Jayaprakasam <i>et al.</i> , 2003) |
|  <p>Physagulin H</p> | Aerial part (Nagafuji <i>et al.</i> , 2004) | Trypanocidal activity against epimastigotes and trypomastigotes of <i>T. cruzi</i> <i>in vitro</i> (Nagafuji <i>et al.</i> , 2004). |

| | | |
|--|---|--|
|  <p>Physagulin I</p> | Aerial part (Nagafuji <i>et al.</i> , 2004) | |
|  <p>Physagulin J</p> | Aerial part (Nagafuji <i>et al.</i> , 2004) | |
|  <p>Physanolide A</p> | Whole plant (Kuo <i>et al.</i> , 2006) | |
| <p>Carotenoids</p> | | |
|  <p>all-trans-β-carotene</p> | Fruits (De Rosso and Mercadante, 2007) | |
| <p>Others</p> | | |
|  <p>Myricetin 3-O-neohesperidoside</p> | Leaves (Ismail and Alam, 2001) | Strong cytotoxicity against three cell lines (P-388, KB-16 and A-549) (Ismail and Alam, 2001). |
|  <p>Oleanolic Acid</p> | Leaves (Shim <i>et al.</i> , 2002) | Antibacterial activity against <i>Streptococcus mutans</i> and <i>Porphyromonas gingivalis</i> (Shim <i>et al.</i> , 2002) |

| | | |
|--|---|--|
|  <p style="text-align: center;">Phygrine</p> | Roots and aerial parts (Basey <i>et al.</i> , 1992) | |
| | | |

Other

A flavonol glycoside, myricetin 3-*O*-neohesperidoside was isolated from cytotoxic MeOH extract of leaves *P. angulata* (Ismail and Alam, 2001). In study realized by Shim *et al.* (2002) isolated and identified oleanolic acid from *P. angulata*, showing antibacterial activity against oral pathogens. Phygrine is an alkaloid that is present in *Physalis* species, including *P. angulata* (Basey *et al.*, 1992).

BIOLOGICAL ACTIVITY

The uses of natural products to treat variety of diseases have increased due to large number of medicinal plants that have shown biological activity.

Scientific research on the medicinal properties of that specie began in the 90's, with a significant rise in the last few years. A resume of results of researches carried out are presented below.

Antiparasitic activity

Schistosomiasis is debilitating chronic disease, which appears in every tropical country in the world, and affects thousands of people specially those who had contacts with water hosting infected mollusks: rural workers, children, washerwomen in areas without treated water supply or drains. Tests carried out over *Biomphalaria tenagophila* mortality in regards to different extracts of *P. angulata*, shown that extracts with ethyl acetate (LD₅₀ = 55.3 mg/l) and acetone (LD₅₀ = 178 mg/l) from entire plant presented good molluscicidal activity (Dos Santos *et al.*, 2003).

Isolated components of the aerial part of *P. angulata* showed good activity against epimastigotes of *Trypanosoma cruzi*, etiologic agent for Chagas' disease, *in vitro* tests of cells counting Kit-8 (Nagafuji *et al.*, 2004).

Studies carried out by Freiburghaus *et al.* (1996) on *in vitro* antitrypanosomal activity of twenty-four African plant species against *Trypanosoma brucei rhodesiense*, determined that highest activity was found in dichloromethane stem extract of *P. angulata*, with an IC₅₀ value of 0.1 µg/ml.

Anti-inflammatory activity

Choi y Hwang (2003) have demonstrated that metanol extract from flowers shows anti inflammatory action against edema in rats paw, induced by carragenin, edema of ear induced by araquidonic acid and arthritis induced by formaldehyde and also antiallergic properties against hypersensitivity reaction of contact type IV induced by 2,4-dinitrofluorobenzene in rats. It has been proved that aqueous extract from root, by inhibition of different ways in rats, has powerful anti inflammatory and immunomodulatory activity, interfering with ciclooxigenase way, lymphocyte proliferation and production of TGF-β (Bastos *et al.*, 2008).

The anti-inflammatory effect of physalin E, a steroid isolated from *P. angulata*, has been evaluated in sharp and chronic models of dermatitis induced respectively by 12-*O*-tetradecanoyl-phorbol-13-acetate (PTA) and oxazolone, in rats. The good results of topic application of physalin E, on experimental dermatitis in mice ear, (significantly reduce the ear edema response by 33%, 38% and 39% with 0.125, 0.25 and 0.5 mg/ear, respectively) suggests that it could be a powerful and effective local anti-inflammatory drug, useful for treatment of acute peel and chronic inflammatory diseases (Pinto *et al.*, 2010). Moreover, Brustolim *et al.*, (2010), established physalin F's effects, in a model of arthritis induced by collagen, where rats were treated by oral way after the apparition of an edema of paw. After 20 days treatment with physalin F, observed a significant reduction of edema.

Antinociceptive effect

Bastos *et al.* (2006) shows that aqueous extract obtained from roots of *P. angulata*, when given intraperitoneally or orally, produces dose-related and significant antinociception according to assessment of abdominal constrictions elicited by acetic acid, model used to evaluate the potential analgesic activity of drugs.

Antimicrobial activity

The essential oil extracted by hydro distillation of the aerial part and the roots, has antimicrobial properties

as evidenced by Osho *et al.* (2010), using the diffusion technique in agar against *Bacillus subtilis* (MIC₅₀ = 4.0 mg/ml) and *Klebsiella pneumoniae* (MIC₅₀ = 4.0 mg/ml); moreover it has antifungic activity with *C. albicans* (MIC₅₀ = 4.0 mg/ml), *C. stellatoidea* (MIC₅₀ = 3.75 mg/ml) and *C. torulopsis* (MIC₅₀ = 4.0 mg/ml), which are resistant to many antibiotics. Lopes *et al.* (2006) analyzed antimicrobial activity of different extracts of the fruit and root of *P. angulata*, using the agar diffusion method against *Staphylococcus aureus* ATCC 6538, of which the ethanol extract of the fruit showed better bacterial activity, showing significant response when compared to ampicillin, which was prepared in water at concentrations ranging from 0.25 to 4090 µg/ml. The extract showed an inhibition of 11.17 mm, matching the range of linearity of curve of the antibiotic, which ranged from 9.60 to 20.30 mm. Silva *et al.*, (2005) conducted a comparative study between physalin B and enriched physalin fractions (mixture of B, D, F and G physalins) at three different concentrations using the agar diffusion technique, against pathogenic gram positive and gram negative microorganisms, demonstrating that, at concentration of 200 µg/ml, pure physalin B exhibited ± 85% of the inhibitory zone observed with the pool of physalins, at same concentration. The physalin pool at 200 µg/ml yielded 100% inhibition for *Staphylococcus aureus* ATCC 29213, *S. aureus* ATCC 25923, *S. aureus* ATCC 6538P, and *Neisseria gonorrhoeae* ATCC 49226.

The ethanolic extract of the flowers of *P. angulata*, exhibit noticeable antibacterial activity against *Streptococcus mutans* causing dental caries at all concentration tested. The bactericidal test showed that methanol extract of *P. angulata* conferred fast killing effect against *S. mutans* in 2 min at 50 mg/ml concentration (Hwang *et al.*, 2004).

The ethanolic extract of the fruit of *P. angulata* show antibacterial activity against *Staphylococcus aureus* at all concentration used (100 mg g⁻¹, 125 mg g⁻¹ and 150 mg g⁻¹) with inhibition zones between 34.5 mm and 50.5 mm as compared to standard antibiotic (chloramphenicol) which gave a mean zone inhibition diameter of 79.8 mm at 100 mg g⁻¹ concentration (Donkor *et al.*, 2012).

Studies undertaken by Pietro *et al.* (2000) on natural antimicrobial agents from plant extracts through bioassay-guide fractionation, by *in vitro* determination of minimum inhibitory concentration (MIC) using the microdilution method with Alamar blue oxidation-reduction dye, demonstrated that crude

CHCl₃ extracts from aerial parts (500 µg/ml) of *P. angulata* caused total growth inhibition of *Mycobacterium tuberculosis* H37 Rv cells. Moreover, 32 µg/ml and 625 µg/ml of the physalin-containing fractions were necessary to inhibit 100% of *M. tuberculosis* and *M. avium*, respectively. Purified physalin B showed MIC values against *M. tuberculosis* H37 Rv strain of 32 µg/ml (Januário *et al.*, 2002).

Antimalarial effect

The methanol extract from leaves of *P. angulata* showed a very interesting antiplasmodial activity against 3D7 (chloroquine sensitive) and W2 (chloroquine resistant) strains of *Plasmodium falciparum* (IC₅₀ = 1.27 and 3.02 µg/ml). Similar activity showed the chloroform extract from leaves with an IC₅₀ = 1.96 and 2.00 µg/ml, respectively (Luzakibanza *et al.*, 2010). In other studies, the hydroalcoholic extract (EtOH/H₂O; 70/30) from *P. angulata* showed antiplasmodial activity *in vitro* on *Plasmodium falciparum* chloroquine resistant strain (FCR-3) with an IC₅₀ = 4.6 µg/ml (Ruiz *et al.*, 2011).

Antileishmanial activity

Guimarães *et al.* (2009) showed antileishmanial activity of steroids purified from *P. angulata*. Whereas physalins B and F had potent antileishmanial activity against intracellular amastigotes of *Leishmania amazonensis* and *Leishmania major*. Topical treatment with physalin F significantly reduced the lesion size, parasite load and histopathological alterations in BALB/c mice infected with *L. amazonensis*.

Immunosuppressive effect

Soares *et al.* (2003) report that physalins B, F and G isolated from ethanolic extract of the *P. angulata* have potent immunosuppressive activities in macrophages and in lipopolysaccharide-induced shock. Withangulatin A, an active withanolides compound isolated from *P. angulata*, exhibits compelling immunosuppressive activity and directly induces HO-1 expression to restrict the T lymphocytes from over-expression and modulates Th1/Th2-type balance (Sun *et al.*, 2011).

Antiasthmatic activity

Asthma is a chronic inflammatory disease of the airways with a wide range of presentations. In studies carried out by Rathore *et al.* (2011), the methanolic

extract of *P. angulata* leaves was exhibit inhibition of histamine response on guinea pig ileum preparation; indicate that extract may be acting through H₁ receptor as antagonists. Also was inhibited responses of 5-hydroxytryptamine on rat fundus preparation, that indicate the antagonistic activity of extract on serotonergic receptor, thus showing antagonistic activity on both histaminergic and serotonergic receptors.

Diuretic activity

Diuretics are chemicals that increase the rate of urine formation. Methanolic leaf extract of *P. angulata* increases urine volume significantly and also potentiate excretion of Na⁺ in urine output in rats (Nanumala *et al.*, 2012), the results this study provides a quantitative basis to explain the traditional folkloric use of *P. angulata* as a diuretic agent.

Anticancer/antitumour effect

Studies by Hseu *et al.* (2011) indicate that ethyl acetate extracts of *P. angulata* exerts an inhibitory effect on several essential steps of metastasis, including migration and invasion of human oral squamous carcinoma cells (HSC-3).

He *et al.* (2007) report the cytotoxic properties of eleven withanolides isolates from MeOH extract of the aerial parts of *P. angulata* towards NCI-H460 (lung) and HCT-116 (colon) cancer cells. Where withangulatin A exhibited the highest anticancer activity against the HCT-116 cell line, with an IC₅₀ value of 1.64±0.06 µM, while physagulin B exhibited highest cytotoxicity towards NCI-H460 cell line, with an IC₅₀ value of 0.43±0.02 µM.

Methanolic extract from leaves of *P. angulata* demonstrated significant *in vitro* cytotoxicity (IC₅₀ = 5.7±0.3 µg/ml) against human cell line HL60 (acute promyelocytic leukemia-ATCC CCL-240) (Faria *et al.*, 2006).

Ferreira *et al.* (2006) evaluated the *in vitro* and *in vivo* antitumour activity of physalin B and physalin D isolated from the aerial parts of *P. angulata*. *In vitro*, both compounds displayed considerable cytotoxicity against several cancer cell lines, showing IC₅₀ values in the range of 0.58 to 15.18 µg/ml for physalin B, and 0.28 to 2.43 µg/ml for physalin D. The antitumour activity of both compounds was confirmed *in vivo* using mice bearing sarcoma 180 tumour cells.

Fractions obtained from methanolic extract of the fruit of *P. angulata*, showed significant inhibition

values against mouse lymphoma (97%) and Erlich carcinoma strains (93%) (Ribeiro *et al.*, 2002).

Myricetin 3-*O*-neohesperidoside, a flavonol glycoside isolated from a cytotoxic methanolic extract of the leaves of *P. angulata*, showed remarkable cytotoxicity *in vitro* against murine leukemia cell line P-388, epidermoid carcinoma of the nasopharynx KB-16 cells, and lung adenocarcinoma A-549 with ED50 values of 0.048, 0.50 and 0.55 µg/ml, respectively (Ismail and Alam, 2001).

Hsieh *et al.* (2005) showed that extracts from *P. angulata* L. induced G2/M phase arrest in human breast cancer cells. Wu *et al.* (2012) reported that Physalin F induced cell apoptosis through the Reactive Oxygen Species-mediated mitochondrial pathway and suppressed NF-κB activation in human renal cancer A498 cells.

TOXICOLOGY

In acute toxicity study, methanolic extract of *P. angulata* leaves showed no mortality at 2000 mg/kg, so the extract are safe for *in vivo* studies (Rathore *et al.*, 2011). Assay conducted by Bastos *et al.* (2006) demonstrated that the treatment of mice with aqueous extract obtained from roots of *P. angulata* (10-60 mg/kg) produces no changes in behavior, such as the appearance of involuntary movements, piloerection, stimulatory or sedative effects, respiratory depression or other signs at 4, 24 or 48 h after administration of the aqueous extract. This data indicates that the aqueous extract of *P. angulata* present a low acute toxicity. Moreover Alves *et al.* (2008) demonstrated the genotoxic effects of aqueous extract of *P. angulata* on human lymphocytes *in vitro*, using the comet assay and the micronucleus assay in human lymphocytes provided by six healthy donors.

CLINICAL STUDIES

In the review of clinical studies of *P. angulata*, only one reference was found, indicating that the species is a component used in the formulation for the treatment of malaria. "Study realized for Ankrah *et al.* (2003) for determined the efficacy and safety of a decoction formulated (AM-1) from *Jatropha curcas*, *Gossypium hirsutum*, *Physalis angulata* and *Delonix regia*. AM-1 was used to treat malaria at an herbal clinic in Ghana. Results this study showed progressive elimination of *Plasmodium falciparum* and *P. malariae* parasites from the peripheral blood of the patients who were treated with the decoction, all without apparent toxic effects to humans".

CONCLUSIONS

Physalis angulata has a traditional use for 26 types of diseases ten tropical countries.

Most of chemicals in this species correspond to group withanolides and physalins isolated from the roots, stems and leaves. Also fruits contain carotenoids.

For pharmacological activities are ten types of studies, eight studies of the effect anticancer/antitumour, followed by seven antimicrobial activity and other activities with lowers numbers.

The pharmacological studies conducted on *P. angulata* indicate the immense potential of this plant in the treatment of conditions such as schistosomiasis, Chagas' disease, trypanosomiasis, inflammatory ailments including dermatitis and arthritis, pain, malaria, leishmania, asthma, tuberculosis, liquid retention, cancer, etc.

However, the diverse pharmacological activities of *P. angulata* extracts and isolated phytochemicals have only been assayed *in vitro* tests using laboratory animals, and the results obtained may not necessarily be portable to the situation in humans. For the case of the overhaul in clinical studies, are only have access to one publication, indicating that this species is potentiated, for its in malaria when combining with other plant species.

While there are gaps in the studies conducted so far, which need to be bridged in order to exploit the full medicinal potential of *P. angulata*, it is still very clear that this is a plant with tremendous widespread use a now and also with extraordinary potential for the future.

On the basic of the low toxicity of *P. angulata* extracts and derived phytochemicals and their use as nutraceutical (fruit) and medicinal (leaves, stems and roots) agents, backed by proven activity of both the traditional formulation (macerations, infusions, decoctions, topical applications) and their derived phytochemicals (withanolides, physalins, carotenoids and others), further research, clinical trials and product development can only cement this species as a very Important part of our biodiversity to respect and sustainably use for generations to come.

It should increase the comprehensive studies for this species, as a source of resource to be transformed in diverse products, such as pharmaceuticals, food intake, essential oils and preserves.

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