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Universidad de Santiago de Chile
Santiago, Chile

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

Elsa RENGIFO-SALGADO¹ & Gabriel VARGAS-ARANA²

¹Instituto de Investigaciones de la Amazonía Peruana, Av. José A. Quiñones Km 2.5, Iquitos, Perú.
²Universidad Científica del Perú, Av. José A. Quiñones N° 2500, Iquitos, Perú.

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, antinoceptive, antimalarial, antileishmanial, immunosuppressive, antiasmatic 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, antiflamatorias 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 witanólicos. Los estudios farmacológicos revelan que tiene actividad antiparasitaria, antiflamatoria, antimicrobiana, antinoceptiva, antimalárica, antileishmanía, inmunosupresor, antiasmático, 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.
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 make 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 evidence the great interest about this plant. Therefore, the objective of this review was to get updated comprehensive information about *P. angulata* including their deferments uses in traditional medicine, phytochemistry and pharmacology. It performed an articles selection of last thirty years with the purpose of find 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 Pará, 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

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

### 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 know 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 8-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).


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

Fractionation of CHCl₃ 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, withangulatins 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>
<thead>
<tr>
<th>BCPL2</th>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemical structure of the main constituents of <em>Physalis angulata</em></strong></td>
<td></td>
</tr>
<tr>
<td>Structure</td>
<td>Plant part (Bibliographic reference)</td>
</tr>
<tr>
<td>--------</td>
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</tr>
<tr>
<td><img src="image" alt="Physalin F" /></td>
<td>Leaves (Row <em>et al</em>., 1978)</td>
</tr>
<tr>
<td>Compound</td>
<td>Source</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Physalin B</td>
<td>Leaves (Row et al., 1978)</td>
</tr>
<tr>
<td>Physalin D</td>
<td>Leaves (Row et al., 1980)</td>
</tr>
<tr>
<td>Physalin E</td>
<td>Leaves (Row et al., 1978)</td>
</tr>
<tr>
<td>Physalin G</td>
<td>Leaves (Row et al., 1980)</td>
</tr>
<tr>
<td>Physalin H</td>
<td>Leaves (Row et al., 1978)</td>
</tr>
<tr>
<td>Physalin I</td>
<td>Leaves (Row et al., 1980)</td>
</tr>
</tbody>
</table>
### Physalis angulata: traditional uses, chemistry and pharmacology

<table>
<thead>
<tr>
<th>Compound</th>
<th>Source</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physalin U</td>
<td>Whole plant (Kuo et al., 2006)</td>
<td>Weak cytotoxicity against different cell lines (Damu et al., 2007).</td>
</tr>
<tr>
<td>Physalin W</td>
<td>Whole plant (Kuo et al., 2006)</td>
<td></td>
</tr>
</tbody>
</table>

#### Whithanolides

<table>
<thead>
<tr>
<th>Compound</th>
<th>Source</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withangulatin A</td>
<td>Whole herb (Chen et al., 1990)</td>
<td>Anticancer against the HCT-116 cell line (He et al., 2007), trypanocidal activity against epimastigotes and trypomastigotes of T. cruzi in vitro (Nagafuji et al., 2004), inhibitory activities against COLO 205 and AGS cancer cells (Lee et al., 2008).</td>
</tr>
<tr>
<td>Withangulatin B</td>
<td>Whole plant (Damu et al., 2007)</td>
<td>Strong cytotoxic against multiple tumour cell lines (Damu et al., 2007).</td>
</tr>
<tr>
<td>Withangulatin I</td>
<td>Whole plant (Lee et al., 2008)</td>
<td>Inhibitory activities against COLO 205 and AGS cancer cells (Lee et al., 2008).</td>
</tr>
<tr>
<td>Compound</td>
<td>Source</td>
<td>Activity Description</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Physagulin A</td>
<td>Leaves and stems (Shingu et al., 1992)</td>
<td>Trypanocidal activity against epimastigotes and trypomastigotes of <em>T. cruzi</em> in <em>vitro</em> (Nagafuji et al., 2004).</td>
</tr>
<tr>
<td>Physagulin B</td>
<td>Leaves and stems (Shingu et al., 1992)</td>
<td>Trypanocidal activity against epimastigotes and trypomastigotes of <em>T. cruzi</em> in <em>vitro</em> (Nagafuji et al., 2004).</td>
</tr>
<tr>
<td>Physagulin C</td>
<td>Leaves and stems (Shingu et al., 1991)</td>
<td>Trypanocidal activity against epimastigotes and trypomastigotes of <em>T. cruzi</em> in <em>vitro</em> (Nagafuji et al., 2004).</td>
</tr>
<tr>
<td>Physagulin D</td>
<td>Leaves and stems (Shingu et al., 1992)</td>
<td>Either weak or no activity against different human tumour cell lines (Jayaparakasam et al., 2003).</td>
</tr>
<tr>
<td>Physagulin H</td>
<td>Aerial part (Nagafuji et al., 2004)</td>
<td>Trypanocidal activity against epimastigotes and trypomastigotes of <em>T. cruzi</em> in <em>vitro</em> (Nagafuji et al., 2004).</td>
</tr>
<tr>
<td>Compound</td>
<td>Source</td>
<td>Properties</td>
</tr>
<tr>
<td>--------------------------</td>
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</tr>
<tr>
<td>Physagulin I</td>
<td>Aerial part (Nagafuji et al., 2004)</td>
<td></td>
</tr>
<tr>
<td>Physagulin J</td>
<td>Aerial part (Nagafuji et al., 2004)</td>
<td></td>
</tr>
<tr>
<td>Physanolide A</td>
<td>Whole plant (Kuo et al., 2006)</td>
<td></td>
</tr>
<tr>
<td>Carotenoids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>all-trans-β-carotene</td>
<td>Fruits (De Rosso and Mercadante, 2007)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myricetin 3-O-neohesperidoside</td>
<td>Leaves (Ismail and Alam, 2001)</td>
<td>Strong cytotoxicity against three cell lines (P-388, KB-16 and A-549) (Ismail and Alam, 2001).</td>
</tr>
<tr>
<td>Oleanolic Acid</td>
<td>Leaves (Shim et al., 2002)</td>
<td>Antibacterial activity against <em>Streptococcus mutans</em> and <em>Porphyromonas gingivalis</em> (Shim et al., 2002).</td>
</tr>
</tbody>
</table>
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 (LD$_{50}$ = 55.3 mg/l) and acetone (LD$_{50}$ = 178 mg/l) from entire plant presented good molluscidal 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* anttrypanosomal 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 IC$_{50}$ 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 cilcloxygenase 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 (MIC<sub>50</sub> = 4.0 mg/ml) and Klebsiella pneumoniae (MIC<sub>50</sub> = 4.0 mg/ml); moreover it has antifungal activity with C. albicans (MIC<sub>50</sub> = 4.0 mg/ml). C. stellatoidea (MIC<sub>50</sub> = 3.75 mg/ml) and C. torulopsis (MIC<sub>50</sub> = 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<sup>-1</sup>, 125 mg g<sup>-1</sup> and 150 mg g<sup>-1</sup>) 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<sup>-1</sup> concentration (Donkor et al., 2012).

Studies undertaken by Pietro et al. (2000) on natural antimicrobial agents form 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 CHCl<sub>3</sub> 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 (IC<sub>50</sub> = 1.27 and 3.02 µg/ml). Similar activity showed the chloroform extract from leaves with an IC<sub>50</sub> = 1.96 and 2.00 µg/ml, respectively (Luzakibanza et al., 2010). In other studies, the hydroalcoholic extract (EtOH/H<sub>2</sub>O; 70/30) from P. angulata showed antiplasmodial activity in vitro on Plasmodium falciparum chloroquine resistant strain (FCR-3) with an IC<sub>50</sub> = 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. Withangulin 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 withanones isolates from MeOH extract of the aerial parts of *P. angulata* towards NCI-H460 (lung) and HCT-116 (colon) cancer cells. Where withangulanin 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.

Methanol 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).


**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”.

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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, leishmaniasis, 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 basis 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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