# Physalis alkekengi L. var. franchetii (Mast.) Makino

Subjects: Pharmacology & Pharmacy

Contributor: Jing Yang

The calyxes and fruits of *Physalis alkekengi* L. var. *franchetii* (Mast.) Makino (*P. alkekengi*), a medicinal and edible plant, are frequently used as heat-clearing and detoxifying agents in thousands of Chinese medicine prescriptions. For thousands of years in China, they have been widely used in clinical practice to treat throat disease, hepatitis, and bacillary dysentery.

the calyxes and fruits of P. alkekengi | structural analysis | quality control | pharmacology | pharmacokinetics

## 1. Introduction

*P. alkekengi* is a perennial plant (**Figure 1**a) belonging to the genus *Physalis* of the family Solanaceae. The calyxes and fruits of *P. alkekengi* (known as Jindenglong in Chinese) (**Figure 1**b) are distributed in Europe and Asia. The use of the calyxes and fruits of this plant was first recorded in the prestigious monograph *Shennong Bencao Jing* in China [1]. Subsequently, it was included as an important traditional Chinese medicine (TCM) in the *Ben Cao Gang Mu* and pharmacopoeia [2]. Calyxes are green, self-expanded into an oocyst shape, slightly concave at the base, 2.5–5 cm in length, 2.5–3.5 cm in diameter, have thin leathery skin, and are orange-red or fire-red when mature (**Figure 1**c). Fruits are spherical, orange-red, and 10–15 mm in diameter (**Figure 1**d). This plant has been used for >2000 years in China, and its activities have been defined as "heat-clearing and detoxifying, relieving sore throat to reducing phlegm and inducing diuresis for treating strangurtia" in TCM theory [3][4]. In clinical practice, *P. alkekengi* is often used in combination with other TCMs for the treatment of cough, excessive phlegm, pharyngitis, sore throat, dysuria, pemphigus, eczema, and jaundice [5]. Currently, the 12 TCM formulae and modern pharmaceutical preparations of the calyxes and fruits of *P. alkekengi* are listed in the Pharmacopoeia of the People's Republic of China and used in folk medicine [6]. For example, qing guo ointment, a TCM formula composed of seven medicinal herbal plants (i.e., the calyxes and fruits of *P. alkekengi*, *Cannarii Fructus*, *Sophorae Tonkinensis* Radix et Rhizoma, *Sterculiae Lychnophorae Semen*, *Trichosanthis Radix*, *Ophiopogonis Radix*, and *Chebulae Fructus*), is effective for clearing the throat and quenching thirst, treating aphasia and hoarseness, and relieving sore throat, dry mouth, and dry tongue [1].

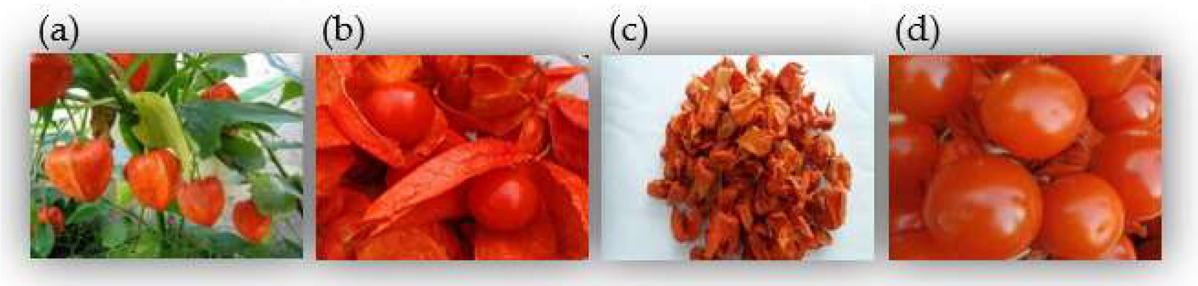



**Figure 1.** Images of *P. alkekeng*. (**a**) The whole plant; (**b**) Calyxes and fruits; (**c**) Calyxes; (**d**) Fruits.

In the last decades, reviews concerning research progress on the calyxes and fruits of *P. alkekengi* have been published, mainly focusing on the chemical components, traditional uses, toxicology, and pharmacological activities [6]; however, thus far, there are no reports on structural analysis, quality control, and pharmacokinetics. In recent years, new pharmacological activities have been discovered, and the main active ingredients in *P. alkekengi* are physalins and flavonoids [7]. Therefore, we herein provide a literature review on the structural analysis of physalins and flavonoids in the calyxes and fruits of *P. alkekengi*. We have also prepared a comprehensive and up-to-date report for the known pharmacological activities. In addition, the quality control and pharmacokinetics studies are summarized in detail. We hope that the current review will provide a theoretical basis and valuable data for future in-depth studies and the development of useful applications.

## 2. Pharmacology

Pharmacological experiments showed that the various crude extracts and compounds isolated from *P. alkekengi* have diverse biological activities (e.g., anti-inflammatory, anti-tumor, immunosuppressive, anti-microbial, anti-leishmanial, anti-asthmatic, anti-diabetic, etc.). In addition, the mechanisms of action of the anti-inflammatory and anti-tumor activities were also reported. The main pharmacological activities of crude extracts and compounds are shown in **Table 1**.

**Table 1.** Pharmacological effects of *P. alkekengi*.

| Pharmacological Activity | Animal/Cell Models | Constituent/Extract | Detail | Dosage | Reference |
|---|---|---|---|---|---|
| Anti-inflammatory activity | LPS-induced 264.7 cells | Physalins A, O, L, G Isophysalin A | Induced NO production | 20 μM | [8] |
| | IFN-γ-stimulated macrophages LPS-stimulated macrophages | Physalins B, F, G | Reduced NO production; inhibited TNF-α, IL-6, IL-12 | 2 μg/mL | [9] |
| | C57BL/6 mice | Physalins B, F | Suppressed the increase in TNF-α; increased vascular | 20 mg/kg | [10] |

| Pharmacological Activity | Animal/Cell Models | Constituent/Extract | Detail | Dosage | Reference |
|---|---|---|---|---|---|
| | | | permeability; prevented neutrophil influx | | |
| | LPS-induced 264.7 cells | Physalin B | Decreased the levels of TNF-α, IL-6, IL-1β | 0.25, 0.5, 1.0 μM | [11] |
| | LPS/IFN-γ-induced macrophages IL-4/IL-13-induced macrophages LPS-induced C57BL/6 mice | Physalin D | In vitro: activated signal transducer and activator of STAT6 pathway; suppressed STAT1 activation; blocked STAT1 nuclear translocation In vivo: reduced inducible iNOS cell number; increased CD206+ cell number | 5 μM | [12] |
| | LPS-stimulated RAW 264.7 cells | Physalin E | Inhibited the generation of TNF-α, IL-6, NF-κB p65; reduced the degradation of I-kappa B protein | 12.5, 25, 50 μM | [13] |
| | TPA-induced acute ear edema in mice Oxazolone-induced chronic dermatitis in mice | Physalin E | Reduced ear edema response and myeloperoxidase activity; suppressed increase in ear thickness and levels of TNF-α and IFN-γ | 0.125, 0.25, 0.5 mg/ear | [14] |
| | DBA/1 mice | Physalin F | Decreased paw edema and joint inflammation | 60 mg/kg | [15] |
| | LPS-induced macrophages | Physalin X Aromaphysalin B | Inhibited NO production | $IC_{50}$ = 68.50, 29.69 μM, | [16] |

| Pharmacological Activity | Animal/Cell Models | Constituent/Extract | Detail | Dosage | Reference |
|---|---|---|---|---|---|
| | | | | respectively | |
| | LPS-induced macrophages | Physalins B, F, H, V, D1, VII, I<br>Isophysalin B | Inhibited NO production | $IC_{50}$ = 0.32–4.03, 12.83–34.19 μM, respectively. | [17] |
| | LPS-induced macrophages | Physalins A, B, F<br>Ombuine<br>Luteolin | Inhibited NO production | $IC_{50}$ = 2.57 ± 1.18, 0.84 ± 0.64, 0.33 ± 0.17, 2.23 ± 0.19, 7.39 ± 2.18 μM, respectively. | [18] |
| | LPS/IFN-γ-stimulated macrophages<br>ICR mice | Luteolin | In vitro: suppressed the production of IL-6, IL-12, and TNF-α<br>In vivo: inhibited paw edema | 20 μM<br>20 mg/kg | [19] |
| | KF-8 cells | Apigenin<br>Lutelin | Inhibited NF-κB activation and the expression of CCL2/MCP-1 and CXCL1/KC | 20 μM | [20] |
| | LPS-induced macrophages | Kaempferol<br>Quercetin | Inhibited STAT-1 and NF-κB activation, iNOS protein and mRNA expression, and NO production | 100 μM | [21][22] |
| | LPS-stimulated THP-1 cells<br>ICR mice | 70% ethanol extract | In vitro: reduced the production of NO, PGE2, TNF-α, IL-1, iNOS, and COX-2<br>In vivo: reduced ear edema; induced granulomatous tissue formation | 500 μg/mL | [23] |
| | Wistar rats | Methanol extract | Reduced the | 500 mg/kg | [24] |

| Pharmacological Activity | Animal/Cell Models | Constituent/Extract | Detail | Dosage | Reference |
|---|---|---|---|---|---|
| | | | paw volume | | |
| | LPS-induced macrophages | Physanosides B | Inhibited NO production | $IC_{50}$ = 9.93 μM | [25] |
| | LPS-induced macrophages | (6S,9R)-roseoside | Inhibited NO production | $IC_{50}$ = 7.31 μM | [26] |
| Anti-tumor activity | HepG2 cells | Physalin A | Activated the Nrf2–ARE pathway and its target genes | 20 μM | [26] |
| | Non-small cell lung cancer BALB /c mice | Physalin A | In vitro: suppressed both constitutive and induced STAT3 activity<br>In vivo: suppressed tumor xenograft growth | 5,10, 15 μM<br>40, 80 mg/kg | [27] |
| | Human melanoma A375-S2 cells | Physalin A | Activated transmembrane death receptor; Induced poptosis via apoptotic (intrinsic and extrinsic) pathway; up-regulated p53-NOXA-mediated ROS generation | 15 μM | [28] |
| | Human HT1080 fibrosarcoma cells | Physalin A | Upregulated CASP3, CASP8 expression | $IC_{50}$ = 10.7 ± 0.91 μM | [29] |
| | Human melanoma A375-S2 cells | Physalin A | Repressed the production of RNS and ROS; triggered the expression of iNOS and NO | 15 μM | [30] |
| | Non-small cell lung cancer | Physalin A | Induced G2/M cell cycle arrest; increased the | $IC_{50}$ = 28.4 μM | [31] |

| Pharmacological Activity | Animal/Cell Models | Constituent/Extract | Detail | Dosage | Reference |
|---|---|---|---|---|---|
| | | | amount of intracellular ROS | | |
| | Prostate cancer cells (CWR22Rv1, C42B) | Physalins A, B | Inhibited the growth of two cells; activated the JNK and ERK pathway | $IC_{50}$ = 14.2, 9.6 μM, respectively | [32] |
| | Non-small cell lung cancer | Physalin B | Exhibited anti-proliferative and apoptotic activity; downregulated the CDK1/CCNB1 complex; upregulated p21 | 5, 10, 20 μmol/L | [33] |
| | Human melanoma A375 cells | Physalin B | Activated the expression of the NOXA, BCL2 associated X (Bax), and CASP3 | 3 μg/mL | [34] |
| | Human HCT116 colon cancer cells | Physalin B | Activated the ERK, JNK, and p38 MAPK pathways; increased ROS generation | $IC_{50}$ = 1.35 μmol/L | [35] |
| | Human DLD-1 colon cancer cells | Physalin B | Inhibited TNFα-induced NF-κB activation; induced the proapoptotic protein NOXA generation | 5 μM | [36] |
| | Breast cancer cells (MCF-7, MDA-MB-231, T-47D) | Physalin B | Induced cell cycle arrest at G2/M phase; promoted the cleavage of PARP, CASP3, CASP7, and CASP9; inactivated Akt | 2.5, 5, 10 μM | [37] |

| Pharmacological Activity | Animal/Cell Models | Constituent/Extract | Detail | Dosage | Reference |
|---|---|---|---|---|---|
| | | | and P13K phosphorylation | | |
| | TNF-α-stimulated HeLa cells | Physalins B, C, F | Inhibited the phosphorylation and degradation of IκBα and NF-κB activation | $IC_{50}$ = 6.07, 6.54, 2.53 μM, respectively | [38] |
| | Tumor cells (A549, K562) | (17S,20R,22R)-5β,6β-epoxy-18,20-dihydroxy-1-ox-owitha-2,24-dienolide withaphysalin B | Suppressed the PI3K/Akt/mTOR signaling pathway | $IC_{50}$ = 1.9–4.3 μM | [39] |
| | Tumor cells (B-16, HCT-8, PC3, MDA-MB-435, MDA-MB-231, MCF-7, K562, CEM, HL-60)<br>Swiss mice | Physalins B, D | In vitro: displayed activity against several cancer cell lines<br>In vivo: inhibited the proliferation of cells; reduced Ki67 staining | 0.58–15.18, 0.28–2.43 μg/mL, respectively<br>10, 25 mg/kg | [40] |
| | Human cancer cells (C4-2B, 22Rv1, 786-O, A-498, ACHN, A375-S2) | Physalins B, F | Showed anti-proliferative activities | $IC_{50}$ = 0.24–3.17 μM | [17] |
| | Human T cell leukemia Jurkat cells | Physalins B, F | Inhibited PMA-induced NF-κB and TNF-α-induced NF-κB activation | 8, 16 μM, respectively | [41] |
| | HEK293T cells<br>BALB/c-nu/nu mice | Physalin F | In vitro: decreased TOPFlash reporter activity; promoted the proteasomal degradation of β-catenin<br>In vivo: downregulated β-catenin | 4 μM<br>10, 20 mg/kg | [42] |
| | T-47D cells | Physalin F | Activated the CASP3 and c- | $IC_{50}$ = 3.60 μg/mL | [43] |

| Pharmacological Activity | Animal/Cell Models | Constituent/Extract | Detail | Dosage | Reference |
|---|---|---|---|---|---|
| | | | myc pathways | | |
| | Human renal, carcinoma cells (A498, ACHN, UO-31) | Physalin F | Induced cell apoptosis through the ROS-mediated mitochondrial pathway; suppressed NF-κB activation | 1, 3, 10 μg/mL | [44] |
| | PC-3 cancer cell lines | 7β-ethoxyl-isophysalin C | Showed apparent moderate activities | $IC_{50}$ = 8.26 μM | [45] |
| | Human osteosarcoma cells | Physakengose G | Inhibited the epidermal growth factor receptor/mTOR (EGFR/mTOR) pathway; blocked autophagic flux through lysosome dysfunction | 5, 10, 20 μM | [46] |
| Immunosuppressive activity | *Trypanosoma cruzi (T. cruzi)*-infected insects | Physalin B | Decreased number of *T. cruzi* Dm28c and *T. cruzi* transmission; inhibited the development of parasites | 1 mg/mL<br>20 ng<br>57 ng/cm$^2$ | [47] |
| | H14 *Trypanosoma rangeli*-infected *Rhodnius prolixus* larvae | Physalin B | Reduced the production of hemocyte microaggregation and NO | 0.1, 1 μg/mL | [48] |
| | *T. cruzi* trypomastigotes BALB/c mice macrophages | Physalin B<br>Physalin F | Displayed strongest effects against epimastigote forms of *T. cruzi* | $IC_{50}$ = 5.3 ± 1.9, 5.8 ± 1.5 μM, respectively<br>$IC_{50}$ = 0.68 ± 0.01, 0.84 ± 0.04 μM, respectively | [49] |

| Pharmacological Activity | Animal/Cell Models | Constituent/Extract | Detail | Dosage | Reference |
|---|---|---|---|---|---|
| | Con A-induced spleen cells<br>CBA mice | Physalins B, F, G | In vitro: inhibited MLR and IL-2 production<br>In vivo: prevented the rejection of allogeneic heterotopic heart transplant | 2 μg/mL<br>1 mg/mouse/day | [50] |
| | Human T-cell lymphotropic virus type 1 (HTLV-1)-infected subjects | Physalin F | Inhibited spontaneous proliferation; reduced the levels of IL-2, IL-6, IL-10, TNF-α, and IFN-γ | 10 μM | [51] |
| | T cells<br>BALB/c mice | Physalin H | In vitro: suppressed proliferation and MLR<br>In vivo: inhibited delayed-type hypersensitivity reactions and T-cell response | $IC_{50}$ = 0.69, 0.39 μg/mL, respectively<br>$IC_{50}$ = 2.75 or 3.61 μg/mL | [52] |
| | ICR mice | Polysaccharides | Enhanced specific antibody titers immunoglobulin G (IgG), IgG1, and IgG2b, as well as the concentration of IL-2 and IL-4 | 40 μg/mice | [53] |
| Anti-microbial activity | Gram-positive bacteria: *Staphylococcus epidermidis* (*S. epidermidis*), *Enterococcus faecalis* (*E. faecalis*), *Staphylococcus aureus* (*S. aureus*), *Bacillus subtilis* | Methanol extract<br>Dichloromethane extract<br>Physalin D | Displayed moderate antibacterial activity | MIC = 32–128 μg/mL | [54] |

| Pharmacological Activity | Animal/Cell Models | Constituent/Extract | Detail | Dosage | Reference |
|---|---|---|---|---|---|
| | (*B. subtilis*), *Bacillus cereus* (*B. cereus*) | | | | |
| | *Escherichia coli* (*E. coli*), *B. subtilis* | Physalins B, J, P | Showed high antibacterial activity | MIC = 12.5–23.7, 23.23–24.34, 22.8–27.98 μg/mL, respectively | [55] |
| | *Mycobacterium tuberculosis* H37Rv | Trichlormethane extract Physalins B, D | Showed antibacterial activity | MIC = 32, >128, 32 μg/mL, respectively | [56] |
| | *Lactobacillus delbrueckii* (*L. delbrueckii*), *E. coli* | 70% ethanol extract | Promoted the growth of *L. delbrueckii*; inhibited the growth of *E. coli* | 0.78–1.56 mg/mL | [57] |
| | Gram-positive bacteria: *S. aureus, S. epidermidis, Staphylococcus saprophyticus* (*S. saprophyticus*), *Enterococcus faecium* (*E. faecium*) Gram-negative bacteria: *Pseudomonas aeruginosa* (*P. aeruginosa*), *Streptococcus pneumoniae* (*S. pneumoniae*), *E. coli* | 70% ethanol extract | Showed antibacterial activity | MIC = 0.825–1.65 mg/mL | [23] |
| | *S. aureus, B. subtilis, P. aeruginosa, E. coli* | Physakengoses B, E, F, G, H, K, L, M, N, O | Showed potent inhibitory effects | MIC = 2.16–14.9 μg/mL | [58][59] |
| Anti-leishmanial | *Leishmania*-infected | Physalins B, F | In vitro: reduced the percentage | $IC_{50}$ = 0.21 and 0.18 μM, | [60] |

| Pharmacological Activity | Animal/Cell Models | Constituent/Extract | Detail | Dosage | Reference |
|---|---|---|---|---|---|
| | macrophages *Leishmania amazonensis* -infected BALB/c mice | | of macrophages In vivo: reduced the lesion size, the parasite load, and histopathological alterations | respectively | |
| Others | Kunming mice | Water extract | Decreased the expression of white blood cells and eosinophils, IL-5, IFN-γ, Th1, and Th2 | 0.25, 5, 1 g/mL | [61] |
| | 3T3-L1 pre-adipocyte cells HepG2 cells Male Sprague–Dawley (SD) rats | Ethyl acetate extract | In vitro: relieved oxidative stress; inhibited α-glucosidase activity. In vivo: decreased FBG, TC, and TG | 300 mg/kg | [62] |
| | Alloxan-induced mice | Polysaccharides | Decreased FBG and GSP; increased FINS; upregulated the PI3K, Akt, and GLUT4 mRNA | 200, 400, 800 mg/kg | [63] |
| | High-fat diet-fed and streptozotocin-induced diabetic SD rats | Ethyl acetate extract | Reduced the FBG, TC, TG, and GSP; increased FINS | 300, 600 mg/kg | [64] |
| | Wistar rats Albino mice | Aqueous methanolic extract | Reduced the intensity of gastric mucosal damage; inhibited pain sensation | 500 μg/mL 500 mg/kg | [24] |
| | LPS-induced acute lung injury in BALB/c mice | 70% ethanol extract | Reduced the release of TNF-α and the accumulation of oxidation products; | 500 mg/kg | [65] |

…, mouse
…nethanol
…nhibiting
…1 (IL-1),
…[23][58] …d from *P.*
…physalin
…ysalin A
…[8][9] …I, and I,
…-12, and
…d 12-*O*-
… through
…r factor-

κB (NF-κB) and the STAT1 signaling pathway [9][10][12][13][14][16][17]. The anti-inflammatory effects of four flavonoids (i.e., luteolin, apigenin, kaempferol, and quercetin) were related to inhibition of the production of NO, IL-6, IL-12, TNF-α, STAT-1, and NF-κB, the expression of C–C motif chemokine ligand 2/monocyte chemoattractant protein-1

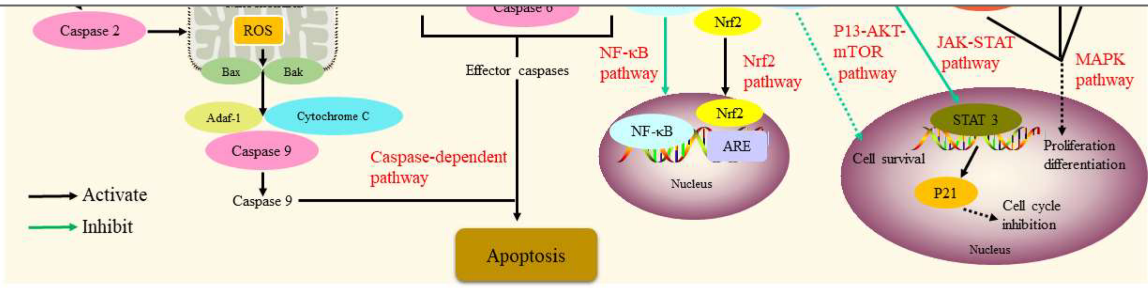
| Pharmacological Activity | Animal/Cell Models | Constituent/Extract | Detail | Dosage | Reference |
|---|---|---|---|---|---|
| | | | decreased the levels of NF-κB, phosphorylated-p38, ERK, JNK, p53, CASP3, and COX-2 | | |
| | 4% dextran sulfate sodium--induced colitis in BALB/c mice | Physalin B | Reduced MPO activity; suppressed the activation of NF-κB, STAT3, arrestin beta 1 (ARRB1), and NLR family pyrin domain containing 3 (NLRP3) | 10, 20 mg/kg | [11] |
| | N2a/APPsw cells | Physalin B | Downregulated β-amyloid (Aβ) secretion and the expression of beta-secretase 1 (BACE1) | 3 μmol/L | [66] |
| | DPPH<br>TBA | Physalin D | Exhibited antioxidant activity | $IC_{50} \geq 10 \pm 2.1$ μg/mL | [54] |
| | *Plasmodium berghei*-infected mice | Physalins B, D, F, G | Caused parasitemia reduction and delay | 50, 100 mg/kg | [67] |
| | High glucose-induced primary mouse hepatocytes<br>Oleic acid-induced HepG2 cells<br>Kunming mice | 75% ethanol extract<br>Luteolin-7-*O*-β-d-glucopyranoside | In vitro: decreased the levels of TG in HepG2 cells<br>In vivo: decreased the levels of TC and TG | 50, 100 μg/mL, respectively<br>1 or 2 g/kg, 0.54 g/kg, respectively | [68] |
| | SD mice | Luteolin | Increased NO; activated PI3K/Akt/NO signaling pathway; enhanced the | 7.5 μg/mL | [69] |

[18][19][20][21]
50 [18]
[27][28][30][31][33][34]
50 [26][28][29][32]
[38][35][36][37][41]
[42][43][44]
[27][42]
[40]

ombuine
entration
cancer,
A and B
S2 cells.
n, JAK3
species
the p53-
K/ROS)
induced
e effects
2–ARE),
signaling
types of
La, and
TNF-α-
pted the
OPFlash
chondrial
-bearing
bearing
sociated
sitide-3-
ed to the
signaling

| Pharmacological Activity | Animal/Cell Models | Constituent/Extract | Detail | Dosage | Reference |
|---|---|---|---|---|---|
| | | | activity of endothelial NOS | | |
| | SD rats | Luteolin | Conferred a cardioprotective effect; ameliorated $Ca^{2+}$ overload | 7.5, 15, 30 μmol/L | [70] |

e 2.




Signaling pathways involved in the antitumor activity of *P. alkekengi* and its constituents.

## 2.3. Immunosuppressive Activity

The immunosuppressive activity of *P. alkekengi* mainly focused on immune cells and *Trypanosoma* infection. Previous studies utilizing concanavalin A (Con A)-activated spleen cells suggested that physalin B inhibited Con A-induced lymphoproliferation, mixed lymphocyte reaction (MLR), and IL-2 production [50]. Yu et al. [52] found that physalin H also significantly inhibited the proliferation of Con A-induced T cells and MLR in vitro, with $IC_{50}$ values of 0.69 and 0.39 μg/mL, respectively. In vivo, physalin H dose-dependently inhibited CD4+ T cell-mediated delayed-type hypersensitivity reactions and antigen-specific T-cell response in ovalbumin-immunized mice, with $IC_{50}$ values of 3.61 μg/mL for 48 h and 2.75 μg/mL for 96 h. The mechanisms may be related to the modulation of T-helper 1/T-helper 2 (Th1/Th2) cytokine balance, inhibition of T cell activation, and proliferation and induction of HO-1 in T cells. Moreover, at the concentration of 40 μg, polysaccharides from fruits of *P. alkekengi* showed good immunosuppressive effects in mice [53]. Physalin B decreased the number of *T. cruzi* Dm28c and *T. cruzi* transmission in the gut at doses of 1 mg/mL (oral administration), 20 ng (topical application), and 57 $ng/cm^2$ (contact treatment), and suppressed epimastigote forms of *T. cruzi*, with an $IC_{50}$ value of 5.3 ± 1.9 μM [47][49]. At a concentration of 1 μg/mL, physalin B significantly increased the mortality rate (78.1%) among *Rhodnius prolixus* larvae infected with *Trypanosoma rangeli* [48]. Physalin F prevented the rejection of allogeneic heterotopic heart transplants in vivo in a concentration-dependent manner. Moreover, it inhibited the spontaneous proliferation of peripheral blood mononuclear cells in patients with human T-cell lymphotropic virus type 1-related (HTLV1-related) myelopathy at 10 μM, suggesting its potential for treatments of pathologies in the inhibition of immune responses [50][51].

## 2.4. Antibacterial Activity

In vitro, at the concentration of 100 μg/mL, physalin D isolated from *P. alkekengi* was found to be effective against *Staphylococcus epidermidis* (*S. epidermidis*), *Enterococcus faecalis* (*E. faecalis*), *Staphylococcus aureus* (*S.*

*aureus*), and *Bacillus subtilis* (*B. subtilis*) [54]. Yang et al. [55] reported that physalins B, J, and P exhibited a good antibacterial activity against *Escherichia coli* (*E. coli*) and *B. subtilis*. Additionally, trichlormethane, ethanol, methanol, or aqueous extracts from *P. alkekengi* were also active against some Gram-positive and Gram-negative bacteria [23][56][57][58]. Janua'rio et al. [56] found that the crude trichlormethane extract (fraction A1-29-12) inhibited the *Mycobacterium tuberculosis* H37RV strain at a minimum concentration of 32 μg/mL. Li et al. [57] found that the 70% ethanol extract stimulated the growth of probiotic bacteria (*Lactobacillus delbrueckii*) and inhibited that of pathogenic bacteria (*E. coli*) in a dose-dependent manner. Moreover, a study indicated that physakengoses also have potent antibacterial activity against *S. aureus*, *B. subtilis*, and *Pseudomonas aeruginosa* (*P. aeruginosa*). The minimum inhibitory concentration (MIC) values of physakengoses B, E, F, G, and H for *S. aureus* were 9.72 ± 2.83, 9.81 ± 1.48, 5.32 ± 1.47, 6.57 ± 0.86, and 5.78 ± 0.96 μg/mL, respectively. For *B. subtilis*, these values were 8.89 ± 1.63, 5.59 ± 0.85, 3.50 ± 1.49, 8.78 ± 1.67, and 3.57 ± 1.02 μg/mL, respectively. For *P. aeruginosa*, these values were 14.91 ± 2.56, 13.12 ± 2.42, 5.79 ± 1.15, 4.51 ± 3.02, and 3.21 ± 0.95 μg/mL, respectively [58]. Zhang et al. showed that physakengoses K, L, M, N, and O had potent antibacterial activity, with MIC values ranging from 2.16 to 12.76 mg/mL [59]. However, the mechanism involved in the antibacterial activity of *P. alkekengi* has not been reported yet, warranting further research. The antibacterial activity is illustrated in **Figure 3.**

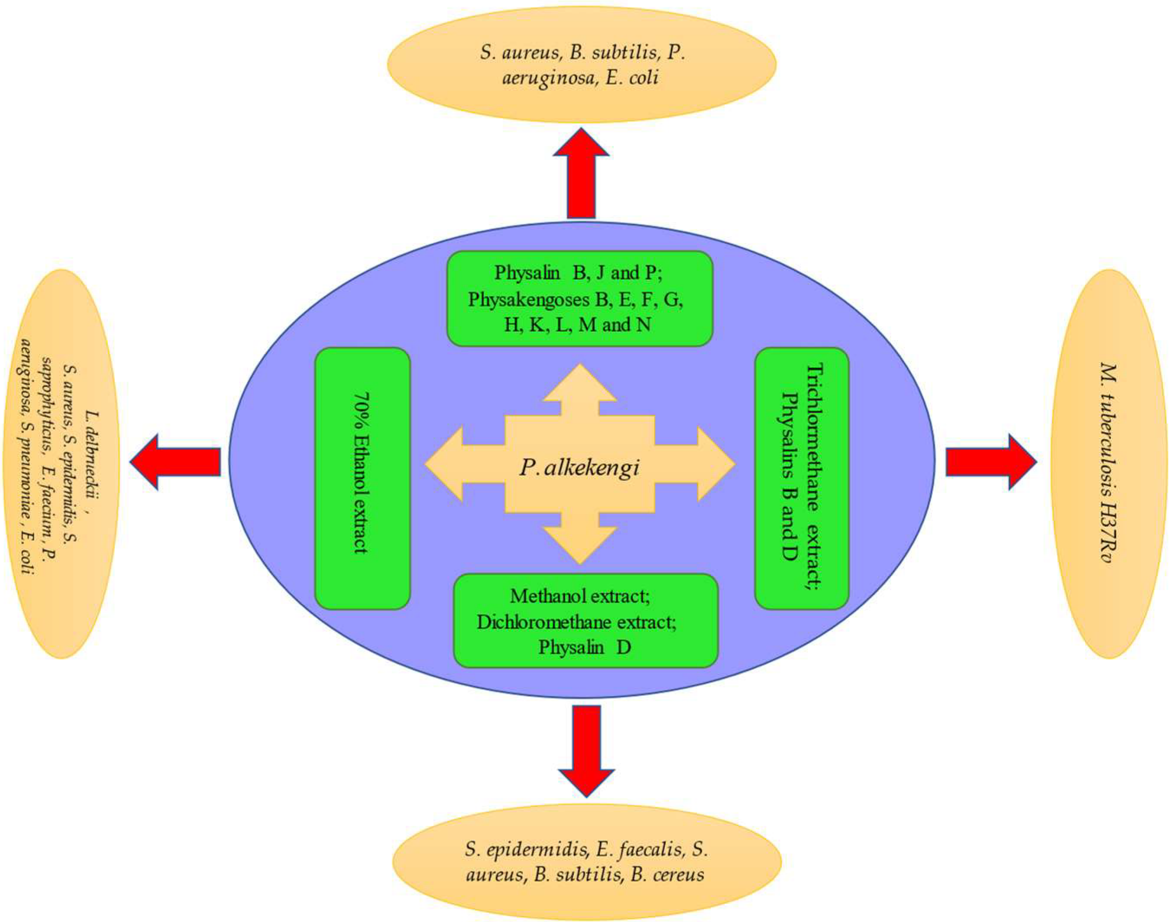



**Figure 3.**

Schematic representation of antibacterial activity of *P. alkekengi* and its constituents.

## 2.5. Antileishmanial Activity

Physalins exhibit potent antileishmanial activity against the cutaneous leishmaniasis [71][72]. Guimarães et al. [60] reported that physalins B and F exerted in vivo antileishmanial effects in BALB/c mice infected with *Leishmania amazonensis* (*L. amazonensis*); in vitro, they demonstrated an effect against intracellular amastigotes of *Leishmania*. In vitro, physalins B and F inhibited the infection of macrophages with *L. amazonensis*, with $IC_{50}$ values of 0.21 and 0.18 μM, respectively. Physalin F markedly reduced the lesion size and number of parasites in vivo. However, physalin D did not show this activity. This effect was associated with the inhibition of NO and proinflammatory cytokines (e.g., IL-12 and TNF-α) by physalins B and F; however, physalin D lacked immunomodulatory/anti-inflammatory activity [9][50]. Meanwhile, the results suggest that anti-inflammatory and antileishmanial activities by physalins play a role in the treatment of cutaneous leishmaniasis.

## 2.6. Others

The anti-asthmatic activity of physalins has been increasingly reported over the years. In an in vitro study, following the oral administration of a water extract from *P. alkekengi*, the number of white blood cells and eosinophils in mice, as well as the expression of IL-5 and IFN-γ in lung tissue, were reduced. These findings indicated its potency as a drug for the treatment of allergic asthma in children [61]. Moreover, some studies showed that luteolin effectively inhibited inflammation in asthmatic models [73]. The relevant mechanisms may be related to the inhibition of iNOS/NO signaling. Thus, more studies are required to explain the mechanisms involved in the anti-asthmatic activity of the *P. alkekengi* extract.

Thus far, most scientific investigations on the anti-diabetic activity of *P. alkekengi* have been carried out using the fruits, aerial parts, and polysaccharides obtained from the calyxes of *P. alkekengi*. For the fruits and aerial parts, the ethyl acetate extract effectively decreased the levels of fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG), and glycated serum protein, whereas it significantly increased those of fasting insulin (FINS) [62][64]. Moreover, polysaccharides showed anti-hyperglycemic activity on alloxan-induced mice. Although research is currently at a preliminary stage, the possible mechanisms are related to the enhancement of PI3K, Akt, and glucose transporter type 4 (GLUT4) mRNA expression, as well as the inhibition of FNG and GSP expression, indicating that they are promising candidates for the development of new anti-diabetic agents [63].

The anti-ulcer and anti-*Helicobacter pylori* effects are newly discovered pharmacological effects of *P. alkekengi*. Wang et al. reported that the *P. alkekengi* extract showed anti-*Helicobacter pylori* and gastroprotective activities by reducing the intensity of gastric mucosal damage and mitigating pain sensation [24]. It was recently reported that the 70% ethanol extract of *P. alkekengi* treated LPS-induced acute lung injury by: (1) reducing the release of TNF-α and the accumulation of oxidation products; (2) decreasing the levels of NF-κB, phosphorylated-p38, ERK, JNK, p53, caspase 3 (CASP3), and COX-2; and (3) enhancing the translocation of Nrf2 from the cytoplasm to the nucleus [65]. It was also shown that the mechanism of *P. alkekengi*, which is involved in the improvement of oxidative stress damage and inflammatory response induced by acute lung injury, was related to the inhibition of NF-κB and the MAPK signaling pathway and the transduction of the apoptotic pathway, as well as the activation of the Nrf2 signaling pathway. Physalin B could be used in the treatment of dextran sulfate sodium-induced colitis in BALB/c mice by suppressing multiple inflammatory signaling pathways [11]. In addition, physalin B is effective against Alzheimer's disease through downregulation of β-amyloid (Aβ) secretion and beta-secretase 1 (BACE1) expression by activating forkhead box O1 (FoxO1) and inhibiting STAT3 phosphorylation [66]. In the diphenyl-2-picrylhydrazyl (DPPH) and thiobarbituric acid (TBA) test, physalin D showed antioxidant activity, with an $IC_{50}$ value ≥10 ± 2.1 μg/mL [54]. Physalins B, D, F, and G showed low anti-plasmodial activity; nevertheless, physalin D markedly caused parasitemia and a delay in mortality in mice infected with *Plasmodium berghei* [67]. Furthermore, a study demonstrated that 75% ethanol extract of calyxes and fruits of *P. alkekengi* significantly decreased the serum's total cholesterol and TG levels in vivo. Moreover, luteolin-7-*O*-β-d-glucopyranoside isolated from *P. alkekengi* decreased the TG levels induced by oleic acid in HepG2 cells and by high glucose in primary mouse hepatocytes, thereby exhibiting hypolipidemic activity [68]. Luteolin effectively relaxed the blood vessels and preserved the rat heart, mainly through activation of the PI3K/Akt/NO signaling pathway and enhancement of the activity of endothelial NOS, as well as amelioration of the $Ca^{2+}$ overload in rat cardiomyocytes [69][70].

## 3. Summary

In summary, *P. alkekengi* is an excellent, abundant, inexpensive, and edible drug. The synthesis of the main active components of *P. alkekengi* must be further analyzed using additional biological and chemical techniques to further expand their potential applications. In addition, the quantitative analysis of the chemical constituents of *P. alkekengi* should be employed for the purpose of standardization and quality control of extracts. Lastly, additional in vivo animal research and clinical trials are needed to determine whether various applications of *P. alkekengi* are effective and safe in a larger population.

## References


1. Chinese Pharmacopoeia Commission. Pharmacopoeia of the People's Republic of China Part I; People's Medical Publishing House: Beijing, China, 2020; p. 360. (In Chinese)
2. Zheng, W.J.; Fu, L.G. Flora of China; Editorial Committee of Flora of China, Chinese Academy of Sciences, Science Press: Beijing, China, 1978; p. 54. (In Chinese)
3. Shu, Z.P.; Xu, B.Q.; Xing, N.; Li, X.L.; Wang, Q.H.; Yang, B.Y.; Kuang, H.X. Chemical constituents of Physalis Calyx seu Fructus. Zhong Guo Shi Yan Fang Ji Xue Za Zhi 2014, 20, 99–102.
4. Gao, P.Y.; Jin, M.; Du, C.L.; Liu, X.G. Research progress of Physalis alkekengi var. franchetii. Shenyang Yao Ke Da Xue Xue Bao 2014, 31, 732–737.
5. Wen, X.; Erşan, S.; Li, M.; Wang, K.; Steingass, C.B.; Schweiggert, R.M.; Ni, Y.; Carle, R. Physicochemical characteristics and phytochemical profiles of yellow and red Physalis (Physalis alkekengi L. and P.pubescens L.) fruits cultivated in China. Food Res. Int. 2019, 120, 389–398.
6. Li, A.L.; Chen, B.J.; Li, G.H.; Zhou, M.X.; Li, Y.R.; Ren, D.M.; Lou, H.X.; Wang, X.N.; Shen, T. Physalis alkekengi L. var. franchetii (Mast.) Makino: An ethnomedical, phytochemical and pharmacological review. J. Ethnopharmacol. 2018, 210, 260–274.

7. Yang, L.J.; Wang, D.D.; Wu, H.J.; Chen, D.Z. Study on the action targets for anti-inflammatory bioactive components of Physalis alkekengi L. var. franchetii (Mast.) Makino based on network pharmacology. J. Tianjin Univ. Tradit. Chin. Med. 2018, 37, 399–403.
8. Ji, L.; Yuan, Y.; Luo, L.; Chen, Z.; Ma, X.; Ma, Z.; Cheng, L. Physalins with anti-inflammatory activity are present in Physalis alkekengi var. franchetii and can function as michael reaction acceptors. Steroids 2012, 77, 441–447.
9. Soares, M.B.; Bellintani, M.C.; Ribeiro, I.M.; Tomassini, T.C.; dos Santos, R.R. Inhibition of macrophage activation and lipopolysaccaride-induced death by seco-steroids purified from Physalis angulata L. Eur. J. Pharmacol. 2003, 459, 107–112.
10. Vieira, A.T.; Pinho, V.; Lepsch, L.B.; Scavone, C.; Ribeiro, I.M.; Tomassini, T.; Ribeiro-dos-Santos, R.; Soares, M.B.; Teixeira, M.M.; Souza, D.G. Mechanisms of the anti-inflammatory effects of the natural secosteroids physalins in a model of intestinal ischaemia and reperfusion injury. Br. J. Pharmacol. 2005, 146, 244–251.
11. Zhang, Q.; Xu, N.; Hu, X.; Zheng, Y. Anti-colitic effects of physalin B on dextran sodium sulfate-induced BALB/c mice by suppressing multiple inflammatory signaling pathways. J. Ethnopharmacol. 2020, 259, 112956.
12. Ding, N.; Wang, Y.; Dou, C.; Liu, F.; Guan, G.; Wei, K.; Yang, J.; Yang, M.; Tan, J.; Zeng, W.; et al. Physalin D regulates macrophage M1/M2 polarization via the STAT1/6 pathway. J. Cell. Physiol. 2019, 234, 8788–8796.
13. Yang, Y.J.; Yi, L.; Wang, Q.; Xie, B.B.; Dong, Y.; Sha, C.W. Anti-inflammatory effects of physalin E from Physalis angulata on lipopolysaccharide-stimulated RAW 264.7 cells through inhibition of NF-κB pathway. Immunopharmacol. Immunotoxicol. 2017, 39, 74–79.
14. Pinto, N.B.; Morais, T.C.; Carvalho, K.M.; Silva, C.R.; Andrade, G.M.; Brito, G.A.; Veras, M.L.; Pessoa, O.D.; Rao, V.S.; Santos, F.A. Topical anti-inflammatory potential of physalin E from Physalis angulata on experimental dermatitis in mice. Phytomedicine 2010, 17, 740–743.
15. Brustolim, D.; Vasconcelos, J.F.; Freitas, L.A.; Teixeira, M.M.; Farias, M.T.; Ribeiro, Y.M.; Tomassini, T.C.; Oliveira, G.G.; Pontes-de-Carvalho, L.C.; Ribeiro-dos-Santos, R.; et al. Activity of physalin F in a collagen-induced arthritis model. J. Nat. Prod. 2010, 73, 1323–1326.
16. Sun, C.P.; Oppong, M.B.; Zhao, F.; Chen, L.X.; Qiu, F. Unprecedented 22,26-seco physalins from Physalis angulata and their anti-inflammatory potential. Org. Biomol. Chem. 2017, 15, 8700–8704.
17. Sun, C.P.; Qiu, C.Y.; Zhao, F.; Kang, N.; Chen, L.X.; Qiu, F. Physalins V-IX, 16,24-cyclo-13,14-seco withanolides from Physalis angulata and their antiproliferative and anti-inflammatory activities. Sci. Rep. 2017, 7, 4057.

18. Qiu, L.; Zhao, F.; Jiang, Z.H.; Chen, L.X.; Zhao, Q.; Liu, H.X.; Yao, X.S.; Qiu, F. Steroids and flavonoids from Physalis alkekengi var. franchetii and their inhibitory effects on nitric oxide production. J. Nat. Prod. 2008, 71, 642–646.
19. Ziyan, L.; Yongmei, Z.; Nan, Z.; Ning, T.; Baolin, L. Evaluation of the anti-inflammatory activity of luteolin in experimental animal models. Planta Medica 2007, 73, 221–226.
20. Funakoshi-Tago, M.; Nakamura, K.; Tago, K.; Mashino, T.; Kasahara, T. Anti-inflammatory activity of structurally related flavonoids, apigenin, luteolin and fisetin. Int. Immunopharmacol. 2011, 11, 1150–1159.
21. Hämäläinen, M.; Nieminen, R.; Vuorela, P.; Heinonen, M.; Moilanen, E. Anti-inflammatory effects of flavonoids: Genistein, kaempferol, quercetin, and daidzein inhibit STAT-1 and NF-κB activations, whereas flavone, isorhamnetin, naringenin, and pelargonidin inhibit only NF-κB activation along with their inhibitory effect on iNOS expression and NO production in activated macrophages. Mediat. Inflamm. 2007, 2007, 045673.
22. Kim, H.P.; Son, K.H.; Chang, H.W.; Kang, S.S. Anti-inflammatory plant flavonoids and cellular action mechanisms. J. Pharmacol. Sci. 2004, 96, 229–245.
23. Shu, Z.; Xing, N.; Wang, Q.; Li, X.; Xu, B.; Li, Z.; Kuang, H.X. Antibacterial and anti-inflammatory activities of Physalis alkekengi var. franchetii and its main constituents. Evid.-Based Complement. Altern. Med. 2016, 2016, 4359394.
24. Wang, Y.; Wang, S.L.; Zhang, J.Y.; Song, X.N.; Zhang, Z.Y.; Li, J.F.; Li, S. Anti-ulcer and anti-Helicobacter pylori potentials of the ethyl acetate fraction of Physalis alkekengi L. var. franchetii (Solanaceae) in rodent. J. Ethnopharmacol. 2018, 211, 197–206.
25. Qiu, L.; Zhao, F.; Liu, H.; Chen, L.; Jiang, Z.; Liu, H.; Wang, N.; Yao, X.; Qiu, F. Two New Megastigmane Glycosides, Physanosides A and B, from Physalisalkekengi L. var. franchetii, and Their Effect on NO Release in Macrophages. Chem. Biodivers. 2008, 5, 758–763.
26. Shin, J.M.; Lee, K.M.; Lee, H.J.; Yun, J.H.; Nho, C.W. Physalin A regulates the Nrf2 pathway through ERK and p38 for induction of detoxifying enzymes. BMC Complement. Altern. Med. 2019, 19, 101.
27. Zhu, F.; Dai, C.; Fu, Y.; Loo, J.F.; Xia, D.; Gao, S.P.; Ma, Z.; Chen, Z. Physalin A exerts anti-tumor activity in non-small cell lung cancer cell lines by suppressing JAK/STAT3 signaling. Oncotarget 2016, 7, 9462–9476.
28. He, H.; Zang, L.H.; Feng, Y.S.; Chen, L.X.; Kang, N.; Tashiro, S.; Onodera, S.; Qiu, F.; Ikejima, T. Physalin A induces apoptosis via p53-Noxa-mediated ROS generation, and autophagy plays a protective role against apoptosis through p38-NF-kappaB survival pathway in A375-S2 cells. J. Ethnopharmacol. 2013, 148, 544–555.

29. He, H.; Zang, L.H.; Feng, Y.S.; Wang, J.; Liu, W.W.; Chen, L.X.; Kang, N.; Tashiro, S.; Onodera, S.; Qiu, F.; et al. Physalin A induces apoptotic cell death and protective autophagy in HT1080 human fibrosarcoma cells. J. Nat. Prod. 2013, 76, 880–888.
30. He, H.; Feng, Y.S.; Zang, L.H.; Liu, W.W.; Ding, L.Q.; Chen, L.X.; Kang, N.; Hayashi, T.; Tashiro, S.; Onodera, S.; et al. Nitric oxide induces apoptosis and autophagy; autophagy down-regulates NO synthesis in physalin A-treated A375-S2 human melanoma cells. Food Chem. Toxicol. 2014, 71, 128–135.
31. Kang, N.; Jian, J.F.; Cao, S.J.; Zhang, Q.; Mao, Y.W.; Huang, Y.Y.; Peng, Y.F.; Qiu, F.; Gao, X.M. Physalin A induces G2/M phase cell cycle arrest in human non-small cell lung cancer cells: Involvement of the p38 MAPK/ROS pathway. Mol. Cell. Biochem. 2016, 415, 145–155.
32. Han, H.; Qiu, L.; Wang, X.; Qiu, F.; Wong, Y.; Yao, X. Physalins A and B inhibit androgen-independent prostate cancer cell growth through activation of cell apoptosis and downregulation of androgen receptor expression. Biol. Pharm. Bull. 2011, 34, 1584–1588.
33. Cao, C.; Zhu, L.; Chen, Y.; Wang, C.H.; ShenTu, J.Z.; Zheng, Y.L. Physalin B induces G2/M cell cycle arrest and apoptosis in A549 human non-small-cell lung cancer cells by altering mitochondrial function. Anti-Cancer Drugs 2019, 30, 128–137.
34. Hsu, C.C.; Wu, Y.C.; Farh, L.; Du, Y.C.; Tseng, W.K.; Wu, C.C.; Chang, F.R. Physalin B from Physalis angulata triggers the NOXA-related apoptosis pathway of human melanoma A375 cells. Food Chem. Toxicol. 2012, 50, 619–624.
35. Ma, Y.M.; Han, W.; Li, J.; Hu, L.H.; Zhou, Y.B. Physalin B not only inhibits the ubiquitin-proteasome pathway but also induces incomplete autophagic response in human colon cancer cells in vitro. Acta Pharmacol. Sin. 2015, 36, 517–527.
36. Vandenberghe, I.; Créancier, L.; Vispé, S.; Annereau, J.P.; Barret, J.M.; Pouny, I.; Samson, A.; Aussagues, Y.; Massiot, G.; Ausseil, F.; et al. Physalin B, a novel inhibitor of the ubiquitin-proteasome pathway, triggers NOXA-associated apoptosis. Biochem. Pharmacol. 2008, 76, 453–462.
37. Wang, A.; Wang, S.; Zhou, F.; Li, P.; Wang, Y.; Gan, L.; Lin, L. Physalin B induces cell cycle arrest and triggers apoptosis in breast cancer cells through modulating p53-dependent apoptotic pathway. Biomed. Pharmacother. 2018, 101, 334–341.
38. Ozawa, M.; Morita, M.; Hirai, G.; Tamura, S.; Kawai, M.; Tsuchiya, A.; Oonuma, K.; Maruoka, K.; Sodeoka, M. Contribution of Cage-Shaped Structure of Physalins to Their Mode of Action in Inhibition of NF-κB Activation. ACS Med. Chem. Lett. 2013, 4, 730–735.
39. Sun, Y.; Guo, T.; Zhang, F.B.; Wang, Y.N.; Liu, Z.; Guo, S.; Li, L. Isolation and characterization of cytotoxic withanolides from the calyx of Physalis alkekengi L. var franchetii. Bioorg. Chem. 2020, 96, 103614.

40. Magalhães, H.I.; Veras, M.L.; Torres, M.R.; Alves, A.P.; Pessoa, O.D.; Silveira, E.R.; Costa-Lotufo LV de Moraes, M.O.; Pessoa, C. In-vitro and in-vivo antitumour activity of physalins B and D from Physalis angulata. J. Pharm. Pharmacol. 2006, 58, 235–241.
41. Jacobo-Herrera, N.J.; Bremner, P.; Marquez, N.; Gupta, M.P.; Gibbons, S.; Muñoz, E.; Heinrich, M. Physalins from Witheringia solanacea as modulators of the NF-kappaB cascade. J. Nat. Prod. 2006, 69, 328–331.
42. Chen, C.; Zhu, D.; Zhang, H.; Han, C.; Xue, G.; Zhu, T.; Luo, J.; Kong, L. YAP-dependent ubiquitination and degradation of beta-catenin mediates inhibition of Wnt signalling induced by physalin F in colorectal cancer. Cell Death Dis. 2018, 9, 591.
43. Ooi, K.L.; Muhammad, T.S.; Sulaiman, S.F. Physalin F from Physalis minima L. triggers apoptosis-based cytotoxic mechanism in T-47D cells through the activation caspase-3- and c-myc-dependent pathways. J. Ethnopharmacol. 2013, 150, 382–388.
44. Wu, S.Y.; Leu, Y.L.; Chang, Y.L.; Wu, T.S.; Kuo, P.C.; Liao, Y.R.; Teng, C.M.; Pan, S.L. Physalin F induces cell apoptosis in human renal carcinoma cells by targeting NF-kappaB and generating reactive oxygen species. PLoS ONE 2012, 7, e40727.
45. Sun, J.L.; Jiang, Y.J.; Cheng, L. Two new physalin derivatives from Physalis alkekengi L. var. franchetii (Mast.) Makino. Nat. Prod. Res. 2021, 35, 203–206.
46. Lin, H.; Zhang, C.; Zhang, H.; Xia, Y.Z.; Zhang, C.Y.; Luo, J.; Yang, L.; Kong, L.Y. Physakengose G induces apoptosis via EGFR/mTOR signaling and inhibits autophagic flux in human osteosarcoma cells. Phytomedicine 2018, 42, 190–198.
47. Castro, D.P.; Moraes, C.S.; Gonzalez, M.S.; Ribeiro, I.M.; Tomassini, T.C.; Azambuja, P.; Garcia, E.S. Physalin B inhibits Trypanosoma cruzi infection in the gut of Rhodnius prolixus by affecting the immune system and microbiota. J. Insect Physiol. 2012, 58, 1620–1625.
48. Garcia, E.S.; Castro, D.P.; Ribeiro, I.M.; Tomassini, T.C.; Azambuja, P. Trypanosoma rangeli: Effects of physalin B on the immune reactions of the infected larvae of Rhodnius prolixus. Exp. Parasitol. 2006, 112, 37–43.
49. Meira, C.S.; Guimarães, E.T.; Bastos, T.M.; Moreira, D.R.; Tomassini, T.C.; Ribeiro, I.M.; Dos Santos, R.R.; Soares, M.B. Physalins B and F, seco-steroids isolated from Physalis angulata L., strongly inhibit proliferation, ultrastructure and infectivity of Trypanosoma cruzi. Parasitology 2013, 140, 1811–1821.
50. Soares, M.B.; Brustolim, D.; Santos, L.A.; Bellintani, M.C.; Paiva, F.P.; Ribeiro, Y.M.; Tomassini, T.C.; Dos Santos, R.R. Physalins B, F and G, seco-steroids purified from Physalis angulata L., inhibit lymphocyte function and allogeneic transplant rejection. Int. Immunopharmacol. 2006, 6, 408–414.

51. Pinto, L.A.; Meira, C.S.; Villarreal, C.F.; Vannier-Santos, M.A.; de Souza, C.V.; Ribeiro, I.M.; Tomassini, T.C.; Galvão-Castro, B.; Soares, M.B.; Grassi, M.F. Physalin F, a seco-steroid from Physalis angulata L., has immunosuppressive activity in peripheral blood mononuclear cells from patients with HTLV1-associated myelopathy. Biomed. Pharmacother. 2016, 79, 129–134.
52. Yu, Y.; Sun, L.; Ma, L.; Li, J.; Hu, L.; Liu, J. Investigation of the immunosuppressive activity of physalin H on T lymphocytes. Int. Immunopharmacol. 2010, 10, 290–297.
53. Yang, H.; Han, S.; Zhao, D.; Wang, G. Adjuvant effect of polysaccharide from fruits of Physalis alkekengi L. in DNA vaccine against systemic candidiasis. Carbohydr. Polym. 2014, 109, 77–84.
54. Helvacı, S.; Kökdil, G.; Kawai, M.; Duran, N.; Duran, G.; Güvenç, A. Antimicrobial activity of the extracts and physalin D from Physalis alkekengi and evaluation of antioxidant potential of physalin D. Pharm. Biol. 2010, 48, 142–150.
55. Yang, Y.K.; Xie, S.D.; Xu, W.X.; Nian, Y.; Liu, X.L.; Peng, X.R.; Ding, Z.T.; Qiu, M.H. Six new physalins from Physalis alkekengi var. franchetii and their cytotoxicity and antibacterial activity. Fitoterapia 2016, 112, 144–152.
56. Januário, A.H.; Filho, E.R.; Pietro, R.C.; Kashima, S.; Sato, D.N.; França, S.C. Antimycobacterial physalins from Physalis angulata L. (Solanaceae). Phytother. Res. 2002, 16, 445–448.
57. Li, X.; Zhang, C.; Wu, D.; Tang, L.; Cao, X.; Xin, Y. In vitro effects on intestinal bacterium of physalins from Physalis alkekengi var. Francheti. Fitoterapia 2012, 83, 1460–1465.
58. Zhang, C.Y.; Luo, J.G.; Liu, R.H.; Lin, R.; Yang, M.H.; Kong, L.Y. 1H NMR spectroscopy-guided isolation of new sucrose esters from Physalis alkekengi var. franchetii and their antibacterial activity. Fitoterapia 2016, 114, 138–143.
59. Zhang, C.Y.; Luo, J.G.; Liu, R.H.; Lin, R.; Yang, M.H.; Kong, L.Y. Physakengoses K-Q, seven new sucrose esters from Physalis alkekengi var. franchetii. Carbohydr. Res. 2017, 449, 120–124.
60. Guimarães, E.T.; Lima, M.S.; Santos, L.A.; Ribeiro, I.M.; Tomassini, T.B.; dos Santos, R.R.; dos Santos, W.L.; Soares, M.B. Activity of physalins purified from Physalis angulata in in vitro and in vivo models of cutaneous leishmaniasis. J. Antimicrob. Chemother. 2009, 64, 84–87.
61. Bao, C.L. Curative Effect of Chinese Physalis Alkekeng on Mice Allergic Asthuma; Yanbian University: Yanji, China, 2008.
62. Hu, X.F.; Zhang, Q.; Zhang, P.P.; Sun, L.J.; Liang, J.C.; Morris-Natschke, S.L.; Chen, Y.; Lee, K.H. Evaluation of in vitro/in vivo anti-diabetic effects and identification of compounds from Physalis alkekengi. Fitoterapia 2018, 127, 129–137.
63. Guo, Y.; Li, S.; Li, J.; Ren, Z.; Chen, F.; Wang, X. Anti-hyperglycemic activity of polysaccharides from calyx of Physalis alkekengi var. franchetii Makino on alloxan-induced mice. Int. J. Biol. Macromol. 2017, 99, 249–257.

64. Zhang, Q.; Hu, X.F.; Xin, M.M.; Liu, H.B.; Sun, L.J.; Morris-Natschke, S.L.; Chen, Y.; Lee, K.H. Antidiabetic potential of the ethyl acetate extract of Physalis alkekengi and chemical constituents identified by HPLC-ESI-QTOF-MS. J. Ethnopharmacol. 2018, 225, 202–210.
65. Yang, Y.; Ding, Z.; Wang, Y.; Zhong, R.; Feng, Y.; Xia, T.; Xie, Y.; Yang, B.; Sun, X.; Shu, Z. Systems pharmacology reveals the mechanism of activity of Physalis alkekengi L. var. franchetii against lipopolysaccharide-induced acute lung injury. J. Cell. Mol. Med. 2020, 24, 5039–5056.
66. Zhang, W.; Bai, S.S.; Zhang, Q.; Shi, R.L.; Wang, H.C.; Liu, Y.C.; Ni, T.J.; Wu, Y.; Yao, Z.Y.; Sun, Y.; et al. Physalin B reduces Aβ secretion through down-regulation of BACE1 expression by activating FoxO1 and inhibiting STAT3 phosphorylation. Chin. J. Nat. Med. 2021, 19, 732–740.
67. Sá, M.S.; de Menezes, M.N.; Krettli, A.U.; Ribeiro, I.M.; Tomassini, T.C.; dos Santos, R.R.; de Azevedo, W.F.J.; Soares, M.B. Antimalarial activity of physalins B, D, F, and G. J. Nat. Prod. 2011, 74, 2269–2272.
68. Yang, Y.; Piao, X.; Zhang, M.; Wang, X.; Xu, B.; Zhu, J.; Fang, Z.; Hou, Y.; Lu, Y.; Yang, B. Bioactivity-guided fractionation of the triglyceride-lowering component and in vivo and in vitro evaluation of hypolipidemic effects of Calyx seu Fructus Physalis. Lipids Health Dis. 2012, 11, 38.
69. Yang, Y.; Chen, B.; Liang, K.L.; Su, J.; Chen, S.H.; Lv, G.Y. Relaxation effect of buddleoside combined with luteolin on isolated vessels in vivo and its mechanism. China J. Chin. Mater. Med. 2017, 42, 1370–1375.
70. Yan, Q.; Li, Y.; Yan, J.; Zhao, Y.; Liu, Y.; Liu, S. Effects of luteolin on regulatory proteins and enzymes for myocyte calcium circulation in hypothermic preserved rat heart. Exp. Ther. Med. 2018, 15, 1433–1441.
71. Tariq, A.; Adnan, M.; Amber, R.; Pan, K.; Mussarat, S.; Shinwari, Z.K. Ethnomedicines and anti-parasitic activities of Pakistani medicinal plants against Plasmodia and Leishmania parasites. Ann. Clin. Microbiol. Antimicrob. 2016, 15, 52.
72. Guimarães, E.T.; Lima, M.S.; Santos, L.A.; Ribeiro, I.M.; Tomassini, B.C.; Santos, R.R.; Santos, L.C.; Soares, B.P. Effects of seco-steroids purified from Physalis angulata L., Solanaceae, on the viability of Leishmania sp. Rev. Bras. Farmacogn. 2010, 20, 945–949.
73. Tan, X.; Jin, P.; Feng, L.; Song, J.; Sun, E.; Liu, W.; Shu, L.; Jia, X. Protective effect of luteolin on cigarette smoke extract-induced cellular toxicity and apoptosis in normal human bronchial epithelial cells via the Nrf2 pathway. Oncol. Rep. 2014, 31, 1855–1862.