Journal of Ethnopharmacology 210 (2018) 260–274

Contents lists available at ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jep

Review

Physalis alkekengi L. var. *franchetii* (Mast.) Makino: An ethnomedical, phytochemical and pharmacological review

Ai-Ling Li[a], Bang-Jiao Chen[b], Guo-Hui Li[c], Ming-Xing Zhou[a], Yan-Ru Li[a], Dong-Mei Ren[a], Hong-Xiang Lou[a], Xiao-Ning Wang[a,*], Tao Shen[a,*]

[a] Key Lab of Chemical Biology (MOE), School of Pharmaceutical Sciences, Shandong University, Jinan, PR China
[b] Department of Pharmacy, The Third Hospital of Jinan, Jinan, PR China
[c] Department of Pharmacy, Jinan Maternity and Child Care Hospital, Jinan, PR China

ARTICLE INFO

Chemical compounds studied in this article:
calystegin B1 (PubChem CID: 164245)
calystegin B2 (PubChem CID: 443000)
chlorogenic acid (PubChem CID: 1794427)
ferulic acid (PubChem CID: 445858)
isophysalin A (PubChem CID: 101575890)
luteolin (PubChem CID: 5280445)
luteolin-7-*O*-β-D-glucopyranoside (PubChem CID: 5280637)
physalin A (PubChem CID: 44577487)
physalin B (PubChem CID: 101650337)
physalin D (PubChem CID: 431071)
physalin F (PubChem CID: 101528280)
physalin L (PubChem CID: 101637227)

Keywords:
Physalis alkekengi var. *franchetii*
Phytochemistry
Pharmacology
Ethnomedical uses

ABSTRACT

Ethnopharmacological relevance: The calyxes and fruits of *Physalis alkekengi* L. var. *franchetii* (Mast.) Makino (Physalis Calyx seu Fructus), have been widely used in traditional and indigenous Chinese medicines for the therapy of cough, excessive phlegm, pharyngitis, sore throat, dysuria, pemphigus, eczema, and jaundice with a long history.

Aim of the review: The present review aims to achieve a comprehensive and up-to-date investigation in ethnomedical uses, phytochemistry, pharmacology, and toxicity of *P. alkekengi* var. *franchetii*, particularly its calyxes and fruits. Through analysis of these findings, evidences supporting their applications in ethnomedicines are illustrated. Possible perspectives and opportunities for the future research are analyzed to highlight the gaps in our knowledge that deserves further investigation.

Material and Methods: Information on *P. alkekengi* var. *franchetii* was collected *via* electronic search of major scientific databases (*e.g.* Web of Science, SciFinder, Google Scholar, Pubmed, Elsevier, SpringerLink, Wiley online and China Knowledge Resource Integrated) for publications on this medicinal plant. Information was also obtained from local classic herbal literature on ethnopharmacology.

Results: About 124 chemical ingredients have been characterized from different parts of this plant. Steroids (particularly physalins) and flavonoids are the major characteristic and bioactive constituents. The crude extracts and the isolated compounds have demonstrated various *in vitro* and *in vivo* pharmacological functions, such as anti-inflammation, inhibition of tumor cell proliferation, antimicrobial activity, diuretic effect, anti-diabetes, anti-asthma, immunomodulation, and anti-oxidation.

Conclusions: *P. alkekengi* var. *franchetii* is an important medicinal plant for the ethnomedical therapy of microbial infection, inflammation, and respiratory diseases (*e.g.* cough, excessive phlegm, pharyngitis). Phytochemical and pharmacological investigations of this plant definitely increased in the past half century. The chemical profiles, including ingredients and structures, have been adequately verified. Modern pharmacological studies supported its uses in the traditional and folk medicines, however, the molecular mechanisms of purified compounds remained unclear and were worth of further exploration. Therefore, the researchers should be paid more attention to a better utilization of this plant.

1. Introduction

Physalis Calyx seu Fructus, named as 'Jin-Deng-Long' (锦灯笼) in Chinese, is the calyxes and fruits of *Physalis alkekengi* L. var. *franchetii* (Mast.) Makino, and has a long history of the treatment of human diseases in China. Its medical values have been recorded in many Chinese medical documents, exemplified by 'Shennong's Classic of Materia Medica' (*Shen Nong Ben Cao Jing*, 神农本草经), and 'Compendium of Materia Medica' (*Ben Cao Gang Mu*, 本草纲目). According to traditional Chinese medicine (TCM) theory, it is com-

Abbreviation: ERK, extracellular signal-regulated kinase; EtOAc, ethyl acetate; EtOH, ethyl alcohol; COX-2, cyclooxygenase-2; IL, interleukin; INF-γ, interferon γ; JAK, Janus kinases; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MIC, minimum inhibitory concentration; MIR-2 , Macrophage inflammatory protein-2; MMP, matrix metalloproteinase; NF-κB, nuclear factor κB; NO, nitric oxide; iNOS, inducible nitric oxide synthase; PGE2, prostaglandin E2; ROS, reactive oxygen species; STAT3, the signal transducers and activators of transcription; TNF-α, tumor necrosis factor α; WSP, water soluble polysaccharide

* Correspondence to: School of Pharmaceutical Sciences, Shandong University, 44 Wenhua Xi Road, Jinan 250012, PR China.
E-mail addresses: wangxn@sdu.edu.cn (X.-N. Wang), shentao@sdu.edu.cn (T. Shen).

http://dx.doi.org/10.1016/j.jep.2017.08.022
Received 5 April 2017; Received in revised form 14 August 2017; Accepted 18 August 2017
Available online 31 August 2017
0378-8741/

monly used for the treatment of cough, excessive phlegm, pharyngitis, sore throat, dysuria, pemphigus, and eczema (Pharmacopoeia Commission of PRC, 2015).

Since the wide applications of *P. alkekengi* var. *franchetii* in indigenous medicines, plenty of investigations on the phytochemical and pharmacological aspects of this plant have been developed, and given rise to many interesting and attractive results. Chemical constituents covering steroids, flavonoids, phenylpropanoids, and alkaloids, have been isolated from different parts of the plant. Crude extracts and isolated ingredients of this plant demonstrated various pharmacological effects, such as anti-inflammation, inhibition of tumor cell proliferation, antimicrobial, diuretic effect, anti-diabetes, anti-asthma, immunomodulation, and anti-oxidation, verified by the bioassay *in vitro* and *in vivo* (Gao et al., 2014; Guo et al., 2012).

Although several concise reviews concerning the phytochemical and biological aspects have been published, these reviews were composed in Chinese and not comprehensive. Different from above literatures, the present review provides a comprehensive and up-to-date survey on ethnomedical uses, phytochemistry, pharmacology, and toxicology of this plant. More importantly, correlations of ethnomedical uses, pharmacology, toxicology, and phytochemical aspects have been discussed on the basis of the research findings in these fields. Besides, the major achievements, shortcomings, as well as the possible perspectives and trends for future studies of the calyxes and fruits of *P. alkekengi* var. *franchetii* have also been put forward.

2. Botanical characterization and distribution

Five synonyms are known for *Physalis alkekengi* var. *franchetii* (Solanaceae), including '*Physalis franchetii* Mast., *Physalis franchetii* var. *bunyardii* Makino, *Physalis glabripes* Pojark., *Physalis praetermissa* Pojark., and *Physalis szechuanica* Pojark.' (The Plant List, 2017).

P. alkekengi var. *franchetii* is a perennial herb growing to the height of 40–80 cm. The stem is little branched, nodes sometimes inflated, and pubescent. Leaf is blade narrowly to broadly ovate, 5–15 cm long, 2–8 cm broad, glabrescent and sometimes ciliate, base oblique, cuneate, margin entire or coarsely dentate, sometimes with salient, unequal deltate lobes, and apex acuminate. Pedicel is 0.6–1.6 cm in length, glabrescent, puberulent or densely and persistently villous. Fruiting calyx is red, ovate, rounded, 2.5–4 × 2 – 3.5 cm, subleathery, invaginated at base, and glabrescent. Fruiting pedicel is 2–3 cm in length. Berry is shiny, orange-red, globose, and 1–1.5 cm in diameter. The seeds are *ca.* 2 mm in diameter, pale yellow, and reniform. Pictures of *P. alkekengi* var. *franchetii* have been shown in Fig. 1. It is widely distributed in Asia and Europe. In China, it mainly grows in Gansu, Shanxi, Henan, Hubei, Sichuan, Guizhou, and Yunnan provinces (Editorial board of flora of China, 1978; Zhang et al., 1994).

3. Ethnomedical uses and preparations

Ethnomedical uses of *P. alkekengi* var. *franchetii* date back to over 2000 years ago. Its medical values were firstly recorded in the Shennong's Classic of Materia Medica' (*Shen Nong Ben Cao Jing*, 神农本草经) arisen in the period of the Warring States, the Qin and Han Dynasties (B. C. 475–A. D. 220). In this TCM monograph, *P. alkekengi* var. *franchetii* was classified into a 'medium grade' drug with undefined toxicity, and was described as an agent of treating dysuria and dystocia (Gu and Yang, 2007). Subsequently, its medical uses were documented in plenty of well-known TCM classics, such as *Shen Nong Ben Cao Jing Ji Zhu* (神农本草经集注, A. D. 480), *Xin Xiu Ben Cao* (新修本草, A. D. 659), *Dian Nan Ben Cao* (滇南本草, A. D. 1436), Compendium of Materia Medica (*Ben Cao Gang Mu*, 本草纲目, A. D. 1578), and Chinese Pharmacopoeia (2015 Edition). Based on the descriptions in these TCM monographs and traditional applications by local residents in folk medicines, it is concluded that the calyxes and fruits of *P. alkekengi* var. *franchetii* are externally and/or internally used to treat cough, excessive phlegm, pharyngitis, sore throat, dysuria, dermatosis, dystocia, jaundice, hemorrhoids, and bronchocephalitis. The clinical dosages for adults suggested by the TCM monographs and Chinese Pharmacopoeia are 5 – 9 g/day for internal use, and reasonable amount for external application. The usages of this plant have been summarized as follows. Infusion tea of the calyxes of *P. alkekengi* var. *franchetii* was able to cure cough, excessive phlegm, sore throats and laryngeal cancer (Liaoning College of Traditional Chinese Medicine, 1973). The dry powder of fruits was used for the therapy of bronchocephalitis (Ye, 1953). Administration of its fruits could relieve the infant jaundice (Tao and Shang, 1987). The aerial parts of *P. alkekengi* var. *franchetii* were externally used for the therapy of hemorrhoids. The fresh jam and powders of dry fruits were applied externally for the treatment of dermatosis, such as felon, pemphigus, and eczema (Guiyang Health Bureau, 1959; Li, 1978). In Turkish folk medicine, the plant was used as diuretic, antipyretic, and sedative agents (Baytop, 1999). It has also been adopted for the treatment of cough, urinary problem, middle ear infection, and sore throats in Eastern Asia and European folk medicines (Hong et al., 2015; Kim et al., 1997). Beside these ethnomedical applications in the form of single medicine, the calyxes and fruits of *P. alkekengi* var. *franchetii* (Physalis Calyx seu Fructus) were commonly used in multi-component preparations to improve their therapeutic efficacy because of the TCM's synergic effects, such as Jin Deng Shan Gen Decoction (金灯山根汤). Moreover, the calyxes and fruits of *P. alkekengi* var. *franchetii* were developed into modern pharmaceutics preparation [*e.g.* Ju Hong Hua Tan Pill (橘红化痰丸)]. The traditional uses of the calyxes and fruits of *P. alkekengi* var. *franchetii* in the form of compound and modern pharmaceutical preparations have been summarized in Table 1. The names of crude drugs in Table 1 were established on the basis of Chinese Pharmacopoeia (2015 Edition).

4. Phytochemistry

Phytochemical investigations of *P. alkekengi* var. *franchetii* date back to the year of 1965 (Yamaguchi and Nishimoto, 1965). The information of the isolated constituents has been briefly provided by two Chinese reviews (Gao et al., 2014; Guo et al., 2012). Up to date, approximately 124 ingredients covering steroids, flavonoids, phenylpropanoids, and alkaloids, have been isolated from different parts of this plant (Table 2). Among them, steroids (mostly physalins) and flavonoids have been regarded to be the characteristic and principal bioactive substances of *P. alkekengi* var. *franchetii*.

4.1. Steroids

About fifty-eight steroids have been reported from the calyxes, fruits and aerial parts of *P. alkekengi* var. *franchetii*. Among them, a group of steroids bearing 13, 14-seco-16, 24-cycloergostane skeletons, named as physalins, are the predominate steroids in this plant. Physalin A (**1**), isolated from the leaves of *P. alkekengi* var. *franchetii* in 1969, was the first member of this group (Matsuura et al., 1969). Subsequently, a series of physalins with complex and diverse structures were reported from the genus *Physalis*. Up to now, phytochemical investigations of *P. alkekengi* var. *franchetii* lead to the isolation of fifty physalins (**1**–**49** and **53**), and most of which are firstly discovered structures (Table 2 and Fig. 2). The structural diversity of physalins is produced by cyclization, changes in the degree of unsaturation, and the variations in the substitution pattern of rings. For example, physalins F (**12**), J (**15**), and III (**34**) contain 5, 6-epoxy moiety (Qiu et al., 2008c; Yang et al., 2016; Xu et al., 2013). Physalins K (**16**) and Q (**22**) are 2α, 5α-epidioxy derivatives (Makino et al., 1995a). An additional bond between C-11 and C-16 exists in the structure of physalin R (**23**) (Makino et al., 1995b). Physalin S (**25**) possesses a 6β-hydroxy-3, 5-cyclo steroidal skeleton which might be produced by an acid catalyzed