

БИОЛОГИЧЕСКАЯ АКТИВНОСТЬ
РАСТЕНИЙ

BIOLOGICALLY ACTIVE COMPOUNDS AND BIOLOGICAL ACTIVITY
OF *PHYSALIS ALKEKENGII* (SOLANACEAE)

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Physalis alkekengi L. was well known as a medicinal plant in Ancient China. Fruits, calyx, and plant roots have been used to treat a number of ailments, including sore throat, cough, eczema, hepatitis, and tumours. In the Unani system of medicine, Kaknaj, the dried fruits of *P. alkekengi* are valued primarily as a source of vitamin C and used as a diuretic, antiseptic and sedative. Modern medical research has shown that *P. alkekengi* is effective in therapy of the disorders of immune system, thyroid hormones, liver enzymes, reproductive sex hormones, against cancer. The plant owes its beneficial properties to the presence of biologically active compounds, such as alkaloids, flavonoids, steroids, vitamin C, etc. The purpose of this study is to summarize literature data on the results of experimental studies of the component composition and biological activity of *P. alkekengi*. The results of the chemical study of *P. alkekengi* shows that fresh fruits, calyx, roots and leaves are rich in various biologically active substances such as flavonoids, steroids, alkaloids, etc. Chemical composition of various organs of *P. alkekengi* as well as antimycobacterial, immunomodulating, antitumour, anti-inflammatory and other properties of groups of substances and individual compounds isolated from *P. alkekengi* extracts were studied. The studied literature data allows to consider *P. alkekengi* as a promising source of substances for medicinal products.

Ключевые слова: *Physalis alkekengi*, biologically active compounds, biological activity

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The genus *Physalis* L. from the *Solanaceae* L. family has from 75 to 120 species in the world flora, widely distributed throughout South and North America, as well as in the temperate regions of Europe and Asia [1–4]. In Azerbaijan, the genus is represented by 2 species. One of them is wild-growing – *Physalis alkekengi* L. is widely distributed in almost all botanical and geographical regions of Azerbaijan, the second is *Physalis ixocarpa* Brot ex Hornem. found only in culture [3]. Among the species belonging to the genus *Physalis* L., *P. alkekengi*. is the most popular food, ornamental and medicinal plant.

P. alkekengi was well known as a medicinal plant in Ancient China. Fruits, calyx, and plant roots have been used to treat a number of ailments, including sore throat, cough, eczema, hepatitis, and tumours [2]. In the Unani system of medicine, Kaknaj, the dried fruits of *Physalis alkekengi* are valued primarily as a source of vitamin C and used as a diuretic, antiseptic and sedative remedies [1]. For centuries, infusion of fruits has been used as an abortive and contraceptive remedy in Iranian traditional medicine [4]. Modern medical research has shown that *P. alkekengi* is effective in therapy of the disorders of immune system, thyroid hor-

mones, liver enzymes, reproductive sex hormones, against cancer. The plant owes its beneficial properties to the presence of biologically active compounds, such as alkaloids, flavonoids, steroids, vitamin C, etc. [5]. The juice form *P. alkekengi* fruit has an antiseptic effect, therefore it is used externally to treat septic wounds and ulcers [6].

The purpose of this study is to summarize literature data on the results of experimental studies of the component composition and biological activity of *P. alkekengi*.

BIOLOGICALLY ACTIVE COMPOUNDS
OF *PHYSALIS ALKEKENGII* L.

About nineteen flavonoids have been isolated and identified from various parts of the *P. alkekengi* in the form of flavones and flavonols. Isolated flavonoids include luteolin and their glycosides, quercetin derivatives and kampferol glycosides, which are widely distributed in medicinal plants [7–13]. In addition, four flavone analogs, apigenin-O- β -D-glucopyranoside, diosmetin-O- β -D-digluco-pyranoside, chryso-riol and its glucopyranoside, as well as three flavonol analogs, 3', 4' dimethoxymyritsetin, ombine and 5,4', 5'-trihy-

droxy-7,3'-dimethoxyflavonol were obtained from sepals [8–10, 14, 15]. These isolated flavonoids were best known for their antioxidant and anti-inflammatory properties [16–18].

As a result of a study conducted by Prokopenko and co-authors, 46 lipophilic compounds were found in the aboveground part of *P. alkekengi*, of which 29 compounds were identified and estimated, including organic acids, phytosterols, hydrocarbons, terpene compounds, etc. Among identified compounds, palmitic and linolenic acids were found [6].

Linoleic acid has a high biological activity and is not produced in the human body. Owing to the high content of linoleic acid, the aboveground parts of *P. alkekengi* are used as raw material for the production of dietary supplements.

In early studies it was reported that only 10 carotenoids are present in the fruits and calyx of *P. alkekengi* [19–21]. The study of 2017 allowed to isolate 69 different carotenoids and carotenoid esters in the fruits and calyx of *P. alkekengi*, of which 45 were identified. Zeaxanthin esters with various fatty acids were the most common carotenoids, accounting for 51–63% of the total carotenoids. The fruits and calyx of plant have been reported to be rich sources of xanthophylls, mainly zeaxanthin esters (6.39 mg zeaxanthin/100 g fresh fruit, 54.89 mg zeaxanthin/100 g fresh sepal), followed by β -cryptoxanthin esters (no data on fruits, 3.92 mg/g of dry sepal). Esters of carotenoids accounted for 94–96% of the total amount of carotenoids in *P. alkekengi* the fruits. Zeaxanthin esters (56–63% of the total amount of carotenoids) were the most common in the fruit, followed by β -cryptoxanthin (18–24%), anterxanthine (4–6%) and violaxanthin esters (2–4%). Small amount of lutein, lutoxanthin, mutatoxanthin, neoxanthin, auroxanthin and zeinoxanthin esters were identified. In addition to carotenoids, a small amount of chlorophyll b, chlorophyll a and pheophytin was also identified in *P. alkekengi* fruits [22]. According to the content as the sum of carotenoids and xanthophylls, the fruits of *P. alkekengi* exceeds fruits of all other plants rich in carotenoids.

Pintea and others showed that *P. alkekengi* calyx contain zeaxanthin and beta-cryptoxanthin esters, which are widely used as nutritional supplements [20].

Physalins have been extensively studied over the past 20 years and are reported to have anti-mycobacterial, immunomodulatory, anti-tumour, and anti-inflammatory effects [23, 24].

Physalins are the main steroid components of *P. alkekengi* and their rare 13,14-seco-16,24-cycloergostane skeletons were first established by x-ray structural analysis [25–27]. Physalin A, isolated from the leaves of *P. alkekengi* in 1969, was the first steroid of this group [28]. Subsequently, a series of physalins

with a complex and diverse structure were obtained from various species of the genus *Physalis*. So far, phytochemical studies of *P. alkekengi* have led to isolation of fifty physalins, most of which were first found while studying this species. The structural diversity of physalins is determined by cyclization, changes in the degree of unsaturation, and changes in the ring substitution structure. For example, W, X, Y, and Z physalins, as well as 3-O-methylphysaline X and isophysalin G, are 3-hydroxyl and/or 3-methoxy-substituted physalins, while fizalin C and 5 α , 6 β -dihydroxyphysaline R are components 5,6-dihydroxyl group [24]. Physalin P was the first neofizalin, isolated from the aboveground part of *P. alkekengi* in 1993 [29]. In 2013, a group of Chinese researchers isolated three new physalins from *P. alkekengi* sepals and named them physalin III, physalin IV, 3-O-methylphysalin X [30]. In 2016, another 6 new physalins 7 β -methoxylisophysalin B, 7 β -methoxyphysaline C, fizalin V, fizalin VI, fizalin VII, isophilin I [31] were determined.

The chemical study of *P. alkekengi* (Table 1) show that fresh fruits, as well as other parts (calyx, roots, leaves) are rich in various biologically active substances (flavonoids, steroids, alkaloids, etc.).

ANTIMICROBIAL AND ANTIFUNGAL ACTIVITY

Species of the genus *Physalis*, including *Physalis alkekengi*, are rich sources of physalins, steroids of the cycloergosterated class, common only in this genus. Chemical composition of various organs of *P. alkekengi* as well as antimycobacterial, immunomodulating, antitumour, anti-inflammatory and other properties of groups of substances and individual compounds isolated from *P. alkekengi* extracts were studied.

Eight phenylpropanoids, consisting of four phenylpropanoic acid derivatives and four lignans, were isolated from *P. alkekengi* var. *franchetii* calyx. The isolated phenylpropanoic acid derivatives are chemical compounds, including ferulic acid methyl ester, 3-caffeoylquinic acid and syringalide, which express antibacterial, antiviral, and anti-inflammatory properties. All isolated lignans possess a tetrahydrofuran-type skeleton and exist in the form of glycosides containing syringaresinol, (+) – pinoresinol-di-O- β -D-glucopyranoside and (+) – medioresinol-di-O- β -D-glucopyranoside [14, 15].

Numerous studies of the antimicrobial and antifungal activities of *P. alkekengi* extracts have been conducted. Thus, the methanol extract from the aboveground parts and the dichloromethane extract from the *P. alkekengi* calyx were tested against five gram-positive and five gram-negative bacteria and five *Candida* species. According to the results of the experiments, the

Table 1. Chemical compounds isolated from various parts of *P. alkekengi* L.

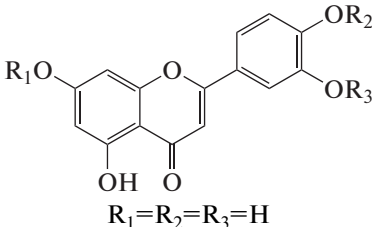
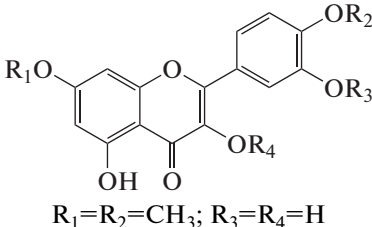
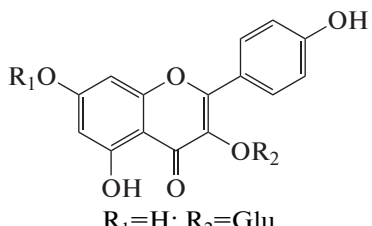
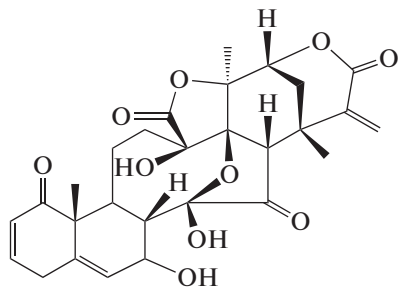
Chemical group	Chemical component	Structure	Part of the plant	References
Flavonoids	Luteolin	 <p style="text-align: center;">$R_1=R_2=R_3=H$</p>	Calyx	[8–10, 13]
	Luteolin-7- <i>O</i> - β -D-glucopyranoside	$R_1=Gluc; R_2=R_3=H$	Calyx	[7–10, 13]
	Luteolin-4'- <i>O</i> - β -D-glucopyranoside	$R_1=R_3=H; R_2=Gluc$	Calyx	[7, 8]
	Luteolin-7,4'-di- <i>O</i> - β -D-glucopyranoside	$R_1=R_2=Gluc; R_3=H$	Calyx	[8]
	Luteolin-7,3'-di- <i>O</i> - β -D-glucopyranoside	$R_1=R_3=Gluc; R_2=H$	Calyx	[7, 8]
	3',7-Dimethylquercetin	 <p style="text-align: center;">$R_1=R_2=CH_3; R_3=R_4=H$</p>	Calyx	[12]
	3',4',7-Trimethylquercetin	$R_1=R_2=R_3=CH_3; R_4=H$	Calyx	[12]
	3',4'-Dimethylquercetin	$R_1=R_4=H; R_2=R_3=CH_3$	Calyx	[11]
	Quercetin-3- <i>O</i> - β -D-glucopyranoside	$R_1=R_2=R_3=H; R_4=Gluc$	Calyx	[7, 8]
	Quercetin-3,7-di- <i>O</i> - β -D-glucopyranoside	$R_1=R_4=Gluc; R_2=R_3=H$	Calyx	[7, 8]
Steroids	Kaempferol-3- <i>O</i> - β -D-Glucose	 <p style="text-align: center;">$R_1=H; R_2=Gluc$</p>	Calyx	[11]
	Physalin A		Calyx	[8, 9, 11, 13, 14, 28, 31, 46–48]

Table 1. (Contd.)

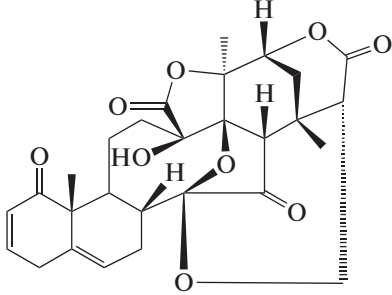
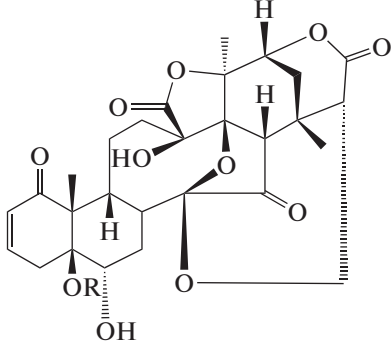
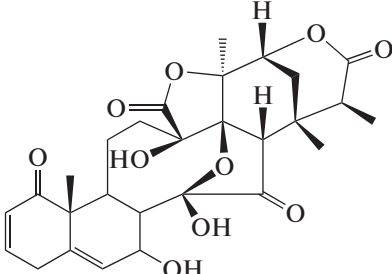
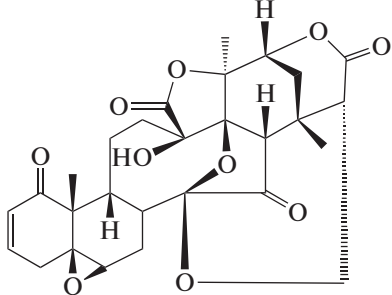
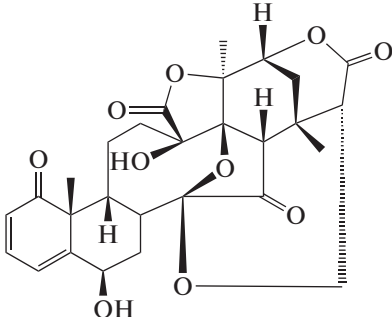
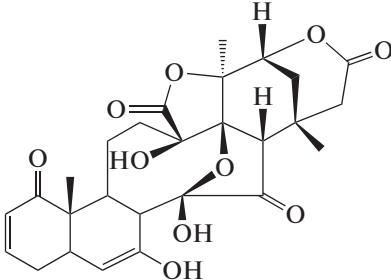
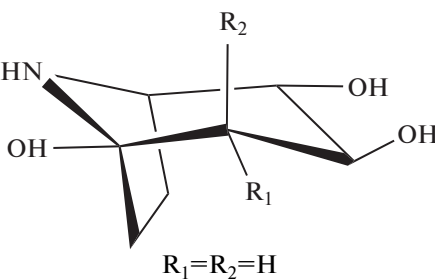
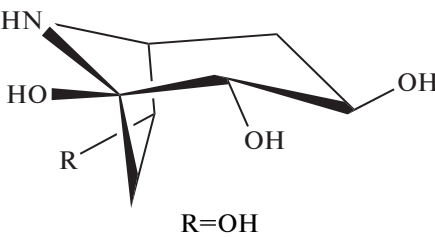
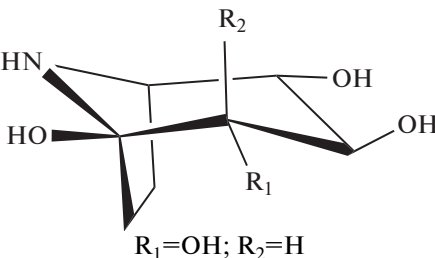
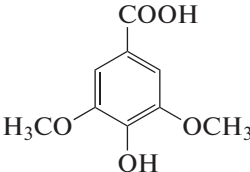
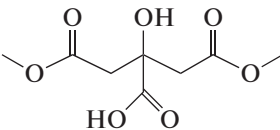
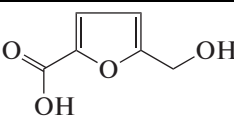
Chemical group	Chemical component	Structure	Part of the plant	References
	Physalin B		Calyx	[8, 9, 11, 12, 14, 31, 46, 47]
	Physalin D		Calyx	[8, 10, 13, 14, 31, 47, 49]
	Physalin O		Calyx	[8, 9, 13, 31, 50]
	Physalin F		Calyx	[8, 11, 31]
	Physalin G		Calyx	[14, 31]

Table 1. (Contd.)

Chemical group	Chemical component	Structure	Part of the plant	References
	Physalin L		Calyx	[8, 9, 13, 23, 31, 46, 47]
Alkaloids	Calystegin A5	 $R_1=R_2=H$	Roots	[14]
	Calystegin B1	 $R=OH$	Roots	[14]
	Calystegin B2	 $R_1=OH; R_2=H$	Roots	[51]
Organic acids	Syringic acid		Calyx	[52]
	1,5-Dimethyl citrate		Calyx	[53]
	5-Hydroxymethylfuroic acid		Calyx	[53]

methanol extract showed moderate antifungal activity with minimum inhibitory concentration (MIC) from 128 to 512 $\mu\text{g/ml}$, dichloromethane extract and fizalin D had low antifungal activity with MIC from 256 to 512 $\mu\text{g/ml}$ [32]. Chlorogenic acid isolated from the aerial parts of *P. alkekengi* showed high antibacterial activity against *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Bacillus subtilis*, *Escherichia coli* and *Shigella dysenteriae* with MIC values ranging from 20 to 80 $\mu\text{g/ml}$. Physalins B, D, F and G showed an antimalarial effect against *Plasmodium falciparum in vitro* with IR 50 values ranging from 2.2 to 55 μM , where physalin F showed the highest effect ($\text{IC}_{50} = 2.2 \mu\text{M}$ and $\text{LC}_{50} = 13.3 \mu\text{M}$) [33].

Six physalins isolated from the plant: 7 β -methoxyphysalin B, 7 β -methoxyphysalin C, physalin V, physalin VI, physalin VII, isophysalin I were tested for antibacterial activity and cytotoxicity against human HL-60, SMMC-7721, A-549, MCF-7 and SW-480. The results showed that these compounds exhibit strong cytotoxicity ($\text{IC}_{50} < 5 \mu\text{M}$) *in vitro*. Antibacterial analysis showed that physalins exhibit high antibacterial activity against *Bacillus subtilis* and *Escherichia coli* [31]. Aqueous, ethanolic, and methanol fruit extracts were used against 3 types of fungi: *Microsporum canis*, *Candida albicans*, *Trichophyton mentagrophytes*. The aqueous extract had a limited spectrum of antifungal effect compared to the other two extracts. Ethanol extract had the strongest effect at $\text{MIC} = 15.62$ against all fungi tested [34].

ANTITUMOUR ACTIVITY

Several authors [35–38] provide information on the antitumour activity of *P. alkekengi*. Taken together, physalins, flavonoids and phenylpropanoids may be considered as the main antitumour substances. Physalins A and B, being representative compounds for the genus *Physalis*, were tested for their antitumor properties using cell analysis. [35, 38]. When studying physalin B, its antiproliferative effect was established. Physalin B was particularly active against human melanoma A375 and A2058 cells ($\text{IC}_{50} < 4.6 \mu\text{g/ml}$) and had lower cytotoxicity on H9c2 rat cells and T/G HA-VSMC

and CCD-966SK human cells. These results have shown that these two physalins A and B may be promising therapeutic agents for the treatment of cancer, especially melanoma.

The antitumour properties of the flavonoids isolated from *P. alkekengi*, including luteolin, quercetin and their analogues, have been thoroughly investigated [39, 40]. It has been found that these flavonoids can induce apoptosis of cancer cells, stop the cancer cell cycle and inhibit metastasis and angiogenesis.

ANTI-DIABETIC ACTIVITY

Several studies [41, 44] have found that *P. alkekengi* has the potential to reduce serum glucose concentration in alloxan-induced diabetic rats. The reduced glucose levels and activity may be associated with chemical compounds contained in fruits, mainly physalin, flavonoids, citric acid and vitamin C.

Antidiabetic activity of ferulic and chlorogenic acids isolated from *P. alkekengi* was studied. Using various diabetes models *in vivo*, it was found that these two compounds can reduce blood glucose levels, stimulate insulin secretion, improve glucose tolerance and insulin resistance, inhibit lipid absorption and stimulate lipid metabolism *in vivo* [42, 43].

Asano et al. established the antidiabetic potential of polysaccharides (calystegines) isolated from *P. alkekengi* fruits. Administration of isolated polysaccharides (50 and 100 mg/kg) reduced the blood glucose level. Calystegines are a group of structural analogues of glucose and galactose, and, thus, they can block the process of carbohydrate metabolism by competitive inhibition of key glucosidases and galactosidases. It was found that calystegin B2 isolated from *P. alkekengi* is a potent competitive inhibitor of almond β -glucosidase ($K_i = 1.2 \mu\text{M}$) and coffee bean α -galactosidase ($K_i = 0.86 \mu\text{M}$) [45].

Despite using *Physalis alkekengi* for medical purposes, the reasons for its high biological activity have not been fully identified. The analysis of literature data allows to consider *P. alkekengi* as a promising source of substances for medicinal products.

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БИОЛОГИЧЕСКИ АКТИВНЫЕ КОМПОНЕНТЫ И БИОЛОГИЧЕСКАЯ АКТИВНОСТЬ *PHYSALIS ALKEKENGI* (SOLANACEAE)

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Physalis alkekengi L. хорошо знали как лекарственное растение еще в Древнем Китае. Плоды, чашечку и корни растения использовали при лечении ряда заболеваний, включая боль в горле, кашель, экзему, гепатит и опухоли. В системе медицины Унани сухие плоды растения, называемые Какпаж ценятся прежде всего как источники витамина С и используются в качестве мочегонного, антисептического и седативного средства. Современные медицинские исследования показали, что *P. alkekengi* эффективен при нарушениях функций иммунной системы, уровня гормонов щитовидной железы, ферментов печени, половых и репродуктивных гормонов, против рака. Полезными свойствами растение обязано присутствием в его составе биологически активных соединений, таких как алкалоиды, флавоноиды, стероиды, витамин С и др. Цель данной работы – проведение анализа приведенных в литературе результатов экспериментальных исследований, касающихся компонентного состава и биологической активности *P. alkekengi*. Результаты химического изучения растения показывали, что свежие плоды, а также остальные части растения (чашечка, корни, листья) богаты различными биологически активными веществами (флавоноиды, стероиды, алкалоиды и др.). Наряду с изучением химического состава различных органов *P. alkekengi* были широко исследованы антибактериальные, противогрибковые, иммуномодулирующие, противоопухолевые, противовоспалительные и др. свойства группы веществ и индивидуальных компонентов, выделенных из экстрактов данного растения. Результаты анализа литературных данных позволяют рассматривать данное растение в качестве перспективного источника веществ для создания лекарственных средств.

Keywords: *Physalis alkekengi*, биологически активные компоненты, биологическая активность