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Review article

Therapeutic Activities and Phytochemistry of *Physalis* Species Based on Traditional and Modern Medicine

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Abstract

Physalis, the fifth largest genus of the Solanaceae family, consists many species which are used as food and natural remedies. Phytochemical investigations on *Physalis* species have led to characterization of important secondary metabolites such as withaphysalins, physalins and phytosterols which are responsible for wide range of pharmacological effects such as potent cytotoxic activity against various type of human cancer cell lines, immunomodulatory and cancer chemopreventive effects. They are widely used in the indigenous system of medicine for treatment of kidney and urinary disorders, leishmaniasis, inflammations, skin infections and etc. Based on Iranian traditional medicine texts, *Physalis* is effective for treatment of several disorders such as asthma, liver, kidney and bladder dysfunctions, wounds, hemorrhoids, and helminthic diseases. Based on recent surveys, many of the above properties have not been investigated so far except the for the healing effects on liver dysfunction. This review might be a starting point for the development of the new therapeutic applications and more investigations on *Physalis* species in the future.

Keywords: anti-inflammatory; Iranian traditional medicine; physalin; *Physalis*; Solanaceae

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Introduction

Solanaceae or nightshade family consists of nearly 100 genera and 2500 species, distributed in different parts of the world. They include many of our favorite foods with different important phytochemicals [1]. Some of the species such as chili (*Capsicum annuum* L.), tomato (*Lycopersicon esculentum* L.) and potato (*Solanum tuberosum* L.) are cultivated in this family. The family also contains many wild growing species such as *Physalis* which is the fifth largest genus of the *Solanaceae*, comrising of about 70 species. The center of the *Physalis* diversity is located in Mexico (about 50 species) and is endemic to this region [2,3]. Some of the *Physalis* species such as *P. divaricata* and *P. alkegengi* occur jointly in America and Asia. *Physalis alkegengi* is distributed in northern, western, and southern parts of Iran [4,5].

Plants belonging to *Solanaceae* exhibit different growth forms such as trees, shrubs, herbs, climbers, and epiphytes [4]. They have alternate leaves and solitary, bisexual, regular flowers with 5 (rarely 3, 4 or 6) separate or united sepals and 5 united petals. There are 5 stamens inserted on the tube. The ovary is superior. Carpels are bicarpellate with the partition walls, which is obvious in wild species more than domestics containing maturing berry (like the tomato) or a capsule [1].

Physalis is an upright, herbaceous, semi-shrub, perennial species which can grow up to 1 m tall.

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The flowers are bisexual, solitary, and bell-shaped. The specific calyx becomes enlarged to surround the fruit and go downwards similar to a lantern. Because of the inflated calyx it has been named *Physalis* in Greek which means bladder. The juicy berry fruit can reach 1.25 to 2.50 cm in diameter with many small seeds. The ovoid-shape fruit contains an accrescent calyx covered by a brilliant yellow-orange peel [6,7].]. It completely covers the fruit during its growing and ripening, and protects it against insects, birds, diseases and bad climatic conditions [8]. The pattern of *Solanaceae* family and some *Physalis* species has been shown in figures 1 and 2 [1].

Recently, *Physalis* has become an important food crop and widely cultivated in tropical, subtropical and temperate regons. Europe is the main consumer of the *Physalis* fruits as food and in the pharmaceutical industry [6]. Several studies have mentioned the nutritional use of *Physalis* fruits in different parts of the world, including their consumption as raw, or in salads, sauces, compotes and jams [9]. Some *Physalis* species, such as *P. peruviana* (cape gooseberry) and *P. pubescens* (husk tomato) have been cultivated and eaten for their acidulous fruits [10]. The Chinese lantern plant (*P. alkenkengi*) is cultivated for ornamental aspects due to its brilliant orange-red colored and swollen calyces [7]. Fruits of some of *Physalis* species are edible with numerous important therapeutic phytochemicals such as physalins, withanolides, phenolics, phytosterols, carotenoids, vitamins and minerals [2,3,8,11]. The traditional usage of *Physalis* are numerous. It is named "Kakanj" in Iranian traditional medicine texts (ITM) and its potential therapeutic activities are remarkable. It is used for liver, kidney or bladder dysfunctions and many diseases such as jaundice, hemorrhoids, and helminths diseases [12-14]. ITM, known by prominent physicians like Avicenna and Rhazes, has a long history, more than 4000 years. Treatment of diseases and therapeutic principle are documented in many Iranian traditional texts. The bases of etiology and treatment is based on quadruplet pillars, the four elements in ITM [15,16].

Based on recent studies many pharmacological activities are attributed to this genus. Its potential antitumor, immunomodulatory, anti-inflammatory, hepato-renal protection and so on is remarkable [17-20].

Methods

The objective of this review was to get updated comprehensive information about *Physalis* species including their uses in traditional medicine, phytochemistry and pharmacology. It included articles and books selection from 1975 to 2018 with the purpose of finding the best information about this species, by review in following bibliographic databases: Science Direct, WILEY, PubMed and google scholar. We also investigated some data based on important traditional medicine books including The Canon of Medicine (al-qanun), Tuhfat AlMu'minin, Zakhireye Khwarazmshahi, Makhzan ul-Adwia and Ikhtiyarat Badie, which have been written between the 9 and 19 centuries.

Results and Discussion

Uses in ethno-medicine

Recent ethno-pharmacological studies have shown that *Physalis* species have been used in different parts of the world to treat several diseases. *Physalis peruviana* which was locally named "cape gooseberry" or "Uchuva" in Colombia had multiple traditional uses. The fruit juice was used for treating pterygium by applying it directly to the eye [24]. In different regions of Colombia, some of the local traditional healers use *P. peruviana* for purifying kidney blood flow, decreasing albumin, cleaning the cataract, calcifying and controlling amebiasis [8]. In southern Florida *P. angulate* and *P. pubescens* leaves have been used for treatment of some disorders such as gonorrhea, fever and as stomachic [25]. Natives of Omaha and Ponca in northeast Nebraska, United States have used some *Physalis* species roots such as *P. longifolia, P. virginiana, or P. pumila* for treating headache and stomach disorders, and as a dressing for wounds [7]. Native Americans used some *Physalis* species for psychoactive properties such as sedation, hallucination, and analgesia [26]. *Physalis angulata* is one of the medicinal plants of Brazilian Amazon. It has been used for treating malaria and leishmaniasis in the region. It was also utilized by inhabitants of the Brazilian and Peruvian Amazon for liver dysfunctions [27]. In Suni Mirafio, Peru the tea and macerations of the leaves and fruits of *P. angulata* has been used for postpartum infections and itching [28]. It was reported that the root of *P. peruviana* was used for piles (hemorrhoids) among the indigenous people in Morang, Nepal [29]. In Kopaonik Mountain, Central Serbia, *P. alkekengi* fruits have been used for urinary ailments (kidney

stones) due to their strong diuretic properties (10-20 berries a day over a 10-day period taken with honey or jam before breakfast) [30]. *Physalis peruviana* was locally known as "Minathi" in Central Kenya and it has been effective for treatment of helminthic diseases, postpartum pains and typhoid disorders [31]. Leaves and fruits of *P. angulate* have been used for treating generalized oedema, amoebic dysentery and boils (furuncle) in ethno-medicine of the upper Nyong valley forest in Cameroon [32]. Based on a study about using medicinal plants for treatment of chronic inflammation and cancers among two major tribes of northern Nigeria, aerial parts *P. angulata* (locally named "Matsarmamaa") was used for treatment of cancers and inflammations [33]. Leaves and the whole parts of *P. angulata* were used for malaria therapy among indigenous people of Okeigbo, southwest Nigeria [34]. *Physalis minima* is known as "Patakiri" or "Rashbary" among local inhabitants of Himachal Pradesh of India. The fruits and flowers were cooked there for stomach pain and constipation and the herb paste was applied in ear disorders [35]. In the plains area of the Tamilnanu, India, the traditional healers used the whole plant of *P. minima* (Locally known as "Tottakkali") as laxative, expectorant and diuretic agent [36]. In Sri Lanka *P. minima* was used to treat skin disorders (leprosy) and diseases causing bleeding [37]. The decoction of the whole plant has been consumed by Malay community in Malaysia as a remedy for cancer [38]. *Physalis peruvina* was used in some parts of India and islanders of Indian Ocean for abdominal disorders in pregnancy, boils, fever, gout, and heart disorders. It was also used as an emollient and diuretic agent in their ethnomedicine [39].

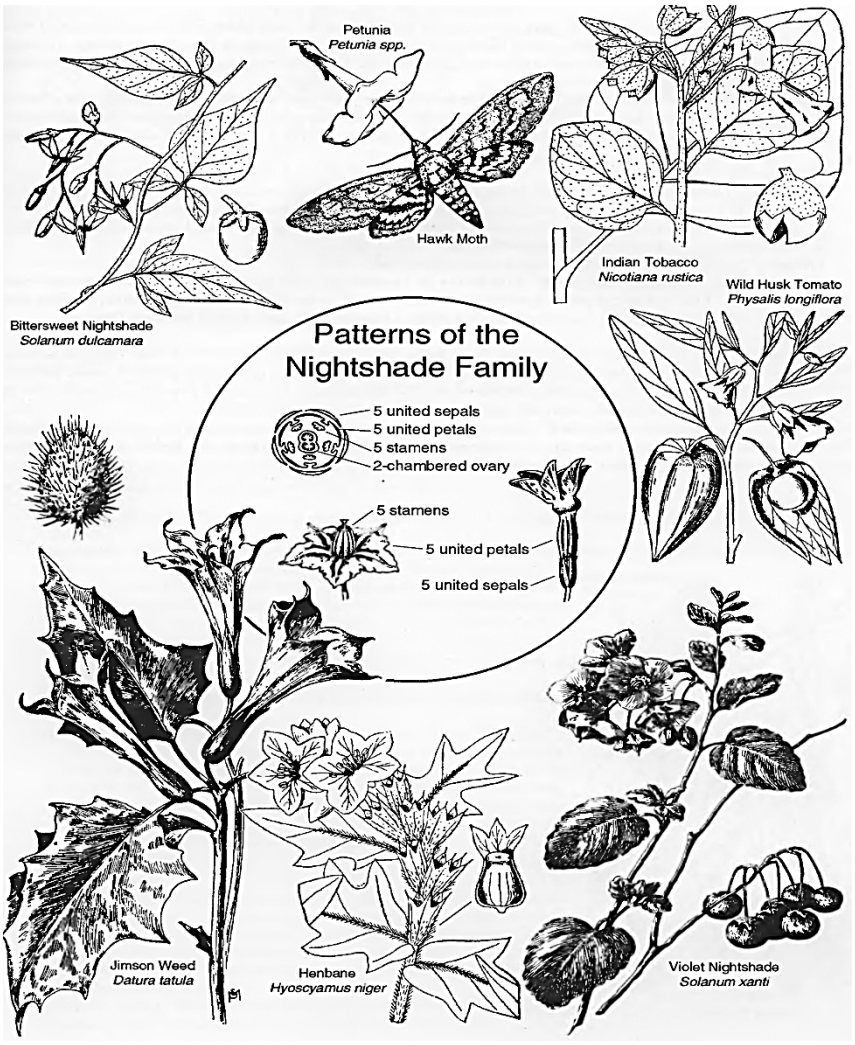
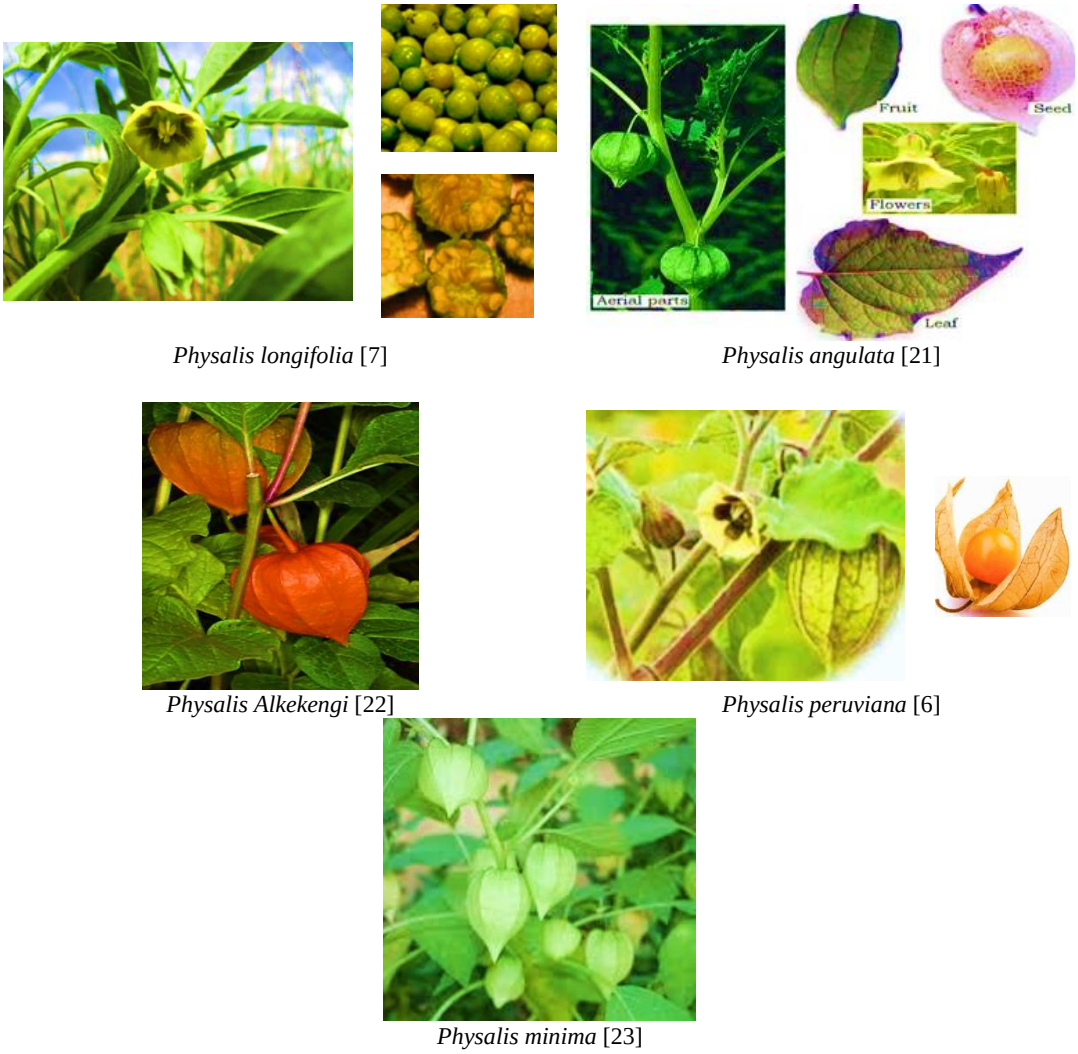


Figure 1. Pattern of Solanaceae [1]



Physalis longifolia [7]

Physalis angulata [21]

Physalis Alkekengi [22]

Physalis peruviana [6]

Physalis minima [23]

Figure 2. The number of *Physalis* species

In folk medicine of Rajshahi District Bangladesh, the whole partsof *P. micrantha* were used for skin infections. The whole plant was dried, fried and powdered followed by its topical application to infected areas [40]. In Garo, an ethnic area of Bangladesh, the mixing of seed and leaf juice of *P. minima* was used in eye disorders [41].

Physalis minima root juice was used as a diuretic agent in Dohanagar Village of Bangladesh [42]. Based on ethno-medicinal study about medicinal plants in Kalanguya tribe of Philipines, decoction of the *P. minima* leaves was used as antitussive and diarrhea [43].In traditional medicine of Thailand and Malaysia, the paste extracted from the leaves and stems of *P. minima* had been used as a medicine to treat cancer [44]. In traditional medicine of Taiwan *P. angulata* extract has been used to treat malaria, hepatitis, rheumatism, liver problems, and tumors [18,45,46]. *Physalis alkekengi* is one of the traditional Chinese herbal plants which is distributed abundantly in the northeast regions of China. Many ethno-pharmacological properties have been reported there, including anti-inflammatory, antitussive and anti-fungal activities [47]. In Unani System of Medicine, *P. alkekengi* fruit was used as anesthetic, anthelmintic, anti-inflammatory, contraceptive, diuretic, hepatoprotective and nephroprotective. It was also effective in wound and scar healing [48]. Based on traditional medicine of clod desert Ladakh, tribal communities inhabited in the remotest region of Indian subcontinent, *P. alkekengi* fruits with admixture of 5 other plants, were used against all kinds of kidney and urinary disorders. It was also effective for healing urine discharge, inflammation and bleeding of the kidney [49].

There are several ethno-medicinal reports about uses of *Physalis* in different parts of Iran. It has been reported that *P. alkekengi* was used for urinary retention, kidney and bladder stones, inflammation, arthritis and rheumatism [50,51]. In an assessment of traditional medicinal plants in the markets of Mashhad, Iran, it was elucidated that the decoction of the *P. alkekengi* ("Arusak posht pardeh" in Persian language) fruits, was effective for treatment of jaundice, kidney stones and irregular menstruation [52]. In Darab, located in south of Iran, the fresh fruits of *P. alkekengi* (known as "Kakanj") was used as contraceptive, diuretic and laxative [53]. In a survey on ethno-botanical uses of anti-cancer herbs in southern region of Ilam, west of Iran, it was reported that *P. divaricata* was effective in kidney cancer. For this purposes the aerial parts of the plant were boiled in water and used twice a day for 2 weeks [54].

Physalis uses in Iranian traditional medicine

Based on the Iranian traditional medicine texts *Physalis* species have different therapeutic properties which are related to the seeds of the plant. Treatment of respiratory disorders such as asthma, liver, kidney and bladder dysfunctions, wounds, hemorrhoids, and helminths diseases are the main and common properties of the species [12-14,55-56]. Using 4.46 g of the seed or its water extract has been mentioned to be effective for jaundice [12,55].

Table 1. The main uses of *Physalis* in Iranian traditional medicine

Part	Uses	Preparation	Reference
Seed	Healing of wound infection and necrosis	Macerated seed in water used as drop	[12]
Seed	Treatment of hemorrhoids	Diluted seed water extract	[12]
Seed	As diuretic, for treatment of kidney and bladder dysfunction, dysuria	-	[12-14,55]
Seed	Liver dysfunction, treatment of Jaundice, increasing bile acid secretion	Oral use of 4.46 g seed powder or its extract	[12-14,55]
Seed	Asthma and shortness of breath	-	[12-14,55]
Seed	Anthelmintic	Oral use of 4.8 g levigated *Physalis* and *Artemisia*	[12-14]
Seed	As an oral contraceptive	Seven seeds taken for seven day every afternoon	[14]
Seed	Sedative and hypnotic	Oral use of 4.46 g seed powder	[12]
Seed	Causing psychosis and hallucination	More than 4.46 g oral use of seed powder	[12]

Biological activity and phytochemistry of *Physalis* species in modern medicine

The benefits associated with *Physalis* species are related to their biologically active components that provide health advantages and reduce risk of certain diseases. Phytochemical examination of *Physalis* species has led to the isolation of many physiologically active compounds, mainly withasteroids (figure 3). Withasteroids have a steroidal backbone bound to a lactone or its derivatives. They are produced via oxidation of C-22 and C-26 ergosterol skeleton to form a δ-lactone by several natural modifications of this steroid backbone, resulting in compounds such as withaphysalins and physalins. This structural variation is responsible for a wide range of pharmacological activities such as potent cytotoxic activity against various type of human cancer cell lines, immune-modulating and cancer chemopreventive effects [17]. The chemical structure and biodiversity of these compounds have been shown in table 2. Based on a recent study, the fruit juice of *P. peruviana* exhibited a potent antitumor effect in hepatocellular carcinoma by modulating the serum inflammatory level, blood indices, hepatic apoptotic markers and significant interruption in hepatic cell cycle [57]. It was showed that *P. peruviana* leaves and stem extracts exhibited cytotoxic effects in colon cancer and chronic myeloid leukemia against cancer cell lines. The extracts were more cytotoxic than reference drug (5-FU) [58]. Based on a recent study, the inhibitory effects of *P. peruviana* ethanolic extracts against human liver cancer cell was due to the inhibition of cell proliferation and changing mitochondrial signaling transduction pathway [59]. Hydroxywithanolide, the isolated pure compound of *P. peruviana* golden berries, has shown inhibitory effects on human lung cancer cell line growth. It could significantly induce DNA damage of the cancer cell line [60]. According to Chiang et al. the isolated Physalins from the ethanolic extract of the whole plant of *P. angulata* showed cytotoxic effects on 8 human and animal cancer cell lines by DEA and MTT assays [61]. Withangulatin, a bioactive withanolide isolated from *P. angulata*, had strong immunosuppressive activity. It could eliminate the T lymphocytes over-expression and modulates T helpers$_1$/T helper$_2$-type balance [62]. Physalins possess many immunosuppressive activities which are widely used to inhibit

unwanted immune responses in autoimmune diseases, allergies and organ transplants [63]. Soares et al. showed that Physalins B, F and G isolated from stems of dried *P. angulata,* possess inhibitory effects on lymphocyte activation and pro-inflammatory cytokine production. This causees the suppressive activity on immune system to inhibit transplant rejection [64]. The immunomodulatory activity of physalins from *P. angulata* stems ethanolic extracts was evaluated in a recent study. The isolated physalins caused reduction in nitric oxide production by macrophages stimulation with lipopolysaccharide and interferon-γ in mice model [65]. The anti-inflammatory effects of physalins B and F in treating immune mediated diseases has been proven recently. They have potent suppressive activities by inhibiting the proliferation of lymphocytes, activation of macrophages and pro-inflammatory cytokines [66].

Physalis species exhibited major anti-inflammatory activities through different pathways. The anti-inflammatory effects of *P. angulata* extract has been evaluated by Bastos et al. in carrageenan induced rats. The aqueous extract from the roots of *P. angulata,* exerts powerful anti-inflammatory and immunomodulatory activities, interfering with the cyclooxygenase pathway, lymphocyte proliferation, nitric oxide, and tumor growth factor production [67]. It has been shown that three physalins isolated from ethanolic extract of *P.alkekengi* calyces, have inhibitory effect on nitric oxide production in lipopolysaccaride-activated macrophages [68]. It has been shown that the anti-inflammatory effect of *P. peruviana* calyces extracts was related to its immunomodulatory effect on macrophages activation and secretion of soluble pro-inflammatory mediators [69].

Phytosterols and phenolic compounds are another group of important bioactive compounds in *physalis* species. Recently, there has been a rise of interest in plant sterols. Most of this interest has been focused on their antioxidant activities and their impact on health, especially the cholesterol-lowering effects. It was reported that feeding *P. peruviana* fruit juice to high-cholesterol diet (HCD)-fed rats, could decreases the levels of total cholesterol, total triacylglycerol and total low-density lipoprotein cholesterol in animal plasma. Analyzing the composition of the fruit juice showed several phytosterols such as Δ5-venasterol, campesterol, ergosterol, lanosterol, stigmasterol, β-sitosterol, Δ7-avenasterol [70,71]. Numerous studies have noted that phytosterols can decrease lipoprotein cholesterol levels in total plasma. It has been hypothesized that these compounds decrease the cholesterol solubility and its absorption across the intestinal barrier, inducing consequently low plasma cholesterol levels [72]. It has been demonstrated that these compounds prevent or delay the development of atherosclerotic lesions in hypercholesterolemic men [73]. Sitosterol, stigmasterol and physalins isolated from *P. angulata* aerial parts extract, have shown protective effects on the intestinal inflammation. The anti-inflammatory activity of the extract is related to its capacity to modulate oxidative stress, immune response and gene expression of inflammatory mediators [74].

Several investigations have been done on *Physalis* species for treating diabetes management. The hypoglycemic effects of *P. minima* were investigated in diabetic rats. The ethanolic extract of the plant had inhibited the intestinal alpha glucosidase activity and showed significant hypoglycemic effect [75]. Based on a recent study, *P. peruviana* fruit extract improves insulin sensitivity and ameliorates hyperglycemia in high-fat diet low dose STZ-induced type 2 diabetic rats [76]. In another study, the effectiveness of *P. peruviana* fruits was evaluated on postprandial glycaemia in young adults. The significant decrease in postprandial glycaemia level was observed in volunteers that consumed the fruits [77]. The hypoglycemic activity of the purified polysaccharide from *P. alkekengi* fruit was evaluated for the hypoglycemic activity in alloxan-induced diabetic mice. The oral administration of polysaccharides could significantly reduce blood glucose levels and water intake, and increase the body weight of diabetic mice [47]. It was reported that *P. pubescens* extract elicited significant reductions in blood glucose of Albino diabetic rats [78].

Other medicinal properties attributed to *Physalis* species are hepato-renal protection, anti-microbial, antifertility activity, antispasmodic, anti-inflammatory, analgesic, antileishmanial, trypanocidal and insecticides activities [18-20,79-83].

Conclusion

Traditional medicine is a comprehensive and dynamic source for treatment of many diseases.

Based on the Iranian traditional medicine references, *Physalis* different exclusive forms of preparations are effective in treatment of several disorders such as jaundice, asthma and shortness of breath, tissue necrosis, liver, kidney and bladder dysfunctions, wounds, hemorrhoids, and helminths diseases. Such properties have not been reported and investigated so far except for the healing effect on liver dysfunction and this might be a starting point for the development of the new therapeutic applications and more investigations on *Physalis* species in the future

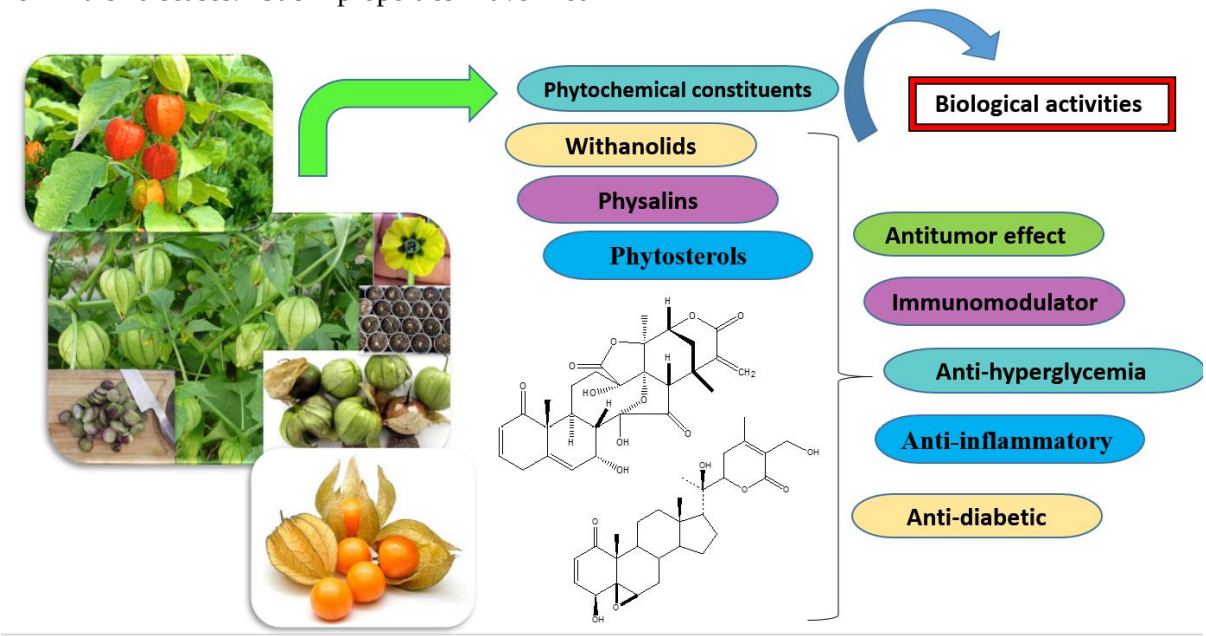


Figure 3. Important *Physalis* phytochemicals and pharmacological activities

Table 2. Chemical structure of withasteroids in *Physalis*

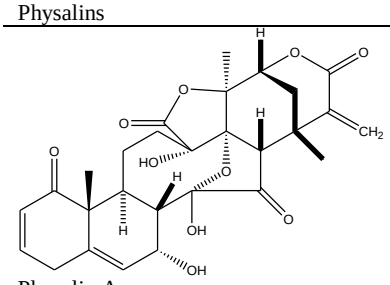
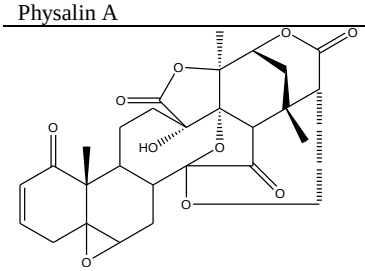
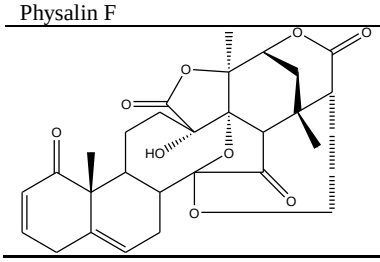
Structure	*Physalis* species and part used	Reference
Physalins		
 Physalin A	*P. alkekengi* leaves and stems	[84]
 Physalin F	*P. angulata* leaves and stems	[85]
	*P. angulata* leaves, *P. alkekengi* leaves and stems, *P. minima* leaves	[84-86]

Table 2. Continued

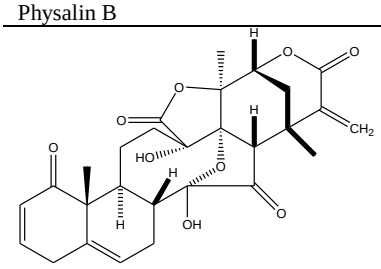
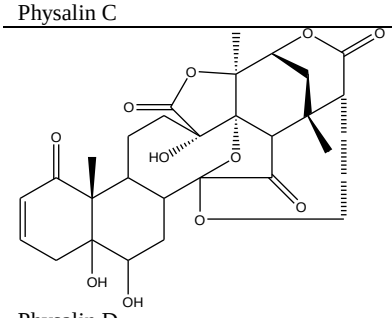
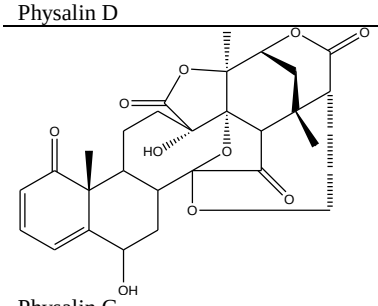
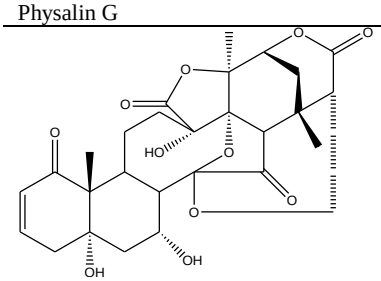
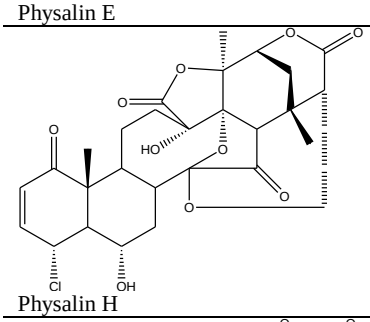
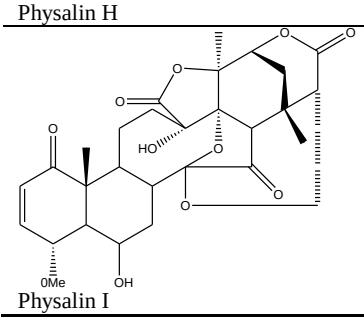
Structure	*Physalis* species and part used	Reference
Physalin B 	*P. alkekengi* leaves and stems	[84]
Physalin C 	*P. angulata* leaves and stems	[85]
Physalin D 	*P. angulata* leaves and stems	[85]
Physalin G 	*P. angulata* leaves and stems	[85]
Physalin E 	*P. angulata* leaves and stems	[85]
Physalin H 	*P. angulata* leaves and stems	[85]
Physalin I		

Table 2. Continued

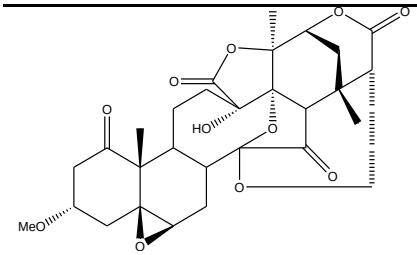
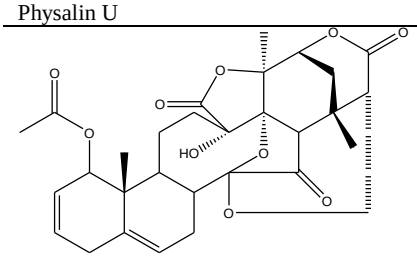
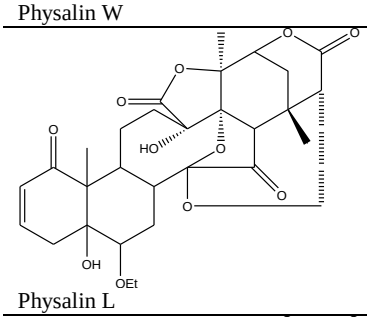
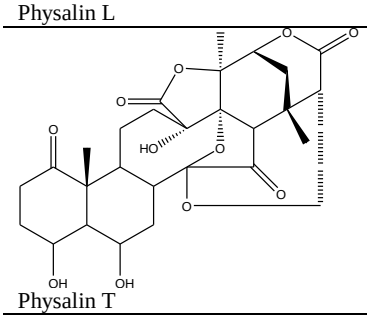
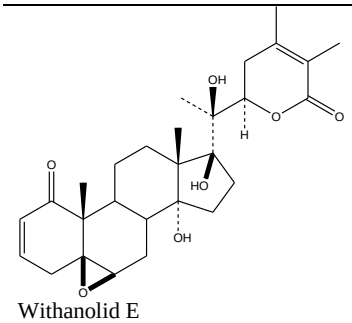
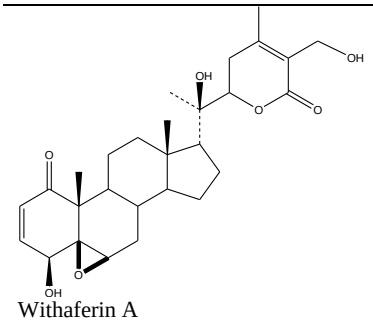
Structure	*Physalis* species and part used	Reference
 Physalin U	*P. angulata* whole plant	[87]
 Physalin W	*P. angulata* whole plant	[87]
 Physalin L	*P. minima* whole fresh plant	[88]
 Physalin T	*P. alkekengi* seed	[89]
Withanolids		
 Withanolid E	*P. peruviana* leaves	[90]
 Withaferin A	*P. peruviana* leaves	[90]

Table 2. Continued

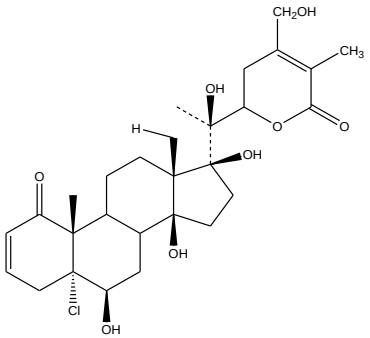
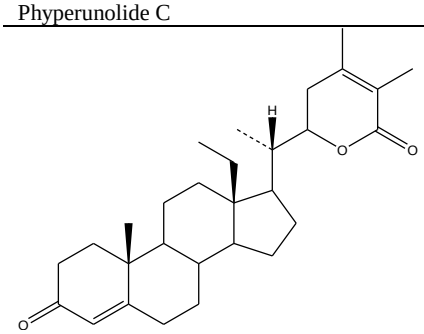
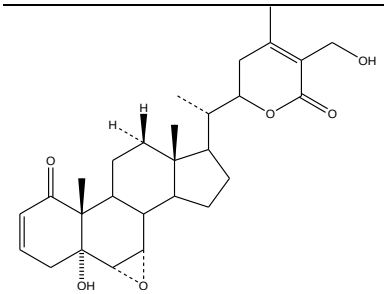
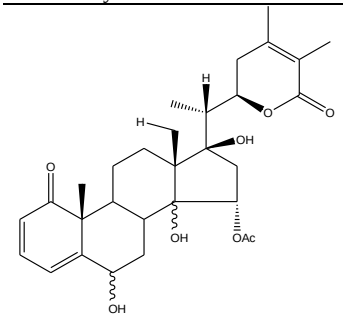
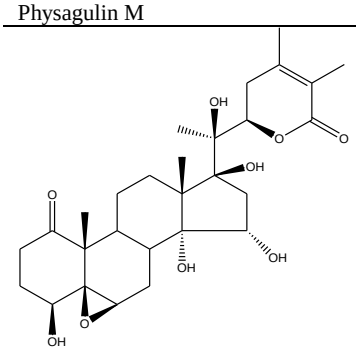
Structure	*Physalis* species and part used	Reference
 Phyperunolide C	*P. peruviana*	[91]
 Minabeolide	*P. alkekengi*	[92]
 12- Deoxywithastramonolide	*P. alkekengi*	[92]
 Physagulin M	*P. angulata*	[91]
 Whithangulatin B	*P. angulata* whole plant	[17]

Table 2. Continued

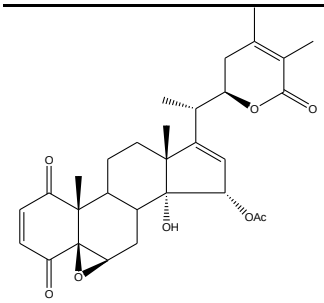
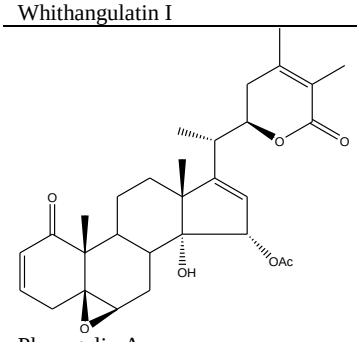
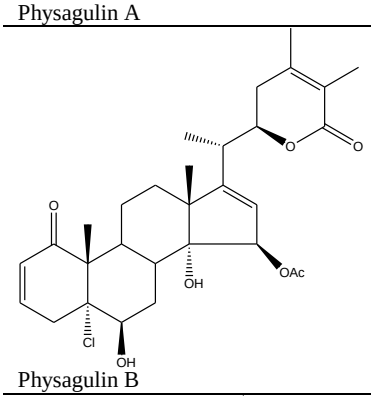
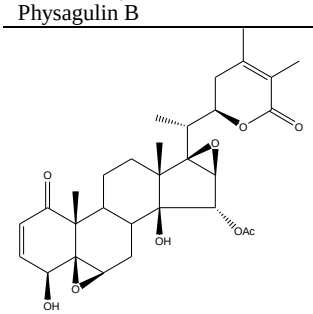
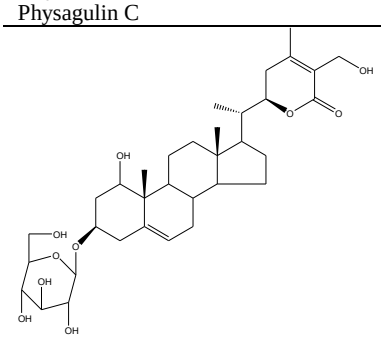
Structure	*Physalis* species and part used	Reference
 Whithangulatin I	*P. angulata* whole plant	[17]
 Physagulin A	*P. angulata* leaves and stems	[93]
 Physagulin B	*P. angulata* leaves and stems	[93]
 Physagulin C	*P. angulata* leaves and stems	[94]
 Physagulin D	*P. angulata* leaves and stems	[93]

Table 2. Continued

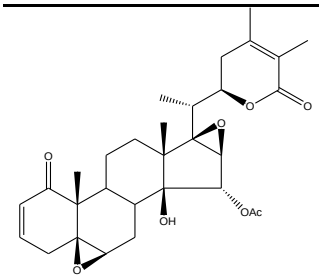
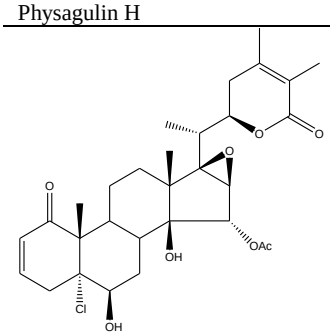
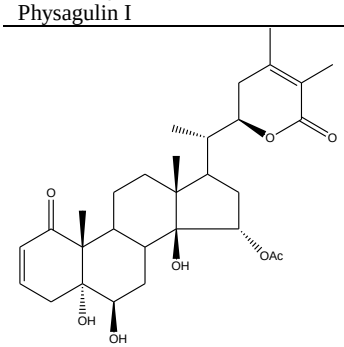
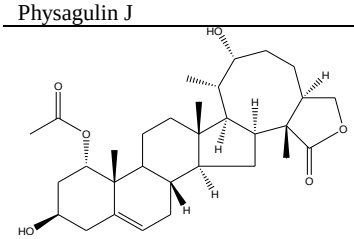
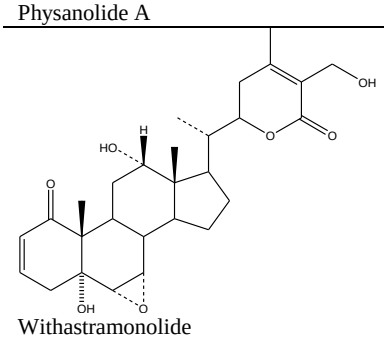
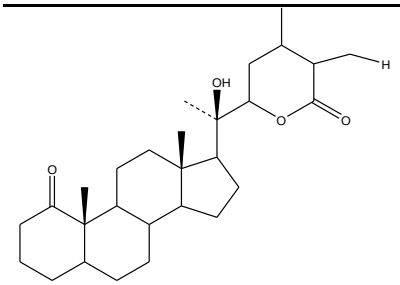
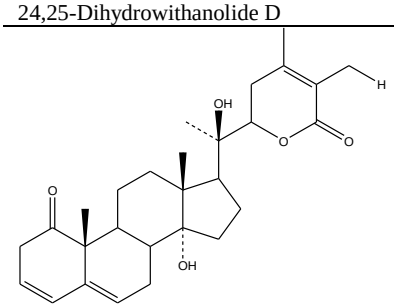
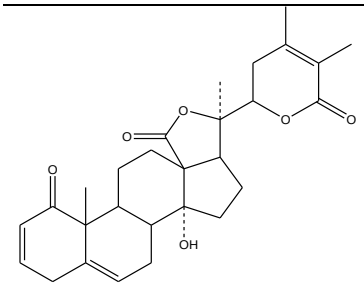
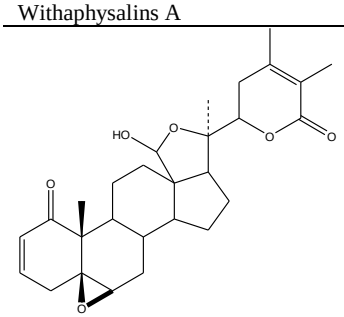
Structure	*Physalis* species and part used	Reference
 Physagulin H	*P. angulata* aerial part	[95]
 Physagulin I	*P. angulata* aerial part	[95]
 Physagulin J	*P. angulata* aerial part	[95]
 Physanolide A	*P. angulata* aerial part	[87]
 Withastramonolide	*P. minima*	[92]

Table 2. Continued

Structure	*Physalis* species and part used	Reference
 24,25-Dihydrowithanolide D	*P. minima*	[92]
 Withanolide K	*P. minima*	[92]
 Withaphysalins A	*P. minima* leaves	[86]
 Withaphysalins B	*P. minima* leaves	[86]

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Author contributions

Fatemeh Mirzaee was the main study investigator and contributed to the collection of the data; Amir Saeed Hosseini participated in the data interpretation and revised the manuscript; Romina Askian participated in the data interpretation; Mohammad Azadbakht was the study investigator, contributed to the collection of the data and critically revised the manuscript.

Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the accuracy and integrity of the paper content.

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Abbreviations

ITM: Iranian traditional medicine