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Exploring the therapeutic landscape of *Physalis* **genus: A pharmacological perspective**

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Abstract

Physalis within the Solanaceae family encompasses numerous edible species such as cape gooseberry, groundcherry, cut leaf groundcherry, hairy groundcherry, tomatillo, Chinese lantern, and strawberry tomato. With an increasing interest in diverse diets for health benefits, these *Physalis* species have attracted attention in preliminary studies evaluating their nutritional and chemical profiles. Exotic fruits play a significant role in nutrition by serving as an excellent base for low-calorie and diet-friendly products. These unique fruits are highly esteemed for their distinct flavours, textures, and vibrant colours. Various research findings revealed significant amounts of essential vitamins and minerals, particularly potassium and immuneboosting vitamin C, fatty acids along with phenolic compounds, and bioactive compounds contributing to antioxidant activity. Along with their nutritional characteristics, these herbaceous fruit crops possess various phytochemicals such as physalin and withanolide, a class of steroidal lactones known for their antitumour, antidiabetic, antimicrobial, anti-inflammatory, hypocholesterolemic, hepatorenal protective and neurotoxicity protective properties. Worldwide, it is employed in herbal medicine to address various human ailments such as malaria, asthma, rheumatism, hepatitis, and dermatitis. A comprehensive understanding of the nutritional benefits of this unique fruit is essential due to its rapidly increasing popularity. This review explores the species description, nutritional profile, and phytochemical aspects of various *Physalis* species and their potential implications for human health.

1. Introduction

Consuming a varied diet, predominantly consisting of fruits and vegetables, is extremely advantageous for human health, aiding in the prevention of chronic ailments. Fruits and vegetables abound with naturally occurring compounds such as antioxidants, providing health benefits that surpass basic nutrition (Siro *et al*., 2008). The well-

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documented advantages have spurred growing curiosity in undiscovered sources of unique vegetables and fruits, recognizing their capacity to offer beneficial compounds and essential nutrients for a healthy diet. In this context, the *Physalis* is an underutilized source within the Solanaceae family, which includes more familiar nightshade crops such as eggplant, tomatoes, peppers, and potatoes. The potential of the *Physalis* as a resource for new food crops has garnered attention due to its numerous edible species. Nevertheless, they remain underutilized in the present food production landscape, resulting in unrealized nutritional benefits. There are approximately 85 species of *Physalis* grown annually and perennial in temperate regions globally (Vargas *et al*., 2001), it is endemic to South America (Wilf *et al*., 2017). Distinguished by its bloated calyx, which forms

a husk surrounding the fruit during maturation, members of the *Physalis* possibly developed this husk to assist in seed dissemination and provide defense against environmental challenges such as pests and diseases (Wilf *et al*., 2017; He *et al*., 2004). *Physalis* has a variety of biological features and strong pharmacological activity such as insect-antifeedants, insect-repellent activities, hepatoprotective effects, immune modulation, antibacterial properties, antiinflammatory attributes, antitumor and cytotoxic activities, also protection against liver damage-induced by CCl₄ (Lan *et al.*, 2009).

Overall, most *Physalis* species thrive in the wild, with only a limited number being deliberately cultivated as food crops or ornamental plants (Khan and Bakht, 2015). Noteworthy among the cultivated species are goldenberry, tomatillo, and groundcherry, all of which are relatives of the tomato. These specific *Physalis* varieties have been grown for both medicinal and nutritional purposes. Over time, there has been an increasing fascination with these edible *Physalis* varieties, driven by their distinctive chemical compounds and culinary attributes (Lim, 2013; Takimoto *et al*., 2014; Kupska and Jelen, 2017; Puente *et al*., 2011; Zhang *et al*., 2016).

2. Different species of *Physalis* **genus**

2.1 *Physalis peruviana* **(Cape gooseberry)**

Physalis peruviana commonly recognized as goldenberry or cape gooseberry, is thought to have originated in Andean regions of Peru and Ecuador in South America (Puente *et al*., 2011). Goldenberry is grown annually in temperate areas and perennially in tropical regions (Morton, 1987). A distinguishing feature of the fruit is covered by a husk, which becomes papery as it matures. The goldenberry is a globular, golden-coloured berry (Figure 1a), measuring 1.25-2.50 cm in diameter and having a weight ranging from 4 to 10 g (Olivares-Tenorio *et al*., 2016). It is consumed as fresh and also used in desserts and preserves and also dried (National Research Council, 1989). Colombia is the largest producer of goldenberries, yielding 7,872 tons annually, ranking second only to banana production (Melo *et al*., 2020).

In India, Kolli Hills tribes use whole plant extract for treating skin diseases, and tribes in Manjoor, Thiashola, and Western Ghats use seeds and leaves to address glaucoma and jaundice (Sharmila *et al*., 2014; Anjalam *et al*., 2016). Overall, the nutritional profile of goldenberry has sparked increasing interest and marketability among food producers and consumers alike.

Figure 1a: Cape gooseberry.

2.2 *Physalis ixocarpa* **(Tomatillo)**

One of the most renowned cultivated crops within the *Physalis* groups is the tomatillo (*P. ixocarpa*), originating from Mexico and continues to be widely regarded as a cultural staple in many parts of Central America and Mexico. Tomatillo comes in varying cultivars, exhibiting either a green or purple hue (Figure 1b) and ranging in diameter from 2.5 to 6.25 cm (Morton, 1987). Noted for its distinctive acidic flavour, tomatillo holds a significant place in Mexican food and is most commonly utilized in salads, salsas, and sauces (Takimoto *et al*., 2014). The optimal conditions for tomatillo cultivation include low altitudes, temperatures ranging from 18 to 25° C, slightly acidic soils, and regions receiving annual rainfall ranging from 60 to 120 cm (SIAP, 2017). Mexico, being the largest producer, cultivates tomatillo year-round. The primary importer of tomatillo is the United States (Bock *et al*., 1995; SIAP, 2017). Xiang *et al*. (2024) found that extracts of the leaf and stem of tomatillo encourage the cytotoxic effect in the tumour cells of humans.

Figure 1b: Tomatillo.

2.3 *Physalis pruinosa***,** *Physalis pubescens***, and** *Physalis grisea* **(Groundcherry)**

Groundcherry, native to North America, bears a striking resemblance to the goldenberry (USDA, 2018). Despite being distinct species, including *P. grisea*, *P. pruinosa,* and *P. pubescens* are often confused and collectively promoted and sold under the name "groundcherry" (Martinez, 1993). Groundcherry also develops within a husk (Figure 1c), but unlike goldenberry, it descends on the ground at different stages of maturity. Groundcherry fruits are smaller than goldenberries, with a milder yet distinctive flavour depicted as both sweet and tart. The fruit is mainly consumed as fresh and also used in jams, pies, and salsas. In ancient Chinese medicine, groundcherry is employed to treat coughs, fever, sore throats, and abscesses (El Sheikha *et al*., 2008). Similar to its species, groundcherry encompasses numerous compounds that contribute beneficial to human health.

Figure 1c: Groundcherry. 2.4 *Physalis angulata* **(Cut leaf groundcherry)**

Physalis angulata is indigenous to warm and temperate regions of the America. Additionally, it is found in Africa, Asia, and South America including the Amazon (Gospel and Chiburuoma, 2023; Januario *et al*., 2002). The flowers are long up to 6 mm, pale yellow

or white, solitary in the leaf axis, and produce tiny, orange berries enclosed within an inflated balloon-shaped ovoid calyx 3-5 mm long (Figure 1d) and distributed as a weed in various environments such as gardens, wastelands, cultivated fields and along a creek near sea levels (Wilf *et al*., 2017). Globally, it is used in herbal medicine for various human ailments such as asthma, hepatitis, malaria, dermatitis, and rheumatism (He *et al*., 2004). Several compounds including glycosides like myricetin-3-o-neohesperidoside and physalin (A, B, D, F), have been extracted from the plant, demonstrating antitumour activities (Takimoto *et al*., 2014).

Figure 1d: Cut leaf groundcherry.

2.5 *Physalis alkekengi* **(Chinese lantern)**

P. alkekengi also known as strawberry groundcherry, winter cherry, and Japanese lantern is indigenous to South and Central Europe and South Asia, including Indochina, China, and Japan has become naturalized in various worldwide regions (Namjoyan *et al*., 2015). This has tailed and paired leaves and produces distinctive lanternlike fruits in shades of orange to red (Figure 1e). The small, globular berries, measuring diameter less than 1-1.5 cm, are orange and shinyred. The plant is rich in alkaloids and glucocorticoids. Its fruit contains lycopene, alkaloids, ethanolic compounds, and vitamin C in a significant quantity (Ge *et al*., 2009; Gharib *et al*., 2008; Namjoyan *et al*., 2015).

In Chinese traditional medicine, various parts of *P. alkekengi*, including the fruit, calyx, roots, and whole plants, are used externally or internally to address various conditions such as cough, sore throat, eczema, urinary problems, tumours, and hepatitis (Shu *et al*., 2016; Qiu *et al*., 2008; Helvaci, 2010; Nasimi, 2008). It also relieves symptoms associated with syphilis and malaria (Bahmani *et al*., 2016; Sharma *et al*., 2015).

Figure 1e: Chinese lantern.

2.6 *Physalis minima* **(Hairy groundcherry)**

Physalis minima, also known as the pygmy ground cherry, is a species indigenous to North America and is characterized by its annual or short-lived perennial herbaceous nature. This plant is recognized for its low-growing habit and cherry-like fruits enclosed

in papery husks (Mazova *et al*., 2020). This species is widely found in subtropical and warm temperate regions worldwide (Usaizan *et al*., 2014), including Asian countries (Chothani and Vaghasiya, 2012). The green fruits enclose an enlarged 10-ribbed, slender reticulately with veined calyx (Figure 1f) and purplish ribs. However, variations exist within this standard description, posing a challenge in distinguishing it from other species (Anjani and Kumar, 2018). The berries exhibit a range of colours from greenish to yellow to orange and maybe purple or red (Ukwubile and Oise, 2016).

Physalis minima have been used for various medicinal purposes, including antifertility, cytotoxic, hypoglycemic, antiulcer, antiinflammatory, antibacterial, antimalarial, analgesic, antipyretic, lipase, amylase, alpha-glucosidase inhibitor and antigonorrhoeal activities. The plant contains steroidal lactones, contributing to its diverse therapeutic properties (Chothani and Vaghasiya, 2012).

Figure 1f: Hairy groundcherry.

2.7 *Physalis lagascae* **(Little gooseberry)**

Physalis lagascae is a perennial herbaceous plant with a height potential of up to 1 meter. The stems are erect, green, and pubescent and may become woody at the base. Its leaves are simple, alternate, and ovate, ranging from 5 to 15 cm in length, with entire to undulate margins. The flowers are solitary and axillary and the berry is globose (Figure 1g), ranging from 10-15 mm in diameter, enclosed within the inflated, papery calyx (Ralte, 2022). It is recognized for its traditional uses in various cultures for its medicinal properties, including the treatment of conditions such as rheumatism, dermatitis, impaludism, tracheitis, hepatitis, and respiratory problems, and flowers against cancer cells when used in conjunction with other treatments (Patel and Singh, 2022; Kasali *et al*., 2021; Singh and Chatterjee, 2021).

Figure 1g: Little gooseberry.

3. Nutritional profile of different *Physalis* **species**

Several investigations have been undertaken to delve deeper into the intrinsic nutritional compositions of various *Physalis* species. Numerous variables such as cultivar disparities and growing environments can impact the fruits nutritional and physio-chemical properties. This review aims to compile studies on the biochemical attributes of these consumable *Physalis* species, offering a comprehensive insight into their nutritional traits. Comparative analyses of their nutritional properties are delineated in Figure 2 and Table 1. As of now, nutritional profiles of *Physalis lagascae* have not been reported yet.

3.1 Proximate analysis

Multiple studies scrutinized the chemical characteristics of *Physalis* species, revealing disparities in pH, TSS, and acidity as reported in Figure 2, and other chemical attributes are mentioned in Table 1. The lowest pH of 3.74 was reported in *Physalis pubescens* subsequent to 3.94 in *P. peruviana*, sufficiently acidic for food preservation and higher than the typical tomatoes (Takimoto *et al*., 2014). The moisture content of *P. ixocarpa* was found to be 91.76%, which was the highest among the species studied following *P. peruviana* had a moisture content of 85.94%. The fresh weight (FW) of protein was highest in *P. alkekengi*, with a value of 5.83% followed by 2.46% in *P. pubescens*. Based on the findings of this study, there is diversity in the moisture content and protein content of *Physalis* species. Further research is needed to explore the underlying mechanisms responsible for these variations and their potential implications for nutrition and health. The higher fat % of 2.91 was reported in *P.*

pubescens subsequent to 2.10% in *P. ixocarpa*, with ash content from 5.58% in *P. pubescens* and 5.75% in *P. alkekengi*. Total dietary fiber varied with species from 4.12% in *P. peruviana* to 3.58% in *P. pubescens*, while higher total carbohydrate was reported at 19.6% in *P. peruviana* followed by 10.85% in *P. pubescens*. The calculated calorific value was approximately 76.8 kcalories 100 g-1 in *P. peruviana* succeeding with 69.36 kcalories 100 g-1 in *P. pubescens*, the reported value is similar to USDA data without any cultivar details (USDA, 2018). Another study reported total soluble solids of 13.46 °Brix in *P. pubescens* followed by 13.0 °Brix in *P. peruviana*. Notably, sugar content variations within goldenberry germplasm were attributed to environmental and genetic factors (Maruenda *et al*., 2018; Wolff, 1991). The titratable acidity of 1.28% in *P. alkekengi* succeeding with 1.26% in *P. peruviana* was reported. Other values from studies for titratable acidity closely matched those reported for the Colombian ecotype (Puente *et al*., 2011).

Figure 2: pH, TSS, acidity, and vitamin C of different *Physalis***.**

3.2 Minerals

Physalis species harbor numerous macro and micronutrients crucial for human health. In mineral content (per 100 g^{-1} FW), various studies reported that *Physalis* is rich in potassium content it varied with species, *i.e*., 556.4 mg in *P. alkekengi*, followed by 373.25 mg in *P. peruviana*. Like numerous other fruits, *P. alkekengi* fruit exhibited a predominance of potassium as the primary macromineral. Despite variations based on region, the potassium concentration remained substantial (Popova *et al*., 2022). The second most is phosphorous which is reported at 55 mg in *P. peruviana* and subsequently 39 mg in *P. ixocarpa*. *P. peruviana* reported 28.0 mg of calcium followed by 12.31 mg in *P. pubescens*. The fruit of *P. peruviana* stands out for its remarkably elevated phosphorus content among fruits, although its calcium levels are comparatively low (Puente *et al*., 2011). In the human body, phosphorus and calcium play crucial roles as primary components of the skeletal system, in addition to serving vital metabolic functions associated with muscle activity, hormonal regulation, and nerve stimulation (Latham, 2002). The magnesium was reported higher 48.7 mg in *P. peruviana* followed by 34.52 mg in *P. pubescens*. High availability of Mg was similarly recorded in

Colombian cape gooseberry (Gabriel *et al*., 2012). The remaining mineral content only the least amount in all species, in that higher amounts, were reported 8.78 mg sodium in *P. peruviana*, 1.18 mg zinc in *P. pubescens*, 0.27 mg manganese in *P. pubescens,* and 2.53 mg iron in *P. pubescens*. The iron content of raw *P. pubescens* juice was higher than that of orange, lemon, and lime juices (El Sheikha *et al*., 2010) (Table 1).

3.3 Vitamins

Physalis species are rich in essential vitamins crucial for human metabolism those vitamins from various species are reported in Figure 2 and Table 1. Among the vitamin contents, Olivares-Tenorio *et al*. (2016) reported higher vitamin C with 40.00 mg 100 g-1 in *P. peruviana* which is closely associated with the report of Singh *et al*. (2014) which is 39.68 mg 100 g⁻¹ in *P. pubescens*. Notably, the Vitamin C (Ascorbic acid) content of *Physalis* has been extensively studied due to its antioxidant properties (El Sheikha *et al*., 2010). This vitamin serves a significant role in human nutrition such as hormone production, immune system responses, neurotransmitters, and maintenance and growth of tissues (Puente *et al*., 2011). Compared

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to vitamin C, the remaining vitamins are present only the least amount in all species except *P. pubescens*. In *P. minima* and *P. angulata are* not yet reported vitamin content, the *Physalis* species rest remain have a source of other vital vitamins, such as vitamins A, E, K, thiamin (B_1) , niacin (B_3) , riboflavin (B_2) , vitamin B_6 , total folate $(B₉)$, and pantothenic acid $(B₅)$ with data obtained from multiple studies, albeit without any cultivar information. Moreover, the vitamin content of goldenberry seeds, pulp, and skin oils has been analyzed and revealed significant amounts of vitamin $K₁$ and E, including various tocopherols.

4. Phytochemicals

As shown in Table 2, *Physalis* contains a diverse array of metabolites isolated from different plant parts. The advantages of plants result from a range of primary or secondary metabolic processes (Shruti *et al*., 2023). Over 40 chemical compounds were identified in this plant, including alkaloids, aldehydes, carotenoids, carbohydrates, flavonoids, esters, lipids, phenols, glycosides, terpenoids, withanolides, and phytosterols. Aperuvin C, peruviose D, ellagic acid, phyperunolide A, physachenolide D, peruvianolides (D, C, B, A), physachenolide C, physapruin A, physalin B, ursolic acid,

Table 2: Phytoconstituents isolated from *Physalis*

physapruin B, 4 β -hydroxywithanolide E, withaperuvin L, withanolides (F, A, C, B, E), withangulatin E and withaferin A. Among the secondary metabolites, physalins stand out as particularly active within the *Physalis* species (Laczko-Zold *et al*., 2017). It is worth noting that the protein content in the fruit is exceptionally high (Wojcieszek and Ruzik, 2015).

4.1 Fatty acids

Fatty acids constitute a key component of lipids, serving as a primary source of energy for animals while also facilitating cellular functions. Two essential fatty acids for humans are linoleic and alpha-linolenic acid i.e. omega-6 and omega-3 fatty acid, respectively. Rodrigues *et al*. (2009) reported the fatty acid profile of goldenberry and illustrated that oil constitutes 2% FW (fresh weight) of the whole berry. The breakdown showed that 72.42% of fatty acids were linoleic, 9.38% palmitic, 10.03% oleic, 2.67% stearic, and other smaller amounts. The majority of these fatty acids were polyunsaturated, followed by monounsaturated and saturated fatty acids. Ramadan and Morsel (2003) examined the fatty acid composition which is 70.6% in whole berries, 76.1% in seed, and 44.4% in pulp oils, showing linoleic acid as the predominant component.

According to USDA (2018), tomatillo fruit comprises 13.9% saturated fats, 15.5% monounsaturated fats, and 41.7% polyunsaturated fats. The primary fatty acid found in linoleic acid, constituting 40.2% of the total. It is followed by oleic acid at 15.5%, palmitic acid at 10.2%, and stearic acid at 4%. In tomatillo seeds, the fatty acid composition remains consistent, with linoleic acid ranging from 83.7% to 95.2%, followed by oleic acid, palmitic acid, and stearic acid. El Sheikha *et al*. (2010) reported in *P. pubescens* juice, where 65.5% of unsaturated fatty acids, with significant proportions of alpha-linolenic acid, linoleic acid, and oleic acid, along with smaller amounts of fatty acids.

4.2 Phytosterols

Phytosterols are a type of compound crucial for human health, naturally occurring in plants, known for their antioxidant activity, and associated with reduced LDL cholesterol levels. Ramadan and Morsel (2003) found that goldenberries contain various phytosterols. In whole berry oil per 100 g, they reported 1.16 g of ergosterol, 6.70 g of campesterol, 4.70 g of Δ 5-avenserol, 2.51 g of lanosterol, 1.21 g of Δ 7-avenasterol, 1.69 g of stigmasterol, and 5.73 g of β -sitosterol. There is no information reported on phytosterol content for the remaining *Physalis* species.

4.3 Antioxidants

Many phytonutrients possess antioxidant properties, which can be quantified based on their ability to inhibit oxidation. Antioxidants are vitamin C and phytonutrients like flavonoids and carotenoids and they have the potential to counteract free radicals detrimental within the body, possibly diminishing the likelihood of developing chronic diseases (Govardhan *et al*., 2023). In a research study that assessed the radical scavenging activity of four tomatillo varieties using the DPPH (2,2-diphenyl-1-picrylhydrazyl) method ranged from 28% to 90% (Gonzalez-Mendoza *et al*., 2013). Bazalar Pereda *et al*. (2019) compared ferric reducing ability of plasma (FRAP) results and DPPH assays for both wild and cultivated goldenberry accessions. The FRAP values consistently exceeded the ABTS values, suggesting a higher reactivity of antioxidant compounds in goldenberry as reducers of ferric ions. Cultivated lines exhibited a greater ability to scavenge the free-radical than wild counterparts, with both showing higher FRAP values compared to several other fruits.

Another study carried out by Torres-Ossandon *et al*. (2018), utilized the oxygen radical absorbance capacity (ORAC) test, it revealed an antioxidant activity of fruit pulp of goldenberry is 6914.10 ± 417.27 μ mol TE 100 g⁻¹ DM and stored under pressurized conditions at 4 for 60 days displayed significantly enhanced antioxidant capacity compared to the non-pressurized conditions (control), indicating a potential influence of postharvest conditions on fruit nutritional quality.

While information on the groundcherry and other species antioxidant activity is lacking, compounds like pyrogallol and vitamin C, known for their antioxidant properties, have been identified in groundcherry. Hence, further investigations into the groundcherry antioxidant activity are warranted (Singh *et al*., 2014; Jing *et al*., 2013).

4.4 Phenolic compounds

Phenolic compounds found in plants are regarded as secondary metabolites that influence fruit characteristics like flavour and colour, while also exhibiting antioxidant activity and other functions (Cheynier, 2012). The soluble phenolic compounds quantification can vary depending on the extraction and solvent method employed (Wu *et al*., 2006). For instance, in a study involving four purple tomatillo cultivars, the soluble phenolic content recorded values differed among cultivars from 5.30 to 10.08 GAE 100 g^{-1} FW (Gonzalez-Mendoza *et al*., 2010). When analyzing the total phenolic content of cape gooseberry on a DM (dry matter) basis, it revealed a measurement of 23.86 mg GAE 100 g⁻¹ in fruit pulp (Torres-Ossandon *et al*., 2018). Bazalar Pereda *et al*. (2019) investigated separately, the phenolic content of fruit pulp on an FW basis was stood at 15.20 mg GAE 100 g^{-1} .

In *P. pubescens*, the pyrogallol phenolic compound was detected in the highest amount, reaching 173.5 mg 100 g⁻¹ of dry weight (Rashwan *et al*., 2017). Pyrogallol is recognized for its antibacterial properties and has been utilized as a pesticide, as well as in pharmaceutical applications for its antipsoriatic effects (Tinh *et al*, 2016; Ozturk Sarikaya, 2015). Additionally, pyrogallol has been studied in litchi for its potential to preserve fruit quality (Jing *et al*., 2013). It is plausible that pyrogallol or similar compounds may contribute to the overall fruit quality of *P. pubescens*.

5. Bioactive compounds from *Physalis*

The *in vivo* and *in vitro* pharmacological research used compounds isolated from several parts of the *Physalis* plant to assess its potential in antidiabetic, anticancer, anti-inflammatory, antioxidant, analgesic, antimicrobial, hormonal, immunomodulatory, neuroprotective, cholesterol-lowering, and hepatorenal protection aspects have been reported. Table 3, highlights the studies, mainly focusing on the antidiabetic, anti-inflammatory, and anticancerous potential of certain compounds. This pharmacological study included inhibition of the cell cycle transition from the G2 phase to the M phase, inducing apoptosis in cancer cells found in breast, toxicity on cell lines of ACHN renal carcinoma, exerted toxic effects on lung, liver, and breast cancer cell strains, modifications of histones and splicing factors, exhibiting cytotoxic effects against LNCaP and 22Rv1 cell lines of prostate cancer, reducing the client proteins expression of Hsp90, disrupt the cell cycle and encourage apoptosis, cancer cells of lung DNA damage, histone modification and cancer cells colorectal cytotoxicity. The anti-inflammatory properties were evaluated by inducing hepatic injury in rats using acetaminophen, oxidative stress inhibition, inhibitory activity of cyclooxygenase-2, inhibition of á-Amylase, prostaglandin E₂ and nitric oxide (NO) by *in-vitro* inhibition, and the overexpression of Nrf2-downstream and Nrf2 genes.

Withanolides belong to the group of steroidal lactones (Mohan *et al*., 2023) that have exhibited remarkable bioactivities, specifically inhibiting tumour growth (Singh *et al*., 2010). Various authors investigated the anticancer potential, specifically toxicity against the cell line of ACHN renal cell carcinoma, cytotoxicity against cancer cells of liver, lung, and breast, and tumour inhibition (Chang *et al*., 2007; Antony *et al*., 2014; Budhiraja *et al*., 2000). White *et al*. (2016) summarised the different cancer types that were treated with withanolides, encompassing head, ovarian, neck, pancreas, colon, glioblastoma, kidney, hematological, and thyroid cancers. Contrastingly, there have been reports of specific modes of action for withanolides as anticancer drugs, such as heat shock protein 90 inhibition (Wang *et al*., 2012), cells resistance to TRAIL-induced apoptosis (Henrich *et al*., 2015), restriction of angiogenesis and metastases (Gao *et al*., 2014), stress responses reduction (Palliyaguru *et al*., 2016), interfering with the neoplastic cells proliferation, cytotoxicity, inhibition of mitosis and proteasome, and transcription factors activation (Samadi, 2015). Currently, restoring the function of p53 wild-type observed in mutant p53Y220C cells (Sundar *et al*., 2019). Carbohydrate esters of Peruvioses A to F have exhibited antiinflammatory effects and antidiabetic potential (Bernal *et al*., 2018; Franco *et al*., 2014).

Table 3: Therapeutic properties of isolated compounds from *Physalis*

Activity	Compounds	Pharmacological properties	References
Anticancer	Physapruin A, Aperuvin J, Withanolide F and Withaperuvin L	Toxicity on cell line of ACHN- renal carcinoma	Xu et al. (2017)
	Withanolide E and Withangulatin E	Renal carcinoma cell sensitizationand cytotoxicity against LNCaP and 22Rv1 of prostate cancer cellular strains	
	Withanolides (E and C), 4β - Hydroxywithanolide E and 7β -Hydroxy-17- epi-withanolide K	Cytotoxic effects on cell lines associated with breast, liver, and lung cancers	
	Physalin B Physalin F	Cells of breast cancer apoptosis and G2/M cell cycle blockage Modulation of histone and splicing factors	Wang <i>et al.</i> (2018) Kasali et al. (2021)
	Phyperunolide A	Cytotoxic effects on cell lines associated with breast, liver, and lung cancers	Lan <i>et al.</i> (2009)
	4β- Hydroxywithanolide E	Inhibit the cell cycle and decrease the levels of Hsp90 client proteins	Park <i>et al.</i> (2016)
		Inhibition of tumor activity during the progression of cancer	You et al. (2014)
		Arrest the proliferation of cancer cells in the human lung by inducing DNA damage, promoting apoptosis, and halting pro- gression in the G2/M phase	Yen et al. (2010)
	4β - Hydroxywithanolide E and 7B-Hydroxywith- anolide F	Inhibiting the proliferation and growth of colorectal cancer cells	Ye et al. (2019)
Anti-inflam- matory	Peruvianolides B, C, D	Nitric oxide inhibition	Dong et al. (2019)
	Peruvioses (B and A)	Prostaglandin E , and nitric oxide (NO) by in vitro inhibition	Franco <i>et al.</i> (2014)
	Physalins B, F, or G	Leaves of P. angulata cause anti-inflammation by in vitro inhibition	Shravan et al. 2011)
	4β - Hydroxywithanolide E	Cyclooxygenase-2 inhibition and inducible nitric oxide synthase transcription	Park <i>et al.</i> (2019)
		COPD suppression	Peng <i>et al.</i> (2016)
Withanolide		Inhibitory action of cyclooxygenase-2 activity	Chen et al. (2011)
		Inhibit the nitric oxide activity	Sang-Ngern et al. (2016)
Antioxidant	4β - Hydroxywithanolide E	The activation of Nrf2-related genes (enzymes that defend against oxidative stress) and genes controlled by Nrf2	Peng et al. (2016)
		Enhancement of intracellular antioxidant activity impedes oxidative stress	Yang et al. (2020)
Antidiabetic	Peruvioses (A, C, B, D, F, E)	α -Amylase	Bernal et al. (2018); Poojari et al. (2014)
Hepatopro- tective	Ellagic acid	Liver injury induced by acetaminophen in rats	Chang et al. (2008)
Insecticidal	Withanolide E	Mortality of Spodoptera littoralis larvae	Mekhlif and Muhammad (2021)
Antibacterial		Inhibit the activity of <i>Staphylococcus aureus</i> against infection	Donkor et al. (2012)
Antileish- manial	Different compounds isolated from Physalis angulate	Bacillus subtilis and Klebsiella pneumoniae inhibited minimally by root and aerial extract	Osho <i>et al.</i> (2010) ; Murali et al. (2013)
Anticancer		HeLa human cancer cell lines inhibited by leaf extract	Ramakrishna Pillai et al. (2022)
Antiasthmatic		Alcoholic extract induces antiasthmatic activity by Ovalbumin	Jyothibasu et al. (2012)
Antidiuretic		The diuretic effect from methanolic leaf extract in rats	Nanumala et al. (2012)
Antiplasmodial		The antiplasmodial activities against two strains of Plasmodium falciparum	Lusakibanza et al. (2010)

5.1 Antidiabetic effect

Diabetes is a persistent medical condition marked by heightened levels of blood glucose (Kanta *et al*., 2023). *Physalis* leaf extract exhibited probable antidiabetic effect and demonstrated the capability to prevent diabetic rat mortality induced by alloxan (Kadima *et al*., 2016). Throughout the 28-day treatment period, no death was reported in the *Physalis* groups, indicating a censored rate of 100%. Zootechnical outlines revealed a highly significant difference in water consumption compared to intake of food, accompanied by observed changes in weight (Kasali *et al*., 2016; Fokunang *et al*., 2017). In obese mice generated by a regular, fat-rich diet, the daily and oral administration of *P. peruviana* extracted fruit pulp (300 mg kg-1 body weight) improved skeletal muscle insulin resistance, leading to reduced blood sugar levels and serum insulin. Additionally, the plant extract enhanced the inflammatory state and protected the liver from oxidative stress (Pino-de la Fuente *et al*., 2020).

The hydroalcoholic *P. peruviana* leaves extract and its fraction (hexane, ethyl acetate, and ethyl acetate residue) exhibited antidiabetic effects in diabetic rats caused by streptozotocin after 28 days of treatment. Sathyadevi *et al*. (2014) found that after the treatments, diabetic insulin-resistant rats exhibited increased insulin levels and elevated hepatic glycogen content. Supplementation with fruit extracts also led to reductions in elevated levels of glycosylated hemoglobin, glucose, alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate transaminase (AST). Rey *et* $al.$ (2015) reported the inhibiting concentrations of α -amylase and α -glucosidase are (IC₅₀: 619.9 g ml⁻¹) and (IC₅₀ = 4191 µg ml⁻¹) respectively.

5.2 Anticancerous property

Cakir *et al*. (2014) found that extracts of shoot and leaf (20 and 30 µg ml-1) effectively protected DNA from hydroxyl radical damage caused by the Fenton reaction. Furthermore, the $100 \mu g$ ml⁻¹ dosage of two extracts showed cytotoxic impacts on HeLa cells. Mier Giraldo *et al*. (2017) discovered the changes in antiapoptotic gene expression by analysis of mRNA expression. For human cervical cancer cells, the fruit of *P. peruviana* showed a half-maximum concentration of inhibition (IC₅₀) that was 60.48 mg ml⁻¹, while for murine fibroblast cells, it was 66.62 mg ml-1. Furthermore, the ethanolic cape gooseberry extract showed greater potency in suppressing cell lines of the colon $(IC_{\rm so}: 142 \mu g \text{ ml}^{-1})$ compared to cell lines of the breast $(IC_{\rm so}: 371 \mu g)$ ml-1) (Ramadan *et al*., 2015). In a rat-induced carcinoma hepatocellular model, cape gooseberry extracts enhanced all parameters, including liver function enzymes, antioxidant system oxidative stress, and alterations in lipid profile. Serag *et al*. (2015) findings also demonstrated, that fruit exhibited higher effectiveness compared to adriamycin and served as a chemosensitizer for treating hepatocellular carcinoma. El-Meghawry *et al*. (2015) invented that ethanol extract from fruit (150 mg kg⁻¹) exhibited protective effects against lung carcinogenesis, attributed to its antiproliferative and antioxidant properties. The ethanolic fruit extract at a concentration of 800 µg/ ml exhibited effectiveness against lung cancer cells, yet its impact on colorectal adenocarcinoma cells was limited (El-Beltagi *et al*., 2019).

5.3 Anti-inflammatory properties

Pardo *et al*. (2008) found that *Physalis* fruit juice had modest antiinflammatory action, promoting pterygium development in the eyes of rabbit compared with the reference (methylprednisolone). Total inflammation scores were 337 for methylprednisolone and 320 for *Physalis* juice. Furthermore, *Physalis* calyx demonstrated significant activity of anti-inflammatory in the colitis model induced by TNBS, leading to colonic tissue enhancements observed at both histological and macroscopic levels (Castro *et al*., 2015). Additionally, the oral administration of the extract from *P. peruviana* (100 mg kg-1) displayed antinociceptive effects against chemically induced pain.

5.4 Antimicrobial activity

Maobe *et al*. (2013) also reported that plant extracts can regulate *Candida albicans*, with inhibitory diameters greater than 12 mm. Furthermore, the calyxes chloroform fraction exhibited a MIC of d< 0.256 mg ml-1. Cueva *et al*. (2017) found that various ethanolic leaf extracts could hinder the 95% microbial activity which is 50 out of 60 strains. These findings underscore the antimicrobial potential of *Physalis peruviana* extracts against a variety of fungal and bacterial strains.

5.5 Antioxidant properties

By increasing the intake of glutathione (GSH), Horn *et al*. (2015) investigate the antioxidant potential of extracted fruits GSH, in turn, repaired lipid and protein damage produced by 2,4-dichlorophenoxyacetic acid at doses of $1 - 10$ g $1¹$. Lipid peroxidation values decreased at the same dosage. According to Mohammed and Ibraheem (2017), 0.500 mg ml⁻¹ concentration of, methanolic extracts removed 95.33% of DPPH radicals, which was much greater than that of 64.67% in vitamin C. Hassan *et al*. (2017) observed the rats daily recommendation of 1 ml kg-1 bw juice had a beneficial effect with hepatocellular carcinoma, leading to a reduction in free radicals, leading to antioxidant biomarkers decreases, including superoxide dismutase, glutathione, catalase and total antioxidant capacity in the examined tissues. In the diabetes rats induced by streptozotocin given to a high-fat diet, the addition of quercetin rich juice enhanced overall antioxidant activity and higher levels of adiponectin. (Dewi and Sulchan, 2018). Guine *et al*. (2020) illustrated a strong association between the presence of phytochemical components (such as ascorbic acid, phenolic compounds, and carotenoids) and the antioxidant capacity as assessed by ABTS and DPPH methods.

5.6 Hormonal protective effect

Abdel Moneim (2016) documented the protective benefits of Physalis juice in mitigating CCl₄-induced toxicity on the reproductive system, thereby addressing diseases and infertility caused by oxidative stress. Furthermore, the study investigated the protective impact of administering the methanol extract of the fruit (200 mg kg⁻¹ body weight for five days) on alleviating cadmium-induced damage to the testicles of rats, with a specific focus on addressing testicular oxidative stress.

5.7 Hepatorenal protective effects

The P*. peruviana* root extracts have demonstrated a protective impact on the liver and kidneys (Hepatorenal) (El-Gengaihi *et al*., 2013). The authors observed improvements in various oxidative stress markers such as superoxide dismutase, malondialdehyde, aspartate, nitric oxide, alkaline phosphatase, alanine aminotransferases, total liver creatinine, bilirubin, serum protein, protein, gamma-glutamyl transferase, and urea. The plant extract effectively shielded the kidney and liver against fibrosis. In a study where the methanolic extract from *Physalis* 200 mg kg⁻¹ d⁻¹ was pre-administered to rats for five

days treated with cadmium (Cd), it mitigated hepato-renal toxicity by reducing nitric oxide and lipid peroxidation levels, while enhancing the activities of glutathione and enzymes in liver and kidney tissues. Additionally, fruit extract reversed the histopathological alterations in liver and kidney tissues and upregulated the expression of Bcl-2. (Dkhil *et al*., 2014). According to Taj *et al*. (2014), the *Physalis peruviana* aqueous extract demonstrated greater exertion in rats poisoned by CCl₄ compared to ethanol and ripe fruit extracts. Ethanol and ripe fruit extracts exhibited moderate levels of activity compared to standard drug (Liv52). Sapna *et al*. (2023) also reported that *Plumeria obtusa* extracts cause hepatoprotective effects against CCl₄ induced rat liver damage.

5.8 Hypocholesterolemic potential

A study involving rats feeding blueberry juice at concentrations of 15% and 5% exhibited lower levels of low-density lipoprotein cholesterol (LDL), total triacylglycerol, and total cholesterol, along with elevated levels of high-density lipoprotein cholesterol (HDL), compared to cholesterol-free diet and animals on a high-cholesterol diet. (HCD) (Ramadan *et al*., 2013). After 60 days of administration, the activity of pyruvic glutamic transaminase decreased in comparison to the control groups. Significantly, there was a notable decrease observed in globulin, serum proteins, and albumin levels in the blueberry juice-treated groups. The group fed 5% fruit juice showed the most significant rise in HDL levels, with a rise of 35 mg $dl⁻¹$. These results suggest that blueberry juice consumption may have beneficial effects on lipid profiles and liver enzyme activity, contributing to a more favourable cardiovascular risk profile in the studied rats (Ramadan *et al*., 2013).

5.9 Neurotoxicity protective potential

A study investigating the impact of *Physalis* fruits on neurotoxicity in rats induced by cadmium revealed noteworthy findings with the administration of the fruit for five days led to a decrease significantly (*p*<0.05) in nitric oxide and lipid peroxidation levels, coupled with an increasing glutathione level. Furthermore, the study observed that rats treated with plant extracts exhibited a noteworthy increase in levels $(p<0.05)$ in the antioxidant enzymes cellular activities, including glutathione peroxidase, glutathione reductase, superoxide dismutase, and catalase. The improvement observed in the brains of the rats subjected to the plant extract reinforces the potential therapeutic benefits of the fruit in mitigating the detrimental effects of cadmium exposure on neurological health (Othman *et al*., 2014).

6. Toxicological studies and clinical trials

Generally, *P. peruviana* extracts exhibit weak toxicity with an LD_{50} (lethal dose for 50% of the population) exceeding 500 mg kg-1 . However, there have been reported cases of toxicity. For instance, the introduction of lyophilized fruit juice at 5000 mg kg $^{-1}$ dose resulted in cardiac toxicity, particularly myocardial damage was observed in male rats after a 90-day treatment period. This was evident from the significant increase in concentration of potassium, and troponin T and troponin I plasma levels (Perk *et al*., 2013). According to Khalaf-Allah *et al*. (2016), rats mortality reached 40% at 1,500 mg kg-1 concentration of leaf extract, while no mortality was observed at a lower concentration which is 500 mg kg⁻¹ of body weight. These findings accentuate the importance of considering dosage levels when assessing the potential toxicity of *P. peruviana* extracts.

In a clinical trial involving 26 volunteers with an average age of 25.03 \pm 2.74 years with a BMI of 22.76 \pm 1.48 kg m⁻¹, participants were separated into two groups randomly. The first group was given 25 g of fruit combined with glucose, followed by the second group receiving glucose alone 40 min later. After a three-day washout period, the treatments were reversed. The results indicated blood glucose values had a significant difference between the two groups at 90 min (*p*< 0.01). Moreover, a highly significant difference was observed at 90 min post-treatment (p < 0.01), and a significant difference at 120 min postprandial (p < 0.05). Fruit juice consumption was related to increased glucose clearance (Rodriguez and Rodriguez, 2007).

7. Conclusion

As consumers increasingly prioritize their well-being and explore alternative nutrition sources, the *Physalis* presents itself as a beneficial choice, providing fruits and vegetables rich in vitamins, minerals, and health-promoting compounds. *Physalis* species with essential vitamins crucial for human health, along with minerals aid in regulating bodily systems. High concentrations of vitamin C, renowned for its antioxidant properties and immune system support, are particularly noteworthy in *Physalis*. Additionally, phenolic compounds in edible *Physalis* varieties contribute to antioxidant activity, effectively neutralizing harmful free radicals. Notably, all the species stand out for containing various levels of withanolides, some of which demonstrate potential antitumor, anticancer, and multiple health properties. Expanding research on the nutritional profile of cut leaf groundcherry, Chinese lantern, hairy groundcherry, and *Physalis lagascae* and the nutritious benefits of goldenberry, tomatillo, and groundcherry should also encompass studies on the bioavailability of various nutritional components. Investigating how these components are absorbed in the gut may reveal unique attributes that contribute to enhanced health advantages in compared to other fruits. The current review shows potential indications for beneficial health effects associated with consuming *Physalis* and it is anticipated that future studies will delve deeper into these mechanisms to offer a more comprehensive understanding of these benefits.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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