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Journal of Herbmed Pharmacology

Chemical constituents and evidence-based pharmacological properties of *Physalis peruviana* L.: An overview

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ARTICLE INFO

Article Type:
Review

Article History:
Received: 16 December 2020
Accepted: 21 January 2021

Keywords:
Physalis peruviana
Phytochemicals
Bioactivity
Pharmacological mechanisms
Therapeutic uses

ABSTRACT

Physalis peruviana L. is among plant species possessing evident nutritional, nutraceutical, and commercial interests. This review highlights the complexity of the chemical composition supporting the multiple pharmacotherapeutic indications and dietary values of this plant through evidence-based studies from Google Scholar, PubMed/Medline, SciFinder, Science Direct, Scopus, the Wiley online library, and Web of Science. The literature mentions at least 40 compounds isolated from different parts; others are still under investigation. High yields in carotenoids, amino acids, minerals, vitamin C, vitamin E, and essential fatty acids have healthy nutritional benefits. Various phytoconstituents, particularly withanolides, exhibit anti-carcinogenic, anti-inflammatory and antidiabetic potentials, as well as cardiovascular and liver protective effects. Prospective studies reveal that the leaves would also provide various beneficial bioactive chemicals worth being isolated. However, clinical evidence-based studies are seldom. Therefore, adequate pharmaceutical formulations and more in-depth controlled clinical trials are needed to fill the gap.

Implication for health policy/practice/research/medical education:
Alongside using *Physalis peruviana* L. fruit in different dietary recipes, medical researchers should also concentrate on formulating and evaluating natural improved medications that can join modern synthetic therapies, particularly to treat cancer, diabetes, and cardiovascular disorders.

Please cite this paper as: Kasali FM, Tuyiringire N, Peter EL, Ahovegbe LY, Ali MS, Tusiimire J, et al. Chemical constituents and evidence-based pharmacological properties of *Physalis peruviana* L.: An overview. J Herbmed Pharmacol. 2022;11(1):35-47. doi: 10.34172/jhp.2022.04.

Introduction

The compilation of various ethnopharmacological surveys worldwide indicates that over 50 000 plants have evident nutritional and therapeutic properties. Around 80% of human beings have used some at least once in their lifetime to deal with their health problems (1). Rarely one plant is used for a single specific disease. Often, the same plant has many indications that can even be contradictory from a pharmacological point of view. It is not surprising to find the same herb used to treat both schizophrenia and depression. However, according to pharmacological principles, schizophrenia is linked to an excess of dopamine, while Parkinson's disease is associated with a dopamine deficit in the brain. The use of a single plant

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for multiple indications may correlate with the chemical content's complexity (2,3).

Physalis peruviana L. is a semi-upright herbaceous shrub or perennial shrub and perennial producing a group of branched stems and native to the Andean region. Numerous studies have been carried out, mainly on the fruit, to determine its chemical content, nutritional value, and pharmacological properties (4-9).

This review aimed to highlight the complexity of its chemical composition that supports its multiple nutritional and pharmacotherapeutic uses.

Literature review method

The search databases were from Google Scholar, PubMed/Medline, SciFinder, Science Direct, Scopus, the Wiley Online Library, Web of Science, and Wikipedia. Useful full articles in different languages without language or time limit restrictions were reviewed.

Plant description

Physalis peruviana (physalis = bladder) is a semi-upright herbaceous shrub or perennial shrub and perennial producing a group of branched stems, native to the Andean region. It has many common names including Cape gooseberry (South Africa), Inca bay, Aztec bay, golden bay, giant ground cherry, African ground cherry, Peruvian groundcherry, Peruvian cherry, pokpok (Madagascar and Hawaii)), rasbhari (India), poha aguaymanto poha aguaymanto (Peru), uvilla (Ecuador), uchuva (Colombia), harankash (Egypt), amour en cage (France, French for love in a cage), and Physalis (United Kingdom) (Figure 1) (10).

Phytochemicals content

As shown in Table 1, *P. peruviana* contains various primary and secondary metabolites isolated from different parts. More than 40 chemical constituents belonging to aldehydes, alkaloids, carbohydrates, carotenoids, esters, flavonoids, glycosides, lipids, phenols, phytosterols, terpenoids, and withanolides have been reported in this plant. Figure 2 shows some chemical structures identified with biological activities, including Aperuvin C, ellagic acid, Peruviose D, Peruvianolides (A, B, C, D), Phyperunolide A, Physachenolide C, Physachenolide D, Physalin B, Physapruin A, Physapruin B, ursolic acid, Withanolides (A, B, C, E, F), 4 beta-hydroxywithanolide E, Withangulatin E, Withaperuvin L, Withaferin A, and analogues. Physalines are the most active representative of secondary metabolites of the genus (11). The protein content is exceptionally high in fruit (12).



Figure 1. Aerial parts and fruit of *Physalis peruviana* L. (Wikipedia photo).

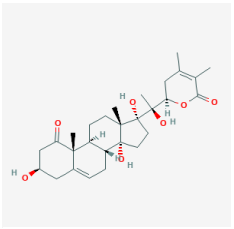
Bioactivity of the isolated compounds

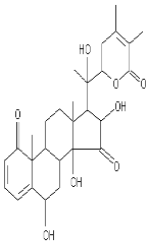
Different researchers have conducted several *in vitro* and *in vivo* pharmacological studies with purified compounds from different parts of the plant to assess the anticancer, antidiabetic, anti-inflammatory, analgesic, hormonal, antioxidant, antimicrobial, immunomodulatory, hepatorenal protection, cholesterol-lowering, and neuroprotective potentials. Table 2 illustrates a couple of studies, mainly for anticancer, anti-inflammatory, and antidiabetic potential of some compounds. The pharmacological study models primarily consisted of the toxicity on ACHN renal carcinoma cell lines, apoptosis in breast cancer cells, block of G2/M cell cycle, cytotoxicity against lung, breast, liver cancer cell lines, cytotoxicity against prostate cancer cell lines LNCaP and 22Rv1, modulation of splicing factors and histone modification, cell cycle arrest and apoptosis, downregulation of Hsp90 client proteins histone modification, human lung cancer cells DNA-damage, and cytotoxicity of colorectal cancer cells. Anti-inflammatory effects were tested using acetaminophen-induced liver injury in rats, cyclooxygenase-2 inhibitory activity, inhibition of oxidative stress, *in vitro* inhibition of nitric oxide (NO) and prostaglandin E2, α-Amylase inhibition, as well as Nrf2 and Nrf2-downstream genes upregulation.

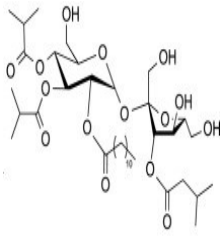
Withanolides are phytoconstituents, which have shown significant bioactivities, in particular the inhibition of tumors (47). They have demonstrated an anticancer potential specifically in the toxicity for the ACHN renal cell carcinoma cell line, tumor inhibition and cytotoxicity activities against prostate, lung, breast, and liver cancers (48–50). White et al (51) summarized other types of cancer treated with withanolides, including ovarian, colon, head and neck, kidney, pancreas, thyroid, glioblastoma, and hematological cancers. On the other hand, certain mechanisms of action of withanolides as anticancer agents are reported, in particular, inhibition of the heat protein 90 (52), a restriction of metastases and angiogenesis (53), cellular resistance to TRAIL (ligand inducing tumor-related apoptosis) - induced apoptosis (54), interference with the proliferation of neoplastic cells, cytotoxicity, inhibition of proteasome and mitosis), activation of transcription factors (55), and reduction of

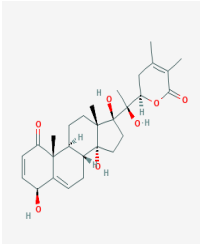
Table 1. Phytoconstituents isolated from *P. peruviana* L.

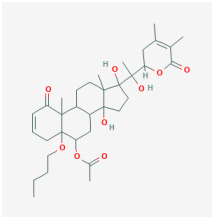
Constituents	Part used	Ref.
Aldehydes		
(E)-non-2-enal	Fruit	(13)
Alkaloids		
(+)-Physoperuvine	Root	(14)
(±)-Physoperuvine	Root	(14)
(+)-N,N-dimethylphysoperuvinium	Root	(14)
Physoperuvine	Root	(15)
Phygrine	Root	(15)
3β-acetoxy-tropane	Root and aerial	(16)
N-methylpyrrolidinylhygrine isomers	Root and aerial	(16)
Cuscohygrine	Root	(17)
Carbohydrates		
3-O-β-D-glucopyranosyl-(1→6)-β-D- glucopyranoside	Fruit	(18)
Diastereomeric 3-O-α-L-arabino-pyranosyl-(1→6)-β-D glucopyranosides	Fruit	(18)
(3S)-butyl 3-hydroxybutanoate	Fruit	(18)
Peruvioses A and B	Calyx	(19)
Peruvioses A,B,C,D,F	Fruit	(20)
Peruvioses F,G,H,I,J,K,L,M	Calyx	(21)
Peruvioses A, B	Calyx	(21)
Nicandrose D	Calyx	(21)
Carotenoids		
Trans-β-Carotene	Fruit	(4)
9-cis-β-carotene	Fruit	(4)
Trans-α-cryptoxanthin	Fruit	(4)
β-carotene and α-carotene	Fruit	(22)
β-carotene and lycopene	Fruit	(23)
Esters		
Ethyl butanoate	Fruit	(13)
Lutein esters	Fruit	(22)
Flavonoids		
Quercetin	Calyx	(24)
Quercetin	Fruit	(25)
Epicatechin	Fruit	(25)
Rutin	Fruit	(25)
Quercetin di-hydrate	Fruit	(25)
Myricetin	Fruit	(25)
Kaempferol	Fruit	(25)
Glycosides		
(1S,2S)-1-phenylpropane-1,2-diol 2- O- β-D-glucopyranoside p-menth4(8)-ene-1,2-diol 1-O-α-L-arabinopyranosyl-(1-6)- β-D-glucopyranoside	Fruit	(26)
1-O-trans-Cinnamoyl-β-D-glucopyranosyl-(1→6)-β-D-glucopyranose	Fruit	(27)
Lipids		
Phytoprostanes	Calyx	(28)
Phenols		
Phenolic acids	Calyx	(28)
Caffeic acid	Fruit, seed	(29)
Chlorogenic acid	-	(30)
Ferulic acid	Fruit	(31)
p-coumaric acid	Fruit	(31)
Gallic acid	Fruit	(31)
Chlorogenic and caffeic acids	Fruit	(31)
Phytosterols		
Campesterol	Fruit	(6)
α-sitosterol	Fruit	(6)
β-sitosterol	Fruit	(6)
Stigmasterol	Fruit	(6)
Δ5-avenasterol	Fruit	(6)
Lanosterol	Fruit	(6)
Δ7-avenastero	Fruit	(6)
Ergosterol	Fruit	(6)
Terpenoids		
Ursolic acid	Leaf	(32)
Lupeol	Fruit	(13)
Linalool	Fruit	(13)
Withanolides		
Irinans A and B	Whole plant	(33)
4 β-Hydroxywithanolide E	Aerial part	(34)
Physalolactone C	Root	(35)
Withaperuvin E	Root	(36)
Withaperuvms F and G	Root	(37)
28-hydroxywithanolide E	Calyx	(38)
4P-hydroxywithanolide E	Calyx	(38)
Phyperunolides A-F	Aerial part	(39)
Blumenol A	Aerial part	(40)
(þ)-(S)-dehydrovomifoliol	Aerial part	(40)
Perulactones A,B,C,D	Aerial part	(40)
Peruvianolides A,B,C,D,E	Whole plant	(41)
Withaperuvin C	Aerial part	(42)
4b-hydroxywithanolide E	Aerial part	(42)
Visconolide	Aerial part	(42)
Withanolide F	Aerial part	(42)
Withaphysanolide	Aerial part	(42)
Withaperuvin H	Root	(43)
Perulactones E-H	Aerial parts	(44)
Withaperuvins I-K	Aerial parts	(44)
Withaperuvins L-N	Aerial parts	(44)
Physaperuvin G	Aerial part	(45)
Physaperuvins I, and J	Aerial parts	(45)
Perulactones I-L	Aeroponical growth	(46)
17-deoxy-23β-hydroxywithanolide E	Aeroponical growth	(46)
23β-hydroxywithanolide E	Aeroponical growth	(46)
4-deoxyphyperunolide A	Aeroponical growth	(46)
7β-hydroxywithanolide F	Aeroponical growth	(46)
7β-hydroxy-17-epi-withanolide K	Aeroponical growth	(46)
24,25-dihydro-23β,28-dihydroxywithanolide G	Aeroponical growth	(46)
24,25-dihydrowithanolide E	Aeroponical growth	(46)

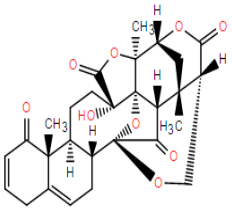

Withanolide F

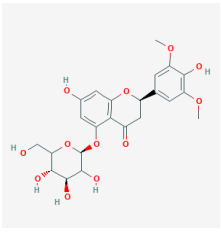

Aperuvin C

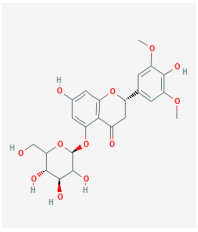

Peruviose D

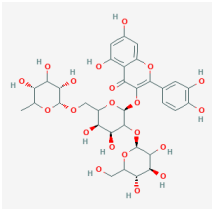

Physapruin A

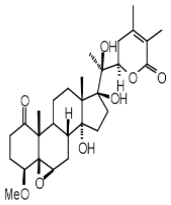

Physapruin B

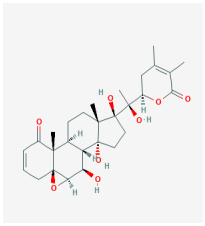

Physalin B

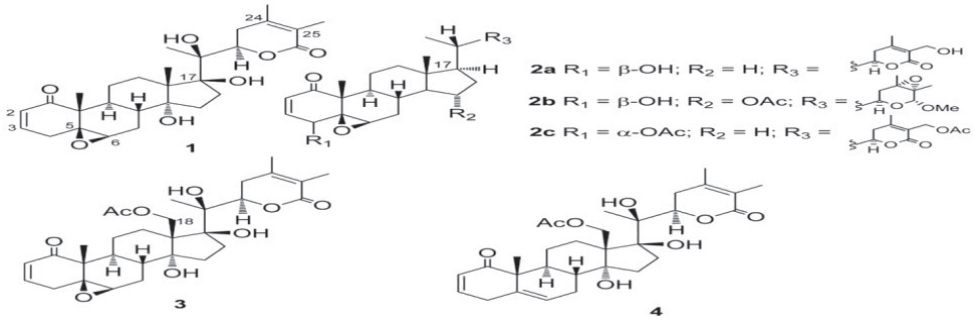

Peruvianolide A


Peruvianolide B

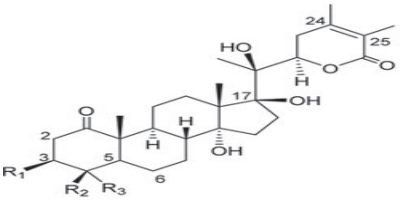

Peruvianolide C


Withangulatin E


Withaperuvin L



Withanolide E (**1**), Withaferin A analogues (**2a, 2b**, and **2c**), Physachenolide C (**3**), and Physachenolide D (**4**).



5 $R_1 = R_3 = H$; $R_2 = OH$; $\Delta^{2,3}$; 5(6)β-epoxy
6 $R_1 = N_3$; $R_2 = OH$; $R_3 = H$; 5(6)β-epoxy
7 $R_1 = R_3 = H$; $R_2 = OAc$; $\Delta^{2,3}$; 5(6)β-epoxy
8 $R_1 = R_3 = H$; $R_2 = OCO_2Me$; $\Delta^{2,3}$; 5(6)β-epoxy
9 $R_1 = R_3 = H$; $R_2 =$  ; $\Delta^{2,3}$; 5(6)β-epoxy
10 $R_1 = H$; $R_2,R_3 = O$; $\Delta^{2,3}$; 5(6)β-epoxy
11 $R_1 = R_2 = H$; $R_3 = OH$; $\Delta^{2,3}$; 5(6)β-epoxy
12 $R_1 = R_2 = H$; $R_3 = OAc$; $\Delta^{2,3}$; 5(6)β-epoxy
13 $R_1 = H$; $R_2,R_3 = O$; $\Delta^{2,3}$; $\Delta^{5,6}$
14 $R_1 = R_2 = H$; $R_3 = OH$; $\Delta^{2,3}$; $\Delta^{5,6}$

Withanolide E analogues (**5–14**).

Figure 2. Structures of some compounds.

stress responses (56). Currently, restoration of wild-type p53 function has been noted in mutant p53Y220C cells (57). Peruvioses (A to F) in the form of carbohydrate esters have an antidiabetic effect and an anti-inflammatory potential (19,20).

Bioactivity of crude extracts

Anticancer property

According to Wu et al (69), a high concentration (50 µg/mL) of the ethanolic extract induced an arrest of the cell cycle, apoptosis via the collapse of the mitochondrial membrane, and the depletion of glutathione content. It also showed a dose-dependent accumulation of the Sub-G1 (hypoploid) peak and caused a stop in the G0/G1 phase. Shu et al (70) demonstrated the potent inhibitory effect of SCEPP-5 (supercritical carbon dioxide extract) on the proliferation of NCI-H661 cells compared to aqueous extract, ethanolic extract, and other supercritical carbon dioxide extracts (SCEPP-0 and SCEPP-4). The SCEPP-5 effectively induced apoptosis of H661 cells, as evidenced by the accumulation of peak Sub-G1 and the fragmentation of DNA, using a DNA ladder and flow cytometry analysis.

According to Çakir et al (71), leaves and shoots extracts (30 and 20 µg/mL) showed significant protection against DNA damage induced by the hydroxyl radical generated by the Fenton reaction. Besides, the two extracts had a cytotoxic effect on HeLa cells when applied at a dose of 100 µg/mL. The analysis of the expression of mRNA by Mier-Giraldo et al (72) showed the alteration of antiapoptotic genes. Isopropanol extract for *P. peruviana* fruit exhibited a half maximum inhibition concentration (IC50) value of 60.48 ± 3.8 mg/mL for cancer cells of the human cervix and 66.62 ± 2.67 mg/mL for murine fibroblast cells. Additionally, for colon or breast cancers, the ethanolic extract of Cape gooseberry was more powerful in inhibiting colon cell lines (IC50: 142 µg/mL) than the breast cell line (IC50: 371 µg/mL) (73). In rat induced hepatocellular carcinoma, Cape gooseberry extract has improved all parameters due to the advancement of alterations in the lipid profile, enzymes of liver function, oxidative stress, and the antioxidant system. The results also demonstrated that the fruit was more effective than the reference (Adriamycin) and that it acted as a chemo-sensitizer for the treatment of hepatocellular carcinoma (74). El-Kenawy et al (75) found that the fruit ethanol extract (150 mg/kg) could protect lung carcinogenesis due to its antioxidant and antiproliferative effects. At a concentration of 800 µg/mL, the ethanolic fruit extract was potent against lung cancer cells, but with a weak effect against colorectal adenocarcinoma cells (76).

Antidiabetic effect

An aqueous decoction of *P. peruviana* leaves (100 mg/kg) induced a significant reduction ($P < 0.05$) in the maximum concentration of hyperglycemia caused in guinea pigs after oral glucose loading (77). Also, the leaf extract of *P. peruviana* showed potential antidiabetic activity and an ability to prevent death in alloxan-induced diabetic rats (78). No death occurred during the observation period in the Harungana and Physalis groups (censored = 100%) after 28 days of treatment. The zootechnical profiles showed a very significant difference ($P < 0.001$) in water consumption as opposed to food intake, and weight changes were observed (79,80). Recently, in obese mice, induced by a regular diet rich in fats, oral and daily administration of pulp extract of (the dose of 300 mg/kg bw) improved insulin resistance in skeletal muscles by reducing both serum insulin and blood sugar levels. Also, the plant extract protected the liver against oxidative stress and improved the inflammatory state (81). The hydroalcoholic extract of the leaves of *P. peruviana* and its fractions (hexane, ethyl acetate, and ethyl acetate residue) showed antidiabetic activity in streptozotocin-induced diabetic rats after 28 days of treatment. The insulin level was improved with an improvement in the hepatic glycogen content of diabetic insulin-resistant rats (82). Supplementation with fruit extracts reduced high levels of glucose, glycosylated hemoglobin, aspartate transaminase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP). Rey et al. (83) reported inhibition of both α-glucosidase (IC50 = 4191 µg/mL) and α-amylase (IC50: 619.9 g/mL).

Anti-inflammatory and analgesic properties

Franco et al (84) studied the anti-inflammatory effect of the ethanolic extract of the calyxes and its fractions in a mouse model of acute atrial edema induced by 12-O-tetradecanoylphorbol-13-acetate. Six extract fractions showed a significant effect ($P < 0.05$), and most of them showed a significant dose-dependent response at doses above 250 µg. According to Pardo et al (85), fruit juice showed moderate anti-inflammatory activity by inducing pterygium formation in rabbit eyes compared to the reference methylprednisolone. The total inflammation scores were 320 for *Physalis* juice and 337 for methylprednisolone. Administration of the calyx showed significant intestinal anti-inflammatory activity in the TNBS-induced colitis model and led to an improvement in colonic tissue at the macroscopic and histological levels (86). Also, the extract of *P. peruviana* (100 mg/kg orally) showed an antinociceptive effect against chemically induced pain. It produced a 40% inhibition of torsions induced by acetic acid (acute visceral nociception) and acute inflammatory nociception of the formalin test (87).

Antimicrobial activity

The experiments of Jaca and Kambizi (88) showed that the aqueous and acetone extracts could inhibit Gram-positive and Gram-negative bacteria with a minimum inhibitory

Table 2. Pharmacological properties of some compounds isolated from *P. peruviana*

Compounds	Activity	Pharmacological model	References
Aperuvin J	Anticancer	Toxicity on ACHN-cell lines	(46)
Ellagic acid	Hepatoprotective	Acetaminophen-induced liver injury in rats.	(58)
Peruvioses (A and B)	Anti-inflammatory	I*n vitro* inhibition of NO and prostaglandin E2	(19)
Peruvioses (A, B, C, D, E, F)	Antidiabetic	α-Amylase	(20)
Physalin B	Anticancer	Apoptosis in breast cancer cells, block of G2/M cell cycle	(59)
Physapruin A	Anticancer	Toxicity on ACHN- renal carcinoma cell line	(46)
Phyperunolide A	Anticancer	Cytotoxicity against lung, breast, and liver cancer cell lines	(39)
Peruvianolides B, C, D	Anti-inflammatory	Inhibition of nitric oxide	(41)
Withanolides	Anti-inflammatory	Cyclooxygenase-2 inhibitory activity	(43)
		Inhibition of nitric oxide activity	(45)
Withanolide E	Anticancer	Sensitization of renal carcinoma cells	(46)
	Anticancer	Cytotoxicity against prostate cancer cell lines LNCaP and 22Rv1	(46)
	Insecticidal	Mortality of *Spodoptera littoralis* larvae	(60)
Withangulatin E	Anticancer	Cytotoxicity against prostate cancer cell lines LNCaP and 22Rv1	(46)
Withanolide F	Anticancer	Toxicity of ACHN-renal carcinoma cell line	(46)
Withaperuvin L	Anticancer	Toxicity of ACHN-renal carcinoma cell line	(46)
Withanolides (C and E)	Anticancer	Cytotoxicity against lung, breast and liver cancer cell lines	(46)
4β-Hydroxywithanolide E	Anticancer	Modulation of splicing factors and histone modification	(61)
	Anticancer	Cytotoxic activity against prostate cancer cell lines LNCaP and 22Rv1	(46)
	Anticancer	Cell cycle arrest and apoptosis downregulation of Hsp90 client proteins histone modification	(62)
	Anticancer	Inhibition of tumor activity in carcinogenic progression	(63)
	Anticancer	Inhibition of growth of human lung cancer cells through DNA-damage, apoptosis, and G2 / M arrest	(64)
	Anticancer	Cytotoxicity activity against lung, breast and liver cancer cell lines	(46)
	Anti-inflammatory	Inhibition of cyclooxygenase-2; transcription of Inducible nitric oxide synthase	(65)
	-		
	Antioxidant,	Improvement of intracellular antioxidant effect inhibition of oxidative stress	(66)
	-		
	Anti-inflammatory	Suppression of COPD.	(66)
	Antioxidant	Upregulation of Nrf2 and Nrf2-downstream genes (antioxidative defense enzymes)	(67)
	-		(67)
4β-Hydroxywithanolide E 7β-Hydroxywithanolide F	Anticancer	Inhibition of tumor growth and the proliferation of colorectal cancer cells	(68)
7β-Hydroxy-17-epi-withanolide K	Anticancer	Cytotoxic activity against prostate cancer cell lines LNCaP and 22Rv1.	(46)
17β-Hydroxywithanolide	Anticancer		(46)
23β-Hydroxywithanolide E	Anticancer		(46)
24,25-Dihydrowithanolide E	Anticancer		(46)

concentration (MIC) ranging from 5.0 to 7.0 mg/mL. For the aqueous extract, the MIC values were 5.0 mg/mL for *Bacillus subtilis, Micrococcus kristinae, Escherichia coli*, and *Serratia marcescens,* and 1.0 mg/mL for *Staphylococcus aureus, Escherichia coli,* and *Proteus vulgaris.* However, the acetone extract was active only against *S. aureus, E. coli, S. marcescens (*7.0 mg/mL), and *P. vulgaris* (5.0 mg/mL).

Maobe et al (89) found the potential of plant extracts to control Candida albicans (with inhibition diameter > 12 mm). Moreover, the chloroform fraction of the calyxes exhibited a MIC ≤ 0.256 mg/mL.

Shoots and leaf extracts showed high activity against Gram-positive bacteria *Lactococcus lactis* (maximum inhibition zone) compared to geneticin (71). Cueva et al (90) indicated that different leaf ethanolic extracts were able to inhibit 50 out of 60 strains (95%).

Antioxidant activity

The results of Wu et al (91) showed that the ethanolic extract of the plant (100 µg/mL) exhibited an inhibition rate of 82.3% on the lipid peroxidation induced by FeCl2-ascorbic acid in the rat liver homogenate. The

aqueous extract produced a dose-dependent increase in antioxidant activity, with an IC50 comparable to vitamin C (0.81 µg/mL; 0.89 µg/mL, respectively) (58). The fresh fruit added in the basal diet at 15% in substitution of the fibers protective rats against gamma irradiation injury. Pretreatment with vegetable powder significantly improved the oxidant/antioxidant status, which was associated with reduced severity of liver damage (92). Horn et al (93) demonstrated the antioxidant capacity of the fruit extracts by stimulating GSH consumption, which in turn was able to repair the damage to lipids and proteins caused by 2,4-dichlorophenoxyacetic at concentrations of 1-10 g/L. At the same dose, there was a decrease in lipid peroxidation levels. Referring to Mohammed and Ibraheem (94), the methanolic extracts eliminated 95.33 ± 2.52% of the DPPH radicals at a concentration of 0.500 mg/mL, which was significantly higher than that of vitamin C (64.67 ± 5.03%). Hassan et al (95) reported that daily administration of Cape gooseberry juice (1 mL/kg bw) in rats with hepatocellular carcinoma produced a beneficial effect on reducing free radicals. There was a decrease in antioxidant biomarkers, including glutathione, total antioxidant capacity, superoxide dismutase, and catalase in the tissues examined. Manal et al (73) have shown that fruit ethanolic extract has a strong antioxidant activity (1.785 ± 0.02 and 1.922 ± 0.03 mmol of TE extract/mL) as determined by the ABTS and FRAB tests. The fruit methanolic extract revealed DPPH free radical scavenging activity, but antioxidant capacity was lower than the standard substances. Eken et al (96) found inhibitory concentrations of 32 mg/mL, 3.8 mg/mL, 3.51 mg/mL and 1.21 mg/mL for *P. peruviana*, ascorbic acid, gallic acid, and BHT, respectively. In streptozotocin-induced diabetic rats subjected to high-fat diet, the juice and quercetin supplement improved the total antioxidant capacity and the concentration of adiponectin (97). Guiné et al (98) showed a strong correlation between the phytochemical constituents (phenolic content, ascorbic acid, and carotenoids) and the antioxidant capacity by DPPH and ABTS methods.

Hepato-renal protective effects

Root extracts have shown hepato-renal protective effect (17). The authors observed improvement in all markers of oxidative stress malondialdehyde, superoxide dismutase, nitric oxide, aspartate and alanine aminotransferases, alkaline phosphatase, gamma-glutamyl transferase, bilirubin, total liver protein, creatinine, urea, and serum protein). The plant extract has successfully protected the liver and kidneys from fibrosis. Pre-administration of methanolic extract of *P. peruviana* (200 mg/kg/d for five days) reduced hepato-renal toxicity in rats treated with cadmium (Cd) by reducing lipid peroxidation, nitric oxide and improving activities enzymes and glutathione in liver and kidney tissue. The extract reversed histopathological changes in liver and kidney tissue and also increased expression of the Bcl-2 (99). One study exploring the antihepatotoxic effect in rats with acute induced liver damage demonstrated the protective effect of different leaf extracts (water, ethanol, and hexane) given at 125 mg/kg bw. Also, the administration of the extract to rats resulted in an increase in hepatic GSH and a decrease in MDA (100). Toro et al (101) demonstrated that the calyx extract significantly inhibited ($P < 0.001$) the hepatic oxidative stress caused by CCl4 while keeping the activities of superoxide dismutase and catalase close to normal. According to Taj et al (102), the aqueous extract of *P. peruviana* showed higher activity in rats poisoned by CCl_4 compared to ripe fruit and ethanol extracts, which showed moderate activity compared to the drug standard (Liv52). On the other hand, pretreatment of rats with the aqueous extract at doses of 150 to 600 mg/kg significantly increased the concentrations of superoxide dismutase, catalase and glutathione peroxidase; it also lowered the level of thiobarbituric acid reactive substances (TBARS) (58).

Hypocholesterolemic potential

Rats fed blueberry juice (5% and 15%) showed lower levels of total cholesterol, total triacylglycerol, and low-density lipoprotein cholesterol, as well as higher levels of HDL compared to animals fed HCD and cholesterol-free diet (103). After 60 days of administration, the activity of pyruvic glutamic transaminase decreased compared to the control groups. There was a remarkable decrease in total serum proteins, albumin, and globulin for the groups treated with blueberry juice. The highest increase in HDL was obtained in a group fed 5% fruit juice (35 mg/dL).

Hormonal protective effect

Abdel (104) demonstrated the preventive effect of the juice against the toxicity of CCl4 on reproduction system. He provided the role of this juice in diseases and infertility induced by free radicals. In the same perspective, he showed the protective effect of the fruit methanol extract (200 mg/kg bw for five days) in testicular toxicity induced by cadmium in rats (testicular oxidative stress).

Neurotoxicity protective potential

A study of the effect of fruits on cadmium-induced neurotoxicity in rats has been performed. After five days, the administration of the fruit resulted in a significant decrease ($P < 0.05$) in lipid peroxidation and nitric oxide levels and increase in the amount of glutathione. In additional, it also noted that activities of cellular antioxidant enzymes, namely superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase significantly increased ($P < 0.05$) in rats treated with plant extract. There has been an improvement in the brains of sick rats (105).

Toxicological studies

In general, *P. peruviana* extracts have weak toxicity (LD50 > 500 mg/kg). However, some cases of toxicity have been reported. Administration of 5000 mg/kg of lyophilized fruit juice induced cardiac toxicity (myocardial damage) in male rats after 90 days of treatment. Also, the potassium concentration, the plasma levels of troponin I, and troponin T increased significantly (106). According to Khalaf-Allah et al (32), 40% of mortality in rats was reached at a concentration of 1,500 mg/kg of leaf extract. No mortality was seen at 500 mg/kg bw. These results of Kasali et al (77) estimated LD50 at around 1.28 mg/kg in guinea pigs.

Clinical trials

A clinical trial was conducted on twenty-six volunteer participants (age 25.03 ± 2.74 years, BMI 22.76 ± 1.48 kg/m) randomly divided into two groups. The first group was treated with 25 g of fruit and glucose, 40 minutes later. The second group received only glucose. After three days of washup, the treatments were reversed. There was a significant difference at 90 minutes ($P<0.01$) At 90 minutes postthere was a very significant difference ($P<0.01$) and at 120 minutes ($P<0.05$) postprandial in blood glucose values in the two groups. The juice increased glucose clearance (107).

Nutritional values

The results of Mokhtar et al (108) showed the following composition in *P. peruviana* powder waste: 5.87% moisture, 15.89% protein, 13.72% fat, 3.52% ash, 74% dietary fiber, and 61% carbohydrates. However, the mineral composition of potassium was high (560 mg/100 g), followed by sodium (170 mg/100 g) and phosphorus (130 mg/100g). The amino acid analysis yielded high levels of cysteine/methionine, histidine, and tyrosine/phenylalanine. The fatty acid profile showed that linoleic acid was the predominant fatty acid, followed by oleic, palmitic, and stearic acids. Iodine index (109.5 g/100g of oil), acid index (2.36 mg KOH/g of oil), saponification index (183.8 mg KOH/g of oil), peroxide index (8.2 mg/kg of oil) and refractive index (1.4735) were comparable to those of soybean and sunflower oils. According to Luz and Tenorio (109), *P. peruviana* was a good source of vitamin C compared to other familiar sources, such as mango (15-36 mg/100 g of fresh weight), comparable to orange (50 mg/100 g FW), but less than guava (120-228 mg/100 g FW) or marula (120 mg/100 g FW). The levels of vitamins B3 and B6 declared for the vegetable pulp were 26.6 ± 0.9 mg/100 g dry weight and 24.8 ± 0.2 mg/100 g DW, respectively (110). The vitamin E content was high, and γ and α-tocopherols were the main components. High levels of β-carotene were also identified in Cape gooseberry juice. Trans-β-carotene was the primary carotenoid, accounting for 76.8% of the total carotenoid content, followed by 9-cis-β-carotene and all-trans-α-cryptoxanthin, representing approximately 3.6 and 3.4%, respectively (5). Higher β-carotene, antioxidants, and vitamin C contents were observed as a result of the application of extraction assisted by high hydrostatic pressure, and the foam required less extraction time compared to other extraction methods (111). Meanwhile, pressurization resulted in a significant increase in fructose and glucose to 300–500 MPa on both day 0 and day 30 ($P<0.05$). The potassium content increased by 8 to 10% at 300 and 500 MPa, while the phosphorus content increased by 65% compared to the control sample at 400 MPa on day 0 ($P<0.05$) (112). The mineral composition analyzed in the methanol extract of calyxes showed calcium at a concentration of 7.50 mg and iron at 1.38 mg (113). The average fiber and ash contents showed nutrient retention during bleaching. Micronutrient estimates also showed retention of β-carotene and vitamin E content, while the average vitamin C content decreased after bleaching (114). The total sugar content in the juice was 4.9 g/100 g and the predominant compounds were sucrose (35 g/100 g sugar) and fructose (29 g/100 g sugar), comparable to the sugar content of most juices. The sugar contents declared in the other juices were as follows: pear 9.8%, orange 7.0%, apple 11.1%, fishing 8.5%, and strawberry 5.7% (4). After treatment with the high hydrostatic pressure of the plant, an increase in soluble dietary fiber was observed for all the treatments compared to the control samples. In addition, a significant increase in the contents of B3 and B6 was observed compared to the control samples (110).

Conclusion

The available studies point out that the numerous therapeutic indications are linked to its phytochemical complexity. The plant has a hepato-renal protective effect and could be explored for the development of promising remedies. Toxicological studies are minimal. Apart from a few cases of poisoning reports, there are no in-depth studies. As a member of the Solanaceae family, the plant could contain solanine, a natural insoluble glycoalkaloid that is very toxic and has been shown to be teratogenic in animal models. The clinical studies do not constitute high-quality clinical trial to answer specific questions about the safety, efficacy, and specific dose required to achieve optimal glycemic control and duration of treatment in T2D patients. The above results validate and support the traditional uses of *P. peruviana*. After all, it is necessary to continue isolating other possible new components and conducting valid pharmacological studies and clinical trials.

Acknowledgment

The authors are grateful to the Mbarara University of Science and Technology (MUST) and Pharm-Bio Technology and Traditional Medicine Centre (PHARMBIOTRAC).

Authors' contributions

FMK wrote the proposal, conducted the internet search, and wrote the first draft. NT, ELP, and LYA contributed to the literature search. MSA corrected the first draft. JT, PEO, and AGA supervised the study and corrected all drafts. JNK contributed to the conception of protocol and revised the final manuscript. All authors have read, approved and confirmed the final manuscript for publication.

Conflict of interests

The authors state that there is no conflict of interest for this review.

Ethical considerations

Not applicaable.

Funding/Support

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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