Review

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Composition and biological effects of goldenberry byproducts: an overview

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Abstract

Goldenberry is a wild fruit that has been widely used for centuries, mainly in folk medicine. Most studies of goldenberry have focused on the fruit, but new research has studied its byproducts, which were considered to be waste until recently. The main objective of our study was to systematize the published information regarding the composition of goldenberry byproducts (calyces, leaves, seeds, and pomace) and their effects on biological systems. Goldenberry byproducts contain minerals, amino acids, withanolides, flavonoids, and essential fatty acids, thus representing good sources of these compounds. Some of their major biological effects include anti-inflammatory, antioxidant, antidiabetic, and antiproliferative effects. Information regarding their toxicity is also presented here. To determine the optimal dosage, further safety studies would be recommended to ensure the best health benefits of these compounds. The available evidence has demonstrated the nutritional value of different byproducts of goldenberry, suggesting them to be potential candidates for use in the cosmetic industry, in the preparation of functional foods, and in phytomedicine for the prevention and adjuvant treatment of some diseases.

Keywords: goldenberry; *Physalis peruviana*; wild fruit; byproducts; waste products

INTRODUCTION

Physalis peruviana Linnaeus is commonly known as goldenberry in English-speaking countries. It is an erect, branching, and densely villous perennial, native to tropical America. It has now been introduced in India and other countries, growing in plains and hills.[1] This plant, belonging to the Solanaceae family, usually grows up to 0.6 to 0.9 m in height, and in some cases, even up to 1.8 m.[2]

Reports on the chemical composition of goldenberry extract have indicated the presence of different chemical compounds, such as withanolides, saponins, peruvioses, irinians, kaempferol, and quercetin di- and tri-glycosides,[3,4] some of which have demonstrated hypoglycemic,[5] antioxidant,[6,7] and anti-inflammatory effects,[8,9] along with significant antiproliferative activity against lung cancer cell lines (H1299),[10] colon cancer cells (colo-205), chronic myeloid leukemia cells (K562),[11] and others, including prostate, renal, colorectal, and mammary cell lines.[12–14]

However, most reports have focused on the properties of goldenberry fruit only, rather than on its byproducts, considering the latter to be waste in the industrial process. Goldenberry calyx represents approximately 33 tons of waste generated per hectare of cultivated goldenberry.[15]

The significant amount of waste generated during the agroindustrial processing of goldenberry may include its byproducts, which are applicable in folk medicine;[16] the calyces, leaves, seeds, and pomace are widely sought for their antiseptic, antiproliferative, and anti-inflammatory effects, as demonstrated by previous research.[17]

Information regarding the composition and biological effects of goldenberry byproducts may form the foundation for future research, taking full advantage of the raw materials and their derivatives. This article aimed to present an overview of the composition of goldenberry byproducts (calyces, leaves, seeds, and pomace) and their effects on biological systems. Reports on their adverse effects and toxicity have also been included for their safe usage.

GOLDENBERRY BYPRODUCTS

Calyces

The calyx that envelops the goldenberry fruit has a cupuliform structure, similar to a Chinese lantern, formed by sepals or modified leaves. Its macro-structures are presented in Fig. 1(A) and

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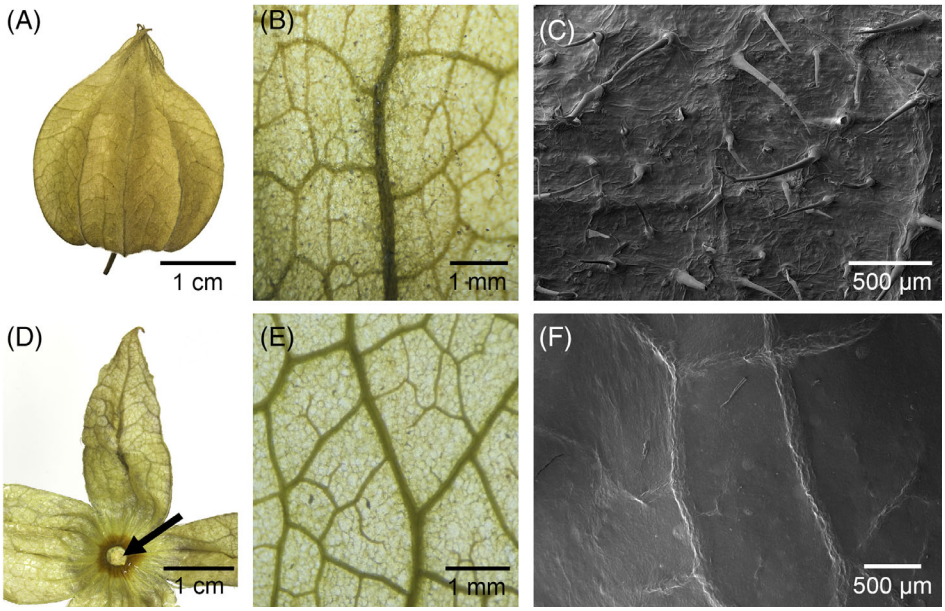

Figure 1. Calyx of goldenberry. (A) External features of the calyx, covering a goldenberry fruit, in a globular shape. (B) Stereoscopic micrograph of the external structure using optical microscope (10×) and (C) scanning electron microscope (50×). (D) Internal appearance of the calyx without the fruit; the site of union of the fruit with calyx can be observed (see arrow). (E) Stereoscopic micrograph of the inner face of the calyx; multiple projections or trichomes are observed (10×). In (F), the same structures are observed in greater detail (100×).

(D), and micro-structures are presented both for the external and internal surface in Fig. 1(B) and (C), and in Fig. 1(E) and (F), respectively.

The goldenberry calyx contributes to the development and maturation of the fruit, protecting it from insects, birds, diseases, and adverse weather conditions.[17] In addition to reporting its protective role, previous studies reported that its presence in post-harvest fruit had positive effects on its preservation and characteristics.[18]

The calyx has typically been used for the preparation of oils and infusions, mainly in folk medicine. Current studies on the goldenberry calyx focus on verifying the bioactivities of both the total extract and isolated constituents, with *in vitro* studies using macrophages and animal models with induced inflammation.[19]

Composition and biological effects

The potential use of the calyx in phytomedicines or in products with nutritional value is based on its constituent elements. The composition and mineral content of goldenberry calyces are shown in Table 1.

The reported data showed that goldenberry calyces present protein levels twice as high as those in the fruit itself,[25] whereas the content was similar to that in leaves. Moreover, carbohydrate content in goldenberry calyx was twice as high as those reported for the leaves, and half of the maximum value reported for goldenberry pomace.

The ash content in the goldenberry calyx was higher than that in its leaves, pomace, and fruit,[25] indicating inorganic material content, such as minerals. Calcium was found to be the main mineral present in goldenberry calyces, playing an important role in cellular physiology. As mentioned above, there is evidence about its role in the post-harvest fruit, impacting the cell turgidity, tissue firmness, and lipid catabolism of the cell membrane,[26] thus moderating the weight loss of the fruit, as confirmed by comparing goldenberry fruits stored with and without calyces.[18]

The level of moisture in this byproduct was found to be similar to that reported for goldenberry pomace, which was 28% below the maximum recommended level, thus allowing reduced microbial growth, ensuring safe storage, and prolonging shelf life.[23]

Goldenberry calyces contain less than 0.5% of both essential and non-essential amino acids – much lower than the proportion reported for goldenberry pomace, as seen in Table 2.

Table 3 presents five main biological effects of goldenberry calyces reported in the literature. These have been found to be essentially sustained in the extracts of goldenberry calyces in the presence of bioactive compounds such as withanolides, flavonoids, phenols, physaperuvin, saponins, and peruvioses [27] possibly through the combined and synergistic actions of these and other compounds present in goldenberry calyces.[28]

According to Wahdan *et al.*, the total flavonoid content of goldenberry calyx extract was 0.61 g quercetin equivalent kg^{-1},[20] the value being lower than that reported for other species of *Physalis*, such as *Physalis subulata* (39.6 g quercetin equivalents kg^{-1}), *Physalis hederifolia* var. *hederifolia* (16.5 g quercetin equivalents kg^{-1}), and *Physalis angulata* (8.8 g quercetin equivalents kg^{-1}).[34] Medina *et al.* had determined rutin (quercetin-3-*O*-rutinoside) to be the main flavonoid present in the goldenberry calyx extract, followed by quercetin-7-*O*-glucoside-3-*O*-rutinoside and kaempferol-3-*O*-rutinoside; the presence of five cinnamoyl acid derivatives was also identified.[27]

The phenolic content of goldenberry calyces was determined to be 5.25 g gallic acid equivalent kg^{-1},[20] and was considered to be responsible for the antioxidant activity, determined by the nitric oxide uptake assay.[35] However, the value mentioned was 4- to 32-fold lower than that determined in the calyces of other six species of *Physalis*.[34]

Two classes of aliphatic sucrose esters, peruvioses A and B, had been reported in goldenberry calyx extracts,[36] these bioactive compounds exhibit biological properties, such as insecticidal, antibacterial, anti-inflammatory, and antifungal properties.[19,36]

Table 1. Proximate analysis results and mineral content of goldenberry byproducts

Constituents	Byproducts			
	Calyces[20]	Leaves[21]	Seeds[22]	Pomace[23,24]
Proximate analysis (g kg^{-1})				
Ash	97.0	8.3	28.4	31.0–35.2
Crude fat	21.0	0.3	146.3	137.2
Fiber	420.0	3.5	315.2	167.4–287.0
Moisture	72.0	756.1	39.2	58.7–66.0
Crude protein	61.0	56.1	145.8	158.9–178.0
Carbohydrates	320.0	175.6	325.1	245.0–610.0
Mineral content	(g kg^{-1})	(g L^{-1})		(g kg^{-1})
Calcium (Ca)	0.08	0.09	NR	0.11
Iron (Fe)	0.01	0.41	NR	0.13
Copper (Cu)	<0.01	<0.01	NR	NR
Zinc (Zn)	<0.01	0.02	NR	0.01
Potassium (K)	NR	0.27	NR	5.60
Sodium (Na)	NR	0.01	NR	1.70
Phosphorus (P)	NR	NR	NR	1.30
Manganese (Mn)	NR	0.02	NR	0.01
Magnesium (Mg)	NR	0.32	NR	NR
Chromium (Cr)	NR	0.01	NR	NR

NR, value not reported.

Table 2. Amino acid composition of goldenberry byproducts

Amino acids	Byproducts	
	Calyx extract[20]	Pomace powder[23]
Non-essential (g kg^{-1})		
Aspartic acid	4.8	78.2
Proline	2.5	39.1
Serine	2.3	47.3
Glutamic acid	4.7	180.9
Glycine	3.0	47.3
Alanine	3.2	42.4
Arginine	2.7	115.7
Essential (g kg^{-1})		
Threonine	2.2	32.6
Valine	2.9	32.6
Isoleucine	2.1	24.4
Leucine	3.5	58.7
Tyrosine	1.8	31.0
Phenylalanine	2.3	39.1
Histidine	1.1	22.8
Lysine	2.8	24.4
Cystine	NR	17.9
Methionine	NR	24.4

NR, value not reported.

The total antioxidant capacity of goldenberry calyx extract was determined to be 3.95 g ascorbic acid equivalent kg^{-1},[20] which is lower than that reported for goldenberry fruit.[25] This activity is partially associated with the presence of carotenoids, which are antioxidant compounds that protect oils from oxidation; the goldenberry calyx extract presents a total carotenoid content of 0.27 g kg^{-1} based on dry weight, which is 18% lower than the reported value for the goldenberry fruit peel, and approximately fourfold lower than that reported for goldenberry fruit pulp.[25] The carotenoid profile revealed high amounts of (all-*E*)-lutein (60%) and (all-*E*)-*β*-carotene (22%), besides (all-*E*)-neoxanthin, (all-*E*)-violaxanthin, (*Z*)-lutein, (all-*E*)-taraxanthin, and (*Z*)-taraxanthin.[37] *β*-Carotene is the most common and most effective provitamin A;[38] goldenberry calyces and their derivatives may therefore serve as an important resource for these compounds.

As stated earlier, multiple bioactive compounds occur in goldenberry calyces, exhibiting potential health benefits in human beings; nevertheless, most of the published research until now has explored the effects on cell lines and animal models, with minimal progress in the field of human research. The latter has been explored essentially through the folk use of calyces and their derivatives in the preparation of infusions; thus, additional studies would be required to support their recommendation in humans.

Adverse effects and toxicity

The extract obtained from goldenberry calyces showed a stronger toxic effect than that obtained from leaves. This toxicity was consistent with the protective function of goldenberry calyces for safeguarding the fruit, suggesting the presence of potent bioactive metabolites.[17]

A study conducted by Ocampo *et al.* showed that the intraperitoneal administration of a mixture of peruvioses A and B into male and female ICR(CD-1) strain mice exerted toxic effects in a dose-dependent manner (at doses ranging from 0.22 to 0.30 g kg^{-1}); however, neither genotoxic effects nor alterations in body weight, vital organs, and biochemical or urine parameters were observed at lower doses.[19]

Leaves

The leaves of goldenberry are simple, alternate, heart shaped, and pubescent, with a size of 5–15 cm in length and 4–10 cm in

Table 3. Biological effects of goldenberry calyx and their derivatives, as reported in the literature

Outcome	Model	Dose	Results	Mechanism	Reference
Antiproliferative	Liver cancer (Hep G2 and Hep 3B), breast cancer (MDA-MB-231 and MCF-7), and lung cancer (A549) cell lines were exposed to a crude ethanolic extract of goldenberry leaves and stems.	Not specified	The extract showed significant antiproliferative activity, with IC_{50} values of 9.91 μg mL^{-1} for Hep G2 cell line, 16.41 μg mL^{-1} for A549, and 4.95 μg mL^{-1} for MDA-MB-231.	Presence of 4-β-hydroxy withanolide E in the extract was associated with the observed antiproliferative activity.	29
	Methanolic extract of calyces was applied to human hepatoma (Hep-3B), human gastric (AGS), and human breast (MDA-MB-231) cancer cell lines.	25–200 μg mL^{-1}	Antitumor activity was more pronounced on AGS than on Hep-3B and MDA-MB-231 cell lines. A dose-dependent effect was observed at the evaluated doses.	Mechanism not described; however, the observed effect could be attributed to the presence of minerals, phenols, flavonoids, and saponins in the extract.	20
	Human colon adenocarcinoma cells (HT-29) and normal human colon fibroblasts (CCD—18Co) received a calyx extract.	6.25–100 μg mL^{-1}	A notable reduction in HT-29 cell (IC_{50} of 6.17 μg mL^{-1}) viability was observed after 48 h of treatment; in contrast, viability of CCD-18Co was not affected.	Transcriptional activation of pro-apoptotic genes, and altered expression of genes related to oxidative stress response in HT-29 cells.	30
Anti-inflammatory activity	Female ICR(CD-1) strain mice with TPA-induced ear edema were supplemented with an ethereal and ethanolic calyx extract (topically).	100–1000 μg per ear	The major fraction of calyx extract (called Pp-D_{28}-LF) showed a significant dose-dependent reduction of edema at doses over 250 μg per ear.	The study did not report the mechanisms underlying the anti-inflammatory effect.	31
	Female Wistar rats received graded doses of peruvioses A and B (intraperitoneally).	0.01–100 μg mL^{-1}	Neither of the peruvioses produced any side effect on the liver and kidneys, and significantly attenuated inflammation.	Induction by λ-carrageenan attenuated inflammation, possibly due to the inhibition of nitric oxide and prostaglandin E2.	13
	Female Wistar rats with 2,4,6-trinitrobenzene sulfonic acid induced colitis received a goldenberry calyx extract intraperitoneally in a preventive and therapeutic approach.	125 mg kg^{-1} day^{-1} (preventive) and 62.5 mg kg^{-1} day^{-1} (therapeutic)	A strong anti-inflammatory effect was observed in the colonic tissue from rats in both preventive and therapeutic approaches.	Significant reduction of tumor necrosis factor alpha, interleukin 1 beta, and nitric oxide levels was seen in the colonic tissue. Additionally, infiltration of neutrophils was reduced.	17
Antioxidant activity	Male Wistar rats with liver inflammation induced by carbon tetrachloride (CCl_4) received an extract of goldenberry calyx (orally).	10 mg mL^{-1}	Significant inhibition of liver oxidative stress was caused by CCl_4. In addition, liver steatosis was attenuated, and hepatic necrosis avoided. Superoxide dismutase and catalase activities were close to normal.	Liver enzyme levels, increased by CCl_4 administration, were reduced significantly; this could be through the bioactivity of flavonoids and withanolides contained in the extract.	28

Table 3. Continued

Outcome	Model	Dose	Results	Mechanism	Reference
Antibacterial activity	Goldenberry calyx extract was applied to *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* cultures.	1.02–6.25 μg mL^{-1}	The minimal inhibitory concentration (in g L^{-1}) was 1.02 and 0.26 for *P. aeruginosa* (ethereal extract and chloroform fraction, respectively) and 1.02 for *K. pneumoniae* (ethanolic fraction).	Mechanism not described.	32
	Methanolic extract of calyces was applied to *Bacillus subtilis*, *Bacillus cereus*, *Escherichia coli*, *Salmonella* sp., and Yeast.	Not specified	The extract had an effect against *B. subtilis*, *Salmonella* sp., *E. coli*, and Yeast with inhibition zones of 27 mm, 24 mm, 24 mm, and 23 mm, respectively.	Mechanism not described; however, the observed effect might be attributed to the presence of phenols, flavonoids, xanthine, and saponins in the extract.	20
Skin antiaging effect	Normal human dermal fibroblast cells in culture were treated with a goldenberry calyx extract.	0.02–100 mg L^{-1}	Significant skin antiaging activity was observed at 0.5 mg L^{-1} concentration.	Up-regulation of type I collagen, elastin, and fibrillin-1 was seen, possibly due to epigenetic changes in DNA and/or histones through acetylation or methylation.	33

width,[39] as shown in Fig. 2(A) and (D). The microstructures on the upper (adaxial) and lower (abaxial) surfaces of goldenberry leaves are presented in Fig. 2(B) and (C), and Fig. 2(E) and (F), respectively. Multiple trichomes may be observed on both the epidermal sides of the leaf, in accordance with the characteristics described by Ahmat *et al.*[40]

Composition and biological effects

The proximate composition and mineral content of goldenberry leaves are shown in Table 1. Among the variables described, it is important to highlight the low content of crude fat (0.83%), which was almost tenfold lower than the values reported for goldenberry calyces, and 76.4% lower than those for goldenberry pomace. In contrast, their moisture content was seen to be similar to that of the goldenberry fruit, approximately tenfold higher than the values determined for calyces and pomace.

In terms of mineral content, the main mineral found in goldenberry leaf extract was iron, which is important for its participation in many metabolic processes, including oxygen transport, deoxyribonucleic acid synthesis, and electron transport.[41] It was followed by magnesium, which is relevant for its role as a co-factor in numerous enzymatic reactions, besides participating in multiple metabolic pathways.[42] Potassium plays an important role in the function of excitable cells like muscle and nerves.[43] The biological importance of calcium has been described in the previous section. Zinc is significant in catalytic, structural, and regulatory functions.[44]

Table 4 shows the fatty acid content of goldenberry leaves; palmitic acid content was approximately fivefold higher than in goldenberry oils from seeds and pomace, as well as from other natural sources like sesame, sunflower, and olive.[45] This fatty acid has several relevant bioactivities based on its effects on the proliferation and apoptosis of cancer cells.[46] Other compounds detected were hexadecene epoxide and phytol, which might be used as a precursor for the manufacture of synthetic forms of vitamins E and K.[47]

In a report by Khalaf-Allah *et al.*, an ethanolic extract of goldenberry leaves was analyzed and the presence of four main constituents was determined: flavonoids (6.838 ± 0.052 g kg^{-1}), glycowithanolydes (0.264 ± 0.004 g kg^{-1}), free withanolides (0.177 ± 0.005 g kg^{-1}), and alkaloids (0.019 ± 0.001 g kg^{-1}).[51] Calderon *et al.* had also reported 1.5 ± 0.7 g kg^{-1} of 4-β-hydroxy withanolide E in leaves,[52] similar to the content determined in the goldenberry fruit (1.4 ± 0.4 g kg^{-1}),[25] although half of that was found in the calyces.

Goldenberry leaf extract presents antiproliferative, antihepatotoxic, antifibrotic, antidiabetic, and antibacterial activity, as summarized in Table 5.

Importantly, goldenberry leaves have been used in folk medicine for centuries, to prepare infusions and perform skin treatments, according to previous reports on indigenous medical knowledge about plants in India.[58] A study performed by Sathyavathi and Janardhanan in the same country had reported the popular use of goldenberry leaves for the treatment of vomiting.[59]

Adverse effects and toxicity

Aqueous extract of goldenberry leaves, applied to male Wistar rats, was found to be devoid of any conspicuous toxicity, either

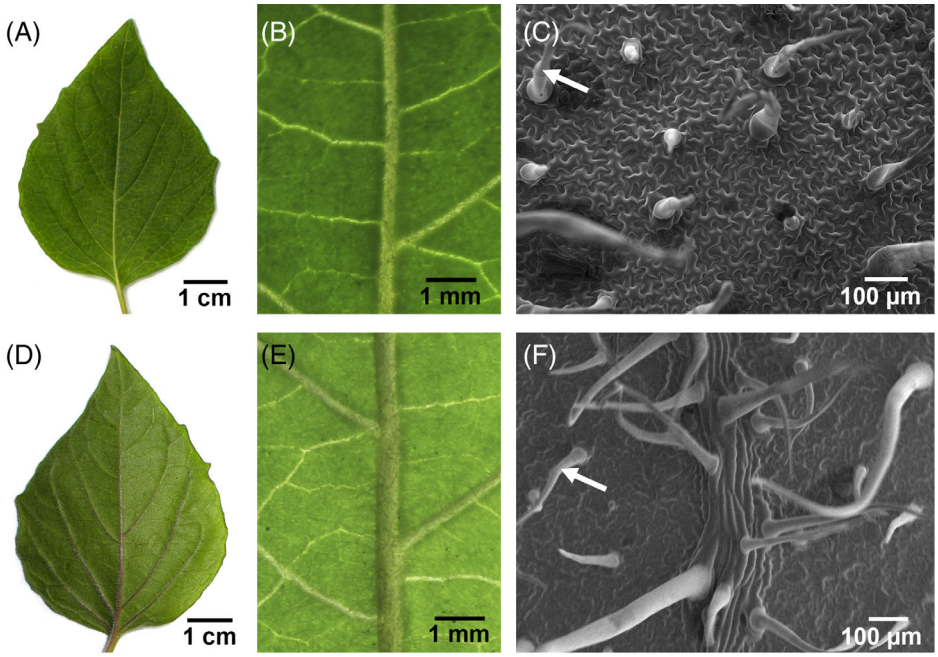

Figure 2. Structure of goldenberry leaves. (A) Features of the adaxial epidermal surface of goldenberry leaves. (B) Stereoscopic micrograph of the adaxial surface of leaf in the midrib region (10×) and (C) under scanning electron microscope (244×). (D) Features of the abaxial epidermal surface of goldenberry leaves. (E) Photomicrograph of the abaxial surface of goldenberry leaf in the midrib region (10×) and (F) under scanning electron microscope (70×). White arrow in (C) and (F) indicates a trichome.

Table 4. Fatty acid, tocopherol, and sterol content of goldenberry byproducts

Compound	Byproduct		
	Leaves[47]	Seeds[38,48,49]	Pomace[23,50]
Fatty acid (g kg^{-1})			
Myristic acid (C14:0)	4.0	10.0	NR
Palmitic acid (C16:0)	428.0	65.0–72.9	73.9–79.5
Palmitoleic acid (C16:1 ω-7)	NR	5.0–5.2	6.2
Stearic acid (C18:0)	7.0	25.0–31.0	26.1–35.1
Oleic acid (C18:1 ω-9)	20.0	113.0–117.0	103.0–113.2
cis-Vaccenic acid (C18:1 ω-7)	NR	6.0	NR
Linoleic acid (C18:2 ω-6)	10.0	761.0–767.0	771.0–777.8
Linolenic acid (C18:3 ω-3)	NR	0.2–3.0	NR
Arachidic acid (C20:0)	NR	4.0	NR
Total saturated	NR	105.0–113.0	109.0–114.0
Total unsaturated	NR	884.0–890.0	881.6–891.0
Tocopherols (g kg^{-1})			
α-tocopherol	NR	0.7–9.0	3.4
β-tocopherol	NR	14.5–113.0	21.0
γ-tocopherol	NR	14.7–91.0	10.8
δ-tocopherol	NR	14.5–84.4	8.5
Sterols (g kg^{-1})			
Campesterol	NR	6.1–65.0	47.0
Stigmasterol	NR	6.2–13.2	2.8
β-sitosterol	NR	12.3–57.1	10.4
δ-5-avenasterol	NR	21.7–45.7	26.3
δ-7-avenasterol	NR	0.5–11.1	5.6

NR, value not reported.

at clinical or at microscopic levels; the results were reported for both doses for therapy (0.13–0.50 g kg^{-1}) and the dose corresponding to acute toxicity (1.25 g kg^{-1}).[1]

These results were consistent, at low doses, with the study conducted by Kasali *et al.* in guinea pigs, where the animals received doses from 0.20 to 3.20 g kg^{-1}, and no observable effect was reported at doses lower than 0.40 g kg^{-1}; nevertheless, with doses of 0.80 g kg^{-1} and higher, the signs appeared in a dose-dependent manner, including effects such as tremors, hesitation, hair rustling, anuria, and eventually death (LD_{50} 1.28 g kg^{-1}).[57] Acute effects were similar to that determined by Khalaf-Allah *et al.*, based on the oral administration of methanolic extract of goldenberry leaves to male Wistar rats, in which mortality rates reached 20% at a dose of 1.00 g kg^{-1} and 40% at 1.50 g kg^{-1}.[51] A possible explanation for the detected toxicity might be the content of solanine in goldenberry plants, which is a toxin belonging to the glycoalkaloid family.[57]

Based on previous information, it would be important to use this preparation carefully, at known and controlled doses. The recommended safe dose of goldenberry leaf extract was 0.50 g kg^{-1} body weight (both in guinea pigs and rats), for which no acute effect or mortality had been observed[51]; consequently, while considering the conversion factors proposed by Reagan-Shaw *et al.*,[60] the safe dose for a 60 kg person would correspond to 0.08 g kg^{-1}.

Seeds

The goldenberry fruit can contain approximately 100–300 small seeds, according to a report by Trillos-Gonzalez *et al.* on 49 genotypes of goldenberry from Colombia, Ecuador, and Europe.[61] The seeds are distributed centrally and peripherally in the fruit, as in a tomato, as is evidenced in both axial and longitudinal sections of the fruit (Fig. 3(A) and (B), respectively).

The mean weight of a goldenberry seed is 0.26 g, and macroscopically it appears to be oval-flat or discoid, of light brown color,

Table 5. Biological effects of goldenberry leaves, as reported in the literature

Outcome	Model	Dose	Results	Mechanism	Reference
Antiproliferative	Oral cancer cells (Ca9-22) received 4-β-hydroxy withanolide E (4βHWE) extract from goldenberry leaves.	1–10 μg mL^{-1}	4βHWE selectively killed oral cancer cells after 24 and 48 h of treatment, with IC_{50} values of 3.6 μg mL^{-1} and 1.9 μg mL^{-1}, respectively.	The results were explained by preferential induction of reactive oxygen species-mediated apoptosis in Ca9-22 over normal oral cells.	53
	Three cancer cell lines (colorectal (HT-29), prostate (PC-3), and human leukemia (K-562)) were evaluated with Vero cell line as the control; all received ethanolic leaf extract.	0.98–62.5 μg mL^{-1}	The extract had less cytotoxicity than positive control drugs in Vero cell line and was more effective than positive control drugs in HT-29, PC-3, and K-562 cell lines.	The inhibition of cell proliferation might be due to the positive regulation of pro-apoptotic proteins (Bax and Bad), and negative regulation of antiapoptotic proteins (Bcl-2, Bcl-xl).	12
	Human lung cancer cells (H661) were exposed to five extracts of goldenberry leaves obtained through different methods.	1–100 μg mL^{-1}	The leaf extract obtained with 5% ethanol as a modifier (called SCEPP-5) showed the most potent inhibitory effect on H661 cell proliferation.	The extract induced cell apoptosis, characterized by cell arrest in S phase, up-regulated expression of Bax, and down-regulated expression of inhibitor of apoptosis protein.	54
	RAW 264.7 murine macrophages were exposed to five extracts of goldenberry leaves obtained through different methods.	10–50 μg mL^{-1}	At 30 μg mL^{-1}, SCEPP-5 extract significantly prevented lipopolysaccharide (LPS)-induced cell cytotoxicity, nitric oxide (NO) release, and prostaglandin E_2 formation.	The reduction of inflammation might be through the inhibition of inducible nitric oxide synthase and cyclooxygenase-2 expression.	55
	Raw 264.7 murine macrophages and transfected human embryonic kidney cells (293/NF-κB-Luc) were used to evaluate the inhibition of NO production on lipopolysaccharide (LPS)-activated and tumor necrosis factor α-induced nuclear factor kappa b (NF-kB) activity, respectively.	Not specified	Exposure to compounds derived from goldenberry calyx was associated with both cell lines showing inhibition of NO production (IC_{50} of 0.32–7.8 μM) and blockade of NF-kB transcription factor (IC_{50} of 0.04–5.6 μM).	The reported results were attributed to the action of three compounds isolated from the aerial parts of goldenberry: 4βHWE, withaperuvin C, and physalactone.	8
	HeLa cells were exposed to an ethanolic leaf extract.	10–200 μg mL^{-1}	The ethanolic extracts of leaf exhibited low cytotoxic activity against HeLa cells at low concentrations (IC_{50} of 100 μg mL^{-1}). The most effective concentration was found to be 200 μg mL^{-1}.	Leaf extract induced apoptosis by altering the mRNA expression of antiapoptotic genes. The extracts damaged mitochondrial membrane potential instead of protecting it.	56
Antihepatotoxic	Male Wistar rats, with acute liver injury induced by carbon tetrachloride (CCl_4), received a goldenberry leaf extract (orally).	125 mg kg^{-1}	Ethanol and hexane extracts presented moderate antihepatotoxic activity compared to water extract. Histopathological changes induced by CCl_4 were significantly reduced by the extract. Serum levels of aspartate transaminase (AST), alanine aminotransferase (ALT), lactate dehydrogenase, and alkaline phosphatase (ALP) were also reduced.	This may be due to the flavonoid, saponin, and phenol content, all of which possess antioxidant properties.	1

Table 5. Continued

Outcome	Model	Dose	Results	Mechanism	Reference
Antifibrotic	Male Wistar rats with hepato-renal fibrosis induced by CCl_4 received a goldenberry leaf extract (orally).	500 mg kg^{-1}	Goldenberry leaf extract diminished lipid peroxidation. The levels of ALT, AST, ALP and gamma-glutamyl transferase were normalized, possibly due to the stabilization of plasma membrane as well as the repair of damaged hepatic tissue.	Scavenging of free radicals through an increase in superoxide dismutase expression leads to reduced inflammation, improved kidney function, and improved health of renal cells.	46
Antidiabetic	Guinea pigs received a goldenberry leaf extract (orally).	3.2–100 mg kg^{-1}	Compared to glibenclamide (reference drug) and negative control, administration of goldenberry leaf extract significantly reduced the glucose peak concentration and revealed hypoglycemic properties.	Some of the effects observed in leaf extracts may be partly due to the action of physalins A, B, D, and F and glycosides present in the leaves of goldenberry.	57
Antibacterial	Ethanolic leaf extract was applied to three gram-positive bacteria (*Staphylococcus aureus* A950277, *Staphylococcus epidermidis* 14990, and *Lactococcus lactis* ATCC 11454) and three gram-negative bacteria (*Escherichia coli* DH5-α, *Chromobacterium violaceum* 12472, and *Erwinia herbicola* pv. *gypsopholia-824*).	100–1000 µg per disc	Leaf extract showed high inhibitory activity against the three gram-positive bacteria evaluated, with minimum inhibitory concentration values of 200 µg per disc for all of them. No response was observed in *Chromobacterium violaceum* 12 472.	Authors hypothesized that the presence of compounds, such as withanolides, in the ethanolic leaf extract might explain the antibacterial effect observed.	56

as shown in Fig. 3(C). The seed has three delimited regions (see Fig. 3(D)); from external to internal, these regions correspond to the 'epidermis', with a protective function, the 'tegmen', with an intermediary function related to gas exchange, and the 'endosperm', a zone associated with embryo nutrition, in which cells present multiple acidophilic inclusions containing nutrients[62] (Fig. 3(E)).

Composition and biological effects

Reported values of the proximate composition of goldenberry seed oil are presented in Table 1. High values of fiber and carbohydrates, and low values of ash and moisture, were obtained. Importantly, seeds present higher content of crude fat and lower content of moisture among the goldenberry byproducts considered in this study.

Regarding the composition of seeds, a study conducted by Ramadan and Mörsel showed that fresh whole berries contain 2.0% oil, of which seed oil was approximately 90% and pulp / peel oil was approximately 10%.[63] A detailed profile of the composition of fatty acids in goldenberry seed oil is presented in Table 4, according to which the fatty acid content of goldenberry seed oil mainly consisted of unsaturated fatty acids (near to 90%), as a result of which it is more sensitive to oxidation.[23] In particular, linoleic acid is the most abundant species in goldenberry seed oil, with values similar to the mean of that reported for goldenberry pomace, and 60% higher than the mean value reported for goldenberry fruit.[25] The values reported were also 19–46% higher than those estimated in the seed oils of grape, apple (Granny Smith, Golden Delicious, Sturmer, and Dougherty varieties), watermelon, black raspberry, and boysenberry. They were 71% higher than those from cherry-seed oil, 75% higher than that from blueberry-seed oil, and nine-fold higher than that from mango-seed oil.[49]

Linoleic acid is an essential fatty acid that has to be obtained through diet. There have been some reports about the protective effects of linoleic acid in cardiovascular disease, hypertension, and arteriosclerosis,[48] and its deficit is known to result in growth deficiencies, skin lesions, fatty liver, and reproductive failure.[64] Thus, the consumption of goldenberry seed oil may be a good dietary source of this compound.

The goldenberry seeds have a total phenolic content 2.3-, 2.7-, and 20-fold higher than that determined for the fruit, leaves, and roots, respectively.[65] As mentioned above, the presence of phenolic compounds contributes to the antioxidant activity of the extract.[35]

The crude oil of goldenberry seeds may be considered a source of four isoforms of tocopherol, as presented in Table 4. These

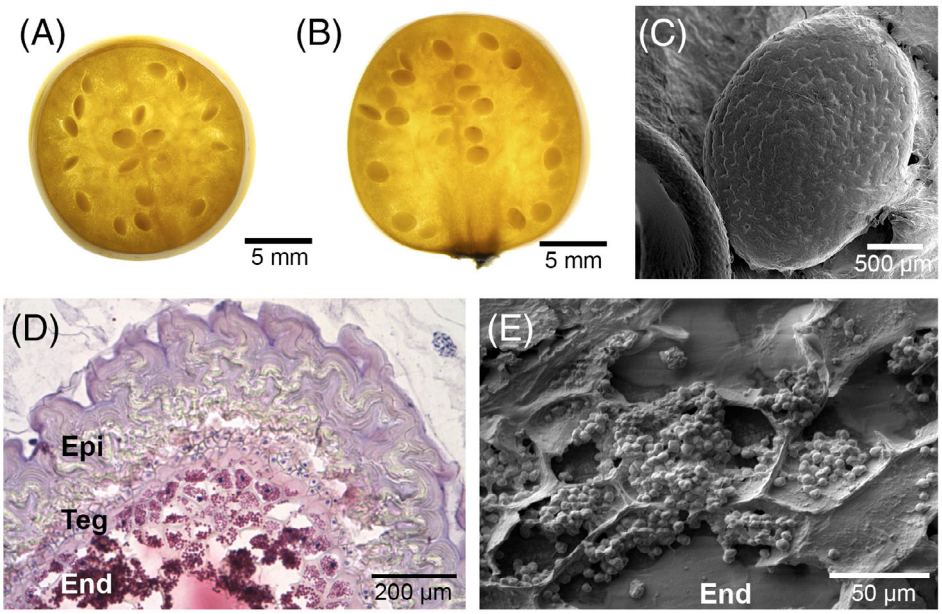

Figure 3. Goldenberry seed characterization. (A) Distribution of goldenberry seeds in an axial section of the fruit and (B) in a longitudinal section of the fruit. (C) Image of a goldenberry seed under the scanning electron microscope. (D) Photomicrograph of an axial section of a goldenberry seed by H&E staining (10×). (E) Image of the goldenberry seed endosperm region under scanning electron microscope (1000×). Epi, epidermis; Teg, tegmen; End, endosperm.

compounds have been shown to be beneficial to health, as they play a role in peroxyl radical scavenging, thereby maintaining the integrity and bioactivity of long-chain polyunsaturated fatty acids in the cell membranes.[66] In particular, α-tocopherol plays a protective role against DNA damage (antioxidant), mitochondrial dysfunction, and decreased memory and learning[48]; β-tocopherol has antioxidant properties and strongly inhibits intracellular tyrosinase[67]; γ-tocopherol is related to reduced neuropathology in Alzheimer's disease,[48] and has natriuretic, anti-inflammatory, and antiproliferative properties[67]; and δ-tocopherol is responsible for a proinflammatory response promoted by reactive oxygen species to prevent hormone-dependent breast-cancer progression.[67]

Five sterols were also found in goldenberry seed oil, the range of reported values (given in Table 4) being higher than that reported for goldenberry pomace; moreover, the highest value detected was for campesterol, followed by β-sitosterol and δ-5-avenasterol. Consumption of these compounds decreased the total cholesterol and LDL-cholesterol concentrations in plasma by inhibiting cholesterol absorption in the intestine in a competitive process, due to the structural similarity between plant sterols and cholesterol.[68]

The total flavonoid content of the ethanol extract of goldenberry seed was 0.74 ± 0.03 g kg^{-1}, which was 74% and 16% higher than that reported for goldenberry fruits and leaves, respectively, and 11-fold higher than the value reported for goldenberry roots.[65] 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging activity was reported for the ethanol extracts of goldenberry, with an SC_{50} of 2.1 g L^{-1} for seeds, which was threefold lower than that reported for leaves (8.0 g L^{-1}).

There is little scientific evidence about the biological effects of goldenberry seeds. A study by Ertürk *et al.* had evaluated the antimicrobial activity of goldenberry fruit and its byproducts (leaf extract, root extract, and seed extract), when applied to 12 microorganisms (10 bacteria, one fungus, and one yeast). The results showed goldenberry seeds to be the most effective antimicrobial among all the byproducts. The seed extract possessed a moderate antimicrobial activity when compared with positive control drugs (ampicillin, cephazolin, and nystatin). The report suggested the values obtained were sufficient for goldenberry (fruit and its byproducts) to be regarded as a potential source of medicinal products for the treatment of several infectious diseases.[65]

However, the report did not mention the concentration of each extract used in the experiment. Additional studies would thus be required to evaluate the antibacterial power of goldenberry seed extract using different extraction methods, at different concentrations, and against a broader spectrum of microorganisms, which would allow a more accurate determination of the dosage, providing clinically detectable effects in both animal models and humans.

A study was performed in India (among the tribes of Thiashola, Manjoor, Nilgiris south division, and the Western Ghats) regarding the use of dried goldenberry seeds and leaves in folk medicine, based on the testimonials of local population. It reported the traditional use of goldenberry byproducts in the treatment of jaundice and glaucoma,[58] which may be useful information for future research regarding its potential use as an alternative in the treatment of various pathological conditions.

Adverse effects and toxicity

No published report has been found regarding the toxic effects of consumption or administration of goldenberry seeds. However, a study of acute and sub-acute toxicity of seeds of *Datura stramonium*, another member of the Solanaceae family, which evaluated its alkaloids by intraperitoneal administration of a dose of 0.1 g kg^{-1} to female albino Wistar rats, did not show mortality or any sign of toxicity for either acute or sub-acute administration over 4 weeks.[69]

These results may provide information for the specific evaluation of goldenberry seeds in future, investigating the occurrence of adverse effects and determining safe doses for administration.

Pomace

The residue after juice extraction, including the seeds, skin, and parts of the pulp, is called pomace, and is generally considered a waste product, despite it being approximately 27.4% of the goldenberry's fruit weight.[50] Previous reports had provided supportive evidence about the nutritional value of goldenberry pomace and its potential health benefits.

Composition and biological effects

The proximate composition and mineral content of goldenberry pomace powder are detailed in Table 1. It shows similar content of crude fat and crude protein as in goldenberry seeds; however, its protein content is higher by 345%, 273% 119%, and 88%, compared to that in pomaces from other fruits like blue grape, pineapple, sweet lemon, and orange, respectively.[70]

Goldenberry pomace powder presents higher carbohydrate content than the other byproducts of goldenberry that were evaluated. Low moisture content, owing to the loss of water in the juice extraction process, allows safe storage of this byproduct. Moreover, the dietary fiber content of goldenberry pomace is lower than that detected in goldenberry seeds (47%) and calyces (60%).

In terms of mineral composition, the reported values have revealed goldenberry pomace powder to be a good source of potassium, followed by iron, sodium, and phosphorous. Potassium in goldenberry pomace powder was twice as high as those reported for goldenberry leaves and fruit itself.[25] Similar iron content was reported for grape pomace flour, although a great difference was observed in the content of potassium and phosphorus between goldenberry and grape pomace flours, the former having 399- and 721-fold higher content respectively.[71]

According to the values reported in Table 2, 30.8% of the amino acid content of goldenberry pomace powder corresponded to essential amino acids, the main compound being leucine, followed by phenylalanine, threonine, and valine. Regarding non-essential amino acids, the most abundant species were glutamic, arginine, and aspartic acid.

The fatty acid composition of goldenberry pomace is detailed in Table 4, according to which the ratio of unsaturated to saturated fatty acids is 1 : 9. As mentioned previously, the oxidation susceptibility is higher in compounds with high concentrations of unsaturated acids, and proper processing, packaging, and storage need to be considered to increase the shelf life of such a byproduct.[23] The content pattern of fatty acids of goldenberry pomace powder was similar to that reported for goldenberry seeds and goldenberry waste powder, with the major content being linoleic acid, followed by oleic acid, and palmitic acid.

Goldenberry pomace samples were found to contain tocopherols and sterols (Table 4). The main tocopherol identified was β–tocopherol, although the values detected were remarkably lower than those for goldenberry seeds. Campesterol was the main sterol detected, followed by δ-5-avenasterol and β-sitosterol, similar to that in goldenberry seeds.

An *in vivo* study was conducted using 20 male albino rats, divided into four groups, two of them being supplemented with goldenberry pomace at a dose of 100 g kg^{-1} (10%) and 300 g kg^{-1} (30%) of feed with 10 g kg^{-1} of cholesterol and 2.5 g kg^{-1} of colic acid. The results showed an increase in the levels of HDL-cholesterol, with a remarkable reduction in the levels of total cholesterol, LDL-cholesterol, total triacylglycerol, total cholesterol, serum alanine aminotransferase (ALT) activity, uric acid, and urea, hence suggesting the consumption of goldenberry pomace to suppress high-cholesterol diet-induced hypercholesterolemia in rats.[50]

Adverse effects and toxicity

No published report is available regarding the toxic effects of consumption or administration of either goldenberry pomace powder or its oil extract. Perk *et al.* had conducted a study for identifying the acute and subchronic toxic effects of lyophilized goldenberry fruit juice on male and female Wistar rats. In the acute approach, the rats received an oral dose of 5.0 g kg^{-1} and effects were observed over a period of 14 days; the LD_{50} value was found to be more than 5.0 g kg^{-1} for both sexes. A subchronic approach, consisting of the intraperitoneal administration of 0.1, 1.0, and 5.0 g kg^{-1} day^{-1} (in a volume of 1 mL 100 g^{-1}) over a period of 90 days, showed that lyophilized goldenberry fruit juice did not induce genotoxicity, and possibly did not result in hematological, hepatic, and / or renal toxicity in either sex; however, cardiotoxicity was observed in males.[72]

CONCLUSIONS AND FUTURE TRENDS

The nutritional value of the different goldenberry byproducts, based on proximate composition, mineral composition, presence of vitamins, antioxidants, amino acids, essential fatty acids, and other compounds specific to this genus, namely peruvioses, physalins and withanolides, makes them potential candidates for use by the cosmetic industry. They can be used in the preparation of functional foods, and as components in phytomedicine for the prevention and adjuvant treatment of pathologies such as diabetes, cancer, and nonalcoholic fatty liver.

The reported studies have concentrated their efforts on the evaluation of the byproducts and their derivatives in cell lines and in animal models, so more scientific evidence would be required to assess their biological activity in human beings, and to identify the required doses of goldenberry byproducts to obtain maximum benefits with minimum harm to human health.

Additional studies, aimed at increasing the extraction efficiency of goldenberry byproduct constituents, maximizing the bioavailability of its components, and improving methods of cultivation, processing, and storage, avoiding the degradation of nutritive components, and increasing cost effectiveness in the use of these raw materials, would open up new possibilities and applications.

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