Citrullus colocynthis (L.) Schrad. and Punica granatum L.: A Review of Phytochemistry, Toxicity, Mitigation Strategies, and Prospects for a Standardized Multi-Fruit Functional Beverage for Diabetes and Cancer Support

Suyash Meena, Khushi Vyas, Manasvi Sharma and Preenon Bagchi*

Dept. of Bioinformatics, School of Life and Basic Sciences, Jaipur National University, Jaipur, India

*Preenon.bagchi@jnujaipur.ac.in

Abstract. Citrullus colocynthis (L.) Schrad., known as bitter apple, Indrayan, or Gaduma, is a desert cucurbit long used in traditional medicine and increasingly studied for its antidiabetic and anticancer bioactivity. Its principal active constituents, the cucurbitacins, are also responsible for a well-documented toxicity profile affecting the gastrointestinal tract, liver, kidneys, and reproductive outcomes, which has historically limited its therapeutic use. This review synthesizes the phytochemical, pharmacological, and toxicological literature on C. colocynthis, examines the biosynthetic origin of its bitterness and toxicity, and evaluates documented and proposed strategies for reducing its toxic load while retaining beneficial activity. Building on this evidence, the review develops the rationale for a standardized functional beverage combining a detoxified C. colocynthis fraction with pomegranate (Punica granatum) and complementary fruits such as amla (Phyllanthus emblica) and jamun (Syzygium cumini), alongside safe, non-bioactive flavor and stability additions. For each documented side effect, corresponding mitigation strategies reported in the literature are identified and discussed. The review concludes with future research directions required before such a formulation could be considered for human use.

Keywords: Citrullus colocynthis, cucurbitacins, pomegranate, functional beverage, antidiabetic activity, anticancer activity, detoxification, nutraceutical formulation.

1 Introduction

Citrullus colocynthis (L.) Schrad. is a perennial, drought-tolerant member of the family Cucurbitaceae distributed across the sandy and semi-arid regions of North Africa, the Middle East, and South and Central Asia [1,2]. The plant is known by many regional names that reflect its long history in folk medicine, including bitter apple and

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colocynth in English, and Indrayan or Gaduma in Hindi- and Rajasthani-speaking parts of India [3]. Traditional applications recorded across these regions include the management of diabetes, constipation, jaundice, asthma, and a range of gastrointestinal complaints [1,2].

Alongside this traditional use, C. colocynthis occupies an unusual position among medicinal plants: the cucurbitacins most often credited with its pharmacological activity are also potent gastrointestinal irritants linked to hepatic, renal, and reproductive toxicity [4,5]. Colocynth-containing laxative products were withdrawn from the United States market in 1991 on safety grounds [6], and case reports continue to describe acute poisoning following ingestion of raw fruit or decoctions [7]. Reconciling this toxicity profile with the plant's demonstrated bioactivity, and identifying a practical route to a safe consumable formulation, is the organizing purpose of this review.

2 Phytochemical Composition

Phytochemical surveys of C. colocynthis have identified more than seventy constituents, spanning cucurbitacins and their glycosides, flavonoids, phenolic acids, alkaloids, saponins, sterols, and fatty acids [8,9]. Cucurbitacins B, E, I, J, K, and L, together with their glucosides, form the plant's chemotaxonomic signature, with cucurbitacin E and its glycosides typically the most abundant forms [8]. Bioassay-guided work continues to identify previously undescribed cucurbitane-type triterpenoids, indicating that the compound inventory of the species is still being resolved [9].

Beyond cucurbitacins, the fruit and seed contain flavonoids such as isovitexin, phenolic acids, and polyphenol-rich fractions that are chemically separable from the cucurbitacin-rich fractions using solvents of increasing polarity [10]. Cucurbitacin content itself varies substantially by plant part, accession, and season [11,12]. This variability, together with the general finding that antioxidant activity tracks with phenolic and flavonoid content while acute toxicity tracks with cucurbitacin content [10,13], forms the pharmacological basis for a detoxification strategy discussed later in this review.

3 Biosynthetic Origin of Bitterness and Toxicity

The bitterness and toxicity of Cucurbitaceae fruits are traceable to a specific enzymatic pathway rather than to a single toxic contaminant. Cucurbitacin biosynthesis begins with the cyclization of 2,3-oxidosqualene into cucurbitadienol, a reaction catalyzed by oxidosqualene cyclase (OSC), encoded by the Bi gene [14,15]. Expression of Bi in fruit tissue is switched on by a basic helix-loop-helix transcription factor, Bt (Bitter fruit); a mutated bt allele underlies the non-bitter cucumber cultivars already used commercially [14]. Downstream, cytochrome P450 enzymes and an acyltransferase further oxidize and acetylate cucurbitadienol into the mature cucurbitacins [9,15]. This genetic pathway means cucurbitacin content is, in principle, tunable through accession selection or breeding, though this route was assessed in this review as impractical for a near-term formulation project (Section 6).

At the cellular level, cucurbitacins exert their effect by disrupting the actin and vimentin cytoskeleton of exposed cells [16,17]. This mechanism underlies both the compound's cytotoxic action against cancer cells and its damage to normal gastrointestinal and hepatic tissue, meaning the beneficial and harmful effects of cucurbitacins are mechanistically inseparable at the molecular level, differing primarily in dose and relative cell sensitivity [16,18]. Separately, cucurbitacin E has been shown to alter hepatic cytochrome P450 2C11 expression and activity in rats, indicating that it can also interfere with the liver's own drug-metabolizing capacity [19].

4 Pharmacological Activities

4.1 Antioxidant Activity

Extracts of C. colocynthis fruit, seed, and leaf show radical-scavenging activity in DPPH and ABTS assays that correlates with total phenolic and flavonoid content rather than cucurbitacin content [10]. In a spontaneously hypertensive rat model, polyphenol-rich fractions reduced oxidative stress markers alongside antihypertensive effects [10].

4.2 Antidiabetic Activity

Forty-six animal studies using streptozotocin- or alloxan-induced diabetic models have reported blood-glucose-lowering effects of C. colocynthis regardless of dose or plant part used [13]. Proposed mechanisms include insulinotropic action in isolated rat islets and perfused pancreas [20,21], enhanced GLUT4-mediated glucose uptake in adipocytes [22], and modulation of hepatic gluconeogenic enzyme expression [23]. A randomized, double-blind, placebo-controlled clinical trial in type II diabetic patients receiving oral fruit capsules alongside standard therapy reported significant reductions in glycated hemoglobin and fasting blood glucose without significant hepatic or renal adverse effects over two months [24]. Reported clinical dose ranges across six identified trials span roughly 125 to 1000 mg per day, most commonly around 300 mg per day in divided doses [13].

4.3 Anticancer Activity

Cucurbitacin B and E glucosides isolated from C. colocynthis leaves inhibit growth of both estrogen-receptor-positive (MCF-7) and estrogen-receptor-negative (MDA-MB-231) breast cancer cell lines, arresting cells at the G2/M checkpoint [25]. Ethyl-acetate fruit extracts show cytotoxicity against pancreatic and epidermoid carcinoma cell lines with comparatively limited effect on normal cells [26], and fruit extracts increase pro-apoptotic Bax expression in human melanoma cells in a dose-dependent manner [27]. This evidence remains preclinical; no human oncological trials were identified in the course of this review.

5 Documented Side Effects and Corresponding Mitigation Strategies

Reported median lethal doses (LD50) for C. colocynthis vary widely by plant part, extract type, and species, ranging from approximately 162 mg/kg for flower extract to over 1000 mg/kg for some fruit methanolic extracts [2,28]. Table 1 summarizes the principal documented side effects together with mitigation strategies reported in the literature, or, where no dedicated study exists, the most defensible interim solution.

Table 1. Documented side effects of Citrullus colocynthis and corresponding mitigation strategies for a standardized functional beverage formulation

Documented side effect / safety concern	Evidence from the literature	Recommended mitigation strategy
Gastrointestinal irritation (watery diarrhea, abdominal cramps, bloody diarrhea)	Cucurbitacins are strong gastrointestinal mucosal irritants and are responsible for the acute laxative and irritant effects of raw fruit and crude extracts.	Siddha Shodhana (purification) of fruit pulp to reduce tannins, resins, and cutin while retaining protective mucilage; avoid raw fruit consumption and use standardized purified fractions.
Hepatotoxicity	High doses and prolonged exposure may cause liver injury, whereas controlled low doses have shown hepatoprotective effects through SIRT1/Nrf2/HO-1 signaling.	Standardize cucurbitacin dose (50–100 mg/kg equivalent preclinical safety range), incorporate antioxidant hepatoprotectants (e.g., curcumin or silymarin), and explore nanoformulation for lower effective doses.
Renal toxicity	Repeated administration has been associated with increased serum urea and creatinine, indicating hepatonephrotoxic effects at higher doses.	Strict dose standardization through the proposed Fractionate–Quantify–Recombine (FQR) protocol and monitoring of renal biomarkers during preclinical and clinical studies.
Teratogenic and reproductive toxicity	Animal studies report fetal resorption, skeletal abnormalities, and abortifacient effects during pregnancy after exposure to fruit pulp extract.	Contraindicate use during pregnancy and breastfeeding; exclude pregnant participants from clinical trials and include mandatory safety labeling.
Acute poisoning	Human poisoning cases include hepatic injury, pseudomembranous colitis, severe diarrhea, and diabetic	Implement batch-release HPLC verification of cucurbitacin concentration before

	ketoacidosis following ingestion of raw fruit or concentrated decoctions.	formulation release to prevent uncontrolled exposure.
Drug interactions from pomegranate co-formulation	Pomegranate juice inhibits CYP3A4 and CYP2C9 enzymes and may alter metabolism of medications such as warfarin and sildenafil.	Conduct pharmacokinetic interaction studies and include package warnings for individuals taking CYP3A4/CYP2C9-metabolized drugs.
Loss of beneficial polyphenols during processing	Heat treatment, solvent extraction, and encapsulation may reduce antioxidant polyphenols during beverage processing.	Use microencapsulation or nanoencapsulation technologies to improve stability, solubility, and bioavailability of antioxidant phytochemicals.

5.1 Gastrointestinal Irritation

Cucurbitacins are potent gastrointestinal mucosal irritants, producing watery or bloody diarrhea and cramping even at doses close to traditional medicinal use [2,5]. A Siddha purification (shodhana) process applied to C. colocynthis fruit pulp has been shown to degrade or remove toxic constituents such as tannins, cutin, and resins while retaining mucilage content, which has a demulcent, mucosa-soothing effect [12]. This purification step is therefore a documented, partial mitigation for gastrointestinal irritation rather than a complete solution.

5.2 Hepatotoxicity

Hepatic effects are the most extensively studied organ-level concern. A dedicated review concluded that C. colocynthis can be hepatotoxic at higher doses or with prolonged exposure but is comparatively well tolerated at 50 to 100 mg/kg, with seed extracts tolerated better than pulp extracts [4]. Notably, this hepatic literature is not uniformly negative: cucurbitacin E glucoside isolated from C. colocynthis fruit has itself been shown to protect against Concanavalin A-induced hepatitis in mice by enhancing SIRT1/Nrf2/HO-1 signaling and suppressing NF-κB/NLRP3 inflammation [29], and cucurbitacin B has been used clinically in China since the 1970s-1980s as an approved adjuvant therapy for chronic hepatitis and liver cancer [30]. This confirms that cucurbitacins are hepatoprotective at controlled low doses and hepatotoxic at higher ones, supporting dose titration rather than elimination as the primary mitigation strategy. Two further approaches are supported by the literature: nanocarrier-based delivery systems, which have been shown to permit effective cucurbitacin B anticancer activity at a lower administered dose, thereby reducing toxicity while preserving efficacy [30]; and co-formulation with an independently documented antioxidant hepatoprotectant, since compounds such as silymarin and curcumin have repeatedly reduced liver enzyme elevation and oxidative stress from a co-administered hepatotoxic agent in unrelated toxicological models [31,32].

5.3 Renal Effects

Animal studies report elevated urea and creatinine following repeated dosing, indicating a combined hepato-nephrotoxic pattern at higher doses [2]. No C. colocynthis-specific renal-protective co-formulation study was identified in this review; the interim mitigation is dose control through the standardization protocol described in Section 6, together with dedicated renal biomarker monitoring in any staged toxicological evaluation.

5.4 Teratogenic and Reproductive Effects

Fetal resorption and skeletal malformation have been reported in rats dosed with fruit pulp extract during early gestation at one-quarter of the determined LD50 [33], and abortifacient effects have been reported in pregnant animals at higher doses. No processing method is expected to eliminate this risk, since it is a property of the compound class rather than a contamination issue. The applicable mitigation is exclusionary rather than technical: labeling the product as contraindicated in pregnancy and excluding pregnant or breastfeeding individuals from any trial cohort.

5.5 Acute Poisoning

Human case reports describe acute colocynth poisoning after ingestion of raw fruit or decoctions, presenting with hepatic injury, pseudomembranous colitis, and, in one diabetic patient, diabetic ketoacidosis [7]. This risk is directly addressed by the batch-release analytical verification step of the standardization protocol proposed in Section 6, which prevents the uncontrolled high-dose exposure responsible for historical poisoning cases.

5.6 Pomegranate Drug Interactions

Pomegranate juice, proposed in this review as the primary complementary fruit (Section 7), is a documented inhibitor of cytochrome P450 enzymes CYP3A4 and CYP2C9 and has been associated with altered pharmacokinetics of drugs including warfarin and sildenafil [34]. No formulation change removes this interaction, since it is an intrinsic pharmacokinetic property of pomegranate itself. The standard mitigation used for other CYP-interacting foods, most notably grapefruit, is a dedicated drug-interaction study combined with a clear package warning, and the same approach is recommended here.

5.7 Polyphenol Degradation During Processing

Heat, solvent extraction, and encapsulation steps used to reduce cucurbitacin content risk degrading the heat- and oxidation-sensitive polyphenols the formulation is intended to preserve. Microencapsulation and nanoencapsulation technologies have a broad evidence base for improving the stability, solubility, and bioavailability of

hepatoprotective and antioxidant phytochemicals during processing, and represent the most directly applicable mitigation [35].

6 A Standardized Fractionate-Quantify-Recombine (FQR) Protocol

Because acute toxicity tracks predominantly with cucurbitacin content while beneficial antioxidant and antidiabetic activity tracks with the polyphenolic fraction, this review proposes a standardization protocol in place of uncontrolled whole-fruit processing. The protocol comprises: (i) solvent fractionation of the fruit extract (hexane, chloroform, ethyl acetate, n-butanol, aqueous) to physically separate the polyphenol-rich fraction from the cucurbitacin-rich fraction [10]; (ii) HPLC/LC-MS quantification of total phenolics and specific cucurbitacins in each fraction; (iii) recombination at a deliberately controlled cucurbitacin dose calculated from purified content rather than crude fruit weight, targeted within the range already shown tolerable in human diabetic trials [13,24]; (iv) bitterness masking of the reconstituted cucurbitacin fraction using β-cyclodextrin inclusion complexation, a technique validated on the chemically analogous triterpene glycosides of bitter gourd, where it achieved full sensory debittering with only a 10% reduction in antidiabetic activity and an increase in phenolic content [36]; and (v) batch-release HPLC verification of the finished bottled product prior to any sensory, in-vitro, or human evaluation. This sequence directly addresses the therapeutic-index problem identified in Section 5.2 and 5.5: rather than eliminating cucurbitacins, which would remove the anticancer-active fraction, or leaving cucurbitacin content uncontrolled, which risks toxicity, the protocol targets a deliberately chosen, analytically verified point on the dose-response curve.

Enzymatic debittering technology developed for citrus juices, in which naringinase hydrolyzes the bitter glycoside naringin into a non-bitter aglycone [37], is mechanistically suggestive for cucurbitacin glucosides but has not yet been demonstrated for this compound class and is identified here as a candidate for future study rather than an established method.

7 Selection of Complementary Fruits for a Multi-Fruit Formulation

7.1 Pomegranate (Punica granatum) as the Primary Complementary Fruit

Pomegranate juice is an extensively documented source of antidiabetic and anticancer polyphenols, principally punicalagin and ellagic acid. These compounds inhibit α-amylase and α-glucosidase, reduce postprandial glycemic response, and improve insulin sensitivity [38,39], with molecular docking work showing punicalagin binding α-glucosidase with affinity exceeding that of the pharmaceutical comparator acarbose [39]. On the anticancer side, punicalagin and ellagic acid induce apoptosis and cell-cycle arrest across multiple cancer cell lines, including hepatoma, leukemia, and cer-

vical cancer models [40,41,42,43]. These mechanisms overlap substantially with those proposed for C. colocynthis, providing a coherent rationale for pairing the two, subject to the drug-interaction caveat discussed in Section 5.6.

7.2 Amla (Phyllanthus emblica) as a Secondary Complementary Fruit

Amla, or Indian gooseberry, is supported by a randomized, double-blind, placebo-controlled crossover trial in healthy adults that reported measurable antioxidant and vascular benefits at 500 mg/day with no observed hepatotoxicity [44]. Separate clinical and animal data document anti-hyperglycemic and lipid-lowering effects in type 2 diabetic patients, with ellagic acid and ascorbic acid shown to inhibit α-glucosidase [45]. Anticancer activity has been reported in cervical and mammary cancer models via G2/M cell-cycle arrest and Bax/Bcl-2 modulation, though this evidence is explicitly characterized in the literature as weak and requiring further study [45,46]. Amla shares the same broad Ayurvedic tradition as C. colocynthis, and its high vitamin C content may additionally help stabilize other polyphenols against oxidative degradation during processing (Section 5.7).

7.3 Jamun (Syzygium cumini) as an Alternative Complementary Fruit

Jamun, or black plum, has a documented antidiabetic history extending over a century [47]. A controlled animal study of a jamun-based drink reported significant reduction in blood glucose in streptozotocin-induced diabetic rats with no adverse renal or pancreatic histology [48], directly relevant to the renal-toxicity concern in Section 5.3. Its anthocyanins (delphinidin, petunidin, malvidin) demonstrate antidiabetic, antioxidant, and anticancer activity, including documented cytotoxicity against MCF-7 breast and HeLa cervical cancer cell lines [49,50]. Evidence for jamun is predominantly preclinical rather than from human clinical trials, and it is proposed here as an alternative rather than a mandatory third component, since additional bioactive fruits compound the unstudied-interaction problem discussed below.

7.4 Non-Bioactive Additions for Taste, Stability, and Overall Quality

To improve palatability and shelf stability without introducing further pharmacological variables, this review recommends restricting non-core additions to ingredients with no meaningful bioactivity or interaction risk at food-use levels: lemon or lime juice, which lowers pH for natural preservation and contributes antioxidant vitamin C; fresh mint, which offsets residual bitterness perception; a small quantity of fresh ginger, which contributes mild antimicrobial shelf stability, noting only a theoretical and dose-dependent interaction with anticoagulant medication at levels far above culinary use [51]; cucumber juice, for dilution and hydration; stevia leaf extract, as a low-glycemic sweetener consistent with the product's diabetic target population; and basil seeds, for texture alone. Restricting these additions to ingredients without independent bioactivity keeps the formulation's toxicological and pharmacokinetic profile tied to

its two functional components, C. colocynthis and pomegranate (and optionally amla or jamun), rather than expanding it further.

8 Limitations

Several limitations constrain the conclusions of this review. First, no published study has evaluated a detoxified C. colocynthis preparation in combination with pomegranate, amla, or jamun; every safety and efficacy figure cited for the individual components must therefore be treated as non-additive until tested directly in combination. Second, every anticancer and antidiabetic finding reviewed here derives from isolated compounds, crude extracts, or animal models rather than from a processed, diluted, juice-blended finished beverage; processing and dilution could reduce potency below any clinically meaningful threshold, and this can only be resolved by testing the finished product directly. Third, batch-to-batch phytochemical variability in a natural product is difficult to eliminate entirely even with analytical verification. Fourth, the regulatory status of a product combining a plant with a history of being withdrawn as unsafe (Section 1) with common fruit juices is ambiguous, particularly if any diabetes- or cancer-related claim is made on packaging.

9 Future Scope

The following research directions follow directly from the gaps identified in this review.

1. Comparative, standardized quantification of cucurbitacin versus phenolic and flavonoid content across candidate processing methods (purification, solvent fractionation, thermal treatment, enzymatic hydrolysis) applied to the same source material.
2. Dose-ranging toxicity studies specific to the low-cucurbitacin, polyphenol-enriched formulation proposed in Section 6, rather than extrapolation from whole-fruit or crude-extract LD50 data.
3. In-vitro confirmation that antidiabetic and anticancer bioactivity is retained after the full FQR standardization sequence, including β-cyclodextrin encapsulation.
4. Feasibility testing of enzymatic glycoside hydrolysis, adapted from citrus naringinase technology, as a possible additional debittering and detoxification route for cucurbitacin glucosides.
5. A dedicated pharmacokinetic interaction study between the C. colocynthis fraction and pomegranate polyphenols, and between the finished beverage and CYP3A4/CYP2C9-metabolized medications.
6. Head-to-head evaluation of amla and jamun as the secondary complementary fruit, including their individual and combined effect on the sensory profile and residual bitterness of the finished beverage.

7. Larger, longer-duration human trials of the standardized combined formulation with systematic hepatic and renal safety monitoring, extending beyond the one- to three-month trials reported for C. colocynthis alone.
8. Stability studies quantifying polyphenol retention across shelf life under the micro-encapsulation and pasteurization conditions proposed for the finished beverage.

10 Conclusion

Citrullus colocynthis is phytochemically rich and pharmacologically promising for antidiabetic and, at a preclinical level, anticancer applications, but its cucurbitacin-driven toxicity profile precludes direct use of raw fruit or unstandardized extracts in a consumable product. This review has mapped each documented side effect to a corresponding mitigation strategy drawn from the existing literature, shown that the toxic and beneficial constituents of the plant are chemically separable, and proposed a standardization protocol together with a rationale for combining the processed fraction with pomegranate and, optionally, amla or jamun, using only non-bioactive ingredients for taste and stability. The central unresolved question identified throughout this review is that no combination of these components has yet been tested together; resolving this is the necessary next step before any efficacy or safety claim could be made for the finished beverage.

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