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Research Article

Development of Sugar-Free Herbal Syrup of *Clerodendrum inerme* Using Stevia for Diabetic Patients

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ABSTRACT

Diabetes mellitus had become a growing global health problem and the limitations of synthetic therapy for a long time related to cost, side effects and adherence challenges have maintained the interest in plant-derived adjuvants. *Clerodendrum inerme* (L.) Gaertn is a shrub used in Ayurveda, Siddha and folk medicine. Pre-clinical investigations show antioxidant, α-amylase and α-glucosidase inhibitory and hypoglycaemic activity. Traditional syrups contain 66% sucrose and are not suitable for diabetics. Stevia (*Stevia rebaudiana* Bertoni) has non-caloric sweetness obtained from steviol glycosides. Stevia has been shown to have antihyperglycemic effects in animal studies. Human studies have reported mixed results. This review integrates the botanical, phytochemical and antidiabetic pharmacological information of *C. inerme*, properties and safety of stevia, and principles of formulation and evaluation of sugar free herbal syrups. Since there has been no published study on a syrup incorporating both *C. inerme* and stevia, the formulation framework here is drawn from adjacent literature, and is advanced as a proposal, rather than a proven product.

INTRODUCTION

Diabetes has become one of the most common chronic metabolic disorders. The IDF Diabetes Atlas (10th edition) forecast 537 million diabetic individuals aged 20 to 79 in 2021, with the figure expected to rise to 643 million by 2030 and 783 million by 2045. India carries much of this burden and the rate of increase in South-east Asia has been more than expected.

Oral hypoglycaemic agents, such as biguanides, sulphonylureas, thiazolidinediones, DPP-4 inhibitors and SGLT2 inhibitors, each have their own risks, including hypoglycaemia, weight gain and gastrointestinal or genitourinary adverse effects. WHO has advocated integration of evidence based traditional medicine in the treatment of diabetes, for which a lot of plants are traditionally used. Liquid dosage forms like syrups are appropriate for elderly patients and those

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who have problems with swallowing. A syrup incorporating sucrose, however, defeats the purpose in a diabetic patient. Thus, replacing sucrose with a natural non-caloric sweetener with its own antidiabetic profile is an attractive formulation strategy.

The ICMR-INDIAB survey of 113,043 adults aged 20 years and above (2008-2020) in India estimated 101 million people (11.4%) affected by diabetes and a further 136 million (15.3%) with prediabetes. The prevalence ranged from 26.4% in Goa to 4.8% in Uttar Pradesh. The prediabetic pool is so vast that the demand for safe, long-standing, adherence-friendly dietary and herbal adjuncts is likely to continue to grow.

Type 2 diabetes is characterized by insulin resistance with progressive β-cell dysfunction and postprandial hyperglycaemia is an early and modifiable aspect. The therapeutic targets are two intestinal enzymes . α-amylase hydrolyzes starch to oligosaccharides and α-glucosidase releases absorbable glucose at the brush border . Inhibited, these enzymes slow the absorption of glucose, which is the mechanism of the drug acarbose. Table 1 summarizes the major drug classes and reasons for patients seeking alternatives or adjuncts.

Table 1: Principal Classes of Oral Antidiabetic Drugs and Their Limitations

Class	Principal action	Common limitations
Biguanides (metformin)	Decreased hepatic glucose production; Improved insulin sensitivity	Gastrointestinal upset; rarely lactic acidosis
Sulfonylureas	Stimulate β-cells insulin release	Hypoglycaemia; weight gain
Thiazolidinediones	PPAR-γ agonists; increase insulin sensitivity	Weight gain; fluid retention
DPP-4 inhibitors	Prolong incretin hormone action	Cost; variable tolerability
SGLT2 inhibitors	Increase urinary glucose excretion	Genitourinary infections; volume loss
α-Glucosidase inhibitors (eg, acarbose)	Slowing down the digestion of carbohydrates in the intestine	Flatulence; abdominal pain

The reason for the proposed syrup is therefore two-fold: a plant whose extracts inhibit carbohydrate-digesting enzymes and reduce oxidative stress delivered in a vehicle adding no sugar load.

2. *Clerodendrum inerme*: The Herbal Component



Figure 2.1: *Clerodendrum inerme*

2.1 Taxonomy and use traditionally

C. inerme (commonly 'garden quinine', 'wild jasmine') is from the Lamiaceae (formerly Verbenaceae). Traditionally used for rheumatic pain, arthritis, skin diseases, wounds, fever, cough and dysentery. *Clerodendrum* is a genus with some 500 species (one estimate) to some 580 species (another estimate) first described by Linnaeus in 1753. The leaf is used in Ayurvedic and Siddha medicines and complete pharmacognostic and physicochemical standards for the leaf have been developed.

2.2 Phytochemistry

C. inerme has over 95 components, including diterpenoids, triterpenoids, steroids, flavonoids, phenolic glycosides, lignans, as well as iridoid and megastigmane glycosides. Of note are

- Neo-clerodane diterpenoids such as 3-epicaryoptin
- Megastigmane glucosides and iridoid glycosides (inerminosides).
- Verbascoside (acteoside), a phenylethanoid glycoside
- The flavone hispidulin, which is quantified alongside total phenolics in leaf extract
- Stigmasterol, studied for antioxidant activity
- Ursolic acid, proposed as a marker compound by HPTLC

A genus-wide review lists 283 compounds and reports anti-inflammatory, antioxidant, antihypertensive, anti-cancer, antimicrobial, hepatoprotective, hypoglycaemic and hypolipidaemic activities across *Clerodendrum* species. A 2022 review of genus diterpenoids and a recent review of *C. trichotomum* gives useful context on extraction and structure activity relationships.

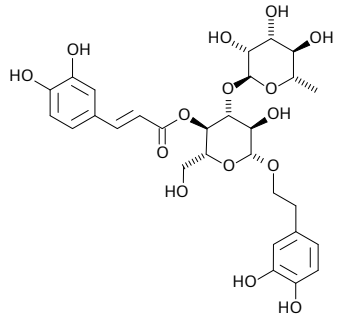


Figure 2.2: Acteoside

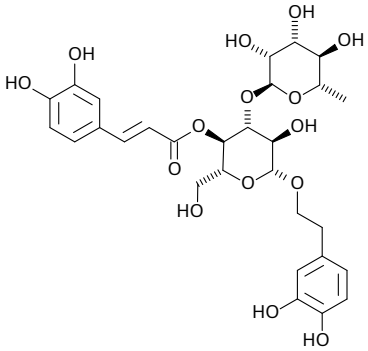


Figure 2.3: Stigmasterol

Table 2 groups the reported constituents by class.

Table 2: Reported Phytoconstituents of *C. inerme* by Class

Class	Examples
Neo-Clerodane diterpenoids	3-Epicaryoptin, cleroinermin and other neo-clerodane diterpenes
Iridoid and megastigmane glycosides	Inerminosides A1, C and D; megastigmane glucosides
Phenylethanoid / phenolic glycosides	Verbascoside (acteoside); a further phenylethanoid glycoside
Flavonoids	Hispidulin; chalcones from the flowers
Triterpenoids and steroids	Lupene-type triterpenic glucoside; 4α-methylsterols; stigmasterol; ursolic acid
Lignans	Lignans from the stems

2.3 General pharmacology

In addition to antidiabetic properties, *C. inerme* extracts have demonstrated antioxidant activity, hepatoprotective activity against CCl4 injury in rats and anti-inflammatory activity by bioassay-guided isolation. The 2024 critical review also lists antimicrobial, anticancer, insecticidal and neuroprotective activities of *C. inerme.*

2.4 Antidiabetic evidence

The evidence supporting antidiabetic activity of *C. inerme* is presented in Table 3.

Table 3: Preclinical Antidiabetic and Related Evidence for *C. inerme*

Study / model	Key finding
Nicotinamide–streptozotocin type 2 diabetic rats, 28 days	Among three plants compared, only the ethanolic extract of *C. inerme* at 400 mg/kg p.o. showed a potent antidiabetic effect
Streptozotocin-induced diabetic mice (343 and 686 mg/kg)	Leaf extract contained flavonoids, alkaloids, tannins, triterpenes and saponins; total phenolics 120.458 mg GAE/g and antioxidant IC_{50} 25.28 µg/mL; authors concluded potent antidiabetic and antioxidant activity
In vitro enzyme inhibition	α-Amylase and α-glucosidase inhibition reported for leaf and root extracts
In vivo / in vitro studies	Antidiabetic activity reported
Network pharmacology (KNApSAcK)	24 compounds identified, with potential activity relevant to diabetes; this is computational and hypothesis-generating

These findings suggest two probable mechanisms: inhibiting carbohydrate digesting enzymes like α-amylase and α-glucosidase, and reducing oxidative stress. Data from additional Clerodendrum species support this concept, although they are outside the scope of this review.

The quantitative enzyme-inhibition results for isolated compounds and extracts from related species of *Clerodendrum* illustrate the extent of activity observed and provide support for the proposed mechanism for *C. inerme* (Table 4). Several of these species share glycoside and phenylpropanoid chemistry with *C. inerme*, but the values below are for other species and should not be mistaken for values for *C. inerme*.

Table 4: In Vitro Carbohydrate-Enzyme Inhibition by Other *Clerodendrum* Species

Species / part	Enzyme	Result (versus acarbose where reported)
C. infortunatum leaf (isolated compounds)	α-Amylase, α-glucosidase	Jionoside D: α-amylase IC_{50} 3.4 ± 0.2 µM versus acarbose 5.9 ± 0.1 µM. Four compounds: α-glucosidase IC_{50} 24.6–96.0 µM versus acarbose 665 ± 42 µM
C. phlomidis root (isolated glycosides)	α-Glucosidase	IC_{50} 1.52 ± 0.14 and 0.78 ± 0.02 mg/mL versus acarbose 0.55 ± 0.03 mg/mL
C. glandulosum leaf (hydromethanolic extract)	α-Glucosidase	IC_{50} 104.11 ± 0.36 µg/mL versus acarbose 232.57 ± 3.28 µg/mL; leaf had the highest phenolic (282.02 mg GAE/g) and flavonoid (276.74 mg QCE/g) content of the parts tested
C. multiflorum stem (methanol and ethyl acetate extracts)	α-Amylase	IC_{50} values of 25.33 and 36.86 reported (units as given in the source)

Across these species, levels of activity were associated with phenolic rich fractions either phenylpropanoid or flavonoid glycosides. This is in line with the high total phenolic content and high DPPH activity reported for *C. inerme* leaf extract. This is also favorable for standardization to the total phenolics or flavonoids of the syrup extract.

2.5 Safety and toxicity

Toxicity of *C. inerme* is reported in some reports and toxicological, preclinical and clinical studies are called for to establish its safety and efficacy. An acute and sub-acute toxicity study has been performed, but lack of human data, and herb–drug interactions with antidiabetic drugs being essentially unstudied, mean for the syrup, that the extract dose would need to be justified via toxicity data and standardised against a marker compound.

3. Stevia as the Sweetener



Figure 3.1: *Stevia rebaudiana* Flower

3.1 Chemistry and sweetness

S. rebaudiana (Asteraceae) generates diterpene glycosides, the most common of which are stevioside and rebaudioside A. Stevioside is 200-300 times sweeter than sucrose, whereas steviol glycosides are 40-300 times sweeter. Rebaudioside A has more appealing taste qualities, while stevioside is associated with bitter aftertaste. This is relevant to a syrup containing a bitter herb, and reviews of stevia as a bio-sweetener have been published. On ingestion, steviol glycosides are hydrolysed to steviol, and the absorption of the intact glycosides is assumed to be very low.

3.2 Antidiabetic and metabolic effects

Reviews on the effects of stevia describe antihyperglycaemic, insulin-mimetic, insulinotropic and glucagonostatic effects, but with few proper randomised controlled trials. Specific findings include:

- Stevioside acts directly on pancreatic β-cells, stimulating insulin production.
- In a test-meal study in type 2 diabetic patients, stevioside reduced the incremental glucose area by 18% and increased the insulinogenic index by about 40% as compared to control.
- A review of the studies in diabetic patients concluded that stevia appears to be safe for diabetics and may have therapeutic effects at pharmacological doses, although few human studies have been carried out.
- The majority of antidiabetic evidence is from in vitro and animal investigations, with few human trials.

Mechanistic and therapeutic reviews have been published.

Human evidence has been summarised in Table 5, and is more mixed than the animal evidence. Long term trials have been performed using 200–1500 mg/day stevioside or 500–1000 mg/day rebaudioside A for periods of 3 days to 2 years.

Table 5: Selected Human Studies of Stevia and Steviol Glycosides in Relation to Glycaemia

Study	Design	Main finding
Gregersen et al. 2004	Acute paired crossover; 12 type 2 diabetic patients; stevioside with a test meal	Incremental glucose AUC reduced by 18% (P = .013); insulinogenic index up about 40% (P < .001); glucagon tended to decrease
Maki et al. 2008	Placebo-controlled RCT of rebaudioside A in adults with type 2 diabetes (16 weeks, n = 122 per a secondary summary)	No effect on blood glucose reported
Stevia vs sucralose as tea sweeteners	RCT in type 2 diabetes patients	No effect on blood glucose, HbA1c, insulin or lipids; stevia a may be an alternative to sucralose
Meta-analysis of RCTs (Nutrients 2019)	Steviol glycosides versus placebo	Significant systolic blood pressure reduction (MD −6.32 mm Hg)
Rebaudioside A crossover trial in T2DM	Placebo-controlled; pharmacokinetics and glucose homeostasis	Authors note chronic-exposure trials showed no glucose lowering and a meta-analysis found non-significant falls in fasting glucose and HbA1c
Roselle–stevia RTD	Healthy volunteers; ISO 26642:2010 glycaemic method, readings every 30 min for 90 min	Stevia version did not raise blood glucose (p > 0.05); the sugar version did (p < 0.05)

Taken together, the strongest and most consistent human conclusion is that stevia consumption does not raise postprandial glucose, and clinically meaningful glucose-lowering benefits have yet to be proven. For the present purpose, therefore, the sweetener should primarily be advocated as a non-glycaemic agent, with the antidiabetic property being an extra.

3.3 Safety and regulatory status

The EFSA's ANS panel determined that steviol glycosides were neither genotoxic nor carcinogenic and defined an acceptable daily dose (ADI) of 4 mg/kg body weight/day, which was consistent with that of JECFA (expressed as steviol equivalents). However, the panel advised that using sweeteners at the maximum recommended doses would result in exceeding the ADI. For the present syrup, which is intended to be taken multiple times a day, the amount of stevia that would be present in a single dose should be calculated according to the ADI.

3.4 Stevia in diabetic formulations

The sweetener has been incorporated into several diabetes-friendly formulations, including

- A comparative study of syrups showed that 1% w/w stevia extract and 5-10% w/w monk fruit extract could be used to make simple syrups comparable to 66.7% w/w sucrose syrups in terms of physicochemical properties.
- A herbal lollipop containing *Costus igneus* and a stevioside jelly.
- A roselle-stevia ready-to-drink formulation in which 0.3% w/v leaves of Stevia did not increase blood glucose in healthy volunteers, unlike the sucrose variant.

4. Syrup as a dosage form for diabetics

4.1 Why to use syrup without sugar?

Most of the syrups contain high concentration of sucrose to obtain the desired consistency and stability due to the combination of osmotic pressure, sweetness and preservation effects. The sucrose is eliminated by substituting three functions: an intense sweetener, a polyol or polymer for viscosity, and a preservative. Sugar-free syrups have been successfully used in traditional medicine. As an example, the Jushanda-Nazla decoction was prepared as sugar and sugar-free syrups and assessed for its physicochemical properties, antimicrobial activity and microbial contamination. The results showed that the preparations met the specifications of ash value, viscosity and specific gravity. However, further studies on stability and the clinical efficacy of sugar-free syrups were recommended.

4.2 Typical formulation components

Table 6: Components of a Sugar-Free Herbal Syrup and Their Roles

Component	Role	Notes from literature
C. inerme leaf extract	Active	Active Extraction with aqueous or hydroalcoholic solvents; standardize to total phenolics/flavonoids or marker
Stevia (Reb A–rich extract preferred)	Sweetener	Keep within ADI; flavour issues from stevioside
Cellulose derivatives (HPMC, CMC) / xanthan gum	Viscosity	Cellulose derivatives have a viscosity similar to that of sucrose syrup
Glycerin / sorbitol	Co-solvent, body	Use cautiously; polyols have some caloric value
Sodium benzoate, parabens	Preservative	Sodium benzoate 0.2% with citric acid used in a sugar-free syrup; 0.05% in a kashaya; benzoate, methyl- and propylparaben compared in a polyherbal syrup
Citric acid / buffer	pH adjustment	Syrup pH commonly kept slightly acidic
Flavour, colour	Palatability	Needed to mask bitterness

Three points follow from the literature. First, the absence of about 66% sucrose allows loss of osmotic preservation, so that the preservative system and the pH are more important and the study of a sugar-free syrup used sodium benzoate at 0.2% plus citric acid. Second, stevia at about 1% w/w was used to produce a stable syrup in a comparative study, but the aftertaste of stevioside means that a Reb A–rich extract, together with flavour and possibly a little polyol, should be screened. Third, aqueous extracts rich in polyphenols can darken or lose phenolics on storage and so amber glass, control of headspace and the addition of an antioxidant such as ascorbic acid should be tested; this is a general formulation point and has not been specifically shown by the studies cited.

4.3 Dose considerations

Stevia. The ADI of 4 mg/kg body weight/day (as steviol equivalents) equates to approximately 240 mg of steviol equivalents per day for a 60 kg adult. This would be approximately 600 mg stevioside or 730 mg rebaudioside A daily, taking into account the molecular weights (approximately 0.40 stevioside and 0.33 rebaudioside A). A 1% w/w syrup would contain roughly 100 mg of glycosides per 10 mL, or about 300 mg per day at three doses, allowing for other dietary intake of stevia. This is an illustrative calculation, dependent upon the purity of the extract and the patient's other intake and the EFSA themselves noted that the ADI could be exceeded at maximum proposed food uses.

Extract. Doses from animals can be converted to an approximate human equivalent dose (HED) by body surface area scaling using Km factors of 3 for mouse, 6 for rat and 37 for human. Table 7 applies this to the two key *C. inerme* antidiabetic studies. These are only starting points for dose-ranging, depending on extraction method and yield, and must be tested against toxicity data.

Table 7: Illustrative Human Equivalent Doses from Animal Studies of *C. inerme*

Source study	Animal dose (mg/kg)	Km ratio	HED (mg/kg)	Per 60 kg adult per day
Ly et al. 2019, mice (low dose) [25]	343	3/37	27.8	about 1.7 g
Ly et al. 2019, mice (high dose) [25]	686	3/37	55.6	about 3.3 g
Bhushan et al. 2015, rats [24]	400	6/37	64.9	about 3.9 g

Grams of dry extract per day is a huge amount to be delivered in a syrup (for instance, 3 doses of 10 mL would require over 50 mg/mL of extract), so extract concentration, dose volume and palatability will probably limit the practical dose. This is thus one of the principal design constraints for the project.

4.4 Preparation outline

The usual procedure is to dry and grind the leaf, make an aqueous extract by maceration or decoction, filter and concentrate, prepare the polymer in hot water and cool, add stevia and

preservative, blend in the extract, adjust pH and volume and fill into amber bottles. More detailed descriptions of the preparation of the syrup are to be found in standard texts.

4.5 Evaluation parameters

Typical quality control tests for herbal syrups are tabulated in Table 8.

Table 8: Suggested Evaluation Parameters for the Finished Syrup

Parameter	Method / instrument	Purpose and reference
Organoleptic	Visual and sensory assessment	Colour, odour, clarity, taste and bitterness masking
pH	Calibrated digital pH meter	Stability and microbial control
Viscosity	Ostwald or Brookfield viscometer	Body and pourability without sucrose
Specific gravity	Specific gravity bottle	Batch consistency
Total phenolics and flavonoids	Folin–Ciocalteu (GAE); aluminium chloride colorimetry (QE)	Standardisation of extract content
Chromatographic fingerprint	TLC / HPTLC against a marker such as ursolic acid	Identity and batch comparison
Microbial limits	Total plate count; yeast and mould	Safety of an aqueous, sugar-free base
Accelerated stability	40 ± 2 °C / 75 ± 5% RH for three months	Shelf-life estimate
Retained bioactivity	In vitro α-amylase / α-glucosidase and DPPH assays	Confirms the syrup still shows the extract's activity

5.Challenges and Gaps

1. **No direct precedent:** No published study of the *C. inerme*–stevia syrup was found and claims are extrapolated.
2. **Standardisation:** *C. inerme* chemistry varies with plant part, season and habitat and a marker such as ursolic acid or total phenolics should be tied to each batch.
3. **Taste:** Both the leaf and stevioside can be bitter and so taste-masking will likely drive formulation optimisation.
4. **Safety**: Reported toxicity of the plant and the stevia ADI both restrict the dose
5. **Deliverable dose:** Doses extrapolated from animal studies are in the gram range per-day which may be greater than what a palatable syrup can deliver (Table 7)
6. **Evidence quality:** Most of the antidiabetic data are from rodent models and assay and clinical trials are required.
7. **Clinical importance of stevia:** Human studies do not consistently indicate glucose reduction, hence the role of stevia should be described as a non-glycemic sweetener.
8. **Drug interaction:** Prescribed antidiabetics can additively cause hypoglycaemia, plausible for both ingredients and unstudied for this combination

6. Future Perspectives

The priorities are standard extracts with validated HPTLC/HPLC methods, dose finding and sub chronic toxicity of the final syrup, head to head comparison with a sucrose based control, enzyme inhibition and in vivo glycaemic studies on the finished formulation and eventually a small clinical study. Network-pharmacology and docking approaches could be helpful to identify the constituents responsible for the activity.

CONCLUSION

C. inerme has pre-clinical evidence of antioxidant, enzyme inhibition and hypoglycaemic activity. Stevia provides non-caloric sweetness which has not been

shown to raise blood glucose in the trials reviewed. Glucose modulating effects seen in mostly animal studies, mixed clinical evidence and an established regulatory safety limit. Using established excipients and evaluation methods it is scientifically sound and technically possible to make a sugar free syrup with them. Its therapeutic efficacy, safety and shelf stability remain to be demonstrated experimentally.

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