

Chaga Human Evidence Program

Proposal for human clinical trials of
Inonotus obliquus (chaga)

A staged, safety-first program to test what chaga actually does in people: oxalate exposure, immune function, glycaemia and lipids, drug interactions, and kidney safety in habitual users.

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Companion document	<i>The True Nutritional Value of Chaga: Evidence Review of Composition, Health Claims, Oxalate Safety and Canadian Regulation</i> (October 2026).
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Executive summary

The companion evidence review concluded that chaga is not a meaningful nutritional food, that it is a real but variable source of bioactive compounds (chiefly β -glucans, phenolics and lanostane triterpenoids), and that every popular health claim rests on cell, animal or uncontrolled human data. The only human trials located in the peer-reviewed literature are two uncontrolled Soviet-era series from 1973 and 1981, and no controlled study designed to assess chaga's safety was found [1]. Memorial Sloan Kettering states that the safety and efficacy of chaga have yet to be evaluated in clinical studies [2]. A live search on 10 October 2026 located no published randomized controlled trial with clinical outcomes.

The best-documented human effect is harm: biopsy-proven oxalate nephropathy after months to years of eating chaga powder [3, 4, 5]. Measured oxalate in commercial powders (2.8–14.2 g/100 g) [4] is about 4- to 70-fold higher than the total oxalate reported in three authenticated sclerotia (about 0.21–0.63 g/100 g) [6, 7]. Nobody knows how much of that oxalate a person actually absorbs from tea, extract or powder.

This proposal therefore designs a **staged program** in which safety and exposure are established before efficacy is tested, and in which each health claim is matched to the outcome a regulator would accept:

Program at a glance

1. **Stage 0 (no participants).** Manufacture and fully characterize one authenticated New Brunswick chaga lot in three formats (tea cut, ground powder, hot-water extract) plus a matched placebo. All doses stay at or below Health Canada's monograph ceiling of 3.6 g dried chaga per day [12].
2. **CHEP-1 — Oxalate and early safety.** A controlled-diet crossover in 42 healthy adults measuring how much 24-hour urinary oxalate rises after tea, extract and powder. This is the gate for everything else.
3. **CHEP-2 — Immune function.** A placebo-controlled trial in 238 adults aged 50–64 using influenza-vaccine antibody response, the type of functional outcome EFSA accepts for immune claims [23].
4. **CHEP-3 — Glycaemia and lipids.** A 16-week placebo-controlled trial in 152 adults with prediabetes or diet-treated type 2 diabetes, primary endpoint A1C, key secondary LDL cholesterol.
5. **CHEP-4A and CHEP-4B — Drug interactions.** A warfarin pharmacokinetic and platelet-function crossover (20 healthy adults) modelled on an established herb-warfarin design [26], and a CGM-monitored hypoglycaemia crossover in 30 adults taking metformin and/or a sulfonylurea.
6. **CHEP-5 — Habitual users.** A 12-month observational kidney-safety cohort of 240 powder users, tea drinkers and non-users. This answers the long-duration, high-dose question that a randomized trial cannot ethically answer.

Two claims are deliberately not put to an efficacy trial now. General nutritional value is a compositional question answered in Stage 0, not a clinical one. Anticancer efficacy is deferred until CHEP-1 shows whether chaga's triterpenoids even reach the bloodstream at permitted doses; chaga must never be tested in a way that diverts people from effective cancer care.

Approximately 722 participants would be randomized or enrolled across six studies over about 42 months (planning estimate). Every study has a pre-specified decision rule, so that a null or harmful result ends a claim rather than being reinterpreted.

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1 Background and rationale

1.1 What the evidence review established

- **Nutrition.** Dried chaga is roughly 2–3% protein, under 3% fat, 10–15% ash and about two-thirds crude fibre and lignin. A 2–5 g serving supplies a few kilocalories. Minerals are present but transfer to tea has not been measured well.
- **Bioactives.** Authenticated wild chaga contained 5.7–11.9% β -glucan by the Megazyme K-YBGL assay and under 2% α -glucan, whereas mycelium-on-grain products contained 1.0–6.9% β -glucan and 33–68% α -glucan, largely from the grain substrate [8]. Most authors of that study are employed by a chaga supplier, which they disclose.
- **Claims.** Antioxidant, immune, anti-inflammatory, glucose, cholesterol, anticancer and gut claims are supported only by in vitro and animal work, plus two uncontrolled human series from 1973 (psoriasis, $n = 50$) and 1981 (peptic ulcer, $n = 58$) [1].
- **Interactions.** Chaga extract inhibited platelet aggregation in a mouse model and showed additive glucose-lowering effects in vitro; Memorial Sloan Kettering describes the clinical relevance of both as unknown [2]. No human interaction study exists.
- **Other signals.** British Columbia's poison centre received five reports (2014–2018) possibly linked to commercial chaga tea, including hepatitis, renal failure, bradycardia and syncope; causality was circumstantial because no product was available for testing [11].

1.2 The kidney signal

Table 1 summarizes the published biopsy-confirmed cases. All involved *eating powder* daily for months to years. One patient began at 3 g/day, below the Health Canada ceiling, for four years before increasing to 9 g/day [4].

Table 1: Published biopsy-confirmed chaga-associated oxalate nephropathy (verified 10 October 2026).

Report	Patient	Exposure	Outcome
Kikuchi et al. 2014, <i>Clin Nephrol</i> [3]	Woman, 72, liver cancer	4–5 teaspoons of powder daily for 6 months [2]	Haemodialysis; renal function did not recover
Lee et al. 2020, <i>J Korean Med Sci</i> [4]	Man, 49, atopic dermatitis	Powder 3 g/day for 4 years, then 9 g/day for about 1 year; estimated oxalate intake 420–1,260 mg/day	End-stage renal disease; maintenance haemodialysis at 18 months
Kwon et al. 2022, <i>Medicine</i> [5]	Man, 69	Powder 10–15 g/day plus vitamin C 500 mg/day for about 3 months	Acute oxalate nephropathy with minimal change disease; recovered after haemodialysis and steroids

1.3 Why the oxalate dose is unknown

Published oxalate values disagree by more than an order of magnitude, and none measures what a person absorbs. Table 2 converts them to a 3.6 g daily dose. The absorbed fraction uses the 5–15% range reported for dietary oxalate in healthy people [9]; it is a planning approximation, because chaga's oxalate may be more or less bioavailable than food oxalate. CHEP-1 replaces these estimates with measurements.

Table 2: Planning estimates of oxalate exposure at the Health Canada ceiling of 3.6 g dried chaga per day.

Source of oxalate value	Reported content	Ingested at 3.6 g/day	Absorbed if 5–15%
Three commercial powders (Korea/Japan) [4]	2.8–14.2 g/100 g total	101–511 mg	≈5–77 mg/day
Three authenticated sclerotia (Russia, Finland, Thailand) [6, 7]	206–625 mg/100 g total	7.4–22.5 mg	≈0.4–3.4 mg/day
Same sclerotia, hot-water-soluble fraction [6, 7]	171–534 mg/100 g	6.2–19.2 mg	≈0.3–2.9 mg/day

For orientation, hyperoxaluria is commonly defined as 24-hour urinary oxalate of 40 mg/day or more, with some publications using 45 mg/day [10]. Dietary oxalate contributes roughly a quarter to a half of urinary oxalate in healthy people on controlled diets, and the share rises when dietary calcium is low [9].

1.4 Canadian regulatory context

- **Monograph ceiling.** Health Canada's *Mushrooms* monograph (25 October 2024) permits chaga as dry powder, aqueous extract (including decoctions and infusions) and ethanolic extract, each not to exceed 3.6 g of dried material per day for adults. Permitted claims are “source of antioxidants” and, for non-ethanolic preparations only, “source of fungal polysaccharides with immunomodulating properties” [12].
- **Clinical trials.** Phase I–III trials of natural health products (NHPs) must be authorized by Health Canada's Natural and Non-prescription Health Products Directorate (NNHPD) under Part 4 of the *Natural Health Products Regulations*; satisfactory applications receive a Notice of Authorization [13, 16]. Phase IV trials within approved conditions of use, and observational studies, do not require Health Canada authorization but still need research ethics board (REB) approval [14].
- **Food status.** A 2018 BC Centre for Disease Control risk assessment reported that Health Canada considered chaga a novel food, so chaga teas sold as foods required a pre-market assessment [11]. This determination should be reconfirmed with Health Canada.

1.5 Design principles that follow

Five rules for the whole program

1. **Safety and exposure before efficacy.** No efficacy trial starts until CHEP-1 shows how much oxalate the efficacy product delivers.
2. **One characterized product.** Every study uses product from the same authenticated, assayed lot, so results are attributable and reproducible.
3. **Stay inside the monograph.** No arm exceeds 3.6 g dried chaga equivalent per day. The program does not test whether higher doses are safe.
4. **Outcomes a regulator would accept.** Biomarkers such as natural killer cell activity or antioxidant capacity are secondary; functional or clinical outcomes are primary.
5. **Not every claim deserves a trial.** Composition questions are answered in the laboratory; claims with no human exposure data are deferred.

2 Program objectives and claim-to-study map

The program's overall question is: *at doses Canadians are permitted to take, what does chaga measurably do to people, and at what cost to their kidneys?* Table 3 maps each claim from the evidence review to the study that tests it.

Table 3: Claim-to-study map.

Claim	Study	Outcome that would count as evidence	Role
Oxalate safety	CHEP-1, CHEP-5	24-h urinary oxalate, eGFR, crystalluria	Primary (both)
Immune support	CHEP-2	Influenza-vaccine haemagglutination-inhibition (HAI) titres	Primary
Blood glucose	CHEP-3	Change in A1C over 16 weeks	Primary
Cholesterol	CHEP-3	Change in LDL-C	Key secondary
Anti-inflammatory	CHEP-2, CHEP-3	hs-CRP, IL-6	Secondary
Antioxidant	CHEP-2, CHEP-3	Urinary F2-isoprostanes	Secondary
Gut health	CHEP-2, CHEP-3	Faecal microbiome, short-chain fatty acids	Exploratory
Anticoagulant / antiplatelet interaction	CHEP-4A	Warfarin INR AUC, S-/R-warfarin, platelet aggregation	Primary
Hypoglycaemic interaction	CHEP-4B	Time below 3.9 mmol/L on CGM	Primary
Triterpenoid bioavailability	CHEP-1	Plasma inotodiol, betulin, betulinic acid	Exploratory (gates anticancer work)
General nutrition	Stage 0	Full compositional panel of trial lot	Analytical, no trial
Anticancer	—	Deferred (Section 5)	Not tested now

3 Cross-cutting methods

3.1 Stage 0: investigational products

Source and authentication

A single harvest of wild *I. obliquus* sclerotium from *Betula papyrifera* in New Brunswick, with documented location, date, host tree and harvester, is milled, homogenized and divided into three formats. Securing the full program requirement as one lot matters: Memorial Sloan Kettering notes that wild chaga is becoming depleted [2], and composition differs with host tree, geography and conk layer. Identity is confirmed by macroscopic and microscopic examination, DNA sequencing of a voucher, and a chromatographic fingerprint; a voucher is deposited with an herbarium.

Formats

- **T — tea cut:** 2–5 mm pieces in pre-weighed 3.6 g sachets, used only in CHEP-1.
- **P — ground powder:** whole sclerotium, finely ground, 3.6 g pre-weighed doses, used only in CHEP-1 for one week.
- **E — hot-water extract:** spray-dried aqueous extract in opaque capsules, dose labelled as dried-chaga equivalent (3.6 g/day) with the drug-to-extract ratio stated. This is the efficacy product for CHEP-2–CHEP-4. A water-only extract is chosen because Health Canada permits the polysaccharide claim only for non-ethanolic preparations [12].
- **Placebo:** identical opaque capsules of microcrystalline cellulose with caramel colour. Health Canada requires a quantitative list of all placebo components [14].

Release specification

Table 4: Proposed release specification. Numerical limits marked * are proposals for the analytical team to finalize.

Attribute	Method	Acceptance
Identity	Morphology; DNA sequence of voucher; chromatographic fingerprint	Conforms to authenticated reference
β -glucan and α -glucan	Megazyme K-YBGL (the assay used by Windsor et al. [8])	Report value; α -glucan < 2%* (absence of grain substrate)
Total and soluble oxalate	Validated chromatographic or enzymatic assay on product and on prepared tea	Report value per dose; this is a required input to CHEP-1
Triterpenoids	HPLC: inotodiol, lanosterol, betulin, betulinic acid	Report value (marker profile)
Total phenolics	Folin-Ciocalteu (non-specific; descriptive only)	Report value
Elemental impurities	ICP-MS	Below Health Canada NHP limits: total As < 10, inorganic As < 2.1, Cd < 6, Pb < 10, total Hg < 20 µg/day [17]
Microbial quality	Total aerobic count, yeasts and moulds, pathogens	Within NHP quality limits [17]
Nutrition panel	Proximate analysis, minerals, vitamins, amino acids, fatty acids	Report value (answers the nutrition claim analytically)
Stability	Real-time and accelerated, all formats	Specifications met for trial duration plus 6 months

Gate A: three consecutive batches of each format meet specification, and the extract's oxalate content per dose is known before any participant is dosed.

3.2 Common eligibility and kidney-safety exclusions

Unless a study specifies otherwise, participants are adults aged 19 or older (the age of majority in New Brunswick) and the following are excluded:

- eGFR below 60 mL/min/1.73 m² by the 2021 race-free CKD-EPI creatinine-cystatin C equation [27]; any history of kidney stones; baseline 24-h urinary oxalate $\geq$ 40 mg/day [10];
- conditions that raise oxalate absorption: inflammatory bowel disease, chronic diarrhoea, bariatric surgery, short bowel or pancreatic insufficiency;
- supplemental vitamin C that cannot be stopped two weeks before and throughout the study (one case involved 500 mg/day [5]);
- anticoagulant, antiplatelet, glucose-lowering or immunosuppressive drugs, except where a study is designed to test them;
- resting heart rate below 50 beats/min or a history of syncope (because of the BC bradycardia reports [11]); ALT or AST above twice the upper limit of normal;

- pregnancy, breastfeeding or planned pregnancy; known mushroom allergy; surgery planned during the study or within two weeks after;
- chaga or other medicinal-mushroom use in the previous four weeks.

3.3 Common safety monitoring and stopping rules

Individual stopping rules (proposed; to be ratified by the safety committee and nephrology advisor)

- Acute kidney injury by KDIGO serum-creatinine criteria (rise of $\geq 26.5 \mu\text{mol/L}$ within 48 h, or ≥ 1.5 times baseline within 7 days) [28]: stop product permanently and refer to nephrology.
- Confirmed eGFR decline of 25% or more from baseline: stop product.
- 24-h urinary oxalate $\geq 80 \text{ mg/day}$ (twice the hyperoxaluria threshold), or $\geq 40 \text{ mg/day}$ with calcium-oxalate crystalluria: stop that product.
- ALT or AST above three times the upper limit of normal: stop product and investigate.
- Symptomatic bradycardia, resting heart rate below 45 beats/min, or syncope: stop product, ECG and clinical review.
- Severe hypoglycaemia needing assistance, or repeated glucose below 3.0 mmol/L (CHEP-4B): stop and review medication.

Serious unexpected adverse reactions are reported to NNHPD within 7 days if fatal or life-threatening and within 15 days otherwise, with a full report within 8 days of a 7-day notice [14]. An independent Data and Safety Monitoring Board (DSMB) with a nephrologist, an endocrinologist and a biostatistician oversees CHEP-2, CHEP-3 and CHEP-4B; a safety review committee covers CHEP-1 and CHEP-4A.

3.4 Randomization, blinding and analysis

Allocation sequences are generated by an independent statistician using permuted blocks of variable size, stratified as specified per study, and concealed through a web-based system. Efficacy studies are double-blind with opaque capsules; tea is used only in the open-label CHEP-1, whose endpoints are laboratory measurements made by staff blinded to period. At the end of each blinded study, participants and assessors guess allocation so that blinding can be assessed. Primary analyses follow the intention-to-treat principle with pre-specified handling of missing data, set out in a statistical analysis plan finalized before database lock. All variance inputs for sample sizes are *assumptions* (Appendix A) and should be checked against a blinded internal pilot where the design allows.

4 Study protocols

4.1 CHEP-1: Oxalate exposure, bioavailability and early safety

Question	How much does 24-hour urinary oxalate rise after a week of chaga tea, hot-water extract or eaten powder at 3.6 g/day, and are triterpenoids detectable in blood?
Design	Randomized, open-label, laboratory-blinded crossover. Everyone completes a no-chaga baseline period, then the three products in one of six Williams-design sequences.
Population	Healthy adults 19–65, both sexes, meeting the common exclusions.
Interventions	T: tea from 3.6 g cut sclerotium daily. E: extract capsules, 3.6 g dried equivalent daily. P: 3.6 g ground powder daily, eaten. Each period lasts 7 days, separated by washouts of at least 14 days.
Controlled diet	Days 4–7 of each period on a provided diet with fixed oxalate, about 1,000 mg calcium and fixed vitamin C, and at least 2 L fluid per day.
Primary endpoint	Mean 24-h urinary oxalate (days 6 and 7) in each product period minus the baseline period.
Sample size	42 randomized (7 per sequence), 35 evaluable.
Duration	About 9 weeks per participant.

Rationale for including powder

Every kidney-injury case involved eaten powder, and the monograph permits dry powder up to 3.6 g/day [12]. A single week at that dose, under daily monitoring and with kidney-risk exclusions, is a small and bounded exposure, while the information is decisive for consumer advice. Longer powder exposure is studied only observationally (CHEP-5).

Tea preparation

Each sachet is steeped in 500 mL of water just off the boil and held at or above 80 °C for 60 minutes, then drunk over the day. An aliquot of every participant's tea from each period is frozen and assayed, so the analysis uses the oxalate actually delivered rather than the label value.

Hypotheses

- H1 (powder): urinary oxalate rises compared with baseline (superiority, two-sided $\alpha = 0.05$).
- H2 and H3 (tea, extract): each is equivalent to baseline within ± 5 mg/day (two one-sided tests, $\alpha = 0.025$ per side per product after Bonferroni correction). The 5 mg/day margin is one-eighth of the 40 mg/day hyperoxaluria threshold; it is a clinical judgement to be confirmed with nephrology input.

Endpoints

- **Secondary:** fractional excretion of the ingested oxalate dose; plasma oxalate; calcium-oxalate supersaturation; crystalluria on fresh urine microscopy; serum creatinine and cystatin C with eGFR [27]; urine albumin-to-creatinine ratio.
- **Exploratory pharmacokinetics:** plasma inotodiol, lanosterol, betulin and betulinic acid by LC-MS/MS before dosing and 1, 2, 4, 8 and 24 hours after the first dose of each product, plus a day-7 trough. Whether these compounds are detectable at all decides whether anticancer research is worth pursuing (Section 5).
- **Safety:** adverse events; liver enzymes; ECG, heart rate and blood pressure; full blood count; INR at baseline and end of the extract period.

Sample size and analysis

Assuming a within-person standard deviation of the difference of 7 mg/day and a true tea or extract effect of 1 mg/day, 35 evaluable participants give 90.6% power for each equivalence test (Monte Carlo, 40,000 simulations). With 15% attrition, 42 are randomized. At this size the 95% confidence interval around any product's increment has a half-width of about 2.4 mg/day. Analysis uses a linear mixed model with condition, period and sequence as fixed effects and participant as a random effect.

Gate B (decision after CHEP-1)

- **Proceed with extract E:** upper 95% confidence limit of the extract increment below 5 mg/day, and no participant meets an acute-kidney-injury criterion.
- **Reformulate first:** extract increment of 5 mg/day or more. Reduce oxalate in the process (or co-formulate with calcium) and repeat a shortened CHEP-1 before any efficacy study.
- **Consumer advice:** the powder result is published regardless and informs labelling and retail guidance.

4.2 CHEP-2: Immune function (influenza-vaccine response)

Question	Does daily chaga extract improve antibody response to seasonal influenza vaccination?
Design	Randomized 1:1, double-blind, placebo-controlled, parallel group. Stratified by age band (50–57, 58–64) and by prior-season vaccination.
Population	Adults 50–64 eligible for, and willing to receive, the same publicly funded seasonal inactivated influenza vaccine product recommended for their age by the National Advisory Committee on Immunization (one product and lot per season).
Intervention	Extract E, 3.6 g dried equivalent daily, or matched placebo, for 28 days before vaccination and 28 days after (8 weeks).
Primary endpoint	Day-28 HAI geometric mean titre (GMT) ratio, chaga versus placebo; A(H3N2) strain tested first, then A(H1N1)pdm09 (hierarchical).
Sample size	238 randomized (119 per arm), 214 evaluable.
Duration	8 weeks per participant; enrolment confined to the autumn vaccination window.

Why vaccine response

Generic “immune support” is not a testable outcome. EFSA’s guidance treats changes in immune markers such as natural killer cell activity or cytokines as supportive evidence that cannot substantiate an immune claim on its own, and it names higher responses to vaccination and clinical infection outcomes as appropriate outcome variables [23]. Infection outcomes would need several thousand participants, so vaccine response is the efficient functional endpoint. Adults aged 50–64 are chosen because responses are lower than in young adults but the group can still receive a uniform vaccine product.

Endpoints

- **Secondary:** seroconversion (pre-vaccination titre below 1:10 and post-vaccination titre of at least 1:40, or a fourfold or greater rise) and the proportion reaching a titre of at least 1:40, using the definitions in FDA’s influenza vaccine guidance [24]; B-strain GMT.
- **Mechanistic and other claims:** natural killer cell cytotoxicity, cytokines (IL-6, TNF- α) and

hs-CRP (anti-inflammatory claim); urinary F2-isoprostanes (antioxidant claim); faecal microbiome and short-chain fatty acids (gut claim).

- **Exploratory:** self-reported respiratory infections over the season (underpowered; descriptive only).
- **Safety:** adverse events, 24-h urinary oxalate at baseline and week 8, eGFR, liver enzymes, heart rate.

Sample size and analysis

Assuming a standard deviation of 1.75 log₂ units in post-vaccination titre, a correlation of 0.5 with baseline titre (analysis of covariance), and a target GMT ratio of 1.5, 107 evaluable participants per arm give 80% power at two-sided $\alpha = 0.05$. Allowing 10% attrition gives 119 per arm. The primary analysis is analysis of covariance on log₂ day-28 titre adjusted for log₂ day-0 titre and stratification factors.

Decision rule: a positive primary result supports a confirmatory multi-season trial; a null result is published and the immune claim is not pursued further with this product.

4.3 CHEP-3: Glycaemia and lipids

Question	Does daily chaga extract lower A1C or LDL cholesterol in people with dysglycaemia?
Design	Randomized 1:1, double-blind, placebo-controlled, parallel group, after a 2-week single-blind placebo run-in to confirm adherence. Stratified by baseline A1C (below 6.5% or 6.5% and above) and sex.
Population	Adults 30–75 with A1C 6.0–7.5% not taking glucose-lowering medication: prediabetes by Diabetes Canada criteria (A1C 6.0–6.4%) or diet-treated type 2 diabetes (A1C $\geq 6.5\%$) [25].
Intervention	Extract E, 3.6 g dried equivalent daily, or placebo, for 16 weeks, with identical standardized lifestyle advice in both arms; 4-week off-product follow-up.
Primary endpoint	Change in A1C from baseline to week 16.
Key secondary	Change in LDL-C (tested after A1C in a fixed sequence).
Sample size	152 randomized (76 per arm), 128 evaluable.

Endpoints

- **Secondary:** fasting plasma glucose; 2-hour glucose on a 75 g oral glucose tolerance test; fasting insulin and HOMA-IR; 14-day blinded continuous glucose monitoring (mean glucose, time in range 3.9–10.0 mmol/L) at baseline and weeks 14–16; non-HDL cholesterol, triglycerides and apolipoprotein B; hs-CRP and IL-6; urinary F2-isoprostanes; faecal microbiome (exploratory).
- **Safety:** hypoglycaemia symptoms and CGM lows; 24-h urinary oxalate at baseline, week 8 and week 16; eGFR; liver enzymes; ECG.

Sample size and analysis

Assuming a standard deviation of A1C change of 0.5 percentage points and a minimal important difference of 0.25 points, 64 evaluable participants per arm give 80% power at two-sided $\alpha = 0.05$; with 15% attrition, 76 per arm are randomized. At this size, the minimal detectable LDL-C difference is about 0.25 mmol/L (assuming a standard deviation of change of 0.5 mmol/L). Analysis is analysis of covariance on week-16 values adjusted for baseline and strata.

Decision rule: an A1C reduction of 0.25 points or more with a confidence interval excluding zero supports a confirmatory trial, which would also need to address the interaction findings from CHEP-4B. A null result on both A1C and LDL-C retires both claims for this product.

4.4 CHEP-4A: Warfarin and platelet-function interaction

Question	Does chaga extract change warfarin's anticoagulant effect or platelet function in people?
Design	Randomized, open-label, two-period crossover modelled on Jiang et al. (2004), who studied St John's wort and ginseng with a single 25 mg warfarin dose in 12 healthy men [26].
Population	Healthy adults 19–55, both sexes (women not pregnant and using effective contraception), normal coagulation, no bleeding history; CYP2C9/VKORC1 genotyped and predicted poor metabolizers excluded for safety.
Interventions	Period A: single oral warfarin 25 mg alone. Period B: extract E (3.6 g dried equivalent daily) for 14 days before and 7 days after a single 25 mg warfarin dose. Warfarin doses separated by at least 14 days. Vitamin K intake standardized.
Primary endpoint	Geometric mean ratio (B/A) of INR area under the curve from 0 to 168 hours, with 90% confidence interval.
Sample size	20 randomized, 16 evaluable.

Endpoints and interpretation

Secondary endpoints are S- and R-warfarin AUC and C_{max} , and platelet aggregation by light-transmission aggregometry (ADP, collagen, arachidonic acid) measured before chaga and after 14 days of chaga but before warfarin. This isolates any antiplatelet effect of chaga itself, which matters for people taking aspirin, clopidogrel or direct oral anticoagulants. No clinically relevant interaction is concluded if the 90% confidence interval of the INR AUC ratio lies within 0.80–1.25. Assuming a within-subject coefficient of variation of 15% and a true ratio of 0.95, 16 evaluable participants give 92.6% power (Monte Carlo); 20 are randomized to allow for 20% attrition.

Decision rule: a ratio outside the bounds, or a meaningful fall in platelet aggregation, leads to an exclusion in all later studies and a labelling warning. If platelet function changes, a dedicated study with a direct oral anticoagulant follows.

4.5 CHEP-4B: Glucose-lowering medication interaction

Question	Does chaga extract increase hypoglycaemia in people taking metformin and/or a sulfonylurea?
Design	Randomized, double-blind, placebo-controlled, two-period crossover (4 weeks each, 2-week washout), stratified by sulfonylurea use.
Population	Adults with type 2 diabetes, A1C 6.5–9.0%, on a stable dose of metformin and/or a sulfonylurea for at least 3 months; insulin users excluded at this stage.
Monitoring	Real-time continuous glucose monitoring throughout with low-glucose alerts; safety takes precedence over blinding of glucose values.
Primary endpoint	Difference in percentage of time below 3.9 mmol/L during weeks 2–4 of each period.
Sample size	30 randomized, 25 evaluable (precision-based).

Secondary endpoints are time below 3.0 mmol/L, symptomatic hypoglycaemia events, mean glucose and time in range, with oxalate and kidney safety as in other studies. Assuming a stan-

dard deviation of the within-person difference of 2.5 percentage points, 25 evaluable participants estimate the difference with a 95% confidence interval half-width of about 1.0 percentage point. Because sulfonylureas carry the higher hypoglycaemia risk, results are reported separately for that stratum. This study informs labelling and clinical advice; it does not test efficacy.

4.6 CHEP-5: Kidney safety in habitual chaga users (observational cohort)

Question	Do people who already consume chaga, especially as eaten powder, have higher urinary oxalate or faster kidney-function decline than non-users?
Design	Prospective observational cohort, 12 months, with a baseline cross-sectional comparison. No product is given.
Groups	(a) habitual powder or capsule users (≥ 1 g/day for ≥ 3 months); (b) habitual tea drinkers (≥ 3 cups/week for ≥ 3 months); (c) non-users matched on age, sex and eGFR band. 80 per group.
Exposure	Structured intake questionnaire plus laboratory assay of each participant's own product for total and soluble oxalate, giving an individual oxalate-dose estimate.
Primary endpoint	Baseline 24-h urinary oxalate by group.
Sample size	240 enrolled.

Secondary endpoints are 12-month eGFR change, albumin-to-creatinine ratio, crystalluria, kidney-stone events, plasma oxalate, liver enzymes, and dose-response against estimated oxalate intake. Assuming a between-person standard deviation of 12 mg/day, 49 per group detect an 8 mg/day difference with 90% power; inflating by 1.25 for confounder adjustment gives 62, and enrolling 80 per group allows for 12-month attrition. eGFR slope over 12 months is descriptive.

Because this is observational, Health Canada authorization is not required, although REB approval is [14]; it can therefore start early and run in parallel. Participants whose results show hyperoxaluria or reduced kidney function are told, with their consent their physician is told, and they are advised to stop chaga. That duty overrides the cohort's integrity, and the analysis accounts for it. An optional descriptive sub-cohort of people with cancer who use chaga may be recruited through oncology clinics with their oncologists' agreement.

5 Claims deliberately not tested now

- **General nutritional value.** Whether a serving supplies meaningful nutrients is answered by the Stage 0 compositional panel on the trial lot. A feeding trial would add nothing and would expose people for no benefit.
- **Anticancer effects.** No efficacy trial is proposed. A future oncology study would be justified only if: (1) CHEP-1 shows that triterpenoids such as inotodiol or betulinic acid reach measurable plasma concentrations at permitted doses; (2) a defined extract has preclinical data translatable to that exposure; (3) the design is led by oncologists as an add-on to standard care, never a replacement; and (4) interactions with the relevant anticancer drugs have been screened. One of the three kidney-injury cases occurred in a woman with liver cancer [3], which underlines why people with cancer need protection rather than encouragement.
- **Broad “immune-boosting” wording.** EFSA regards a claim to strengthen the immune system as insufficiently defined [23]. CHEP-2 tests one specific immune function instead.
- **Antioxidant activity as a health benefit.** Health Canada's “source of antioxidants” wording is compositional. Oxidative-stress biomarkers are secondary outcomes only.

6 Decision gates and program flow

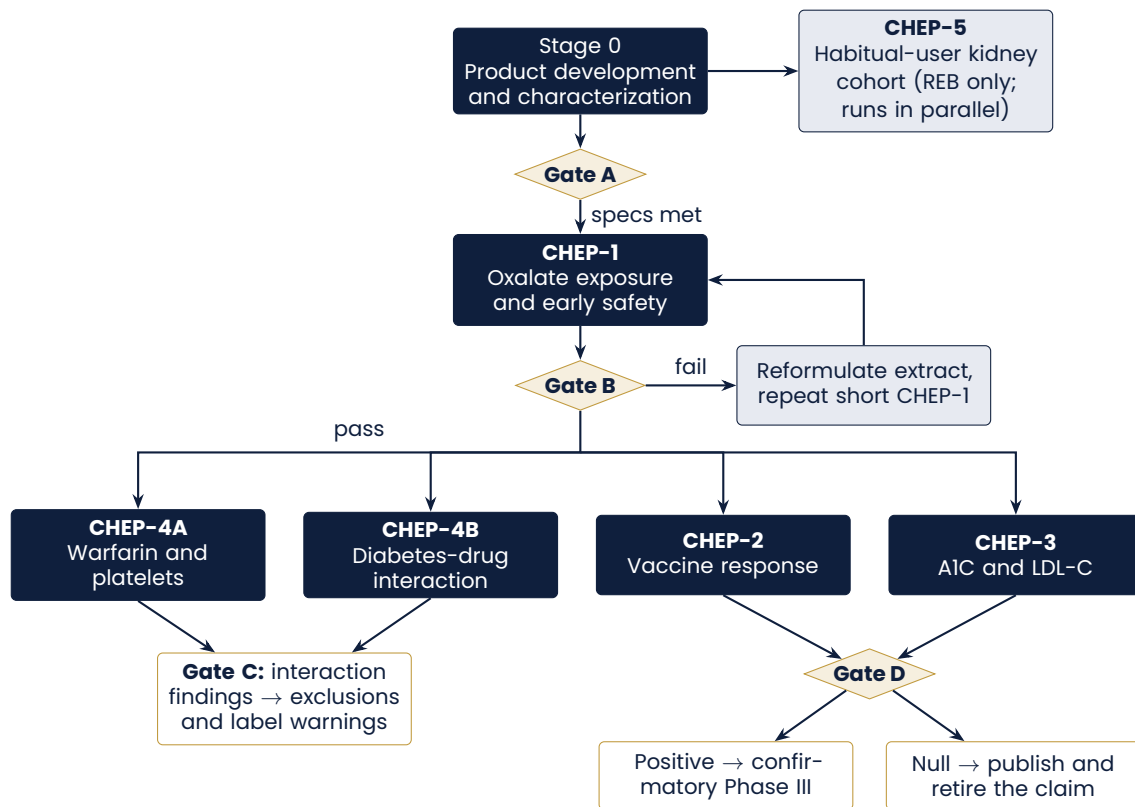


Figure 1: Program flow. Gate C (the interaction results) feeds exclusions and labelling but does not stop the efficacy studies. Gate D applies separately to each efficacy claim.

Table 5: Decision gates.

Gate	When	Go criterion	If not met
A	End of Stage 0	Three consecutive batches per format meet specification; oxalate per dose known	Re-source or re-process; no dosing
B	End of CHEP-1	Extract increment in urinary oxalate: upper 95% limit below 5 mg/day; no acute kidney injury	Reformulate and repeat a shortened CHEP-1
C	End of CHEP-4A/CHEP-4B	INR AUC ratio within 0.80–1.25; no excess time below range	Add exclusions and warnings; consider follow-up studies
D	End of CHEP-2/CHEP-3	Primary endpoint meets pre-specified effect with confidence interval excluding zero	Publish null result; retire claim for this product

7 Governance, ethics and regulatory pathway

7.1 Roles

Landry Industries Inc. would act as sponsor or co-sponsor with an academic or health-authority partner. Because the program needs licensed clinicians, each site requires a Qualified Investigator, documented on Health Canada's Qualified Investigator Undertaking Form [13]. Candidate partners include New Brunswick universities and regional health authorities with REBs and clinical research units; none has been approached, and none is implied to have agreed.

7.2 Ethics

- All studies are reviewed by an REB operating under the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (TCPS 2, 2022) [20].
- Consent materials are provided in English and French.
- If chaga is sourced from, or traditional knowledge is drawn from, First Nations communities, or if studies recruit within those communities, engagement follows TCPS 2's provisions for research involving First Nations, Inuit and Métis peoples [20].
- Payments reimburse time and expenses only and are not structured to induce people to continue a product against medical advice.

7.3 Health Canada

- **Authorization.** CHEP-1–CHEP-4 require a Clinical Trial Application to NNHPD, including the protocol, the Protocol Synopsis and Evaluation Review Template, informed consent documents, REB approvals and site and investigator forms. A Notice of Authorization must be received before the trial starts [13, 15]. Whether any study could be treated as Phase IV should be asked of NNHPD, but because the trial products are not licensed, a full application should be planned. CHEP-5 is observational and needs REB approval only [14].
- **Changes and records.** Substituting a placebo requires an amendment (CTA-A); trial records must be kept for 15 years [14].
- **Good clinical practice.** NNHPD's guidance requires ICH E6 compliance [14]. Health Canada implemented ICH E6(R3) effective 1 April 2026 [18]; that notice is framed for drug trials, so its application to NHP trials should be confirmed with NNHPD.
- **Regulatory watch.** Draft regulations modernizing drug clinical trials were pre-published in December 2025; the commentary located does not say whether NHP trials are in scope [19]. Requirements should be rechecked before submission.

7.4 Transparency and conflicts of interest

- Each trial is registered on ClinicalTrials.gov before the first participant is enrolled. Protocols and statistical analysis plans are also deposited with a DOI (for example on Zenodo) before database lock.
- Protocols follow SPIRIT 2025 (34 items) [21] and reports follow CONSORT 2025 (30 items) [22]. Results are published whatever they show.
- The sponsor declares any commercial interest in chaga. Randomization, the statistical analysis and the DSMB are independent of the sponsor, and investigators keep the right to publish. The supplier-authored glucan study [8] illustrates why this separation matters for credibility.

8 Timeline

The schedule below is a planning estimate assuming a January 2027 start. CHEP-2 must enrol in the autumn vaccination window, so it is placed in months 21-27 (September 2028 to March 2029); missing the window costs a year.

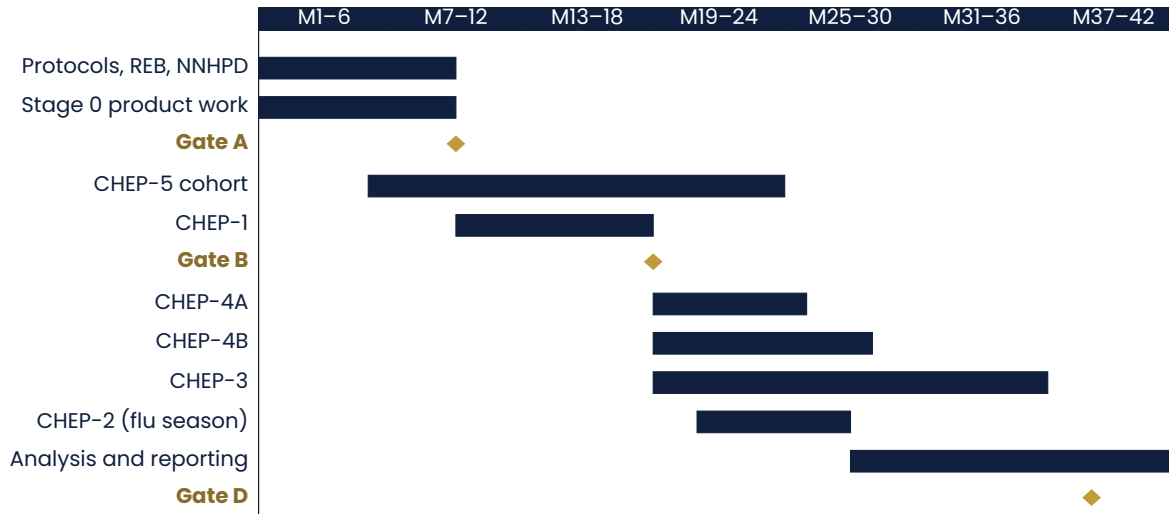


Figure 2: Indicative program timeline in months.

9 Resources required

Costs have not been estimated in this draft; they should be built up with candidate sites and laboratories. The program needs:

- a Qualified Investigator and research coordinator at each site, with nephrology and endocrinology advisors;
- an independent biostatistician and data manager, a DSMB and a safety review committee;
- an NHP manufacturer able to produce the extract and placebo under appropriate good manufacturing practices;
- an accredited analytical laboratory for product release, oxalate in product and tea, and the participant-product assays in CHEP-5;
- a metabolic kitchen able to deliver controlled diets for CHEP-1;
- clinical laboratories for urine and plasma oxalate, kidney and liver panels and coagulation, plus an LC-MS/MS bioanalytical laboratory for triterpenoids and warfarin enantiomers;
- a serology laboratory for HAI assays and a platform for continuous glucose monitoring.

10 Risks and mitigations

Table 6: Program risks.

Risk	Mitigation
Extract carries enough oxalate to fail Gate B	Oxalate-reduction step or calcium co-formulation; shortened repeat of CHEP-1
Missed influenza season (CHEP-2)	Multi-site recruitment; pre-screening in summer; fall-back to a second season
Unblinding from taste or colour	Opaque capsules in all blinded studies; tea used only in the open-label CHEP-1; blinding index reported
Product variability or depletion of wild supply	One homogenized lot secured at the outset; stability programme
Participants already using chaga	Four-week washout; screening questions; urinary oxalate at baseline
Sponsor conflict of interest	Independent statistics, DSMB and registration; pre-committed publication
Assumed variances are wrong	Blinded sample-size re-estimation where designs allow; inputs reported transparently
Null results	Treated as a valid outcome that retires a claim; published regardless

11 Limitations of this proposal

- Every standard deviation, correlation and margin used for sample sizes is an assumption (Appendix A). A trial biostatistician must confirm them before any submission.
- Stopping thresholds for urinary oxalate and the 5 mg/day equivalence margin are proposals that need nephrology consensus.
- The evidence review mentioned a registered crossover study with a chaga arm (NCT07127705); its registry record could not be retrieved during fact-checking, so it is not relied on here. A full registry search is required before submission.
- Whether Health Canada's ICH E6(R3) implementation notice and the draft clinical-trial regulations apply to NHP trials is not confirmed.
- The proposal has not been reviewed by an REB, Health Canada or independent clinicians, and it contains no cost estimate.

Declarations

Preparation. This concept protocol was drafted with AI assistance (Claude, Anthropic) from the companion evidence review, with literature and regulatory facts checked by live web search on 10 October 2026. It requires independent scientific, statistical, ethical and regulatory review before use.

Competing interests. To be completed by the sponsor and all investigators before submission.

A Sample-size assumptions

All calculations were run in Python (SciPy). Monte Carlo results used 40,000 simulated trials with a fixed seed. The script is supplied with this proposal.

Table 7: Inputs and results. Values in the assumption column are planning values, not literature findings.

Study	Test	Assumptions	n
CHEP-1	Paired equivalence (TOST), margin ± 5 mg/day, $\alpha = 0.025$ per side, 90% power	SD of within-person difference 7 mg/day; true effect 1 mg/day; 15% attrition	35 evaluable; 42 randomized
CHEP-2	Two-sample, analysis of covariance, two-sided $\alpha = 0.05$, 80% power	SD 1.75 $\log_2$ units; baseline correlation 0.5; GMT ratio 1.5; 10% attrition	107/arm evaluable; 238 randomized
CHEP-3	Two-sample, two-sided $\alpha = 0.05$, 80% power	SD of A1C change 0.5 points; difference 0.25 points; 15% attrition. LDL-C SD 0.5 mmol/L	64/arm evaluable; 152 randomized
CHEP-4A	2×2 crossover, 90% CI within 0.80–1.25, 90% power	Within-subject CV 15%; true ratio 0.95; 20% attrition	16 evaluable; 20 randomized
CHEP-4B	Precision: 95% CI half-width 1.0 percentage point	SD of within-person difference 2.5 points; 15% attrition	25 evaluable; 30 randomized
CHEP-5	Two-group comparison, two-sided $\alpha = 0.05$, 90% power, design effect 1.25	Between-person SD 12 mg/day; difference 8 mg/day	62/group needed; 80/group enrolled

For reference, an 80% power version of CHEP-2 needs 238 participants; 90% power would need 318. For CHEP-3, 90% power would need 204.

B Schedule of assessments for CHEP-1

Table 8: Assessments in each period (baseline and three product periods). • = performed.

Assessment	Screen	Day 1	Days 4–5	Days 6–7	Day 8
Consent, history, ECG	•				
Product dosing		•	•	•	
Controlled diet			•	•	
24-h urine (oxalate, calcium, citrate, creatinine)	•			•	
Fresh urine microscopy (crystalluria)	•			•	
Plasma oxalate, creatinine, cystatin C	•	•			•
Triterpenoid PK (0–24 h)		•			• (trough)
Liver enzymes, blood count, INR	•				•
Heart rate, blood pressure	•	•	•	•	•
Tea or product aliquot for assay		•		•	
Adverse events		•	•	•	•

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