Protocol

Version 2.3

1 September 2026

Project title: Efficacy and Safety of Ginseng-notoginseng Containing Supplement on Chronic Fatigue in Adults: A Randomized Waitlist-controlled Trial

Introduction

Chronic fatigue is a persistent and unrelenting sense of tiredness or exhaustion that does not improve by rest and not explained by an underlying medical condition. It affect multisystem which also cause sleep disorder, cognitive impairment, and autonomic dysfunction [1]. It is a prevalent health complaint affecting around 10% of adults, especially in females and older population in Hong Kong[2], which significantly impairing work productivity and quality of life. The lack of validated biomarkers, the dependence on subjective self-reported symptomatology, and the marked heterogeneity of underlying pathophysiological mechanisms collectively impede the development of robust diagnostic methodologies and targeted therapeutic interventions [3]. Non-pharmacological approaches, such as cognitive behavioral therapy, graded exercise, and sleep hygiene education, may provide benefits for selected individuals but are often constrained by suboptimal adherence or heterogeneous results in real-world settings [4].

Ginseng and notoginseng are well-known Chinese medicine herbs, has long been used to promote vitality and reduce tiredness. Previous mechanistic studies indicate that ginsenosides, the main active compounds in ginseng, can enhance mitochondrial ATP production [5], modulate neuroendocrine responses to stress [6], and suppress inflammatory pathways [7]—all mechanisms implicated in the pathophysiology of fatigue. Notoginseng (Sanqi), another member of the Panax genus, is rich in notoginsenosides and is traditionally regarded as beneficial for microcirculation, anti-inflammatory actions, and regulation of oxidative stress [8].

Systematic reviews and meta-analyses of randomized controlled trials have shown that ginseng supplementation can reduce fatigue severity in patients with various chronic diseases and [9, 10]. Notoginseng also shows potential in improving fatigue symptoms in an animal model research [11]. However, there are no clinical studies specifically examining the combined effects of Panax Ginseng and Panax notoginseng for chronic fatigue.

Given the high prevalence and personal/social impact of chronic fatigue among adults, coupled with the substantial interest in natural supplements with presumed multi-targeted mechanisms, a randomized controlled trial is needed to assess the

efficacy and safety of a combined ginseng-notoginseng supplement for chronic fatigue in adults. In addition, mechanistic biomarker studies have the potential to clarify the physiological effects of herbal supplementation and identify subgroups most likely to benefit.

Information of the Product

This product is a capsule containing dietary fiber, fermented ginseng extract, Panax notoginseng extract, and Vitamin C. Each capsule contains 81% dietary fiber, which is an excipient and serves as a bulking agent. Dietary fiber is widely used as an ingredient or excipient in dietary supplements and is generally considered safe at appropriate amounts. The recommended dosage is 4 capsules orally daily for 6 weeks. The product should be stored in a cool, dry environment and protected from light exposure. The product was characterized as a supplement, not registered under the *Pharmacy and Poisons Ordinance* or the *Chinese Medicine Ordinance.*

Hypothesis

Based on the literature review and preliminary market observation, we hypothesize that GIN-201 can reduce fatigue in adults who suffer from persistent fatigue. We aim to investigate the efficacy and safety of GIN-201 and its clinical association with multiple factors, including inflammation, stress, aging, neuro-function, and mitochondrial health. The representative workflow chart is shown in Fig. 1.

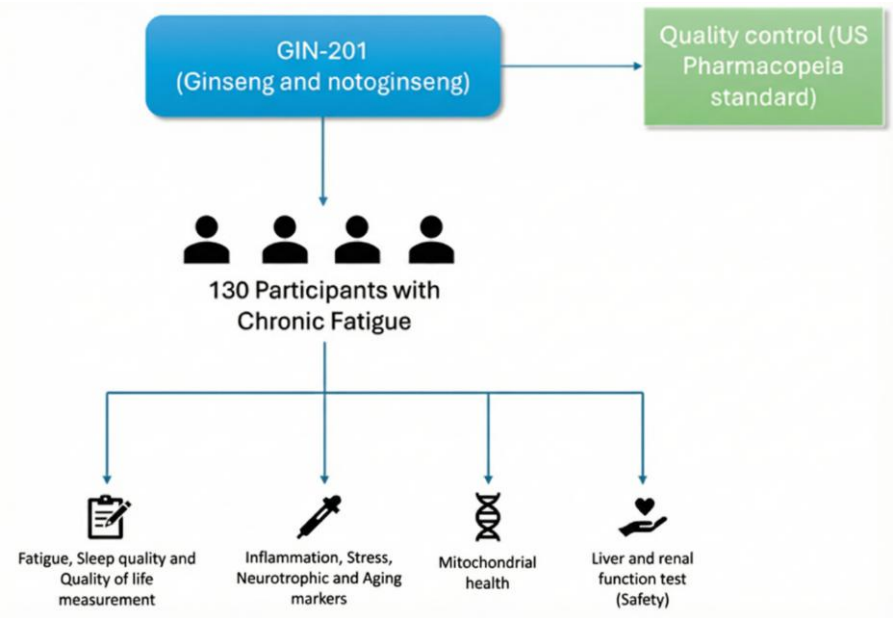


Fig. 1. Research workflow

Method

Study Design

This is a randomized, waitlist-controlled trail on adults stratified by chronic fatigue. Participants will receive the intervention for 6 weeks, followed by a 6-week follow-up. Because there is no approved pharmaceutical intervention for chronic fatigue, a waiting list control without positive drug is designed in this trial. They study protocol will be registered at relevant clinical trial registry platform. The study will be carried out in accordance with the ethical principles of the Declaration of Helsinki and in compliance with the International Council for Harmonisation Good Clinical Practice (ICH-GCP) guidelines. The clinical trial protocol follows the guidelines set by the SPIRIT Statement. The trial's outcomes will be presented in compliance with the CONSORT statement

Participants recruitment

Participants in this trial will be recruited through both advertisements and outpatient clinic enrollments in Hong Kong. Inclusion criteria for targeted participants include: 1) ages 30 to 75 years; 2) self-reported fatigue with Chalder Fatigue Scale ≥4; 3) Self-reported poor sleep quality with Pittsburgh Sleep Quality Index >5; 4) able to complete an online validated fatigue survey, 6-week intervention, and all follow-ups. Exclusion criteria include: 1) diagnosed with dementia or major psychiatric disorder; 2) sleep apnea requiring CPAP; 3) current participation in other trials; 4) unable to comply with study procedures and give informed consent; 5) known allergy to study product or its excipients; 6) abnormal heart, liver or renal function; 7) not pregnant or planning pregnancy with 6 months; 8) using anticoagulants.

Baseline characteristic will be collected after eligibility screening, including 1) demographic information consisting of gender, age, race, height, weight, education, and job; 2) duration of fatigue; 3) self-reported comorbidities; 4) self-reported drugs; 5) outcome measures, including Chalder Fatigue Score (CFS), Fatigue Severity Score (FSS), Patient-Reported Outcomes Measurement Information System (PROMIS) Short Form Fatigue 7A survey, 36-Item Short-Form Health Survey (SF-36), hospital anxiety and depression scale (HADS), Pittsburgh sleep quality index(PSQI), Brief Male Sexual Function Inventory (BMSFI), and Menopause Rating Scale (MRS).

Randomization and Blinding

After screening the baseline assessments, eligible participants will be randomly assigned to an intervention group or a waitlist group at a ratio of 1:1. The random sequences generated in the R statistical package will have a block of 4 in each cycle, consisting of two control groups and two intervention groups. Assignments will be concealed in sealed opaque envelopes and will only open after eligibility is confirmed and consent is obtained. The researcher who recruits and screens the patients, and assessors who conduct the baseline and follow-up assessments, will be blinded to treatment allocation.

Intervention and control

Participants assigned to the intervention group will receive GIN-201 in 4 capsules, once per day, for 6 weeks, according to the manufacturer's guidelines. Then followed by a 6-week follow-up. The quality control will include a similarity of more than 96% tested by UPLC, with a fingerprint for multiple batches. During the intervention period, participants will be asked to fill in the "GIN-201 Intake Record Form" to record if they miss any dose of the trial capsule and if they add any other supplements to their daily life. At the 6-week visit, participants are required to send back all the trial capsules that they have not consumed.

The waiting list control group will wait for 6 weeks after the randomization, and then start to receive GIN-201 in 4 capsules, once per day, for 6 weeks, followed by a 6-week follow-up. During the period of waiting, participants will be asked to fill in a "supplement intake diary" to record if they take any supplements in their daily life. The overview of the study design is shown in Figure 1.

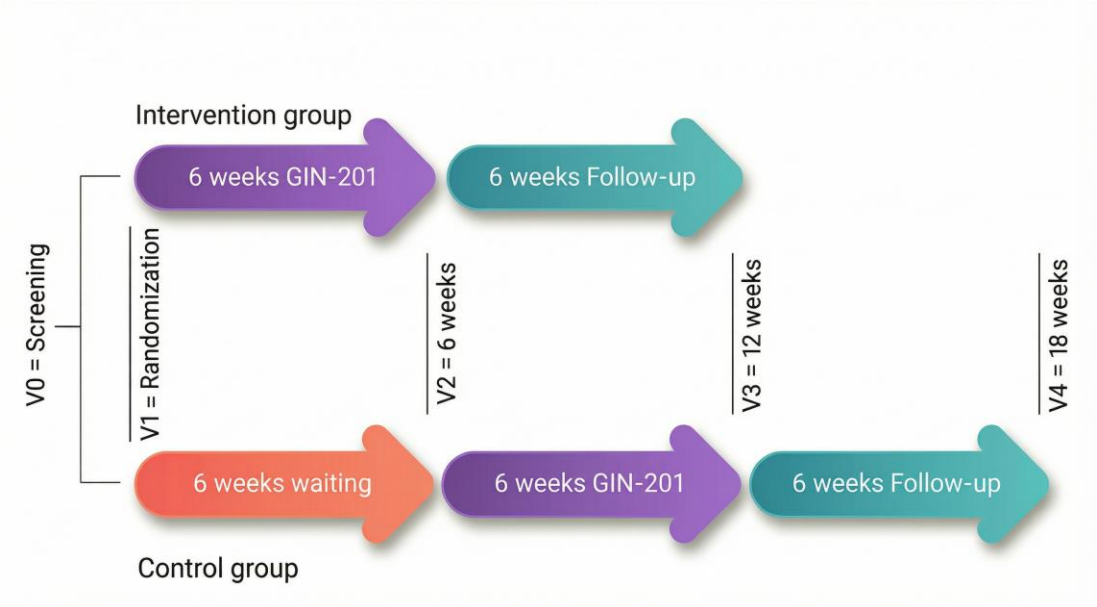


Fig. Overview of the study flow of GIN-201
V1-V4: Visit 1 to 4 for each participant included in this trial.

Outcome Measurement

Measurements in this trial include: **1)** Chalder Fatigue Score (Bimodally score 0-4 of 11-item, higher scores indicating greater fatigue) [12]; **2)** Fatigue Severity Score (Likert score 1-7 of 9-item, higher scores on the scale are indicative of more severe fatigue) [13]; **3)** Patient-Reported Outcomes Measurement Information System (PROMIS) Short Form Fatigue 7A survey (5-point Likert scale of 7-time, higher scores indicating greater fatigue) [14]; **4)** 36-Item Short-Form Health Survey (SF-36, range 0 to 100, with higher scores indicating better health status) [15]; **5)** Hospital Anxiety and Depression Scale (HADS, range 0-21, with higher scores indicating more severe symptoms) [16]; **6)** Pittsburgh sleep quality index (range 0-21, with higher scores indicating worse sleep quality) [17]; **7)** Brief Male Sexual Function Inventory (11-item in 5 divisions, higher score indicates more satisfied sexual function) [18] for men and Menopause Rating Scale (Likert score 0-4 for 11-item, higher indicate severer menopause symptoms) for women [19]; **8)** Biomarkers for inflammation (C-reactive protein, interleukin-6), stress (cortisol), neurotrophic (brain-derived neurotrophic factor), aging (plasma cfDNA telomere length, AGEs level) and mitochondrial health (plasma lactic acid, NAD+/NADH ratio, FGF-21 and GDF-15); **9)** Laboratory test for safety measurement including whole blood count, renal (BUN, creatinine) and liver function (AST and ALT).

The primary outcome is the mean difference in Chalder Fatigue Score from baseline to 6 weeks. The secondary outcome includes **1)** mean difference in Chalder Fatigue Score from baseline to 12 weeks; **2)** mean difference in Fatigue Severity Score from baseline to 6 week and 12 week; **3)** mean difference in PROMIS Short Form Fatigue 7A survey from baseline to 6 weeks and 12 week; **4)** mean difference in 36-Item Short-Form Health Survey from baseline to 6 week and 12 week; **5)** mean difference in Hospital Anxiety and Depression Scale from baseline to 6 week and 12 week; **6)** mean difference in Pittsburgh sleep quality index from baseline to 6 week and 12 week; **7)** Brief Male Sexual Function Inventory and Menopause Rating Scale from baseline to 6 week and 12 week. The explorative outcomes are the mean change in biomarkers of inflammation, stress, neurotrophic, aging, and mitochondrial health from baseline to 6 weeks.

Adverse events will be assessed using the Treatment Emergent Symptom Scale (TESS) throughout the procedure, as well as during laboratory tests (whole blood counts, renal and liver function) if needed. All clinical adverse events will be recorded in terms of intensity (mild, moderate, or severe), duration, action taken, outcome, and relationship to the study. The outcome measures are shown in Table 1.

Outcome Type	**Outcome Measure**	**Baseline to 6 Weeks**	**Baseline to 12 Weeks**	**Baseline to 18 Weeks[#]**
Primary	Chalder Fatigue Score	✓		
Secondary	Chalder Fatigue Score		✓	✓
Secondary	Fatigue Severity Score	✓	✓	✓
Secondary	PROMIS Short Form Fatigue 7A	✓	✓	✓
Secondary	36-Item Short-Form Health Survey (SF-36)	✓	✓	✓
Secondary	Hospital Anxiety and Depression Scale (HADS)	✓	✓	✓
Secondary	Pittsburgh Sleep Quality Index (PSQI)	✓	✓	✓
Secondary	Brief Male Sexual Function Inventory (BMSFI) / Menopause Rating Scale (MRS)	✓	✓	✓
Exploratory	Biomarkers (inflammation, stress, neurotrophic, aging, mitochondrial health)	✓		
Safety	Laboratory Tests (CBC, renal and liver function)	✓		

[#]Only for participants in waiting group

Table 1. Summary of outcome measurements

If participants use a combination of treatments that are prohibited by the study protocol, withdraw their consent, or cease communication, they will be excluded from the study. Researchers will report the reasons for withdrawal and dropout and acquire the time of last treatment and outcome measures, where possible.

Sample size estimation

The sample size was calculated to detect a clinically meaningful difference of 9.9 points on the Chalder Fatigue Scale (CFS), corresponding to a standardized minimal clinically important difference (d) of 0.54 [20]. Assuming a two-sided significance level (α) of 0.05 and a power of 80% (β = 0.20), the sample size was estimated using the formula:

$$n = \left(\frac{(Z_{\alpha/2} + Z_{\beta})^2}{d^2} \right) \times 2$$

The initial sample size required per group is approximately 54 participants. Adjusting for an expected 15% loss to follow-up, the final sample size per group is scaled up to 65, leading to a total required sample size of 130 (65 in each group) to ensure adequate power for detecting the predefined difference.

Statistical Methods

The intention-to-treat approach will be used for data analysis. For participants lost to follow-up or who drop out, inverse probability weighting (IPW) will be used to address missing data and potential selection bias. A generalized linear regression model will be used to determine the comparative effectiveness of the two groups at week 6 and week 12. Baseline score, age, gender, BMI, baseline physical activity, smoking and drinking habits, educational level, and occupational category will be included as covariates to control for confounding factors. Intervention adherence will be incorporated as an interaction term to investigate potential modification effects. Subgroup analyses will be conducted by gender, age category, and menopausal status. Sensitivity analyses will include multiple imputation and adjustment for attendance

rate. Results will be presented as mean differences between groups with 95% confidence intervals. A two-sided P value of <0.05 will be considered statistically significant. All data processing and analysis will be conducted using the R statistical package.

Handling and Storage of Personal Data and Study Data

Data will be solely managed throughout the study period, accessible only to authorized investigators and designated personnel on a password-protected system (REDCap). Additionally, an independent data and safety monitoring committee, separate from sponsors, researchers, and stakeholders, will convene quarterly to oversee the research's safety and efficacy in the medium term.

The Principal Investigator and co-investigators will have access to the personal and study data during the study; after study completion, the Principal Investigator will retain access to the study data for the period required by applicable regulatory requirements, subject to inspection by authorized regulatory authorities and sponsor representatives as per ICH GCP. Our project team will ensure the security of raw data by storing it in a locked cabinet within a secure room with limited access. Data entry will be performed on a password-protected computer accessible solely to team members. Throughout and following the study, only designated team members will have the authority to access raw data or study records.

Upon study completion, personal and study data storage period of 5 years will be preserved for a period of five years and subsequently disposed of, unless an application for extended retention is sanctioned by the Institutional Review Board (IRB). Prior to statistical analyses, any personal identifying information will be expunged from the dataset.

Traffic reimbursements

Participation in the project is entirely voluntary, and patients are not charged anything associated with it. To assist with patients' travel to the Specialist Clinical Teaching and Research Centre, HKU (at Sasson Road), Clinical Centre for Teaching and Research, HKU (at Queen's Road Central), and the blood draw center, they will be reimbursed 400 HKD to cover travel expenses. This reimbursement will be provided after the completion of

all follow-ups and is intended purely to compensate for travel costs incurred by participating in the study. Patients' participation or decision to withdraw will not affect their access to medical care in these centers.

Funding

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