

N Northeastern Experiential Network

Title:

++HENCE GREENS STACK Food Supplements- XN Project



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I. Introduction

Hence Nutritional Super Stacks, a UK-based company, is positively impacting millions with health-focused performance supplements. Their mission: to enhance overall health, performance, quality of life, and longevity through holistic mind and body advancement, prioritizing health, honesty, and sustainability.

In their pursuit of scientific inquiry, Hence Nutritional Super Stacks is initiating a study on its Greens Stack Supplement to define the research question or objective. This study aims to evaluate the supplement's impact on antioxidant and adaptogenic activity, as well as its potential health benefits. Key aspects include designing a randomized controlled trial with specific participant selection criteria and defining appropriate outcome measures.

Critical considerations such as dosage, supplementation duration, and potential interactions with other medications or supplements will be thoroughly addressed. Additionally, a comprehensive literature review will be conducted to assess existing research on the ingredients present in the Greens Stack Supplement. This scientific examination seeks to deepen understanding of the supplement's effects on health and performance.

Ultimately, the goal is to support marketing endeavors compliant with regulations outlined by the European Union (EU) or the Food and Drug Administration (FDA) in the United States. Through rigorous scientific research, Hence Nutritional Super Stacks aims to ensure the safety, efficacy, and integrity of their product while providing consumers with accurate information, thereby contributing to the advancement of knowledge in the field of nutrition and supplementation.

II. Objective

The Green Stack supplement is formulated with a unique blend of natural ingredients that offer multifaceted benefits for overall health, performance, and longevity (Green Stack Overview, 2024). To comprehensively evaluate its efficacy, the following research objective is proposed:

Investigate the synergistic effects of the Green Stack formulation on antioxidant status, adaptogenic response, cognitive function, energy levels, and physical performance in healthy adults through a randomized, double-blind, placebo-controlled study.

Randomized Controlled Trial to Assess the Impact of 'Greens Stack' Supplement on Oxidative Stress and Well-being in Healthy Adults

1. Primary Objective:

- Assess the effects of the Greens stack supplement on antioxidant activity and adaptogenic properties in healthy individuals over a 12-week period.

2. Secondary Objectives:

- Evaluate changes in biomarkers of oxidative stress.
- Monitor improvements in physical and mental performance.
- Identify any side effects or interactions with other medications or supplements to ensure safety.

III. Key Areas of Focus

1. Antioxidant and Anti-Inflammatory Properties

Assess the supplement's ability to improve antioxidant status, reduce oxidative stress, and modulate inflammatory markers in the target population (Green Stack Overview, n.d.; Green Stack Research, n.d.).

2. Adaptogenic Effects

Evaluate the formulation's impact on the body's ability to adapt to physical and mental stressors, potentially enhancing resilience and recovery (Green Stack Overview, n.d.; Green Stack Research, n.d.).

3. Cognitive Function

Investigate the effects on cognitive domains such as focus, attention, memory, and overall mental performance (Green Stack Overview, n.d.; Green Stack Research, n.d.).

4. Energy Levels and Physical Performance

Examine the supplement's potential to enhance energy levels, endurance, and physical performance in various activities or exercise regimens (Green Stack Overview, n.d.; Green Stack Research, n.d.; Muscle Hacking Supplements, n.d.).

5. Safety and Long-Term Effects

Monitor and assess the safety profile and potential long-term effects of regular Green Stack consumption in healthy individuals (Green Stack Research, n.d.).

By addressing these key areas through a rigorous study design, valuable insights can be gained into the Green Stack supplement's multifactorial benefits, contributing to the company's mission of promoting health-led performance and longevity.

IV. Major ingredients in Greens Stack Supplement

1. Kale (*Brassica oleracea* var. *sabellica*)

Nutritional Composition: Rich in vitamins A, C, and K; essential minerals such as calcium, potassium, magnesium, and iron; bioactive compounds including flavonoids, polyphenols, and glucosinolates.

Health Benefits: Kale is known for its potent antioxidant and anti-inflammatory properties. It supports immune function and may contribute to stress resilience through its adaptogenic effects.

Clinical studies have demonstrated its ability to reduce oxidative stress and inflammation, potentially lowering the risk of chronic diseases like cancer and cardiovascular disease (Kim et al., 2014; Kim et al., 2016; Li et al., 2019).

2. Maca (*Lepidium meyenii* Walp.)

Nutritional Composition: Contains protein, essential amino acids, vitamins (B complex, C), minerals (iron, magnesium, zinc), and bioactive compounds such as macaenes and macamides.

Health Benefits: Maca is recognized for its ability to enhance fertility and sexual function, reduce fatigue, and improve physical stamina. It also exhibits antioxidant properties, helping to protect cells from oxidative stress. Clinical trials have shown Maca's effectiveness in improving sexual function and physical endurance (Gonzales et al., 2003; Sandoval et al., 2002).

3. Spinach (*Spinacia oleracea*)

Nutritional Composition: High in vitamins A, C, E, and K; minerals such as iron, magnesium, calcium, potassium, and manganese; antioxidants like lutein, betacarotene, and zeaxanthin.

Health Benefits: Spinach provides anti-inflammatory and anti-cancer benefits, supports cardiovascular health, and aids in metabolic regulation. Studies indicate that spinach can reduce inflammation, protect against chronic diseases, and improve overall metabolic health. The antioxidants in spinach are particularly beneficial for eye health, reducing the risk of age-related macular degeneration (Roberts & Moreau, 2016; Clinic, 2024; Bhattarai & Shi, 2021).

4. Black Pepper (*Piper nigrum*)

Nutritional Composition: Contains vitamins K, E, B2, B1; minerals such as manganese, iron, magnesium, and phosphorus; bioactive compound piperine.

Health Benefits: Black pepper enhances nutrient absorption, has antioxidant, antiinflammatory, and anti-carcinogenic properties. Piperine, the active compound in black pepper, significantly increases the bioavailability of various nutrients and drugs, enhancing the overall efficacy of the supplement (Ashokkumar et al., 2021; Stojanović-Radić et al., 2019).

V. Study Design

1. Define the Research Question or Objective

Primary Objective:

- Determine the effects of the Greens stack supplement on antioxidant activity and adaptogenic properties in healthy individuals over a 12-week period.

Secondary Objectives:

- Assess changes in biomarkers of oxidative stress.
- Evaluate improvements in physical performance (endurance and strength).
- Evaluate improvements in mental performance (cognitive function and mood).
- Monitor side effects and potential interactions with other medications or supplements.

2. Design the Study

Study Type: Prospective, double-blind, placebo-controlled, randomized clinical trial.

Participant Recruitment:

- Use online platforms and community bulletin boards for recruitment.
- Screen for eligibility with a detailed medical questionnaire and initial health screening at a local clinic.

Inclusion Criteria:

Age: Participants aged 18 to 60 years. This age range ensures inclusion of both younger and older adults while minimizing variability due to age-related metabolic changes.

General Health: Participants must be generally healthy at the time of enrollment. This includes having no significant acute or chronic medical conditions that could influence the study outcomes or participant safety, except for arthritis.

Arthritis: Individuals with medically diagnosed arthritis can be included. This includes those with rheumatoid arthritis or osteoarthritis, provided their condition is stable and they are not on medications that could interfere with the study outcomes (e.g., high-dose corticosteroids).

Non-Smokers: Only non-smokers will be included to prevent the confounding effects of nicotine and smoking-related oxidative stress.

No Regular Supplements: Participants should not regularly use antioxidant supplements or multivitamins for at least 3 months prior to the study to prevent interference with the baseline and intervention measurements.

Consent: Ability and willingness to provide written informed consent and comply with the study requirements.

Exclusion Criteria:

Uncontrolled Chronic Diseases: Individuals with uncontrolled chronic diseases such as advanced diabetes, severe cardiovascular diseases, or major liver or kidney disorders, which could affect the body's baseline antioxidant levels and inflammatory status.

Pregnancy or Breastfeeding: Women who are pregnant or breastfeeding due to the unknown effects of the supplement's ingredients on fetal and infant development.

Medication Use: Those currently using chronic medications that could interfere with the study outcomes, such as high-dose anti-inflammatory drugs, anticoagulants, or medications affecting liver enzyme activity.

Severe Arthritis: Individuals with severe arthritis requiring high-dose corticosteroids or other immune-suppressive therapies that could confound study results.

Allergies to Ingredients: Individuals with known allergies to any component of the Green Hence Stack supplement.

Substance Abuse: History of substance abuse within the last 12 months, which could affect the metabolic and psychological parameters being studied.

Recent Surgery: Participants who have undergone major surgical procedures within the last 6 months, as this could influence inflammatory and oxidative stress markers.

Dietary Restrictions: Individuals with specific dietary restrictions or diets that could substantially alter baseline nutrient status (e.g., veganism, ketogenic diet) unless they agree to maintain a consistent diet throughout the study period.

Additional Screening:

Initial Health Screening: A physical examination and routine blood tests will be performed to confirm general health status and rule out any underlying conditions that may exclude participation.

Dietary and Lifestyle Questionnaire: To assess and document baseline dietary habits and physical activity levels, ensuring that participants meet the study criteria related to lifestyle factors.

Sample Size:

200 participants (100 in the intervention group and 100 in the placebo group).

3. Intervention:

Group 1 (Intervention Group): Daily intake of the Greens stack supplement.

Group 2 (Placebo Group): Daily intake of a placebo matching the Greens stack supplement in appearance and taste.

Duration:

12 weeks of supplementation with follow-up assessments at 4, 8, and 12 weeks.

Dosage:

The dosage will be based on current recommendations for safe and effective use of the ingredients. Each participant will take the supplement in the form specified (e.g., powder, capsules).

4. Outcome Measures:**Primary Outcomes:**

Levels of antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase).

Levels of oxidative stress markers (malondialdehyde, 8-OHdG).

Secondary Outcomes:

Physical performance (endurance tests such as VO₂ max, strength tests such as grip strength).

Mental performance (cognitive function tests such as memory recall, mood questionnaires).

Quality of life (self-reported questionnaires).

Monitoring side effects and potential interactions with other medications or supplements.

5. Data Collection:

Baseline Measurements: Blood samples, physical performance tests, cognitive function tests, and self-reported health and quality of life questionnaires.

Follow-up Measurements: Similar assessments at 4, 8, and 12 weeks to monitor changes over time.

Data Collection Points:

Initial Assessment (Week 0): Comprehensive health screening, including blood work to assess baseline antioxidant levels and a detailed health and lifestyle questionnaire.

Ongoing Assessments (Every Two Weeks): Collection of blood samples to measure changes in biochemical markers of oxidative stress, inflammation, and general health.

Weekly Health Surveys: Online surveys to record self-reported measures of mood, energy levels, and perceived physical health.

6. Study Procedures:

Recruitment: Participants will be recruited through advertisements in local media and community centers.

Screening: Potential participants will undergo a screening process to ensure they meet the inclusion and exclusion criteria.

Randomization: Eligible participants will be randomly assigned to either the intervention group or the placebo group using a computer-generated randomization sequence.

Blinding: Both participants and researchers will be blinded to the group assignments to prevent bias.

Supplement Administration: Participants will receive their assigned supplement (Greens stack or placebo) and will be instructed to take it daily.

Follow-up Assessments: Participants will visit the research center at baseline, 4, 8, and 12 weeks for assessments. Blood samples will be collected, and physical and cognitive performance tests will be conducted at each visit.

Data Analysis: Data will be analyzed using appropriate statistical methods to compare the outcomes between the intervention and placebo groups.

7. Statistical Analysis:

Use SPSS or a similar statistical software package for data analysis.

Perform intention-to-treat analysis to include all participants who were randomized at baseline.

Utilize mixed-effects models to account for repeated measures and potential confounders.

8. Obtain Ethical Approval

Protocol Submission: Submit the study protocol to the Research Ethics Committee (REC) for review.

Informed Consent: Obtain informed consent from all participants, ensuring they are fully aware of the study's purpose, procedures, potential risks, and benefits.

Compliance: Ensure compliance with all ethical guidelines and regulatory requirements, including those set forth by the Declaration of Helsinki and local regulatory bodies.

Safety Monitoring: Establish a Data and Safety Monitoring Board (DSMB) to oversee the study's progress and address any ethical or safety concerns that arise during the trial.

9. Budget and Funding:

Outline expected costs including personnel, materials, laboratory testing, and participant incentives.

Specify sources of funding and disclose any potential conflicts of interest (Hurrell & Egli, 2010) (Rickman et al., 2007) (Sandoval et al., 2002) (Gonzales et al., 2003) (Ashokkumar et al., 2021).

VI. FDA's approval and Regulations of Green Stack dietary supplement ingredients

1. Spirulina:

Spirulina is approved by the US Food and Drug Administration (FDA) for use as a color additive in certain foods and dietary supplements. Spirulina extract is listed under 21 CFR §73.530 as an approved color additive. Spirulina itself is approved, the FDA does not evaluate or approve spirulina-containing dietary supplements for their claimed health benefits or safety before they are marketed. Like other dietary supplements, spirulina products are not strictly regulated by the FDA for safety and efficacy prior to sale. So, while spirulina can legally be included as an ingredient in dietary supplements sold in the USA, the quality, purity, and safety of these products cannot be guaranteed by the FDA. Some studies have found contamination issues like potentially harmful bacteria and toxins in certain spirulina supplements.

Therefore, while spirulina supplements are allowed on the US market, caution is advised when using them as the FDA does not verify their quality or health claims before they are sold. (Center, 2022) (Rhoades et al., 2023)

2. Matcha:

While matcha itself as a tea product may be allowed for consumption, there is no explicit mention in these results of the FDA approving the use of matcha powder specifically as a dietary ingredient in supplements sold in the United States. The FDA advisories suggest that matcha-containing supplements would need to go through the FDA's registration and evaluation process before being marketed.

So in summary, based on these search results, there is no clear evidence that the FDA has approved the use of matcha powder as a dietary supplement ingredient, though it does not necessarily mean it is prohibited either. More definitive guidance from the FDA would be needed to confirm if matcha is an approved supplement ingredient.

3. Ashwagandha KSM 66:

Ashwagandha is not specifically approved by the FDA for use in dietary supplements. The key points regarding FDA regulation of ashwagandha are:

Ashwagandha is an herbal ingredient, and the FDA does not approve herbal products or other dietary supplements before they are marketed.

As stated by the National Center for Complementary and Integrative Health (NCCIH), "Unlike drugs, dietary supplements are not approved by the U.S. Food and Drug Administration (FDA) before they are sold to the public."

While the FDA regulates dietary supplements containing ashwagandha, it does not evaluate their safety and efficacy before they are sold. Manufacturers must comply with certain labeling and quality control guidelines, but FDA approval is not required.

The FDA does not approve or reject individual dietary supplement ingredients like ashwagandha. It is the responsibility of manufacturers to ensure their products are safe and their claims are truthful. (*FDA-Registered Ashwagandha Powder Supplier | Nutri Avenue, 2024*) (Ashwagandha, 2019)

4. Yamabushitake (Lion's Mane):

There is no evidence that Yamabushitake (also known as *Hericium erinaceus* or Lion's Mane mushroom) is specifically approved by the FDA for use as a dietary supplement ingredient. The FDA does not approve or reject individual dietary ingredients like Yamabushitake before they are marketed. As stated in, "FDA approves a new drug on the basis of scientific data and information demonstrating the drug is safe and effective." But dietary supplements are not subject to the same approval process as drugs.

The FDA issued a warning letter to a company selling Lion's Mane and other mushroom supplements, stating that the products "are not generally recognized as safe and effective" for the claimed uses, and are considered "new drugs" requiring FDA approval before being marketed.

While Yamabushitake supplements may be legally sold in the US, the FDA does not specifically approve or reject individual supplement ingredients like this mushroom before they are marketed. The FDA's regulation focuses more on manufacturing practices, labeling, and marketing claims rather than pre-approving ingredients. (Center, 2021) (Center, 2021) (rjbonaobra, 2023)

5. Turmeric (Curcumin):

Turmeric and its components like curcumin are approved by the FDA for certain uses in foods and dietary supplements, but with some important caveats:

Turmeric (the ground rhizome of *Curcuma longa*) is approved by the FDA as a color additive in foods (21 CFR 73.600). It is also considered GRAS (generally recognized as safe) by the FDA for use as a spice and flavoring agent (21 CFR 182.10, 182.20).

Turmeric oleoresin (solvent extract of turmeric) is also approved by the FDA as a color additive in foods (21 CFR 73.615).

The FDA issued a "no questions" letter in 2013 for a GRAS notice (GRN 460) on the use of curcuminoids (compounds found in turmeric like curcumin) as a flavor, flavor enhancer or nutrient up to certain use levels in foods. (*CFR - Code of Federal Regulations Title 21*, 2023)

6. Stevia:

Stevia is approved by the FDA for use as a dietary ingredient in supplements. In 1995, the FDA revised its import alert to allow the use of stevia leaves and extracts as dietary ingredients in dietary supplements. The FDA has evaluated and not objected to over 50 GRAS notices for the use of various high purity steviol glycosides as sweeteners. While the FDA regulates stevia-derived ingredients used in foods through the GRAS notification process, it specifically allows the use of stevia leaves and crude extracts as ingredients in dietary supplements without needing FDA approval as a food additive. Manufacturers must still comply with supplement labeling and quality control regulations. (Perrier et al., 2018)

7. Maca Root:

Maca root is not specifically approved by the FDA for use as a dietary supplement ingredient.

The key points are:

The FDA warning letter states that "Maca Root is credited by many with possessing immunostimulating qualities that help to build the body's defenses", indicating the FDA does not consider maca root as an approved ingredient for claimed therapeutic uses.

The FDA advisory lists "VITACIO MACA ROOT EXTRACT COMPLEX, 500MG" as an unregistered food supplement product that has not gone through the FDA's evaluation process,

meaning its quality and safety cannot be guaranteed. The FDA does, in fact, evaluate nutritional supplements for their content as foods." This confirms the FDA does not approve maca root specifically for use in supplements. (*FDA Advisory No. 2019-155 || Public Health Warning against the Purchase and Consumption of the Following Unregistered Food Supplements: - Food and Drug Administration, 2019*) (Office, 2020) (*Is Maca FDA-Approved?, 2023*)

8. Kale:

There is no evidence that kale is specifically approved by the FDA for use as a dietary supplement ingredient. The FDA advisory warns against several unregistered food supplement products, but kale is not mentioned. Manufacturers of kale-containing supplements must ensure their products comply with FDA regulations for dietary supplements, such as proper labeling and following current good manufacturing practices (cGMPs). But there is no specific FDA approval required for the use of kale as a dietary ingredient based on these search results. (*FDA Advisory No. 2019-155 || Public Health Warning against the Purchase and Consumption of the Following Unregistered Food Supplements: - Food and Drug Administration, 2019*)

9. Dang-gui Buxue Tang:

there is no evidence that Dang-gui Buxue Tang (DBT), the traditional Chinese herbal decoction containing Astragali Radix and Angelicae Sinensis Radix, is specifically approved by the FDA for use as a dietary supplement ingredient.

an Amazon product listing for a DBT supplement, which states "Statements regarding dietary supplements have not been evaluated by the FDA." Manufacturers of DBT-containing supplements must ensure their products comply with FDA regulations for dietary supplements, such as proper labeling and following current good manufacturing practices (cGMPs). But there does not appear to be any specific FDA approval required for the use of DBT itself as a dietary ingredient based on these search results. (*Amazon.com: Dang GUI Bu Xue Tang - Dong Quai Astragalus Combination, 100gm,(E-Fong) : Health & Household, 2024*)

10. Moringa Oleifera:

moringa oleifera (also known as the drumstick tree) is allowed by the FDA for use in dietary supplements. Moringa is mentioned in FDA and European food safety documents as a food plant, suggesting its general acceptance as a food ingredient, which extends to supplements. Manufacturers of moringa supplements must ensure they follow FDA regulations for dietary supplements, such as proper labeling, avoiding drug claims, and adhering to current good manufacturing practices (cGMPs). (Klimek-Szczykutowicz et al., 2024) (Center, 2021)

11. Black Pepper Extract:

There is no evidence that the FDA has specifically approved black pepper for use as a dietary supplement ingredient. The NRDC comments raise concerns about the scientific evidence and procedures used by the company Sabinsa to claim that their black pepper extract BioPerine® is Generally Recognized as Safe (GRAS) for use as a flavoring agent in foods. This suggests the FDA has not definitively approved it. While the FDA has designated black pepper itself, its essential oil, oleoresin, and natural extractives as GRAS for use in foods (21 CFR 182.20), and approved piperine (the main component) as a synthetic flavoring (21 CFR 172.515), this does not necessarily extend to highly concentrated extracts. The other results do not provide any

information about FDA regulation or approval of black pepper extract for use in dietary supplements. (Weleff et al., 2022)

12. Spinach:

None of the results directly state that the FDA has approved or rejected the use of spinach powder, spinach extract, or any other spinach-derived ingredient in dietary supplements. (*Center for Infectious Disease Research and Policy*, 2008) (Office, 2021) (Office, 2020)

13. Broccoli Sprout:

There is no evidence that the FDA has specifically approved broccoli sprouts for use as a dietary supplement ingredient.

The key points are:

The FDA warning letter to Natural Sprout Co. LLC states that the company's broccoli sprout products are considered "new drugs" because the claims made on their website establish the products are intended for use in "the cure, mitigation, treatment, or prevention of disease." This means the FDA has not approved broccoli sprouts for those therapeutic uses. (Center, 2022) The warning letter also mentions the FDA's position that broccoli sprout products from Sunny Creek Farm are "not generally recognized as safe and effective" for the disease treatment claims made, and therefore require FDA approval as "new drugs" before marketing, which they do not have. (News Desk, 2022)

The potential health benefits of compounds like sulforaphane found in broccoli sprouts, they do not indicate the FDA has approved broccoli sprouts themselves as a dietary supplement ingredient. (Fahey & Kensler, 2021)

So, in summary, while broccoli sprouts may be legally sold as a food item, the FDA does not appear to have explicitly approved broccoli sprouts or their extracts/compounds for use as dietary supplement ingredients making disease treatment claims. The FDA regulates supplements differently than drugs, focusing more on manufacturing practices and labeling rather than pre-approving specific ingredients like broccoli sprouts.

FDA's labeling requirements

1. Statement of Identity: The product must be identified as a "dietary supplement" on the label.
2. Net Quantity of Contents: The net contents must be displayed in terms of weight, measure, or numerical count.
3. Nutrition Labeling: Most dietary supplements must have a "Supplement Facts" panel that lists the amounts of nutrients and ingredients per serving. This includes listing dietary ingredients, vitamins, minerals, herbs, amino acids, etc.
4. Name and Place of Business: The name and place of business of the manufacturer, packer, or distributor must be listed.
5. Ingredient List: All ingredients must be listed in descending order by weight.
6. Directions for Use: Directions for the intended use must be provided.

7. Domestic Address or Phone Number: A domestic address or phone number must be included to report adverse events.
8. Health/Nutrient Content Claims: Any nutrient content or health claims must comply with FDA regulations and have proper scientific substantiation.
9. Supplement Facts Formatting: The Supplement Facts panel must follow specific FDA formatting rules for type size, bolding, enclosure in a box, etc. (Center, 2024) (Center, 2022).

VII. New Dietary Ingredients (NDI) Notification Process

New Dietary Ingredients: Manufacturers must notify the FDA about new dietary ingredients before marketing.

To submit a New Dietary Ingredient (NDI) notification to the FDA for dietary supplements, you must follow these steps:

1. Determine if your ingredient qualifies as a "new dietary ingredient" under the Federal Food, Drug, and Cosmetic Act (FD&C Act). A new dietary ingredient is one that was not marketed in the U.S. before October 15, 1994.
2. At least 75 days before introducing the NDI or dietary supplement containing the NDI into interstate commerce, you must submit a premarket notification to the FDA.
3. The notification must contain the following information:
 - a) Your name and complete address
 - b) Name of the new dietary ingredient (including Latin binomial name if botanical)
 - c) Description of the dietary supplement containing the NDI, including the level of NDI, conditions of use, history of use, or evidence establishing safety
 - d) Data and information that provide the basis for your conclusion that the dietary
4. Supplements containing the NDI will reasonably be expected to be safe under the recommended conditions of use.
5. Submit the notification electronically via the FDA ePortal system (COSM). Paper submissions are also accepted. You must submit an original and two copies of the notification and all its attachments.
6. FDA regulations require that you submit an original and two (2) copies of the notification and all its attachments. You must also provide in the notification:
 - a) Your name and complete address.
 - b) The name of the new dietary ingredient. If the new dietary ingredient is an herb or other botanical, you must include the Latin binomial name (including the author).
 - c) A description of the dietary supplement or dietary supplements that contain the new dietary ingredient, including the:
 - level of the new dietary ingredient in the product.
 - conditions of use of the product stated in the labelling or if no conditions of use are stated, the ordinary conditions of use; and
 - history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in

the labelling of the dietary supplement, will be reasonably be expected to be safe.

- d) Any reference to published materials must be accompanied by reprints or photostatic copies.
- e) Any material in a foreign language must be accompanied by an English translation.
- f) A signature by a person designated by you who can be contacted if we have questions.
- g) If you send a written submission, please follow-up with an email including the subject line -- NDIN Written Submission -- to NDITeam@fda.hhs.gov. Failure to follow these processes may add to further delays in receiving and processing your written submission.
- h) **Send written submissions to:**

Office Center Food 5001	of for Food and	Dietary Safety and Drug Campus	Supplement and Programs Applied Nutrition Administration Drive	(HFS-810)
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College Park, MD 20740-3835

FDA provides an ePortal (CFSAN Online Submission Module or COSM) for electronic submissions. You may use the same COSM account for future submissions. (Center, 2024)

The notification must be submitted by the manufacturer, distributor, or other responsible party intending to market the NDI or dietary supplement containing it.

FDA will review the notification and may respond with objections, request more information, or take no action which allows marketing after 75 days. (Center, 2024)

Post-Market Responsibilities and Compliance

The manufacturing facility and processes must comply with the FDA's current Good Manufacturing Practices (cGMPs) for dietary supplements. This ensures the product is consistently produced and meets quality standards.

It's important to note that the FDA does not approve dietary supplements before they are marketed. The manufacturers and distributors of dietary supplements are responsible for making sure their products are safe before they go to market. If the dietary supplement contains a new dietary ingredient, the manufacturer must notify the FDA about that ingredient prior to marketing. However, the manufacturer does not have to provide the FDA with the evidence it relies on to substantiate safety or effectiveness before or after it markets its products.

Once the product is on the market, the company must have a system in place to report any serious adverse events associated with the use of the dietary supplement to the FDA. (Center, 2024) (Center, 2023)

VIII. Proposal for a Randomized Clinical Trial (RCT) on a Multi-Ingredient Plant-Based Supplement

1. Title

A Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Assess the Efficacy of a Multi-Ingredient Plant-Based Supplement on Quality of Life, Adaptogenic Response, Antioxidant Capacity, Inflammation, Detoxification, and Micronutrient Status.

2. Objectives

- Primary Objective:

- Assessment of Vitamins and mineral levels in serum and overall quality of life.

- Secondary Objectives:

- To assess the impact of the multi-ingredient plant-based supplement on the overall quality of life.
- To evaluate the supplement's effects on adaptogenic response, antioxidant capacity, inflammation, detoxification, and micronutrient status. (Panossian, 2010)

3. Study Design

- Type: Double-blinded, placebo-controlled, randomized clinical trial. (Lopresti, 2022)
- Duration: 12 weeks.
- Population: Healthy adults aged 18-60.
- Sample Size: 200 participants (100 in the supplement group and 100 in the placebo group).

4. Intervention

Supplement Group: Receives the plant-based food supplement. (Floyd, 2022)

Placebo Group: Receives a placebo identical in appearance to the supplement.

5. Primary Outcome Measure

Quality of Life:

- Assessed using the WHOQOL-BREF questionnaire and Fatigue Severity Scale (FSS) at baseline, 6 weeks, and 12 weeks.
- The blood levels of vitamins and minerals will be assessed at 6 week and 12 week points from baseline.

6. Secondary Outcome Measures

Adaptogenic Response: Measured using the Perceived Stress Scale (PSS) and cortisol levels in saliva at baseline, week -3, 6, 9 and 12. (Lopresti, 2022)

Antioxidant Capacity: Evaluated through blood tests for total antioxidant capacity (TAC) and levels of glutathione at baseline, week -3, 6, 9 and 12. (Silvestrini, 2023)

Inflammation: Measured by assessing C-reactive protein (CRP) and interleukin-6 (IL-6) levels at baseline, week -3, 6, 9 and 12. (Bermudez, 2002)

Detoxification: Assessed through liver function tests (ALT, AST, bilirubin) and urinary excretion of toxins at baseline, week -3, 6, 9 and 12. (Rincon, 2012)

Micronutrient Status: Measured by assessing blood levels of key vitamins and minerals (e.g., vitamin C, vitamin D, zinc, magnesium) at baseline, week -3, 6, 9 and 12.

7. Tests and Assessments

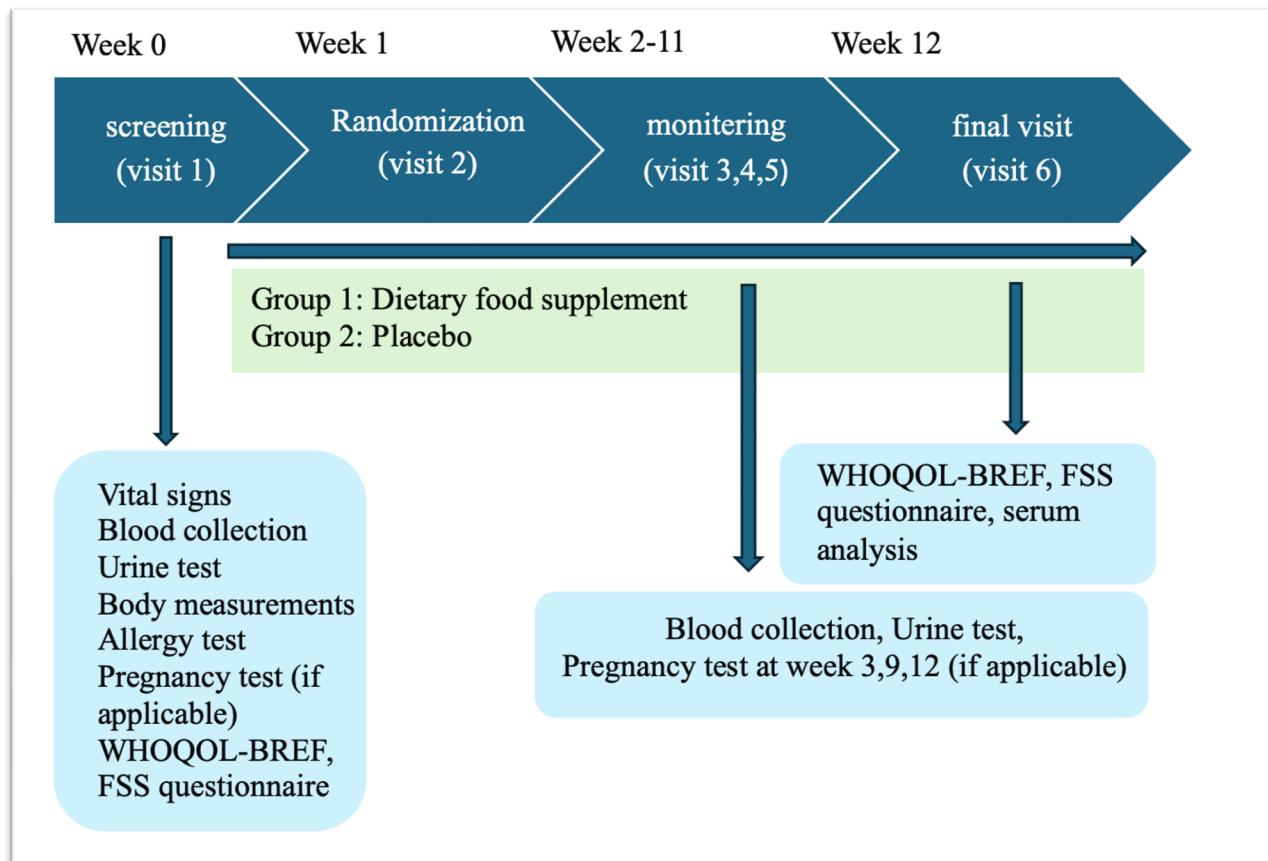
1. **Quality of Life:** WHOQOL-BREF questionnaire, Energy Levels: Fatigue Severity Scale (FSS). (WHO, 2012)
2. **Adaptogenic Response:** Perceived Stress Scale (PSS), Salivary cortisol levels. (Panossian, 2010)
3. **Antioxidant Capacity:** Total antioxidant capacity (TAC) in blood, Blood glutathione levels. (Lopresti, 2022)
4. **Inflammation:** C-reactive protein (CRP) levels, Interleukin-6 (IL-6) levels. (Bermudez, 2002)
5. **Detoxification:** Liver function tests (ALT, AST, bilirubin), Urinary excretion of toxins. (Rincon, 2012)
6. **Micronutrient Status:** Blood levels of vitamins and minerals (vitamin C, vitamin D, zinc, magnesium).

8. Procedure

1. **Recruitment, Screening and Baseline Assessment:** Obtain informed consent, Recruit participants through advertisements and conduct initial screening based on inclusion/exclusion criteria. Perform baseline assessments (questionnaires, blood tests, saliva tests, urine tests).
2. **Randomization and Blinding:** Participants are randomly assigned to supplement or placebo group and distribute the assigned supplements/placebo.
3. **Intervention Period:** Participants take the supplement or placebo daily for 12 weeks, with follow-up assessments conducted at weeks 3, 6, 9, and 12.
4. **Data Collection:** Collect data on primary and secondary outcomes at each assessment point, monitor adherence to the intervention, and record any adverse events.
5. **Data Analysis:**
 - Use intention-to-treat analysis.
 - Compare primary and secondary outcomes between the supplement and placebo groups using appropriate statistical tests (e.g., t-tests, chi-square tests).

Figure 1 illustrates a schematic representation of the overall study duration from screening to completion of the clinical trial.

Figure 1: Study Timeline and Procedure for the Randomized Controlled Trial



9. Clinical study Overall Timeline

Month 1-3: Active Patient recruitment, screening, and randomization.

Month 1-6: Ongoing trial for safety and efficacy evaluation of the dietary supplement.

Month 6: Completion of the study including final follow-up with the last study participant.

Month 7-9: Comprehensive data analysis.

Month 10: Reporting and dissemination of results.

IX. INFORMED CONSENT FORM

This section contains the informed consent form (U.S. Food and Drug Administration, 2024), for the randomized, double-blind, placebo-controlled clinical trial assessing the efficacy of **Hence Greens Stacks** on health parameters. Please read on to understand the study's objectives, potential benefits, and risks involved (U.S. Food and Drug Administration, 2015).

**PARTICIPANT INFORMED CONSENT FORM AND AUTHORIZATION TO USE AND
DISCLOSE MEDICAL INFORMATION**

STUDY TITLE: A randomized controlled trial over a 12-week period to assess the impact of Greens Stack supplement in healthy adults on quality of life, adaptogenic response, antioxidant capacity, inflammation, detoxification, and micronutrient status.

PROTOCOL NO:

STUDY:

INVESTIGATOR:

STUDY SITE:

TELEPHONE:

SPONSOR: Luke Backhouse

CONCISE SUMMARY:

This study is a randomized, double-blind, placebo-controlled clinical trial designed to assess the efficacy of a multi-ingredient plant-based supplement, known as Hence Greens Stacks, on various health parameters over a 12-week period. The primary objective is to evaluate the effects on vitamins and mineral levels in serum and overall quality of life. Secondary objectives include assessing adaptogenic response, antioxidant capacity, inflammation, detoxification, and micronutrient status.

No immediate risks are expected with this study. However, introducing new products may cause some people to have adverse reactions. If you are interested in learning more about this study, please continue to read below.

INTRODUCTION

In a world where unhealthy dietary patterns, irregular energy levels and suboptimal quality of life are common, there's a growing interest in interventions that may promote general health and wellness, including metabolic health and other aspects of overall well-being.

Micronutrient deficiencies can disrupt your body's balance. These essential elements, crucial for energy production, brain function, and immunity, can be depleted in our diets due to factors like soil quality and food processing. Lack of these micronutrients can lead to fatigue, brain fog, and diminished overall well-being. Furthermore, micronutrient deficiencies can weaken

the immune system, making us more susceptible to infections, and hinder our body's natural repair processes. In some cases, they may even contribute to the development of chronic health conditions.

This study is evaluating the potential benefits of a Greens Stack supplement by monitoring its effects on a group of participants over a defined period.

You are invited to take part in a research study. The decision to participate in this study is entirely voluntary. Your involvement will provide information that could help with the development of programs to improve human health and well-being. This Informed Consent Form (ICF) provides details about the study so that you are well-informed before deciding to participate.

Luke Backhouse is sponsoring this research study.

Please read this form carefully. Take your time to ask the study investigator or study staff as many questions about the study as you would like. The study investigator or study staff can explain words or information that you do not understand. Reading this form and talking to the study investigator or study staff may help you decide whether to take part or not. The decision to participate in this study is entirely voluntary. If you decide to take part in this study, you must sign your name at the end of this form and date it.

STUDY PROCEDURE

If you decide to participate, you will be one of the 200 participants in this study. The study will last for 12 weeks (about 3 months) and will involve the following procedures:

1. **Screening:** You will complete a medical questionnaire and undergo an initial health screening, including routine blood tests, to ensure you meet the eligibility criteria.
2. **Randomization:** You will be randomly assigned to one of two groups:
 - **Intervention Group:** You will receive the Greens Stack supplement.
 - **Placebo Group:** You will receive a placebo that looks and tastes like the Greens Stack supplement but does not contain the active ingredients.
3. **Supplementation:** You will take your assigned supplement daily for 12 weeks (about 3 months).
4. **Assessments:** You will visit the research center at baseline (week 0), 4 weeks, 8 weeks, and 12 weeks for assessments. These will include:
 - Blood samples to measure antioxidant enzyme levels and oxidative stress markers.
 - Physical performance tests (e.g., endurance and strength tests).
 - Mental performance tests (e.g., memory recall and mood questionnaires).
 - Quality of life questionnaires.

- 5. Follow-up Surveys:** You will complete weekly online surveys to report your mood, energy levels, and any allergies or side effects you may experience.

An institutional review board (IRB) is an independent committee established to help protect the rights of research subjects. XXX Institutional Review Board has reviewed the information in this consent document and has given approval for the study investigator to do the study. This does not mean the IRB has approved your participation in the study. You must think about the information in this consent document for yourself. You must then decide if you want to be in the study.

This study will use competitive enrollment. This means that when a target number of subjects begins the study, all further enrollments will be closed. Therefore, it is possible that you could be in the screening phase, ready to begin the study, and be removed without your consent if the target number of subjects has already begun the study.

WHAT WILL WE ASK YOU TO DO?

If you decide to participate in this study, participation in this study will last approximately 84 days (about 3 months) and will include 03 visits to the study center on week 04, 08 & 12 for the follow up assessments and includes weekly online health surveys to record self-reported measures. The study test products and study materials will be given to you at the local clinic.

You will be assigned by chance, like the flip of a coin, to **GROUP A (Intervention group)** or **GROUP B (Placebo)**. You will have an equal chance of being in each group. You will be instructed on how to use the product daily, follow a recommended diet, physical activity, and hydration plan and complete daily mindfulness practices for the entire study duration as described in the following table.

Program Intervention	GROUP A	GROUP B
(1) Green stack supplement	1 serving - morning	
(2) Placebo supplement	1 serving - morning	
Recommended Diet	High fiber, plant-forward, Mediterranean-like diet	
Physical activity plan	7,000-10,000 steps per day + 75 minutes of exercise per week	
Hydration plan	At least 0.5 oz of water/per 1 lb of body weight of water or other non-caffeinated unsweetened beverages	
Mindfulness activities	At least one (1) activity per day of your choice (diaphragmic breathing, stretching/yoga, prayer, meditation, mindful eating)	

Each study product listed below will be taken as a powder.

(1) Green stack supplement containing:

Allergens: none. Not tested for potential gluten content

(2) Placebo

Allergens: none. Not tested for potential gluten content

The study products should be kept out of the reach of children and stored as instructed.

In addition to following the program and taking the products, you will be required to wear a fitness tracker and provide daily feedback about your activities, sleep, stress, and wellbeing. This will involve recording the fitness tracker data and completing online questionnaires at predetermined time intervals.

Over the course of the study, you will be asked to record the following tracking and health data and transfer it online at least once a week:

- Daily tracking of program activities completed, from Day 1 through Day 84
- Body self-measurements (weight, height, and waist circumference) need to be taken on Day 1,2, 16 and 30, each month.
- Validated online questionnaires on Day 1, 16, 30, each month.

To ensure the study's results are as accurate as possible, you must take the product as recommended and follow the program guide consistently.

You will be asked to avoid additional drastic changes to your lifestyle during the study period (extended travel, relocation, major life events). This helps ensure that any observed effects can be attributed primarily to the program and not external factors.

If you experience significant life events, sickness, or changes during the study, please inform the study team.

HOW LONG IS THE STUDY?

You will participate in the program for 12 weeks (about 3 months).

ANY POTENTIAL RISKS, SIDE EFFECTS, AND/OR DISCOMFORTS

There are no known risks or side effects anticipated from following this program. However, as with any new food or dietary supplement, or lifestyle intervention there's always a potential for individual reactions. While the program is intended to support - antioxidant status, oxidative stress, adaptogenic response, cognitive function, energy levels and physical performance, metabolic health, stress management and other aspects of well-being, you might experience initial discomfort as your body adjusts to the new products and life-style regiment. The study products are formulated with natural plant-based ingredients and contain no known allergens.

Any discomfort or unusual feelings from the time of study product consumption until 24 hours following final day of consumption should be reported.

You will be provided with a telephone number for the study site and instructions to contact the study site if they experience an adverse event requiring medical care.

ALTERNATIVES TO PARTICIPATION

This study is for research purposes only. The only alternative is to not participate in this study.

NEW FINDINGS

Any new important information that is discovered during the study and which may influence your willingness to continue participation in the study will be provided to you.

POTENTIAL BENEFITS

This study is for research purposes. You might experience improvements in your antioxidant status, oxidative stress status, adaptogenic response status, cognitive functions, energy levels and overall well-being, however this cannot be guaranteed and not limited to. You may not experience any benefit from being in this study. There are no other known benefits to participants for participating in this study.

Information learned from this study may help in the development of a program for improving antioxidant, oxidative and adaptogenic response and overall well-being.

CONFIDENTIALITY

Records of your participation in this study will be held confidential except when sharing the information is required by law or as described in this informed consent form. The study investigator, the sponsor or persons working on behalf of the sponsor, and under certain circumstances, the United States Food and Drug Administration (FDA) and the Institutional Review Board (IRB) will be able to inspect and copy confidential study-related records which identify you by name. The Sponsor, P&K Research and IRB will keep your data confidential.

The study's overall results may be published; however, the identity of participants will not be included. Your name and other identifying information (such as date of birth) will never be used in any presentations, reports, or public documents related to this research study. Your data and information will be analyzed as part of a group and that all study results will be presented as a group.

COMPENSATION FOR INJURY

If you become ill or are injured while you are in the study, get the medical care that you need right away. You should inform the healthcare professional treating you that you are participating in this study. If you tell the study staff that you think you have been injured, then they will help you get the care you need.

If you are injured as a result of taking the study product or from procedures done for the purpose of this study, the sponsor will pay for those medical expenses necessary to treat your injury that are not covered by your medical insurance or any other third-party coverage. You will not lose any of your legal rights or release the sponsor, the study investigator, the study staff, or study site from liability for mistakes by signing and dating this consent document. To pay medical expenses, the sponsor will need to know some information about you like your name, date of birth, and social security number or Medicare Health Insurance Claim Number. This is because the sponsor has to check to see if you receive Medicare and if you do, report the payment it makes to Medicare.

You do not waive any of your legal rights by signing this form.

COSTS

There will be no charge to you for your participation in this study. The study products and study- related materials will be provided at no charge to you or your insurance company.

WHOM TO CONTACT ABOUT THIS STUDY

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns, or complaints about the study, please contact the study investigator at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

If you have questions regarding your rights as a research participant, or if you have questions, concerns, complaints about the research, would like information, or would like to offer input, you may contact the *XX Institutional Review Board Regulatory Department, XXX (mailing address)* at telephone number *XXX* or *XXX@gmail.com*.

VOLUNTARY PARTICIPATION / WITHDRAWAL

Your decision to participate in this study is voluntary. You may choose to not participate or you may withdraw from the study for any reason without penalty or loss of benefits to which you are otherwise entitled and without any effect on your future medical care. However, please note that the FDA requires that any information collected up to the point of your withdrawal cannot be removed from the study.

Your decision to withdraw will bring no negative consequences to you.

The study investigator or the sponsor can stop your participation at any time without your consent for the following reasons:

- If it appears to be medically harmful to you.
- If you fail to follow directions for participating in the study.
- If it is discovered that you do not or no longer meet the study requirements.
- If the study is canceled.

- For administrative reasons.

If you leave the study for any reason, the study investigator may ask you to have some end-of-study tests for your safety.

CONSENT

By signing this form, I confirm the following:

- I have read all of this consent form.
- All of my questions have been answered to my satisfaction.
- I can leave the study at any time without giving a reason and without penalty.
- I agree to the collection, use, sharing, and analysis of my personal health information and study information collected as part of this study by the sponsor and other authorized persons and regulatory agencies as described in this form.
- I will be given a copy of this signed and dated consent form to keep.
- I do not give up any legal rights that I would otherwise have if I were not in this study.

Your signature will be electronically captured if you agree to participate.

Participant Name	Signature	Date
Signature of Person Explaining Consent		

AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION

If you decide to be in this study, to confirm your identity, communicate with you, determine your eligibility, and send you the product, we will collect your name, address, phone number, email address, and date of birth. Through the surveys, we will collect personal health information related to the study. As a result, the study investigator and research team may collect the following personal and health data about you:

- Your name.
- Address.
- Phone number.
- Date of birth.
- Medical history.
- Information from your study records, measurements, and responses

Health data may come from your study records or from existing records kept by your investigator or other health care workers.

For this study, the research team may share health data about you with authorized users. Authorized users may include:

- Representatives of Hence Greens Stack.
- Representatives of IRB (an Institutional Review Board that reviews this study).
- The Food and Drug Administration (FDA) and other US federal and state agencies.
- Government agencies to whom certain diseases (like HIV, hepatitis, and STDs) must be reported.
- Governmental agencies of other countries.
- Other companies, research investigators and medical centers, such as laboratories and data storage companies, that work with the researchers and sponsor and need to access your information to conduct this study or evaluate the study results.
- A data safety monitoring board which oversees this research, if applicable.

Your health data will be used to conduct and oversee the research, including for instance:

- To see if the study products and program work and are safe.
- For other research activities related to the products and program.

Once your health data has been shared with authorized users, it may no longer be protected by federal privacy law and could possibly be used or disclosed in ways other than those listed here.

Your permission to use and share health data about you will end in 50 years unless you revoke it (take it back) sooner.

You may revoke (take back) your permission to use and share health data about you at any time by writing to the study investigator at the address listed on the first page of this form. If you do this, you will not be able to stay in this study. No new health data that identifies you will be gathered after your written request is received. However, health data about you that has already been gathered may still be used and given to others as described in this form.

Your right to access your health data in the study records will be suspended during the study to keep from changing the study results. When the study is over, you can access your study health data.

If you decide not to sign and date this form, you will not be able to take part in the study.

STATEMENT OF AUTHORIZATION

I have read this form and its contents were explained. My questions have been answered. I voluntarily agree to allow study staff to collect, use and share my health data as specified in this form. I will receive a copy of this form for my records. I am not giving up any of my legal rights by agreeing to participate.

Your signature will be electronically captured if you agree to participate.

Participant Name

Signature

Date

X. FDA Approval Process for New Dietary Ingredients (NDIs) in Dietary Supplements(U.S. Food and Drug Administration. (2023)).

1. Determine if the ingredient is an NDI:

Definition: Verify that the ingredient was not marketed in the U.S. before October 15, 1994.

Documentation: Manufacturers must provide evidence such as marketing records or publications. (U.S. Food and Drug Administration. (2023, February 9))

2. Prepare a Premarket Notification:

Who Must Notify: Manufacturers or distributors intending to market an NDI or dietary supplement containing an NDI.

Timing: Notify the FDA at least 75 days before introducing the product into the market.

3. Compile Necessary Documentation:

Contents:

Name and address of the notifier.

Name of the NDI (including Latin binomial for botanicals).

Description of the dietary supplement containing the NDI.

Conditions of use recommended in labeling.

History of use or evidence of safety.

Signature of the responsible person.

4. Submit the Notification:

Submission Methods: Notifications can be submitted electronically or via hard copy.

Contact Information: Email the Office of Dietary Supplement Programs at NDIN@fda.hhs.gov for assistance.

5. FDA Review Process:

Review Period: The FDA has 75 days to review the notification.

Evaluation: Assess the safety evidence and compliance with regulations.

Confidentiality: The FDA keeps the notification confidential for the first 90 days.

6. Public Disclosure:

Post-Review: After 90 days, the notification becomes public unless it contains trade secrets or confidential information.

Access: Information can be accessed through the FDA's Dockets Management Staff or regulations.gov.

7. FDA's Decision:

Approval: If the FDA finds the evidence satisfactory, the NDI can be marketed.

Denial: If the FDA finds issues, the product cannot be marketed until concerns are addressed. For more detailed guidance, visit the FDA's page on NDIs (FDA).

XI. SUMMARY

This document outlines a rigorous research proposal for a randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of the Greens Stack dietary supplement. The study aims to assess the supplement's impact on various health parameters, including antioxidant activity, adaptogenic properties, physical and cognitive performance, inflammation, detoxification, and micronutrient status in healthy adults over a 12-week period.

The study design involves recruiting 200 participants who meet the inclusion criteria and randomly assigning them to either the intervention group (receiving the Greens Stack supplement) or the placebo group. Participants will undergo comprehensive assessments at baseline, 4 weeks, 8 weeks, and 12 weeks, including blood samples, physical and cognitive performance tests, and quality of life questionnaires.

The primary outcomes will focus on measuring antioxidant enzyme levels and oxidative stress markers, while secondary outcomes will evaluate changes in physical endurance, strength, cognitive function, mood, and overall quality of life. Strict protocols will be followed to ensure participant safety, data integrity, and ethical conduct throughout the study.

The study will employ rigorous statistical analyses, including intention-to-treat analysis and mixed-effects models, to compare outcomes between the supplement and placebo groups. Comprehensive data analysis will be conducted, and the results will be disseminated through appropriate scientific channels.

The document also includes a detailed informed consent form, outlining the study's objectives, procedures, potential risks and benefits, confidentiality measures, and participants' rights. Additionally, it provides guidance on the FDA approval process for new dietary ingredients (NDIs) in dietary supplements, emphasizing the importance of premarket notification, safety documentation, and compliance with current Good Manufacturing Practices (cGMPs).

Overall, this study aims to contribute valuable insights into the multifaceted benefits of the Greens Stack supplement, supporting the company's mission of promoting health-led performance and longevity. The comprehensive approach ensures a rigorous evaluation of the supplement's efficacy and safety while prioritizing ethical conduct and participant well-being.

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