A PROPOSAL SUBMITTED TO NASENI GRANTS PROGRAMS

TITLE: SCALING UP PRODUCTION OF A PLANT-BASED ANTIFUNGAL OINTMENT: A Health Innovation for Accessible and Affordable Fungal Infection Treatment

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Executive Summary

Fungal infections represent a pressing but often underappreciated global health challenge, with both superficial and systemic manifestations contributing significantly to morbidity and, in some cases, mortality. Globally, more than one billion people are affected by superficial fungal infections annually, and approximately 150 million people suffer from serious or life-threatening fungal diseases[1]. In Nigeria and other tropical countries, the warm, humid climate creates conditions that favor the persistence and spread of dermatophytes and opportunistic fungal pathogens, amplifying the burden of disease in already resource-limited health systems[2]. Despite the availability of conventional antifungal drugs, their clinical effectiveness is undermined by multiple challenges including emergence of antifungal resistance, toxicity concerns, high cost of therapy, and limited availability of certain drugs in rural and peri-urban communities[3]. Herbal medicines on the other hand, are relatively cheap, easily affordable and accessible in addition to being readily accepted due to its purported claim of relative safety, these can bridge the gap between rising demands and limited therapeutic options. By utilizing the healing properties of medicinal herbs, we have created a new herbal antifungal ointment (NIPRIFAN^{TM}) that has shown great potential as a potent topical antifungal agent in initial laboratory studies. However, clinical research on the efficacy of this formulation is lacking.

NIPRIFAN^{TM} is a formulation of the extract of the aerial parts of the plant *Mitracarpus villosus*, locally known as “Irawo-ile” by the Yoruba tribe of Nigeria, “Obuobwa” in Igbo, “Gududal” by the Hausas and Fulani is traditionally, the plant is used in treatment of fungal skin infections. Based on the hypothesis that NIPRIFAN^{TM} is efficacious and cheap for the treatment of topical fungal infection, the goal of this project is to scale up and validate a novel herbal antifungal ointment, ensuring its stability, safety, and efficacy for widespread and affordable use in the management of fungal infections.

The objectives of the project are:

1. To scale up the production of NIPRIFAN^{TM} to pilot-scale manufacturing ensuring reproducibility, cost-effectiveness and Good Manufacturing Practices (GMP).
2. To conduct accelerated and real-time stability testing under varying storage conditions to establish physicochemical integrity, quality, shelf-life and storage requirements of the ointment

3. To generate and compile necessary data for regulatory approval laying the foundation for introduction to the drug market.

This concept is unique because it seeks to develop a completely indigenous product and scale-up same to make it assessable and available to the Nigerian populace. The proposed pilot scale-up production and clinical trials will be initiated and completed within 24 months. The project is estimated to cost N28,800,000.00 (Twenty-eight million, eight hundred thousand naira only) only. Upon completion of this project, it is expected that a safe, effective, affordable and accessible antifungal topical product with potential to strengthen local manufacturing and reduce dependence on imported products would have been developed.

BACKGROUND

Fungal infections represent a diverse spectrum of diseases caused by yeasts, dermatophytes, and molds. They range from superficial infections, such as tinea corporis and onychomycosis, to invasive systemic infections caused by opportunistic fungi like *Candida spp*. and *Aspergillus spp*.[4]. These infections contribute significantly to the global disease burden with increasing incidence and prevalence, particularly in low- and middle-income regions such as Asia and Sub-Saharan Africa. The World Health Organization (WHO) estimates that approximately 1.7 billion individuals suffer from superficial fungal infections each year, and over 150 million people experience severe fungal diseases with high mortality rates[1].

In Sub-Saharan Africa, including Nigeria, the burden is magnified due to environmental and socio-economic factors. Warm and humid climates favour fungal growth, while limited access to healthcare, overcrowding, and poverty contribute to the persistence and spread of infection. A recent survey in Nigeria found dermatophytic infections to be one of the most common skin diseases among children and adults, with prevalence rates ranging from 10–35% depending on the region[2]. In immunocompromised individuals particularly those living with HIV/AIDS, cancer, or diabetes, fungal infections pose a significant threat, often leading to systemic complications.

Over the past several decades, antifungal therapy has relied heavily on polyenes (e.g., amphotericin B), azoles (e.g., fluconazole, itraconazole), echinocandins (e.g., caspofungin), and allylamines (e.g., terbinafine). These drugs have revolutionized clinical practice, but they are not without limitations such as high cost, limited accessibility, emergence of drug-resistant strains, adverse reactions like nephrotoxicity and poor patient adherence[3]. These health trend analysis highlights the critical need for effective, accessible, and cost-effective antifungal therapies, including options derived from herbal and natural sources to address this public health challenges.

Phytomedicines, derived from plant-based bioactive compounds, offer a promising avenue for addressing the limitations of conventional antifungals. Ethnomedicinal practices across cultures have long utilized plants like *Punica granatum* (pomegranate), *Eucalyptus globulus*, *Azadirachta indica* (neem), *Syzygium aromaticum*, essential oils from cinnamon (*Cinnamomum zeylanicum*) and *Peganum harmala* for treating fungal infections, with modern studies validating their efficacy.

The plant *Mitracarpus villosus*, family, Rubiaceae which was formerly referred to as *Mitracarpus scaber* Zac is a small herbaceous plant that is widely distributed in the tropical countries including Nigeria. It is locally known as “Irawo-ile” by the Yoruba tribe of Nigeria,

"Obuobwa" in Igbo, "Gududal" by the Hausas and Fulani and traditionally used against ringworm, eczema, scabies, and other dermatophytic infections[5]. Preliminary phytochemical and pharmacological investigations confirm that the aerial parts of the plant contain bioactive compounds such as tannins, flavonoids, and saponins, which have demonstrated antimicrobial and antifungal properties[6]. Scientific studies have also demonstrated that incorporation of the extracts of *Mitracarpus villosus* into various cream bases have inhibited *Trichophyton*, *Microsporum*, *Epidermophyton species*, *Candida albicans* and *Aspergillus flavus* [7,8]. However, despite its traditional popularity and scientific claims, the antifungal property of the plant remains underexplored in terms of standardized pharmaceutical formulation and clinical evaluation.

In response to this identified gap, we have developed and trademarked a novel herbal ointment with demonstrated antifungal activity. The product (NIPRIFAN^{TM}) has been trademarked by the National Agency for Food and Drug Administration and Control (NAFDAC) and is now ready to move forward into large manufacturing, stability validation and clinical testing. The National Institute for Pharmaceutical Research and Development (NIPRD) where this product originates from has extensive background in herbal formulation and pharmaceutical development as such, it is uniquely positioned to lead and advance this project. Promotion of our innovation (NIPRIFAN^{TM}) would improve access to affordable topical antifungal treatment, reduce dependency on costly imported antifungal products, boost local manufacturing and contribute to sustainability of public health impact.

PROBLEM STATEMENT

Topical fungal infections are a major public health issue, despite their global prevalence and significant socioeconomic burden. In Sub-Saharan Africa, it affects mostly school-aged children and young adults while also contributing to morbidity and mortality in immunocompromised populations[2]. In Nigeria, challenges with treatment of fungal infections includes high cost of conventional agents, poor affordability, reduced accessibility, particularly in rural and underserved areas. Rise of antifungal resistance especially among *Candida species* compromises conventional therapeutic effectiveness, making some of these agents unreliable[3] while nephrotoxicity, and drug–drug interactions, restrict their clinical utility. Although herbal medicines offer promising antifungal activity, most remain confined to traditional use without validation for stability, safety, and efficacy. This lack of standardization creates a gap that limits their integration into mainstream healthcare. This project addresses this critical gap by advancing the scale up of a novel, already trademarked herbal antifungal ointment

(NIPRIFAN^{TM}), from laboratory development to scale-up production. Thus, reducing dependence on costly imported antifungal products, boosting local pharmaceutical manufacturing and improving health outcome of the Nigerian populace.

SIGNIFICANCE OF THE STUDY

Superficial fungal infections are a persistent challenge in the tropical and subtropical regions including Nigeria. These infections not only cause physical discomfort but also contribute to absenteeism, reduced productivity, and social stigma as a result of their visible manifestations. Conventional antifungal agents like the azoles although widely effective are limited by challenges of high costs, limited accessibility, emerging resistance and undesirable adverse effects. This underscore the urgent need for alternative therapeutic options that are affordable, safe, culturally acceptable, and effective. Our herbal topical antifungal preparation; NIPRIFAN^{TM}, has been developed to meet this need. Advancing NIPRIFAN^{TM}, to clinical effectiveness offers a practical intervention capable of to reducing morbidity, improving quality of life, and mitigating the psycho-social burden associated with these skin conditions. This innovation also serves to reduce dependence on imported synthetic drugs and provides an alternative with lower treatment cost for patients. In addition, this advancement represents an important step toward strengthening local pharmaceutical innovation with a potential to contribute to the diversification and expansion of the National Formulary with a credible plant-based topical alternative for treatment of fungal infections. Significantly, this endeavor aligns with the World Health Organization's advocacy for the integration of scientifically validated herbal medicines into formal healthcare systems[1]. Summarily, advancing the development of NIPRIFAN^{TM} holds considerable public health, pharmaceutical, socioeconomic, and scientific significance.

PROJECT GOALS AND OBJECTIVES

The overall **goal** of this project is to prepare our herbal antifungal ointment, NIPRIFAN^{TM}, for commercialization by scaling up production, evaluating its safety *in vitro*, and validating its stability in compliance with Good Manufacturing Practices (GMP).

The specific objectives include;

1. To scale up the production of the herbal antifungal ointment NIPRIFAN^{TM} from laboratory to pilot batch level using Good Manufacturing Practice (GMP) guidelines.
2. To carry out quality control and standardization of the ointment by establishing analytical parameters that ensures batch-to-batch consistency.

3. To conduct *in vitro* safety evaluation of NIPRIFAN^{TM} (e.g., skin irritation potential, tolerability) to establish preliminary safety data supporting further product development.
4. To perform pre-clinical *in vitro* antifungal activity studies on the scaled-up batches to confirm and validate the product's efficacy against common fungal pathogens.
5. To carry our accelerated and real-time stability studies on the scale-up batches under various storage conditions following the ICH guideline to determine its shelf-life and optimal storage conditions.
6. To generate scientific data for regulatory purposes that can facilitate wider approval, market expansion, and possible export of the product.
7. To build local capacity for the scientific development, testing, and commercialization of indigenous herbal medicines, especially those of topical formulations, thereby contributing to national self-reliance and healthcare improvement.

METHODOLOGY

a. Collection of raw materials and preparation of extract

The aerial parts of *Mitracarpus villosus* will be collected and validated as per earlier methods. The ethyl-acetate extract will be prepared by earlier standardized methods and stored appropriately.

b. Validation and optimization of the benchtop production of NIPRIFAN^{TM}

NIPRIFAN^{TM} is a topical ointment containing the ethyl-acetate extract of aerial parts of *Mitracarpus villosus* (*M. villous*). The ointment, weighing 100 g per batch, will be prepared following already established standardized methods according to the composition in Table 1. Appropriate quantities of emulsifying wax, BP, would be melted over a water bath at 70- 80 ^{o}C, appropriate quantities of liquid paraffin will be heated to 70- 80 ^{o}C and the white soft paraffin will be melted in the paraffin at 70- 80 ^{o}C. The melted liquid paraffin mixture would be incorporated into the melted wax at the same temperature (70- 80 ^{o}C). The melted bases would be integrated in the appropriate quantity of extract and homogenized to give a consistent mixture. The prepared ointment (NIPRIFAN^{TM}) will be packaged into air-tight containers and stored until further analysis.

Table 1: Composition of ingredients for the preparation of NIPRIFAN™

Ingredients	Quantity
Extract of *M. villous* (g)	1.5
Emulsifying wax BP (g)	30
White soft paraffin (g)	48.50
Liquid paraffin (g)	20
Total (g)	**100**

c. **Pilot scale production of NIPRIFAN™**

The above composition will be directly scaled up by a factor of 100. In-process quality control will be carried out during production and packaging cycles. Final quality control and shelf-life determination will be carried out on the finished products randomly selected from the batches. The product of this pilot scale up production will be used for the clinical trial.

d. Quality control

Various parameters like color, consistency, texture, temperature monitoring and mixing speed would be evaluated during production. The final product would be evaluated for appearance, texture, consistency, pH, viscosity, spreadability test, assay of active marker in extract using the UV Vis spectrophotometer (UV). Microbial contamination assessment and antifungal efficacy of the product will also be evaluated.

e. Stability testing

Accelerated stability studies would be conducted on the prepared ointment according to ICH guidelines[9] for 6 months while real-time stability testing would be conducted at room temperature for 12 months. Samples would be collected at 0, 3, 6 and 0, 3, 6, 9 and 12 months respectively for accelerated and real-time stability testing. Collected samples would be evaluated for appearance, consistency, pH, viscosity, assay of extract active marker and antifungal efficacy of the product. Data obtained would be used to determine storage conditions and shelf-life of the product.

PRELIMINARY DATA

Preliminary data of microbial on efficacy of different batches of the extract of *Mitracarpus villosus* shows the ethylacetate extract has significant extended activity against *Trichophyton rubrum* and *Trichophyton schoeleenii* for 7 days. It also showed suppressive activity against *Aspergillus niger* and *Aspergillus fumigatus* for 72 hours. Other types of extracts including water, methanol and hexane extracts showed no inhibition of growth of the selected microorganisms.

TIMELINES WITH MILESTONES

ACTIVITIES/MONTH	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Project Initiation and Team Meeting																								
Preparation of Standard Operating Procedures (SOPs)																								
Procurement of Raw material, Authentication,																								
Procurement of Equipment																								
Raw material Processing and Phytochemical testing																								
Formulation Development and Validation																								
Scale-up manufacture and Quality Assurance testing																								
Physicochemical evaluation																								
In vitro dermal safety testing																								
Pre-clinical *in vitro* antifungal activity																								
Stability testing (Accelerated and Real-time)																								
Data Analysis and Report Writing																								
Dissemination of Project Reports to Funding Agency																								

RESEARCH MANUFACTURING ENVIRONMENT

The manufacturing activities for this project will be conducted in the National Institute for Pharmaceutical Research and Development (NIPRD), Abuja, a Federal Government institution under the Federal Ministry of Health which is mandated to conduct research, development, and production of pharmaceutical products from indigenous resources. NIPRD is an ISO 17025:2017 certified laboratory, which provides assurance of quality management systems and compliance with global regulatory expectations for pharmaceutical research and production. NIPRD has qualified and experienced technical staff with different areas of specialization and expertise. In addition, NIPRD has a Drug Manufacturing Unit (DMU) that is fairly equipped for small- and medium-scale formulation, scale-up, and pilot production of pharmaceutical dosage forms and can be optimized to accelerate the translation of research findings into viable products such as NIPRIFAN^{TM}. Conducting the project within NIPRD's research manufacturing environment guarantees enhances the credibility of the project and lays a foundation for future scale-up and regulatory submission of such herbal products.

EXPECTED OUTCOMES AND BENEFITS

Upon successful completion of this project, a GMP-compatible pilot manufacturing process, validated quality control methods, and stability data supporting a defined shelf-life for a herbal antifungal ointment would have been developed. In addition, this project will produce a regulatory dossier, lay the foundation for commercialization, job creation, and technology transfer to small and medium-scale enterprises (SMEs) in the pharmaceutical and herbal product sectors.

DETAILED BUDGET FOR SCALE-UP PRODUCTION OF NIPRIFAN™

Description of Item		**Total (N)**
Item	**Description/ Justification**	
Personnel Costs/Allowances		
Principal Investigator	Project leadership, supervision of scale-up, regulatory coordination	2,000,000
Co-Investigators (3)	Laboratory supervision, data analysis, technical reporting	1,500,000
Research Assistants/Technicians	Laboratory work, animal studies, stability monitoring	1,000,000
Raw Materials and Consumables		
Herbal raw materials	Bulk procurement of plant material	1,000,000
Preparation of extract	For preparation of extract and solvents for extraction	1,200,000
Excipients and formulation materials	Ointment base materials, emulsifiers	1,500,000
Packaging materials	Tubes, jars, cartons, labeling for pilot and validation batches	1,200,000
Laboratory reagents and solvents	For microbial, antifungal	500,000
Animals, animal feed, bedding, and welfare supplies	For *in vivo* safety evaluation	1,000,000
Miscellaneous consumables	Glassware, PPE, disposables	500,000
Equipment and Scale-Up Infrastructure		
Pilot-scale mixer and homogenizer	For batch uniformity during scale-up	1,500,000
Semi-automatic filling and sealing machine	For packaging of test and validation batches	1,000,000
Stability chamber / environmental cabinet	For real-time and accelerated stability studies	2,500,000
Laboratory upgrades and calibration	Maintenance, minor tools, installation	1,000,000
Laboratory Testing and Analysis		
Antifungal efficacy tests	Evaluation against *Candida*, *Aspergillus*, *Trichophyton*, etc.	1,500,000
In vivo safety studies	Acute, sub-acute, and dermal irritation studies in animals	1,000,000
Stability studies	Accelerated (6 months) and real-time (12 months)	2,000,000
Microbial limit, preservative efficacy, and physicochemical tests	Required by GMP and NAFDAC standards	1,000,000
Data analysis and validation report	Statistical and scientific reporting	500,000
Regulatory Documentation and Quality Assurance		
GMP and SOP documentation	Development of production records, QC templates	500,000

Product dossier preparation and printing	Compilation for commercialization	700,000
Travel, Logistics, and Local Operations		
Transportation	Material sourcing	400,000
Team meetings and workshops	Team coordination, progress review	500,000
Dissemination and Reporting		
Interim and final report writing	Printing, binding, submission	300,000
Dissemination: Workshop/seminars/Conference	Dissemination of reports	600,000
Contingency		
Exigencies	Price variation, additional testing	1,000,000
TOTAL DIRECT COST		**27,400,000**
INDIRECT COST		**1,400,000**
GRAND TOTAL		**28,800,000**

NARRATIVE FOR JUSTIFICATION OF BUDGET

The total proposed budget of ₦28,800,000 million only has been judiciously structured to deliver the project objectives to support local innovation, value addition, and commercialization of indigenous technologies. The budget covers costs for personnel, raw materials and consumables, equipment and infrastructure, laboratory testing and analysis, Regulatory documentation and quality assurance, travel/local operations and logistics, dissemination, reporting and contingencies.

INVESTIGATOR'S CONTRIBUTIONS

S/No.	Name	Highest Qualification	Area of Specialization	Contribution
1.	Dr. Olubunmi J. Olayemi (Principal Investigator)	Ph.D.	Pharmaceutical Technology, Formulation and Quality control of phytomedicines	Pilot scale production of NIPRIFAN®. General co-ordination of project
2.	Dr. Jemilat Ibrahim (Co-investigator)	Ph.D.	Medicinal Plant Research and Traditional Medicine	Raw material sourcing and extraction
3.	Dr. Mercy I. Aboh (Co-investigator)	Ph.D.	Pharmaceutical Microbiology and Biotechnology	Microbiological studies including microbial limit and efficacy test
4.	Dr. Lucy B. John-Africa (Co-investigator)	Ph.D	Pharmacology and Toxicology	Safety studies in laboratory animals
5.	Pharm. Ekere E. Kokonne (Research Assistant)	M. Pharm.	Pharmaceutical Technology and Stability evaluation of Phytomedicines	Stability Studies and Determination of Shelf-life
6.	Pharm. Rashida Abdullahi (Research Assistant)	B. Pharm.	Pharmaceutical Technology	Formulation Studies and Quality Control

SOME of NIPRD's PUBLISHED ARTICLES SHOWING EFFECTIVENESS OF *Mitracarpus villosus*

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