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UFZ

Workshop

Drug lifecycle control in Subsaharan Africa

From production to responsible safe disposal and elimination in wastewater treatment plants

(Med4Africa)

Faculty of Pharmacy
University of Ibadan, Nigeria

AUGUST 29, 2022

Manufacturing Skills Building in Africa: Experience from Nigeria

Presented by

Professor Chinedum Peace Babalola *(B.Pharm, FAS, FAAS)*

Centre for Drug Discovery, Development and Production (CDDDP)

University of Ibadan, Ibadan, Nigeria

During workshop on Drug Lifecycle Control in Sub-Saharan Africa,
Gold Crest Hotel, Arusha Tanzania
29 August 2022

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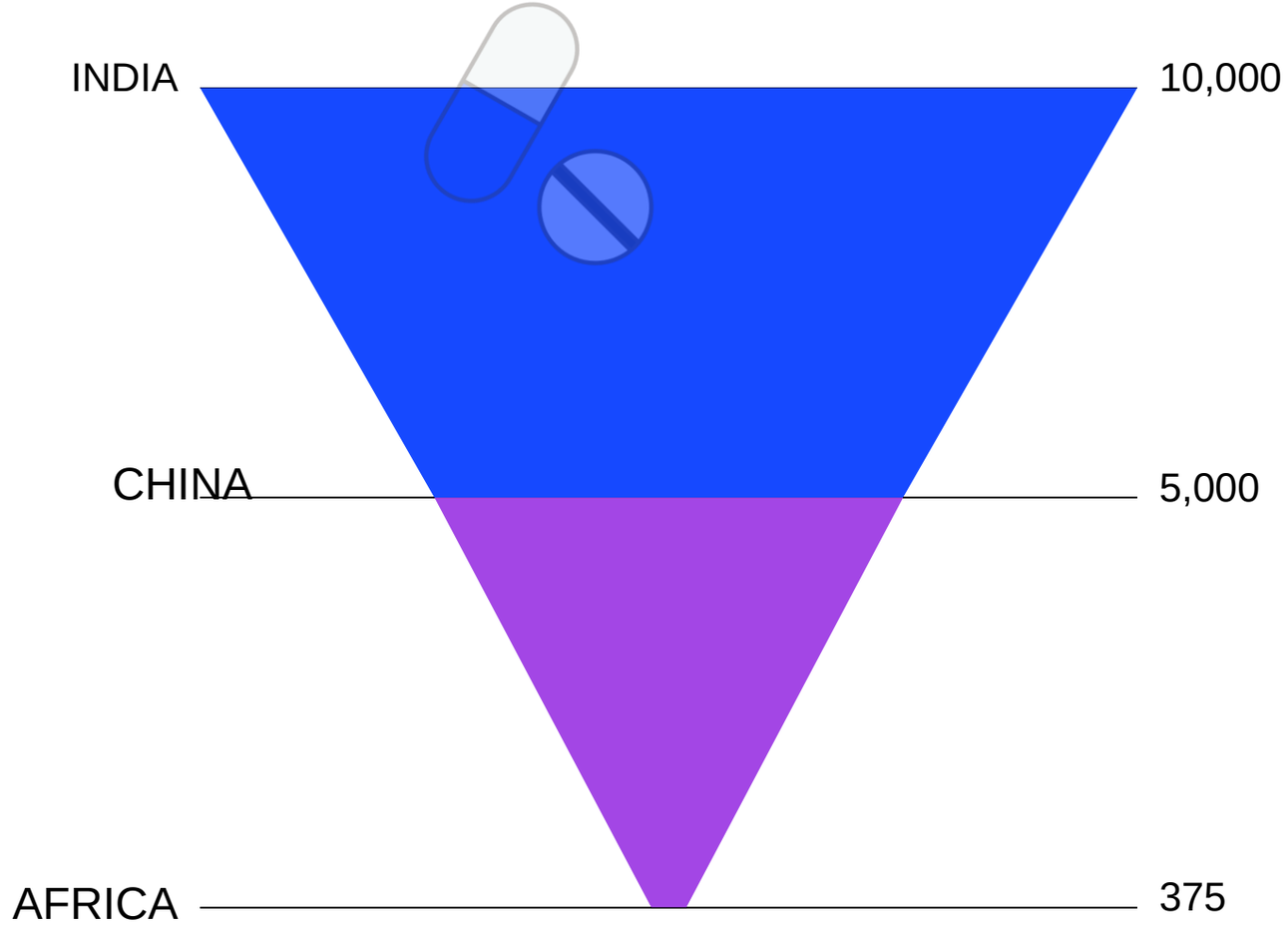
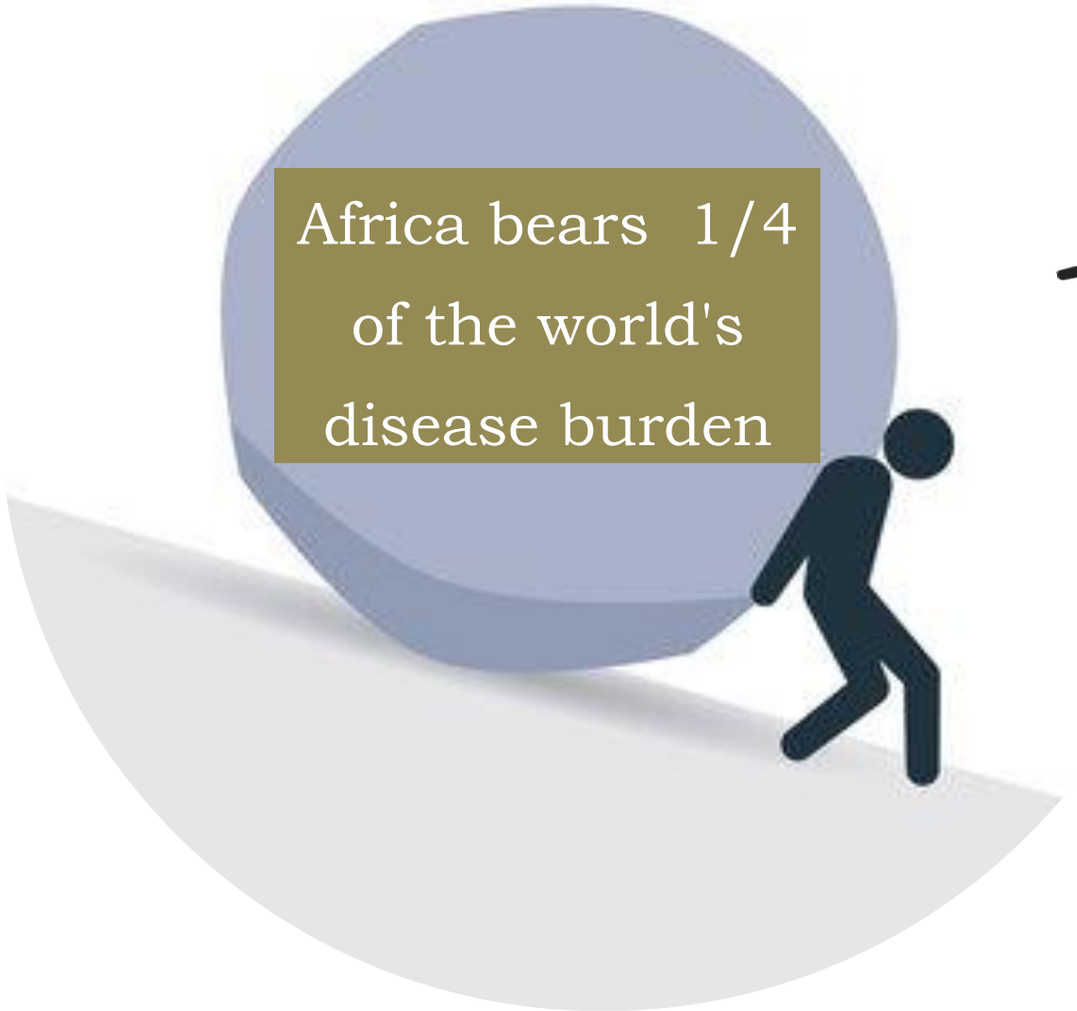


Approximate number of Pharma Manufacturers

WITH ROUGHLY THE SAME POPULATION

>90% of the drugs available in Sub-Saharan Africa are imported

There are too few Pharma companies manufacturing in Africa



Yet, consumes only 1.2% of pharmaceutical products indicating lack of access

Improving health outcomes in the continent strongly requires an increase in its manufacturing capacity and output

Challenges faced by Pharma in Nigeria

- The Pharmaceutical Manufacturers Group of the Manufacturers Association of Nigeria (PMG-MAN), has the capacity to be a giant in the manufacturing, distribution in Sub-Saharan Africa
- Significant attention has not been paid to the local production of raw materials, pharmaceutical dosage formulations, or processing equipment.
- Due to the lack of domestic of APIs and excipients, the country is forced to rely on India and China for supply. This causes a hike in prices and foreign exchange difficulties.
- Over the last few years, Nigeria has struggled with a lack of foreign exchange, which has contributed to a 200% rise in the cost of imported drugs.
- Interestingly, over the past two decades, the Nigerian pharmaceutical industry has invested more than NGN400 billion (USD 969 million) in boosting its infrastructure in order to obtain the WHO prequalification required for foreign competition. Despite these investments and big steps, the sector still faces multifaceted challenges

DRUG LIFECYCLE

RESEARCH

Drug Discovery and Development in the Lab

MANUFACTURING

Local Manufacturing Companies must be able to develop local drugs for use

REGULATION

Need for Registration and Approval for use

DISTRIBUTION

Post-Manufacturing distribution and in fact, exportation of finished drug products also relies on Pharma companies.

- The Intrinsic role of Manufacturing in the Drug Lifecycle indicates its urgent need for improvement and progress.

- Manufacturing skills building involves the ability of Pharma companies to produce drugs starting from the Active Pharmaceutical Ingredient, creating Original formulations, and enabling self-sufficiency of the continent to rely on its natural flora for drug discovery useful in tropical diseases.

African Pharma manufacturing status

- In North Africa and South Africa, the status of local manufacturing of pharmaceutical products is high
- Egypt and Tunisia produce most of their national requirements for essential medicines.
- Morocco, the second largest African pharmaceutical producer, after South Africa,
- Morocco has 40 pharmaceutical industrial units supplying 70% of domestic demand and exporting 10% to neighbouring African countries.
- Nigerian pharma of 180 produce at less than 40% capacity

MANUFACTURING SKILLS ALSO RELY ON

1

Capacity of Regulatory agencies to provide guidelines

2

Training status of staff

3

Industrial incentives from Government

4

Consumer attitude

CURRENT STATE OF MATTERS

WHO-cGMP

Only about four (4) out of 180 companies are WHO- cGMP qualified in Nigeria

INPUTS

Unavailability of inputs and infrastructure from the Government to support production locally.

PERSONNEL

Insufficient number of well-trained Personnel to undertake Manufacturing projects in Pharma Industries

HIGH COST

High cost of Pilot medicine projects on a Production Scale

Increasing Pharma Manufacturing Skills relies on marrying the "town" and "gown"

EFFECTIVE TRANSLATION OF ACADEMIC RESEARCH IS VERY IMPORTANT

The "Prototype Pipeline"

EFFECTIVE SKILL BUILDING FOR THE PHARMACEUTICAL SECTOR

Roadmap To Increasing Drug Manufacturing in Nigeria

1. TRAINING IN PHARMACY SCHOOLS

Increasing Capacity starts with equipping the future Pharmacy workforce with skiils required to carry out novel industrial production

2. INCREASING INDUSTRIAL CAPACITY

Creating guidance documents and projects to enable Pharma companies embark on primary drug manufacturing.

3. CERTIFICATION AND QUALIFICATION

Equipping Pharma Companies with necessary capacity building and requirements to attain qualification status.

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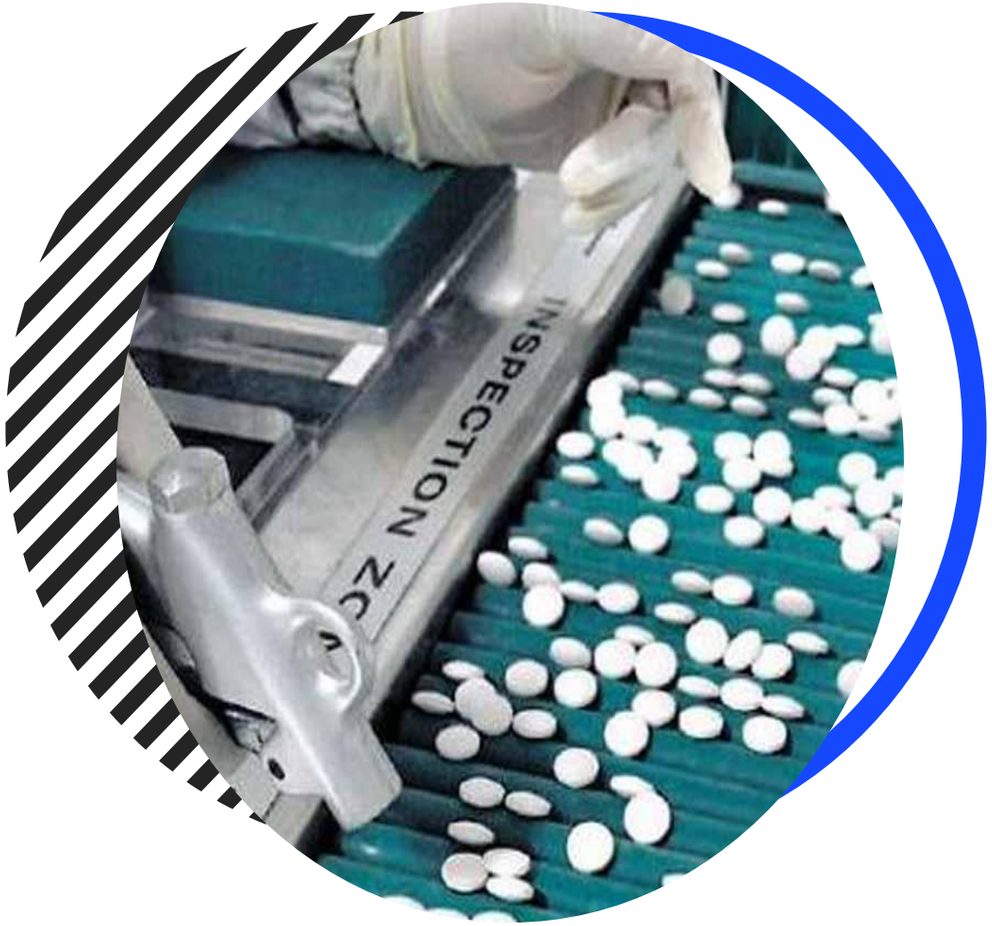


EXPERIENCE FROM NIGERIA

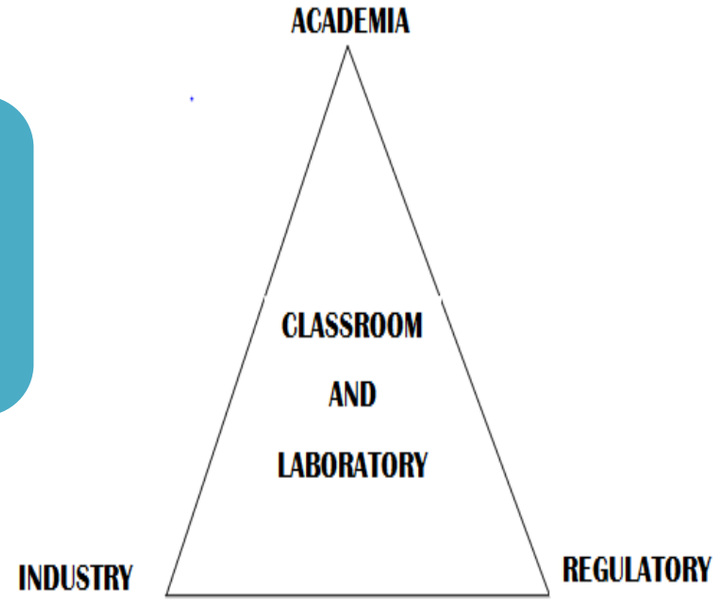
CDDDP – An Academic Initiative

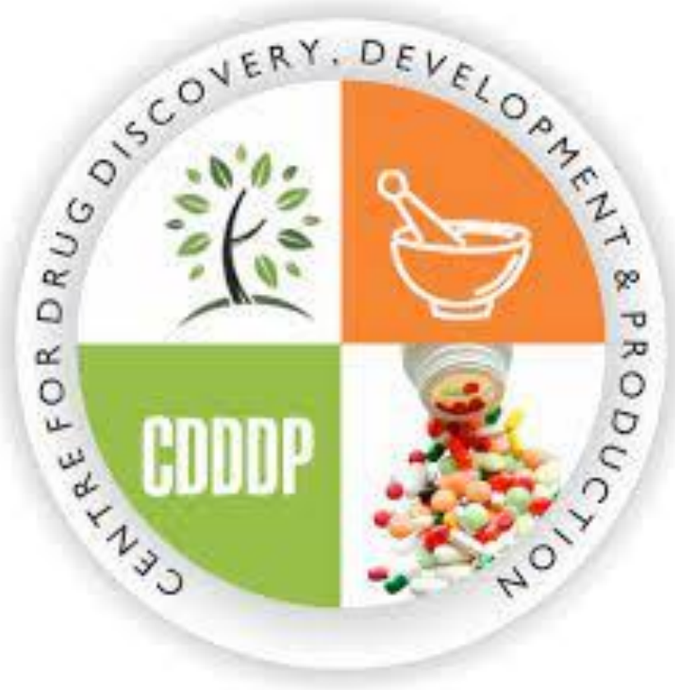
Proposal writing & Grant winning

Postgraduate curricula development and Senate approvals

Short courses on GxP academy

Research to medicinal products





- ~~T~~he Centre for Drug Discovery Development and Production (CDDDP), University of Ibadan was set up in 2012 through a grant from the MacArthur Foundation (USA)

- A platform for world-class training in drug discovery, development, production and medicine regulation as well as to provide opportunities and services for research and development of quality medicines that meet the specific needs of Nigeria, sub-Saharan Africa and the whole of Africa in general.

- In 2014 became recognized as a NEPAD Regional Centre for Regulatory Excellence (RCORE) for oversight functions in medicine regulation

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SPECIFIC OBJECTIVES

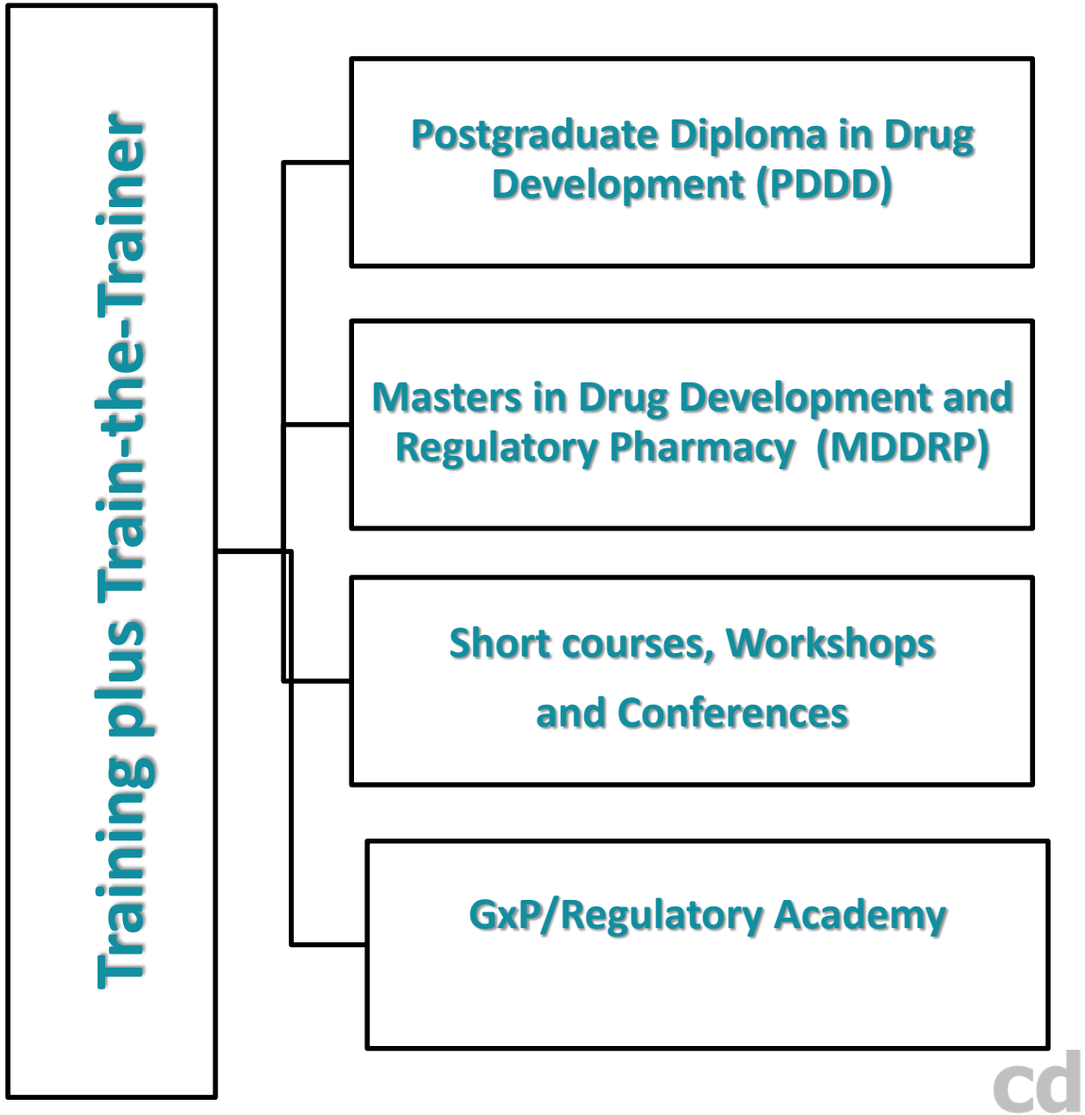
- Running Postgraduate Diploma in Drug Development (PDDD) & Masters in Drug Development and Regulatory Pharmacy (MDDRP)
- Establishing pilot cGMP facilities pre-qualifiable by WHO for medicine development (API, FPP)
- Offering services such as quality assurance of drugs, bioequivalence studies, clinical trials, etc
- Translating research findings to finished products
- Establishing GxP academy via short courses/workshops

Preamble

- The vision of the centre was born after attending my first module of IPAT programme in KSP, Tanzania on Industrial and Regulatory Pharmacy

- A life-transforming experience indeed!!!

Training Profile of CDDDP



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Postgraduate Diploma (PDDD) and Masters Programme (MDDRP)

Students in group discussion

Lecture session by Prof. Joe Fortunak

Courses

Some of the courses include:

- Fundamentals of Drug Discovery
- Drug Development, Regulatory and Quality Compliance
- Drug Manufacturing Processes
- Regulatory Documents and Generic Drug Approval Submissions.
- Basics of Clinical Trials and Bioethics in Drug Development

Short Courses and Conferences

- A one-day workshop for manufacturers titled ‘From Powder to Tablet’ was held in conjunction with BASF.
- About 70 people from top pharmaceutical companies in Nigeria were trained on several topics.
- Some of the participants thereafter registered as pioneer students of PDDD.

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Workshops and Conferences

- The Centre has successfully organized four workshops
- Two international conferences: NAFDAC DG present; together with Reckitt Benckiser
- Conference stakeholders included policy makers, pharma industrial professionals, academia, regulators and medicine endusers
- It was a characteristic marriage of **‘town’** and **‘gown’**

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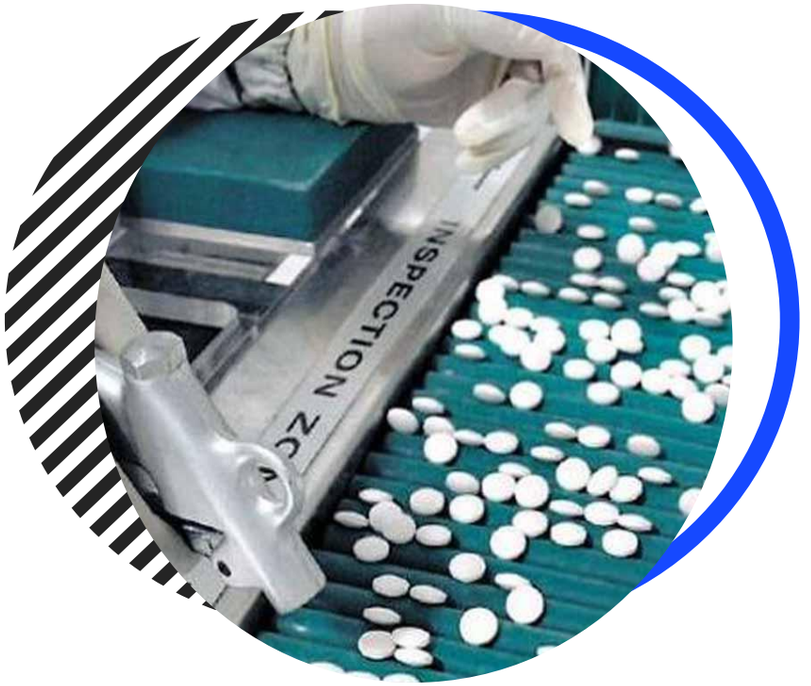
Presentation of some research products from CDDDP

COVID-19 AND POST-COVID ERA



Roadmap to Search for Anti-Covid Medicine from natural sources

1. Holistic Literature review on indigenous plants with antiviral activity
2. Identify existing herbal formulations with mere anti-COVID-19 claims
3. *In silico* analysis with a focus on SARS-Cov-2 virus
4. Selection of candidate plant(s) based on strong evidence
5. Acute and subacute toxicity investigation
6. *In vitro* antiviral studies
7. Pharmacognostic & Pharmaceutical Standardization of identified therapies
8. Formulation of COVID-19/antiviral phytomedicines into Dosage forms for clinical trial/application

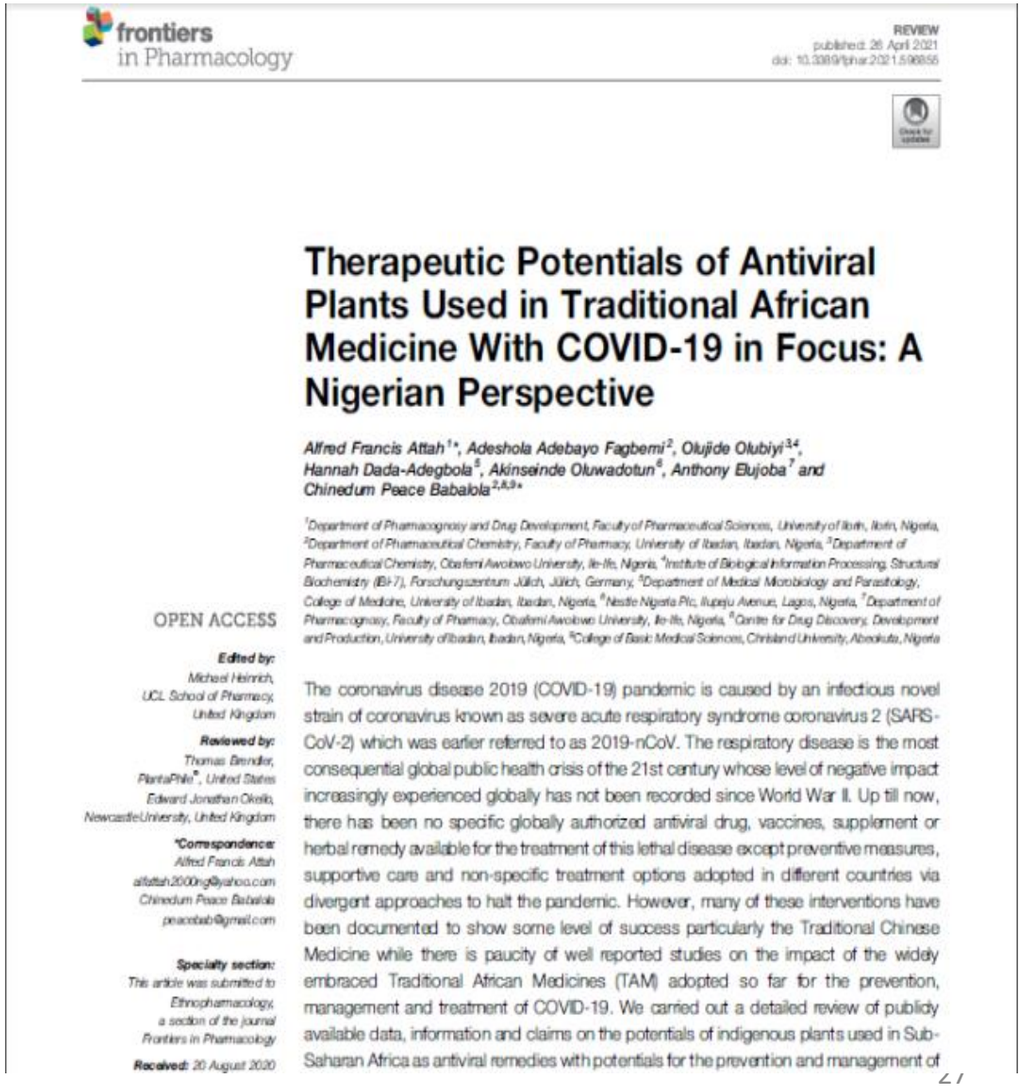
Literature Review

- Evidence-based documented scientific publications on the antiviral and immuno-modulatory potentials shows that African plants could help in the management of COVID 19

- Some of these African plants are referred to as immunue boosters. These include: *Vernonia amygdalina*, *Moringa oleifera*, *Telfairia occidentalis*, among others.

- We carried out an extensive literature review on African traditional plants and our findings have been published in a leading academic journal, **FRONTIERS IN PHARMACOLOGY (Impact Factor: 5.810)**

- **DOI:**10.3389/fphar.2021.596855



frontiers in Pharmacology

REVIEW
published: 26 April 2021
doi: 10.3389/fphar.2021.596855

Therapeutic Potentials of Antiviral Plants Used in Traditional African Medicine With COVID-19 in Focus: A Nigerian Perspective

Alfred Francis Attah[1], Adeshola Adebayo Fagbemi[2], Olujide Olubiyi[3,4], Hannah Dada-Adegbola[5], Akinseinde Oluwadotun[6], Anthony Elujoba[7] and Chinedum Peace Babalola[2,8,9]**

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The coronavirus disease 2019 (COVID-19) pandemic is caused by an infectious novel strain of coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which was earlier referred to as 2019-nCoV. The respiratory disease is the most consequential global public health crisis of the 21st century whose level of negative impact increasingly experienced globally has not been recorded since World War II. Up till now, there has been no specific globally authorized antiviral drug, vaccines, supplement or herbal remedy available for the treatment of this lethal disease except preventive measures, supportive care and non-specific treatment options adopted in different countries via divergent approaches to halt the pandemic. However, many of these interventions have been documented to show some level of success particularly the Traditional Chinese Medicine while there is paucity of well reported studies on the impact of the widely embraced Traditional African Medicines (TAM) adopted so far for the prevention, management and treatment of COVID-19. We carried out a detailed review of publicly available data, information and claims on the potentials of indigenous plants used in Sub-Saharan Africa as antiviral remedies with potentials for the prevention and management of

Virtual screening of >1.2million compounds against SARS-CoV2 main protease

molecules

MDPI

Article

High Throughput Virtual Screening to Discover Inhibitors of the Main Protease of the Coronavirus SARS-CoV-2

Olujide O. Olubiyi [1,2,*], Maryam Olagunju [1], Monika Keutmann [1] and Jennifer Loschwitz [1,3] and Birgit Strodel [1,3,*]

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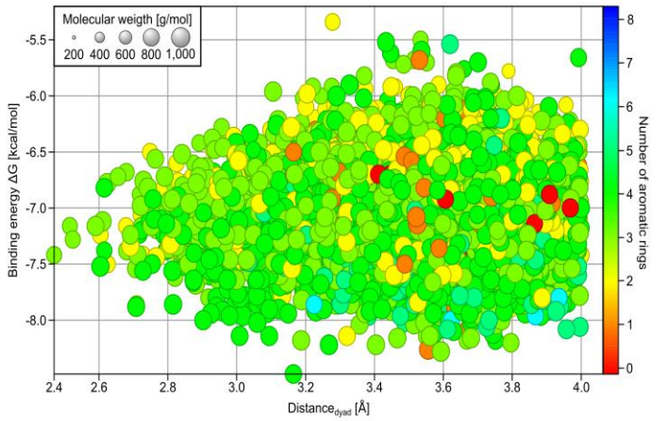


Figure 2. Distribution of the best binding synthetic compounds in terms of $\mathbf{d}_{dyad}$ (**x**-axis), **ΔG** (**y**-axis), number of aromatic rings (color), and molecular weight (circle size). The ΔG and d_{dyad} values are averages obtained from ensemble docking. Only compounds with $\Delta G < -5.0$ kcal/mol and $d_{dyad} \leq 4$ Å are shown.

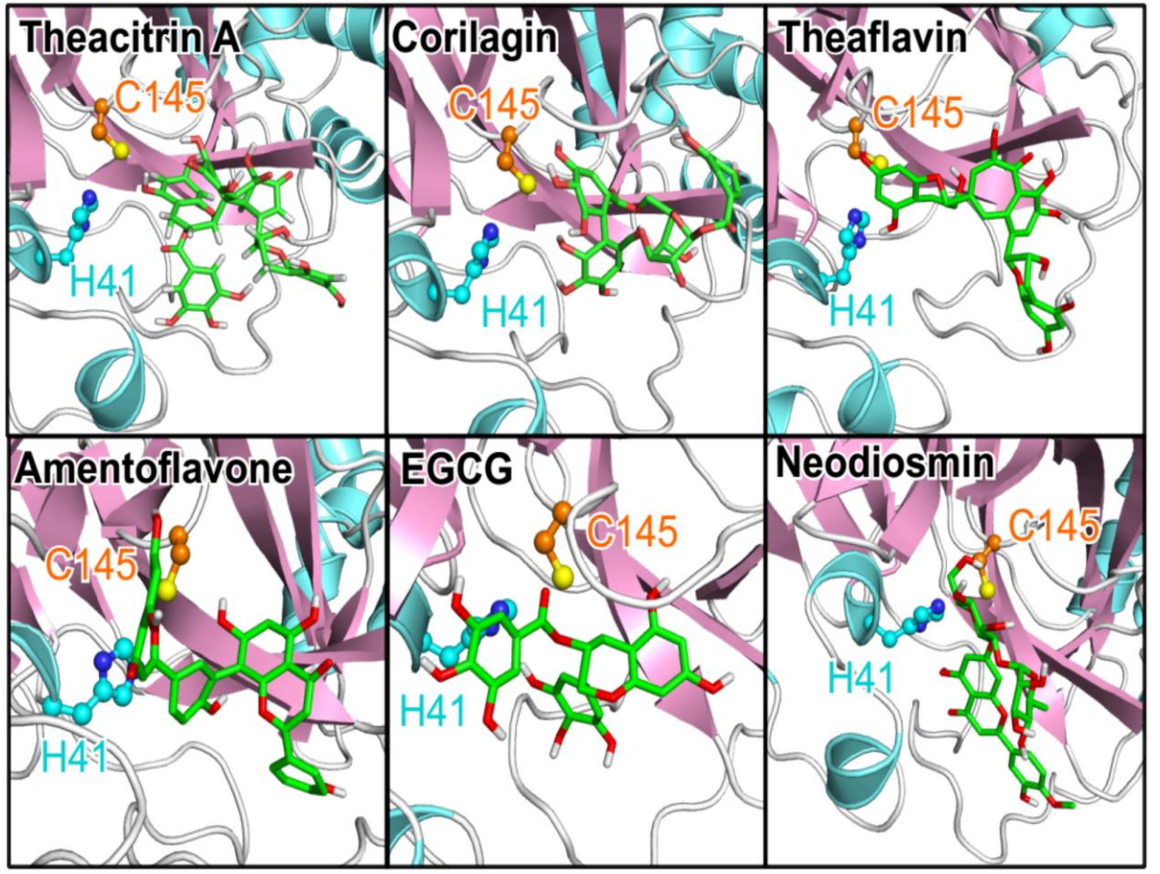


Figure 7. The poses of the six best natural drugs. The top six compounds bind well to the substrate site in terms of both ΔG and closeness to the catalytic dyad of $3CL^{pro}$. The same protein and ligand representation as well as color scheme as in Figure 1 are used.

The NPs can be seen interacting closely with the virus' 3CLpro **catalytic dyad** amino acids **Histidine 41** and **Cysteine145**.

Plants with potential activities against SARS CoV-2 based on CADD – Vive Forte

Name: *Andrographis paniculata*

- Andrographolide; constituent of plant with good antiviral property
- IC_{50} of 0.036μM & 0.034 μM against SARS-CoV2 infected Calu-3 cells for *A. paniculata* and andrographolide, respectively; covalent inhibitory mechanism

Name: *Scoparia dulcis*

- Scutellarin; phytochemical in plant reported to have high antiviral activity
- IC_{50} of 0.86 μM against 3CLpro and helicase

Name: *Terminalia catappa*

- Chebulagic acid; molecule present in this plant; exhibits profound antiviral activity
- IC_{50} of 8.6 μM against Plpro

Name: *Allium cepa*

- Plant rich in quercetin which displayed IC_{50} of 8.6 μM against Plpro

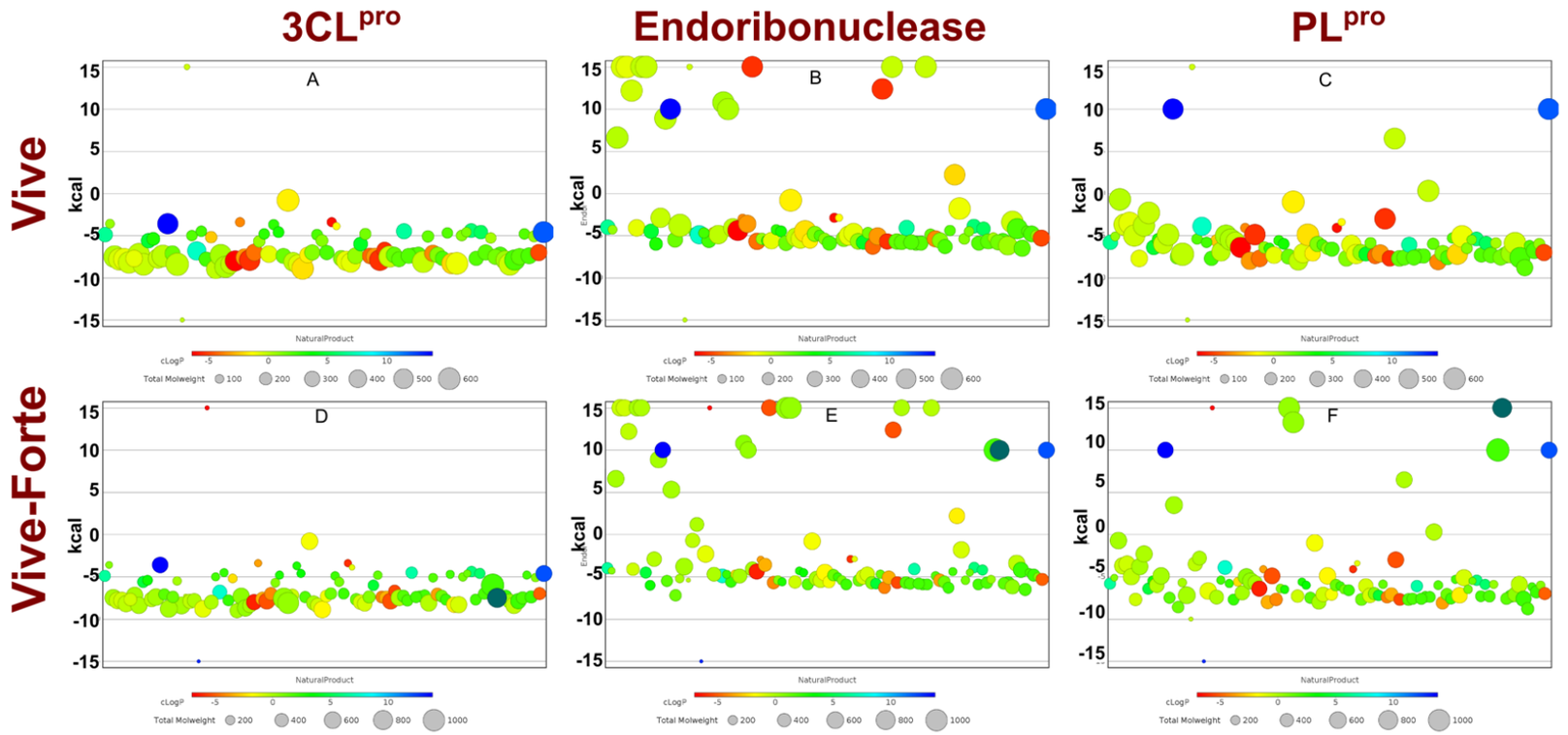
Identified herbal preparations with potential anti-COVID activity

VIVE®: Polyherbal formulations rich in flavonoids. Fortified with antiviral plants to **VIVE FORTE**

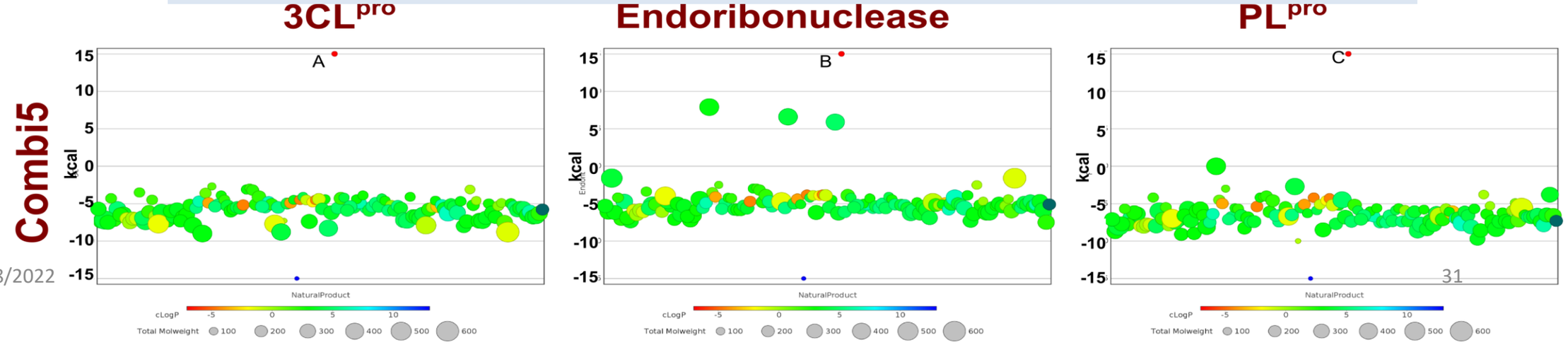
COMBI-5: A polyherbal supplement made up antiviral phytochemicals and micronutrients such as Zn and Se; capable of limiting viral replication and oxidative stress

Antiviral Polyorganic (MO) whose main Active Plant Ingredient (API) has been freed of its potentially toxic component. An accidental discovery

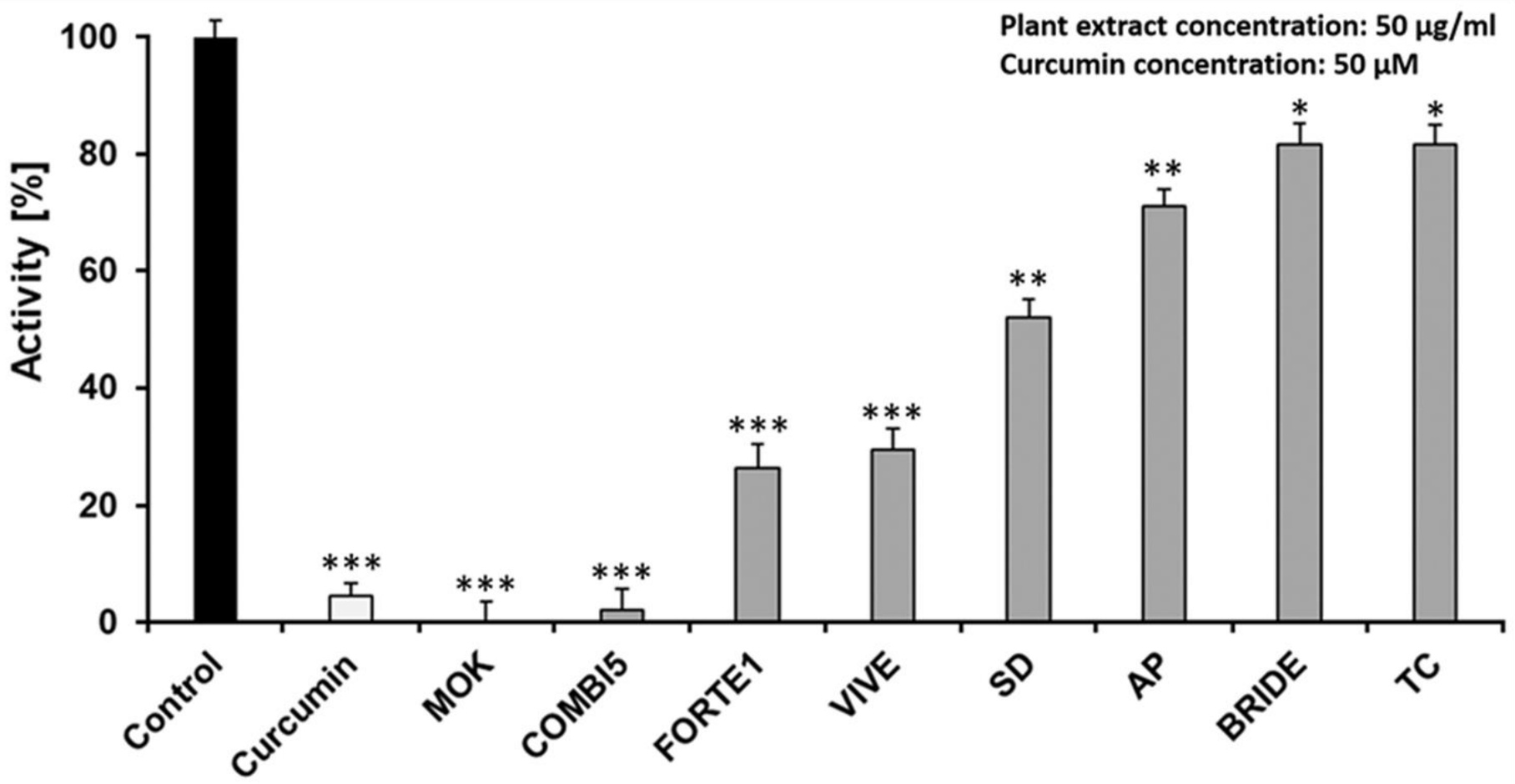
IN SILICO EVIDENCE OF ACTIVITIES



Vive-Forte: Vive + *Andrographis paniculata*, *Scoparia dulcis*, *Terminalia catappa*

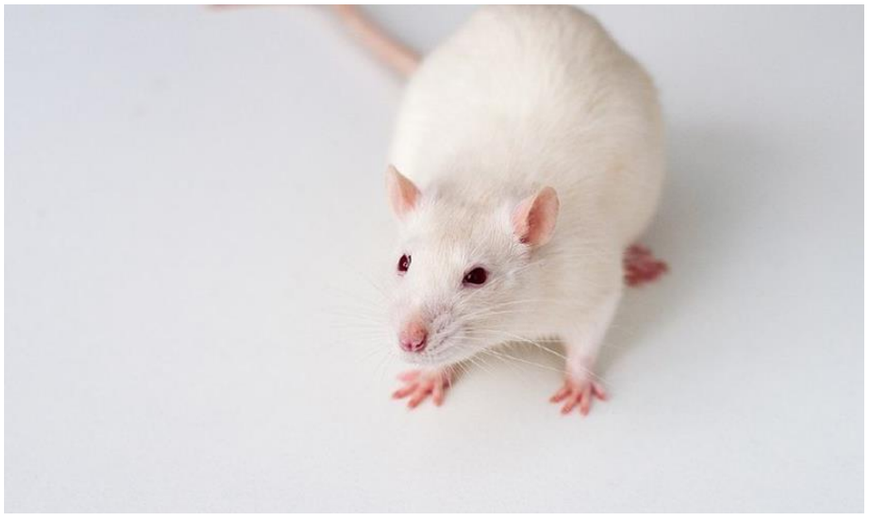


IN VITRO EVIDENCE OF ANTIVIRAL ACTIVITY



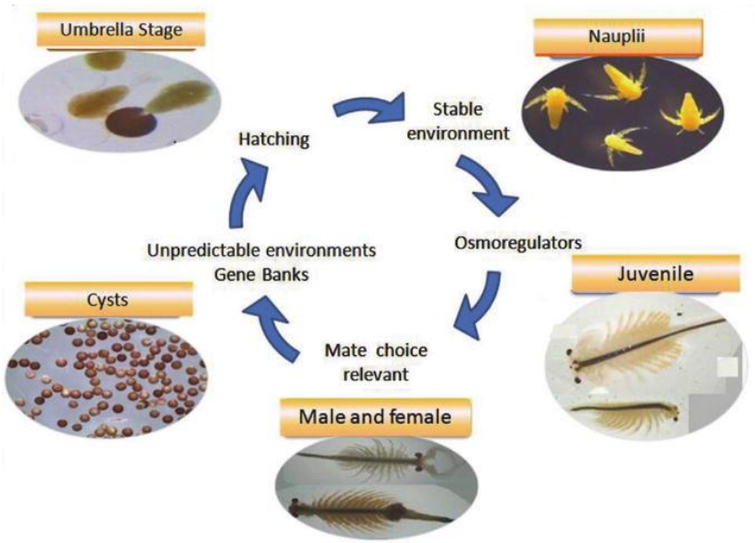
Preliminary findings of *in vitro* screening. A comparative graph showing activities of the four phytomedicines, positive control – Curcumin and other antiviral plant extracts screened for the residual activity of SARS-CoV-2 $3CL^{pro}$

In vivo evidence of safety of novel antiviral phytomedicines



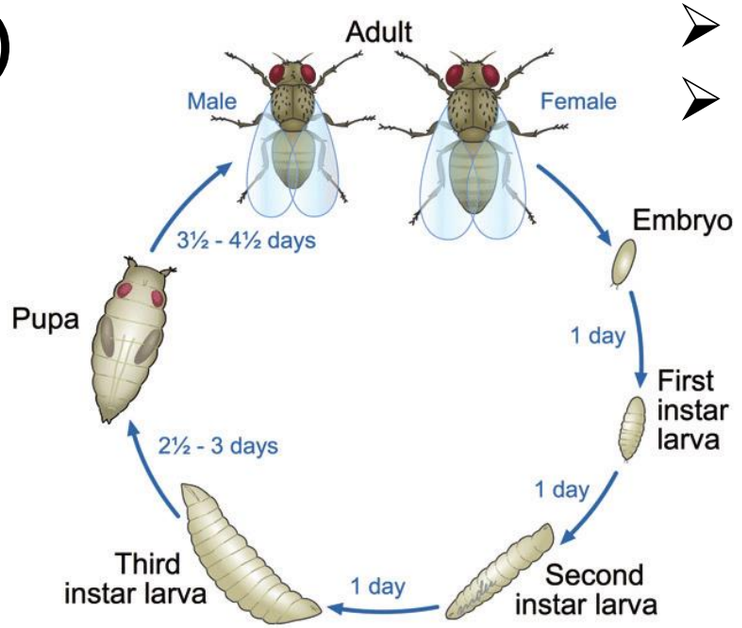
1. VIVEFORTE
2. COMBI5
3. MO Polyorganic

1. 200.198
2. 91.698
3. 115.1337



LD50 and subacute toxicity
In rodents

- ❖ **Acute toxicity (>2000 mg/kgbw)**
- ❖ **Subacute toxicity**
- ❖ **Histopathological examination**
- ❖ **Biochemical analysis**
- ❖ **Haematological analysis**



Brine shrimp cytotoxicity

- ➢ **Safety**
- ➢ **Pharmacology**

Drosophila melanogaster
✓ **Mechanistic assessment of safety – on-going**

Published Case Report on Combi-5

Managing Mild and Moderate Symptoms of COVID-19 in Infected Subjects using Combi-5 Herbal Supplement: Case Series.

Running Title: Combi-5 Herbal Supplement in Managing COVID-19 Symptoms.

[1,2]Augustine Anayochukwu Onyeaghala, [3, 4, 5] Chinedum Peace Babalola, [6]Emmanuella Ogechi Onyeaghala, [7]Olujide O.Olubiyi, [8]Francis Alfred Attah,

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DE GRUYTER J Complement Integr Med 2021; aop

Case Report

Augustine Anayochukwu Onyeaghala*, Emmanuella Ogechi Onyeaghala, Chinedum Peace Babalola, Oluwasanmi Olayinka Aina and Dadik Jelpe

Herbal supplement (Combi-5) in the management of COVID 19 individual with mild to moderate symptoms: a case report

https://doi.org/10.1515/jcim-2020-0430
Received October 15, 2020; accepted November 16, 2020; published online May 7, 2021

Abstract

Objective: To explore repurposing known natural products for managing patients with mild to moderate symptoms of COVID-19.
Case presentation: We present a case report of a middle aged woman, who was positive to COVID 19, with mild to moderate symptoms; who self –managed at home using well formulated herbal supplement (Combi-5) taken along with vitamin C and Zinc supplements. She recovered within a short time.
Conclusions: While we may not conclude from this report that Combi-5 was solely responsible for the recovery of the patient, we strongly believe that it played significant role through different mechanisms in facilitating early recovery from the infection. Further studies are needed to evaluate the phytochemical and pharmacological constituents of CoV-2 and conduct randomized controlled trial to elucidate its clinical benefits.

Keywords: Combi-5; COVID 19; SARS CoV-2.

Introduction

The corona virus disease 2019 (COVID 19) caused by severe acute respiratory syndrome novel coronavirus 2 (SARS-nCoV-2), since reported has infected over 37,807,136 million of individuals and caused 1,082,246 mortalities across the globe [1]. The pandemic has caused significant social, economic and health disruptions and impact across countries. As at the time of documenting this report, neither a therapeutic cure nor preventive solution has been developed, but efforts are being targeted towards repurposing drugs for COVID 19 including traditional therapies [2]. In the instance, non-pharmacological approaches have been implemented with a view to limiting the spread of the virus.

Organogram of Collaborators

Babalola Research Team

University of Ibadan	Chrisland University	UCH	RX Agro processing (MSME)	OAU	Unilorin	Nnamdi Azikiwe University
Dr. Amos Abolaji	Tosin Ayodele	Dr. Augustine	Pharm. Dotun	Prof. Elujoba	Dr. Attah	Prof. Uzochukwu
Dr. Olayinka Kotila		Dr. Hannah Dada-Adegbola		Prof. Olubiyi		

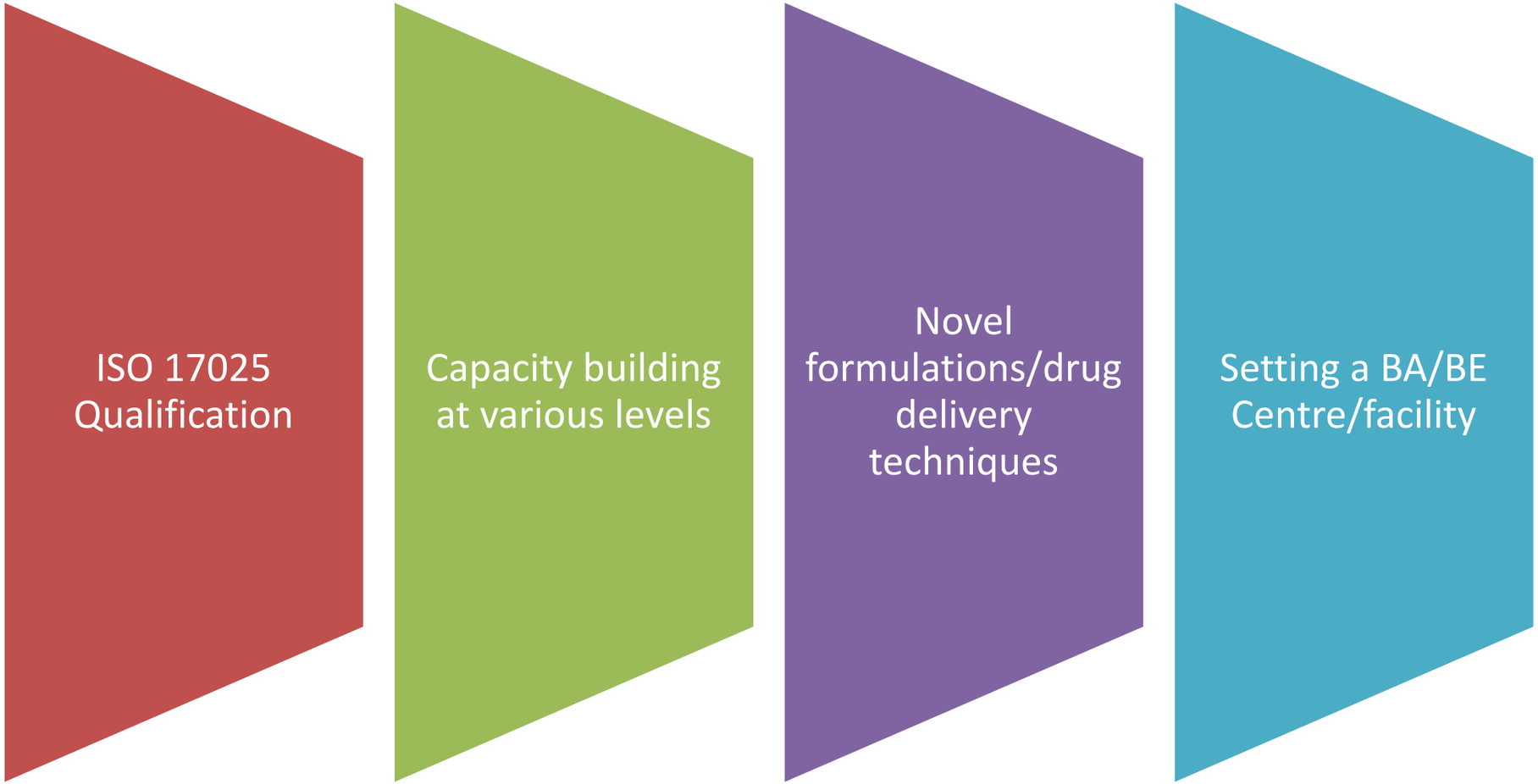
Institute of Biological Information Processing, Germany (enzyme studies & *in silico assay*) & Department of chemistry

Capacity strengthening on Pharma in Nigeria

USP-PQM+ Trainings

- Quality Risk Management
- Good Manufacturing Practices Guidelines on Factory Inspection
- Virtual training on Essential Requirements for Developing Quality-Assured, Generic Active Pharmaceutical Ingredients and Finished Dosage Forms (other African Pharma companies participated)
- CDDDP a core-flex partner on PQM+

Future Prospects



Ensuring Medicine Quality in Africa: USP-PQM PROGRAMME

- **AIM - the incorporation of Pharmaceutical Quality Assurance within the curriculum of Nigerian University programmes**
  - Pharma industry may go extinct if pharmacists don't occupy that space or focus only on clinical pharmacy
  - Nucleus committee - academics, industry practitioners and regulators between 2015-2016
  - Partnership between USP and PCN (Regulatory agency for Pharmacy Practise in Nigeria)
  - Designed curricular for undergraduate programme on Pharmaceutical Quality Systems (PQS)
  - To run from 200 t0 600 levels
  - Mainly basic knowledge

Some topics covered:

A) Pharmaceutical Quality System

- Pharmaceutical Supply Chain;
- Good Practices (GxAcademy)
- ICH Series;
- ISO Standards;
- Quality Risk Management;

B) Regulatory

- Good Regulatory Practices
- Good Pharmacovigilance Practices;
- Pre-Approval Inspections; Imports and Exports Inspections;
- Clinical Trial Site Inspections;
- CTD Dossier Development;
- Drug Substance (API)

Mode of deployment

- USP and stakeholders to provide models and materials
- Lectures form lecturers and practitioners
- Case-based lectures/case studies
- At least 3 months rotation in the industry and regulatory
- USP to identify centres of excellence
- Pharma and USP to support
- Support from PCN, NUC, Deans of faculties
- Deans are to deploy through PharmD programme
- Awka has started implementing the curricular designed

Conclusion

- Tripartite model of Government + Academia + Industry an excellent leverage for African Pharmas to adopt
- Exploration of Africa's rich biodiversity a low hanging fruit for addressing indigenous health challenges on the continent
- Strong North-South and South-South partnerships will add boost to achievements already recorded
- More training on skill acquisition in manufacturing of API and FPP
- Strengthening of the pharma sector
- More funding and commitment by government

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