RESEARCH

A. Completed

a. Quality Control – Surveillance of quality of Panadol and Panadol extra circulating in Nigeria

b. Metabolic and toxicological studies of phytomedicines of Aqueous extract of Azadirachta indica (Neem tree)

c. Pharmacokinetic/Pharmacogenetic studies

i. Drug analysis from biological matrices and drug products (Method development) and Physicochemical properties of drugs using HPLC and spectrophotometric methods including quinine, pyronaridine, halofantrine, Beta Lactams antibiotics, Lumefantrine, artemisins and derivatives, sulphadoxine-pyrimethamine, sulphamethoxazole-trimethoprim etc.

ii. Pharmacokinetics (PK) studies of quinine in an African population (Nigerians) both in healthy and malaria patients 5. Pharmacokinetics of oral paracetamol in Nigerians which revealed a two-compartment model and for the first time.

iii. Pharmacokinetic/biopharmaceutical Relationship between in vitro and in vivo availability of 3 different brands of paracetamol tablets

iv. Formulation of Suppository of antimalarials (quinine and chloroqine) with bases such as cocoa butter, polyethylene glycols (PEGs), shear butter, witepsol and different absorption

v. Metabolic studies of quinine - metabolite of quinine in humans, 3- hydroxy quinine was fully characterized for the first time by mass spectrophotometer and H – NMR.

vi. Genetic polymorphic metabolic oxidation of proguanil (a prophylactic antimalaria drug) in healthy Nigerians as an indication of phenotype status of CYP2C19 isozyme

vii. Genotyping and phenotyping comparison of genetic polymorphism of CYP2C19 among sickle cell patients and non-sickle cell patients in Nigeria.

viii. Genetic polymorphism of NAT2 enzyme in HIV and non-HIV individuals in Nigeria

d. Drug interaction studies

i. Drug interaction between Magnesium trisilicate (an antacid) and proguanil in healthy volunteers.

ii. Drug interactions(in vitro and in vivo) between various antimalarials and beta Lactam antibacterials – including chloroquine vs ampicillin-coxacillin, quinine vs ampicillin –cloxacillin, proguanil vs ampicillin-cloxacillin, artesunate vs ampicillin-cloxacillin, various antimalarials and amoxicillin etc

iii. Interaction studies between halofantrine (HF), caffeine, caffeine-containing foods and anti microbials (e.g. fluconazole, penicillins etc).

iv. Effect of caffeine co-administration with halofantrine and other antimalarials on parasite clearance in *Plasmodium berghei* infected mice.

v. Effect of antacids on artemether-lumefantrine

e. Pharmacodynamic (PD) studies of antimalarials and antibacterials

i. Evaluation of the clinical, parasite kinetics and drug level parameters in children with chloroquine resistant strains and those with sensitive strains.

ii. Evaluation of changes in electrocardiography with time; called 'Disposition of the relative increase in electrocardiographic time intervals' (DISKRIETI) was applied to children with acute falciparum malaria treated with halofantrine (HF) and chloroquine plus chlorpheniramine (CQCP) since CP reverses CQ resistance.

iii. Evaluation of the risk factors associated with hyperparasitaemia in children.

iv. The effects of co-trimoxazole (Co-T) and pyrimethamine-sulphadoxine (PS) on gametocytes prevalence carried out in children with acute falciparum malaria.

f. Pharmacodynamic studies with antibacterial agents

i. The synergy between two glycopeptides, vancomycin (old) and teicoplanin (new) versus an aminoglycoside – streptomycin was studied by time-kill method using five clinical vanB resistant *Enterococcus feacalis* (ENC) isolates.

ii. The use of immunomodulators/cytokines such as interferon-gamma (IFN-γ) and granulocyte colony-stimulating factor (G-CSF) along with ceftazidime (TAZ) was carried out in both immunocompromised (neutropenic - NT) and non-neutropenic (NN) mouse models induced with acute *Pseudomonas aeruginosa* (PSA) pneumonia.

iii. The pharmacodynamics of Ertapenem, a new beta-lactam antibiotic was evaluated in a neutropenic mouse model thigh infection with extended beta-lactamase (ESBL)-positive and ESBL-negative strains of *Escherichia coli* and *Klebsiella pneumonia*.

iv. The penetration, efflux and intracellular activity of tigecycline (a novel tetracycline/glycycline derivative active against gram-positive and gram-negative anaerobic bacteria) were carried out in human polymorphonuclear neutrophils (PMNs).

g. Clinical trials

i. Comparative trial on two magnesium antacid suspensions; Phillips Milk of Magnesia (PMM) and Supermag (SPM) was carried out in patients with acid peptic disease. Clinical, laboratory investigations as well pH monitoring of the gastric fluid after endoscopy were used as markers for clinical outcome.

ii. Neo-adjuvant Capecitabine Chemotherapy in Women with Newly Diagnosed Locally Advanced Breast Cancer in a Resource-poor Setting (Nigeria): Efficacy and Safety in a Phase II Feasibility Study'.

iii. Pre-cilinical trials of imipenem in mouse model

B. **<u>Work in progress</u>**

a. **Investigation of the effects of surfactants on the release rate of Artemeter-Lumefantrine and Quinine Suppositories.** Parenteral Artemeter and Quinine, though have been indicated in the treatment of uncomplicated and severe malaria respectively, and provide rapid onset of action, require, among other factors, administration by trained personnel, which is not readily available in rural areas. Consequently, these challenges will be addressed by the formulation of Artemeter

and Quinine suppositories, which require no special technique for administration. The formulation of Artemeter, Lumefantrin, Artemeter-Lumefantrin and quinine suppositories can serve as an alternative to oral dosage forms (syrup, tablet, and capsule) for treating malaria especially in children who are unable to tolerate oral Artemeter-Lumefantrin and Quinine due to the bitter taste and those who are vomiting, comatose or uncooperative.

Research objectives include

- To formulate, improve and enhance absorption of Artemeter-Lumefantrin and quinine suppositories by the incorporation of absorption enhancers, such as surfactants [14], and the use of Fattibase® as the suppository base, which is expected to give optimal release of the model drugs and consequently good bioavailability profiles
- To establish the pharmacokinetics and bioavailability profile of Artemeter-Lumefantrin and quinine suppositories
- To determine the efficacy of the Artemeter-Lumefantrin and quinine suppositories in cerebral malaria therapy.
- Various quinine formulations have been made with different suppository bases. Drug release studies have been done and bioavailability has been carried out on one of the formulations but a suitable formulation is yet to be obtained. Fattibase is being used to formulate artemether-lumfantrine

b. **Drug-drug interactions of antimalarials and antibacterial drugs.** This was started in 2001 and interesting findings have led to more work. We are currently looking at the clinical implications of these interactions in children with malaria and bacterial infections who are taking the drugs concurrently. Outcome of these studies will definitely alter the practice of co-administering antimalarial and antibacterial drugs.

c. **Efavirenz Pharmacokinetics And Pharmacogenetics; Relationship With Neurocognitive Functioning In HIV Infected Cohort In Nigeria.** The aim of this study is to determine relationship between *CYP2B6* polymorphism, hair and blood efavirenz concentration and neuropsychiatric/neurocognitive side effects in patients treated with efavirenz-based regimen. One time point hair-DBS pair will

be collected from each subject 14 to 22 hours post dose and efavirenz levels will be determined using LC-MS. Additional once DBS sample will also be collected for genotyping of subjects for genetic polymorphism in *CYP2B6* while neurocognitive/neuropsychiatric function testing will also be carried out at the time of DBS and hair samples collection. The mean efavirenz concentration for patients who are neurocognitively impaired or have neuropsychiatric adverse event will be compared to the patients without neurocognitive impairment using t-test. The results of this study will provide insight as to whether monitoring efavirenz levels in HIV-positive patients on long term efavirenz-based regimens using DBS or hair as a biomatrix may optimize treatment outcomes with respect to neuropsychiatric adverse events. We will also derive information on the contribution of *CYP2B6* polymorphism to drug levels and neurocognitive/neuropsychiatric performance in our Nigerian cohort. Questionnaire sampling is completed. Sample collection in PEPFAR clinic UCH is ongoing

d. **Pharmacokinetics, drug-drug interaction and Bioavailability of different brands of Artemether – Lumefantrine (an antimalarial) in Nigerians.** This was partly supported by EMZOR pharmaceutical. The in vitro equivalence studies (disintegration, dissolution, chemical potency, content uniformity etc) of Artemether-lumefantrine (A-L) have been completed in 3 brands. The in vivo trials in human are ongoing including effect of antacid on is being awaited. In vivo trial on effect of antacids on A-L, effect of Moringa leaf and effect dose size on pharmacokinetics of A-L.

e. **Identifying Lead Antiadhesins against Enteroaggregative *Escherichia Coli* (EAEC) causing Diarrhea In Children.** Childhood diarrhoea accounts for high death rates globally with EAEC identified as the most common pathogen causing persistent diarrhoea. Despite the burden of EAEC infections, no known specific chemotherapy exits either for prophylactic or therapeutic purposes for EAEC infections Antibiotics currently in use are not EAEC-specific and could enhance selection pressure which will consequently facilitate mutant species that might become antibiotic resistant. Additionally, EAEC adhesins have only been partially investigated, the study present a good chance of improving our understanding of

known adhesins and potentially discovering novel EAEC adhesins. We hypothesize that the Pathogen Box contains molecules that can interfere with or inhibit EAEC adherence to host cells either by structurally modifying adhesins or competing for their receptors.

The objectives of this study include:

- To determine the structure and binding sites of known EAEC adhesins computationally.
- To determine binding affinities of molecules from the Pathogen Box to EAEC adhesins using a known EAEC antiadhesin as a reference probe in order to screen for molecules (hits) with similar bioactivity from the Pathogen Box.
- To identify hit molecules from the Pathogen Box with antiadherance activities using medium throughput biofilm and heamagglutination assay screens.
- To utilize computational methods in optimizing lead molecules potentially useful as prophylactic or therapeutic agents in infantile diarrhoea.

Preliminary work is ongoing on computational methods and training

C. **Dissertation and Thesis**

Anyabuike, C. P. (1983). Marine Natural Products in Drug Development B.Pharm. Dissertation, University of Ife.

Anyabuike, C. P. (1986). Biochemical Aspects of Hepatotoxicity of Azadirachta indica. M.Sc. Thesis, University of Ife.

Babalola, C. P. (1996). Pharmacokinetic Studies of Quinine in Man. Ph.D. Thesis, Obafemi Awolowo University, Ile-Ife.