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USING "REVERSE PHARMACOLOGY" TO CREATE A PLANTDRUG THAT FIGHTS MALARIA

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ABSTRACT
After six years of study, a novel standardised herbal anti-malarial is created in Mali using a "reverse pharmacology" strategy to producing an anti-malarial phytomedicine. The initial step is to choose through a retrospective treatment-outcome investigation, a development therapy. The second phase is choosing the safest and most effective dose by a dose- escalating clinical experiment that demonstrated a dose-response phenomena. A randomised controlled trial was the third step, which compared the phytomedicine to the conventional first-line therapy. Finding active substances that can be utilised as markers for standardisation and quality control was the final step. This illustration of "reverse pharmacology" demonstrates that standardised phytomedicines can be created more quickly and affordably than traditional medications. Even though both methods are Despite not being completely similar, their effectiveness in promoting public health and their complementarity should be carefully taken into account. It Describes and evaluates the reverse pharmacology approach for Malarial Plant Drug.

KEYWORDS: Reverse Pharmacology, Antimalarial Phytomedicine, traditional medicine, Argemone Mexicana decoction, soumaya, kono, artemether Lumefantrine.

INTRODUCTION
Malaria elimination sweats will lead to the important wider use of the many presently effective anti-malarial medicines, similar as artesunate/ amodiaquine, artesunate/ sulphation pyrimethamine (SP), and artemether/ lumefantrine. There is formerly discussion about intermittent plausible treatment of babies, children, pregnant women, and indeed mass medicine administration in some settings.[1] Resistance formerly exists to amodiaquine and SP, and will presumably increase as a result of the increased medicine pressure. The first signs of resistance to artemisinin derivations are appearing in Cambodia.[2] In environment it's important to maximize the lifetime of being anti-malarial, and to consider all options for the development of new anti-malarial. Traditional medicinal shops have handed the source of the two major families of anti-malarial medicines still in use moment, artemisinin and quinine, so numerous experimenters are webbing shops for new chemical realities to develop as 6 "lead composites" for new anti-malarial medicines.[3] Still conventional medicine development is slow and precious, taking up to 15 times and up to $ 800m to develop a new medicine,[5] likewise, the finished products are frequently unapproachable and unaffordable to the poorest cases in remote areas, unless they're part of a heavily subsidized scheme. In discrepancy the resemblant development of standardized phytomedicines can be done briskly, more cheaply, and more sustainably for remote areas. They could also be proposed and tested as a complement to being strategies, for illustration as first aid in remote areas in case there is some detention until ACT treatment can be started. Their use might also delay the development of resistance to current standard medicines. The conception of "reverse pharmacology" was chased in India to develop Medicinals from Ayurvedic drugs, and was also supported by the Chinese in the 1950s,[6] but still involved a classical pathway of segregating composites for farther development.[7] The saving in time and cost comes from the fact that substantial experience of mortal use increases the chances that a remedy will be effective and safe, and that preventives will be known. still, as with classic medicine discovery, there's no guarantee of successfully developing new treatments. In order to develop a standardized phytomedicine, a "reverse pharmacology" approach was tested, where clinical evaluation was prioritized from the launch. insulation of composites was done only at the end of the pathway, substantially for the purposes of quality control, agronomic selection and standardization, if justified by the clinical results. This experience led to the

development of anew Argemone Mexicana decoction, a traditional herbal cure that is currently being licencedin Mali, is an anti-malarial phytomedicine. As opposed to new medications, herbal remedies have entirely different criteria. It should be stressed that the project discussed here has the improvement of the usage of currently available herbal medicines as its main goal rather thanthe development of new pharmaceuticals. The Ethics Committee of the Institute National de Recherche end Santa Pulque (INRSP) in Mali examined and approved each of the clinicalresearch listed below. This procedure cost roughly 400,000 euros and took six years.

MATERIALS AND METHODS

Stage 1

How to choose herbal medicine Classical method for determining medicinal plants Further research is done through ethnobotanical studies. Yet Traditional ethnobotanical studies rarelyinvolve clinicians. They can and should provide more clinical information if the ultimate goalis to know which one of many treatments for a particular disease, it has the best effect.[8]

Although specifying Plants are generally of good standard, definition The diseases they treat are not. is rarely enough investigation of observed patient condition and progress, perceivedefficacy and resource limitations; And whether these are really the "treatments of choice".

Many plants are said to be effective against diseases. or other, but not really the preferred treatment Used in daily life. To circumvent these problems, Graz et al. developed a new method called the Retrospective Treatment Outcome Study (RTO)[9] This It just adds two important elements to ethnobotany.

METHOD

Clinical information and statistical analysis. Clinical information is collected retrospectively on Presentation and course of a defined disease episode. Analyse treatment and subsequent clinical outcomes to generate statistically significant correlations. between them. Such an approach would require a large number of samples for a large number of different treatments. The method makes it possible to identify the remedy. It has the highest statistical correlation with reported clinical recovery. The hypothesis is that this correlation is Efficacy markers that can be further tested Prospective clinical studies of selected agents. It has also been hypothesized that this is a marker of ineffectiveness when treatments often lead to failure. With RTO, the first step was to locally understand Disease concepts and terms. The aim was to maximize the chances given by respondents Information about diseases of interest to researchers. The definition of uncomplicated malaria was 'fever'. There is no other obvious cause during the rainy season." In severe malaria, "fever with convulsions or Unconsciousness during the rainy season"[10] In Mali these correspond to the local Bambara words 'soumaya' and 'kono'. Of course not Very precise, but these are the same definitions as these used in questionable treatments.[11] and the best can be done later if a blood test is done impossible. In the second step, a representative random sample of households within the study area was selected (according to cluster sampling), ask everyone if anyone has anything disease of recent interest. Timing It is the end of the malaria season (e.g. Mali starts to rain in July, the best time for rain Such surveys he conducted from November to December). For Her recall time for uncomplicated malaria was 2 weeks is used (this is common and Too long a collection period leads to inaccurate information long).[10]

Severe malaria (rare and more common) A dramatic (i.e. more likely to be remembered)recall period of 6 months was used. Sample size was determined based on estimated prevalence Malaria in the area and an estimated number of different treatments (from previous information). Third step when respondents have conditions I am interested in asking in detail what kind of treatment they do In what order and at what stage they recovered from the disease and whether the healing was complete. with consequences. I amable to understand it like this Treatments actually used by patients.

And what kind of results do you get?

In Mali, the use of this method resulted in Treatment of malaria cases in 952 households. The analysis A statistician's help starting with correlation tests between reported clinical results and plants used. Because in some cases the recipe contains more than one The system consists of a second stage that takes this into account in the analysis, To determine whether individual components are associated with clinical outcome. Of 66 plants used to treat malaria in two regions The districts studied alone or in various combinations in Mali were thedistricts associated with the best results Decoction of Argemone Mexicana (Table 1).

Clinical The results were not better when used in combination.[12] This agent was selected forfurther study. At this stage, I had the opportunity to test some of plants for antimalarial activity in vitro (Table 2). Argemone mexicana activity was the best In vitro, the extract in a polar solvent and Aqueous Brew.[12] Methanol IC50 The extract is 1.0 µg/ml, which is about the same size. Ethanol extract of Artemisia annua.[13] It's important to do so before proceeding to clinical trials Make sure your remedy is safe. WHO guidelines.[14] say: "If the product is traditionally used Where there is no proven harm, no specific restrictive regulatory action should be taken unless there is new evidence A revised risk-benefit assessment is required. WHO's position is that there is no need. preclinical toxicology studies; rather evidence of traditional use or recent clinical experience is sufficient.[15] In fact, the same plant is often used traditionally As a food and drug[16] not toxicological Foods that are normally consumed require testing more than medicine. Preclinical toxicity Examination is required only for new herbal medicines, including those

without a traditional history use.

Therefore, a preliminary field survey (RTO studies) show that the preparation has been widely and anciently used, even if important aspects are unknown No toxicological studies are required.[17] The literature has been extensively searched.[18] whether the drug is already safe established in previous studies. The aim was to find studies on the same plant parts withsimilar extractions.

Table 1: Sample results from RTO study for 3 Promising Plants.

Plant	Preparation	No. of case Reporting Use	No. of casesReporting Clinical Recovery	No. of treatment failure	P Log P
ArgemonaMexicana (Papavaraceae)	Aerial Parts Decoction	30	30	0	NA
Carica Papaya	Leaves	33	28	5	0.05
Anegeisus Lelocarpus	Leaves	33	27	6	0.03

Table 2: Invitro Antimalarial Activity of Plant extract identified in retrospective Treatment Outcome Study for Plants with aqueous extracts having IC 50 < 10 ug/ml.

Plant	Plant Part	Extract	IC50
Argemone Mexicana	Aerial part	Methanol	1.00
Argemone Mexicana	leaves	Dichloromethane	1.25
Optilia Celfitolia	leaves	Aqueous maceration	6.22
Feretia Apondather	leaves	Aqueous maceration	7.66

Stage 1: Selection of a remedy
- Retrospective Treatment Outcome Study
- Literature review (selected remedy)

Stage 2: Dose-escalating clinical trial
- Increase dose sequentially
- Observe clinical effects x Assess safety x Choose optimal dose

Stage 3: Randomized controlled trial
- Pragmatic inclusion criteria and outcomes
- Compare to standard first-line drug x Test effectiveness in the field

Stage 4: Isolation of active compounds
- In vitro antiplasmodial tests of purified fractions and isolated compounds from thedecoction
- To permit standardization and quality control of phytomedicine
- For agronomic selection x For pharmaceutical development

Summary of the methodology used to develop an anti-malarial phytomedicine by“reverse pharmacology”.

How to answer the following questions
1. Are there reports of relevant human toxicity?

Ingestion of plants? If so, which part plants, in what preparations, in what doses, what didResult is?
1. Are laboratory toxicity studies performed? About proper preparation of plants? if yes, whatDid you see results?
2. What do pharmacologically active compounds do Is this plant species included? which part of the plant have they been found? What are their main pharmacological effects and dosages? Search terms included plant species and primary

Compounds known to occur in plants (mainly berberine for Argemone Mexicana). None of the present databases or books can cowl all posted records on a given topic, and consequently as many reasserts of records as viable had been consulted: first of all, freely to be had on line databases,[19,20] then reference books inclusive of pharmacopoeia and comparable monographs,[21] and texts on plant toxicology and natural medication safety,[22-24] and finally, different databases:

EMBASE, CAB Global Health, and the Allied and Complementary Medicine database. In the case of Argemone Mexicana, the literature seeks discovered no toxicology research however there had been reviews of “epidemic dropsy” in India attributed to the ingestion of the seed oil containing sanguinarine, as a contaminant in culinary oils.[25] This changed into of a few concerns, consequently the conventional healer changed into requested to put off seed tablets from the practise used for medical research in Mali. However, there had been no references to toxicity from an aqueous decoction of the leaves and stems (which changed into the conventional practise in question), and this treatment changed into mentioned withinside the ethnobotanical literature as being utilized in Benin, Mali, India and Colombia.[26,29]

Level 2: Dose escalation clinical trial

As patients, they definitely A literature review revealed no concerns and an observational clinical study was conducted in a small number of patients. is a prerequisite for such an implementation study in areas where patients are already taking it Therefore, no new treatments have been proposed (e.g., for comparative prospective studies – cuff below) without some clinical evidence of effect size safety.

Traditional formulations were given to patients Uncomplicated malaria meeting the following criteria:

1. Inclusion Criteria

a. Symptoms of malaria (fever) within the last 24 hours

b. Parasitaemia > 2000/mcl and < 200,000/mcl microscopy

c. Informed consent from patient or parent

2. Exclusion Criteria:

- Signs of severe malaria
- Age < 3 months
- Pregnancy

I. Other concomitant febrile illnesses

e. Administration of full antimalarial therapy(modern or traditional) within the last week

f. Inability to return to follow-up care.

Patients were followed closely on days 1, 2, 3, 7 and 14 And at 28 I am advised to return anytime soon

Another time their condition worsens. Monitoring Efficacy parameters included (temperature, symptoms, parasite counts) and safety (new symptoms/undesirable Events, ECG, blood tests to monitor bone marrow function, renal function and liver function). Design

The whole study Patients using lower doses than the first group. The one traditionally used (but dates back to when it was proposed modified by traditional healers), then and above the normal dose range (see Figure 1). In this Patients always received the best dose Current state of knowledge. the incidence is significant undesirable effects have reached unacceptable levels, Of course the process can be aborted. compliance is Monitored by direct observation of several doses Treatment (first dose for each of the first 3 days when the patient comes to follow-up care) and by asking questions Whether the patient took what was recommended.

The rest of her daily dosage. This also allowed us to assess whether the optimal dosage was realistic and feasible on-site. Selected outcome measures were appropriate Situations in which phytomedicine use was envisaged, i.e., areas of high infection (Table 3 and four). In low-infection areas, the WHO-recommended outcome is an Adequate Clinical and Parasitic Response (ACPR), which includes requirements. A reduction in the number of parasites to <. 25% discount Baseline and that complete parasite clearance is achieved Day 7, maintained until day 28.[30] But WHO now recommends total elimination of parasites. In all circumstances this may not be necessary in areas of high infection where the population is partially increasing Immunity is present from an early age, and even if infected, it is easy to re-infect. Parasite elimination is achieved. With such high transmittance Area is the most clinically useful outcome measure rather than parasites. One of these is the "adequate clinical response" rate (ACR, see Table 3). Correction of ACPR. Criteria for parasitaemia.

The third day should be <. 25% of the amount per day 0 was developed for fast-acting drugs such as chloroquine and artemisinin derivatives. not required Testing criteria for slow-acting drugs such as quinine and herbal remedies can be omitted Such attempts.[31] Whether the patient has clinically deteriorated Recovered (i.e., "treatment failure").

Alternative treatments (nationally recommended antimalarial drugs). Chloroquine dose administered once daily 3 days). Then he revealed that he was actually normal Explainedhow to make remedies and gave advice to patients Try to drink as much as possible.

Therefore, 2 Other standard doses have been agreed. 2 glasses a day 7 days (B), initially by glass 4 times a day 4 days, then 2 glasses per day for up to 7 days (C). Increasing the dose from A to B improved efficacy (proportion of ACR patients increased 35% to 73%) with noincrease in side effects.

However, at maximum dose there was no additional dose (ACR 65%), and two patients showed prolongation of his QTc interval on electrocardiogram. Therefore, the intermediate dose (B) was chosen as the safest and most effective dose. To the next level.[32]

Specimens of plants harvested for crafting Phytomedicine was deposited in the Herbarium of. Department of traditional medicine. thin layer plant extract (methanol) and Decoctions are used to identify those already published. constituents. HPLC and mass spectrometry later confirmed this exploratory investigation. In the methanol extract, sanguinarine and berberine were found. However, there was no sign of sanguinarine in the decoction. The employed phytomedicine's lyophilized samples were saved for future phytochemical fingerprinting and reference. Although it would not have been required by WHO criteria, the chance to undertake toxicological tests occurred. These were carried out concurrently with the clinical trial with dose escalation. Since neither rats or mice were harmed even at this high dose, the LD50 of the freeze-dried decoction of the aerial portions was evaluated twice in two different laboratories, both of which revealed that it was >3000mg/kg.[33,34] It's a constant worry that certain harmful compounds won't be absorbed by rodent species, however was 1.9% in both groups (Argemone Mexicana and ACT) in during the first 28 days of follow-up. Follow-up was extended to three months, during which the age-adjusted incidence of severe malaria was 2% per month in the herb group and 1% permonth in the ACT group. At 95% confidence, the age-adjusted incidence of severe malaria was 6% per month in both groups.[37]

Final Step

Isolation and Testing of Active Compounds

This is the final step of "reverse pharmacology". Herbal medicine can be developed without isolating the active ingredient, but this is useful for two reasons.

First, there must be a phytochemical marker for quality control and standardization of herbal medicines and agronomic selection of the best plants. Second, it is possible that the pharmaceutical industry could develop new modern medicines in parallel. However, it makes more sense to do this after clinical safety and efficacy have already been demonstrated, as there may be a greater likelihood that the isolated compound (or derivative) will also be safe and effective. A lot of time and money is wasted on the development of drugs that turn out to be dangerous or ineffective in humans.[38] Isolationof pure active ingredients from herbal medicines is not easy. Most phytomedicines contain compounds with additive or synergistic effects, or even prodrugs. Argemone Mexicana contains at least three protoberberine alkaloids in equal amounts (about 0.5% in Malian plants) with similar antimalarial activity: berberine, protopine and effects, or (IC50 in vitro = 0.32, 0.32 mcg/ml). Although all are active in vitro, absorption of -berberine is poor in some animal models, although this can be improved with P-glycoprotein inhibitors. It is not knownwhether A. Mexicana contains inhibitors of P-glycoproteins, but if so, their concentration would also be significant. The pharmacokinetics of protopine and effects, or have not yet been studied in humans, so it is not known which is the best marker or if there is synergy between them (perhaps all should be used as markers for. Unlike berberine, protopine and effects, or have good selectivity against Plasmodium and low cytotoxicity.[39] Since initial in vivo tests with lyophilized AM broth were unsuccessful in both murine and rat models (Plasmodium Bergheim and Plasmodium Chabad, unpublished results), the plan isnow to investigate the ant plasmodial activity of in vitro in plasma samples. of healthy volunteers to identify substances or metabolites of plant origin associated with such activity.

DISCUSSION

Development of new compounds derived from nature. The product could be an important source of new antimalarial drugs in the long term, and it is possible to develop them Botanical medicines standardized and validated faster and cheap. The scheme used already saves a lot of time and money when developing new herbs Malaria control in Mali. Since the plants under study are pantropical weeds, results are obtained from such research programs inthis case, it may apply in many countries Local quality control of plants. It is most important to do one Ethical research and all clinical trials Submitted to and approved by the Ethics Committee. To be ethical, noninferiority studies should test strategies that can be maintained after the study has ended. Appropriate safety precautions should be taken during the study.

A place to ensure patient safety, according to medical organizations All the time the team wasstationed in the village Get immediate care if needed. the result is to Inform villagers of the traditional remedies they use What doses are clinically proven to be effective antimalarials and what precautions are necessary? ready, and they should look for the latest soon.

Treatment if no improvement or at-risk characters are displayed. This knowledge is likely to be more Long-term profit, therefore more ethical Short-term, unsustainable interventions. thishypothesis Will be tested in future public health studies Meaning of such information. Quite a lot in hindsight Improvements that can be made to the system. Of First selection of plants, the decisive factor Must be an observed correlation between treatment and effect RTO rather than possible in vitro activity misleading. In this case, in vitro activity was greater Due to poor absorption of berberine, probably (or directly) not responsible for human activity. A dose escalation trial is better Start by talking to someone who knows how to treat About the minimum and maximum dose administered by the patient Make sure the traditional healer has suggested his usual dose range for the study. This information, 2 or 3 different standard doses of phytomedicine test protocol. Of course, the same recording standards Patients, as they must be used throughout the study as similar as possible in each group.

Depending on the situation, the goals of treatment may differ. For example, in Brazil Artemisia annua is infused. Tested as a situational backup No recommended first-line treatment available. This These include shortages of standard medicines and remote areas Notreachable from medical infrastructure. Brazil is a low-infection area and a complete parasite Release is considered mandatory. in this context ACPR is the selected outcome measure.

Other herbal medicines against malaria have already been developed Developed in Burkina Faso and state approved Faso (Cochlospermum planchoii rootstock), Ghana (Cryptolepis sanguinolenta root injection),[41] Democratic Republic of the Congo (Artemisia) Anamed leaf infusion). lots of development.

This is already working: It has been proven and appears to be effective in preliminary clinical studies. However, more work is needed determine how they fit into public health strategies Control or eliminate malaria. it's important develop cost-effective and reliable tests for quality control, Standardization of plant material. Main clinical Research is required.

Risk of severe malaria in the future Validated and officially recommended phytomedicine users. This is not the case in Mali where this is the case. Proposed testing health policies on asmall scale.

Contains Argemone mexicana decoction for home treatment of malaria in patients over 5 years of age Years of ACT savings in high-infection areas for children under the age of 5.[35] There are many other promising antimalarial herbal drugs that could be developed much more quickly. cheaper than new compounds.

Preliminary work has already provided some information on their safety and efficacy.[42] such herbal medicines in addition to treating malaria as well as prophylactic and intermittent suspected process. The proposed methodology is Adapted for the development of herbal prophylaxis starting from Good ethnomedical observation and progress clinical trials (although protocols may differ from those described here evaluation of possible treatments).

Funding bodies need to support opportunities to develop new types of medicines, including herbal medicines, rather than restricting funding solely to the development of traditional isolated compounds. Sustainable improvement of public health in remote areas is an important aspect in such discussions. Innovative Public-private partnerships are also possiblewith companies that are already manufacturing experts Standardized herbal medicines.

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