The whole story

Dr Stephen Rich describes his work validating the efficacy of malaria treatments derived from whole plants rather than extracts, and explains why science should not be too quick to judge more natural options.

Artemisinin is unique among 21st Century malaria chemotherapy in that it is derived from plant material and not manufactured synthetically. Some would argue that this isn’t particularly novel since the plant from which it is derived has been used for millennia to treat fever in the tropics, by diffusing active ingredients from the leaves into a tea-like preparation. In the 1970s artemisinin was identified as the plant’s key constituent, and research efforts have since focused primarily on maximising the production of the extract as, to date, there has been no scalable and cost-effective means of synthesising it. The plant-derived nature of artemisinin sets it apart. It is also unique in that it is the first drug to be deployed as a combination therapy with other antimalarials. The World Health Organization (WHO) now prescribes artemisinin combination therapies (ACTs) as the only sustainable antimalarial strategy.

Could you explain the significance of Artemisia annua and its drug derivative artemisinin?

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Your experiments utilised Plasmodium chabaudi, a malarial species which affects rodents. How relevant will your findings from this parasite, and from the mouse model in general, be to humans and P. falciparum, the most deadly human strain?

We’ve actually confirmed our findings in another rodent malaria parasite as well – P. yoelii. Every human antimalarial drug, and the resulting resistance to that drug, has been modelled on the pattern of rodent malaria. Moreover, the resistance mechanisms – the genetic mutations in the parasites that allow them to be resistant – are homologous. We feel confident that these models are ideal for testing proofs of principle regarding whole plant efficacy and resilience, but we are also working on novel ex vivo methods for testing this against human parasites.

Because of the increased bioavailability of artemisinin in whole plant applications of A. annua, you theorised that this treatment could be used to overcome resistance in parasite populations. What have your experiments in this area revealed?

We’ve done some preliminary investigations using rodent malaria models resistant to artemisinin to show that whole plant A. annua overcomes this resistance. That is, it kills parasites that are not affected by artemisinin. A. annua is not as effective against resistant parasites as it is against wild type parasites; however A. annua is significantly better at killing artemisinin-resistant parasites than artemisinin alone. While more work is needed here, this holds some promise that A. annua may work as an antimalarial therapy where artemisinin is failing.

Are the hundreds of additional phytochemicals present in whole plant treatments helpful in preventing, or at least delaying, the development of resistant parasite populations?

At this point, we cannot say for certain, however our laboratory studies in rodent models suggest that resistance to A. annua develops much slower than resistance to artemisinin under experimental evolution conditions set up to select for resistance. As for the mechanisms underlying this empirical observation, there is still much work to be done.

This research demonstrates the potential efficacy and clinical application of a remedy that has been in use for thousands of years. Do you think that with the rise of drug resistance there will be an increased movement to investigate other ancient traditional therapies?

Unfortunately, efforts to develop herbal therapies rather than specific moieties of synthetic or natural origin are met with skepticism by Western science. This skepticism may be valid, given the preponderance of failed potions and remedies – but to reject out of hand the notion that a whole plant therapy could work against malaria is to take an unnecessarily chauvinistic position.

Furthermore, I think the nature of reductionist science will always limit the effectiveness of these efforts. I would argue that the complex nature of natural therapies makes easy identification of the component interactions a daunting, if not impossible task. We should not stop trying, but it’s important not to overlook the empirical evidence of efficacy for lack of a specific mechanism to which we can attribute that efficacy. After all, vaccines and drugs proved effective in combating human diseases long before we completely understood their modes of action.

While it would be imprudent, if not irresponsible, to deploy therapies that have not been rigorously tested and hence may render parasites resistant to the last line of defence we have (as was done by the Global Eradication campaign of the 1950-60s), I would like to see more balance in weighing the observed empirical efficacy against the reductionist inclination to understand its mode.
An overlooked opportunity

A group of parasitologists at the University of Massachusetts Amherst has postulated that the most widely-used form of malaria therapy could be delivered in a significantly cheaper and more effective way.

MALARIA HAS BEEN around for a very long time, but it is only within the last 100 years or so that humanity has begun to understand its mechanisms. The name ‘malaria’, which is Latin for ‘bad air’, is a reminder of how mysterious the disease must have been for earlier civilizations to whom the idea of protozoan parasites in the bloodstream would have been laughable. However, while modern understanding of the disease and its mechanisms is more complete, this does not mean that the ancient response to malaria was entirely ineffectual. In fact, one of the earliest and most effective modern treatments for malaria, quinine, was derived from the bark of Cinchona trees – found in the South American highlands – and probably first used by the Incas.

Likewise, the World Health Organization’s (WHO’s) current suggestion for sustainable antimalarial treatment, artemisinin combination therapies (ACTs), are based on a substance derived from Artemisia annua – a plant that has been used as a ‘heat cleaning’ herb in Chinese traditional medicine for thousands of years. Modern medical research tends to emphasise the identification of active ingredients, and so the general approach to A. annua was first to identify artemisinin, then extract it and finally develop more efficient methods for extraction – as well as attempting to synthesise it. The extracted chemical was then combined with other antimalarials to make ACTs, on the basis that combination therapies are less likely to promote resistance in parasite populations.

MAKING UP FOR LOST TIME

Unfortunately, artemisinin resistance is still developing in parts of Southeast Asia – the same area where parasites first became resistant to chloroquine and its derivatives decades ago. The reason for ACTs failing is not yet fully understood, but it is likely that incorrect doses and non-standard combinations of drugs have contributed to the problem. Antimalarials are available from black market sources, and the counterfeit and substandard drugs acquired this way may be a factor. After a few short years, it seems that time is already running out for artemisinin – and when it does, clinicians will have lost another weapon in the war against malaria.

One lab at the University of Massachusetts Amherst (UMass), USA, has evidence to suggest that something major has been overlooked in the investigative process that led to A. annua being developed into ACTs. Recent research led by parasitologist Dr Stephen Rich has shown that treatments using the whole plant rather than just the extract are proportionally far more effective for eradicating malaria parasites, and this opens up new realms of possibility for antimalarial treatments. Not only is this whole plant treatment more effective, it is also capable of dealing with parasites resistant to artemisinin – and its basis in the whole plant rather than extracts would make it far cheaper to produce than ACTs.

MALARIAL MICE

The studies performed by Rich’s team rely on rodent models of malaria; as part of their initial investigation whole plant therapy was tested in several mice and compared with artemisinin. The mice were infected with malaria parasites, and then – several days after the infection was established – half of them were given dried A. annua leaves by gastro-oral gavage. The remaining mice received doses of pure artemisinin in their conventional rodent chow and acted as controls. Parasitaemia was then monitored in both groups by counting the parasites highlighted in thin blood smears by Giemsa staining. The results were surprising, and showed not only that administration of the whole plant in just one dose produced a marked decrease in parasitaemia, but also that it took five times as much artemisinin to have the same parasite-killing effect as whole plant treatments.

This impressive increase in efficacy could be achieved very easily, it seems – but its mechanisms are still not well understood, as the studies of the UMass group are still in their early stages. The researchers hypothesise that one of the main reasons A. annua might be better than pure artemisinin is that the whole plant treatment may be a combination therapy in itself. It is possible that other antimalarial compounds in the plant may synergise with the known active chemical, creating a multi-effective antimalarial that is resilient to resistance – and this is one aspect of the treatment that the team plans to further investigate. Rich has theorised that these mechanisms may have evolved in the plants to cope with multi-resistant pathogens.

BRINGING TREATMENT TO THE WORLD

One of the great advantages of using the whole plant is that it eliminates costly extraction processes, effectively making the manufacture of treatments substantially cheaper. Plant biomass remains the primary source of artemisinin used in ACTs, but the low supply of suitable plants and affordable processing has thwarted the efforts to make these therapies fully available where they are most needed, despite WHO’s endorsement. The UMass scientists are collaborating with Dr Pam Weathers of the Worcester Polytechnic Institute, also in Massachusetts, to develop forms of delivery for the whole plant therapy that might easily be mass produced and
A diagram showing the sharp decrease in parasitaemia in A. annua treated mice (WP), reflecting significantly greater reduction in parasite load compared to mice treated with a comparable dose of artemisinin (AN) or the no-treatment group mice (CON).

DISTRIBUTED TO MALARIA-STRICKEN AREAS. The dried leaves of the whole plant can easily be pulverised or ground up, homogenising their content, before being pressed into tablets for consumption. The ACTs currently being used require multiple daily doses, and it is likely that the whole plant therapy will require a similar dosage.

Another possibility is that A. annua as a crop could be made available to at-risk communities, who could then grow and harvest it themselves. The plant grows as a weed in a variety of climates, making its cultivation feasible on a local scale. This would be a highly effective method of bringing treatment to critical areas, and would help to eradicate the commodity value of pharmaceuticals – thus reducing the potential for black market sellers. What is more, if the plant is a true combination therapy, as Rich and his collaborators suspect, then it could eliminate the problem of ensuring that drugs are taken as combinations. Capsules of dried plant leaves would contain all the necessary components naturally and inextricably.

MOVING FORWARD

The research being pursued by Rich and his team has a long way to go before it can produce definite answers on the mechanisms of whole plant treatment – but this is beside the point. This work draws on a simple fact that more reductionist science has failed to spot, and its focus on developing routes to manufacture and distribution rather than pausing to dismantle the healing action of its treatment will serve malaria patients well. This is a project that is making swift progress in an area where time is of the essence, and it is possible that many lives could be saved in the near future by a treatment that can tackle the whole of the problem.

Giemsa stained blood smears from mice showing erythrocytes infected with P. chabaudi, 30 hours after treatment with: (A) WP-LO (24 mg/kg whole plant delivered artemisinin), (B) AN-LO (24 mg/kg pure drug artemisinin) and (C) Placebo control.