Artemisia annua leaves improved solubility of antimalarial drug, artemisinin

Artemisia annua L., also known as Sweet Annie, is a Chinese medicinal herb that produces the important antimalarial drug, artemisinin. Artemisinin is the most powerful antimalarial ever discovered and its derivatives are the main component of artemisinin combination therapies (ACTs), the current global treatment for malaria. Unfortunately, a large portion of people most in need of ACTs do not have access to or financial means to afford these drugs and as a result, 438,000 people died of malaria in 2015. As an alternative to ACTs for those living in rural, poverty stricken communities, we proposed oral consumption of dried *A. annua* leaves as a treatment. Artemisinin itself has low bioavailability, meaning it does not readily enter into the bloodstream where it is needed to kill the parasites that cause malaria. This low bioavailability has led doctors to discourage use of artemisinin because it is difficult to achieve effective therapeutic doses with this drug Interestingly, it has been shown that delivery of artemisinin as dried leaves of *A. annua* as opposed to pure drug results in more than 40 times greater bioavailability, making it easy to achieve adequate therapeutic blood concentrations of artemisinin.

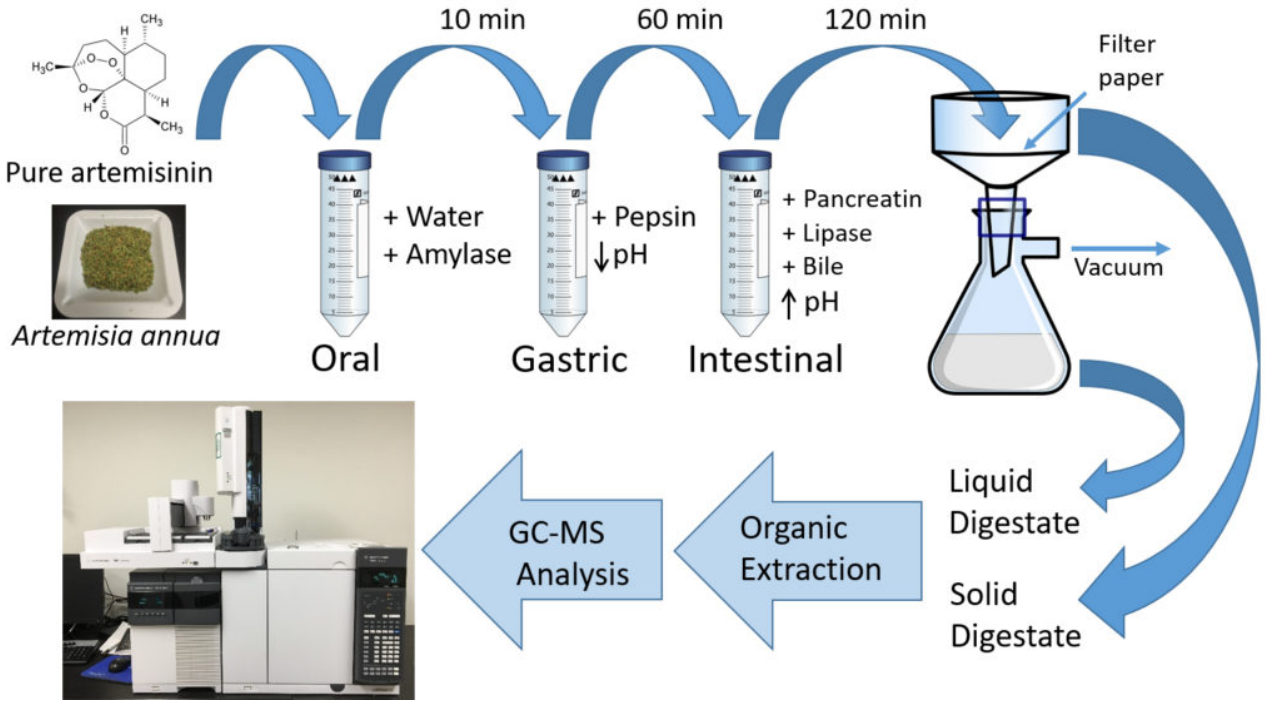

Fig. 1. Simulated digestion. Pure artemisinin or Artemisia annua leaves containing an equal amount of artemisinin are artificially digested in three stages. The resulting digestate is filtered into separate liquid and solid fractions, each of which is analyzed to measure artemisinin content.

Our studies aimed to determine how this greater bioavailability of artemisinin occurs, and which components of the plant might enhance transport of artemisinin into the blood. This particular study focused on solubility of the drug, in other words, how much drug dissolves in the intestinal fluid. The solubility of a drug is often correlated with how well it is absorbed and thus the overall bioavailability. Drugs that dissolve easily into the intestinal fluid (where most drug absorption occurs) are easily absorbed into the blood, while drugs that do not easily dissolve have lower bioavailability. We performed simulated digestions in a test tube that allowed us to mimic human digestion (Fig. 1). With this system we were able to add either pure artemisinin or dried *A. annua* leaves containing artemisinin. Then we measured the solubility of the drug in the intestinal fluid after simulated digestion. We showed that when artemisinin is delivered in the form of dried *A. annua* leaves, the solubility of the drug is about 4 times higher than when it is delivered as pure artemisinin. This means that the drug is likely better absorbed into the bloodstream when it is orally consumed as plant material. We next set out to determine what component of the plant may effect this increased solubility of artemisinin.

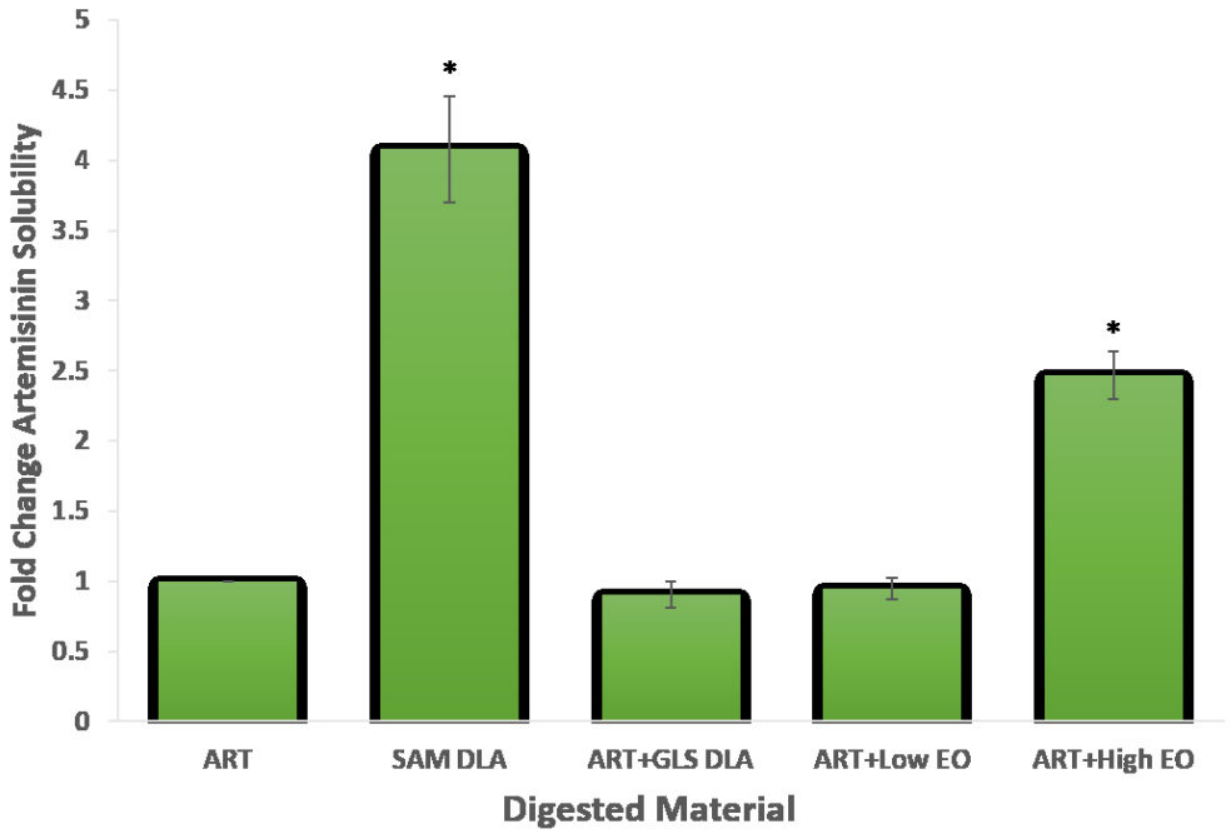

Fig. 2. Differences in solubility after simulated digestions of pure artemisinin (ART), dried leaves of A. annua (DLA), ART-free essential oil-free DLA (GLS DLA) plus added artemisinin, or ART plus high or low amount of essential oil (EO). SAM DLA is about 4 fold more soluble than pure ART after digestion while solubility of ART digested with GLS DLA or a low concentration of EO does not change compared to pure ART. Solubility of ART digested with a high concentration of EO is

about 2.5 fold higher than pure ART.

We tested many different phytochemicals found in *A. annua* and found that when we combined artemisinin with essential oils from *A. annua* the solubility was about 2.5 times higher than pure artemisinin alone (Fig. 2). We therefore concluded that the essential oil in the plant leaves was partly responsible for increasing artemisinin solubility. In our study, we demonstrated that drug solubility can differ significantly when the drug is delivered in the form of a medicinal plant as opposed to a purified drug. These changes in solubility are likely to affect the overall bioavailability, and therefore the efficacy, of the drug. In the case of artemisinin, these results partly explain why artemisinin delivered orally as *A. annua* has over 40 fold higher bioavailability in the blood versus pure artemisinin.

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