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Bioavailability of the Antimalarial Drug Artemisinin Delivered Orally as Dried Leaves of 
_Artemisia annua:_ the Role of Solubility and Protein.

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Malaria treatment using orally consumed dried leaves of the artemisinin producing GRAS plant 
_Artemisia annua_ has recently shown promise. Previously we showed, oral consumption of A. 
_annua_ dried leaves (DLA) yielded >40 times more artemisinin in the blood of mice than 
treatment with pure artemisinin. Using the Caco-2 cell culture model of the human intestinal 
epithelium, we also showed that compared to pure artemisinin, digested DLA doubled the 
permeability (P_{app}). Here, using simulated human digestion, we show that artemisinin solubility is 
about seven times higher in digestates of DLA than in digestates of pure artemisinin, likely 
contributing to its enhanced bioavailability. Digestion with pure artemisinin combined with levels 
of essential oils comparable to that in DLA increased the solubility of artemisinin 2.5 times 
indicating essential oils play a role in increasing artemisinin solubility. Interestingly, increasing 
the starting concentration of artemisinin in Caco-2 transport studies did not alter P_{app}. 
Considering malaria affects mostly young children and about 60% of the population experiences 
DLA as unpleasant tasting, we also tested several protein rich foods as potential flavor-masking 
agents for their effects on bioavailability. We showed that while taste was masked, peanuts and 
a peanut-based paste used to treat malnutrition, PlumpyNut, reduced artemisinin and flavonoid 
levels in simulated digestates, respectively, likely decreasing their bioavailability. Experiments to 
{further investigate the role of several compounds such as camphor, a principle component of 
the essential oil fraction, and flavonoids on artemisinin solubility and bioavailability are ongoing. 
The results of these experiments are helping to explain the increased bioavailability afforded by 
DLA seen in mice.

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