Towards continuous and efficient production of artemisinin

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Artemisinin-based combination therapies (ACTs) are the most active medications against malaria currently available on the market. Due to the high price of the base compound artemisinin, however, the availability of these medications is limited especially for the population in developing countries, who are particularly threatened by malaria. An industrial process based on biotechnological and chemical conversion implemented by Sanofi met strong market resistance leading to the shutdown of the plant [1]. Currently, artemisinin is still mainly produced by extraction of the plant *Artemisia annua*, where it is formed as secondary metabolite.

Our approach to make ACTs less cost-intensive is to increase the amount of artemisinin obtained from the plant by following two main research directions: 1) Utilization of co-extracted dihydroartemisinic acid (DHAA) as additional source for artemisinin and 2) application of advanced technologies together with optimized conditions to the initial extraction and the final purification step to increase the efficiency of the overall process (Figure 1).

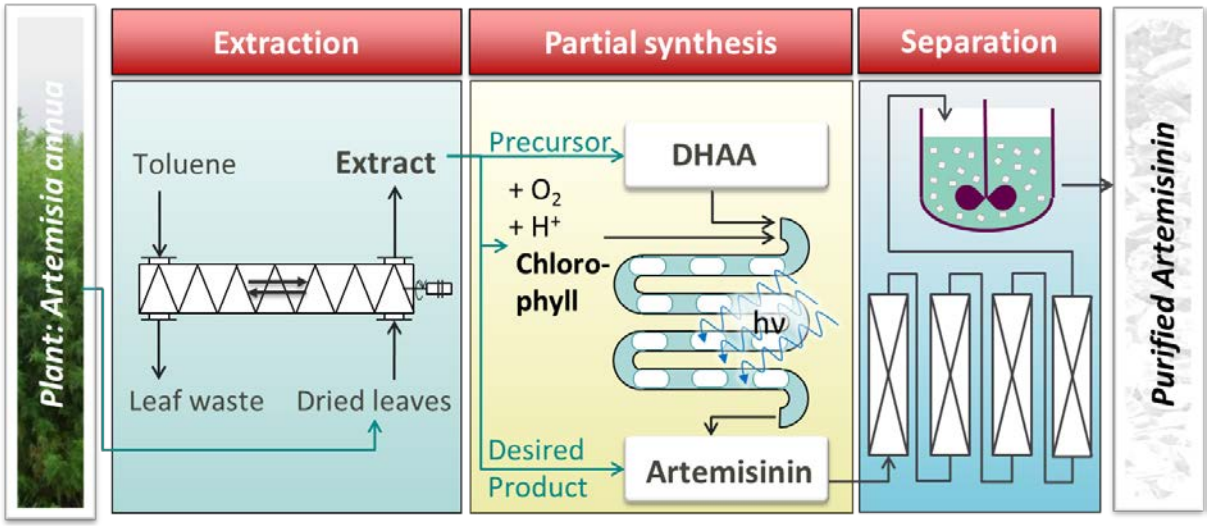

Figure 1: Illustration of the process for continuous artemisinin production using the plant *Artemisia annua*.

The extraction of dried *A. annua* leaves can be either performed in batch – the conventional method – or in a continuous counter-current screw extractor. In the latter case the leaves and the solvent are transported in opposite directions through the extraction unit by a screw and a pump, respectively. This flow arrangement leads to intensified mass transfer from the solid to the liquid phase [2] and, thus, enables almost complete extraction of artemisinin from the plant material in a single step.

Besides artemisinin, the obtained extract contains a variety of other metabolites besides artemisinin, e.g. dihydroartemisinic acid (DHAA) - a biological precursor of the active substance. DHAA can be converted to additional artemisinin via a photooxidation and subsequent acid-catalyzed reaction sequence [3]. The obtained extract is pumped in a mini-channel tubular reactor, contacted with oxygen in a T-mixer, and illuminated by high-intensity LED lamps. To initiate the photooxidation, a photoactive compound is required which transfers absorbed light energy to triplet oxygen forming singlet oxygen. Recently, we demonstrated that chlorophyll, another available byproduct of the extraction, can be utilized to initiate the photooxidation making the addition of other, often toxic photosensitizers unnecessary [4]. Thus, artemisinin can be synthesized out of crude extract of *A. annua* – which contains *both* the reactant and the photosensitizer – by treating it just with oxygen, visible light, and acid. In this way 67 % of the co-extracted dihydroartemisinic acid can be utilized.

The reactor effluent obtained from the synthesis step constitutes a complex mixture containing a wide range of metabolites extracted from the plant and the side products formed in the partial synthesis. In a first study, a process of continuous chromatography coupled with a crystallization step was developed to purify artemisinin from the reaction solution [5]. Recently, we could also show that pure artemisinin (>99%) can be obtained more easily from the reactor effluent after combined extraction and synthesis just by a single cooling crystallization step [6].

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