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Role of impurities in purification of artemisinin from *Artemisia annua* extracts

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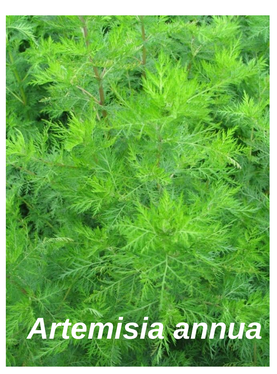
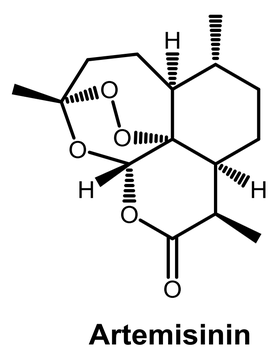
INTRODUCTION

Artemisinin is used in combination with other drugs against *Plasmodium falciparum* induced malaria. Artemisinin is obtained mainly from dried leaves of *Artemisia annua* L. (sweet wormwood). Existing processes include extraction of leaves of *A. annua* by using organic solvents, ionic liquids, or supercritical fluids and subsequent purification of artemisinin from crude extract [1]. Most of the processes used for manufacturing of artemisinin report poor yield during crystallization and attribute it to the interference of impurities on the crystallization of artemisinin [2]. Understanding the role of impurities is therefore essential for the design of an optimal process for recovery of artemisinin. The aim of this study was to investigate the effect of impurities in extracts on the overall recovery of artemisinin.





Artemisinin

EXTRACTION AND PROCESS FOR RECOVERY OF ARTEMISININ

Dried leaves of *A. annua*

Organic solvent

Extraction

Crude extract

Mobile phase: *n*-hexane–ethyl acetate

Flash CC

Fractions with artemisinin

Crystallization

Artemisinin

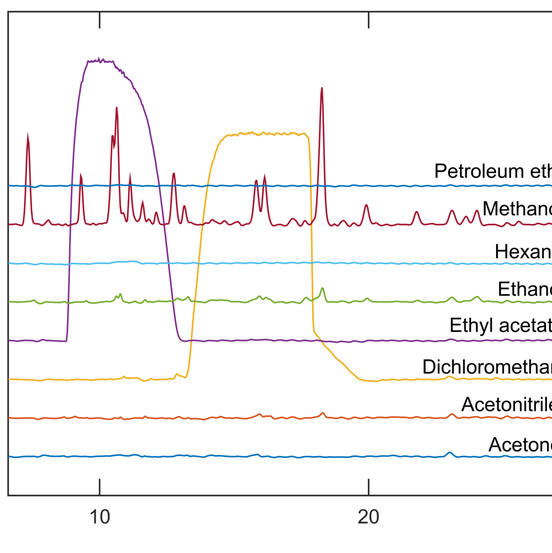


Fig. 1. HPLC chromatograms of *A. annua* extracts obtained with different solvents.

- Extracts obtained with different solvents showed different yield of artemisinin; *e.g.*, methanol (1.47 wt %), ethyl acetate (1.13 wt %), acetone (1.02 wt %), dichloromethane (0.45 wt%), and *n*-hexane (0.34 wt %).
- Composition of extracts was also different; *n*-hexane and petroleum ether extracts contained fewer impurities while methanol extract contained most impurities (Fig. 1).

PURIFICATION OF ARTEMISININ FROM DICHLOROMETHANE EXTRACT

- Dichloromethane extract of *A. annua* leaves partially purified with flash CC.
- Fractions containing artemisinin combined and analyzed by LC-MS.
- Solubility of artemisinin was measured in the mobile phase *n*-hexane–ethyl acetate (77.7:22.3 v/v) together with impurities (Table 1, Fig. 2**)**.
- Crystallization of artemisinin from combined flash CC fraction was performed (Fig. 3).

Table 1. Composition of combined fraction containing artemisinin

Compound	Concentration (mg/mL)
Artemisinin	1.82
Artemisitene	0.015
Dihydroartemisinic acid	0.0745
Artemisinic acid	0.01
Arteannuin B	< 0.001
Coumarin	0.0051

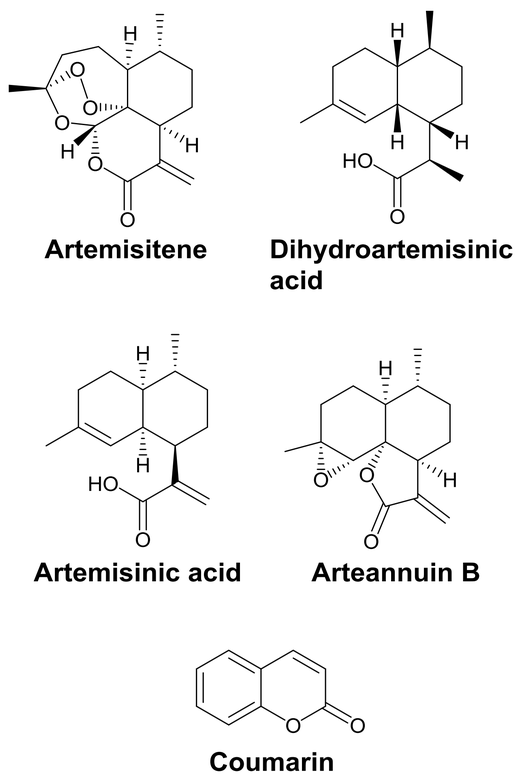


Fig. 2. Structures of impurities found in dichloromethane extract of *A. annua* leaves

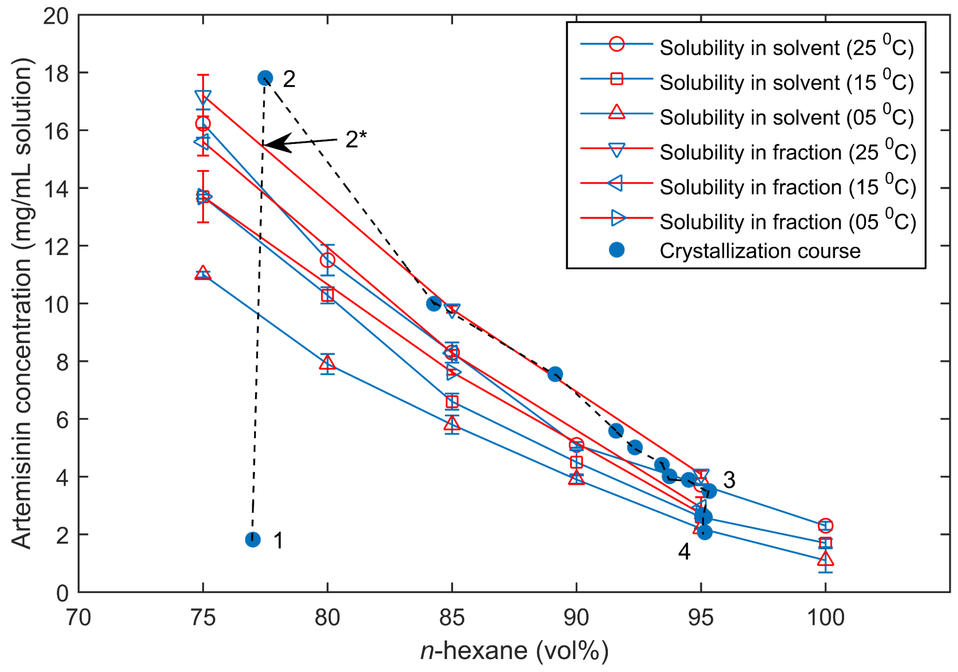


Fig. 3. Crystallization of artemisinin from combined fraction and solubility of artemisinin in *n*-hexane−ethyl acetate mixtures (**blue lines**) and the combined fraction reconstituted in *n*-hexane−ethyl acetate mixtures (**red lines**).

CONCLUSIONS

- Impurities in the dichloromethane extract increased solubility of artemisinin, *i.e*., showed co-solvency effect.
- Impurities in the dichloromethane extract did not affect the yield of artemisinin in the crystallization step.
- Maximum yield of artemisinin in the overall process was obtained with acetone (0.29 wt %), followed by ethyl acetate (0.26 wt %), methanol (0.18 wt %), *n*-hexane (0.15 wt %) and dichloromethane (0.11 wt %).
- The composition of extracts, *i.e.*, impurities may in some cases have a significant effect on the purification of artemisinin.

REFERENCES

[1] *Malwade CR, Qu H, Rong BG, Christensen LP*. Ind Eng Chem Res 2013; 52: 7157−7169
[2] *Malwade CR Qu H, Rong BG, Christensen LP*. Ind Eng Chem Res 2014; 53: 5582−5589

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