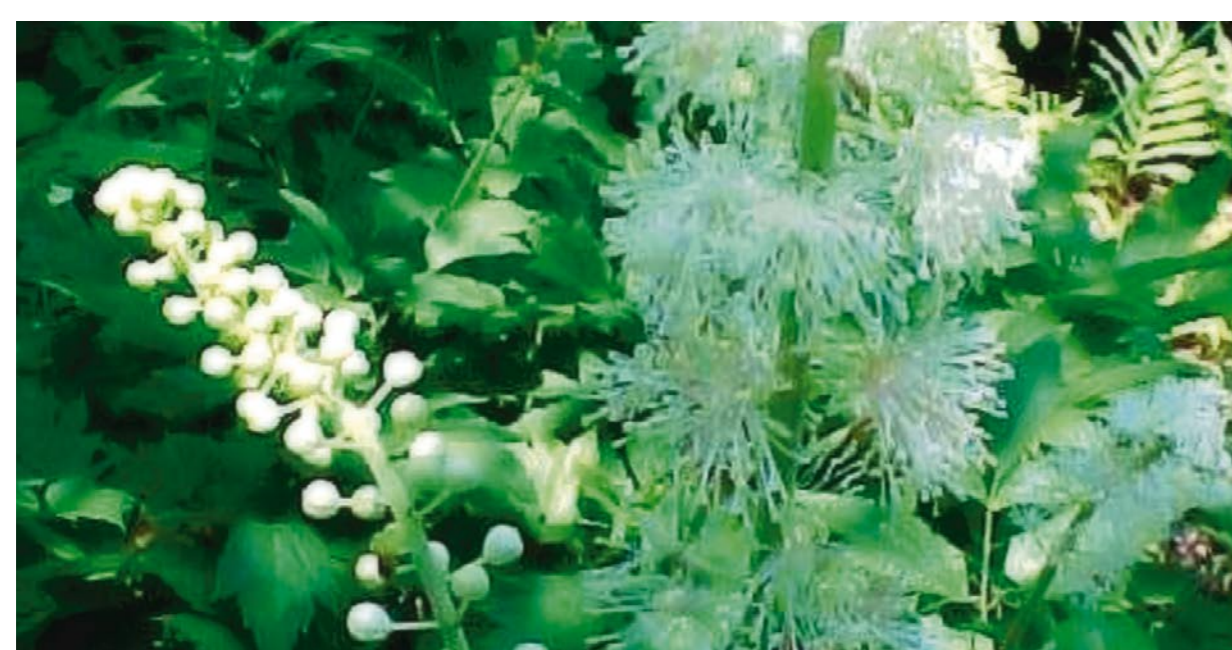


Cimicifuga racemosa L. Nutt. (Black cohosh) and anaphylactic reactions, including face and oral oedema.

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Introduction

Cimicifuga racemosa L. Nutt. (a.k.a Black cohosh or *Actaea racemosa* L.) is a perennial plant native to North America and its roots and rhizomes have been used for traditional medicinal purposes by Native Americans. The underground parts contain cycloartane-type triterpene glycosides including actein. Its modern day application is in the treatment of menopausal symptoms. *Cimicifuga racemosa* has been used in Germany for over 40 years.



Picture 1: *Cimicifuga racemosa* L. Nutt. showing leaves, buds and flowers.

A range of adverse drug reactions (ADRs) has been associated with the use of *Cimicifuga racemosa*. Authoritative herbal texts list mild gastrointestinal upset as the most frequent adverse effect and mention other minor ADRs such as headache, vertigo, mastalgia, weight gain, and heavy feelings in the legs.^{1,2} The Swedish SPC for Remifemin® lists nausea, diarrhoea and allergic skin reactions as well as transient changes in hepatic function test results as rarely reported ADRs for *Cimicifuga racemosa*.³ It points out, however, that no clear causality can be determined between liver function and the use of *Cimicifuga racemosa*. Some consumers may assume *Cimicifuga racemosa* to be safer than hormone replacement therapy because of its natural origins, but data to support this are scarce.

Aim

The aim of this review was to analyse the suspected association between the use of *Cimicifuga racemosa* and spontaneous reports of anaphylactic reactions including facio-oral oedemas.

Method

A search of the WHO database, Vigibase, was performed to identify reported ADRs on *Cimicifuga racemosa*. Vigibase contains spontaneous ADR reports from member countries of the WHO Programme for International Drug Monitoring. For the purpose of this review, spontaneous case reports citing anaphylactic reaction and facio-oral oedema after use of *Cimicifuga racemosa* were extracted and analysed. The reason being that, the combination of the use of *Cimicifuga racemosa* and the ADRs mentioned above is reported to the database more often than statistically expected from the rest of the case reports in the database. This means, the combination stands out from the background of the database which makes it interesting for a closer review. The suspected association has not been previously reported.

Results

The database cites 122 suspected spontaneous ADR reports for *Cimicifuga racemosa* from twelve countries with the majority of the reports from 2001–2004. Five of these ADR case reports from three different countries have been extracted and analysed for this review.

These reports describe anaphylactic reactions and oedema of the face and mouth.

Case report 1

A 48 year old female patient developed oedema of face, tongue and mouth, oral pain dyspnoea, glossodynia and a feeling of strangeness after treatment with *Cimicifuga racemosa*. The patient concomitantly used rofecoxib, sertraline and multivitamins. It is not known if she recovered from her symptoms.

Case report 2

A 52 year old female patient developed respiratory distress, pruritus, rash and flushing one day after using *Cimicifuga racemosa*. The concomitant drug here was celecoxib. The outcome is unknown and there is no information about dechallenge or rechallenge.

Case report 3

A female patient of unknown age developed oedema pharynx, rhinitis and erythematous rash after seven days of using *Cimicifuga racemosa*. It was the sole drug used according to the report. The patient recovered from her symptoms.

Case report 4

A 51 year old female patient presented peripheral and face oedema and malaise after one day use of *Cimicifuga racemosa*. She used alprazolam concomitantly. She recovered from her symptoms on dechallenge.

Case report 5

There is also a report of face oedema and chest pain occurring in a 41-year-old woman five days after beginning treatment with Remifemin® for menstrual disorders. There is no dechallenge or rechallenge information and the woman is reported to have recovered. There were no other concomitant drugs.

In addition to the five reports described above, there is a further report describing a 59 year old woman who developed face oedema and abnormal vision after starting treatment with Remifemin Plus® (a combination product which contains *Cimicifuga racemosa* and *Hypericum perforatum* L., St. John's wort). The reaction abated when the drug was withdrawn, and there was also a positive rechallenge in this case confirming a possible causality.

Discussion

Over time, the formulation of Remifemin®, one of several *Cimicifuga racemosa* preparations has changed from a solution to tablets, and the medium of extraction has changed from ethanol to isopropyl alcohol. The effects of a standardised extract of *Cimicifuga racemosa* (containing 1 mg triterpene glycosides, calculated as 27-deoxyactein, in each 20mg tablet), Remifemin®, have been investigated in a total of six clinical trials, to date, involving women with menopausal symptoms.⁴ 27-deoxyactein has now been determined to be 23-epi-26-deoxyactein.⁵ These studies are heterogeneous in design and most have methodological limitations, so the use of black cohosh for the relief of menopausal symptoms is not at present supported by convincing clinical trial data.^{4,6,7} There is not yet any conclusive evidence to explain the mechanism behind the suspected association. Can the change in the medium of extraction have a role to play? Can an allergic reaction linked to the physiology of the patients be involved or could it possibly be the result of an interaction? We believe that further studies may throw more light on the issue.

Conclusion

Our data suggests that there is an association between the use of *Cimicifuga racemosa* and anaphylactic facio-oral oedema. However, there is a need for further studies to determine causality.

Acknowledgement

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