Putative pharmacokinetic interactions due to Remifemin®

One human clinical trial addressed the question of pharmacokinetic drug-drug interactions, investigating influences of black cohosh on CYP P450 isoenzymes *(Gurley et al. 2005)*. The authors investigated the potential of various herbal pharmaceuticals to interact with ezymes involved in drug metabolism. Twelve healthy volunteers, of which 6 were women, were treated for 28 days with black cohosh capsules. Investigations were performed on the CYP isoenzymes 1A2, 2D6, 2E1 und 3A4/5.

An extract of black cohosh (Actaea/Cimicifuga racemosa) reduced the activity of isoenzyme CYP2D6 by approx. 7%, which was, however, statistically significant. The authors themselves concluded that this reduction was most probably of minor clinical relevance. No other isoenzyme was influenced by the black cohosh extract.

The tested material were Cimicifuga hard capsules, batch no. 060706 distributed by the North American company Solaray Inc (Park City, Utah, USA). According to package information, each capsule contains 545 mg of a black cohosh extract which is standardized to contain 0.2% triterpene glycosides. Package information guarantees a minimum content of 1 mg triterpene glycosides (TTG) per capsule. Although the extraction medium is not explicitly stated, it can be assumed that a mixture of ethanol and water was used.

The standardization of the product on a pre-defined amount of triterpene glycosides implies the dilution of the extract with an excipient mixture, thus transmuting the de facto declaration for each capsule from a “fixed amount of extract” to a “fixed amount of an extract preparation”. The given amount itself is well plausible: 545 mg of an extract standardized to 0.2 % TTG sum up to 1.09 mg TTG per capsule.

The recommended dosage comprises two capsules taken twice daily, however, another statement within this publication sets the recommendend daily dose at 1 - 4 capsules. In the referenced study, the highest dose was administered, i.e. 2 capsules in the morning and 2 capsules in the evening.

Within this meticulously conceived and executed trial, marker substances characteristic for the study medication were quantified in the capsules. For cimicifuga analytics the authors used an HPLC-technique with light scatter detection (HPLC/ELSD) thus quantifying the TTGs cimiracemoside, 27-deoxyactein and actein. This gave the following results:

cimiracemoside	0.2 ± 0.02 mg / capsule
27-deoxyactein	0.6 ± 0.01 mg / capsule
actein	1.9 ± 0.06 mg / capsule

Thus, a daily dose of 4 capsules results in a TTG-uptake of 10.8 mg per day.
The daily uptake of actein would be 7.6 mg.

Each Remifemin® tablet contains 2.5 mg native dry extract of Cimicifugae racemosae rhizoma. The content of actein in this extract is approx. 3% as determined by HPLC/ELSD. It is of utmost importance that here, in Remifemin® tablets, the given amount of actein refers to this extract, which is in contrast to the preparation tested by Gurley et al., which is referenced to an extract preparation, also including the excipient mixture.

Therefore, direct comparison of extract amounts is illegitimate. It can however be said that the Remifemin® recommended daily dose, i.e. 5 mg primary extract, results in a daily uptake of approx. 120 µg actein.

Consequently, compared to Remifemin®, the black cohosh preparation investigated by Gurley et al. was approx. 60fold (7600µg /120 µg) higher concentrated. The absence of clinically relevant interactions even at that high a dosage makes it rather probable that the recommended daily dose of Remifemin® does not imply the risk of CYP450-mediated drug-interactions.

In addition to this, Gurley et al. investigated possible influences of black cohosh (Cimicifuga racemosa) on the intestinal P-gp transporter system. A daily dose of 40 mg herbal drug Cimicifugae racemosae rhizoma for 14 days had no effect on the pharmacokinetics (AUC(0-3), AUC(0-24), C(max), clearance and elimination half life) of digoxin. In parallel controls, rifampine and clarithromycine induced resp. inhibited the transporter system and thus proved the validity of the test system. Thus black cohosh appears safe also when combined with pharmaceuticals depending in pharmacokinetics on the intestinal P-gp transporter system (Gurley et al. 2006).

Interactions between three different black cohosh extracts and various cytostatics or radiation therapy have been investigated by Rockwell et al. (2005). They used an estrogen-insensitive mouse mammary carcinoma cell line. Of importance is the fact that one of the tested extracts is claimed to be standardized for the phytoestrogenic isoflavone formononetin, which has repeatedly been shown to be absent in either plant material or the iCR-extract preparation Remifemin®. The test substances should therefore be regarded of dubious authenticity. In this model the only relevant results were an increase in cytotoxicity of doxorubicine due to a concomitant treatment with black cohosh. Based on the content of triterpene glycosides, the corresponding dose resulting in a significant increase would correspond to ~25 times the recommended daily dose of Remifemin®. In spite of the way the results are presented, the actual increase in cytotoxicity was only from 99 % (without black cohosh) to 99.3 % (with black cohosh) (Rockwell et al. 2005).

Therefore, when taking the very recent results from Gurley et al. (2005, 2006) and Rockwell et al. (2005) into consideration, which at close inspection can only be deemed irrelevant, it can be said that no clinically relevant pharmacokinetic drug interactions of C. racemosa extracts with other drugs are to be expected.