



DPHG/ÖPhG-Jahrestagung 2007 Erlangen

Nachsymposium der DPhG-Fachgruppe „Pharmazeutische Biologie“  
in Kooperation mit der  
„Gesellschaft für Arzneipflanzenforschung e.V.“ (GA)

## Arzneimittelinteraktionen mit Phytopharmaka: Relevanz, Bewertung, Testung, Regularien

**Datum:** Freitag, 12.10.2007, 14:00 – 18:00  
**Ort:** Hörsaal 7 (Raum 00.222), Hörsaalgebäude der Technischen Fakultät  
Universität Erlangen-Nürnberg  
Erwin-Rommel-Straße 60, 91058 Erlangen  
**Organisation:** Prof. Dr. S. Alban (CAU Kiel), Prof. Dr. W. Blaschek (CAU Kiel)  
**Moderation:** Prof. Dr. V. Schulz (Berlin)

**DPhG**



Die Organisatoren danken den Sponsoren für die großzügige  
Unterstützung der Veranstaltung

Bundesverband  
der Arzneimittel-  
Hersteller e.V. **B.A.H.**  
beraten · analysieren · handeln

Bundesverband der  
Pharmazeutischen  
Industrie e.V.  
**BPI**  
Leben ist Vielfalt

**KFN**  
Komitee  
Forschung  
Naturmedizin e.V.

**PhytoLab**

**Finzelberg**

## PROGRAMM

- 14:00 – 14:05 Begrüßung (Susanne Alban, Wolfgang Blaschek)
- 14:05 – 14:30 **Phyto-Interaktionen: Last oder Lust?**  
Vorbemerkungen aus der Sicht eines Kliniklers  
Volker Schulz, Berlin
- 14:30 – 15:00 **Transportproteine für Arzneimittel:**  
Bedeutung für Arzneimittelinteraktionen und pharmakogenetische  
Aspekte  
Martin F. Fromm, Uni Erlangen
- 15:00 – 15:30 **Flavonoide:**  
Bioverfügbarkeit und potentielle Interaktionen mit Arzneimitteln  
Rainer Cermak, Uni Leipzig
- 15:30 - 16:00 KAFFEEPAUSE
- 16:00 – 16:30 **Interaktionen von Phytopharmaka mit chemisch definierten  
Arzneimitteln im Spiegel der Pharmakovigilanz**  
Hartwig Sievers, PhytoLab, Vestenbergsgreuth
- 16:30 – 17:00 **Arzneimittelinteraktionen durch Phytopharmaka -  
Kritische Bewertung und klinische Relevanz**  
Mathias Unger, Uni Würzburg
- 17:00-17:30 **Regulatorische Bewertung von  
Interaktionen bei pflanzlichen Arzneimitteln**  
Werner Knöss, BfArM, Bonn
- 17:30 – 18:00 **Diskussion und Schlussfolgerungen**
- 
- 18:00 Mitgliederversammlung der FG „Pharmazeutische Biologie“



## ABSTRACT 1

### Drug transporters: importance for drug interactions and pharmacogenetic aspects

Fromm MF

Uptake and efflux transporters are expressed in all organs (e.g. small intestine, liver, kidney), which are important for drug disposition. The efflux transporter P-glycoprotein (PGP, *ABCB1*) is a major determinant for oral bioavailability of drugs due to its expression in the apical (luminal) membrane of the small intestine. Induction of intestinal PGP by drugs (e.g. rifampicin) and St John's wort is the underlying mechanism of drug interactions with a broad variety of PGP substrates (e.g. digoxin) in humans. Moreover, bioavailability of PGP substrates increases in humans during coadministration of drugs, which are PGP inhibitors (e.g. digoxin-quinidineinteraction). There are in addition to efflux transporters uptake transporters (e.g. OATPs, organic anion transporting polypeptides), which are expressed for example in the luminal membrane of enterocytes and the basolateral membrane of hepatocytes. One of the hepatic OATPs is OATP1B1 (*SLCO1B1*), which mediates uptake of statins (e.g. pravastatin) into the hepatocyte. Recent data indicate that the *SLCO1B1* 521T>C polymorphisms, which has an allele frequency in Caucasians of 15 %, has *in vitro* a clearly reduced uptake capacity. Accordingly, carriers of 521C have clearly elevated plasma concentrations (e.g. of pravastatin) compared to carriers of at least one T allele. Taken together, inhibition or induction of drug transporters are new mechanisms of drug interactions in humans. Moreover, genetic polymorphisms in genes encoding for uptake or efflux transporters contribute to the interindividual variability in pharmacokinetics and effects of drugs.

## ABSTRACT 2

### Flavonoids: Bioavailability and potential interactions with therapeutic drugs.

Cermak R

Flavonoids are plant polyphenols that are very abundant in plants and plant extracts. Many of the over 6000 known different flavonoids are present as glycosides. The ability of intestinal enzymes to hydrolyse these glycosides has a strong impact on flavonoid bioavailability because only the released aglycones can be absorbed in the small intestine. Most of the absorbed polyphenols are conjugated in enterocytes and the liver. Subsequent intestinal secretion and biliary excretion of these conjugates diminishes flavonoid bioavailability. Non-absorbed glycosides as well as secreted conjugates are subject to bacterial metabolism in the large intestine. Microbial hydrolysis releases the aglycones that can be further broken down into phenolic acids and short chain fatty acids which, themselves, can be absorbed in the lower intestinal tract.

During the course of absorption, flavonoids share the same metabolic pathways with therapeutic drugs. A number of *in vitro* studies have shown effects of various flavonoids on drug metabolism by cytochrome P450 monooxygenases and by phase II conjugation enzymes, as well as on membrane transporters involved in drug excretion. The *in vivo* relevance of such drug-flavonoid interactions has been demonstrated in several studies which reported changes of drug bioavailability by certain flavonoids. A drastic example was a lethal digoxin intoxication observed in pigs due to a co-administration of the cardiac glycoside together with the flavonol quercetin. However, due to the countless drug-flavonoid combinations which are possible, it is difficult to make exact predictions about all of the interactions which are potentially harmful. It is necessary to select characteristic flavonoids and drugs and to test them in bioavailability studies with relevant animal models in order to be able to provide a qualified risk assessment.



### ABSTRACT 3

#### Interactions of herbal medicinal products in the mirror of pharmacovigilance

Sievers H

Like any xenobiotics herbal medicinal products may interact with other xenobiotic substances in the human body, particularly with chemically defined drugs. Based on such interactions the efficacy and/or pharmacokinetics of chemical drugs may be affected. As the word says, any such interaction needs at least two partners to come about, i.e. the herbal and the chemical drug. Consequently, any interaction potential of a herbal product, how strong it may be, does not render the herbal product risky or dangerous per se. Triggered by the "hypericum case" the scientific and public interest in the issue of herbal interactions has sharply increased since about 1999, as demonstrated by the number of publications. While the mere number of publications does not necessarily correlate with the real relevance of the phenomenon, both pharmaceutical companies holders and regulatory authorities have to consider all available information which may strongly vary regarding its scientific validity. Following European pharmacovigilance regulations producers of herbal medicinal products are performing research of literature and data bases for case reports and in addition perform periodic safety update reports encompassing the completeness of any information possibly affecting the risk/benefit balance of herbal products for several years now. Within this scope of activities, the absolute number of reports concerning herb-/drug interactions is low considering the broad and worldwide use of many herbal drugs. While the assumption of a considerable under-reporting seems plausible but remains however unproven, the discrepancy between the proven safety of the majority of herbal medicinal products as such and the potentially severe risk of the supposed interaction potential of some herbs recently under discussion strongly raises the question for an adequate handling of the issue, particularly regarding labelling requirements and distribution channels.

### ABSTRACT 4

#### Arzneimittelinteraktionen durch Phytopharmaka - Kritische Bewertung und Klinische Relevanz

Unger M, Frank A

Berichte über pharmakokinetische Arzneimittelinteraktionen zwischen Arzneipflanzenextrakten und synthetischen Arzneistoffen haben in den letzten Jahren die Unbedenklichkeit pflanzlicher Arzneimittel in Frage gestellt. Während in vivo nur wenige klinisch relevante Interaktionen zu verzeichnen sind, haben zahlreiche Veröffentlichungen über die In-vitro-Inhibition von Cytochrom-P450-Enzymen durch Pflanzenextrakte für Verwirrung gesorgt. Für In-vitro-Untersuchungen stehen verschiedene Verfahren zur Verfügung, welche sich hauptsächlich in der Detektion der zu quantifizierenden Metabolite unterscheiden. Da vom Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) In-vitro-Untersuchungen zur Beeinflussung des Metabolismus von Arzneistoffen gefordert werden, sollen die etablierten In-vitro-Methoden vorgestellt und die Aussagekraft sowie Eignung dieser Methoden ausführlich bewertet und diskutiert werden. Auch die In-vitro-in-vivo-Korrelation der mit diesen Methoden erhaltenen Ergebnisse wird anhand von Beispielen ausführlich besprochen. Die Überwachungsbehörde fordert zusätzliche In-vitro-Untersuchungen zur Induktion von CYP-Enzymen sowie zur Inhibition bzw. Induktion von Transportproteinen, wie zum Beispiel P-Glykoprotein. Da diese In-vitro-Untersuchungen nur mit Hilfe von geeigneten Zellkulturmodellen durchgeführt werden können, sind solche Assays sehr aufwändig und teuer. Ebenso stellt die fehlende „Selektion“ der Extraktinhaltsstoffe im Verdauungstrakt den Einsatz solcher zellbasierten Systeme in Frage. Da zahlreiche Pflanzeninhaltsstoffe im Dünndarm einem ausgeprägten Phase-II-Metabolismus unterliegen, soll auch die Möglichkeit von Arzneimittelinteraktionen aufgrund einer Inhibition von Glucuronosyltransferasen diskutiert werden.



## ABSTRACT 5

### Regulatory evaluation of interactions of (traditional) herbal medicinal products

Knöss W; Werner C, Reh K, Koch J

It is known that some herbal medicinal products may cause interactions of clinical relevance. In Germany a pharmacovigilance action was made concerning St. John's wort in order to address suitable regulatory requirements. This has to be considered when assessing (traditional) herbal medicinal products for marketing authorisation or registration. In literature there are reports on induction or inhibition of Cytochrom P450- enzymes or induction of P-Glykoprotein which could be the reason of pharmacokinetic interactions. Safety is a basic requirement for marketing authorisation or registration of medicinal products. The risk assessment is based on all data available for the active substance. BfArM has already addressed this topic by publishing a draft announcement discussing the requirements concerning assessment of interactions. The basic strategy was to suggest different levels of action based on the evaluation of all available data - e.g. in-vitro data on interactions could be a minor regulatory action, irrespectively of the methodological limitation.

Examples of plants used in herbal medicinal products for which data on interactions are available are: Peppermint, Eucalyptus, Artichoke, Milk Thistle, Liquorice, Nettle, Curcuma, St. John's Wort, Ginkgo, Allium, Chamomile, Colchicum. The data represent different levels of scientific evidence. Actually, more than 180 plant species are used in (traditional) herbal medicinal products. A major problem in assessment of the data is the poor quality of some references in literature as well as insufficient reports on adverse reactions. In general, it has to be considered that suitable instruments for systematic collection of data are to be developed. The evaluation of interaction data could be improved by a few reliable experimental studies. The discussion for suitable regulatory approaches could be shortened.

## ADRESSEN

Prof. Dr. Susanne Alban  
Pharmazeutisches Institut, Abt. Pharm. Biologie  
Christian-Albrecht-Universität zu Kiel  
Gutenbergstrasse 76  
D-24118 Kiel  
[salban@pharmazie.uni-kiel.de](mailto:salban@pharmazie.uni-kiel.de)

Prof. Dr. Wolfgang Blaschek  
Pharmazeutisches Institut, Abt. Pharm. Biologie  
Christian-Albrecht-Universität zu Kiel  
Gutenbergstrasse 76  
D-24118 Kiel  
[wbla@pharmazie.uni-kiel.de](mailto:wbla@pharmazie.uni-kiel.de)

Prof. Dr. Rainer Cermak  
Veterinär-Physiologisches Institut  
An den Tierkliniken 7  
D-04103 Leipzig  
[cermak@vetmed.uni-leipzig.de](mailto:cermak@vetmed.uni-leipzig.de)

Prof. Dr. Martin F. Fromm  
Institut für Experimentelle und Klinische Pharmakologie und Toxikologie  
Lehrstuhl für Klinische Pharmakologie und Klinische Toxikologie  
Friedrich-Alexander-Universität Erlangen-Nürnberg  
Fahrstr. 17  
91054 Erlangen  
[Martin.Fromm@pharmakologie.med.uni-erlangen.de](mailto:Martin.Fromm@pharmakologie.med.uni-erlangen.de)

PD Dr. Werner Knöss  
Leiter der Abteilung Besondere Therapierichtungen und Traditionelle Arzneimittel  
Bundesinstitut für Arzneimittel und Medizinprodukte  
Kurt-Georg-Kiesinger-Allee 3  
D-53175 Bonn  
[w.knoess@bfarm.de](mailto:w.knoess@bfarm.de)

Prof. Dr. med. Volker Schulz  
Oranienburger Chaussee 25  
D-13465 Berlin  
[v.schulz.berlin@t-online.de](mailto:v.schulz.berlin@t-online.de)

Dr. Hartwig Sievers  
PhytoLab GmbH & Co. KG  
Dutendorfer Straße 5-7  
D-91487 Vestenbergsgreuth  
[hartwig.sievers@phytolab.de](mailto:hartwig.sievers@phytolab.de)

Dr. Matthias Unger  
Institut für Pharmazie und Lebensmittelchemie  
Lehrstuhl für Pharmazeutische Chemie  
Am Hubland  
D-97074 Würzburg  
[unger@pharmazie.uni-wuerzburg.de](mailto:unger@pharmazie.uni-wuerzburg.de)