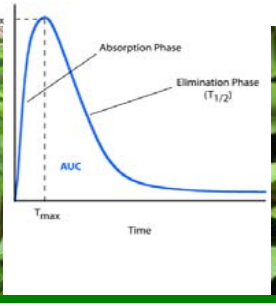


Workshop WS2, Sept. 3, 2007

GRAZ 2007

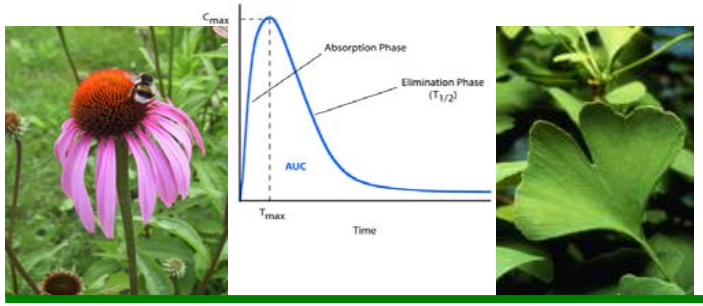
Pharmacokinetics of Herbal Medicinal Products:

Useful or not?

Karin Wölkart

Institute of Pharmaceutical Sciences

Karl-Franzens-University Graz



Scientific approach

- to link results from pharmacological *in vitro* assays and clinical studies

Clinical studies

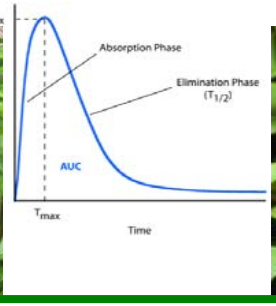
Pharmacokinetics

Bioavailability?

Metabolic pathways?

first step

phytochemical analyses and pharmacological *in vitro* studies



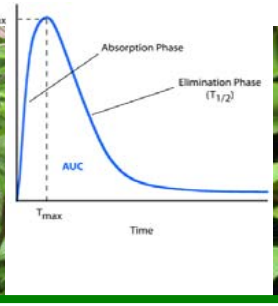
Constituents relevant for activity

Otherwise, the performance of pharmacokinetic studies is useless!

- The role of <u>alkamides</u> as the active principle of Echinacea

  - significant anti-inflammatory and immunomodulatory properties [Woelkart et al. 2007]
  - inhibition of COX-2 activity with a significant decline of the PGE_2 levels [Hinz et al. 2007]
  - modulation of TNF-α gene expression and an *ex vivo* significant decrease in production of pro-inflammatory cytokines [Gertsch et al. 2004, Woelkart et al. 2006]

- Echinacea alkamides trigger most of their effects via CB-2-binding [Woelkart et al. 2005, Gertsch et al. 2004, Raduner et al. 2006]



Preparation of new galenic formulations or comparison of different formulations/1

Echinaforce Junior tablets with 95 % (380 mg) *Echinaceae purpureae* herba and 5 % (20 mg) *Echinaceae purpureae* radix, but **beta-cyclodextrin (betadex)** as excipient

To what extent the Echinacea alkamides are bioavailable?

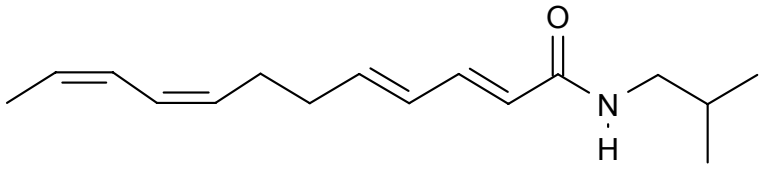
- randomized, open crossover study with 8 volunteers

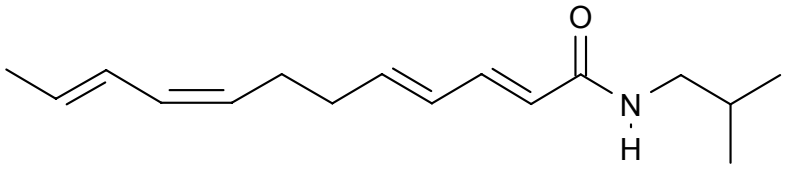
  Single oral dose of

  10 Echinaforce® Junior tablets (beta-Cyclodextrin; Betadex) or

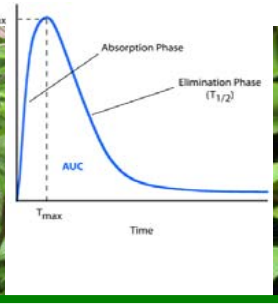
  12 Echinaforce® tablets from *Echinacea purpurea*

  (Tetraene concentration: 141,3 µg or 143,2 µg/Dosis)

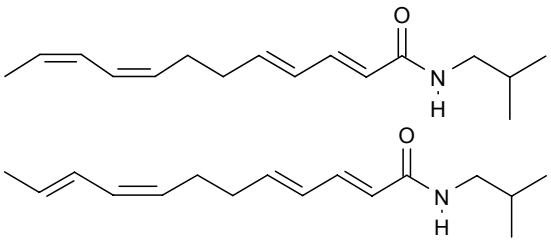


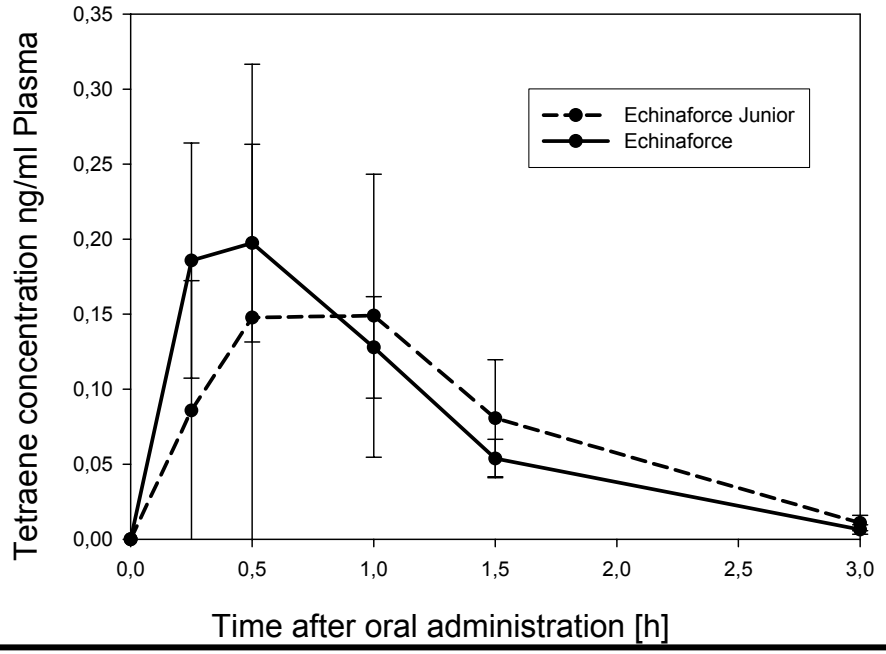


The study was approved by the „Ethics Committee of the University of Medicine Graz“, Austria (**EK-No.: 17-112 ex 05/06**) and by „AGES PharmMed“ Vienna, Austria. (**EudraCT 2005-005853-23**)



Pharmacokinetic results of the new galenic formulation (Betadex Echinaforce tablets)/2

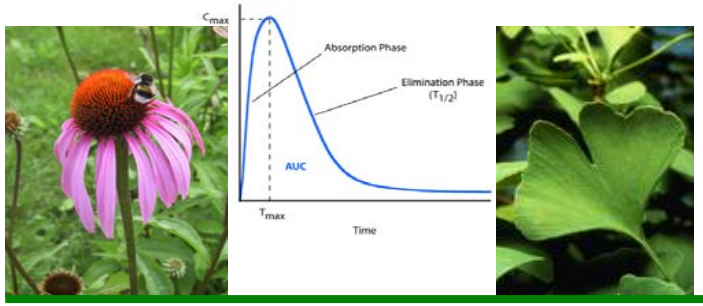




Echinaforce Junior tablets (Betadex)

and Echinaforce® tablets

Dodeca-2*E*,4*E*,8*Z*,10*E/Z*-tetraenoic acid isobutylamides (Tetraene)			
	Echinaforce Junior tablets (Betadex)	Echinaforce® tablets	
Dose	0.1413 mg	0.1432 mg	
C_{max} [ng/ml]	0.22 ± 0.15	0.22 ± 0.07	
T_{max} [h]	1.13 ± 0.35 (~68 min)	0.47 ± 0.25 (~28 min)	
AUC [ng/ml*h]	0.22 ± 0.09	0.23 ± 0.05	



Pharmacokinetic of two different Echinaforce® formulations/3

Pharmacokinetic/Pharmacodynamic modelling

Pharmacokinetic:

- randomized, open crossover study with 8 volunteers

  Single oral dose of

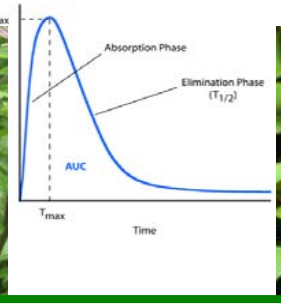
  4 ml Echinaforce® tincture or

  12 Echinaforce® tablets from *Echinacea purpurea*

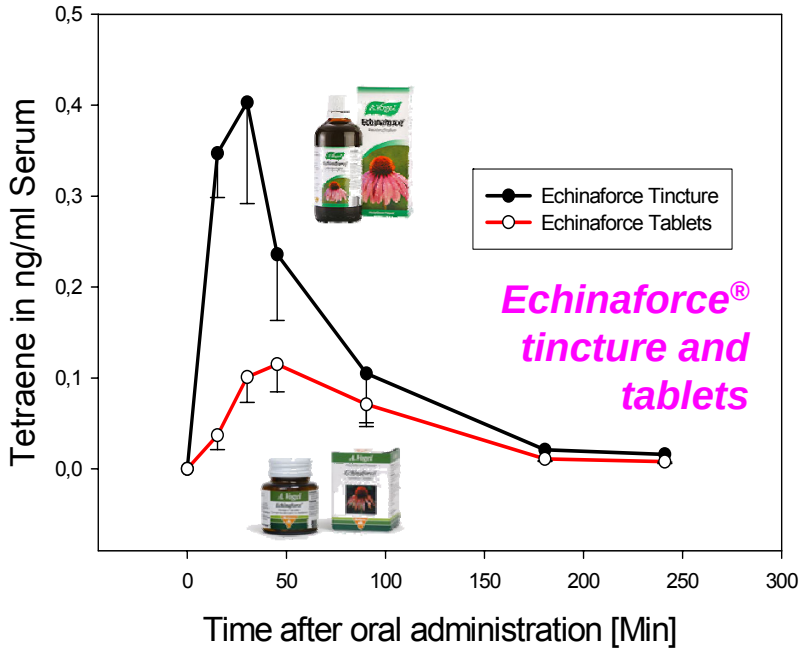
  (Tetraene concentration: 0.07 mg/Dose)

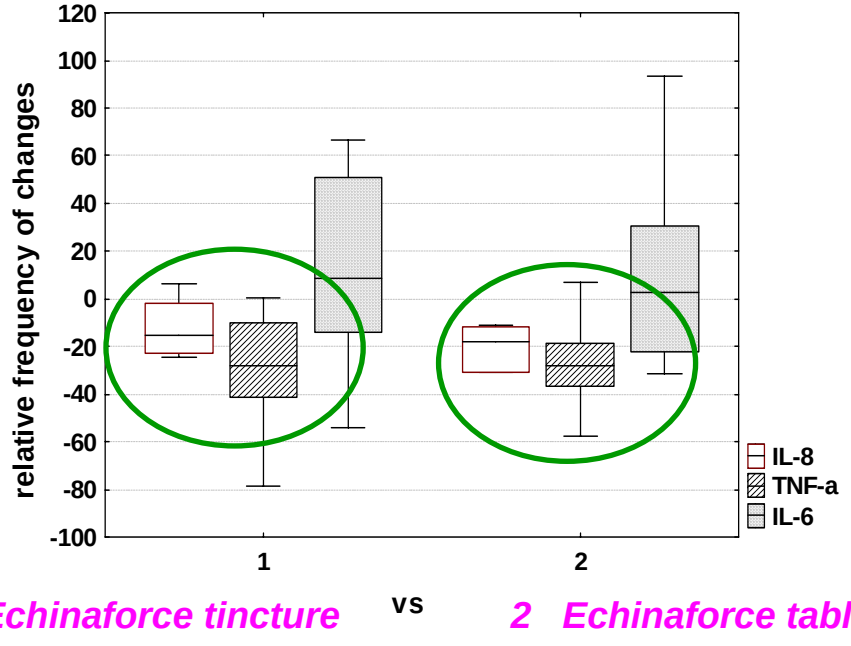
The study was also approved by the „Ethics Committee of the University of Medicine Graz“, Austria (**EK-No.: 16-009 ex 04/05**) and by „AGES PharmMed“ Vienna, Austria (**EudraCT 2004-002632-26**)

[K. Woelkart et al. R. Bauer; Int J Clin Pharmacol & Ther, 2006, 44 (9), 401 - 408]



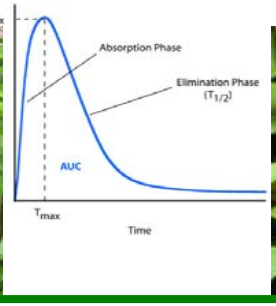
Pharmacokinetic results of the two different formulations (Echinaforce® tincture and tablets)/4





1 Echinaforce tincture vs *2 Echinaforce tablets*

Dodeca-2*E*,4*E*,8*Z*,10*E/Z*-tetraenoic acid isobutylamides (Tetraene)		
	Echinaforce® tincture	Echinaforce® tablets
Dose	0.07 mg	0.07 mg
C_{max} [ng/ml]	0.40 ± 0.11	0.12 ± 0.03
T_{max} [min]	30.1 ± 0.1	45.3 ± 0.4
AUC [ng*min/ml]	27.55 ± 8.94	11.36 ± 2.74



Ginkgo pharmacokinetic study (commercial Ginkgo tincture and Ginkgo tablets, new Ginkgo tablets)

- to demonstrate, that a new product is in the range of commercial available products
- randomized, open parallel study with 24 volunteers

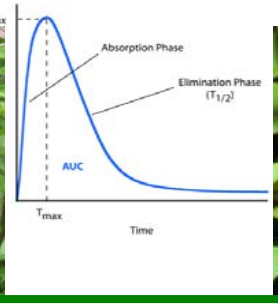
  Single oral dose of

  a commercial available *Ginkgo biloba* tincture or

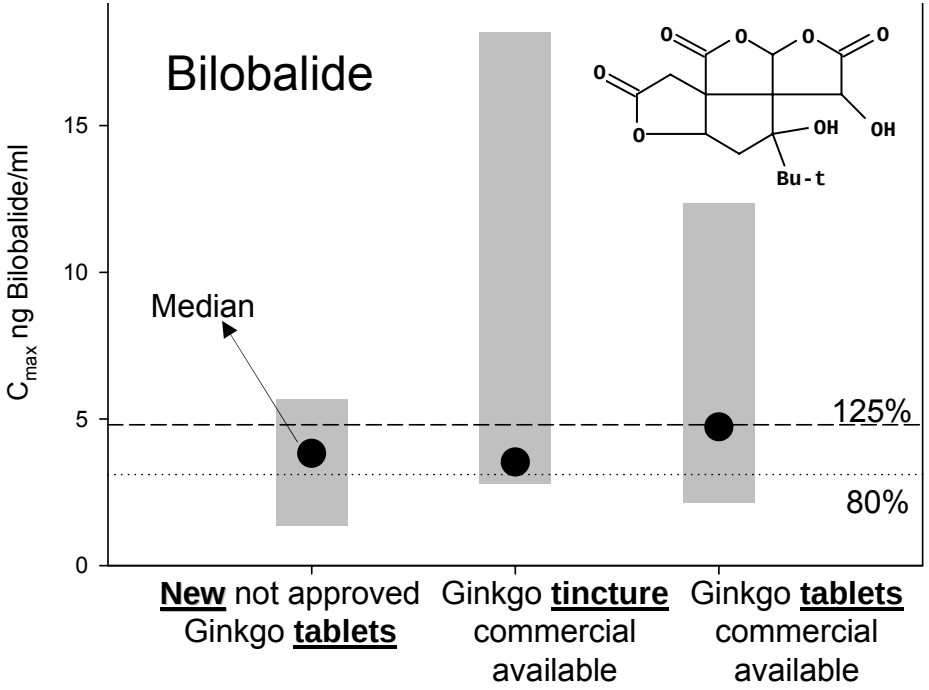
  commercial available *Ginkgo biloba* tablets or

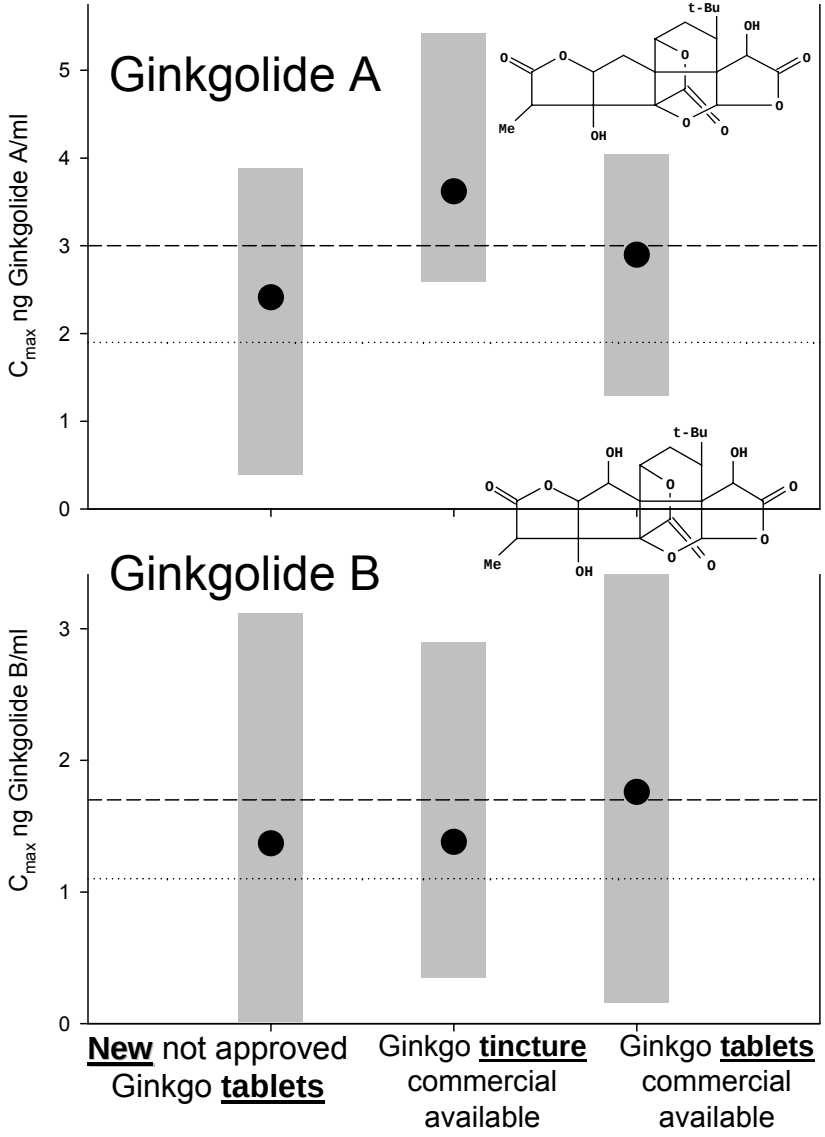
  the new, not approved, *Ginkgo biloba* tablets

The study was also approved by the „Ethics Committee of the University of Medicine Graz“, Austria (**EK-No.: 18-142 ex 06/07**) and by „AGES PharmMed“ Vienna, Austria (**EudraCT 2007-000539-25**)

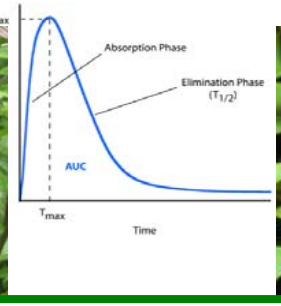


Pharmacokinetic results/ comparison of c_{max}

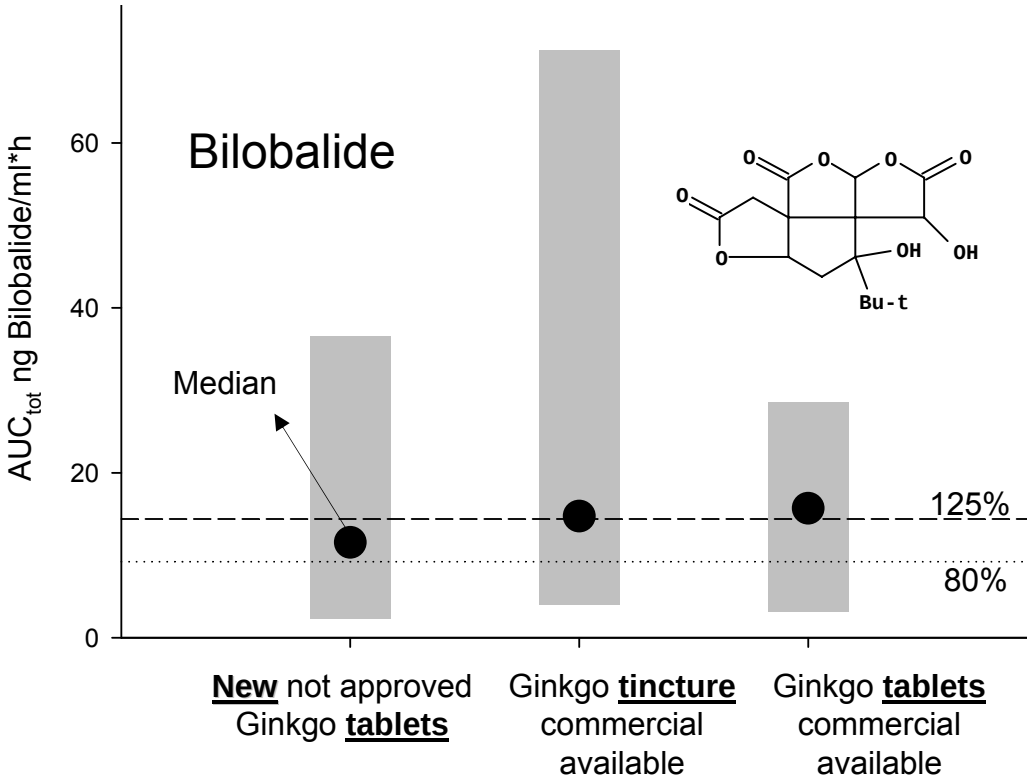


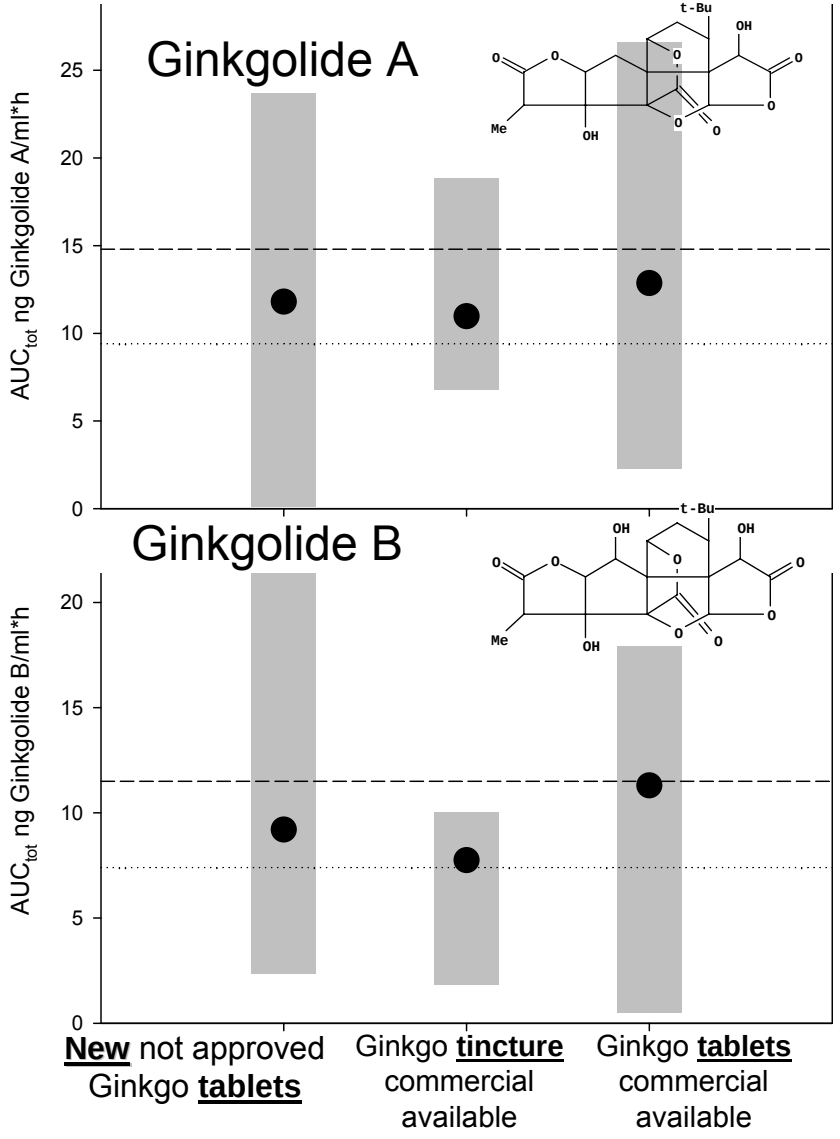


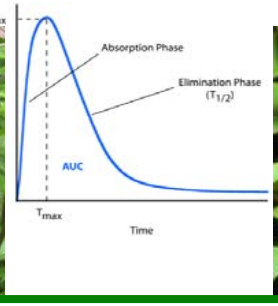
new not approved *Ginkgo biloba* tablets are highly comparable with commercial available preparations



Pharmacokinetic results/ comparison of AUC_{tot}

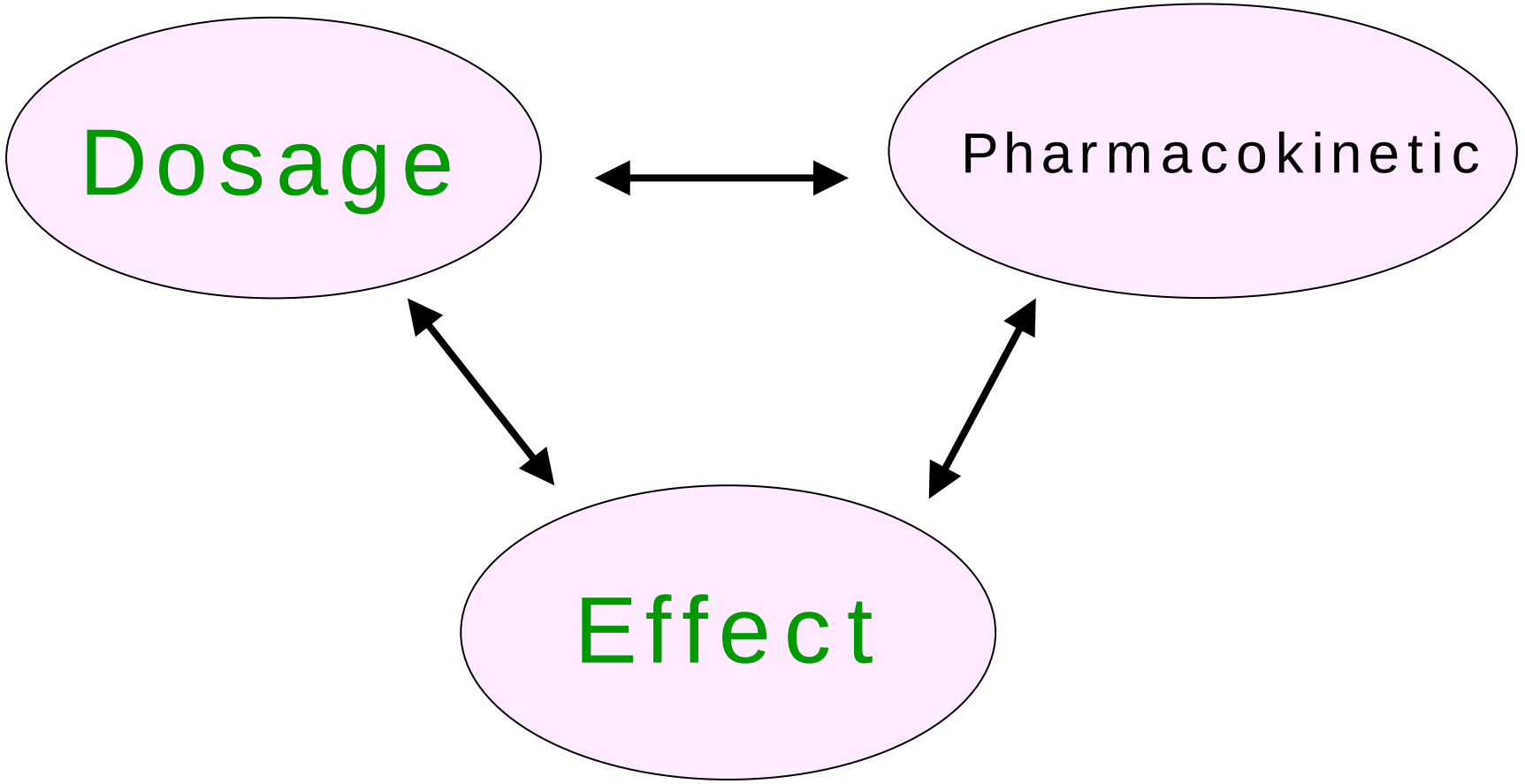


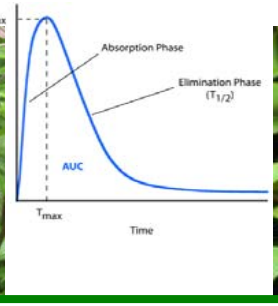




PK/PD studies for designing rational dosage regimes

Pharmacological active constituents are known





Pharmacokinetic interactions – for safety reasons

- a result of activity changes of drug-metabolizing and transporting proteins (CYP enzymes, P-gp)

Pharmacokinetic herb-drug interaction studies are important for most of the common used HMPs

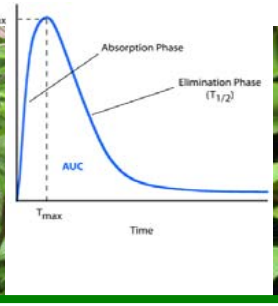
Problem:

most of the performed studies used phytochemically uncharacterized HMPs

Intention:

Phytochemically define the test product to make statements:

- which group of compounds are responsible for any obtained effect
- for which preparation, species, plant part and extraction procedure care must be taken when coadministered with prescription medications



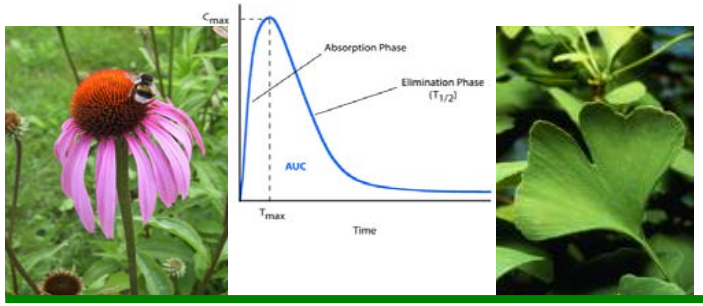
Summary and Conclusion

pharmacokinetic studies are only meaningful, if the pharmacological active constituents are known

Accordingly you can use pharmacokinetic studies to

- link results from pharmacological *in vitro* assays and clinical studies
- get information to what extent the active constituents are bioavailable from new galenic formulations, or to compare two different formulations
- demonstrate that a new formulation is in the range of commercial available products
- adjust the dosage to a more rational use of the HMPs
- perform pharmacokinetic herb-drug interaction studies for safety reasons

➢ much more work is needed to characterize the bioavailability and pharmacokinetics of HMPs in order to fully take advantage of their therapeutic potential



Acknowledgements

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All volunteers, who participated in the studies

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