

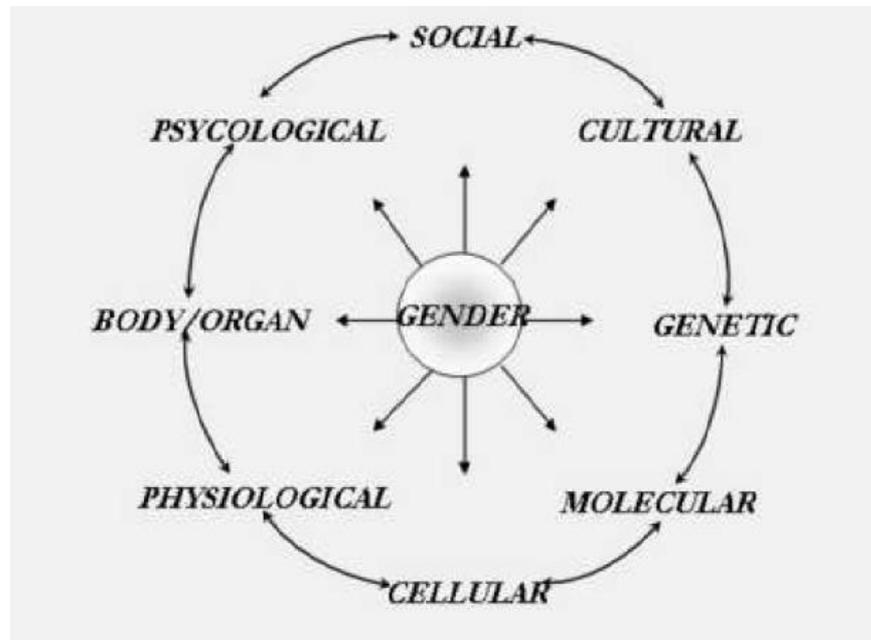
# Gender-related differences in pharmacotherapy: Is this the case for phytopharmaceuticals, too?



Prof. Dr. Karen Nieber  
University of Leipzig  
Institute for Pharmacy  
[nieber@rz.uni-leipzig.de](mailto:nieber@rz.uni-leipzig.de)

# Gender-related aspects: Why is this topic relevant?

Several factors (nutrition or chemical compounds including drugs), especially during specific windows of life, can influence health and diseases, in a sex/gender-related manner.



The recognition of differences and similarities between men and women can impact on the prevention, diagnosis, development of diseases and outcomes, and on the efficacy and safety of treatments.

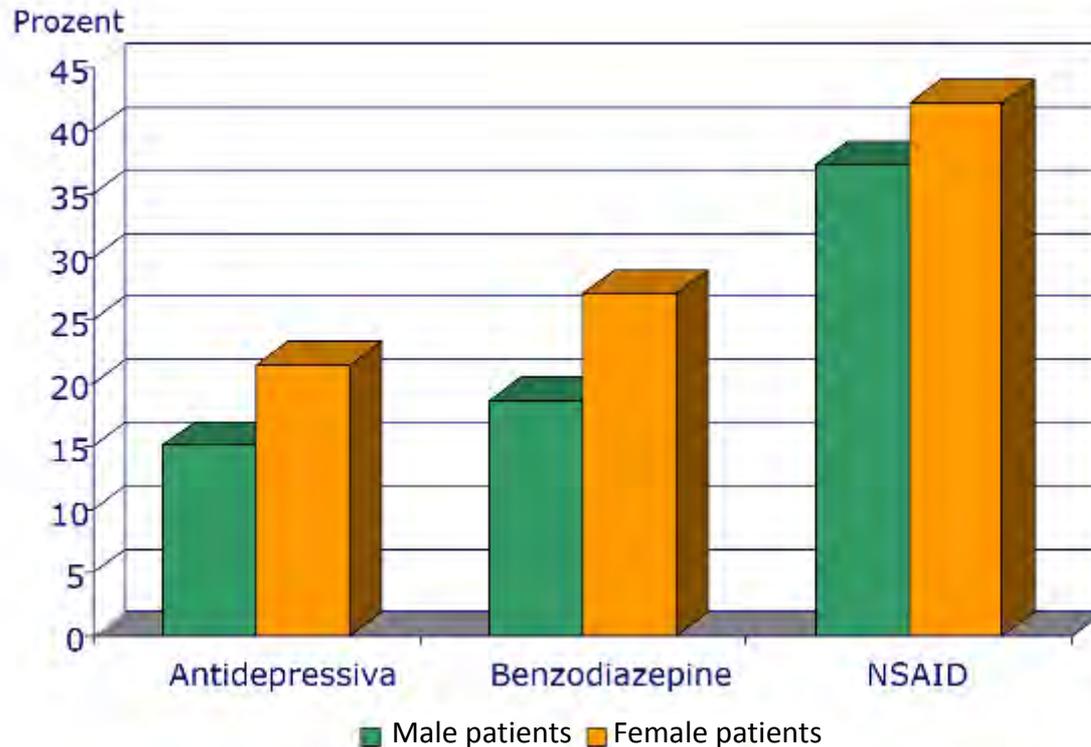
# Gender aspects in frequent diseases

The physiologic differences between men and women play an important role in disease prevalence and outcomes.

<i>Disease</i>	<i>Risk</i>
Cancer	Bladder, lung, kidney, and pancreatic cancers are more common in men; thyroid cancer is more common in women
Depression	Twice as common in women
Fibromyalgia	Nine times more common in women
Gout	More common in men
Hearing loss	More common in men
Irritable bowel syndrome	More common in women
Lupus	Nine times more common in women
Migraine	Three times more common in women
Myocardial infarction	Men are more likely to have a heart attack, but women are more likely to die within a year after a heart attack; women tend to be diagnosed with heart disease seven to 10 years later than men
Nearsightedness (myopia)	More common in women up to 60 years of age
Osteoporosis	More common in women
Rheumatoid arthritis	Two to three times more common in women
Stroke	Men are more likely to have a stroke, but women are more likely to die from a stroke; women are generally older than men when they have a stroke

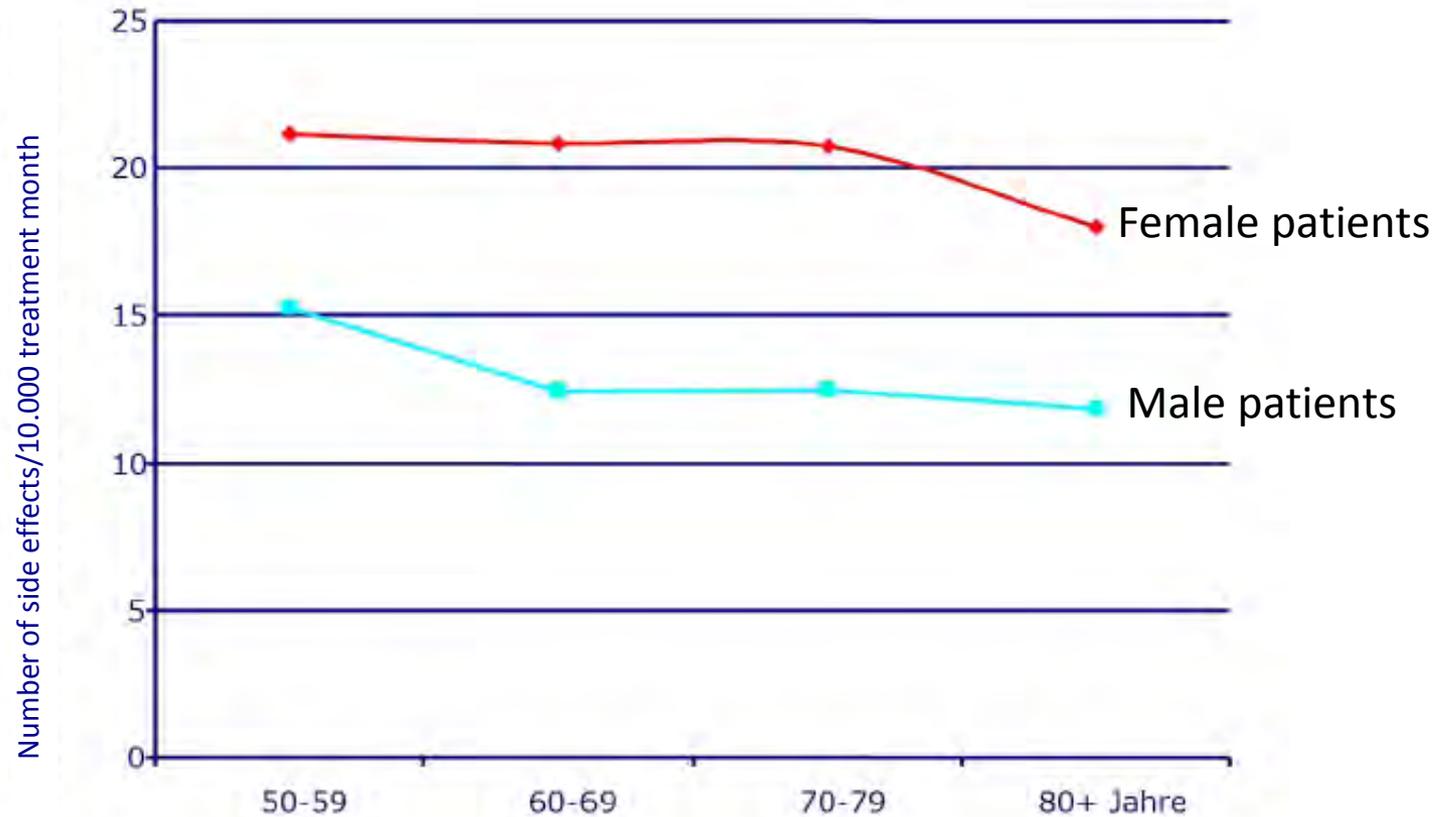
*Adapted from Bren L. Does sex make a difference? FDA Consum. 2005;39(4):10-15.*

# Gender-related aspects: Prescription of drugs in patients with ischaemic heart disease



Number (%) of patients with ischemic heart diseases who received a prescription for an antidepressant, benzodiazepine, or NSAID.

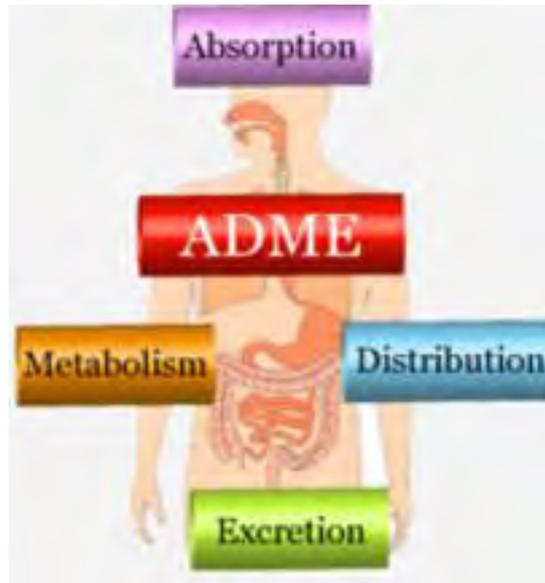
# Gender-related aspects: Side effects



Martin et al. Br J clin Pharmacol 1998, 46, 501-11

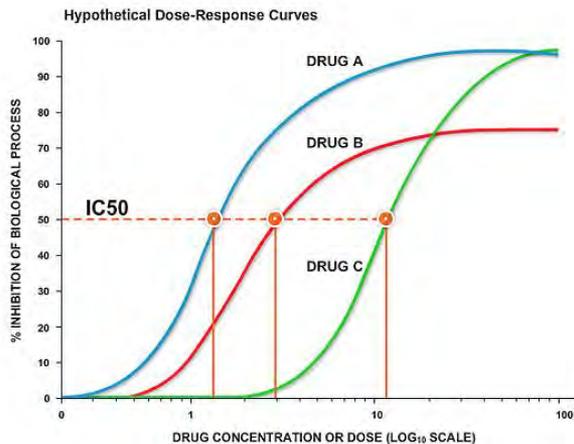
**Women are 50 to 75 % more likely than men to experience an adverse drug reaction.**

# What are the mechanisms underlying gender-related drug actions?



Gender-related differences can be divided into three categories:

- ✓ Physiological differences
- ✓ Pharmacokinetics/Pharmacodynamics
- ✓ Socio-medical aspects



Side effects



# Physiological differences between Men and Women

Parameter	Reference Adult Male	Reference Adult Female	Pregnant Female
Body Weight (kg) <sup>*</sup>	78	68	72.5
Body Length (cm) <sup>*</sup>	176	162	162
Body Surface Area (cm <sup>2</sup> )	18,000	16,000	16,500
Total Body Water (L)	42.0	29.0	33.0
Extracellular Water (L)	18.2	11.6	15.0
Intracellular Water (L)	23.8	17.4	18.8

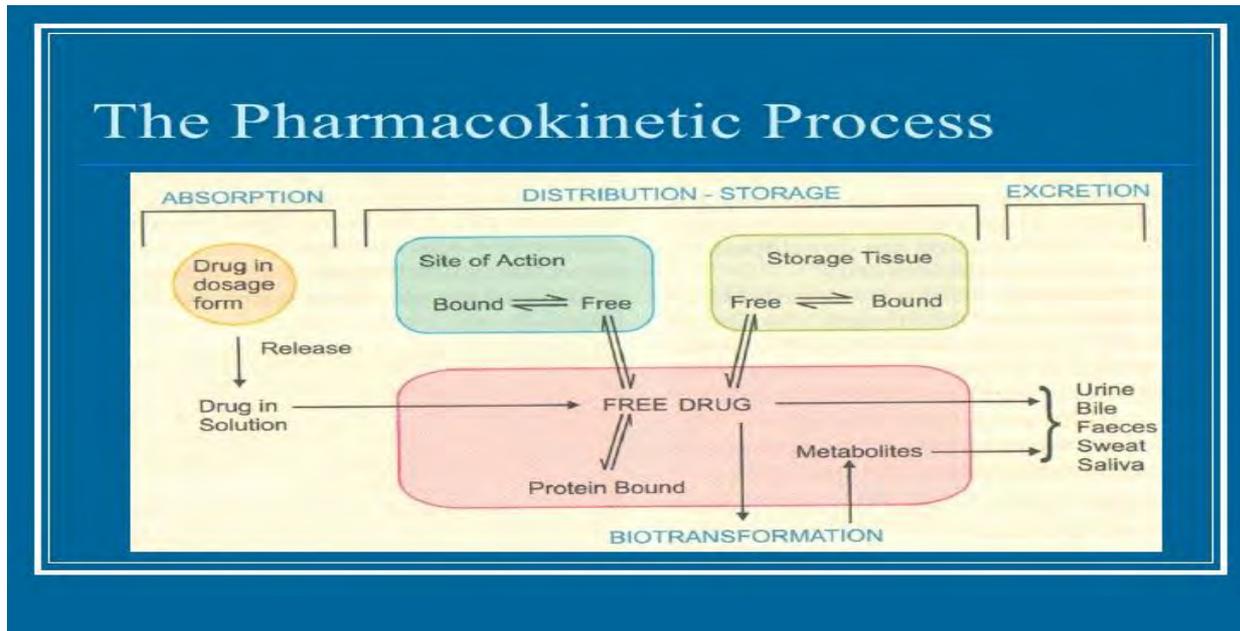
<sup>\*</sup>CDC Advance Data No. 347 October 27, 2004

Soldin and Mattison. Clin Pharmacokinet 2009;48;143-157

As our knowledge of drug toxicology and pharmacology is expanding it has become clear that men and women differ in response to drug treatment.

This could be the result of the physiological differences such as body weight, length, surface area, as well as differences in total body water.

# Molecular factors: Pharmacokinetics



Gender-related differences have been found in 4 pharmacokinetic areas:

- ✓ Absorption
- ✓ Distribution
- ✓ Biotransformation
- ✓ Excretion

# Gender-related aspects: Absorption

Some mechanisms which may contribute in absorption rate and duration have been reported for several drugs.

The rate of absorption is influenced by multiple factors:

(Caballeria J, et al. Gastroenterology. 1989;96:388–92):

- ✓ Women secrete less gastric acid.
- ✓ Mean gastrointestinal transit times is shorter in men (44.8 hrs) than in women (91.7 hrs).
- ✓ Lipid solubility of some drugs is grater in women than in men.
- ✓ pH at the site of absorption differs between men and women. There are changes during the menstrual cycle.
- ✓ Differences in plasma protein binding secondary to hormonal characteristics are documented.

**Generally, the clinical relevance of these mechanisms is questionable.**

# Gender-related aspects: Distribution

PARAMETER	PHYSIOLOGIC DIFFERENCE	PHARMACOKINETIC IMPACT
Plasma Volume	pregnant F>M>F	Decreased concentration in pregnancy
Body Mass Index (BMI)	M>F	Higher in men
Average organ blood flow	Pregnant F>M>F	Higher in men
Total Body Water	M>pregnant F>F	Decreased concentration
Plasma Proteins	M, F>pregnant F	Free concentration increases in pregnancy
Body Fat	pregnant F>F>M	Increase body burden of lipid- soluble drug in women
Cardiac Output	M>pregnant F>F	Increase rate of distribution in men

Soldin and Mattison. Clin Pharmacokinet 2009;48;143-157

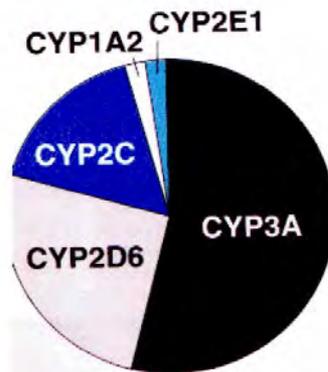
## Consequences:

If an average male and an average female are exposed to the same dose of a hydrophilic drug, the greater total body water, plasma volume, extracellular as well as intracellular water will increase the volume of distribution followed by decreasing drug concentration. On the other hand, hydrophilic drugs, such as alcohol or fluoroquinolone antibiotics, distribute into smaller volumes in women, producing higher initial plasma concentrations and greater effects.

# Gender-related differences: Biotransformation

PARAMETER	PHYSIOLOGIC DIFFERENCE	PHARMACOKINETIC IMPACT
Hepatic	higher basal metabolic rate (BMR) in M; hepatic metabolism in pregnant F	Increased metabolism
Extra-Hepatic	metabolism by fetus/placenta	Decreased metabolism
Plasma Proteins	free concentration increase in pregnant F	Increased metabolism

- ✓ Drug metabolism and biotransformation occurs predominantly in the liver, as well as in extra hepatic sites of metabolism such as lung, kidney, intestinal tract, and skin.
- ✓ Lipid solubility, protein binding, dose, and route of exposure all affect the rate of biotransformation.
- ✓ The initial phase of metabolism oxidizes, reduces, or hydroxylates drugs through CYP enzymes.



# Gender-related aspects: Biotransformation

	Men > Women	Men = Women	Women > Men
Bioavailability			
Oral			X
Transdermal		X	
Bronchial	X		
Distribution volume*			
Water soluble, nonlipophilic	X		
Lipophilic			X
Protein binding			
Albumin		X	
Alpha-1-acidglycoprotein	X		
Renal drug clearance			
Glomerular filtration	X		
Tubular reabsorption	X		
Tubular secretion	X		
Hepatic Drug Clearance			
Phase I			
CYP1A, 2D6, 2E1	X		
CYP 2C9, 2C19		X	
CYP3A			X (?)
Phase II	X		
(conjugation, glucuronidation, catechol-O-methyltransferase, thiopurine methyltransferase)			

\*In general, total volumes are greater in men because of greater body size.

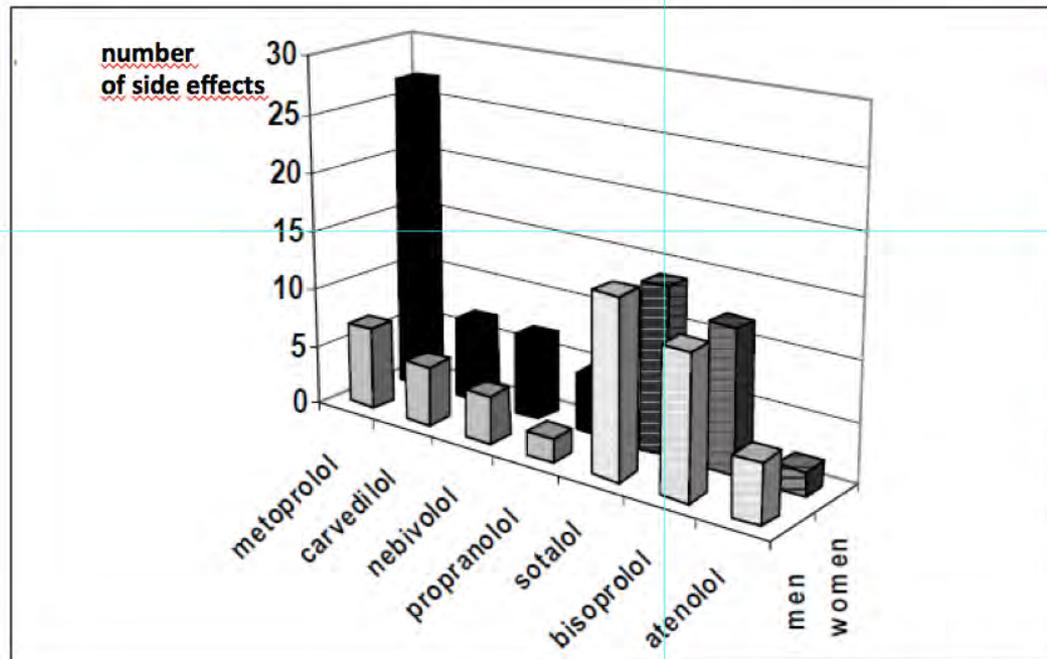
There is evidence for females having lower activity of CYP1A2, CYP2E1, and CYP2D6; higher or equivalent activity of CYP3A4 ; and no differences in CYP2C9 and CYP2C19 activity.

# Gender-related aspects: Biotransformation

Phase II reactions produce polar conjugates for renal excretion.

Men show a faster clearance of drugs that are eliminated by glucuronidation, causing some medications to clear faster, including paracetamol, caffeine, digoxin, doxorubicin, fluorouracil, levodopa, mercaptopurine, and some beta-blockers.

## Consequence:



**CYP2D6-  
dependent:**

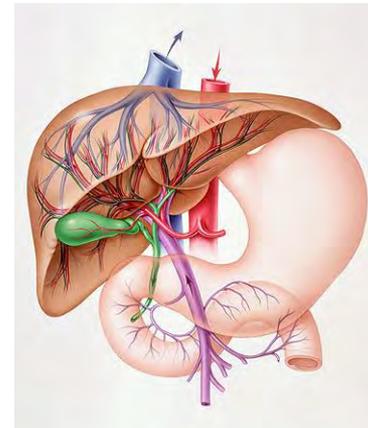
**Metoprolol,  
Carvedilol,  
Nebivolol,  
Propranolol**

**CYP2D6-  
independent:**

**Sotalol,  
Bisoprolol,  
Atenolol**

# Gender-related aspects: Excretion

- ✓ Sometimes clinically relevant gender differences could be identified for excretion and were predominantly linked to the gender-specific expression of metabolic enzymes.
- ✓ Both renal blood flow and glomerular filtration rate (GFR) are higher in men than in women. Therefore, women show a slower clearance of drugs that are actively eliminated via the kidney. Examples of these drugs include digoxin, methotrexate, gabapentin, and pregabalin (Soldin and Mattison. Clin Pharmacokinet 2009;48;143-157; Whitley H, Lindsey W.. Am Fam Physician. 2009;80:1254–1258).
- ✓ Significant hormonal changes and hormonal replacement therapy in menopausal and postmenopausal women can also lead to altered drug disposition in women (Spoletini et al. Handb Exp Pharmacol. 2012;214:91–105).



# Gender-related aspects: Pharmacodynamics

With regard to pharmacodynamics, gender differences have been observed in baseline characteristics as well as in drug response, which might be the consequence of modulation by sex hormones (Melbohm et al. Clin Pharmacokinet 2002;41:329-342).

<b>CLINICAL RECOMMENDATION</b>	<b>EVIDENCE RATING</b>
For the treatment of depression, men respond better to tricyclic antidepressants and women respond better to selective serotonin reuptake inhibitors.	C
Women require lower dosages of antipsychotic medications to control symptoms.	C
Opioids produce a stronger analgesic response in women compared with men.	C
Women have an increased response to beta-blocker therapy.	C
Aspirin therapy has a better protective effect against stroke in women and against myocardial infarction in men.	C
Women with heart failure have an increased risk of mortality when using digoxin therapy.	C

# Consequences

- ✓ The differences in pharmacokinetics and pharmacodynamics as well as the subsequent differential adverse drug effects between men and women have gained more awareness in recent years.
- ✓ For a few drugs, e.g. verapamil, beta-blockers and selective serotonin reuptake inhibitors, gender-related differences have been shown to result in different pharmacological responses, but their clinical relevance remains unproven.
- ✓ In contrast, gender differences of clinical importance have clearly been identified for pharmacodynamic processes such as QTc prolongation (Melbohm et al. Clin Pharmacokinet 2002;41:329-342).
- ✓ For example, to reduce the risk of morning-after activity impairment in women, the FDA has recommended lowering the dosages of zolpidem by 50% for women ([www.fda.gov/drugs/drugsafety/ucm334033.htm](http://www.fda.gov/drugs/drugsafety/ucm334033.htm)).

# Phytopharmaceuticals

- ✓ According to the World Health Organization, 80% of the world population cover their need of drugs through herbal preparations.
- ✓ The use of herbal medicines is increasing in Western countries.
- ✓ Herbal medicines are considered to have a broad therapeutic range.
- ✓ Herbal medicines are quite safe.
- ✓ Women have often used herbal medicines to treat pregnancy-related diseases and for their own health and well-being in pregnancy.
- ✓ Studies from Western countries show that the use of herbal drugs during pregnancy varies between 7 and 45% (Nordeng and Havnen Acta Obstet Gynecol Scand 2005: 84: 26—33).
- ✓ The side effects of herbal medicines depend from the herbal remedy, the dosage, and interaction with other pharmaceutical medications taken by the patient.

# Gender-related aspects: Population study

- ✓ In a Swedish population study, 58% of the subjects used prescribed pharmaceuticals (women 70.0%, men 46%) and 53.7% used non-prescribed pharmaceuticals (women 62.3%, men 44,2%) during a year.
- ✓ The figures for herbal medicines were 31.8% (women 39.2%, men 23.7%).
- ✓ The proportion of women was significantly higher than of men for all these categories of use.

	<i>n</i>	Prescribed pharmaceuticals (%)	Non-prescribed pharmaceuticals (%)	Herbal medicines (%)	Self-care products (%)
Age (years)					
16-44	357	52	57	32	21
45-64	268	56	54	34	25
65+	183	75	47	29	29
<i>P</i> value		< 0.0001	0.0631	0.0809	> 0.20
Gender					
Men	338	46	44	24	16
Women	420	70	62	39	31
<i>P</i> value		< 0.0001	< 0.0001	< 0.0001	< 0.0001

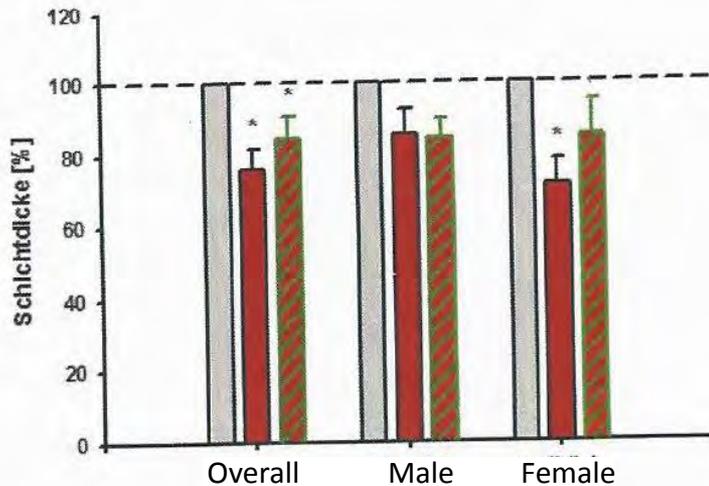
# Gender-related aspects: Facts

- ✓ Herbal products share the same metabolic processes and can act on the same targets as chemical drugs.
- ✓ Therefore, interactions between herbs and chemical drugs can be elicited by either pharmacodynamic or pharmacokinetic mechanisms.
- ✓ There is limited information on the pharmacokinetics of herbs even though their use either alone or in addition to chemical drugs is increasing.
- ✓ One of the major reasons for most of these multi-component drugs is that their active ingredient(s) are often not known.
- ✓ Nevertheless some in vitro and in vivo studies as well as clinical studies were published indicating gender-related differences or even no effects.

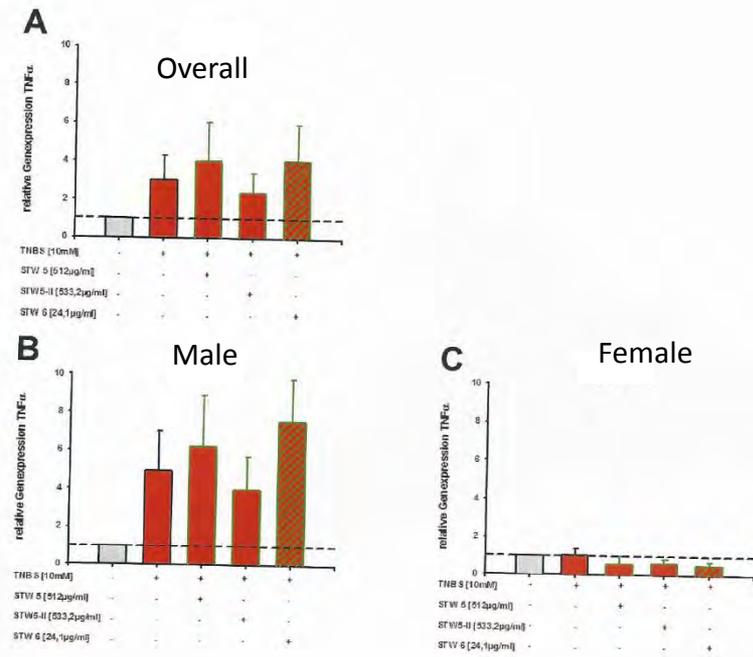
# Gender-related aspects: in vitro studies

- ✓ IBS is a common functional bowel disorder and most studies indicate a female predominance (Saito et al. Am J Gastroenterol 2002;97:1910-1915).
- ✓ There is growing evidence that STW 5, a fixed combination of 9 herbal extracts, besides being effective in functional dyspepsia, also improves symptoms in IBS.
- ✓ Gender-related effects were evaluated using an established inflammation in vitro model.

Muscle layer (colon preparation)



TNF-α release (colon preparation)



# Gender-related aspects: in vivo studies

*Zingiber officinale* exhibits behavioral radioprotection against radiation-induced CTA in a gender-specific manner. Haksa et al. Pharmacol Biochem Behav. 2006;84(2):179-88.

**Results:** A comparison of the efficacy of zingiber extract with two antiemetic drugs, ondasteron and dexamethasone, revealed that the extract induced protection against radiation-induced taste aversion. The significant dose in males was 200mg/kg KW and in females 250 mg/kg KW. The observed gender variations were hypothesized to be a result of hormonal fluctuations and differences in pharmacokinetic parameters in male and female rats.



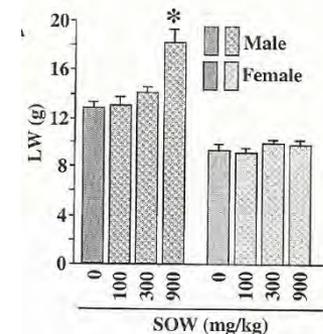
Gender-related variation in the effective dose

*An aqueous extract of Salacia oblonga* root, a herb-derived peroxisome proliferator-activated receptor- $\alpha$  activator, by oral gavage over 28 days induces gender-dependent hepatic hypertrophy in rats. Rong et al. Food Chem Toxicol. 2008 Jun;46(6):2165-72.

**Results:** An extract of *Salacia oblonga* root (SOW) has anti-diabetic and anti-obesity properties. The study show that SOW elicited dose-related increases in liver weight in male but not in female rats.



Gender-related effects



## Gender-related aspects: Clinical studies

*Effect of Acute Administration of an Herbal Preparation on Blood Pressure and Heart Rate in Humans.* Seifert et al. *Int J Med Sci* 2011;8:192-197

**Results:** The results of this study indicate that acute ingestion of a dietary supplement containing caffeine, bitter orange extract (*p*-synephrine) and green tea extract did not lead to significant cardiovascular effects as reflected by blood pressure and heart rate in men and women.



No gender-related differences

*Herbal treatment of allergic rhinitis: the use of Nigella sativa.* Nikakhlagh et al. *Am J Otolaryngol* 2011;32:402-407

**Results:** The results show that *N. sativa* could reduce the presence of allergic symptoms (nasal mucosal congestion, nasal itching, runny nose, sneezing attacks, hypertrophy, and mucosal pallor) during the first 2 weeks both in males and females.



No gender-related differences

# Gender-related aspects: Clinical studies

*St. John's wort treatment in women bears risks beyond pharmacokinetic drug interactions.* Hohmann et al. Arch Toxicol 2015, DOI 10.1007/s00204-015-1532-7

**Results:** The study analysed adverse events in a clinical phase I trial to assess dose-dependent effects of St. John's wort co-administered with rifampicin in 6 female and 6 male healthy volunteers. 5 of 6 female volunteers developed ambient temperature-dependent allodynia and paresthesia in sun-exposed areas. None of the male volunteers showed any of these effects.



Gender-related pharmacokinetic effects resulting in higher side effects

Colocynthis fructus extract (Arhama<sup>®</sup>-Tinktur N) has been well studied for different diseases of the gastrointestinal tract. It is used in combination products for treating constipation or liver and gallbladder problems. The HED was calculated from rat experiments. (Bombastus Werke AG, personal communication)

**Results:** The HED and therefore the Safety Factor is different in men and women, indicating a higher toxicity in men.



Gender-related toxic dose

	Human Equivalent Dose (HED; mg/kg KG)	Safety factor (HED/TD Arhama Tinktur N)
female	1158	733
male	Ca. 450	285

# Conclusion

- ✓ Despite the differences in drug pharmacokinetics between men and women, gender-specific recommendations in dosage do not exist for most drugs.
- ✓ Pregnancy, oral contraceptive use, and hormonal replacement therapy can significantly change drug metabolism and drug clearance as well as the affinity to the targets.
- ✓ For the majority of investigated drugs, however, no or only very minor gender differences could be detected in pharmacokinetics and/or pharmacodynamics.
- ✓ Only few studies with herbs were reported in which gender-related aspects were studied and evaluated.
- ✓ It seems that in vitro and in vivo gender-related effects could be confirmed but all identified studies were made under laboratory conditions and a transfer to human situation is questionable.
- ✓ The results of the identified clinical studies with herbs are controversially discussed, the most of them are in a preliminary stage.
- ✓ Overall, gender-related aspects with herbs are of minor importance in comparison to chemical drugs.
- ✓ In addition, the clinical significance of gender differences identified with herbs seem very limited and was only very rarely linked to treatment success or failure.