

# Pumpkin Seed and Hormonal Imbalance

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# Directory

- Short Introductions to
  - Urinary Incontinence and
  - Benign Prostate Hyperplasia (BPH)
- Pumpkin Seed: Selection of Compounds
- Mode of Action and Active Fraction
- Pre-Clinical and Clinical Trials
- Technical Background, Quality and Safety
- Final Summary of Effects of EFLA®940

# Urinary Incontinence: General Data

- definition: inability to control urination (approx. 5 % of population affected)
- psychological: shame, depression, hygiene, isolation
- patients: men and women
- therapy:
  - medical treatment, physiotherapy, diapers
  - treatment of psychological and social problems

# Urinary Incontinence: Classifications

- stress incontinence:  
weak pelvic muscle or sphincter, occurrence in context with coughing, sneezing or lifting weight
- pressure/urge incontinence:  
irritable detrusor, high frequency of contraction
- overflow incontinence:  
constriction of the urethra in the prostate gland caused by BPH

# Urinary Incontinence: Dependence on age

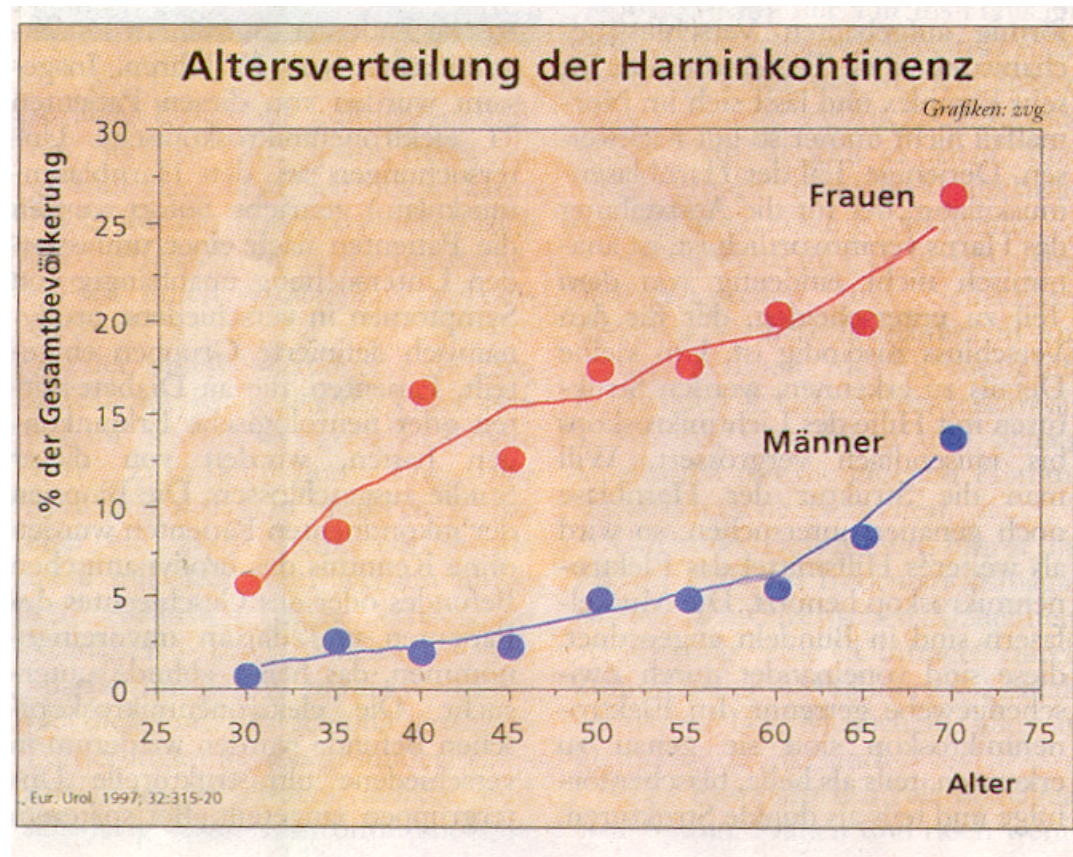


Fig.: Medizinzeitung, 5, 2000

# Urinary Incontinence: Pathophysiology

Stress incontinence and overflow incontinence are closely linked to hormonal deficits and shifts in hormonal balances:

stress incontinence:

in postmenopausal women:

- estrogen deficit:  
atrophy of urethra
- insufficient androgen effect: weak pelvic floor

→ **aromatase**

overflow incontinence:

benign prostate hyperplasia in men:

- testosterone deficit  
→ **5 $\alpha$ -reductase**

# Urinary Incontinence: Pathophysiology

## Overflow incontinence

### functional

weakness of  
bladder muscle

### overstretching of bladder wall

*both sexes  
affected*

metabolic disturbance, side effects  
of remedies, parkinson etc.

### obstructive

narrowing of the urethra caused  
by prostate growth

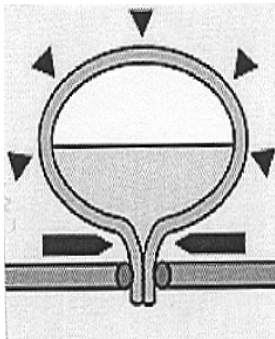
### benign prostate hyperplasia (BPH)

*men at advanced age*

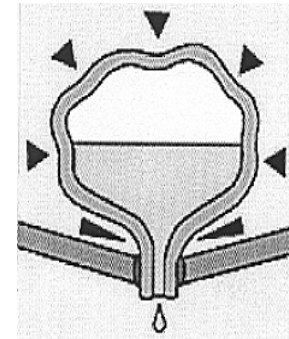
cause not clear yet, hypothesis:  
endocrine changes or disturbances

# Urinary Incontinence: Pathophysiology

## Stress incontinence

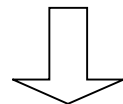


weakening of the sphincter muscle caused by the relaxation of the pelvic floor muscles



***affected: mostly women***

**further cause in postmenopausal women:  
atrophy in urethral epithelium caused  
by hormonal changes**



**menopause influences control over  
function of bladder**

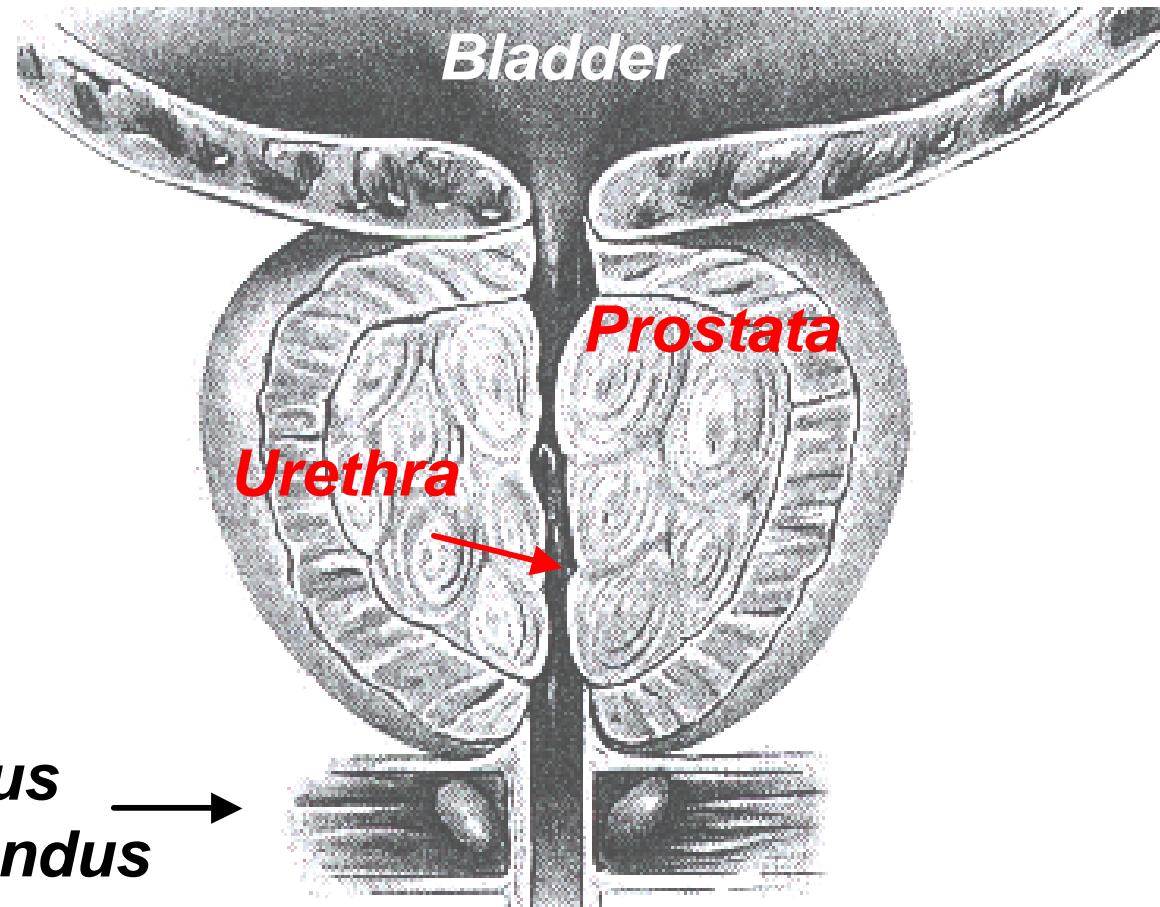
# Benign Prostate Hyperplasia: **General Data**

- definition: non malignant enlargement of fibromuscular and epithelial structures within the gland (approx. 60 % of men older 50 y)
- symptoms: urinary symptoms as: hesitancy, incomplete voiding of the bladder, terminal dribbling, urgency, frequency and nocturia
- cause: not clear
- hypothesis: hormonal imbalance

# Benign Prostate Hyperplasia: **Classifications**

- stage I: obstructive and irritant symptoms
- stage II: begin of decompensation of the voiding mechanism, residual urine of 100-150 ml, pollakisuria (frequency↑ )
- stage III: decompensation of the bladder: chronic and complete retention of urine or overflow incontinence, reduction of renal function, uremia.

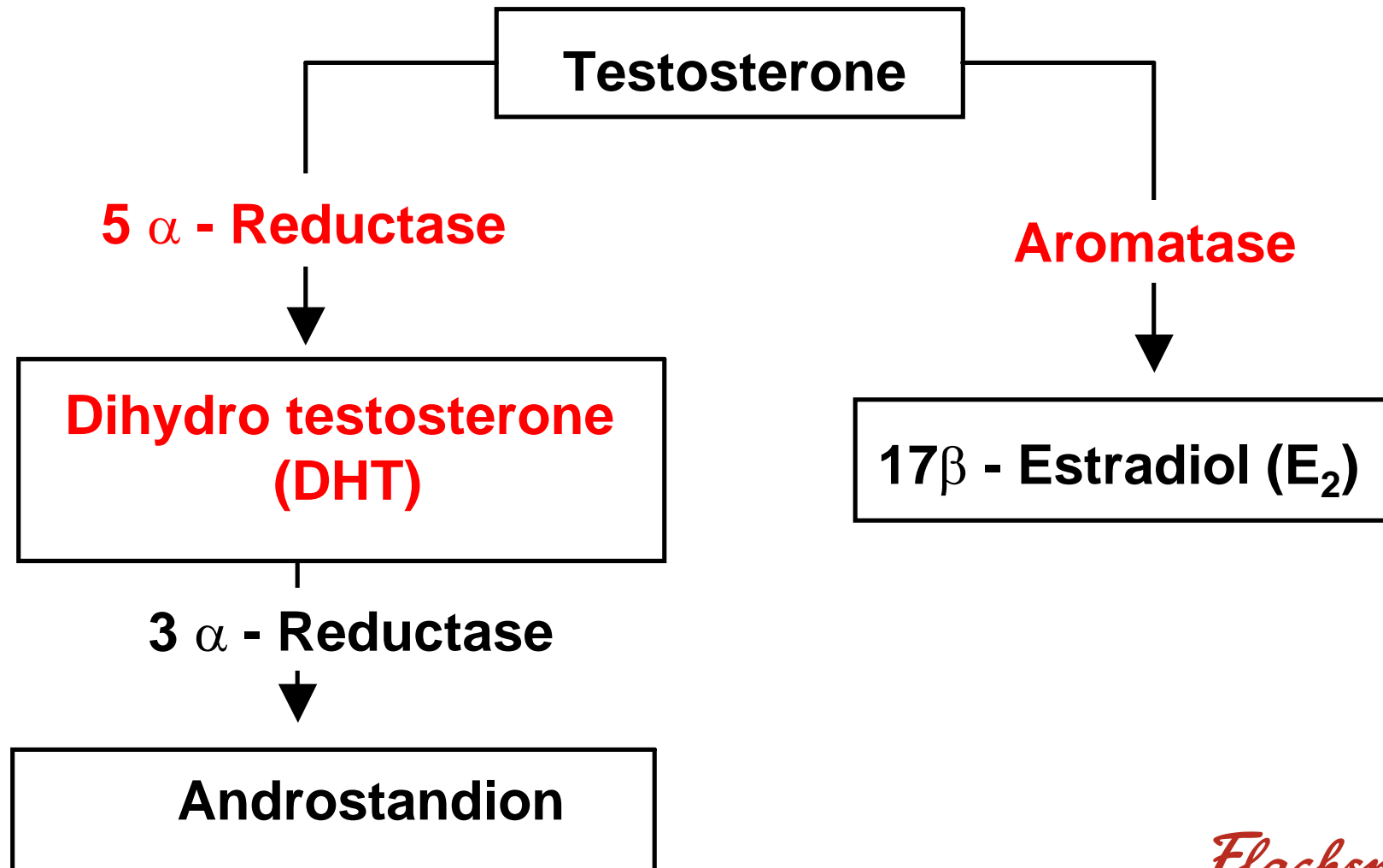
# Benign Prostate Hyperplasia: Pathophysiology



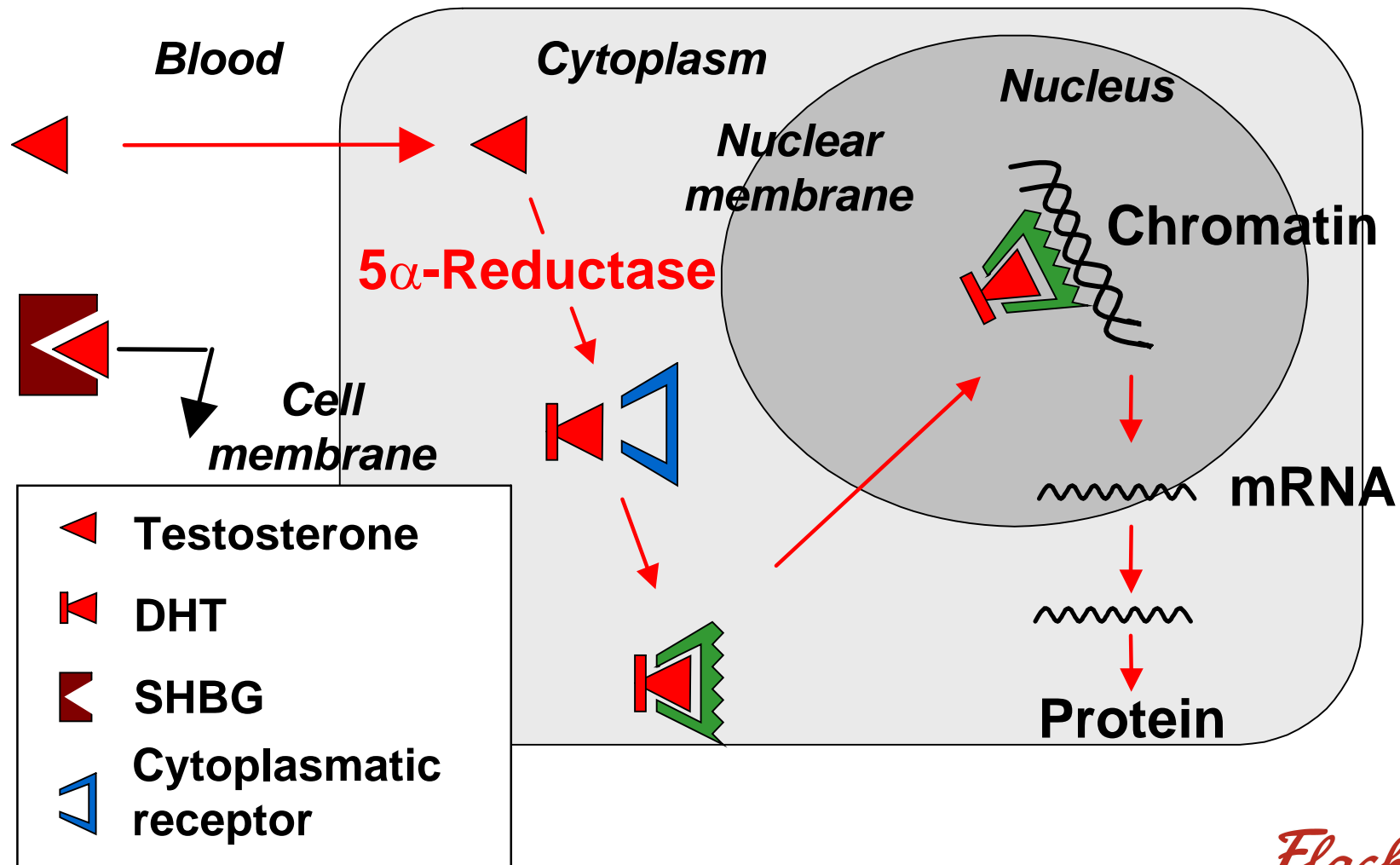
***M. transversus  
perinei profundus*** →

(Fig. from: Schunack, W.: BPH-Die Leiden des älteren Mannes. DAZ 1998; 138 (46): 62-63)

# Benign Prostate Hyperplasia: Pathophysiology



# Benign Prostate Hyperplasia: Pathophysiology



# Pumpkin Seed: **Indications**

According to the Commission E recommendations:

- Irritable bladder condition
- micturition problems caused by benign prostate hyperplasia (BPH) stage I and II (relief of the symptoms, no reduction of the prostate growth)

recommended average daily dosage:  
10 g of seed or equivalent preparations

# Pumpkin Seed: Selection of Compounds

## lipid fraction

nutritional value as food  
less suited as medicinal  
drug

linoleic acid 50 %

oleic acid 35 %

palmitic acid 10 %

stearic acid 5 %

delta-7-sterols 0.2 - 0.4 %

tocopherol

fat free, polar part  
of pumpkin seeds:

-proteins

-phenols (lignans)

belonging to the family of

**phytoestrogens**

secoisolariciresinol

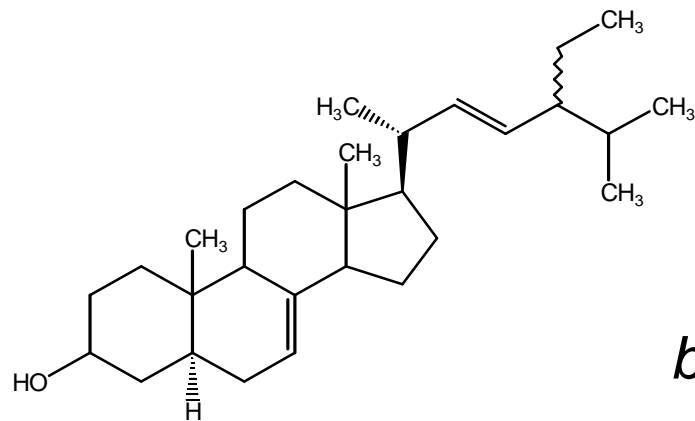


enterodiol / enterolactone

# Pumpkin Seed: Selection of Compounds

## Lipid fraction

potential effective substance:



Spinasterol;  
a  $\Delta^7$ -sterol from *C. pepo* L.

*but:*

- sterols are not absorbed in the intestines
- efficient doses are unrealistic high



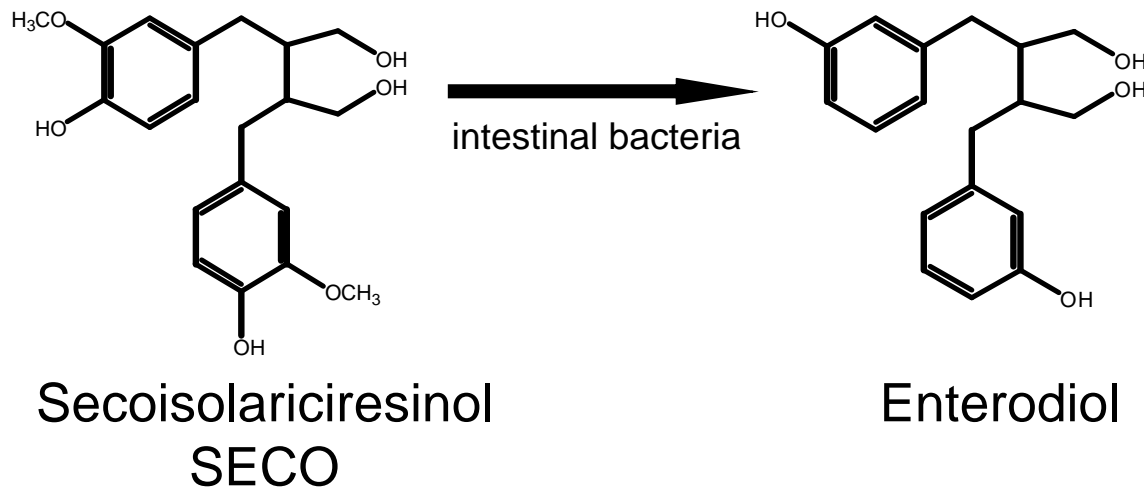
no rational therapy with phytosterols

# Pumpkin Seed: Selection of Compounds

## Polar Fraction

potential effective substance:

Phytoestrogens (e.g. Lignans)



Enterodiol found in:

- urine
- feces
- prostate
- bile
- plasma
- saliva
- breast milk

Murkies A, (1998) *Aust Fam Physician*, 27

(Suppl. 1), 47-51

➔ ***promising rational therapy***

# Pumpkin Seed: Mode of Action

the **polar** fraction reveals the following effects:

- inhibition of peripheral and placental aromatase
- inhibition of  $5\alpha$ -reductase type II
- Phytoestrogens bind to estrogen receptors
- Phytoestrogens interfere with binding of testosterone,  $5\alpha$ -dihydrotestosterone and estradiol to SHBG

Schottner M, et al. (1998) *J Nat Prod.* 61(1): 119-21

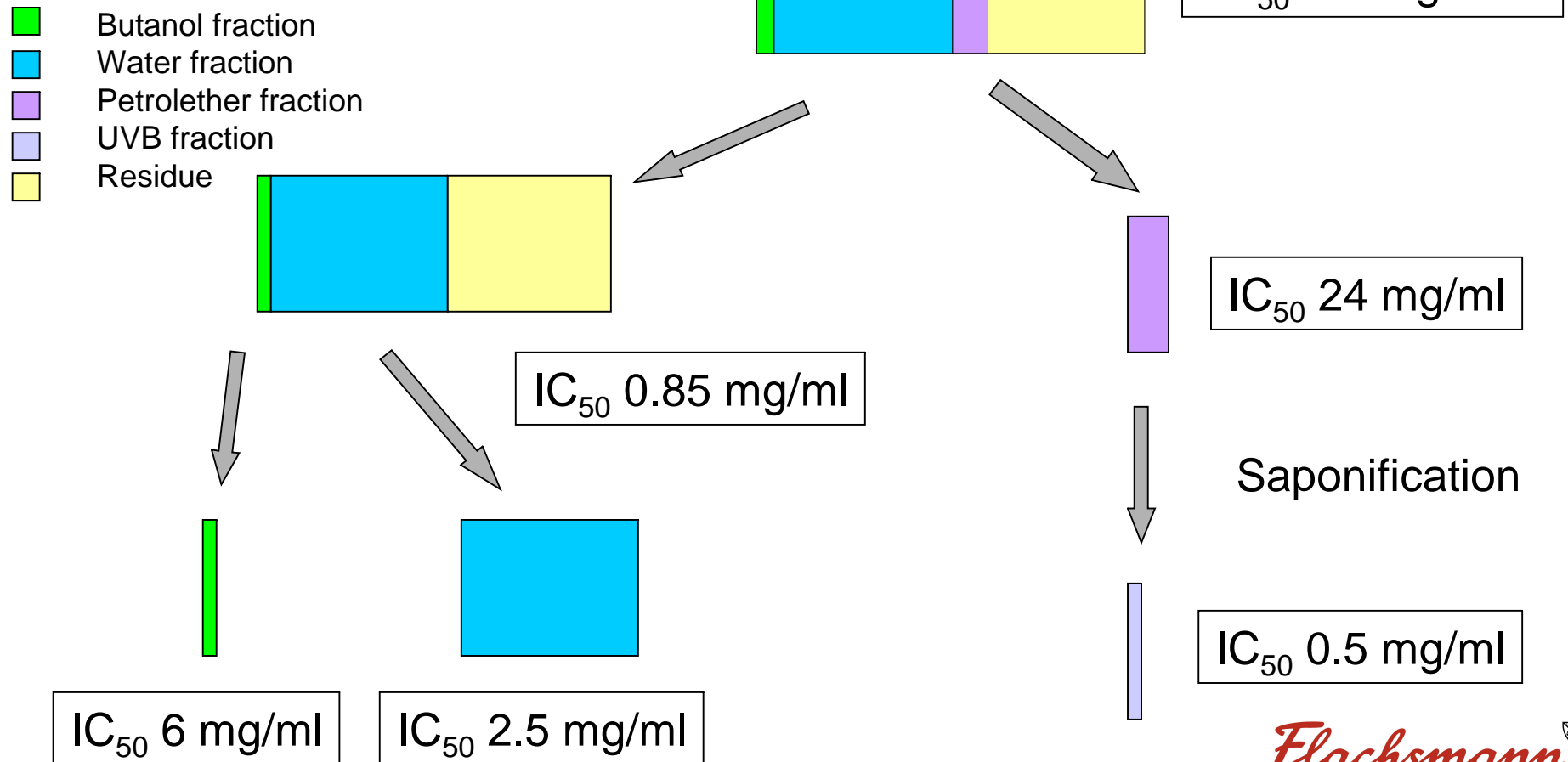
Schottner M, et al. (1997) *Z Naturforsch[C]* 52(11-12): 834-43.

Schottner M, et al. (1997) *Planta Med.* 63(6): 529-32.

Martin ME, et al. (1996) *Life Sci.* 58(5): 429-36.

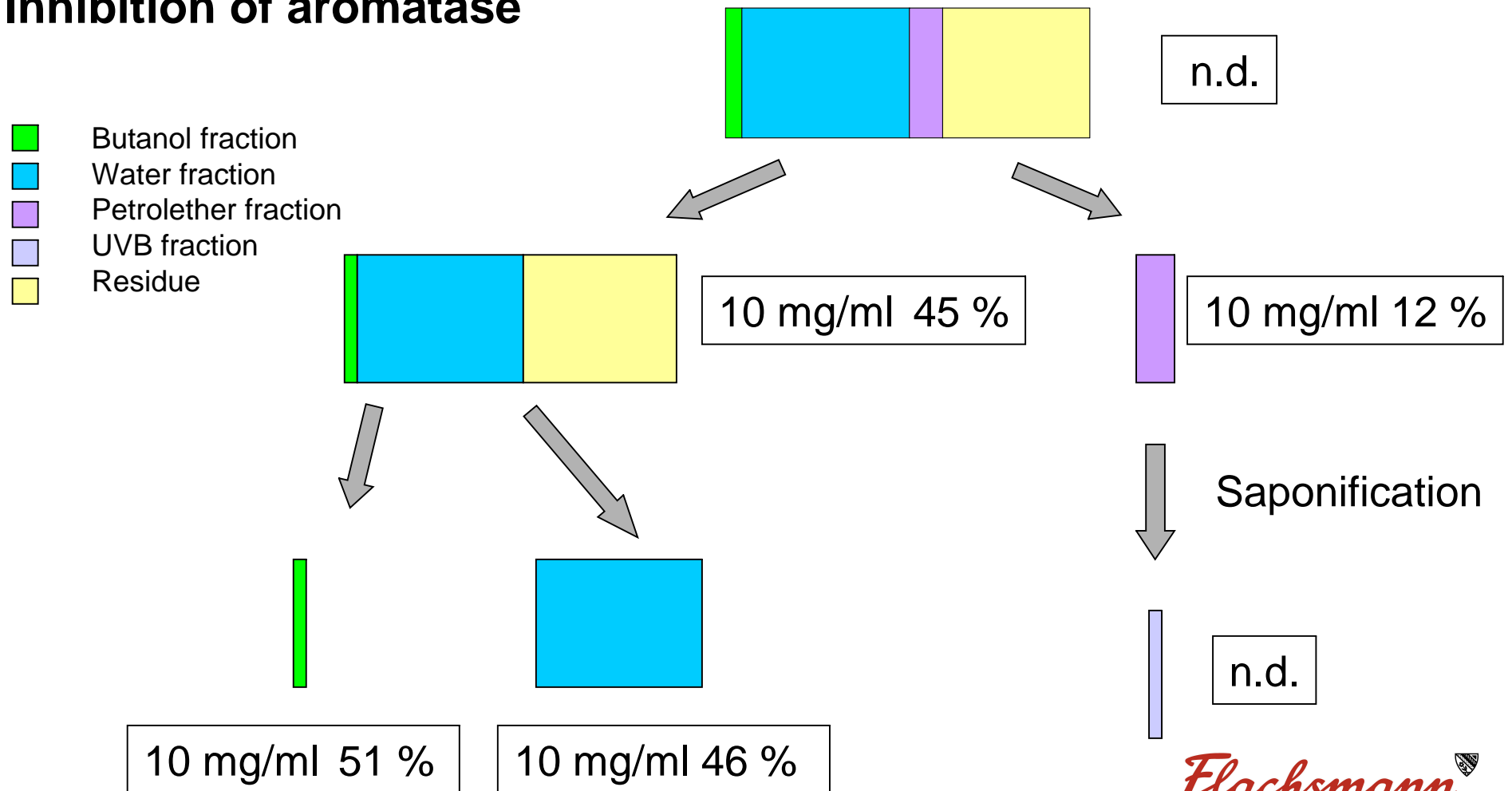
# Pumpkin Seed: Active Fraction

## Inhibition of 5 $\alpha$ -reductase



# Pumpkin Seed: Active Fraction

## Inhibition of aromatase



# Pumpkin Seed: *in vitro* Inhibition of Aromatase

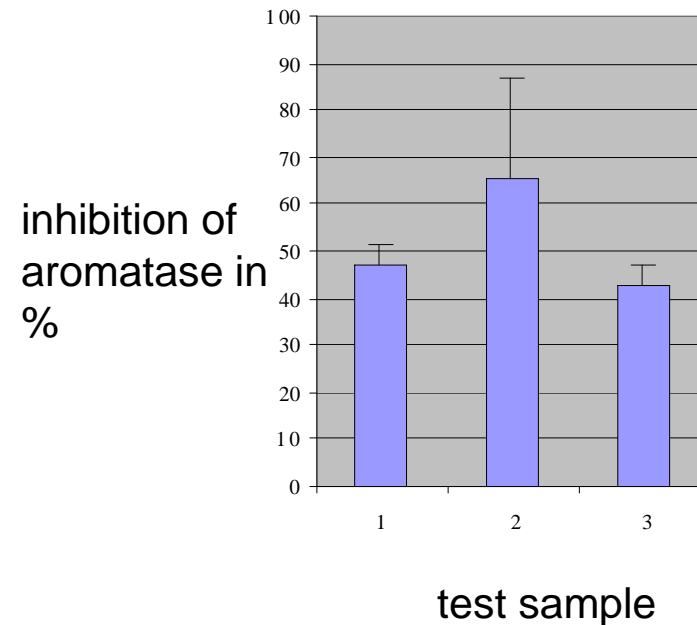
## Experimental design:

- standard test to determine directly the ability of different extract fractions to inhibit aromatase from human placenta homogenate
- incubation of the enzyme with  $^3\text{H}$ -testosterone
- determination of radioactive  $^3\text{H}_2\text{O}$  generated from testosterone by aromatase

# Pumpkin Seed: *in vitro* Inhibition of Aromatase

## Results *in vitro*:

- aromatase inhibition tested in 3 series.
- inhibition with 10 mg/ml amounts to
  - 46.8 +/- 5.0 %
  - 65.4 +/- 21.4 %
  - 43.0 +/- 4.2 %
- IC<sub>50</sub> about 10 mg/ml



# Pumpkin Seed: *in vitro* Inhibition of Aromatase

## Discussion

- lignans assumed responsible for the inhibition of aromatase are present but bound to glycosides
- *in vitro* with 10 mg/ml extract remarkable inhibition of the aromatase achievable.

# Pumpkin Seed: *in vivo* Phytoestrogenic Effect

## Phytoestrogenic effect

### Assessment with the aid of the induction of the growth of rat uterus

- application once daily in juvenile female Sprague Dawley rats (5 mg, 10 mg and 20 mg/kg)
- treatment during 4 or 8 days
- determination of the uterus weight

# Pumpkin Seed: *in vivo* Phytoestrogenic Effect

## Result: experiment I

4 days  
application

Treatment	Uterine wet weight (mg/100 g b.w.) Mean ± SEM	Uterine dry weight (mg/100 g b.w.) Mean ± SEM
Vehicle treated control (CMC)	78.2 ± 8.9	13.6 ± 1.2
85940 (mg/kg) 5	68.8 ± 3.2	11.7 ± 0.6
10	72.3 ± 9.6	12.5 ± 1.5
20	70.6 ± 2.8	12.9 ± 0.6

8 days  
application

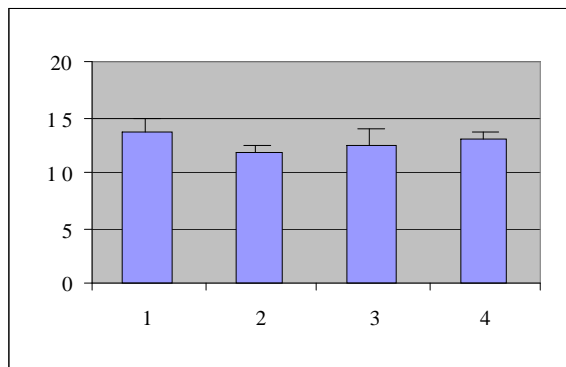
Treatment	Uterine wet weight (mg/100 g b.w.) Mean ± SEM	Uterine dry weight (mg/100 g b.w.) Mean ± SEM
Vehicle treated control (CMC)	108.8 ± 22.0	17.5 ± 3.1
85940 (mg/kg) 5	128.5 ± 32.1	18.5 ± 4.0
10	129.5 ± 34.9	21.1 ± 4.9
20	182.6 ± 65.7	23.6 ± 6.4

# Pumpkin Seed: *in vivo* Phytoestrogenic Effect

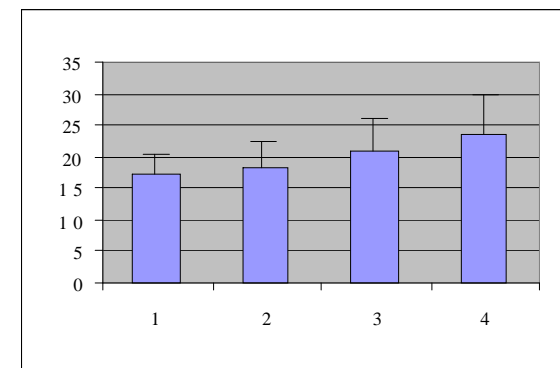
## Result: experiment I

- 4 days of treatment reveals no effect
- 8 days of treatment shows an increase of the dry weight of uterus of 34.9 %

4 days



8 days



1: control  
2: 5 mg/kg  
3: 10 mg/kg  
4: 20 mg/kg

dry uterus weight mg/100 g b.w.

# Pumpkin Seed: *in vivo* Phytoestrogenic Effect

## Result: experiment II

8 days treatment  
relative values

Treatment		Uterine wet weight (mg/100 g b.w.) Mean ± SEM	Uterine dry weight (mg/100 g b.w.) Mean ± SEM
Vehicle treated control (CMC 0.5%)		61.0 ± 4.4	11.4 ± 0.6
85940 (mg/kg)	5	58.0 ± 3.3	10.9 ± 0.5
	10	69.3 ± 6.5	14.4 ± 1.3 *
	20	56.3 ± 1.7	11.9 ± 0.5

8 days treatment  
absolute values

Treatment		Uterine wet weight (mg) Mean ± SEM	Uterine dry weight (mg) Mean ± SEM
Vehicle treated control (CMC 0.5%)		42.4 ± 3.3	8.0 ± 0.5
85940 (mg/kg)	5	39.2 ± 2.6	7.3 ± 0.4
	10	42.5 ± 4.4	8.7 ± 0.8
	20	37.3 ± 1.3	7.8 ± 0.3

# Pumpkin Seed: *in vivo* Phytoestrogenic Effect

## Discussion

- experiment I shows dose dependent increase of the uterus weight
- no significance caused by strong deviation
- phytoestrogenic effect is possible
- no reproducibility yet (experiment II)

# Pumpkin Seed: *in vitro* Inhibition of 5 $\alpha$ -Reductase

## Experimental design:

- standard test to determine directly the ability of different extract fractions to inhibit 5 $\alpha$ -reductase type II in human prostate homogenate
- incubation of the enzyme with <sup>3</sup>H-testosterone
- separation by HPLC and determination of radioactive testosterone and its metabolite dihydrotestosterone
- ratio of peak areas correlates quantitatively with the degree of enzyme inhibition
- different sample concentrations allow determination of IC<sub>50</sub> value

# Pumpkin Seed: *in vitro* Inhibition of 5 $\alpha$ -Reductase

## Results *in vitro*:

- polar (lipid free) fraction of EFLA®940 inhibits the activity of 5 $\alpha$ -Reductase type II (IC<sub>50</sub> 0.85 mg/ml)

# Pumpkin Seed: *in vivo* Inhibition of 5 $\alpha$ -Reductase

## Experimental design:

- standard test to evaluate directly the potency of EFLA®940 / positive control (finasteride)
- investigation of the inhibitory influence of EFLA®940 on increase of prostate weight *in vivo*
- immature castrated male rats
- testosterone propionate for the stimulation of increase of prostate weight
- oral application of EFLA®940

# Pumpkin Seed: *in vivo* Inhibition of 5 $\alpha$ -Reductase

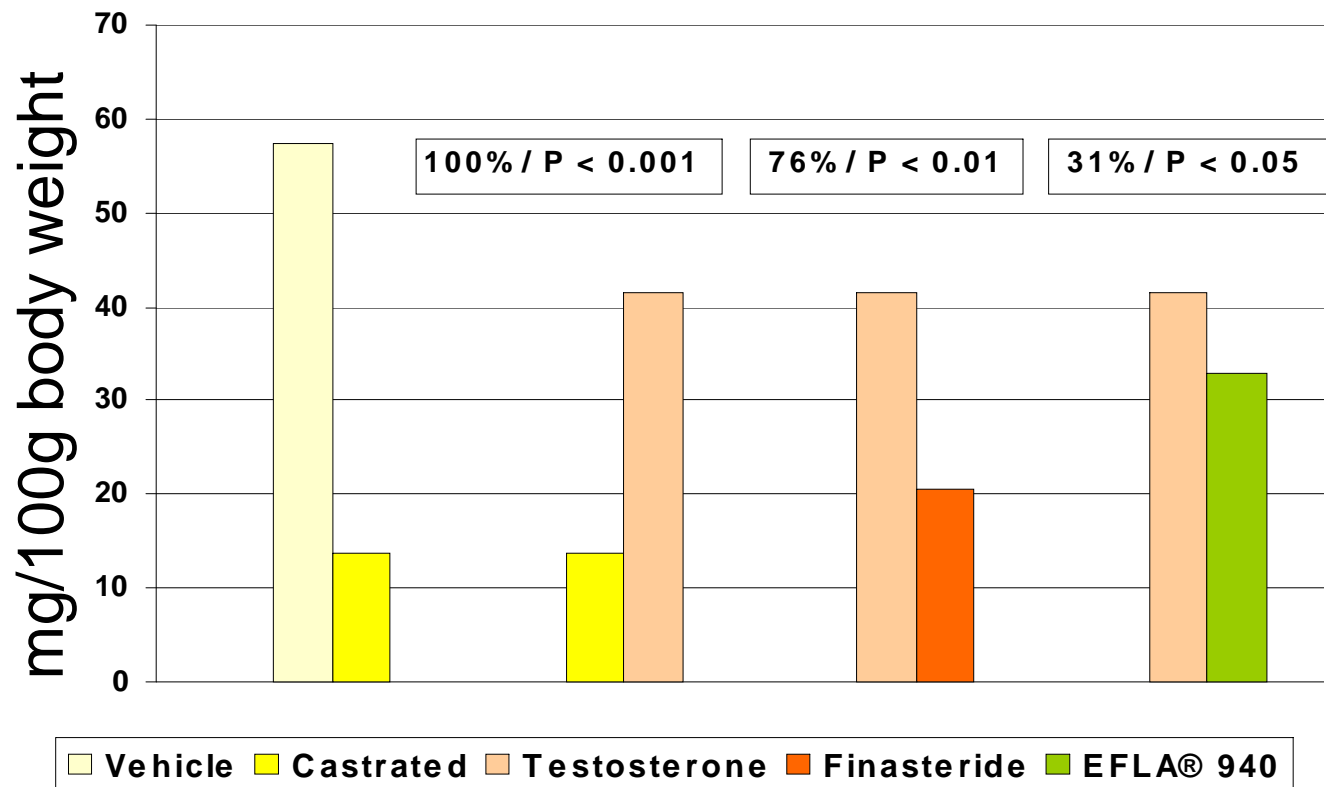
## Design:

- All animals except in group I are castrated 3 days before start of study.
- All groups were treated during 4 consecutive days according the following scheme:

Groups	Treatment				
	Castrated	Vehicle	Testosterone	Finasteride	EFLA® 940
Vehicle-treated Control	-	+	-	-	-
Castrated Vehicle-treated Control	+	+	-	-	-
Testosterone prop., sc 1 mg/kg	+	+	+	-	-
Finasteride, sc 1 mg/kg	+	+	+	+	-
Cucurbitae extr., po 100 mg/kg	+	+	+	-	+

# Pumpkin Seed: *in vivo* Inhibition of 5 $\alpha$ -Reductase

## Result



# Pumpkin Seed: Inhibition of $5\alpha$ -Reductase

## Discussion

- Remarkable inhibition of  $5\alpha$ -reductase in vitro
- EFLA®940 is absorbed and intestinally metabolised
- EFLA®940 reaches its destination
- Significant reduction of the prostate weight increase

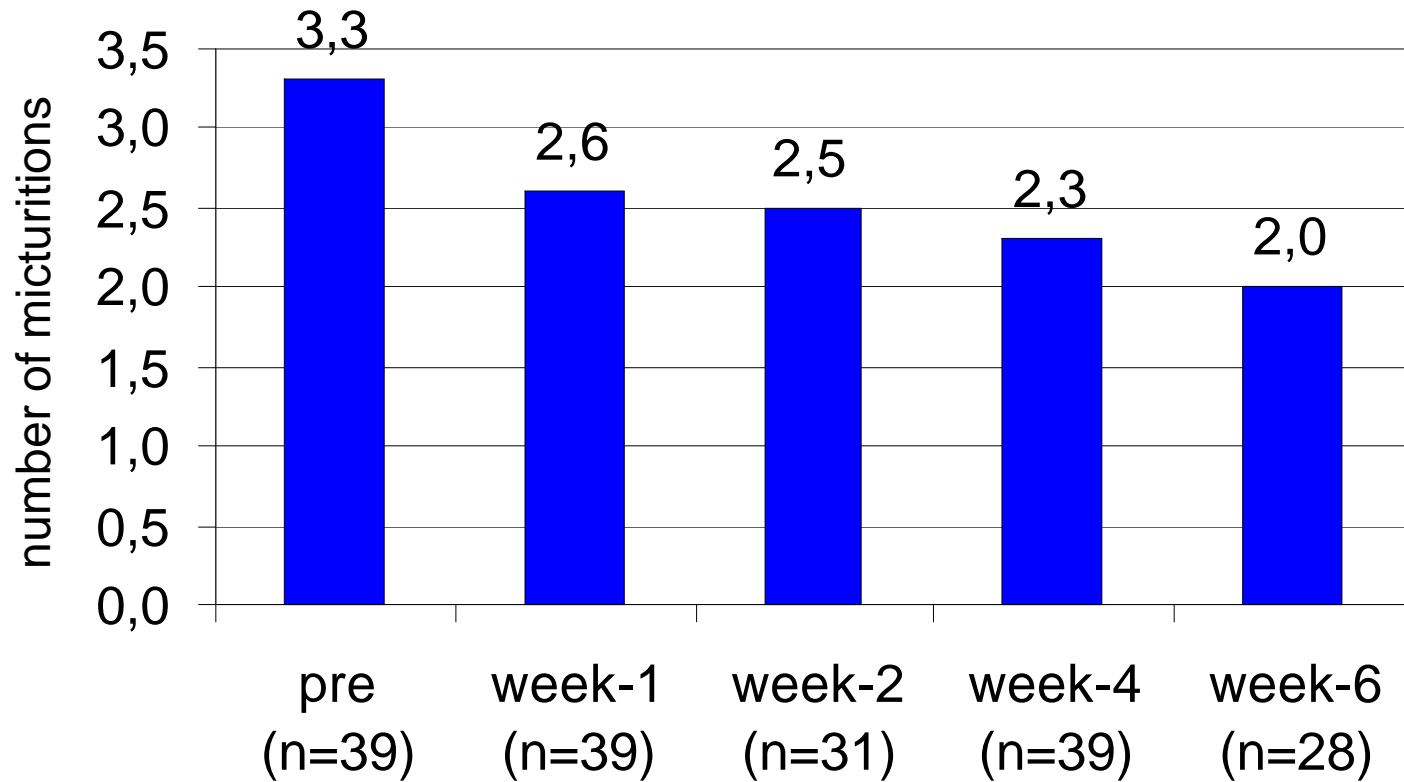
# Urinary Incontinence: Open Clinical Trial

## Aim and design of the study:

- reduction of number of nocturnal and diurnal micturitions and number of incontinence episodes
- **study design:**  
39 postmenopausal women / 6 weeks
- **study medication:**  
tablets containing 87.5 mg Cucurbitae seed extract EFLA®940 and 16.6 mg soybean germ extract (PEP)

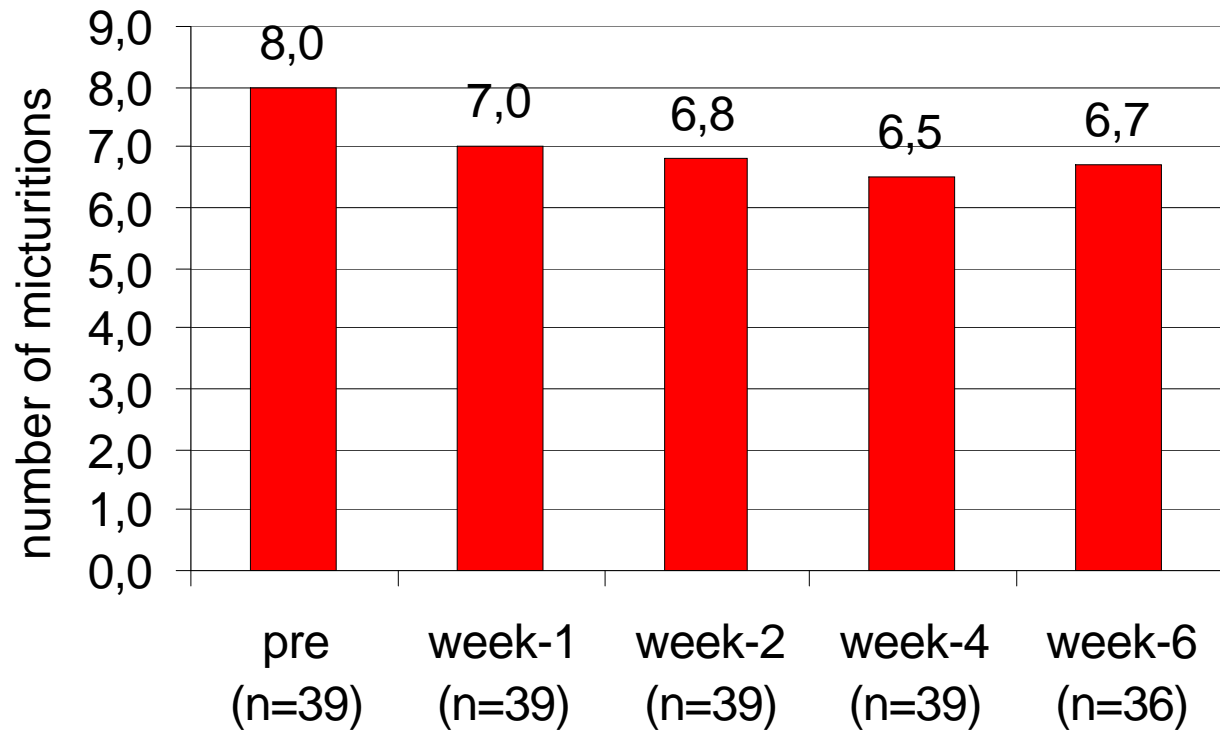
# Urinary Incontinence: Open Clinical Trial

**Results: number of nocturnal micturitions**



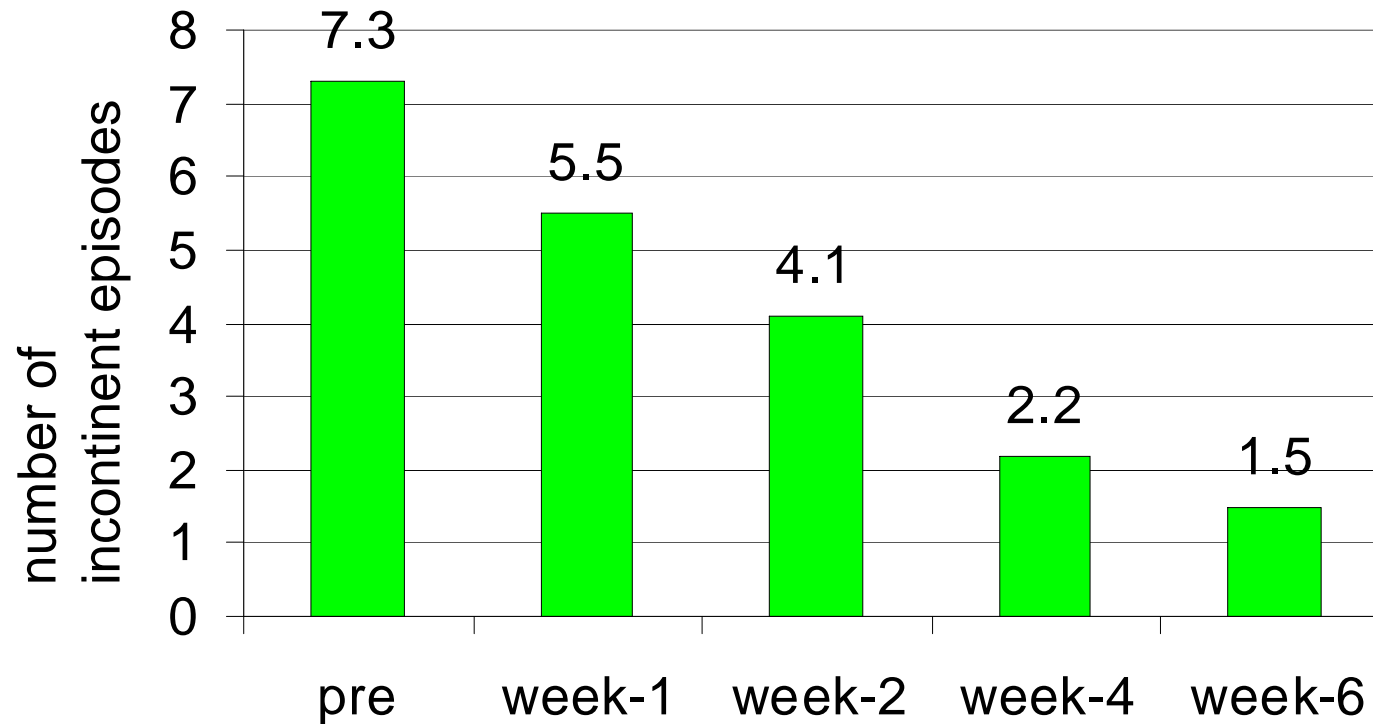
# Urinary Incontinence: Open Clinical Trial

**Results: number of diurnal micturitions**



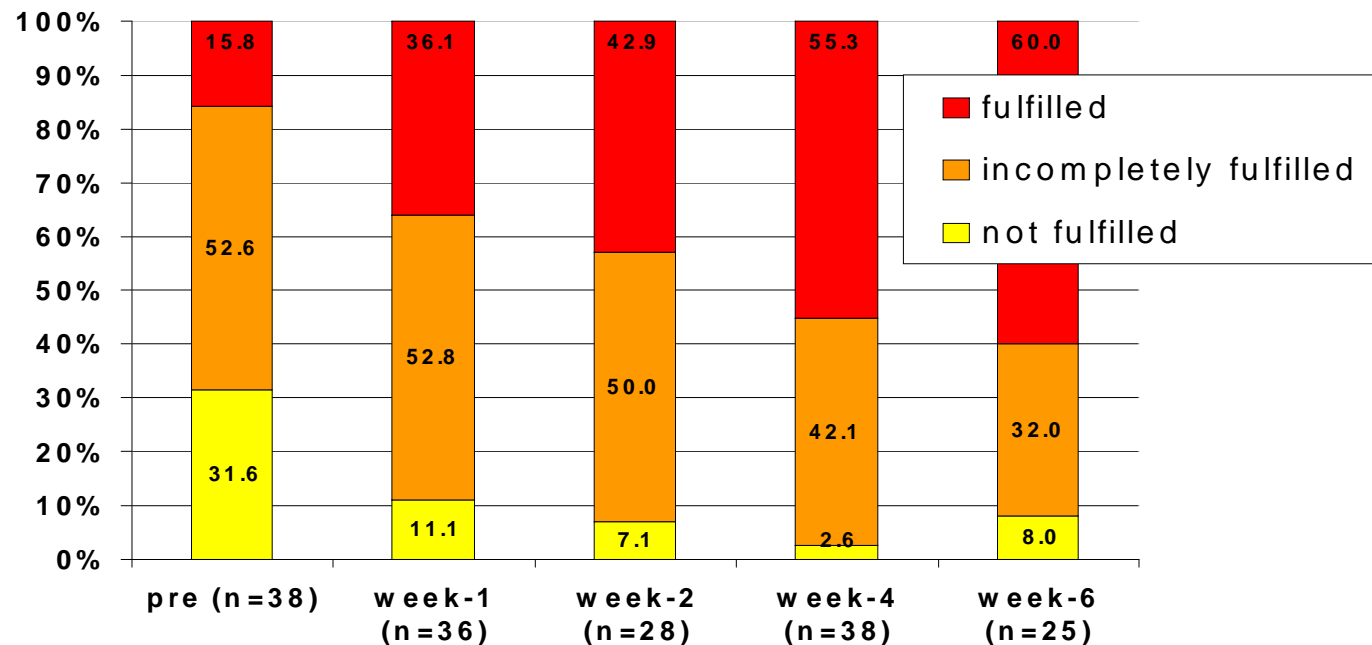
# Urinary Incontinence: Open Clinical Trial

**Results:**      **number incontinent episodes**



# Urinary Incontinence: Open Clinical Trial

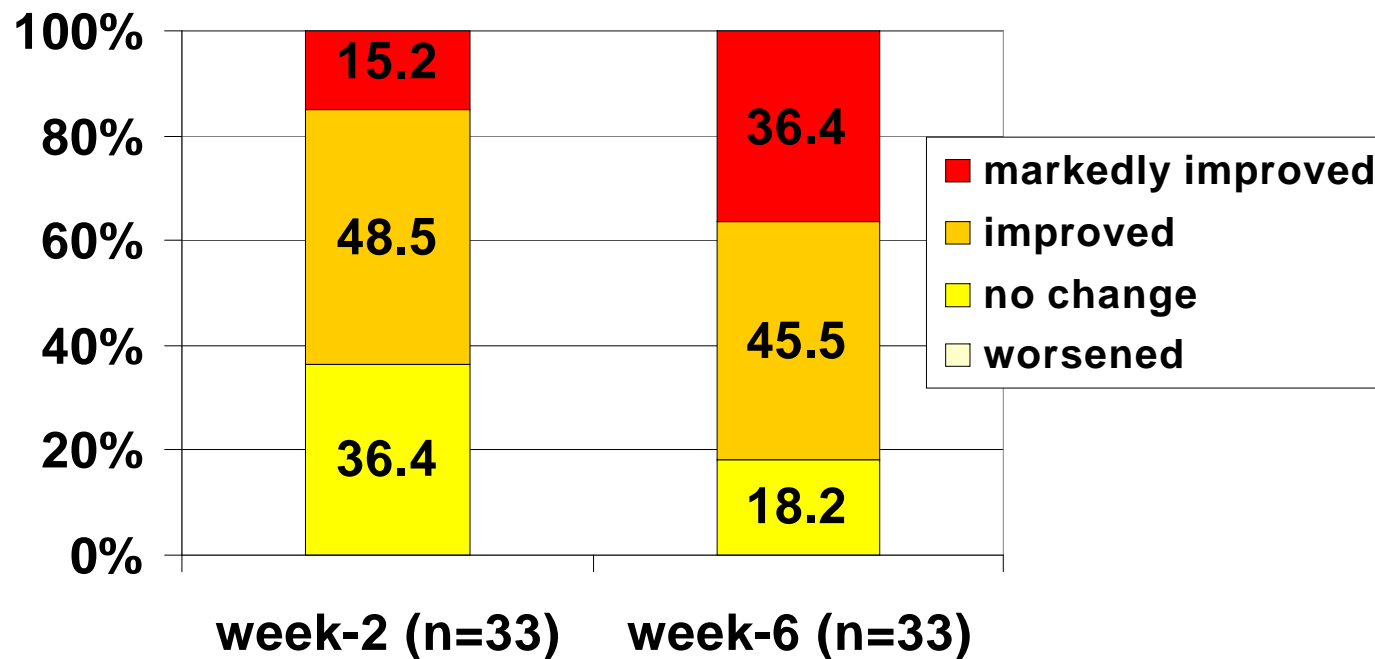
**Results: subjective improvement**



# Urinary Incontinence: Open Clinical Trial

## Results: total ratio of improvement

subgroup of 33 individuals with 2 to 4 micturitions per night



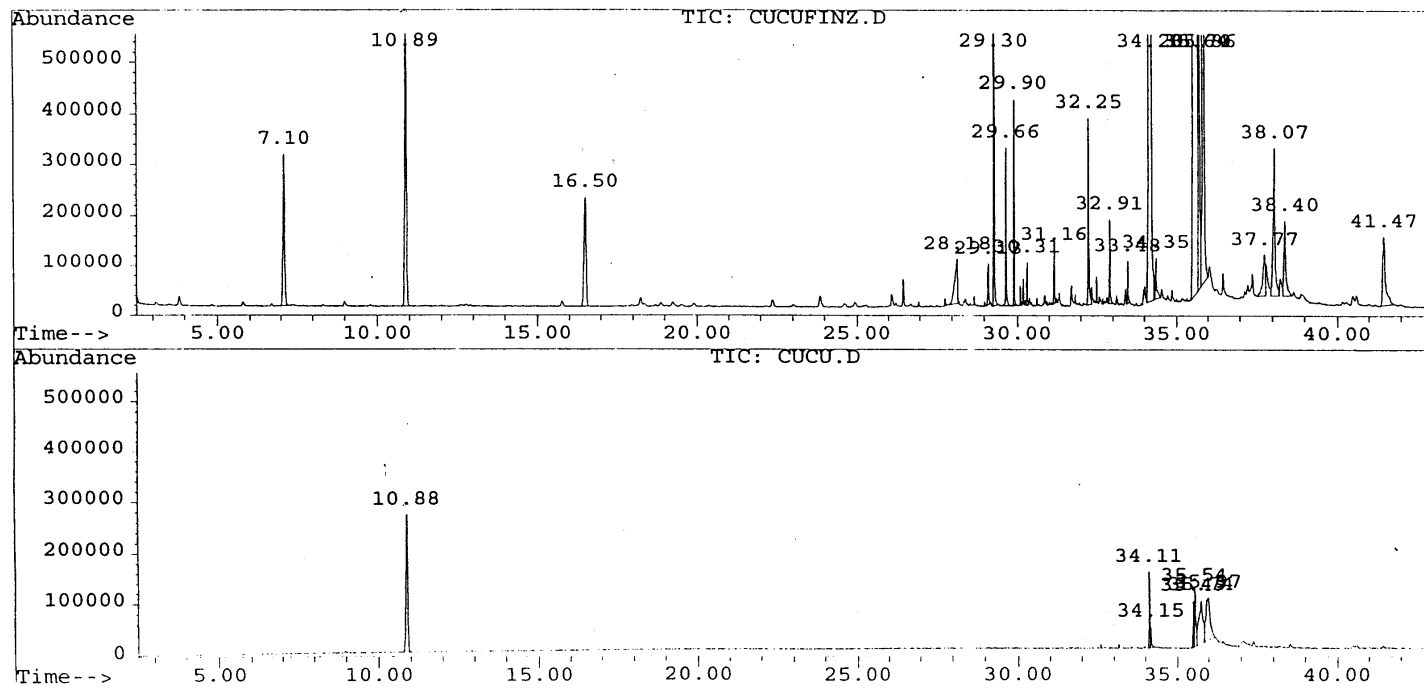
# Urinary Incontinence: Open Clinical Trial

## Discussion:

- PEP reduces the number of incontinent episodes and the number of nocturnal and diurnal micturitions
- The effect increases with the progress of the treatment => hint at a causal mechanism
- EFLA®940 may possess estrogen-like effects

# Pumpkin Seed: **Technical Background**

## Comparison: extract with lipophilic phase versus EFLA®940



GC-diagrams: above: extract with lipophilic phase, below: EFLA®940

# Pumpkin Seed: **Technical Background**

## **Specific manufacturing procedure**

- effective substances in hydrophilic phase  
(for the inhibition of aromatase as well as for the inhibition of 5 $\alpha$ -reductase)
- patented method for the elimination of lipophilic substances
- no rancidity in EFLA®940

# Pumpkin Seed: Safety of EFLA®940

## experimental design

- oral application of 5 mg, 10 mg, 20 mg, 30 mg, 100 mg and 300 mg/kg body weight of EFLA®940 a day in juvenile female SD rats
- oral application of 100 mg/kg body weight of EFLA®940 a day in immature male SD rats
- treatment for 4 consecutive days
- assessment of the mortality

# Pumpkin Seed: Safety of EFLA®940

## results and conclusion

- no rat died during the experiment
- EFLA®940 is well tolerated in the experiment
- Commission E recommends 500 mg of extract a day for humans. For a man weighing 70 kg this recommendation corresponds to about 7 mg/kg body weight a day.

# Pumpkin Seed: Quality of EFLA®940

- raw material tested in conformity with official monographs
- standardized and validated manufacturing procedure
- transparency of patented manufacturing procedures
- quality controls during manufacture (in process controls)

# Pumpkin Seed: Quality of EFLA®940

- extract high quality standard controls
- extract long-term stability
- detailed and comprehensive extract documentation (drug master file)

# Pumpkin Seed: Final Summary of Effects

- Active phase of pumpkin seed extract EFLA®940 is the hydrophilic phase
- Inhibition of aromatase in vitro
- Possible phytoestrogenic effect
- Inhibition of 5 $\alpha$ -reductase in vitro and in vivo, significant reduction of prostate growth in rat
- Decrease of nocturnal and diurnal micturitions
- Significant decrease of incontinent episodes