

Phytotherapie

Phytoöstrogene in der Therapie

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Phytotherapy for gynaecological disorders

| | |
|---------------------------|--------------|
| Urinary tract infections: | Cranberry |
| Overactive bladder: | Pumpkin |
| Liver disorders: | Milk thistle |
| Dyspepsia: | Artichocke |



Phytotherapy for gynaecological disorders

Fever, pain:

Willow bark

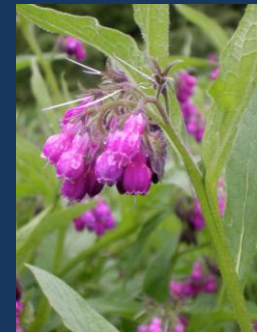
Inflammation, rheumatic pain:

Frankincense,

Devil's claw

Blunt injuries, wounds:

Comfrey



Phytotherapy for gynaecological disorders

| | |
|-------------------------|----------------------------------|
| Pre-menstrual syndrome: | Chasteberry |
| Menopause: | Black cohosh, Soy, Red clover |

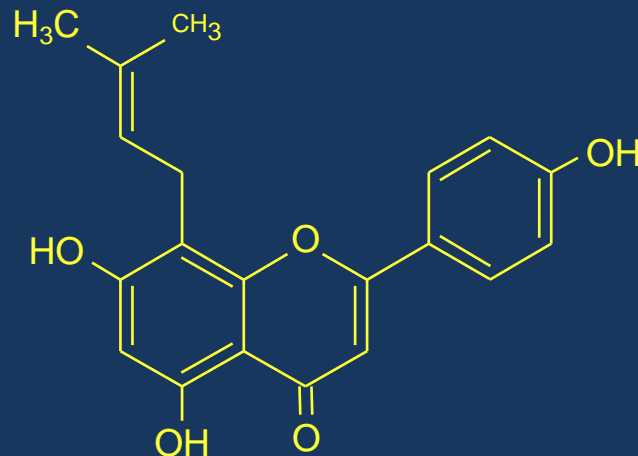
→→ Phyto-“Estrogens“?
→→ Rather Phyto-SERMS!



Discovery of the „Phyto-Estrogens“

Observation of effects similar to those of hormones in female pickers of hop strobiles:

→→ Cycle anomalies due to contact with hops

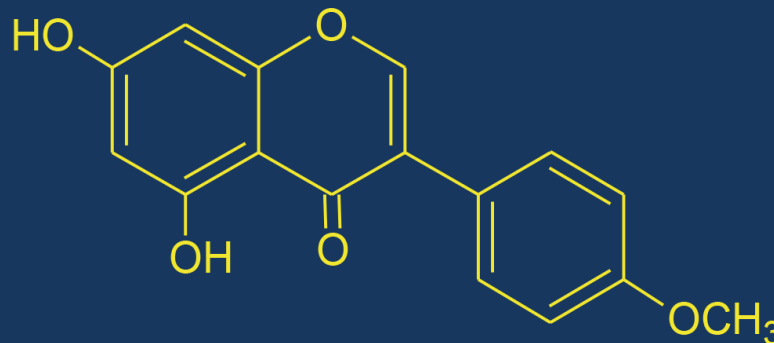


8-Prenylnaringenin
(Flavone derivative)

Phyto-“Estrogens“ in red clover

Alleged observation on Australian pastures with grazing sheep (Bennets et al. 1946):

- Fertility disorders in sheep grazing on pastures with red clover
- Highly questionable: corresponding observations have never been made in Europe!

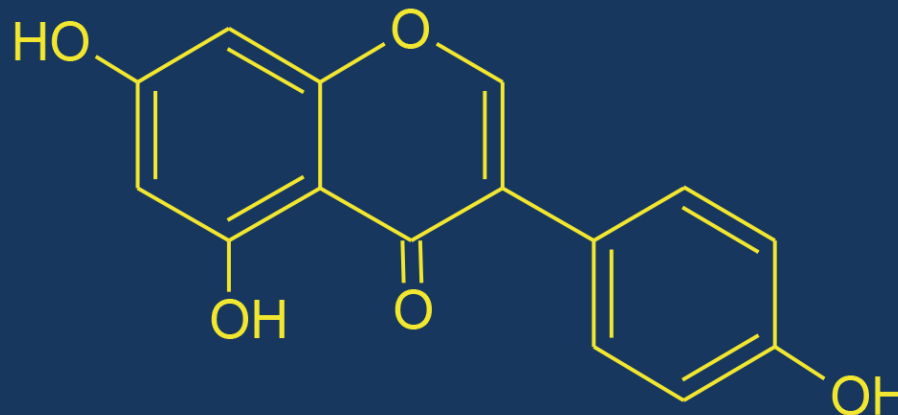


Biochanin A
(Isoflavone)

Phyto-“Estrogens“ in soy

Epidemiological and clinical observations:

- Soy-based nutrition is associated with less menopausal complaints, osteoporosis or breast/endometrial cancer
- Safety and long-term effects are well-examined

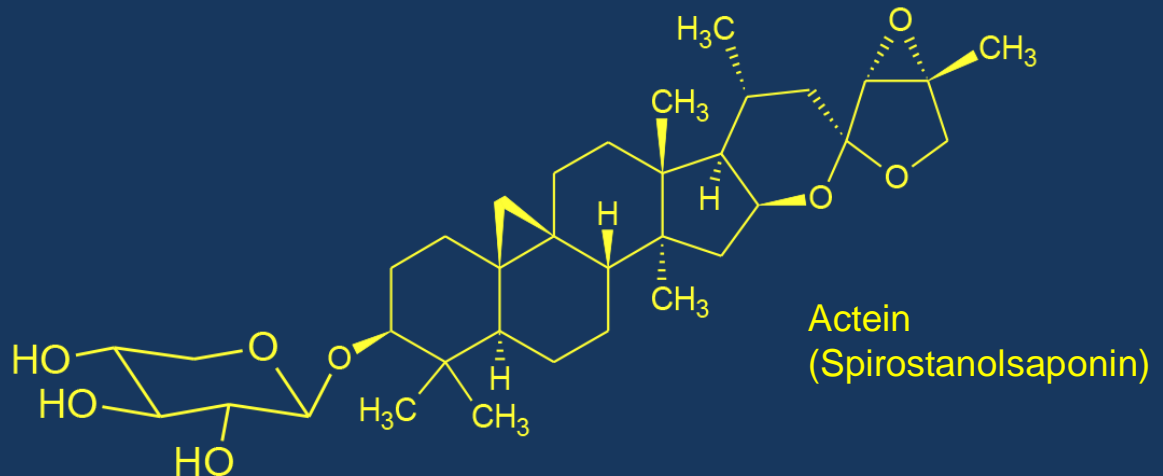


Genistein
(Isoflavone)

Phyto-“Estrogens“ in Black cohosh

Clinically proven:

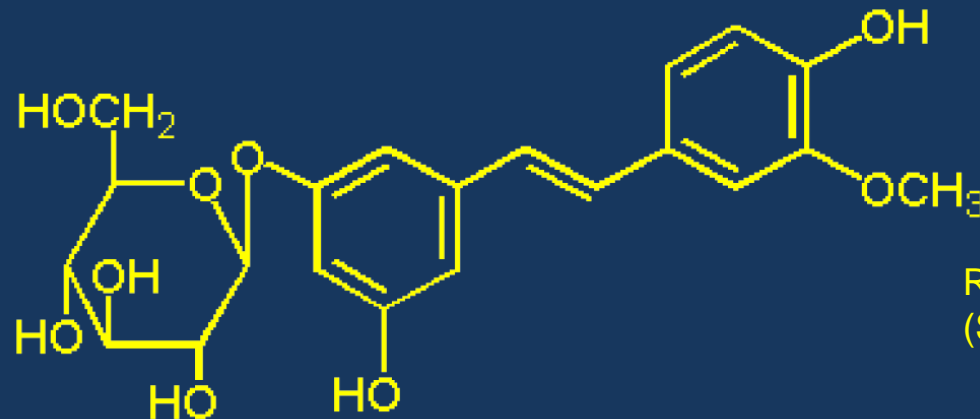
→→ Extracts of the roots of *Cimicifuga racemosa* reduce hot flashes when applied over a few weeks. Probably effects on the level of the CNS (Schmidt et al. 2005)



Phyto-“Estrogens“ in Sibirian rhubarb

Relatively new to the drug market:

- Extracts of the root of *Rheum rhaponticum* alleviate hot flushes (Kaszin-Bettag et al. 2007)
- Potentially problematic due to effects at the estrogen- alpha-receptor and constituents such as oxalic acid



Rhaponticin
(Stilbestrol derivative)

What are „Phyto-Estrogens“?

The perspective of phytochemistry:

- Structures not similar to that of estrogen
- Assumed to „act like estrogen“
 - pharmacological definition, not a chemically defined class
- Very different structures

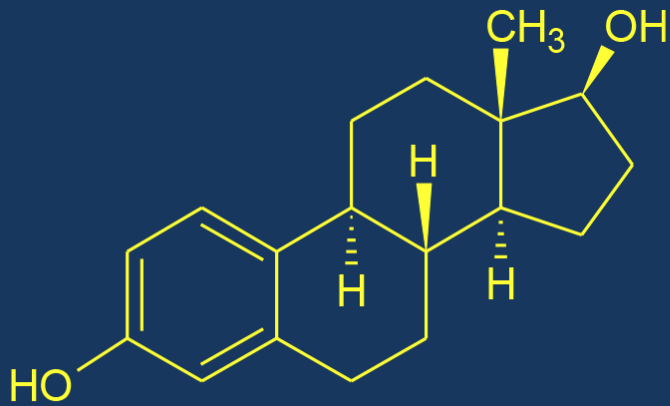
Structures of „phyto-estrogens“

- Flavones in hops (mixed ER-agonists)
- Isoflavones in red clover and soy (ER- β -agonists)
- Saponins in Black cohosh (Mechanism unknown)
- Stilbestrols in rhubarb (ER- α -agonist)

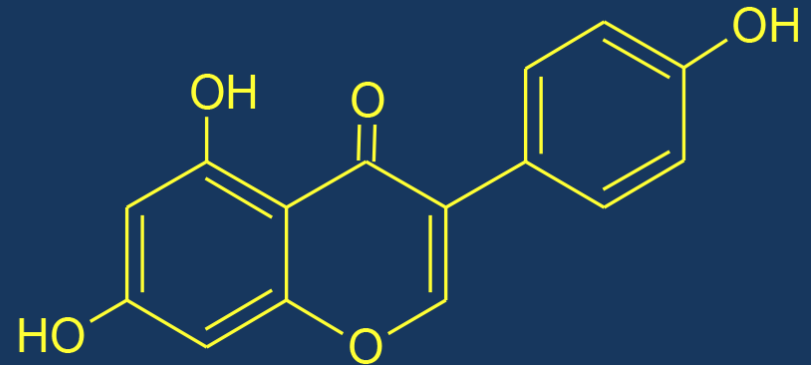
Very different mechanisms of action!

Example: Isoflavones

Acting „like estrogen“?



Estradiol



Genistein

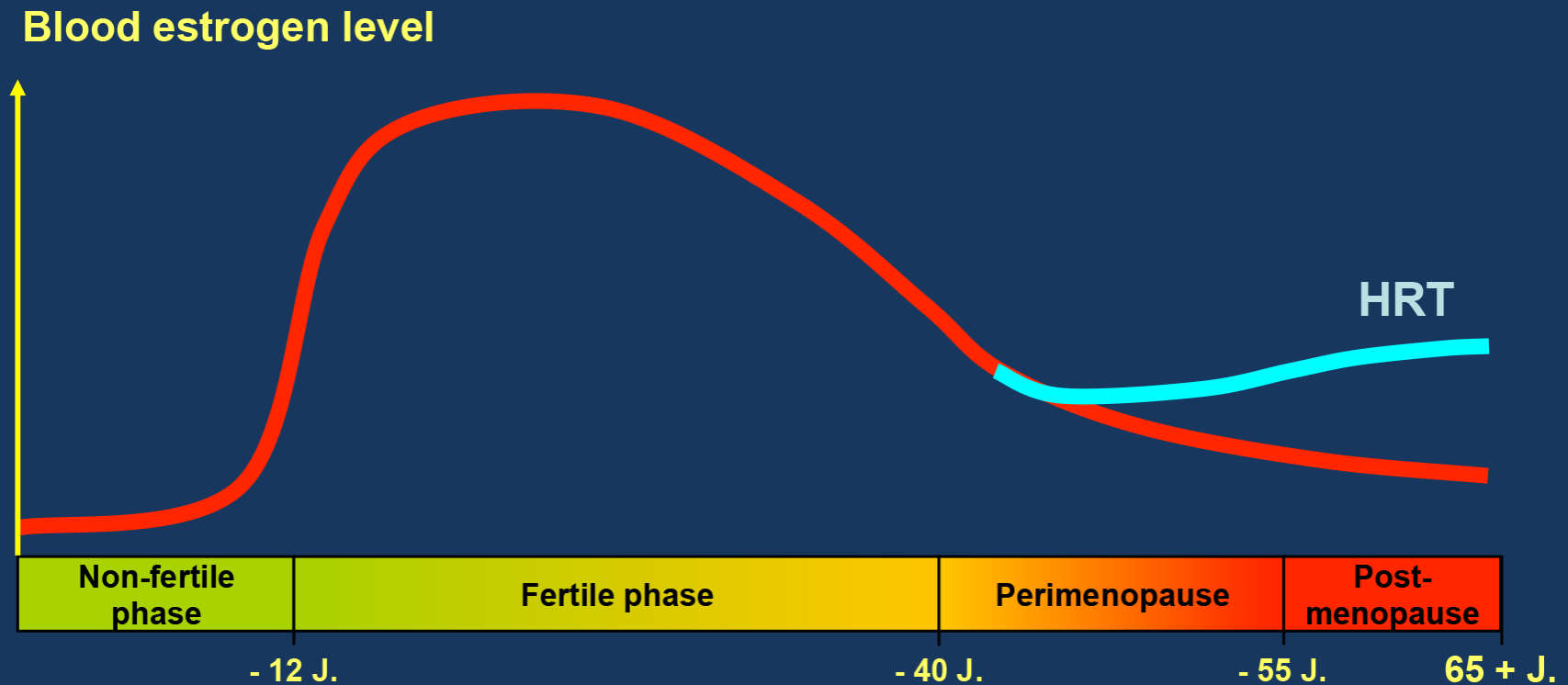
Isoflavones do not act exactly like estrogen!

Short detour:

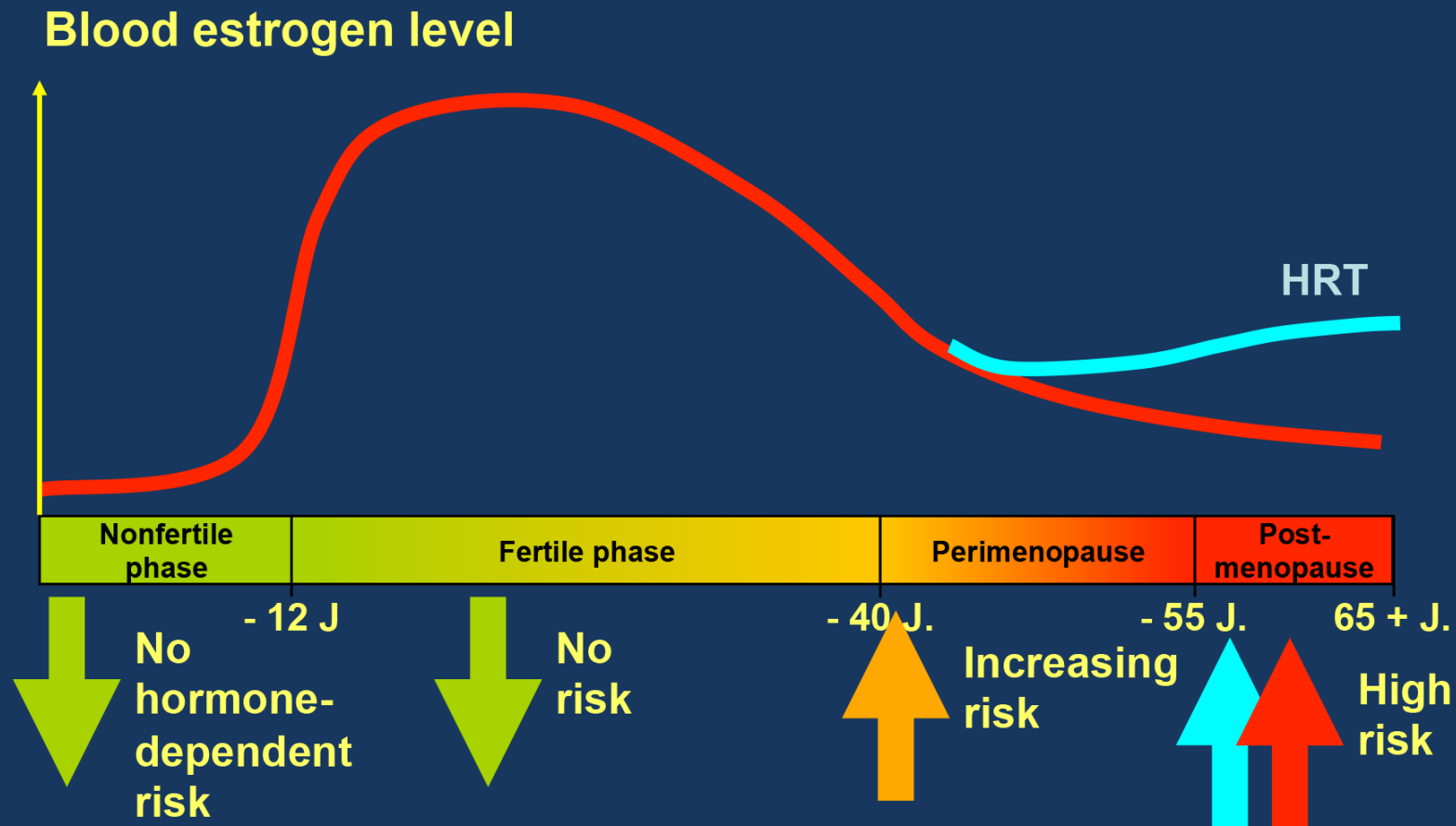
What is the relation between estrogens and menopausal complaints?



Changes in estrogen levels in women



Discrepancy between cancer risk and hormone levels

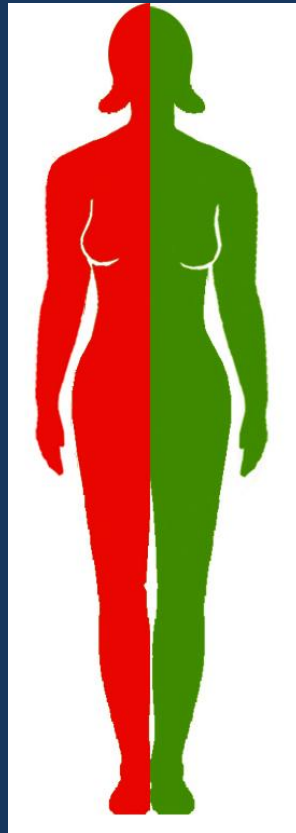


Estrogen receptors

ER- α –
Up to 1998 the only
known estrogen
receptor.

Activated by
17 β -estradiol

α



β

ER- β –
Discovered 1998 as a
new receptor type.

Activated by

- 17 β -estradiol
- 5 α -androstane-3 β ,
17 β -diol (3 β -Adiol)
- Soy isoflavones

Estrogen receptors

ER- α : Enhances proliferation of breast and uterus, important for female cycle and pregnancy

ER- β : Inhibitor of proliferation, counteracts ER- α .



Further effects: Increases bone formation, antidepressant, protects the cardiovascular system, reduces menopausal vasomotor complaints

Location of ER- β

→→ Breast

→→ Uterus

→→ Ovaries

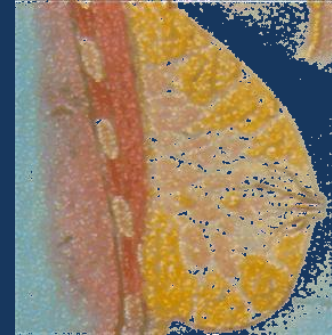
→→ Bones

→→ Brain

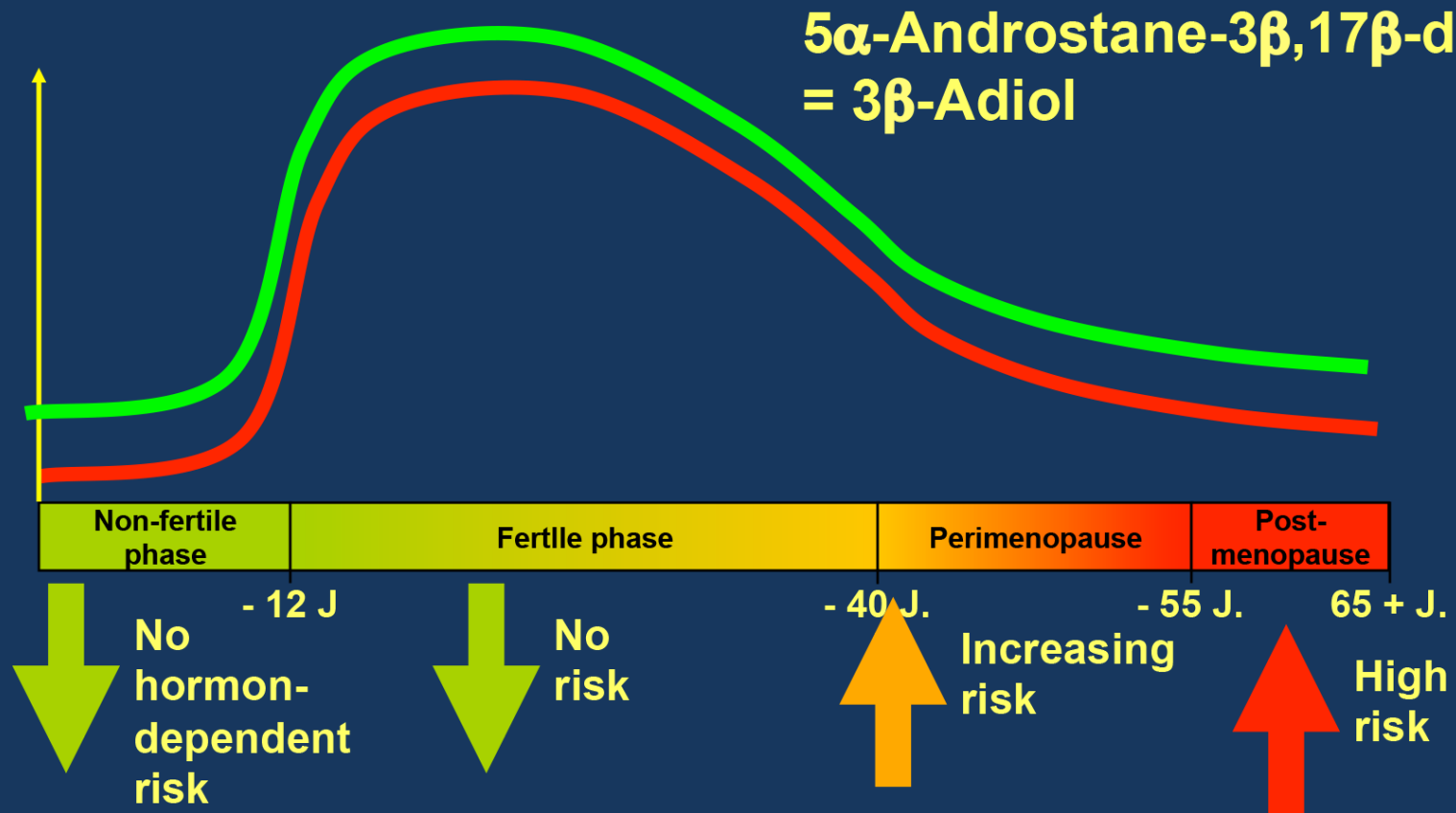
→→ Control of ER- α -induced proliferation

→→ Protection from bone resorption

→→ Protection from hot flushes and depression



3β -Adiol as a protective factor



ER- β -agonists as therapeutical targets

- Potential benefit in osteoporosis
- Currently tested as supportive anti-cancer medication (antiangiogenetic effects, improved effect of cytostatics)
- Model compound: Genistein

ER- β -agonists as therapeutic targets

ER- β Patents

Wyeth

Estrogen-receptor (ER) beta agonists, for the potential treatment of inflammatory diseases, including Crohn's disease and other inflammatory bowel diseases (IBD), as well as rheumatoid arthritis (RA) and endometriosis

Schering

ER β agonists for the prevention or treatment of **hypertensive heart disease**.

ER β antagonists - useful as male or female contraceptives and for the treatment of benign or malignant ovarian proliferative disorders.

ER β -selective agonists for anti-catabolic therapy in an aging organism.

Merck

ER β agonist for the treatment of **hypertension, cardiac dysfunction or stroke**.

ER modulators for the treatment of e.g. depression, estrogen-dependent cancer and hot flashes. ER β agonists for inducing tryptophan hydroxylase and treating depression or other CNS disorders. **Eli Lilly**

Selective ER β agonists - useful for the treatment of prostate cancer and BPH.

Others

Bionovo is developing an ER β agonist, for the potential treatment of hot flashes and night sweats in perimenopausal and menopausal women. **ACADIA** is investigating a series of ER β agonists for the potential treatment of chronic intestinal and joint inflammation

GlaxoSmithKline is investigating a series of ER β modulators for the potential treatment of osteoporosis, atherosclerosis, Alzheimer's disease and breast cancer

Soy: A true „Health Food“

The physiological benefits of soy-rich nutrition are well-documented by epidemiology. Soy protects against

- Menopausal vasomotor complaints
- Osteoporosis
- Cancer



Latest findings:

Soy isoflavone supplementation improves cognitive function in menopausal women (meta-analysis)

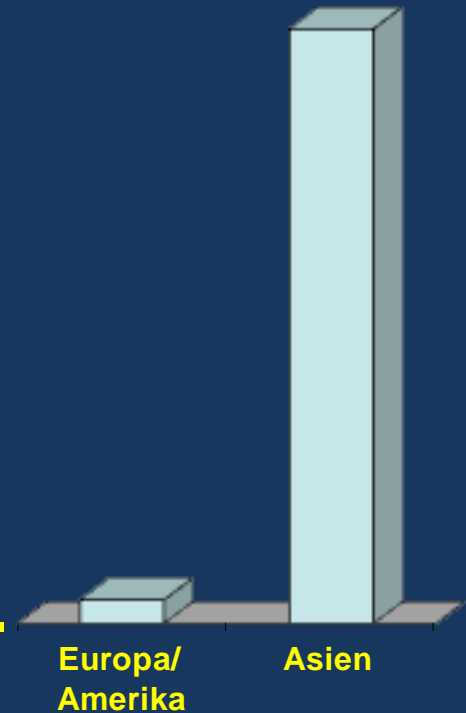
Cheng et al. (2015) Menopause 22(2): 198-206



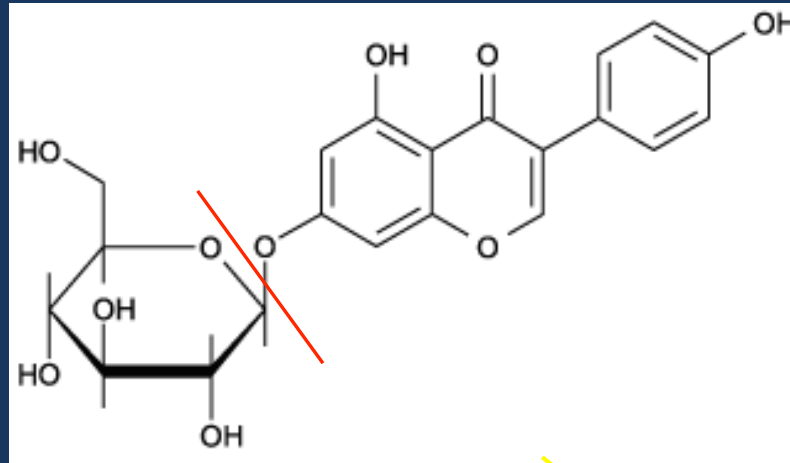
Which constituents cause the effect?

The fraction of isoflavones has been associated with the effect.

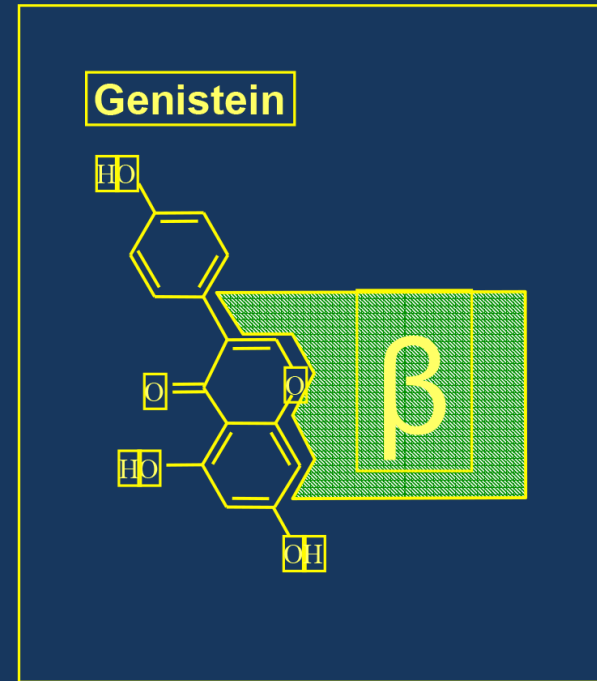
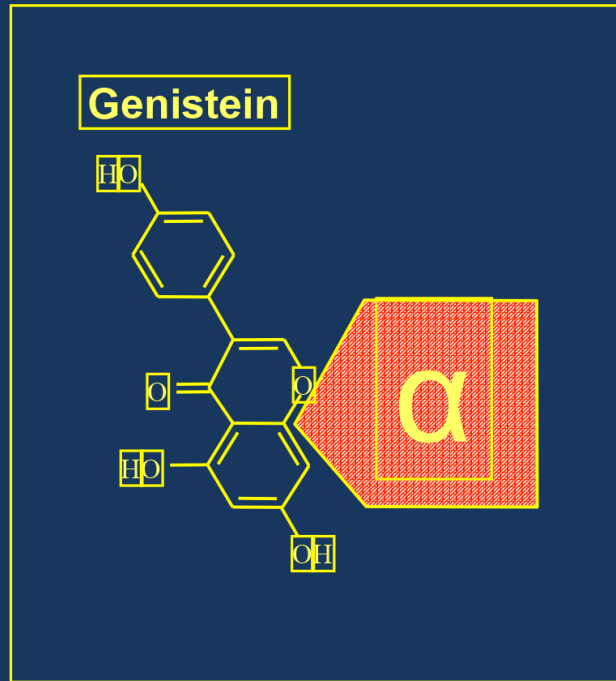
Daily exposure in Asian countries: 30-100 mg/day
(calculated as aglycons)



Glykoside vs. aglycone

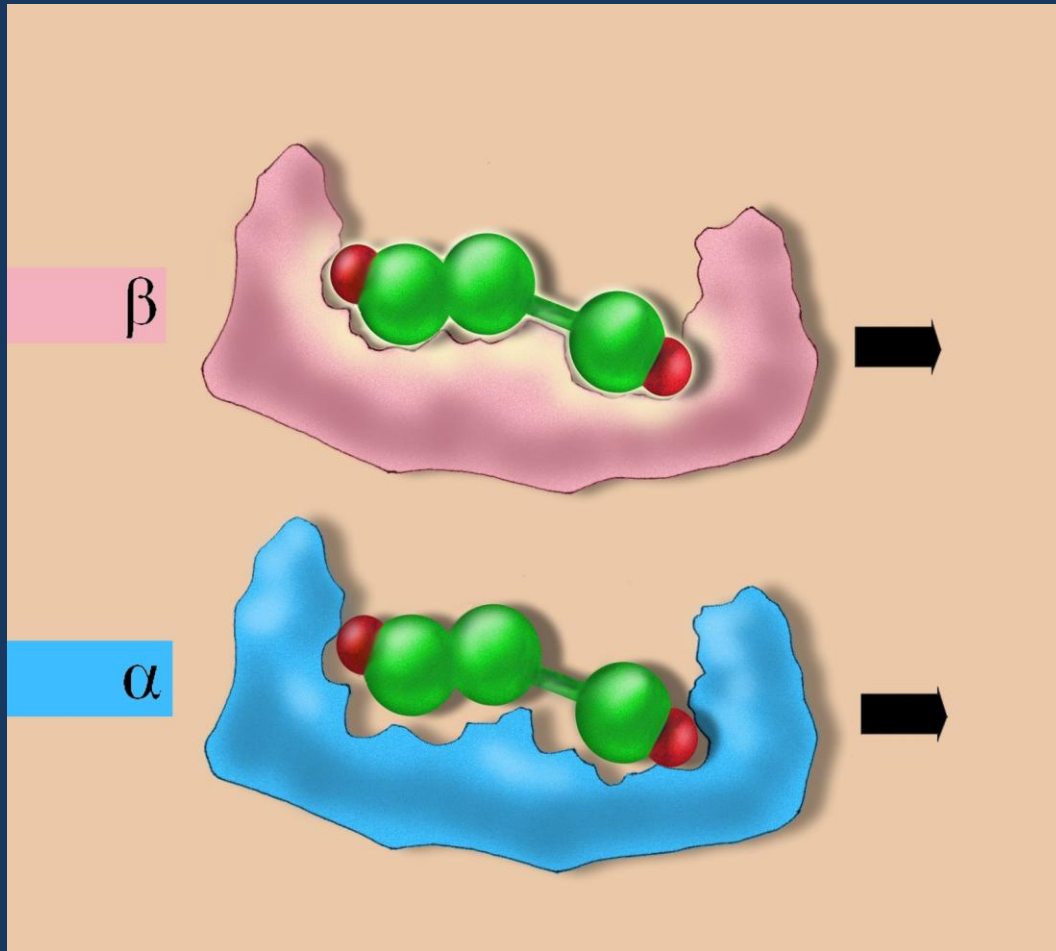


Binding of isoflavones to estrogen receptors



Preferential binding to ER- β

Key-lock-principle: Agonistic and antagonistic effects



Good signal
Translates into
hormonal effects

Weak signal
insufficient
activation

Affinities at ER

| Ligand | EC ₅₀ at ER-⟨ | EC ₅₀ at ER-® |
|---------------|---------------------------|--|
| 17®-Estradiol | 6,4 · 10 ⁻¹¹ M | 3,9 · 10 ⁻¹¹ M |
| Genistein | 4,6 · 10 ⁻⁷ M | 3,4 · 10 ⁻⁹ M (x 218 % in the presence of 15 pM estradiol) |

→→ The EC₅₀ of genistein and daidzein at ER-® is in the range of blood levels after soy-rich nutrition (approx. 1 · 10⁻⁶ M)

Harris et al. (2005)

Phyto-SERM vs. Phyto-Estrogen:

Isoflavones are **selective Estrogen-Receptor-Modulators**

- Isoflavones share the effects of estrogen at ER- β (albeit to a much weaker extent)
- They have no influence on the female cycle (→→ this would require an ER- α -effect)
- They do not increase the proliferation of breast and uterine tissue (→→ no ER- α -effect)
- They have a positive impact on bone density (ER- β - effect)
- They reduce hot flushes (ER- β -effect)

Isoflavones in studies on menopausal complaints

- Recent meta-analysis of 10 double-blind studies: Isoflavones are significantly superior over placebo (Chen et al. 2014)
- Recent review of 16 double blind studies: The effect of isoflavones is 25 % better than that of placebo. Isoflavones reach up to 57 % of the efficacy of estrogen (Li et al. 2014)

Isoflavones in studies on menopausal complaints

Detailed meta-analysis of 17 studies (Taku et al. 2012)

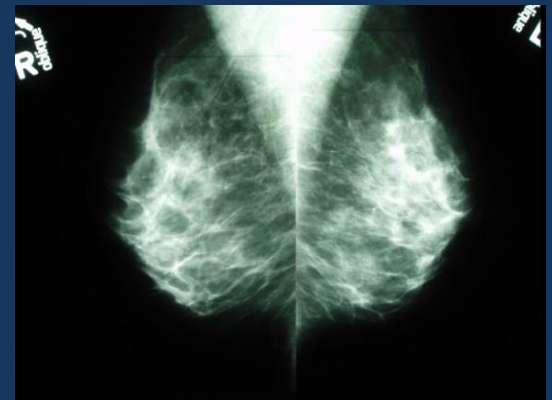
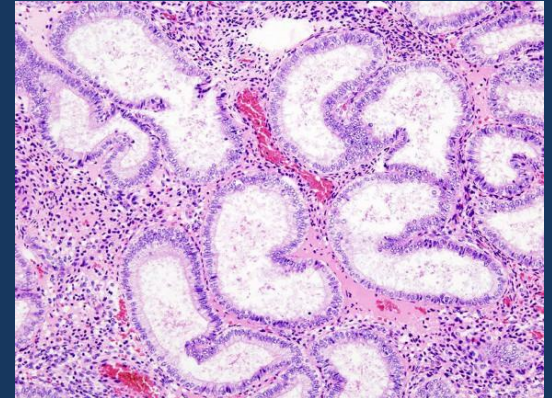
- Frequency of hot flushes:
Isoflavones 25 % better than placebo
- Severity: Isoflavones 26% better than placebo
- Extract composition: High proportions of genistein within the total isoflavones may be advantageous

Safety of Application

Estrogens are suspected to increase the risk of hormone- dependent tumours.

What about Phyto-Serms?

Isoflavones have been shown to be safe or even protective in practically all clinical examinations!



Safety of estrogens

WHI-Study: Hormone replacement therapy* in menopausal women possibly increases the relative risk of

- **Stroke by 41 %**
- **Cardiac infarction by 29 %**
- **Thrombosis by 50 %**
- **Breast cancer by 26 %**

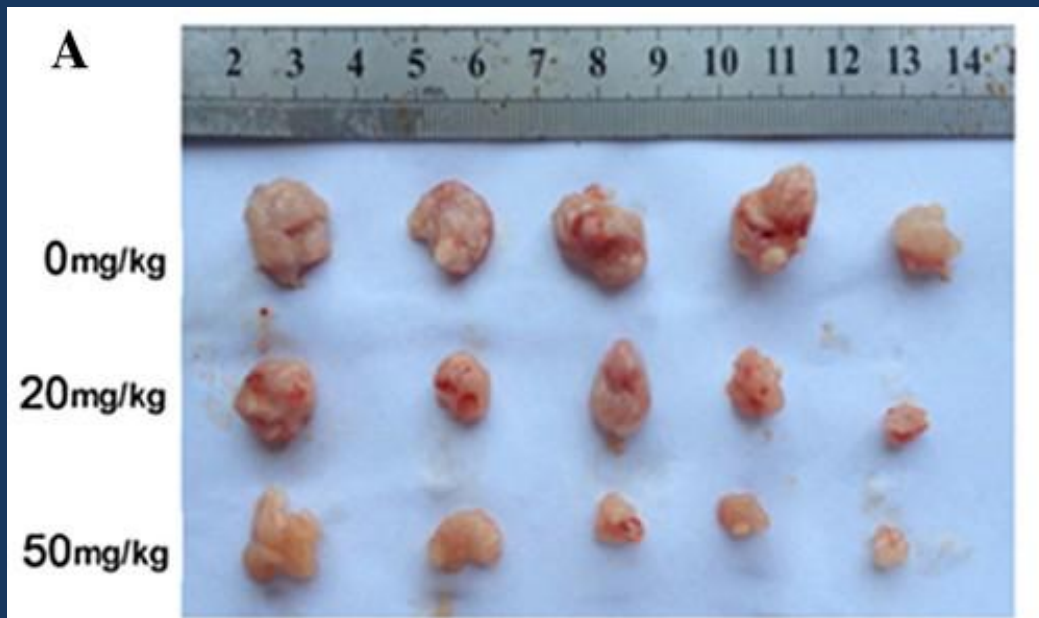
Rossouw et al 2002 and subsequent publications

* Probably associated with gestagens, not estrogens!

Safety of isoflavones in animal experiments

Effect of genistein on tumour volume and weight with breast cancer induced by MCF-7-cells (Fan et al. 2013):

→→ Distinct reduction of the tumour!



Safety of isoflavones in clinical studies

Explicit measurement of hormonal safety parameters:

- ≥ 14 open studies with isoflavone exposure of at least 2630 women
- ≥ 44 double-blind studies with more than 3400 women exposed to isoflavones
- Study durations of up to three years
- Exposure to isoflavones: 36-300 mg/day

Safety parameters in clinical trials

- Mammography and breast tissue density
- Nipple aspirate
- Activation of tumour-promoting genes
- Biopsies of the endometrium
- Thickness of the endometrium (ultrasound)
- Maturation of vaginal epithelium (PAP-smears)
- Hormonal levels (E2, LH, FSH, SHBG)
- Thyroidal hormones

Results of safety studies

→→ Safety supported by double-blind long-term studies with high doses

(Alekel et al. 2015; Alekel et al. 2014; Quas et al. 2013)

Example: Alekel et al. (2015): Menopause 22(2): 185-197

- Study duration three years
- Placebo-controlled, double-blind
- 80 or 120 mg of soy isoflavones daily for three years
- No effect on endometrium thickness
- No effect on circulating hormone levels
- No adverse effect on thyroidal function

Results of safety studies

→→ **No increased, but rather a decreased breast cancer risk observed in women diagnosed with and treated for breast cancer!**

(Hooper et al. 2009; Kang et al. 2012)

→→ **Isoflavones act synergistically with tamoxifen**

(Mai et al. 2007; Wu et al. 2007; Guha et al. 2009)

Soy and breast cancer epidemiology

≥ 45 studies; > 500,000 women exposed to isoflavone-containing soy preparations

→→ Cancer protective effects or lack of cancer-inducing effects (breast and endometrium)

→→ Meta-analyses confirm dose-dependent risk reduction: 16 % reduction of the relative risk per each 10 mg isoflavones/day (Wu et al. 2008)

Recent epidemiology

Multiethnic cohort study

84,450 women, 13 years of follow-up

- Isoflavones do not increase the breast cancer risk
- Protective effect correlates with dose

Morimoto et al. (2014)

Soy and breast cancer

Canadian case-control study (6500 women)

- Isoflavones reduce the risk of breast cancer by 32 % on average
- Long-term exposure protects (5 years: -25 %)
- The combination of high doses and long-term exposure raises the risk reduction effect to 45 %

Boucher et al. (2013)

Conclusions

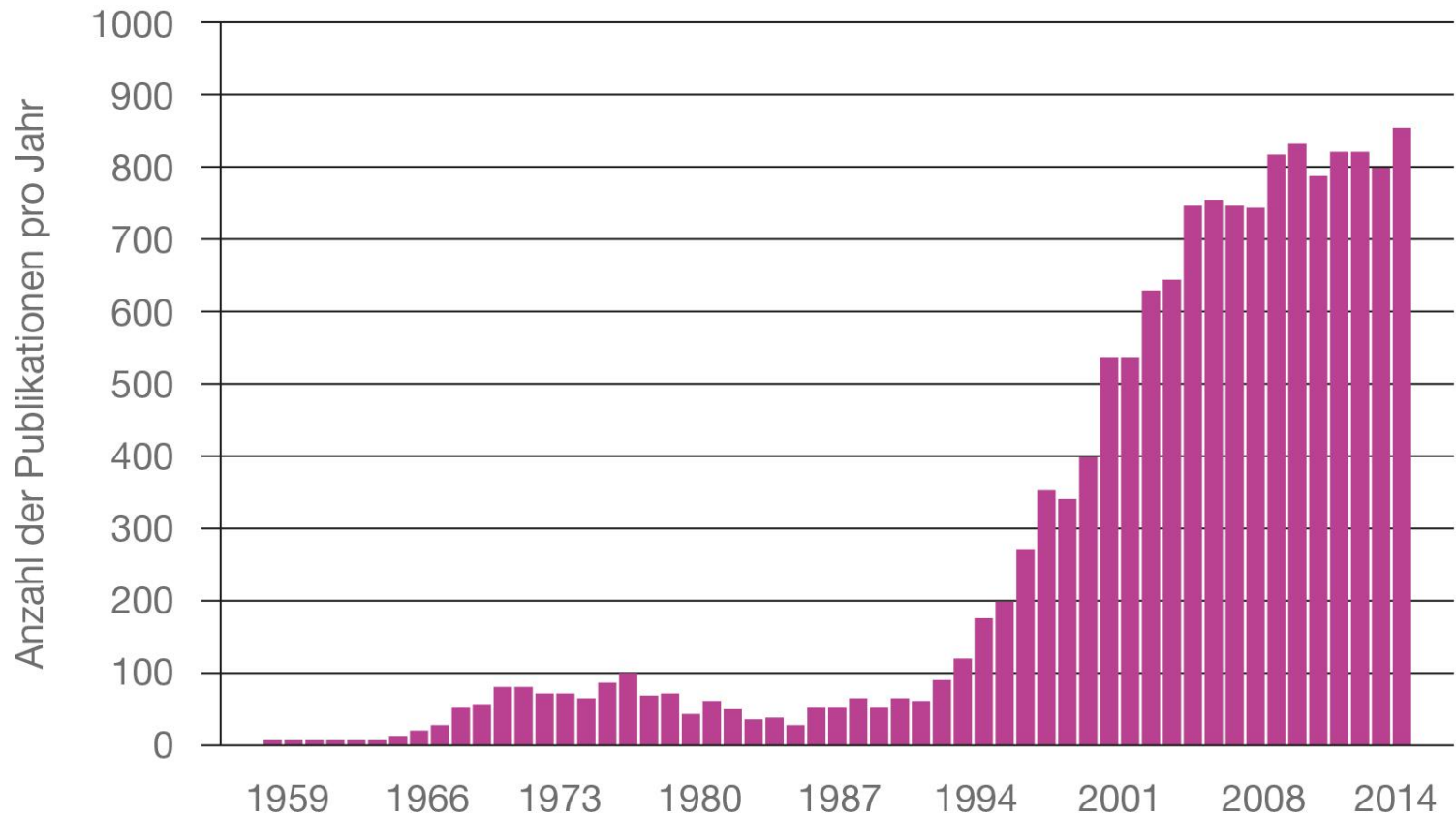
Efficacy against menopausal complaints confirmed in meta-analyses

(recent: Chen et al. 2014)

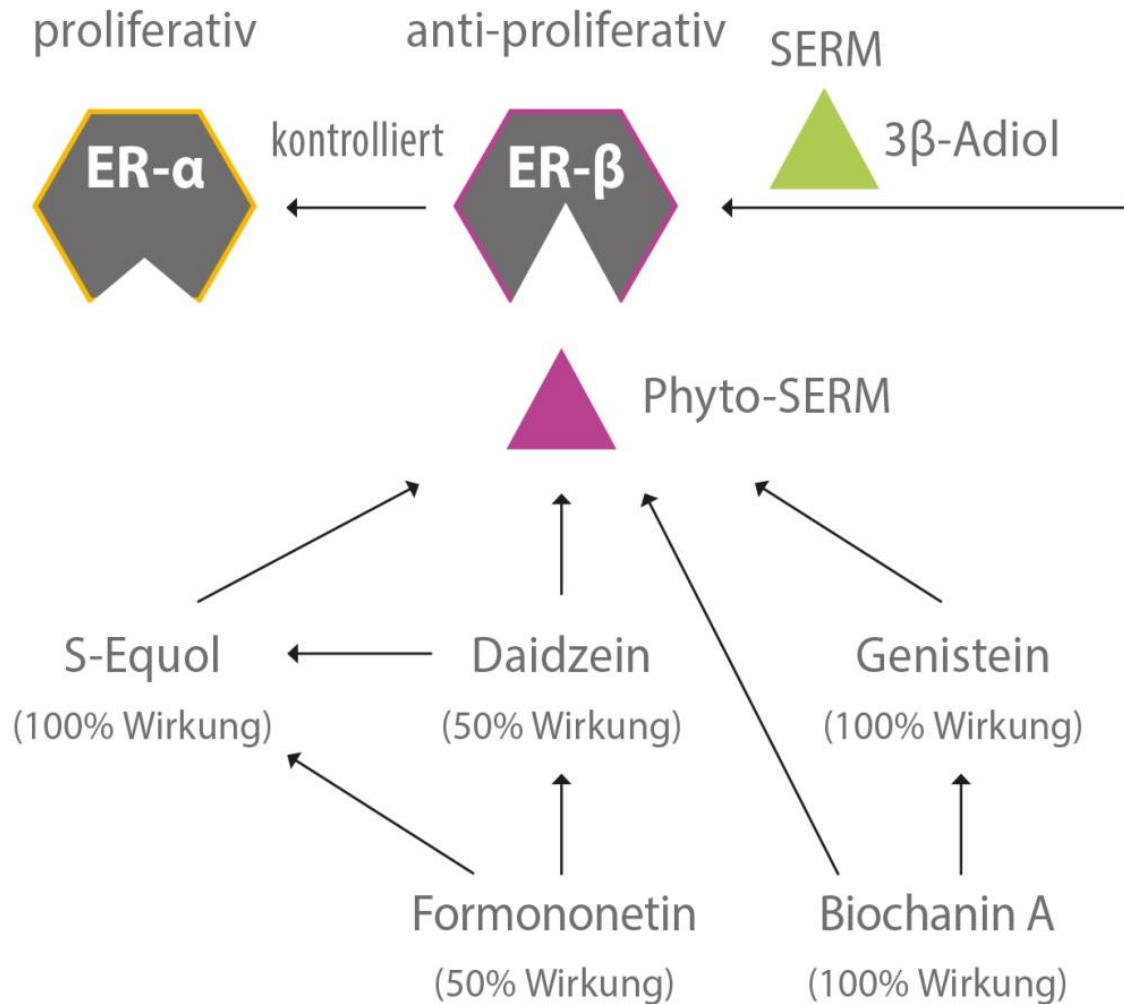
Safety: Long-term studies with partly very high doses confirm the absence of estrogenic risks. This is also applicable to women with a history of breast cancer.

→→ The benefit-risk ratio of isoflavones is clearly positive!

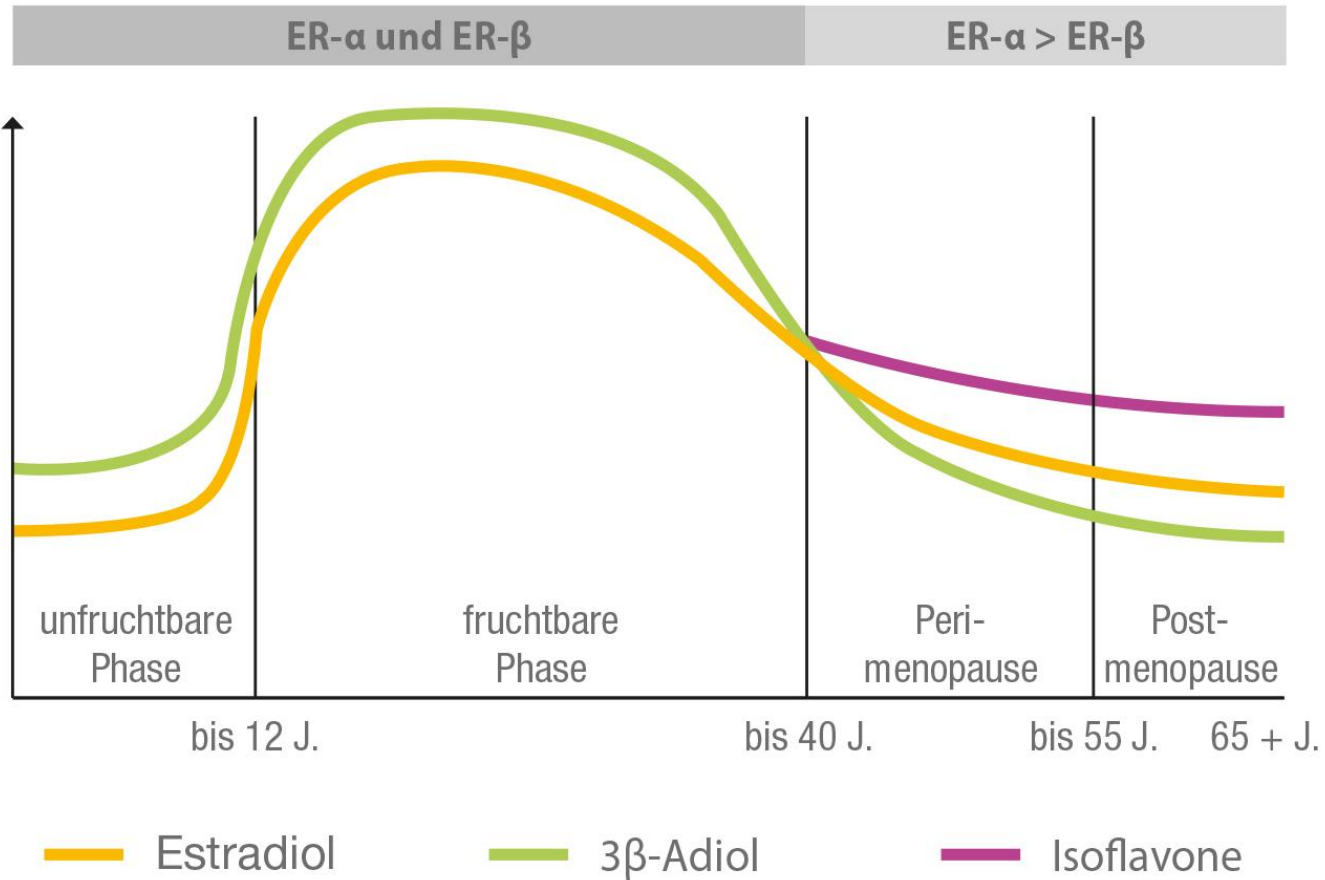
PubMed – Isoflavon Publikationen

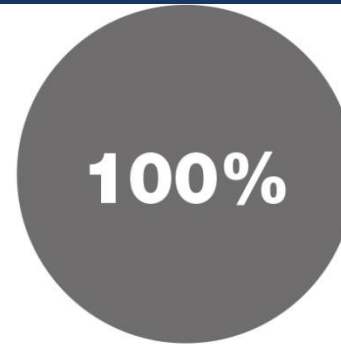
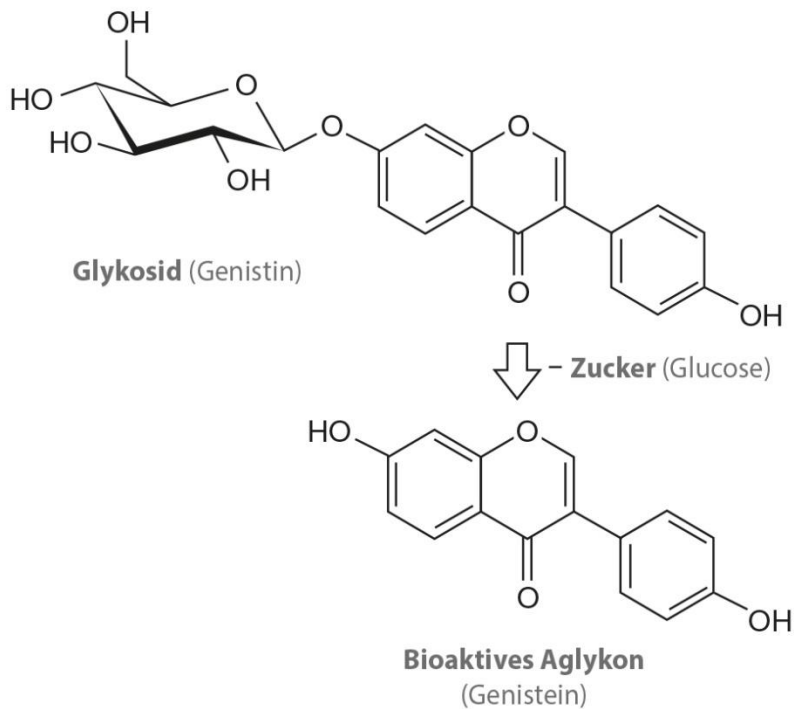


Selektive Rezeptorbindung



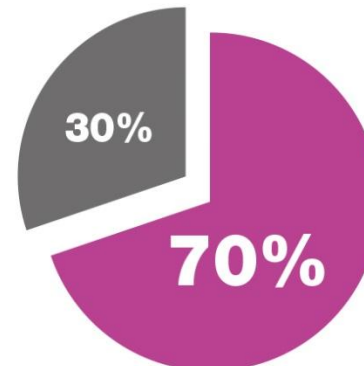
Schutzwirkung der Isoflavone





Glykosidische Konzentrate
aus Tofuherstellung
und Sojakeimlingen

■ Glykoside



Genuine Pflanzenextrakte
aus Soja und Rotklee
mit hohem bioaktiven
Aglyka-Anteil

■ Isoflavon-Aglyka
■ Glykoside

Efficacy of phytoestrogens for menopausal symptoms: a meta-analysis and systematic review

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Key words: CLIMACTERIC, ESTROGEN, HOT FLUSH, ISOFLAVONE, LIGNAN, MENOPAUSE, META-ANALYSIS