„Naturhormone"

aus gyn-endokrinologischer Sicht

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MEDIZINISCHE UNIVERSITÄT WIEN

Die menschliche Größe

Naturhormone

Bioident(isch)e Hormone

Pflanzliche Stoffe

Was sind „Phyto-Östrogene"?

Aus Sicht der Phytochemie:
Sehr unterschiedliche Strukturen

→ Flavone (gemischte ER-Agonisten)
→ Isoflavone (ER-β)
→ Saponine (Mechanismus unbekannt)
→ Stilbestrole (ER-α): Diethylstilbestrol, Fosfestrol, Dienestrol
→ (Stilbenoide: Resveratrol, Pterostilbene)
→ (Lignane)

Begriff „**Phyto-SERMs**" seit einigen Jahren gebräuchlich

Allgemeine Effekte der Phyto-Östrogene

- *Weibliche Fertilität*: Progesteronproduktion, Oozytenmaturation, Entwicklung der Zygote
- Verbesserung *Klimakterischer Beschwerden*
- Direkte und indirekte *Kardiovaskuläre Effekte*
- *Gewichtsverlust*
- *Antikanzerogene Eigenschaften*
- Zunahme der *Knochendichte*
- Verminderung des Risikos für *Morbus Alzheimer*
- Einfluss auf das *Immunsystem*

Desmawati & Sulastri Macedonian Journal of Medical Sciences 2019

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Desmawati & Sulastri Macedonian Journal of Medical Sciences 2019

Isoflavone

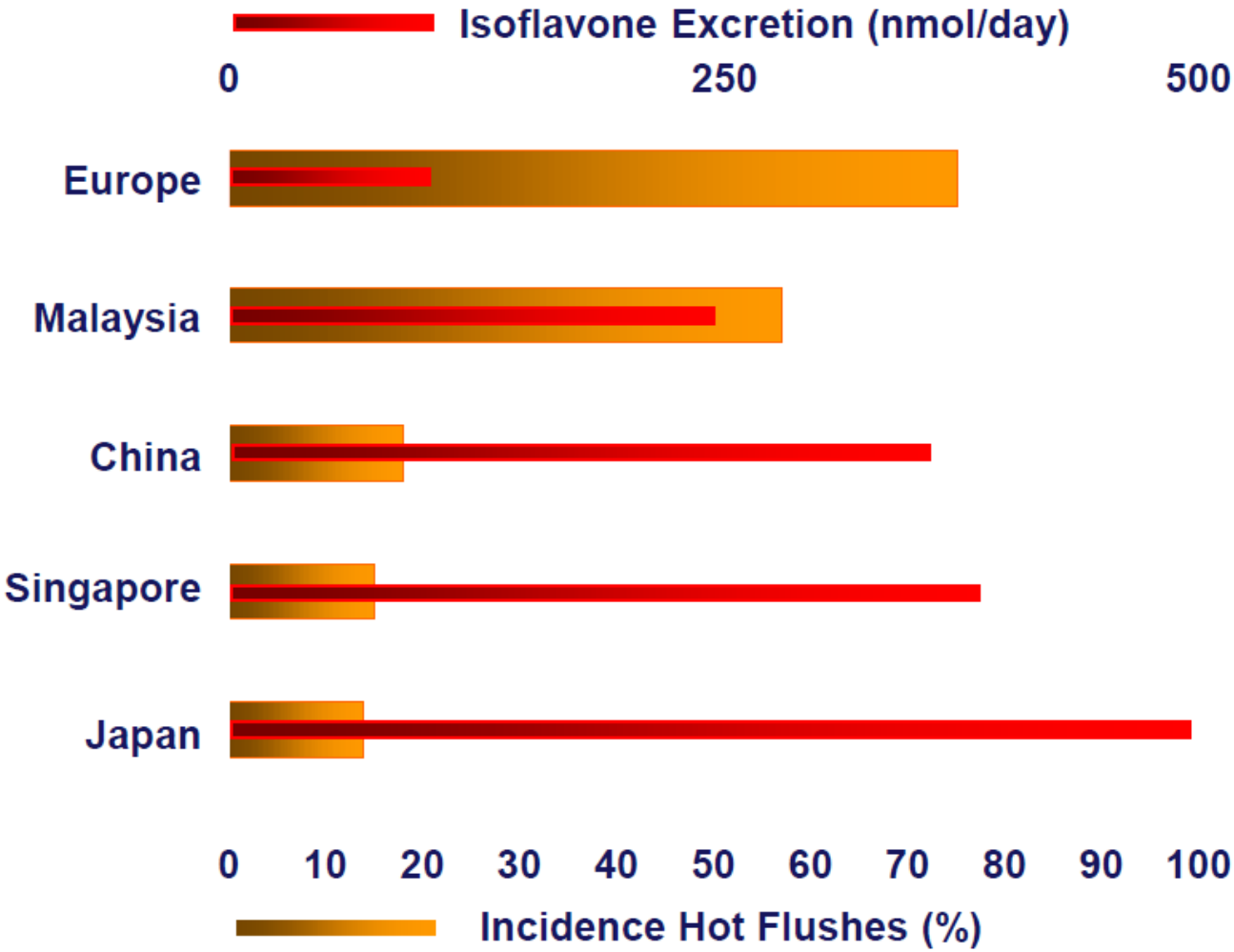
- Isoflavone kommen in **Soja**, verschiedenen **Kleearten**, **Traubensilberkerze** sowie **Hopfen** vor

- Soja-Bohnen enthalten 12 verschiedene Isoflavone
  - Genistein ~ 50%
  - Daidzein ~ 40%
  - Glycitein ~ 10%
  - (Formononetin, Biochanin A…)

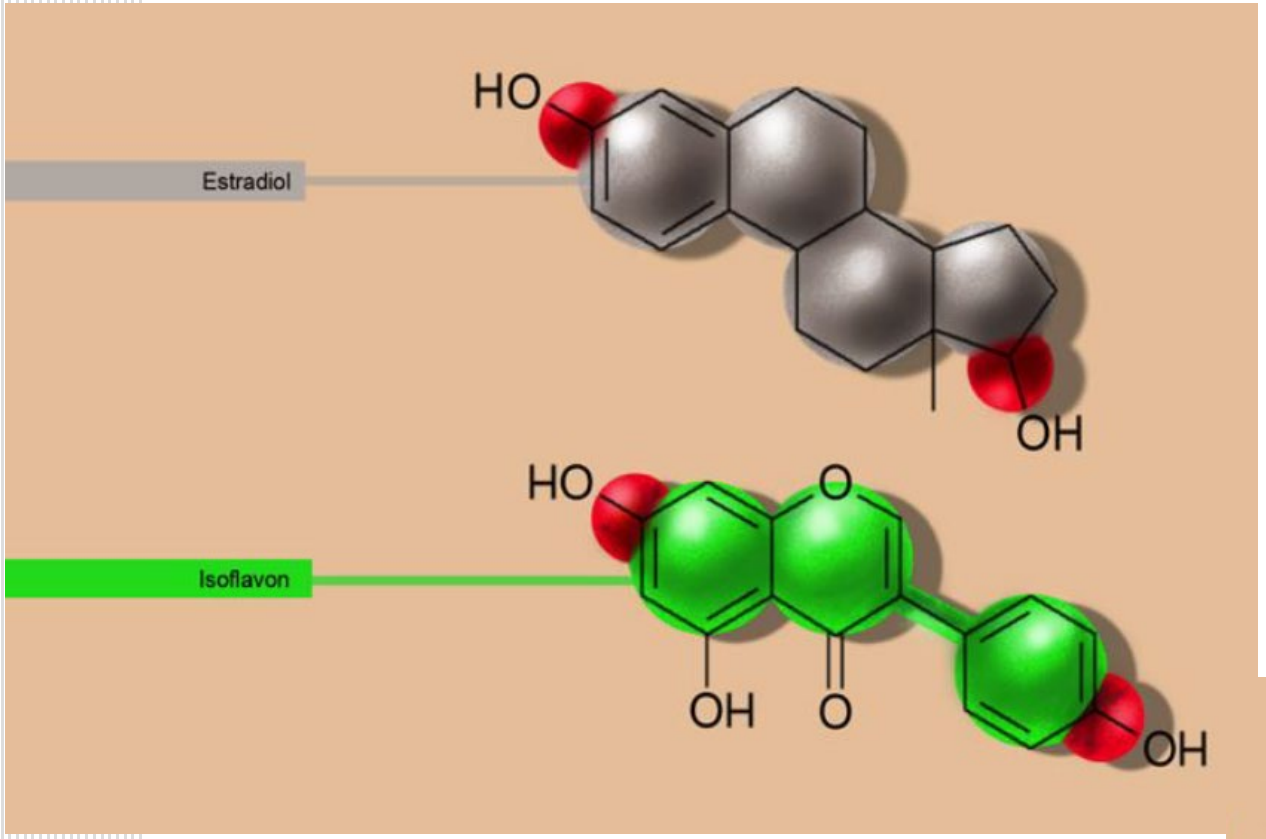
- Sojanahrung wird in Asien seit Jahrhunderten verstärkt konsumiert
  - > 70% Verlust an Isoflavonen durch Nahrungsverarbeitung (z.B. Soja-Protein)
  - täglich ~10 - 15 mg Hong Kong, ~30 - 45 mg Japan und Shanghai
  - inter-individuelle Metabolisierung
  - Europäer, Nordamerikaner: 30-40% Equolproduktion aus Genistein, Daidzein – deutlich höher bei den Asiaten
  - Abhängig von der Darmflora!

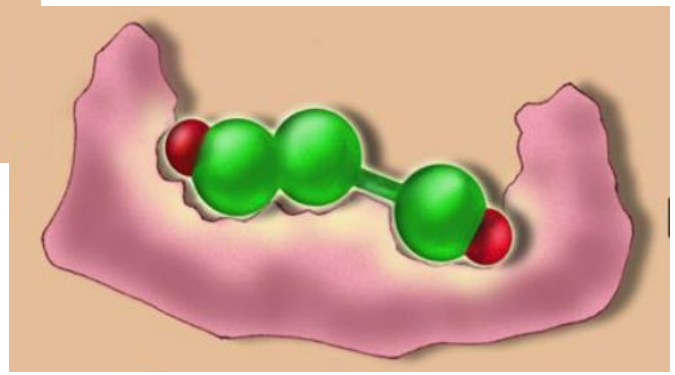
Messina M. Am J Clin Nutr 2014

Klimakterische Symptome & Isoflavone



Isoflavone & Östrogene

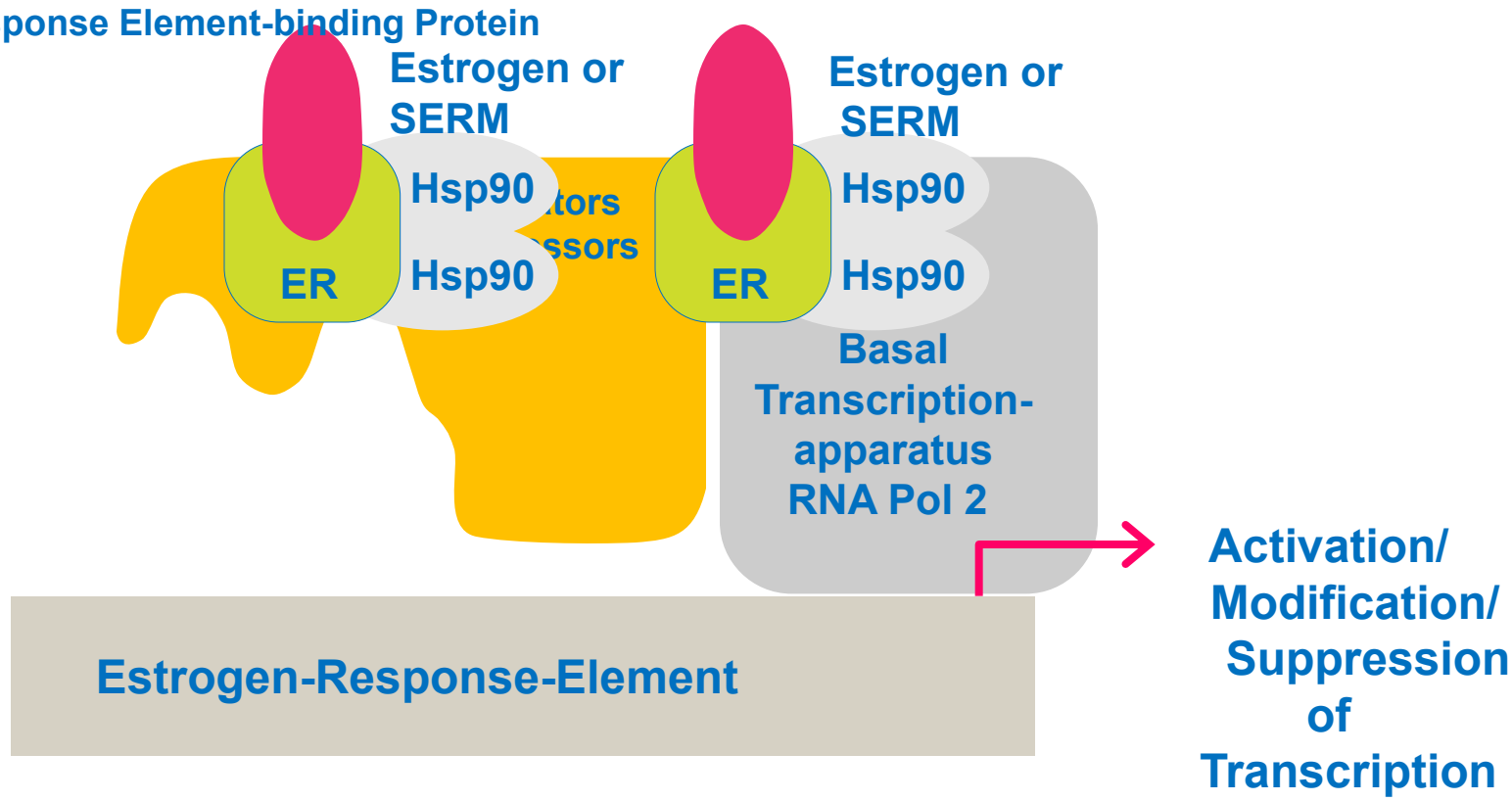




Bindung an den Östrogen Rezeptor

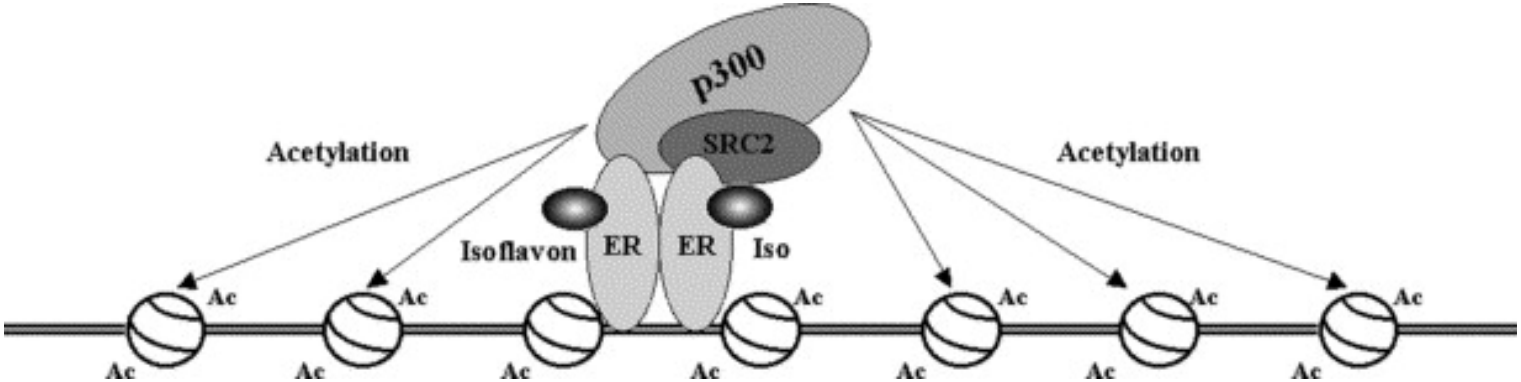
Steroid Receptor Co-activator (SCR 1/3)
Vitamin D Receptor-interacting Protein (DRIP205)
Nuclear Receptor-interacting Protein (NRIP1II)
cAMP Response Element-binding Protein (CREB)

Nuclear Receptor Co-repressor (NCoR)
Silencing Mediator of Retinoic Acid and Thyroid Hormone (SMRT)



Adaptiert von: Tata JR Nat Rev Mol Cell Biol 2002

Isoflavone und ER
Co-Aktivator P300



Equol, Genistein und Daidzein weisen eine starke Stimulation der ERβ-mediierten Core-Histon-Acetylierung (HAT) auf

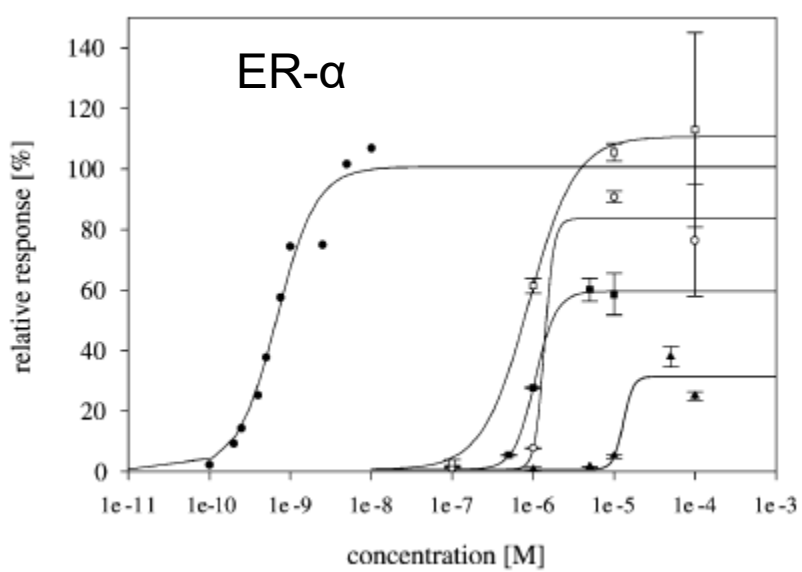
Binding to Estrogen

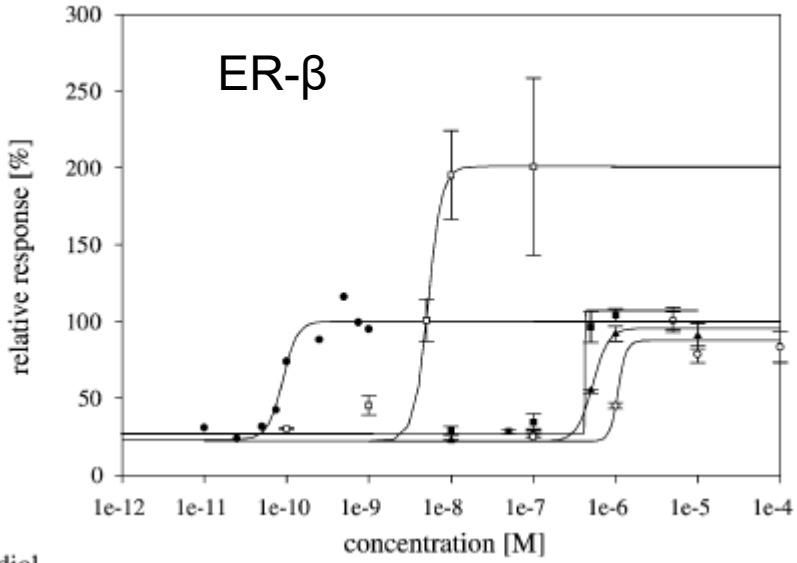
Binding to SERM

Hong T. et al. Biochem Biophy Res Comm 2004

17β Estradiol und Isoflavone

Vergleich von ER-α und ER-β

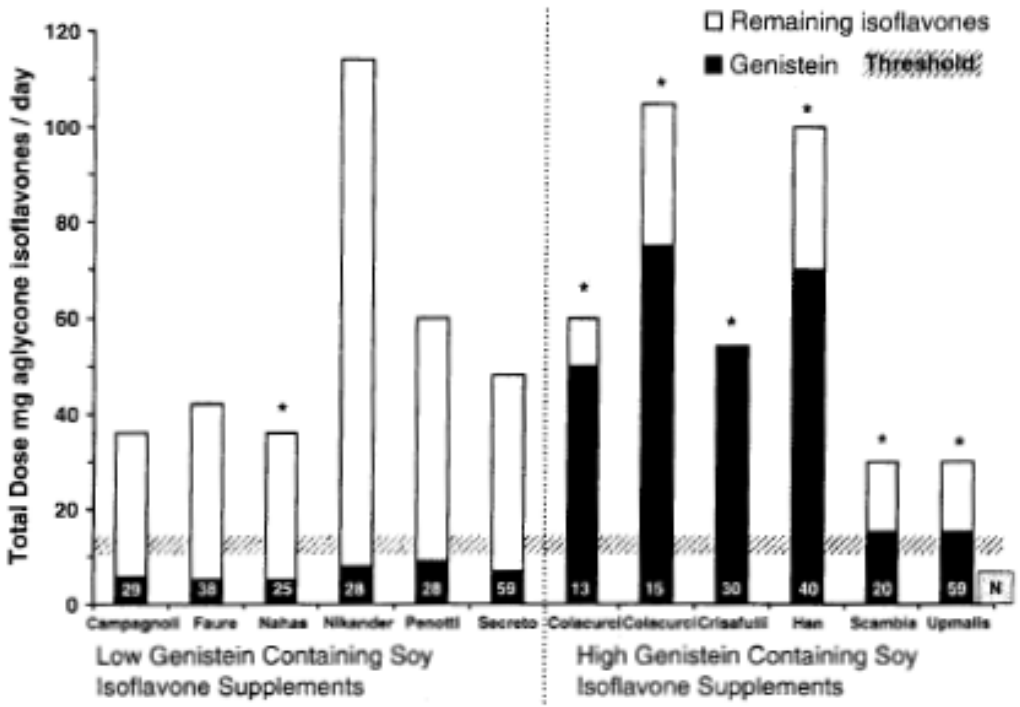




- 17beta-Estradiol
- Biochanin A
- Daidzein
- Formononetin
- Genistein

Beck V. et al. J Steroid Biochem Mol Biol 2003

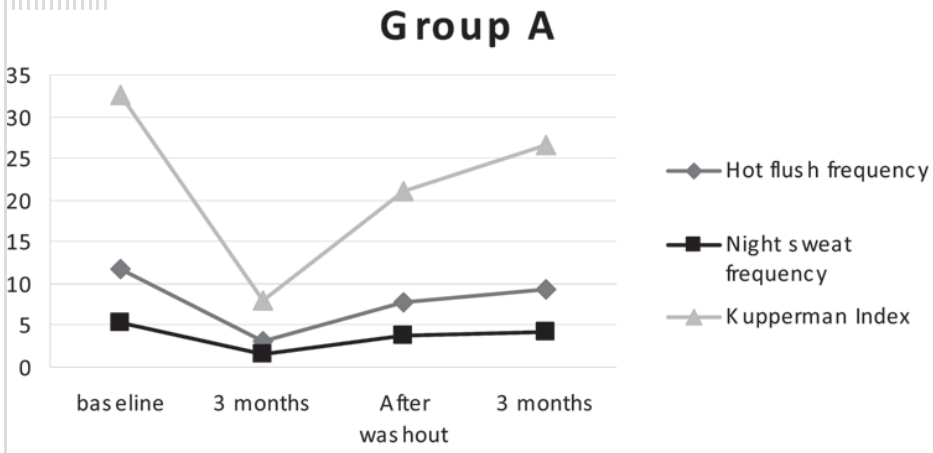
Isoflavon Dosierungen
Genistein

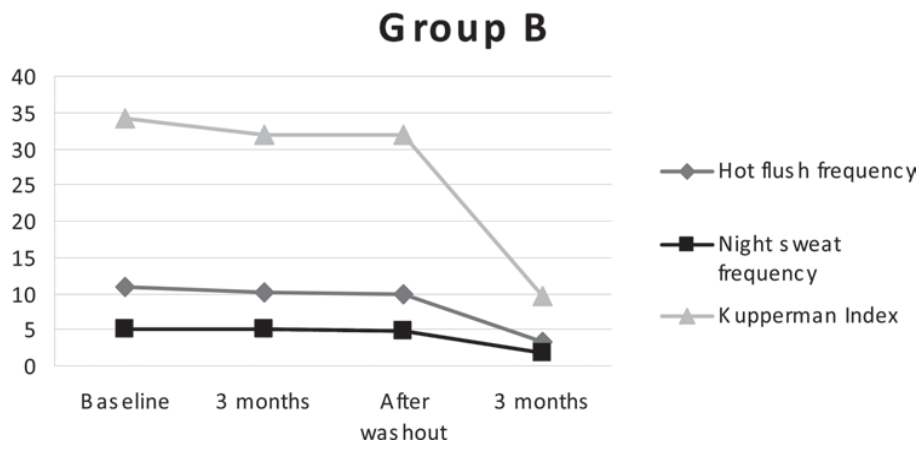


Minimum of 10 to 15 mg genistein per day as effective for treatment of hot flushes

Williamson-Hughes PS et al. Menopause 2006

Hitzewallungen und Rotklee



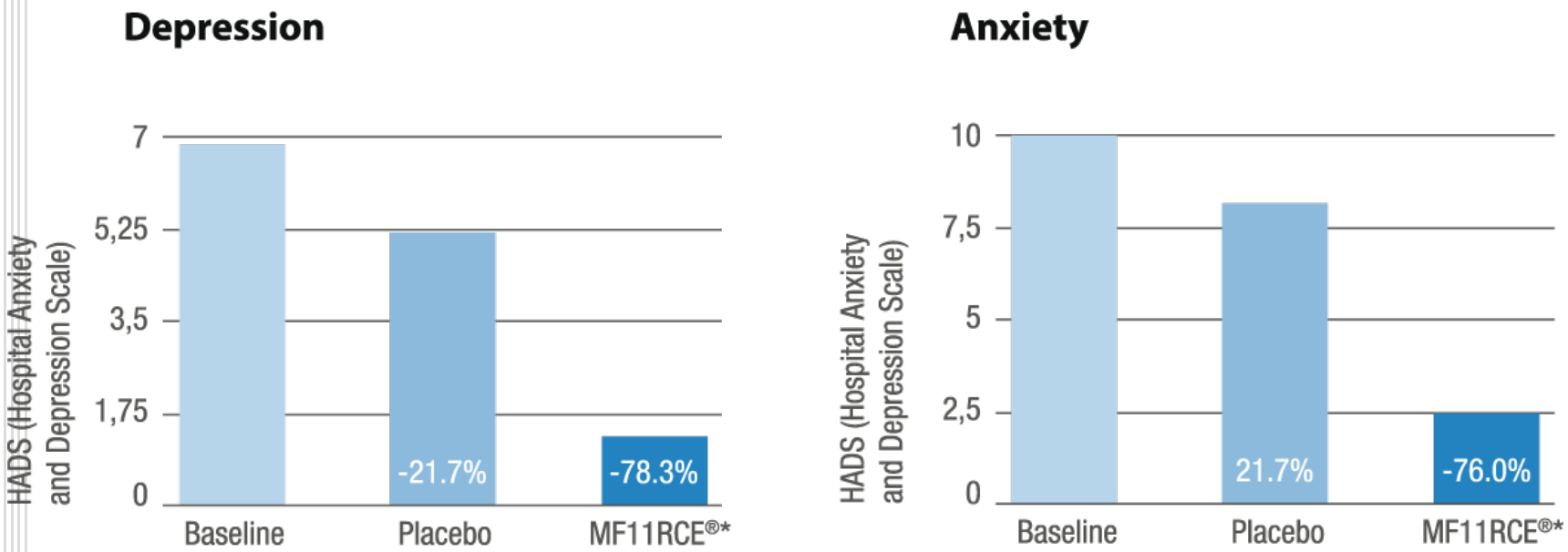


Group A: 80 mg red clover isoflavones (n=53)
Group B: Placebo (n=60)
Cross over design after 7-day wash-out

Lipovac M et al. Gyn Endocrinol 2011

Klimakterische Symptome
Depression/Ängstlichkeit und Rotklee

HADS scoring after each treatment phase:

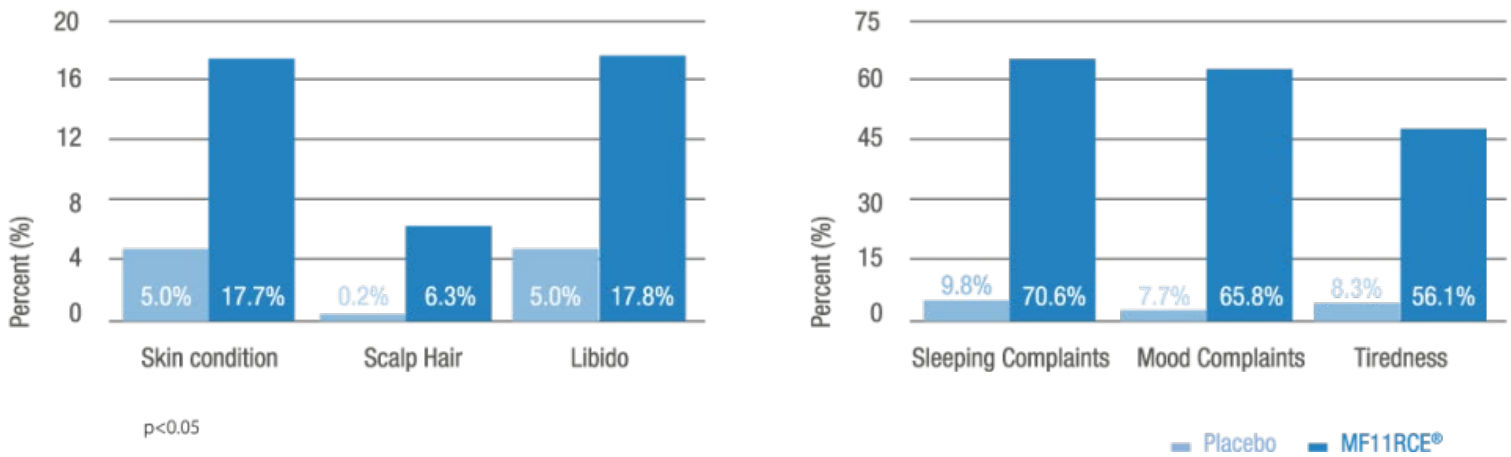


* p<0.001 to baseline and placebo

Lipovac M et al. Maturitas 2010

Klimakterische Symptome
Haut/Libido und Rotklee

Subjective symptom or condition improvement after treatment as assessed with the VAS

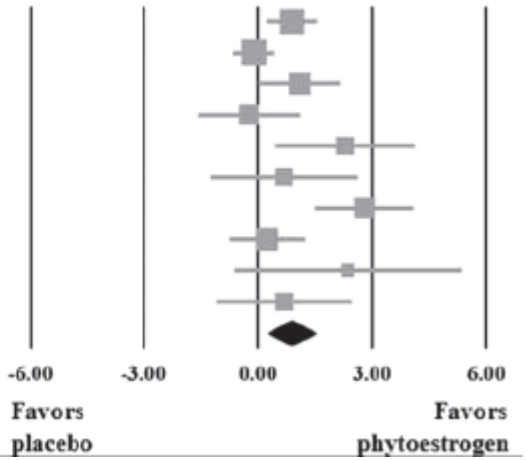


Lipovac M et al. Obstet Gyn Int 2011

Klimakterische Symptome

Study name	Sample size	Mean difference (95%CI)	P-value
Aso T (2012)	60 vs. 66	0.90 (0.24, 1.56)	0.008
Atkinson C (2004)	103 vs. 102	-0.10 (-0.64, 0.44)	0.714
Ferrari A (2009)	94 vs. 82	1.10 (0.03, 2.17)	0.044
Lewis JE (2006)	33 vs. 33	-0.22 (-1.55, 1.11)	0.746
Nahas EA (2007)	38 vs. 38	2.30 (0.47, 4.13)	0.014
Penotti M (2003)	34 vs. 28	0.70 (-1.22, 2.62)	0.474
Petri Nahas E (2004)	25 vs. 26	2.80 (1.53, 4.07)	0.000
Tice JA (2003)	85 vs. 167	0.25 (-0.74, 1.24)	0.620
van de Weijer PH (2002)	14 vs. 16	2.37 (-0.60, 5.34)	0.118
Van Patten CL (2002)	64 vs. 59	0.70 (-1.06, 2.46)	0.435
Pooled mean difference in random model		0.89 (0.26, 1.52)	<0.005

Forest plot for mean difference (95% CI)

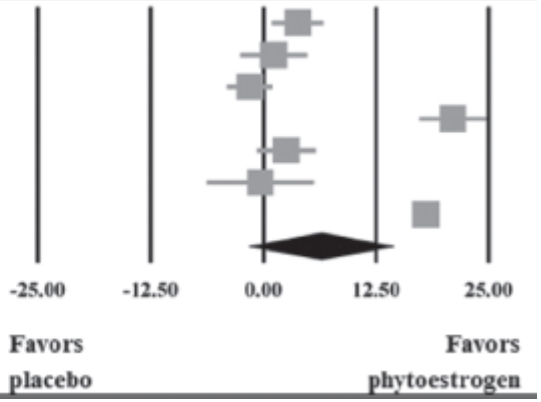


Hitzewallungen

Kuppermann Index

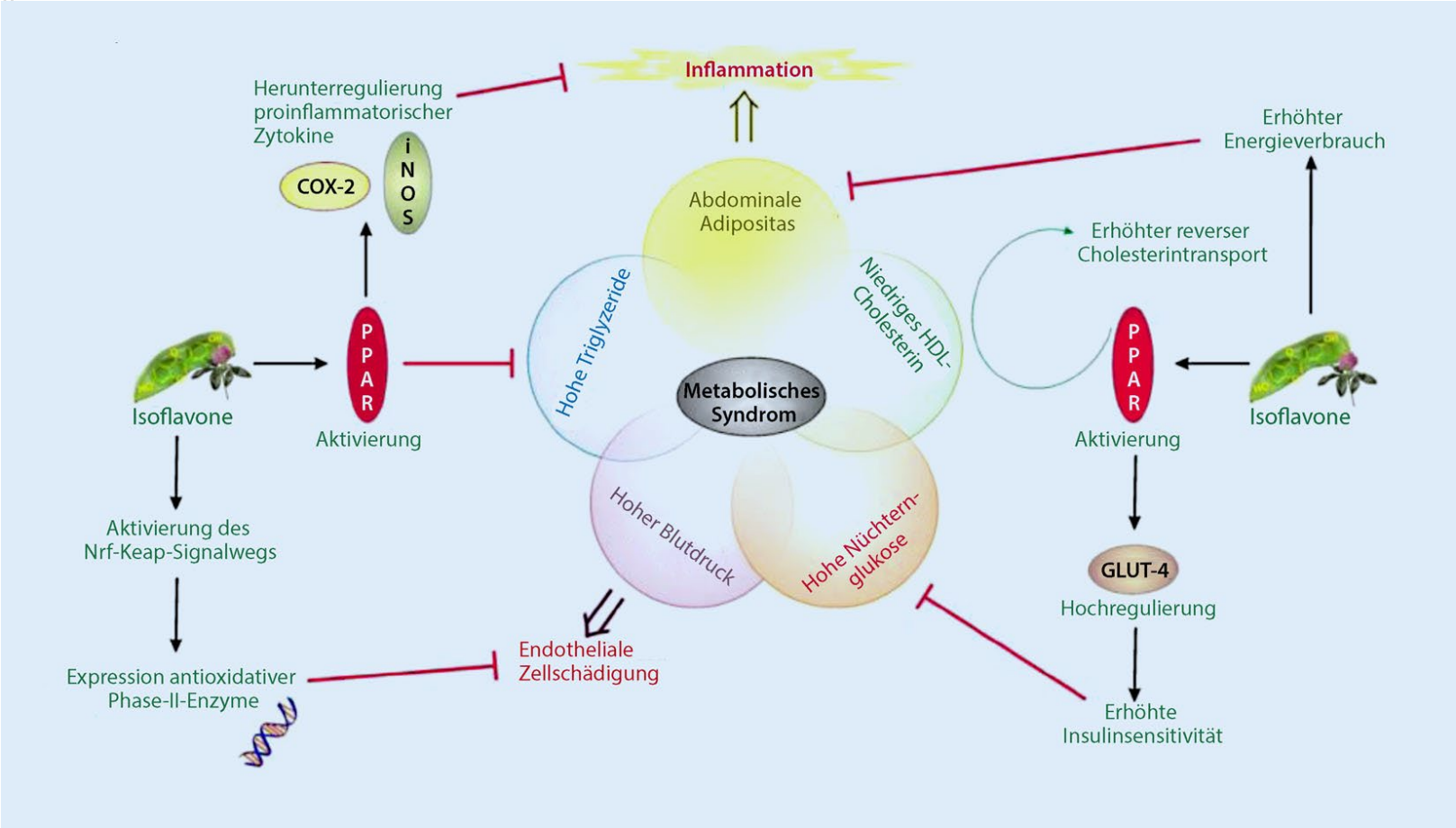
Study name	Sample size	Mean difference (95%CI)	P-value
Cancellieri F (2007)	65 vs. 60	3.80 (1.01, 6.59)	0.008
Del Giorno C (2010)	50 vs. 50	1.11 (-2.52, 4.74)	0.549
Ferrari A (2009)	94 vs. 82	-1.50 (-3.96, 0.96)	0.232
Han KK (2002)	40 vs. 40	21.00 (17.31, 24.69)	<0.001
Petri Nahas E (2004)	25 vs. 26	2.55 (-0.67, 5.77)	0.121
Riesco E (2011)	21 vs. 19	-0.30 (-6.16, 5.56)	0.920
Sammartino A (2006)	36 vs. 39	18.00 (16.90, 19.10)	<0.001
Pooled mean difference for all studies (random model)		6.44 (-1.45, 14.34)	0.110

Forest plot for mean difference (95% CI)



Chen M et al. Climacteric 2014

Molekulare Mechanismen der Isoflavone
Metabolisches Syndrom



Jungbauer A. et al. J Steroid Biochem Mol Biol 2014

Isoflavone und Atherosklerose

Direkte Effekte

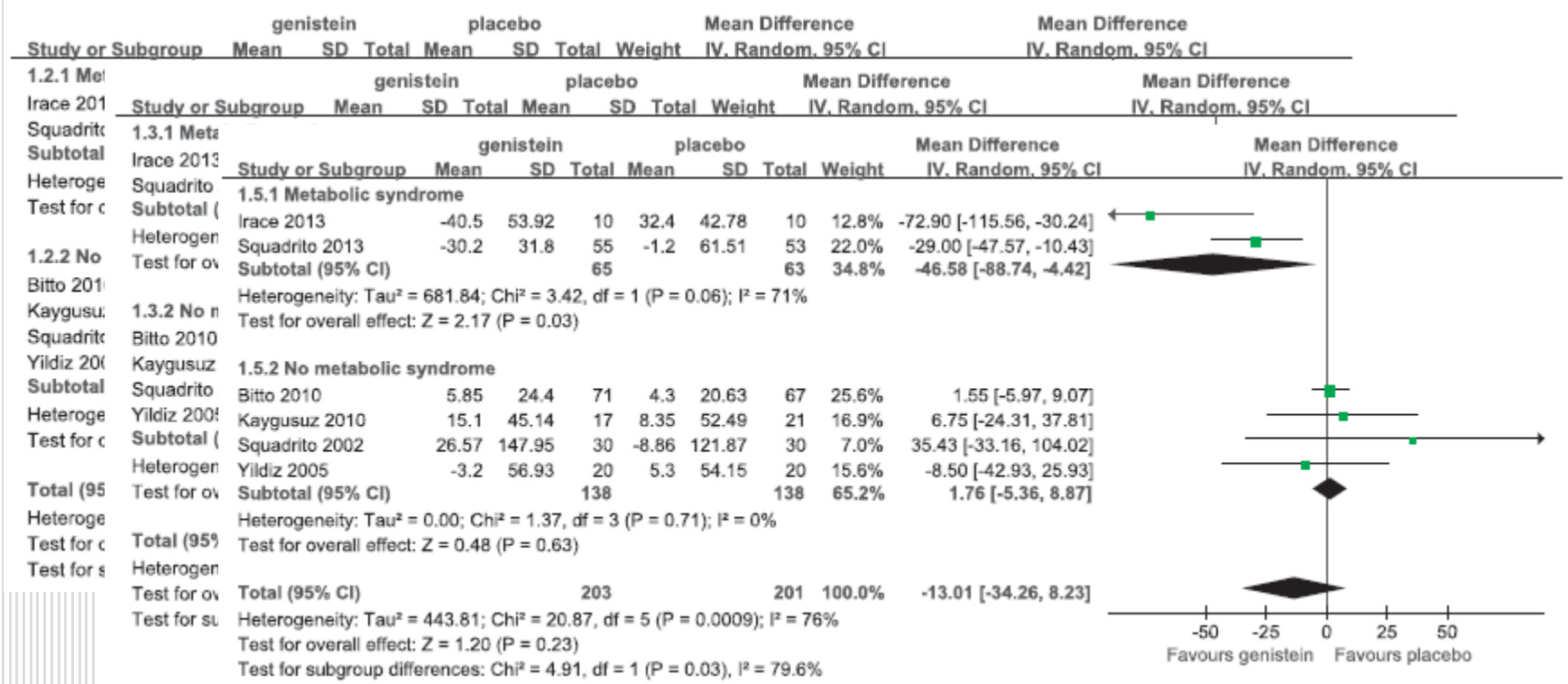
- Atherosklerotische Plaques ↓
- Kardiomyocyten
  - Ischaemia ↓
  - Reperfusion ↑
- Zytokin Freisetzung ↓
- Inflammation ↓
- Endothelzell Wachstum ↑
- VSMC Wachstum↓

Indirekte Effekte

- Lipoprotein Metabolismus
  - LDL ↓ HDL ↑ TG ↓
- Glukose Metabolismus
  - Nüchternglukose ↓
  - Insulin Sensitivität ↑
- Blutdruck ↓
- Homocystein ↓

Isoflavone und Atherosklerose

HDL, LDL, Triglyzerid Plasmaspiegel



Li J. et al. Climacteric 2016

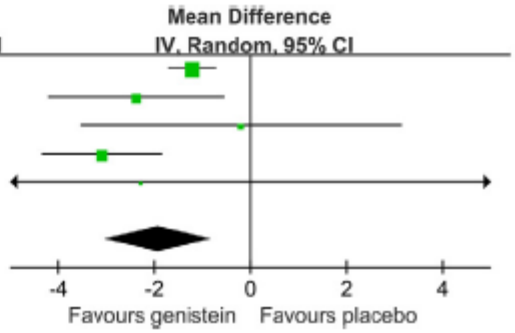
Isoflavone und Atherosklerose
Insulinresistenz

Effects of genistein on fasting glucose

Effects of genistein on fasting insulin

Study or Subgroup	genistein Mean	genistein SD	genistein Total	placebo Mean	placebo SD	placebo Total	Weight	Mean Difference IV, Random, 95% CI
Atteritano 2007	-0.53	2.27	178	0.69	2.49	172	41.0%	-1.22 [-1.72, -0.72]
Crisafulli 2005	-0.76	2.78	30	1.63	4.32	30	20.3%	-2.39 [-4.23, -0.55]
Irace 2013	-0.3	3.45	10	-0.1	4.15	10	9.0%	-0.20 [-3.54, 3.14]
Squadrito 2013	-3.1	3.83	60	0	3.12	58	28.6%	-3.10 [-4.36, -1.84]
Villa 2009	-2	15.93	28	0.3	15.88	15	1.2%	-2.30 [-12.27, 7.67]
Total (95% CI)			**306**			**285**	**100.0%**	**-1.92 [-3.04, -0.79]**

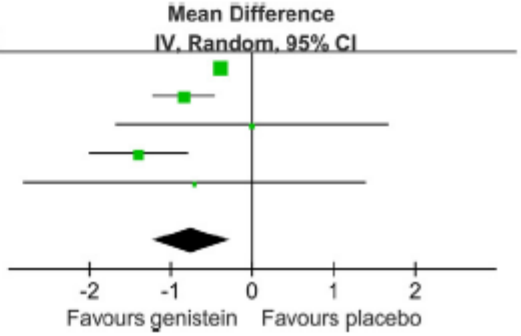
Heterogeneity: Tau² = 0.73; Chi² = 8.92, df = 4 (P = 0.06); I² = 55%
Test for overall effect: Z = 3.35 (P = 0.0008)



Effects of genistein on HOMA-IR

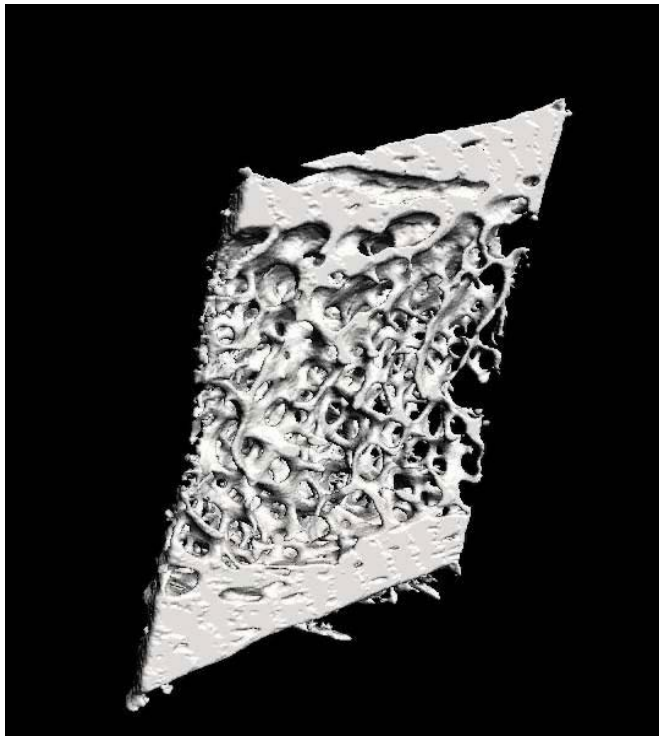
Study or Subgroup	genistein Mean	genistein SD	genistein Total	placebo Mean	placebo SD	placebo Total	Weight	Mean Difference IV, Random, 95% CI
Atteritano 2007	-0.18	0.34	178	0.21	0.45	172	36.6%	-0.39 [-0.47, -0.31]
Crisafulli 2005	-0.29	0.5	30	0.55	0.94	30	29.8%	-0.84 [-1.22, -0.46]
Irace 2013	-0.5	1.67	10	-0.5	2.13	10	6.4%	0.00 [-1.68, 1.68]
Squadrito 2013	-1.6	1.96	60	-0.2	1.37	58	22.8%	-1.40 [-2.01, -0.79]
Villa 2009	-0.69	5.66	28	0.02	0.31	15	4.4%	-0.71 [-2.81, 1.39]
Total (95% CI)			**306**			**285**	**100.0%**	**-0.74 [-1.21, -0.28]**

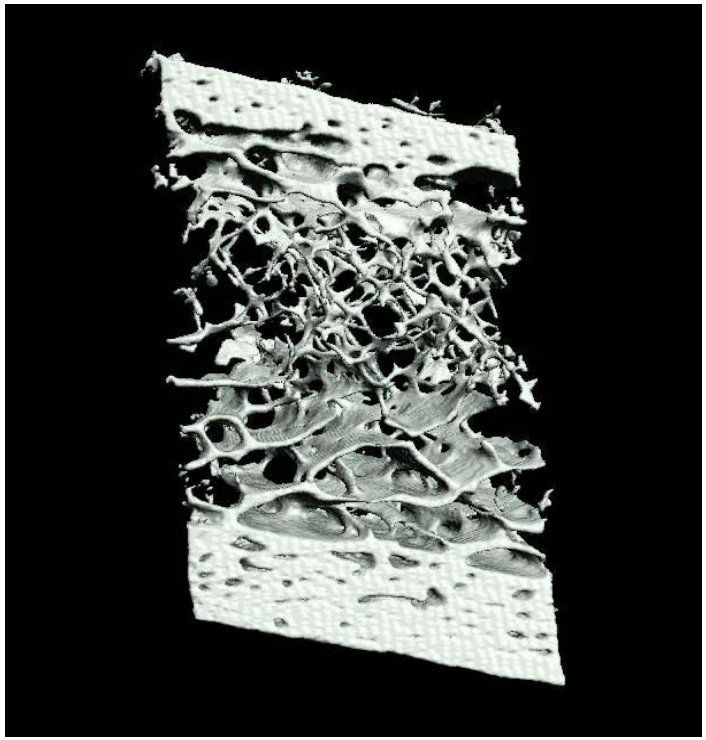
Heterogeneity: Tau² = 0.15; Chi² = 15.40, df = 4 (P = 0.004); I² = 74%
Test for overall effect: Z = 3.11 (P = 0.002)



Liu Y et al. Maturitas 2017

Isoflavone und Knochen





In früher Postmenopause vor allem zunächst Verlust des trabekulären Knochens

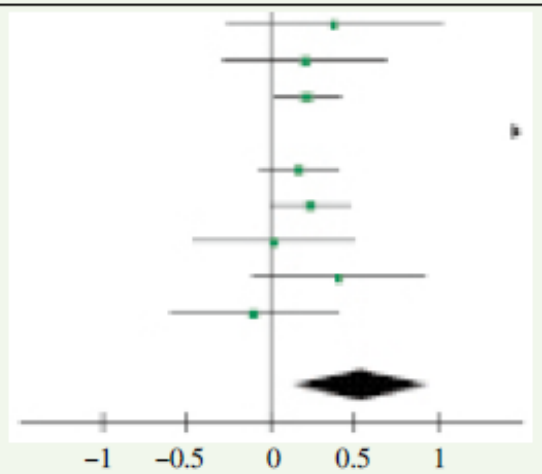
Zebaze RM et al. Lancet 2010; Dufresne TE et al. Calcif Tissue Int 2003

Isoflavone und Knochen

Study of subgroup	Experimental			Control		
	Mean	*SD*	Total	Mean	*SD*	Total
Harkness 2004	0.890	0.030	19	0.880	0.020	19
Kenny 2009	1.106	0.085	32	1.086	0.103	33
Marni 2007	0.850	0.080	198	0.830	0.100	191
Shao 2007	0.879	0.070	30	0.544	0.050	30
Wong 2009a	1.115	0.090	135	1.100	0.084	134
Wong 2009b	1.121	0.093	134	1.100	0.084	134
Wu 2005	0.996	0.105	34	0.994	0.089	34
Ye 2006a	0.904	0.149	30	0.851	0.102	30
Ye 2006b	0.841	0.108	30	0.851	0.102	30
Total (95% *CI*)			642			635

Heterogeneity: $Tau^2=0.32$; $Chi^2=85.18$, $df=8$ ($P<0.000\,01$); $I^2=91\%$

Test for overall effect: $Z=2.60$ ($P=0.009$)

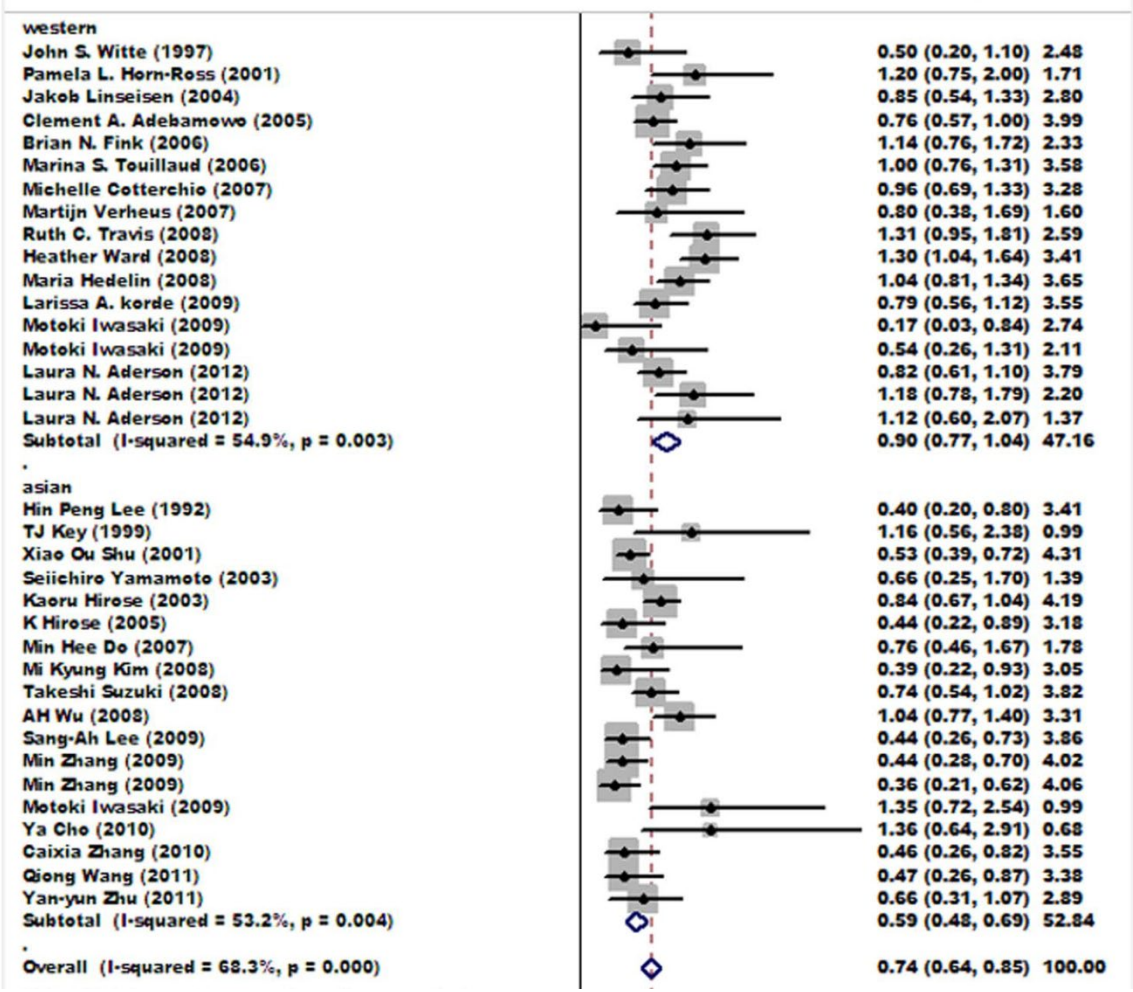


Variables		Trials	Sample size	P value for heterogeneity
Menopausal status	Perimenopausal	1	269/268	–
	Postmenopausal	6	423/416	0.001
Isoflavone dose	⩽75 mg/d	1	34/34	–
	>75 mg/d	6	658/650	<0.001

BMD 54%↑
uDPD 23%↓

Wie P et al. Asian Pacific J Trop Med 2012

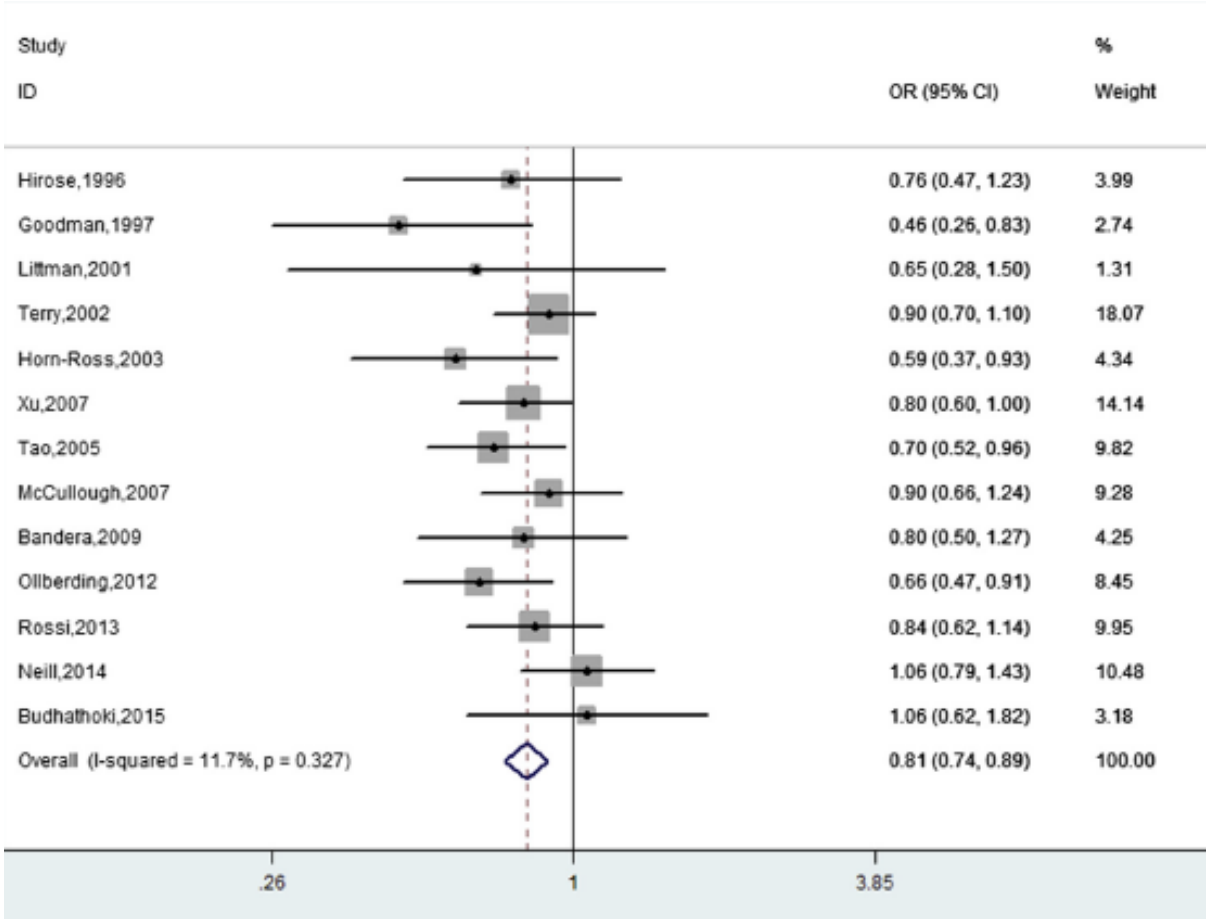
Isoflavone und Mammakarzinom Risiko
Metaanalyse epidemiologischer Studien



Favours control I Favours treatment

Chen M et al. PLOS 2014

Isoflavone und EM-Karzinom Risiko
Metaanalyse epidemiologischer Studien



Favours treatment I Favours control

Zhong X et al. J Acad Nutr Diet 2016

Isoflavone und Patientensicherheit

European Food Safety Authority 2015

EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS)

The EFSA ANS Panel was asked to deliver a scientific opinion on the possible association between the intake of isoflavones from food supplements and harmful effects on mammary gland, uterus and thyroid in peri- and post-menopausal women. Isoflavones are naturally occurring substances which can be found in, among other sources, soy, red clover and kudzu root. The main isoflavones are genistein, daidzein, glycitein, formononetin, biochanin A and puerarin. …. Food supplements targeted at peri- and post-menopausal women typically provide a daily dose of isoflavones in the range of 35–150 mg/day. A systematic review … of human data **did not support the hypothesis of an increased risk of breast cancer from observational studies nor of an effect on mammographic density nor on proliferation marker Ki-67 expression** in interventional studies. No effect was found on endometrial thickness and histopathological changes in the uterus up to 30 months of supplementation with 150 mg/day of soy isoflavones. … **Thyroid hormones levels were not changed** following intake of isoflavones from food supplements.

Naturhormone

Bioident(isch)e Hormone

Pflanzliche Stoffe

Bioidente Hormone

- Rationale: möglichst risikofrei und „bekömmlich“
- Definition?
  - Alles, was auf irgendeine Art primär oder sekundär aus der Natur kommt?
- In der Hormon(ersatz)therapie:
  - Progesteron
  - Östradiol (E2)
  - Testosteron, DHEA

Mück 2017 Gynäkologische Endokrinologie

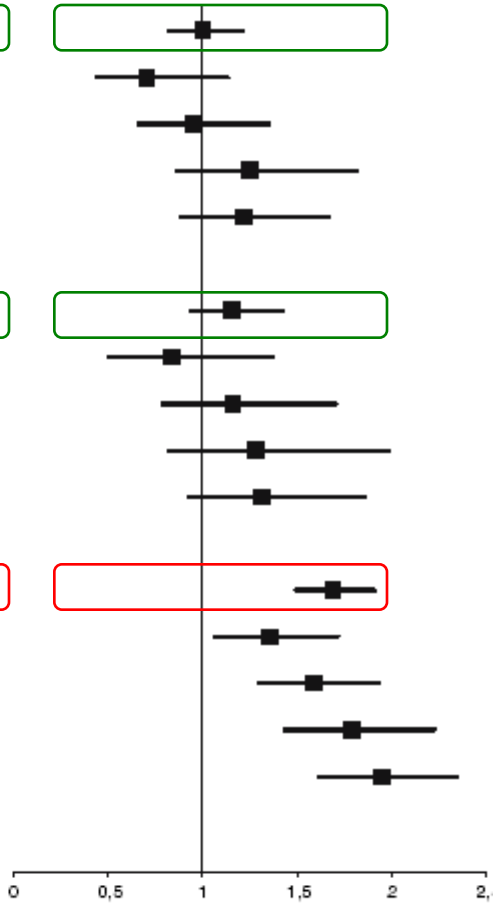
Bioidente Hormone

	Uterus	Ovary	Mammary Gland
E_2	Promotes cell proliferation and carcinogenesis[1, 2, 3, 4]	No studies reported comparing E_2 to CEE within the same study	Promotes cell proliferation and carcinogenesis[4, 5, 6, 7, 8, 9, 10]
CEE	Promotes cell proliferation and carcinogenesis[1, 2, 3, 4]	No studies reported comparing E_2 to CEE within the same study	Promotes cell proliferation and carcinogenesis[4, 5, 6, 8, 9, 10]
P_4	Induces less cell proliferation than MPA; Inhibits carcinogenesis[11,12,13, 14, 15, 16]	Neutral effect on carcinogenicity[17]	Induces less cell proliferation than MPA[11, 18, 19, 20, 21, 22, 23]
MPA	Induces more cell proliferation than P_4; Inhibits carcinogenesis[11, 12, 13, 14, 15, 16]	Stimulates carcinogenesis at low concentration; Inhibits carcinogenesis at high concentration[17]	Induces more cell proliferation than P_4[11, 18, 19, 20, 21, 22, 24]
E_2 + P_4	Induces less cell proliferation than E_2 + MPA[11]	No studies reported comparing CEE + MPA to E_2 + P_4 within the same study	Induces less cell proliferation than E_2 + MPA[11, 18, 19] Promotes more cellular differentiation than E_2 + MPA [19] Inhibits carcinogenesis to a greater extent than E_2 + MPA[20, 21, 22]
CEE + MPA	No studies reported comparing CEE + MPA to E_2 + P_4 within the same study	No studies reported comparing CEE + MPA to E_2 + P_4 within the same study	No studies reported comparing CEE + MPA to E_2 + P_4 within the same study

Atwood & Ekstein 2019 Mol Cell Endocrinol

Risiko für das Mammakarzinom

Estrogen + progesterone	**129/40,537**	**1.00 (0.83-1.22)**
<2	18/8,697	0.71 (0.44-1.14)
[2-4[	33/11,647	0.95 (0.67-1.36)
[4-6[	30/7,619	1.26 (0.87-1.82)
6+	43/10,111	1.22 (0.89-1.67)
p for trend		0.04
Estrogen + dydrogesterone	**108/31,045**	**1.16 (0.94-1.43)**
<2	16/6,923	0.84 (0.51-1.38)
[2-4[	28/8,697	1.16 (0.79-1.71)
[4-6[	21/5,590	1.28 (0.83-1.99)
6+	35/7,876	1.32 (0.93-1.86)
p for trend		0.16
Estrogen + other progestagens	**527/104,243**	**1.69 (1.50-1.91)**
<2	86/22,792	1.36 (1.07-1.72)
[2-4[	134/30,189	1.59 (1.30-1.94)
[4-6[	106/19,942	1.79 (1.44-2.23)
6+	156/23,817	1.95 (1.62-2.35)
p for trend		0.01



(2354 Fälle / 80377 Patientinnen)

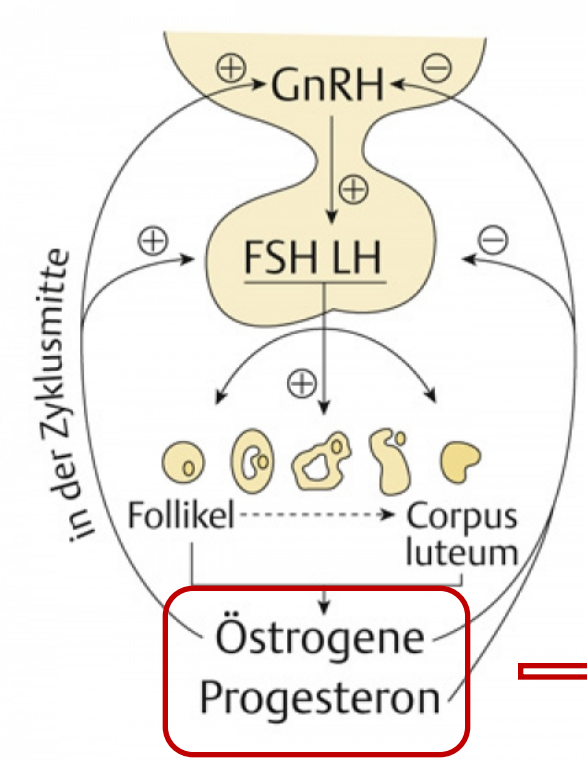
Fournier 2008 Breast Cancer Res Treat

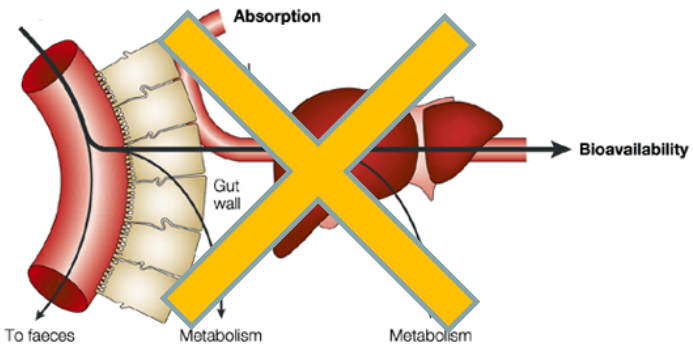
Equine Östrogen

- „conjugated equine estrogens“ (CEE)
- Aus Pferdeurin
- Beinhalten insg. Etwa 200 verschiedene Steriode
  - Unter anderem Östrogene, Androgene, Gestagene und Kortikoide
- → für den Menschen nicht „bioident“!

Bhavnani 2014 J Steroid Biochem Mol Biol

Applikationsweg





⟹ Gelangen direkt ins Blut

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Georg Thieme Verlag KG, Stuttgart · New York · 2011
G. Spinas, S. Fischli: Endokrinologie und Stoffwechsel kompakt · 2. Auflage

Applikationsweg

- Bei der HRT werden venös etwa 25–100µg Estradiol gebraucht, um an den Zielorganen zu wirken

- Orale Applikation: 1-2mg (95% hepatische Metabolisation!)
- Transdermale Applikation: 25–100µg

- → orale Applikation führt zu stärkeren hepatischen Effekten wie z.B. Aktivierung der hepatischen Gerinnungsfaktoren, vermehrte Bildung von SHBG, CBG, TBG etc.

Mück 2017 Gynäkologische Endokrinologie

Transdermal versus oral

Table 1. Relative risks (RR) of thromboembolic accident in users of menopausal hormone therapy (estrogens-only and combined estrogen–progestogens) according to the route of estrogen administration. Adapted from Renoux *et al.* (*J Thromb Haemost* 2010;8:979–86).

Route of estrogen administration	*Daily estrogen dose*	*Relative risk (95% confidence interval)*
Oral	Low (<0.625 mg CEE or <2 mg E2)	1.19 (1.04–1.35)
	Standard (0.625 mg CEE or 2 mg E2)	1.55 (1.45–1.65)
	High (>0.625 mg CEE or >2 mg E2)	1.84 (1.63–2.09)
Transdermal	Patches ≤50 μg	0.99 (0.87–1.12)
	Patches >50 μg	1.05 (0.81–1.36)

CEE, conjugated equine estrogens; E2, estradiol

Table 3. Relative risk (RR) of hospitalization for gallbladder disease (including cholecystectomy) in actual users of menopausal hormone therapy, according to the route of estrogen administration, compared to never-users. Adapted from Liu *et al.* (*Br Med J* 2008;337:a386).

Route of estrogen administration	*Duration of estrogen use (years)*	*Cases/controls*	*Relative risk (95% confidence interval)*
Oral	6.6	6914/263 871	1.74 (1.68–1.80)
Transdermal	7.2	1249/60 247	1.17 (1.10–1.24)

Table 2. Relative risks (RR) or odds ratios (OR) of ischemic stroke from menopausal hormone therapy (estrogen-only and combined estrogen–progestogens) according to the route of estrogen administration and to the dose administered. Adapted from Renoux *et al.* (*Br Med J* 2010;340:c2519) and from Canonico *et al.* (*Stroke* 2016;47:1734–41).

	Renoux et al., 2010		*Canonico et al., 2016*	
Route of estrogen administration	*Dose*	*Adjusted RR (95% CI)*	*Dose*	*Adjusted OR (95% CI)*
Oral	≤0.625 mg CEE or ≤2 mg E2	1.25 (1.12–1.40)	≤1 mg E2	1.39 (1.00–1.99)
	>0.625 mg CEE or >2 mg E2	1.48 (1.16–1.90)	1.5 mg E2	1.84 (1.02–3.30)
			≥2 mg E2	2.41 (1.43–4.07)
Transdermal	≤50 μg	0.81 (0.62–1.05)	<50 μg	0.69 (0.37–1.28)
	>50 μg	1.89 (1.15–3.11)	50 μg	0.79 (0.40–1.58)
			>50 μg	0.88 (0.57–1.37)

CEE, conjugated equine estrogens; E2, estradiol

L'Hermite 2017 Climacteric

Schlussfolgerungen

- *Bioidentische HRT*: Estradiol + Progesteron, transdermale Applikation!

- *Isoflavone* sind „Phyto-SERMs“ und binden an ER-β (und ER-α)
  - Umfangreiche präklinische Daten (in-vitro, in-vivo) zeigen einen Einfluss von Isoflavonen auf verschiedene Stoffwechselvorgänge
    Klinische RCT und Metaanalysen ergeben einen gewissen Effekt auf Hitzewallungen
  - Studienlage heterogen (unterschiedliche Phytoöstrogene, Dosierungen, inter-individuelle Metabolisierung, ethnische Aspekte, etc.)
    Effekte auf Surrogatparameter des kardiovaskulären Risikos und Osteoporose durch Isoflavone nachweisbar, jedoch keine harten Endpunktstudien (Herzinfarkt, Schlaganfall, Frakturrate etc.)
  - Lt. EFSA keine Hinweise auf Risiko↑ bezüglich Mamma Ca, Endometrium-Stimulation oder Schilddrüse mit typischer Dosierung von 35–150 mg/d

source: https://memegenerator.net/img/instances/65777355/thank-you-for-your-attention-please-clap-and-dont-ask-questions.jpg