Soya, soya isoflavones and health effects

Angela Mörixbauer

eatconsult - agentur für ernährungskommunikation

Soya foods are very popular not only in Asia but now also in Europe and the USA – not least because of the trend towards vegan and vegetarian diets as well as for sustainability reasons to reduce meat consumption. Soya products are versatile in the kitchen and enrich a plant-based diet due to their high nutrient density and biological value of the protein. In particular, the high phytoestrogen content has a number of health-promoting effects [1–3]. At the same time, however, it is precisely this content that makes people feel unsure since the opposite is often claimed on the internet and in social media, as it is shown in the review of over 500 prints, online and social media clippings in the period from October to December 2018 [4]. In particular, feminisation in men, reduced fertility, breast cancer-promoting properties and adverse effects on thyroid function are concerns. However, the current scientific literature does not confirm this but rather points to the positive health effects of soya foods and ingredients.

Legumes Translated Special Report 2

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Legumes Translated

Introduction

Anyone surfing the web on soya and its health effects will find a whole range of contradictory information, from the "super bean" to "toxic waste". The situation in the scientific literature does not seem clear at first glance either. Around 2,000 scientific studies are published annually. Concerns that were justified two decades ago have now been waived – such as those about adverse effects on breast cancer patients. But opponents of soya often base their arguments on obsolete sources and simply transfer results from in vitro studies and animal experiments to humans. Caution is advised here, particularly with soya, because most animals, including rodents and primates, metabolise isoflavones (phytoestrogens) significantly different than humans [5].

In 2016, Kopp Verlag, a publishing house, published a 500-page work on soya, which at first glance seems quite reliable: "Soja – Die ganze Wahrheit. Die Schattenseiten der 'gesunden Ernährung' (original title: "The Whole Soya Story: The Dark Side of America's Favourite Health Food")[6]. The author, an American nutritionist, backs up her anti-soya campaign with hundreds of thoroughly serious studies from reputable journals. However, and this is the crux of the matter, almost all references to the literature date to the period before 2004, which is when the book was published in the USA. But the German translation was published in 2016.

Often, varying research results are based on differences in the study design and the population studied. For example, data from observational studies in Asia show a stronger correlation between soya and health than Caucasian cohorts. The reasons are manifold. Observational studies, especially in Asia, are mainly based on the consumption of traditional, mostly fermented soya products such as tofu, miso, tempeh or soya milk. Studies with Caucasian cohorts or test persons often do not reach clear-cut results because the amount of soya products consumed in Europe and the USA is apparently too low, and especially in the USA, isolates and highly processed soya products are often consumed [1].

Clinical trials, in turn, focus on isolated individual components, mainly soya protein and isoflavones, sometimes in amounts that could not be ingested with conventional soya foods. However, soya contains a number of other ingredients that have different physiological effects, both individually and in combination. Production, processing and preparation processes also influence nutrient and isoflavone content. Furthermore, it is also important which soya components are processed because, just like cereals, soybeans also consist of the seed coat, seedling and endosperm. It is also relevant whether someone has been consuming soya since childhood, from adulthood or only for the duration of the study [2].

In recent years, more and more research has indicated that the ability to metabolise the soya isoflavone daidzein to the more bioavailable equol differs both between individuals and depending on the population and thus has a significant influence on the results of the studies [3, 7].

Soya foods

Soya foods are very popular not only in Asia but also in Europe and the USA - not least because of the trend towards vegan and vegetarian diets but also for sustainability reasons to reduce meat consumption. The characteristics of the popular soya foods are given in table 1.

Table 1. Description of soya products

Soya products	Main characteristics
Edamame	its own variety of soybeans; cooked unripe green soybeans, eaten directly from the pod
Miso	Steamed soybeans, grain and water are fermented with koji (noble mould) to form a creamy, aromatic paste.
Natto	cooked and fermented soybeans
Nimame	cooked whole soybeans
Okara	soya pulp, a by-product of soya drink production
Silk tofu	non-drained tofu with particularly high water content and pudding-like consistency
Soya flakes	peeled, toasted soybeans, pressed into flakes
Soya yoghurt	fermented product from soya drink
Soya flour	steamed, dried, ground soybeans
Soya "Milk"/Soya drink	Soaked and drained soybeans are pureed, mixed with water, boiled and strained. Legally, only the term "soya drink" may be used for such products.
Soya nuts	dry roasted soybeans
Soybean Oil	Edible oil obtained from soybeans by pressing or extraction; as soybeans are not suitable for cold pressing, they are refined.
Soya sprouts	The "real" soya sprouts must be cooked before consumption. In these climes, the sprouts from the mung bean are usually called soya sprouts.
Soya sauce	Seasoning sauce made of water, soybeans, salt and possibly grain, fermented with special mould fungi (koji); the process can take up to five years for fine soya sauces.
Sufu	similar to tofu, a fermented, cheese-like soya product
Tempeh	Cooked, hulled soybeans are inoculated with mould, packed in perforated plastic bags and fermented at approx. 30°C for one day to form a firm block.
Textured soya (TVP, textured vegetable protein)	Ground soybeans are degreased in several pressing steps and brought into the desired shape (e.g., steak, medallion, cubes, granules) by means of an extruder.
Tofu	Soya drink is coagulated with nigari (sea salt bitter extract), magnesium chloride or calcium sulphate; the soya curd is drained and then pressed into blocks. The production process is similar to cheese production.
Yuba	skin that forms on heated soya drink and is then dried

Soya isoflavones

Isoflavones belong to the group of phytoestrogens. Although they are found in numerous plants, soya stands out due to its strikingly high content.

The isoflavones contained therein are almost exclusively present as inactive glycosidic compounds. In the gastrointestinal tract, these are then hydrolysed into aglycons, which makes them much more readily bioavailable to humans [8]. In fermented soya foods, bacteria take over this hydrolysis already during the fermentation process. The most important isoflavonoids in soya are genistein (50%), daidzein (40%) and glycitein (10%) in the protein content [5, 9].

Isoflavones are similar in structure to the female sex hormone estrogen. But they are not "plant estrogens" because they bind selectively and almost exclusively to the cell-protecting estrogen receptor beta (ERBeta, estrogen receptor). The binding affinity to ERAlpha is marginal. Compared to oestradiol, the binding affinity of genistein to ERAlpha is only 4%, while that of ERBeta is 87% (more on the mode of action in the section "Breast cancer").

To determine direct interaction with the ER, the relative binding affinity (RBA) of isoflavones and some metabolites has been determined, assuming the effect of oestradiol at 100%. An RBA of >1% was only measured for genistein and equol, for all other isoflavones the values were between <0.01 and 0.5%, for both ERAlpha and ERBeta [10].

The term selective estrogen receptor modulator ("PhytoSERM") is, therefore, more appropriate because soya isoflavonoids act as ERAgonists at low endogenic estrogen levels and as ERAntagonists at high estrogen levels [11]. Pharmaceutical SERMs such as tamoxifen and raloxifene have been used for a long time to treat breast cancer, and raloxifene is also used to treat osteoporosis [12].

Due to the estrogen-like effect of isoflavones, safety concerns have arisen in the past, especially concerning menopausal women, especially when high amounts of isoflavones are ingested via supplements. Based on a comprehensive evaluation of the literature, the European Food Safety Authority (EFSA) concluded in 2015 that isoflavones in post-menopausal women with a daily intake of 35–150 mg as supplements have no adverse effects on the mammary and thyroid glands as well as the uterus [13].

Heavily processed soya products contain up to 90% less isoflavones than traditional and fermented soya foods, depending on the processing method. Photograph: photo-ac.com

Equol

One of the main reasons for the disagreement in the results of studies seems to be the different individual ability to produce equol. Some people are able to convert the soya isoflavone daidzein into the metabolite equol by means of certain intestinal bacteria. Among vegetarians and in Asia, where soya products are part of the daily diet, this is on average about one in two (50–60%), in the USA and Europe only about one in four (20–35%). However, equol is much more bioavailable to humans than other soya isoflavones [7, 14].

Equol producers, therefore, benefit more from soya consumption because the metabolite has a much higher affinity to bind to ERBeta than the precursor daidzein. Therefore, it is important to determine the equol production capacity of study participants when investigating the relationship between soya consumption and health outcomes. This is done by measuring daidzein and equol in urine. Unfortunately, only a few studies have taken this into account. Compared to subjects who do not consume soya food, soya consumers have a significantly higher probability of producing equol.

Regular soya consumption, therefore, seems to be positively related to the ability to produce equol [7].

Factors influencing intestinal colonisation, such as antibiotic use or changes in nutritional habits, thus also affect the ability to produce equol [14].

Soya consumption

Another factor in result variations is differences in soya consumption between Asian and non-Asian countries. For example, the average intake of soya isoflavones in Japan is 23–54 mg/day, while in the USA and Europe, it is less than 3 mg/day (Table 2). There is a clear north-south gradient with higher intake in northern European countries, so that the range of isoflavone intake in European countries is between 0.37 and 4.5 mg/day. Overall, it is extremely difficult to give average intakes because of the large differences in soya consumption between populations.

Not only the intake quantity but also the isoflavone sources differ. In the USA, highly processed soya products are the main item on the menu, while Asians eat mainly traditional and often fermented soya foods [1]. This influences the intake of isoflavones, as their content in highly processed soya products and depending on the processing method can decrease by up to 90% [3].

Table 2. Soya consumption per day [3], n/a = not available

Region	Soya and soya food (g)	Soya protein (g)	Isoflavones (mg)
USA	n/a	n/a	0.73–3.3
Europe	n/a	n/a	0.37–4.5
Vegetarians and soya consumers (Europe)	n/a	8.42–9.25	3.2–30
China	23.5–135.4	2.5–10.3	6.2–75.7
Japan	50.7–102.1	6–11.3	22.6–54.3
Korea	21.07	7.4–8.5	14.88

In Asia, soya is typically consumed in the form of whole soybean products: edamame, nimame, soya nuts, tempeh, natto, soya milk, tofu, yuba and okara (table 1). In the USA, soya products made of isolated and highly processed soya components are typical: energy or protein bars made of isolated soya protein, protein powder, drinks and ice cream based on soya protein, meat replacement products made of textured soya protein or cereal flakes enriched with soya flour, as well as soya isoflavone supplements [2].

The main sources of soya isoflavones are soybeans, soya protein isolate, tofu, soya milk and fermented products such as miso, natto and tempeh. However, various factors influence the isoflavone content (Table 3) and bioavailability: variety, climate, cultivation area, degree of ripeness, processing or texture [3, 8].

An analysis of US and Japanese soybeans showed an isoflavone content of 1.2–4.2 mg/g. Processing steps reduce the isoflavone content. The second generation of soya products, such as tofu, contains only 6–20% of the isoflavone content in unprocessed soybeans [15]. Deep-freezing for 30 minutes reduced the isoflavone content in natto by almost 45% [16]. Soya drink and tofu provide about 2 mg of isoflavones per 100 g of soya protein, whereas soya flour provides about 5 mg because the baking process hardly influences the content [17].

Soya drink and textured soya protein (TVP) contain mainly glycosides, while tempeh, miso, natto and fermented soya drink tend to contain aglycones due to the microbiological activity during the ripening process. Furthermore, the bioavailability of isoflavones in the liquid matrix is higher than in the solid matrix [3].

Recommended dosage

To benefit from the positive effects of soya isoflavones, a daily intake of 50–100 mg seems to be appropriate [3].

Study results and recommendations often refer to the consumption of "moderate" amounts of soya isoflavones. The American Institute for Cancer Research (AICR) defines this as one or two servings of traditional soya products per day, and that quantities of up to three servings a day are considered safe. A portion is defined as the quantity that provides approx. 7 g soya protein and 25 mg soya isoflavones, which corresponds to 100 g tofu, 250 ml soya drink or 20 g soya nuts, for example. According to the AICR, two servings a day also correspond to the quantities usually consumed in Asia. Asian women after menopause eat on average two to three servings a day [18].

Traditional soya products usually consist of the whole soybean. Photograph: Hui Wang (pixabay.com) and photo-ac.com

Table 3. Isoflavone contents of different soya products (according to [3])

Soya product	Total isoflavone content (mg/100g)
Soya flour	173
Raw soybeans	155
Soya flour degreased	151
Soya nuts	149
Soya protein isolate (SPI)	91
Natto	82
Yuba	45
Miso	41
Tofu	13–35
Edamame	18
Soya lecithin	16
Sufu	14
Soya drink	1–11
Okara	9
Tempeh	4
Soya sauce (Shoyu)	1
Soybean oil	0

Soya and cancer

Studies on the correlation between soya food or soya isoflavones and cancer risk show promising results. For example, there is evidence that regular consumption of soya products can reduce the risk of gastrointestinal cancer [19-22]. The same applies to cancer of the endometrium (uterine lining) [23, 24]. In both cases, however, the data situation is (still) not uniform.

This is different in the case of breast and prostate cancer, two hormone-associated cancers: here, the evidence for a preventive effect of soya or soya isoflavones is now very good.

Breast cancer

Breast cancer is the most common cancer in women and the second most common type of cancer. Breast cancer is much less common in Asian countries than in Europe and the USA [25]. The main factor in the different incidences of breast cancer is probably the high soya consumption in Asian countries compared to Western eating habits.

Concerns repeatedly arise that soya foods, due to their high phytoestrogen content, have an adverse effect on the risk of breast cancer or worsen the prognosis of breast cancer patients. However, extensive clinical and epidemiological data shows that these concerns are unfounded [12, 26]. Furthermore, the International and Austrian Menopause Society found in a 2016 consensus paper that high soya isoflavone intake is associated with a lower risk of breast cancer [27]. It is certain that soya products or soya isoflavones do not increase the risk of breast cancer [28]. On the contrary: systematic reviews and meta-analyses have shown a consistent preventive effect [29-34]. Chen et al. [30] evaluated 35 cohort and case-control studies and showed that the intake of soya isoflavones in Asian countries significantly reduce both the pre- and post-menopausal breast cancer risk. Xie et al. [31] came to comparable results, who in their meta-analysis assessed the dose-dependent effect of isoflavone intake on the risk of pre- and post-menopausal breast cancer in 22 observational studies. Nagata and colleagues [32] confirm the breast cancer preventive effect of high levels of soya consumption in Japanese women, Wu et al. [33] in Chinese women. The evaluations for women from Western countries, on the other hand, showed no correlation. This is probably due to the generally lower soya consumption and the associated low isoflavone intake. Surprisingly, the data from the Oxford arm of the EPIC study, which investigated the relationship between a vegetarian diet with a high soya content and breast cancer, did not show a reduction in breast cancer risk, although the amounts consumed were roughly the same as those of Asian cohorts [35]. Another EPIC evaluation of more than 330,000 women from ten European countries also found no correlation between breast cancer risk and soya or isoflavone intake [36].

These results may be due to the so-called early-intake hypothesis. According to this hypothesis, there is strong evidence that women who regularly eat soya products in childhood and adolescence reduce their risk of breast cancer particularly strongly [37-40]. In connection with the EPIC studies, this hypothesis suggests that the women observed only changed or increased their soya consumption when they reached adulthood.

Tofu and tempeh. Photograph: pixabay.com

Recurrences of breast cancer

For a long time, there was particular uncertainty among women with diagnosed breast cancer. Previous animal studies indicated that soya could stimulate cell growth in this case. Soya isoflavones were assumed to increase the body's estrogen concentrations through their estrogen-like effect and cause cancer cells to grow.

Meanwhile, it has been proven that soya isoflavones act as selective estrogen receptor modulators ("phytoSERMs"). They activate above all ERBeta, which has the task of protecting against excessive estrogen effects and slowing down the ERAlpha induced cell division.

The AICR [18] refers to the current report of the World Cancer Research Fund (WCRF) [41] to make clear that soya products are safe for cancer patients, and the evidence is consistent.

Prospective cohort studies even show that soya improves breast cancer prognosis in both Asian and North American women and reduces the recurrence rate [42, 43]. The best effect was observed with a daily intake of about 11 g soya protein or 30–70 mg isoflavones [42]. In two meta-analyses [44, 45] with over 11,000 and 6,300 breast cancer patients, respectively, soya consumption significantly reduced the frequency of recurrence and increased survival. No undesirable interactions with breast cancer drugs were observed. Smaller studies [46, 47] even suggest that soya products can support the effects of breast cancer drugs like tamoxifen and aromatase inhibitors like Anastrozole. The Austrian Menopause Association [27] therefore points out that breast cancer patients should be advised to take soya isoflavone-supplements.

Both in vitro and animal, as well as human studies, refute the amateurish idea that isoflavones from soya foods act like the body's own estrogen. Rather, they show anti-estrogenic effects and do not seem to influence endogenous estrogen level [34, 41].

In vitro and animal studies provide insight into the physiological mechanisms behind the protective effect of soya isoflavones. They can inhibit the proliferation of blood vessels in tumour tissue, compete with endogenous estrogens and show additional apoptosis-promoting, anti-angiogenetic, antioxidative and anti-inflammatory effects. This is mainly attributed to the preferential binding of soya isoflavones to ERBeta. In contrast to ERAlpha, these act as tumour suppressors and prevent cell growth. Activated ERAlpha, in contrast, promote cell proliferation [10, 32, 33].

Prostate cancer

Prostate cancer is the second most common cancer in men worldwide. As with breast cancer, the incidence is lowest in Asian countries [48]. A number of reviews and meta-analyses show a significant inverse relationship between the consumption of soya food and soya isoflavones and the incidences of prostate cancer for both Asians and Caucasians [49-56].

The exact mechanisms are still unclear. Androgens such as testosterone and androgen receptors (AR) play an important role in the development of prostate carcinoma. However, soya products and isolated soya isoflavones do not alter the testosterone concentrations in men but rather influence AR in several ways, which ultimately appears to induce apoptosis and inhibit cancer cell growth [56]. In addition, the described binding of preferred genistein to ERBeta and the associated antiproliferative and proapoptotic effect could also play a role (Figure 1) since this receptor is also expressed in epithelial prostate cells [3, 57]. Intervention studies in prostate cancer patients generally show that isoflavone intake slows down the increase in prostate-specific antigen (PSA) but does not significantly reduce the overall PSA concentration [58]. However, the evidence on this is still thin. PSA is a protein produced in the prostate and is an indicator of prostate cancer. Low levels of PSA are found in the blood of all men, while higher levels indicate that there is carcinoma [59].

Menopausal hot flashes

Hormonal changes during menopause cause instability in the body's temperature regulation [60]. Hot flashes are the most common menopausal symptoms, which is why women seek medical advice. About half of the women in Western countries choose complementary methods of treatment for menopausal symptoms [61].

Similar to breast cancer, the incidence of menopausal hot flashes is significantly lower among Asian women (18–25%) than among Caucasian women (70–85%). It is assumed that regular consumption of soya foods and the associated high intake of soya isoflavones, which are like estrogen, compensates for the hormone decline in menopause [8]. Soya could thus offer some of the advantages of the classic hormone replacement therapy, but without its undesirable side effects [10].

In 2013, a Cochrane meta-analysis did not yet come to a conclusive result [62]. In the meantime, however, several systematic reviews and meta-analyses [61, 63–67], as well as experts from Cochrane Austria [60], have confirmed the inverse relationship between soya isoflavone intake, genistein in particular, and the frequency and severity of hot flashes during and after menopause. Compared to placebo, these symptoms are about 20–25% less frequent [64, 65] and reduce the severity of symptoms by about 26% [64]. Clinical trials have generally investigated the effect of isolated isoflavone supplements. It is apparent that equol-producers benefit significantly better from the effects of soya isoflavones [66], which is why equol supplements are already being used in Asia to treat menopausal symptoms in women who are unable to produce equol [68].

There is also a dose-response relationship. Taku et al. [64] showed in their meta-analysis that higher-dose genistein supplements (>18.8 mg/day) were 50–200% more effective than lower-dose ones (<18.8 mg/day). Women with frequent hot flashes may benefit more from isoflavone intake than those with less frequent hot flashes [63].

However, the decrease in the frequency of hot flashes takes much longer compared to oestradiol administration. Soya isoflavones need at least 48 weeks to reach 80% of their maximum effect. This should also be considered for future study designs [64, 65, 69]. The North American Menopause Society (NAMS) has already pointed out the efficacy of isoflavones against hot flashes in its report for 2011 and has demonstrated this in predominantly Caucasian women in early menopause with at least four hot flashes per day [70]. In a comprehensive review, soya isoflavones were even more effective than many other non-hormonal drugs [69]. A position paper of the International and Austrian Menopause Society classifies the efficacy of isoflavones in menopausal hot flashes as evidence level 1. Soya isoflavones are therefore classified as a first-line approach for the treatment of menopausal hot flashes [27].

Concerns that the estrogen-like effect of soya isoflavones would have adverse effects in postmenopausal women are not supported by the present clinical and epidemiological evidence.

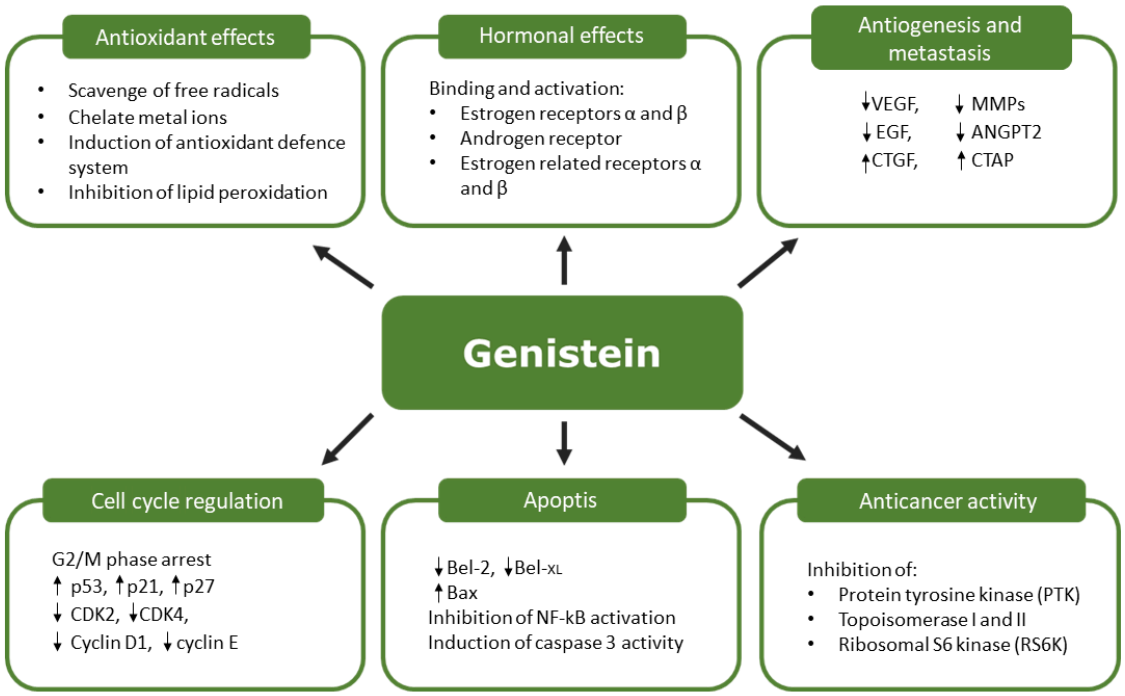

Figure 1. Overview of the effects of genistein (after [56])
↑ Upregulation; ↓ downregulation; ANGPT2 = Angiopoietin 2; CDK = Cyclin-dependent kinase; CTAP = connective tissue activation peptide; CTGF = connective tissue growth factor; EGF = Epidermal growth factor; MMPs = Matrix-metalloproteinases; NF-kB = nuclear factor Kappa B; VEGF = Vascular endothelial growth factor

Premenstrual syndrome

Premenstrual syndrome (PMS) covers a range of psychological and physical complaints in the late phase of the cycle, although the exact pathophysiology is unclear [11]. A few, mostly small studies suggest that isoflavones can modulate cycle-dependent estrogen fluctuations and relieve certain PMS symptoms [71-75]. Again, the ability to produce equol seems to play a role. Women suffering from PMS symptoms are less likely to be equol producers. Takeda et al. [76] showed that out of 98 women without PMS, 42% were equol producers, compared to 24% of 46 PMS patients. The authors conclude that the lack of equol-producing capacity is a risk factor for PMS. In a double-blind, placebo-controlled cross-over study [75] of 23 women with PMS over seven menstrual cycles, taking isolated soya protein (68 mg/day isoflavones) showed better results than placebo (milk protein): headaches, breast tenderness, cramps and swelling were less common in the isoflavone group. In contrast, a systematic review of 2009 [77] could not prove any correlation between soya consumption and PMS complaints.

Nagata et al. [78] and McFadyen et al. [79] also came to this conclusion but pointed out that soya consumption and compliance were possibly too low in their studies. Overall, the data on the effect of soya on PMS symptoms is weak. However, there is also no evidence that soya or isoflavones would increase PMS symptoms.

Cardiovascular diseases

Inconsistent data situation

The data on the effect of the consumption of soya foods on cardiovascular diseases is mixed. In the USA, the Food and Drug Administration (FDA) initiated a procedure in October 2017 [80] to re-evaluate the health claim on soya protein and its cholesterol-lowering effect, which was approved in 1999 [81]. In 2012, the European Food Safety Authority (EFSA) rejected the application for a comparable Article 14 health claim because the evidence for a clear cause-effect relationship was lacking [82]. Canada, on the other hand, approved such a claim in 2014 [83]. The situation is similarly inconsistent when reviewing epidemiological data, although most observed a reduced risk of cardiovascular disease, especially for (postmenopausal) women. For example, the Shanghai Women's Health Study [84], the WHO-CARDIAC Study [85], the Japan Public Health Center-Based (JPHC) Study Cohort I [86], the Ohsaki National Health Insurance (NHI) Cohort Study [87] and the Takayama Study [88]. A large case-control study [89] of Chinese women and men aged 60 years and older (about 21,000 cases and 11,000 controls) found that consumption of soya products at least four times a week or more compared with less than once a month was associated with both significantly reduced all-cause and myocardial infarction mortality. Again, the effect was more pronounced in women. Another Chinese case-control study (377 cases, 753 controls) [90] found no association between urinary isoflavone concentration (a biomarker of soya or soya isoflavone intake) and coronary heart disease (CHD), but the sub-analysis showed a significant inverse association between urinary equol concentration and cardiovascular risk in women.

In contrast, the evaluations of the Dutch EPIC cohort [91] and the Singapore Chinese Health Study [92] did not find an association between the consumption of soya products and cardiovascular risk. However, soya isoflavone intake in this cohort was extremely low (less than 1 mg/day). The Shanghai Men's Health Study [93] even found a positive association between soya product consumption and CHD incidence. Three current meta-analyses summarise the status of epidemiological studies on the association between soya consumption and cardiovascular diseases and do not allow a clear evaluation. In 2016, Lou et al. [94] could not prove any influence of soya consumption on the risk of myocardial infarction or CHD based on the analysis of five prospective cohort studies, while the analysis of data from six case-control studies showed a significant risk reduction for myocardial infarction (standardised relative risk [SSR] = 0.54; 95% confidence interval [95 % CI]: 0.34–0.87) and CHD (SSR = 0.66; 95 % CI: 0.56–0.77). The meta-analysis by Yan et al. from 2017 [95] was somewhat more comprehensive, with ten prospective cohorts and seven case-control studies. The authors found negative associations between soya consumption and cardiovascular disease (SSR = 0.84; 95% CI: 0.75–0.94), risk of myocardial infarction (SSR= 0.82; 95% CI: 0.68–0.99) and CHD (SSR = 0.83; 95% CI: 0.72–0.95). A sub-analysis indicated that the preventive effect was mainly observed in case-control studies and Asian populations. The meta-analysis by Namazi et al. [96] published in 2018 evaluated four cohort studies on soya consumption and cardiovascular mortality and found no significant association.

Tofu. Photograph: Wichai Bopatay (pixabay.com)

The data on the preventive effect of soya and soya foods on cardiovascular diseases is mixed but promising. In part, the effects can probably also be explained by replacing animal protein sources that often go hand in hand with it.

Attempts to explain inconsistency

The inconsistency of the results so far may have various reasons. For example, the individually different ability of the intestinal flora to produce the biologically more active metabolite equol from the soya isoflavone daidzein apparently plays a role. In studies that take this into account, equol producers (whose proportion is higher in Asian populations) often show more positive results or significant improvements in cardiovascular risk parameters [90, 97–102]. Some authors [103] even assume that equol is a key factor for the antiatherogenic effect of soya isoflavones. Menopausal status in women is also an influencing factor due to the estrogen-modulating effect of soya isoflavones [104].

Soya foods provide not only protein and isoflavones but numerous other ingredients that can influence heart health. Therefore, it is not surprising that the results of studies with isolated substances and those with traditional soya foods do not always coincide [105–107]. For example, although the cholesterol-lowering properties of soya are mainly attributed to the isoflavone content, other soya ingredients such as lecithin, phytosterols, saponins and β-glucans also have an influence [108, 109].

The hypolipidemic properties of soya peptides have also been demonstrated in various research designs. Many lower cholesterol and triglyceride levels and inhibit fat synthesis and storage. Several meta-analyses and systematic reviews show that soya products significantly reduce total and LDL cholesterol levels and to a clinically relevant extent [106, 110–119]. Soya isoflavones are also potent antioxidants, specifically reducing serum levels of oxidised LDL, which plays an essential role in the pathogenesis of atherosclerosis [102]. Another novel approach is provided by spermidine research (box "Hopeful spermidine"). Soya is rich in peptides with ACE-inhibiting effects. ACE, the angiotensin-converting enzyme, converts angiotensin I to the vasoconstrictor angiotensin II, thus raising blood pressure. In this way, regular soya consumption can contribute to blood pressure modulation, although the exact mechanisms are not yet clear [120, 121]. However, several meta-analyses support the hypotensive effect of soya ingredients [122–125].

Last but not least, preventive cardiovascular effects of soya foods can also be explained by the replacement of animal protein sources with soya products, which often goes hand in hand with this, changing the fatty acid pattern, cholesterol intake and fibre content of the diet, among other things [112–126].

Spermidine

Research on a substance that is contained in particularly high amounts in soya products is highly topical [127, 128]: spermidine. This natural polyamine has a life-prolonging effect and is associated with reduced mortality from cardiovascular and cancer diseases [129–131]. Spermidine is produced by all body cells and is found in particularly high concentrations in semen. In addition, there are two external sources: production by certain intestinal bacteria and ingestion via food [130]. Spermidine causes an epigenetic change in the cell nucleus so that autophagy processes are stimulated, and the cell nucleus programme is set to "youthful". In the sense of a self-cleaning process, defective or no longer needed cell components are broken down and recycled. Autophagy loses efficiency with advancing age, and disease-relevant deposits occur in the cells.

In 2018, an international team of researchers led by the Medical University of Innsbruck was able to prove this effect for humans for the first time. In a prospective cohort study with 829 participants, subjects who consumed at least 80 μmol of spermidine per day in their diet had a significantly lower mortality risk. The survival advantage of a high-spermidine diet compared to a low-spermidine diet (less than 60 μmol/day) over the 20-year observation period was around five years [132].

Fermentation processes further increase spermidine concentrations, so fermented soya products are particularly good sources [127, 130] and have been shown to increase blood levels of spermidine when consumed regularly [133].

Allergy

Despite opinions contrary in large parts of the population, food allergies have not increased in the last one to two decades. According to this, the lifetime prevalence of medically diagnosed food allergies for adults of all age groups in Germany remained at the same level from 1998 to 2011 and is 4.7% (95% CI: 4.1–5.4) [134]. The frequency of food allergies is also usually overestimated. For example, a recent survey in the USA [135] showed that about 19% of Americans self-report that they have a food allergy, but in fact, only about 11% of respondents have convincing symptoms and medical histories, and only 5% have been diagnosed with a food allergy by a doctor. The most common food allergens were crustaceans and shellfish (2.9%), cow's milk (1.9%), peanuts (1.8%), nuts (1.2%) and fish (0.9%). Soya, at 0.6%, was still behind eggs and wheat (0.8% each) and about the same as walnuts and hazelnuts.

Soya allergy

Just like other foods, soya can also trigger an allergy. Although soybeans, together with cow's milk, eggs, wheat, peanuts, nuts, fish and seafood, are among the foods that most frequently trigger allergies, there are hardly any reliable prevalence data. A meta-analysis [136] of data from Europe conducted in 2012 showed a prevalence of 0.3% (basis: provocation test) or 0.4% (basis: self-report) for soya allergy across all age groups. In 2013, a review commissioned by EFSA [137] showed that only one study from Sweden on the prevalence of soya allergy was available for European countries, which was not based on self-reporting but clinical diagnosis. According to this, the prevalence was 0.2% in one-year-old children and 0.8% in 4 to 8-year-olds. Four studies with clinical diagnoses from other countries observed prevalences between 0% (infants and toddlers up to 2 years in Israel) and 0.6% (in 11 to 13-year-olds in the USA). In childhood, soya allergy disappears spontaneously in many cases – in about half by school age. By the age of ten, about 70% of affected children have developed soya tolerance [138].

Immediate type

In so-called immediate-type allergy, type E immunoglobulins (IgE antibodies) react with allergens and trigger allergic reactions. The presence of IgE antibodies is an absolute prerequisite for the clinical expression of an allergy, i.e., the symptoms that occur. This is called allergic sensitisation. However, allergic sensitisation can also be present without symptoms occurring on contact with the allergen. In Germany, 25.5% (95% CI: 24.2–26.9) of adults and 20% of children and adolescents are sensitised to at least one food allergen, but less than 5% are affected by a clinical allergy [139].

Cross-sensitivity

Pollen-associated food allergy to soya protein is a special form of soya allergy that requires primary sensitisation to pollen, especially birch. The main allergen of soya (rGly m 4) is very similar in structure to that of birch (rBet v 1). Therefore, cross-allergies with soya can occur in birch pollen allergy sufferers. The prevalence of sensitisation to rGly m 4 is about 10% in Germany. The prevalence of sensitisation to soybeans is 3.7%, significantly lower than the prevalence of sensitisation to other commonly consumed foods such as carrots, celery, tomatoes, potatoes or rice (Figure 2) [139].

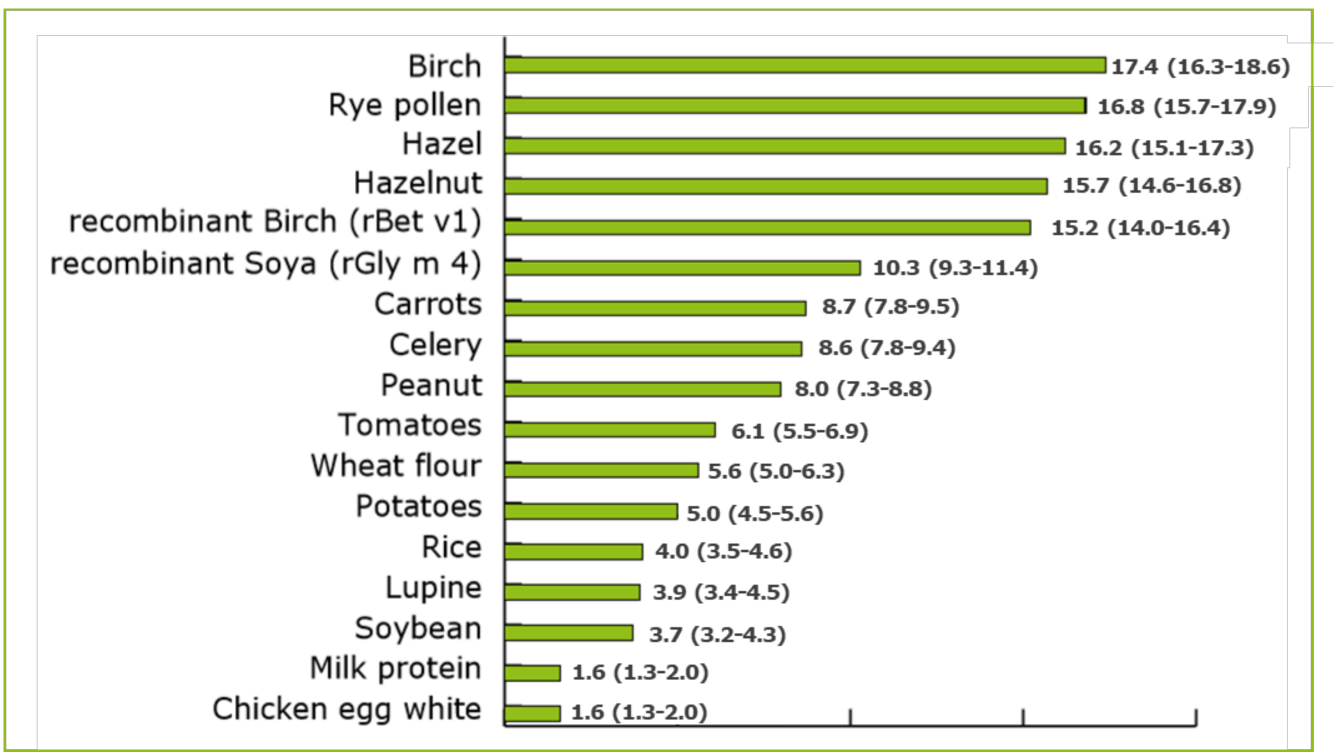

Figure 2. Prevalence (in percent, weighted; 95 % confidence intervals in parentheses) of sensitisation to selected allergens in the German adult population (DEGS1, n = 7 025) (mod. after [139])

Whether birch pollen allergy sufferers react with complaints to soya products is closely related to the type of food and its processing. A Leipzig survey [140] showed that 72% of birch pollen allergy sufferers were also sensitised to Gly m 4, but only some had problems. According to interviews, soya drinks seem to lead to immediate reactions, as large amounts of low-processed soya protein are supplied in a short time. In many other soya products, fermentation and processing processes lead to complete or partial hydrolysis of the allergen so that the allergenicity decreases significantly. Swiss researchers [141] arrived at comparable figures: 71% of a group of birch pollen allergy sufferers with high Bet v 1 values also had specific IgE for the main soya allergen Gly m 4. In a telephone survey, 70% of the patients reported consuming soya products, but only 9.6% experienced symptoms after consumption. The concentration of Gly m 4 increases with the maturity stage and the storage time of the soybeans. Heating, however, significantly reduces the content. In particular, the combination of heat and fermentation seems to be particularly effective and reduces the IgE binding capacity for the allergen by 65–99%. In highly fermented foods such as soya sauce and miso, but also roasted soybeans, the allergen is usually no longer detectable. The highest levels of Gly m 4 were found in soya drinks based on soya protein isolates and soya protein powder [141, 142]. Therefore, allergy sufferers can consume most products with soya components without causing complaints [143].

Due to cross-allergies, birch pollen allergy sufferers also react to numerous other foods such as apples, strawberries, hazelnuts, carrots, and celery. Therefore, the Federal Institute for Risk Assessment rejects a warning label on soya products, as some call for [144], especially since the EU Allergen Regulation already requires that packaged food must state whether it contains soya. However, nutritionists and doctors should point out the possibility of such cross-allergies to patients with known birch pollen allergies and advise them accordingly when choosing and preparing food.

Atopic dermatitis

Together with egg, cow's milk, peanut and wheat, soya is one of the foods most likely to trigger atopic dermatitis in children – a chronic, intermittent, inflammatory skin condition. Children with atopic dermatitis react to soya protein in 2–4.4% of cases. However, severe anaphylactic shocks are rare [144]. Adolescents with atopic dermatitis show sensitisation to soya protein in 30% of cases. However, according to a Czech study of 175 patients, less than 3% showed clinical symptoms when eating soya products [145].

Pills – medication. Photograph: pixabay.com

Soya protein – like some herbs, fibre, calcium supplements or medications – affects the absorption of the T4 drug levothyroxine. Therefore, if thyroxine is taken and soya products are consumed regularly, the dose of medication may need to be increased.

Thyroid gland

Soya has repeatedly been associated with negative effects on thyroid function, and even thyroid cancer, especially in people with subclinical hypothyroidism (latent hypothyroidism). In this case, the TSH (thyroid-stimulating hormone) level is elevated, but the thyroid hormones T3 and T4 are within the normal range. It is estimated that about 5 out of 100 people have latent hypothyroidism. In adults, the most common trigger is Hashimoto's disease, an autoimmune disorder.

As a rule, subclinical hypothyroidism is not associated with any symptoms. In the course of time, about every second to third person with this clinical picture develops a manifest form of the disease. The suspicion that soya isoflavones could play a role in this is not supported by meaningful long-term studies, according to the summary of the experts from the Department of Evidence-Based Medicine and Clinical Epidemiology at the Danube University Krems and from Cochrane Austria [146].

Among other things, observations from animal and cell studies triggered concerns. In these studies, the soya isoflavones genistein and daidzein were able to inhibit thyroid peroxidase activity, which is necessary for the synthesis of thyroid hormones. However, this inhibition is reversible in the presence of iodine [147]. Isoflavones compete with tyrosine in iodination and can thus theoretically reduce the synthesis of thyroid hormone. However, clinical studies show that the extent of isoflavone iodination is not clinically relevant [120, 148]. A recent review [28] points out that results of studies on the effect of isoflavones on thyroid function that do not consider the iodine status of the test persons are questionable.

From a preventive point of view, risk groups – persons with insufficient iodine supply, latent hypothyroidism and genetically determined thyroid dysfunction – are advised against taking high-dose isoflavone supplements. However, the consumption of conventional soya foods in quantity common in Asian countries and corresponds to the intake of 50 mg/day of soya isoflavones is considered safe [28]. Patients who take thyroid hormones due to hypothyroidism may have to increase the necessary dose of medication if they consume soya foods regularly. However, this is not because of a direct effect on the thyroid gland, but because soya protein – like some herbs, dietary fibres, calcium supplements or medicines – can influence the absorption of the T4 drug levothyroxine. It is usually sufficient to slightly increase the dosage of the replacement hormone to compensate for the absorption inhibition [120].

There is no evidence that soya isoflavones affect thyroid function in people with normal thyroid function and adequate iodine status [3, 13, 28, 149–152]. Claims that soya promotes the development of thyroid cancer have no scientific basis. Instead, the opposite may be true: In the San Francisco Bay Thyroid Cancer Study, consumption of soya foods was associated with a lower risk of thyroid cancer [153].

Osteoporosis

Menopause is often accompanied by lower bone mineralisation due to the drop in estrogen. Postmenopausal women, therefore, have an increased risk of osteoporosis and fractures. Soya products can have a preventive effect here by contributing to the maintenance of bone mineral density (BMD), as the authors of several (systematic) reviews from recent years emphasise [3, 10, 27, 120, 154–156].

Large prospective cohort studies, such as the Shanghai Women's Health Study [157] and the Singapore Chinese Health Study [158], observed a significant inverse association between soya product intake and fracture risk. A meta-analysis found that soya isoflavone supplements significantly increased bone mineral density and decreased bone resorption markers. The effects were particularly pronounced in postmenopausal women and at doses above 75 mg/day [159]. Isoflavone mixtures, as also found in natural soya foods, are apparently more effective than isolated genistein [160]. The results from epidemiological and clinical studies are promising. Nevertheless, the evidence is currently insufficient to make concrete recommendations. Several factors such as the dosage of isoflavone supplements, isolated soya isoflavones versus soya foods, the ability to produce equol, study duration, population, age, gender, selected endpoints or menopausal status make comparisons and interpretations difficult [161–164].

Testosterone levels and "feminisation"

Soya consumption for men: Epidemiological studies in populations with high soya consumption as well as clinical studies with partly high isoflavone doses do not give cause for concern.

In social media, soya is often attributed with a feminising effect on men, a negative influence on testosterone levels and libido and fertility disorders. Results from animal studies and individual case reports support these fears [165, 166].

A crossover study of 99 men [167] found an inverse relationship between soya consumption and sperm concentration, particularly in overweight and obese men, and when soya consumption was at the upper end of the distribution (70th and 90th percentiles). Relatively, the subjects were selected from couples with fertility disorders. Moreover, the data on soya consumption were not detailed, and isoflavone intake was estimated by food frequency questionnaires and not determined by blood analysis. In contrast, soya consumption had no influence on sperm motility, sperm morphology or ejaculate volume.

In contrast, a pilot study [168] – 48 men with impaired semen quality and 10 controls – concluded that a higher intake of the two most important soya isoflavones, genistein and daidzein, was associated with significantly better semen quality (sperm count and motility). And the authors of a meta-analysis [169] found no correlation between the intake of soya protein or isoflavones and parameters of testosterone levels.

Although the scientific data is thin and partly contradictory [170], observations from epidemiological studies in populations with high soya consumption as well as clinical studies with partly high doses of isoflavones do not give cause for concern [3, 171, 172].

Child nutrition

Some paediatricians advise concerned parents against soya products in childhood. According to the Federal Centre for Nutrition (BZfE), however, there is nothing to be said against the occasional consumption of soya products as part of a balanced diet, even in this age group. The experts only point out that soya products that are to serve as a substitute for cow's milk should be enriched with calcium to guarantee the calcium supply [173].

So far, only a few, mostly small studies, exist on the influence of isoflavone intake from soya in children. Their results indicate that soya consumption in childhood has no undesirable effects, for example, on the sex hormone status or sexual maturity [174].

For women, the so-called "early intake" hypothesis rather assumes that the risk of breast cancer is reduced if soya products are already regularly included in the diet during childhood and adolescence. This is supported by several case-control studies that show a strong and consistent inverse association between soya consumption in childhood and later breast cancer risk [37, 39, 175, 176].

In a recent US study [177] with 248 male adolescents between 12 and 18 years of age, the intake of soya isoflavones and the time of onset of sexual maturity was assessed. The total isoflavone intake was in a wide range between 0.8 and 54.9 mg/day. Sexual maturity tended to occur up to five months earlier in boys with moderate and high soya consumption than in the low soya consumption group but was still within the normal range. The same group of authors [178] came to similar conclusions in 2014 in 339 girls aged 12–18 years and found no effect of soya consumption on the timing of the onset of first menstruation. A study published in 2018 [179] investigated the influence of soya protein on sexual maturity in 51 prepubertal children using Tanner stages. For a period of one year, 29 of the subjects received 45 g of a commercially available soya protein supplement daily. This corresponded to 0.13 mg isoflavones per kg body weight and day. The results showed no difference between the verum and placebo groups.

Antinutritive ingredients

Raw soybeans contain antinutritive ingredients such as protease inhibitors (inhibit protein digestion), lectins (especially soybean agglutinin [SBA], which can affect the mucosa of the small intestine and inhibit disaccharidases and proteases) and phytates (chelating agents that reduce the bioavailability of certain minerals, especially calcium, zinc and iron).

Soybeans can therefore not be eaten raw, and all soya foods are heated during their production. The majority of the antinutritive ingredients are also inactivated or their content is significantly reduced in the course of other processing steps. For example, heat (boiling, roasting) inactivates protease inhibitors and lectins. The germination process of soybean sprouts, soaking (e.g., during tofu or soya milk production) and fermentation reduce the phytate content in particular and thus improve the bioavailability of minerals [180]. During fermentation, but also through soaking and cooking, the oligosaccharide content decreases, responsible for gastrointestinal gas formation (flatulence) [181, 182].

The content of antinutritive ingredients in raw soybeans is reduced by heating, germination and fermentation. Photograph: photo-ac.com

Ecological aspects

EAT-Lancet Commission

Since the report of the EAT-Lancet Commission [183] at the beginning of 2019, it has become clear that the menu in wealthy countries must change not only for health reasons but also for ecological reasons. Our eating habits are already a risk to climate stability. 37 experts from 16 countries, together with the journal The Lancet, have for the first time presented comprehensive and detailed science-based goals for a diet that protects both human health and the planet. Based on average eating habits in this country, these include doubling the proportion of vegetables and halving the consumption of red meat and sugar [184]. A study by the Institute for Ecological Economics at the Vienna University of Economics and Business Administration on behalf of WWF Austria [185] has calculated that around a quarter of the ecological footprint of every Austrian is attributable to diet. Meat is the largest factor – accounting for only 9% of the volume of food consumed, it causes 43% of greenhouse gas emissions.

Vegetable protein sources such as soya play a special role as an alternative to meat in this context. The experts of the EAT-Lancet Commission recommend an average of 25 g of soya per day as a source of protein to reduce the amount of meat in the diet [183].

Nitrogen fertiliser

The soya plant is an ecologically valuable and very grateful crop: due to the symbiosis with nodule bacteria in its roots, it can bind nitrogen from the air and normally manages without nitrogen fertiliser. In this respect, soya is more efficient than other legumes. Soya plants improve the soil structure by enriching the soil with humus and loosening it up through their distinctive root system. They are also particularly suitable as a preceding crop in crop rotation, as they prepare the soil for subsequent plants and reduce the need for nitrogen fertiliser [191].

Soya cultivation

The EU's main producing countries and trading partners for soya are the USA, Brazil and Argentina. In these countries, soya is often grown in large monocultures. For this purpose, considerable areas of rainforest are cleared every year, and grasslands and savannahs are destroyed. This is associated with high greenhouse gas emissions, increasing soil erosion and water pollution, reduced biodiversity and social conflicts around land use rights in the countries of origin [186]. According to estimates, over 80% of the soya grown worldwide is genetically modified. In the main cultivation countries, the USA and Brazil, 93% and 94% respectively genetically modified soya is grown, and in Argentina, the figure is as high as 100%. An estimated 80% worldwide, the majority, ends up in the trough as animal feed, mainly pig and poultry fattening. The rest goes into the production of biodiesel and cosmetic products, and only about 5% of the global soya harvest is directly processed into food [187]. In the EU, genetically modified soybeans are not approved for cultivation.

Consumers cannot see whether meat, eggs, or milk products come from animals fed with genetically modified soya. This is because there is no legal obligation to label such products. For this reason, private initiatives such as the Europe-wide Donau Soja association are committed to ensuring that not only food soya but also soya feed increasingly comes from European production. In Austria, milk and chicken meat production are now entirely GMO-free due to the voluntary commitment of producers. This applies to organic food anyway due to the EU organic regulation.

Soy from Europe and in D-A-CH

Currently, the protein gap in the EU is very large, with demand for plant protein sources significantly exceeding the EU's own production. Therefore, the European Parliament adopted a European strategy for the promotion of protein crops in April 2018. The demand for plant protein in Europe is growing strongly and amounted to around 27 million tonnes of crude protein in 2016/2017. 17 million tonnes of this had to be imported, 13 million tonnes of which was soy-based alone.

The self-sufficiency level for soy in the EU was just 5% in 2018, with a production of 2.8 million tonnes [188]. While Europe will never become self-sufficient in protein crops, increased independence from soy imports is one of the most important issues for the future of European agriculture. In addition, regional cultivation also stands for high environmental and quality standards as well as freedom from genetic engineering.

Over the past two decades, numerous soy farmers from Germany and Austria have recognised this opportunity: The areas under cultivation are steadily increasing (Figure 3) [189]. In Switzerland, soy cultivation is difficult due to climatic conditions. But the small country is a pioneer in other ways: as the initiator of the Basel criteria for responsible soy cultivation and as the only country in the world that imports only sustainably certified and GMO-free soy. And: In the last four years, Switzerland has been able to increase the share of soy from Europe from 1 to 40% [190].

Initiatives such as the Deutsche Sojaförderring e. V. (www.sojafoerderring.de), the Donau Soja association (www.donausoja.org), the Verein Soja aus Österreich (www.soja-aus-oesterreich.at) and the Soja Netzwerk Schweiz (www.sojanetzwerk.ch) campaign for sustainable soy cultivation in Europe. Unfortunately, far too few consumers know that soy grows in their region without having to clear virgin forests.

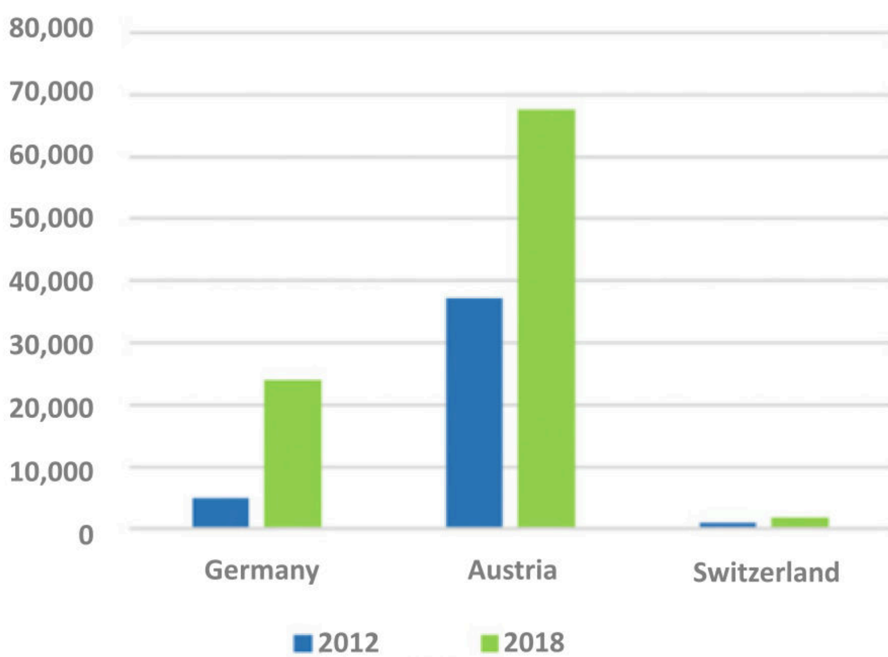

Figure 3. Soybean cultivation areas in D-A-CH in ha (according to [117])

Conclusion

Concerns about the consumption of soya food, which are frequently voiced, especially in the lay media, are unjustified: There is no scientific evidence that soya would increase the risk of hormone-dependent cancers or worsen PMS symptoms. On the contrary, regular soya consumption in quantities common in Asia is even associated with positive effects in this respect.

High consumption of soya or an appropriate intake of soya isoflavones very probably even reduces the risk of breast and prostate cancer, improves the prognosis for breast cancer patients, relieves menopausal hot flashes, and there are indications that women with premenstrual syndrome could also benefit from soya isoflavones.

The data on the preventive effect of soya on cardiovascular diseases is inconsistent but promising. Some influencing variables and effective ingredients such as the isoflavone metabolite equol or the polyamine spermidine have only recently become known and were therefore not considered in older study designs. In post-menopausal women, the regular consumption of soya foods contributes to bone preservation. Men need not worry about the alleged "feminising" effects of the phytoestrogens typical of soya. And parents should whet young girls' appetites for soya foods because this is apparently particularly effective in reducing their later risk of breast cancer. Moreover, data to date do not give cause for concern, either in girls or boys, that soya isoflavones could have undesirable effects on sex hormone status or sexual maturity.

Like other foods, soya protein can also be allergenic. Of particular relevance for nutritional counselling is a possible cross-allergy with birch pollen and the advice for patients with hypothyroidism treated with medication to avoid high-dose isoflavone preparations. Antinutritive ingredients do not play a practically relevant role due to the processing procedures in the production of soya foods.

In the future, the importance of soya products in the context of a health-promoting and ecologically compatible diet is likely to increase significantly in our latitudes as well. Europe is preparing intensively for this with a strategy to promote protein crops in the region.

Literature

1. Tucker, K.L., Qiao, N., Maras, J.E., 2010. Simulation with soya replacement showed that increased soya intake could contribute to improved nutrient intake profiles in the U.S. population. J. Nutr. 140: 2296S-2301S
2. Reinwald, S., Akabas, S.R., Weaver, C.M., 2010. Whole versus the piecemeal approach to evaluating soya. J. Nutr. 140: 2335S-2343S
3. Rizzo, G., Baroni, L., 2018. Soya, soya foods and their role in vegetarian diets. Nutrients 10: 43
4. Mörixbauer, A., 2019. Own data, content analysis of print, online and social media clippings of a commissioned media monitoring in the period October to December 2018 [unpublished].
5. Messina, M., 2016. Soya and health update: re-evaluation of the clinical and epidemiologic literature. Nutrients 8: 754
6. Daniel, K.T., 2016. Soja - The whole truth. The dark sides of "healthy" nutrition. Kopp, Rottenburg
7. Ideno, Y., Hayashi, K., Nakajima-Shimada, J. et al., 2018. Optimal cut-off value for equol-producing status in women: The Japan Nurses' Health Study urinary isoflavone concentration survey. PLoS ONE 13: e0201318
8. Xiao, Y., Zhang, S., Tong, H. et al., 2017. Comprehensive evaluation of the role of soya and isoflavone supplementation in humans and animals over the past two decades. Phytother. Res. 32: 384-394
9. Izumi, T., Piskula, M.K., Osawa, S. et al., 2000. Soya isoflavone aglycones are absorbed faster and in higher amounts than their glucosides in humans. J. Nutr. 130: 1695-1699
10. Egarter, C., 2018. Update on isoflavones in the menopause. First choice remedy for mild climacteric complaints. J. Gynaecol Endocrinol [published online: 6 March 2018]
11. Takeda, T., Shiina, M., Chiba, Y., 2018. Effectiveness of natural S-equol supplement for premenstrual symptoms: protocol of a randomized, double-blind, placebo-controlled trial. BMJ Open 8: e023314
12. Messina, M., 2016. Impact of soya foods on the development of breast cancer and the prognosis of breast cancer patients. Forsch Komplementmend 23: 75-80
13. EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), 2015. Risk assessment for peri- and post-menopausal women taking food supplements containing isolated isoflavones. EFSA Journal 13: 4246
14. Setchell, K.D.R., Clerici, C. 2010. Equol: pharmacokinetics and biological actions. J. Nutr. 140: 1363S-1368S
15. Pilsáková, L., Riecansk'y, I., Jagla, F., 2010. The physiological actions of isoflavone phytoestrogens. Physiol. Res. 59: 651-664
16. Haron, H., Ismail, A., Azlan, A. et al., 2009. Daidzein and genestein contents in tempeh and selected soya products. Food Chemistry 115: 1350-1356
17. Coward, L., Smith, M., Kirk, M. et al., 1998. Chemical modification of isoflavones in soyfoods during cooking and processing. Am. J. Clin. Nutr. 68(6 Suppl): 1486S-1491S
18. American Institute for Cancer Research, 2018. Foods that fight cancer - soya. URL: www.aicr.org/foods-that-fight-cancer/soya. html Zugriff 11.02.19
19. Yu, Y., Jing, X., Li, H. et al., 2016. Soya isoflavone consumption and colorectal cancer risk: a systematic review and meta-analysis. Sci. Rep. 6: 25939
20. Tse, G., Eslick, G.D., 2016. Soya and isoflavone consumption and risk of gastrointestinal cancer: a systematic review and meta-analysis. Eur. J. Nutr. 55: 63-73
21. Lu, D., Pan, C., Ye, C. et al., 2017. Meta-analysis of soya consumption and gastrointestinal cancer risk. Sci. Rep. 7: 4048
22. Weng, K.G., Yuan, Y.L., 2017. Soya food intake and risk of gastric cancer. A dose-response meta-analysis of prospective studies. Medicine 96: e7802
23. Zhang, G.Q., Chen, J.L., Liu, Q. et al., 2015. Soya intake is associated with lower endometrial cancer risk. Medicine 94: e2281
24. Zhong, X.S., Ge, J., Chen, S.W. et al., 2016. Association between dietary isoflavones in soya and legumes and endometrial cancer: a systematic review and meta-analysis. J. Acad. Nutr. Diet. 118: 637-651

25. Global Cancer Observatory, World Health Organization (WHO), International Agency for Research on Cancer, 2019. Cancer fact sheet breast cancer. URL: http://gco.iarc.fr/ today/data/factsheets/cancers/20-Breast- fact-sheet.pdf Zugriff 16.02.19

26. Eakin, A., Kelsberg, G., Safranek, S., 2015. Does high dietary soya intake affect a woman's risk of primary or recurrent breast cancer? Fam Pract 64: 660-662

27. Schmidt, M., Arjomand-Wölkart, K., Birkhäuser, M.H. et al., 2016. Soya isoflavonoid as the first choice for vasomotor complaints during menopause. Gynecol. Endocrinol. 32: 427-430

28. Hüser, S., Guth, S., Joost, H.G. et al., 2018. Effects of isoflavones on breast tissue and the thyroid hormone system in humans: a comprehensive safety evaluation. Archives of Toxicology 92: 2703-2748

29. Dong, J.Y., Qin, L.Q., 2011. Soya isoflavones consumption and risk of breast cancer incidence or recurrence: a meta-analysis of prospective studies. Breast Cancer Res. Treat. 125: 315-323

30. Chen, M., Rao, Y., Zheng, Y. et al., 2014. Association between soya isoflavone intake and breast cancer risk for pre- and post-menopausal women: a meta-analysis of epidemiological studies. PLoS ONE 9: e89288

31. Xie, Q., Chen, M.L., Quin, Y. et al., 2013. Isoflavone consumption and risk of breast cancer: a dose-response meta-analysis of observational studies. Asia Pac. J. Clin. Nutr. 22: 118-128

32. Nagata, C., Mizoue, T., Tanaka, K. et al., 2014. Soya intake and breast cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. Jpn. J. Clin. Oncol. 44: 282-295

33. Wu, Y.C., Zheng, C., Sun, J.J. et al., 2015. Meta-analysis of studies on breast cancer risk and diet in Chinese women. Int. J. Clin. ExpMed. 8: 73-85

34. Fritz, H., Seely, D., Flower, G. et al., 2013. Soya, red clover, and isoflavones and breast cancer: a systematic review. PLoS ONE 8: e81968

35. Travis, R.C., Allen, N.E., Appleby, P.N. et al., 2008. A prospective study of vegetarianism and isoflavone intake in relation to breast cancer risk in British women. Int. J. Cancer 122: 705-710

36. Zamora-Ros, R., Ferrari, P., González, C.A. et al., 2013. Dietary flavonoid and lignan intake and breast cancer risk according to menopause and hormone receptor status in the European Prospective Investigation into Cancer and Nutrition (EPIC) Study. Breast Cancer Res. Treat. 139: 163-176

37. Korde, L.A., Wu, A.H., Fears, T. et al., 2009. Childhood soya intake and breast cancer risk in Asian American women. Cancer Epidemiol. Biomarkers Prev. 18: 1050-1059

38. Lee, S.A., Shu, X.O., Li, H. et al., 2009. Adolescent and adult soya food intake and breast cancer risk: results from the Shanghai Women's Health Study. Am. J. Clin. Nutr. 89: 1920-1926

39. Wu, A.H., Wan, P., Hankin, J. et al., 2002. Adolescent and adult soya intake and risk of breast cancer in Asian-Americans. Carcinogenesis 23: 1491-1496

40. Baglia, M.L., Zheng, W., Li, H. et al., 2016. The association of soya food consumption with the risk of subtype of breast cancers defined by hormone receptor and HER2 status. Int. J. Cancer. 139: 742-748

41. Douglas, C.C., Johnson, S.A., Arjmandi, B.H., 2013. Soya and its isoflavones: the truth behind the science in breast cancer. Anti-Cancer Agents in Medicinal Chemistry 13: 1178-1187

42. World Cancer Research Fund, American Institute for Cancer Research, 2018. Diet, nutrition, physical activity and cancer: a global perspective. Continuous update project expert report 2018. URL: dietandcancerreport.org Zugriff 16.02.19

43. Shu, X.O., Zheng, Y., Cai, H. et al., 2009. Soya food intake and breast cancer survival. JAMA 302: 2437-2443

44. Nechuta, S.J., Caan, B.J., Chen, W.Y. et al., 2012. Soya food intake after diagnosis of breast cancer survival: an in-depth analysis of combined evidence from cohort studies of US and Chinese women. Am. J. Clin. Nutr. 96: 123-132

45. Zhang, F.F., Haslam, D.E., Terry, M.B. et al., 2017. Dietary isoflavone intake and all-cause mortality in breast cancer survivors: The Breast Cancer Family Registry. Cancer 123: 2070-2079

46. Chi, F., Wu, R., Zeng, Y.C. et al., 2013. Post-diagnosis soya food intake and breast cancer survival: a meta-analysis of cohort studies. Asian Pacific J. Cancer Prev. 14: 2407-2412

47. Kang, X., Zhang, Q., Wang, S. et al., 2010. Effect of soya isoflavones on breast cancer recurrence and death for patients receiving adjuvant endocrine therapy. CMAJ 182: 1857–1862

48. Global Cancer Observatory, World Health Organization (WHO), International Agency for Research on Cancer, 2019. Cancer fact sheet prostate cancer. URL: http://gco.iarc. fr/today/data/factsheets/cancers/27-Pros tate-fact-sheet.pdf Zugriff 16.02.19

49. Yan, L., Spitznagel, E.L., 2005. Meta-analysis of soya food and risk of prostate cancer in men. Int. J. Cancer 117: 667-669

50. Yan, L., Spitznagel, E.L., 2009. Soya consumption and prostate cancer risk in men: a revisit of a meta-analysis. Am. J. Clin. Nutr. 89: 1155-1163

51. Hwang, Y.W., Kim, S.Y., Jee, S.H. et al., 2009. Soya food consumption and risk of prostate cancer: a meta-analysis of observational studies. Nutr. Cancer 61: 598-606

52. van Die, M.D., Bone, K.M., Williams, S.G. et al., 2014. Soya and soya isoflavones in prostate cancer: a systematic review and meta-analysis of randomized controlled trials. BJU Int. 113: E119-E130

53. He, J., Wang, S., Zhou, M. et al., 2015. Phytoestrogens and risk of prostate cancer: a meta-analysis of observational studies. World J. Surg. Oncol. 13: 231

54. Zhang, M., Wang, K., Chen, L. et al., 2016. Is phytoestrogen intake associated with decreased risk of prostate cancer? A systematic review of epidemiological studies based on 17,546 cases. Andrology 4: 745-756

55. Zhang, Q., Feng, H., Qluwakemi, B. et al., 2017. Phytoestrogens and risk of prostate cancer: an updated meta-analysis of epidemiological studies. Int. J. Food. Sci. Nutr. 68: 28-42

56. Sivonová, M.K., Kaplan, P., Tatarkova, Z. et al., 2019. Androgen receptor and soya isoflavones in prostate cancer (Review). Mol. Clin. Oncol. 10: 191-204

57. Sak, K., 2017. Current epidemiological knowledge about the role of flavonoids in prostate carcinogenesis. Exp. Oncol. 39: 98-105

58. Zhang, H.Y., Cui, J., Zhang, Y. et al., 2016. Isoflavones and prostate cancer: a review of some critical issues. Chin. Med. J. 129: 341–347

59. Applegate, C.C., Rowles, J.L., Ranard, K.M. et al., 2018. Soya consumption and the risk of prostate cancer: an updated systematic review and meta-analysis. Nutrients 10: E40

60. Harlfinger, J., Kerschner, B., Mahlknecht, P., 2015. Menopause: Using plant power against hot flushes? medizin-transparent ent.at of 27 August 2015, a project of Cochrane Austria. URL: www.mediz in-transparent.at/phytohormone-change complaints Access 16.02.19

61. Franco, O.H., Chowdhury, R., Troup, J. et al., 2016. Use of plant-based therapies and menopausal symptoms: a systematic review and meta-analysis. JAMA 315: 2554-2563

62. Lethaby, A., Marjoribanks, J., Kronenberg, F. et al., 2013. Phytoestrogens for menopausal vasomotor symptoms. Cochrane Database Syst. Rev. 12: CD001395

63. Howes, L.G., Howes, J.B., Knight, D.C., 2006. Isoflavone therapy for menopausal flushes: a systematic review and meta-analysis. Maturitas 55: 203-211

64. Taku, K., Melby, M.K., Kronenberg, F. et al., 2012. Extracted or synthesized soybean isoflavones reduce menopausal hot glash frequency and severity: systematic review and meta-analysis of randomized controlled trials. Menopause 19: 779-790

65. Li, L., LV, Y., Xu, L. et al., 2015. Quantitative efficacy of soya isoflavones on menopausal hot flashes. Br. J. Clin. Pharmacol. 79: 593- 604

66. Thomas, A.J., Ismail, R., Taylor-Swanson, L. et al., 2014. Effects of isoflavones and amino acid therapies for hot flashes and co-occurring symptoms during the menopausal transition and early postmenopause: a systematic review. Maturitas 78: 263-276

67. Chen, M.N., Lin, C.C., Liu, C.F., 2015. Efficacy of phytoestrogens for menopausal symptoms: a meta-analysis and systematic review. Climacteric 18: 260-269

68. Aso, T., Uchiyama, S., Matsumura, Y. et al., 2012. A natural S-equol supplement alleviates hot flushes and other menopausal symptoms in equol nonproducing postmenopausal Japanese women. J. Womens Health (Larchmt) 21: 92-100

69. Li, L., Xu, L., Wu, J. et al., 2016. Comparative efficacy of nonhormonal drugs on menopausal hot flashes. Eur. J. Clin. Pharmacol. 72: 1051-1058

70. Clarkson, T.B., Utian, W.H., Barnes, S. et al., 2011. The role of soya isoflavones in menopausal health: report of The North American Menopause Society/Wulf H. Utian Translational Science Symposium in Chicago, IL (October 2010). Menopause 18: 732-753

71. Ingram, D.M., Hickling, C., West, L. et al., 2002. A double-blind randomized controlled trial of isoflavones in the treatment of cyclical mastalgia. Breast 11: 170-174

72. Ishiwata, N., Uesugi, S., Uehara, M. et al., 2004 Effects of soya isoflavones on premenstrual syndrome. Poster Abstract (S. 1281S). Fifth International Symposium on the Role of Soya in Preventing and Treating Chronic Disease. J. Nutr. 134: 1248S-1293S

73. Kim, H.W., Kwon, M.K., Kim, N.S. et al., 2006. Intake of dietary soya isoflavones in relation to perimenstrual symptoms of Korean women living in the USA. Nurs. Health. Sci. 8: 108-113

74. Kim, H.W., Hil, J.M., 2007. A study on isoflavones intake from soya foods and perimenstrual symptoms. Taehan Kanho Hakhoe Chi. 37: 276-285

75. Bryant, M., Cassidy, A., Hill, C. et al., 2005. Effect of consumption of soya isoflavones on behavioural, somatic and affective symptoms in women with premenstrual syndrome. Br. J. Nutr. 93: 731-739

76. Takeda, T., Ueno, T., Uchiyama, S. et al., 2016. Relation between premenstrual syndrome and equol-production status. J. Obstet. Gynaecol. Res. 42: 1575-1580

77. Whelan, A.M., Jurgens, T.M., Naylor, H., 2009. Herbs, vitamins and minerals in the treatment of premenstrual syndrome: a systematic review. Can. J. Clin. Pharmacol. 16: e407-e429

78. Nagata, C., Hirokawa, K., Shimizu, N. et al., 2004. Soya, fat and other dietary factors in relation to premenstrual symptoms in Japanese women. BJOG 111: 594-699

79. McFadyen, I.J., Chetty, U., Setchell, K.D. et al., 2000. A randomized double blind-cross over trial of soya protein for the treatment of cyclical breast pain. Breast 9: 271-276

80. FDA, 2017. Food labelling: health claims; soya protein and coronary heart disease. A proposed Rule by the Food and Drug Administration on 10/31/2017. URL: www.federalregister.gov/docu ments/2017/10/31/2017-23629/food-labeling-health-claims-soya-protein-and-coronary-heart-disease Zugriff 19.05.19

81. FDA, 1999. Food labelling: health claims; soya protein and coronary heart disease. Food and Drug Administration, HHS. Final rule. Fed. Regist. 64: 57700–57733

82. EFSA, 2012. Scientific opinion on the substantiation of a health claim related to isolated soya protein and reduction of blood LDL-cholesterol concentrations pur- suant to Article 14 of Regulation (EC) No 1924/2006. EFSA J. 10: 2555

83. Benkhedda, K., Boudrault, C., Sinclair, S.E. et al., 2014. Health Canada's proposal to accept a health claim about soya products and cholesterol lowering. Int. Food Risk Anal. J. 4: 1–12

84. Zhang, X., Shu, X.O., Gao, Y.T. et al., 2003. Soya food consumption is associated with lower risk of coronary heart disease in Chinese women. J. Nutr. 133: 2874–2878

85. Yamori, Y. on behalf of the WHO-CARDIAC study group, 2006. Food factors for atherosclerosis prevention: Asian perspective derived from analyses of worldwide dietary biomarkers. Exp. Clin. Cardiol. 11: 94–98

86. Kokubo, Y., Iso, H., Ishihara, J. et al., 2007. Association of dietary intake of soya, beans, and isoflavones with risk of cerebral and myocardial infarctions in Japanese populations. The Japan Health Center-Based (JPHC) Study Cohort I. Circulation 116: 2553–2562

87. Shimazu, T., Kuriyama, S., Hozawa, A. et al., 2007. Dietary patterns and cardiovascular disease mortality in Japan: a prospective cohort study. Int. J. Epidemiol. 36: 600–609

88. Nagata, C., Wada, K., Tamura, T. et al., 2017. Dietary soya and natto intake and cardiovascular disease mortality in Japanese adults: The Takayama study. Am. J. Clin. Nutr. 105 :426–431

89. Ho, S.Y., Schooling, M., Hui, L. L et al., 2006. Soya consumption and mortality in Hong Kong: proxy-reported case-control study of all older adult deaths in 1998. Prev. Med. 43: 20–26

90. Zhang, X., Gao, Y.T., Yang, G. et al., 2012. Urinary isoflavonoids and risk of coronary heart disease. Int. J. Epidemiol. 41: 1367–1375

91. van der Schouw, Y.T., Kreijkamp-Kaspers, S., Peeters, P.H.M. et al., 2005. Prospective study on usual dietary phytoestrogen intake and cardiovascular disease risk in Western women. Circulation 111: 465–471

92. Talaei, M., Koh, W.P., van Dam, R..M et al., 2014. Dietary soya intake is not associated with risk of cardiovascular disease mortality in Singapore Chinese adult. J. Nutr. 144: 921–928

93. Yu, D., Zhang, X., Xiang, Y.B. et al., 2014. Association of soya food intake with risk and biomarkers of coronary heart disease in Chinese men. In. J. Cardiol. 172: e285–e287

94. Lou, D., Li, Y., Yan, G. et al., 2016. Soya consumption with risk of coronary heart disease and stroke: a meta-analysis of observational studies. Neuroepidemiology 46: 242–252

95. Yan, Z., Zhang, X., Li, C. et al., 2017. Association between consumption of soya and risk of cardiovascular disease: a meta-analysis of observational studies. Eur. J. Prev. Cardiol. 24: 735–747

96. Namazi, N., Saneei, P., Larijani, B., Esmaill-zadeh, A., 2018. Soya product consumption and the risk of all-cause, cardiovascular and cancer mortality: a systematic review and meta-analysis of cohort studies. Food Funct. 9: 2576–2588

97. Nestel, P., Fujii, A., Zhang, L., 2007. An isoflavone metabolite reduces arterial stiffness and blood pressure in overweight men and postmenopausal women. Atherosclerosis 192: 184–189

98. Usui, T., Tochiya, M., Sasaki, Y. et al., 2013. Effects of natural S-equol supplements on overweight or obesity and metabolic syndrome in the Japanese, based on sex and equol status. Clin. Endocrinol. 78: 365–372

99. Curtis, P.J., Potter, J., Kroon, P.A. et al., 2013. Vascular function and atherosclerosis progression after 1 y of flavonoid intake in statin-treated postmenopausal women with type 2 diabetes: a double-blind randomized controlled trial. Am. J. Clin. Nutr. 97: 936–942

100. Hazim, S., Curtis, P.J., Schär, M.Y. et al., 2016. Acute benefits of the microbial-derived isoflavone metabolite equol on arterial stiffness in men prospectively recruited according to equol producer phenotype: a double-blind randomized controlled trial. Am. J. Clin. Nutr. 103: 694–702

101. Ahuja, V., Miura, K., Vishnu, A. et al., 2017. Significant inverse association of equol-producer status with coronary artery calcification but not dietary isoflavones in healthy Japanese men. Br. J. Nutr. 117: 260–266

102. Sekikawa, A., Ihara, M., Lopez, O. et al., 2019. Effect of S-equol and soya isoflavones on heart and brain. Current Cardiology Reviews 15: 114–135

103. Birru, R.L., Ahuja, V., Vishnu, A. et al., 2016. The impact of equol-producing status in modifying the effect of soya isoflavones on risk factors for CHD: a systematic review of randomized controlled trials. J. Nutr. Sci. 5(e30) [doi: 10.1017/jns.2016.18]

104. Hodis, H.N., Mack, W.J., Kono, N. et al., 2011. Isoflavone soya protein supplementation and atherosclerosis progression in healthy post-menopausal women: a randomized controlled trial. Stroke 42: 3168–3175

105. Liu, Z.M., Ho, S.C., Chen, Y.M. et al., 2014. Whole soya, but not purified daidzein, had a favorable effect on improvement of cardiovascular risks: a 6-month randomized, double-blind, and placebo-controlled trial in equol-producing postmenopausal women. Mol. Nutr. Food. Res. 58: 709–717

106. Tokede, O.A., Onabanjo, T.Y., Yansane, A. et al., 2015. Soya products and serum lipids: a meta-analysis of randomized controlled trials. Br. J. Nutr. 114: 831–843

107. Chalvon-Demersay, T., Azzout-Marniche, D., Arfsten, J. et al., 2017. A systematic review of the effects of plant compared with animal protein sources on features of metabolic syndrome. J. Nutr. 147: 281–292

108. Pirro, M., Vetrani, C., Bianchi, C. et al., 2017. Joint position statement on "Nutraceuticals for the treatment of hypercholesterolemia" of the Italian Society of Diabetology (SID) and of the Italian Society for the Study of Arteriosclerosis (SISA). Nutr. Metab. Cardiovasc. Dis. 27: 2–17

109. Ramdath, D.D., Padhi, E.M.T., Sarfaraz, S. et al., 2017. Beyond the cholesterol-lowering effect of soya protein: a review of the effects of dietary soya and its constituents on risk factors for cardiovascular disease. Nutrients 9: 324

110. Anderson, J.W., Johnstone, B.M., Cook-Newell, M.E., 1995. Meta-analysis of the effects of soya protein intake on serum lipids. N. Engl. J. Med. 333: 276–282

111. Zhan, S., Ho, S.C., 2005. Meta-analysis of the effects of soya protein containing isoflavones on the lipid profile. Am. J. Clin. Nutr. 81: 397–408

112. Sacks, F.M., Lichtenstein, A., van Horn, L. et al., 2006. Soya protein, isoflavones, and cardiovascular health. An American Heart Association science advisory for professionals from the Nutrition Committee. Circulation 113: 1034–1044

113. Reynolds, K., Chin, A., Lees, K.A. et al., 2006. A meta-analysis fo the effect of soya protein supplementation on serum lipids. Am. J. Cardiol. 98: 633–640

114. Harland, J.I., Haffner, T.A., 2008. Systematic review, meta-analysis and regression of randomized controlled trials reporting an association between an intake of circa 25 g soya protein per day and blood cholesterol. Atherosclerosis 200: 13–27

115. Jenkins, D.J.A., Mirrahimi, A., Srichaikul, K. et al., 2010. Soya protein reduces serum cholesterol by both intrinsic and food displacement mechanisms. J. Nutr. 140: 2302S–2311S

116. Anderson, J.W., Bush, H.M., 2011. Soya protein effects on serum lipoproteins: a quality assessment and meta-analysis of randomized, controlled studies. J. Am. Coll. Nutr. 30: 79–91

117. Yang, B., Chen, Y., Tongchen, X. et al., 2011. Systematic review and meta-analysis of soya products consumption in patients with type 2 diabetes mellitus. Asia Pac. J. Clin. Nutr. 20: 593–602

118. Li, J., Liu, Y., Wang, T. et al., 2016. Does genistein lower plasma lipids and homocysteine levels in postmenopausal women? A meta-analysis. Climacteric 19: 440–447

119. Zhang, X.M., Zhang, Y.B., Chi, M.H., 2016. Soya protein supplementation reduces clinical indices in type 2 diabetes and metabolic syndrome. Yonsei Med. J. 57: 681–689

120. Messina, M., 2016. Soya and health update: evaluation of the clinical and epidemiological literature. Nutrients 8: 75

121. Chatterjee, C., Gleddie, S., Xiao, C.W., 2018. Soybean bioactive peptides and their functional properties. Nutrients 10: 1211

122. Taku, K., Umegaki, K., Sato, Y. et al., 2007. Soya isoflavones lower serum total and LDL cholesterol in humans: a mata-analysis of 11 randomized controlled trials. Am. J. Clin. Nutr. 85: 1148–1156

123. Taku, K., Lin, N., Cai, D. et al., 2010. Effects of soya isoflavone extract supplements on blood pressure in adult humans: systematic review and meta-analysis of randomized placebo-controlled trials. J. Hypertens. 28:1971–1982

124. Liu, X.X., Li, S.H., Chen, J.Z. et al., 2012. Effect of soya isoflavones on blood pressure: a meta-analysis of randomized controlled trials. Nutr. Metab. Cardiovasc. Dis. 22: 463–470

125. Kou, T., Wang, Q., Cai, J. et al., 2017. Effect of soybean protein on blood pressure in post-menopausal women: a meta-analysis of randomized controlled trials. Food Funct. 8: 2663–2671

126. Li, S.S., Mejia, S.B., Lytvyn, L. et al., 2017. Effect of plant protein on blood lipids: a systematic review and meta-analysis of randomized controlled trials. J. Am. Heart. Assoc. 6: e006659

127. Atiya Ali, M., Poortvliet, E., Strömberg, R., Yngve, A., 2011. Polyamines in foods: development of a food database. Food Nutr. Res. 55: 5572

128. Kalac, P., 2014. Health effects and occurrence of dietary polyamines: a review for the period 2005-mid 2013. Food Chem. 161: 27–39

129. Eisenberg, T., Abdellatif, M., Schroeder, S. et al., 2016. Cardioprotection and lifespan extension by the natural polyamine spermidine. Nat. Med. 22: 1428–1438

130. Madeo, F., Eisenberg, T., Pietrocola, F., Kroemer, G., 2018. Spermidine in health and disease. Science 359: eaan2788

131. Nilsson, B.O., Persson, L., 2019. Beneficial effects of spermidine on cardiovascular health and longevity suggest a cell type-specific import of polyamines by cardiomyocytes. Bichem. Soc. Trans. 47: 265–272

132. Kiechl, S., Pechlanerm, R., Willeit, P. et al., 2018. Higher spermidine intake is linked to lower mortality: a prospective population-based study. Am. J. Clin. Nutr. 108: 371–380

133. Soda, K., Kano, Y., Sakuragi, M. et al., 2009. Long-term oral polyamine intake increases blood polyamine concentrations. J. Nutr. Sci. Vitaminol. 55: 361–366

134. Langen, U., Schmitz, R., Steppuhn, H., 2013. Häufigkeit allergischer Erkrankungen in Deutschland. Ergebnisse der Studie zur Gesundheit Erwachsener in Deutschland (DEGS1). Bundesgesundheitsbl 56: 698–706

135. Gupta, R.S., Warren, C.M., Smith, B.M. et al., 2019. Prevalence and severity of food allergies among US adults. JAMA Network Open 2: e185630

136. Nwaru, B.I., Hickstein, L., Panesar, S.S. et al., 2014. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. Allergy 69: 992–1007

137. University of Portsmouth, 2013. Literature searches and reviews related to the prevalence of food allergy in Europe. EFSA supporting publication 2013: EN-506

138. Savage, J.H., Kaeding, A.J., Matsui, E.C., Wood, R.A., 2010. The natural history of soya allergy. J. Allergy Clin. Immunol. 125: 683–686

139. Haftenberger, M., Laußmann, D., Ellert, U. et al., 2013. Prävalenz von Sensibilisierungen gegen Inhalations- und Nahrungsmit- telallergene. Ergebnisse der Studie zur Gesundheit Erwachsener in Deutschland (DEGS1). Bundesgesundheitsbl 56: 687–697

140. Treudler, R., Werner, M., Thiery, J. et al., 2008. High risk of immediate-type reactions to soya drinks in 50 patients with birch pollinosis. J. Investig. Allergol. Clin. Immunol. 18: 483–484

141. Mittag, D., Vieths, S., Vogel, L. et al., 2004. Soybean allergy in patients allergic to birch pollen: clinical investigation and molecular characterization of allergens. J. Allergy Clin. Immunol. 113: 148–154

142. Verhoeckx, K.C.M., Vissers, Y.M., Baumert, J.L. et al., 2015. Food processing and allergenity. Food Chem. Toxicol. 80: 223–240

143. Bundesinstitut für Risikobewertung, 2007. Birkenpollenallergiker können auf Sojaprodukte besonders empfindlich reagieren. Presseinformation vom 28.6.2007.

144. Bundesinstitut für Risikobewertung, 2007. Sojaprodukte können bei Birkenpollen-Allergikern schwere allergische Reaktionen auslösen. Stellungnahme Nr. 016/2007 des BfR vom 17. April 2007

145. Celakovská, J., Ettlerova, K., Ettler, K. et al., 2013. Soya allergy in patients suffering from atopic dermatitis. Indian J. Dermatol. 58: 325

146. Harlfinger, J., Kerschner, B., Christof, C., 2016. Soja-Lebensmittel: Riskant für die Schilddrüse? Medizin-transparent.at. URL: www. medizin-transparent.at/soja-lebensmittel- riskant-fuer-die-schilddruese Zugriff 19.05.19

147. Bundesinstitut für Risikobewertung, 2007. Isolierte Isoflavone sind nicht ohne Risiko. Aktualisierte Stellungnahme Nr. 039/2007 des BfR vom 3. April 2007

148. Sosvorová, L., Miksátkova, P., Bicicová, M. et al., 2012. The presence of monoiodinated derivates of daidzein and genistein inhuman urine and its effect on thyroid gland function. Food Chem. Toxicol. 50: 2774–2779

149. Messina, M., Redmond, G., 2006. Effects of soya protein and soybean isoflavones on thyroid function in healthy adults and hypothyroid patients: a review of the relevant literature. Thyroid 16: 249–258

150. Marini, H., Polito, F., Adamo, E.B. et al., 2012. Update on genistein and thyroid: an overall message of safety. Front. Endocrinol. 3: 94

151. Alekel, D.L., Genschel, U., Koehler, K.J. et al., 2015. Soya Isoflavones for Reducing Bone Loss (SIRBL) Study: effect of a three-year trial on hormones, adverse events, and endometrial thickness in postmenopausal women. Menopause 22: 185–197

152. Tonstad, S., Jaceldo-Siegl, K., Messina, M. et al., 2016. The association between soya consumption and serum thyroid-stimulating hormone concentrations in the Adventist Health Study-2. Public Health Nutr. 19: 1464–1470

153. Horn-Ross, P., Hoggatt, K.J., Lee, M.M., 2012. Phytoestrogens and thyroid cancer risk: The San Francisco Bay Area Thyroid Cancer Study. Cancer Epidemiol Biomarkers Prev. 11: 43–49

154. Castelo-Branco, C., Cancelo Hidalgo, M.J., 2011. Isoflavones: effects on bone health. Climacteric 14: 204–211

155. Taku, K., Melby, M.K., Nishi, N. et al., 2011. Soya isoflavones for osteoporosis: an evidence-based approach. Maturitas 70: 333–338

156. Abdi, F., Alimoradi, Z., Haqi, P., Mahdizad, F., 2016. Effects of phytoestrogens on bone mineral density during the menopause transition: a systematic review of randomized, controlled trials. Climacteric 19: 535–545

157. Zhang, X., Shu, X.O., Li, H. et al., 2005. Prospective cohort study of soya food consumption and risk of bone fracture among postmenopausal women. Arch. Intern. Med. 165: 1890–1895

158. Koh, W.P., Wu, A.H., Wang, R. et al., 2009. Gender-specific associations between soya and risk of hip fracture in the Singapore Chinese Health Study. Am. J. Epidemiol. 170: 901–909

159. Wei, P., Liu, M., Chen, Y., Chen, D.C., 2012. Systematic review of soya isoflavone supplements on osteoporosis in women. Asian Pac. J. Trop. Med. 5: 243–248

160. Pawlowski, J.W., Martin, B.R., McCabe, G.P. et al., 2015. Impact of equol-producing capacity and soya-isoflavone profiles of supplements on bone calcium retention in post-menopausal women: a randomized crossover trial. Am. J. Clin. Nutr. 102: 695–703

161. Ricci, E., Cipriani, S., Chiaffarino, F. et al., 2010. Soya isoflavones and bone mineral density in perimenopausal and postmenopausal western women: a systematic review and meta-analysis of randomized controlled trials. J. Womens Health (Larchmt) 19: 1609–1617

162. Lagari, V.S., Levis, S., 2013. Phytoestrogens in the prevention of postmenopausal bone loss. J. Clin. Densitom. 16: 445–449

163. Castelo-Branco, C., Soveral, I., 2013. Phytoestrogens and bone health at different reproductive stages. Gynecol. Endocrinol. 29: 735–743

164. Zheng, X., Lee, S.K., Chun, O.K., 2016. Soya isoflavones and osteoporotic bone loss: a review with an emphasis on modulation of bone remodeling. J. Med. Food. 19:1–14

165. Martinez, J., Lewi, J.E., 2008. An unusual case of gynecomastia associated with soya product consumption. Andocr. Pract. 14: 415–418

166. Siepmann, T., Roofeh, J., Kiefer, F.W., Edelson, D.G., 2011. Hypogonadism and erectile dysfunction associated with soya product consumption. Nutrition 27(7–8): 859–862

167. Chavarro, J.E., Toth, T.L., Sadio, S.M., Hauser, R., 2008. Soya food and isoflavone intake in relation to semen quality parameters among men from an infertility clinic. Hum. Reprod. 23: 2584–2590

168. Song, G., Kochman, L., Andolina, E. et al., 2006. Beneficial effects of dietary intake of plant phytoestrogens on semen parameters and sperm DNA integrity in infertile men. Fertil. Steril. 86: S49

169. Hamilton-Reeves, J.M., Vazquez, G., Duval, S.J. et al., 2010. Clinical studies show no effects of soya protein or isoflavones on reproductive hormones in men: results of a meta-analysis. Fertil. Steril. 94: 997–1007

170. Cederroth, C.R., Auger, J., Zimmermann, C. et al., 2010. Soya, phyto-oestrogens and male reproductive function: a review. Int. J. Androl. 33: 304–316

171. Messina, M., 2010. Soybean isoflavone exposure does not have feminizing effects on men: a critical examination of the clinical evidence. Fertil. Steril. 93: 2095–2104

172. Messina, M., Magee, P., 2018. Does soya protein affect circulating levels of unbound IGF-1? Eur. J. Nutr. 57: 423–432

173. Krüger, M., 2014. Expertenforum: Säuglings- und Kinderernährung (0 – 10 Jahre). Frage: Sojaprodukte im Krippen- und Kindergarten als Milch- und Fleischersatz. Expertenantwort. URL: www.bzfe.de/forum/index.php/forum/showExpMessage/id/45910/searchstring/soja/page1/1/forumId/8/datumvon/+/datumbis/+/searchpattern/1/searchconcat/1 Zugriff 19.05.19

174. Messina, M., Rogero, M.M., Fisberg, M., Waitzberg, D., 2017. Health impact of childhood and adolescent soya consumption. Nutr. Rev. 75: 500–515

175. Shu, N.X., Jin, F., Dai, Q. et al., 2001. Soyfood intake during adolescence and subsequent risk of breast cancer among Chinese women. Cancer Epidemiol. Biomarkers Prev. 10: 483–488

176. Thanos, J., Cotterchio, M., Boucher, B.A. et al., 2006. Adolescent dietary phytoestrogen intake and breast cancer risk (Canada). Cancer Causes Control 17: 1253–1261

177. Segovia-Siapco, G., Pribis, P., Oda, K., Sabaté, J., 2018. Soya isoflavone consumption and age at pubarche in adolescent males. Eur. J. Nutr. 57: 2287–2294

178. Segovia-Siapco, G., Pribis, P., Messina, M., 2014. Is soya intake related to age at onset of menarche? A cross-sectional study among adolescents with a wide range of soya food consumption. Nutr. J. 13: 54

179. Duitama, S.M., Zurita, J., Cordoba, D. et al., 2018. Soya protein supplement intake over12 months has no effect on sexual maturation and may improve nutritional status in prepubertal children. J. Paediatr. Child Health 54: 997–1004

180. Boye, J., Ribéreau, S. Assessing compositional differences in soya products and impacts on health claims. In: El-Shemy H (Hg). Soya- bean and nutrition. InTech, Rijeka, 2011. 453–476. URL: www.intechopen.com/ books/soybean-and-nutrition Zugriff 19.05.19

181. Reinwald, S., Akabas, S.R., Weaver, C.M., 2010. Whole versus the piecemeal approach to evaluating Soya. J. Nutr. 140: 2335S–2343S

182. Zaheer, K., Humayoun Akhtar, M., 2017. An updated review of dietary isoflavones: nutrition, processing, bioavailability and impacts on human health. Crit. Rev. Food Sci. Nutr. 57: 1280–1293

183. Willet, W., Rockström, J., Loken, B. et al., 2019. Food in the anthropocene: the EAT-Lancet Commission on healthy diets from sustainable food systems. Lancet 393: 447–492

184. Potsdam-Institut für Klimafolgenforschung, 2019. Lancet Report: Gesund leben auf einem gesunden Planeten – anders essen und anders produzieren. Pressemitteilung vom 17.01.2019. URL: www.pik-potsdam. de /aktuelles/pressemitteilungen/ lancet-report-gesund-leben-auf-einem- gesunden-planeten-anders-essen-und- anders-produzieren Zugriff 19.05.19

185. de Schutter, L., Bruckner, M., Giljum, S. WWF Studie 2015. Achtung: Heiß und fettig – Klima und Ernährung in Österreich. Aus- wirkungen der Österreichischen Ernährung auf das Klima. WWF Österreich (Hg). Wien, 2015. URL: www.wwf.at/de/ ernaehrungsstudie/Zugriff 19.05.19

186. WWF Deutschland, 2016. Soja: Wunderbohne mit riskanten Nebenwirkungen. Stand: 21.4.2016. URL: www.wwf. de/themen-projekte/landwirtschaft/produkte-aus-der-landwirtschaft/soja/soja-wunderbohne-mit-riskanten-nebenwirkungen/ Zugriff 19.05.19

187. Soja Netzwerk Schweiz, 2019. Soja Fakenblätter. URL: www.sojanetzwerk.ch/fileadmin/user_upload/soja-fact sheet-de_180618_update.pdf Zugriff 19.05.19

188. Europäische Kommission, 2018. Bericht der Kommission über die Entwicklung von Eiweißpflanzen in der EU. Pressemitteilung vom 22. November 2018. URL: http://europa.eu/rapid/press-release_IP-18-6495_de.htm Zugriff 19.05.19

189. Verein Donau Soja, 2018. Donau Soja Statistics. Soybean area by country in Europe (2011–2018). Last update: 07.12.2018. URL: www.donausoja.org/de/innovation/ markt-statistik/marktinfos/ Zugriff 19.05.19

190. Verein Donau Soja, 2019. Schweiz unterzeichnet Europa Soja Erklärung. Pressemitteilung vom 28. Jänner 2019. URL: www.donausoja.org/fileadmin/user_upload/Press/Press_Release/PA_Schweiz_unterzeichnet_Europa_Soja_Erkla__rung_012019.pdf Zugriff 19.05.19

191. Bundesministerium für Ernährung und Landwirtschaft (Hg), 2016. Ackerbohne, Erbse & Co. Die Eiweißstrategie des Bundesministeriums für Ernährung und Landwirtschaft zur Förderung des Leguminosenanbaus in Deutschland. URL: BMEL - Publikationen - Ackerbohne, Erbse & Co. - Die Eiweißpflanzenstrategie des Bundesministeriums für Ernährung und Landwirtschaft zur Förderung des Leguminosenanbaus in Deutschland, Zugriff 19.05.19

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Author: Angela Mörixbauer, eatconsult – agentur für ernährungskommunikation, am@eatconsult.at, https://www.eatconsult.at

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Conflict of interest: Angela Mörixbauer has been working as a self-employed nutrition scientist in the private sector since 2003 and receives fees for her services. Among other things, she has been providing PR support to the non-profit association 'Verein Soja aus Österreich' since 2018 and advises companies in the soya sector. The author has not received any fees from companies or associations for the preparation of this article.