Figure A: Forest plot of systolic blood decrease of studies in which median and standard deviation is detailed.

Figure B: Forest plot of diastolic bood pressure decrease of all studies included in the meta-analysis.

Figure C: Forest plot of diastolic blood pressure decrease of studies whose primary outcome was decrease of blood pressure.

Figure D: Forest plot of diastolic blood decrease of studies in which median and standard deviation is detailed.

Figure E: Funnel plot with Egger line to evaluate the effect of small studies.

Figure F: Sensitivity analysis of studies with high (Jadad score >= 3 points) or low quality (Jadad < 3 points)

Figure G: Scatter plot and regression line to evaluate relationship between systolic blood pressure decrease and quality of the study (Jadad scale)

Figure H: --------------------------------------------------------------------------------

Figure I: Sensitivity analysis of studies with parallel or cross-over design.

Figure J: Scatter plot and regression line to evaluate the relationship between systolic blood pressure decrease and amount of ingested isoflavones.

Figure K: Scatter plot and regression line to evaluate the relationship between systolic blood pressure decrease and amount of ingested soy protein.

Figure L: Relationship between systolic blood pressure decrease and % of women in included studies.

Figure M: Relationship between systolic blood pressure decrease and median age of patients in included studies.

Figure N: relationship between systolic blood pressure decrease and Impact Factor of journal where the study was published.

Table A: Other search strategies.

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| --- |
| * EMBASE: (`soy´ OR ´phytoestrogen?´ OR ´isoflavon$´ AND [humans]/lim) AND ((´randomized controlled trial`/exp OR ´randomized controlled trial´) OR (´clinical trial´/exp OR ´clinical trial´)). We found 562 studies. * Cochrane Central Register of Controlled Trials (Mesh): “phytoestrogens” (183 clinical trials), “isoflavones” (579), “soy foods” (495) and “soy beans” (403). * ClinicalTrials.gov: “phytoestrogens” (99 studies), “isoflavones” (120), “soy foods” (175), “soy beans” (514) and “daidzein” (15), a lot of them ongoing.   TRIPDATABASE with “*title*” “phytoestrogens OR isoflavones OR soy foods OR soy meals OR daidzein”: 401 clinical trials and 19 systematic reviews. |

Table B: Mathematical analysis of data recovered of studies included in the meta-analysis.

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| --- |
| We must have a value of BP decrease, a value of standard deviation (SD), and the population size (N) in each branch of the study, to make numerical calculations of the meta-analysis. We found information about BP decrease in the clinical trials of our meta-analysis in different ways.   * In a few studies, these 3 values are detailed, and are directly included in the estimate; * In other jobs, authors detailed values of median blood pressure decrease and population size, and the value of standard error (SE). According to an easy formula ( SE = SD / √N, N = population size), we calculated the corresponding SD; * In several works, authors showed values of median blood pressure decrease and SD, but referred in percentage (%) according to basal values. We calculated the integer values by multiplying by the basal blood pressure value.   And finally, in a lot of works authors showed values of mean final and initial blood pressure and SD. We calculated the mean difference as the difference of these values, final minus initial blood pressure; and the mean standard deviation as the weighted mean of final and initial blood pressures. |

Table C: Characteristics of all studies included in the systematic review. BMI: body mass index; DB double blind; wk weeks; Jadad: scoring according to Jadad´s scale (citation # 12); ISP isolated soy proteins; SBP systolic blood pressure; CVD cardiovascular disease; PM postmenopausal; MS metabolic síndrome; HT hypertension; SP soy protein; HOMA-IR: homeostasis model assessment for insulin resistance; TLC Therapeutic Lifestyle Changes.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Author year | Participants | Intervention | Primary outcomes | Notes |
| Allison 2003 | N=70 obese volunteers (BMI 28-41). Median BP 117,7 / 76,9 mmHg | Soy-based meal replacement formula (Scan diet) vs dietary counselling describing good weight loss practices. 12 wk. Not blinded | Weight, body fat, serum lipid concentrations | USA. Jadad 2 |
| Anderson 2005 | N=90 obese (BMI 27-40) volunteers. Excluded uncontrolled HT. 125,6/69,3 mmHg | Soy-based versus milk-based replacement meals (low energy diets, 1200 Kcal/day).12 wk. Not blinded | Weight loss, lipid changes | USA. Jadad 0 |
| Anderson 2007 | N=43 obese women. Excluded uncontrolled HT. 124/81 mmHg | 3 soy-based replacement shakes daily vs 3 casein-based shakes, as part of a 16-wk, energy restricted diet | Weight loss, body composition, waist circumference | USA. 150 mg isoflavones/day. Jadad 2 |
| Appel 2005 | N= 161 preHT or HT grade 1. 131,2/77 mmHg | 3 healthy diets: rich in carbohydrates, rich in protein (about half from plant sources, also soy), and rich in unsaturated fat (monounsaturated). Cross-over. 6 wk. | LDL-cholesterol, SBP | USA. 7,3 g SP. Jadad 2. |
| Atkinson 2004 | N=177 periMP women, 126,5/81 mmHg | Capsules of red-clover derived dietary supplement vs placebo. 52 wk. | Lipid profile, CVD, fibrinogen, PAI-1 | 43,5 mg isoflavones/day. UK. Jadad 4 |
| Aubertin 2008 | N=50 obese PM women. 125,8/78,3 mmHg | Capsules of isoflavones supplementation vs placebo. 26 wk | Lipid profile, body composition, factors predisposing to CVD | 70 mg isoflavones /day. Canada. Jadad 3. |
| Azadbakht 2003 | N=14 type 2 diabetic patients with nephropathy. BP>140/90 mmHg | Follow a diet containing 35% soy protein, 30% vegetable protein and 35% animal protein; vs 70% animal and 30% vegetal protein (an usual nephropathy diet). 7 wk. Cross-over | Lipid profile, kidney function | 18,9 g SP. Iran. Jadad 1. |
| Azadbakht 2007 | N=42 PM women with MS. 136/87 mmHg. Included hypertensives with definition of MS | DASH (Dietary Approaches to Stop Hypertension) diet vs similar diet in which red meat is replaced by soy protein. 8 wk. Cross-over | MS, insulin resistance, fasting plasma glucose | 84 mg isoflavones. Iran. Jadad 2. |
| Azadbakht 2009 | N=14 type 2 diabetics with proteinuria, and HT with antiHT medication. 153,5/95 mmHg | Diet containing 0,8 g protein/kg weight, with 35% SP, 35% animal protein and 30% vegetal protein vs 70% animal protein and 30% vegetal protein. 7 wk. Cross-over | Renal function markers | 42,3 mg isoflavones, 17,8 g SP. Iran. Jadad 2. |
| Azadbakht 2011 | N=23 overweight and obese women. 101,5/66 mmHg | All patients were on a weight reducting diet. 1 glass (240 ml) of soy drink vs cow´s milk. 6 wk. Cross-over | Anthropometric values and BP | Iran. Jadad 1 |
| Bakhtiary 2012 | N= 75 women with MS. 127,4/80,4 mmHg | Receive 35 g of soy nut/day vs control (nothing). Patients were asked not to change their habitual diet. 12 wk | Lipid profile | Iran. Jadad 3 |
| |  | | --- | | Beavers 2015 | | N=24 older, abdominally obese adults. 136/72,6 mmHg. Excluded uncontrolled HT | In a weight loss intervention, SP vs non-SP based replacement (whey and eggs proteins). 12 wk | Body and composition weight | 97,5 mg isoflavones, 44 g SP. USA. Jadad 3 |
| Brussaard 1981 | N= 49 young healthy volunteers. Excluded BP>150/95mmHg 123,5/69 mmHg | Diet containing SP vs diet containing control (casein). 4 wk | Lipid profile | Netherlands. Jadad 0 |
| Burke 2001 | N= 18 treated hypertensive patients with <= 2 antihyper-tensive agents. 131,3/75,8 mmHg | Soy vs maltodextrine supplement (drink mixed with juice or water). 8 wk | BP | 66 g SP. Australia. Jadad 3 |
| Cancellieri 2007 | N= 125 postMP women. Excluded patients taking antiHT drugs. 126,1/78,4 mmHg | 1 tablet daily of an herbal product from soybean and red clover vs placebo. 26 wk. | Kupperman menopause index | 72 mg isoflavones. Italia. Jadad 3 |
| Casiglia 1991 | N= 109 non-diabetic adults. Any antyHT treatment must be discontinued. 145,1/86,7 mmHg | Intake of 50 g soybean oil, 500 ml of soybean milk and 10 g soybean lecitine vs normal dietary fats. 13 wk. | Lipid profile | Italia. Jadad 0 |
| Chan 2008 | N=102 patients with prior ischaemic stroke. 141/77,5 mmHg | Intake of isoflavone supplement vs placebo. 12 wk. | Brachial flow-mediated dilatation | 80 mg isoflavones. China. Jadad 5 |
| Cheng 2007 | N=51 postMP women. | Daily nutritional addition of a fruit drink containing isoflavones vs placebo. 3 months | Climacteric symptoms | 65 mg isoflavones. Sweden. Jadad 3 |
| Chiechi 2002 | N=67 asymptomatic healthy postMP women. 130,6/81,4 mmHg | Continue their usual diet, asked to add a soy food serving every day (soy milk, miso soup, tofu) vs no add soy food. 6 months | Lipid profile | 47 mg isoflavones. Italy. Jadad 2 |
| Clerici 2007 | N=62 newly diagnosed hypercholestero-lemia. Excluded patients taking antiHT drugs | Intake of a daily serving of pasta naturally enriched with isoflavones vs conventional pasta. 4 wk. Cross-over. | Lipid profile | 33 mg isoflavones. Italy. Jadad 2 |
| Clifton 2015 | N=147 postMP women. 126,6/75 mmHg | Intake of 2 tablets daily of Rimostil (isoflavones) vs placebo. 2 years | Bone mineral density | 50 mg isoflavones. Australia Jadad 4 |
| Colacurci 2005 | N=57 postMP women. 120,5/78 mmHg. Not included hyper-tensive patients | Inkate of 1 tablet/day of isoflavone vs placebo tablet. 6 months | Endothelium-dependent vasodilatation | 60 mg isoflavones. Italia. Jadad 3 |
| Colado 2010 | N=30 women with MS. 136,4/89,2 mmHg. >70% hypertensive patients taking antiHT drugs | Intake of SP (kinako) vs usual diet. 90 days. | Serum nitric oxide metabolites | 50 mg isoflavones, 12,95 g SP, Brasil. Jadad 2 |
| |  | | --- | | Colado 2012 | | N=30 women with MS. 134/87,8 mmHg | Intake of soyabean + isoflavones vs maintained their usual diet. 90 days. | BP | 50 mg isoflavones, Brazil, Jadad 1 |
| Cuevas 2003 | N= 18 postMP women with hypercholesterolemia. 132/73 mmHg. None of patients were receiving antiHT drugs | Intake of isolated powder SP vs matching (casseinate). 4 wk. Cross-over | Lipid profile | 80 mg isoflavones,  40 g SP, Chile, Jadad 3 |
| Curtis 2012 | N= 93 patients with type 2 diabetes and postMP women. Excluded raised BP at screening. 133,68 mmHg SBP | Intake of split (flavonoid enriched chocolate dose) vs matched placebo. 1 year | Estimated peripheral insulin resistance (HOMA-IR) | 100 mg isoflavones, UK, Jadad 2 |
| Dodin 2005 | N= 199 healthy postMP women. Excluded BP>140/90. 123,9/78,7 mmHg | Intake of 40 g flaxseed/day vs wheat germ placebo. 12 months | Lipid profile | Canada. Jadad 4 |
| Evans 2007 | N= 22 postMP normotensive women. 123,5/69,1 mmHg | Intake of isoflavone protein, soy lecithin and soy isoflavone protein vs placebo. 4 wk. Cross-over | Endothelial function (flow-mediated dilatation) | 25 g SP. USA. Jadad 3 |
| Fauré 2002 | N= 75 postMP women. | Intake of capsules of soy isoflavone extract vs cellulose microcrystalline placebo. 4 months | Hot flushes | 70 mg isoflavones. France. Jadad 3 |
| Garrido 2006 | N= 29 healthy postMP women. 121,5/77,3 mmHg. Excluded arterial HT | Intake of capsules with phytoestrogens vs placebo. 12 wk | Lipid profile | 100 mg isoflavones, Chile. Jadad 4 |
| Gleason 2009 | N= 30 older non demented healthy patients free of major medical illnesses | Intake of isoflavones capsules vs placebo (maltodextrin and caramel food). 6 months. | Cognitive effects | 100 mg isoflavones, USA. Jadad 4 |
| González 2007 | N= 32 women with diet-controlled type 2 diabetes. 131,5/74 mmHg | Intake of tablets of soy preparation vs placebo (microcrystalline cellulose). Cross-over. 12 wk | Glycemic control, insulin resistance, lipid profile | 132 mg isoflavones, UK. Jadad 3 |
| Guevara 2012 | N=67 patients with MS. 109,4/75,4 mmHg. Excluded patients taking antiHT drugs | A dietary pattern including nopal, chia seed, SP and oat vs placebo, added to a reduced energy diet. 2 months. | Anthropometric and glycemic measures | 32 g SP, Mexico. Jadad 3 |
| Hale 2002 | N= 29 healthy postMP women. patients could not be taking beta-alfa blockers or calcium channel blockers 123,2/75,7 mmHg | Intake of an oral soy isoflavone concentrate or placebo. 2 wk. | Brachial artery reactivity test | 80 mg isoflavones, USA. Jadad 4 |
| Hall 2006 | N= 117 healthy postMP women. Excluded if were taking previously antiHT drugs. 120,6/76,1 mmHg | Intake of isoflavone enriched bars vs placebo (cereal) bars. Cross-over. 8 wk. | Lipid profile. Glucose metabolism | 50 mg isoflavones, Western Europe (UK, Germany, Denmark, Italy). Jadad 3 |
| Hallund-Bugel 2006 | N=30 volunteers postMP women without antiHT drugs. 126/77 mmHg | Intake of 2 soy isoflavone -enriched bars vs cereal bars per day. Cross-over. 8 wk. | Vascular risk markers associated. Endothelial function | 50 mg isoflavones, Western Europe (UK, Germany, Denmark, Italy). Jadad 2 |
| Hallund-Tetens 2006 | N= 22 postMP women. BP<160/90. 124/75 mmHg | Intake of a low-fat muffin, with vs without a lignin complex. Cross-over. 12 wk. | Flow-mediated endothelium dependent vasodilatation | Western Europe (UK, Germany, Denmark, Italy). Jadad 2 |
| Han 2002 | N=80 postMP women. Excluded if history of uncontrolled HT. 132/84 mmHg | Intake of 3 capsules/day of isoflavones vs placebo. 4 months. | Menopausal Kupperman index | 100 mg isoflavones, 0,151 g SP, China, Jadad 5 |
| He 2005 | N= 302 pre-hypertensive or mild hypertensive patients. 135/84,7 mmHg | Intake of cookies with SP vs complex carbohydrate from wheat. 12 wk | BP | 80 mg isoflavones, 40 g SP, China. Jadad 5 |
| He 2011 | N= 352 pre-hypertensive or stage 1 hypertension (excluded if taking antiHT drugs). 126,7/82,4 mmHg | Intake of a SP, vs carbohydrate complex supplement. Cross-over. 8 wk | BP | 40 g SP, China, Jadad 5 |
| Heger 2006 | N= 41 women periMP with climacteric complaints | Intake of 1 enteric-coated tablet (containing Rheum rhaponticum dry extract) vs placebo. 12 wk | Menopause Rating Scale (MRS II) | Ukraine. Jadad 5 |
| Hermansen 2001 | N=20 type 2 diabetic outpatients. 130/78 mmHg | Dietary supplement of SP, isoflavones and cotyledon fiber vs placebo (casein + cellulose). Cross-over. 6 wk | Lipid profile | 165 mg isoflavones, 50 g SP, Denmark, Jadad 1 |
| Hermansen 2005 | N= 89 hypercholesterolemic subjects. Excluded severe HT. 133/80,8 mmHg | Intake of an oral supplement (SP, cotyledon fiber, isoflavones) vs placebo (casein). 24 wk | Lipid profile | 100 mg isoflavones, 30 g SP, Denmark, Jadad 3 |
| Hidalgo 2005 | N=53 MP women. 118,3/76,6 mmHg | Intake of capsules (red clover extracts vs placebo). Cross-over. 90 days | MP symptoms | 80 mg isoflavones, Ecuador, Jadad 4 |
| Hoïe-Graubaum 2005 | N= 117 hypercholesterolemic patients. Excluded BP>160/100 mmHg | Intake of a soy-based protein supplement vs placebo (milk protein). 8 wk | Lipid profile | 25 g SP, Norway-Germany. Jadad 3 |
| Hoïe-Morgenstern 2005 | N=121 hypercholesterolemic adults. Excluded BP>160/100 mmHg | Intake of soy-based vs milk supplement. 8 wk | Lipid profile | 96,6 mg isoflavones, 25 g SP, Norway-Germany. Jadad 2 |
| Hoïe 2007 | N=120 hypercholesterolemic outpatients. Excluded severe cardiovascular diseases | Intake of preparations of isolated SP vs milk protein, stirred into cold water and taken with meals. 8 wk | Lipid profile | 25 g SP, Germany, Jadad 2 |
| Howes 2000 | N=66 postMP women with mild-moderate hypercholesterolemia | Intake of purified extract of red clover vs placebo. 12 wk | Lipid profile | 87 mg isoflavones, Australia, Jadad 2 |
| Howes 2004 | N=28 postMP women. 142/81,5 mmHg. Excluded patients with treatment with betablockers or centrally acting antiHT drugs | Intake of tablets containing isoflavones vs placebo. Cross-over. 6 months | Cognitive function | 58 mg isoflavones, Australia, Jadad 5 |
| Hussain 2015 | N=61 postMP women. 123,6/80,4 mmHg | Intake of a supplementation with biscuits of isoflavones vs placebo. 8 wk | Kupperman index (MP symptoms) | 54 mg isoflavones, Iran, Jadad 1 |
| Imhof 2006 | N= 109 postMP women. | Intake of 2 capsules of red clover extract vs placebo. Cross-over. 90 days | Sex hormones, endometrium thickness | 80 mg isoflavones, Austria, Jadad 4 |
| Jayagopal 2002 | N=32 postMP women with diet-controlled type 2 diabetes. 147,1/82,1 mmHg | Intake of dietary supplementation with phytoestrogens vs placebo (cellulose). Cross-over. 12 wk | Glycemic control | 132 mg isoflavones, 30 g SP, UK, Jadad 5 |
| Jenkins 1999 | N= 31 hyperlipidemic men and potMP women. 120/79,5 mmHg | Combination of 2 plant components (SP and soluble fiber) incorporated into low-saturated –fat diet. Cross-over. 1 month | Lipid profile | 33 g SP, Canada, Jadad 1 |
| Jenkins 2000 | N=25 hyperlipidemic men and postMP women. 129/82,5 mmHg | Soy vs control of breakfast supplements. Cross-over. 3 wk | Lipid profile | 168 mg isoflavones, 36 g SP, Canada, Jadad 1 |
| Jenkins 2002 | N= 41 hyperlipidemic men and postMP women. 12% taking antiHT drugs. 124/78 mmHg | Comparison of diets: high soyfood diets vs low-fat dairy food (control) diet. Cross-over. 1 month | Lipid profile | 73 mg isoflavones, 50 g SP, Jadad 2 |
| Jorissen 2002 | N=120 elderly with criteria for age-associated memory impairment. 129,7/79,2 mmHg | Intake of phostatidil-serine soy-derived or placebo. 12 wk | Neurological evaluation, memory impairment | Netherlands. Jadad 3 |
| Katz 2007 | N=22 postMP women. 126,9/71,5 mmHg | Intake of soy phytoestrogens capsules vs placebo. Cross-over. 6 wk | Flow-mediated vasodilatation | 60 mg isoflavones, USA. Jadad 4 |
| Khaodhian 2008 | N=147 postMP women. 120,5/77 mmHg | Intake of daidzein-rich isoflavone vs placebo. 12 wk | Frecuency of hot flashes | 50 mg isoflavones, USA, Jadad 3 |
| Kreijkamp 2005 | N=202 postMP women. 140,9/75,3 mmHg | Intake of a isoflavone-rich supplement, mixed with food or dring, vs control (milk protein). 12 months | Flow-mediated dilatation (endothelial function) | 99 mg isoflavones, 25,6 g SP, Netherlands, Jadad 5 |
| Kurowska 1997 | N=34 patients with moderately elevaled serum colesterol levels. 131/77 mmHg | Incorporate into their normal diet: 2 soybeand products vs cows´milk. Cross-over. 4 wk | Lipid profile | 31 g SP, UK, Jadad 1 |
| Kwak 2012 | N=64 overweighted subjects. Excluded hypertensive patients. 122,5/85,5 mmHg | Intake of 3 pouches containing black soy peptide vs placebo (casein), and patients advised to mildly restrict their caloric intake. 12 wk | Body weight, body mass index | Korea. Jadad 3 |
| Lee 2012 | N=51 overweighted subjects. Excluded if taking medications, or chronic disorder. 118,1/75,6 mmHg | Intake of Korean fermented soy paste “doenjang” into supplement vs placebo tablets. 12 wk | Body mass index | 29,7 g SP, Korea, Jadad 2 |
| Levis 2011 | N=192 postMP women. | Intake of daily soy isoflavones vs identical placebo tablets. 2 years | Bone mineral density | 200 mg isoflavones, USA. Jadad 5 |
| Liao 2007 | N=30 obese adults. No history of chronic or cardiovascular disease. 112,6/76,5 mmHg | Intake of soy-based vs traditional (animal and vegetal) low-caloric diet. 8 wk | Body weight, body fat % | 45 g SP, Taiwan-China. Jadad 2 |
| Liu 2013 | N=60 postMP women with mildly hyperglucemia. 72% are pre o hyperten-sive patients. 127,1/77,8 mmHg | Diet of a SP and isoflavones vs milk protein basis. 6 months | BP, endothelial citokines | 100 mg isoflavones, 15 g SP, Hong-Kong-China. Jadad 5 |
| Liu 2015 | N=253 postMP women. Prehypertensive and grade 1 HT. 133,6/80,1 mmHg | Intake of soy flour vs low-fat milk powder. 6 months | BP | 49,3 mg isoflavones, 12,8 g SP, Hong-Kong-China. Jadad 5 |
| Llaneza 2010 | N=116 postMP women, non antiHT drugs users. 129,5/76,6 mmHg | Intake of a Mediterranean diet and exercise plan vs all this recommendations plus soy isoflavones supplement. 24 months | HOMA-IR | 40 mg isoflavones, Spain. Jadad 3 |
| Luckaczer 2006 | N=59 postMP women. Excluded uncontrolled hypertension (>140/90). 126,5/83,5 mmHg | Low glycemic index diet with a functional food delivering of SP and phytoestrogens vs AHA step I standard dietary program. 12 wk | Body weight. Lipid profile | 34 mg isoflavones, USA. Jadad 3 |
| Mathan 2007 | N=28 hypercholesterolemic subjects free of chronic diseases | SP based diets vs animal-protein diet. Cross-over. 6 wk | Lipid and glycemic profile | 132 mg isoflavones, USA. Jadad 1 |
| Meyer 2004 | N=26 mildly hypercholesterolemic and/or hypertensive volunteers, no farmacologic treatment. 132/77 mmHg | Foods containing whole-soybean and yoghurt vs equivalent dairy products. Cross-over. 5 wk | Lipid profile. Ambulatory BP | 80 mg isoflavones, 30 g SP, Australia, Jadad 1 |
| Miragharani 2013 | N=25 type2 diabetic patients with nephropathy. 85% with antiHT drugs. 136,6/87,5 mmHg | Diet containing soy milk (1 glass of 240 cc/day) vs cow´s milk. Cross-over. 4 wk | Anthropometric and biochemical measurements | Iran. Jadad 3 |
| Nasca 2008 | N=60 normotensive and hypertensive healthy postMP women | Intake of soy nuts vs therapeutic life change diet alone. Cross-over. 8 wk | Markers of inflammation –VCAM-1, sICAM-1, CRP, IL-6- | 101 mg isoflavones, 25 g SP, USA, Jadad 1 |
| Nestel 1999 | N=13 postMP women | Intake of tablets with isoflavones vs placebo. 5 wk | Systemic arterial compliance | 80 mg isoflavones, Australia, Jadad 3 |
| Nikander 2003 | N=56 postMP women with breast cancer. 8 patients take antiHT medication. 134,9/87,2 mmHg | Intake of tablets containing isoflavonoids vs similar looking placebo. Cross-over. 3 months | Kuppeman index (MP symptoms) | 114 mg isoflavones, Finland, Jadad 4 |
| Osmers 2005 | N= 304 postMP women. | Intake of 1 tablet of black cohosh extract vs matching placebo. 12 wk | Menopause Rating Scale I (climacteric complaints) | Germany. Jadad 5 |
| Oztürk 2009 | N=90 healthy early postMP women. Excluded uncontrolled hypertension (>170/105). 114/79 mmHg | Intake of isoflavones vs placebo tablet twice a day. 6 months | Serum homocysteine, nitrites, nitrates | 80 mg isoflavones, Turkey, Jadad 4 |
| Puska2004 | N=143 hypercholestero-lemic patients without significant signs of cardiovascular, renal disease. 131,2/80,8 mmHg | Intake of yoghurt containing isolated SP vs jplacebo matched in appearance. 8 wk | Lipid profile | 153 mg isoflavones, 41,4 g SP, Finland, Jadad 3 |
| Radhakrish-nan 2009 | N=100 postMP women. Excluded patients with hypertension. 123/80,4 mmHg | Intake of a supplementation (sackets of powders) of isoflavones vs placebo (casein protein). 6 months | Kupperman index, lipid profile | 75 mg isoflavones, 25 g SP, Pakistan, Jadad 3 |
| Rivas 2002 | N= 40 patients with mild-moderate HT. 153,4/99,8 mmHg | Intake of soya vs cow´s milk (500 ml, twice a day). 3 months | BP | 143 mg isoflavones, 18 g SP, Spain, Jadad 4 |
| Sagara 2003 | N=61 men with relatively high BP (SBP>=130) and/or total cholesterol. 138/84 mmHg | Diets contatining SP and isoflavones vs placebo diet. 5 wk | Urinary soflavones, BP | 80 mg isoflavones, 20 g SP, Scotland, Jadad 3 |
| Santo 2008 | N=19 healthy volunteers. Excluded cardiovascular history. 110,8/69,5 mmHg | Intake of supplements with isoflavone-rich SP vs milk protein. 4 wk | Lipid profile | 96,4 mg isoflavones, USA, Jadad 4 |
| Sathyapalan 2011 | N=60 patients with subclinical hypothyroidism. Excluded patients taking antiHT drugs. 141,1/76,3 mmHg | Comparison of high-dose phytoestrogens, representative of a vegetarian diet, vs low dose of phytoestrogens (western diet). Cross-over. 8 wk | Progression to overt hypothyroidism | 16 mg isoflavones, 30 g SP, USA, Jadad 4 |
| Simons 2000 | N=20 healthy volunteers postMP women. 135/85 mmHg | Intake of a commercial preparation of phytoestrogens (2 tablets/day) vs matching placebo. Cross- over. 8 wk | Flow-mediated endothelium-dependent vasodilatation | 80 mg isoflavones, Australia, Jadad 2 |
| Sirtori 1999 | N=21 severely hypercholesterolemic patients with resistance/intolerance to statins | Intake of a soya drink vs cow´s milk (similar composition and taste). Cross-over. 4 wk | Lipid profile | 35 g SP, Italy, Jadad 3 |
| Squadrito 2002 | N=60 healthy postMP ambulatory women | Intake of tablets of genistein vs placebo. 6 months | Flow-mediated endothelium dependent vasodilatation | 54 mg isoflavones, Italy, Jadad 2 |
| Squadrito 2013 | N=120 postMP women with MS. 135,4/78,4 mmHg | Intake of 2 tablets daily of genistein vs placebo. 1 year | HOMA-IR | 54 mg isoflavones, Italy. Jadad 5 |
| Takahira 2011 | N=48 obese adults with treatment for visceral, fat obesity. 138,5/83,2 mmHg | Formulas food with SP vs milk protein. 20 wk | Visceral fat area, subcutaneous fat area | 12 g SP, Japan. Jadad 4 |
| Teede 2001 | N=179 healthy men and post MP women. Excluded hypertensive patients. 132/78,5 mmHg. | Supplements of powder sackets SP/isoflavones vs placebo (casein). 3 months | BP, vascular compliance, endothelial function. | 118 mg isoflavones, 40 g SP, Australia, Jadad 3 |
| Teede 2003 | N=80 healthy men and postMP women. Excluded hyper-tensive patients. 127/72,5 mmHg | Intake of isoflavones enriched in biochanin or formonotein vs placebo. Cross-over. 6 wk | 24 hour ambulatory BP | 80 mg isoflavones, Australia, Jadad 3 |
| Teede 2006 | N=41 hypertensive but otherwise healthy men and postMP women 141/83,1 mmHg | Dairy supplement in breakfast with SP/isoflavones vs placebo (Sorghum, gluten, sugar, salt).Cross-over. 6 months | Isoflavones concentration in urine. | 118 mg isoflavones, 40 g SP, Australia, Jadad 3 |
| Tice 2003 | N=252 symptomatic recently menopausal women | Intake of 2 tablets once daily of isoflavones vs placebo. 12 wk | Change in frecuency of hot flashes | 82 mg isoflavones, USA. Jadad 5 |
| Uesugi 2004 | N=58 climacteric women (48% hypertensives). 140/84 mmHg | Intake of tablets of isoflavone supplements vs placebo. Cross-over. 4 wk | Bone mineral density. Climacteric symptoms | 42,2 mg isoflavones, Japan. Jadad 1 |
| vanHorn 2001 | N=127 postMP women with mild-moderate hypercholesterole-mia | Lipid lowering diet (motivational intervention techniques), with intake of soy vs milk. 6 wk | Lipid profile | 58,2 mg isoflavones, USA, Jadad 3 |
| vanNielen 2014 | N=15 postMP women with abdominal obesity. 122/71 mmHg | Controlled weight-maintaining, moderately high-protein diet rich in soy vs “traditional Dutch diet”.Cross-over. 4 wk | Insulin sensitivity, lipid profile | 48 mg isoflavones, Netherlands, Jadad 2 |
| Vigna 2000 | N=104 postMP women with hot flushes. 128,6/82,2 mmHg | To replace breakfast by beverages containing soy powder vs caseinate). 12 wk. | Lipid profile | 76 mg isoflavones, Italy Jadad 2 |
| Washburn 1999 | N=51 periMP women non hypercho-lesterolemic, non hypertensive. 132/82,2 mmHg | Isocaloric supplements given in a powder containing phytoestrogens vs complex carbohydrates.Cross-over.6 wk | Cardiovascular disease risk factors, menopausal symptoms | 68 mg isoflavones, USA, Jadad 4 |
| Welty 2007 | N=60 healthy postMP (pre, hyper and normotensive) women | TLC diet alone vs TLC diet + soy nuts. Cross-over. 8 wk | BP, lipid profile | 101 mg isoflavones, USA, Jadad 1 |
| Wong 2010 | N=23 men and postMP women with hyperlipidemia. 121,9/75,3 mmHg | Low-fat vs soy food-containing diet. Cross-over. 4 wk | Lipid profile | 61 mg isoflavones, 30 g SP, Canada, Jadad 2 |
| Wong-Kendall 2012 | N=85 men and postMP women. Excluded non treated HT. 124,7/77,3 mmHg | Weight-mantaining or reducting diet, with soy-phases vs control. Cross-over. 1 month | Lipid profile | 43 mg isoflavo-nes, 41 g SP, Canada, Jadad 2 |
| Wong-Taylor 2012 | N=24 postMP women with high-normal BP (prehyperten-sives). 140,4/82,5 mmHg | Intake of 2 tablets each day (isoflavones vs placebo). 6 wk | Changes in nitric oxide metabolism | 80 mg isoflavo-nes, Canada, Jadad 5 |
| Yildiz 2005 | N=80 healthy postMP women without cardiovascular disease. 127,5/77,6 mmHg | Intake of capsules of genistein vs placebo. 6 months | C-reactive protein levels | 40 mg isoflavones, Jadad 2 |

Table D: Calculating the number of unpublished trials using the Glesser-Olkin´s method.

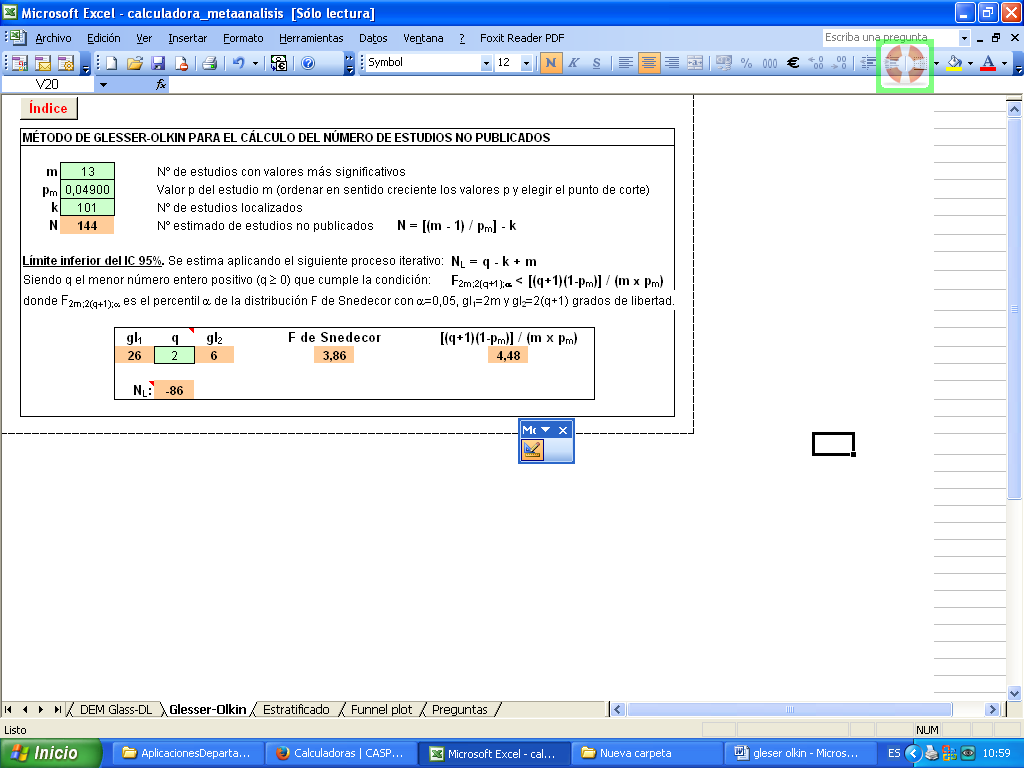


Table E: Special characteristics in several clinical trials included in the meta-analysis.

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| * The Garrido´s study (#30, Appendix) provides mean and SD, but values of diastolic BP are disproportionally low; perhaps it is a tipographical error. * Hall and Hallund´s team published 3 works in 2006 (#35, 36 and 37, Appendix) about postmenopausal women, whose numeric results are not identical; the first and second one can be made in subpopulations of the same work; Hallund and Tetens´ work (#37) seems different, with different active principle and length. * The 2 performed works by He et al (#39 and 40), developed in different countries (China and USA, respectively) describe similar results, which is against the idea that the decline in BP is higher in Eastern countries. |

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