Table 1. Overview of rodent studies, clinical trials and *in vitro* assays addressing BAT-mediated thermogenesis by phytochemicals and their impact on energy expenditure and weight control.

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| ***Pterostilbene*** | blueberries, berries, wine, wine grapes, sorghum(1) |
| Reference and model | Design | Sex and N  | Treatment | Outcome |
| (2) Golden Syrian Hamsters | DI | male n=8-10 per group | 2.5 mg/kg BW/d in HFD3 weeks | -BWplasma ↓C, ↓LDL, ↓LDL:HDL |
| (2)rat hepatic H4IIEC3 cells |  | male | 1,10,100 or 300 µM PTS30 min | ↑PPARα reporter activity |
| (3)Zucker fa/fa rats | DI | male n=10 per group | 15 mg/kg BW/d in HFD6 weeks | ↓BW, ↓fat massplasma ↓C, ↓insulin |
| (4)Wistar rats | DI | malen=9 per group | 15 or 30 mg/kg BW/d in HFHS6 weeks | ↓BW gain,↓total fat mass, ↓vWAT, ↓sWAT↑hepatic CPT1α and ACOX activity  |
| (5)Zucker fa/fa rats | orogastric catheter | malen=10 per group | 0, 15 or 30 mg/kg BW/d in chow diet,6 weeks | ↓BW, ↓AT weight↑iBAT mRNA/protein: NRF1, UCP1, PPARα↑iBAT CPT1b activity |
| (6)OLETF rats | DI | malen=6 per group | 300 mg/kg BW/d in chow4 weeks,  | -BW, ↓abdominal WAT, ↓total WAT ↓RER, ↑FO, ↑EE↓WAT FAS mRNA |
| (7)C57BL/6 mice | DI | male and femalen=8 per group/sex | 90 mg/kg BW/d in HFD30 weeks | ↓BW, ↑glucose tolerance (after 18 weeks)↑iWAT thermogenic genes (PPARγ, PGC1α, SIRT1, CIDEA, TBX1), ↑iWAT UCP1 protein* effects in m+f, stronger than in f vs m
 |
| (7) 3T3-L1 adipocytes | acute | male | 5 µM PTS for 24 hours, d12 | ↑UCP1 protein, ↑CIDEA, FGF21 mRNA |
| (8)hypercholesterolaemicCaucasian, AA | placeboparallel | male and female100 mg/d, n=20 (m5/f15)250 mg/d, n=20 (m6/f14)placebo, n=20 (m7/f13) | 100 or 250 mg/d* 1. weeks
 | -BMI (if stratified for C medication ↓BMI)plasma ↑total C, ↑LDL, -HDL |
| ***Resveratrol*** | peanuts and peanut products, grapes, red wine, soy, herbal remedies(9) |
| (10)C57Bl/6J mice | DI | malen=8-10 per group | 400 mg/kg BW/d in HFD15 weeks | ↓weight gain, ↓final BW, ↓WAT mass↑VO2, ↑cold-resistance (rectal T)↑iBAT mito content, ↑iBAT thermogenic genes (UCP1, PGC1α, PPARα)↑mito gene enrichment in muscle, ↑IS |
| (11)C57BL/6NIA | DI | malen=6-9 per group | 22.4 mg/kg BW/d in HFDmiddle aged mice,for 55 weeks | -fat distribution, -BW (trend for↓), ↑IS, -BT ↑survivalplasma -TAG, ↑C, ↓GLC, ↓insulin |
| (12)grey mouse lemur (*Microcebus murinus*) | DIBefore-after | malen=6 | 200 mg/kg BW/d4 weeks | ↑RER, ↓weight gain vs baseline week↓food intake, -locomotor activity |
| (13)mice (strain unknown) | DI | malen=8 per group | 0.4% w/w in chow diet8 weeks | ↓WAT mass, -BW, ↑VO2, -locomotor activity↑iBAT thermogenic genes (UCP1, PRDM16, SIRT1), plasma -C, -TAG, -GLC |
| (14)CD-1 mice | DI | femalen=6 per group | 0.1% w/w in HFD4 weeks | ↓BW gain, ↑VO2, ↓RER, ↑EE (p=0.065),↑UCP1+ in iWAT sections, ↓iWAT adipocyte size ↑pAMPK, UCP1, PRMD16 protein in iWATplasma ↓insulin, ↓TAG, -GLC |
| (14)SVF from iWAT of CD-1 mice | long-term | unknown | 10 µM RSVduring differentiation with brown adipogenic cocktail | ↑thermogenic genes (UCP1, ELOVL3, PGC1α, CIDEA, PRDM16), ↑UCP1, PRDM16 protein ↑respiration, ↑pAMPK* effects AMPK-dependent
 |
| (15)CD-1 mice | DI | female | 0.1% RSV w/w in HFD4 weeks | ↓BW gain, ↑BA number in iBAT sections ↑iBAT UCP1. PRDM16 and pAMPK protein |
| (16)Spargue-Dawley rats | DI | malen=8 per group | 30 mg/kg BW/d in HFHS6 weeks | -BW, ↓fat mass↑BAT thermogenic genes (UCP1, PGC1α, TFAM) ↑iBAT UCP1 protein, ↓acetylated PGC1α (muscle) |
| (17)obese, healthy (BMI>30)Denmark | placeboparallel | malen=12 per group | 500 mg RSV or placebo tablet/d4 weeks | -BW, -total fat mass, -vWAT mass, plasma –GLC, -C, -TAG,-ALT, -HbA1c-acetylated lysine, pAMPK in muscle |
| (18)non-obese, normoglycaemicCaucasian  | placeboparallel | femaleRSV n=15placebo n=14 | 75 mg RSV/d12 weeks | -BW, -fat mass, -sWAT mass, -vWAT massplasma -leptin,-C, -TAG, -NEFA, -GLC-REE, -BP, -IS-WAT microarray: -mito function, -FO genes-muscle SIRT1 activity |
| (19)older adults with IGTUS | before-after | male n=3female n=7 | 1, 1.5 or 2 g RSV/d4 weeks | -BW, -fat mass, -BPplasma –C, -TAG, -insulin, -ALT, -insulin↓post-meal GLC, ↓post-meal insulin |
| (20)obese, healthy men | placebocrossover | male n=11 | 150 mg RSV/d (resVida) or placebo, 30 days per treatment | -BW, -fat mass↓SEE (caloric restriction), ↑diurnal RERmuscle ↑pAMPK, ↑mito activity, ↑SIRT1, PGC1α protein  |
| ***Quercetin*** | apples, onions, black currants, red wine, black tea, nuts, seeds, shallots(21) |
| (22)Sprague–Dawley rats | DI | malen=7 per group | 0.36% or 0.72% w/w OPE in HFD, 8 weeks | ↓BW, ↓intra-abdominal fat mass |
| (23)Wistar rats | DI | malen=12 per group | 185, 270, 925 mg/kg BW/d in HFD8 weeks | ↓BW gain, ↓total fat mass, ↓vWATplasma ↓TAG, ↓NEFA, -C, ↓GLC at high dose↓hepatic fat content, ↑fecal lipids↑PPARα, ↑SIRT1, ↓ACC, ↓FAS mRNA (WAT) |
| (24)Zucker fa/fa rats | oral gavage | malen=7 per group | 10 mg/kg BW/d RSV or vehicle with HFD10 weeks | ↓BW gainplasma ↓TAG, ↓C, ↓GLC, ↓insulin, ↓HOMA-IR↓TNFα production, iNOs protein in vWAT |
| (25)C57BL/6 | DI | malen=6 for OPEn=9 for control | 0.5% w/w OPE in HFD8 weeks | -BW gain, -eWAT mass, -rWAT mass ↑thermogenic genes (UCP1, PRDM16, CIDEA, PGC1α) in rWAT |
| (25)3T3-L1 adipocytes | long-term | male | 100 µM quercetin at d5, 7, 9 | ↑ UCP1, SIRT1, PGC1α mRNA and protein↑pAMPK, pHSL, ↓lipogenic genes (FAS, ACC) |
| (26)C57BL/6 | DI | malen=8-10 per group | 0.1% w/w quercetin in HFD8 weeks | -BW, -fat mass,-EE, -RER, -FO, -CHO, ↓plasma TAG ↑sWAT thermogenic genes (UCP1, ELOVL3)↑UCP1+ cells in sWAT, ↑FA uptake in sWAT-mito content sWAT, -BAT morphology/genes |
| (27)C57BL/6J  | DI | malen=8 per group | 0.8% w/w in HFD8 weeks | -BW, -adiposity, -EE, -RER↓plasma inflammatory cytokines (INFγ, IL1, IL4) |
| (28)C57BL/6 | DI | malen=6 per group | 0.05% w/w quercetin in HFD9 weeks | -BW, ↓WAT adipocyte size ↑UCP1+ cells, ↑UCP1, ↑PGC1α protein in iWAT↑iWAT thermogenic genes (UCP1, PRDM16, MEM26, NRF-1) ↑PKA, pAMPK protein in iWAT↑plasma NE, ↑iBAT UCP1 |
| (29)isolated Wistar rat adipocytes  | acute | male | 0, 1, 10, 100 or 250 µM quercetin, 15 min | ↑PDE activity, ↑cAMP, ↑epinephrine-stimulated lipolysis |
| (30)C57BL/6 | DI | malen=8 per group | 0.1% w/w quercetin in HFD12-17 weeks | ↓BW, ↓sWAT mass, ↓eWAT mass, ↓eWAT cell size, plasma ↓leptin, ↓insulin, ↓TNFα, ↓IL6↓mast cell infiltration eWAT↓eWAT TNFα, IL6↑eWAT SIRT1, pAMPK protein↑iBAT UCP1 mRNA,  |
| (31)university studentshealthyKorean | placebocrossover | female n=12 | 100 mg/d quercetin or placebo capsule for 2 weeks each | -BW, -fat mass, -WHR, -BMI, -SBP, -DBPplasma –TAG, -C, -LDL |
| (32)overweight/obese subjects(BMI>23 kg/m2)Korean | placebocrossover | femalequercetin n=18placebo n=19 | 100 mg/d quercetin or placebo capsules12 weeks | -BW, -fat mass, -BMIplasma –ALT,-leptin, ↑adiponectin, -TNFα, -IL4 |
| (33)overweight/obese subjectsKorean | placebocrossover | male n=5female n=31 | 100 mg/d quercetin or placebo capsules12 weeks | -BW, -fat mas, -BMI, -WC, -RER, -REEplasma –GLC, -C, -LDL, ↓TAG, -leptin -before-after effects on REE, BW, RER, BMI within quercetin group |
| (34)Meta-analysis | 9 RCTs | male=189female=336 | 100 to 1000 mg/d2 to 12 weeks | -BW, -WC, -WHR, -BMI |
| ***Luteolin*** | peppers, carrots, cucumber, pomegranate, herbal spices, cabbage, broccoli, medicinal herbs (sage)35  |
| (36)C57BL/6 | DI | malen=8 per group | 0.01% w/w in HFD12 weeks | ↓BW, ↓sWAT mass, ↓vWAT mass, ↓BAT mass↓eWAT adipocyte size, ↑IS↓mast cell infiltration eWAT plasma –insulin, ↓leptin, ↑adiponectin |
| (37)C57BL/6 | DI | malen=13 per group | 0.005% w/w in HFD16 weeks | ↓BW, ↓sWAT mass, ↓vWAT massplasma ↓TAG, ↓C, ↓NEFA, ↑IS↑eWAT FAO genes (PGC1α, ADRB3, CPT2, PNP2, ACAD) |
| (38)C57BL/6 | DI | malen=8 per group | 0.01% w/w in HFD20 weeks | ↓BW, ↑IS↓plasma MCP1, IL6, TNFα↓macrophage infiltration vWAT, ↓M1/M2-ratio |
| (39)C57BL/6 | DI | malen=12 per group | 0.01% w/w in HFD12 weeks | ↓BW, ↓weight gain, ↓fat mass↑VO2, ↑CO2, ↑RER, ↑BAT UCP1 protein↑UCP1+ cells in sWAT, ↑thermogenic genes (PGC1α, UCP1, SIRT1, PPARα, ELOVL3)↑SIRT1, pAMPK, pACC protein in BAT, sWAT |
| (39)primary subcutaneous and brown adipocytes | acute | unknown | 24 hours of 100 nM luteolin on differentiated cells | ↑SIRT1, UCP1, PGC1α protein↑pAMPK, ↑pACC↑thermogenic genes (UCP1, PRDM16, ELVOL6, PPARα)* effects AMPK-dependent
 |
| ***Catechins*** | grapes, apples, strawberries, apricots, broad beans, cocoa-products, green/black/oolong tea(40,41) |
| (42)Sprague-Dawley rat | DI | malen=8 per group | 2% w/w green tea extract in HFD, 2 weeks | -BW, ↓fat mass, ↑BAT weight↑BAT DNA/protein content↑EE, propranolol prevented ↑EE  |
| (43)Sprague-Dawley rat | DI | malen=8 per group | 0.5% w/w catechins in chow8 weeks | -BW↑BAT mass, ↓pWAT mass, ↓eWAT mass↑BAT UCP1 expressionplasma ↓TAG, GLC, leptin |
| (44)New Zealand black mice | gavageshort-term | malen=6 per group | 3x 500 mg/kg EGCG or placebo, chow diet | -BW, -fat mass-EE, ↓RER (p=0.053), -activity |
| (44)New Zealand black mice | DI | malen=11 per group | 0.1% w/w EGCG in HFDDIO 4 weeks, DI 4 weeks | ↓BW, ↓fat mass, -food intake, ↓eWAT weightplasma ↓TAG, -NEFA-UCP1 mRNA in BAT |
| (45)iBAT depots from Sprague-Dawely rat | acute | male | 100 or 200 µM green tea extract for 40-90 min | ↑iBAT respiration (100 µM)↑norepinephrine (0.1 µM) stimulated respiration at 100 or 200 µM |
| (46)healthy menGeneva, CH | placebocrossover | malen=10 | 3x daily capsule with 50mg caffeine and 80 mg EGCG, 50 mg caffeine or placebo | ↑diurnal EE, ↑total EE, -nocturnal EE↓total, diurnal and nocturnal RER ↑FO, ↑urinary norepinephrine excretion |
| (47)young, healthy subjectsLausanne, CH | placebocrossover | male n=15female n=16 | 3x daily beverage with 100 mg caffeine and 180 mg catechins or placebo, 3 days | ↑total EE, diurnal EE, nocturnal EE-substrate oxidation-catecholamine secretion |
| (48)healthy men(BMI 23-27 kg/m2)Laval University, CA | placebo crossover | malen=14 | 3x daily capsule with 200 mg caffeine plus 90, 200, 300 or 400 mg EGCG or placebo | ↑total EE, -SEE-RER,-FO-catecholamine secretion |
| (49)overweight/obese men(BMI=31 kg/m2)Berlin, DE | placebocrossover | male n=10 | 300 or 600 mg EGCG or placebo capsule for 3 days | -EE (pre- and post-meal)↓post-meal RQ, ↑post-meal FO (300 mg), ↓post-meal CHO (300 mg)plasma -NEFA,-insulin, GLC |
| (50) Meta-analysiseffect of EGCG on EE or anthropometric measures | 8 RTC | n=268  | EGCG:300 or 600 mg/d for 2-3 days300 to 800 mg/d for 2-12 weeks | ↑EE, ↓RER, -FO, - BMI, ↓WC, -fat percentage |
| (51)healthy menJapanese | placebocrossover | male n=15low BAT activity (mean SUV=1.9) | 615 mg catechins plus 77 mg caffeine or placebo (81 mg caffeine), 2x daily as beverage for 5 weeks | -BMI, -fat mass, -WC, -EE↑cold-induced thermogenesis, ↑cold-induced FO |
| (51)healthy menJapanese | acutecrossover | male n=15 | 615 mg catechins plus 77 mg caffeine or placebo (81 mg caffeine), single beverage | ↑post-drink EE,↑EE in high BAT (SUV>2) vs low BAT subjects, pre-assessed by 2 hours cold-exposure  |
| (52)healthy university studentsJapanese | placeboparallel | femalecatechin n=10placebo n=11 | 640 mg catechins/d or placebo, beverage12 weeks | -BMI, -fat mass, -BW↑BAT density in supraclavicular regionneg. correlation between EMCL and BAT density |
| (53)overweight/obese childrenJapanese | placeboparallel | catechin group (m21, f5)placebo group (m13, f6) | 576 mg/d catechins or placebo (75 mg/d catechins),as Oolong tea, 12weeks | -no changes in anthropometric or metabolites in catechin vs control↓WC, ↓SBP, ↓LDLC in catechin group when stratified to baseline values |
| (54)normal to overweight menJapanese(36) | placeboparallel | malecatechin group n=17placebo group n=19 | 690 mg/d catechins or placebo (22 mg/d),as Oolong tea, 12weeks | ↓WC, ↓skinfold thickness, ↓total fat area↓visWAT and sWAT areaplasma –NEFA, -TAG, -C, -GLC, -insulin |
| (55)obese adult Thais(BMI>25kg/m2) | placeboparallel | catechin group:(m21, f9) placebo group:(m21, f9) | 3x daily 250 mg catechins or placebo in capsule12 weeks | ↓BMI, ↓BW, ↓fat mass, ↓WC, -HC↓RER, ↑REE |
| (56)overweight/obese adults(BMI >25-32 kg/m2)Caucasian | before-after | female n=63male n=7 | 270 mg/d EGCG in capsule | -BW, ↓WC-SBP, -DBPplasma -C |
| (57)Meta-analysiseffect of green tea extracts on anthropometry | 15 RTCs | n=1243 | catechin intake combined with caffeine intake (141 up to 1207 mg/d)8 to 24 weeks | ↓BMI, ↓BW, ↓WC, -WHR when compared to caffeine-intake only |
| ***Phytoestrogens*** | kidney beans, mung bean sprouts, Japanese arrowroot, soybean, soy products (tofu, soy milk, soy flour, soy sauce)(58) |
| (59)C57/B6J mice | DI | malen=7-8 | 5% isoflavone-rich fraction of *Puerariae* flower in HFD,7 weeks | ↓BW, ↓WAT mass, ↓BAT mass-food intake, -fecal lipid content↑VO2, -RER, ↑UCP1+ cells in BAT sections |
| (60)CD-1 mice | DI | male n=12female n=12 | 25% w/w soy-rich diet (150 pmm daidzein, 190 ppm genistein) vs soy-free diet16 weeks | ↓BW, ↓intra-abdominal fat mass, ↓iWAT, ↓eWAT/ovWAT, ↓WA adipocyte size↓BAT mass (male), ↑brown appearance, ↓lipid droplet size↑cold-resistance (rectal T), ↑VO2, ↓RER (only male data available) |
| (61)Sprague-Dawley rats | ovxDI | femalen=10 per group | isoflavone-rich (200 µg/g) or isoflavone-free diet13 days | ↓BW gain, ↓abdominal fat mass↓serum leptin |
| (62)Long-Evans rats | DI | male | isoflavone-rich (600 ppm) or isoflavone-free (10-15 ppm) dietup to 75 days of age | ↑food intake, ↓BW gain, ↓WAT mass, ↓BAT massplasma ↑T3, ↓insulin, leptin↑UCP1 protein in BAT |
| (63)Wistar rats | DIO with DI | malen=16 per group | 50 mg/kg BW daidzein or vehicle, i.p.DIO 10 weeks, 14 d treatment | ↓caloric intake, ↓BW gain↓hepatic liver content plasma ↓TAG, -C, ↑GLC, -ALT ↑UCP1 protein in BAT  |
| (64)ICR mice | DIO with gavage | male | 0, 25, 50 or 100 mg/kg BWDIO 8 weeks, 30 d treatment | ↓BW. ↓vWAT mass, ↓sWAT massplasma ↓C, ↓LDL, ↓NEFA, -TAG, ↑HDL |
| (64)primary adipocytes differentiated from eWAT SVF | acute | male | 0, 1, 3, 16, 64 µM daidzein 24 hours | ↑glycerol release (dose-dependent) |
| (65)adipocytes from Wistar rats | acute | male | 0.01, 0.1 or 1 mM daidzein | ↑basal lipolysis (dose-dependent)↑epinephrine-stimulated lipolysis (0.1 mM)↓lipogenesis from GLC (0.1 and 1 mM) |
| (66)C57BL/6 | DI | femalen=8 per group | 0.25% w/w genistein in HFD8 weeks | ↓BW, -sWAT weight, -vWAT weight↓BAT weight (ns), ↑IS plasma –TAG, -C, HDL-, ↓LDL, ↓NEFA↑iWAT browning (UCP1, CIDEA mRNA)↑ hypothalamic UNC3 mRNA |
| (67)C57BL/6 | DI | malen=7-8 per group | 0.2% w/w genistein in casein diet or casein only (control)60 days | -BW, ↑glucose tolerance↑thermogenic genes in sWAT (UCP1, PGC1α)↑UCP1 protein in sWAT,-BAT↑EE, ↑VO2, ↑cold-resistance (rectal T), -RERplasma –TAG, ↓GLC, ↓insulin |
| (67)primary adipocytes from iWAT of mice | acute | unknown | 0, 5, 15, 30 µM genistein for 1 hour | -basal respiration↑maximal respiration |
| (68)immortalized brown adipocytes | long-term | unknown | 0, 0.1, 1 or 40 µM of genistein on differentiated adipocytes, 3 days treatment | ↑UCP1 promoter activity (luciferase)↑UCP1 activity (immunofluorescence intensity) |
| (69)C57BL/6 | oral gavage | male and female | 50 to 200 mg/kg BW genistein or vehicle for 15 d | ↓BAT mass, ↓eWAT (m), ↓abdominal WAT (f)plasma ↓TAG, ↓C for 50 mg/kg BW |
| (70)postmenopausal women (BMI=23.6 kg/m2)Chinese, equol-producer | placeboparallel | femalen=90 per group | 40 g soy flour, 40 g low-fat milk powder with 63 mg daidzein, 40 g low fat milk powder (placebo)daily, 6 months | -BW, -BMI, -WC, -HC, -WHR, -fat mass |
| (71)adolescent malesTasmania | placeboparallel | maleisoflavone n=69placebo n=59 | 50 mg isoflavone equivalents or placebo tablets daily6 weeks | -BW |
| (72)obese women (20-65 yrs)(BMI 30-40 kg/m2)USA | placeboparallel | femalesoy group n=22casein group n=21 | 3x daily soy (50 mg isoflavone) or casein (3.5 mg isoflavone) shake, 16 weeks | -WC, -weight loss, -fat mass, -truncal fat-SBP, -DBP |
| (73)impaired glycemic controlChinese women (30-70 yrs) | placeboparallel | female daidzein n=55genistein n=56placebo n=54 | 10 g soy protein with no addition, 50 mg daidzein or 50 mg genistein24 weeks | -BMI, -WC, -fat mass-IS |
| (74)patients with NAFLDIranian (16-69 yrs) | placeboparallel | genistein group(m30, f11)placebo group(m31, f10) | 250 mg daidzein or placebo capsules8 weeks | -BW, ↓fat percentage, ↓WHR, ↓WC, -BMIplasma ↓TAG, -C, -LDL, -HDL, ↓insulin↓HOMA-IR |
| (75)postmenopausal women(BMI>30 kg/m2)Caucasian or AA | placeboparallel | soy group (n=17)8 AA, 9 Caucasianplacebo (n=16)8 AA, 8 Caucasian | soy protein with isoflavones (160 mg) or placebo casein, shake3 months | -BW, -total fat, -lean mass↓abdominal, ↓subcutaneous abdominal fat, ↓vWATfor AA: weight loss more than for Caucasianfor Caucasian: vWAT loss bigger than for AAplasma ↓IL6, -CRP, -TNFα, -leptin, -HDL, -LDL, -C, -TAG |
| (76)postmenopausal women(mean BMI=30.5)Caucasian | placeboparallel | femalesoy group n=9placebo n=6 | soy protein with isoflavones (160 mg) or placebo casein,shake3 months | -BMI, -BW, -total fat mass, -IS↓subcutaneous abdominal fat, ↓intra-abdominal fatplasma -GLC, -insulin |
| (77)Meta-analysisEffect of soy-isoflavones on BW in non-Asian, postmenopausal women | 9 RCTs | isoflavones n=272placebo n=256 | 40 to 160 mg/d of isoflavones8 weeks to 1 year | ↓BW with isoflavone intake<100 mg or <6 months more effective more effective with BMI<30 kg/m2 |
| (78)Meta-analysiseffect of soy and isoflavones on anthropometric measures | 24 soy RTCs17 isoflavones RTCs | soy: f1265, m45 (1 RTC)m/f =74 (mixed)isoflavones:f1177, m0 | soy protein: 7.5 to 116 mg/d4 weeks to 2 yearsisoflavones: 33.3 to 300 mg/d8 weeks to 2 years  | soy:-BW, >40 g/d ↑BW, 1-3 months ↑weight gain-WC, -fat massisoflavones:↓BMI for postmenopausal and Caucasian women<100 mg and 2-6 months more effective-fat mass, -WC |
| ***Capsaicinoids*** | chili, bell peppers, jalapenos, habaneros, cayenne pepper, red pepper(79,80) |
| (81)Std ddY mice | intragastric tube | unknownn=6-8 | vehicle, 10 mg/kg BW capsaicin or 10, 50 mg/kg BW capsiate, 2 weeks | ↓BW (ns), -food intake-BAT mass, ↓eWAT for capsiate, ↓pWAT for capsaicin and 50 mg/kg capsiate |
| (81)Std ddY mice | intragastric tube, acute | unknownn=6-8 | Vehicle, 10 mg/kg BW capsaicin or 10 mg/kg BW capsiate, 3 hours | ↑VO2 for capsaicin and capsiate, ↑serum adrenalineplasma ↑NEFA, ↓TAG |
| (82)C57BL/6 or TRPV1 -/- mice | intragastric tube, acute | malen=5-18 | vehicle, 10 mg/kg BW capsaicin or 10 mg/kg BW capsiate, 3 hours | ↑VO2 (capsaicin, capsiate at 10 mg/kg BW) ↑FO (capsaicin, capsiate at 10 mg/kg BW), ↓CHO↑BAT and colonic T (50 mg/kg capsinoids, 10 mg/kg capsaicin) ↓T increase after denervation of jejunal nerves at 50 mg/kg capsinoid* effects in wt but not TRPV-/- mice
 |
| (83)TRPV1 -/- or wt miceB6.129X1 | DI | male | 0.01% w/w capsaicin in HFD32 weeks | ↓weight gain, ↓BW, ↑BAT UCP1, BMP8b protein↑activity, ↑RER, -food intake, ↓BAT TAG content, ↑BAT glycerol release (basal or forskolin-stimulated) ↑TRPV1 protein in BAT↑Ca2+ influx in isolated BA (2 µM CAP)↑pAMPK, pSIRT1 in BAT↓PRDM16, PPARγ acetylation (HEK293 1 µM CAP), ↑PRDM16 and PPARγ interaction in BAT lysate* effects blunted in TRPV-/- vs wt mice
 |
| (84)TRPV1 -/- or wt miceB6.129X1 | DI | malen=40 per group | 0.01% w/w capsaicin in HFD26 weeks | ↓weight gain, ↑TRPV1 mRNA in iWAT, eWAT↑EE, ↑activity, -fecal lipid content, ↑RER, ↑VO2↑UCP1, BMP8b, PPARα/γ protein in s/eWAT, ↑sWAT lipolysis (basal, forskolin-stimulated)↓PRDM16, PPARγ acetylation in sWAT↑pAMPk, CaMKKII activation in sWAT↑Ca2+ influx in isolated WA (2 µM CAP)* effects blunted in TRPV-/- vs wt mice
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| (85)C57BL/6 | DIO+DI | malen=6 per group | 0.01% w/w capsaicin in HFDDIO 10 weeks, 10 week DI | ↓BW, ↓weight gain, ↑eWAT, ↓rWAT mass-food intake, ↓WAT adipocyte size ↑glucose tolerance, ↑adiponectin, ↓leptin↑TRPV1 expression WAT |
| (86)Sprague-Dawley rats | intra-muscular | femalen=9-18 per group | 0.6, 0.7, 0.8 mg/kg BW capsaicin or DMSO, 80 to 120 min | ↑BAT and rectal T with 0.8 mg/kg BW-BAT weight, -mito content↑BAT respiration |
| (87)Std ddY mice | intragastric tube | malen=9-10 | 10 mg/kg BW capsiate or vehicle, 2 weeks | -BAT mass, ↓eWAT, ↓pWAT↑VO2, ↑FO, ↑CHO, ↑UCP1 protein (BAT)↑UCP1 mRNA (eWAT, BAT),  |
| (87)Std ddY mice | intragastric tube, acute | malen=4 per group | 10 mg/kg BW capsiate or vehicle for 30 min | ↑UCP1 mRNA in BAT |
| (88)healthy young menBritish | acute | male | breakfast with 3g chili sauce | ↑post-meal EE |
| (89)long distance runnersJapanese | acutecrossover | malen=8 | breakfast with or without 10 g red pepper | ↑post-meal EE (30 min)↑RER, ↑CHO, ↓FO* effect blocked by propranolol
 |
| (90)healthy young menCaucasian | placebocrossover | male n=10 | appetizer with or without 6 g of red pepper | ↓energy intake at lunch and dinner↑sympathetic: parasympathetic nerve activity |
| (91)healthy lean subjectsCaucasian  | placebo crossover | male n=11female n=19 | 1030 mg red pepper in lunch | -EE post-meal-RER-CHO, -FO, ↑peak plasma GLP-1,-ghrelin |
| (92)overweight subjects(mean BMI=29.4 kg/m2)Caucasian, AA, other | placeboparallel | male (ethnicity)Placebo (16,9,3)3 mg (15, 9, 1)9 mg (10, 4, 2) | 0, 3, 9 mg dihydrocapsiate in gel capsule4 weeks | -RMR (p=0.054 for 3 mg vs placebo)↑RMR dihydrocapsiate vs placebo |
| (93)Meta-analysis effect of capsaicin or capsiate on EE, RER | capsiate on EE 13 RCTscapsiate on RER 9 RCTscapsaicin on EE 13 RCTscapsaicin on RER 10 RCTsfemale/male unknown | capsaicin doses: <7, 20-35 mg, 135-150 mg/ddihydrocapsiate doses: <1.5, 2-4 or 6-9 mg/d | ↑EE at 2-9 mg/d for capsiate ↑EE at 135-150 mg/d for capsaicin↑FO at 6-9 mg/d capsiate↑FO at 20-150 mg/d for capsaicin↑SNS activity (1 RCT) |
| (94)healthy adult participants (BMI 20-30)Caucasian | acutecontrolled | N=15 per group(m8, f7) | 0 or 7.68 mg/d capsaicin with 100% or 75% of daily energy requirements26 hours | -TEE 100% CAP vs 100% control (c) -DIT 75% CAP vs 100% c, ↓75 % c vs 100% -REE 75% CAP vs 100% c, ↓75 % c vs 100% ↑FAO 75% CAP vs 100% c, -75 % c vs 100%↓CHO 75% CAP vs 100% c  |
| (95)healthy adults BMI 25-30 kg/m244% Hispanic, 41% white, non-Hispanic, 13% black, 2% others | placeboparallel | capsinoids (m21, f22)Placebo(m17, f20) | 6 mg capsinoids or placebo capsule with MCTG, rapeseed oil12 weeks | -BW, -fat mass, -abdominal fat-EE (only m): 54 kcal/d higher with CAP (p=019)-FO (only m): 21 mg/min higher with CAP (p=0.06) |
| (96)lean, healthy subjectsSingapore | crossovercold vs capsinoids | Male n=8, female n=12BAT+ m6/f6BAT- m2/f6 | 12 mg capsinoids in capsule with rapeseed oil and MCTG | ↑FDG-uptake in BAT↑EE, higher in BAT+ subjects↑FO, ↓RERplasma –GLC, -TAG, ↑C, ↑NEFA |
| (97)young healthy menJapanese | placebocrossoveracute | male n=18BAT+ n=10BAT- n=8 | 9 mg capsinoids or placebo capsule with rapeseed oil, MCTG2 hours | ↑EE in BAT+ with capsinoids vs placebo-RER, -skin T |
| ***Berberine*** | barberry, supplements from bark, root, stems or leaves from plants of the *Berberis* genus (e.g. goldenseal, goldthread, Oregon grape, tree turmeric)(98) |
| (99)db/db mice | i.p. | maleBBR n=17vehicle n=16 | 5 mg/kg BW on chow diet26 days | ↓BW, ↓eWAT mass, ↓sWAT adipocyte size ↓intra-abdominal fat, ↑IS,↑BAT mRNA, PPARα, PGC1α ↓FAS↓WAT mRNA FAS, PPARγ, SREBP1c, aP2 |
| (99)3T3-L1 adipocytes | acute | male | 5 µg/mL BBR for 60 min | ↑pAMPK, ↑pACC |
| (100)db/db mice | long-termi.p | malen=5 per group | 5 mg/kg BW on chow diet26 days at 22°C or 30°C | ↓BW, ↓fat mass, ↓plasma NEFA↑rectal T, ↑VCO2, ↑VO2, ↑EE↑cold-resistance (core T)↑BAT activity (PET/CT)↑BAT mito content, ↑oxphos, ↓BAT mass↑BAT UCP1, PGC1α, CPT1, pAMPK protein↑iWAT thermogenic genes (UCP1, NRF1) ↑UCP1+ cells, ↑mito content, ↑UCP1 protein* effects blunted at 30°C
 |
| (101)C57BL/6 | DI | male | 5 mg/kg BW, i.p. on chow diet, 4 weeks | ↑hepatic FGF21 expression, ↑plasma FGF21↑iBAT mRNA (UCP1, DIO2, PRMD16) |
| (102)C57BL/6 | DIO | malen=7-8 | 1.5 mg/kg BW/d on HFDDIO 8 weeks, DI 6 weeks | ↓BW gain, ↓pWAT, iWAT mass↑rectal T, ↑EE, ↑VO2, ↑BAT activity, volume (PET/CT), ↑UCP1+ cells in BAT↓BAT PRDM16 promoter methylation* effects blunted in adiponectinCre AMPKα1/2 mice
 |
| (102)BAT SVF cells | long-term | male | 250 nM BBRduring differentiation until d8 | ↑basal and uncoupled respiration↑BA adipogenesis (↑UCP1+ cells)↑fatty acid oxidative BAT-specific genes↑UCP1, PGC1α, PRDM16 protein |
| (102)patients with NAFLDmean BMI=29 kg/m2China | before-after | not defined | 1.5 g BBR/d1 month | ↓BW, ↓WC, ↓BMI, -total fat mass,↓vWAT mass, ↓sWAT mass↓HOMA-IR↑BAT volume, BAT activity  |
| (103)subjects with NAFLDChina | controlledparallel | LSI (m32/f30)LSI+P (m28/f32)LSI+BBR (m38/f24) | LSI+1.5g BBR/d, LSI+15 mg/d pioglitazone, LSI only16 weeks | ↓hepatic fat content vs LSI, ↓BW, ↓BMI vs LSI and vs LSI+pioglitazone-HbA1c, ↓HOMA-IR vs LSI,  |
| (104)newly diagnosed diabetics no pharmacotherapyChina | placeboparallel | placebo (m38, f28)BBR (m31, f21) | 1.5 g BBR/d or placebo12 weeks | -BW, ↓BMI, -WHRplasma –FBG, ↓PBG, ↓HbA1c, -HOMA-IR, ↓C,- insulin, -TAG |
| (105)type 2 diabetics with poor glycemic controlChina | before-after | n=48sex not stated | 1.5 g BBR/d plus prescribed diabetes medication12 weeks | ↓WC, ↓WHR, -BMIplasma ↓FBG, ↓PBG, -TAG, ↓C, ↓insulin↓HOMA-IR |
| (106)obese adults Caucasian | before-after | male n=2female n=5 | 1.5 g BBR/d 12 weeks | -BMI, -WHR, - fat percentageplasma –GLC,-TAG, ↓C, ↓ALT, ↓AST-plasma inflammatory markers |

AA, African American, BAT, brown adipose tissue; BBR, berberine; BW, body weight; BMI, body mass index, C, cholesterol; CHO, carbohydrate oxidation; d, day; DI, dietary intervention; DIO, diet-induced obesity; DIT, diet-induced thermogenesis; EE, energy expenditure; EMCL, extramyocellular lipid; f, female; FBG, fasting blood glucose; FO, fat oxidation; HC, hip circumference; HFHS, high fat high sucrose; IS, insulin sensitivity, IGT, impaired glucose tolerance; i.p., intraperitoneal; LSI, life style intervention; m, male; MCTG, medium chain triglyceride; mito, mitochondria(l); NAFLD, non-alcoholic fatty liver disease, NEFA, non-esterified fatty acids; ovx, ovariectomized, PBG, postprandial blood glucose; RCT, randomized controlled trial; REE, resting energy expenditure; RER, resting energy expenditure; SEE, sleeping energy expenditure; SUV, standardized uptake value; T, temperature; TAG, triacylglycerol, TEE, total energy expenditure; WC, waist circumference; WHR, waist-hip-ratio; WAT, white adipose tissue, wt, wild-type; - unchanged, ↓decrease, ↑increase compared to placebo or baseline

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