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 HFD  3 weeks | -BW plasma ↓C, ↓LDL, ↓LDL:HDL |
| (2)  rat hepatic H4IIEC3 cells |  | male | 1,10,100 or 300 µM PTS  30 min | ↑PPARα reporter activity |
| (3)  Zucker fa/fa rats | DI | male  n=10 per group | 15 mg/kg BW/d in HFD 6 weeks | ↓BW, ↓fat mass  plasma ↓C, ↓insulin |
| (4)  Wistar rats | DI | male  n=9 per group | 15 or 30 mg/kg BW/d in HFHS  6 weeks | ↓BW gain,  ↓total fat mass, ↓vWAT, ↓sWAT  ↑hepatic CPT1α and ACOX activity |
| (5)  Zucker fa/fa rats | orogastric catheter | male  n=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 | male n=6 per group | 300 mg/kg BW/d in chow 4 weeks, | -BW, ↓abdominal WAT, ↓total WAT  ↓RER, ↑FO, ↑EE  ↓WAT FAS mRNA |
| (7)  C57BL/6 mice | DI | male and female  n=8 per group/sex | 90 mg/kg BW/d in HFD 30 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)  hypercholesterolaemic  Caucasian, AA | placebo  parallel | male and female  100 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 | male  n=8-10 per group | 400 mg/kg BW/d in HFD  15 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 | male  n=6-9 per group | 22.4 mg/kg BW/d in HFD  middle aged mice,  for 55 weeks | -fat distribution, -BW (trend for↓), ↑IS, -BT ↑survival  plasma -TAG, ↑C, ↓GLC, ↓insulin |
| (12)  grey mouse lemur (*Microcebus murinus*) | DI  Before-after | male  n=6 | 200 mg/kg BW/d  4 weeks | ↑RER, ↓weight gain vs baseline week  ↓food intake, -locomotor activity |
| (13)  mice (strain unknown) | DI | male  n=8 per group | 0.4% w/w in chow diet  8 weeks | ↓WAT mass, -BW, ↑VO2, -locomotor activity  ↑iBAT thermogenic genes (UCP1, PRDM16, SIRT1), plasma -C, -TAG, -GLC |
| (14)  CD-1 mice | DI | female  n=6 per group | 0.1% w/w in HFD  4 weeks | ↓BW gain, ↑VO2, ↓RER, ↑EE (p=0.065),  ↑UCP1+ in iWAT sections, ↓iWAT adipocyte size  ↑pAMPK, UCP1, PRMD16 protein in iWAT  plasma ↓insulin, ↓TAG, -GLC |
| (14)  SVF from iWAT of CD-1 mice | long-term | unknown | 10 µM RSV  during 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 HFD  4 weeks | ↓BW gain, ↑BA number in iBAT sections  ↑iBAT UCP1. PRDM16 and pAMPK protein |
| (16)  Spargue-Dawley rats | DI | male  n=8 per group | 30 mg/kg BW/d in HFHS  6 weeks | -BW, ↓fat mass  ↑BAT thermogenic genes (UCP1, PGC1α, TFAM)  ↑iBAT UCP1 protein, ↓acetylated PGC1α (muscle) |
| (17)  obese, healthy (BMI>30)  Denmark | placebo  parallel | male  n=12 per group | 500 mg RSV or placebo tablet/d  4 weeks | -BW, -total fat mass, -vWAT mass,  plasma –GLC, -C, -TAG,-ALT, -HbA1c  -acetylated lysine, pAMPK in muscle |
| (18)  non-obese, normoglycaemic  Caucasian | placebo  parallel | female  RSV n=15  placebo n=14 | 75 mg RSV/d  12 weeks | -BW, -fat mass, -sWAT mass, -vWAT mass  plasma -leptin,-C, -TAG, -NEFA, -GLC  -REE, -BP, -IS  -WAT microarray: -mito function, -FO genes  -muscle SIRT1 activity |
| (19)  older adults with IGT  US | before-after | male n=3  female n=7 | 1, 1.5 or 2 g RSV/d  4 weeks | -BW, -fat mass, -BP  plasma –C, -TAG, -insulin, -ALT, -insulin  ↓post-meal GLC, ↓post-meal insulin |
| (20)  obese, healthy men | placebo  crossover | male n=11 | 150 mg RSV/d (resVida) or placebo,  30 days per treatment | -BW, -fat mass  ↓SEE (caloric restriction), ↑diurnal RER  muscle ↑pAMPK, ↑mito activity, ↑SIRT1, PGC1α protein |
| ***Quercetin*** | apples, onions, black currants, red wine, black tea, nuts, seeds, shallots(21) | | | |
| (22)  Sprague–Dawley rats | DI | male  n=7 per group | 0.36% or 0.72% w/w OPE in HFD, 8 weeks | ↓BW, ↓intra-abdominal fat mass |
| (23)  Wistar rats | DI | male  n=12 per group | 185, 270, 925 mg/kg BW/d in HFD  8 weeks | ↓BW gain, ↓total fat mass, ↓vWAT  plasma ↓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 | male  n=7 per group | 10 mg/kg BW/d RSV or vehicle with HFD  10 weeks | ↓BW gain  plasma ↓TAG, ↓C, ↓GLC, ↓insulin, ↓HOMA-IR  ↓TNFα production, iNOs protein in vWAT |
| (25)  C57BL/6 | DI | male  n=6 for OPE  n=9 for control | 0.5% w/w OPE in HFD  8 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 | male  n=8-10 per group | 0.1% w/w quercetin in HFD  8 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 | male  n=8 per group | 0.8% w/w in HFD  8 weeks | -BW, -adiposity, -EE, -RER  ↓plasma inflammatory cytokines (INFγ, IL1, IL4) |
| (28)  C57BL/6 | DI | male  n=6 per group | 0.05% w/w quercetin in HFD  9 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 | male  n=8 per group | 0.1% w/w quercetin in HFD  12-17 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 students  healthy  Korean | placebo  crossover | female  n=12 | 100 mg/d quercetin or placebo capsule for 2 weeks each | -BW, -fat mass, -WHR, -BMI, -SBP, -DBP  plasma –TAG, -C, -LDL |
| (32)  overweight/obese subjects  (BMI>23 kg/m2)  Korean | placebo  crossover | female  quercetin n=18  placebo n=19 | 100 mg/d quercetin or placebo capsules  12 weeks | -BW, -fat mass, -BMI  plasma –ALT,-leptin, ↑adiponectin, -TNFα, -IL4 |
| (33)  overweight/obese subjects  Korean | placebo  crossover | male n=5  female n=31 | 100 mg/d quercetin or placebo capsules  12 weeks | -BW, -fat mas, -BMI, -WC, -RER, -REE  plasma –GLC, -C, -LDL, ↓TAG, -leptin  -before-after effects on REE, BW, RER, BMI within quercetin group |
| (34)  Meta-analysis | 9 RCTs | male=189  female=336 | 100 to 1000 mg/d  2 to 12 weeks | -BW, -WC, -WHR, -BMI |
| ***Luteolin*** | peppers, carrots, cucumber, pomegranate, herbal spices, cabbage, broccoli, medicinal herbs (sage)35 | | | |
| (36)  C57BL/6 | DI | male  n=8 per group | 0.01% w/w in HFD  12 weeks | ↓BW, ↓sWAT mass, ↓vWAT mass, ↓BAT mass  ↓eWAT adipocyte size, ↑IS  ↓mast cell infiltration eWAT  plasma –insulin, ↓leptin, ↑adiponectin |
| (37)  C57BL/6 | DI | male  n=13 per group | 0.005% w/w in HFD  16 weeks | ↓BW, ↓sWAT mass, ↓vWAT mass  plasma ↓TAG, ↓C, ↓NEFA, ↑IS  ↑eWAT FAO genes (PGC1α, ADRB3, CPT2, PNP2, ACAD) |
| (38)  C57BL/6 | DI | male  n=8 per group | 0.01% w/w in HFD  20 weeks | ↓BW, ↑IS  ↓plasma MCP1, IL6, TNFα  ↓macrophage infiltration vWAT, ↓M1/M2-ratio |
| (39)  C57BL/6 | DI | male  n=12 per group | 0.01% w/w in HFD  12 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 | male  n=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 | male  n=8 per group | 0.5% w/w catechins in chow  8 weeks | -BW  ↑BAT mass, ↓pWAT mass, ↓eWAT mass  ↑BAT UCP1 expression  plasma ↓TAG, GLC, leptin |
| (44)  New Zealand black mice | gavage  short-term | male  n=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 | male  n=11 per group | 0.1% w/w EGCG in HFD  DIO 4 weeks, DI 4 weeks | ↓BW, ↓fat mass, -food intake, ↓eWAT weight plasma ↓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 men  Geneva, CH | placebo  crossover | male  n=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 subjects  Lausanne, CH | placebo  crossover | male n=15  female 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 | male  n=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 | placebo  crossover | 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-analysis  effect of EGCG on EE or anthropometric measures | 8 RTC | n=268 | EGCG:  300 or 600 mg/d for 2-3 days  300 to 800 mg/d for 2-12 weeks | ↑EE, ↓RER, -FO, - BMI, ↓WC, -fat percentage |
| (51)  healthy men  Japanese | placebo  crossover | male n=15  low 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 men  Japanese | acute  crossover | 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 students  Japanese | placebo  parallel | female  catechin n=10  placebo n=11 | 640 mg catechins/d or placebo, beverage  12 weeks | -BMI, -fat mass, -BW  ↑BAT density in supraclavicular region  neg. correlation between EMCL and BAT density |
| (53)  overweight/obese children  Japanese | placebo  parallel | 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 men  Japanese(36) | placebo  parallel | male  catechin group n=17  placebo 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 area  plasma –NEFA, -TAG, -C, -GLC, -insulin |
| (55)  obese adult Thais  (BMI>25kg/m2) | placebo  parallel | catechin group:  (m21, f9)  placebo group:  (m21, f9) | 3x daily 250 mg catechins or placebo in capsule  12 weeks | ↓BMI, ↓BW, ↓fat mass, ↓WC, -HC  ↓RER, ↑REE |
| (56)  overweight/obese adults  (BMI >25-32 kg/m2)  Caucasian | before-after | female n=63  male n=7 | 270 mg/d EGCG in capsule | -BW, ↓WC  -SBP, -DBP  plasma -C |
| (57)  Meta-analysis  effect 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 | male  n=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=12  female n=12 | 25% w/w soy-rich diet (150 pmm daidzein, 190 ppm genistein) vs soy-free diet  16 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 | ovx  DI | female  n=10 per group | isoflavone-rich (200 µg/g) or isoflavone-free diet  13 days | ↓BW gain, ↓abdominal fat mass  ↓serum leptin |
| (62)  Long-Evans rats | DI | male | isoflavone-rich (600 ppm) or isoflavone-free (10-15 ppm) diet  up to 75 days of age | ↑food intake, ↓BW gain, ↓WAT mass, ↓BAT mass  plasma ↑T3, ↓insulin, leptin  ↑UCP1 protein in BAT |
| (63)  Wistar rats | DIO with DI | male  n=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 BW  DIO 8 weeks, 30 d treatment | ↓BW. ↓vWAT mass, ↓sWAT mass  plasma ↓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 | female  n=8 per group | 0.25% w/w genistein in HFD  8 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 | male  n=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), -RER  plasma –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 | placebo  parallel | female  n=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 males  Tasmania | placebo  parallel | male  isoflavone n=69  placebo n=59 | 50 mg isoflavone equivalents or placebo tablets daily  6 weeks | -BW |
| (72)  obese women (20-65 yrs)  (BMI 30-40 kg/m2)  USA | placebo  parallel | female  soy group n=22  casein 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 control  Chinese women (30-70 yrs) | placebo  parallel | female  daidzein n=55  genistein n=56  placebo n=54 | 10 g soy protein with no addition, 50 mg daidzein or 50 mg genistein  24 weeks | -BMI, -WC, -fat mass  -IS |
| (74)  patients with NAFLD  Iranian (16-69 yrs) | placebo  parallel | genistein group (m30, f11)  placebo group  (m31, f10) | 250 mg daidzein or placebo capsules  8 weeks | -BW, ↓fat percentage, ↓WHR, ↓WC, -BMI  plasma ↓TAG, -C, -LDL, -HDL, ↓insulin  ↓HOMA-IR |
| (75)  postmenopausal women  (BMI>30 kg/m2)  Caucasian or AA | placebo  parallel | soy group (n=17)  8 AA, 9 Caucasian  placebo (n=16)  8 AA, 8 Caucasian | soy protein with isoflavones (160 mg) or placebo casein, shake  3 months | -BW, -total fat, -lean mass  ↓abdominal, ↓subcutaneous abdominal fat, ↓vWAT  for AA: weight loss more than for Caucasian  for Caucasian: vWAT loss bigger than for AA  plasma ↓IL6, -CRP, -TNFα, -leptin, -HDL, -LDL,  -C, -TAG |
| (76)  postmenopausal women  (mean BMI=30.5)  Caucasian | placebo  parallel | female  soy group n=9  placebo n=6 | soy protein with isoflavones (160 mg) or placebo casein,  shake  3 months | -BMI, -BW, -total fat mass, -IS  ↓subcutaneous abdominal fat, ↓intra-abdominal fat  plasma -GLC, -insulin |
| (77)  Meta-analysis  Effect of soy-isoflavones on BW in non-Asian, postmenopausal women | 9 RCTs | isoflavones n=272  placebo n=256 | 40 to 160 mg/d of isoflavones  8 weeks to 1 year | ↓BW with isoflavone intake  <100 mg or <6 months more effective  more effective with BMI<30 kg/m2 |
| (78)  Meta-analysis  effect of soy and isoflavones on anthropometric measures | 24 soy RTCs  17 isoflavones RTCs | soy:  f1265,  m45 (1 RTC)  m/f =74 (mixed)  isoflavones:  f1177, m0 | soy protein: 7.5 to 116 mg/d  4 weeks to 2 years  isoflavones: 33.3 to 300 mg/d  8 weeks to 2 years | soy:  -BW, >40 g/d ↑BW, 1-3 months ↑weight gain  -WC, -fat mass  isoflavones:  ↓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 | unknown  n=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 | unknown  n=6-8 | Vehicle, 10 mg/kg BW capsaicin or 10 mg/kg BW capsiate, 3 hours | ↑VO2 for capsaicin and capsiate,  ↑serum adrenaline  plasma ↑NEFA, ↓TAG |
| (82)  C57BL/6 or TRPV1 -/- mice | intragastric tube, acute | male  n=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 mice  B6.129X1 | DI | male | 0.01% w/w capsaicin in HFD  32 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 mice  B6.129X1 | DI | male  n=40 per group | 0.01% w/w capsaicin in HFD  26 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 |
| (85)  C57BL/6 | DIO+DI | male  n=6 per group | 0.01% w/w capsaicin in HFD  DIO 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 | female  n=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 | male  n=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 | male  n=4 per group | 10 mg/kg BW capsiate or vehicle for 30 min | ↑UCP1 mRNA in BAT |
| (88)  healthy young men  British | acute | male | breakfast with 3g chili sauce | ↑post-meal EE |
| (89)  long distance runners  Japanese | acute  crossover | male  n=8 | breakfast with or without 10 g red pepper | ↑post-meal EE (30 min)  ↑RER, ↑CHO, ↓FO   * effect blocked by propranolol |
| (90)  healthy young men  Caucasian | placebo  crossover | 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 subjects  Caucasian | placebo  crossover | male n=11  female 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 | placebo  parallel | male (ethnicity)  Placebo (16,9,3) 3 mg (15, 9, 1)  9 mg (10, 4, 2) | 0, 3, 9 mg dihydrocapsiate in gel capsule  4 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 RCTs  capsiate on RER 9 RCTs  capsaicin on EE 13 RCTs  capsaicin on RER 10 RCTs  female/male unknown | | capsaicin doses: <7, 20-35 mg, 135-150 mg/d  dihydrocapsiate 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 | acute  controlled | N=15 per group  (m8, f7) | 0 or 7.68 mg/d capsaicin with 100% or 75% of daily energy requirements  26 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/m2  44% Hispanic, 41% white, non-Hispanic, 13% black, 2% others | placebo  parallel | capsinoids  (m21, f22)  Placebo  (m17, f20) | 6 mg capsinoids or placebo capsule with MCTG, rapeseed oil  12 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 subjects  Singapore | crossover  cold vs capsinoids | Male n=8,  female n=12  BAT+ m6/f6  BAT- m2/f6 | 12 mg capsinoids in capsule with rapeseed oil and MCTG | ↑FDG-uptake in BAT  ↑EE, higher in BAT+ subjects  ↑FO, ↓RER  plasma –GLC, -TAG, ↑C, ↑NEFA |
| (97)  young healthy men  Japanese | placebo  crossover  acute | male n=18  BAT+ n=10  BAT- n=8 | 9 mg capsinoids or placebo capsule with rapeseed oil, MCTG  2 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. | male  BBR n=17  vehicle n=16 | 5 mg/kg BW on chow diet  26 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-term  i.p | male  n=5 per group | 5 mg/kg BW on chow diet  26 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 | male  n=7-8 | 1.5 mg/kg BW/d on HFD  DIO 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 BBR  during differentiation until d8 | ↑basal and uncoupled respiration  ↑BA adipogenesis (↑UCP1+ cells)  ↑fatty acid oxidative BAT-specific genes  ↑UCP1, PGC1α, PRDM16 protein |
| (102)  patients with NAFLD  mean BMI=29 kg/m2  China | before-after | not defined | 1.5 g BBR/d  1 month | ↓BW, ↓WC, ↓BMI, -total fat mass,  ↓vWAT mass, ↓sWAT mass  ↓HOMA-IR  ↑BAT volume, BAT activity |
| (103)  subjects with NAFLD  China | controlled  parallel | LSI (m32/f30) LSI+P (m28/f32) LSI+BBR (m38/f24) | LSI+1.5g BBR/d, LSI+15 mg/d pioglitazone, LSI only  16 weeks | ↓hepatic fat content vs LSI,  ↓BW, ↓BMI vs LSI and vs LSI+pioglitazone  -HbA1c, ↓HOMA-IR vs LSI, |
| (104)  newly diagnosed diabetics  no pharmacotherapy  China | placebo  parallel | placebo (m38, f28)  BBR (m31, f21) | 1.5 g BBR/d or placebo  12 weeks | -BW, ↓BMI, -WHR  plasma –FBG, ↓PBG, ↓HbA1c, -HOMA-IR, ↓C,  - insulin, -TAG |
| (105)  type 2 diabetics with poor glycemic control  China | before-after | n=48  sex not stated | 1.5 g BBR/d plus prescribed diabetes medication  12 weeks | ↓WC, ↓WHR, -BMI  plasma ↓FBG, ↓PBG, -TAG, ↓C, ↓insulin  ↓HOMA-IR |
| (106)  obese adults  Caucasian | before-after | male n=2  female n=5 | 1.5 g BBR/d  12 weeks | -BMI, -WHR, - fat percentage  plasma –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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