Table S1.- Reported differences in the circulatory levels of TNF-α between lean, overweight and obese individuals.

	Sample population		TNF-α levels				
Ref.	Country Sex	Body weight phenotype + co-morbidities group, Age[a] (y)	Type of sample Method	Results per group[a] (*N*)[b]	CV%[c]	(Sig) Effect (% change *vs.* Lean)	General message conveyed by the article
[21]	Sweden Women	Lean, 34.4 ± 1.2 Obese, 34.4 ± 1.2	Plasma, ELISA	Protein levels (pg/mL) Lean (*2*): 1.9 ± 0.4 Obese (*2*): 3.2 ± 2.8	 22% 88%	 (NS) ↑ (+68%)	Obesity correlates with increased plasma TNF-α levels. (*N* = only 2 values).
[22]	Spain Women	Lean, 38.4 ± 2.3 Obese, 46.3 ± 1.3 Obese + T2DM, 51.6 ± 2.6 Very obese, 41.5 ± 2.2 Very obese + T2DM, 46.3 ± 1.8	Plasma, ELISA	Protein levels (pg/mL) Lean (*24*): 5.7 ± 9.8 Obese (*63*): 11.6 ± 19.0 Obese + T2DM (*19*): 15.3 ± 17.4 Very obese (*29*): 8.6 ± 12.4 Very obese + T2DM (*22*): 12.0 ± 15.0	 >100%	 (NS) ↑ (+104%) ↑ (+168%) ↑ (+51%) ↑ (+111%)	Increased levels of TNF-α with BMI. Very high variability in the results.
[23]	Poland Women	Lean, 29.4 ± 9.4 Overweight, 32.9 ± 11.3 Obese, 40.7 ± 11.0 Very obese, 40.9 ± 10.4	Serum, ELISA	Protein levels (pg/mL) Lean (*28*): 2.9 ± 2.2 Overweight (*24*): 6.5 ± 3.1 Obese (*81*): 6.8 ± 3.1 Very obese (*21*): 7.4 ± 2.6	 35% 46% 48% 76%	 (p<0.001) ↑ (+124%) ↑ (+135%) ↑ (+155%)	Obesity associates with increased serum TNF-α levels.
[24]	Israel Mixed	Non-obese, 41.9 ± 7.6 Obese, 43.1 ± 12.3	Serum, ELISA	Protein levels (pg/mL) Non-obese (*9*), 0.3 ± 0.3 Obese (*41*), 1.0 ± 0.8	 100% 80%	 (p<0.001) ↑ (+233%)	Obesity associates with increased serum TNF-α levels.
[25]	Korea Mixed	Non obese, 15.4 ± 0.5 Obese, 15.3 ± 0.5	Serum, ELISA	Protein levels (pg/mL) Non-obese (*32*), 5.9 ± 2.0 Obese (*39*), 18.2 ± 6.7	 33% 37%	 (p<0.001) ↑ (+208%)	Obesity associates with increased serum TNF-α levels.
[26]	USA Women	Lean, 36.9 ± 11.8 Obese, 43.2 ± 8.6	Plasma, ELISA	Protein levels (pg/mL) Lean (*16*), 2.7 ± 0.9 Obese (*16*), 3.6 ± 1.8	 34% 50%	 (p<0.05) ↑ (+33%)	Obesity associates with increased serum TNF-α levels.
[27]	USA Mixed	Lean, 42.2 ± 0.2 Obese, 45.2 ± 0.2	Plasma, ELISA	Protein levels (pg/mL) Lean (*84*), 3.8 ± 1.6 Obese (*84*), 4.3 ± 1.6	 42% 36%	 (p<0.05) ↑ (+13%)	Obesity associates with increased serum TNF-α levels.
[28]	USA Mixed	Lean, 11.9 ± 4.0 Obese, 11.6 ± 3.4	Serum, ELISA	Protein levels (pg/mL) Lean (*6*), 3.1 ± 1.8 Obese (*21*), 4.2 ± 2.0	 58% 48%	 (NS) ↑ (+35%)	Serum TNF-α levels is higher in obese but the differences didn't reach significance.

[29]	Netherlands Mixed	Lean, 38.3 ± 2.1 Obese, 37.4 ± 1.2	Plasma, ELISA	Protein levels (ng/L = pg/mL) Lean (*13*), 3.4 ± 0.4 Obese (*15*), 4.5 ± 0.5	 12% 11%	 (NS) ↑ (+32%)	Serum TNF-α levels is higher in obese but the differences didn't reach significance.
[30]	Poland Women	Lean, 32.6 ± 8.6 Obese, 30.1 ± 5.5	Serum, ELISA	Protein levels (pg/mL) Lean (*15*), 4.5 ± 2.3 Obese (*26*), 8.8 ± 7.0	 50% 80%	 (p<0.05) ↑ (+96%)	Obesity associates with increased serum TNF-α levels.
[31]	USA Women	Lean, 31.9 ± 5.8 Obese, 35.7 ± 4.1 Obese + PCOS, 29.6 ± 5.8	Plasma, ELISA	Protein levels (pg/mL) Lean (*15*), 3.1 ± 0.7 Obese (*17*), 3.8 ± 0.8 Obese + PCOS (*42*), 4.1 ± 1.9	 22% 21% 47%	 (NS) ↑ (+23%) ↑ (+32%)	Plasma TNF-α levels are higher in obese but the differences didn't reach significance.
[32]	USA Mixed	Lean, 35.0 Obese, 46.0	Serum, ELISA	Protein levels (pg/mL) Lean (*10*), 82.3 ± 89 Obese (*9*), 0.8 ± 7.2	 >100% >100%	 (p=0.015) ↓ (-99%)	This study indicates opposite results to all the other ones. Very high variability in the data, especially in the obese participants.
[33]	New Zealand Women	Lean, 53 ± 10 Obese, 54 ± 9	Plasma ELISA	Protein levels (ng/L = pg/mL) Lean (*14*), 0.8 ± 0.4 Obese (15), 1.6 ± 1.0	 50% 62.5%	 (p=0.046) ↑ (+100%)	Obese women had higher levels of TNF-α.
[34]	USA Mixed	Lean, 40.0 ± 14 .9 Obese + T2DM, 50 ± 10.8	Plasma, ELISA	Protein levels (pg/mL) Lean (*14*), 2.8 ± 0.5 Obese + T2DM (*13*), 4.3 ± 2.7	 17% 64%	 (p<0.05) ↑ (+53%)	Obesity associates with increased serum TNF-α levels.
[35]	Czech Republic, Women	Lean, 37.7 ± 2.8 Obese, 39.4 ± 9.5	Plasma, ELISA	Protein levels (pg/mL) Lean (*12*), 0.6 ± 0.3 Obese (*20*), 0.7 ± 0.2	 50% 29%	 (p<0.05) ↑ (+16%)	Obesity associates with increased serum TNF-α levels. Data estimated from figures.
[36]	Canada Men	Lean, 42.0 ± 10.7 Obese, 46.2 ± 7.1 Very obese, 43.0 ± 6.9	Plasma ELISA	Protein levels (pg/mL) Lean (*59*), 1.0 ± 1.1 Obese, (*101*), 1.1 ± 1.1 Very obese (*57*), 1.3 ± 1.1	 >100% 92% 90%	 (p<0.05) ↑ (+19%) ↑ (+30%)	TNF-α levels increased with BMI.
[37]	USA NR	Lean, 43 ± 14.4 Overweight, 49 ± 12.6 Obese, 45 ± 20.8 Very obese, 42 ± 12.7 Morbidly obese, 41 ± 19.3	Plasma, ELISA	Protein levels (pg/mL) Lean (*13*), 39.0 ± 50.5 Overweight (*10*), NR Obese (*12*), 294.0 ± 142.0 Very obese (*18*), 478.0 ± 233.3 Morbidly obese (*15*), 713.0 ± 240.1	 >100% ND 48% 49% 34%	 (p<0.001) ND ↑ (+653%) ↑ (+1125%) ↑ (+1728%)	TNF-α positively correlates with BMI.
[38]	Poland Women	Lean, 36.4 ± 8.0 Overweight, 33.3 ± 12.0	Plasma, ELISA	Protein levels (pg/mL) Lean (*14*), 3.1 ± 3.0	 97%	 (p<0.001)	TNF-α positively correlates with BMI.

		Obese, 43.8 ± 10.8		Overweight (*12*), 6.3 ± 3.0 Obese (*57*), 6.9 ± 2.9	48% 42%	↑ (+103%) ↑ (+123%)	
[39]	Poland Women	Lean, 38.0 ± 8.0 Obese, 52.0 ± 9.0 Obese + MetS, 53.0 ± 9.0	Plasma ELISA	Protein levels (pg/mL) Lean (*14*), 5.6 ± 2.0 Obese (*21*), 6.4 ± 5.5 Obese (*71*) + MetS, 6.3 ± 1.9	 38% 86% 30%	 (NS) ↑ (+14%) ↑ (+13%)	Obesity and MetS do not significantly associate with an increase in serum TNF-α levels.
[40]	Egypt Mixed	Men Lean, 32.4 ± 2.89 Class I obese, 33.1 ± 3.13 Class II obese, 32.5 ± 3.14 Class III obese, 32.9 ± 3.06 Women Lean, 31.6 ± 3.15 Class I obese, 31.9 ± 3.0 Class II obese, 32.3 ± 3.4 Class III obese, 32.1 ± 3.1	Serum, ELISA	Protein levels (pg/mL) Men Lean (*15*), 3.0 ± 0.7 Class I obese (*15*), 6.7 ± 1.5 Class II obese (15), 7.3 ± 1.9 Class III obese (*15*), 9.3 ± 2.0 Women Lean (*15*), 2.8 ± 0.7 Class I obese (*15*), 4.8 ± 1.3 Class II obese (*15*), 5.1 ± 2.0 Class III obese (*15*), 7.3 ± 2.1	 23% 22% 26% 21% 15% 27% 39% 29%	 (p<0.05) ↑ (+123%) ↑ (+143%) ↑ (+210%) (p<0.05) ↑ (+71%) ↑ (+82%) ↑ (+161%)	TNF-α positively correlates with BMI. Slightly higher TNF-α levels were detected in men than in women.
[41]	Brazil Mixed	T2DM, 56.0 (12.0) Non diabetes, 53.0 (18.0) Lean Lean + T2DM Overweight Overweight + T2DM Obese Obese + T2DM	Plasma Cytometry Bed Array	Protein levels (pg/mL) T2DM (*102*), Non diabetes (*62*) Lean: 0.090 (0.075) Lean + T2DM: 0.086 (0.048) Overweight: 0.086 (0.068) Overweight + T2DM: 0.092 (0.048) Obese: 0.112 (0.058) Obese + T2DM: 0.092 (0.042)	 ND 	 (NS) ↓ (-4%) ↓ (-4%) ↑ (+2%) ↑ (+24%) ↑ (+2%)	Results converted from fg/mL to pg/mL. Very low values compared to other reports.
[42]	Pakistan Mixed	Lean, 46.5 ± 8.2 Overweight + MetS, 47.08 ± 8.0	Serum ELISA	Protein levels (pg/mL) Lean (*200*): 9.5 (6.1 – 18.0) Overweight + MetS: 20.5 (10.0 – 62.0)	 ND	 (p<0.0001) ↑ (+115%)	Increased levels of TNF-α with increased BMI.
[43]	Australia Mixed	Lean, 33.0 ± 3.2 Overweight, 44.9 ± 4.2 Obese, 43.3 ± 4.5	Serum ELISA	Protein levels (pg/mL) Lean (*12*): 3.6 ± 1.2 Overweight (*9*): 3.1 ± 3.9 Obese (*8*): 4.2 ± 2.3	 33% >100% 55%	 (NS) ↓ (-14%) ↑ (17%)	No significant differences between phenotypes. Results estimated from figure.
[44]	Spain Mixed	Lean, 65.6 ± 0.7 Overweight, 64.9 ± 0.7 Obese, 64.0 ± 0.6	Plasma ELISA	Protein levels (pg/mL) Lean (*50*): 25.0 ± 11.0 Overweight (*50*): 30.0 ± 11.0 Obese (*50*): 34.0 ± 14.0	 41% 37% 44%	 (NS) ↑ (+20%) (p<0.001) ↑ (+36%)	TNF-α increased with BMI. Results estimated from figure.

[45]	Poland Men	Lean, 21.4 ± 1.2 Class I obese, 31.1 ± 3.8 Class II obese, 28.4 ± 3.6	Serum, ELISA	Protein levels (pg/mL) Lean (*9*): 3.5 ± 1.7 Obese (I) (*9*): 3.5 ± 0.9 Obese (II): 5.2 ± 1.3	 49% 26% 25%	 (NS) NC ↑ (+49%)	Data estimated from bar figure. No significant differences between the groups.

Legend: [a]: Most values presented as the mean ± standard deviation (SD), some data indicated as Median (Inter Quartile Range, IQR); [b]: (*N*): sample size per group; [c]: CV%: Coefficient of variation in percentage estimated for each subgroup ((CV%) = (Standard Deviation/Mean) × 100); BMI: Body mass index; MetS: Metabolic syndrome; NC: No change; ND: Not determined; NR: Not reported; NS: Not significant; PCOS: Polycystic Ovary Syndrome; T2DMM: Type 2 diabetes mellitus; TNF-α: Tumour necrosis factor alpha.

Table S2.- Reported changes in the circulatory levels of human TNF-α following dietary intervention with PUFAs-containing foods and products.

	Intervention	Sample population		TNF-α levels				
Ref.	Tested product/main compounds Study design	Country Sex	Body weight phenotype and comorbidities groups, Age[a] (y)	Type of Sample Method	Results per group[a] (*N*)[b]	CV%[c] per group	Sig Effect (%A *vs* B per group[d]; T – C[e] pg/mL)	General messages conveyed by the article
PUFAs (ω-3 PUFAs: EPA, DHA in capsules, oils)								
[63]	T: ω-3 PUFAs (1110 mg/d: 600 mg/d EPA and 510 mg/d DHA) C: PLA (sunflower oil) RCT (crossover), 42 d (14 d washout phase)	The Netherlands Men	Obese healthy 59.0 ± 9.0	Plasma ELISA	Protein levels (pg/mL) T: ω-3 PUFAs (*11*) 0 h: 1.09 ± 0.54; 2 h: 1.39 ± 0.78; 4 h: 1.10 ± 0.65 C: PLA (*11*) 0 h: 1.11 ± 0.64; 2 h: 1.31 ± 0.57; 4 h: 1.37 ± 0.68 T - C	 49% 56% 59% 57% 43% 49%	 (NS) +28% +1% (NS) +18% +23% -0.02 pg/mL (NS)	No significant differences in the levels of TNF-α between T and C at any time point. No effects on body weight.

[64]	T: ω-3 PUFAs (1200 mg/d: 930 mg EPA, 290 mg DHA, 100 mg GLA, 18 mg Vitamin E/d) C: PLA (medium-chain triglycerides) RCT (crossover), 90 d (21 d washout phase)	USA Mixed	Obese 15.7 ± 1.0	Serum ELISA	Protein levels (pg/mL) T: ω-3 PUFAs (*25*) B: NR; A: 5.20 ± 1.0 C: PLA (*25*) B: NR; A: 5.70 ± 1.50 T – C	 ND; 19% ND; 26% 	 ND ND -0.50 pg/mL (p=0.008, based only on values after (A) intervention)	Significant but small reduction of the levels of TNF-α with T. No effect on body weight
[65]	T: Fish oil (900 mg/d: 360 mg DHA and 540 mg EPA) C: PLA (corn starch) RCT (parallel), 30 d	Mexico Mixed	Overweight, IR T: 13.6 ± 1.9 C: 12.9 ± 2.0	Serum ELISA	Protein levels (pg/mL) T: Fish oil (*49*) B: 11.35 ± 4.23; A: NR C: PLA (*27*) B: 10.13 ± 4.98; A: NR T – C	 37%; ND 49%; ND 	 ND ND NR (p=0.052)	Significant reduction of the levels of TNF-α but values not clearly indicated. No information on data after intervention. Effect on body weight only in some children. Some numeric data are missing.
[66]	T: Fish oil (4000 mg/d: 1860 mg EPA and 1500 mg DHA)	USA Mixed	Obese, IR nondiabetic T: 48.8 ± 2.3	Plasma ELISA	Protein levels (pg/mL)			No significant effects on the levels of TNF-α.

	C: PLA (corn oil) RCT (parallel), 84 d		C: 53.3 ± 2.2		T: Fish oil (*19*) B: 17.6 ± 2.9; A: 22.3 ± 3.4 C: PLA (*14*) B: 25.8 ± 4.2; A: 19.6 ±2.6 T – C	16%; 15% 16%; 13%	(NS) +26.7% (NS) -24.03% +10.9 pg/mL (NS)	No effects on body weight.
[67]	T: DHA (500 mg/d during the first 60 d and 250 mg/d till the end of the study) + VLCK diet C: PLA + VLCK diet RCT (parallel), 180 d	Spain Mixed	Obese T: 47.4 ± 9.1 C: 44.3 ± 11.7	Serum ELISA	Protein levels (pg/mL) T: VLCK diet (*14*) B: 5.0 ± 2.5; A: 2.0 ± 0.3 C: VLCK diet (*15*) B: 4.7 ± 2.3; A: 2.0 ± 0.4 T – C	50%; 15% 49%; 20%	(NS) -60% (NS) -57% -0.3 pg/mL (NS)	No significant effects on the levels of TNF-α. Poor indication of TNF-α units. No significant differences in body weight loss between groups.
PUFAs-containing foods								
[68]	T: chia seeds (50 g/d) C: PLA RCT (parallel), 84 d	USA Mixed	Overweight/obese 20 - 70	Plasma ELISA	Protein levels (pg/mL) *Men* T: Chia seeds (*14*) B: 1.63 ± 1.12; A: 1.52 ± 1.01	69%; 66%	(NS) -7%	No effects on the levels of TNF-α. No effect on body weight.

					C: PLA (*14*) B: 1.59 ± 1.12; A: 1.39 ± 0.52 T - C *Women* T: Chia seeds (*25*) B: 1.48 ± 1.25; A: 1.6 ± 1.25 C: PLA (*23*) B: 1.4 ± 0.96; A: 1.41 ± 0.76 T - C	 70%; 37% 85%; 78% 69%; 54%	(NS) -12% +0.11 pg/mL (NS) (NS) +8% (NS) 0% +0.11 pg/mL (NS)	
[69]	T: Flaxseeds (40 g/d) C: PLA RCT (crossover), 84 d (28 d, washout phase)	USA NR	Obese, glucose intolerant 54.7 ± 6.6.	Plasma ELISA	Protein levels (pg/mL) T: Flaxseeds (*7*) B: 0.9 ± 0.4; A: 0.8 ± 0.5 C: PLA (*7*) B: 0.6 ± 0.5; A: 0.7 ± 0.6 T - C	 44% 62% 83% 86%	 (NS) -11% (NS) +13% -0.2 pg/mL (NS)	No significant effect on the levels of TNF-α. No effects on body weight.

[70]	T: *Nigella sativa* oil (3 g/d) + LCD, C: PLA + LCD RCT (parallel), 56 d	Iran Women	Obese, T: 41 ± 11.8 C: 39.5 ± 9.8	Serum ELISA	Protein levels (pg/mL) T: *Nigella sativa* oil (*45*) B: 24.0 ± 17.3; A: 14.2 ± 10.9 C: PLA (*45*) B: 21.7 ± 15.2; A: 18.2 ± 13.5 T - C	 72%, 76% 70%, 74%	 (p<0.05) -41% (NS) -16% -6.3 pg/mL(p=0.03)	Significant reduction of the levels of TNF-α with T. No effects on body weight.
[71]	T: Baru almonds (20 g/d rich in MUFAs 51% and PUFAs 31%); C: PLA RCT (parallel), 56 d	Brazil Women	Overweight/obese 40.0 ± 11.0	Plasma Milliplex	Protein levels (pg/mL) T: Almonds (*24*) B: 2.1 ± 0.1; A: 2.2 ± 0.1 C: PLA (*22*) B: 2.6 ± 0.3; A: 2.0 ± 0.1 T – C	 5%; 5% 16%; 5%	 (NS) +5% (NS) -23% +0.7 pg/mL (NS)	No significant effects on the levels of TNF-α. No effects on body weight.

Legend: [a]: Values are presented as the mean ± SD; [b]:(*N*): Sample size per group; [c]: CV%: Coefficient of variation in percentage estimated for each analyzed subgroup ((CV%) = (Standard Deviation/Mean) × 100); B: Before intervention; A: After intervention; [d]:Difference in % before and after intervention; T: Treatment; C: Control; T – C[e]: effect size calculated as the difference between the T and the C group (pg/mL); DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; GLA: Gamma-linolenic acid; IR: Insulin resistance; LCD: Low calorie diet; MUFAs: Monounsaturated fatty acids; ND: Not determined; NR: Not reported; NS: Not significant; PLA: Placebo; PUFAs: Polyunsaturated fatty acids; RCT: Randomized clinical trial; TNF-α: tumor necrosis factor alpha; VLCK: Very low-calorie ketogenic diet.

Table S3.- Reported changes in the circulatory levels of human TNF-α following dietary intervention with VitD supplements.

	Intervention	Sample population		TNF-α levels				
Ref.	Tested product/main compounds Study design	Country Sex	Body weight phenotype and comorbidities groups Age[a] (y)	Type of Sample Method	Results per group[a] (*N*)[b]	CV%[c] per group	(Sig Effect (% A *vs* B per group[d]; T – C[e] pg/mL)	General messages conveyed by the article
[90]	T: Oily VitD preparation (3332 IU/d) + weight reduction program C: PLA + weight reduction program RCT (parallel), 365 d	Germany Mixed	Overweight T: 47.4 ± 10.0 C: 48.8 ± 10.0	Serum Automated immunoassay	Protein levels (pg/mL) T: Vitamin D + weight reduction program (*82*) B: 7.84 ± 3.15; A: 7.04 ± 2.25 C: PLA + weight reduction program (*83*) B: 8.12 ± 3.43; A: 7.90 ± 2.80 T - C	40%; 32% 42%; 35%	p<0.05 -10% (NS) -2.7% -0.58 pg/mL (p<0.05)	Significant but rather small reduction of the levels of TNF-α with T. No effect on body weight.
[91]	T: VitD (4000 IU/d) + exercise training program C: PLA + exercise training program; RCR (parallel), 84 d	USA Mixed	Overweight/obese T: 26.2 ± 5.1 C: 26.0 ± 4.5	Serum ELISA	Protein levels (pg/mL) T: Vitamin D + exercise (*10*) B: 2.3 ± 1.1; A: 2.1 ± 1.2	48%; 57%	NS -8.7%	No significant effect on the levels of TNF-α. No effect on body weight.

					C: PLA + exercise (*13*) B: 1.9 ± 1.3; A: 1.9 ± 1.2 T - C	68%; 63%	NS -0% -0.2 pg/mL (NS)	
				Supernatant of whole blood ELISA	Protein levels (pg/mL) T: Vitamin D + exercise (*10*) B: 1.5 ± 0.6; A: 0.6 ± 0.5 C: PLA + exercise (*13*) B: 1.6 ± 0.9; A: 0.6 ± 0.5 T - C	40%; 83% 56%; 83%	*p*<0.05 -60% *p*<0.05 -62% +0.1 pg/mL (NS)	
[92]	T: VitD (4000 IU/d) C: PLA; RCT (parallel), 183 d	USA Mixed	Obese and IR T: 14.6 ± 2.3 C: 13.9 ± 2.4	Serum ELISA	Protein levels (pg/mL) T: Vitamin D (*14*) B: 1.85 ± 0.15; A: 1.6 ± 0.15 C: PLA (*15*) B: 1.7 ± 0.15; A: 1.4 ± 0.1 T - C	8%; 9% 9%; 7%	NS -13% NS -17% + 0.05 pg/mL (NS)	No significant reduction in TNF-α levels. No effect on body weight.

[93]	T: Alphacalcidol (1 µg/d 1-α hydroxy-Vitamin D3) C: PLA RCT (parallel), 56 d	Iran Mixed	Obese T: 39 ± 8.9 C: 41 ± 14.5	Serum ELISA	Protein levels (pg/mL) T: Alphacalcidol (*40*) B: 9.83 ± 25.42; A: NR C: PLA (*54*) B: 6.65 ± 14.10; A: NR T – C	 >100%; ND >100%; ND 	 NS -20% NS +25% -3.5 pg/mL (NS)	No significant effect on the levels of TNF-α. Results estimated from Figures. No effect on body weight.
[94]	T: VitD (initial bolus dose of 100,000 IU/d followed by 4,000 IU/d) C: PLA RCT (parallel), 112 d	Australia Mixed	Overweight/obese T: 30.5 (25, 35) C: 29.5 (25, 41)	Serum ELISA	Protein levels (pg/mL) T: Vitamin D (*28*) B: 29.6 (14.6, 55.0); A: 24.3 (11.1, 45.6) C: PLA (*26*) B: 27.6 (16.9, 72.9); A: 21.5 (12.4, 47.4) T – C	 ND ND 	 NS -18% NS -22% + 0.8 pg/mL (NS)	No significant effect on the levels of TNF-α. No effect on body weight.

Legend: [a]: Values are generally presented as the mean ± standard deviation (SD), some data indicated as Median (Inter Quartile Range, IQR); [b]:(*N*): Sample size per group; [c]: CV%: Coefficient of variation in percentage estimated for each analyzed subgroup ((CV%) = (Standard Deviation/Mean) × 100); B: Before intervention; A: After intervention; [d]:Difference in % before and after intervention; T: Treatment; C: Control; T – C[e]: effect size calculated as the difference between the T and the C group (pg/mL); IR: Insulin resistance; ND: Not determined; NR: Not reported; NS: Not significant; PLA: Placebo; RCT: Randomized clinical trial; TNF-α: tumor necrosis factor alpha; VitD: Vitamin D.

Table S4.- Reported changes in the circulatory levels of human TNF-α following dietary intervention with products containing mixed bioactive (micro)nutrients.

	Intervention	Sample population		TNF-α levels				
Ref.	Tested product/main compounds Study design	Country Sex	Body weight phenotype and comorbidities groups Age[a] (y)	Type of Sample Method	Results per group[a] (*N*)[b]	CV%[c]	(Sig) Effect (% A vs B[d] per group T – C[e] pg/mL)	General message conveyed by the article
[95]	T: NuFit active blend (3 times/d, 2.25g leucine and 30 mg vitamin B6), C: PLA RCT (parallel), 28 d	USA Mixed	Overweight/obese T: 33 ± 5.1 C: 25 ± 5.8	Plasma ELISA	Protein levels (pg/mL) T: NuFit (*10*) B: 408 ± 22; A: 334 ± 38 C: PLA (*10*) B: 411 ± 40; A: 393 ± 29 T - C	 5%; 11% 10%; 7%	 (p<0.01) -18% (NS) -4% -56 pg/mL (NR)	Reduction in TNF-α levels. No effects on body weight.
[96]	T: L-arginine (9 g/d) C: PLA RCT (parallel), 90 d	Poland Mixed	Obese T: 43.8 ± 8.2 C: 41.0 ± 8.8	Serum ELISA	Protein levels (pg/mL) T: L-arginine (*30*) B: 4.6 ± 2.0; A: 4.3 ± 1.8 C: PLA (*30*) B: 4.6 ± 1.8; A: 4.5 ± 1.5 T - C	 43%; 41% 39%; 33%	 (NS) -7% (NS) -2% -0.2 pg/mL (NS)	Non-significant tendency to decrease of TNF-α levels. No effects on body weight.
[97]	T: Black soy peptide (4.5 g/d) C: PLA RCT (parallel), 84 d	Korea Mixed	Overweight/obese T: 39 ± 10.3 C: 36.2 ± 8.1	Serum ELISA	Protein levels (pg/mL) T: Black soy peptide (*35*) B: 4.84 ± 0.67; A: 3.97 ± 0.65 C: PLA (*29*) B: 5.97 ± 0.97; A: 4.49 ± 0.78 T - C	 14%; 16% 16%; 17%	 (p= 0.017) -18% (NS) -25% +0.61 pg/mL (NR)	Reduction of TNF-α levels in the T group. Significant reduction of body weight.
[98]	T: Zinc (30 mg/d) C: PLA RCT (parallel), 56 d	Korea Women	Obese 20.8 ± 2.2	Serum ELISA	Protein levels (pg/mL) T: Zinc (*20*) B: 16.1 ± 7.1; A: 13.9 ± 4.9 C: PLA (*20*) B: 13.0 ± 5.0; A: 14.7 ± 4.7	 44%; 35% 38%; 32%	 (NS) -14% (NS) +13%	No reduction in TNF-α levels. No effects on body weight.

					T - C		-3.9 pg/mL (NS)	
[99]	T: Yeast β–Glucan 1 capsule/d for the first 14 d followed by 2 capsule/d for the other 28 d (477 mg/capsule) C: PLA RCT, 42 d	Thailand Mixed	Overweight/obese 41.3 ± 10.7	Serum ELISA	Protein levels (pg/mL) T: Yeast β–Glucan 1 (*22*) B: 10.5 ± 5; A: 10.2 ± 4 C: PLA (*22*) B: 10.2 ± 3; A: 10.5 ± 1.5 T - C	 47%; 40% 29%; 14%	 (NS) -3% (NS) +3% -0.6 pg/mL (NS)	Significant reduction of TNF-α levels (only after 14 d). Reduction of waist circumference.
[100]	T: Hydrolyzed cod proteins (4 g/d) C: PLA RCT (parallel), 56 d	Norway Mixed	Obese, MetS T: 52.8 ± 6.2 C: 53.4 ± 6.8	Serum ELISA	Protein levels (pg/mL) T: Cod proteins (*15*) B: 0.57 (0.22, 0.93) A: 0.93 (0.22, 0.93) C: PLA (*15*) B: 0.22 (0.11, 0.93) A: 0.57 (0.22, 0.93) T - C	 ND ND ND ND	 (NS) +63% (NS) +159% +0.01 pg/mL (NS)	No effect on the levels of TNF-α. No effects on body weight.

Legend: [a]: Values are generally presented as the mean ± standard deviation (SD), some data indicated as Median (Inter Quartile Range, IQR); [b]:(*N*): Sample size per group; [c]: CV%: Coefficient of variation in percentage estimated for each analyzed subgroup ((CV%) = (Standard Deviation/Mean) × 100); B: Before intervention; A: After intervention; [d]:Difference in % before and after intervention; T: Treatment; C: Control; T – C[e]: effect size calculated as the difference between the T and the C group (pg/mL); MetS: Metabolic syndrome; ND: Not determined; NR: Not reported; NS: Not significant; PLA: Placebo; RCT: Randomized clinical trial; TNF-α: tumour necrosis factor alpha.

Table S5. Reported changes in the circulatory levels of human TNF-α following dietary intervention with different products containing polyphenols and other phytochemicals.

	Intervention	Sample population		TNF-α levels				
Ref.	Tested product/main compounds Study design	Country Sex	Body weight phenotype and comorbidities groups Age[a] (y)	Type of Sample Method	Results per group[a] (*N*)[b]	CV%[c]	(Sig) Effect (% A *vs* B[d] per group T – C[e] pg/mL)	General message conveyed by the article
Polyphenol-containing products								
[114]	T: Quercetin (150 mg/d) C: PLA RCT (crossover), 42 d (35 d washout phase)	Germany Mixed	Overweight/obese 45.1 ± 10.5	Plasma ELISA	Protein levels (pg/mL) T: Quercetin (*93*) B: 2.62 ± 2.40; A: 2.37 ± 2.45 C: PLA (*93*) B: 2.48 ± 2.37; A: 2.40 ± 2.50 T - C	 91%; >100% 95%; >100%	 (p<0.01) -9.5% (NS) -3.22% -0.17 pg/mL (NS)	No significant effect on the levels of TNF-α. No effects on body weight.
[115]	T: Curcuminoids (1 g/d; curcumin, demethoxycurcumin, and bisdemethoxycurcumin) C: PLA RCT (crossover), 30 d (15 d washout phase)	Iran NR	Obese 18 – 65	Serum Chemiluminescent immunoassay	Protein levels (pg/mL) *Phase 1* T: Curcuminoids (*15*) B: 2.63 ± 2.81; A: 1.50 ± 0.69	 >100%; 46%	 (NS) -43%	No effects on the levels of TNF-α. Effects on body weight not reported.

					C: PLA (*15*) B: 2.72 ± 1.17; A: 0.92 ± 0.29 T – C *Phase 2* T: Curcuminoids (*15*) B: 1.29 ± 0.92; A: 1.09 ± 0.46 C: PLA (*15*) B: 1.33 ± 0.64; A: 1.52 ± 0.82 T - C	 43%; 31% 71%; 42% 48%; 54% 	(NS) -66% +0.67 pg/mL (NS) (NS) -15.5% (NS) +14.2% -0.39 pg/mL (NS)	
[116]	T: Curcumin (500 mg/d) or Nano-curcumin (80 mg/d) C: PLA RCT (parallel), 60 d	Iran NR	Overweight cardiac patients T (Curcumin): 55.3 ± 7.1 T (Nano-curcumin): 56.2 ± 6.9 C: 54.1 ± 5.2	Serum ELISA	Protein levels (pg/mL) T: Curcumin (*30*) B: 19.61 ± 4.72; A: 16.01 ± 3.52 T: Nano-curcumin (*30*) B: 18.95 ± 4.09; A: 14.06 ± 3.27 C: PLA (*30*): B: 19.11 ± 4.23; A: 19.02 ± 4.1	 24%; 22% 21%; 23% 22%; 21%	 (p<0.05) -18.3% (p<0.05) -25.8% (NS) -0.47%	Significant reduction of TNF-α levels. No effects on body weight.

					T – C (Curcumin) T – C (Nano-curcumin)		-3.5 pg/mL (p<0.01) -4.8 pg/mL (p<0.01)	
[117]	T: Cocoa extract (1.4 g/d, 645 mg of polyphenols) + 15 % energy restricted diet C: PLA + 15% energy restricted diet RCT (parallel), 28 d	Spain Mixed	Overweight/obese 57.3 ± 5.2	Plasma ELISA	Protein levels (pg/mL) T: Cocoa extract (*23*) B: 1.31 ± 0.60; A: 1.13 ± 0.50 C: PLA (*24*) B: 1.28 ± 0.63; A: 1.09 ± 0.49 T - C	 46% 44% 49% 45% 	 (p<0.05) -13.7% (NS) -14.8% +0.01 pg/mL (NS)	No significant effect on TNF-α levels. No effects on body weight
[118]	T: Grape extract capsules (≈ 70 mg mix polyphenols) or Grape extract + Resveratrol capsules (+8 mg Resveratrol) C: PLA RCT (parallel), 1 capsule/d 180 d, 2 capsules/d for another 180 d	Spain Mixed	Overweight/obese with CAD 58 ± 9 59 ± 10 60 ± 12	Serum ELISA	Protein levels (pg/mL) T: Grape extract (*25*) B: 14.2 ± 8.7; A180d: 14.4 ± 8.6; A365d: 14.7 ± 9.9; T: Grape extract + Resveratrol (*25*) B: 14.9 ± 8.6;	 61% 60% 67% 58%	 (NS) +1.4% +3.5% (NS)	No significant effect on TNF-α levels. No changes in body weight.

					A180d: 14.4 ± 8.6; A365d: 13.8 ± 8.2; C: PLA (25) B: 13.7 ± 8.6; A180d: 14.5 ± 9.2; A365d: 15.2 ± 7.0; T – C (Grape extract, 180d) T – C (Grape extract, 365d) T – C (Grape extract + Resveratrol, 180d) T – C (Grape extract + Resveratrol, 365d)	60% 59% 63% 63% 46%	-3.3% -7.3% (NS) +6% +11% -0.6 pg/mL (NS) -1.0 pg/mL (NS) -1.3 pg/mL (NS) -2.6 pg/mL (NS)	

[119]	T: Grape extract capsules (≈ 70 mg mix polyphenols) or Grape extract + Resveratrol capsules (+8 mg Resveratrol); C: Placebo (PLA); RCT (parallel), 1 capsule/d 180 d, 2 capsules/d for another 180 d	Spain Men	Overweight/obese with CAD, T2DM, Hypertension 57 ± 10 60 ± 10 63 ± 12	Serum ELISA	Protein levels (pg/mL) T: Grape extract (*13*) B: 12.1 ± 6.6; A365d: 11.9 ± 5.1; T: Grape extract + Resveratrol (*13*) B: 11.7 ± 5.5; A365d: 10.7 ± 5.8; C: PLA (*9*) B: 12.5 ± 6.4; A365d: 13.9 ± 6.9; T – C (Grape extract) T – C (Grape extract + Resveratrol)	55% 43% 47% 54% 51% 50%	(NS) -1.6% (NS) -8.5% (NS) +11.2% -1.6 pg/mL (NS) -2.4 pg/mL (NS)	No significant effect on TNF-α level. No changes in body weight with any of the two treatments. In the Grape extract + Resveratrol group down-regulation of *TNF-α* gene expression but not of protein release in PBMCs.
[120]	T: Freeze-dried Grape Powder (46 g/day, 15.6 mg /d of polyphenols) C: PLA RTC (crossover), 21 d (15 d washout phase)	USA Mixed	Obese 20-60	Plasma ELISA	Protein levels (pg/mL) T: Grape powder (*24*) B: 3.93 ± 1.92; A: 3.75 ± 2.18 C: PLA (*24*) B: 3.81 ± 2.05; A: 3.76 ± 2.00	49% 58% 54% 53%	(NS) -4.5%, (NS) 1.3%	No significant effects on the levels of TNF-α. No effect on body weight.

					T – C		-0.13 pg/mL (NS)	
[121]	T: Grape powder (60 g/d, rich in polyphenols ~300 mg/d; mostly anthocyanins, flavonols) C: PLA RCT (crossover), 2-phases: post-prandial and 28 d treatment	USA Mixed	Obese 48.6 ± 15.4	Plasma ELISA	Protein levels (pg/mL) *Post-prandial (5 h)* T: Grape powder (*20*) B: 1.5 ± 0.6; A: 1.3 ± 0.5 C: PLA (*20*) B: 1.4 ± 0.4; A: 1.3 ± 0.6 T – C *28 d* T: Grape powder (*20*) B: 1.5 ± 0.6; A: 1.3 ± 0.6 C: PLA (*20*) B: 1.4 ± 0.4, A: 1.4 ± 0.6 T – C	 40%, 39% 29%, 46% 40%, 46% 29%, 43%	 (NS) -13.3% (NS) -7.1% -0.1 pg/mL (NS) (NS) -13.3% (NS) 0% -0.2 pg/mL (NS)	No significant effects on the levels of TNF-α. The effects on body weight were not reported.
[122]	T: Grape pomace extract + Omija fruit (342.5 mg/d + 57.5 mg/d for low dose	Korea Mixed	Overweight/obese 30–70	Plasma ELISA	Protein levels (pg/mL)			Significant but rather small reduction of TNF- α levels with high dose of Grape

	group and 685 mg/d + 11 5 mg/d for high dose group) C: PLA RCT (parallel), 70 d				T: Grape pomace extract-high dose (*26*) B: 5.56 ± 2.96; A: 3.56 ± 2.79 T: Grape pomace extract-low dose (*26*) B: 4.56 ± 2.66; A: 3.78 ± 2.47 C: PLA (*24*) B: 4.87 ± 2.28; A: 4.24 ± 2.41 T – C (high dose) T – C (low dose)	53% 78% 58% 65% 47% 57%	(p<0.05) -36% (NS) -17% (NS) -13% -1.37 pg/mL (p<0.05) -0.15 pg/mL (NS)	pomace extract + Omija fruit. No effect on body weight.
[123]	T: Grape seed extract (300 mg/d containing 85% polyphenols) + LCD C: PLA + LCD RCT (parallel), 84 d	Iran Mixed	Overweight/obese T: 35.0 ± 1.9 C: 33.5 ± 2.0	Serum ELISA	Protein levels (pg/mL) T: Grape seed extract (*20*) B: 24.3 ± 3.55 A: 17.9 ± 4.6 C: PLA (*20*) B: 17.6 ± 0.74 A: 23.1 ± 3.48 T – C	15% 26% 4% 15%	(p<0.01) -26.3%, (p<0.01) +31.25%	Significant reduction of TNF-α levels. Significant decreased in body weight.

							-11.9 pg/mL (p=0.0001)	
[124]	T: Pomegranate peel extract (250 mg/d, C: Placebo; RTC (parallel), 56 d	Bosnia and Herzegovina Mixed	Overweight, T2DM T: 57.9 ± 6.1 C: 56.9 ± 6.7	Plasma ELISA	Protein levels (pg/mL) T: Pomegranate peel extract (*30*) B: 0.17 (0.8 – 0.27); A: 0.13 (0.6 – 0.23) C: PLA (*14*) B: 0.18 (0.3 – 0.34) A: 0.19 (0.5 – 0.33) T - C	 ND ND ND ND 	 (p<0.05) -23% (NS) -5% -0.05 pg/mL (p<0.05)	Values estimated from figures (median (IQR)). Significant but rather small reduction of the levels of TNF-α with T. Effects on body weight not reported.
[125]	T: Freeze-dried strawberries (50 g/d) C: PLA RCT (crossover), 84 d (14 d washout phase)	USA Mixed	Obese, knee OA 57 ± 7	Serum ELISA	Protein levels (pg/mL) T: Freeze-dried strawberries (*8*) B: 5.5 ± 1.5; A: 2.8 ± 2.6 C: PLA (*8*) B: 5.5 ± 1.5; A: 5.2 ± 2.1 T – C	 27% 93% 27% 40% 	 (p<0.05) -49% (NS) 5% -2.7 pg/mL (p=0.02)	Significant reduction of the levels of TNF-α with T. No effects on body weight.

[126]	T: Frozen red raspberry (250 g/d containing 11.5 g fiber and 343 mg polyphenols, mostly anthocyanins, ellagitannins) C: PLA RCT (crossover), 2 phases: post-prandial and 28 d	USA Mixed	Obese, T2DM 54.0 ± 4.2	Serum ELISA	Protein levels (pg/mL) *Post-prandial (4 h)* T: Frozen red raspberry (*25*) B: 6.3 ± 12.5; A: 9.3 ± 32.5 C: PLA (*25*) B: 4.7 ± 7.5; A: 18.7 ± 37.5 T – C *28 d* T: Frozen red raspberry (*22*) B: 5.5 ± 7.0; A: 3.2 ± 9.8 C: PLA (*22*) B: 5.5 ± 11.7; A: 5.3 ± 15.5 T – C	 >100% >100% >100% >100% 	 (NS) +47% (NS) +297% -11.0 pg/mL (p<0.05) (p<0.05) -42% (NS) -4% -2.1 pg/mL (p<0.05)	Significant reduction of the levels of TNF-α with T. Effect on body weight not reported.
[127]	T: Black soybean testa extracts (2.5 g/d rich in anthocyanins) C: PLA (starch 2.5 g/d)	Korea Mixed	Overweight/obese T: 30.30 ± 9.42 C: 30.88 ± 9.18	Plasma ELISA	Protein levels (pg/mL) T: Soybean extract (*32*) B: 15.96 ± 3.73;	 23%	 (p<0.05)	No significant effects on the levels of TNF-α. No effect on body weight.

	RCT (parallel), 56 d				A: 15.17 ± 2.97 C: PLA (*31*) B: 43.01 ± 19.49; A: 39.63 ± 12.69 T – C	19% 45% 32%	-5% (p<0.05) -8% +2.61 pg/mL (NS)	
Other phytochemical-containing products								
[128]	T: Fruit + Vegetable concentrate powder (6 capsules/d, β-carotene, α-tocopherol, vitamin C, folate, polyphenols) C: PLA RCT (parallel), 56 d	UK Mixed	Overweight/obese T: 61.4 ± 1.5 C: 57.9 ± 1.4	Plasma ELISA	Protein levels (pg/mL) T: Fruit + Vegetable (*28*) B: 1.04 (0.87, 1.41) A: 1.02 (0.55, 1,41) C: PLA (*28*) B: 1.07 (0.79, 1.22) A: 0.94 (0.82, 1.26) T - C *Subgroup (CRP ≥3.0 mg/mL)* T: Fruit + Vegetable (*16*)	 ND ND	 (p=0.037) -2% (NS) -12% +0.11 pg/mL (NS)	For all subjects: No reduction in TNF-α levels. No effects on body weight. For subjects with CRP (≥3.0 mg/mL): Reduction in TNF-α levels. No effects on body weight.

					B: 1.13 (0.95, 1.52) A: 0.95 (0.70, 1.40) C: PLA (*15*) B: 1.07 (0.79, 1.30) A: 0.96 (0.87, 1.26) T - C	 ND ND 	(p=0.07) -16% (NS) -10% -0.07 pg/mL (p=0.035)	
[129]	T: Juice Plus+ Premium® (6 capsules/d, 2.91 mg carotene, 18.7 mg Vitamin E, 159 mg Vitamin C, 318 μg folate, 6.1 mg lutein, 1 mg lycopene and 0.15 mg astaxanthin) C: PLA RCT (crossover), 112 d (28 d washout phase)	Spain Mixed	Mixed subjects (BMI between 18.5 and 35) 34 ± 11	Serum ELISA	Protein levels (pg/mL) T: Juice Plus (*92*) B: 5.82 ± 1.14; A: 5.22 ± 1.21 C: PLA (*92*) B: 5.69 ± 1.02; A: 5.30 ± 0.87 T - C	 18%; 16% 19%; 23%	 (p<0.01) -10% (p<0.05) -7% -0.21 pg/mL (NS)	No reduction in TNF-α levels. No effects on body weight.
[130]	T: Melatonin (6 mg/d) + LCD C: PLA + LCD RCT (parallel), 40 d	Iran Women	Obese T: 33.8 ± 6.9 C: 34.8 ± 7.3	Serum ELISA	Protein levels (pg/mL) T: Melatonin (22) B: 3.52 ± 0.72; A: 1.73 ± 0.07 C: PLA (22)	 20%; 4% 18%; 19%	 (p<0.05) -50% (NS)	Reduction of TNF-α levels. No effect on body weight.

					B: 2.82 ± 0.52; A: 2.01 ± 0.38 T - C		-29% -0.98 pg/mL (p=0.02)	
[131]	T: Garlic tablets (1000 mg/d containing 2.5 mg of allicin), C: PLA RCT (parallel), 84 d	Iran Women	Overweight/obese, knee OA, 58.7 ± 7.4	Serum NR	Protein levels (pg/mL) T: Garlic tablets (39) B: 62.8 ± 73.3; A: 64.1 ± 73.5 C: PLA (37) B: 61.8 ± 64.7; A: 49.1 ± 40.5 T - C	 117%; 115% 105%; 82%	 (NS) +2% (NS) -21% +14.0 pg/mL (NS)	No effect on the levels of TNF-α. No effects on body weight.

Legend: [a]: Most values presented as the mean ± standard deviation (SD), some data indicated as Median (Inter Quartile Range, IQR); [b]:(*N*): Sample size per group; [c]: CV%: Coefficient of variation in percentage estimated for each analyzed subgroup ((CV%) = (Standard Deviation/Mean) × 100); B: Before intervention; A: After intervention; [d]:Difference in % before and after intervention; T: Treatment; C: Control; T – C[e]: effect size calculated as the difference between the T and the C group (pg/mL); BMI: Body mass index; CAD: Coronary artery disease; LCD: Low calories diet; ND: Not determined; NR: Not reported; NS: Not significant; OA: Osteoarthritis; PBMCs: Peripheral blood mononuclear cells; PLA: Placebo; RCT: Randomized clinical trial; T2DM: type 2 diabetes mellitus; TNF-α: tumor necrosis factor alpha.

Table S6. Reported changes in the circulatory levels of human TNF-α following dietary intervention with foods rich in mixed bioactive phytochemicals.

	Intervention	Sample population		TNF-α levels				
Ref.	Tested product/main compounds Study design	Country Sex	Body weight phenotype and comorbidities groups Age (y)[a]	Type of Sample Method	Results per group[a] (*N*)[b]	CV%[c]	(Sig) Effect (% A *vs* B[d] per group T – C[e] pg/mL)	General message conveyed by the article.
[132]	T: Juçara pulp (5 g/d; phenolics, flavonoids) C: PLA RCT (parallel), 42 d	Brazil Mixed	Obese T: 45.1 ± 3.4 C: 45.8 ± 2.6	Supernatant of isolated PBMC ELISA	Protein levels (pg/mg of proteins) T: Jucara pulp (*10*) B: 650 ± 200; A: 300 ± 150 C: PLA (*10*) B: 780 ± 200; A: 300 ± 100 T - C	 30% 50% 25% 33%	 (NS) -54% (NS) -61% +130 (NS)	No significant effect on the expression and release of TNF-α by isolated PBMC. Effect on body weight not reported.
[133]	T: Queen Garnet plums juice (250 mL/d; anthocyanins, quercetin) C: PLA (Raspberry cordial) RCT (parallel), 84 d	Australia Mixed	Overweight/obese with Hypertension 20-60	Plasma ELISA	Protein levels (pg/mL) T: QG juice (*15*) B: 5.6 ± 2.6; A: 3.4 ± 3.4 C: Raspberry cordial (*14*) B: 7.2 ± 5.9; A: 7.0 ± 3.2 T - C	 46% 100% 82% 46%	 (p<0.05) -39% (NS) -3% -2.0 pg/mL (p<0.05)	Significant reduction of the levels of TNF-α with T. No effect on body weight.
[134]	T: Tart cherry juice (240 mL/d; anthocyanins, flavonoids, phenolics) C: PLA RCT (crossover), 28 d (14 d washout phase)	USA Mixed	Overweight/obese 38.1 ± 12.5	Plasma ELISA	Protein levels (pg/mL) T: Tart cherry juice (*10*) B: 5.83 ± 1.14; A: 5.53 ± 0.94 C: PLA (*10*) B: 5.56 ± 1.07; A: 5.47 ± 0.94 T – C	 19% 17% 19% 17%	 (NS) -5% (NS) -1% -0.21 pg/mL (NS)	No significant effect on the levels of TNF-α. No effect on body weight.
[135]	T: Tomato juice (330 mL/day; carotenoids, phytosterols, phenolics, flavonoids, anthocaynins) C: PLA	Iran Women	Overweight/obese T: 23.3 ± 3.6 C: 23.2 ± 2.9	Serum ELISA	Protein levels (pg/ml) T: Tomato juice (*53*) B: 73.2 ± 92.45; A: NR	 ND	 ND	Authors did not present TNF- α values before and (or) after the treatment but they reported a significant reduction of TNF- α levels, especially in the

	RCT (parallel), 20 d				C: PLA (*51*) B: 66.7 ± 84.5; A: NR T – C *Subgroup overweight* T: Tomato juice (*43*) B: NR; A: NR C: PLA (*42*) B: NR; A: NR T – C *Subgroup Obese* T: Tomato juice (*10*) B: NR; A: NR C: PLA (*9*): B: NR; A: NR T – C	ND ND ND ND ND	ND -8.3 pg/mL (p<0.05) ND ND -5.3 pg/mL (p<0.05) ND ND +21.3 pg/mL (NS)	overweight subgroup. No effect on the levels of TNF- α in obese subgroup. Effect on body weight not reported.
[136]	T: Red sorghum flaked biscuits (45 g/d; carotenoids, phytosterols, phenolics, flavonoids) + LCD; C: Wheat biscuits (45 g/d) + LCD RCT (parallel), 84 d	Australia Mixed	Overweight/mildly obese T: 48.1 ± 10.3 C: 48.6 ± 11.4	NR	Protein levels (pg/mL) T: Sorghum biscuits (*26*) B: 3.2 ± 1.2; A: NR C: Wheat biscuits (*30*) B: 2.9 ± 1.3; A: NR T – C	 37% ND 45% ND	 ND ND -0.3 pg/mL (NS)	No significant effect on the levels of TNF-α. No effect on body weight.

Legend: [a]: Values are presented as the mean ± SD; [b]:(*N*): Sample size per group; [c]: CV%: Coefficient of variation in percentage estimated for each analyzed subgroup ((CV%) = (Standard Deviation/Mean) × 100); B: Before intervention; A: After intervention; [d]:Difference in % before and after intervention; T: Treatment; C: Control; T – C[e]: effect size calculated as the difference between the T and the C group (pg/mL); LCD: Low calorie diet; ND: Not determined; NR: Not reported; NS: Not significant; PBMCs: peripheral blood mononuclear cells; PLA: Placebo; QC: Queen Garnet; RCT: Randomized clinical trial; TNF-α: tumor necrosis factor alpha.

Table S7. Circulating levels of TNF-α across different genotypes for various SNPs located within the regulatory region of the *TNFα* gene.

	Genetic variant	Sample population			Genotype Protein levels[a] (pg/mL) (CV%)[c]				
Ref	SNP	Country Sex	Phenotype group Age[a] (y)	*N*[b]	Sample Method	Homozygous reference (*N*)[d]	Heterozygous (*N*)[d]	Homozygous variant (*N*)[d]	(Sig) Effect (pg/mL)[e]
[137]	*(-308 G/A)* *rs1800629*	Brazil Mixed	High cardiometabolic risk (pre-diabetes or MetS) 56.5 ± 11.6	138	Plasma Immuno-enzyme chemi-luminescent assay	GG (107) 0.11 (0.09 – 0.13)[f] (ND)	GA+AA (28) 0.11 (0.09 – 0.14)[f] (ND)		(NR) (NC)
[139]	*(-308 G/A)* *rs1800629*	Spain Mixed	Obese patients 45.8 ± 16.4	128	Unclear ELISA	GG (91) 1.4 ± 0.6 (42.9%)	GA+AA (37) 1.6 ± 1.3 (81.3%)		(NR) +0.2
				133		GG (106) 2.01 ± 1.8 (89.6%)	GA+AA (27) 1.8 ± 2.1 (>100%)		(NR) +0.2
[41]	*(-308 G/A)* *rs1800629*	Brazil Mixed	Mix (normal, overweight, T2DM) 56.0 (12.0)[f] 53.0 (18.0)[f]	264	Plasma Cytometric bed array	GG (125) 0.095 (0.055)[f] (ND)	GA (38) 0.090 (0.063)[f] (ND)	AA (1) 0.048 (ND)	(NS) -0.005, -0.047
			T2DM 56.0 (12.0)[f]	102		GG (45) 0.095 (0.045)[f] (ND)	GA (44) 0.085 (0.044)[f] (ND)	AA (1) 0.048 (ND)	(NS) -0.01, -0.047
[140]	*(-308 G/A)* *rs1800629*	Brazil Mixed	General population 38.4 ± 12.5, 38.2 ± 12.1	280	Plasma Multiplex	GG (226) 4.9 ± 2.0 (41%)	GA+AA (54) 4.8 ± 1.8 (38%)		(NS) -0.1
	(-857C/T) *rs1799724*		General population 37.8 ± 12.2, 40.7 ± 12.6			CC (227) 4.9 ± 2.0 (41%)	CT+TT (52) 4.6 ± 2.0 (43%)		(NS) -0.2
	(-1031T/C) *rs17999964*		General population 37.9 ± 12.7, 38.9 ± 11.9			TT (152) 4.9 ± 1.8 (37%)	TC+CC (128) 4.6 ± 1.9 (41%)		(NS) -0.3
	(-238G/A) *rs361525*		General population 38.2 ± 12.6,			GG (243) 4.8 ± 1.9	GA+AA (37) 5.5 ± 2.1		(*p*=0.033) +0.7

			39.5 ± 10.9			(40%)	(38%)		
[141]	*(-308 G/A) rs1800629*	Poland Women	MetS 53.0 ± 5.0	253	Serum ELISA	GG (191) 3.5 ± 14.9 (>100%)	GA (54) 3.2 ± 8.4 (>100%)	AA (8) 4.0 ± 4.4 (>100%)	(NS) -0.3, +0.5
				90		GG (65) 4.2 ± 9.2 (>100%)	GA (25) 3.4 ± 6.1 (>100%)	NR	(NS) -0.8
[142]	*(-308 G/A) rs1800629*	India Mixed	NAlb 53.9 ± 10.9	196	Plasma ELISA	GG (121) 56.2 (48.7 – 65.9) (ND)	GA (47) (NR)	AA (28) 99.1 (46.2 – 143.6) (ND)	(NR) +42.9
[42]	*(-308 G/A) rs1800629*	Pakistan Mixed	Healthy normoweight 46.5 ± 8.2	200	Serum ELISA	GG (102) 14.0 (5.5 – 20.5)[f] (ND)	GA (76) 8.0 (6.0 – 13.5)[f] (ND)	AA (22) 18.0 (7.0 – 83.0)[f] (ND)	(NS) -6.0 +4.0
			MetS overweight 47.0 ± 8.0	224		GG (100) 13.0 (7.0 – 43.0)[f] (ND)	GA (101) 30.0 (12.0 – 60.0)[f] (ND)	AA (23) 68.0 (26.0 – 146)[f] (ND)	(*p*=0.060) +17.0 (*p*=0.001) +38.0
[143]	*(-308 G/A) rs1800629*	Iraq Mixed	Patients with vitiligo 33.0 ± 12.7 28.8 ± 12.4	40	Serum ELISA	GG (27) 6.9 ± 4.8 (70%)	GA (11) 5.8 ± 2.9 (50%)	AA (2) 4.1 ± 0.6 (15%)	(NR) -1.1 -2.5
				80		GG (46) 13.5 ± 16.5 (>100%)	GA (21) 11.5 ± 7.8 (68%)	AA (13) 12.9 ± 14.5 (>100%)	(NS) -2.0 -0.6
[144]	*(-308 G/A) rs1800629*	Austria Mixed	Patients with AAA 69.7 ± 9.6 70.5 ± 7.0	216	Plasma ELISA	GG (115) 28.1 (31.6)[f] (>100%)	GA+AA (101) 78.2 (93.3)[f] (>100%)		(*p*=0.045) +50.1

Legend: [a]: Data are shown as the mean value ± SD unless otherwise indicated; [b]: Sample size of the full genotyped group; [c]: CV%: Coefficient of variation (%) ((CV%) = (Standard Deviation/Mean) × 100); [d]: Sample size of each of the genotype subgroups; [e]: Change (effect size) attributed to a different genotype estimated as the difference between heterozygous – homozygous reference and between homozygous variant – homozygous reference; [f]: median (IQR); A: Adenine; AAA: Abdominal aortic aneurism; C: Cytosine; G: Guanine; MetS: Metabolic syndrome; NAlb: Normoalbuminuria; NC: No change; ND: Not determined; NR: Not reported; NS: Not significant; T: Thymine; T2DM: Type 2 diabetes mellitus.

Table S8. Circulating levels of TNF-α across different genotypes for different SNPs located in various genes related to obesity, inflammatory and metabolic disorders.

	SNP description		Sample population			Genotype Protein levels[a] (pg/mL) (CV%)[c]				
Ref	Gen/ SNP	Metabolic association	Country Sex	Phenotype group Age[a] (y)	*N*[b]	Sample Method	Homozygous reference (*N*[d])	Heterozygous (*N*[d])	Homozygous variant (*N*[d])	(Sig) Effect (pg/mL)[e]
[145]	*MTHFR*/ C677T	Body fat accumulation Inflammatory response	Brazil Women	Overweight/ Obese 44.3 ± 9.3	24	Serum Chemi-luminiscent solid-phase system	CC (8) 5.8 ± 8.3 (>100%)	CT (8) 9.5 ± 8.6 (90.5%)	TT (8) 3.1 ± 2.3 (74.2%)	(NR) +3.7 -2.7
				Overweight/ Obese 44.8 ± 12.5	24		CC (8) 7.7 ± 12.4 (>100%)	CT (8) 5.0 ± 4.6 (92.0%)	TT (8) 6.8 ± 5.2 (76.5%)	(NR) -2.7 -0.9
[146]	*PPARD*/ -87T>C	Plasma lipid profile	China Mixed	T2DM 63.5 ± 10.5	286	Plasma ELISA	TT (136) 12.8 ± 7.4 (57.8%)	TC (128) 11.1 ± 4.8 (43.2%)	CC (22) 9.7 ± 4.2 (43.3%)	(p<0.05) -1.7 -3.1
				Normal glucose 64.6 ± 12.6	158		TT (75) 11.0 ± 6.7 (61.0%)	TC (72) 11.1 ± 7.5 (67.6%)	CC (11) 12.1 ± 8.8 (72.7%)	(NS) +0.1 +1.1
[147]	*VDR*/ FOK1	Bone mineral density	Iran Women	Obese 37.8 ± 11.1, 42.0 ± 13.1	264	Serum (NR)	FF (184) 5.1 ± 6.4 (>100%)	Ff + ff (80) 12.6 ± 26.6 (>100%)		(p=0.01) +7.5
[148]	*CLOCK*/ rs3749474	Circadian rhythm and energy balance	USA Mixed	GOLDN population (overweight) 48.5 ± 16.3	1110	Plasma Enzyme-linked immune sorbent assay	CC (427) 3.3 ± 8.3 (>100%)	TT+CC (666) 3.6 ± 6.7 (>100%)		(NS) +0.3
	CLOCK/ rs4580704						CC (481) 3.6 ± 7.0 (>100%)	GG+CG (619) 3.3 ± 8.0 (>100%)		(NS) -0.3
	CLOCK/ rs1801260						AG+AA (914) 3.5 ± 12.7 (>100%)		GG (183) 3.1 ± 5.7 (>100%)	(NS) -0.4
[149]	*IL6*/ rs1800795	Inflammation, lipid metabolism, energy balance	Poland Women Post-menopause	Central obesity + ≥1 feature MetS 60.5	144	Serum ELISA	GG (36) 8.2 ± 3.6 (43.9%)	GC+CC (108) 11.3 ± 7.3 (64.6%)		(NS) +3.1
[150]	*UCP3*/	Energy balance	Spain		64	Unclear	CC (NR)	CT+TT (NR)		(NR)

	-55CT		Mixed	Obese non diabetic NR			3.9 ± 2.7 (69.2%)	2.3 ± 2.7 (>100%)		-1.6
					67		CC (NR) 4.3 ± 2.8 (65.1%)	CT+TT (NR) 4.2 ± 2.9 (69.0%)		(NR) -0.1
[151]	*FTO*/ rs9939609	Associated with obesity	Spain NR	Obese (BMI>40) 50.0 (17.3)[f] 48.9 (16.2)[f]	129	Serum ELISA	TT (41) 7.0 (6.3)[f] (ND)	AT+AA (88) 6.3 (4.4)[f] (ND)		(NS) -0.7
[152]	*TLR1*/ A743G & T1805G	Immune response to infections and vaccination. Levels of cytokines and age.	Germany/ Italy Mixed	Elderly sample population 70.0 70.5 92.8	187	Plasma Multiplex beads	*TLR1* – AA/GG (66-76) ≈90 ± 60* (44.4%)	(all) *TLR1* + AG+GG/TG+TT (88-89) ≈80 ± 70* (87.5%)		(NS) -10
[153]	*CAT*/ rs769214	Glucose homeostasis; malnutrition	France Mixed	Malnourished elderly 83.3 ± 6.8	33	Serum Bio-Plex	GG (8) 6.9 ± 6.8 (98.6%)	GA (17) 3.7 ± 0.8 (21.6%)	AA (8) 3.0 ± 1.1 (36.7%)	(p<0.001) -3.2 -3.9
[154]	*TGFB*/ rs1800471	Fibrosis; heart failure	Poland Mixed	Heart failure patients 63.0 ± 11.0	110	Serum ELISA	CC (88) 21 (10 - 31)[f] (ND)	CG (22) 14 (2.9 - 21.0)[f] (ND)	NR	(p=0.042) -7
[137]	*IL6*/ -174 G/C	Adiposity, inflammation and metabolic disturbances	Brazil Mixed	High cardio-metabolic risk (pre-diabetes, MetS) 56.5 ± 11.6	138	Plasma Immuno enzyme chemiluminescent assay	GG (47) 0.11 (0.09 – 0.14)[f] (ND)	GG+CC (86) 0.11 (0.09 – 0.13)[f] (ND)		(NS) NC
	ADIPOQ/ 45 T/G	Hypo-adiponectinemia, risk of T2DM and MetS					TT (94) 0.11 (0.09 – 0.13)[f] (ND)	TG+GG (37) 0.11 (0.10 – 0.13)[f] (ND)		(NS) NC
[155]	*ZIP2*/ A/G/T rs2234632	Severe carotid artery disease and inflammation	Italy, Poland, Germany, Greece, France Mixed	ZINCAGE population (healthy elderly people) 74.9 ± 8.5	1090	Plasma Multiplex bead-based assay	Leu – (535) 76.6 ± 43.9 (57.3)	Leu + (555) 70.5 ± 43.2 (61.3)		(p=0.011) -6.1
[156]	*TNF-LTA* cluster/ rs2229094	Metabolic traits including susceptibility to	Canada Mixed	Healthy, normal	191	Plasma ELISA	TT (108) ≈1.9 ± 2.0 (>100%)	CT (66) ≈1.5 ± 0.5 (33.3%)	CC (17) ≈1.6 ± 0.5 (31.3%)	(NS) -0.4 -0.3

		T2DM, MetS, IR, and increased BMI		weight, overweight 30.8 ± 8.7						
[157]	*TMEM182*/ Rs141764639	Strongly associated with WC	Korea Mixed	Normal 48.5 ± 0.30	1314	Serum Bio-Plex	TT (1252) ≈10.0 ± 35.0 (>100%)	TC (62) ≈14.5 ± 32.0 (>100%9	CC (32) (NR)	(p<0.05) +4.5
				Central obese 51.4 ± 0.42	827		TT (749) ≈9.5 ± 14.0 (>100%)	TC (78) ≈23.0 ± 26.0 (>100%)	CC (39) (NR)	(p<0.001) +13.5
[158]	*TLR2*/ rs4696480	Receptors of bacterial products.	Spain Mixed	BMI < 30 49 ± 15	104	Serum ELISA	Wild type (47) ≈5.3 ± 2.5 (47.2%)	Variant (57) ≈4.2 ± 3.9 (92%)	-	(NS) -1.1
	TLR9/ rs187084						Wild type (65) ≈5.5 ± 3.8 (69%)	Variant (39) ≈4.2 ± 4.2 (100%)	-	(NS) -1.3
	TLR4/ rs4986790						Wild type (99) ≈6.5 ± 3.8 (58.5%)	Variant (5) ≈4.9 ± 2.5 (51%)	-	(NS) -1.6
	TLR2/ rs4696480			BMI > 30 49 ± 14	211		Wild type (89) ≈5.5 ± 4.7 (85%)	Variant (122) 3.8 ± 2.7 (71%)	-	(NS) -1.7
	TLR9/ rs187084						Wild type (131) ≈4.2 ± 2.7 (64%)	Variant (80) ≈4.4 ± 3.3 (75%)	-	(NS) +0.2
	TLR4/ rs4986790						Wild type (202) ≈4.2 ± 2.5 (60%)	Variant (9) ≈4.4 ± 3.1 (70%)	-	(NS) +0.2

Legend: [a]: Data are shown as the mean value ± SD unless otherwise indicated; [b]: Sample size of the full genotyped group; [c]: CV%: Coefficient of variation (%) ((CV%) = (Standard Deviation/Mean) × 100); [d]: Sample size of each of the genotype subgroups; [e]: Change (effect size) attributed to a different genotype estimated as the difference between heterozygous – homozygous reference and between homozygous variant – homozygous reference; [f]: median (IQR); BMI: Body mass index; IR: Insulin resistance; MetS: Metabolic syndrome; NC: No change; ND: Not determined; NR: Not reported; NS: Not significant; T2DM: Type 2 diabetes mellitus; WC: Waist circumference; ≈: Values estimated from bars figure. G: Guanine; A: Adenine; C: Cytosine; T: Thymine. Genes: *MTHFR*: Methylenetetrahydrofolate reductase; *PPARD*: POeroxisome proliferator activated receptor delta; *VDR*: Vitamin D receptor; *CLOCK:* Clock circadian regulator.*; IL6:* Interleukin 6*; UCP3:* Uncoupling protein 3*; FTO:* FTO alpha-ketoglutarate dependent dioxygenase*; TLR:* Toll like receptor; *CAT:* Catalase; *TGFB*: Transforming growth factor; *ADIPOQ:* Adiponectin; *ZIP2*: Zinc transporter protein; *TNF-LTA*: TNF-LTA gene cluster; *LTA*: Lymphotoxin alpha; *TMEM182:* Transmembrane protein 182.

Table S9. Reported changes on the circulatory levels of human TNF-α following intervention with specific drugs in relation with obesity treatment.

	Intervention	Sample population		TNF-α levels				General message conveyed by the article
Ref.	Tested drug Study design	Country Sex	Body weight phenotype and co-morbidities group, Age[a] (y)	Type of Sample Method	Results per group[a] (*N*)[b]	CV%[c] per group	(Sig) Effect (%A *vs* B per group; T – C[e] pg/mL)	
Chemical drugs								
[163]	T: Orlistat (360 mg/d) + LCD C: LCD RCT, 365 d	Turkey Mixed	Obese, T2DM C: 53.2 ± 9.9 T: 53.7 ± 9.4	Plasma ELISA	Protein levels (pg/mL) T: Orlistat + LCD (*190*) B: NR A: 13.6 (0.1 – 89.8)[d] C: LCD (*186*) B: NR A: 14.1 (0.3 – 96.1)[d] T - C	ND	% ND -0.5 pg/mL (based only on values after intervention)	Body weight reduction in both C and T groups. Association with lower levels of TNF-α in both groups but slightly lower in the Orlistat group than in the C subjects. Insufficient information on the statistical differences between the two groups and it is not possible to ascribe any clear effect to Orlistat.
[164]	T: Orlistat (NR mg/d) + LCD C: LCD RCT (open-label), 183 d	Greece Women	Obese C: 35.4 ± 9.2 T: 38.0 ± 7.1	Serum ELISA	Protein levels (pg/mL) T: Orlistat + LCD (*35*) B: 43 ± 15.9 A: 22.3 ± 7.5 C: LCD (*36*) B: 41.1 ± 12.7 A: 32.5 ± 10.3 T – C	31% 32% 37% 34% 	(p<0.001) (-48%) (p<0.001) (-21%) (-12.1 pg/mL) (p<0.001)	Body weight and TNF-α reduction in both groups. Significant differences between T and C and thus, Orlistat potentiated the effect of a LCD in the reduction of TNF-α. It also potentiated the improvements in metabolic and inflammatory dysregulation.
[165]	T: Orlistat (360 mg/d) + LCD C: LCD RCT (open-label), 60 d	Brazil Women	Obese, Hypertensive C: 46.8 ± 5.8 T: 47.9 ± 9.3	Serum ELISA	Protein levels (pg/mL) T: Orlistat + LCD (*14*) B: 24.5 ± 13.4 A: 9.7 ± 7.0	55% 72%	(p<0.05) (-60%)	Reduction of body weight and TNF-α levels in both groups, but no significant differences between T and C. Orlistat did not clearly

					C: LCD (*10*) B: 18.8 ± 7.1 A: 8.2 ± 1.2 T – C	 38% 15% 	 (*p*<0.05) (-56%) -4.2 pg/mL (NS)	improved the effect of a LCD on TNF-α and did not add any further metabolic and/or anti-inflammatory improvements.
[166]	T: Orlistat (120 mg ×3/d)+ L-Carnitine (2 g/d) C: Orlistat (120 mg ×3/d) RCT double-blind controlled, 90 d, 180 d, 270 d, 365 d	Italy Mixed	Obese, T2DM C: 53.0 ± 6.0 T: 51.0 ± 4.0	Unclear ELISA	Protein levels (pg/mL) T: Orlistat+ L-Carnitine (*132*) B: 4.8 ± 2.1 A (90 d): 4.3 ± 1.7 A (180 d): 3.4 ± 1.1 A (270 d): 3.1 ± 0.9 A (365 d): 2.8 ± 0.7 C: Orlistat (*126*) B: 4.4 ± 1.8 A (90 d): 4.0 ± 1.5 A (180 d): 3.8 ± 1.3 A (270 d): 3.7 ± 1.2 A (365 d): 3.3 ± 1.0 T – C (365 d)	 44% 50% 32% 29% 25% 41% 40% 34% 32% 30% 	 (NS) (-10%) (*p*<0.05) (-29%) (*p*<0.02) (-35%) (*p*<0.01) (-42%) (NS) (-9%) (NS) (-14%) (NS) (-16%) (*p*<0.05) (-25%) -0.9 pg/mL (NS)	Body weight and TNF-α levels decreased in both groups but no significant differences between T and C for the levels of TNF-α. The authors claim that Orlistat + L-Carnitine led to a better improvement in body weight, metabolic profile and inflammatory parameters than Orlistat, but differences were small.
[167]	T: Sibutramine (10 mg/d) + LCD (+ exercise) C: No control group 60 d	South Korea Mixed	Obese T: LCD + Sibutramine: 38.5 ± 11.8	Serum ELISA	Protein levels (pg/mL) T: Sibutramine + LCD (+ exercise) (78) B: 2.94 ± 0.9 A: 2.48 ± 0.7 C: NR T – C	 31% 27% 	 (*p*<0.001) (-16%) ND ND	Body weight loss upon caloric restriction + Sibutramine (+ exercise) was accompanied by a reduction of TNF-α and improve metabolic risk factors. Since there wasn't a C group, it was not possible to differentiate the LCD effect from the drug effect.
[168]	T1: Sibutramine (10 mg/d) T2: Sibutramine (15 mg/d) RCT (prospective open), 570 d	Turkey Women	Obese T1: 39.6 ± 2.1 T2: 40.6 ± 8.1	Plasma ELISA	Protein levels (pg/mL) T1: Sibutramine 10 mg/d (*30*) B: 3.0 ± 1.1 A: 2.5 ± 1.09 T2: Sibutramine 15 mg/d (*30*) B: 3.4 ± 1.5	 37% 43.6% 44% 29%	 (*p*<0.04) (-17%,) (*p*<0.001) (-30%)	The two doses of Sibutramine reduced body weight and TNF-α levels but no information on significant differences between groups.

					A: 2.4 ± 0.7 T2 – T1		 -0.5 pg/mL (NR)	It is not addressed if this effect is associated with body weight reduction.
[169]	T: Sibutramine (10 mg/d) + LCD (+ exercise) C: LCD (+ exercise) RCT, 365 d	Italy Mixed	Obese, T2DM C: 53.0 ± 6.0 T: 51.0 ± 4.0	Serum NR	Protein levels (pg/mL) T: Sibutramine + LCD + exercise (*110*) B: 4.9 ± 2.2 A (90 d): 4.3 ± 1.7 A (183 d): 4.2 ± 1.6 A (270 d): 3.7 ± 1.3 A (365 d): 3.2 ± 1.1 C: LCD + exercise (*112*) B= 4.5 ± 1.9 A (90 d): 4.4 ± 1.8 A (183 d): 4.3 ± 1.7 A (270 d): 4.1 ± 1.5 A (365 d): 3.8 ± 1.4 T – C (365 d)	 45% 40% 38% 35% 34% 42% 41% 40% 37% 37%	 (NS) (-12%) (NS) (-14%) (p<0.05) (-25%) (*p*<0.01) (-35%) (NS) (-2%) (NS) (-4%) (NS) (-9%) (*p*<0.05) (-16%) -1.0 pg/mL (NS)	Body weight reduction more significant in the Sibutramine group. TNF-α levels significantly reduced in both the T and the C groups. TNF-α significant predictor of BMI changes.
[170]	T: Diacerein + LCD + Sibutramine (+ exercise) C: LCD + Sibutramine (+ exercise) (doses not reported) RCT, 84 d	South Korea Mixed	Obese, T2DM, Hypertensive, Dyslipidaemia T: 39.0 ± 1.0 C: 37.0 ± 1.0	NR EIA	Protein levels (pg/mL) T: Diacerein + Sibutramine + LCD (*12*) B: 15.7 ± 1.4 A: 10.3 ± NR C: Sibutramine + LCD (*7*) B: 11.5 ± 2.7 A: 5.3 ± NR T – C	 9% ND 23% ND 	 (NS) (-34%) (NS) (-54%) +0.8 pg/mL (NS)	Body weight and TNF-α levels reduction in both groups but no significant differences between them. Diacerein (anti-IL-1 drug), given on top of Sibutramine, did not produce additional weight or metabolic improvement.
[29]	T: Troglitazone (2×200 mg/d) C: PLA RCT (double-blind crossover,), 56 d	The Netherlands Mixed	Obese 37.4 ± 1.2	Plasma ELISA	Protein levels (pg/mL) Participants (*126*) T: Troglitazone A: 3.4 ± 0.5	 15%	 ND	No changes observed for body weight. Lower levels of TNF-α in obese participants treated with troglitazone as compare to PLA

					C: PLA A: 4.5 ± 0.5 T – C	 11% 	ND -1.1 pg/mL (based only on values after intervention)	(↓ -24%, p<0.01) but there is no information on baseline values.
[171]	T: Rosiglitazone ± MET (8 mg/d + 1500 ± 500 mg/d) (controlled energy diet) C: MET (2500 ± 500 mg/d) (controlled energy diet) RCT (single-blind placebo-controlled), 90 d, 180 d	Italy Mixed	Overweight/ Obese, T2DM C: 54.0 ± 3.0 T: 55.0 ± 4.0	Plasma ELISA	Protein levels (ng/mL) T: Rosiglitazone + MET (*56*) B: 3.2 ± 0.6 A (90 d): 2.8 ± 0.5 A (180 d): 2.5 ± 0.4 C: MET (*61*) B= 3.5 ± 0.9 A (90 d): 3.3 ± 0.8 A (180 d): 3.2 ± 0.7 T – C (180 d)	 19% 18% 16% 26% 24% 22% 	 (NS) (-13%) (p<0.05) (-22%) (NS) (-6%) (NS) (-9%) -0.4 pg/mL (NS)	There was no body weight reduction in any group. No significant differences reported between groups for TNF-α levels.
[172]	T: HCQ (400 mg/d) C: PLA RCT double-blind, parallel-arm, 93 d	USA Mixed	Overweight/ Obese, IR non-diabetic patients (> 18.0)	NR ELISA	Protein levels (pg/mL) T: HCQ (*13*) B: NR, A: NR C: PLA (*15*) B: NR, A: NR T – C	 ND 	 No effect ND	There were no significant changes in body weight or any other inflammatory cytokine except for adiponectin. No values reported.
[173]	T: Rimonabant (20 mg/d) C: MET (500 mg 3x/d) RCT (open labelled parallel), 84 d	UK Women	Obese, PCOS NR	Serum Bio-Plex 200 system	Protein levels (pg/mL) T: Rimonabant (*10*) B: 8.7 ± 3.9 A: 8.7 ± 3.7 C: MET (*10*) B: 7.1 ± 2.9 A: 7.9 ± 4.3 T – C	 45% 45% 41% 54% 	 (NS) No change (NS) (+11%) -0.8 pg/mL (NS)	Significant reduction of body weight with Rimonabant but, no effects on TNF-α levels in any group.

[174]	T: Combined Lacidipine (2 and 4 mg) + Candesartan (4, 8, 16 mg) Not a RCT, 56 d	Ukraine Mixed	Overweight/ Obese, Hypertensive T: 54.7 ± 5.8	Serum ELISA	Protein levels (pg/mL) T: combined drugs (*30*) B: 132.6 ± 22.6 A: 44.9 ± 5.6 C: NR T – C	 17% 13% 	 (p<0.05) (-66%) ND ND	It does not indicate results for a control group neither on body weight changes.
[175]	T: MET (dose1:1000, dose2: 2000, dose3: 3000 mg/d) Cross-sectional study	Ghana Mixed	Mostly overweight, T2DM responsive to MET T: 61 to 80 y	Serum ELISA	Protein levels (pg/mL) dose1: 125.0 ± 61.0 dose2: 95.0 ± 57.0 dose3: 60.0 ± 63.0 dose3 – dose1	 49% 60% >100% 	 (p<0.0001) (-52%) (dose3 *vs* dose1) -65 pg/mL (p<0.001)	A significant reduction of TNF-α levels with a higher dose. Not an intervention study or clinical trial. No control group.
Protein/peptide drugs								
[176]	T: Etanercept (50 mg ×2 weekly for 90 d, then 50 mg ×1 weekly for 90 d); TNF-α inhibitor C: PLA RCT, 180 d	USA Mixed	Obese T: 41.0 ± 2.0 C: 47.0 ± 2.0	Serum ELISA	Protein levels (pg/mL) T: Etanercept (*12*) B: 3.4 ± 6.2 A (90 d): NR A (180 d): NR C: PLA (*22*) B: 0.9 ± 2.3 A (90 d): NR A (180 d): NR T – C	 >100% >100% 	 (NS) (+55%) (p<0.03) (+51%) ND	The levels of TNF-α were increased in both the T and C groups but no values after treatment reported. No effects on body weight. No significant correlation between BMI and TNF-α expression in adipose tissue.
[177]	T: Exenatide (5.0 µg s.c.i. + 0.5 g MET x2/d for 28 d, then 10.0 µg s.c.i. + 0.5 g MET x2/d for 168 d: GLP-1 C: No control group included, comparison women *vs* men	China Mixed	Overweight/ Obese, T2DM Females: 49.1 ± 10.4 Males: 48.4 ± 9.8	Serum ELISA	Protein levels (pg/mL) Women T: Exenatide (+ MET) (*54*) B: 34.6 ± 85.2 A (196 d): 28.0 ± 89.0 Men T: Exenatide (+ MET) (*51*) B: 33.5 ± 70.0 A: 30.3 ± 85.6	 >100% >100% >100% >100%	 (p=0.001) (-19%) (p=0.039) (-10%)	Reduction of body weight and TNF-α levels in both groups but significantly better in women than in men.

					T - C		ND	
[178]	T: Exenatide (5.0 µg s.c.i. + 0.5 g MET x2/d for 30 d, then 10.0 µg s.c.i. + 0.5 g MET x2/d for 90 d: GLP-1 C: Acarbose 50-100 mg oral + 0.5 g MET 90 d) RCT (prospective open), 120 d	China Mixed	Obese, T2DM T: 44.4 ± 11.1 C: 38.7 ± 10.3	NR NR	Protein levels (pg/mL) T: Exenatide (+ MET) (*15*) B: 25.1 ± 10.7 A: 18.1 ± 6.8 C: Acarbose (+ MET) (*16*) B: 23.2 ± 10.4 A: 22.2 ± 8.0 T – C	 43% 38% 45% 36%	 (p<0.001) (-28%) (NS) (-4%) -6.0 pg/mL (NS)	Exenatide/MET reduced significantly intra-abdominal fat content in comparison with the C group. BMI is reduced in both groups. TNF-α levels significantly reduced with T but difference between the T and C group did not reach significance.
[179]	T: Liraglutide (s. c. i. ×1/d from 0.6 mg to 1.8 mg within 28 d) + MET (orally from 0.5 g ×2/d to 1 g ×2/d within 28 d); GLP-1 C: PLA + MET RCT (double-blind cross-over), 84 d	Denmark Mixed	Overweight/ Obese, CAD, T2DM on stable statin therapy 62.3 ± 7.6	Plasma ELISA	Protein levels (pg/mL) Patients (*28*) T: Liraglutide B: 6.1 (5.3, 7.0)[d] A: NR C: PLA + MET B: NR A: NR -0.2 (-0.6, 0.2) T – C	 ND ND	 No effect (p<0.05) ND ND	No significant different results between groups. Lack of data and unclear results but apparent lack of effect of the drug liraglutide on TNF-α levels. No clear information on body weight changes but the authors claim no correlation between TNF-α and body weight changes.

Legend: [a]: Results are presented as the mean ± SD unless otherwise stated; [b]: *N*: group sample size; [c]: CV%: Coefficient of variation ((CV%) = (Standard Deviation/Mean) × 100); [d]: median (IQR); [e]: calculated as ΔT - ΔC; Δ= A – B unless otherwise indicated; A: After treatment; B: Before treatment; C: Control group; CAD: Coronary Artery Disease; d: day; EIA: Enzyme immune assay; GLP-1: Glucagon-like peptide 1; HCQ: Hydroxychloroquine (anti-malarial drug with anti-inflammatory properties); IR: Insulin resistance; LCD: Low Calorie Diet; MET: Metformin; ND: Not determined; NR: Not reported; NS: Not significant; PLA: Placebo; PCOS: Polycistic ovary syndrome; RCT: Randomized controlled trial; SAT: Subcutaneous abdominal adipose tissue; s.c.i.: subcutaneous injection; T: Treatment group; T2DM: Type 2 Diabetes Mellitus; TNF-α: Tumour necrosis factor alpha.