Study	Mean Difference	MD 95%-Cl
ZELBER–SAGI, 2006 Harrison, 2009		-17.90 [-45.38; 9.58] -10.00 [-41.97; 21.97]
Harte, 2010 Ye, 2019		- 2.00 [-44.67; 48.67] -10.90 [-22.45; 0.65]
Feng, 2023 Zahmatkesh, 2023		-12.20 [-26.15; 1.75] -4.26 [-7.24; -1.28]
Random effects model Heterogeneity: $l^2 = 0\%$, $\tau^2 = 8.3522$, $p = 0.66$		-6.79 [-11.96; -1.63]
	-40 -20 0 20 40	

Figure S1. Forest plot describing the effect of orlistat administration on ALT levels (in RCTs)



Figure S2. Funnel plot for the studies describing the effect of orlistat administration on ALT levels (in RCTs and single-arm trials)



Figure S3. Forest plot describing the effect of orlistat administration on ALT levels (in RCTs and singlearm trials) (Subgroup analysis based on age of participants)

Study	proportion	MRAW	95%-CI
Dose = 120 mg TDS ZELBER–SAGI, 2006 Harrison, 2009 Ye, 2019 Feng, 2023 Harrison, 2004 Hussein, 2007 Khazal, 2007 Random effects model Heterogeneity: l^2 = 95%, τ^2 = 166.4146, $p < 0.01$	*	-55.00 [- -16.50 [- 17.20 [-39.00 [- -41.00 [- -14.00 [-	-55.83; -5.37] 82.30; -27.70] -27.12; -5.88] -29.92; -4.48] 53.51; -24.49] 44.51; -37.49] 17.51; -10.49] 39.46; -17.54]
Dose = 120 mg BD Harte, 2010 Iranparvar Alamdari, 2020 Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.61$	-	-31.60 [-	-44.05; -9.95] 35.60; -27.60] 35.26; -27.46]
Dose = 120 mg daily Zahmatkesh, 2023 Random effects model Heterogeneity: l^2 = 97%, τ^2 = 145.9210, $p < 0.01$ Test for subgroup differences: χ_2^2 = 93.99, df = 2 ($p < 0.01$)-60		2000 000 100 100 100 100 100 100 100 100	-11.72; -6.86] 34.70; -17.76]

Figure S4. Forest plot describing the effect of orlistat administration on ALT levels (in RCTs and singlearm trials) (Subgroup analysis based on intake dose)



Figure S5. Forest plot describing the effect of orlistat administration on ALT levels (in RCTs and singlearm trials) (Subgroup analysis based on study duration)

Study	proportion	MRAW	95%-CI
Assessment = biopsy			
ZELBER–SAGI, 2006 –		-30.60 [-	55.83; -5.37]
Harte, 2010		-27.00 [-	44.05; -9.95]
Harrison, 2004		-39.00 [-	53.51; -24.49]
Hussein, 2007		-41.00 [-4	44.51; -37.49]
Random effects model	-	-38.66 [-4	4.62; -32.71]
Heterogeneity: $I^2 = 3\%$, $\tau^2 = 10.0163$, $p = 0.38$			
Assessment = NAS	8 9 9		
Harrison, 2009 🗸 👘		-55.00 [-8	82.30; -27.70]
Zahmatkesh, 2023		-9.29 [-	11.72; -6.86]
Random effects model		-30.04 [-7	74.64; 14.56]
Heterogeneity: $I^2 = 91\%$, $\tau^2 = 946.9288$, $\rho < 0.01$			
Assessment = MRI-PDFF			
Ye, 2019	÷ • •	-16.50 [-	27.12; -5.88]
Feng, 2023		-17.20 [-	29.92; -4.48]
Random effects model		-16.79 [-	24.94; -8.64]
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.93$			
Assessment = US			
Khazal, 2007		-14.00 [-	17.51; -10.49]
Iranparvar Alamdari, 2020		-31.60 [-3	35.60; -27.60]
Random effects model		-22.77 [-	40.02; -5.52]
Heterogeneity: $I^2 = 98\%$, $\tau^2 = 151.1914$, $p < 0.01$			
Random effects model	-	-26.23 [-3	84.70; -17.76]
Heterogeneity: $l^2 = 97\%$, $\tau^2 = 145.9210$, $p < 0.01$			
Test for subgroup differences: $\chi_3^2 = 18.87$, df = 3 ($p < 0.01$)-60	-50 -40 -30 -20 -10	0	

Figure S6. Forest plot describing the effect of orlistat administration on ALT levels (in RCTs and singlearm trials) (Subgroup analysis based on NAFLD detection method)

Study	Mean Difference	MD 95%-CI
ZELBER–SAGI, 2006 Harrison, 2009 Ye, 2019 Feng, 2023 Zahmatkesh, 2023		-10.10 [-25.87; 5.67] 1.00 [-14.73; 16.73] -5.10 [-9.99; -0.21] -5.90 [-11.48; -0.32] -3.33 [-5.41; -1.25]
Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.74$	-20 -10 0 10 20	-3.86 [-5.64; -2.08]





Figure S8. Funnel plot for the studies describing the effect of orlistat administration on AST levels (in RCTs and single-arm trials)



Figure S9. Forest plot describing the effect of orlistat administration on AST levels (in RCTs and singlearm trials) (Subgroup analysis based on age of participants)



Figure S10. Forest plot describing the effect of orlistat administration on AST levels (in RCTs and single-arm trials) (Subgroup analysis based on intake dose)



Figure S11. Forest plot describing the effect of orlistat administration on AST levels (in RCTs and single-arm trials) (Subgroup analysis based on study duration)

Study	proportion	MRAW	95%-CI
Assessment = biopsy	1	40.00	
ZELBER-SAGI, 2006	100	지금 위험 집 것같이 지난 것 같아. 지난 것 같아.	33.01; -4.79]
Harrison, 2004		Second States and States	4.86; -17.14]
Hussein, 2007			4.27; -35.73]
Random effects model		~31.41 [-4	3.81; -19.00]
Heterogeneity: $I^2 = 77\%$, $\tau^2 = 88.9152$, $p = 0.01$			
Assessment = NAS			
Harrison, 2009		-28.00 [-3	9.16; -16.84]
Zahmatkesh, 2023		1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	-7.93; -4.95]
Random effects model		-16.48 [-	37.56; 4.60]
Heterogeneity: $l^2 = 93\%$, $\tau^2 = 215.9274$, $\rho < 0.01$			
Assessment = MRI-PDFF			
Ye, 2019		8.30 [-	12.86; -3.74]
Feng, 2023		~~ 고려한 것같아. 말 수 있다.	14.68; -5.32]
Random effects model			12.39; -5.86]
Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.61$		L.	
Assessment = US			
Iranparvar Alamdari, 2020	in the second se	-18.50 [-2	20.19; -16.81]
Random effects model		-19.62 [-2	8.33; -10.92]
Heterogeneity: $l^2 = 98\%$, $\tau^2 = 141.2809$, $p < 0.01$, · - ,
Test for subgroup differences: $\chi_3^2 = 30.39$, df = 3 ($p < 0.01$)-50	-40 -30 -20 -10	0	
	10 00 20 10	M	

Figure S12. Forest plot describing the effect of orlistat administration on AST levels (in RCTs and single-arm trials) (Subgroup analysis based on NAFLD detection method)



Figure S13. Funnel plot for the studies describing the effect of orlistat administration on ALP levels



Figure S14. Forest and funnel plot for the studies describing the effect of orlistat administration on FBS

	Standardised Mean		
Study	Difference	SMD	95%-CI
Dose = 120 mg TDS	8 f		
ZELBER-SAGI, 2006		-0.58	[-1.18; 0.03]
Harrison, 2009			[-0.12; 1.14]
Ye, 2019			[-0.46; 0.24]
Feng, 2023			[0.01; 0.96]
Random effects model			[-0.41; 0.56]
Heterogeneity: $l^2 = 71\%$, $\tau^2 = 0.1745$, $p = 0.02$	T	0.00	[-0.41, 0.30]
Dose = 120 mg BD			
Harte, 2010 —		-1 55	[-2.81; -0.30]
10.10, 2010		1.00	[2.01, 0.00]
Dose = 120 mg daily			
Esmail, 2020		-0.47	[-1.03; 0.09]
Zahmatkesh, 2023			[-1.44; -0.31]
Random effects model	\bigcirc		[-1.07; -0.27]
Heterogeneity: $I^2 = 0\%$, $\tau^2 = < 0.0001$, $p = 0.32$			An other strength and
Random effects model	$\langle \rangle$	-0.28	[-0.76; 0.19]
Heterogeneity: $I^2 = 77\%$, $\tau^2 = 0.3094$, $p < 0.01$		Commission and Sold 2	
Test for subgroup differences: $\chi_2^2 = 8.72$, df = 2 ($p = 0.01$)	-2 -1 0 1 2		

Figure S15. Forest plot for the studies describing the effect of orlistat administration on FBS (Subgroup analysis based on intake dose)

Study	Standardised Mean Difference	SMD	95%-CI
Duration = 6			
ZELBER-SAGI, 2006		-0.58 [-1.18; 0.03]
Ye, 2019		-0.11 [-0.46; 0.24]
Feng, 2023		0.49	0.01; 0.96]
Random effects model		-0.05 [-	0.62; 0.53]
Heterogeneity: $l^2 = 75\%$, $\tau^2 = 0.1973$, $p = 0.02$			
Duration = 9			
Harrison, 2009		0.51 [-0.12; 1.14]
Duration = 12			
Harte, 2010 —		-1.55 [·	-2.81; -0.30]
Duration = 3			
Esmail, 2020		-0.47 [-1.03; 0.09]
Zahmatkesh, 2023		-0.88 [-1.44; -0.31]
Random effects model	\diamond	-0.67 [-	1.07; -0.27]
Heterogeneity: $I^2 = 0\%$, $\tau^2 = < 0.0001$, $p = 0.32$			
Random effects model		-0.28 [·	-0.76; 0.19]
Heterogeneity: $I^2 = 77\%$, $\tau^2 = 0.3094$, $p < 0.01$			
Test for subgroup differences: χ_3^2 = 14.30, df = 3 (p < 0.01)-2 -1 0 1 2		

Figure S16. Forest plot for the studies describing the effect of orlistat administration on FBS (Subgroup analysis based on study duration)



Figure S17. Forest and funnel plot for studies describing the effect of orlistat administration on HOMA



Figure S18. Forest and funnel plot for studies describing the effect of orlistat administration on BMI



Standardised Mean Difference

Figure S19. Forest and funnel plot for studies describing the effect of orlistat administration on TG levels

Study	Standardised Mean Difference	SMD	95%-CI
ZELBER–SAGI, 2006 Harte, 2010 Ye, 2019 Esmail, 2020 Zahmatkesh, 2023		0.00 [- 0.20 [- 0.19 [-	0.62; 0.57] 1.06; 1.06] 0.15; 0.55] 0.37; 0.74] 1.34; -0.22]
Random effects model Heterogeneity: l^2 = 56%, τ^2 = 0.1083, p = 0.06	-1 -0.5 0 0.5 1	-0.07 [-0	0.46; 0.32]

Figure S20. Forest plot for studies describing the effect of orlistat administration on TG levels (after removal of Feng's study)



Figure S21. Forest and funnel plot for studies describing the effect of orlistat administration on cholesterol levels

Study	Standardised Mean Difference	SMD	95%-CI
ZELBER-SAGI, 2006		-0.61 [-1.22; -0.01]
Harrison, 2009		-0.45 [-1.08; 0.17]
Harte, 2010		0.00 [-1.06; 1.06]
Ye, 2019		-0.22 [-0.57; 0.13]
Esmail, 2020		0.05 [-0.51; 0.60]
Zahmatkesh, 2023		-0.92 [-1.49; -0.35]
Random effects model Heterogeneity: $l^2 = 34\%$, $\tau^2 = 0.0469$, $p = 0.18$		-0.38 [·	0.67; -0.08]
	-1 -0.5 0 0.5 1		

Figure S22. Forest plot for studies describing the effect of orlistat administration on cholesterol levels (after removal of Feng's study)



Figure S23. Forest and funnel plot for studies describing the effect of orlistat administration on insulin levels





Figure S24. Forest and funnel plot for studies describing the effect of orlistat administration on LDL levels

Standardised Mean Difference

Study	Standardised Mean Difference	SMD	95%-CI
Harrison, 2009		-0.41 [-	1.03; 0.21]
Harte, 2010		-0.37 [-	1.44; 0.70]
Ye, 2019		0.10 [-	0.25; 0.45]
Esmail, 2020		-0.05 [-	0.60; 0.50]
Zahmatkesh, 2023		-0.72 [-	1.28; -0.16]
Random effects model		-0.24 [-	0.58; 0.11]
Heterogeneity: $l^2 = 42\%$, $\tau^2 = 0.0667$, $p = 0.14$	-1 -0.5 0 0.5 1		

Figure S25. Forest plot for studies describing the effect of orlistat administration on LDL levels (after removal of Feng's study)



Figure S26. Forest and funnel plot for studies describing the effect of orlistat administration on WC



Figure S27. Forest and funnel plot for studies describing the effect of orlistat administration on SBP

RCT studies included	1	2	3	4	5	6	7	8	9	10	11	12	13
Zahmatkesh et al. ^[15]	Yes	No	Yes	No	No	Yes							
Feng et al. ^[16]	Yes	Yes	Yes	Yes	Yes	Yes	n/a	Yes	Yes	Yes	Yes	Yes	Yes
Wasta Esmail et al. ^[14]	Yes	No	Yes	No	No	Yes	n/a	Yes	Yes	Yes	Yes	Yes	Yes
Ye et al. ^[17]	Yes	No	Yes	No	No	Yes	n/a	Yes	Yes	Yes	Yes	Yes	Yes
Harte et al. ^[18]	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Harrison et al. ^{[19}]	Yes	No	Yes	No	No	Yes							
Zelber–Sagi et al. ^[20]	Yes	Yes	Yes	Yes	Yes	Yes	n/a	Yes	Yes	Yes	Yes	Yes	Yes

Table S1. JBI critical appraisal checklist for randomized controlled trials

- 1- Was true randomization used for assignment of participants to treatment groups?
- 2- Was allocation to treatment groups concealed?
- 3- Were treatment groups similar at the baseline?
- 4- Were participants blind to treatment assignment?
- 5- Were those delivering the treatment blind to treatment assignment?
- 6- Were treatment groups treated identically other than the intervention of interest?
- 7- Were outcome assessors blind to treatment assignment?
- 8- Were outcomes measured in the same way for treatment groups?
- 9- Were outcomes measured in a reliable way?
- 10- Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?
- 11- Were participants analyzed in the groups to which they were randomized?
- 12- Was appropriate statistical analysis used?
- 13- Was the trial design appropriate and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

Single-arm trials included	1	2	3	4	5	6	7	8	9
Iranparvar Alamdari et al. ^[21]	Yes	No	Yes						
Khazal et al. ^[13]	Yes	No	Yes						
Hussein et al. ^[22]	Yes	No	Yes						
Harrison et al. ^[23]	Yes	No	Yes						

Table S2. JBI critical appraisal checklist for quasi-experimental studies

- 1- Is it clear in the study what is the "cause" and what is the "effect" (i.e. there is no confusion about which variable comes first)?
- 2- Was there a control group?
- 3- Were participants included in any comparisons similar?
- 4- Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?
- 5- Were there multiple measurements of the outcome, both pre and post the intervention/exposure?
- 6- Were the outcomes of participants included in any comparisons measured in the same way?
- 7- Were outcomes measured in a reliable way?
- 8- Was follow-up complete and if not, were differences between groups in terms of their follow-up adequately described and analyzed?
- 9- Was appropriate statistical analysis used?

Study	Estimate	CI_lb	CI_ub	p_value	Tau2	I2
ZELBER– SAGI	0.5589	-0.77799	1.895794	0.41257	2.206851	96.29354
Harte	0.544935	-0.77555	1.86542	0.418611	2.187304	96.79489
Ye	0.514243	-0.84422	1.872707	0.458124	2.269922	95.36896
Esmail	0.516276	-0.83592	1.868477	0.454266	2.258144	96.26787
Feng	-0.07074	-0.46142	0.319943	0.722672	0.108736	57.7949
Zahmatkesh	0.712844	-0.50195	1.927641	0.2501	1.799965	95.37402

Table S3. Sensitivity analysis for studies assessing TG levels

Table S4. Sensitivity analysis for studies assessing cholesterol levels

Study	Estimate	CI_lb	CI_ub	p_value	Tau2	I2
ZELBER– SAGI	-0.02513	-0.672	0.621734	0.939294	0.55273	87.65158
Harrison	-0.05281	-0.71398	0.608357	0.875598	0.582644	88.31157
Harte	-0.12379	-0.77349	0.525905	0.708812	0.582994	89.31295
Ye	-0.08874	-0.77257	0.595082	0.799222	0.616837	86.267
Esmail	-0.13712	-0.81169	0.537461	0.690345	0.606665	88.31534
Feng	-0.37592	-0.66872	-0.08311	0.01186	0.047308	36.49487
Zahmatkesh	0.030263	-0.56862	0.62915	0.921105	0.458542	85.20076

Table S5. Sensitivity analysis for studies assessing LDL levels

Study	Estimate	CI_lb	CI_ub	p_value	Tau2	I2
Harrison	-0.58087	-1.29994	0.138199	0.113358	0.569794	88.06166
Harte	-0.57903	-1.26635	0.108283	0.098702	0.540852	88.84267
Ye	-0.70468	-1.35436	-0.055	0.033513	0.431989	80.88303
Esmail	-0.65704	-1.34244	0.028372	0.060268	0.504801	86.14197
Feng	-0.23803	-0.58207	0.106012	0.175092	0.066837	45.24189
Zahmatkesh	-0.51718	-1.23872	0.204365	0.16007	0.570103	87.54376

Table S6. Sensitivity analysis for studies assessing FBS levels

Study	Estimate	CI_lb	CI_ub	p_value	Tau2	I2
ZELBER-	-0.24824	-0.80909	0.312607	0.38566	0.38823	83.57852
SAGI						
Harrison	-0.41123	-0.89844	0.075982	0.098066	0.272885	78.34587
Harte	-0.16758	-0.61696	0.281803	0.46485	0.24191	78.16519
Ye	-0.33762	-0.92707	0.251819	0.261591	0.42588	81.5384
Esmail	-0.26809	-0.84157	0.305382	0.359529	0.407805	83.91835
Feng	-0.42207	-0.89049	0.046342	0.077386	0.238131	73.96895
Zahmatkesh	-0.17993	-0.6824	0.322533	0.482762	0.292321	78.92562