EVIDENCE BASED LDL LOWERING OPTIONS

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CONFLICT OF INTEREST STATEMENT

- Dr White is a coinvestigator on a project assessing the risk of bias in andexanet alfa and prothrombin complex concentrate products for reversal of factor Xa inhibitors
- This project is funded by AstraZeneca Pharmaceuticals
- No AstraZeneca products or its competitors' products are being reviewed in this presentation

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OBJECTIVES

- At the end of this lecture, the successful learner will be able to:
  - Describe the role of dietary modification for LDL modification
  - Identify how some dietary supplement ingredients mimic the mechanisms of action of prescription drugs
  - Describe the magnitude of plant sterols and stanols, red yeast rice, Silybum M, berberine, cinnamon, green tea extract, and garlic LDL reduction as monotherapy
    - The potential for combination therapy to increase the magnitude of benefit
  - Compare and contrast with prescription LDL lowering options
  - Describe risks of contamination and adulteration with dietary supplements

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DIETARY MODIFICATIONS TO REDUCE LDL

Lifestyle Change	Magnitude of LDL Reduction
Reduce excess body weight	Up to 5%
Preferentially use monounsaturated or polyunsaturated fats over saturated/ trans fats	Up to 8%
Preferentially use MCTs over saturated/ trans fats	Up to 4%
Use fat-based products enhanced with plant sterols and stanols for saturated fat/ trans fats	Up to 8%
Increase intake of soluble fiber	Up to 6%
Increase use of almonds over other protein sources including other nut products	Up to 4%

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WEIGHT LOSS AND LDL CHOLESTEROL

- During active weight loss, LDL levels tend to rise slightly (~1-2%) while the body is using adipose tissue to supply triglycerides to the blood for fuel
- With successful weight loss, the LDL goes down ~5% over time

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LOWDOWN ON FATS AND LDL CHOLESTEROL

	LDL (Bad)	HDL (Good)
Trans Fats (Partially Hydrogenated Oil)	+++	--
Long Chain Saturated Fat (Animal Fat/Oil)	+++	++
Medium Chain Saturated Fat (Coconut, Palm Oil)	++	++
Monounsaturated Fat	0	+
Polyunsaturated Fat (Fish/Krill Oil, Flaxseed Oil)	0	++

Switching to mono/poly-unsaturated reduces LDL by 8%

Switching to mono/poly-unsaturated reduces LDL by 4%

Trans and saturated fats increase hs-CRP
MCTs and PUFAs reduce hs-CRP
MUFAs impact on hs-CRP unclear

Am J Clin Nutr. 1992 Nov;56(5):895-8.
Am J Clin Nutr. 1997 Jan;65(1):41-5.
J Am Coll Nutr. 2008 Oct; 27(5): 547–552.

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DIETARY SOLUBLE FIBER

- Forms gel that removes intestinal dietary fat and bile which contains LDL
- Soluble fiber is found in oats, beans/legumes, apples, pears, apricots, avocados, Brussel sprouts, sweet potato
- 10 grams or more of soluble fiber a day decreases your LDL cholesterol by 6%
  - One serving of oatmeal or oat bran provides 3 to 4 grams of fiber
- USDA recommends 25g of fiber a day

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MEDITERRANEAN DIET VERSUS STANDARD EATING PLANS

Table 2. Effect of the Mediterranean diet on anthropometric, blood pressure, biochemical, insulin resistance, oxidative stress, inflammatory, and endothelial function markers related to the metabolic syndrome *.

Outcome	No. of Studies	No. of Participants	Effect Estimate (MD, 95% CI)	*p*-Value	I^2
Anthropometric markers					
Body weight (kg)	40	12,571	−1.72 (−2.40, −1.05)	<0.001	98.6%
Body mass index (kg/m^2)	37	5679	−0.41 (−0.71, −0.10)	0.010	98.6%
Waist circumference (cm) (MetSyn component)	27	9690	−1.47 (−2.54, −0.39)	0.007	99.6%
Total fat mass (kg)	9	963	−0.47 (−1.53, 0.60)	0.389	85.1%
Total body fat (%)	8	661	−0.12 (−1.60, 1.37)	0.878	89.7%
Blood pressure (MetSyn component)					
Systolic blood pressure (mm Hg)	27	4930	−1.34 (−2.00, −0.67)	<0.001	93.6%
Diastolic blood pressure (mm Hg)	27	4930	−0.81 (−1.30, −0.32)	0.001	92.8%
Biochemical and insulin resistance markers					
Glucose (mg/dL) (MetSyn component)	31	3662	−2.98 (−4.54, −1.42)	<0.001	98.1%
Insulin (μU/mL)	20	2184	−0.94 (−1.72, −0.16)	0.019	97.2%
HOMA-IR index	18	2098	−0.42 (−0.70, −0.15)	0.003	97.7%
HbA1c (%)	18	869	−0.15 (−0.41, 0.12)	0.274	81.3%
Total cholesterol (mg/dL)	37	4603	−5.70 (−9.96, −1.43)	0.009	98.6%
LDL-cholesterol (mg/dL)	29	3633	−8.24 (−13.50, −2.99)	0.002	99.6%
HDL-cholesterol (mg/dL) (MetSyn component)	36	4433	1.30 (0.38, 2.21)	0.005	98.1%

Eating plan includes more MUFA and PUFA, less red meat, more whole grains and fruits and vegetables

Net effect: ~4% reduction in LDL without losing weight

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MEDITERRANEAN DIET REDUCES ASCVD ENDPOINTS BUT DOES NOT REDUCE NEED FOR LIPID THERAPY

Table 3. Effect of the Mediterranean diet on metabolic syndrome-related comorbidities and pharmacologic treatment for metabolic syndrome components and related comorbidities *.

Outcome	No. of Studies	Intervention		Control		Effect Estimate (RR, 95% CI)	*p*-Value	I^2
		Events	Total	Events	Total			
Metabolic Syndrome-related comorbidities								
CVD mortality	3	90	5503	96	2955	0.72 (0.43, 1.01)	0.090	0.0%
CVD incidence	2	119	703	201	703	0.61 (0.42, 0.80)	<0.001	0.0%
Sudden cardiac death	2	15	703	34	703	0.45 (−0.15, 1.04)	0.142	0.0%
Stroke incidence	2	88	5496	71	2951	0.67 (0.35, 0.98)	<0.001	0.0%
Heart failure incidence	2	73	5470	67	2933	0.69 (0.08, 1.30)	0.300	59.4%
Non-fatal myocardial infarction	2	26	801	60	804	0.45 (−0.001, 0.900)	0.051	0.0%
Fatal myocardial infarction	2	30	703	44	703	0.68 (0.23, 1.12)	0.090	0.0%
Type 2 diabetes incidence	2	207	2598	144	1349	0.81 (0.61, 1.02)	0.051	0.0%
Pharmacotherapy								
Use of blood pressure lowering drugs	3	2444	3299	1130	1657	0.99 (0.96, 1.02)	0.550	0.0%
Use of lipid-lowering agents	2	1552	2738	602	1090	1.01 (0.95, 1.08)	0.690	0.0%
Use of anti-platelet therapy	2	818	2738	338	1090	0.99 (0.90, 1.08)	0.830	0.0%
Use of insulin	2	271	2738	109	1090	0.99 (0.78, 1.20)	0.890	0.0%
Use of oral antidiabetic agents	3	1112	2846	520	1197	0.83 (0.58, 1.09)	0.230	64.2%

CVD, cardiovascular disease; RR, risk ratio. * Findings are based on random-effects meta-analysis (inverse variance). I^2 represents the magnitude of heterogeneity.

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SELF ASSESSMENT QUESTION 1

1. Which of the following fats has the worst effects on the LDL to HDL ratio?
   A. Trans fats
   B. Saturated fats
   C. MUFAs
   D. PUFAs

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SELF ASSESSMENT QUESTION 1

1. Which of the following fats has the worst effects on the LDL to HDL ratio?
   - **A. Trans fats (RAISE LDL AND LOWER HDL)**
   - B. Saturated fats
   - C. MUFAs
   - D. PUFAs

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SELF ASSESSMENT QUESTION 2

- 2. Which of the following describes the impact of the Mediterranean diet on patients?
  - A. It reduces cardiovascular events significantly and LDL by a large amount
  - B. It reduces cardiovascular events significantly and LDL to a modest amount
  - C. It reduces the need for lipid lowering therapy by a large amount
  - D. It does not impact cardiovascular events or LDL significantly

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SELF ASSESSMENT QUESTION 2

- 2. Which of the following describes the impact of the Mediterranean diet on patients?
  - A. It reduces cardiovascular events significantly and LDL by a large amount
  - **B. It reduces cardiovascular events significantly and LDL to a modest amount (CVD incidence and stroke incidence were significantly reduced while LDL was reduced by 8mg/dL or ~4%)**
  - C. It reduces the need for lipid lowering therapy by a large amount
  - D. It does not impact cardiovascular events or LDL significantly

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REALITY CHECK

- Fixing your diet will have a modest effect on LDL in most people
  - LDL receptor polymorphisms, PCSK9 polymorphisms, issues in LDL receptor re-expression, genetic issues in the overproduction of LDL, and loss of hepatocytes are the main drivers of elevated circulating LDL
- The use of dietary supplements, OTC products, or prescription drugs may still be needed regardless of dietary change

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MECHANISM OF ACTION OF DIETARY SUPPLEMENTS AND OTC PRODUCTS

- Plant sterols/stanols, soluble fiber, green tea extract
  - Partial blockade of LDL in secreted bile and dietary fats from being (re)absorbed in the small intestine
    - Almonds have both plant sterol (primary) and soluble fiber mechanisms
  - These drugs work tangentially to bile acid sequestrants
- Red yeast rice
  - What makes tandoori chicken red
  - Has natural lovastatin and other natural statins in it, works exactly like statins
- Silybum M
  - From Milk Thistle
  - Mechanism not known, possibly a hepatocyte restoration phenomenon (Milk Thistle used a "liver tonic")
- Berberine
  - Blocks the production of PCSK9
  - Works similarly to inclisiran and tangentially to evolocumab and alirocumab
- Cinnamon and garlic – Mechanism not known.

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PLANT STANOLS/STEROLS (PHYTOSTEROLS)

- Binds to intestinal fat and bile preventing some absorption into the body
- A typical eating plan contains around 200-400mg of sterols and stanols a day
- Plant stanols and sterols are added to certain foods such as fat-based spreads or dairy-type foods like milk and yogurt
  - 0.75 to 2g per serving size
- 1.5g to 3g of plant stanols and sterols daily can lower LDL by 8% when eaten regularly
  - There does not seem to be a difference in the effect between stanols and sterols
  - This is in addition to the reduction achieved by statins alone

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SOLUBLE FIBER OTC

- Psyllium (Metamucil) and methylcellulose (Citrucel) are viscous soluble fiber products.
  - Psyllium comes from the seed husks from the psyllium plant (Plantago ovata) while methylcellulose comes from plant cell walls.
  - Psyllium has been the most extensively studied soluble fiber and 6 and 15 grams per day are able to lower LDL levels ~12%
- Chitosin is soluble fiber from ground crustacean shells sold as a dietary supplement
  - Standard doses 1.5-3.0 grams per day reduces LDL by ~6%
- Polycarbophil (FiberCon, FiberLax, Store Brands) and wheat dextrin (Benefiber) are not soluble, gel forming fiber and do not lower LDL

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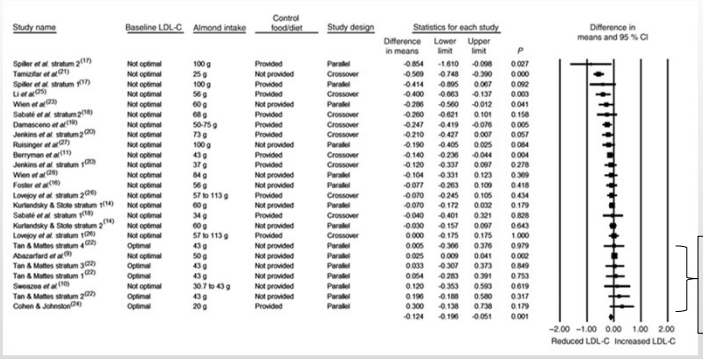
ALMONDS

https://www.cambridge.org/core/services/aop-cambridge-core/content/view/F83DA25317E0AB280F9BF556CF5197A1/S2048679016000197a.pdf/effects_of_almond_consumption_on_fasting_blood_lipid_levels_a_systematic_review_and_metaanalysis_of_randomised_controlled_trials.pdf

- Meta-analysis of 18 RCTs found an LDL reduction of 6mg/dL (~3%)
  - If >1.5 oz per day of almonds (45g/day), 8mg/dL (~4%)



Almonds were used in people with normal LDL at baseline, no benefit, maybe worse

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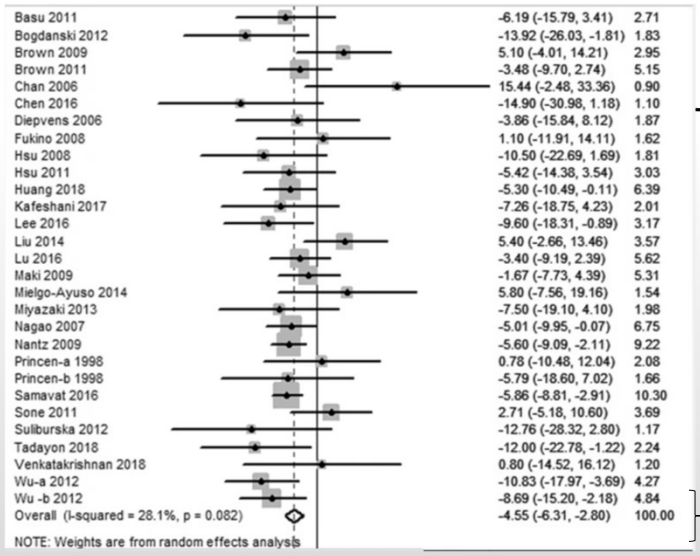
GREEN TEA EXTRACT IMPACT ON LDL



Green tea extract has a modest effect on LDL levels ~2.3%

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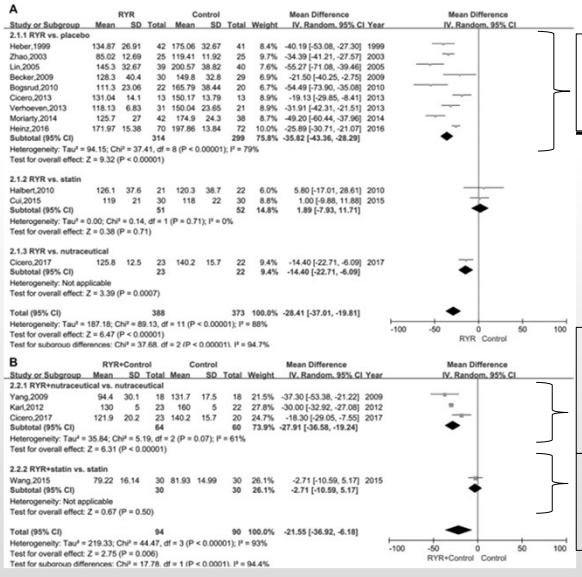
RED YEAST RICE



Red Yeast Rice better than placebo. Lowers LDL by 35.8mg/dL or ~18%

Red Yeast Rice can enhance other dietary supplement ingredients LDL effects by 28mg/dL or ~14%

Adding Red Yeast Rice to statin no better than statin alone

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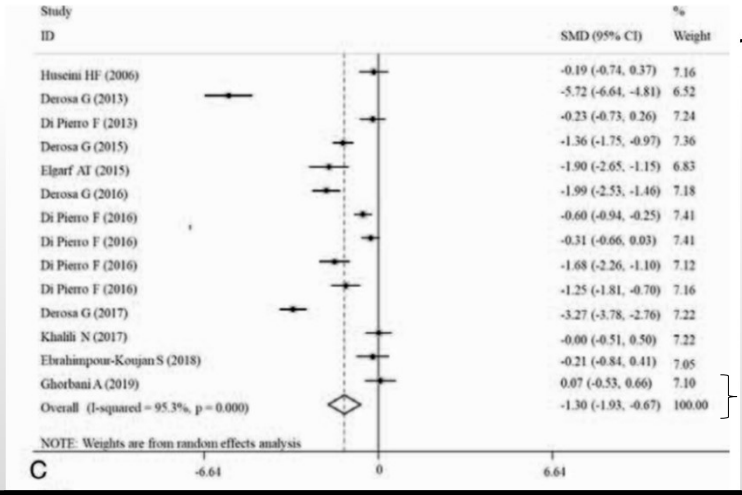
SILYBUM MARINARIUM



Pooled effect is LDL reduction of 50mg/dL (converted from mmol/L) or ~25% but high statistical heterogeneity

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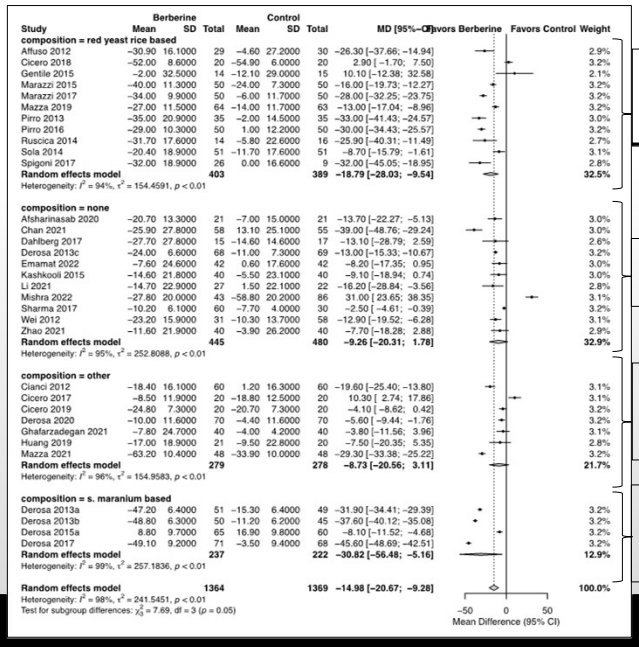
BERBERINE



Combo with berberine + red yeast rice reduced LDL by 19mg/dL or ~9.5%

Berberine alone reduced LDL by 9mg/dL or ~4.5%

Combo with berberine and lots of other ingredients no better than berberine alone

Combo with berberine + Silybum M reduced LDL by 31mg/dL or ~15.5%

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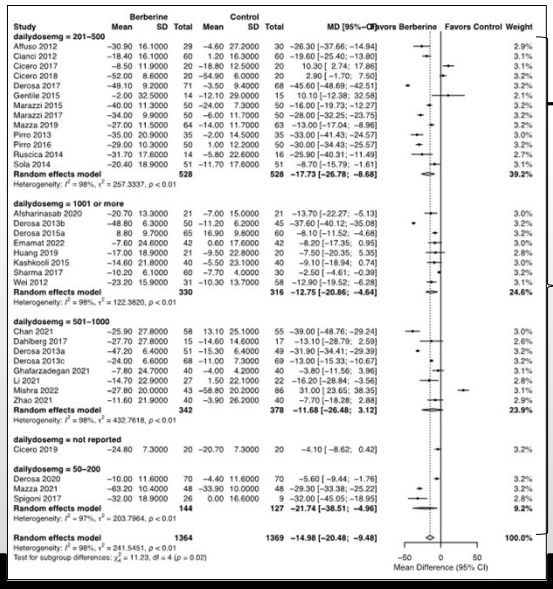
BERBERINE: IMPACT OF DOSE



The dose of berberine did not drive the lipid lowering effects, no dose response relationship noted

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CINNAMON LDL EFFECTS

B. LDL Cholesterol (mg/dL)

Study name	Sample size: Cinnamon	Sample size: Control	Relative weight	Difference in means	Lower limit	Upper limit
Khan et al, 2003-1	10	10	11.60	-3.12	-9.07	2.83
Khan et al, 2003-2	10	10	11.06	-32.37	-40.15	-24.59
Khan et al, 2003-3	10	10	10.67	-20.67	-29.64	-11.70
Mang et al, 2006	33	32	11.42	-0.78	-7.36	5.80
Vanschoonbeck et al, 2006	12	13	6.11	2.34	-20.13	24.81
Blevins et al, 2007	29	28	12.30	1.00	-1.34	3.34
Akilen et al, 2010	30	28	9.78	-1.17	-12.66	10.32
Khan et al, 2010	7	7	4.66	-20.40	-48.92	8.12
Wainstein et al, 2011	29	30	8.83	-18.30	-32.41	-4.19
Lu et al, 2012-1	23	10	7.28	-8.19	-26.77	10.39
Lu et al, 2012-2	23	10	6.28	-2.73	-24.59	19.13
Combined	**216**	**188**		**-9.42**	**-17.21**	**-1.63**

Difference in Means and 95% CI

-50.00 -25.00 0.00 25.00 50.00

Favors Cinnamon Favors Control

I^2 = 88.6%; Egger's P = .12

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Figure 3 continues

Note: Squares represent individual studies, and size of the square represents the weight given to each study in the meta-analysis. Error bars represent 95% confidence intervals. The diamonds represent the pooled results. The solid vertical line extending upward from 0.00 is the null value.

Cinnamon has a modest effect on LDL levels ~4.5%

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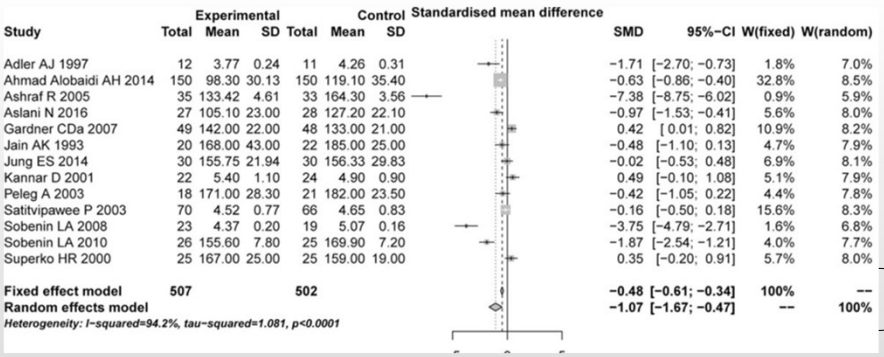
GARLIC AND LDL REDUCTION



Study	Experimental Total	Mean	SD	Control Total	Mean	SD	SMD	95%-CI	W(fixed)	W(random)
Adler AJ 1997	12	3.77	0.24	11	4.26	0.31	−1.71	[−2.70; −0.73]	1.8%	7.0%
Ahmad Alobaidi AH 2014	150	98.30	30.13	150	119.10	35.40	−0.63	[−0.86; −0.40]	32.8%	8.5%
Ashraf R 2005	35	133.42	4.61	33	164.30	3.56	−7.38	[−8.75; −6.02]	0.9%	5.9%
Aslani N 2016	27	105.10	23.00	28	127.20	22.10	−0.97	[−1.53; −0.41]	5.6%	8.0%
Gardner CDa 2007	49	142.00	22.00	48	133.00	21.00	0.42	[0.01; 0.82]	10.9%	8.2%
Jain AK 1993	20	168.00	43.00	22	185.00	25.00	−0.48	[−1.10; 0.13]	4.7%	7.9%
Jung ES 2014	30	155.75	21.94	30	156.33	29.83	−0.02	[−0.53; 0.48]	6.9%	8.1%
Kannar D 2001	22	5.40	1.10	24	4.90	0.90	0.49	[−0.10; 1.08]	5.1%	7.9%
Peleg A 2003	18	171.00	28.30	21	182.00	23.50	−0.42	[−1.05; 0.22]	4.4%	7.8%
Satitvipawee P 2003	70	4.52	0.77	66	4.65	0.83	−0.16	[−0.50; 0.18]	15.6%	8.3%
Sobenin LA 2008	23	4.37	0.20	19	5.07	0.16	−3.75	[−4.79; −2.71]	1.6%	6.8%
Sobenin LA 2010	26	155.60	7.80	25	169.90	7.20	−1.87	[−2.54; −1.21]	4.0%	7.7%
Superko HR 2000	25	167.00	25.00	25	159.00	19.00	0.35	[−0.20; 0.91]	5.7%	8.0%
Fixed effect model	**507**			**502**			**−0.48**	**[−0.61; −0.34]**	**100%**	--
Random effects model							**−1.07**	**[−1.67; −0.47]**	--	**100%**

Heterogeneity: I-squared=94.2%, tau-squared=1.081, p<0.0001

Standardised mean difference

Garlic has very minimal effects on LDL levels ~0.5%

https://journals.lww.com/md-

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DIETARY SUPPLEMENTS TO REDUCE LDL: EFFECTS ARE MODEST AT BEST WITH HIGH HETEROGENEITY THAT IS NOT FULLY BEEN RECONCILED (REDUCED STRENGTH OF EVIDENCE)

Lifestyle Change	Magnitude of LDL Reduction
Rice Yeast Rice	8-18%
Berberine	4.5%
Silybum M	(25%)??
Berberine + Red Yeast Rice or Berberine + Silybum M	10-16%
Cinnamon	4.5%
Green Tea Extract	2.3%
Garlic	0.5%

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SELF ASSESSMENT QUESTION 3

3. Which of the following drug is linked correctly to its likely mechanism of action?

A. Berberine – Block the enzyme HMG CoA Reductase
B. Red Yeast Rice – Block formation of the protein PCSK9
C. Green Tea Extract – Block the enzyme HMG CoA Reductase
D. Sterols/Stanols – Block LDL reabsorption & fat absorption

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SELF ASSESSMENT QUESTION 3

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A. Berberine – Block the enzyme HMG CoA Reductase
B. Red Yeast Rice – Block formation of the protein PCSK9
C. Green Tea Extract – Block the enzyme HMG CoA Reductase
D. Sterols/Stanols – Block LDL reabsorption and fat absorption (Well, this is how it, Soluble Fiber, Green Tea Extract, and Almonds work…)

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SELF ASSESSMENT QUESTION 3

3. Which of the following drug is linked correctly to its likely mechanism of action?

A. Berberine – Block HMG CoA Reductase
B. Red Yeast Rice – Block formation of PCSK9
C. Green Tea Extract – Block HMG CoA Reductase
D. Plant Sterols/Stanols – Block reabsorption of LDL in bile and reabsorption of fats in the diet (Well, this is how it, Soluble Fiber, Green Tea Extract, and Almonds work…)

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SELF ASSESSMENT QUESTION 4

4. Tobias Whale is a 50 year old super villain in the series Black Lightening. In addition to killing the innocent and extorting small business owners, he also has a poor baseline diet. He requires a 6% reduction in his LDL in order to reach his goal. Which of the following natural products will get him to goal?

A. Cinnamon
B. Garlic
C. Green tea
D. Red Yeast Rice

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SELF ASSESSMENT QUESTION 4

4. Tobias Whale is a 50 year old super villain in the series Black Lightening. In addition to killing the innocent and extorting small business owners, he also has a poor baseline diet. He requires a 6% reduction in his LDL in order to reach his goal. Which of the following natural products are MOST LIKELY to get him to goal?

A. Cinnamon
B. Garlic
C. Green tea
D. Red Yeast Rice (Red Yeast Rice, Berberine + Red Yeast Rice, and Berberine + Silybum M can all be used to help get him to goal)

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REALITY CHECK

- Prescription lipid reducers can be more effective than dietary supplements and with high strength of evidence
  - High intensity statins can reduce LDL by up to 50%
  - Low intensity statins can reduce LDL by up to 30%
  - PCSK9 monoclonal antibody inhibitors can reduce LDL by over 60%
  - Ezetimibe reduces LDL by ~18%
- All these prescription options have proven ability to reduce ASCVD events in addition to LDL
  - There is no ASCVD data with dietary supplements
- Some dietary supplements can cost as much or more than generic statins and ezetimibe

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INDEPENDENT LABORATORY VERIFICATION OF DIETARY SUPPLEMENTS IS CRITICAL

- USP, NSF, ConsumerLabs, or another independent laboratory certification assures:
  - A lack of heavy metal or microbial contamination
  - That the active ingredient you are paying for is in the pills you are buying
  - That there is not adulteration with prescription drugs
- Be concerned about any dietary supplements without independent laboratory certification
  - The FDA cannot protect you in real time

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SELF ASSESSMENT QUESTION 5

5. What does a USP of NSF seal on a bottle of Red Yeast Rice tell you?
   A. That the product will reduce your LDL by 30% under normal circumstances
   B. That the product will reduce your risk of ASCVD events
   C. That the specified active ingredient is actually in the pills
   D. That the product was FDA approved

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SELF ASSESSMENT QUESTION 5

5. What does a USP of NSF seal on a bottle of Red Yeast Rice tell you?

A. That the product will reduce your LDL by 30% under normal circumstances

B. That the product will reduce your risk of ASCVD events

C. That the specified active ingredient is actually in the pills (It certifies that an independent lab verified the active ingredient is in the bottle and a lack of product contamination and adulteration at the time of manufacturing)

D. That the product was FDA approved

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CONCLUSIONS

- Weight loss and changes in an eating plan can modestly reduce the LDL cholesterol
  - Eat less trans and saturated fat, eat more MUFA and PUFA
  - Eat more dietary fiber, especially soluble fiber
  - Soluble fiber OTC products with psyllium or methylcellulose are reasonable if patients will not/cannot change diet to get recommended amounts of fiber
  - Substituting almonds for other snack foods that might be higher in saturated/trans fats is a reasonable trade off

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CONCLUSIONS

- Since statins and PCSK9 inhibiting drugs are complementary in LDL lowering, combining red yeast rice and berberine should be as well
  - Studies suggest that this is true
- While combining berberine + red yeast rice or berberine + Silybum M is better than berberine alone, whether berberine + red yeast rice + Silybum M is even better is unknown
  - Adding chromium, curcuma, lipoic acid, isoflavones, cinnamon, resveratrol, or quercetin to berberine did not enhance the LDL lowering effects
- When used in people with lower baseline LDLs, the impact of therapy like almonds was muted
  - Since almonds, soluble fiber, sterols/stanols, and green tea extracts work through a unique mechanism – it is a future target for combination therapy with red yeast rice, berberine, and Silybum M
- Cinnamon and garlic has very modest effects on reducing LDL
- There are limitations to using dietary supplements for LDL reduction such as lack of ASCVD risk reduction evidence and lower LDL reducing potency
- Only independent laboratory verified products should be used

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