

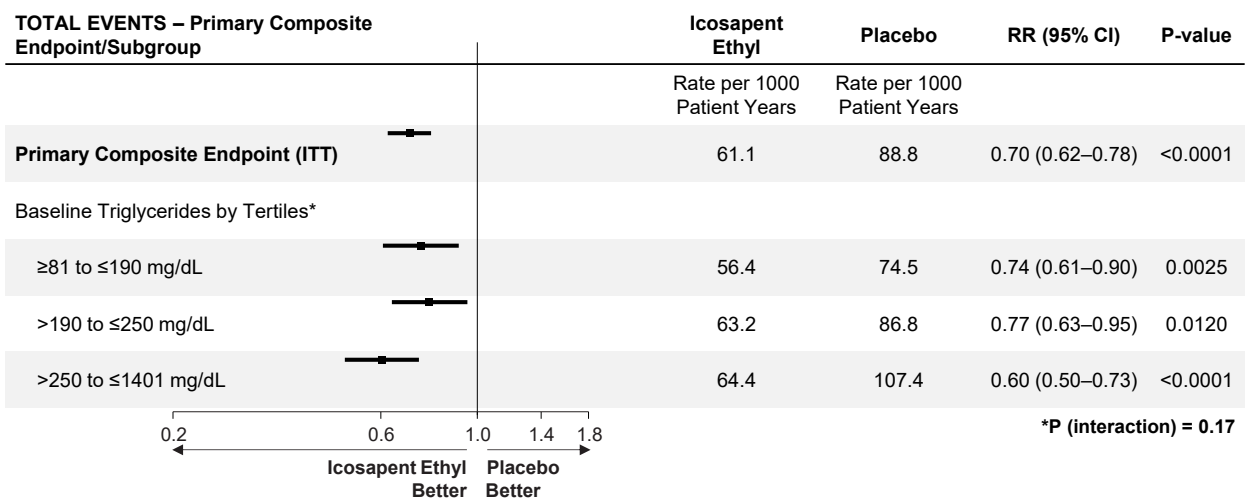
What is the MOA for EPA's Effect on ASCVD?

R. PRESTON MASON, PHD



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Primary Composite Endpoint: Total Endpoint Events by Baseline TG Tertiles

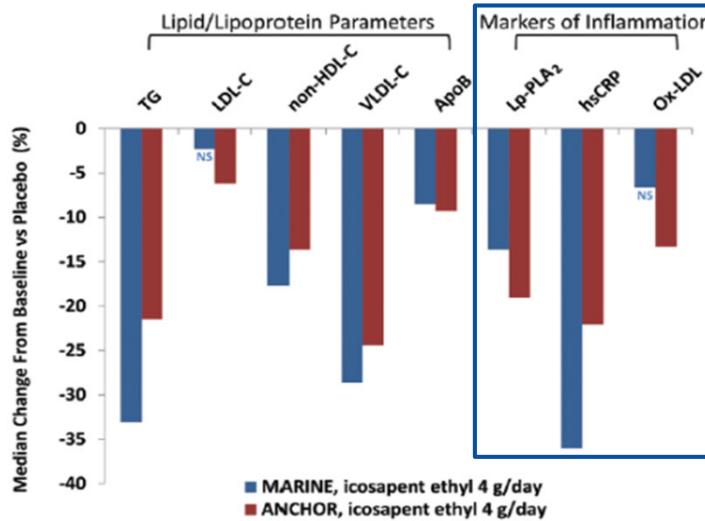


Bhatt DL. ACC 2019, New Orleans.

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Effects of EPA on Non-HDL-C and Inflammatory Markers in Patients With Elevated TGs at 4 g/d



Bays HE et al. *Am J Cardiovasc Drugs*. 2013;13:37-46.

3

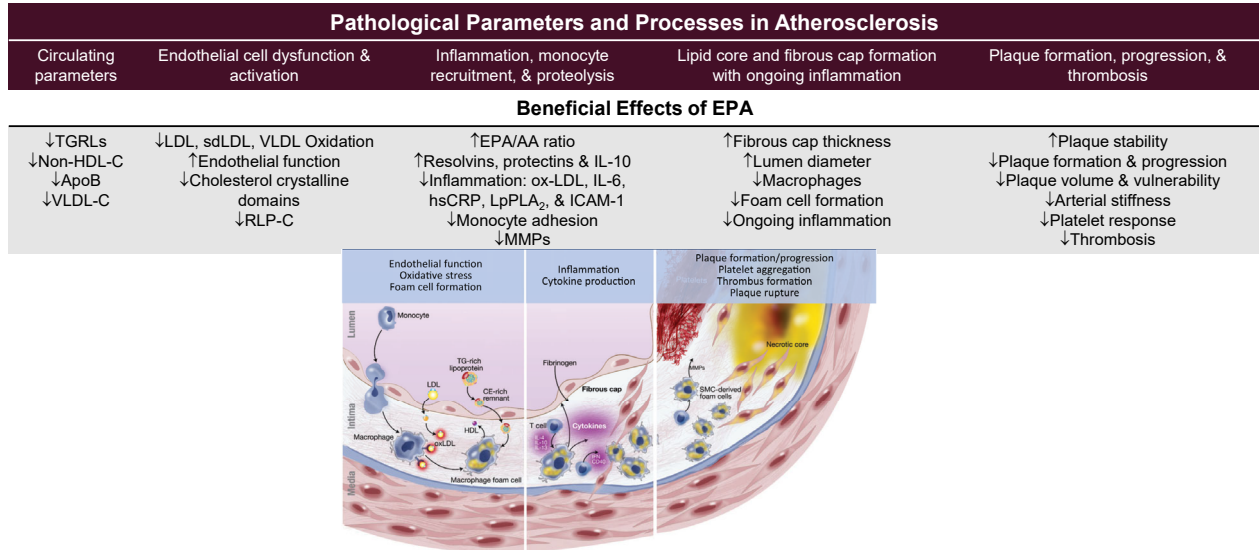
Lipid Therapies Have Different Effects on hsCRP

Lipid Therapy	hsCRP Levels
Statins	↓
EPA (4 g)	↓
EPA (4 g) + Statin	↓ ↓
EPA/DHA (4 g)	↔
Ezetimibe	↔
Ezetimibe + Statin	↓
PCSK9i + Statin	↔

Bays HE et al. *Am J Cardiovasc Drugs*. 2013;13:37-46. Dunbar RL et al. *Lipids Health Dis*. 2015;14:98. Ridker PM et al. *N Engl J Med*. 2008;359:2195-207. Bohula EA et al. *Circulation*. 2015;132:1224-33. Pradhan AD et al. *Circulation*. 2018;138:141-9.

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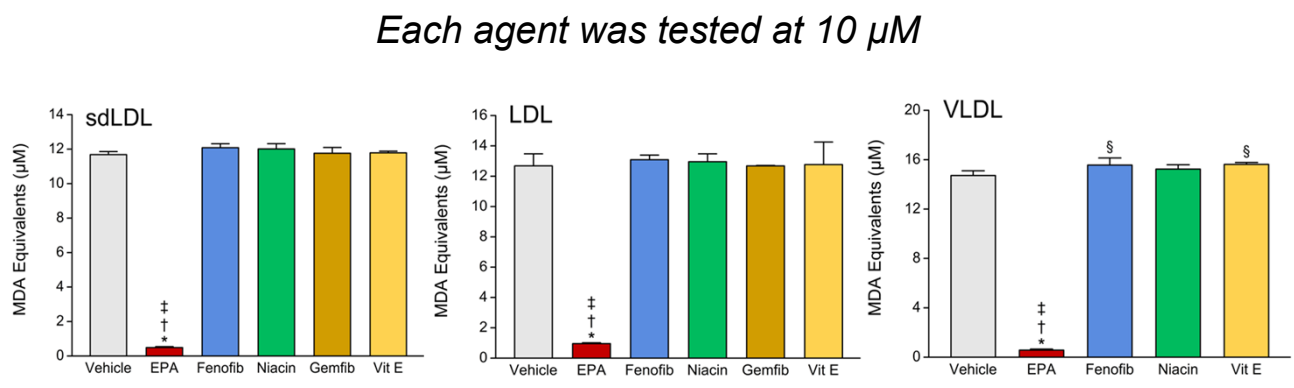
EPA Interferes with Plaque Development at Multiple Stages Beyond TG-Lowering



Borow K, Nelson JR, Mason RP. *Atherosclerosis* 2015;242:357-366
 Budoff M, et al. *Clinical Cardiology* 2018;41:13-19

5

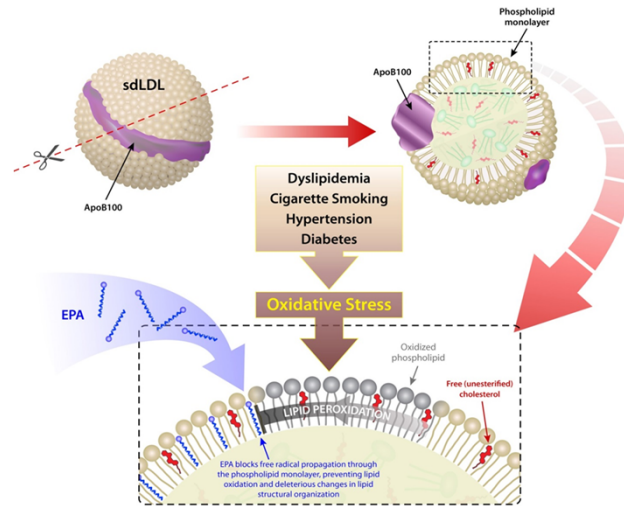
Comparative Effects of EPA (4 g/d) and TG-Lowering Agents on Lipoprotein Oxidation



Mason RP, et al. *J Cardiovasc Pharmacol* 2016;68:33-40.

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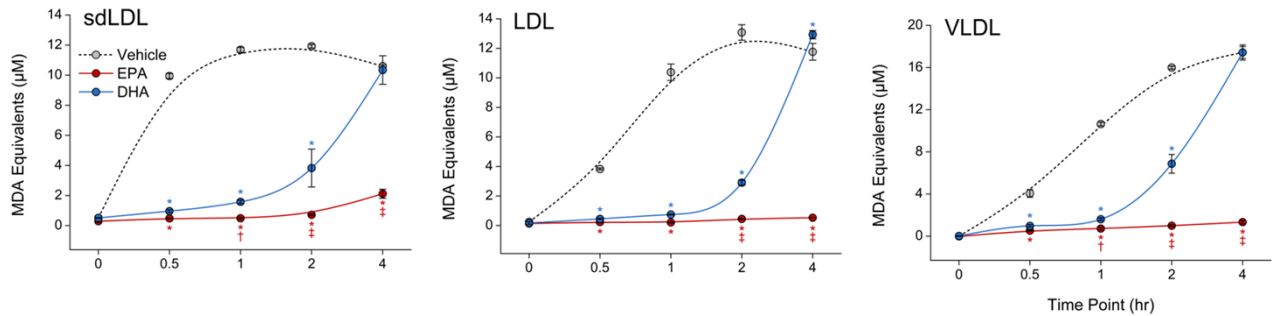
Schematic Illustration of the Protective Effects of EPA on sdLDL Lipid Oxidation



Adapted from: Mason RP, Jacob RF. *Diabetes*. 2015;64(Suppl 1):A178-A179.

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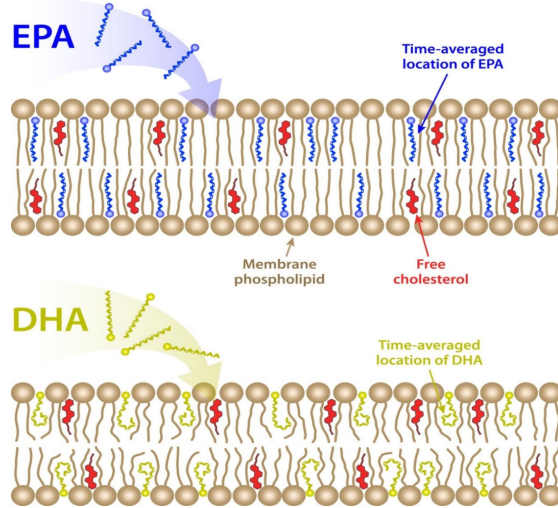
Comparative Effects of EPA and DHA on Oxidation in Different ApoB Particles



Mason RP et al. *J Cardiovasc Pharmacol* 2016;68:33-40.

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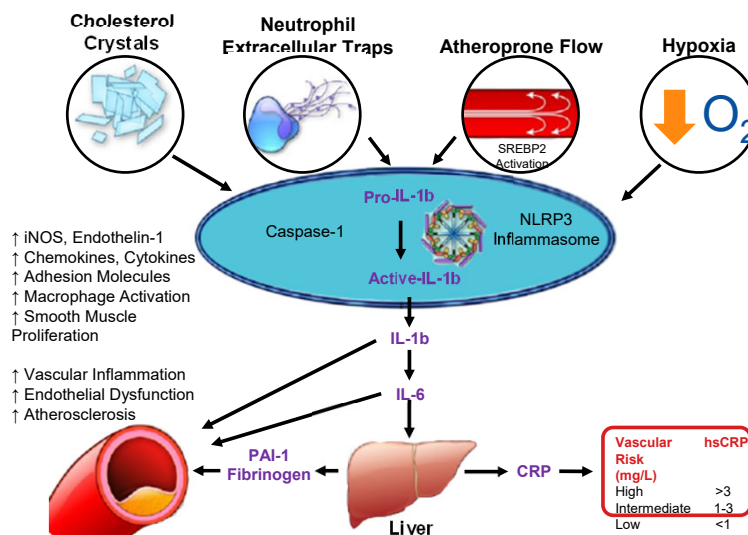
Biophysical Analysis: EPA Has Stable Extended Conformation in the Membrane While DHA Has Disordering Effect



Sherratt SCR, Mason RP. *Chem Phys Lipids* 2018;212:73-79.

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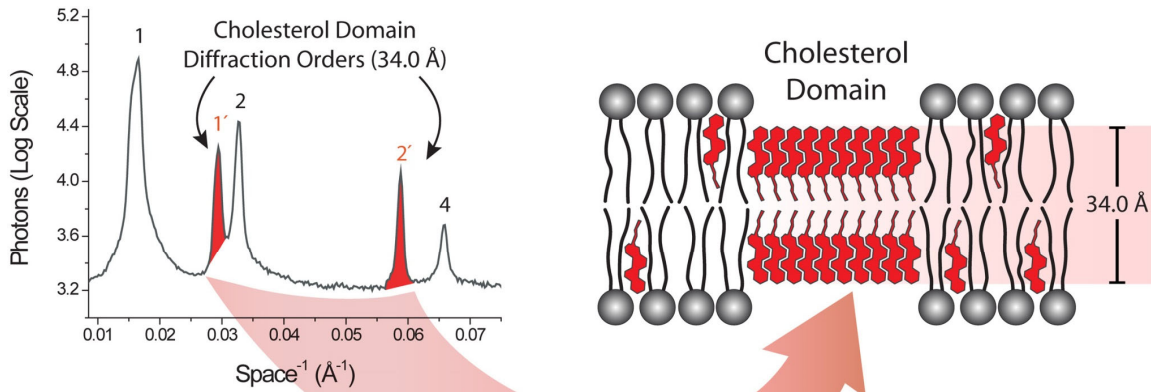
Cholesterol Crystals Trigger IL-1 β Formation



Ridker PM. *Circ Res* 2016;118:145-156.

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Characterizing Membrane Cholesterol Crystalline Domains by X-ray Diffraction

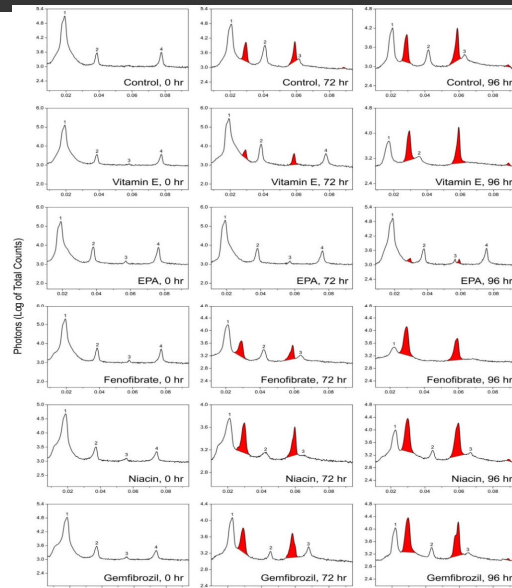


Mason RP et al. *J Biol Chem.* 2006;281:9337-9345.

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Effects of TG-Lowering Agent on Cholesterol Crystalline Domains

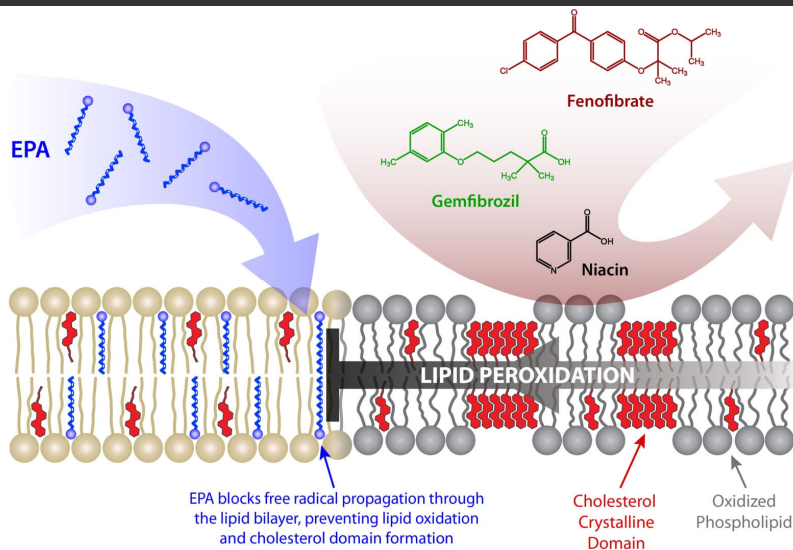
- Comparison of Vitamin E, EPA, Fenofibrate, Niacin, and Gemfibrozil



Mason RP, et al. *Biochim Biophys Acta* 2015;1848:502-509.

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EPA, But Not Other TG-lowering Agents, Inhibits Lipid Oxidation & Cholesterol Domain Formation



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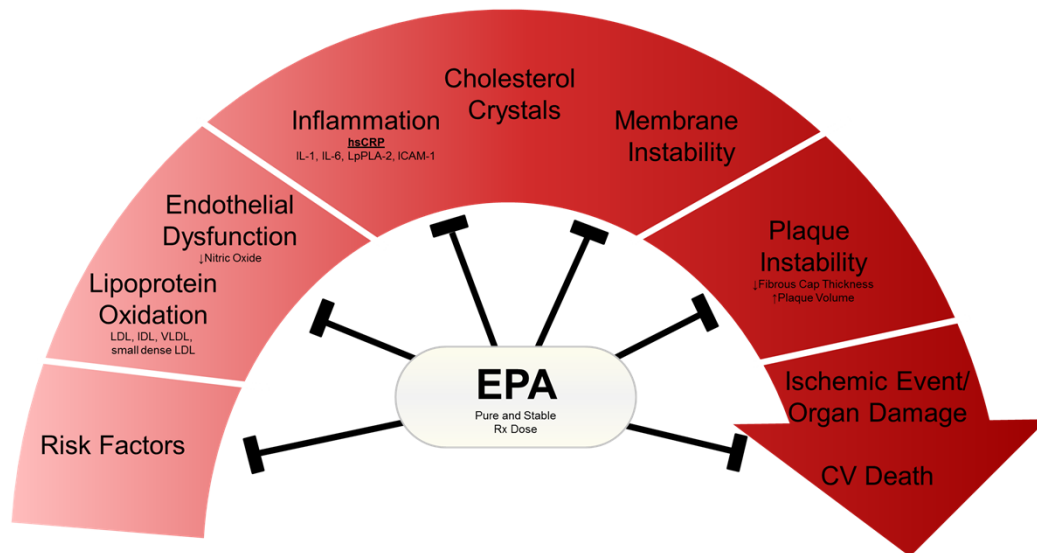
Distinct Effects of EPA on Plaque Development

- Reverses human endothelial dysfunction: enhanced with a statin;
- Inhibits cholesterol crystal formation linked to inflammation and plaque destabilization;
- Membrane stabilizing in contrast to DHA;
- Prevents membrane damage with hyperglycemia;
- Preserves HDL function

Mason RP and Jacob RF. *Biochim Biophys Acta* 2015;1848:502-509; Mason RP et al. *Biomed Pharmacother*. 2018;103:1231-1237; Sherratt SCR and Mason RP. *Biochem Biophys Res Comm*. 2018; 496:335-338; Mason RP et al. *J Cardiovasc Pharmacol* 2016;68:33-40; Mason RP et al. *Biochim Biophys Acta*. 2016;1858:3131-3140; Mason RP. *Curr Atheroscler Rep*. 2019;21:2

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EPA Interferes with the Cardiovascular Disease Continuum at Multiple Points to Reduce CV Events



Bays HE et al. *Am J Cardiovasc Drugs*. 2013;13:37-46; Borow KM, Nelson JR, Mason RP. *Atherosclerosis*. 2015;242:357-66; Bhatt DL et al. *N Engl J Med*. 2019;380:11-22; Ganda OP et al. *J Am Coll Cardiol*. 2018;72:330-43; Jia X et al. *Curr Atheroscler Rep*. 2019;21:1; Mason RP et al. *Biomed Pharmacother*. 2018;103:1231-7; Ference BA et al. *JAMA*. 2019;321:364-73. Sherratt SCR and Mason RP. *Biochem Biophys Res Comm*. 2018; 496:335-338.

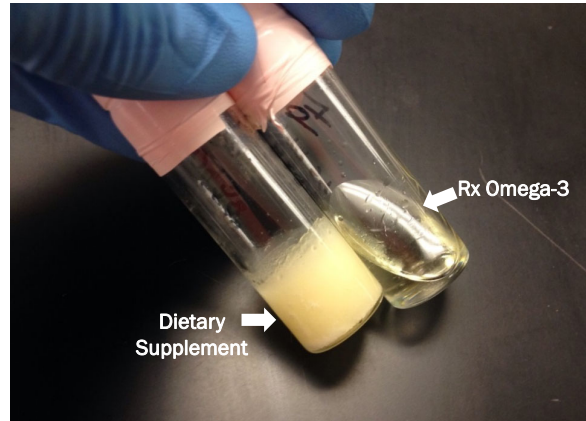
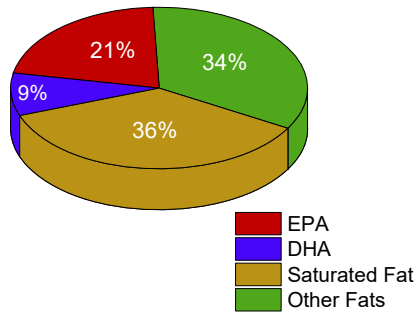
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What's the Basis for Benefit with EPA in REDUCE-IT?

- Right dose (4 g/d)
- Right formulation (EPA)
- Right patients (↑ TGs, ↑ CV risk)

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Fatty Acid Content of Leading US Fish Oil Supplement


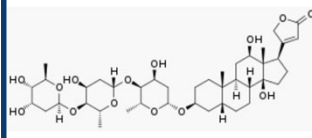

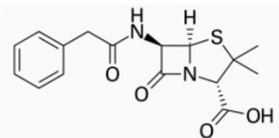

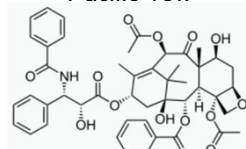

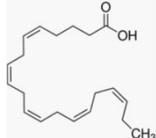


Saturated fatty acid content in fish oil supplement results in solid mass following isolation

Mason RP, Sherratt SCR. *Biochem Biophys Res Commun.* 2017;483:425-429.

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Transformational Medicines Isolated from Nature: Unique Molecules with Proven Clinical Efficacy

<p>Digoxin</p>  <p><i>Purple Foxglove</i></p> 	<p>Penicillin</p>  <p><i>Penicillium Mold</i></p> 	<p>Paclitaxel</p>  <p><i>Pacific Yew</i></p> 	<p>Icosapent ethyl</p>  <p><i>Marine Fish</i></p> 
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Lero M, Sherratt SCR, Mason RP (2019)

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