SUMMARY OF THE INVENTION

[0005] The subject application provides compositions, methods, and kits for treating hyperlipidemia in a subject. The compositions, methods, and kits can include leucine and/or leucine metabolites in combination with nicotinic acid. The present invention addresses the negative side effects of treating subjects with high doses of nicotinic acid.

[0006] The subject compositions can be administered orally or through other routes such as intravenous administration. Compositions for oral administration can include pills, tablets, capsules, and the like.

[0007] In one aspect, the present invention refers to a composition comprising (a) at least 250 mg-1300 mg of L-leucine in free form and/or at least 25 mg of one or more leucine metabolites in free form; and (b) at least 1 mg of nicotinic acid and/or nicotinamide riboside and/or one or more nicotinic acid metabolites, wherein the composition is free of arginine, isoleucine and valine, wherein the one or more leucine metabolites are selected from the group consisting of keto-isocaproic acid (KIC), alpha-hydroxy-isocaproic acid, and HMB, and wherein the one or more nicotinic acid metabolites are selected from the group consisting of nicotinyl CoA, nicotinuric acid, nicotinate mononucleotide, nicotinate adenine dinucleotide, and nicotinamide adenine dinucleotide. In one example, there are disclosed compositions comprising at least about 250 mg of leucine and/or about 25 mg of one or more leucine metabolites; and at least about 1 mg of nicotinic acid and/or nicotinamide riboside and/or one or more nicotinic acid metabolites.

[0007a] In another example, there is disclosed a composition comprising: (a) at least 250 mg-1300 mg of leucine in free form and/or at least 25 mg of one or more leucine metabolites in free form; and (b) at least 1 mg of nicotinic acid and/or nicotinamide riboside and/or one or more nicotinic acid metabolites, wherein the composition is free of isoleucine and valine.

[0007b] In another aspect, there is provided a kit comprising a multi-day supply of unit dosages of the composition as described herein, and instructions directing the administration of said multi-day supply over a period of multiple days.

[0007c] In another aspect, the present invention refers to a composition comprising (a) L-leucine and/or one or more leucine metabolites; and (b) at least 1 mg of nicotinic acid and/or nicotinamide riboside and/or one or more nicotinic acid metabolites, wherein the molar ratio of component (a) to (b) in said composition is greater than 5, and wherein the composition is free of arginine, isoleucine and valine, wherein the amount of L-leucine and/or one or more leucine metabolites is less than 1300 mg, wherein the one or more leucine metabolites are selected from the group consisting of keto-isocaproic acid (KIC), alpha-hydroxy-isocaproic acid, and HMB, and wherein the one or more nicotinic acid metabolites are selected from the group consisting of nicotinyl CoA, nicotinuric acid, nicotinate mononucleotide, nicotinate adenine dinucleotide, and

nicotinamide adenine dinucleotide. In one example, there is disclosed a composition comprising (a) leucine and/or one or more leucine metabolites; and (b) at least 1 mg of nicotinic acid and/or nicotinamide riboside and/or one or more nicotinic acid metabolites, wherein the molar ratio of component (a) to (b) in said composition is greater than 5, and wherein the composition is free of isoleucine and valine.

[0007d] In another aspect, there is provided a use of the composition as described herein, in the manufacture of a medicament for lowering total cholesterol level in a subject in need thereof.

[0007e] In another aspect, there is provided a use of the composition as described herein, in the manufacture of a medicament for lowering total cholesterol level or total lipid content in a subject in need thereof.

[0008] In another example, there are disclosed compositions are provided that comprise at least about 250 mg of leucine and/or about 25 mg of one or more leucine metabolites; and an amount of nicotinic acid and/or nicotinamide riboside and/or one or more nicotinic acid metabolites, wherein the composition is substantially free of each of alanine, glycine, glutamic acid, and proline.

[0009] In yet another example, there are disclosed compositions comprising at least about 250 mg of leucine and/or about 25 mg of one or more leucine metabolites; and an amount of nicotinic acid and/or nicotinamide riboside and/or nicotinic acid metabolites, wherein the amount of nicotinic acid and/or nicotinic acid metabolites is insufficient to reduce lipid content in the absence of component (a).

[0010] In still yet another example, compositions are disclosed that comprise an amount of leucine and/or one or more leucine metabolites; and an amount of nicotinic acid and/or nicotinamide riboside and/or one or more nicotinic acid metabolites, wherein the composition is administered to a subject in need thereof, further wherein the composition causes a reduced degree of cutaneous vasodilation in the subject administered as compared to a dose of nicotinic acid alone that has the same effectiveness as the composition in lowering lipid content in the subject.

[0011] In another example, there are disclosed compositions comprising leucine and/or one or more leucine metabolites; and at least about 1 mg of nicotinic acid and/or nicotinamide riboside and/or one or more nicotinic acid metabolites, wherein the molar ratio of component (a) to (b) in said composition is greater than about 20.

What is claimed is:

1. A composition comprising:
   a. at least 250 mg-1300 mg of L-leucine in free form and/or at least 25 mg of one or more leucine metabolites in free form; and
   b. at least 1 mg of nicotinic acid and/or nicotinamide riboside and/or one or more nicotinic acid metabolites,

   wherein the composition is free of arginine, isoleucine and valine,
   wherein the one or more leucine metabolites are selected from the group consisting of keto-isocaproic acid (KIC), alpha-hydroxy-isocaproic acid, and HMB, and
   wherein the one or more nicotinic acid metabolites are selected from the group consisting of nicotinyl CoA, nicotinuric acid, nicotinate mononucleotide, nicotinate adenine dinucleotide, and nicotinamide adenine dinucleotide.
2. The composition of claim 1, wherein the composition is free of nicotinamide.
3. The composition of claim 1 wherein the composition is free of nicotinic acid metabolites.
4. The composition of claim 1, wherein the component (a) in the composition is L-leucine and the component (b) in the composition is nicotinic acid.
5. The composition of claim 1, wherein the component (a) in the composition is L-leucine.
6. The composition of claim 1, wherein the amount of nicotinic acid and/or nicotinamide riboside and/or one or more nicotinic acid metabolites is less than 1g.
7. The composition of claim 1, wherein the amount of nicotinic acid and/or nicotinamide riboside and/or one or more nicotinic acid metabolites is less than 250 mg.
8. The composition of claim 1, wherein the amount of nicotinic acid and/or nicotinamide riboside and/or one or more nicotinic acid metabolites is between 1-100 mg.
9. The composition of claim 1, wherein the composition is effective in reducing triglyceride level, total cholesterol or LDL level in a subject by at least 5% and the amount of nicotinic acid and/or nicotinamide riboside and/or nicotinic acid metabolites is insufficient to effectuate such reduction in the absence of the L-leucine and/or one or more leucine metabolites.
10. The composition of claim 1, wherein the composition further comprises resveratrol.
11. The composition of claim 1, wherein the composition is formulated for oral administration.

12. The composition of claim 1, wherein the composition is a tablet, a capsule, or a pill.
13. The composition of claim 1, wherein component (a) and component (b) are separately packaged.
14. The composition of claim 1, wherein component (a) and component (b) are mixed.
15. The composition of claim 1, wherein the composition is free of each amino acid selected from the group consisting of alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, valine, isoleucine and tyrosine.
16. The composition of claim 1, wherein the composition contains less than 0.1% of each free amino acid selected from the group consisting of alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, valine, isoleucine and tyrosine.
17. The composition of claim 1, wherein the composition contains less than 10% of non-leucine amino acids.
18. The composition of claim 1, further comprising one or more therapeutic agents that is capable of lowering lipid accumulation.
19. The composition of claim 1, further comprising one or more therapeutic agents selected from the group consisting of HMG-CoA inhibitor, fibrate, bile acid sequestrant, ezetimibe, lomitapide, phytosterols, CETP antagonist, orlistat, and any combination thereof.
20. The composition of claim 1, wherein the molar ratio of component (a) to (b) in said composition is greater than 20.
21. The composition of claim 1, wherein the composition is formulated in a unit dosage form.
22. A kit comprising a multi-day supply of unit dosages of the composition of claim 21, and instructions directing the administration of said multi-day supply over a period of multiple days.
23. A composition comprising:
    a. L-leucine and/or one or more leucine metabolites; and
    b. at least 1 mg of nicotinic acid and/or nicotinamide riboside and/or one or more nicotinic acid metabolites,

    wherein the molar ratio of component (a) to (b) in said composition is greater than 5, and

wherein the composition is free of arginine, isoleucine and valine,

wherein the amount of L-leucine and/or one or more leucine metabolites is less than 1300 mg,

wherein the one or more leucine metabolites are selected from the group consisting of keto-isocaproic acid (KIC), alpha-hydroxy-isocaproic acid, and HMB, and

wherein the one or more nicotinic acid metabolites are selected from the group consisting of nicotinyl CoA, nicotinuric acid, nicotinate mononucleotide, nicotinate adenine dinucleotide, and nicotinamide adenine dinucleotide.

24. The composition of claim 23, where the molar ratio of component (a) to (b) is less than 100.
25. The composition of claim 23,wherein the composition comprises at least 250 mg of L-leucine and/or 25 mg of one or more leucine metabolites.
26. The composition of claim 23, wherein the composition is free of nicotinamide.
27. The composition of claim 23, wherein the component (a) in the composition is L-leucine and the component (b) in the composition is nicotinic acid.
28. The composition of claim 23, wherein the amount of nicotinic acid and/or nicotinamide riboside and/or one or more nicotinic acid metabolites is between 1-100 mg.
29. The composition of claim 23, wherein a portion of the L-leucine and/or one or more leucine metabolites is in a free form.
30. The composition of claim 23, wherein the composition is a tablet, a capsule, or a pill.
31. The composition of claim 23, wherein the composition is formulated in a unit dosage form.
32. Use of the composition of claim 1, in the manufacture of a medicament for lowering total cholesterol level in a subject in need thereof.
33. Use of the composition of claim 23, in the manufacture of a medicament for lowering total cholesterol level or total lipid content in a subject in need thereof.