Nutraceutical & Functional Foods Research & Development, Patents and Independent Research

Claims Substantiation & Claims Summary

February 2015

Production of Functional Ingredients

Raw Rice Bran
(sourced in USA)

Trade Secret Process

Proprietary, non-chemical stabilization process

Four locations:
Lake Charles, LA
Mermentau, LA
West Sacramento, CA
Arbuckle, CA

RiBran
(stabilized rice bran)

Raw Rice Bran
(sourced in Brazil)

Hexane extraction & separation

Pelotas, Brazil

cRBO
(crude rice bran oil)

RiBran DF
(defatted rice bran)

Dillon, MT

Patented Process

RiBran

Amylase treatment

RiBalance™
(dextrinized rice bran)

Separation of solubles from solids

RiSolubles™
(Water-soluble rice bran)

RiFiber
(fiber-rich rice bran)

RiBran

Experimental (lab scale)

Hydro-ethanolic extraction

Hydro-ethanolic & SCCO2 extraction

RBExt-GLC
(Rice bran extract)

RBExt-INF
(rice bran extract)

Summary of IP & Studies on RiceBran Technologies Ingredients

All RiceBran Technolgies ingredients are: Non-GMO; Gluten-Free; Wheat-Free; Soy-free; Dairy-Free; Zero Cholesterol; Made from whole grain

						Cholesterol Lipid			**Glucose Metabolism**				**Weight Satiety**			**GI Health**			**Inflammation Joint Health**				
						Human clinical: Reduction in serum cholesterol, LDL-cholesterol, apolipoprotein B and triglycerides			Human clinical: Reduction in serum glucose and glycosylated hemoglobin, and increase in insulin In vitro: increase glucose uptake into adipocytes and inhibition of FABP4				Human clinical: Induces satiety			Animal study: Reduction of adenoma development in the intestine; inceases faecal transit; enhances GI microflora			Animal study: Formulations comprised or RiSolubles or Rice Oil combined with other active ingredients to provide inflammation relief and joint health in horses In vitro: Inhibition of COX1,2 and 5-LOX Human PK: biouptake of active compounds				
Ingredient	Trade Secret	Patent	Trade Mark	Manufacture	Product Data Sheet	Human Clinical	Pub	IP	Human Clinical	In Vitro Studies	Pub	IP	Human Clinical	Pub	IP	Animal Studies	Pub	IP	Human PK	Animal Studies	In Vitro Studies	Pub	IP
RiBran	yes			US - powder	yes	yes	1	4	yes		1,5,6	5,6				Mouse	11, 12						
Ribalance™		7	yes	US - powder	yes																		
RiSolubles™		7	yes	US - powder	yes	yes	1, 8	4,8	yes yes		1,5,6 2,3	5,6 2	Yes	2	2				Horse			9	9
RiFiber		7		US - powder	yes	yes	1, 8	4,8	yes		1,5,6	5,6				Mouse	11b						
RiBran DF				Brazil - powder	yes																		
cRBO				Brazil - oil	yes															Horse		9	9
RBExt-INF				R&D only															10, 14		10, 14	10,15	
RBExt-GLC				R&D only					PK, 13	13,16	16												

1. J. Nutritional Biochemistry (2002) 175-187 Effects of stabilized rice bran, its solubles and fiber fractions on blood glucose levels and serum lipid parameters in humans with diabetes mellitus types I and II
2. US Patent Application # 12/253,481 Methods for treating obesity, insulin resistance and inducing satiety
3. Final Report from Glycemic Index Laboratories(June 2007) Glycemic and Insulinemic Response and Glycemic Index Determination of: RiSolubles
4. US Patent # 6,126,943 (Oct 2000) Method for treating hypercholesterolemia, and artherosclerosis (26 claims: SRB derivatives effectively reduce serum lipids and cholesterol and prevent heart disease)
5. US Patent # 6,303,586 B1 (Oct 2001) Supportive therapy for diabetes, hyperglycemia, and hypoglycemia (11 claims: SRB derivatives normalize glucose levels in hyperglycemic and hypoglycemic subjects
6. US Patent # 6,350,473 B1 (Feb 2002) Method for controlling serum glucose (22 claims: SRB derivatives effectively reduce serum glucose levels and glycosylated hemoglobin in diabetic subjects
7. US Patent #6,558,714 B2 (May 2003) Method for treating hypercholesterolemia, and artherosclerosis (13 claims: A process of enzymatic treatment of stabilized rice bran to obtain RiSolubles and RiceMucil)
8. US Patent #6.733,799 B2 (May 2004) Method for treating hypercholesterolemia, and artherosclerosis (20 claims: A method for inhibiting platelet aggregation, inhibiting HMG CoA Reductase and reducing the cardiovascular disease risks in a mammal)
9. US Patent # 6,902,739 B2 (June 2005) Method for treating joint inflammation, pain and loss of mobility (11 claims: Methods and formulations for treating an inflammatory disease or reducing inflammatory reaction in all mammals, inhibiting prostaglanding synthetase activity and a method for treating pain, lameness or loss of mobility in a mammal
10. Journal of Medical Food (2009) 615-623 Pro-Inflammatory Enzymes, Cyclooxygenase 1, Cyclooxygenase 2, and 5-Lipooxygenase, Inhibited by Stabilized Rice Bran Extracts
11. British J. Cancer (2007) 248-254 Evaluation of the cancer chemopreventive efficacy of rice bran in genetic mouse models of breast, prostate and intestinal carcinogenesis
11b. University of Leicester Report (2012) Prevention of gastrointestinal adenomas in ApcMin mouse by high-fiber rice bran RiFiber
12. US Patent Application #12/346,736 Methods for treatment of intestinal carcinogenesis with rice bran (Abandoned)
13. US Patent Application # 12/467,848 Rice bran extracts and methods of use thereof (Abandoned)
14. Detailed R&D Report from RiceScience (May 2008) Arthitis/Anti-Inflammation SRB Extract
15. US Patent Application # 12/467,835 Rice Bran Extracts for inflammation and methods of use thereof (Abandoned)
16. Detailed R&D Report from RiceScience (January 2009) Optimized SRB Extracts for Metabolic Syndrome

RiSolubles™ – Supporting Evidence

		Healthy Metabolism Glucose Regulation	Weight Management	Performance/Energy	Joint Health	Cardiovascular Health	GI Health
RiceBran Technologies Studies on **RiSolubles**	**Human Clinical** (Type I & Type II diabeteic subjects)	↓ Serum Glucose (1,5,6) ↓ Glyco. Hemoglobin (1,5,6) ↑ Insulin (1,5,6)				↓ Cholesterol (1,4,8) ↓ LDL-Cholestrol (1,4,8) ↓ Serum Apo B (1,4,8)	
	Human Clinical (Healthy subjects)	↓ serum Glucose & low Glycemic Index (2,3)	↑ Satiety (2)				
	Animal				↑ joint mobility (9)		
	Testimonial			Mike Bridges World Record Powerlifter			
Supporting Scientific Evidence (not conducted on RiSolubles but on related ingredients or compounds present in RiSolubles)	**γ-Oryzanols** (248 mg/100g)	Inhibits NF-κβ resulting in ↑ adiponectin (17,18,19,20,23,25,30)	Inhibits NF-κβ resulting in ↑ adiponectin (17,18,19,20,23,25,30)	Inhibits NF-κβ resulting in ↑ adiponectin (17,18,19,20,23,25,30) Ergogenic aid (39,40)	Inhibits mast cell degranulation (23,24) Anti-inflammatory (25) ↓ Bone loss (33) Inhibits TPA-induced inflammation mice (45)	↓ Cholesterol absorption (37) ↓ plasma lipid & lipoprot cholesterol (38)	
	Tocopherols + Tocotrienols (18 mg/100g)	Activate PPARγ resulting in ↑ adiponectin (27,28,29)	Activate PPARγ resulting in ↑ adiponectin (27,28,29)	Activate PPARγ resulting in ↑ adiponectin (27,28,29)			
	Phytosterols (413 mg/100g)					FDA Health Claim (31)	
	Tricin (5-10 mg/100g)* (21,41)				COX Inhibition (21,22)		↓ Intestinal carcinogenesis (22)
	Rice Bran Extracts				COX1/2 & 5-LOX Inhibition (10)		
	Rice Bran	↑ Human Adiponectin (26)	↑ Human Adiponectin (26)	↑ Human Adiponectin (26)			

* Tricin levels in RiSolubles have not been determined

RiSolubles Characteristics

Bulk Density	(0.31 g/cc)
ASTM Mesh	(20)
Pass-Throguh	(99.8%)
Water Dispersible	
Nutty Flavor	

- High in Antioxidants
- Hypoallergenic
- High in Vitamins & Minerals
- Low Sodium
- Zero Trans Fat
- All Natural
- Low Glycemic Index
- Kosher / Halal Certified

Applications

- Dietary Supplements
- Nutritional Beverages
- Meal Replacements
- Nutritional Bars
- Sports Beverages
- Weight Control Foods
- Muscle Maintenance

Unique Attributes of RiSolubles

- Contains unique phytochemicals (i.e. γ-Oryzanols) present at much lower levels in other botanicals
- Clinically shown to support healthy glucose and lipid metabolism and to induce satiety
- Patents cover method of making and methods of use
- Naturally rich in phytochemicals including vitamins, minerals and antioxidants
- Natural, non-GMO, non-allergenic and made from a sustainable resource in the United States
- Dispersible powder that is amenable to multiple applications including beverages

RiFiber – Supporting Evidence

		Healthy Metabolism Glucose Regulation	Weight Management	Performance/Energy	Joint Health	Cardiovascular Health	GI Health
RiceBran Technologies Studies on RiFiber	Human Clinical (Type I & Type II diabeteic subjects)	↓ Serum Glucose (1,5,6) ↓ Glyco. Hemoglobin (1,5,6)				↓ Cholesterol (1,4,8) ↓ LDL-Cholestrol (1,4,8) ↓ Serum Apo B (1,4,8) ↓Triglycerids (1,4,8)	
	Animal						↓ Adenoma burden and numbers ↑ haemocrit values
Supporting Scientific Evidence (not conducted on RiFiber but on related ingredients or compounds present in RiFiber)	γ-Oryzanols (174 mg/100g)	Inhibits NF-κβ resulting in ↑ adiponectin (17,18,19,20,23,25,30)	Inhibits NF-κβ resulting in ↑ adiponectin (17,18,19,20,23,25,30)	Inhibits NF-κβ resulting in ↑ adiponectin (17,18,19,20,23,25,30) Ergogenic aid (39,40)	Inhibits mast cell degranulation (23,24) Anti-inflammatory (25) ↓ Bone loss (33) Inhibits TPA-induced inflammation mice (45)	↓ Cholesterol absorption (37) ↓ plasma lipid & lipoprotein cholesterol (38)	
	Tocopherols + Tocotrienols (3.7 mg/100g)	Activate PPARγ resulting in ↑ adiponectin (27,28,29)	Activate PPARγ resulting in ↑ adiponectin (27,28,29)	Activate PPARγ resulting in ↑ adiponectin (27,28,29)			
	Phytosterols (315 mg/100g)					FDA Health Claim (31)	
	Dietary Fiber (42 g/100g)		↑ Satiety ↓ Energy intake (34)				FDA Health Claims (32)
	Protein (20 g/100g)			Non-allergenic protein			
	Rice Bran					↓ Cholesterol (35,36)	

RiFiber Characteristics

Bulk Density (~0.25 g/cc)
Nutty Flavor

High in Antioxidants
Hypoallergenic
High in Vitamins & Minerals
Low Sodium
Zero Trans Fat
All Natural
Low Glycemic Index
Kosher / Halal Certified

Applications

Dietary Supplements
Meal Replacements
Nutritional Bars
Weight Control Foods
Muscle Maintenance
Pre-Biotics

Unique Attributes of RiFiber

- Contains unique phytochemicals (i.e. γ-Oryzanols)
- Clinically shown to support healthy lipid metabolism
- Patents cover method of making and methods of use
- Naturally rich in phytochemicals including vitamins, minerals and antioxidants
- Natural, gluten-free, soy-free, source of dietary fiber from a non-GMO sustainable grain source

RiBalance™ – Supporting Evidence

		Healthy Metabolism Glucose Regulation	Weight Management	Performance/Energy	Joint Health	Cardiovascular Health	GI Health
Supporting Scientific Evidence (not conducted on RiBalance but on related ingredients or compounds present in RiBalance)	**γ-Oryzanols** (230 mg/100g)	Inhibits NF-κβ resulting in ↑ adiponectin (17,18,19,20,23,25,30)	Inhibits NF-κβ resulting in ↑ adiponectin (17,18,19,20,23,25,30)	Inhibits NF-κβ resulting in ↑ adiponectin (17,18,19,20,23,25,30) Ergogenic aid (39,40)	Inhibits mast cell degranulation (23,24) Anti-inflammatory (25) ↓ Bone loss (33) Inhibits TPA-induced inflammation mice (45)	↓ Cholesterol absorption (37) ↓ plasma lipid & lipoprotein cholesterol (38)	
	Tocopherols + Tocotrienols (23 mg/100g)	Activate PPARγ resulting in ↑ adiponectin (27,28,29)	Activate PPARγ resulting in ↑ adiponectin (27,28,29)	Activate PPARγ resulting in ↑ adiponectin (27,28,29)			
	Phytosterols (520 mg/100g)					FDA Health Claim (31)	
	Tricin (5-10 mg/100g)* (21,41)				COX Inhibition (21,22)		↓ Intestinal carcinogenesis (22)
	Protein (15.2 g/100g)			Non-allergenic protein			
	Dietary Fiber (22.9 g/100g)		↑ Satiety ↓ Energy intake (34)				FDA Health Claims (32)
	Rice Bran	↑ Human Adiponectin (26)	↑ Human Adiponectin (26)	↑ Human Adiponectin (26)			

* Tricin levels in RiBalance have not been determined

RiBalance Characteristics

Bulk Density (0.37 g/cc)
Nutty Flavor

High in Antioxidants
Hypoallergenic
High in Vitamins & Minerals
Low Sodium
Zero Trans Fat
All Natural
Low Glycemic Index
Kosher / Halal Certified

Applications

Dietary Supplements
Meal Replacements
Nutritional Bars
Weight Control Foods
Muscle Maintenance
Pre-Biotics

Unique Attributes of RiBalance

- Contains unique phytochemicals(i.e. γ-Oryzanols)
- Clinically shown to support healthy lipid metabolism
- Patents cover method of making and methods of use
- Naturally rich in phytochemicals including vitamins, minerals and antioxidants
- Natural, non-GMO, non-allergenic and made from a sustainable resource in the United States
- Natural, gluten-free, soy-free, source of dietary fiber from a non-GMO sustainable grain source

cRBO – Supporting Evidence

		Healthy Metabolism Glucose Regulation	Performance/Energy	Joint Health	Cardiovascular Health
RiceBran Technologies Studies on cRBO	**Animal**			↑ joint mobility (8)	
Supporting Scientific Evidence (not conducted on cRBO but on related ingredients or compounds present in cRBO)	**γ-Oryzanols** (1000 mg/100g)	Inhibits NF-κβ resulting in ↑ adiponectin (17,18,19,20,23,25,30)	Inhibits NF-κβ resulting in ↑ adiponectin (17,18,19,20,23,25,30) Ergogenic aid (39,40)	Inhibits mast cell degranulation (23,24) Anti-inflammatory (25) ↓ Bone loss (33) Inhibits TPA-induced inflammation mice (45)	↓ Cholesterol absorption (37) ↓ plasma lipid & lipoprotein cholesterol (38)
	Tocopherols + Tocotrienols (200 mg/100g)	Activate PPARγ resulting in ↑ adiponectin (27,28,29)	Activate PPARγ resulting in ↑ adiponectin (27,28,29)		
	Phytosterols (>400 mg/100g)				FDA Health Claim (31)
	Tricin (>45 µg/100g)* (21)			COX Inhibition (21,22)	
	Unsaponifiable Matter (3-5 g/100g)				↓ Cholesterol (42,43)
	Rice Bran Oil				↑ LDL-Receptor mRNA ↑ HMG-CoA Red. mRNA ↑ Insulin sensitivity 44)

* Tricin levels in cRBO have not been determined

cRBO Characteristics

Opaque, brown liquid

High in Antioxidants
Hypoallergenic
High in Vitamins & Minerals
Zero Trans Fat
Kosher / Halal Certified

Applications

Dietary Supplements

Unique Attributes of cRBO

- High content of unsaponifiable matter •
1% naturally occuring g-Oryzanols
- Naturally rich in phytochemicals including vitamins, minerals and antioxidants
- Non-GMO, non-allergenic and made from a sustainable resource
- Gluten-free, soy-free, source of dietary fiber from a non-GMO sustainable grain source

Additional Citations

17. Phytomedicine (2011) 669-671 g-Oryzanol recovers mouse hypoadiponectinemia induced by animal fat ingestion
18. Current Nutrition & Food Science (2011) Gamma-Oryzanol - A multi-purpose steryl ferulate
19. Phytomedicine (2011) 655-660 Oral Administration of g-Oryzanol prevents stress-induced hypoadiponectinemia
20. Phytomedicine (2009) 130-137 The effects of hydroxycinnamic acid derivatives on adiponectin secretion
21. Cancer Epidiol Biomarkers Prev (2000) 1163-1170 Characterization of potentially chemopreventative phenols in extracts of brown rice that inhibit the growth of human breast and colon cancer cells
22. Mol Can Ther (2005) 1287-1292 The rice bran consituent tricin potently inhibits cyclooxygenase enzymes and interferes with intestinal carcinogenesis in ApcMin mice
23. Phytomedicine (2010) 152-156 Cycloartenyl ferulate, a component of rice oil-derived g-oryzanol, attenuates mast cell degranulation
24. Arthritis Res. Ther (2005) 1-11 Mast cells in inflammatory arthritis
25. Biochemical and Biophysical Res. Com. (2007) 615-619 Anti-inflammatory effects of hydroxycinnamic acid derivatives
26. Nutrition & Metabolism (2010) 45-51 Ameliorative effects of stabilized rice bran on type 2 diabetes patients
27. Nutrition Reviews (2011) 155-161 Vitamin E and adiponectin: proposed mechanisms for vitamin E-induced improvement in insulin sensitivity
28. Theriogenology (2011) 482-491 Effect of tocopherol supplementation on serum 8-epi-prostaglandin F2 alpha and adiponectin concentrations, and mRNA expression of PPARg and genes in ovine placenta and uterus
29. Biological Chemistry (2005) Regulation of gene expression by a α-tocopherol
30. Int. J. of Obesity (2007) 1104-1109 Adiponectin gene expression and NF-κβ transcriptional activity in elderly overweight and obese women
31. FDA Phytosterol health claims for risk of cardiovascular disease http://www.fda.gov/food/labelingnutrition/labelclaims/healthclaimsmeetingsignificantscientificagreementssa/ucm074779.htm
32. FDA Dietary Fiber health claims http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr;sid=502078d8634923edc695b394a357d189;rgn=div8;view=text;node=21%3A2.0.1.1.2.5.1.7;idno=21;cc=ecfr
33. Masters Thesis (2002) The effects of oryzanols on bone mineral density in ovariectomized, retired breeder rats (etd.lsu.edu/docs/available/etd-0710102-160310/
34. Nutrition Bulletin (2007) 32-42 Dietary Fibre and Satiety
35. J. Nutrition (1998) 865-869 Full-fat rice bran and oat bran similarly reduce hypercholesterolemia in humans
36. Nutrition Research (1993) 387-398 Stabilized rice bran and oat bran lower cholesterol in humans
37. Lipids (1997) 303-309 Oryzanol decreases cholesterol absorption and aortic fatty streaks in hamsters
38. J. Nut. Biochem. (2007) 105-112Rice bran oil and oryzanol reduce plasma lipid and lipoprotein cholesterol concentrations and aortic cholesterol ester accumulation to a greater extent than ferulic acid in hypercholesterolemic hamsters
39. J. Am. Diet Assoc. (1992) 1264-1265 Comtemporary ergogenic aids used by strength/power athletes
40. Int J. Sport Nutr. (1997) 318-329 The effects of g-Oryzanol supplementation during resistance exercise training
41. Plant Foods Hum Nutr (2011) 91-96 Isolation, characterization and quantification of tricin and flavonolignans in the medicinal rice Njarvara (Oryza sativa), as compared to staple varieties
42 Cereal Chemistry (1996) 69-74 Cholesterol lowering by rice bran and rice bran oil unsaponifiable matter in hamsters
43 Am J Clin Nutr (2005) 64-68 Rice bran oil, not fiber, lowers cholesterol in humans
44. J. of Nutrition (2010) 1472-1476 A rice bran oil diet increases LDL-receptor and HMG-CoA reductase mRNA expressions and insulin sensitivity in rats with streptozotocin/nicotimanimde-induced type 2 diabetes
45. J. Agric. Food Chem. (2000) 2313-2319 Triterpene alcohol and sterol ferulates from rice bran and their anti-inflammatory effects

(Copies of these citations are not included in the packet)

MEDICUS Research

Claims Substantiation

& Claims Summary

2015

CLAIMS SUBSTANTIATION

RiceBran Technologies

Ri-Solubles®

Claims Substantiation – Rice Bran Technologies – RI-Solubles®

The following is a summary of the scientific and clinical research related to the Rice Bran Technologies – RI-Solubles®, the water-based soluble fiber fraction from rice bran, and its effects on reduction of hyperglycemia, improvement of insulin levels and insulin sensitivity, and increase in adiponectin levels.

- We performed a comprehensive review of the totality of evidence regarding rice bran in general, RI-Solubles® specifically, and their major component, gamma-oryzanol on reduction of hyperglycemia, improvement of insulin levels and insulin sensitivity and increase in adiponectin levels.

- From this comprehensive review, we have generated evidence tables aimed at representing each of the physiologic processes.

- From these tables, we have analyzed the totality of evidence and have created substantiated scientific statements that we believe represent an accurate summary of this evidence.

- Based on these statements, we have worked with the client to generate claims that are based solely on the substantiated statements that summarize the totality of evidence from the evidence tables.

Ingredients reviewed in this substantiation document for Rice Bran Technologies include:

- RI-Solubles® (branded ingredient)
- Rice bran in general
- Gamma-Oryzanol (generic ingredient/rice bran component)

These following evidence tables are based on the totality of the evidence. Each statement outlined below is supported by an evidence table, which is attached. We have graded each third party literature review based on the following grading criteria:

- Class A Evidence: Randomized, controlled trials
- Class B Evidence: Non randomized prospective studies, Cross-sectional studies
- Class C Evidence: Retrospective studies
- Class E Evidence: Reviews, Expert Opinion, Guidelines
- Class M Evidence: Meta-analyses
- Class S Evidence: Systematic reviews

Current Claims – The following table demonstrates claims that can be substantiated based on our research. In our opinion, these claims can be substantiated scientifically based on the level of scientific evidence found in the available literature. As we are not a law firm, the use of this scientific substantiation for specific purposes should be evaluated by your legal counsel to confirm that it meets your individual needs.

Claim	Substantiated Statements & Evidence Tables
Reduces hyperglycemia	• Two human clinical studies have shown that RI-Solubles® can reduce serum glucose levels in both diabetic and healthy subjects (Evidence Table 1). • One human study, eight preclinical studies and one in vitro/in vivo study have shown that gamma-oryzanol and rice bran in general can reduce glucose levels (Evidence Table 2).
Improves insulin levels and insulin sensitivity	• Two human clinical studies have shown that RI-Solubles® can improve insulin levels and insulin sensitivity in diabetic and healthy subjects (Evidence Table 1). • Six preclinical studies, one in vitro/in vivo study and one review have shown that gamma-oryzanol and rice bran in general can improve insulin levels insulin sensitivity (Evidence Table 2).
Increases adiponectin levels	• Four human clinical studies, one in vitro/in vivo study, and two reviews have revealed that plasma adiponectin is positively correlated with insulin sensitivity and lower risk of impaired glucose metabolism (Evidence Table 2). • Two human studies, three preclinical studies and two in vitro studies have shown that gamma-oryzanol and rice bran in general can increase adiponectin levels through NF-kappaB inhibition (Evidence Table 2).

Summary of Substantiated Scientific Statements

1. **RI-Solubles® and Reduction of Hyperglycemia** – Two human clinical studies have shown that RI-Solubles® can reduce serum glucose levels in both diabetic and healthy subjects (Evidence Table 1).

   A. One (1) Grade-A study, consisting of a total sample size of n=68 Type I and n=80 Type II diabetes patients, demonstrated that stabilized rice bran (A), rice bran water soluble (B) and rice bran fiber concentrates (C), each administered at 20g/day for 8 weeks with a 4-week washout period between study products can reduce hyperglycemia. In particular, B and C non-significantly decreased glycosylated hemoglobin while A, B, and C significantly reduced fasting serum glucose in Type II diabetes subjects. On the other hand, only B and C showed a significant reduction in fasting serum glucose in Type I diabetes subjects (Evidence Table 1, Qureshi, 2002).

   B. One (1) Grade-A study, with a total sample size of n=10 healthy subjects, showed that 45g RI-Solubles® significantly lowered postprandial glucose levels at 15, 30, 45 and 60min after consumption compared to the glucose control. Moreover, GI value of the RI-Solubles® was also significantly lower than the glucose GI, thereby classifying it as a low GI food (Evidence Table 1, Vuksan, 2007).

2. **RI-Solubles® and Improvement of Insulin Levels and Insulin Sensitivity** – Two human clinical studies have shown that RI-Solubles® can improve insulin levels and insulin sensitivity in diabetic and healthy subjects (Evidence Table 1).

   A. One (1) Grade-A study, consisting of a total sample size of n=68 Type I and n=80 Type II diabetes patients, demonstrated that rice bran water soluble (B) at 20g/day for 8 weeks significantly increased serum insulin levels in subjects by 4% in both Type I and II diabetes patients, thereby indicating that consumption of rice bran water solubles can control blood glucose levels in human diabetes (Evidence Table 1, Qureshi, 2002).
   B. One (1) Grade-A study, with a total sample size of n=10 healthy subjects, showed that 45g RI-Solubles® significantly reduced postprandial insulin levels at 45 minutes compared to glucose control, suggesting improvement in insulin sensitivity (Evidence Table 1, Vuksan, 2007).

3. **Adiponectin and Glucose Metabolism / Insulin Sensitivity –** Four human clinical studies, one in vitro/in vivo study, and two reviews have revealed that plasma adiponectin is positively correlated with insulin sensitivity and lower risk of impaired glucose metabolism (Evidence Table 2).

   A. Two (2) Grade-B prospective studies have found that high adiponectin levels are strongly associated with lower risk of impaired glucose metabolism, type II diabetes and insulin sensitivity (Evidence Table 2, Snijder, 2006; Tschritter, 2003).

   B. Two (2) Grade-B studies consisting a total sample size of n=190 subjects have demonstrated that plasma adiponectin is negatively associated with percent body fat, visceral fat, subcutaneous abdominal fat, insulin resistance, and leptin levels and positively associated with glucose utilization (Evidence Table 2, Ryan, 2003; Reinehr, 2004).

   C. One (1) In vitro /in vivo study has shown that adiponectin activated 5'-AMP-activated protein kinase (AMPK), thereby directly regulating glucose metabolism and insulin sensitivity in vitro and in vivo (Evidence Table 2, Yamauchi, 2002).

D. One (1) Review discussed that adiponectin stimulates glucose uptake by skeletal and cardiac muscle, and inhibits glucose production by the liver; consequently decreasing blood glucose levels (Evidence Table 2, Karbowska 2006).

E. One (1) Review noted that full-length versions of adiponectin or its proteolytic fragments improve post-absorptive insulin-mediated suppression of hepatic glucose output. A strong correlation between plasma adiponectin levels and systemic insulin sensitivity is also well established (Evidence Table 2, Berg, 2002).

4. **Gamma-Oryzanol / Rice Bran and Adiponectin Levels –** Two human studies, three preclinical studies and two in vitro studies have shown that gamma-oryzanol and rice bran in general can increase adiponectin levels through NF-kappaB inhibition (Evidence Table 2).

A. One (1) Grade-A study, consisting of a total sample size of n=28 patients with Type II diabetes, demonstrated that daily consumption of 20g of stabilized rice bran for 12 weeks significantly increased adiponectin concentrations by 40% compared to placebo group (Evidence Table 2, Cheng, 2010).

B. One (1) Grade-B, with a total sample size of n=27 elderly women, demonstrated that abdominal adiposity is negatively associated with adiponectin mRNA, and with adipocyte IkB-a mRNA suggesting that if there is high adiponectin gene expression, there is higher expression of IkB-a and an inhibition of NF-kB transcriptional activity resulting in lower inflammation in the adipocytes (Evidence Table 2, Zamboni, 2007).

C. One (1) Preclinical study on mice with hypoadiponectinemia induced by administration of beef tallow and palmitate, demonstrated that administration of gamma-oryzanol (ORZ) from crude rice bran oil recovered hypoadiponectinemia and increased adiponectin levels (Evidence Table 2, Nagasaka, 2011).

D. One (1) Preclinical study on mice with hypoadiponectinemia induced by immobilization stress demonstrated that GABA, gamma-oryzanol, and their combination significantly increased relative LMW and HMW adiponectin levels (Evidence Table 2, Ohara, 2011).

E. One (1) Preclinical study on a total of n=42 obese Zucker rats and lean Zucker rats, demonstrated that 5% rice bran enzymatic extract (RBEE) containing gamma-oryzanol, for 20 weeks recovered adiponectin levels in obese animals (Evidence Table 2, Justo, 2013).

F. One (1) In vitro / in vivo study found that in mice, serum adiponectin concentrations were increased by gamma-ORZ administration but it did not enhance adiponectin secretion of 3T3-L1 adipocytes. Moreover, the results of the study suggested that inhibition of NF-kappaB activation by gamma-oryzanol might lead to regulation of adiponectin secretion (Evidence Table 2, Ohara, 2009).

G. One (1) In vitro study on macrophages demonstrated that cycloartenyl ferulate, a natural product derived from gamma-oryzanol, significantly inhibited DNA-binding of NF-kappaB, which may result in an increase in adiponectin levels (Evidence Table 2, Nagasaka, 2007).

5. **Gamma-Oryzanol / Rice Bran and Reduction of Hyperglycemia –** One human study, eight preclinical studies and one in vitro/in vivo study have shown that gamma-oryzanol and rice bran in general can reduce glucose levels (Evidence Table 2).

   A. One (1) Grade-A study consisting of a total sample size of n=28 subjects with Type II diabetes demonstrated that daily consumption of 20g of stabilized rice bran for 12 weeks significantly decreased postprandial glucose and AUC glucose compared to baseline, as well as HbA1c compared to baseline (Evidence Table 2, Cheng, 2010).

   B. One (1) Preclinical study on a total of n=65 mice with acute and long-term dyslipidemia found that 5-50 mg/kg gamma-oryzanol for 14 days for long-term model reduced glucose and total cholesterol levels (Evidence Table 2, Arruda Filho, 2014).

   C. One (1) Preclinical study on type II diabetic NSY/Hos mice found that wx/ae brown rice containing greater amounts of gamma-oryzanol compared to Koshihikari rice, for 10 weeks, significantly lowered fasting blood glucose level and pathological score of glycosuria compared to the Koshihikari group (Evidence Table 2, Matsumoto, 2012).

   D. One (1) Preclinical study on male C57BL/6J mice, found that 20, 80, or 320 mg/g body weight gamma-oryzanol for 13 weeks improved high fat diet-induced glucose dysmetabolism (Evidence Table 2, Kozuka, 2012).

   E. One (1) Preclinical study on male C57BL/6N mice, demonstrated that high-fat diet supplemented with gamma-oryzanol and ferulic acid for 7 weeks, significantly lowered blood glucose level and G6pase and PEPCK activities, and enhanced GK activity compared to the control groups (Evidence Table 2, Son, 2011).

   F. Three (3) Preclinical studies on rats with hyperglycemia and diabetic neuropathy found that gamma-oryzanol derived from crude rice bran oil at 50 and 100 mg/kg/day for 8 weeks resulted in reduced blood glucose and improved glycemic status (Evidence Table 2, Ghatak, 2012; Ghatak, 2012; Ghatak, 2014).

   G. One (1) Preclinical study on C57 BL/6 J mice, demonstrated that intake of HFD-diet with rice powder resulted in significantly lowered blood glucose and ameliorated glucose responses compared with HFD-fed mice. Also, rice powder enhanced glucose uptake by activating AMP-activated protein kinase and downstream glucose transporter 4 in the skeletal muscle (Evidence Table 2, Choi, 2014).

   H. One (1) In vitro/in vivo study on rats found that Egyptian stabilized rice bran and standardized to contain 2% gamma-oryzanol have antidiabetic effects as shown in the in vivo study on rats (Evidence Table 2, Kaup, 2013).

   I. One (1) Review study discussed that the potential properties exhibited by gamma-oryzanol include anti-diabetic, anti-hyperlipidemic, and anti-inflammatory effects (Evidence Table 2, Ghatak, 2011).

   J. One (1) Systematic review noted that germinated brown rice can be attributed to its bioactive compounds including gamma-oryzanol that has been shown to possess antihyperglycemia and hypercholesterolemic effect (Evidence Table 2, Imam 2012).

6. **Gamma-Oryzanol / Rice Bran and Improvement of Insulin Levels and Insulin Sensitivity –** Six preclinical studies, one in vitro/in vivo study and one review have shown that gamma-oryzanol and rice bran in general can improve insulin levels insulin sensitivity (Evidence Table 2).

   A. Three (3) Preclinical studies on at least n=48 rats with streptozotocin/nicotinamide-induced type 2 diabetes demonstrated that rice brain oil with 5.25 g gamma-oryzanol and tocotrienol for 4-5 weeks, resulted in increased insulin sensitivity and lower area under the curve for insulin, suggesting suppression of the hyperinsulinemic response in rats with streptozotocin/nicotinamide-induced T2DM (Evidence Table 2, Cheng 2010; Chou, 2009; Chen, 2006).

   B. One (1) Preclinical study on a total of n=42 obese Zucker rats and lean Zucker rats, demonstrated that 5% rice bran enzymatic extract (RBEE) containing gamma-oryzanol, for 20 weeks improved insulin resistance and HOMA-IR index without affecting serum glucose levels (Evidence Table 2, Justo, 2013).

   C. One (1) Preclinical study on male C57BL/6N mice, demonstrated that high-fat diet supplemented with gamma-oryzanol and ferulic acid for 7 weeks, significantly increased insulin concentrations compared to the control groups (Evidence Table 2, Son, 2011).

   D. One (1) Preclinical study on C57 BL/6 J mice, demonstrated that intake of HFD-diet with rice powder resulted in significantly lowered insulin and leptin levels and lowered HOMA-IR compared with HFD-fed mice. (Evidence Table 2, Choi, 2014).

   E. One (1) In vitro/in vivo study on rats found that Egyptian stabilized rice bran and standardized to contain 2% gamma-oryzanol have insulinotropic effects in vitro (Evidence Table 2, Kaup, 2013).

   F. One (1) Review discussed that gamma-oryzanol, may have potential for treatment of obesity and type II diabetes in humans as it improves beta-cell function and enhances glucose-stimulated insulin secretion (GSIS) (Evidence Table, Kozuka, 2013).

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CLAIMS SUBSTANTIATION

RiceBran Technologies

Ri-Fiber®

Claims Substantiation – Rice Bran Technologies – RI-Fiber®

The following is a summary of the scientific and clinical research related to the Rice Bran Technologies – RI-Fiber®, the insoluble fiber fraction from rice bran, and its effects on reduction of total cholesterol, LDL cholesterol, and triglycerides, reduction of cholesterol absorption, and reduction of plasma lipid and lipoprotein cholesterol.

- We performed a comprehensive review of the totality of evidence regarding rice bran and insoluble fiber in general, RI-Fiber®, as well as one of its component, gamma-oryzanol on reduction of total cholesterol, LDL cholesterol, and triglycerides, reduction of cholesterol absorption, and reduction of plasma lipid and lipoprotein cholesterol.

- From this comprehensive review, we have generated evidence tables aimed at representing each of the physiologic processes.

- From these tables, we have analyzed the totality of evidence and have created substantiated scientific statements that we believe represent an accurate summary of this evidence.

- Based on these statements, we have worked with the client to generate claims that are based solely on the substantiated statements that summarize the totality of evidence from the evidence tables.

Ingredients reviewed in this substantiation document for Rice Bran Technologies include:

- RI-Fiber® (branded ingredient)
- Insoluble fiber (generic ingredient)
- Gamma-Oryzanol (generic ingredient/rice bran component)

These following evidence tables are based on the totality of the evidence. Each statement outlined below is supported by an evidence table, which is attached. We have graded each third party literature review based on the following grading criteria:

- Class A Evidence: Randomized, controlled trials
- Class B Evidence: Non randomized prospective studies, Cross-sectional studies
- Class C Evidence: Retrospective studies
- Class E Evidence: Reviews, Expert Opinion, Guidelines
- Class M Evidence: Meta-analyses
- Class S Evidence: Systematic reviews

Current Claims – The following table demonstrates claims that can be substantiated based on our research. In our opinion, these claims can be substantiated scientifically based on the level of scientific evidence found in the available literature. As we are not a law firm, the use of this scientific substantiation for specific purposes should be evaluated by your legal counsel to confirm that it meets your individual needs.

Claim	Substantiated Statements & Evidence Tables
Reduces total cholesterol, LDL cholesterol, and triglycerides	• One human clinical study has shown that RI-Fiber® can improve lipid parameters in diabetic subjects (Evidence Table 3). • Seven human clinical studies and ten preclinical studies have demonstrated that insoluble fibers from various sources can reduce total cholesterol LDL cholesterol, and triglycerides (Evidence Table 4). • Five human studies, three preclinical studies and one in vitro study have shown that gamma-oryzanol and rice bran in general can reduce total cholesterol, LDL cholesterol and triglyceride levels (Evidence Table 2).
Reduces absorption of cholesterol	• One human clinical study and ten preclinical studies have shown that insoluble fiber from various sources can reduce cholesterol absorption resulting in increased fecal cholesterol excretion (Evidence Table 4). • Two preclinical studies have shown that gamma-oryzanol can reduce cholesterol absorption (Evidence Table 2).
Reduces plasma lipid and lipoprotein cholesterol	• One human clinical study has shown that RI-Fiber® can reduce plasma lipid and lipoprotein cholesterol levels (Evidence Table 3). • Six human clinical studies, two preclinical studies and three reviews have shown that insoluble fiber consumption can reduce lipid and lipoprotein cholesterol levels (Evidence Table 4). • Five human studies and three preclinical studies have shown that gamma-oryzanol and rice bran in general can reduce plasma lipid and lipoprotein cholesterol (Evidence Table 2).

Summary of Substantiated Scientific Statements

1. **RI-Fiber® and Reduction of Total Cholesterol, LDL Cholesterol, and Triglycerides** – One human clinical study has shown that RI-Fiber® can improve lipid parameters in diabetic subjects (Evidence Table 3).

   A. One (1) Grade-A study, consisting of a total sample size of n=68 Type I and n=80 Type II diabetes patients, demonstrated that stabilized rice bran fiber concentrate administered at 20g/day for 8 weeks can improve serum total cholesterol, LDL cholesterol, apolipoprotein B, and triglycerides levels (Evidence Table 3, Qureshi, 2002).

2. **Insoluble fiber and Reduction of Total Cholesterol, LDL Cholesterol, and Triglycerides** – Seven human clinical studies and ten preclinical studies have demonstrated that insoluble fibers from various sources can reduce total cholesterol LDL cholesterol, and triglycerides (Evidence Table 4).

   A. Two (2) Grade-A studies, with a total sample size of n=117, demonstrated that insoluble fiber from carob pod at 8-15 g/day, significantly reduced the levels of total cholesterol, LDL cholesterol, LDL:HDL cholesterol ratio, and triglycerides (Evidence Table 4, Ruiz-Roso, 2010; Zunft, 2003).

   B. One (1) Grade-A study consisting of a total sample size of n=53 healthy volunteers, demonstrated that subjects who consumed Group II diet containing 4.11 g soluble fiber and 25.08 g insoluble fiber (hemicelullose, cellulose and lignins) had a significant decrease in LDL cholesterol from baseline (Evidence Table 4, Aller, 2004).

   C. One (2) Grade-A study a total sample size of n=108 healthy subjects, demonstrated that wheat fiber or wheat bran as sources of insoluble fiber at 16.4-21g/day significantly reduced total cholesterol, LDL cholesterol, as well as LDL:HDL ratio compared to baseline (Evidence Table 4, Vuksan, 1999; Kashtan, 1992).

   D. One (1) Grade-A study, with a total sample size of n=12 men subjects, found that carboxymethylcellulose gum, locust bean gum, and karaya gum resulted in lower total cholesterol, LDL cholesterol and triglycerides compared to the insoluble fiber, cellulose (Evidence Table 4, Behall, 1984).

   E. One (1) Grade-B study with a total sample size of n=8 healthy males, demonstrated that 3-6/day of water-insoluble chitosan for 14 days, reduced total serum cholesterol and increased HDL cholesterol (Evidence Table 4, Maezaki, 1993).

   F. Five (5) Preclinical studies demonstrated that the administration of insoluble dietary fiber from various sources, including carob pod, starfruit bagasse, *Tremella fuciformis* Berk edible mushroom, and whole Gracilaria, can significantly reduce serum and hepatic concentrations of total cholesterol, LDL cholesterol and triglycerides (Evidence Table 4, Valero-Muñoz, 2014; Herman-Lara, 2014; Safaa, 2014; Cheng, 2002; Lin, 2011).

   G. Three (3) Preclinical studies on hamsters found that a insoluble fiber rich fraction (FRF) from defatted *Passiflora edulis* seed and from carrot pomace, and a water-insoluble fiber-rich fraction (WIFF) isolated from the pomace of *Averrhoa carambola* effectively decreased the levels of

serum triglyceride, serum total cholesterol and liver cholesterol (Evidence Table 4, Chau, 2004; Chau, 2005; Hsu, 2006).

H. One (1) Preclinical study on n=16 male Golden-Syrian hamsters found that cellulose containing 12.7g insoluble fiber and oat bran containing 5.7g insoluble fiber for 4 weeks significantly lowered VLDL+LDL cholesterol concentrations while only oat bran reduced total cholesterol levels (Evidence Table 4, Jonnalagadda 1993).

I. One (1) Preclinical study on a total of n=60 hamsters demonstrated that Cholazol H, a chemically functionalized insoluble fiber, significantly lowered plasma total cholesterol and plasma very low and low-density lipoprotein cholesterol with no significant effects on plasma HDLC or triglycerides (Evidence Table 4, Wilson, 1998).

3. **Insoluble fiber and Reduction of Cholesterol Absorption –** One human clinical study and ten preclinical studies have shown that insoluble fiber from various sources can reduce cholesterol absorption resulting in increased fecal cholesterol excretion (Evidence Table 4).

   A. One (1) Grade-B study with a total sample size of n=8 healthy males, demonstrated that 3-6/day of water-insoluble chitosan for 14 days significantly increased excreted amounts of primary bile acids and deceased the resorption of bile acids, so that the cholesterol pool in the body was decreased and the level of serum cholesterol consequently decreased. (Evidence Table 4, Maezaki, 1993).

   B. Three (3) Preclinical studies on hamsters demonstrated that water-insoluble fiber-rich fraction (WIFF) isolated from the pomace of *Averrhoa carambola* and insoluble fiber rich fraction (FRF) from defatted *Passiflora edulis* seed and from carrot pomace, increased the concentrations of fecal total lipids, fecal cholesterol, and fecal bile acids and increased the fecal bulk and moisture (Evidence Table 4, Chau 2004; Chau, 2005; Hsu, 2006).

   C. One (1) Preclinical study on hamsters demonstrated that the water insoluble fiber-rich fraction (WIFF) from pineapple peel enhanced the total amounts of short-chain fatty acid in the cecal content and the growth of gut microflora such as Lactobacillus spp and Bifidobacterium spp. (Evidence Table 4, Huang, 2014).

   D. One (1) Preclinical study on Male Sprague Dawley rats has found that young barley leaf powder containing water-insoluble dietary fiber fraction is the major component responsible for increased the fecal weight and volume (Evidence Table 4, Ikeguchi, 2014).

   E. One (1) Preclinical study on rat experimental model of diet-induced hypercholesterolemia demonstrated that insoluble fiber residue increased fecal fat excretion, and improved parameters of large intestine physiological status due to its fermentative and water holding capacity (Evidence Table 4, Kapravelou 2013).

   F. One (1) Preclinical study on n=16 male Golden-Syrian hamsters found that oat bran containing 5.7g insoluble fiber and 4.2g soluble fiber for 4 had the highest total fecal cholesterol excretion among fiber groups (Evidence Table 4, Jonnalagadda 1993).

G. One (1) Preclinical study on a total of n=60 hamsters demonstrated that Cholazol H, a chemically functionalized insoluble fiber, produced a significantly greater concentration of fecal total bile acids (Evidence Table 4, Wilson, 1998).

H. Two (2) Preclinical study on rat found that the soluble fraction isolated from bilberry, black currant, and raspberry or from guar resulted in lower amounts of liver cholesterol and greater amounts of cecal short-chain fatty acids compared to the insoluble fraction (Evidence Table 4, Jakobsdottir, 2014; Isken, 2010).

4. **RI-Fiber® and Reduction of Plasma Lipid and Lipoprotein Cholesterol Levels** – One human clinical study has shown that RI-Fiber® can reduce plasma lipid and lipoprotein cholesterol levels (Evidence Table 3).

   A. One (1) Grade-A study, consisting of a total sample size of n=68 Type I and n=80 Type II diabetes patients, demonstrated that stabilized rice bran fiber concentrate administered at 20g/day for 8 weeks can improve serum total cholesterol, LDL cholesterol, apolipoprotein B, and triglycerides levels (Evidence Table 3, Qureshi, 2002).

5. **Insoluble Fiber and Reduction of Plasma Lipid and Lipoprotein Cholesterol Levels –** Six human clinical studies, two preclinical studies and three reviews have shown that insoluble fiber consumption can reduce lipid and lipoprotein cholesterol levels (Evidence Table 4).

   A. One (1) Grade-A study consisting a total sample size of n=130 subjects free of diabetes mellitus, found that insoluble fiber from *Aspergillus niger* mycelium, CG for 6 weeks at 4.5g/day significantly reduced oxidized LDL compared with placebo. Moreover, CG at 1.5 g/day significantly lowered LDL cholesterol (Evidence Table 4, Bays, 2013).

   B. One (1) Grade-A study consisting a total sample size of n=19 healthy subjects found that insoluble fiber from carob fiber at 50g/day increased plasma ghrelin accompanied by enhanced lipid metabolism suggesting higher lipid utilization and suppressed lipolysis (Evidence Table 4, Gruendel, 2007).

   C. One (1) Grade-B study on patients with Type 2 diabetes demonstrated that diet containing food rich in soluble and insoluble fiber had significant improvements in lipid panels when compared with patients who consumed a diet with moderate amounts of fiber (Evidence Table 4, McIntosh, 2001).

   D. One (1) Grade-B pilot human study on a total sample size of n=30 subjects with slight hypercholesterolemia found that 4.5 g of chitin-glucan/day for 4 weeks decreased oxidized LDL by 29% and 26% after 2 and 4 weeks of treatment, respectively (Evidence Table 4, Deschamps, 2009).

   E. One (1) Grade-B prospective study has found that water-insoluble fiber intake is positively associated with low-density lipoprotein levels (Evidence Table 4, Lin, 2014).

   F. One (1) Grade-B prospective study, with a total sample size of n=51,529, showed that intake of insoluble fiber (from whole grains) has an inverse association with hypertension as it reduces cholesterol levels (Evidence Table 4, Flint, 2009).

G. One (1) Preclinical study on a total of n=32 rats found that insoluble fiber from Jabuticaba [Pliniajaboticaba (Vell.) Berg] skins at 27.51g/100g for 4 weeks reduced lipid peroxidation (oxidized LDL) in the liver by about 50% (Evidence Table 4, Fonseca, 2014).

H. One (1) Preclinical study on n=6 mice found that insoluble fiber intake from chitosan or cellulose at 7.5% for 3 weeks prevented the increase in serum cholesterol due to high fat/high cholesterol diet (Evidence Table 4, van Bennekum, 2005).

I. Three (3) Reviews showed that also insoluble/non-digestible fibers can reduce cholesterol and have favorable effects on fasting and postprandial serum lipoprotein levels although it was also notable that soluble fibers appear to have a greater potential to alter serum lipid levels than do insoluble fibers (Evidence Table 4, Anderson, 1999; Glore, 1994; Tungland, 2002).

6. **Gamma-Oryzanol / Rice Bran and Reduction of Total Cholesterol, LDL Cholesterol, and Triglyceride Levels –** Five human studies, three preclinical studies and one in vitro study have shown that gamma-oryzanol and rice bran in general can reduce total cholesterol, LDL cholesterol and triglyceride levels (Evidence Table 2).

   A. Two (2) Grade-A studies, consisting of a total sample size of n=55 have shown that the addition of stabilized rice bran in the diet of hyperlipidemic adults significantly reduced serum total cholesterol levels, LDL cholesterol, VLDL cholesterol, and apoB (Evidence Table 2, Gerhardt, 1998; Hegsted, 1992).

   B. One (1) Grade-A study, consisting a total sample size of n=30 mildly hypercholesterolemic men, found that rice bran oil containing 0.05or 0.8 g/day gamma-oryzanol for 6 weeks reduced total plasma cholesterol, LDL cholesterol and the LDL:HDL ratio (Evidence Table 2, Berger, 2005).

   C. Two (2) Grade-B open-label studies, consisting of a total sample size of n=60, have shown that gamma-oryzanol administration at 300mg-1500mg/day significantly reduced total cholesterol, triglyceride, LDL cholesterol apolipoprotein B, and apo B/apo A-I ratio as well as lipid peroxidation in subjects with hyperlipidemia (Evidence Table 2, Sasaki, 1990; Ishihara, 1982).

   D. Three (3) Preclinical studies on a total of n=145 hypercholesterolemic hamsters and mice demonstrated that gamma-oryzanol reduced total cholesterol, non-HDL cholesterol and triacylglycerols levels (Evidence Table 2, Arruda Filho, 2014; Rong, 1997; Wilson, 2007).

   E. One (1) In vitro study on Caco-2 human intestinal cells, demonstrated that gamma-oryzanol significantly inhibited the incorporation of cholesterol into synthetic micelles and decreased apical uptake of cholesterol (Evidence Table 2, Makyen, 2001).

   F. One (1) Review showed that rice bran oil and gamma-oryzanol can improve the plasma lipid pattern of rodents, rabbits, primates and humans; reduce total plasma cholesterol and triglyceride concentration and increase the high density lipoprotein cholesterol level (Evidence Table 2, Cicero, 2001).

7. **Gamma-Oryzanol and Cholesterol Absorption** – Two preclinical studies have shown that gamma-oryzanol can reduce cholesterol absorption (Evidence Table 2).

   A. One (1) Preclinical study on n=32 hypercholesterolemic hamsters demonstrated that gamma-oryzanol for 8.5 weeks resulted in 25% reduction in percent cholesterol absorption compared to control animals (Evidence Table 2, Rong, 1997).

   B. One (1) Preclinical study on n=48 hamsters found that rice bran oil with gamma-oryzanol for 10 weeks resulted in the increase of fecal excretion of cholesterol and its metabolites (Evidence Tale 2, Wilson 2007).

8. **Gamma-Oryzanol / Rice Bran and Reduction of Plasma Lipid and Lipoprotein Cholesterol Levels –** Five human studies and three preclinical studies have shown that gamma-oryzanol and rice bran in general can reduce plasma lipid and lipoprotein cholesterol (Evidence Table 2).

   A. Two (2) Grade-A studies, consisting of a total sample size of n=55 have shown that the addition of stabilized rice bran in the diet of hyperlipidemic adults significantly reduced serum total cholesterol levels, LDL cholesterol, VLDL cholesterol, and apoB (Evidence Table 2, Gerhardt, 1998; Hegsted, 1992).

   B. One (1) Grade-A study, consisting a total sample size of n=30 mildly hypercholesterolemic men, found that rice bran oil containing 0.05or 0.8 g/day gamma-oryzanol for 6 weeks reduced total plasma cholesterol, LDL cholesterol and the LDL:HDL ratio (Evidence Table 2, Berger, 2005).

   C. Two (2) Grade-B open-label studies, consisting of a total sample size of n=60, have shown that gamma-oryzanol administration at 300mg-1500mg/day significantly reduced total cholesterol, triglyceride, LDL cholesterol apolipoprotein B, and apo B/apo A-I ratio as well as lipid peroxidation in subjects with hyperlipidemia (Evidence Table 2, Sasaki, 1990; Ishihara, 1982).

   D. Three (3) Preclinical studies on a total of n=145 hypercholesterolemic hamsters and mice demonstrated that gamma-oryzanol reduced total cholesterol, non-HDL cholesterol and triacylglycerols levels (Evidence Table 2, Arruda Filho, 2014; Rong, 1997; Wilson, 2007).

   E. One (1) Review showed that rice bran oil and gamma-oryzanol can improve the plasma lipid pattern of rodents, rabbits, primates and humans; reduce total plasma cholesterol and triglyceride concentration and increase the high density lipoprotein cholesterol level (Evidence Table 2, Cicero, 2001).

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RI-Fiber®

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Insoluble fiber

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CLAIMS SUMMARY

RiceBran Technologies

Ri-Solubles®

Claims Summary – Rice Bran Technologies – RI-Solubles®

The following summary discusses claims for which we believe to be substantiated for the Rice Bran Technologies – RI-Solubles®, rice bran and gamma-oryzanol. In our opinion, these claims can be substantiated scientifically based on the level of scientific evidence found in the available literature. As we are not a law firm, the use of this scientific substantiation for specific purposes should be evaluated by your legal counsel to confirm that it meets your individual needs.

The following claims can be substantiated for this product when taken as directed.

1) *Reduces hyperglycemia*

RI-Solubles®

There are two (2) Grade-A studies which demonstrated that RI-Solubles® can reduce serum glucose levels in both diabetic and healthy subjects. In particular, one (1) Grade-A study, consisting of a total sample size of n=68 Type I and n=80 Type II diabetes patients, demonstrated that rice bran water soluble (B) and rice bran fiber concentrates (C), each administered at 20g/day for 8 weeks decreased glycosylated hemoglobin and significantly reduced fasting serum glucose in Type II and Type I diabetes subjects (Qureshi, 2002). In addition, one (1) Grade-A study, with a total sample size of n=10 healthy subjects, showed that 45g RI-Solubles® significantly lowered postprandial glucose levels at 15, 30, 45 and 60min after consumption compared to the glucose control. Moreover, GI value of the RI-Solubles® was also significantly lower than the glucose GI, thereby classifying it as a low GI food (Vuksan, 2007).

Gamma-oryzanol/Rice bran

Moreover, one human study, eight preclinical studies and one in vitro/in vivo study have demonstrated that gamma-oryzanol and generic rice bran can elicit similar effects. Specifically, one (1) Grade-A study demonstrated that daily consumption of 20g of stabilized rice bran for 12 weeks can decrease postprandial glucose levels, AUC glucose and HbA1c compared to baseline (Cheng, 2010). Three (3) Preclinical studies on rats with hyperglycemia and diabetic neuropathy found that gamma-oryzanol derived from crude rice bran oil at 50 and 100 mg/kg/day for 8 weeks resulted in reduced blood glucose and improved glycemic status (Ghatak, 2012; Ghatak, 2012; Ghatak, 2014). Also, one (1) Preclinical study on C57 BL/6 J mice, demonstrated that intake of HFD-diet with rice powder resulted in significantly lowered blood glucose and ameliorated glucose responses compared with HFD-fed mice. Also, rice powder enhanced glucose uptake by activating AMP-activated protein kinase and downstream glucose transporter 4 in the skeletal muscle (Choi, 2014). In addition, two (2) Preclinical study on male C57BL/6J mice, found that 20, 80, or 320 mg/g body weight gamma-oryzanol for 13 weeks improved high fat diet-induced glucose dysmetabolism and significantly lowered blood glucose level and G6pase and PEPCK activities, and enhanced GK activity compared to the control groups (Kozuka, 2012; Son, 2011). One (1) Preclinical study on a total of n=65 mice with acute and long-term dyslipidemia found that 5-50 mg/kg gamma-oryzanol for 14 days reduced glucose and total cholesterol levels (Arruda Filho, 2014). Furthermore, one

(1) Preclinical study on type II diabetic NSY/Hos mice found that wx/ae brown rice containing greater amounts of gamma-oryzanol compared to Koshihikari rice, for 10 weeks, significantly lowered fasting blood glucose level and pathological score of glycosuria compared to the Koshihikari group (Matsumoto, 2012). Lastly, one (1) In vitro/in vivo study on rats found that Egyptian stabilized rice bran and standardized to contain 2% gamma-oryzanol have antidiabetic effects (Kaup, 2013).

Summary

In summary, based on two (2) Grade-A studies on RI-Solubles® and one (1) Grade-A study on stabilized rice bran, we believe that there is adequate substantiation for the claim of *reduces hyperglycemia* for Rice Bran Technologies – RI-Solubles® at 20g/day, and for generic stabilized rice bran and gamma-oryzanol at 20g/day.

2) *Improve insulin levels and insulin sensitivity*

RI-Solubles®

There are two (2) Grade-A studies which have shown that RI-Solubles® can improve insulin levels and insulin sensitivity in both diabetic and healthy subjects. In particular, one (1) Grade-A study, consisting of a total sample size of n=68 Type I and n=80 Type II diabetes patients, demonstrated that rice bran water soluble (B) at 20g/day for 8 weeks significantly increased serum insulin levels in subjects by 4% in both Type I and II diabetes patients, thereby indicating indicate that consumption of rice bran water solubles can control blood glucose levels in human diabetes (Qureshi, 2002). Also, one (1) Grade-A study, with a total sample size of n=10 volunteers, showed that 45g RI-Solubles® significantly reduced postprandial insulin levels at 45 minutes compared to glucose control, suggesting improvement in insulin sensitivity in healthy subjects (Vuksan, 2007).

Gamma-oryzanol/Rice Bran

On the other hand, six (6) preclinical studies have shown that gamma-oryzanol and rice bran can improve insulin levels and insulin sensitivity. Specifically, one (1) Preclinical study on a total of n=42 obese Zucker rats and lean Zucker rats, demonstrated that 5% rice bran enzymatic extract (RBEE) containing gamma-oryzanol at 1260 mg/kg for 20 weeks improved insulin resistance and HOMA-IR index without affecting serum glucose levels (Justo, 2013). Moreover, one (1) Preclinical study on male C57BL/6N mice, demonstrated that high-fat diet supplemented with oryzanol and ferulic acid for 7 weeks, significantly increased insulin concentrations compared to the control groups (Son, 2011). One (1) Preclinical study on C57 BL/6 J mice, demonstrated that intake of HFD-diet with rice powder resulted in significantly lowered insulin and leptin levels and lowered HOMA-IR compared with HFD-fed mice. (Choi, 2014). Also, three (3) Preclinical studies on at least n=48 rats demonstrated that rice brain oil with 5.25 g gamma-oryzanol and tocotrienol for 4-5 weeks, resulted in increased insulin sensitivity and lower area under the curve for insulin, suggesting suppression of the hyperinsulinemic response in rats with streptozotocin/nicotinamide-induced Type II diabetes mellitus (Cheng 2010; Chou, 2009; Chen, 2006). In

addition, one (1) In vitro/in vivo study on rats found that Egyptian stabilized rice bran and standardized to contain 2% gamma-oryzanol have insulinotropic effects in vitro (Kaup, 2013). One (1) Review discussed that gamma-oryzanol, may have potential for treatment of obesity and type II diabetes in humans as it improves beta-cell function and enhances glucose-stimulated insulin secretion (GSIS) (Kozuka, 2013).

Summary

In summary, based on the two (2) Grade-A studies on RI-Solubles®, we believe that there is adequate substantiation for the claim of *improves insulin levels and insulin sensitivity* for Rice Bran Technologies – RI-Solubles® at 20g/day.

However, although these preclinical studies do support the claim of *improves insulin levels and insulin sensitivity*, there are no human studies evaluating the roles of generic rice bran and gamma-oryzanol relating to improvement of insulin levels and insulin sensitivity, therefore claims as they pertain to direct effect on humans cannot be substantiated.

3) *Increase adiponectin levels*

Adiponectin is a hormone secreted by adipocytes that regulate energy homeostasis and glucose and lipid metabolism. This is associated with glucose levels as it directly regulates glucose metabolism and insulin sensitivity. There are two (2) Grade-B prospective studies which have shown that high adiponectin levels are strongly associated with lower risk of impaired glucose metabolism, type II diabetes and insulin sensitivity (Snijder, 2006; Tschritter, 2003). Moreover, two (2) Grade-B studies consisting a total sample size of n=190 subjects have demonstrated that plasma adiponectin is negatively associated with insulin resistance and positively associated with glucose utilization (Ryan, 2003; Reinehr, 2004). In addition, one (1) In vitro /in vivo study has shown that adiponectin activated 5'-AMP-activated protein kinase (AMPK), thereby directly regulating glucose metabolism and insulin sensitivity in vitro and in vivo (Yamauchi, 2002). Lastly, two (2) reviews noted that adiponectin improve post-absorptive insulin-mediated suppression of hepatic glucose output, consequently decreasing blood glucose levels and that plasma adiponectin levels is strongly correlated with insulin sensitivity (Karbowska 2006; Berg, 2002).

Gamma-oryzanol/Rice Bran

In line with this, studies have shown that gamma-oryzanol and rice bran has can increase adiponectin levels through NF-kappaB inhibition. In particular, one (1) Grade-A study, consisting of a total sample size of n=28 patients with Type II diabetes, demonstrated that daily consumption of 20g of stabilized rice bran for 12 weeks significantly increased adiponectin concentrations by 40% compared to placebo group (Cheng, 2010). One (1) Grade-B, with a total sample size of n=27 elderly women, demonstrated that abdominal adiposity is negatively associated with adiponectin mRNA, and with adipocyte IkB-a mRNA suggesting that if there is high adiponectin gene expression, there is higher expression of IkB-a and an inhibition of NF-kB transcriptional activity resulting in lower inflammation in the adipocytes (Zamboni, 2007). Preclinical studies have also shown similar results. Specifically, two (2) Preclinical studies on

mice with hypoadiponectinemia, demonstrated that administration of gamma-oryzanol from crude rice bran oil recovered hypoadiponectinemia and increased adiponectin levels (Nagasaka, 2011; Ohara, 2011). Moreover, one (1) Preclinical study on a total of n=42 obese Zucker rats and lean Zucker rats, demonstrated that 5% rice bran enzymatic extract (RBEE) containing gamma-oryzanol, for 20 weeks recovered adiponectin levels in obese animals (Justo, 2013). Lastly, two (2) In vitro/in vivo studies on adipocytes and macrophages found that gamma-oryzanol increased serum adiponectin concentrations via inhibition of NF-kappaB activation (Ohara, 2009; Nagasaka, 2007).

Summary

In summary, based on one (1) Grade-A study on generic stabilized rice bran and gamma-oryzanol, we believe that there is adequate substantiation for the claim of *increases adiponectin levels* for generic stabilized rice bran at 20g/day.

However, as there are no human studies evaluating the roles of Rice Bran Technologies – RI-Solubles® relating to increase in adiponectin levels, claims as they pertain to direct effect on humans also cannot be substantiated.

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CLAIMS SUMMARY

RiceBran Technologies

Ri-Fiber®

Claims Summary – Rice Bran Technologies – RI-Fiber®

The following summary discusses claims for which we believe to be substantiated for the Rice Bran Technologies – RI-Fiber®, generic rice bran, insoluble fiber and gamma-oryzanol. In our opinion, these claims can be substantiated scientifically based on the level of scientific evidence found in the available literature. As we are not a law firm, the use of this scientific substantiation for specific purposes should be evaluated by your legal counsel to confirm that it meets your individual needs.

The following claims can be substantiated for this product when taken as directed.

1) *Reduces total cholesterol, LDL cholesterol, and triglycerides*

RI-Fiber®

There is one (1) Grade-A study which demonstrated that RI-Fiber® can improve lipid parameters in diabetic subjects. In particular, one (1) Grade-A study, consisting of a total sample size of n=68 Type I and n=80 Type II diabetes patients, demonstrated that stabilized rice bran fiber concentrate administered at 20g/day for 8 weeks can improve serum total cholesterol, LDL cholesterol, apolipoprotein B, and triglycerides levels (Qureshi, 2002).

Insoluble fiber

Moreover, seven human clinical studies and ten preclinical studies have demonstrated that insoluble fibers from various sources can reduce total cholesterol LDL cholesterol, and triglycerides. Specifically, two (2) Grade-A studies, with a total sample size of n=117, demonstrated that insoluble fiber from carob pod at 8-15 g/day, significantly reduced the levels of total cholesterol, LDL cholesterol, LDL:HDL cholesterol ratio, and triglycerides (Ruiz-Roso, 2010; Zunft, 2003). Moreover, one (1) Grade-A study consisting of a total sample size of n=53 healthy volunteers, demonstrated that subjects who consumed Group II diet containing 4.11 g soluble fiber and 25.08 g insoluble fiber (hemicelullose, cellulose and lignins) had a significant decrease in LDL cholesterol from baseline (Aller, 2004). In addition, one (2) Grade-A study a total sample size of n=108 healthy subjects, demonstrated that wheat fiber or wheat bran as sources of insoluble fiber at 16.4-21g/day significantly reduced total cholesterol, LDL cholesterol, as well as LDL:HDL ratio compared to baseline (Vuksan, 1999; Kashtan, 1992). Also, one (1) Grade-A study, with a total sample size of n=12 men subjects, found that carboxymethylcellulose gum, locust bean gum, and karaya gum resulted in lower total cholesterol, LDL cholesterol and triglycerides compared to the insoluble fiber, cellulose (Behall, 1984).One (1) Grade-B study with a total sample size of n=8 healthy males, demonstrated that 3-6/day of water-insoluble chitosan for 14 days, reduced total serum cholesterol and increased HDL cholesterol (Maezaki, 1993).

Preclinical studies have also demonstrated similar results. Specifically, five (5) Preclinical studies on mice, rabbits and broilers, demonstrated that the administration of insoluble dietary fiber from various sources, including carob pod, starfruit bagasse, *Tremella fuciformis* Berk edible mushroom, and whole

Gracilaria, can significantly reduce serum and hepatic concentrations of total cholesterol, LDL cholesterol and triglycerides (Valero-Muñoz, 2014; Herman-Lara, 2014; Safaa, 2014; Cheng, 2002; Lin, 2011). Moreover, three (3) Preclinical studies on hamsters found that a insoluble fiber rich fraction (FRF) from defatted *Passiflora edulis* seed and from carrot pomace, and a water-insoluble fiber-rich fraction (WIFF) isolated from the pomace of *Averrhoa carambola* effectively decreased the levels of serum triglyceride, serum total cholesterol and liver cholesterol (Chau, 2004; Chau, 2005; Hsu, 2006). Also, one (1) Preclinical study on n=16 male Golden-Syrian hamsters found that cellulose containing 12.7g insoluble fiber and oat bran containing 5.7g insoluble fiber for 4 weeks significantly lowered VLDL+LDL cholesterol concentrations while only oat bran reduced total cholesterol levels (Jonnalagadda 1993). Lastly, one (1) Preclinical study on a total of n=60 hamsters demonstrated that Cholazol H, a chemically functionalized insoluble fiber, significantly lowered plasma total cholesterol and plasma very low and low-density lipoprotein cholesterol with no significant effects on plasma HDLC or triglycerides (Wilson, 1998).

Gamma-oryzanol/Rice bran

Five human studies, three preclinical studies and one in vitro study have also shown that rice bran in general as well as gamma-oryzanol can reduce total cholesterol, LDL cholesterol and triglyceride levels. Two (2) Grade-A studies, consisting of a total sample size of n=55 have shown that the addition of stabilized rice bran in the diet of hyperlipidemic adults significantly reduced serum total cholesterol levels, LDL cholesterol, VLDL cholesterol, and apoB (Gerhardt, 1998; Hegsted, 1992). Moreover, one (1) Grade-A study, consisting a total sample size of n=30 mildly hypercholesterolemic men, found that rice bran oil containing 0.05 or 0.8 g/day gamma-oryzanol for 6 weeks reduced total plasma cholesterol, LDL cholesterol and the LDL:HDL ratio (Berger, 2005). Two (2) Grade-B open-label studies, consisting of a total sample size of n=60, have shown that gamma-oryzanol administration at 300mg-1500mg/day significantly reduced total cholesterol, triglyceride, LDL cholesterol apolipoprotein B, and apo B/apo A-I ratio as well as lipid peroxidation in subjects with hyperlipidemia (Sasaki, 1990; Ishihara, 1982).

Preclinical studies and in vitro studies have also found the same results. Three (3) Preclinical studies on a total of n=145 hypercholesterolemic hamsters and mice demonstrated that gamma-oryzanol reduced total cholesterol, non-HDL cholesterol and triacylglycerols levels (Arruda Filho, 2014; Rong, 1997; Wilson, 2007). One (1) In vitro study on Caco-2 human intestinal cells, demonstrated that gamma-oryzanol significantly inhibited the incorporation of cholesterol into synthetic micelles and decreased apical uptake of cholesterol (Makyen, 2001). Lastly, one (1) Review showed that rice bran oil and gamma-oryzanol can improve the plasma lipid pattern of rodents, rabbits, primates and humans; reduce total plasma cholesterol and triglyceride concentration and increase the high density lipoprotein cholesterol level (Cicero, 2001).

Summary

In summary, based on one (1) Grade-A study on RI-Fiber®, six (6) Grade-A studies on generic insoluble fiber, and three (3) Grade-A studies on generic stabilized rice bran and gamma-oryzanol, we believe that there is adequate substantiation for the claim of r*educes total cholesterol, LDL cholesterol, and triglycerides* for Rice Bran Technologies – RI-Fiber® at 20g/day, for generic insoluble fiber at 15g/day, and for generic stabilized rice bran/gamma-oryzanol at 50mg/day.

2) *Reduces absorption of cholesterol*

Insoluble fiber

One human clinical study and eight of ten preclinical studies have shown that insoluble fiber from various sources can reduce cholesterol absorption resulting in increased fecal cholesterol excretion. In particular, one (1) Grade-B study with a total sample size of n=8 healthy males, demonstrated that 3-6/day of water-insoluble chitosan for 14 days significantly increased excreted amounts of primary bile acids and deceased the resorption of bile acids, so that the cholesterol pool in the body was decreased and the level of serum cholesterol consequently decreased (Maezaki, 1993).

In addition, three (3) Preclinical studies on hamsters demonstrated that water-insoluble fiber-rich fraction (WIFF) isolated from the pomace of *Averrhoa carambola* and insoluble fiber rich fraction (FRF) from defatted *Passiflora edulis* seed and from carrot pomace, increased the concentrations of fecal total lipids, fecal cholesterol, and fecal bile acids and increased the fecal bulk and moisture (Chau 2004; Chau, 2005; Hsu, 2006). One (1) Preclinical study on hamsters demonstrated that the water insoluble fiber-rich fraction (WIFF) from pineapple peel enhanced the total amounts of short-chain fatty acid in the cecal content and the growth of gut microflora such as Lactobacillus spp and Bifidobacterium spp. (Huang, 2014). Moreover, one (1) Preclinical study on Male Sprague Dawley rats has found that young barley leaf powder containing water-insoluble dietary fiber fraction is the major component responsible for increased the fecal weight and volume (Ikeguchi, 2014). Also, one (1) Preclinical study on rat experimental model of diet-induced hypercholesterolemia demonstrated that insoluble fiber residue increased fecal fat excretion (Kapravelou 2013). Furthermore, one (1) Preclinical study on n=16 male Golden-Syrian hamsters found that oat bran containing 5.7g insoluble fiber and 4.2g soluble fiber for 4 had the highest total fecal cholesterol excretion among fiber groups (Jonnalagadda 1993). One (1) Preclinical study on a total of n=60 hamsters demonstrated that Cholazol H, a chemically functionalized insoluble fiber, produced a significantly greater concentration of fecal total bile acids (Wilson, 1998). However, two (2) Preclinical study on rat found that the soluble fraction isolated from bilberry, black currant, and raspberry or from guar resulted in lower amounts of liver cholesterol and greater amounts of cecal short-chain fatty acids compared to the insoluble fraction (Jakobsdottir, 2014; Isken, 2010).

Gamma-oryzanol/Rice Bran

Furthermore, two preclinical studies have shown that gamma-oryzanol can reduce cholesterol absorption. One (1) Preclinical study on n=32 hypercholesterolemic hamsters demonstrated that gamma-oryzanol for 8.5 weeks resulted in 25% reduction in percent cholesterol absorption compared to control animals (Rong, 1997). One (1) Preclinical study on n=48 hamsters found that rice bran oil with gamma-oryzanol for 10 weeks resulted in the increase of fecal excretion of cholesterol and its metabolites (Wilson 2007).

Summary

In summary, although there are several preclinical studies which could support the claim of *reduces absorption of cholesterol*, there is only 1 grade-B human study on generic insoluble fiber and there are no human studies on Rice Bran Technologies – RI-Fiber®, generic rice bran nor gamma-oryzanol relating to reduction of absorption of cholesterol, therefore claims as they pertain to direct effect on humans cannot be substantiated.

3) *Reduces plasma lipid and lipoprotein cholesterol*

RI-Fiber®

There is one (1) Grade-A study, consisting of a total sample size of n=68 Type I and n=80 Type II diabetes patients, which demonstrated that stabilized rice bran fiber concentrate administered at 20g/day for 8 weeks can improve serum total cholesterol, LDL cholesterol, apolipoprotein B, and triglycerides levels (Qureshi, 2002).

Insoluble fiber

Six human clinical studies, two preclinical studies and three reviews have shown that insoluble fiber consumption can reduce lipid and lipoprotein cholesterol levels. Specifically, one (1) Grade-A study consisting a total sample size of n=130 subjects free of diabetes mellitus, found that insoluble fiber from *Aspergillus niger* mycelium, CG for 6 weeks at 4.5g/day significantly reduced oxidized LDL compared with placebo. Moreover, CG at 1.5 g/day significantly lowered LDL cholesterol (Bays, 2013). One (1) Grade-A study consisting a total sample size of n=19 healthy subjects found that insoluble fiber from carob fiber at 50g/day increased plasma ghrelin accompanied by enhanced lipid metabolism suggesting higher lipid utilization and suppressed lipolysis (Gruendel, 2007). One (1) Grade-B study on patients with Type 2 diabetes demonstrated that diet containing food rich in soluble and insoluble fiber had significant improvements in lipid panels when compared with patients who consumed a diet with moderate amounts of fiber (McIntosh, 2001). One (1) Grade-B pilot human study on a total sample size of n=30 subjects with slight hypercholesterolemia found that 4.5 g of chitin-glucan/day for 4 weeks decreased oxidized LDL after 4 weeks of treatment (Deschamps, 2009). One (1) Grade-B prospective study has found that water-insoluble fiber intake is positively associated with low-density lipoprotein levels (Lin, 2014). Moreover, one (1) Grade-B prospective study, with a total sample size of n=51,529, showed that intake of insoluble fiber (from whole grains) has an inverse association with hypertension as it reduces cholesterol levels (Flint, 2009).

One (1) Preclinical study on a total of n=32 rats found that insoluble fiber from Jabuticaba [Pliniajaboticaba (Vell.) Berg] skins at 27.51g/100g for 4 weeks reduced lipid peroxidation (oxidized LDL) in the liver by about 50% (Fonseca, 2014). In addition, one (1) Preclinical study on n=6 mice found that insoluble fiber intake from chitosan or cellulose at 7.5% for 3 weeks prevented the increase in serum cholesterol due to high fat/high cholesterol diet (van Bennekum, 2005). Moreover, three (3) Reviews

showed that also insoluble/non-digestible fibers can reduce cholesterol and have favorable effects on fasting and postprandial serum lipoprotein levels although it was also notable that soluble fibers appear to have a greater potential to alter serum lipid levels than do insoluble fibers (Anderson, 1999; Glore, 1994; Tungland, 2002).

Gamma-oryzanol/Rice bran

Five human studies and three preclinical studies have also shown that rice bran and gamma-oryzanol can reduce plasma lipid and lipoprotein cholesterol levels. Two (2) Grade-A studies, consisting of a total sample size of n=55 have shown that the addition of stabilized rice bran in the diet of hyperlipidemic adults significantly reduced serum total cholesterol levels, LDL cholesterol, VLDL cholesterol, and apoB (Gerhardt, 1998; Hegsted, 1992). Moreover, one (1) Grade-A study, consisting a total sample size of n=30 mildly hypercholesterolemic men, found that rice bran oil containing 0.05 or 0.8 g/day gamma-oryzanol for 6 weeks reduced total plasma cholesterol, LDL cholesterol and the LDL:HDL ratio (Berger, 2005). Two (2) Grade-B open-label studies, consisting of a total sample size of n=60, have shown that gamma-oryzanol administration at 300mg-1500mg/day significantly reduced total cholesterol, triglyceride, LDL cholesterol apolipoprotein B, and apo B/apo A-I ratio in subjects with hyperlipidemia (Sasaki, 1990; Ishihara, 1982).

Preclinical studies and in vitro studies have also found the same results. Three (3) Preclinical studies on a total of n=145 hypercholesterolemic hamsters and mice demonstrated that gamma-oryzanol reduced total cholesterol and non-HDL cholesterol (Arruda Filho, 2014; Rong, 1997; Wilson, 2007). Lastly, one (1) Review showed that rice bran oil and gamma-oryzanol can improve the plasma lipid pattern of rodents, rabbits, primates and humans; reduce total plasma cholesterol and triglyceride concentration and increase the high density lipoprotein cholesterol level (Cicero, 2001).

Summary

In summary, based on one (1) Grade-A study on RI-Fiber®, two (2) Grade-A studies on generic insoluble fiber, and three (3) Grade-A studies on generic stabilized rice bran and gamma-oryzanol, we believe that there is adequate substantiation for the claim of *reduces plasma lipid and lipoprotein cholesterol* for Rice Bran Technologies – RI-Fiber® at 20g/day, for generic insoluble fiber at 1.5g/day, and for generic stabilized rice bran/gamma-oryzanol at 0.8g/day.

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