



Probiotic *Lactobacillus reuteri* NCIMB 30242
(**LRC™**) for Heart Health Benefits



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HEALTHY IS HAPPY: *Lactobacillus reuteri* NCIMB 30242 (LRC™) heart health benefits help keep your heart healthy and happy.

PROBIOTIC *LACTOBACILLUS REUTERI* NCIMB 30242 (LRC™) FOR HEART HEALTH BENEFITS

Introduction

Cardiovascular disease is considered the principal global cause of morbidity and mortality by the World Health Organization (WHO 2011). In the United States, one in three deaths occurs as a result of CVD; half of these due to coronary artery disease (CAD). Estimated costs associated with CVD and stroke in the United States reached nearly \$300 billion in 2008 and are projected to triple by 2030 (Roger et al. 2012). Cardiovascular disease is a progressive disease that starts in childhood and manifests itself with aging. A number of modifiable risk factors have been identified; adopting healthy and therapeutic lifestyle habits is an important part of managing cardiovascular risk and reducing costs associated with the disease (WHO 2007; Lichtenstein et al. 2006; Grundy et al. 2002; Grundy et al. 2004). A healthy lifestyle comprises a range of habits including: maintaining a healthy body weight, regular physical activity, consuming an overall healthy diet, reducing intakes of saturated fats, trans fatty acids and cholesterol, avoiding the use of tobacco products and routine medical check-ups for blood pressure and cholesterol (WHO 2007; Lichtenstein et al. 2006; Grundy et al. 2002; Grundy et al. 2004). While sharing the same facets as a 'healthy lifestyle', a 'therapeutic dietary lifestyle' also includes consuming foods and supplements that help maintain healthy cholesterol levels that are already in the normal range.

Cholesterol fulfills multiple functions in the body, forming part of cell membranes, hormones, and detergents that solubilize consumed fats. Ingested or produced by the organism, cholesterol transits the

digestive and vascular systems and is transported through arteries and veins to its metabolic destinations in lipoproteins, such as LDL-C and HDL-C. Elevated LDL-C (“the bad cholesterol”) is a major risk factor for CAD and is the primary target for lipid-lowering therapy (Grundy et al. 2002; Grundy et al 2004; Grundy et al. 2008). LDL-C has been shown to initiate and promote the progression of the disease, including plaque formation, growth, destabilization and rupture (WHO 2011; Grundy et al. 2008). Additional risk factors or predictors of CAD include inflammatory markers such as fibrinogen (a precursor of the blood clot component fibrin), and C-reactive protein (hs-CRP, a protein that is present at high levels in inflammation). While inflammatory risk factors are of importance, targeting them for therapy is considered secondary to LDL-C (Grundy et al. 2002). Further, cholesterol lowering therapies aimed at LDL-C often reduce inflammation through interrelated or independent mechanisms.

Understanding the gastrointestinal (GI) system and its interaction with resident microorganisms may provide possible means to support heart health. The GI lining consists of a surface with an estimated area of the size of a football field with great access to the circulatory system due to its high irrigation. The GI tract is exposed to a multitude of resident, non-harmful, microorganisms called “the gut microbiome”, distributed throughout its length that include bacteria, fungi and viruses. The microbial genes in the gut outnumber their human counterparts by 150-fold and many of these genes help their host organism to perform metabolic functions. In fact, many essential processes that take place in the gut are performed by our resident microorganisms and would not occur in their absence. Probiotic bacteria are defined as “live microorganisms that when administered in adequate amounts confer a health benefit on the host” (WHO/FAO 2002). This definition has undergone a recent review with a slight grammatical change, resulting in a working definition of “Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host” (Hill et al. 2014). These species may interact and alter the GI flora or release a number of molecules including enzymes that can improve digestion, metabolism, positively influence the immune system, and even affect the nervous system to control pain (Hord et al. 2008; Sanders et al. 2013). Probiotics have gained great interest among consumers of health products, physicians, and scientists, and a remarkable research focus is examining the role of these microorganisms on metabolic functions.

Bile Salt Hydrolase Active Bacteria and Cholesterol Management

Bile acids are natural detergents synthesized in the liver from cholesterol, stored in the gall bladder, and released into the duodenum with the purpose of transporting dietary fat and other ingested lipophilic compounds into the circulation. Bile acids get reabsorbed in the distal ileum and return to the liver with only a small percentage being eliminated through feces. In order to improve their solubility, bile acids can get conjugated to hydrophilic compounds such as glycine, and thus form conjugated bile acids. Bile salt hydrolase (BSH) is an enzyme present in many commensal bacteria that breaks down conjugated bile acids in the luminal side of the GI. Bile acid deconjugation has been implicated in several key transcriptional changes in circulation, liver and the GI tract. As bile acids deconjugate, hydrophobicity increases and cholesterol absorption is affected, which can influence LDL-C levels in blood. Recent evidence shows that deconjugated bile acids are natural ligands of the farnesoid X receptor (FXR), a nuclear receptor present mainly in enterocytes and hepatocytes that plays an important role in the regulation of cholesterol uptake, metabolism, synthesis and efflux (Matsubara et al. 2013). In the intestines, this stimulation helps reduce lipid absorption. In the liver, FXR helps decrease bile acid uptake and stimulates elimination of bile acids and cholesterol by increasing expression of ATP-binding cassette (ABC) transporters from the liver to the gall bladder. Of note, mice colonized with active BSH bacteria resulted in significantly reduced weight gain, plasma cholesterol and liver triglycerides (Joyce et al. 2014).

LRC™ Is A Highly BSH-Active Probiotic And Has Been Extensively Characterized

Lactobacillus reuteri NCIMB 30242, or LRC™ was selected from a screening for BSH activity of over 100 strains, based on the aforementioned rationale. The strain has been named LRC™ and is currently deposited in the National Collection of Industrial and Food Bacteria international culture collection. LRC™ has been fully characterized both genotypically and phenotypically. The strain did not show any resistance to tested antibiotics with minimum inhibitory concentrations at or below the established guidelines of the European Food Safety Authority (EFSA 2012). A careful analysis of the genomic sequence revealed no virulent genes, extra chromosomal DNA or mobile elements (Branton et al. 2011). In addition, the strain tested negative for production of the antimicrobial agent reuterin, as typically released by other *L. reuteri*. Furthermore, co-administration of indicator microorganisms with LRC™ ferments did not result in growth inhibition, in contrast with ferments of positive controls, implying that the selected BSH-active strain is unlikely to produce the bacterial bacteriocin. Finally no detectable release of biogenic amines such as histamine, tyramine, putrescine and cadaverine was observed in growth media fermented by LRC™.

An evaluation of the resistance of LRC™ to biological fluids was performed to help functionally characterize the strain. LRC™ showed superior resistance, as compared to commercial reference strains, when exposed to biological processes, including human and simulated gastric juice, simulated pancreatic secretion and human bile. Further, the long-term stability and suitability of LRC™ was confirmed in various commercial environments (Roy et al. 2016). Safety of LRC™ was evaluated in vivo in rats and hamsters over a period of up to 8 weeks. No changes were observed in weight, animal activity, hematological parameters and serum chemistry markers (unpublished observations). Finally, histological analysis of tissues from major organs collected at necropsy at the end of these studies showed no pathologies.

Clinical Safety of LRC™

Clinical safety of LRC™ was thoroughly evaluated in randomized controlled trials (Jones et al. 2012c, Jones et al. 2012d). No serious adverse events were reported in either test group during the course of these studies. Additionally, no effects in weight, body mass index (BMI), systolic and diastolic blood pressure, heart rate or oral temperature were observed. Hematological parameters (RBC, WBC, hematocrit, hemoglobin, and platelets) showed no changes over the duration of the studies and no clinical significance was observed in the changes of blood chemistry parameters (urea, ALT, AST, GGT, alkaline phosphatase, bilirubin, creatinine, lipase, glucose, calcium, potassium, sodium, and chloride) before and after at least 9 weeks of use.

Regulatory Status of LRC™

Numerous strains of *L. reuteri* have a long history of safe use in the food industry as a fermentation culture for the production of sourdough breads. Various strains of *L. reuteri* also have a history of safe use in food and supplement probiotic products. LRC™ has been issued a product license by Health Canada's Natural and Non-prescription Health Products Directorate (NNHPD) based on its heart health properties. Products with a license have been assessed by Health Canada and found to be safe, effective and of high quality under their recommended conditions of use. It is identifiable by its Natural Product Number (NPN 80038469). Furthermore, LRC™ has self-affirmed Generally Recognized as Safe (GRAS) designation in the United States (U.S. Food and Drug Administration) and a full FDA GRAS notification has been completed (GRN No. 440, No NDI is required).

In the European Union, the *L. reuteri* probiotic species has Qualified Presumption of Safety (QPS) status. This assessment process recognizes that many microorganisms have long-histories of safe use by the food industry, and is based on four essential pillars of information: established identity, body of knowledge,

possible pathogenicity, and end use. The European Food Safety Authority (EFSA 2008) concluded that the current food and feed uses of *L. reuteri* do not present cause for safety concern, and QPS status was granted for the species (EFSA 2008). In Australia, the *L. reuteri* probiotic species is on the Therapeutic Goods Administration's (TGA) approved list of medical ingredients (Therapeutic Goods Administration 2007). Lastly, the *L. reuteri* probiotic species is listed in the Inventory of Microorganisms With Documented History of Use in Human Food (Mogensen et al. 2002) as well as the list of Microorganisms with Technological Beneficial Use (Bourdichon et al. 2012).

FREQUENTLY ASKED QUESTIONS

What Is LRC™?

LRC™ (*Lactobacillus reuteri* NCIMB 30242) is an award-winning, effective and clinically documented probiotic strain. With multiple patents and more pending, LRC™ is shown to naturally support:

- Healthy total and LDL-cholesterol levels (Jones 2012a,b,c,d) already within the normal range.
- Healthy Vitamin D levels in blood (Jones 2013a).
- Healthy levels of the biomarkers hs-CRP and fibrinogen (Jones 2012b).
- LRC™ may also help promote overall digestive health and help maintain a healthy digestive system (Jones 2013b).

How Was LRC™ Discovered?

LRC™ was discovered through ProSelect, UAS Labs' proprietary discovery enabling technology that identifies non-GMO probiotic candidates with the potential to promote better metabolic health and natural balance through the microbiome. LRC™ was carefully selected for its ability to naturally help support total and LDL-cholesterol levels already within the normal range.

Is LRC™ A Supplement Or An Ingredient?

LRC™ can be used both as a supplement and as an ingredient. As a supplement, LRC™ can be utilized for its heart healthy properties on its own, or in combination with a wide array of vitamins, minerals or other heart healthy ingredients including CoQ₁₀, fiber, and phytosterols.

LRC™ can also be used as an ingredient in a variety of functional food items. Please see below for more information on how.

Is LRC™ Safe?

Yes. LRC™ is a natural, over-the-counter probiotic supplement and ingredient for a wide range of foods and beverages that is safe to consume daily (Jones 2012c; Jones 2012d). *L. reuteri* are used frequently and have a long history of safe use within foods.

- LRC™ is Generally Recognized as Safe (GRAS) by U.S. Food and Drug Administration (US FDA, GRN440).
- Health Canada has determined that LRC™ is not a novel food and has approved a Product License Application for LRC™ (Health Canada. Natural Product Number 80038469).
- Food Standards Australia New Zealand has determined LRC™ is not a novel food.
- LRC™'s probiotic species, *L. reuteri*, has Qualified Presumption of Safety (QPS) status in Europe (EFSA 2008) and is on the Therapeutic Goods Administration's approved list of medicinal ingredients in Australia (TGA).

In fact, in infant formula trials, *Lactobacillus* species including *L. reuteri*, have been shown to be safe and well tolerated by infants (Alsheikh 2005; Alsheikh 2006).

How Does LRC™ Work?

LRC™ healthy bacteria supports healthy total cholesterol and LDL-cholesterol levels in two possible ways:

1. By helping keep the amount of cholesterol your body produces within healthy ranges.
2. By supporting your body's natural elimination of cholesterol.

LRC™ produces an enzyme called bile salt hydrolase that deconjugates bile acids. These bile acids are neutral detergents made by the liver from cholesterol and are released into the intestine with the purpose of transporting dietary fat and cholesterol into the circulation. As bile acids are naturally deconjugated by LRC™ in the intestines, dietary and biliary cholesterol absorption is normalized by the body, and the recirculation of bile is altered helping keep LDL-C levels already within normal ranges in blood.

What Does The Science In LRC™ Show?

- LRC™ is a natural probiotic that has been shown in peer reviewed and published clinical trials to safely support healthy mean LDL-cholesterol levels, already within the normal range, as compared to the placebo (Jones 2012a; Jones 2012b).
- Two well-powered randomized double-blind, placebo controlled, multicenter trials have shown that LRC™ supported healthy total and LDL-cholesterol levels already within a normal range in adults (Jones 2012a; Jones 2012b).
- In all clinical trials performed, LRC™, was shown to help support healthy cholesterol levels already within the normal range in adults when consumed at only 200 mg a day. Most dietary cholesterol management products (phytosterols, soluble oat fibers and soy protein) require consumption between 2-25 g (equal to 2,000-25,000 mg) per day (Demonty 2009).
- The ability of LRC™ to support healthy blood C-reactive protein levels is demonstrated (Jones 2012b).
- LRC™ is the first and only probiotic to clinically demonstrate support for healthy vitamin D levels in blood (Jones 2013a).
- LRC™ natural bacteria may help to promote overall digestive health and help maintain a healthy digestive system (Jones 2013b).

Can LRC™ Be Used In Functional Foods?

LRC™, is an effective and well documented heart health probiotic strain. It has been shown to naturally support healthy cholesterol levels already within a normal range in multiple gold standard, double-blind, placebo controlled clinical trials (Jones 2012a; Jones 2012b).

What makes LRC™ unique in terms of probiotic bacteria, is that it can be added as an ingredient to a wide array of dairy-based functional food products, effectively lending its heart healthy properties to the medium it is included in.

The plan to use LRC™ to create heart healthy functional foods is supported by data suggesting the strain is suitable for use in such products. Not all probiotics have such formulation flexibility. A probiotic strain can be effective when it is freeze-dried in capsule form, but ill-suited for use in foods. Issues with quality, quantity and storage can render probiotics ineffective or non-viable in foods. Equally, some strains affect the taste and texture of the food, making it undesirable.

LRC™ has come through multiple tests suggesting it is unaffected by these shortcomings. The first randomized controlled trial showed LRC™ supports healthy levels of cardiovascular health biomarkers already within a normal range when formulated in a yogurt. Data from the yogurt clinical trial were comparable to those generated by the study of LRC™ in capsule form.

Subsequent formulation studies found LRC™ is a good candidate for addition alongside the starter culture

or after the yogurt has been through this initial process. Adding a probiotic to the starter culture enables formulators to use less of the strain — as it grows with the yogurt — but some formulators prefer to add it later. LRC™ gives companies both options.

UAS Labs has also looked at how LRC™ copes with the commercial storage conditions of yogurts and consumption in this formulation. One study showed levels of LRC™ remain high throughout the shelf life of yogurts when kept in real-world conditions (Champagne 2016). Another project found LRC™, a hardy strain in itself, survives simulated gastrointestinal transit even better when formulated in yogurt (Champagne 2015). This performance is the result of the extra buffering from stomach acid provided by the yogurt.

Buoyed by these findings, UAS Labs has looked at how LRC™ copes with being formulated into fruit juices and soy-based beverages. As fruit juice is acidic and soy-based beverages are alkaline, these formulations present contrasting challenges to probiotic strains. LRC™ coped well with both environments (Roy 2016)..

Over 60 days in a fruit juice with a starting pH of 3.9, LRC™ experienced minimal losses, suggesting the formulation is commercially viable. Stability in the soy-based beverage was better still. Potency in the soy-based drink was virtually the same after 60 days as it was at the start of the study. Importantly, strain survival rates in both formulations were comparable regardless of whether the product was kept at 4 or 8 degrees Celsius (Roy 2016).

In addition to yogurts, soy beverages, and fruit juices, LRC™ has been found to be viable in additional functional food items such as frozen dairy desserts, chocolates, and oils.

Does LRC™ Have Anything To Do With The Microbiome In The Gut?

Yes, LRC™ is the most researched probiotic that has been shown to naturally help support total cholesterol and LDL-cholesterol levels, already within the normal range, through the microbiome in the gut. Scientific and public health leaders from around the world are putting significant effort into better understanding the microbiome, and its role and impact on human health. Emerging science is evaluating whether the microbiome, and gut bacteria specifically, can play a role in health and specifically heart health. Probiotics (live healthy bacteria that confer a health benefit to the host) are being studied to determine if they may have a role in improving specific health markers to maintain and improve health and wellness through the gut.

Who Can Benefit from LRC™?

Many adults are interested in natural ways of maintaining healthy cholesterol levels that are already within the normal range. Also, healthy people who like the digestive benefits of probiotics and are also interested in maintaining healthy and normal levels of cholesterol already within the normal range may benefit from LRC™.

Where is LRC™ Sold?

LRC™ is available now through UAS Labs (www.uaslabs.com) or contact sales at sales@uaslabs.com.

What Formats is LRC™ Available In?

- 20 kg drums of freeze dried powder at 50 billion CFU/g or more
- 1 kg bags of frozen pellets at not less than 20 billion CFU/g
- 24 months, frozen in original sealed package

Questions About LRC™?

To learn more visit www.uaslabs.com/LRC or email us at sales@uaslabs.com.

ABOUT UASLabs

Founded in 1979, UAS Labs, LLC has delivered the highest quality, science-backed probiotics to the marketplace for more than thirty years. Strictly dedicated to probiotic manufacturing, UAS Labs is committed to designing innovative and effective formulations including strains such as *Lactobacillus acidophilus* DDS®-1 and patented superstrain LRC™ for cholesterol support. This GMP and organic certified company is fully integrated from formulation through manufacturing, packaging and marketing, and adheres to the highest quality standards.

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