Obesity has become a worldwide health concern with a constantly rising prevalence. Obesity is defined by WHO as excess weight gain for a given height with BMI ≥ 30 kg/m^2. The prevalence of obesity in the US is 31%. Obesity is associated with increased cardio-metabolic risk, insulin resistance, type 2 diabetes due to increased cytokine production and sub-clinical inflammation. Besides diet and exercise, gut microbiome has been recognized as a major factor in the pathophysiology of obesity and dysbiosis can contribute to the pathophysiology of obesity.

Recent research results have suggested that the shift from healthy symbiosis to persistent dysbiosis can increase bacterial metabolites, such as short-chain fatty acids (SCFAs) causing host energy homeostatic changes, and elevate bacterial components, such as lipopolysaccharides (LPS) triggering low-grade inflammation leading to excess fat deposition and resultant obesity.

1. Dysbiosis causes increased diet energy extraction leading to obesity

Healthy human gut microbiota consists of over 1000 phylotypes classified into six bacterial phyla shown in Table 1: Firmicutes, Bacteroidetes, Proteobacteria, Fusobacteria, Actinobacteria and Verrucomicrobia. Gut microbiota comprises mainly (>90 %) Firmicutes and Bacteroidetes. The Firmicutes are Gram-positive bacteria including *Lactobacillus*, *Mycoplasma*, *Streptococcus* and *Clostridium*, while Bacteroidetes are Gram-negative bacteria and include about twenty genera and species, such as, *Bacteroides thetaiotaomicron*. Most of these organisms are usually benign inhabitants of the intestinal ecosystem coexisting with the host in a commensal and symbiotic relationship. But, a few can be pathogenic especially when they gain access to the circulation or peritoneal cavity.

Phylum	Genera	Change trend
Firmicutes	*Bacillus*	↑
	Clostridium	↑
	Lactobacillus	↓
Bacteroidetes	*Bacteroides*	↓
	Prevotella	↑
Actinobacteria	*Bifidobacterium*	↓
Verrucomicrobia	*Akkermansia*	↓
Euryarchaeota (domain archaea)	*Methanobrevibacter*	↑

Table 1. Obesity-associated changes in gut microbiota

The composition of the gut microbiota is relatively diverse in healthy individuals. However, obese people are associated with a low bacterial gene count with a reduced proportion of Bacteroidetes and higher levels of Firmicutes. Increased Firmicutes is associated with energy intake than expended by the body causing weight gain and obesity. Research results have suggested that obesity due to energy imbalance is determined by the Firmicutes:Bacteroidetes (F:B) ratio. Obese gut microbiota exhibit significantly elevated F:B ratio while lean gut microbiota show preponderance of Bacteroidetes (up to 50 % more). Some obese individuals have shown up to 90 % less Bacteroidetes and much more Firmicutes than lean individuals. Consumption of high-fat/carbohydrate diet favors increased Firmicutes dominance.

Firmicutes play a significant role in the relationship between gut bacteria and human health and Firmicutes dominance can significantly increase energy harvest from diet. Firmicutes consists of diverse members. Many members including Lactobacillus, Faecalibacterium, Eubacterium, Roseburia, and Anaerostipes are capable of efficiently ferment dietary fiber and resistant starch to produce metabolites such as short-chain fatty acids (SCFAS),

like butyrate, acetate, and lactate. Butyrate has many health benefits and helps prevent gut inflammation and fuels the gut lining cells. However, enhanced energy extraction from the diet can cause corresponding weight gain and obesity. In contrast, consumption of low fat and sugar diet increases Bacteroidetes dominance, which encourages weight loss by stimulating increased expression of fasting-induced adipocyte factor (FIAF) and subsequent increase in energy expenditure and reduced fat storage.

2. Dysbiosis promotes chronic inflammation causing liver inflammation, insulin resistance causing obesity

Among the Firmicutes members, some of them are some pathogenic gram-positive species. For example, Staphylococcus aureus is a common cause of serious infection. Some other pathogenic members produce bacterial endotoxins which can cause chronic low-grade inflammation of the gut due to the initiation of sub-clinical, persistent innate immune response. Such low-grade gut inflammation can disrupt the tight-junction of the intestinal epithelium cause increase permeability which allow enhanced passage of bacteria and bacterial LPS to the circulation. LPS is able to activate macrophages in different organs including adipose tissue and the liver resulting in the production of proinflammatory factors (factor nuclear Kappa B; NF-κB) and macrophage infiltration in adipose tissue. Adipocytes inflammation trigger systemic low-grade inflammation by releasing increased levels of proinflammatory mediators such as TNF-*α*, IL-1 and IL-6. These cytokines stimulate further release of cytokines and chemokines leading to lipogenesis and obesity by acting on adipocytes in a paracrine and/or autocrine fashion.

Insulin resistance plays a key role in the development of obesity. Insulin regulates blood glucose by stimulating glucose uptake and utilization by muscle and adipose tissues and inhibit hepatic glucose production. Increased cytokines such as TNF-*α* and IL-6 released by adipocytes are able to block the key step of insulin signal transduction with reduced glucose uptake causing insulin resistance especially in muscle. Inflamed adipocytes also secrete hormones such as Resistin which can reduce glucose uptake causing insulin resistance in adipose tissue.

Enlarged adipocytes output increase FFAs into circulation and result in more TAG stored in the liver causing fatty liver disease leading to insulin resistance. Excess triglycerides act as *a* toxin to liver cells and cause liver inflammation leading to increased glucose and VLDL output into the blood, since excessive triglycerides in the liver can activate specific enzymes that interfere with a key step of insulin signal transduction pathway and, therefore, impairs insulin action resulting in hepatic insulin resistance with increased hepatic glucose and VLDL output.

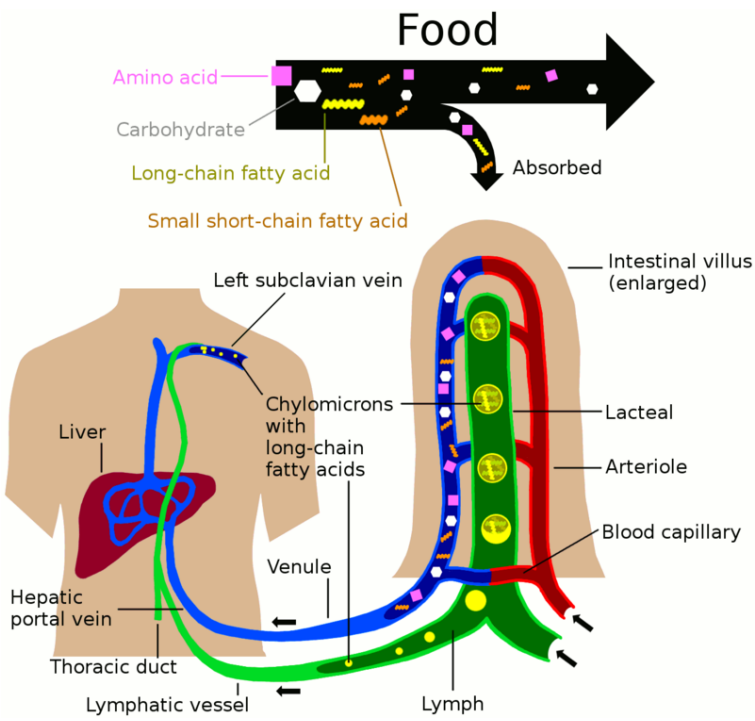
Increased blood sugar levels due to impaired insulin function stimulates the pancreas to secrete more insulin to control the blood sugar levels. Increased insulin levels enhance more free fatty acid delivery to the liver and further increase hepatic fat accumulation. Dysregulation of insulin function in adipose tissue can further increase its release of inflammatory signals. The combination of these processes creates a vicious cycle of metabolic dysfunction leading to obesity, hyperlipidemia and type II diabetes.

Increased insulin levels also suppress fasting-induced adipocyte factor (FIAF) expression in adipose tissue. Fat metabolism and storage is regulated by FIAF expressed in adipose tissue. Fat storage in peripheral white adipose tissue or lipogenesis is catalyzed by lipoprotein lipase. FIAF inhibits lipoprotein lipase activity and stimulates white adipose tissue lipolysis leading to a reduction in adipose tissue mass. Insulin suppresses FIAF activity and increased insulin levels due to insulin resistance block the lipolysis process causing obesity.

3. Dysbiosis causes GI lymphatic dysfunction and obesity

A number of recent studies have shown that obesity is associated with lymphatic dysfunction and vice versa – lymphatic dysfunction promotes obesity. Lymphatic system functions as the 'sewage system' by removing body fluid and metabolic wastes from the cells and returning them to blood circulation. The lymphatic network consists of blind-ended capillaries located in most tissues that funnel into progressively fewer and larger pre-collecting and collecting vessels.

Lymphatics in the gut perform essential transport and serve as a second line of defense against possible bacterial infections. In addition to collecting fluid, gut lymphatics also absorbs and transports dietary lipids through lymphatic capillaries, called lacteals, in the intestinal villi. Most types of dietary nutrients including small and medium chain fatty acids are absorbed and entered to the portal vein for liver processing. Dietary fats are converted by intestinal enterocytes into triglyceride-rich lipoproteins enveloped by proteins and cholesterol, which are called chylomicrons, and are absorbed and transported by the intestinal lacteals. The collected chylomicrons pass through the mesenteric lymph nodes, ultimately draining into the venous circulatory system via the thoracic duct, bypassing the portal system.



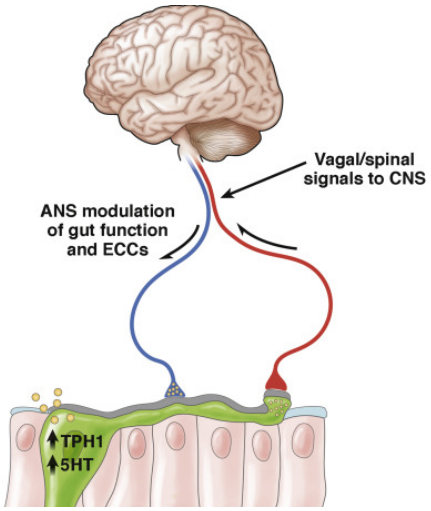
Throughout the body, lymphatics are anatomically co-localized with adipose tissue. Major lymphatic vessels are always surrounded by adipose tissues and lymph nodes are maintained in thick fat pads even in highly lean individual.

Damage to the intestinal epithelial cells due to bacterial infection and/or inflammation allows passage of bacterial pathogens and LPS into the villi interstitial space and subsequent drainage to the lymphatic system. The lacteals wall is not able to selectively avoid these toxins allowing entrance into the lymphatic circulation causing damage to the lymphatic vessels leading to lymph leakage into the surrounding visceral adipose tissue. Lymph leakage triggers adipose tissue inflammation and stimulates adipose tissue proliferation resulting in weight gain in the abdomen.

The interaction between obesity and lymphatic dysfunction is bi-directional not only in the abdomen but also on a systemic level. Once the obesity process starts, circulation of the free fatty acid levels in the lymph will be elevated including oleic acid, α-linoleic acid, and palmitic acid. Free fatty acids have toxic effects to the epithelial lining of the lymphatic vessels and induce systemic lymphatic system inflammation which causes reduced lymphatic circulation, lymphatic vessel leakage, and lymphedema. Markedly impaired lymphatic function caused by obesity leads to further worsening of the obesity condition.

4. Dysbiosis causing Food cravings and obesity

The enteric nervous system (ENS) senses and reacts to the dynamic ecosystem of the GI tract. The ENS communicates to the brain via brain-gut-axis which includes the vagus nerve and autonomic nervous system (ANS). Signals flow in both directions. The brain-gut axis is involved in many regular functions and systems within our body, including the regulation of eating.



When food arrives in the stomach, certain appetite-suppressing hormones peptide hormones such as cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), and peptide YY (PYY) are secreted by the neuroendocrine cells in the ileum and colon in response to protein and fat intake, carbohydrate intake, and fat and fermentable carbohydrate intake respectively. They either bind to the receptors in the vagus nerve terminals relaying satiety signals to the hypothalamus to suppress appetite or directly to the receptors in the CNS to

generate satiety signals. When the body needs food on an empty stomach, the peptide hormone, Ghrelin is released from cells in the gastric mucosa to generate the feeling of hunger. Ghrelin exerts its effects through binding to the ghrelin receptor, called growth hormone secretagogue receptor (GSHR) in the vagal afferent system.

There is growing evidence to support the role of gut microbiota in influencing food craving through regulating the peptide hormone expression and signaling pathway. The secretion and signaling of the GI peptide hormones that suppress or enhance appetite can be modulated by commensal bacteria present in our GI tract. Research focusing on the orexigenic hormone, ghrelin has revealed that the gut microbiota may directly or indirectly influence secretion of ghrelin, similar to the modulation of satiety inducing GI hormones. Changes in circulating ghrelin levels concomitant with specific gut microbiota changes. The gut microbiome impacts on ghrelinergic signaling through its metabolites by enhancing or attenuating the ghrelin receptor, GSHR activity. Dysbiosis can result in increased secretion and enhanced signaling of ghrelin and/or decreased secretion and suppressed signaling of GI hormones induced by satiety causing food craving and leading to the development of obesity.

Leptin is a peptide hormone synthesized by white adipose tissue in relation to the amount of body fat. Leptin's function in the body pertains to balancing food intake and energy expenditure by regulating appetite. Leptin's principal site of action is in the brainstem and hypothalamus where it modulates satiety and the control of reward and aversion. Leptin deficiency can lead to obesity. However, most obese subjects are not deficient in leptin, and the circulating levels of leptin are elevated compared to those in non-obese subjects reflecting a state of leptin resistance. Reduced sensitivity to leptin causes an increase in leptin levels and leads to the intake of extra calories and prevents sustained weight loss. Obesity, leptin resistance and insulin resistance are interrelated. Studies have suggested that hyperinsulinemia can be a potential cause of leptin resistance, eventually leading to obesity and metabolic syndrome.

Wellness Recommendation

To help patients achieve a healthy weight, Reduce 4 is recommended to address the root cause of obesity. Ingredients in Reduce 4 help reduce weight and support weight management through the following mechanisms.

1. Reduce gram-positive bacterial population and clear pathogenic bacteria to resolve gut dysbiosis

Berberine is a major herbal ingredient in Reduce 4. Berberine is a plant alkaloid with many therapeutic effects. Its anti-obesity action has also been well-documented. Berberine exhibits potent antibacterial activity against gram-positive bacteria and, therefore, helps reduce the population of gram-positive bacteria in the gut including pathogenic bacteria such as Streptococcus agalatiae. Berberine also enhances the expression of the AMPK-dependent adipose tissue triglyceride lipase leading to long-term weight loss and prevention of obesity. It helps regulate blood sugar level, LDL levels and decreases insulin resistance. It also has an anti-inflammatory properties which help reduce gut inflammation.

Herbal ingredient Rhubarb, also in Reduce 4, has been suggested as a long-term weight loss or management therapeutic. Rhubarb extracts and compounds have also shown strong broad-spectrum antibacterial activity against pathogenic Gram-negative bacteria, *E. coli* and *Aggregatibacter actinomycetemcomitans*, and Gram-positive bacteria, *S. aureus*. It preferentially kills slow-growing bacteria and has shown great potential as a strong bactericidal antibiotic and as an anti-proliferative drug.

Rhubarb also has shown preventative effects against high-fat/high-sucrose diet induced obesity, diabetes, visceral adiposity, adipose tissue inflammation and liver triglyceride accumulation, without any modification in food intake in animal models. Such prevention effect is associated with a blooming of *Akkermansia muciniphila,* which is strongly correlated with increased colon expression of *Reg3γ*, an antimicrobial peptide that maintains the distance between the gut bacteria and the host which prevents bacterial translocation and regulates intestinal inflammation. Rhubarb supplementation also helps maintain gut barrier integrity by increasing goblet cell number and mucus production.

Components such as hydroxyanthraquinones (HAQs), from rhubarb have been shown to exhibit antiadipogenic activity to lower the body's lipids and has been recommended as a potential therapeutic for obesity management. Rhubarb HAQs efficiently suppress lipid formation in differentiated adipocytes and promote fat loss in vivo. Rhubarb HAQs also exhibit superior inhibition of BUN, CRE, AST, ALT, and total cholesterol levels. The steatosis hypertrophy was significantly diminished by the treatment of rhubarb HAQs.

2. Reduce inflammation and insulin resistance

Herbal ingredients in Reduce 4 have also been shown to increase energy metabolism, lower total cholesterol, increase lipid export, and reduce fatty liver deposits. They help improve blood circulation through the hepatic artery to provide adequate oxygenated blood flow to the liver to improve the function and structure of the liver to help aid the breakdown of fats and increase insulin sensitivity to promote weight loss.

Red Peony Root has been shown to have powerful healing properties within the human body. It decreases pro-inflammatory cytokines and is commonly used in the treatment of chronic inflammatory conditions such as rheumatoid arthritis, systemic lupus erythematosus, and hepatitis. This herb can help reduce the low-grade inflammation and the resulting metabolic syndrome in obese patients. Research has also shown that the compound paeniflorin in Red Peony Root can help increase probiotic activity in the gut, which can help balance gut bacteria in the body and prevent intestinal inflammation.

Cassia obtusifolia seed have been used as an effective medicinal food for the prevention and improvement of fatty liver disease. Clinical research has shown that oral administration of processed Cassia obtusifolia seed powder reduces body weight and cholesterol in overweight patients. Compounds in Cassia obtusifolia seed can inhibit α-glucosidase and human protein tyrosine phosphatases 1B to restore insulin sensitivity.

Herbal ingredient King Solomonseal Rhizome has been shown to lower serum total cholesterol, triglyceride and fasting blood glucose, improve glucose tolerance test and insulin tolerance test.

3. Improve lymphatic circulation

Herbal ingredients in Reduce 4 have also been shown to help improve GI and systemic lymph fluid recycling and circulation to reduce lymph leakage and promote weight loss. In Traditional Chinese Medicine (TCM) terms, the herbs exert their effects by clearing phlegm damp and removing Qi stagnation.

Animal studies showed that Perilla Seed Oil alleviates gut dysbiosis, intestinal inflammation and metabolic disturbance in obese-induced-insulin-resistant rats. Treatment with Perilla Seed Oil not only effectively attenuated HFD induced gut dysbiosis, but also improved gut barrier integrity and decreased gut inflammation. It helps decrease oxidative stress, metabolic endotoxemia, and insulin resistance. Improved gut integrity will in turn help the GI lymphatic system to avoid toxin damage and restore its normal functionality.

White mustard seeds have been traditionally used as a weight loss ingredient which also has various health benefits. It helps stimulate the lymphatic system for improved lymphatic drainage which helps reduce lymph edema and swelling to aid in weight loss. Mustard seeds contain compounds that help increase metabolism and help the body burn more calories to support weight loss. Mustard seeds are rich in compounds that can help reduce appetite and cravings to help reduce overall calorie intake. It also helps regulate blood sugar levels, preventing spikes and crashes in energy levels and improve digestion and promote healthy bowel movements. Mustard seeds contain anti-inflammatory compounds, which can help reduce inflammation to aid in weight loss.

Qiancao, also known as Rubia Cordifolia Root, has powerful beneficial effects on the lymph system and has been known as a powerful lymph cleanser. This bitter, astringent herb was traditionally used and valued for its extreme effectiveness in cleansing and purifying the blood, liver, and lymphatic system. It supports the lymphatic function by allowing nutrition to feed the cells and wastes to be removed from the body in an optimal fashion. It is known to

detoxify and cleanse the blood and the organs by helping the lymph system remove toxins from the body which ultimately leads to boosting the body's immune functions to help restore lymphatic structure and function.

4. Restore healthy appetite regulation

Herbal ingredients in Reduce 4 such as Berberine and rhubarb help reduce undesirable gut bacteria and inflammation. This may help alleviate the negative influence on the expression and signaling of GI peptide hormones to restore healthy appetite regulation and reduce food cravings. Herbal ingredient in Reduce 4 also have been shown to function as appetite suppressants to help reduce food intake to support weight loss.

Ginseng has been shown to have anti-obesity effects in high-fat diet-fed rats. Research on rats demonstrated that several ginsenosides reduce HFD-induced obesity and adipose tissue mass by controlling appetite and food consumption as well as attenuating HFD-induced chronic inflammation of the hypothalamus, improving leptin resistance, and regulating the hypothalamic secretion of neuropeptide Y and CCK.

Ginseng also demonstrated other health benefits which can be more beneficial to obese patients including reducing inflammation, lowering blood sugar and cholesterol levels, as well as reducing oxidative stress and increasing energy production in cells to help decrease fatigue. Ginseng possesses potent anti-bacterial, anti-fungal, and anti-viral properties and may enhance the function of the immune system.

Astragalus has also been shown to possess an anti-obesity effect in HFD fed mice by suppressing appetite and increasing leptin sensitivity by enhancing leptin signaling transduction. More specifically the components, Astragaloside IV in astragalus is able to prevent obesity and weight gain by enhancing expression of leptin and its receptors, as well as leptin sensitivity. Astragaloside IV also helps reduce blood sugar levels, lower serum triglyceride and total cholesterol levels, mitigate liver lipid accumulation, reduce fat tissues and decrease the enlargement of adipose cells. Astragalus also is used to protect and support the immune system through protecting the liver.

Expected Results and Timeframe

Patients can experience less bloating, better digestion, increased emotional stability and stress tolerance, enhanced energy levels, and a change in eating habits with less cravings for sugar, sweeteners and carbohydrates in 2-3 weeks and reduced body weight in 4-6 weeks. 3 months of the protocol is recommended for significant improvement in the body weight. It is recommended to continue taking Reduce 4 to help prevent weight gain.

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