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# Accumulating Body Flab as You Age? Help Stop It With This

Analysis by Dr. Joseph Mercola Fact Checked | June 08, 2022

## STORY AT-A-GLANCE

- Bilirubin inhibits NOX, a metabolic enzyme that reduces NADPH, which is the most important antioxidant recharging molecule in your body. Phycocyanobilin found in spirulina can inhibit NOX and increase NADPH
- Elevated bilirubin might aid weight control by preventing the development of leptin resistance, and spirulina may therefore be an effective way to combat leptin resistance
- Bilirubin also appears to have anti-inflammatory, antioxidant and atheroprotective properties, and spirulina mimics those effects as well
- Most overweight Americans have some degree of insulin and leptin resistance. This also includes diabetics and many with high blood pressure or high cholesterol
- If you fall into this category, it would be prudent for you to restrict fructose to about 15 to 25 grams per day from all sources. Spirulina supplementation may also be an effective treatment for leptin resistance

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In 2018, James DiNicolantonio, co-author of my book, "Superfuel," published a groundbreaking paper,[1] "Antioxidant Bilirubin Works in Multiple Ways to Reduce Risk for Obesity and Its Health Complications."

Bilirubin is a breakdown product of red blood cells (heme) and the chemical responsible for the yellow color of bruises, urine and jaundice.

In that paper, DiNicolantonio explains how bilirubin inhibits NADPH oxidase (typically abbreviated as NOX) — a metabolic enzyme activated in a large number of pathological conditions that generates a great deal of oxidative stress — and how phycocyanobilin found in spirulina can exert similar effects.

The reason for this is because the phycocyanobilin found in spirulina is rapidly reduced to phycocyanorubin, a close homolog of bilirubin, in mammalian cells.[2,3] In a follow-up paper[4] published March 2019, DiNicolantonio, et.al, propose that elevated bilirubin might aid weight control by preventing the development of leptin resistance, and discuss evidence suggesting spirulina may be an effective way to combat leptin resistance as well.

## Bilirubin Can Play a Role in Chronic Disease

When a newborn baby gets jaundice, he is placed under "bili lights" in the hospital nursery to prevent brain damage (kernicterus), should his bilirubin levels become too high. The blue lights break down the bilirubin so it can be excreted. However, at appropriate levels, bilirubin has a strong free radial scavenging effect.

Until recently, scientists were unaware that bilirubin may actually have anti-inflammatory, antioxidant and atheroprotective properties, and there is a growing body of scientific and clinical evidence to support this.

From an evolutionary/biological perspective, it also makes sense that nature would have created a way for your body to break down heme,[5] which can be toxic if it accumulates. The way bilirubin is thought to provide these health benefits is through its ability to inhibit NOX.

In fact, NOX overactivity appears to play a significant role in a wide range of health conditions, including but not limited to vascular diseases and vascular complications of other diseases (diabetes, kidney failure, blindness and heart disease, for example),

insulin resistance, neurodegenerative disorders such as Alzheimer's and Parkinson's, cancer, glaucoma, pulmonary fibrosis and erectile dysfunction.

It follows then that preventing many chronic diseases would require finding a means of inhibiting or modulating NOX. Bilirubin is believed to assist with this modulating effect.

People with Gilbert Syndrome comprise 3 to 7% of the population[6,7] and illustrate this phenomenon quite nicely, as they are genetically predisposed to chronically elevated levels of unconjugated bilirubin.

These individuals, having two to three times as much bilirubin as the rest of us after a 24-hour fast,[8] enjoy a greatly reduced risk for coronary artery disease, hypertension, carotid atherosclerosis and overall mortality, and this protection is thought to be related to their high bilirubin levels.[9]

## Spirulina — An Effective NADPH Oxidase Inhibitor

Since phycocyanobilin is a very close relative of bilirubin — and spirulina is a great source of phycocyanobilin — spirulina has enormous clinical potential due to its NOX inhibiting effect. This is why phycocyanobilin has been the focus of a large amount of research.

Phycobilin extracts have been shown to inhibit NOX activity in human aortic endothelium, aortic smooth muscle and renal cell cultures. And bilirubin protects against diabetic nephropathy via downregulation of NOX in rats.

As DiNicolantonio's 2018 paper[10] explains, bilirubin reduces the risk for obesity and related health problems through a number of mechanisms, but primarily by inhibiting NOX complexes.

Downregulating NOX activity — which can be done with spirulina, thanks to its bilirubin-mimicking phycocyanobilin — could therefore have "profound implications for preservation of metabolic and vascular health." As further explained by the authors:

*"Expression of inducible form of heme oxygenase, HO-1, can be boosted by oxidative stress — often derived from NADPH oxidase [NOX] activity; the resultant production of bilirubin feeds back to quell this oxidative stress …*

*[Phycocyanobilin, which is covalently attached to phycocyanin] is readily converted by biliverdin reductase to the bilirubin analogue phycocyanorubin, which appears to share bilirubin's ability to inhibit NADPH oxidase [NOX] complexes. Arguably, this may largely explain the versatile antioxidant and anti-inflammatory properties of oral spirulina … in rodent studies …*

*A recent cross-sectional epidemiological study evaluating subjects with [Gilbert Syndrome] has discovered that [Gilbert Syndrome] is associated with a reduced tendency to gain body fat in later life … A reasonable deduction is that chronically elevated free unconjugated bilirubin — and perhaps an upregulation in intracellular bilirubin generation — somehow opposes age-related gain in body fat.*

*Of related interest is a study showing that intraperitoneal administration of bilirubin — administered daily for 14 days — inhibits weight gain in rats fed a diet high in fats and sugar. Bilirubin injections were also found to prevent deterioration of glucose tolerance …*

*A credible case can be made that the favorable impact of elevated bilirubin on risk for undesirable weight gain reflects preservation of hypothalamic leptin sensitivity …*

*Activation of NADPH oxidase [NOX] is a key mediator of proinflammatory microglial activation; hence, elevated bilirubin might be expected to support effective leptin function in the arcuate nucleus, thereby aiding appetite control.*

*Oxidative stress in adipocytes, stemming largely from NADPH oxidase [NOX] activity, appears to play a key role in the induction of insulin resistance and the skewing of adipokine and cytokine production in hypertrophied adipocytes.*

*Hence, bilirubin and heme oxygenase activity could be expected to aid maintenance of adipocyte insulin sensitivity. Indeed, plasma levels of unconjugated bilirubin have been found to correlate inversely with risk for metabolic syndrome and diabetes in prospective epidemiological studies, as confirmed in a recent meta-analysis.*

*In both cross-sectional and prospective studies, higher plasma bilirubin levels are associated with better insulin sensitivity and decreased risk for metabolic syndrome and Type 2 diabetes — independent of BMI … A direct protective effect of bilirubin on adipocyte function may be largely responsible for this phenomenon."*

## Leptin Resistance: A Hallmark of Obesity and Type 2 Diabetes

In order for you to significantly gain weight, you must first become leptin resistant. Leptin is a hormone that helps you regulate your appetite. When your leptin levels rise, it signals your body that you're full, so you'll stop eating.

However, as you become increasingly resistant to the effects of leptin, you end up eating more. The question then is: what drives this basic process? Why do you become leptin resistant in the first place?

Research by Dr. Richard Johnson — head of nephrology at the University of Colorado who has published more than 500 medical papers and written a number of books on obesity — clearly shows that refined sugar (in particular fructose) is exceptionally effective at causing leptin resistance in animals and blocks the burning of fat.

Most overweight Americans have some degree of insulin and leptin resistance. This also includes people with diabetes, and many individuals with high blood pressure or high cholesterol. If you fall into this category, it would be prudent for you to restrict fructose to about 15 to 25 grams per day from all sources.

In his most recent paper,[11] DiNicolantonio and his co-authors hypothesize that spirulina supplementation may also be an effective treatment for leptin resistance.

## Bilirubin Protects Against Weight Gain

As mentioned earlier, people with Gilbert Syndrome are genetically predisposed to chronically elevated levels of unconjugated bilirubin. This not only appears to protect them from heart disease and overall mortality, but also prevents body fat accumulation, especially during later years, and hypothalamic leptin resistance is one known condition that promotes weight gain as you grow older.[12]

Research has shown that leptin injections have no effect on obesity. "Studies in rodents with diet-induced obesity suggest that this phenomenon reflects a loss of leptin responsiveness that is specific to the arcuate nucleus," DiNicolantonio notes.[13]

Research also suggests that diet-induced obesity is related to the activation of microglia (glial cells that function as scavengers) in the mediobasal hypothalamus (MBH).[14] Again, NOX plays an important role. Activation of microglia also leads to the production of toxic oxidants such as peroxynitrite and other proinflammatory cytokines.

As noted by DiNicolantonio, "Hence, it is straightforward to propose that bilirubin may have the ability to downregulate microglial activation by diminishing NADPH oxidase activation." That said, bilirubin does not appear to be able to influence leptin activity until or unless leptin resistance has actually developed.

## Spirulina May Combat Leptin Resistance by Mimicking Bilirubin

Now, while raising your bilirubin level could potentially protect you from obesity and diabetes, it's not a useful nutraceutical in and of itself, and this is where spirulina comes in, as the phycocyanobilin found in spirulina is very similar to bilirubin. DiNicolantonio sums it up as follows:[15]

> *"If the hypothesis presented here is correct, the far lower body fat in older subjects with Gilbert Syndrome reflects the ability of bilirubin to suppress the activation and proliferation of microglia in the MBH.*

*The extent to which this expansion of activated microglia — and the associated impact on the function of leptin-responsive neurons — can be reversed by elevation of bilirubin (or administration of phycocyanobilin) in patients who have already developed obesity with leptin resistance remains to be seen.*

*Particularly because microglial mass increases, it may be rash to assume that this syndrome is fully reversible. If phycocyanobilin does prove to have utility for controlling hypothalamic inflammation, its greatest impact on obesity will likely be achieved by long-term administration in a preventive mode.*

*In any case, studies evaluating the impact of bilirubin or phycocyanobilin administration on the development of hypothalamic leptin resistance in fat-fed rodents appear to be warranted … Two studies have been published very recently in which inclusion of spirulina in the diet has been shown to inhibit gain in body weight and fat in rats fed a high-fat diet; these appear to be the first studies to have evaluated spirulina's impact in this regard.*

*Although neither of these studies focused on leptin function, the fact that markers of adipose tissue browning were higher in rats receiving spirulina is consistent with effective leptin function in these rats.*

*Moreover, a double-blind, placebo-controlled clinical trial has also emerged, in which spirulina supplementation (at only 2 grams daily) was found to potentiate loss of body fat, body weight, waist circumference and BMI in overweight subjects placed on a calorie-restricted diet; reductions in triglycerides and C reactive protein were also greater in the spirulina group.*

*Bilirubin mimesis [imitation or mimicry] may represent one example of a more general strategy for preventing or reversing inappropriate weight gain: counteracting hypothalamic leptin resistance or upregulating hypothalamic leptin signaling."*

## Spirulina Types, Dosing and Potential Adverse Reactions

There are many types of spirulina on the market, so do your homework before making a purchase. Since spirulina grown in an uncontrolled environment has the potential to become contaminated with heavy metals and other toxins, it is important to choose organic spirulina from a reputable source.

Spirulina comes in capsules, tablets, powders and flakes. Dosing depends on what you plan to use it for and to whom it is given. A general starting dose for adults is typically around 3 grams. For disease prevention, you may work your way up to 20 grams per day. The adult maintenance dose is typically around 10 grams a day.

Remember to increase your intake of spring water or filtered water when taking spirulina to help it absorb into your system. Also be aware that spirulina is a potent detoxifier, so depending on your toxic burden, you may or may not experience a detox reaction. For that reason, it is best to start with a small dose and work your way up.

Though there are no known side effects associated with spirulina, your body may react to it based on your current state of health. Some of the most prominent reactions you may experience include:

**Slight fever —** The high protein content in spirulina increases metabolism, which may elevate body temperature

**Dark green stool —** Spirulina can remove accumulated waste products in your colon, which may cause darker stool. Also, spirulina is high in chlorophyll, which turns your stool green

**Gas —** Buildup of gas may indicate that your digestive system is not functioning properly

**Excitability —** Your body is converting protein into heat energy, which may cause temporary feelings of restlessness

**Breakouts and/or itchy skin —** This is caused by the colon cleansing process and is a temporary reaction

**Sleepiness —** This is caused by the detoxification process and may indicate your body is exhausted and needs more rest

Also keep in mind that while spirulina is entirely natural and generally considered a healthy food, there are some important contraindications you need to be aware of. Avoid spirulina if you are:[16]

- Severely allergic to seafood
- Allergic to iodine
- Pregnant
- Nursing

If you have hyperthyroidism (overactive thyroid), consult your health care provider before taking spirulina. Also avoid taking spirulina if you are currently running a fever, as it may raise it further. Also, do not take spirulina if you have an autoimmune diseases such as multiple sclerosis or rheumatoid arthritis, or if you a metabolic condition called phenylketonuria (PKU).

## Chlorella — An Alternative if You Can't Tolerate Spirulina

Chlorella is another form of algae that is sometimes confused with spirulina. The fundamental difference between spirulina and chlorella is that spirulina does not possess the hard cell wall that makes chlorella closer to a plant than algae. Note, however, that chlorella does not have the phycocyanobilin so it will not inhibit NOX and increase NADPH.

Chlorella is an excellent way to detoxify your body from mercury, a common problem if you have amalgam dental fillings, have received a thimerosal-containing vaccine or regularly eat contaminated fish. It is also one of nature's highest source of chlorophyll, which has many biological benefits.

Spirulina is unable to remove heavy metals, as it lacks a cell membrane. It can, however, protect your liver against the toxic effects of heavy metals, and help eliminate other toxins, including arsenic. If for whatever reason you cannot tolerate spirulina, chlorella could be a viable alternative to obtain some of its benefits described above.

## Sources and References


- [1] Open Heart 2018; 5: e000914 (PDF)
- [2] RSC Advances 2015, Issue 76
- [3] Journal of Medicinal Food December 25, 2007; 10(4)
- [4, 11, 12, 13, 14, 15] Open Heart 2019; 6: e000897
- [5] Pediatrics June 2004; 113(6)
- [6] Rare Disease Database 2015
- [7] NIH Genetics Home Reference, April 2, 2019
- [8] Science Direct, Jaundice, 2018
- [9] World J Gastrointest Pharmacol Ther, November 6, 2016
- [10] BMJ Open Heart 2018;5:e000914
- [16] Mount Sinai. Spirulina