

Berberine and Metformin for Longevity

Aging and decreased longevity are a function of the body's decreasing ability to refresh and repair itself over time. As the human body ages, there is decreased rebuilding of structures such as bone and muscle, decreased turnover of cells (autophagy) as well as cellular components, decreased suppression of harmful oxidation and inflammation, and decreased tumor fighting activity. Although these processes do diminish over time naturally, they still do occur, even at the extremes of old age. These systems only continue when they are given a healthy environment and healthy tools to do so.

There are various ways to support the body's repair function and adopt a longevity lifestyle, including changes to exercise and diet. According to anti-aging research, two geroprotectors (substances that support healthy aging) that may support the body's repair function are the supplement *berberine* and the well-known Diabetes drug *metformin*.

Berberine is a compound found in various plants such as the barberry shrub. Traditionally, berberine uses have included treatment for diarrhea, dysentery, stomatitis, and hepatitis. Berberine also helps control blood sugar in diabetics. It has also been observed to decrease total cholesterol and LDL cholesterol.

Berberine is associated with increased lifespan in animal models, potentially by slowing a metabolic pathway that causes inflammation and increasing activity of the *AMPK* enzyme which plays a role in cellular energy homeostasis, largely by activating glucose and fatty acid uptake and oxidation when cellular energy is low.

Metformin is a compound originally derived from French lilac. The most common metformin uses are related to blood glucose control primarily in type 2 diabetes. At least part of its effect is credited to its influence on increasing the activity of the *AMPK* enzyme. The most common metformin side effects are gastrointestinal, including abdominal discomfort, lack of appetite, bloating, and diarrhea.

Metformin treatment is associated with decreased mortality in people with type 2 diabetes. Metformin has been shown to improve not only the lifespan (length of life) but more importantly the healthspan (length of healthy life) in mice. A metformin aging clinical trial, the TAME study (Targeting Aging with Metformin), is testing the potential to extend healthy years of life for humans who do not have diabetes.

Both supplements are usually very well tolerated but they can cause some abdominal discomfort, lack of appetite, bloating, and diarrhea. Metformin tends to cause this to a greater degree.

Berberine vs Metformin. Berberine and metformin share many health outcomes, the most well-known of which is improved blood glucose control however other similarities can be found when looking at cellular level effects. Both compounds appear to increase *AMPK* activity. This enzyme is biologically stimulated when there is a deficit of energy, like during fasting or exercise. By stimulating *AMPK*, the cell works to increase its access to energy by facilitating glucose and fatty acid uptake from the blood, increasing fat and glycogen breakdown, and inhibiting both glucose and fat storage. *AMPK* acts by directly phosphorylating enzymes for a more immediate effect, and also by phosphorylating the transcription factors of enzymes, giving it a longer lasting effect. Both berberine and metformin increase the cellular uptake of energy compounds and break down energy storage.

In addition to stimulating *AMPK* activity, glucose consumption is increased by influencing the electron transport chain. Metformin and berberine can each inhibit the electron transport chain making the

process less efficient at producing ATP, thereby wasting energy and potentially mimicking a restricted calorie diet which has many health benefits. These compounds basically trick the body into thinking it is starving which sets off a series of healthful, protective reactions, without the discomfort of actually restricting calories (although EVERYONE can do with some caloric restriction).

Exact mechanisms of action are not clear but it appears that the different compounds have different areas of influence. Berberine has been shown to decrease total cholesterol and LDL cholesterol (the bad one) while metformin has been shown to decrease both of those, in addition to fatty acid and triglyceride levels.

Both compounds can be taken together. When using berberine with metformin, berberine potentially corrects dangerously high levels of lactic acid that some people experience when using metformin.