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The therapeutic benefits of berberine and its effectiveness compared to metformin

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Abstract: Berberine is a plant extract that exhibits an impressive array of therapeutic properties, including accelerated weight loss, improved insulin sensitivity, and protection from numerous chronic, degenerative diseases. Berberine exerts its effects in several ways, including by activating AMP- activated protein kinase (AMPK), an enzyme that governs metabolism and maintains whole-body energy homeostasis. Since AMPK influences the ageing process, long-term berberine consumption may extend lifespan by decelerating one's rate of ageing. Besides its impact on AMPK, berberine also profoundly alters the gut microbiome, specifically in ways that reduce metabolic endotoxemia, a condition that promotes obesity and other metabolic disorders.

Berberine's physiological effects are similar to those of metformin, but in comparative studies, berberine either matches or outperforms metformin. Considering metformin's minor side effects, berberine's absence of side effects, and berberine's therapeutic potential against neurological degenerative diseases and a host of other chronic conditions, berberine is quickly gaining recognition for being one of the most powerful and most effective nutritional agents for weight loss, disease prevention, anti-ageing, and overall wellness.

Keywords: Activated protein kinase (AMPK), ageing process, long-term berberine consumption.

Introduction: Berberine is a bitter-tasting, vibrant yellow alkaloid, which is extracted from the roots, rhizomes, and stem bark of many plants, including Hydrastis canadensis (goldenseal), Coptis chinensis (coptis or golden thread), Berberis aquifolium (Oregon grape), Berberis vulgaris (barberry), and Berberis aristata (tree turmeric). Berberine has been used therapeutically for at least 3,000 years, including

extensive use in Traditional Chinese Medicine and Ayurvedic Medicine.1

Despite its long, illustrious history, interest in berberine has surged during the past decade. The PubMed database, for example, contains roughly 4,700 published articles referencing berberine, 2,800 of which have been published during the past ten years. The recent buzz surrounding berberine isn't surprising, considering the wide array of therapeutic benefits attributed to the molecule. For example, research shows berberine to be protective against cancer, obesity, inflammation, atherosclerosis, neurodegenerative diseases, rheumatoid arthritis, cardiovascular disease, diabetes, and various metabolic disorders, plus many other benefits.2, 3, 4, 5 For those seeking a "panacea" nutritional supplement, which promotes overall wellbeing and even has anti- ageing properties, berberine is a prime candidate.

This review focuses on berberine's usefulness in weight loss while examining the two primary mechanisms by which berberine exerts its powerful therapeutic effects, namely by activating AMP-activated protein kinase (AMPK) and by modulating the gut microbiome. We also compare berberine with metformin, one of the most widely prescribed pharmaceutical drugs for treating diabetes. Finally, we assess berberine's usefulness in anti-ageing therapy while summarizing some of its other key benefits.

Weight Loss through AMPK Activation

Physical exercise increases energy expenditure, thereby contributing to weight loss, primarily by activating AMP-activated protein kinase (AMPK), an enzyme that plays a critical role in controlling whole-body energy homeostasis.6 Besides exercise, AMPK can be activated pharmacologically (by drugs, such as metformin), through plants (berberine), and through other activities, such as fasting. In fact, AMPK arose during early eukaryotic evolution as a regulatory pathway that enables organisms to survive periods of food scarcity.7

Commonly regarded as the "master regulator of metabolism," AMPK restores energy imbalances caused by metabolic stress at both the cellular and physiological levels.8, 9 AMPK functions as a "cellular fuel gauge," meaning it senses low-fuel situations, at which time it switches off energy- consuming activities while switching on energy producing activities.10 If AMPK were a computer's battery sensor, for example, it would sense when battery reserves were low, subsequently sending recharge notifications while attempting to conserve energy by hibernating certain apps.

With respect to AMPK's energy regulation, we are referring specifically to adenosine triphosphate (ATP), the so-called "molecular currency" of intracellular energy transfer, a molecule that stores and transports chemical energy within the cells. AMPK is activated when the ratio between 5'-adenosine monophosphate (AMP) and ATP becomes too high. To restore cellular energy homeostasis, AMPK activates catabolic pathways that generate ATP, including the burning of excess fat (fatty acid oxidation).11 Simultaneously, AMPK switches off ATP- consuming activities that aren't essential to short-term cell survival, including almost all anabolic pathways (e.g. fatty acid synthesis, sterol synthesis, cell growth and proliferation).12

Besides burning fat cells, AMPK also improves blood glucose homeostasis and lipid profiles, while preventing insulin resistance, partly by inhibiting pathways that antagonize insulin signaling.13 In simpler terms, as the master regulator of metabolism, AMPK prevents energy balance disorders, including type-2 diabetes and obesity, as well as metabolic derangements, including cancer and various inflammatory diseases. Since being discovered and formally defined in the late 1980s, over 9,000 papers have been published concerning the AMPK system.14, 15

Berberine is a potent AMPK activator, which has been demonstrated to activate AMPK in both fat cells and muscle cells, thereby resulting in reduced fat accumulation and improved insulin sensitivity. For example, the authors of a 2006 study published by the American Diabetes Association's Diabetes Journal, observed, "Strikingly, berberine acutely stimulated AMPK activity in both myotubes [fibers involved with muscle generation] and adipocytes [fat cells] in vitro, contributing to enhanced GLUT4 translocation in myotubes and reduced lipid mass in adipocytes."16 They went on to suggest that berberine could become a major therapeutic tool for treating obesity and insulin resistance.

Weight Loss through Gut Microbiome Modulation

Energy imbalances are just one of many factors that contribute to weight gain and obesity. For example, an imbalanced gut microbiome can also promote these conditions. Poor diet and lifestyle choices, for example, can undermine the gut microbiome, causing changes that decrease mucosal barrier function, meaning the intestinal barrier becomes compromised.17, 18 This leads to intestinal permeability and access to the bloodstream by microbiome-derived lipopolysaccharides (LPS).

Metabolic endotoxemia (ME) is a condition characterized by elevated serum LPS.19 ME triggers a signaling cascade of pro-inflammatory pathways, which

leads to chronic low-grade inflammation and oxidative stress, both of which are associated with obesity. Recent research suggests, "metabolic endotoxemia may serve [as] a key mediator of metabolic derangements observed in obesity" and cardio-metabolic disease.20 In 2007, for example, Cani et al. induced obesity in mice through a high-calorie diet rich in corn oil. The stages leading to obesity were a) alterations of the gut microbiota, including reductions in Bifidobacterium and Eubacterium spp, b) two- to threefold increases in circulating LPS levels (which classifies as ME), and c) 30 and 40% increases in subcutaneous and visceral fat deposits, respectively.21

Berberine has been shown to protect against obesity by regulating ME. In 2017, for example, Xu et al. induced obesity in rats and then tested berberine's effects. 22 Berberine significantly altered the rats' gut microbiomes, including increases in the abundance of 14 genera, and decreases in 20 genera. This led to decreased intestinal permeability (via improved expression and distribution of tight junctions), reduced ME, and reduced inflammation. Moreover, berberine caused significant improvements regarding weight loss, fasting blood insulin, and insulin resistance.

For a similar study, published in 2018 in Atherosclerosis, researchers used berberine to alter the gut microbiomes of mice, including increases in the abundance of Akkermansia, which caused increased intestinal expression of tight junction proteins and increased thickness of the colonic mucus layer. 23 These changes restored gut integrity and reduced ME, while also reducing arterial and intestinal expression of pro-inflammatory cytokines.

Berberine versus Metformin

In 2008, berberine captured the attention of the healthcare community when it outperformed metformin, the popular diabetes drug, in a comparative study published in Metabolism. After treating 36 recently diagnosed type-2 diabetes patients with diet alone, researchers randomly assigned the patients to receive either berberine or metformin, three times daily (500mg doses) for a period of 13 weeks.24

The berberine group matched or outperformed the metformin group in all categories. With respect to glucose metabolism, including improvements in HbA1c, fasting blood glucose (FBG), postprandial blood glucose (PBG), fasting insulin, and postprandial insulin, both groups exhibited similar improvements. With respected to lipid metabolism, however, including triglycerides and total cholesterol, the berberine group exhibited significantly better results compared to the metformin group.

For a 2012 study published in the European Journal of Endocrinology, researchers compared the effects of berberine and metformin on women diagnosed with polycystic ovary syndrome, a

common reproductive and metabolic disorder associated with insulin resistance.25 Eighty-nine subjects were randomized into one of three groups, corresponding to a three-month treatment regimen inclusive of berberine (1500mg daily), metformin (1500mg daily), or placebo.

The berberine group, compared to the metformin group, exhibited significant reductions in waist circumference, waist-to-hip ratio, total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDLC), as well as significant increases in high-density lipoprotein cholesterol (HDLC) and sex hormone-binding globulin.

So berberine and metformin both activate AMPK, and both modulate the gut microbiome. Both have similar effects on glucose metabolism, lipid metabolism, and weight loss, but when compared in head-to-head clinical trials, berberine has thus far performed better. Regarding side effects, berberine has no significant side effects, whereas for metformin there are some concerns.

Metformin and Gastrointestinal Distress

Around 20-30% of patients taking metformin suffer gastrointestinal side effects, including 5% for whom these side effects are so severe that they warrant discontinuation of the drug.26 In 2016, researchers publishing in Diabetic Medicine identified a genetic component to this metformin side effect. Specifically, they found that patients with specific variants of the OCT1 gene have more than double the odds of experiencing common metformin-induced gastrointestinal side effects.

Berberine, on the other hand, has been used since ancient times to treat gastrointestinal disorders. Recent studies confirm berberine's significant therapeutic impact on the gastrointestinal tract, including effectiveness against diarrhea and gastroenteritis.27 Additionally, as discussed above, berberine modulates the gut microbiome, thereby protecting the mucosal lining of the gut and preventing "leaky gut" by attenuating disruptions of tight junctions in the intestinal epithelium.28 Berberine is not associated with any significant adverse gastrointestinal side effects.

Metformin and Liver Risks

The risks of metformin for those who suffer from advanced liver inflammation have been hotly contested. Until recently, doctors typically discontinued metformin for patients diagnosed with cirrhosis due to fears of

adverse reactions. A 2014 study conducted by the Mayo Clinic, however, found that continuation of metformin after a cirrhosis diagnosis reduces the risk of death by 57 percent.29

Despite persistent concerns, metformin appears to be safe and effective, even for those with weakened livers. In fact, for a 2012 mouse study, metformin reversed steatosis and inflammation in non-diabetic subjects afflicted by nonalcoholic steatohepatitis (NASH).30

Despite a limited number of quality trials, for a 2016 meta-analysis regarding the effects of berberine on non-alcoholic fatty liver disease (NAFLD), researchers concluded that berberine positively affects blood lipids, blood glucose, liver function, insulin resistance, and fatty liver condition, with respect to NAFLD patients.31 Berberine's liver-protective properties are attributable primarily to its ability to suppress inflammation.32 Additionally, researchers have demonstrated berberine's ability to modulate gene expression with respect to hundreds of genes associated with liver metabolism and NAFLD-related functions, thereby conferring additional protective effects against NAFLD.33

Metformin and Vitamin B12 Deficiency

Long-term use of metformin has been shown in cross-sectional, retrospective, and longitudinal observational studies to be associated with vitamin B12 deficiency. This side effect is attributed to metformin's interference with vitamin B12-intrinsic factor absorption.34

Metformin and Renal Impairment

Metformin belongs to a class of glucose-lowering drugs called biguanides. Other biguanides, such as phenformin and buformin, were previously pulled from the market based on compelling evidence linking them to lactic acidosis.35 Metformin poses similar risks, but only for a small subset of the population, including those with impaired renal function, impaired hepatic function, and/or circulatory dysfunction.

Metformin-associated lactic acidosis (MALA) is a condition characterized by increased serum lactate along with impaired clearance ability. This occurs in people with impaired renal function and/or impaired hepatic metabolism, including those who acutely develop impaired renal function via dehydration, vomiting, diarrhea, or simply through old age (based on age-related renal decline).36, 37, 38

With mortality rates ranging from 25 to 50%, the consequences of MALA are severe.39 The prevalence of MALA, however, is very low – 7.4 cases per 100,000 patient-years for metformin users, compared to 2.2 cases of lactic acidosis per 100,000 person-years for nonusers of metformin.40 Nevertheless, in the interest of preventing MALA, metformin is currently contraindicated for those diagnosed with moderate to severe renal impairment.

As discussed throughout this article, berberine delivers all the benefits of metformin (and more), but without metformin's side effects. With respect to lactic acidosis, this is also the case.

Berberine not only doesn't cause lactic acidosis, but it may also protect against lactic acidosis caused by metformin.

For a 2017 study, scientists induced diabetes in rats before randomizing them into groups receiving metformin alone or metformin plus berberine (at 50 or 100 mg/kg body weight). Serum lactate (an indicator of lactic acidosis) was observed at 1.87 mmol/L for the metformin group, compared to 1.62 for the metformin plus 50mg/kg berberine group and 1.47 for the metformin plus 100mg/kg berberine group. Additionally, the berberine groups fared better with respect to fasting glucose, fasting insulin, insulin resistance, and HOMA-IR.41

Besides its apparent benefits vis-à-vis MALA, berberine also provides general kidney support and protection. For a 2017 study published in Molecular Medicine, for example, scientists concluded that berberine can inhibit renal fibrosis while improving symptoms associated with diabetic nephropathy (kidney damage caused by diabetes).42 Moreover, for a 2015 study published in Natural Product Communications, scientists demonstrated that long-term berberine treatment attenuates renal injury in spontaneously hypertensive rats (rats with kidney damage resembling that observed in some cases of human essential hypertension).43

Additional Berberine Benefits

Anti-Ageing Properties

AMPK is one of the key governors of the ageing process due to its impact on metabolic homeostasis, stress resistance, and cellular maintenance/upkeep, all of which are hallmarks of improved quality of life and extended lifespan. It has been demonstrated that the ageing process diminishes the responsiveness of AMPK activation.44 The mechanisms responsible for this diminished responsiveness are currently unknown, but researchers suspect that inflammation, cellular stress, and age-related changes to protein phosphatase function are involved.45 Berberine, based on its remarkable ability to activate AMPK, is regarded as one of the plant kingdom's most powerful anti-ageing molecules.

Berberine and the Brain

Cognitive dysfunction is a consequence of chronic hyperglycemia, oxidative stress, and cholinergic dysfunction, all of which are associated with type-2 diabetes and metabolic syndrome. When diabetes is induced in rats, they suffer severe deficits in learning and memory, which is associated with increased lipid peroxidation, decreased glutathione levels, and elevated choline esterase (ChE) activity. In multiple studies, berberine has been shown to improve learning and memory impairment by reducing synaptic dysfunction and by lowering hyperglycemia, oxidative stress, and ChE activity.46, 47

Berberine also exhibits mood enhancing and antidepressant-like properties, thanks to its ability to boost neurotransmitter activity, specifically in the hippocampus and frontal cortex, but also in the entire brain.48 In mice, acute administration of berberine (5 mg/kg) increased norepinephrine (31%), serotonin (47%), and dopamine (31%) levels. Chronic administration for 15 days was shown to maintain these elevated levels, while mitigating behavioral patterns of despair vis-à-vis forced swim tests and tail-suspension tests.49

A follow-up study published in The Pharmacogenomics Journal was designed to test berberine's effect on serotonin transporter (5-HTT), which indirectly regulates mood, emotion, and appetite by modulating extracellular fluid serotonin concentrations.50 Depending on genetic variations concerning 5-HTT expression, berberine increased 5-HTT promoter activities from 28 to 129%, thereby providing "a convincing example of how herbal compounds influence the expression of one of the most intensively studied psychiatric candidate genes, the serotonin transporter."51

Finally, berberine is emerging as a promising candidate for therapeutic approaches to preventing or delaying the process of Alzheimer's disease (AD).52 The two hallmark pathologies of AD are the accumulation of β-amyloid (Aβ) plaque deposits and the accumulation of neurofibrillary tangles (NFTs) of tau proteins. Berberine has been shown in numerous studies to decrease the accumulation of both antagonists, although the mechanisms behind these improvements remain unclear.53 What is clear, however, is that berberine crosses the blood-brain barrier, thereby conferring numerous neuro-protective benefits, including the reduction of oxidative stress and the reduction of neuro-inflammation.54

During the past several years, the pharmaceutical industry has suffered many setbacks regarding Alzheimer's research. "The large number of major failed trials in Alzheimer's is quite frightening. It has really scared off big pharma," explained Lennart Mucke, director of the Gladstone Institute of Neurological Disease at UC San Francisco.55 In fact, in January 2018, Pfizer announced it would be abandoning research aimed at developing drugs to treat AD and Parkinson's disease.56 Perhaps this astonishing announcement signals a new era during which herbal and botanical treasures like berberine will rise to prominence.

CONCLUSION

Berberine is an ancient herbal medicine, which, during the past decade, has emerged as a superstar of naturopathy. Berberine has been shown in clinical trials to have a wide range of therapeutic benefits, including weight loss, improved insulin sensitivity, and protection against many chronic diseases, including cancer, atherosclerosis, cardiovascular disease, various neurodegenerative diseases, diabetes, and various metabolic disorders.

With respect to weight loss, two of the most important mechanisms behind berberine's effects are its impact on AMPK and on the gut microbiome. Berberine activates the AMPK, thereby regulating metabolism and prompting the body to burn stored fat deposits. With respect to the gut microbiome, berberine alters the gut microbiome in ways that restore gut integrity and prevent metabolic endotoxemia, thereby reducing inflammation and promoting weight loss.

Metformin, one of the most prescribed diabetes medications, has similar effects compared to berberine, but in head-to-head studies, berberine equals or outperforms metformin, and without any significant side effects. Finally, the vast array of therapeutic benefits attributed to berberine cannot be overstated. During the next several years, berberine has the potential to gain widespread recognition among the general public as one of the world's most important nutritional treasures.

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