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## Hyperinsulinemia, cancer and maqui berry: The promise of nutritional supplementation

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### ABSTRACT

Nutritional supplementation has long been studied as a possible treatment alternative or as an adjunct to the standard treatments for common ailments and diseases. According to the latest research, the Chilean maqui berry, *Aristotelia chilensis*, has been shown to reduce postprandial insulin levels by as much as fifty percent. The berry, which has been shown to be as effective as metformin at increasing insulin sensitivity and controlling blood glucose levels, follows a simple mechanism of action that involves the inhibition of sodium dependent glucose transporters in the small intestine, slowing the rate at which sugars enter the bloodstream and thereby decreasing blood sugar spikes and the corresponding increase in insulin levels. Chronically high blood glucose levels have been proven to play a significant role in the development of cancers, as diabetics and prediabetics have been proven to have elevated risk of developing cancerous growth. Consistent dietary supplementation with maqui berry may therefore indirectly reduce the risk of cancer, as well as other diseases which respond negatively to hyperglycemia and hyperinsulinemia.

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### 1. Introduction

Insulin insensitivity and hyperinsulinemia create a predisposing or gateway environment to a significantly greater risk of cancer. This paper reviews the pathogenesis of this process, the literature that supports the efficacy of nutritional supplementation against cancer, and the new data that suggests that the Chilean maqui berry extract may help to control or reduce the incidence of hyperinsulinemia, and therefore indirectly help reduce the risk of various cancers. The berry extract works via the mechanism of slowing gastric emptying, thereby reducing spikes in blood glucose and insulin, and does not require massive dietary changes which patients have typically demonstrated low compliance with. The berry extract is inexpensive, widely available, and to date has shown minimal side effects.

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### 2. Claim

Insulin insensitivity, also known as insulin resistance, and hyperinsulinemia are typically products of a sedentary lifestyle and poor dietary habits which often include significant amounts of high glycemic index, or rapidly absorbed, carbohydrates. Historically, hyperinsulinemia and insulin insensitivity were thought to have been separate conditions, exclusive from one another. However, research now suggests that hyperinsulinemia and insulin insensitivity are directly and causally linked. One condition cannot exist if the other condition does not also concurrently exist [1]. With an increased duration and consistent ingestion of high glycemic food sources which rapidly elevate blood sugar levels, and along with increased adipose deposition (increased body fat levels and or obesity), cells in the body become more insulin resistant. As insulin becomes progressively less effective in modulating blood glucose levels, blood sugar levels rise, initiating additional secretion of insulin. The chronic, recurrent continuation of this process leads to hyperinsulinemia. If the chronic increase in insulin and blood glucose levels are not addressed through dietary changes, lifestyle changes, medications, or with dietary supplements, then the risk of diabetes, cancer, and age-related diseases increases significantly.

Longer duration postprandial blood sugar increases are a primary indicator of insulin insensitivity. New research, as discussed below, has shown that regular dietary supplementation with a



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Chilean berry extract may help slow the absorption of carbohydrates, thus reducing or blunting the degree of postprandial blood glucose elevations by 15% and postprandial insulin secretion by more than 50%. This would make dietary supplementation with maqui berry a potentially significant discovery in the clinical approach to reducing insulin insensitivity, hyperinsulinemia, obesity, diabetes, and cancer [2,3].

### 3. Epidemiology of cancer and hyperinsulinemia

Diabetes and its most important predisposing factor obesity are becoming progressively more prevalent in the U.S. and worldwide. There are over thirty million diabetics in the U.S. and there are over eighty million people that are considered prediabetic [4]. The incidence of cancer is also growing, with a projected increase of fifty percent in cancer cases by 2030 [5]. Recent research suggests that there are strong correlations between obesity, diabetes, and cancer-related morbidity and mortality. A study conducted in 2017 aimed to determine where and how hyperinsulinemia played a role in the pathogenesis of obesity, diabetes, and cancer-related death. In this study, the participants had no previous history of cancer or diabetes. Among nearly ten thousand participants, thirty percent of non-obese participants were found to have hyperinsulinemia while seventy-five percent of obese participants were found to have hyperinsulinemia. This suggests a link between obesity and a higher risk, if not causation, of developing hyperinsulinemia. Hyperinsulinemia can potentially magnify the likelihood of becoming diabetic. This study also highlighted the finding that the risk of cancer mortality was far greater in participants with hyperinsulinemia, whether they were obese or not [6]. Given the magnitude of this health issue, these new findings regarding the efficacy of the maqui extract in reducing postprandial insulin and glucose spikes are relevant and important.

### 4. Mechanisms of hyperinsulinemia and cancer

Mounting research suggests a significant correlation between a greater risk of developing cancer when hyperinsulinemia is involved. There is a two to three-fold greater risk of developing breast cancer if a patient has hyperinsulinemia [7]. There is a two to three-fold greater risk of developing liver cancer if a patient has hyperinsulinemia [8]. Hyperinsulinemia is also responsible for a more than two-fold increase in the risk of developing malignant prostate cancer [9]. Cancers generally cause an increased reliance on glucose as a primary fuel source at a cellular level. Cancers tend to form and grow more rapidly in patients with chronically high blood sugar levels, including those with obesity and or diabetes.

While cancer can potentially stem from long term hyperinsulinemia, hyperinsulinemia and insulin insensitivity can begin, or be concurrent with, obesity as discussed in a 2007 study [10]. When the body is subjected to low exercise levels and a caloric surplus provided by high carbohydrate, high glycemic food sources, fat is more rapidly stored. As adipose tissue deposition increases, the body accumulates more visceral fat mass. Visceral fat is responsible for releasing polypeptides, called cytokines. Cytokines are the cause of increased systemic inflammation [11]. A 1993 study showed that cytokines cause cells to produce proteolytic enzymes and free radicals, both of which negatively affect the cells of the pancreatic inlet where insulin is produced [12]. Long term insulin levels and postprandial insulin response can both be compromised, eventually causing hyperinsulinemia, which can lead to an increased risk of cancer. This relationship was clearly represented in a 2009 study conducted by Currie et al., which retrospectively examined over 60,000 diabetic patients. Participants were divided

into groups based on the treatment they received, whether it was metformin, sulfonylurea, or strictly insulin. Cancer risk was measured by tumor progression or incidences of breast cancer, colon cancer, pancreatic cancer, or prostate cancer. Participants that received treatment with metformin, one of the most commonly prescribed medications for diabetics, showed the lowest risk of developing cancer. Metformin functions as somewhat of an antagonist to insulin, decreasing the amount of glucose absorbed by cells. It also increases insulin sensitivity, reducing the amount of insulin required to respond to blood sugar spikes, and, therefore, excess insulin in the bloodstream. The participants treated only with insulin showed the highest risk of developing cancers, particularly colorectal and pancreatic cancers. However, this increased risk was nearly eliminated when patients combined metformin with their original treatment with insulin. Considering metformin's mechanism of action, this study may present a direct correlation, although not causation, between hyperinsulinemia and cancer risk [13]. Many different types of cancer cells have been shown to grow and metastasize more readily when blood glucose levels are chronically high [14–16]. Additionally, insulin is a highly anabolic hormone that may increase the rate of cancerous cell proliferation.

This data suggests the following mechanism for the correlation between hyperinsulinemia and the increased risk of cancers:

HYPERGLYCEMIA →	HYPERINSULINEMIA →	INCREASED CANCER RISK
- high carbohydrate diet	- insulin insensitivity	- increased glucose metabolism
	- obesity, diabetes	- increased cytokine production
	- increased inflammation	
	- increased free radicals and oxidative damage	

### 5. Nutritional supplementation, cancer, and hyperinsulinemia

Growing research suggests the association between high insulin levels and the development of malignancies. According to the literature, the idea that nutritional supplementation could potentially reduce the risk of cancer, or support immune system function, is not new. This very idea was elaborated on in a review published in 1995. Nutritional supplementation has a long-standing track record of providing efficacious nutritional support in cancer patients or in helping to reduce risks. Suboptimal levels of some essential vitamins, minerals and nutrients can increase the likelihood of mortality [17].

### 6. Vitamins C and D supplementation

Larger doses of intravenous vitamin C and vitamin D have both been used as nutritional support to treat diseases by bolstering the immune system and by reducing systemic inflammation that may correlate with disease. A 2010 review showed that the likelihood of developing cardiovascular disease was 50% lower in individuals that had plasma vitamin C levels in the upper 25<sup>th</sup> percentile of the 25,000 participants studied. This may be due, at least in part, to vitamin C's role as an antioxidant that can improve arterial longevity and reduce plaque buildup, as was suggested by Linus Pauling. Vitamin C has also been shown to decrease the risk of cancer by influencing gene expression and protecting cells from genetic mutations that may lead to cancerous growth. Vitamin C has also been used to treat fatigue, infection, and cold symptoms [18]. The potential anticancer effects of vitamin D have also been explored recently. Extensive research has been conducted cover-

ing a possible link between vitamin D and breast cancer. It has been shown that there is a significant negative correlation between circulating vitamin D levels and the risk of developing breast cancer. Other research has proposed that the physiology that explains this phenomenon has to do with the malfunctioning of proper vitamin D metabolism in breast epithelial tissue. This may suggest that vitamin D has a propensity to affect the cell cycle, cell proliferation, and cell death. Additionally, symptoms of depression, chronic fatigue, and joint pain have been shown to positively correlate with low vitamin D levels. Some instances of these symptoms have been ameliorated with vitamin D supplementation [19].

## 7. Berberine and cinnamon supplementation

Berberine is a plant derivative that has been used to treat ailments for thousands of years. Berberine has been linked to the reduction of blood glucose levels and insulin levels. In fact, berberine has been shown to be as effective as metformin, the most commonly prescribed drug for diabetics, at controlling blood sugar levels in diabetics. Berberine causes a decrease in HbA1c which leads to a hypoglycemic effect [20,21]. Even cinnamon has been implicated in the reduction of blood sugar. Cinnamon helps to make cells more insulin sensitive and can also help with more efficient utilization of sugar for energy [22,23].

## 8. Maqui berry supplementation

New research shows that while the maqui berry extract operates through a different mechanism of action than the nutritional supplements discussed, it has been shown to be effective. In addition to being a rich source of antioxidants, maqui berry acts to decrease postprandial changes in blood glucose levels by slowing the rate that sugar enters the blood stream, allowing for a smaller, more gradual rise in blood glucose levels, resulting in less insulin secretion.

The mechanism of action is based on the fact that maqui berry contains powerful peptides called delphinidins that inhibit sodium dependent glucose transporters located in the small intestine [23]. Therefore, nutrients and sugars that can potentially spike blood glucose and insulin levels are absorbed through the intestinal wall and into the portal vein at a slower rate. A recent study showed that participants taking maqui berry extract had 15% less increase in blood glucose levels when compared to the placebo group. Insulin levels were even more heavily affected in the experimental group, as participants taking maqui berry extract showed more than a 50% lower peak insulin level post meal when compared to the control group [3].

MAQUI BERRY → SLOWED GLUCOSE ABSORPTION → LESS INCREASE IN BLOOD GLUCOSE → LOWER INSULIN RESPONSE

Given the mechanism discussed above, maqui berry may play a key, albeit indirect role, in reducing cancer risk by decreasing hyperglycemia, which would decrease hyperinsulinemia.

## 9. Potential side effects and safety of maqui berry

A review of the literature cited in this article revealed no findings regarding the safety or potential toxicity issues of maqui berry, though some nutritionists may advise mothers to avoid use of such nutritional supplements during pregnancy or breastfeeding. In addition, there were no findings regarding maqui berry drug interactions. Literature sources, in general, tend to suggest that as a natural berry, it is non-toxic. None of the discussed publications made mention of study participants having to discontinue use of maqui berry due to a negative response. In rare cases, an allergy to maqui berry may cause an undesirable reaction. Further research

is needed in this area. However, as compared to the numerous side effects of using oral or injectable medications used to treat hyperglycemia, maqui berry appears to have significant promise in terms of being a relatively safe alternative.

## 10. Discussion

Cancer has been described as a metabolic disorder, and as such, incidences may be influenced by a variety of factors including lifestyle, exercise, nutritional choices, body composition, and hormonal levels. The most significant risk factors of cancer may, therefore, be controllable, such as diet (in terms of total calories, macronutrient ratios, fiber, and sugar intake), exercise, supplementation, and body fat levels. In a broader sense, hyperinsulinemia and insulin resistance can affect the occurrence of diabetes, cancer, and age-related diseases.

A 2016 study conducted by Alvarado et al. sampled 43 individuals between the ages of 19 and 50, both male and female. All subjects presented hypertension, prediabetes, or a high body mass index. Participants were given maqui berry extract, delphinol, in doses between 60 and 180 mg one hour before meals. Postprandial glucose and insulin dynamics were recorded thirty minutes after meals, and the results proved to be consistent and dose-dependent. Higher doses of delphinol showed a lower average postprandial blood glucose level among participants. Administering higher doses of delphinol also showed a lower required insulin response to the same amount of glucose. This suggests that delphinol may help to manage the same amount of glucose more effectively and with less insulin [2].

A 2014 study composed and conducted by a Chilean university managed to elaborate on the reduced rate of gastric emptying that maqui berry extract may be responsible for. Delphinidins, derived from maqui berry extract, were shown to inhibit the sodium-dependent glucose symports, especially in the jejunum, in humans and rats. This would, therefore, slow the absorption rate of glucose in the gastrointestinal tract and minimize spikes in blood glucose levels. Diabetic rats that were given delphinol for four months showed a significant reduction in fasted blood glucose levels. After four months of supplementation, fasting blood glucose levels in diabetic rats were nearly indistinguishable from fasted blood glucose levels in healthy rats. Compared to placebo, pre-prandial delphinol consumption showed a statistically significant reduction in postprandial blood glucose and insulin levels in human subjects [3].

## 11. Conclusion

Obesity and diabetes-related diseases, such as cancer, continue to increase, despite the increase in free or cost-efficient access to exercise programs, body fat reduction dietary programs, and lower carbohydrate diets. Given the impact and new-found dependence on technology, sedentary lifestyle habits compound this trend. Consumers, in general, looking for convenient, cost-efficient, relatively passive solutions to weight gain and dietary challenges.

Other nutritional supplements have shown promising results in reducing blood sugar and insulin levels and further research is warranted to explore how these ingredients may work most effectively in concert in the battle against diabetes and its role as a gateway to cancer.

By introducing the long-term supplementation of the maqui berry, the mechanism that leads from obesity and hyperinsulinemia to cancer may be impeded or even prevented. While further research is necessary, implementing maqui berry as a nutritional supplement, it is possible that chronic insulin levels will be reduced, insulin sensitivity will be greater, and the risk of developing cancer will be reduced. The availability, affordability, relative

safety, and minimally invasive nature and ease of compliance of the maqui berry supplementation make these results even more exciting.

### Declaration of Competing Interest

We would like to confirm that there are no known conflicts of interest associated with this publication and there has been no financial support for this work that could have influenced its outcome. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

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