well-being
by nature

dianafood

GLUCOSE REGULATION

glucophenol®

A healthy blend of polyphenols from the first nutraceutical variety of strawberries ever produced, the Orleans, and cranberries.

Glucophenol®: promoter of your health

What is Glucophenol®?

Glucophenol® is a mixture of polyphenols obtained through water and ethanol extraction from the Orleans variety of strawberries and american cranberries. The Orleans is a new and unique strawberry cultivar characterized by unusually high levels of antioxidants (such as p-coumaroyl hexose).

Cranberries are a major source of A-type proanthocyanidins (PACs). These organic molecules are concentrated according to a manufacturing process developed by **Diana Food** in order to achieve highly purified extracts while maintaining the integrity of the molecules, thus preserving their inherent activities. The concentration of polyphenols in **Glucophenol®** reaches 18 to 20 %, according to the Folin-Ciocalteu method. The ingredient comes in powder form and is low in calories.

Glucophenol®: what for?

According to the International Diabetes Federation, up to 592 million people (1 adult/10) will suffer from type 2 diabetes by the year 2035, an increase of 55 % over 2013. The raising prevalence of the condition has been associated with several factors, including changes in eating habits and increasingly sedentary lifestyles that together lead to obesity. The economic burden of type 2 diabetes affects governments as well as individuals. In the US, the lifetime health care costs related to the treatment of one individual with the disease is estimated at $283,000 (*Seuring et al, 2015*). Moreover, peoples with diabetes have worse employment opportunities globally. For instance, the annual income loss for an affected American woman has been estimated at nearly $22,000. per year. Thus, better prevention and management of type 2 diabetes has the potential to not only bring good health but also economic gains.

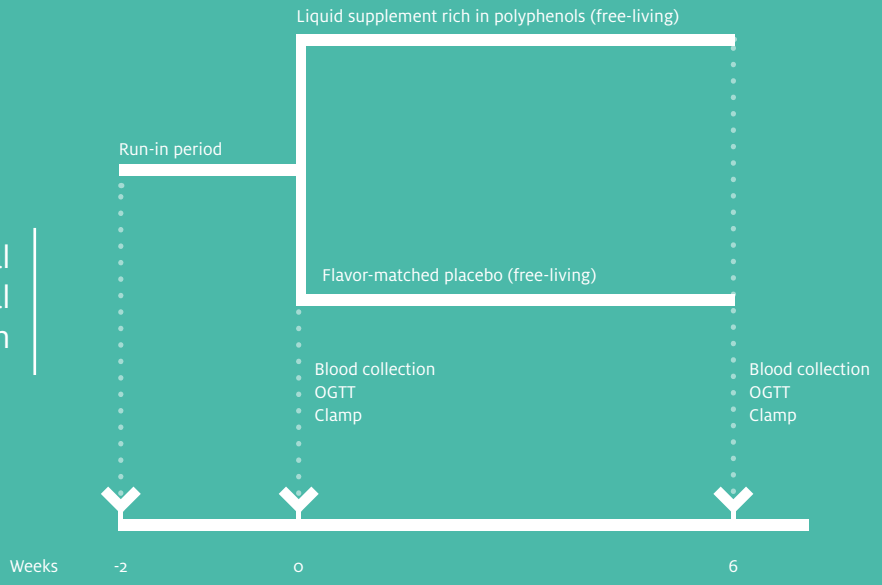
With their anti-oxidant and anti-inflammatory properties polyphenols have found multiple health applications. Recently there have been indications that dietary polyphenols may influence glucose metabolism by various mechanisms. Polyphenols were reported to inhibit carbohydrate digestion and glucose absorption in the intestine, to stimulate insulin secretion from the pancreatic beta-cells, to modulate glucose release from liver, to activate insulin receptors and glucose uptake in tissues, and to modulate hepatic glucose output.

Clinical research

Given the polyphenol profile of **Glucophenol®, Diana Food** and the Institute of Nutrition and Functional Foods (INAF) at Laval University decided to investigate the potential of the ingredient to modulate insulin sensitivity in a randomized, parallel-arm, doubled-blind, and placebo-controlled clinical trial.

A total of 41 non-diabetic insulin-resistant subjects, with excess weight, completed the 6-week study. The supplement was taken once a day, in a liquid form. In order to limit their intake of additional polyphenols, subjects were asked not to consume red wine and small fruits and berries during the study. **Glucophenol®** performed well on all accounts.

Clinical experimental design

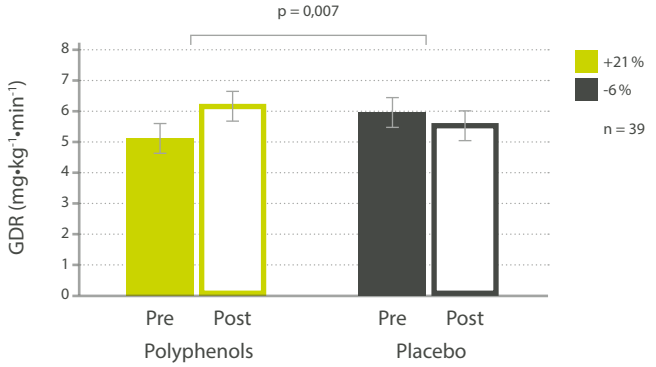


Glucophenol® supplementation improves glucose disposal rate and insulin sensitivity

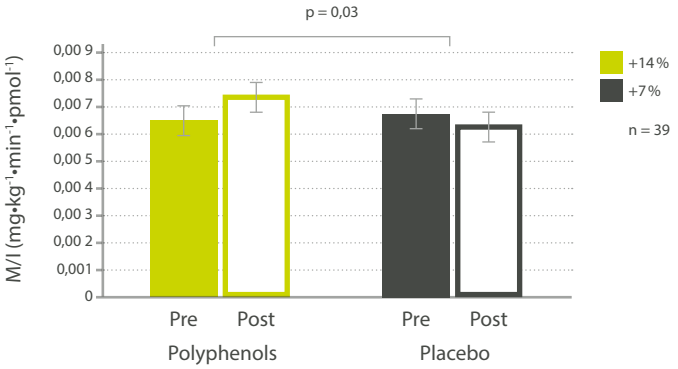
Following overnight fast, a 120-min hyperinsulinemic-euglycemic clamp was performed, at the beginning and at the end of the study, to assess insulin sensitivity in volunteers. In this technique, plasma insulin concentration is acutely raised and kept at 100 µU/ml by a continuous infusion of insulin, while normal plasma glucose concentration is maintained using a variable glucose infusion. Once the steady-state is achieved, the glucose infusion rate equals glucose uptake by all the tissues in the body and is therefore a measure of tissue insulin sensitivity (M/I). The glucose disposal rate (GDR or M) is calculated from the glucose infusion rate (mg·min-1) divided by the body weight (kg) during the final 30 min of the clamp. The M/I value is calculated from the GDR divided by the mean insulin concentration during the final 30 minutes of the clamp.

Glucophenol® supplementation for 6 weeks improved GDR rate by +21% (p=0.007) and M/I by +14% (p=0.03). In contrast, the placebo had a negative effect on both parameters, decreasing GDR by -6% and M/I by -7%. Thus, **Glucophenol®** has a positive impact on both insulin sensitivity and glucose uptake by tissues has just the right polyphenol profile to support such neuroprotective, antioxidant, and anti-inflammatory activities.

Glucose disposal rate (GDR)



Insulin sensitivity (M/I)

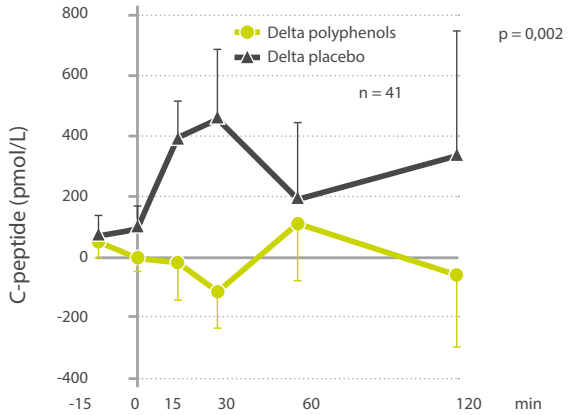


Glucophenol® supplementation normalizes insulin secretion

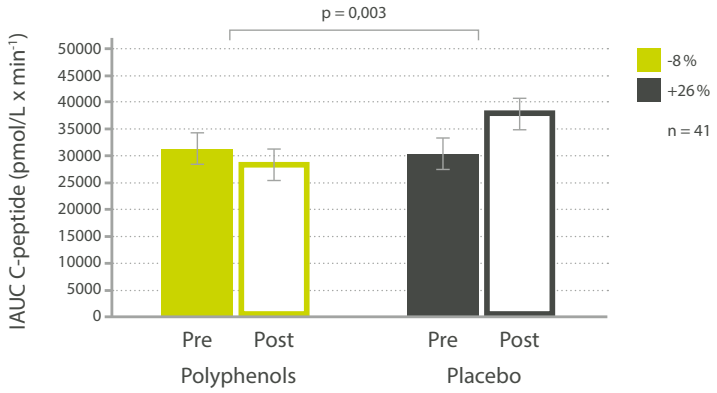
An insulin C-peptide test was also performed, in the course of an oral glucose tolerance test (OGTT), to assess the level of insulin production in volunteers. Insulin C-peptide is a blood test that measures the amount of C-peptide, a breakdown product that is released as new insulin is secreted by beta-cells in the pancreas.

The production of C-peptide was sharply increased at 30 minutes in the placebo group, while it remained rather constant throughout the test for the group supplemented with **Glucophenol®**. The difference between treatments was statistically significant. Noteworthily, this timing corresponds to the peak in biodisponibility registered in humans for phenolic metabolites such as p-coumaric acid, following ingestion of the extract. From these results, we conclude that **Glucophenol®** is able to normalize insulin secretion when the body is challenged by high levels of glucose intake.

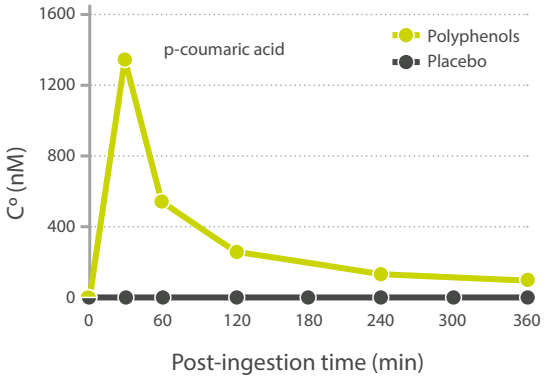
Delta C-peptide



IAUC C-peptide 30 min



Biodisponibility of *p*-coumaric acid



Glucophenol® supplementation works at low dose

The clinical results described above were obtained with a daily dose of 300mg/day of polyphenols from **Glucophenol®**, over a period of 6 weeks.

Starting 2 weeks prior to the study start, until its completion, all participants were instructed to ban wine and berries from their diet. To verify if **Glucophenol®** could be efficient at a lower dose, in normal life conditions, a 2nd trial was run with 8 volunteers under a normal diet (no restriction), at a dosage of 277 mg/day of **Glucophenol®**. Although not statistically significant due to the small size of the group, a similar tendency toward improvement of insulin sensitivity was observed with the low dose group.

GLUCOPHENOL® EFFECT ON INSULIN SENSITIVITY IN THE HIGH DOSE VERSUS LOW DOSE COHORT

No of volunteers	Dose	Result	Duration
20	1660 mg	+14 %	6 weeks
8	*277 mg	+10 %	6 weeks

*1660 mg of Glucophenol® contains 300 mg of polyphenols and 277 mg of Glucophenol® contains 50 mg of polyphenols.

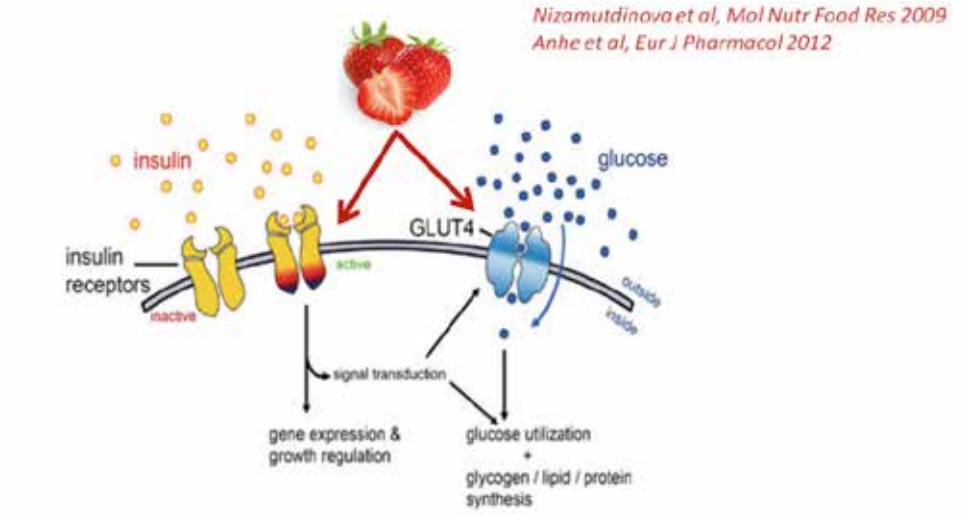
* dose taken in supplementation to a normal diet

How Glucophenol® works

Most likely molecular mechanisms of action

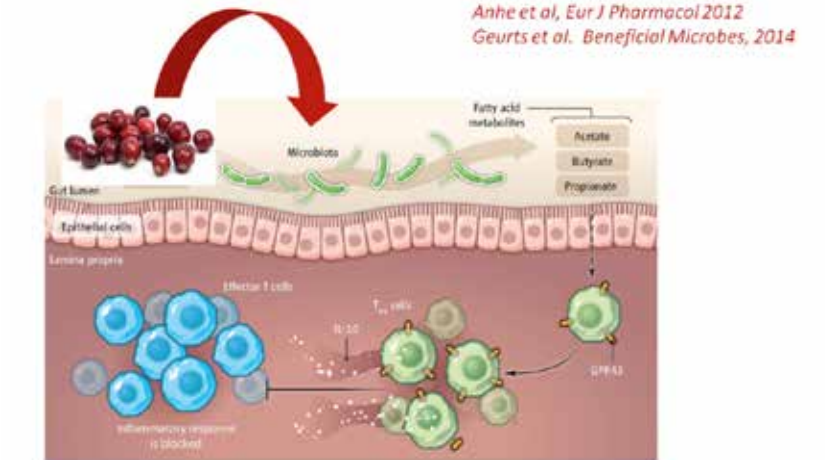
Polyphenols such as those found in Orleans™ strawberries improve insulin sensitivity by stimulating phosphorylation and activation of the insulin receptor, and by increasing expression of the glucose transporter (GLUT4) responsible for glucose uptake in skeletal muscles and adipose tissue.

Molecular mechanisms of strawberry polyphenols



Polyphenols from cranberries rather have a prebiotic action. They improve insulin sensitivity through the modulation of the gut microbiota which in turn releases signaling molecules that counteract inflammation in both intestinal and hepatic tissues. Inflammation is a major factor in the development of insulin resistance.

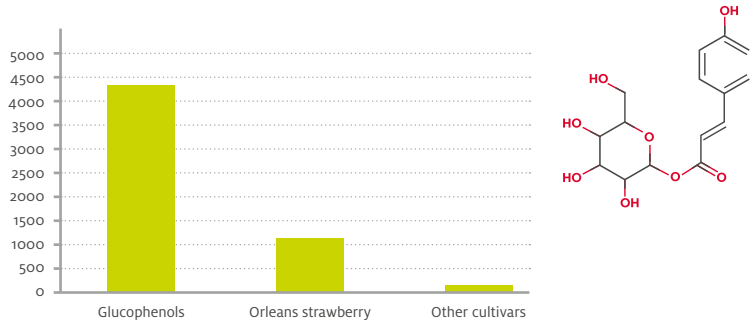
Molecular mechanisms of cranberry polyphenols



The importance of the Orleans variety of strawberries for Glucophenol® activity

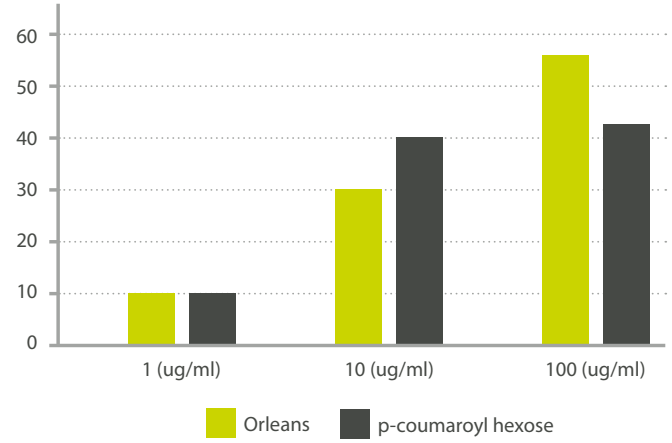
The polyphenol concentration and profile of the Orleans™ strawberry differ significantly from other varieties. The cultivar has a higher content of flavanols and hydroxycinnamic acids and provides an extract that is particularly enriched in p-coumaroyl hexose, a derivative of coumaric acid. Incidentally, the peak in plasma coumaric acid levels correlated with the normalization of insulin production in the clinical trial.

Content in p-coumaroyl-hexose (ppm)



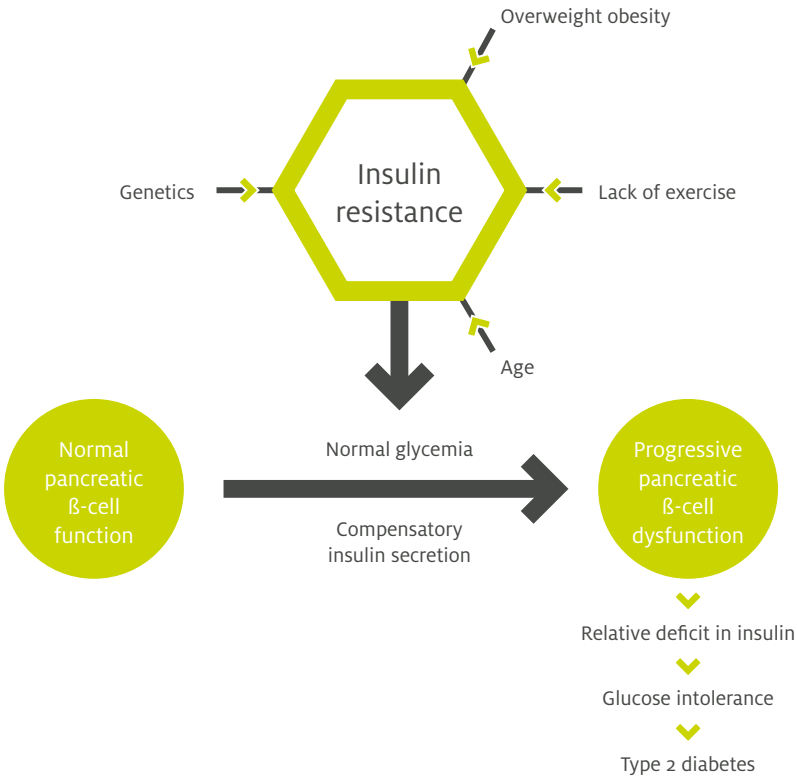
Moreover, the Orleans™ strawberry extract was able to inhibit nitric oxide (NO) secretion in mouse macrophage challenged *in vitro* with lipopolysaccharides (LPS) to create a pro-inflammatory environment. Type 2 diabetes is increasingly recognized as an inflammatory process. In the early stage of the disease, macrophages invade pancreatic tissue, releasing pro-inflammatory cytokines that help destroy beta cells. In more advanced stages, macrophage dysfunction is a likely mechanism underlying common diabetic complications such as increased susceptibility to infection, accelerated atherosclerosis, and disturbed wound healing. NO production is known to be increased in diabetic peoples. Keeping NO release under control, with the help of Orleans™ strawberry extract, may represent a good strategy to halt or prevent the development of type II diabetes.

% Inhibition of LPS-stimulated NO production in mouse macrophages



How insulin resistance may lead to type-2 diabetes

Insulin resistance is a common condition associated with excess weight, sedentary lifestyle, ageing, and genetic predispositions. In people with such profile, there is an overproduction of inflammatory and pro-oxidative molecules that progressively alter the metabolism of glucose. In such conditions, although the body produces insulin, cells inexorably lose their ability to respond to it. When this happens, insulin secretion is increased in a compensatory manner by the pancreas. However with time, the beta-cells responsible for insulin secretion eventually become exhausted, leading to high glucose level and decompensation toward diabetes-2. It is thus important to act early in the presence of predisposing factors, in order to prevent or reverse insulin resistance.



Glucophenol® versus Metformin

Metformin is a hypoglycemic agent commonly used to help control blood sugar levels. It is the first-line drug of choice for treatment of type 2 diabetes, in particular, in overweight and obese people, and those with normal kidney function. Metformin may also decrease the chances of developing the disease in people at risk. Unfortunately, metformin use is sometimes associated with severe adverse reactions, such as lactic acidosis, as well as milder effects, including gastrointestinal irritation, diarrhea, cramps, nausea, vomiting, and increased flatulence.
In a recent study, the efficacy of Metformin at preventing progression to the metabolic syndrome in people with impaired glucose tolerance was evaluated at 17% after 3 years of treatment (*Orchard et al, 2005*). (By comparison, in a similar population, **Glucophenol®** was able to improve insulin sensitivity by 21% within 6 weeks, without any adverse effect.) **Glucophenol®** may thus represent a fair alternative alternative to Metformin, in the prevention of type II diabetes and other conditions associated with it.

People who may benefit from Glucophenol® supplementation

People with increased body mass index, at risk of, or having developed insulin resistance, and also people with normal body mass index with a genetic background or lifestyle predisposing to the development of insulin resistance may benefit from **Glucophenol®** supplementation.

RECOMMENDED DOSAGE		
Glucophenol®	Loading	Maintenance
Suggested dosage	2 x 277 mg/day	277 mg/day
Duration	2 weeks	Minimum 4 weeks
277 mg of **Glucophenol®** contains 50 mg of polyphenols.		

Stability data

Stability curves were performed on **Glucophenol®**. Results showed that the polyphenol content of the extract remains stable for at least 3 years.

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