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Grape Seed Procyanidin Extract (GSPE): Findings From Lab-based Research and Implications for Improving Human Health and Nutrition

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This publication highlights the beneficial effects of a grape seed extract in a rat model of the metabolic syndrome. Grape seed extract significantly reduced serum triglycerides and improved signs of fatty liver in fructose-fed rats. While results from animal studies are not generalizable to humans, this research provides compelling evidence suggesting that clinical intervention trials are warranted to assess whether this extract may indeed have similar effects in humans.

Introduction

This publication summarizes ongoing USDA-funded research in the Department of Agriculture, Nutrition and Veterinary Sciences, focused on understanding the potential health effects of a grape seed procyanidin extract (GSPE). Laboratory-based research in rats suggests that GSPE may play an important role in mitigating a variety of human health problems. However, additional research is necessary in order to fully understand the effects of GSPE in alleviating a suite of human health problems commonly referred to as the *"Metabolic Syndrome"*. **Table 1** provides a collection of terms, abbreviations and definitions useful in understanding the research results presented.

Table 1: Terms, abbreviations and definitions.

Term	Abbreviation	Definition
Cholesterol	CHOL	A lipid found in most human tissues, including blood, that is important in a variety of bodily functions
Flavonoid		A large class of plant pigments
Grape Seed Procyanidin Extract	GSPE	An extract from the seeds of white grapes, *vitis vinifera*, that contains a high concentration of procyanidins
Hyperlipidemic		An abnormally high concentration of fats or lipids in the blood
Hypertriglyceridemia		Elevated triglyceride levels in the blood
Lipogenesis		Synthesis of fat
Lipid		A class of compounds that includes triglycerides and cholesterol
Metabolic Syndrome	MetS	A clustering of metabolic risk factors that increases the risk of cardiovascular disease mortality
Procyanidins		Water-soluble plant pigments
Triglyceride	TG	A type of lipid commonly known as fat

The Metabolic Syndrome

The epidemic of obesity in the U.S. is a primary contributor to the metabolic syndrome (MetS), which is characterized by a clustering of metabolic risk factors, including elevated serum triglyceride levels (hypertriglyceridemia), fatty liver, poor ability to use the hormone insulin (also known as insulin resistance), increased abdominal fat and high blood pressure (hypertension). MetS currently affects approximately one in four adults in the U.S. (Beltran-Sanchez, Harhay, Harhay, & McElligott, 2013). The collective presence of such risk factors doubles the risk of cardiovascular disease and increases the risk for type II diabetes five-fold (Andersen & Fernandez, 2013). Additionally, MetS may increase susceptibility to fatty liver, cholesterol gallstones, asthma and certain forms of cancer (Grundy et al., 2004).

MetS and fructose

Along with MetS, consumption of fructose, a simple sugar that is abundant in processed foods, is on the rise (Vos, Kimmons, Gillespie, Welsh, & Blanck, 2008), and it is estimated that over 10 percent of calories consumed by the average American come from fructose alone (Vos et al., 2008). Excess fructose intake is correlated with increased serum triglyceride levels and fatty liver in humans and animals, therefore inducing MetS (Nomura & Yamanouchi, 2012; Stanhope & Havel, 2010). This occurs because excess fructose consumption has two major metabolic effects. First, it decreases the breakdown and tissue uptake of lipoproteins that are rich in triglycerides, such as low-density lipoproteins (LDLs). This leaves these triglyceride-rich particles to circulate in the blood stream,

leading to elevated serum triglyceride levels. Second, excess fructose intake also increases fat synthesis in the liver, leading to the development of fatty liver (Nomura & Yamanouchi, 2012; Stanhope & Havel, 2010). Fatty liver disease, also referred to as non alcoholic fatty liver disease, is a disorder that is closely related to obesity and diabetes and affects more than 70 million people in the U.S. It causes extensive damage to the liver and in more serious cases, can lead to liver cancer. Currently this disorder has no established treatment.

It is important to note that naturally occurring fructose, such as that found in fruits and vegetables, does not stimulate fat synthesis to the same extent as refined forms of fructose. Most of the fructose consumed in the U.S. originates from sources that are low in fiber and high in simple carbohydrates, such as sugar-sweetened beverages and baked goods, which are more conducive to weight gain (Park & Yetley, 1993). Fruits and vegetables, however, contain smaller amounts of fructose that are absorbed more slowly, due in part to the presence of fiber, leading to a negligible rise in serum fructose levels (Gaby, 2005).

Procyanidins protect against MetS

Diets rich in fruits and vegetables may have protective effects against MetS, since such diets tend to be high in flavonoids (a class of plant pigments), which show cardioprotective effects in humans (Hertog, Feskens, Hollman, Katan, & Kromhout, 1993; Hertog et al., 1995). Dietary procyanidins, a class of flavonoids commonly found in grapes, apples and red wine, have demonstrated an ability to lower risk factors associated with MetS (Kastorini et al., 2011; Rasmussen, Frederiksen, Krogholm, & Poulsen, 2005). Our laboratory research focuses on the molecular actions of a grape seed procyanidin extract (GSPE), which is rich in low molecular weight procyanidins that are more easily taken up in the digestive tract and into the body. In particular, GSPE has shown an ability to decrease serum triglyceride levels in healthy mice (Del Bas et al., 2008; Del Bas et al., 2009; Heidker, Caiozzi, & Ricketts, 2016a, 2016b), rats (Del Bas et al., 2005) and hamsters (Jiao, Zhang, Yu, Huang, & Chen, 2010), making it an attractive natural treatment for lowering high triglyceride levels. The research presented here aimed to determine whether GSPE is effective in lowering serum triglyceride levels in a hyperlipidemic state, meaning in a state where there is an abnormally high concentration of fats or lipids in the blood (Downing et al., 2015). The research presented herein is a condensed version of the full scientific research report, which can be found at the journal website: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0140267.

Methods

The experimental design, shown in **Figure 1**, consisted of laboratory rats that were fed for eight weeks with either: 1) a high-fructose diet (65 percent fructose) to induce hypertriglyceridemia (n=10) or 2) a standard rodent diet (formulated to deliver constant and complete nutrition throughout the rat's life cycle) (n=5). After eight weeks, the rats continued on their respective diets for one additional week, and the high-fructose treatment group was divided into two treatment sub groups (n=5 per group). One group was administered GSPE (250 mg/kg) (Fructose-GSPE), while the other group was administered water (Fructose-Vehicle). The control group (standard rodent diet) was also administered water (Control-Vehicle). After seven days of treatment with GSPE or water, liver and blood specimens were collected from the rats for analysis.

High-fructose diets are known to contribute to elevated triglycerides and fatty liver in experimental models (Bremer et al., 2014; Gao et al., 2012; Kelley & Azhar, 2005). This study was designed to use acute amounts of fructose to potently induce such characteristics in the rats, so that the effects of GSPE in a hyperlipidemic state could be assessed. However, it is important to note that, while humans don't consume fructose at the levels used in this study on a daily basis, chronically

consuming relatively high levels of fructose over an extended period of time in a refined form (e.g. high-fructose corn syrup) is associated with the development of fatty liver and increased serum triglyceride levels in humans (Cox et al., 2012; Perez-Pozo et al., 2010; Stanhope, 2012).

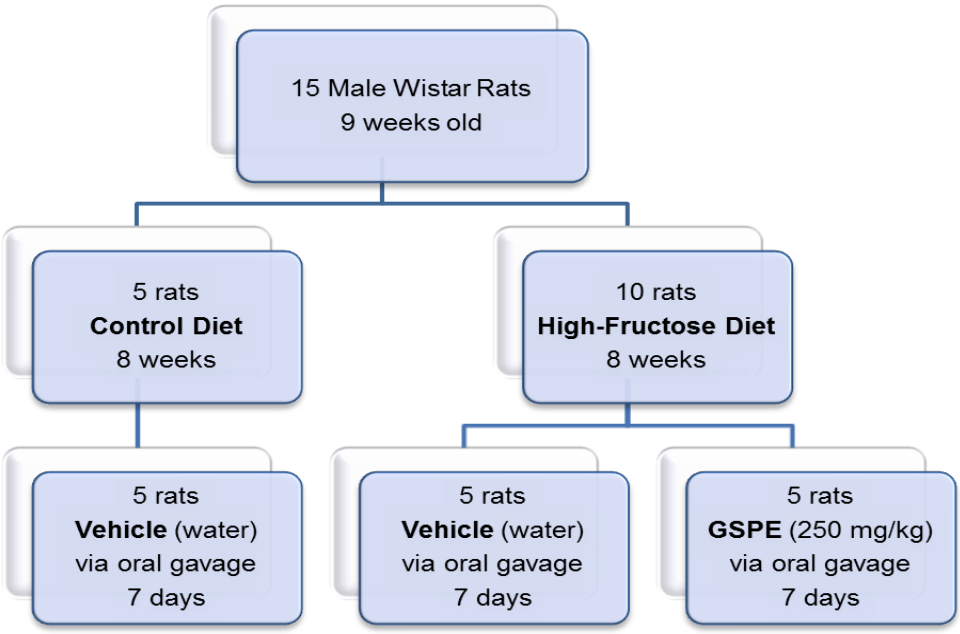

Figure 1: Dietary intervention and group assignment during the nine-week study.

Results

Effects on serum triglyceride levels

The high-fructose diet increased serum triglyceride levels in the fructose-vehicle treatment group by 171 percent, compared to the control group (standard rodent diet), indicative of hypertriglyceridemia (**Figure 2**). GSPE administration in the presence of the high-fructose diet decreased serum triglyceride levels by 41 percent, compared to the fructose-vehicle group (**Figure 2**). In comparison to this 41 percent decrease observed in the presence of GSPE, *fenofibrate*, a pharmaceutical commonly prescribed to treat hypertriglyceridemia, lowers serum triglycerides by only 36 percent (Birjmohun, Hutten, Kastelein, & Stroes, 2005; Moutzouri, Kei, Elisaf, & Milionis, 2010).

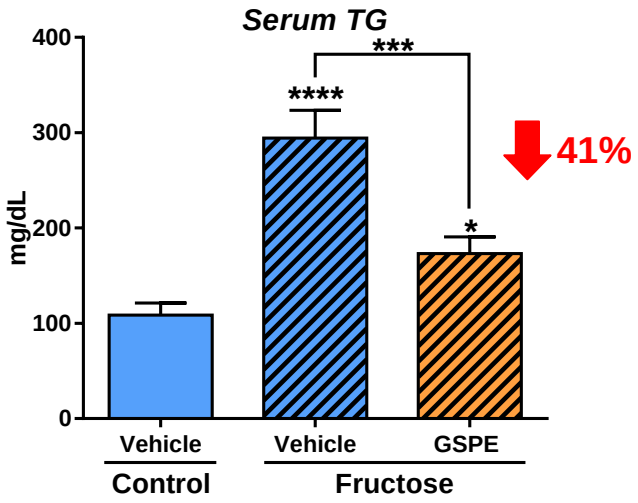

Figure 2: GSPE reduces serum triglycerides by 41 percent in rats in the presence of fructose. TG: Triglycerides. (n=4 or 5 per treatment, per group, in triplicate). Statistical significance: *p<0.05, ***p<0.001, ****p<0.0001. Asterisks above the bars are in comparison to the control unless otherwise indicated. Reproduced with modification from (Downing et al., 2015).

Liver lipids

The high-fructose diet increased lipid accumulation in the liver, compared to the control diet, and this effect was reduced by GSPE treatment (**Figure 3**). The white dots on the liver histology sections shown below the graph indicate lipid droplets, which were higher in number and larger in size in the animals fed fructose without GSPE treatment. There are fewer, and smaller, lipid droplets present in the livers of the fructose-fed animals that also received GSPE. Hepatic cholesterol, an indicator of liver fat accumulation (Fernandez, Colell, Garcia-Ruiz, & Fernandez-Checa, 2008), was also decreased with GSPE treatment (results not shown).

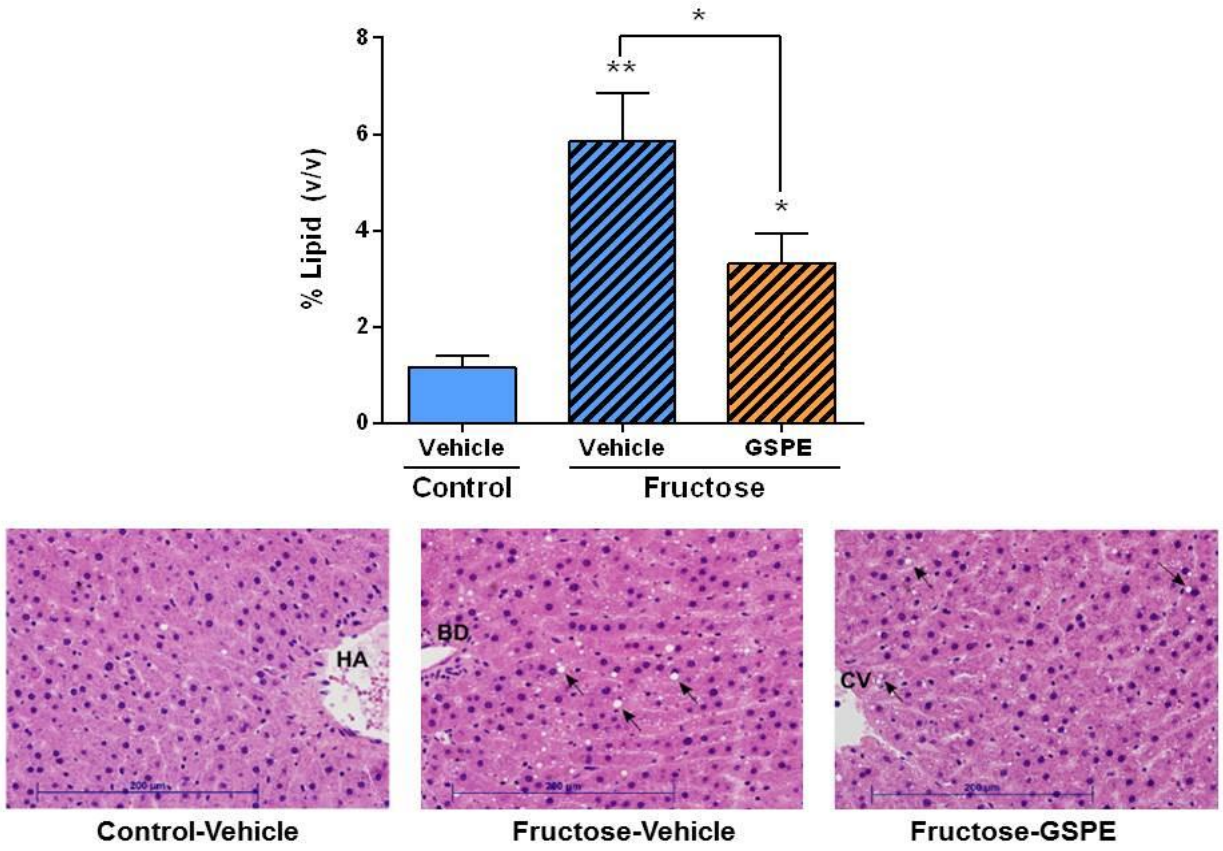

Figure 3: GSPE decreases hepatic lipid accumulation in the presence of fructose. (n=4 or 5 per treatment, per group, in triplicate). Statistical significance: *p<0.05, **p<0.01. Asterisks above the bars are in comparison to the control unless otherwise indicated. Reproduced with modification from (Downing et al., 2015).

Gene expression

The expression of several genes was altered by fructose feeding. Furthermore, consumption of GSPE in conjunction with fructose led to differing gene expression profiles. These alterations in gene expression resulted in the following physiological changes:

- High levels of fructose in the diet caused an increase in the amount of fat produced by the liver.
- The expression of genes involved in the synthesis of triglycerides (i.e. fat) in the liver was decreased following GSPE treatment.
- In order to prevent the continued production of fat within the liver (induced by the high levels of fructose consumed from the diet) GSPE redirected the by-products from fructose metabolism to be converted into cholesterol instead of fat. This cholesterol was then removed from the liver and eventually excreted from the body via the feces (**Figure 4**).
- Removal of this cholesterol from the liver is an important step in protecting the health of the liver, since cholesterol is a major driving force in the development of fatty liver disease (Min et al., 2012; Wouters et al., 2008).
- GSPE treatment not only increased the excretion of cholesterol via the feces, but also total lipids (**Figure 4**).
- These results indicate a possible avenue through which the excess cholesterol produced in the liver was removed from the body.

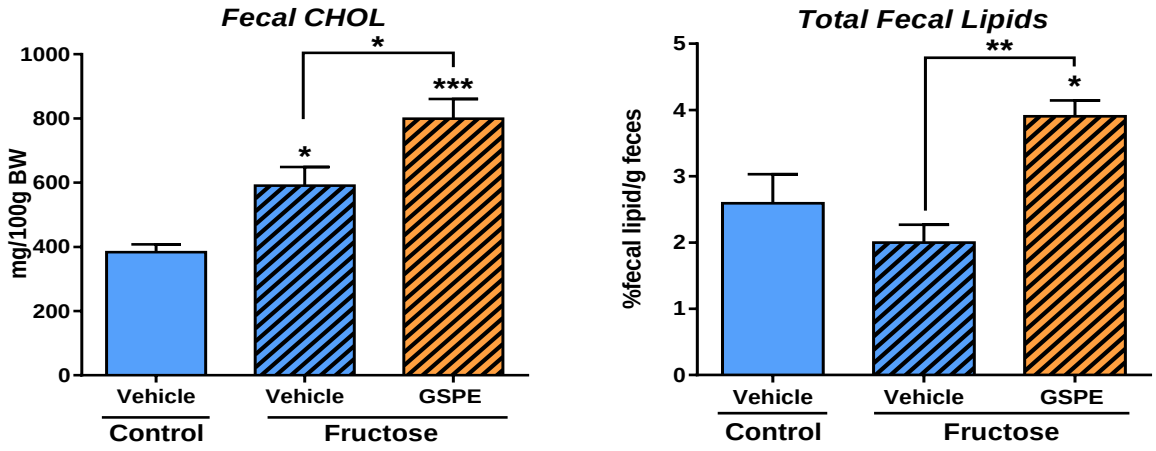

Figure 4: GSPE increases fecal cholesterol and total fecal lipid excretion in rats in the presence of fructose. CHOL: Cholesterol (n=4 or 5 per treatment, per group, in triplicate). Statistical significance: *p<0.05, **p<0.01, ***p<0.001. Asterisks above the bars are in comparison to the control unless otherwise indicated. Reproduced with modification from (Downing et al., 2015).

What the findings of this study reveal:

The key findings regarding the effects of GSPE obtained from this laboratory-based research in a rat model are as follows:

- GSPE decreases the synthesis of triglycerides in the liver and reduces serum triglyceride levels in the presence of a diet containing high levels of fructose
- As a result of reducing triglyceride synthesis in the liver, GSPE increases the synthesis of cholesterol in the presence of a diet containing high levels of fructose
- In order to protect the liver from the increased accumulation of fats, initiated by the high-fructose diet, and therefore prevent the development of fatty liver, GSPE directs this newly made cholesterol to be excreted from the body via the feces

Relevance of dose used

It is important to note that the dose used in the current study involving laboratory rats (250 mg/kg GSPE) is equivalent to approximately 1800 mg in humans, based on metabolic comparison (Clifton, 2004). The mean procyanidin intake by adults in the U.S. from dietary sources is reported to be 95 mg per day (Wang et al., 2011). However, in comparison, the mean intake in Finland ranges from 448 to 1278 mg per day (Ovaskainen et al., 2008), levels which were achieved by increased dietary consumption of fruits and vegetables. The evidence from Finland strongly suggests that a substantial increase in procyanidin intake can be achieved through dietary means.

Healthy Eating:

Eating the recommended five servings per day of fruits and vegetables is an important aspect of a healthy eating plan. Since procyanidins are a major component of a plant-based diet, and have important implications for health, it is important that the average American diet provides more than the reported current intake of approximately 95 mg of procyanidins per day (Wang, Chung, Song, & Chun, 2011). Increased intake of fruits and vegetables would increase the potential for health benefits associated with procyanidin intake. Combined with reduced consumption of sugary drinks, soda, and baked and processed foods, modification of the American diet could lead to a reduction in the incidence of obesity, cardiovascular disease, fatty liver and the metabolic syndrome. Based on the results of this study in rats, taking a grape seed extract that is rich in procyanidins, may also be beneficial for both liver and heart health, suggesting that further studies in human subjects is warranted.

Conclusion

Our results using a rat model demonstrate that GSPE, in the presence of fructose, exerts a potent triglyceride-lowering effect by altering gene expression patterns to decrease fat synthesis in the liver and excrete more cholesterol in the feces. The changes induced by GSPE aim to protect the liver from the deleterious effects of consuming a high-fructose diet. The results from this study provide important insight into the actions of GSPE at the molecular level and increase our understanding regarding the beneficial effects of grape seed procyanidins. Ultimately this knowledge will aid in future studies to assess the beneficial effects of dietary procyanidins in human subjects.

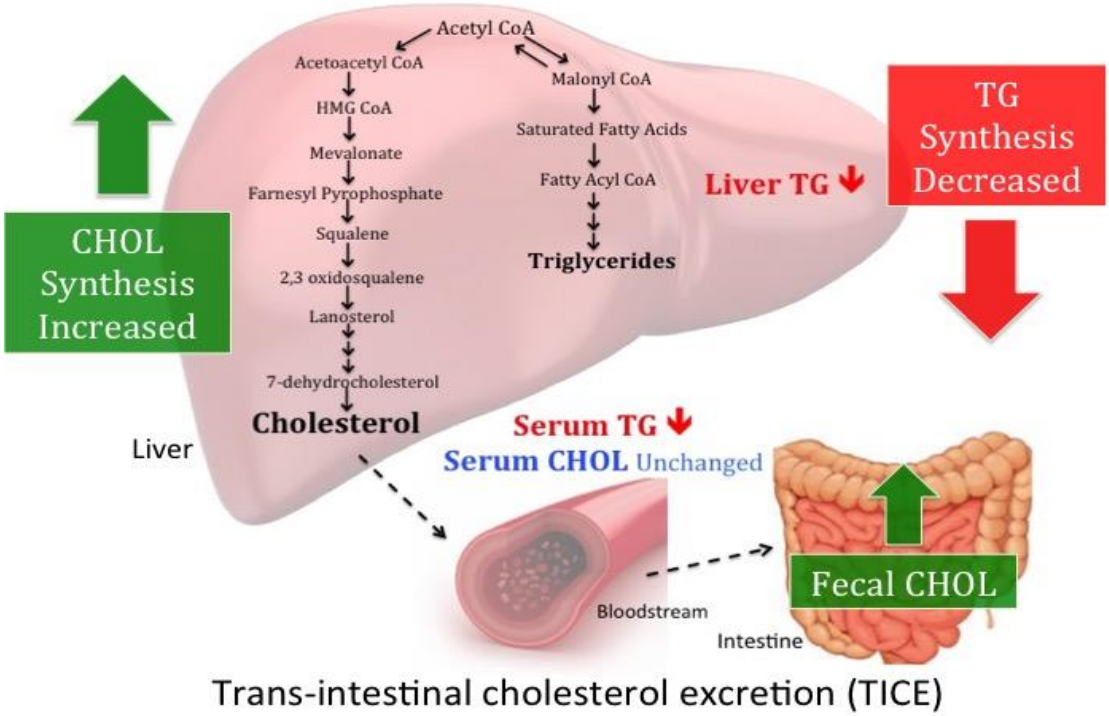

Figure 5: The proposed mechanism through which GSPE acts in the liver to maintain lipid homeostasis and decrease serum triglyceride levels.

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