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Pharmacy Research at URI: Mining Red Maple (*Acer rubrum*) Trees for Novel Therapeutics to Manage Diabetes

Navindra P. Seeram, PhD, Jialin Xu, PhD, Liya Li, PhD, and Angela Slitt, PhD

TYPE 2 DIABETES MELLITUS (T2DM) accounts for about 90% of all diagnosed cases of diabetes in adults. Over 200 million people suffer from this disease worldwide. In the United States alone, in 2007, 10% of American adults had diabetes and the cost of management was $174 billion and this figure is expected to skyrocket (Centers for Disease Control and Prevention, 2010). Plants and their derived products have been used for centuries by various cultures as traditional medicines for the management of diabetes. Plants contain secondary metabolites (known as phytochemicals; 'phyto' means plant), which are implicated in the prevention and treatment of several chronic human diseases, including diabetes. Among these natural products, polyphenols and phenolic glycosides, have attracted significant interests for their anti-diabetic properties.

Plant polyphenols as α-glucosidase inhibitors. Dietary carbohydrates are hydrolyzed by pancreatic α-amylase with absorption aided by α-glucosidases and thus, inhibition of the activities of these enzymes is a promising approach for managing T2DM. In fact, the clinical α-glucosidase inhibitor, acarbose, has been shown to effectively reduce glycated hemoglobin levels when given as monotherapy or as an add-on to other antidiabetic drug treatment.[1] Additionally, a fixed dose combination of acarbose and metformin was reported to be superior to metformin alone in controlling HbA1c, fasting blood glucose, and post prandial blood glucose levels in T2DM patients,[2] as well as, enhancing the blood glucose control.[3] Multiple plant-derived polyphenols have been investigated as α-glucosidase inhibitors. Extracts from grape seeds and green tea been demonstrated to exert inhibition on α-glucosidase activity.[4] We recently have shown a similar activity for phenolic-enriched extracts from the bark of *Acer rubrum*, commonly known as red maple.

Study of maple for novel therapeutics. The sugar maple (*Acer saccharum*) and red maple plant species are native to eastern North America and highly regarded for their sap which is used to produce the natural sweetener, maple syrup. Our laboratory has recently identified a number of phenolic compounds native in maple plant parts that are also present in maple syrup.[5]

Here we report a case study in which the ability of **red maple bark extract (MBE)** to decrease elevation of blood glucose levels was investigated. Male adult C57BL/6 mice were administered MBE in combination with a bolus sucrose challenge to evaluate the effect of MBE or acarbose on α-glucosidase activity *in vivo* according to described methods.[6] As expected, mice receiving a bolus sucrose challenge increased blood glucose concentration 30, 60, and 90 minutes after administration compared to initial blood glucose concentration. (Figure 1) Both MBE and acarbose significantly lowered blood glucose concentrations at these time intervals after the sucrose challenge. Compared to acarbose, MBE was less effective, but did impart a significant inhibitory effect. We now hope to further purify and evaluate individual phytochemicals of MBE to evaluate for activity against sucrose-induced glucose elevation.

We have demonstrated that phenolic glycosides are present in various maple constituents. The isolated compounds and extracts inhibit α-glucosidase activity *in vitro*.[7,8] Recently, multiple gallotannins, named maplexins A-E, were isolated from red maple stems and bark.[7,8] These maplexin compounds were shown *in vitro* to possess more activity than acarbose for inhibition of α-glucosidase activity (IC_{50} = 8 vs. 160 μM; maplexin E vs. acarbose, respectively). These interesting maplexin compounds, that are as effective as acarbose *in vitro*, will be further evaluated and developed to determine whether they impart beneficial properties in preventing blood glucose elevations *in vivo*. Overall, we determined that MBE contains bioactive constituents that can potentially aid

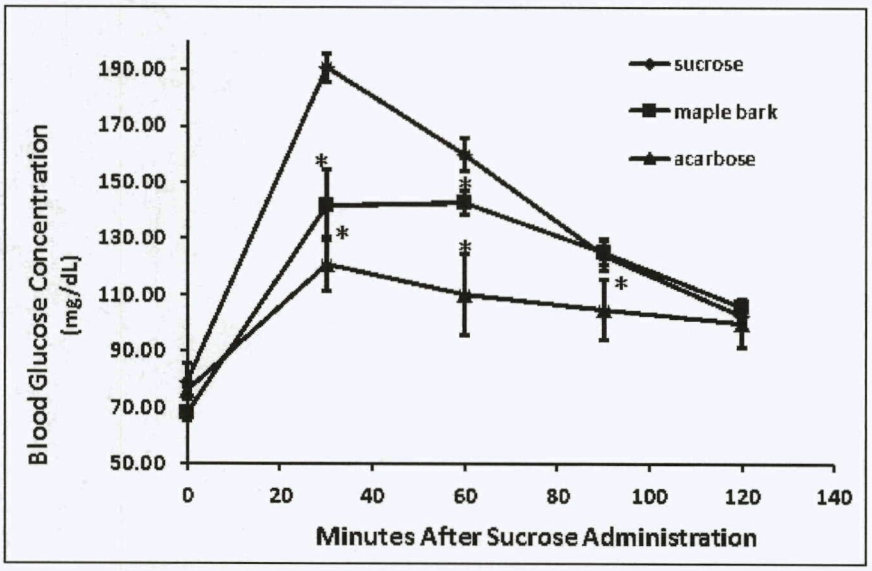

Figure 1. Adult male C57BL/6 mice were administered sucrose (3g/kg BW), sucrose and acarbose (3g/kg BW + 3 mg/kg BW), or 3) sucrose and maple bark extract (3g/kg BW+150mg/kg BW) by oral gavage. Blood glucose levels were determined by tail bleed at 0, 30, 60, 90, and 120 minutes post sucrose administration. An asterisk (*) denotes statistical significance ($p<0.05$) from the sucrose treatment group.

in the regulation of blood glucose control after a carbohydrate challenge.

We will continue to explore how bioactive extracts and molecules isolated from plants can impart beneficial effects on metabolic syndrome. As metabolic syndrome encompasses T2DM, dyslipidemia, systemic inflammation, and non-alcoholic fatty liver disease, the potential therapeutics isolated will be tested in various cell-based and in vivo models. We are currently exploring anti-inflammatory effects of maple-derived extracts and compounds, as well as, the potential for plant-derived extracts to augment weight loss and T2DM therapies. Ultimately, we hope that identification of beneficial components in foods commonly consumed can arm the consumer with information to make better food choices that can be synergistic with drug therapies used to treat T2DM. We also will continue to mine botanicals for potential therapies to treat T2DM or enhance activity of commonly prescribed anti-diabetes therapies.

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Disclosure of Financial Interests

The authors and/or their spouses/significant others have no financial interests to disclose.

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