UNIVERSITY OF SÃO PAULO

School of Pharmaceutical Science

Graduate Program in Food Science

Field of Study Bromatologie

Biomarker exposure of phenolic compounds from grumixama (*Eugenia
brasiliensis* Lam.) in healthy human model: Metabolomic approach

Luciane de Lira Teixeira

Thesis for obtaining DOCTORAL degree
in Science

Advisor: Profa. Dra. Neuza Mariko
Aymoto Hassimotto

São Paulo

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Corrected version of Thesis according to resolution CoPGr 6018.

The original version is available at the Post-Graduation Service of FCF/USP

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2016

Ficha Catalográfica
Elaborada pela Divisão de Biblioteca e
Documentação do Conjunto das Químicas da USP.

Teixeira, Luciane de Lira
T266b Biomarker exposure of phenolic compounds from grumixama
 (*Eugenia brasiliensis* Lam.) in healthy human model: metabolomics
 approach / Luciane de Lira Teixeira -- São Paulo, 2016.
 157p.

 Thesis (doctorate) -- School of Pharmaceutical Science of
University of São Paulo. Department of Food and Experimental
Nutrition.
 Advisor: Hassimotto, Neuza Mariko Aymoto.

 1. Alimento : Composto fenólico : Ciência dos alimentos
2. Metabólitos I. T. II. Hassimotto, Neuza Mariko Aymoto,
advisor.

Luciane de Lira Teixeira

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Referee Commission

Thesis for obtaining doctoral degree in Science

Profa. Dra. Neuza Mariko Aymoto Hassimotto

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1° Examiner

2° Examiner

3° Examiner

4° Examiner

São Paulo, _____ of _____ of 2016

ACKNOWLEDGMENTS

I would like to thank God to make me strong during my four years of doctoral course.

To my family and friends, including my ex-husband, to encourage me to do my doctoral course at University of São Paulo.

To my advisor, Professor Neuza Mariko Aymoto Hassimotto, for being the best advisor I could have here.

Special thanks to Professor Franco Maria Lajolo, Professor Ernani Pinto, Professor Thomas Prates Ong, PhD Fabiane Dörr, PhD Felipe Dörr and Msc Gabriela Rezende Souza to collaborate with my work.

Special thanks to the laboratory technicians, PhD Tânia Shiga, Lúcia Helena Justinos and Elias Araújo to the great work and support.

I would like to thank PhD Silas G. Villas-Bôas to advise me about the metabolomic analysis and for the great opportunity of a short internship at University of Auckland (Auckland, New Zealand), as well to all friends that I made in his laboratory. Thanks for Núcleo de Apoio a Pesquisa em Alimentos e Nutrição (NAPAN) for providing the scholarship.

I would like also to thank PhD André Marette, PhD Geneviève Pilon and PhD Yves Desjardans to receive me for an internship at Université Laval (Québec, Canadá), specially to Geneviève Chevrier for being a great friend. Thanks for CAPES for providing the scholarship.

Thanks to CNPq for providing scholarship and FAPESP (Forc-CEPID) for financial support.

I learned a lot in all opportunities that I received during my doctoral course and I am sure that these learning made me a better researcher and person.

Resumo

TEIXEIRA, L.L. **Identificação de biomarcadores de exposição de compostos fenólicos de grumixama (*Eugenia brasiliensis* Lam.): Abordagem metabolômica.** 2016. 157f. Tese (Doctoral degree) - Faculdade de Ciências Farmacêuticas, Universidade de São Paulo, São Paulo, 2016.

O consumo de frutas e verduras na dieta está associado à redução da incidência de doenças crônicas não transmissíveis entre eles câncer, síndrome metabólica e doenças cardiovasculares. A atividade biológica atribuída à ingestão desses alimentos é relacionada principalmente à presença de compostos bioativos, entre eles os compostos fenólicos, tais como flavonoides e elagitaninos. Contudo, a biodisponibilidade e a influência destes compostos no metabolismo humano não estão estabelecidas. Assim, o objetivo geral do presente estudo foi investigar as alterações no metaboloma humano decorrente da ingestão de uma fonte rica em compostos fenólicos, o suco da grumixama roxa (*Eugenia brasiliensis* Lam.), buscando identificar possíveis pontos de regulação do metabolismo. Para isto, a grumixama, variedades amarela e roxa, foram caracterizadas quanto ao seu perfil de compostos fenólicos e administradas na forma de suco, em dose única, a voluntários saudáveis. A grumixama roxa se mostrou rica em antocianinas e elagitaninos, principalmente cianidina 3-*O*-glicosídeo e a strictinina, respectivamente. Para o ensaio clínico, 15 voluntários saudáveis consumiram, em dose única, suco de grumixama roxa (10 ml de suco/kg de peso corporal). Amostras de plasma e urina foram coletadas em diferentes tempos durante 24 h após ingestão e analisados por CG-MS e LC-ESI-MS/MS. Os metabólitos exógenos excretados na urina foram identificados como urolitinas e ácidos fenólicos, derivados da degradação, principalmente, pela microbiota dos elagitaninos e das antocianinas, respectivamente. Quatro urolitinas (A, B, C e D) foram encontradas na urina, principalmente como metabólitos de fase II, detectados a partir de 4 h após a ingestão do suco com aumento na concentração observado até 24h. Além disso, quatro ácidos fenólicos foram identificados, destes o ácido hipúrico como majoritário. 114 metabólitos, entre eles, 17 aminoácidos, 47 ácidos orgânicos, 7 outras classes de compostos e 43 compostos desconhecidos foram identificados por CG-MS, para os tempos de coleta de urina antes da ingestão de suco de grumixama (T0) e para os períodos de 1-2 h e 2-4 h após a ingestão. A OPLS-DA foi utilizada para discriminar os metabólitos alterados pela ingestão de suco de grumixama. A análise das vias metabólicas mostrou que a ingestão do suco de grumixama influenciou principalmente em três vias metabólicas: metabolismo do glioxilato e dicarboxilato (*up-regulated*), da beta-alanina (*down-regulated*) e da fenilalanina (*up-regulated*), sendo essas direcionadas ao metabolismo energético. Além disso, os extratos de grumixama roxa e amarela também foram testados em modelo animal (camundongo C57BL/6J) de obesidade e resistência à insulina induzido por uma dieta rica em lipídeos e açúcares. O tratamento com os extratos, concomitante à dieta e durante 8 semanas, promoveu modulação significativa do metabolismo lipídico. Como conclusões, a grumixama roxa mostrou ser uma boa fonte de antocianinas e elagitaninos, e a interação entre metabólitos oriundos da ingestão do fruto e dos metabólitos endógenos podem estar relacionados com alterações nos metabolismos de aminoácidos e energético. No entanto, mais estudos são necessários para elucidar e validar as hipóteses geradas.

Palavras-chave: grumixama, antocianinas, elagitaninos, urolitinas, aminoácidos, ácidos orgânicos, metabolômica.

ABSTRACT

TEIXEIRA, L.L. **Biomarker exposure of phenolic compounds from grumixama (*Eugenia brasiliensis* Lam.) in healthy human model: Metabolomic approach.** 2016. 157f. Tese (Doutorado) - School of Pharmaceutical Sciences, University of São Paulo, São Paulo, 2016.

The fruits and vegetables intake has been associated to the reduction of chronic non-communicable disease incidence, such as cancer, metabolic syndrome and cardiovascular diseases. The biological activities attribute to them has been related mainly to the phenolic compounds, such as flavonoids and ellagitannins, presents in their composition. However, the bioavailability and influence of these compounds under human metabolism still unclear. Thus, the objective of the present study was investigate changes in human metaboloma as a result of the acute intake of the polyphenol-rich source from purple grumixama juice (*Eugenia brasiliensis* Lam.), searching to identify possible sites of metabolic regulation. In this way, purple and yellow grumixama varieties were characterized to polyphenol profile, and a single dose of the purple grumixama juice was administered to healthy human. The purple grumixama showed be a good source of anthocyanins and ellagitannins, mainly cyanidin 3-*O*-glucoside and strictinin, respectively. In the clinical trial, 15 healthy subjects intake a single dose of purple grumixama juice (10 ml of juice/kg of body mass). Plasma and urine samples were collected, before and after intake (over 24 h), and analyzed by GC-MS and LC-MS. The exogenous metabolites excreted and identified in urine samples by LC-MS were identified as urolithins and phenolic acids, gut microbiota catabolites of ellagitannins and anthocyanins, respectively. Four urolithins were detected beginning excretion 4 h after juice intake, increasing over 24 h. Furthermore, four phenolic acids were identified, being the hippuric acid the majority of them. 114 metabolites were identified to urine collection points before and after intake (1-2 h and 2-4 h) by CG-MS, being 17 amino acids, 7 other classes, 47 organic acids and 43 unknown compounds. A OPLS-DA discriminated the metabolites changed by the grumixama juice intake. The pathway analysis showed that juice intake influenced mainly three metabolic pathways: glyoxylate and dicarboxylate metabolism (up-regulated), betalanine metabolism (down-regulated), and phenylalanine metabolism (up-regulated), being these pathways related to energetic metabolism. Furthermore, the purple and yellow grumixama fruits extracts were evaluated in animal model of obesity and insulin resistance (C57BL/6J mice) induced by high fatty and high sugar diet. The treatment, during 8 weeks, promoted lipid metabolism modulation. As conclusions, purple grumixama showed to be a good source of anthocyanins and ellagitannins, and the interaction among the metabolites from fruits and endogenous metabolites can be related to changes in energetic metabolism and amino acid metabolism. However, more studies are necessary to elucidate and validate these hypotheses.

Key-words: grumixama, anthocyanins, ellagitannins, amino acids, organic acids, metabolomic.

1 INTRODUCTION

The healthy conditions have been associated to the food quality intake during the life. The intake of fruits and vegetables has been related to the reduction of incidence of chronic diseases such as cancer, metabolic syndrome and cardiovascular diseases (PAREDES-LÓPEZ *et al.*, 2010). The health benefits associated to fruits and vegetables-rich diets have been attributed to bioactive compounds that can be essential nutrients, such as ω 3-fatty acids and vitamin C, and non-essential nutrients, such as carotenoids and phenolic compounds (CLIFFORD and BROWN, 2006; SCALBERT *et al.*, 2014).

Nutritional intervention studies have been looking for explanations to biological activities attributed to nutrients and non-nutrients bioactive compounds and their role on health promotion (SCALBERT *et al.*, 2014). These bioactive compounds can interact with human organism playing an important role by modulating enzyme systems (SZOTAKOVA *et al.*, 2013), transcription factors (SALAMONE *et al.*, 2016), proteins expression, signaling cascade (EDWARDS *et al.*, 2015) and showing more directly antioxidant activity (DÍAZ-RUBIO *et al.*, 2015).

The metabolomic approach shows to be a powerful tool to help to explain these biological activities, attributed to nutrients and non-nutrients compounds.

Among the “omics” (Proteomic, Genomic, Metabolomic and Transcriptomic), the metabolomic approach showed to be the most directly related to possible biological effects of the nutrition intervention (HERRERO *et al.*, 2012; SCALBERT *et al.*, 2014), due to its search for metabolites, which could express an end product of the biological system. Metabolomic studies are used to identify biomarkers of exposure from food and endogenous metabolome, trying to understand the interaction among them (SCALBERT *et al.*, 2014) and their interaction with also gut microbiota (VERNOCCHI *et al.*, 2012). Usually, the metabolites are separated in endogenous and exogenous compounds (SCALBERT *et al.*, 2014), but it is also possible to identify metabolites that can be both or be formed from gut microbiota (VERNOCCHI *et al.*, 2012, JACOBS *et al.*, 2012). The metabolomic studies can be classified in targeted and untargeted studies, being the search for metabolites specific and unspecific, respectively. This classification is a direct consequence of sample preparation and extraction which will direct the findings to specific (targeted) or unspecific metabolites (untargeted).

Among the non-nutrients, bioactive compounds, the phenolic compounds present in high amount in fruits and vegetables have been associated to the biological activities, such as

flavonoids and ellagitannins (ETs) (PAREDES-LÓPEZ *et al.*, 2010, LLORACH *et al.*, 2014; DÍAZ-RUBIO *et al.*, 2015). Flavonoids have showed modulate some important pathways as amino acid metabolism (JACOBS *et al.* 2012) and steroid biosynthesis (MEDINA *et al.*, 2013). However, most of the studies involving metabolomic approach search for exogenous metabolites (LLORACH *et al.*, 2014).

Several biological activities have been attributed to phenolic compounds, including anti-inflammatory, antioxidant and anti-proliferative activities and apoptosis (LI *et al.*, 2009; LI *et al.*, 2011). However, the biological relevance of anthocyanin and ETs intake have been discussed extensively due to the low bioavailability of the native structure, and the beneficial effects have been attributed to the catabolites formed by gut microbiota degradation (KAY, KROON and CASSIDY, 2009; WILLIAMSON and CLIFFORD, 2010). The main catabolites associated with anthocyanins and ETs metabolism are phenolic acids (VITAGLIONE *et al.*, 2007; CZANK *et al.*, 2013) and urolithins (GONZALEZ-BARRIO *et al.*, 2010; GARCÍA-VILLALBA *et al.*, 2013; GARCÍA-MUÑOZ *et al.*, 2014), respectively, which shows the importance of gut microbiota in polyphenol bioavailability assessment.

Anthocyanin bioavailability has been found to be less than 1% of intake (DEL RIO *et al.*, 2013) (considering 690 mg intake) (WU *et al.*, 2002). Overall, 70% disappeared from the gastrointestinal tract after 4 h through gut microbiota action and also by spontaneous degradation by neutral pH (VITAGLIONE *et al.*, 2007; FANG, 2014). When the catabolites, such as phenolic acids, were considered, the bioavailability increased to approximately 12% (CZANK *et al.*, 2013).

Similarly, ETs were not bioavailable and were metabolized by gut microbiota to form dibenzopyranone compounds, which are also known as urolithins (GONZALEZ-BARRIO *et al.*, 2010; GARCÍA-VILLALBA *et al.*, 2013; TULIPANI *et al.*, 2012; SELMA *et al.*, 2014; LUDWIG *et al.*, 2015). The urolithins can be transformed by the ellagic acid (EA) that is already present in the food matrix or by the EA formed by the action of gut microbiota under the ETs (GARCÍA-VILLALBA *et al.*, 2013; GARCÍA-MUÑOZ *et al.*, 2015).

The grumixama (*Eugenia brasilienses* Lam.) is a cherry, approximately 2.0 cm in diameter, containing one or many seeds, and is somewhat sweet. It belongs to the Myrtaceae family and is a native fruit of the southern and southeastern regions of the Atlantic Forest of Brazil. Three varieties were recognized by Cambessèdes (1832–1833) according to their fruit colors: The α -variety or purple fruit is the most common and is known as the Brazilian cherry (MORENO *et al.*, 2007; FLORES *et al.*, 2012). The β -variety has red fruit, and the γ -variety has white fruit, although it was also described by Mattos (1984) as being yellow (MORENO

et al., 2007). Despite belonging to the same species, the yellow and purple varieties show distinct chemotypes with respect to the terpene profiles in the leaves and fruits (MORENO *et al.*, 2007). Grumixama is rarely consumed as a fresh fruit, but is commonly used to produce fruit juice and frozen pulp, with the pulp frequently containing a mixture of the purple and yellow forms. Although still limited, commercial cultivation has begun in recent years, and this plant represents economic potential due to the attractive sensory attributes and phenolic compounds in its composition, including ellagitannins and flavonoids (REYNERTSON *et al.*, 2008; FLORES *et al.*, 2012; ABE *et al.*, 2012).

In general, fruits belonging to this family are known to be good sources of bioactive compounds (REYNERTSON *et al.*, 2008; FRACASSETTI *et al.*, 2013). The purple grumixama fruit was shown to be rich in anthocyanins, mainly cyanidin-3-glucoside, and carotenoids, mainly monohydroxy carotenoids such as all-trans- β -cryptoxanthin (Flores *et al.*, 2012; SILVA *et al.*, 2014). High antioxidant capacity (REYNERTSON *et al.*, 2008) and anti-inflammatory activity (FLORES *et al.*, 2012) have been demonstrated. However, no information about phenolic composition, the antioxidant capacity, or other biological activities of the yellow fruit was previously available.

As a member of the Myrtaceae family, in addition to the flavonoids, grumixama would also be expected to be rich in ETs and EA derivatives, another class of phenolic compounds. This class of phenolics is relatively uncommon in dietary fruits and vegetables, although a few berries, such as strawberry, raspberry, blackberry, and pomegranate, have substantial contents of these compounds (KASIMSETTY *et al.*, 2010; LANDETE *et al.*, 2011; SANGIOVANNI *et al.*, 2013). It has been suggested that ETs as well as flavonoids may prevent chronic diseases such as cancer and cardiovascular diseases. These protective activities are attributed to both classes of phytochemicals, which are thought to provide antiproliferative (ASCACIO-VALDÉS *et al.*, 2011), anti-inflammatory, and antioxidant activities (SANGIOVANNI *et al.*, 2013; MORTON *et al.*, 2000; NIJVELDT *et al.*, 2001; CLIFFORD and BROWN, 2006) and to function as glycemic regulators (ASCACIO-VALDÉS *et al.*, 2011; ȘTEFĂNUȚ *et al.*, 2013; SEPÚLVEDA *et al.*, 2011).

Several biological activities have been attributed to both phenolic compounds, including anti-inflammatory, antioxidant and anti-proliferative activities and apoptosis (LI *et al.*, 2009; LI *et al.*, 2011). Among the biological activities, the antiproliferative activity of metabolites in breast cancer cells and the effects of polyphenols against non-alcoholic fatty liver disease had been explored in this thesis.

The anti-tumor activity of anthocyanins and ETs from many fruit and vegetable extracts have been explored in mammal cells. Berries such as blackberry, raspberry, blueberry and strawberry have demonstrated inhibitory activity and apoptosis in oral (KB, CAL-27), breast (MCF-7), colon (HT-29, HCT116), and prostate (LNCaP) cancer cells (SEERAM *et al.*, 2006). Anthocyanin has been found in raspberry extract, but the anti-proliferative activity on HeLa cancer cells was mainly associated with ETs (ROSS *et al.*, 2007). In addition, EA also demonstrated anti-proliferative activity against lung (NCI 460), breast (MCF-7) and ovary (OVCAR03) cancer cells, and the activity was more efficient compared to strawberry and strawberry' ETs extracts (PINTO *et al.*, 2010). Additionally, urolithins strongly inhibited both androgen-dependent and androgen-independent prostate cancer cells (CaP) (KASIMSETTY *et al.*, 2010).

Non-alcoholic fatty liver disease (NAFLD) is extensively reported worldwide and it is related to metabolic syndrome associated to insulin resistance and obesity (ROY *et al.*, 2013; CUI *et al.*, 2014). NAFLD can carry out to development of liver inflammation, steatohepatitis, hepatic fibrosis and cirrhosis (PAN *et al.*, 2015). The pathogenesis of NAFLD has showed be deeply associated to metabolism disorders that promote the energy storage as triglycerides in steatotic hepatocytes in adipocyte-packed vacuoles. Insulin resistance and fatty acid metabolism disorders and inflammatory disorders have been usually associated with NAFLD (BERLANGA *et al.*, 2014).

Polyphenol-rich sources can be helpful to inhibit NAFLD disease progression as well as health melioration (SALAMONE *et al.*, 2012; ANHÊ *et al.*, 2014). Phenolic compounds can act by modulation the antioxidant enzymatic systems (ANHÊ *et al.*, 2014), modulation of lipogenesis (SALAMONE *et al.*, 2012), inflammation inhibition (SALAMONE *et al.*, 2016), directly action as antioxidant (DIAZ-RUBIO *et al.*, SALAMONE *et al.*, 2016) and also by change gut microbiota. The gut microbiota composition has been also appointed as an important factor in NAFLD development. Awhere, a gut microbiota more responsive to a high fatty diet increasing de-novo lypogenesis and triglycerides in liver (ROY *et al.*, 2013). However, the mechanisms of polyphenol activity in NAFLD prevention and inhibition progression still under-recognized with much unknowns.

7 CONCLUSION

The grumixama showed to be a good source of flavonoids and ellagitannins and the interaction among exogenous and endogenous metabolites following an acute intake can be related to changes in amino acids and energetic metabolisms.

In addition, the polyphenols metabolites had also demonstrated potencial antiproliferativy activity for human breast cancer cells, as well as induced protection against non-alchoolic fatty liver disease in animal model.

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