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# THE EFFECTS OF STRESS AND A HIGH-ANTIOXIDANT SPICE BLEND ON POSTPRANDIAL LIPOPOLYSACCHIDE SERUM CONCENTRATIONS

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# ABSTRACT

Inflammation is related to the development of a wide-ranging assortment of chronic diseases, especially atherosclerosis. To protect against detrimental inflammatory conditions in the body, an emphasis has been placed on the use of therapeutic methods, such as diet, to reduce the effects of stress-induced inflammation. As a result, the consumption of antioxidants has been closely studied; however, the *in vivo* effects of antioxidants in the attenuation of chronic disease risk has been disputed despite the positive health effects that have been shown in preclinical *in vitro* analyses. Further, the specific mechanisms of action underlying inflammation in human populations are unclear, particularly those in relation to the role of LPS and metabolic endotoxemia. Through the observation of postprandial LPS serum values, the present study assessed the potential buffering ability of antioxidants to attenuate stress-induced inflammation in a human model. Unexpectedly, there was no significant treatment effect (spice vs. control) on postprandial LPS serum concentrations across conditions (rest vs. stress). However, there was a trend for lower postprandial LPS serum concentrations when the meal contained the high-antioxidant spice blend versus when the meal was served devoid of spices (0.0684). This finding was not influenced by the consumption of the preloaded spice meal 48 hours prior to each test day. Our analysis demonstrates the need for continued investigation into the ability of antioxidant-rich spices to mediate postprandial LPS concentrations, a precursor to inflammation, in human populations.

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# Chapter 1

# Introduction

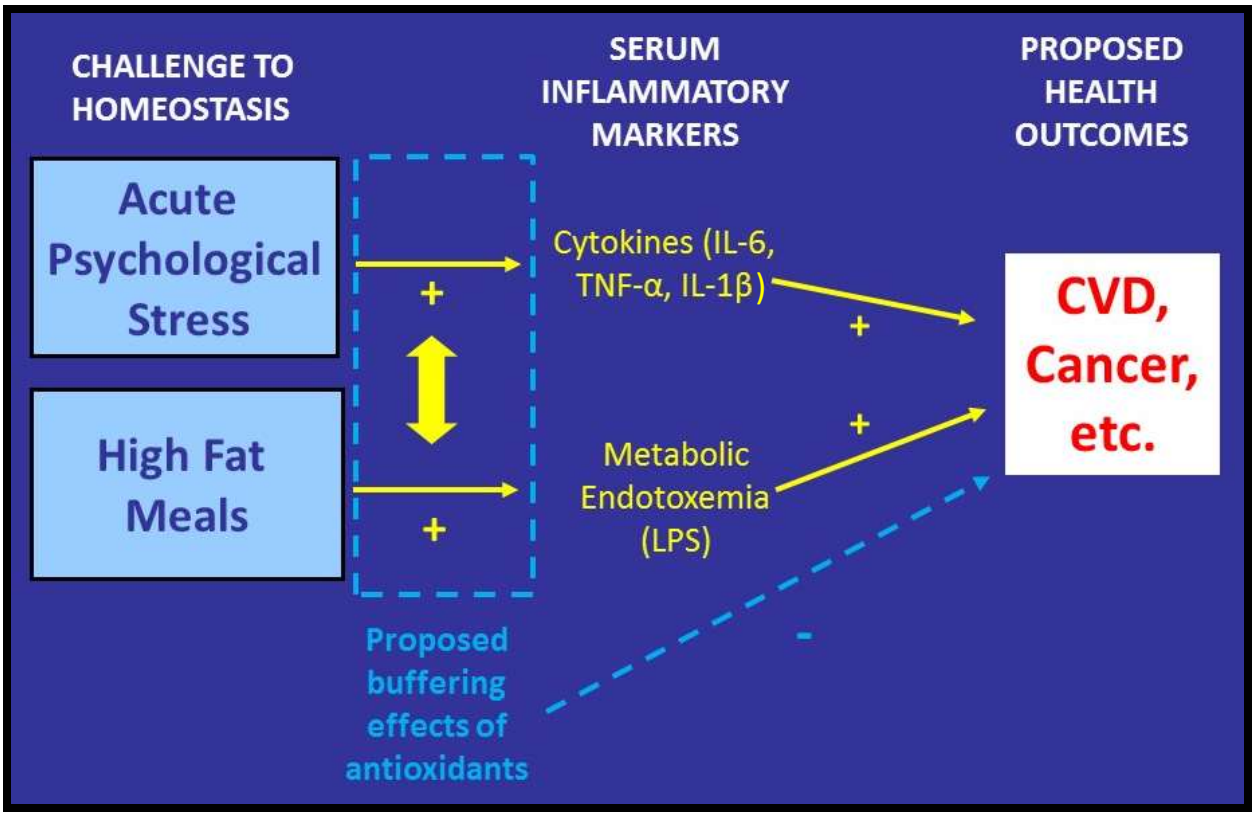
## 1.1 A Model to Explain Chronic Disease:

According to the most recent reports from the World Health Organization (2015), the incidence of cardiovascular disease, cancer, respiratory diseases, and diabetes accounts for over 80% of all mortality rates relating to chronic disease. Hyperlipidemia, hyperglycemia, high blood pressure, and obesity are the four most influential risk factors in the onset of chronic disease (World Health Organization, 2015). In efforts to explain the development of chronic disease, research has focused on investigations into the physiological mechanisms associated with changes in homeostasis, specifically those relating to stress and diet.

Evidence suggests that both exposure to acute psychological stress and consumption of high fat meals can upset normal physiological functioning and increase a variety of proinflammatory markers, such as interleukin-1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α) (Calcagni & Elenkov, 2006; Black & Garbutt, 2002; de La Serre et al., 2010; Cani et al., 2008). Further, these homeostatic challenges appear to affect serum concentrations of lipopolysaccharide (LPS), a component of the cell wall of Gram-negative bacteria found in the gut of even healthy individuals (Sperandeo, Villa, Dehò, & Polissi, 2014; Raetz & Whitfield, 2002; Pendyala, Walker, & Holt, 2012; Guo, Al-Sadi, Said, & Ma, 2013). When the intestinal epithelium is compromised, LPS is able to enter the bloodstream, resulting in a condition referred to as metabolic endotoxemia (Pendyala et al., 2012; Andreasen et al., 2008). It is

proposed that this surge of LPS into circulation causes an inflammatory response (Andreasen et al., 2008). Such inflammation is established as a contributor to the development of chronic disease (Clemente-Postigo et al., 2012; Golia et al., 2014). Although disputed, the consumption of antioxidants may help to disrupt the relationship between homeostatic changes and damaging inflammation (Willcox, Ash, & George, 2004). Ultimately, this buffering effect of antioxidants may reduce the risk of cancer, cardiovascular disease, and other chronic ailments. This paper will explore in depth the known evidence and suggested links associated with this hypothesis, as described in Figure 1.

***Figure 1: A model of serum inflammatory markers' impact on proposed health outcomes***




**In Figure 1, a (-) identifies a decrease in effect and a (+) indicates an increase in effect*

**1.2 The Stress-Inflammation Connection:**

The term "stress" was first coined by Hans Selye in 1936 while exploring the "syndrome of just being sick" and experimenting with the pathophysiological responses of animal ovarian tissue. Based on his observations, Selye (1936; 1973) newly defined stress as "the non-specific response of the body to any demand for change" and "the rate of wear and tear on the body". The stressors which he employed in his experiments resulted in repeatable, characteristic symptoms, such as stomach ulcers, enlarged adrenal glands, and diminished lymphoid tissues (Selye, 1936; Selye, 1973). Selye (1936; 1973) hypothesized that such symptoms ultimately developed into many diseases commonly seen in humans, such as rheumatoid arthritis, ulcers, and myocardial infarction.

Since the time of Hans Selye's preliminary findings and further research into both pro- and anti-inflammatory stress responses, extensive evidence has linked stress to the onset of chronic inflammatory conditions in humans. Resulting inflammation from stress is known to be associated with cardiovascular disease risk, particularly atherosclerosis (Gu, Tang, & Yang, 2012; Yudkin, Kumari, Humphies, & Mohamed-Ali, 2000; Black & Garbutt, 2002). The American Heart Association, as well as a multitude of research findings, pinpoint inflammation as a foundation in which atherosclerosis develops, progresses, and hastens the onset of imminent heart complications ("Inflammation and Heart Disease"; Libby, Ridker, & Maseri, 2002; Libby, 2012; Golia et al., 2014). In fact, findings have revealed that nearly 4 of every 10 atherosclerosis cases are the direct result of stress-induced inflammation with no other evident risk factors, such as high cholesterol (Black & Garbutt, 2002).

It has been demonstrated that inflammatory conditions have the potential to be produced from prolonged psychological stress conditions or repeated acute psychological stress conditions

in both animal and human populations (Black 2003; Seematter, Binnert, Martin, & Tappy, 2004; Ait-Belgnaoui et al., 2012; Gu et al., 2012; Black & Garbutt, 2002). Psychological distress can be elicited from daily life events, but in human clinical trials, the Trier Social Stress Test (TSST) is a gold standard for investigating the psychobiological effects of stress (Krischbaum, Pirke, & Hellhammer, 1993; Harmon-Jones & Winkielman, 2007). The standard TSST protocol involves subjecting participants to psychologically demanding tasks, including the preparation and delivery of a speech, as well as serial subtraction (Krischbaum, Pirke, & Hellhammer, 1993; Harmon-Jones & Winkielman, 2007). Today, the TSST is the most widely accepted method of stimulating acute stress responses in clinical trials because it has been shown to stimulate the hypothalamic-pituitary-adrenal (HPA) axis (Krischbaum et al., 1993; Harmon-Jones & Winkielman, 2007). In this way, changes in cortisol, prolactin, acetylcholine, and growth hormone are produced during the TSST that are representative of novel stress reactions (Krischbaum et al., 1993; Harmon-Jones & Winkielman, 2007).

The body's reaction to both inflammation and stress are linked in a myriad of ways (Gu et al., 2012; Black & Garbutt, 2002; Black & Berman, 1999; Kop & Cohen, 2001; Black, 2003; Black, 2006). Because the stress response triggers the nonspecific, systemic inflammatory response, the development of inflammation is a fundamental element of the body's reaction to internal or external strains on homeostasis (Black, 2006). The exposure to a physical or psychological stressor stimulates the hypothalamus to produce corticotrophin-releasing hormone, commonly referred to as CRH (Seematter et al., 2004; Black, 2003; Black 2006). CRH activates both the HPA-axis, resulting in the release of cortisol, and the sympathetic nervous system (SNS), resulting in norepinephrine and epinephrine distribution (Black & Garbutt, 2002; Black, 2006). The activation of the SNS catalyzes the renin-angiotensin cascade to yield angiotensin II

(Chae, Lee, Rifai, & Ridker, 2001; Black, 2003; Black, 2006). Angiotensin II is a known precursor to an increase in oxidative stress and inflammation (Black, 2003; Black, 2006; Saavedra, Sánchez-Lemus, & Benicky, 2011).

**1.3 Diet-Influenced Inflammation:**

The consumption of diets high in fat, sucrose, and caloric value is associated with increased inflammation and incidence of metabolic diseases (Reuter, Gupta, Chatuvedi, & Aggarwal, 2010; Zhou et al., 2014). Consequently, in recent years, diets that are comprised of whole grains, vegetables, fruits, legumes, and foods that contain natural antioxidants, especially vitamins, minerals, proteins, and phenolic compounds, are recommended (Kevers, Sipel, Pincemail, & Dommes, 2014; Hu & Willet, 2002; Zhou et al., 2014; Esposito & Giugliano, 2005). Likewise, the limitation of "western diet" foods, such as those with added sugars or full-fat dairy products, is commonly endorsed (Esposito & Giugliano, 2005; Hu & Willet, 2002; Zhou et al., 2014). By adhering to these guidelines, an individual may reduce his or her risk of developing chronic health conditions, such as obesity, cancer, diabetes, metabolic syndrome, and cardiovascular diseases (Esposito & Giugliano, 2005; Hu & Willet, 2002). When an individual consumes an excessive amount of lipids and carbohydrates, there is an escalation of proinflammatory cytokine production in the body (Esposito & Giugliano, 2005). Even in healthy participants, the consumption of excessive lipids and carbohydrates is connected to an increased production of reactive oxygen species (ROS) and inflammatory cytokines characteristically found when the body is undergoing a stress response (Nappo et al., 2002). Surprisingly, the

concentration of proinflammatory markers, like TNF-α, can increase in plasma after the consumption of only one high-fat meal (Ghanim et al., 2009; Nappo et al., 2002).

**1.4 The Power of Antioxidant Defense:**

In the 1990s, polyphenols became a groundbreaking topic of discussion among both the general public and researchers because of their antioxidant properties, although the latter were discovered many years prior (Manach, Scalbert, Morand, Rémésy, & Jiménez, 2004; D'Archivio, Filesi, Varí, Scazzocchio, & Masella, 2010). Records show that since ancient times, Indian Ayurveda and traditional Chinese medicinal practices have relied upon the antioxidant properties of natural sources for the treatment of various conditions (Devasagayam et al., 2004). Yet, it was not until the 20th century that researchers began to postulate that free radical damage was associated with the early stages of atherosclerosis and other common chronic health conditions, such as cancer (Mitchell, 2004; Devasagayam et al., 2004).

It is suggested that in order for the body to function properly, a balance between antioxidants and free radicals produced from ROS must be achieved and maintained (Mitchell, 2004; Lobo et al., 2010; Birben, Sahiner, Sackensen, Erzurum, & Kalayci, 2012). *In vitro* studies demonstrate that a heightened concentration of free radicals results in cell damage, and, subsequently, oxidative stress (Birben et al., 2012; Lobo et al., 2010). Prolonged exposure to oxidative stress has been linked to mitochondrial DNA damage and chronic inflammation in the body, contributing to the incidence of cancer, neurological disorders, diabetes, asthma, acute respiratory distress syndrome, and atherosclerosis (Valko et al., 2007; Tucker & Robards, 2008;

Birben et al., 2012; Hulsmans, De Keyzer, & Holvoet, 2011; Ding et al., 2012; Reuter et al., 2010).

It is proposed that antioxidants have the ability to neutralize the negative effects of oxidative stress in the human body (Sies, 1986; Mitchell, 2004). Supporting research indicates that antioxidants have a free radical scavenging property, which enables them to contest free radical buildup (Kevers et al., 2014; Lobo et al., 2002). Antioxidants' stability and ease of donating an electron to the electron-deficient free radical make them a paramount contributor to homeostasis (Lobo et al., 2002). Some antioxidants, such as uric acid, are created during normal metabolism (Sautin & Johnson, 2008; Birben et al., 2012). However, other antioxidants, such as vitamin E, vitamin C, and beta-carotene, are taken into the body solely through food and dietary supplementation (Birben et al., 2012; Lobo et al., 2002). Recently, studies in animal models have reported that butylated hydroxyanisole and other man-made antioxidants have deleterious effects on normal physiological functioning (Weber, 2014). As a result, there has been a surge of investigation into the effectiveness of natural antioxidant sources on bodily processes, and many researchers are assessing antioxidants of plant origin (Lobo et al., 2002).

In preclinical epidemiological studies, antioxidants have been linked to a multitude of health benefits, such as improvement in endothelial function (Franzini et al., 2012; Buscemi et al., 2012; Kahn et al., 2014). When observed through *in vitro* studies, these advantageous changes are associated with a reduced risk for atherosclerosis (Devasagayam et al., 2004; Khan et al., 2014; D'Archivio et al., 2010). However, evidence from many clinical trials has failed to confirm the hypothesized reduction in risk of chronic disease development when single antioxidants are consumed (Lonn et al., 2005; Devasagayam et al., 2004). For example, daily supplementation of vitamin E, a potent antioxidant, in a population of patients with preexisting

diabetes mellitus or vascular disease, surprisingly did not delay the onset of cardiovascular complications or cancer (Mitchell, 2004; Lonn et al., 2005). In this study population, as well as a sample of older males, rates of heart failure unexpectedly increased (Lonn et al., 2005; Wannamethee et al., 2013). Because of this disconnect between the biochemical effects of antioxidants and their role in chronic disease progression, this hypothesis warrants further inquiry in human populations.

### 1.5 Spice Antioxidant Capability:

Spices have been proposed to possess antioxidant capabilities since the 1950s (Chipault, Mizuno, Hawkins, & Lundberg, 1952). Since then, the potential health effects of spices have been studied extensively in various populations, ranging from healthy to diabetic individuals. In recent years, research interest in spices has sparked, particularly because each spice type consists of varied compositions, and, thus, each type has diverse antioxidant properties (Paur, Carlsen, Halvorsen, & Blomhoff, 2011). Therefore, when a spice blend is added to a food, that food gains the added health benefit of multiple antioxidant properties working together in the same mixture (Paur et al., 2011)

The term ORAC, oxygen radical absorbance capacity, was developed as a unified, standardized measure to assess the *in vitro* antioxidant capabilities of food products in a standardized assay (Prior, Wu, & Schaich, 2005). A higher ORAC value indicates that a food has a greater antioxidant potential; similarly, a lower ORAC value indicates that a food has poor antioxidant power. Based on a prior ORAC database produced by the U. S. Department of Agriculture (USDA), common spices have the highest ORAC value per gram compared to other

food products (Skulas-Ray, 2011; U.S. Department of Agriculture NDL, 2007). However, because of the controversy over the meaning of ORAC scores, the USDA has been pressured to remove the database from the public domain (U.S. Department of Agriculture NDL, 2012).

Despite this debate, researchers have indicated that spices are powerful sources of phenolic antioxidants compared to other foods (Naidu & Thippeswamy, 2002; Ninfeli et al., 2005; Paur, Carlsen, Halvorsen, & Blomhoff, 2011; Shan, Cai, Sun, & Corke, 2005). Ninfali and colleagues (2005) compared the total phenol content and ORAC value of salad dressings, vegetables, and spices to find those with the greatest antioxidant power. Oregano (Origanum vulgare) was determined to have a total phenol content of 435 ± 41.0 mg/100g with an ORAC value of 13970.2 ± 1090 μmolTE/100g (Ninfali et al., 2005). In comparison, extra virgin olive oil, a staple in the Mediterranean diet, was determined to have a total phenol content of only 16.50 ± 1.50 mg/100g and an ORAC value of 1150 ± 103.0 μmolTE/100g (Bogani, Galli, Villa, & Visioli, 2007; Covas, 2007; Ninfali et al., 2005).

Similarly, by analyzing the antioxidant content of commonly consumed foods, Paur et al. (2011) demonstrated that plant-based foods contained an average antioxidant content of 11.57 mmol/100g and animal-derived foods contained a mere 0.18 mmol/100g. Out of all plant-derived foods analyzed, the 425 spices and herbs included contained an average antioxidant content of 29.02 mmol/100g, while a group of commonly consumed berries contained an average of 9.86 mmol/100g (Paur et al., 2011). Berries, especially blueberries, have been commonly identified and advertised as powerful dietary sources of antioxidants (Heinonen & Meyer, 2002). Yet, spices and herbs are estimated to be nearly three times more potent in their antioxidant content compared to berries (Paur et al., 2011). Thus, spices remain a promising possible intervention to combat oxidative stress and its detrimental physiological effects.

Previous research has recognized that spices and herbs contain biologically active compounds derived from plant origins, which may contribute to their functioning (Rubió, Motilva, & Romero, 2013; Naidu & Thippeswamy, 2002). These compounds include, but are not limited to, phenolic terpenes, flavonoids, and phenolic acids (Lindsay & Astley, 2002; Naidu & Thippeswamy, 2002; Rubió et al., 2013). Foods rich in phenols, such as spices, are comprised phytochemicals that are advantageous for improving aspects of physiological health (Paur et al., 2011; Ninfali et al., 2005). The phytochemicals found in commonly used high-antioxidant spices, such as thyme, cloves, and oregano, include eugenol, rosmarinic acid, and gallic acid; these phytochemicals have been shown to block transcription factors from stimulating the onset of inflammation and immune system activation (Ocaña-Fuentes, Arranz-Gutiérrez, Señorans, & Reglero, 2010; Shan et al., 2005; Lee et al., 2006; Chainy, Manna, Chaturvedi, & Aggarwal, 2000; Paur et al., 2011). Moreover, recent work suggests that spices with high antioxidant activity also work to regulate lipids and glucose in the body (Skulas-Ray, 2011; Tapsell et al., 2006; Jagetia & Aggarwal, 2007; Aggarwal, Van Kuiken, Iyer, Harikumar, & Sung, 2009). However, clinical data which explain the specific mechanisms through which spices produce these beneficial health effects is sparse.

Among the commonly consumed antioxidant spices, cinnamon has been studied extensively in clinical trials that assess glucose metabolism (for review, see Appendix A). The weight of the evidence from previous research has shown conflicting findings, especially in non-diabetic populations. The effects of cinnamon on metabolism in a population of healthy adults at risk for developing metabolic syndrome remains to be clearly defined. Studies which have related cinnamon intake to changes in fasting plasma glucose, postprandial glucose, fasting insulin, gastric emptying rate, and oxidative stress are inconsistent in showing benefits. Multiple

factors, such as the cinnamon species used, the dose of cinnamon supplementation, duration of cinnamon exposure, and even the method of cinnamon administration, lack standardization and produce inconsistent results.

### 1.6 Metabolic Endotoxemia: An Overview

In the broadest definition, endotoxemia describes the presence of bacterial endotoxin in the bloodstream (Andreasen et al., 2008). Metabolic endotoxemia is a term used to describe a physiological condition in which bacterial endotoxin concentrations reach heights above the average baseline concentration (Cani et al., 2007; Chang &Li, 2011). Chronic health conditions, such as metastasizing cancer, type II diabetes mellitus, Parkinson's disease, obesity, and inflammation-related conditions, have a hypothesized link to increased bacterial endotoxin levels in blood plasma (de Kort, Keszthelyi, & Masclee, 2011; Sun et al., 2010; Hawkesworth et al., 2013; G. Zaman, F. Zaman, & Rasul, 2014; Chang & Li, 2011; Zhou et al., 2014). Although the exact etiology of metabolic endotoxemia is still unclear, bacterial endotoxin levels have been connected to the inflammation that provides the foundation for chronic disease progression (Hawkesworth et al., 2013; Chang & Li, 2011). The majority of information understood about endotoxemia has been gained through observation of septic shock, sepsis, and the induction of "experimental" endotoxemia in clinical trials—a condition in which bacterial endotoxin is purposefully injected (van den Boogaard et al., 2010; Change & Li, 2002; Andreasen et al., 2008). However, more research is needed to better understand the functioning of metabolic endotoxemia in human chronic disease progression.

Common sources of endogenous exposure to low-grade bacterial endotoxin are varied, but may include smoking, aging, prolonged physical exertion, stress, chronic alcohol intake, localized chronic infections, periodontal disease, and high fat diets (Erridge, Atinna, Spickett, & Webb, 2007; Chang & Li, 2011; Guo et al., 2013). It is proposed that each of these sources causes an increase in bacterial endotoxin concentrations because of any one of the following reasons: increased intestinal bacteria, intestinal permeability, or susceptibility to infection because of the body's decreased immune system capability (de Kort et al., 2011; Chang & Li, 2002; Guo et al., 2013). Most clinical trials assessing the effects of LPS on physiological changes utilize high doses of infused bacterial endotoxin between 10 ng/ml and 200 ng/ml, but low exposures to the same endotoxin, between 1pg/ml and100pg/ml, can also elicit significant effects when observed in the bloodstream (Chang & Li, 2011).

**1.7 The Link to Bacterial Endotoxin:**

LPS, referred to interchangeably as bacterial endotoxin in literature, is found in the gut of all people, including those who are healthy and those afflicted by disease (Guo et al., 2013; Berg, 1996). In healthy individuals, the epithelial cells of intestinal tissue act as an efficient barrier to prevent large amounts of LPS from being transported from the intestine to blood circulation or other areas of the body (Gu et al., 2013; Neves, Coelho, Couto, Leite-Moreira, & Roncon-Albuquerque, 2013; Zhou et al., 2014). However, when an individual is obese, experiences Non-alcoholic Fatty Liver Disease, has diabetes, or eats a high-fat diet, the intestinal epithelium becomes more porous, or "leaky" (de Kort et al., 2011; Neves et al., 2013; Zhou et al., 2014).

LPS is released in excess because the intestinal epithelium's permeability is amplified (Guo et al., 2013).

As intestinal permeability increases, the ease in which LPS can pass from the intestine into the liver, bloodstream, and adipose tissue also increases (Yue, Ma, Zhao, Q. Li, & J. Li, 2012; Neves et al., 2013). This directly proportional relationship creates an environment in which metabolic endotoxemia can potentially develop (Neves et al., 2013).When LPS is released from the intestinal lumen, it often travels into portal circulation to be cleared by Kupffer cells in the liver and, thus, is discarded as bile (Munford, Hall, Lipton, & Dietschy, 1982; Mathison & Ulevitch, 1979; Coulthard, Swindle, Munford, Gerard, & Meidell, 1996; Zhou et al., 2014; Neves et al., 2013). LPS that does not immediately come in contact with Kupffer cells may begin to circulate in the blood. CD14 recognizes the presence of residual LPS in the bloodstream. As a result, the bacterial endotoxin's harmful effects are quickly neutralized by lipoproteins and LPS-binding protein (Munford, Hall, & Dietschy, 1981; Parker et al., 1995; Kitchens, 2000; Neves et al., 2013; Chang & Li, 2011; Kim et al., 2007).

The response of the body to excessive LPS translocation from the gut into circulation is similar to its reaction to other inflammatory precursors. Like that of any other invading microbe in the body, the pathogen-associated patterns on LPS bind to pattern-recognition receptors on cell surfaces (Andreasen et al., 2008; Kawai & Akira, 2010). LPS signaling occurs in conjunction with toll-like receptor 4, which is commonly discussed in literature as TLR4 (Chang & Li, 2011; Kim et al., 2007). The toll-interleukin-1 receptor domain of TLR4 is essential to the initiation of downstream signaling that ultimately increases proinflammatory cytokine production (Lu, Yeh, & Ohashi, 2008; Chang & Li, 2011). TLRs are used in the functioning of the body's innate immunity and are readily located on surfaces of monocytes, which are the

primary leukocytes supporting this type of immunity (Kawai & Akira, 2010; Andreasen et al., 2008; Chang & Li, 2011). Once LPS is bound to TLRs, it is identified by macrophages, endothelial cells, and epithelial cells (Andreasen et al., 2008). The binding of LPS to TLR4 catalyzes the progression of transcription factors, including nuclear factor-kB (NF-kB), mitogen-activated protein kinases, and activator protein-1 (Andreasen et al., 2008; Chang & Li, 2011). NF-kB facilitates proinflammatory cytokine production, especially IL-1β and TNF-α (Andreasean et al., 2008; Change & Li, 2011; Pahl, 1999). Thus, LPS-induced inflammation is the result of multiple connected events. LPS induces a rise in proinflammatory cytokines, which leads to activation of the complement system and other inflammatory phases through the stimulation of adhesion molecules and leukocytes (Andreasen et al., 2008; Neves et al., 2013).

**1.8 Evidence of LPS Outcomes:**

There is a lack of understanding of the exact mechanisms through which LPS functions in both human and animal models. LPS functioning has previously been investigated through either the injection of low-dose LPS or exposure to endogenous LPS levels. The majority of studies that assess LPS utilize rodent populations, but researchers are beginning to find links connecting LPS to harmful effects in the human body (Hietbrink et al., 2009). As a result of recent research, LPS has been found to increase inflammatory responses, insulin resistance, triglyceride levels, and gut permeability.

*Inflammatory Response:*

In humans, low-dose LPS injections is used to stimulate experimental endotoxemia to study the detrimental changes in metabolism that result from inflammatory conditions (Andreasen et al., 2008; Mehta et al., 2010; Agwunobi, Reid, Mayeock, Little, & Carlson, 2000; Hudgins et al., 2003; Anderson et al., 2007). It is proposed that aspects of the inflammatory response are similar when comparing psychosocial stress conditions and LPS-induced stress conditions (Black & Garbutt, 2002). Cani et al. (2007) demonstrated that a mouse population treated with LPS had increased expression of proinflammatory cytokine-coding genes in adipose, liver, and muscle tissue, which ultimately resulted in inflammation.

*Triglycerides:*

The presence of LPS in serum is suggested to induce hypertriglyceridemia because of its ability to slow lipoprotein lipase (LPL) enzymatic activity (Feingold et al., 1992). LPL is an enzyme in the bloodstream that helps the body maintain homeostasis by hydrolyzing triglycerides and encouraging hepatic clearance of lipoproteins (Rip et al., 2006). When LPL activity is diminished, lipoproteins carrying triglycerides remain circulating in the bloodstream for a longer period of time. Feingold et al. (1992) demonstrated that the administration of exogenous LPS to a rodent population can produce an increase in serum triglyceride levels in as early as a two hour time span. The work of Feingold and colleagues (1992) demonstrates that LPS itself may have the capability of altering lipid metabolism. Other recent animal models support this directly proportional relationship between postprandial LPS concentrations and postprandial triglyceride concentrations after LPS injections (Cani et al., 2007). Although

limited, clinical data in human populations have also replicated this link. More specifically, in one clinical trial, baseline LPS concentrations predicted an increase in triglyceride levels after the ingestion of a high fat meal (Clemente-Postigo et al., 2012). However, because the stimulus of a high fat meal increases both postprandial triglyceride and LPS concentrations, the two are highly confounded.

*Insulin Resistance:*

In 2007, Cani and colleagues identified LPS as a causative factor in the development of insulin resistance. Mice infused with an exogenous source of LPS developed insulin resistance in their liver (Cani et al., 2007). It is interesting to note that mutant mice lacking receptors for CD14 were resistant to the majority of physiological changes caused by the LPS injections (Cani et al., 2007). These findings demonstrate that the association between LPS and CD14 may be critical in the development of insulin resistance or sensitivity (Cani et al., 2007). Similarly, a study investigating the effects of LPS on insulin in human muscle in a population of obese, type 2 diabetes mellitus (T2DM) participants showed that LPS injection hinders insulin signaling and glucose transport in human muscle cells (Liang, Hussey, Sanchez-Avila, Tantiwong, & Musi, 2013). Because human muscle is the primary location for glucose removal, an inhibition of insulin signaling in this region could reflect the same effects in an individual's entire body (Liang et al., 2013; DeFronzo et al., 1981). This outcome is supported further by evidence such as that gathered by Mehta et al. (2010), which demonstrates that systemic insulin resistance can be achieved through the injection of LPS in a healthy adult population.

*Gut Permeability:*

Even in individuals free of chronic disease, it is not uncommon for intestinal permeability to increase after exposure to LPS (Andreasen et al., 2008). This outcome is seen in both human and animal models. For example, Ait-Belgnaoui et al. (2012) investigated the effects of stress on gut permeability in a female rodent population. Findings from this study demonstrate an increase in gut permeability in the rodents after exposure to psychologically stressful conditions (Ait-Belgnaoui et al., 2012). The increased gut permeability resulted in LPS crossing the intestinal epithelium through both paracellular and transcellular pathways (Ait-Belgnaoui et al., 2012). Moreover, the outcomes suggest that the degree of stress exposure influences the extent of the metabolic endotoxemia observed (Ait-Belgnaoui et al., 2012). Likewise, Hietbrink et al. (2009) demonstrated that gut permeability increases in a human sample injected with LPS. This increase was recognized as being solely connected to paracellular changes in the gut epithelium caused by LPS-induced inflammation in the intestinal tract (Hietbrink et al., 2009).

## 1.9 Purpose and Goals of Study:

In their 2007 study analyzing postprandial LPS serum concentrations, Erridge and colleagues suggested the need for future investigation into possible methodologies that would reduce the movement of LPS from the gut to circulation as a way of preventing atherosclerosis. As outlined in Figure 1, antioxidants may have the ability to buffer the increase in metabolic endotoxemia and proinflammatory serum markers elicited from acute psychological stress and high fat meal consumption. **Through the analysis of the relationship between spice consumption and postprandial LPS serum concentrations, this study will test the potential**

**for an antioxidant-rich spice meal to reduce the translocation of LPS into the bloodstream as a method of attenuating inflammation.**

Furthermore, as previously mentioned, most clinical trials assessing the effects of LPS on physiological changes assess high doses of infused bacterial endotoxin between 10 ng to 200 ng/ml (Chang & Li, 2011). However, studies have indicated that low exposure to endogenous bacterial endotoxin between 1pg to 100pg/ml can also elicit significant effects when observed in the bloodstream (Chang & Li, 2011). This study will contribute to the sparse clinical knowledge associated with exposure to low doses of endogenous LPS concentrations in a human sample of overweight, healthy individuals who consumes a high fat meal and are exposed to acute psychological stress.

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# Chapter 2

# Methods

## 2.1 Study Design:

The analysis of LPS concentrations in serum samples was carried out after the completion of a larger clinical trial at the Pennsylvania State University in University Park, PA (McCrea et al., 2015). The larger clinical trial was a randomized, controlled, four-period crossover study. There was at least one week separating each testing session. The conditions used in this study design were presented to all subjects in a random order. The conditions were the following: (1) a spice meal and rest condition, (2) a spice meal and stress condition; (3) a control meal and rest condition, and (4) a control meal and stress condition.

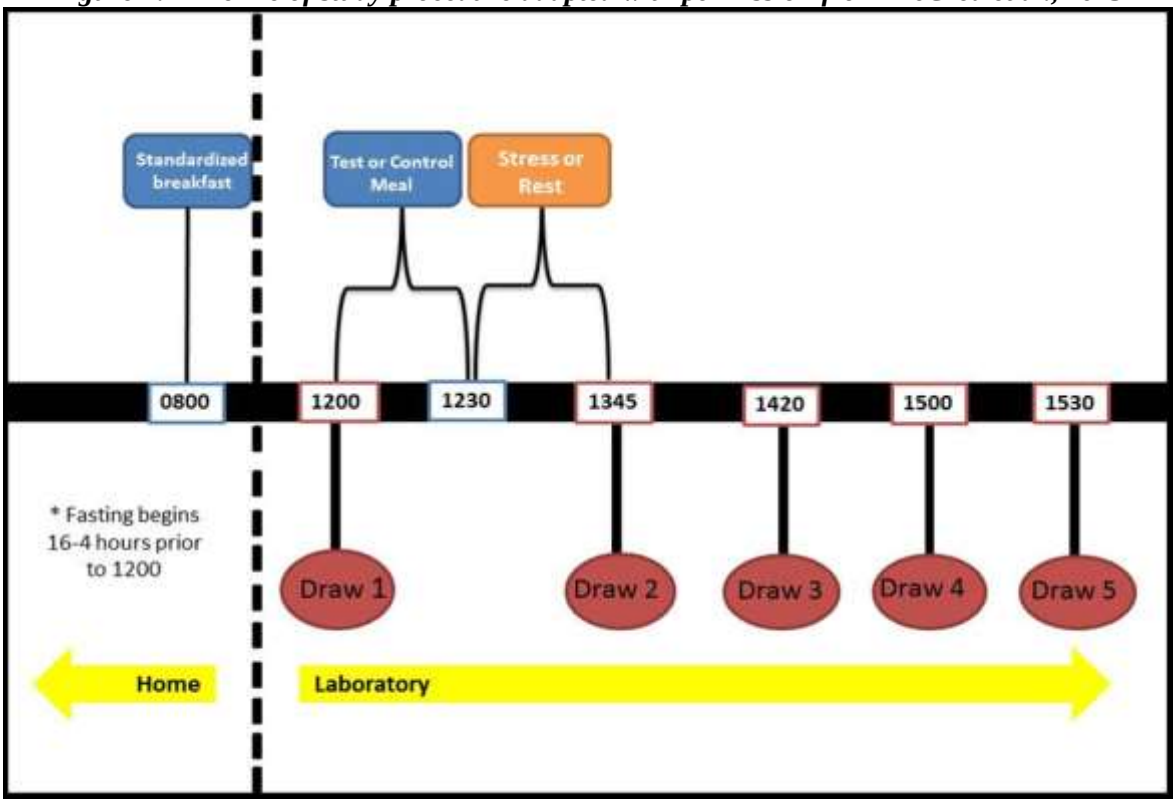
## 2.2 Subjects:

Participants were included if they were males or females between the ages of 30 and 65 who had a BMI in the range of 25 to 40 $kg/m^2$. According to CDC BMI guidelines, these participants were categorized as overweight (BMI 25.0-29.9) or obese (BMI 30.0 or above) (Centers for Disease Control & Prevention [CDC], 2014). Included participants were required to have a resting blood pressure of less than 160/100 mmHg and a fasting glucose level of less than 126. Also, subjects were required to be free of any serious medical illness or condition. Ultimately, 6 males and 14 females met these criteria and completed the study.

**2.3 Timeline of Study Procedure:**

At 0800 in the morning of testing day, participants consumed a standardized breakfast consisting of a bagel and low-fat cream cheese 4 hours prior to consuming the test meal. At 1200, a baseline blood sample was taken. Beginning at 1200, participants were instructed to begin eating the test meal and were given 30 minutes to finish. From 1230 to 1245, participants either has a rest period or stress period in which they completed the TSST depending on the randomized condition they were given. At 1345, 1420, 1500, and 1530 a blood sample was taken from the participant. Thus, serum samples used for analysis were taken at baseline, as well as at 105 minutes, 140 minutes, 180 minutes, and 210 minutes after the baseline measurement. See figure 1 for details regarding the timeline of events.

***Figure 2: Timeline of study procedure adapted with permission from McCrea et al., 2015***



**2.4 Visit Preparation:**

Prior to the testing day, a participant was required to abstain from high-antioxidant foods and consume a preloaded high-antioxidant spice meal 48 hours prior to arriving at the Clinical Research Center. Between 16 and 4 hours prior to the test meal, participants were instructed to begin a fasting regime.

**2.5 Stress Condition:**

Each "stress condition" consisted of the TSST. This protocol was chosen because it is a standardized method used to produce significant increases in blood pressure, heart rate, and up to a 4-fold increase in cortisol concentrations compared to baseline values (Krischbaum et al., 1993; Harmon-Jones & Winkielman, 2007; Birkett, 2011). Before the stress segments of the TSST began, participants engaged in a 20 minute rest period in which they listened to calming music. During the TSST, subjects were instructed to prepare a public speech for 10 minutes, and, after, present the speech for 5 minutes to researchers who provided only negative commentary on the participant's actions (Krischbaum et al., 1993; Harmon-Jones & Winkielman, 2007; Birkett, 2011). Moreover, the participant was instructed to complete a serial subtraction sequence for eight minutes in front of researchers who once again only provided negative commentary (Krischbaum et al., 1993; Harmon-Jones & Winkielman, 2007; Birkett, 2011). Each subsequent stress period utilized different speech topics and serial subtraction sequences to prevent familiarization and adaptation to the procedure. After the TSST speech and serial subtraction segment, participants engaged in a 10 minute recovery period. The instrumentation used to

measure both blood pressure and heart rate throughout the duration of the study was a standard blood pressure cuff (Pro 100 oscillometric monitor, GE Medical Systems).

**2.6 Meals:**

The spice meal consisted of 14.5 g of spices cooked into chicken, white rice, a corn muffin, and a pastry. Table 1 lists the composition of spices in each food item consumed by participants during this phase of the study. The control meal consisted of the same chicken, white rice, a corn muffin, and a pastry, but no spices were added to the food items. When eating the control meal, participants were given a placebo capsule and told they were consuming "antioxidants" in capsule-form instead of consumption through food. For both control and spice meals, the calorie intake was 1000 kcal and contained approximately 45 g of fat.

***Table 1: Amount of each spice added to spice meal adapted with permission from McCrea et al., 2015***

| **Spice:** | **Amount Added (g):** | **Food Item:** |
|---|---|---|
| Paprika | 2.85 | Chicken, Rice, Muffin |
| Turmeric | 2.79 | Chicken, Rice, Muffin |
| Oregano (Mediterranean) | 2.26 | Chicken, Rice, Muffin |
| Garlic Powder | 1.81 | Chicken, Rice, Muffin |
| Ginger | 1.51 | Chicken, Rice, Cookie |
| Cinnamon | 1.11 | Chicken, Rice, Cookie |
| Black Pepper | 0.91 | Chicken, Rice, Muffin |
| Rosemary | 0.61 | Muffin |
| Cloves | 0.61 | Chicken, Rice, Cookie |

**2.7 LPS Assay:**

Analysis of LPS concentration was carried out by the assay method detailed in the LONZA Limulus Amebocyte Lysate (LAL) QCL-1000 protocol and a full explanation of assay procedures is described in this manual (Lonza, 2014). This protocol specifies an assay detection range of 0.1 – 1.0 EU/ml. Samples were run in duplicate to allow for later assessment of accuracy.

The LONZA protocol specifies that under standard conditions, absorbance at 405-410 nm is linear in the specific concentration range of 0.1 to 1.0 ml of endotoxin. For the two presented methods of calculating endotoxin concentration as described by LONZA, the mean Δ absorbance of the blanks is first subtracted from the mean absorbance of the standards. To use the graphical method, the mean Δ absorbance of each of the four standards is plotted on a y-axis. The corresponding endotoxin concentration in EU/ml is plotted on the x-axis. A best fit line is drawn between these plotted points on a graph. The linear equation of this best fit line is then used to calculate the endotoxin concentration of each sample tested in the assay. To use the spreadsheet method, a calculator with linear regression capability is used, and the mean Δ absorbance is inputted. Next, the each of the four concentrations of the standards used is entered. Then, linear regression is used to calculate the endotoxin concentration of each sample by their absorbance. The LPS concentrations calculated in this analysis were determined using the graphical method because of its ease of calculation.

**2.8 Accuracy Calculation Method:**

Coefficient of variation (CV) was used to assess the accuracy between the calculated duplicate LPS concentrations. CV is a normalized measure that can be used on unit-less values to indicate dispersion between two variables (Brown, 1998; Abdi, 2010.). CV is calculated by dividing the standard deviation by the average of the values and multiplying by 100 (Abdi, 2010.). A low CV is indicative of low dispersion between variables; conversely, a high CV is indicative of great dispersion between variables (Brown, 1998; Abdi, 2010). In order to ensure a standardized level of accuracy among all data values used, LPS concentrations were only included in our data analysis procedures if they had a calculated CV less than 15.00, indicating that the difference between the duplicate values was low.

# Chapter 3

# Results

## 3.1 Participant Characteristics:

The characteristics of recruited participants can be found in Table 2 below. These values were obtained during each participant's fasted screening visit. Additionally, Table 3 contains details regarding the baseline blood sample values following the preloaded meal at the spice and placebo treatment visits. Systolic blood pressure and diastolic blood pressure remained unchanged over the two days (data not shown).

***Table 2: Characteristics of study participants adapted with permission from McCrea et al., 2015***

| **Characteristic:** | **Mean ± SEM** |
|---|---|
| Age (years) | 43.2 ± 2.3 |
| BMI ($kg/m^2$) | 30.4 ± 0.9 |
| Systolic BP (mmHg) | 117.8 ± 2.2 |
| Diastolic BP (mmHg) | 81.8 ± 1.3 |
| Triglycerides (mmol/L) | 1.54 ± 0.14 |
| Glucose (mmol/L) | 5.23 ± 0.12 |
| C-reactive protein (mg/L) | 12.95 ± 2.00 |

***Table 3: Baseline blood values at meal treatment visits adapted with permission from McCrea et al., 2015***

| **Characteristics** | **Control Visits** | **Spice Visits** | ***p*** |
|---|---|---|---|
| Heart Rate (bpm) | 64.43 ± 1.56 | 64.98 ± 1.84 | 0.56 |
| Triglycerides (mmol/L) | 1.76 ± 0.13 | 1.82 ± 0.49 | 0.51 |
| Glucose (mmol/L) | 5.00 ± 0.18 | 5.01 ± 0.18 | 0.28 |
| Insulin (pmol/L) | 63.00 ± 9.69 | 60.56 ± 9.11 | 0.77 |

**The values in Table 3 were taken during control/spice visits and are the average of values over the course of 2 days*

### 3.2 Data Inclusion Criteria:

Out of the 400 possible samples (20 participants x 4 visits each x 5 timepoints each), serum was unavailable for LPS analysis for just 7 timepoints. Thus, 393 samples were analyzed in duplicate. If the coefficient of variation (CV) between each set of duplicate samples exceeded 15.00, then the value was considered unreliable and excluded from analysis (n=16). A total of 86 LPS values fell outside the assay range of 0.1-1.0 EU/ml of endotoxin (LONZA, 2014). Seventy of these values were retained in the analysis and treated as follows: negative values were converted to 0.0 (n=4), values between 0.0 and 0.1 were not rounded (n=19), and values between 1.0 and 1.5 were converted to 1.0 (n=47). LPS values greater than 1.5 were excluded from analysis (n=16).

### 3.3 Statistical Analysis Methods:

The mixed models procedure (PROC MIXED, SAS v9.3, Cary, NC) was used to test the fixed effects of treatment (spice or placebo), trier (stress or rest testing session), and their

interaction modeled with subject treated as a random effect. Least-squares means and standard errors are reported. Model selection was based on optimizing fit statistics (evaluated as lowest Bayesian Information Criterion). A paired t-test was used to test the effects of preload on baseline LPS concentrations.

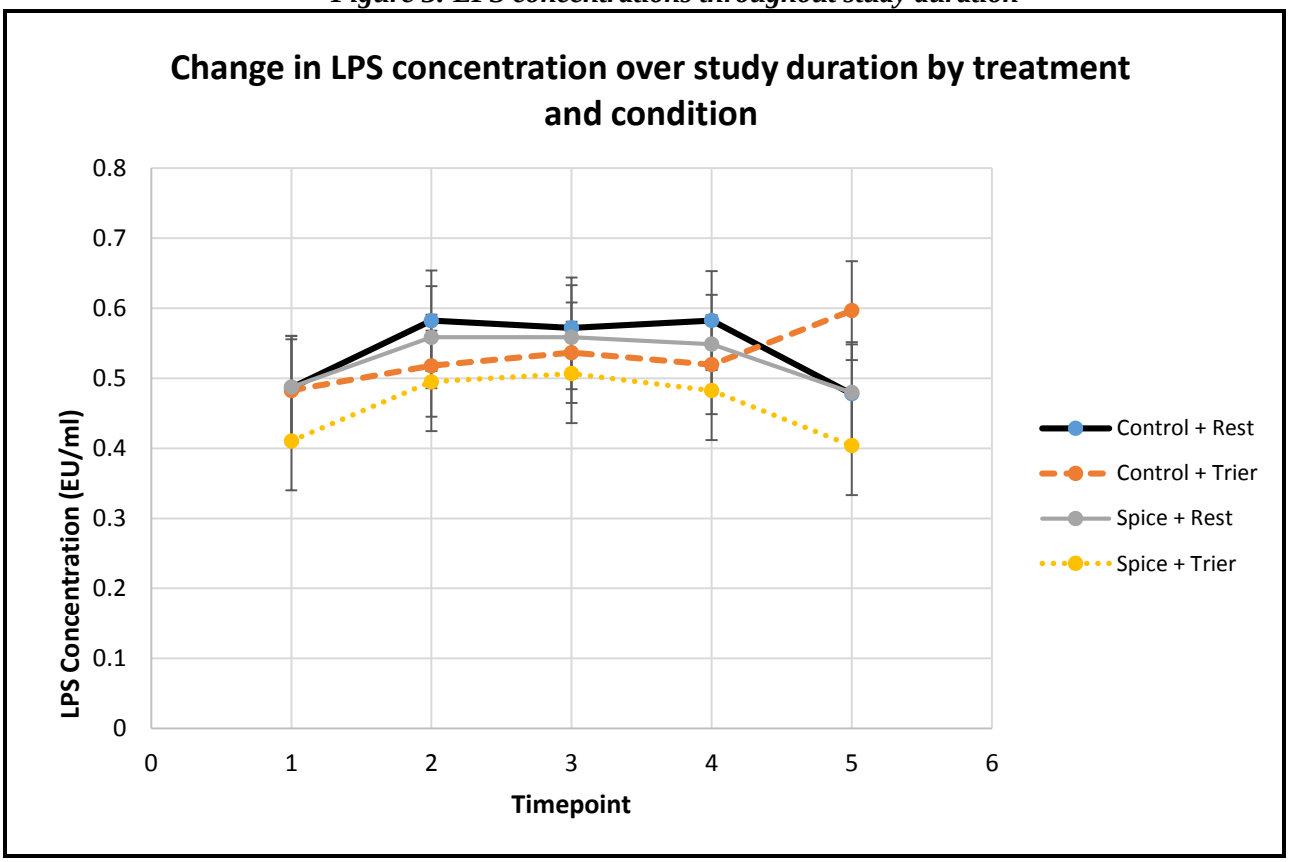
### 3.4 Baseline LPS Measurements:

The mean LPS concentration at baseline was 0.45 ± 0.28 EU/ml. LPS concentrations after 48 hours of preload with spices (0.46 ± 0.06 EU/ml) were not significantly different than after preload with control (0.48 ± 0.05 EU/ml) as determined by a paired t-test (t-Value = 0.77, d.f. = 18, $p = 0.45$).

### 3.5 Treatment Effects:

LPS values by treatment (spice or control) and condition (stress or rest) throughout the time course of the visit can be viewed in Figure 2. No statistically significant effects of condition (stress vs. rest) were observed ($p = 0.11$). However, there was a trend for a treatment effect on LPS ($p = 0.0684$); spices tended to result in reduced LPS levels when compared to control (LS mean for spice ± SE vs. LS mean for control ± SE).

***Figure 3: LPS concentrations throughout study duration***




**"Spice" and "control" indicate the treatment. "Rest" and "trier" indicate the condition. Note that "trier" signifies exposure to the TSST stressor. Meals (spice treatment or control treatment) were consumed within 30 minutes after timepoint 1 indicated on the x-axis of Figure 3. Stress conditions (trier condition or rest condition) were carried out within 75 minutes prior to timepoint 2 indicated on the x-axis of Figure 3.*

# Chapter 4

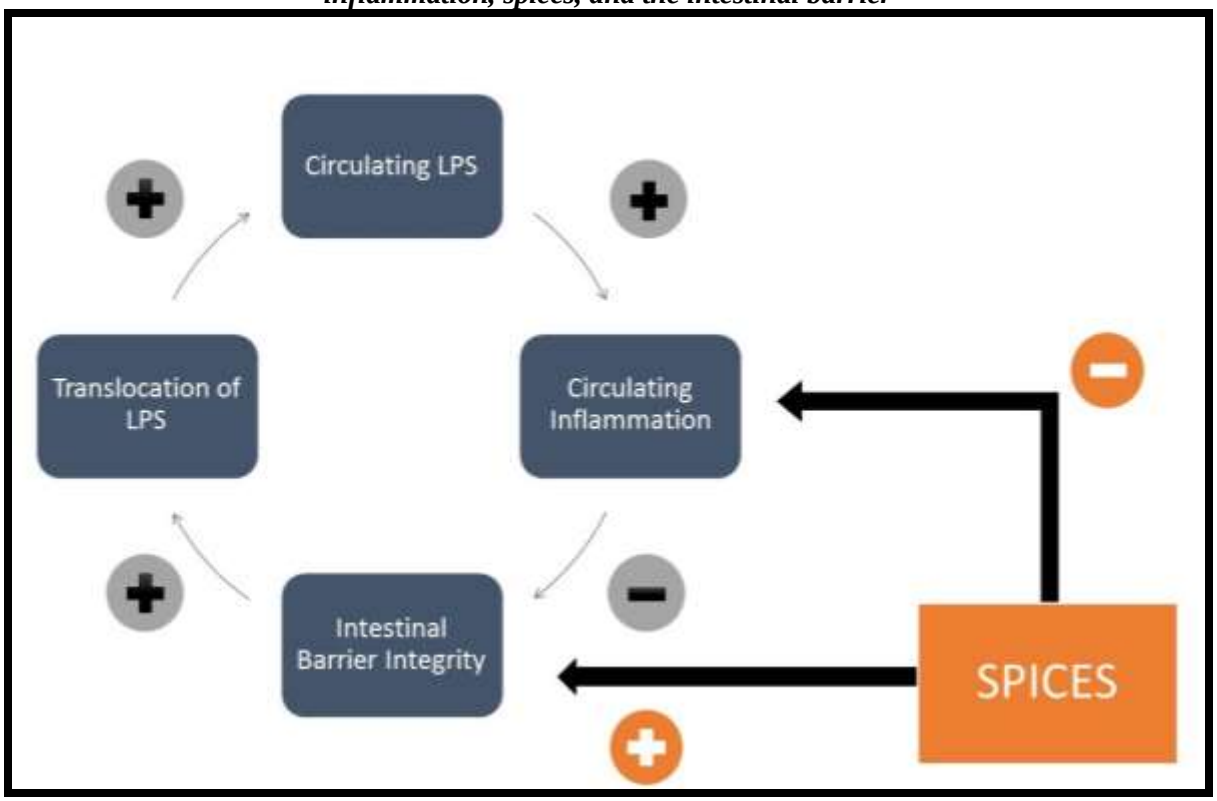
## Discussion

The goal of this analysis was to investigate the effects of a high-antioxidant spice blend on postprandial LPS serum concentrations in healthy overweight subjects. Others have shown that spices may have the ability to mediate inflammatory responses because of their antioxidant-rich composition. We found that 48 hours of preload with high-antioxidant spices compared to placebo capsules had no effect on serum concentrations of LPS. Further, when measured up to 4 hours following the high fat meal, stress did not induce changes in LPS serum concentrations compared to rest. Despite these findings, there was a trend for lower postprandial LPS serum concentrations when the meal contained the high-antioxidant spice blend versus when the meal was served devoid of spices (0.0684).

Two possible mechanisms for the spice blend's tendency to reduce circulating LPS are displayed in Figure 4. First, the polyphenols in the spice blend may have influenced LPS levels by means of their effects on tight junction permeability of intestinal epithelial cells. Given the size of polyphenol molecules, it has been postulated that only a small portion of those consumed are absorbed in their entirety (D'Archivio et al., 2010). Thus, part of the health benefits of polyphenols is assumed to be dependent on actions in the gut. Adjoining intestinal epithelial cells have tight junctions closely connecting them to help the intestine maintain paracellular impermeability (Guo et al., 2013). When this barrier is compromised, LPS passes through the

junctions and enters the bloodstream (Guo et al., 2013). Polyphenols, including curcumin, are hypothesized to increase the functioning of epithelial cell tight junctions in mice (Shigeshiro, Tanabe, & Suzuki, 2013). Additionally, LPS and gut permeability have a self-perpetuating relationship; in both *in vitro* and *in vivo* animal models, an increase in circulating LPS can decrease the ability of these tight junctions to form an efficient, strong barrier (Guo et al., 2013). Ait-Belgnaoui and colleagues (2012) suggested that in rodents, the obstruction of epithelial cell cytoskeleton movement hinders the ability for excess LPS to readily cross from the intestine into circulation. Therefore, the polyphenol rich spices fed to participants in our protocol may have improved the integrity of the intestinal barrier, resulting in a statistical tendency to decrease circulating LPS.

***Figure 4: Proposed mechanistic explanation of findings relating the connections between LPS, inflammation, spices, and the intestinal barrier***




**In Figure 4, a (+) indicates an increase in effect and a (-) indicates a decrease in effect.*

An alternative mechanism for the observed trend may involve the more traditional effects of antioxidants. The spices used (paprika, turmeric, oregano, garlic power, ginger, cinnamon, black pepper, rosemary, and cloves) were selected because of their high antioxidant capacity *in vitro*. Additionally, our previous work also demonstrates that this blend increases *in vivo* antioxidant measures, such as FRAP (McCrea et al., 2014; Skulas-Ray et al., 2014). Oxidative stress is known to potentiate inflammation (Bondia-Pons, Ryan, & Martinez, 2012). Thus, by buffering oxidative stress, the antioxidant activity of the spice blend may have reduced systemic inflammation. The resulting reduction in inflammation results in a less permeable intestinal barrier, which may have more effectively prevented LPS from entering circulation.

Unexpectedly, stress did not induce statistically significant increases in LPS concentrations during either treatment period (spice or control). This may be because the TSST stress protocol used in this study elicits an acute psychological stress response, not chronic psychological stress. Previous investigation in animal models yielded the claim that both chronic and acute stress can increase gut leakiness, increasing the bacterial endotoxin that is able to pass from the interior of the intestine to other areas of the body (Ait-Belgnaoui et al., 2012; Ait-Belgnaoui et al., 2005; Zareie et al., 2006). Further, both chronic and acute stress conditions have the proposed ability to increase the incidence of proinflammatory cytokines in circulation (Ait-Belgnaoui et al., 2012; Ait-Belgnaoui et al., 2005; Zareie et al., 2006). Yet, evidence shows that this effect is less pronounced in animals during exposure to acute psychological stress, such as acute social defeat, compared to chronic stress (Goshen & Yirmiya, 2009; Hueston et al., 2011).

Although preliminary, our findings suggest novel evidence for a trend that should be further explored by future research. However, there are several limitations to our conclusions. First, the sample size was relatively small (n=20). One participant was unable to complete the

stress conditions due to adverse psychological response to the stressor. Our analysis was further limited by the lack of serum samples for 7 timepoints. Moreover, the population studied reflects only a very specific subgroup of individuals, which includes only overweight individuals who identified as being absent of chronic disease. Therefore, these outcomes cannot be generalized to all individuals, especially those with chronic disease or who maintain a healthy weight. Moreover, the study design did not allow for investigation into dose-dependent responses because only one amount of the spice mixture (14.5 g) was added to each spice treatment.

An additional limitation to the study design is the lack of traditional blinding of subjects during our treatment and condition interventions. Strong, distinguishable contrasts in flavor exist between the spice and control treatment, and there are distinct differences in the activity between the stress and rest condition. However, an attempt at blinding (presentation of placebo capsules with the control meal as a test comparing food derived antioxidants and food derived antioxidants) may have controlled for a subject's expectations of possible antioxidant effects. Further, data analysis of LPS concentrations in serum samples was performed in a blinded fashion.

Although this analysis did not reveal statistically significant differences in effects of treatment (spice vs. control) or condition (rest or stress), the trend for a treatment effect has potential clinical implications. The ability of spices, antioxidant-rich food products, to reduce the risk for chronic inflammatory disease has been debated. Similarly, there is sparse evidence that analyzes the link between endogenous LPS exposure to chronic disease progression in human populations. Therefore, the trend of reduced postprandial LPS serum values after the ingestion of spices warrants more detailed exploration. Future research that analyzes postprandial LPS levels should consider the use of more sensitive LPS detection methods and consider the possible

confounding effects of hypertriglyceridemia. Previous findings demonstrate that LPS concentrations in the body vacillate quickly in healthy subjects and are fleeting in nature (Erridge et al., 2007). This rapid fluctuation may account for the large standards of error observed in this analysis. An assay method with greater sensitivity may produce more reliable results in future investigations.

In conclusion, our study offers added insight into the functioning of low exposure to endogenous LPS in a human sample through two plausible mechanisms. Based on our findings, the use of a mixture containing multiple antioxidant-rich spices with high ORAC values is believed to facilitate both a reduction in circulating inflammation and an increase in intestinal barrier integrity. Therefore, the use of antioxidant-rich foods, especially a combination of those containing various compositions, should not be omitted from further investigation into the health effects of therapeutic diets on inflammation. The continued exploration into the underlying mechanisms that connect metabolic endotoxemia to inflammation may offer more a detailed understanding of how LPS contributes to the human chronic disease progression.

**Appendix A**

# The Effects of Cinnamon Intervention on Metabolism in Healthier Adult Populations

## 5.1 Introduction:

Recent research has investigated the effects of cinnamon on human health. The type of cinnamon used varies in clinical trials, but frequently includes *Cinnamomum cassia*, *Cinnamomum zeylanicum*, and a supplement, known as Cinnulin PF. Each form of cinnamon is a derivative of the product taken from the insides of evergreen bark and varies in concentration of coumarins – compounds identified as having anticoagulant characteristics (Ranasinghe et al., 2012). *C. cassia* is most frequently sold in grocery stores in the United States and has a higher concentration of coumarins compared to other types of cinnamon (Ranasinghe et al., 2012). *C. zeylanicum* is known as a "gourmet" cinnamon type and has lower concentrations of coumarin (Ranasinghe et al., 2012). Cinnulin PF is an aqueous extract of *Cinnamomum burmannii*, and is advertised to consumers as a supplement that will enhance insulin signaling (Qin, Panickar, & Anderson, 2010; Miller, T. Romero, Bolin, & A. Romero, 2011).

Previously, cinnamon's ability to act as an effective bioactive supplement was determined by Broadhurst, Polansky, & Anderson (2000), based on previous findings that suggest cinnamon can have an insulin-potentiating effect in regards to metabolism (Khan, Bryden, Polanksy, & Anderson, 1990). Cinnamon consumption has been linked to a heightening of glucose uptake associated with improved activity of glycogen synthase, insulin receptor kinase, and insulin receptor auto-phosphorylation (Qin et al., 2003; Jarvill-Taylor, Anderson, & Graves, 2001; Imparl-Radosevich et al., 1998; Cao, Polanksy, & Anderson, 2007). It was at first

believed that cinnamon was able to act as a bioactive compound because it included methylhydroxychalcone polymer (MHCP) in its composition, which acts in a similar fashion as insulin (Jarvill-Taylor et al., 2001). However, it has been more recently proposed that it is not MHCP that performs this action, but instead water-soluble polyphenolic type-A polymers (Anderson et al, 2004).

The National Institute of Health (NIH) recognizes individuals with diagnosed metabolic syndrome as those who have a combination of at least three major risk factors (2011). These can include abdominal-centered obesity, elevated blood pressure, an increased triglyceride concentration in the blood, a consistent diminished HDL cholesterol level, or significantly elevated fasting blood glucose (NIH, 2011). If an individual has a fasting blood glucose level that ranges from 100 to 125mg/dL they are considered to have a form of prediabetes called impaired fasting glucose (NIH, 2011). Fasting blood glucose levels that extend upward of 125mg/dL are characteristically seen in individuals with diagnosable diabetes (NIH, 2011). Thus, because of cinnamon's suggested role in enhancing insulin sensitivity, insulin response, and ability to improve metabolic factors, such as blood glucose levels, inclusion of cinnamon supplementation into everyday diet must be further investigated. Such evidence can be beneficial when evaluating the dieting strategies of individuals at risk for acquiring metabolic syndrome and associated health conditions, including type 2 diabetes, stroke, and heart disease.

Several clinical trials have investigated the effects of *C. cassia*, *C. zeylanicum*, and Cinnulin PF supplementation on physiological factors that contribute to the efficiency of metabolism. However, the majority of these studies focus on animal subjects or individuals already diagnosed with type 2 diabetes. The later human clinical trials have shown varying results. For example, after a 40-day investigation of the effects of 1g, 3g, and 6g of daily *C.*

*cassia* supplementation in type 2 diabetic subjects from a Pakistani population with poor glycemic control, findings demonstrated that cinnamon significantly reduced serum glucose levels by 18-29%, serum triglyceride levels by 23-30%, serum cholesterol levels by 13-26%, and LDL cholesterol levels by 10-24% (Khan, Safdar, Khan, Khattak, & Anderson, 2003). Such findings suggested that a wide range of cinnamon doses have the potential to elicit sustained effects (Khan et al., 2003). In an attempt to replicate the same effects using 3g of daily cinnamon supplementation over a 4-month period among a Western population with type 2 diabetes, Mang et al. (2006) discovered conflicting evidence. In this population of individuals with type 2 diabetes who managed their fasting glucose levels according to recommended guidelines, fasting plasma glucose was only moderately reduced by 10.3%; there was no significant effect on any other measured variables, including lipid profiles, HbA1c levels, blood coagulation parameters, or serum lipids after the cinnamon intervention (Mang et al., 2006). However, because there was still a significant reduction in plasma glucose levels, the advantageous health effects of cinnamon supplementation may still be a potentially valid outcome when used in healthier populations. Such findings warrant the need for further exploration.

The purpose of this literature review is to identify if cinnamon supplementation can have a beneficial effect on metabolism in healthy adult subjects or adults at-risk for developing metabolic syndrome. This literature review is based on the findings of 8 published journal articles that evaluate the outcomes of postprandial blood glucose, fasting blood glucose, postprandial insulin, fasting insulin, oxidative stress, and gastric emptying rate (GER). The goal of this literature review is to generalize the implications of cinnamon use on metabolism of a meal for a population of adults without metabolic syndrome.

## 5.2 Methods:

### *Identifying Relevant Publications:*

To be included in this literature review, research studies had to be randomized placebo-controlled trials or randomized crossover trials that used cinnamon supplementation as an intervention. Data on fasting blood glucose, postprandial blood glucose, fasting insulin, postprandial insulin, insulin sensitivity, or other related metabolic factors, such as GER or oxidative stress must have been reported as outcomes. Additionally, included clinical trials needed to use subjects who were considered "healthy" or "at risk" for metabolic syndrome. Thus, studies were included if subjects were healthy, sedentary, overweight, had impaired fasting glucose, or impaired glucose tolerance, but did not yet meet the standard criteria for diagnosable metabolic syndrome as defined by the previously stated NIH guidelines. The type of cinnamon used was not limited to any one type or species. Therefore, *C. cassia, C. zeylanicum*, and Cinnulin PF were all considered during the collection of relevant publications.

In order to find a comprehensive array of all journal articles published regarding the metabolic effects of cinnamon supplementation in healthy adult subjects, various databases were utilized such as Google Scholar, Science Direct, and PubMed. Searches in these databases were carried out using a combination of any of the following terms: "cinnamon supplementation", "metabolism", "metabolic effects", "GER", "insulin", "healthy adults", "blood glucose", "oxidative stress", and other similar words and phrases. Once relevant articles were found, their references were analyzed for other pertinent scientific articles. Moreover, some databases, such as Science Direct, have the capability of identifying similar articles viewed under the same topic;

this feature was used in the manual search and identification of relevant publications for this specific cinnamon literature search.

Journal articles were excluded if they described studies with subjects who were already clinically diagnosed with metabolic syndrome, type 2 diabetes, and type 1 diabetes. Exclusion criteria also included clinical trials with subject pools consisting of animals or adolescents. Studies were excluded if interventions included the use of spice mixes without a clearly stated, identifiable amount of cinnamon. Studies were also excluded if they were meta-analyses.

## 5.3 Results:

### *Overview of the Publications:*

The association between cinnamon supplementation and metabolic effects was examined in 8 journal articles included in this literature review. The types of cinnamon species investigated included *C. zeylanicum, C. cassia,* Cinnulin PF, and an unspecified cinnamon species. Subjects were healthy or at-risk for metabolic syndrome, male and female adults, and had a BMI within the range of 19.8 to 45kg/$m^2$. Three studies included subjects who were healthy (Hlebowicz, Darwiche, Björgell, & Almér, 2007; Hlebowicz et al., 2009; Markey et al., 2011). Subjects in 5 of the 8 journal articles met criteria for being at-risk for metabolic syndrome because they were characterized as having at least one risk factor for developing metabolic syndrome, but were not yet clinically diagnosed with metabolic syndrome (Roussel, HIninger, Benaraba, Ziegenfuss, & Anderson, 2009; Wickenberg, Lindstedt, Berntorp, Nilsson, & Hlebowicz, 2012; Solomon & Blannin, 2007; Solomon & Blannin, 2009; Skulas-Ray et al., 2011). Therefore, subjects included were classified as sedentary, overweight, impaired fasting glucose, or impaired glucose

tolerance. One study included subjects who had impaired fasting glucose (Roussel et al., 2009). One study included subjects who were known to have impaired glucose tolerance (Wickenberg et al., 2012). Two studies included healthy, but sedentary subjects (Solomon & Blannin, 2007; Solomon & Blannin, 2009). One study investigated subjects that were healthy, but overweight (Skulas-Ray et al., 2011)

It should also be noted that among the 8 journal articles analyzed, the metabolic outcomes of either short-term or long-term cinnamon exposure was observed. Further, 2 of the 8 journal articles described study designs consistent with the investigation of the long-term effects of cinnamon on metabolic factors (Roussel et al., 2009; Solomon & Blannin, 2009). The remaining 6 journal articles described study designs consistent with the investigation of short-term cinnamon exposure on metabolic factors (Hlebowicz et al., 2007; Helbowicz et al., 2009; Markey et al., 2011; Wickenberg et al., 2012; Skulas-Ray et al., 2011). Of the 8 journal articles included, 6 utilized randomized crossover study designs (Hlebowicz et al., 2009; Markey et al., 2011; Wickenberg et al., 2012; Solomon & Blannin, 2007; Solomon & Blannin, 2009; Skulas-Ray et al., 2011), and only 2 employed randomized placebo-controlled parallel arm study designs (Hlebowicz et al., 2007; Roussel et al., 2009)

Three studies did not specify the cinnamon type used, one of which used a specific amount of cinnamon in combination with other spices (Hlebowicz et al., 2007; Hlebowicz et al, 2009; Skulas-Ray et al., 2011). One study used *C. zeylanicum* (Wickenberg et al., 2012). One study used Cinnulin PF, an aqueous extract form of cinnamon (Rousssel et al., 2009). Three studies used *C. cassia* (Markey et al., 2011; Solomon & Blannin, 2007; Solomon & Blannin, 2009). The cinnamon distribution method was addition directly into food as described by 3 of the 8 journal articles (Hlebowicz et al., 2007; Hlebowicz et al., 2009; Skulas-Ray et al., 2011).

Capsules of cinnamon were used to distribute cinnamon supplementation in the remaining 5 studies (Markey et al., 2011; Roussel et al., 2009; Wickenberg et al., 2012; Solomon & Blannin, 2007; Solomon & Blannin, 2009). Of these 5 journal articles, 3 identified the use of oral glucose tolerance tests (OGTT) to assess metabolic factors after consumption of cinnamon capsules (Wickenberg et al., 2012; Solomon & Blannin, 2007; Solomon & Blannin, 2009).

GER was analyzed in 3 of the 8 included journal articles (Hlebowicz et al., 2007; Hlebowicz et al., 2009; Markey et al., 2011). Fasting blood glucose levels were investigated as outcomes in 3 studies (Roussel et al., 2009; Solomon & Blannin, 2007; Solomon & Blannin, 2009). The same 3 studies also examined fasting plasma insulin levels (Roussel et al., 2009; Solomon & Blannin, 2007; Solomon & Blannin, 2009). Postprandial blood glucose was examined in 4 studies (Hlebowicz et al., 2007; Hlebowicz et al., 2009; Markey et al., 2011; Wickenberg et al., 2012). Postprandial insulin levels were analyzed in 3 of the same studies (Hlebowicz et al., 2009; Markey et al., 2011; Wickenberg et al., 2012). Additionally, oxidative stress was assessed in 2 of the 8 included journal articles (Markey et al., 2011; Roussel et al., 2009). A detailed overview of the study design and outcomes of each of the 8 studies is shown in Table 4.

***Table 4: Details of study designs and outcomes of the 8 included journal articles***

| Year/ Reference | # of Subjects/ Type | BMI ($kg/m^2$) | Study Design: | Cinnamon Distribution Method | Control Distribution Method | Cinnamon Type | Duration of Exposure | Metabolic Factors Analyzed* | Main Outcome Results |
|---|---|---|---|---|---|---|---|---|---|
| **2007/ Hlebowicz et al.** | 8 M, 6 F/ Healthy | 22.6 (±2.2) | -RCT parallel arm<br>- 8h fast prior to intervention<br>- 1 visit<br>- Ingestion of test or control meal<br>- Blood samples taken every 15 min up to 120 min | 6 g. in 300g rice pudding | 300g rice pudding | Not Specified | Short-term | - GER<br>- Postprandial blood glucose concentrations<br>- Reduction in GER | - Reduction in postprandial blood glucose concentrations<br>- Reduction in GER |
| **2009/ Roussel et al.** | 22/ Impaired fasting glucose | Range: 25-45 | - RCT parallel arm<br>- 2 capsules each day for 12 weeks<br>- Fasting blood test at wk 0, 6, 12<br>- No lab meals | 2 capsules (250 mg) | 2 capsules of placebo | Cinnulin PF | Long-term | - Fasting glucose<br>- Fasting insulin<br>- Plasma oxidative stress | - Reduction in oxidative stress<br>- Reduction in fasting glucose<br>- No effect on fasting insulin |
| **2011/ Skulas-Ray et al.** | 6 M/ Healthy, overweigh t | 26.4 (±0.4) | - Randomized cross-over<br>- 1 visit per intervention<br>- 1 week separating intervention periods<br>- 12 h fasting except 4h prior ingestion of low antioxidant breakfast at home<br>- Ingestion of lab meal<br>- Blood samples post intervention every 30 min up to 4 hr | 0.61 g in 14 g spices added to chicken curry, cinnamon biscuit | Coconut chicken, desert biscuit | 0.61 g cinnamon mixture with other spices | Short-term | - Postprandial blood glucose<br>- Postprandial insulin | - Reduction in postprandial insulin<br>- No effect on postprandial glucose |
| **2007/ Solomon & Blannin** | 7 M/ Healthy, sedentary | 24.5 (±0.3) | - Randomized cross-over<br>- 3 interventions ($OGTT_{control}$, $OGTT_{cin}$, $OGTT_{cin12h}$)<br>- 8 h fasting prior to intervention<br>- Blood samples post every 30 min up to 120 min<br>- $OGTT_{control}$: ingestion of 5 g placebo capsules 12 h prior and immediately prior OGTT<br>- $OGTT_{cin}$: ingestion of 5 g placebo capsule 12 h prior and 5 g cinnamon immediately prior OGTT<br>- $OGTT_{cin12h}$: ingestion of 5 g cinnamon 12 h prior and 5 g placebo immediately prior OGTT | 5 g immediately prior or 12 h prior | 5g vegi-capsulated wheat flour placebo | *C. cassia* | Short-term | - Fasting serum insulin<br>- Fasting plasma glucose | - No effect on fasting serum insulin<br>- No effect on fasting plasma glucose |

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|---|---|---|---|---|---|---|---|---|---|
| **2009/ Solomon & Blannin** | 8 M/ Healthy, sedentary | 24.0 (±0.7) | - Randomized crossover<br>- Two 20-day interventions (cinnamon and control)<br>- ***Control trial:*** 8h fast prior to intervention, OGTT on days 1, 14, 16, 18, 20 with ingestion of 6 placebo pills at 2030 hrs on days 0-14 and 15-19 after meal<br>- ***Cinnamon trial:*** 8 h fast prior to intervention, OGTT on days 1, 14, 16, 18, 20 with ingestion of 6 cinnamon pills at 2030 hrs with meal on days 0-14 and ingestion of 6 placebo pills at 2030 hrs on day 15<br>-Blood samples taken every 30 min up to 120 min post OGTT<br>- 2 week washout separation period | 500 mg vegi-capsules w/ cinnamon on days 0-14, then six pills per day (3 g each day) after evening meal, placebo pills on days 15-19 after evening meal | 500 mg wheat flour capsules on days 0-14, then six pills per day (3 g each day) after evening meals, then placebo pills on days 15-19 after evening meal | *C. cassia* | Long-term | - Fasting serum insulin<br>- Fasting blood glucose | - Reduction in glucose response on day 1 and 14<br>- Reduction in serum insulin response on day 14 |
| **2009/ Hlebowicz et al.** | 9 M, 6 W/ Healthy | 22.5 (±2.7) | - Randomized crossover<br>- 8 h fast prior to intervention<br>- Random order of meals in 1 week intervals<br>- Meal ingested in 5 min<br>- Test duration around 2 months<br>- Blood samples prior and post every 15 min up to 150 min | 3 or 1 g of cinnamon in 300g rice pudding | 300 g rice pudding | Not Specified | Short-term | - GER<br>- Postprandial blood glucose<br>- Postprandial plasma insulin | - Reduction in postprandial plasma insulin response (Slight for 1g)<br>- No effect on postprandial blood glucose response<br>- No effect on GER |
| **2011/ Markey et al.** | 3M, 6F/ Healthy | 22.4 (±2.5) | - Randomized cross-over<br>- Two 1-day trials separated<br>- 28 day wash-out period<br>- 12 h fast prior to intervention<br>- Meal ingested within 15 min<br>- Subjects ingested 8 capsules (cinnamon or control)<br>- Blood samples taken each hour post intervention up to 260 min | 3 pancakes and 8 gelatin capsules with 3 g powered cinnamon | 3 pancakes and 8 gelatin capsules with wheat flour placebo | *C. cassia* | Short - term | - GER<br>- Postprandial plasma glucose<br>- Postprandial serum insulin<br>- Oxidative stress | - No effect on GER<br>- No effect on postprandial blood glucose<br>- Reduction in postprandial serum insulin<br>- No effect on oxidative stress |
| **2012/ Wickenberg et al.** | 6 M, 4 F/ Impaired glucose tolerance | 26.3 (±4.2) | - Randomized cross-over<br>-12 h fast prior to intervention<br>- OGTT with 75 g glucose with 6.9g lactose ingested with 15 capsules of cinnamon or placebo<br>-1 week intervals between intervention<br>- Blood samples taken prior to OGTT and post every 15 min up to 180 min | 400 mg *C. zeylanicum* and 100 mg lactose capsules | 560 mg lactose capsules | *C. zeylanicum* | Short-term | - Postprandial blood glucose<br>- Postprandial insulin | - No effect on postprandial glucose<br>- No effect on postprandial insulin |

**The studies included in this literature review investigated other outcomes in addition to those listed. Those outcomes not listed in Table 4 were deemed irrelevant to the scope of this particular literature review, and thus, were not included in the column entitled "Metabolic Factors Analyzed".*

***Summary of Included Journal Articles***

*Effect of cinnamon on postprandial blood glucose, gastric emptying, and satiety in healthy subjects (Hlebowicz et al., 2007)*

In a study with 8 healthy male and 6 healthy female subjects, the consumption 6g of unspecified cinnamon species in 300g of rice pudding was investigated to determine the effects on GER and postprandial blood glucose response. This intervention yielded reducing effects on postprandial blood glucose concentrations and GER. Yet, it should be noted that the reduction in postprandial blood glucose was more noticeable than the reduction in GER. Such findings suggest that cinnamon has a potential beneficial metabolic effect in healthy adult subjects because of its ability to lower postprandial glucose responses when added to food, explainable by a delay in GER.

*Effects of 1 and 3 g cinnamon on gastric emptying, satiety, and postprandial blood glucose, insulin, glucose-dependent insulinotropic polypeptide, glucagon-like peptide 1, and ghrelin concentrations in healthy subjects (Hlebowicz et al., 2009)*

In a study with 9 healthy male and 6 healthy female subjects, the consumption of 3g and 1g of unspecified cinnamon species in 300g of rice pudding was analyzed. Main results showed a significant reducing effect on postprandial insulin response for both 1g and 3g of the unspecified cinnamon, with a less profound effect on those consuming 1g of cinnamon. Additionally, study outcomes demonstrated no significant effects on postprandial blood glucose response or GER for either 1g or 3g of the unspecified cinnamon type used. Therefore, it is suggested that despite

reducing postprandial insulin response, the addition of 1g or 3g of unspecified cinnamon to food does not elicit beneficial effects on metabolism in healthy adults. Higher doses of cinnamon are most likely needed to impact GER and postprandial blood glucose response.

*Effect of cinnamon on gastric emptying, arterial stiffness, postprandial lipemia, glycemia, and appetite responses to high-fat breakfast (Markey et al., 2011)*

In a clinical trial with 3 healthy male and 6 healthy female subjects, the supplementation of 3g *C. cassia* in 8 capsules each day in combination with 3 pancakes over the span of 28 days was studied. The findings suggest evidence for a reduction in postprandial insulin response, but no significant effect on blood glucose response, GER, or oxidative stress. Thus, aside from reducing postprandial insulin response, there are no significant beneficial metabolic impacts implied by supplementing meals with 3g of *C. cassia* in healthy adult subjects. Lack of statistically significant evidence questions the reliability of using *C. cassia* supplementation to treat or prevent metabolic syndrome.

*Antioxidant effects of a cinnamon extract in people with impaired fasting glucose that are overweight or obese (Roussel et al., 2009)*

In a clinical trial with 22 subjects with impaired fasting glucose, the supplementation of two 250mg capsules of Cinnulin PF twice daily for 12 weeks was studied. Main results showed significant effects after 12 weeks, but not after 6 weeks. There was a reducing effect on fasting blood glucose and oxidative stress, but there was no significant effect on fasting insulin levels. For that reason, the supplementation of 500mg of Cinnulin PF each day may have some beneficial effects on metabolism in adult populations at risk for developing metabolic syndrome.

Additionally, because oxidative stress and hyperglycemia are risk factors for metabolic syndrome, such supplementation should be considered when treating and preventing diabetes and cardiovascular disease.

*A high antioxidant spice blend attenuates postprandial insulin and triglyceride response and increases some plasma measure of antioxidant activity in healthy, overweight men (Skulas-Ray et al., 2011)*

In a study with 6 healthy, overweight male subjects, the consumption of a meal with 0.61g of unspecified cinnamon type was investigated. Results demonstrated a reducing effect on postprandial insulin response, but no significant effect on postprandial blood glucose response. Therefore, the addition of 0.61g of unspecified cinnamon type to a meal demonstrated no beneficial effects on metabolism of a meal in healthy, overweight adult subjects, except for reducing postprandial insulin levels. This trial is important because it suggests that the addition of such cinnamon dosages to meals can help normalize postprandial insulin levels.

*Ceylon cinnamon does not affect postprandial plasma glucose or insulin in subjects with impaired glucose tolerance (Wickenberg et al., 2012)*

In a clinical trial with 6 male and 4 female subjects with impaired glucose tolerance, the supplementation of 400mg capsules of *Cinnamon zeylanicum* was studied. Such supplementation suggested no effect on postprandial blood glucose, postprandial insulin, fasting blood glucose, or fasting insulin. Thus, the supplementation of *Cinnamon zeylanicum* demonstrates no beneficial impacts on metabolism in healthy adult subjects.

*Effects of short-term cinnamon ingestion on in vivo glucose tolerance (Solomon & Blannin, 2007)*

In a study with 7 healthy, sedentary male subjects, the supplementation of 5g capsules of *C. cassia* was investigated. Main results showed a significant reduction in total glucose response and increase in insulin sensitivity, but no effects on insulin response or fasting blood glucose. Therefore, the supplementation of 5g *C. cassia* may have some beneficial effects of metabolism in healthy adult subjects. Because the effects were prevalent immediately and as much as 12 hours later, such evidence implicates this dosage of *C. cassia* as being potentially important in regulating glycemic control and insulin sensitivity.

*Changes in glucose tolerance and insulin following 2 weeks of daily cinnamon ingesting in healthy humans (Solomon & Blannin, 2009)*

In a clinical trial with 8 healthy, sedentary men, the supplementation of 500g capsules of *C. cassia* was studied. Findings suggest that this dosage of cinnamon supplementation can reduce glucose response and insulin response; additionally, insulin sensitivity will improve. However, these effects subside as soon as individuals stop taking cinnamon supplementation. Therefore, 500g of *C. cassia* can have beneficial effects on metabolism of a meal in healthy subjects, but the supplementation must be consistent and routine for the impact to sustain.

## 5.4 Discussion:

### *Description of Outcome Results*

#### *Fasting Plasma Glucose*

The use of two 250mg capsules of Cinnulin PF twice daily for 12 weeks suggests reducing effects on fasting plasma glucose (Roussel et al., 2009). Previous studies identified similar reducing effects from 1000mg cinnamon extract for 60 days and 3g cinnamon powder for 3 months in subjects with type 2 diabetes (Khan et al., 2003; Mang et al., 2006). The ability to reduce fasting plasma glucose levels in healthy adult subjects further exemplifies the health benefits of cinnamon in normalizing hyperglycemia.

Cinnamon supplementation of 5g of *C. cassia* has no significant effect on fasting plasma glucose levels in healthy adult subjects (Solomon & Blannin, 2007). These findings are similar to Vanschoonbeek et al. (2006) whose outcomes were based on the use of 1500mg of *C. cassia* supplementation each day for 6 weeks in postmenopausal type 2 diabetic females.

#### *Postprandial Blood Glucose*

The use of 6g of unspecified cinnamon type in 300g of rice pudding has a reducing effect on postprandial blood glucose levels (Hlebowicz et al., 2007). Because these findings indicate that the reduction of postprandial blood glucose levels were much lower than that of GER, it is evidence that the reduced postprandial blood glucose levels could be explained by cinnamon's ability to improve insulin receptor activity (Qin et al., 2003; Imparl-Radosevich et al., 1998).

Out of the 8 included articles, 4 suggest that the cinnamon supplementation used had no significant effect on postprandial blood glucose levels (Hlebowicz et al., 2009; Markey et al., 2011; Wickenberg et al., 2012; Skulas-Ray & Etherton, 2011). These findings were based on the clinical trial methods used in Markey et al. (2011) with short-term exposure of 3g of *C. cassia* capsules, Hlebowicz et al. (2009) with short-term exposure of 1g or 3g of unspecified cinnamon type in 300g of rice pudding, Skulas-Ray et al. (2011) with short-term exposure of 0.61g cinnamon in a spice-added meal, and Wickenburg et al. with short-term exposure of 400mg *of C. zeylanicum* capsules (2012).

*Fasting Insulin*

The supplementation of two 250mg capsules of Cinnulin PF twice daily has no effect on fasting insulin levels in healthy adult subjects (Roussel et al., 2009). Additionally, Wickenburg et al. (2012) found that the supplementation of 400mg of *C. zeylanicum* also has no effect on fasting insulin levels in healthy adult subjects.

*Postprandial Insulin*

The supplementation of 3g of *C. cassia* (Markey et al., 2011) and 1g or 3g of unspecified cinnamon type added to 300g of rice pudding (Hlebowicz et al., 2009) suggests a reducing effect on postprandial insulin levels. It should be noted that Hlebowicz et al. (2009) only noticed a slight reduction in postprandial insulin when analyzing 1g of unspecified cinnamon type.

However, findings from Wickenburg et al. suggest that 400mg of *C. zeylanicum*, coupled with 100mg lactose capsules, does not have any significant effect on postprandial insulin levels

(2012). Skulas-Ray et al. demonstrated similar findings; in this case, the cinnamon supplementation of 0.61g of unspecified cinnamon has no effect on postprandial insulin levels when consumed in combination with other spices added to a chicken meal (2011).

*Gastric Emptying Rate (GER)*

The use of 6g of unspecified cinnamon in combination with 300g of rice pudding has been shown to cause a reduction in GER (Hlebowicz et al., 2007). However, the use of 3g *C. cassia* powder in capsule form shows no significant effect on GER (Markey et al., 2011). Similar dosages of an unspecified cinnamon type added to 300g rice pudding replicate these findings (Hlebowicz et al., 2009). No significant effect was found by Hlebowicz et al. (2009) for 1g unspecified cinnamon type as well. This may suggest that the dosages of 3g and 1g of cinnamon are not substantial enough to elicit such results. As such, a dosage of cinnamon as great as 6g might be necessary to demonstrate statistically significant reductions in GER.

*Oxidative Stress*

The use of 250mg of dried aqueous Cinnulin PF in 2 capsules twice a day has demonstrated the potential of reducing oxidative stress in subjects with diagnosed impaired fasting glucose (Roussel et al., 2009). However, Markey et al. (2011) demonstrated different results, as 3g of *C. cassia* in 8 capsules showed no significant effect on oxidative stress. The significant reduction in oxidative stress as seen in Roussel et al. (2009) was demonstrated in individuals with impaired fasting glucose. The insignificant effect on oxidative stress as seen in Markey et al. (2011) was demonstrated in healthy subjects.

### *Explanation of Proposed Theoretical Mechanisms*

There have been various suggested mechanisms associated with cinnamon supplementation that influence the reduction of plasma glucose levels in human subjects. These proposed mechanisms can be found in Figure 4. Because the scope of this literature review is focused on cinnamon's effects on glucose, insulin, GER, and oxidative stress, the main mechanisms described by Figure 4 only include insulin sensitivity, plasma glucose, oxidative stress, and GER. Other common factors associated with these mechanisms have been included to provide a more comprehensive view of the model. For example, it is known that physical activity can directly influence insulin sensitivity and BMI, both of which contribute to blood glucose concentrations. Moreover, diet can influence blood glucose concentrations directly or indirectly by contributing to BMI. However, the main mechanisms evaluated in regards to the included journal articles are insulin sensitivity, oxidative stress, and GER.

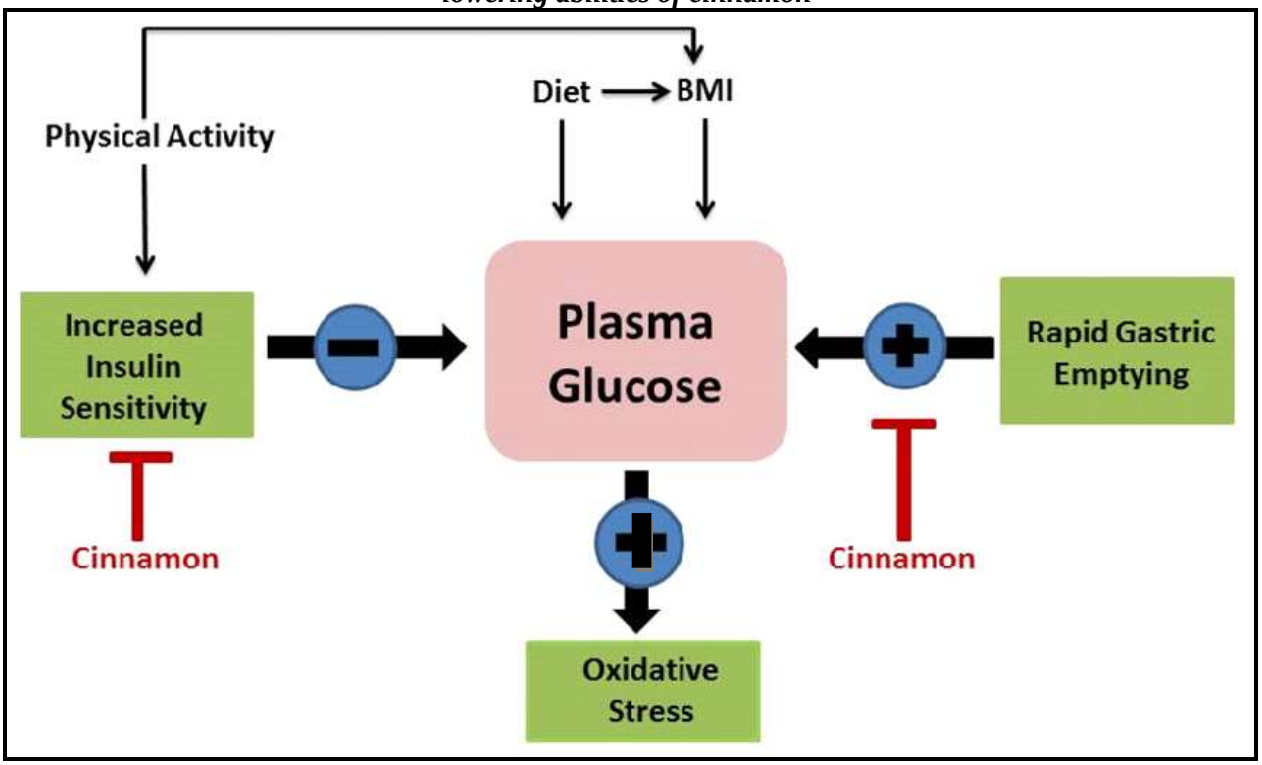
It is known that increased insulin sensitivity causes a decrease in blood glucose levels. When an individual has high insulin sensitivity, the ability to lower blood glucose concentrations will only require small amounts of insulin. Conversely, individuals with low insulin sensitivity will not have this capability; much greater amounts of insulin are needed to detect and lower elevated blood glucose levels. Such individuals are said to be "insulin resistant". Investigations into factors contributing to insulin resistance have revealed that even healthy adults can develop low insulin sensitivity associated with increased postprandial blood glucose and insulin concentrations when eating a normal everyday meal (Dickinson, Colagiuri, Faramus, & Petocz,

2002). Many previous studies have suggested that cinnamon has insulin-sensitizing abilities (Couturier et al., 2010). Thus, a proposed mechanism for cinnamon's ability to reduce blood glucose is through an indirect increase in insulin sensitivity.

Moreover, GER has been shown to potentially assist in the regulation of postprandial blood glucose response. Thus, GER has a crucial role in contributing to the homeostasis of blood glucose levels. Decreased GER has been linked to a reduction in blood glucose levels because the transit time for carbohydrates to be moved into the small intestine is decreased (Horowitz, Edelbroek, Wishart, & Straathof, 1993; Blair, Wing, & Wald, 1991). Thus, it was proposed that the intervention of cinnamon may help to blunt rapid gastric emptying, leading to a reduction in postprandial glucose levels in humans.

Prolonged, poorly managed, elevated blood glucose levels may contribute to an increased production of reactive oxygen species (ROS) in cells, which, in turn, increases oxidative stress (Wright, Scism-Bacon, & Glass, 2006). This can potentiate risk for improper cardiovascular function. For example, oxidative stress has been connected to an increased production of circulating inflammatory cytokines during spikes in blood glucose concentrations in healthy subjects, as well as those with impaired glucose tolerance (Wright et al., 2006). Moreover, oxidative stress caused by elevated blood glucose levels can increase the production of endothelial cellular adhesion molecules, and, as a result, lead to an increased risk for plaque buildup associated with atherosclerosis (Wright et al., 2006; Ceriello et al., 2004). Polyphenols in cinnamon are thought to have antioxidant effects that can aide in reducing oxidative stress when added to the diet. Thus, by implementing a cinnamon supplementation intervention, oxidative stress was thought to be indirectly reduced via reduction in blood glucose concentrations.

***Figure 5: A model of the main mechanisms thought to be associated with the blood glucose-lowering abilities of cinnamon***




**A (-) indicates a decrease and a (+) indicates an increase.*

***Summary of Support for Mechanistic Findings from Studies:***

Of the 5 included studies that analyzed postprandial blood glucose levels after the cinnamon intervention used in each respective trial, 1 study demonstrated a reduction in postprandial blood glucose levels (Hlebowicz et al., 2007), while the remaining 4 studies found no such significant effect on postprandial blood glucose levels in the test groups (Hlebowicz et al., 2009; Markey et al., 2011; Wickenberg et al., 2012; Skulas-Ray et al., 2011). An additional 3 studies investigated fasting blood glucose as a measured outcome (Roussel et al., 2009; Solomon & Blannin, 2007; Solomon & Blannin, 2009). Of these, 2 studies found a significant reduction in fasting blood glucose levels after cinnamon supplementation (Roussel et al., 2009; Solomon &

Blannin, 2009); however, 1 study did not find similar effects (Solomon & Blannin, 2007). Postprandial insulin levels after cinnamon supplementation were investigated in 4 of the included studies (Hlebowicz et al., 2009; Markey et al., 2011; Wickenberg et al., 2012; Skulas-Ray et al., 2011), but only 3 of these studies demonstrated findings consistent with a significant reduction in postprandial insulin levels after exposure to the cinnamon intervention (Hlebowicz et al., 2009; Markey et al., 2011; Skulas-Ray et al., 2011). In addition, 3 studies looked into the effects of cinnamon exposure on fasting insulin levels (Roussel et al., 2009; Solomon & Blannin, 2007; Solomon & Blannin, 2009), with only 1 of these trials identifying a significant reduction after cinnamon supplementation (Solomon & Blannin, 2009). Thus, there is evidence that cinnamon may have potential beneficial reducing effects on postprandial blood glucose, postprandial insulin, fasting blood glucose, and fasting insulin levels – all of which are associated with insulin sensitivity. Yet, the evidence is not concrete. It may be plausible that cinnamon can increase insulin sensitivity in order to decrease blood glucose levels. Thus, this mechanism should not be ignored in the analysis of how cinnamon can benefit the human metabolism. Yet, more investigation is needed to confirm specific details about the correct dosage and species of cinnamon to use, as well as the specific health conditions that will benefit most from such intervention.

Of the 3 studies that analyzed GER, 2 trials found that supplementation of cinnamon had no significant effect on GER (Hlebowicz et al., 2009; Markey et al., 2011), and 1 found that supplementation of cinnamon resulted in only a minor reduction in GER (Hlebowicz et al., 2007). It is interesting to note that the 1 study that found a small reduction in GER also found a much more prominent reduction in overall blood glucose levels after cinnamon supplementation (Hlebowicz et al., 2007). Although the 2 studies that found non-significant GER results also

found no significant reduction in postprandial plasma glucose, such findings demonstrate that reduced GER is not the only major mechanism contributing to the reduction in blood glucose levels after cinnamon consumption (Hlebowicz et al., 2009; Markey et al., 2011).

Of the 2 studies that analyzed oxidative stress as an outcome measure after cinnamon supplementation, 1 study found a significant reduction in oxidative stress (Roussel et al., 2009) and 1 trial did not (Markey et al., 2011). A possible explanation for the differences in results may be in part because of the difference in subject pool. The study that found significant reduction in oxidative stress employed subjects who were diagnosed with impaired fasting glucose with a BMI of 25-45 $kg/m^2$ (Roussel et al., 2009). The study that found no significant effect on oxidative stress recruited subjects who were classified as being "healthy" with a BMI of 22.4 $\pm 2.5$ $kg/m^2$ (Markey et al., 2011). Additionally, the duration of exposure to cinnamon supplementation may be a contributing factor to differences as well. Markey et al. (2011) found no significant effects on levels of oxidative stress when investigating short term cinnamon exposure (Markey et al., 2011). In contrast, Roussel et al. (2009) found a significant reduction in oxidative stress when investigating long term cinnamon exposure. Moreover, Rousel et al. (2009) utilized Cinnulin PF and Markey et al. (2011) employed *C. cassia* in their respective trials. Cinnulin PF is recognized as being an aqueous cinnamon extract, and therefore, may have an increased concentration of bioactive components compared to whole cinnamon species, such as *C. cassia*. However, more investigation is needed to confirm this possible explanation.

**5.5 Conclusion:**

The conflicting findings of the 8 included journal articles in this literature review may be explained by a variety of factors including the difference in type of cinnamon species used, health condition of the subjects studied, dosage of cinnamon used, duration of cinnamon supplementation exposure, and method of cinnamon distribution. For example, *C. zeylanicum* is a species of cinnamon known to have significantly less coumarin in it than *C. cassia* (Ranasinghe et al., 2012; Jayatilaka, Poole, Poole, & Chichila, 1995; Pari & Rajarajeswari, 2009; Guerro-Analco, Hersch-Martínez, Pedraza-Chaverri, Navarrete, & Mata, 2005). In past studies, coumarin has exhibited reducing effects on glucose and metabolism in diabetic rats (Pari & Rajarajeswai, 2009; Guerro-Analco et al., 2005; Feuer, Golberg, & Gibson, 1966). If coumarin has the same effects in humans, it is plausible that for small effects, or potentially even no significant effects, on fasting insulin to be expected when consuming *C. zeylanicum*. However, more investigation into this concept is needed to confirm coumarin's effects in the human body. Moreover, even though the same species of cinnamon may be used in more than one study, the cinnamon may have variances due to method of production, location it was produced in, and way that it was distributed. Additionally, the blood glucose-lowering effect of the cinnamon intervention used may be altered depending on the health of the study subjects. As demonstrated by the studies of Kahn et al. (2003) and Mang et al. (2006), individuals may experience different outcomes when utilizing a cinnamon intervention in diet depending on their health and baseline blood glucose levels. Individuals with poorly managed glycemic control may experience more extreme outcomes, compared to healthier individuals (Mang et al., 2006).

As such, the comparison of results from this overview should be interpreted with caution. More research should be done that includes larger subject pools to enhance generalizations and

standardization of results. Clinical trials using the same cinnamon type as an intervention, but different dosages may have conflicting results. Thus, more research should be carried out to investigate the exact amount of each cinnamon supplementation type needed to generate beneficial metabolic effects for healthy adult subjects, and which dose, if any, is most effective.

**5.6 Clinical Implications:**

These studies indicate that including cinnamon in the diet may have the potential for lowering postprandial glucose, reducing oxidative stress, reducing impaired fasting glycaemia, reducing fasting blood glucose, normalizing insulin levels, and enhancing antioxidant defenses. Implications of these studies suggest that cinnamon supplementation may have protective effects for individuals at risk for diabetes and cardiovascular disease. However, further investigation is crucial for a more comprehensive understanding of the mechanisms related to cinnamon's blood glucose-lowering abilities. Additional consistent evidence is required to confirm cinnamon's hypothesized ability to improve metabolism functioning in healthier adult populations.

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# ACADEMIC VITA

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## Education

The Pennsylvania State University, University Park, PA
B. S., Biobehavioral Health with Honors in Biobehavioral Health, Expected May 2015
Schreyer Honors College

## Honors and Awards

Schreyer Honors College Academic Excellence Scholarship (2011-2015)
Dean's List, The Pennsylvania State University (2012-2015)
Omega Bank Academic Excellence Scholarship (2013-2015)
Fasola Family Trustee Scholarship (2013-2014)
Schreyer Honors College Research Grant (Summer 2014)
Schreyer Honors College Travel Grant (Spring 2012)

## Certifications

New Jersey Certified Nurse Aide (01/2014-Present)
American Heart Association: Basic Life Support for the Healthcare Provider (09/2014-Present)
Federal Education Rights and Privacy Act (09/2014-Present)

## Research Experience

Vascular Health Interventions Laboratory (Sheila West, PI)
*Pennsylvania State University; Department of Biobehavioral Health*

- Undergraduate Research Assistant (2013-Present)
- Observe and assist with clinic patient visits; carry out blood processing, data entry, and blood bag assembly
- Attend and participate in weekly lab meetings with undergraduate and graduate students to discuss current lab proceedings and review current relevant literature
- Conduct honors thesis research and writing

Mind-Body Cardiovascular Psychophysiology Lab (William Gerin, PI)
*Pennsylvania State University; Department of Biobehavioral Health*

- Undergraduate Research Assistant (2012-2013)
- Assessed participant cardiovascular changes during series of stress tests in laboratory setting
- Performed data analysis of study results
- Trained new lab members on procedure and protocols of ongoing studies

## Healthcare Experience

The Meadows Psychiatric Facility
*Centre Hall, PA*

- Adolescent Mental Health Technician on unit with male and female patients, ages12-17
- Maintained 1 to 4 ratio of mental health technicians to patients on a unit with maximum occupancy of 17
- Monitored patient safety on unit, in cafeteria, and in group activities
- Completed patient observational rounds every 15 minutes to assess for changes in behavior and location
- Performed vital checks as directed for each patient
- Carried out safety searches upon arrival for new admits

## Activities & Community Service

College of Health & Human Development Honors Society
*Pennsylvania State University*

- Active Member since 2013

Biobehavioral Health Society
*Pennsylvania State University*

- Active Member since 01/2014; Distinguished Member during fall 2014 - spring 2015

Omega Phi Alpha National Community Service Sorority – Alpha Theta Chapter
*Pennsylvania State University*

- Active Sister since 09/2012; Morale Chair during fall 2013
- Completed 50 or more hours of community service each active semester
- Participated in service activities to benefit the university community, State College community, and international organizations

Development Center for Adults – Centre County
*Centre County, PA*

- Adult Basic Education Tutor during fall 2013
- Completed 30 hours of tutoring during semester

- Tutored adult learners in mathematics, vocabulary, grammar, reading comprehension, and writing composition basics

Global Medical Brigades
*Pennsylvania State University*

- Active Member 2011-2012; Panama brigade member March 2012; Charla Education Committee March 2012
- Traveled to Panama in March to offer volunteer medical aid to various compounds in Latino and indigenous communities
- Shadowed physicians, dentists, and pharmacists in abroad clinical setting
- Fundraised throughout the semester to raise money for medical supplies to bring to clinics in Panama

## Additional Work Experience

Undergraduate Teaching Assistant for BBH 101 (Sheila West, Professor)
*Pennsylvania State University; Department of Biobehavioral Health*

- Summer 2014
- Created and graded assessments that tested course material
- Held office hours (1.0 hr/week) and attended lectures 5 days a week (1.25 hr/day)
- Answered students' questions through email and in person

Undergraduate Teaching Assistant for BBH 301 (Michele Stine, Professor)
*Pennsylvania State University; Department of Biobehavioral Health*

- Fall 2014
- Lead and graded weekly student discussion assignments
- Held office hours (1.0 hr/week) and attended lectures 3 days a week (1.25 hr/day)
- Answered students' questions through email and in person

Campmor Retail Store
*Paramus, NJ*

- Cashier 05/2013-01/2014 (Seasonal)
- Worked 24-40 hours per week
- Handled all monetary transactions including checks, credit, debit, and cash
- Counted out cash draw at start and end of shift
- Assisted in customer service concerns from customers
- Maintained clean, organized, and professional sales floor and check-out environment