A Proposed Phase I, Randomized Controlled Study to Determine Whether a Combination of Ginger, Turmeric, and Sage Can Reduce C-Reactive Protein in Subjects Undergoing HIV Highly Active Anti-Retroviral Therapy

By

Kyle Burton, L.Ac.

A Capstone Project

Presented in partial fulfillment of the requirement for the

Doctor of Acupuncture and Oriental Medicine Degree

Capstone Project Advisor: Rosaleen Ostrick

Yo San University

Los Angeles, California

March 2017

Approval Signatures Page

This Capstone Project has been reviewed and approved for acceptance in fulfillment of DAOM Research Reporting by:

Rosaleen Ostrick, L.Ac.

Capstone Project Advisor

April 30, 2017

Pam Tarlow, PharmD

Integrative Internal Medicine Specialty Co-Chair

April 30, 2017

Laraine Crampton, DAOM, LAc,
Doctoral Program Dean

April 30, 2017

Abstract

Highly active anti-retroviral therapy (HAART) has increased the life expectancy of the HIV-positive patients similar to that of the HIV-negative population. However, those undergoing HAART have shown an increased chance for cardiovascular disease (CVD). Higher levels of C-Reactive Protein (CRP), a risk factor for CVD, are more common for those with HIV. Since HAART is essential for suppressing the viral load, this pilot study will test the safety of adding an herbal formula in combination with HAART to help reduce CRP and potentially CVD. Turmeric, ginger, and sage have been shown to decrease inflammation and do not have any known negative interactions with HAART's absorption or efficacy. **Method**: Patients undergoing HAART will be randomized into either an intervention group that will be given 3 grams of the herbal formula twice a day, or into a control group. The trial will last for six weeks. **Results**: Introductory and final blood draws will be compared to determine whether a significant change in CRP or viral levels occurred. The standard risk factors for CVD will also be tested including: glucose, cholesterol, blood pressure, and weight. The results will show if this herbal combination can safely and effectively reduce the increased risk of CVD in those undergoing HAART.

Acknowledgments

Many people helped make this paper possible; the staff at Yo San University for their overwhelming support, Dr. Laraine Crampton and Dr. Andrea Murchison for their excellent guidance, Dr. Spar and his expertise, and my aunt, Penny Haddad for her life time of inspiration. A special thank you to my family and office staff for their continual support and to my advisor, Rosaleen Ostrick, whom none of this would be possible. Thank you to my fellow cohort for their friendship, humor, and encouragement.

Table of Contents

Signature Page……2

Abstract……3

Acknowledgments……...4

Chapter One: Introduction……...7

Purpose……8
Research Question……...8
Hypothesis……...8
Null Hypothesis……...8
Value of Study……8
Definition of Terms……9

Chapter Two: Literature Review……..……...…11

Overview……..……..11
Inflammation……..……11
Acute vs Chronic……...12
Cardiovascular Disease……12
Inflammatory Enzymes Cyclooxygenase ……14
Inflammatory Proteins: CRP ……..……...14
Inflammatory Cytokines: TNF-alpha, IL-6 ……..15
How CRP Can Increase Risk for CVD…….……15
CRP vs. Highly Sensitive CRP Lab Work……17
Standard of Care Treatment for Inflammation……..17
Diet and CRP……18
HIV / AIDS……19
Highly Active Anti-Retroviral Therapy (HAART)……...19
HAART, HIV and Inflammation……...21
Other Comorbidities……..21
Traditional Chinese Medicine and Thermal Properties…….....23
Ginger……24
Sage……...26
Turmeric……27
Herb / Drug Interactions……....28
Research Synthesis…….……...29

Chapter Three: Methodology……30

Design……..……..30
Sampling Procedures ……...……31
Search Terms……31

Inclusion and Exclusion Factors…….32

Chapter Four: Results…….33
Findings……..33
Ginger and CRP……..33
Ginger and Safety……34
Turmeric and CRP……...34
Turmeric and Safety……36
Sage and CRP…….....37
Sage and Safety……37
Secondary Measurements…….38

Chapter Five: Discussion……41
Implications of Theory……41
Implications of Practice……...42
Challenges and Limitations…….42
Conclusion……...43

References ……..45

Appendices

Appendix A: Pilot Study Design……..……..55

Appendix B: Consent Form…...…….59

Appendix C: Waiver of Liability and Hold Harmless Agreement…….67

Appendix D: Permission to Use Personal Health Information……..69

Appendix E: Breakdown of Cost……...74

Appendix F: Sample Advertisement for Subject Recruitment……..76

Chapter One: Introduction

Background

HIV-positive patients are living longer with the increased success of highly active anti-retrovirus therapy (HAART). HAART keeps the virus at undetectable levels and prevents the patient from developing Acquired Immune Deficiency Syndrome (AIDS). We now have for the first time an aging HIV-positive population. Comorbidities are starting to emerge, and at an earlier age than in the HIV-negative population (Hall, 2011). Large studies have indicated an increased risk of cardiovascular disease (CVD) in HIV patients on HAART (D'Ettorre, 2016). The increased risk is so significant that doctors are suggesting the recommended age for cardiovascular health screenings and prevention should be lowered for those who are HIV-positive (Boccara, 2013).

The exact mechanism of why HIV patients on HAART have an increased chance of developing CVD is not known. It may be due to chronic, low-grade inflammation from the dormant virus or from the daily medication (Triant, 2009). Whatever the cause, we know those undergoing HAART have a higher risk of CVD (Fichtenbaum, 2011).

There are normal risk factors for CVD, such as cholesterol, diabetes, and high blood pressure, but newer research is discovering that certain inflammatory biomarkers found in the blood can be another way to assess the risk for CVD (Ridker, 2005). The American Heart Association suggests monitoring C-reactive protein (CRP), and have established acceptable levels that range depending on age (American Heart Association, 2016). High levels of CRP are considered a risk for CVD (Arnett, 2007). The median level of CRP is higher for those who are HIV-positive (Fichtenbaum, 2011).

Certain herbs have been shown to have anti-inflammatory effects. Several studies have shown ginger, turmeric, and sage to decrease CRP levels (Zhang, 2007; Naderi, 2015; Zhang, 2016). It is possible the combination of these three herbs may decrease the risk for CVD by decreasing CRP levels.

Purpose

The purpose of this capstone is to design a clinical trial, founded in a scholarly literature synthesis, that will show whether a combination of ginger, turmeric, and sage can reduce levels of CRP in HIV-positive patients undergoing HAART.

Research Question

Can a combination of ginger, turmeric, and sage reduce CRP levels in HIV-positive patients who are undergoing HAART?

Hypothesis

HIV-positive patients undergoing HAART who are given ginger, turmeric, and sage will show a decrease in CRP blood serum levels.

Null Hypothesis

There will be no decrease in the CRP serum levels in the treatment group ingesting ginger, turmeric, and sage.

Value of Study

The purpose of this pilot study is to test if an herbal anti-inflammatory formula (HAI) can decrease CRP levels in HIV-positive patients undergoing HAART. This trial may inspire further investigation into herbs and their possible synergistic effects in decreasing inflammation and other comorbidities for those taking HAART. As a further benefit, these herbs might also show the same anti-inflammatory effects in HIV-negative subjects.

Definition of Terms

Acquired Immune Deficiency Syndrome (AIDS) - Acquired Immune Deficiency Syndrome is a condition, caused by HIV, when the body's immune system is unable to fight off secondary infections or diseases due to a weakened immune system. AIDS is diagnosed when the white blood cell count, CD4, is less than 200 cells/mm (CDC, 2016).

Arteriosclerosis - Arteriosclerosis is an abnormal thickening and hardening of the blood vessel wall (Huether, 1996).

Atherosclerosis - Atherosclerosis is a form of arteriosclerosis in which soft deposits of intracellular fat and fibrin on the blood vessel walls harden over time (Huether, 1996).

C-reactive protein (CRP) - A protein involved in inflammation that can be used to monitor the risk of cardiovascular disease (Prasad, 2006).

Cardiovascular disease (CVD) - Cardiovascular disease is a class of diseases that involve the heart and blood vessels. The most common types are coronary artery disease, high blood pressure, cardiac arrest, congestive heart failure, peripheral artery disease, and stroke (Huether, 1996).

Herbal formula - There are many different methods of classifying groups of herbs in a formula. Classifications are based on disease, pattern, symptom, temperatures, taste. Formulas include two or more herbs chosen for their synergetic effects or to balance other included herbs from being too harsh or extreme (Bensky, 1993).

Herbal anti-inflammatory (HAI) - The herbal anti-inflammatory used in this study is a combination of ginger, turmeric, and sage.

Highly active anti-retroviral therapy (HAART) - HAART is a combination of at least three drugs that suppress HIV replication and resistance to medication. HAART can reduce viral levels to an undetectable level. This helps prevent the development of AIDS and decreases the chance of transmitting the virus to others (Hall, 2011).

Human Immunodeficiency Virus (HIV) - Human Immunodeficiency Virus-which if untreated develops into AIDS- attacks a specific white blood cell responsible for preventing infection (CD4), which weakens the immune system over time (CDC, 2016).

Interleukin-6 (IL-6) - Interleukin 6 is an inflammatory cytokine that has been observed in chronic diseases, including cardiovascular disease (Neal, 2008).

Metabolic syndrome (MS) - A group of risk factors for cardiovascular disease (Guarner, 2012).

Myocardial infarction - Prolonged, unrelieved ischemia that interrupts blood supply to the myocardium (Huether, 1996).

Prostaglandins - Long chain fatty acids produced from arachidonic acid, which increase vascular permeability during inflammation (Huether, 1996).

Qi - Various translation including energy, life force, matter-energy, qi is difficult to define (Maciocia, 1989).

Traditional Chinese Medicine (TCM) - Including acupuncture, herbs, diet, and massage, TCM dates back more than 2,000 years (Maciocia, 1989).

Tumor Necrosis Factor-Alpha (TNF-alpha) - Produced primarily by macrophages in response to infection, TNF-alpha causes vascular endothelial cells to become stickier by increasing surface adhesion molecules (Huether, 1996).

Viral reservoir - A viral reservoir is a cell type or anatomical site in association with which a replication-competent form of the virus accumulates and persists (Blankson, 2002).

Chapter Two: Literature Review

Overview

This chapter will provide a review of inflammation, CVD, and associated biomarkers involved in inflammation. It will further explore HIV and HAART's independent risks of CVD. Next, a literature review of the efficacy of ginger, turmeric, and sage to decrease inflammatory biomarkers will provide the rationale for this pilot study.

Search Terms

Research information for the literature review was obtained from: Pubmed, Google Scholar, National Institute of Health, Journal of Chinese Medicine, Journal of Acquired Immune Deficiency Syndromes, Louise M. Darling Biomedical Library at UCLA, HIV/AIDS in the Post-HAART Era, Chinese Herbal Medicine Materia Medica, Foundations of Chinese Medicine. Key search words included HIV, HAART, inflammation, HAART and inflammation, CRP, cardiovascular disease and HAART, ginger and CRP, turmeric and CRP, sage and CRP, ginger and HAART, turmeric and HAART, sage and HAART.

Inflammation

Inflammation is a biological response of body tissue to a foreign stimulus. Its purpose is to eliminate the foreign stimulus and to clear out cells damaged by the stimulus. Harmful stimuli can include bacterial or viral infections, dietary factors, auto-immune diseases, musculoskeletal strains, chemicals, and external injuries. There are two types of inflammation local and systemic. Local inflammation is usually noticeable as swelling, redness and heat from increased blood flow. Systemic inflammation may occur throughout the body, and may be more difficult to detect because of the lack of external physical signs (Huether, 1996).

Acute Inflammation vs Chronic Inflammation

Acute inflammation has a rapid onset after the initial trauma or foreign stimulus. The innate immune response, the non-specific immune system, increases the flow of plasma and leukocytes to the injured tissue. Cytokines help dilate blood vessels so that white blood cells, which are larger than red blood cells, can enter the injured site, which furthers the inflammatory process. This increased dilation of blood vessels is responsible for the heat, redness, swelling, and pain that are the hallmark signs of an acute inflammatory response (Huether, 1996).

Chronic inflammation is defined as inflammation that lasts longer than three months (Huether, 1996). It can occur when the original stimulus has not been eliminated. During chronic inflammation, there is simultaneous destruction and healing of the tissue and, over time, the affected cells begin to change. Such changes can create scar tissue or even thickening of the arteries (arteriosclerosis) (Huether, 1996). Moreover, chronic inflammation is thought to be a driving factor in the aging process (Guarner, 2012).

Cardiovascular Disease

Chronic increased levels of inflammation are an independent risk marker for CVD, beyond the conventionally employed risk factors of metabolic syndrome (MS). Recent studies indicate that vascular inflammation, specifically atherosclerosis, is an independent risk factor for the development of CVD. Inflammation is the catalyst for atherosclerosis, as it requires continuous recruitment of monocytes into the blood vessels, which then form atherosclerotic plaque (Libby, 2009).

MS is a group of risk factors that we know together increases an individual's chance of developing CVD (NIH, 2016). MS is more common within the HIV positive population; a cross-sectional survey of 877 patients revealed that 25% developed MS after prolonged exposure

to HAART (Wu, 2012). Additionally, there is evidence that the risk factors for MS are provoked by chronic inflammation.

The presence of three of the five following risk factors lead to a diagnosis of MS: elevated triglycerides, decreased high density lipids (HDL), increased fasting glucose, hypertension or obesity. Any of these alone also increase the risk of CVD, but they tend to happen concurrently (NIH, 2016).

Some hallmarks of MS such as weight, a sedentary lifestyle, and some types of insulin resistance are controllable. Factors which are not controllable include a person's genetic make-up; an example is insulin-dependent diabetes. Moreover, the risk for MS increases with age.

Most of the risk factors for MS do not have outward signs or symptoms other than a large waistline. High blood sugar can cause increased thirst, urination, fatigue, and blurry vision, but all these symptoms have many causes; it can only be diagnosed accurately through blood work. High blood pressure may cause headaches, dizziness, or nosebleeds, but it is often symptom-free and can only be confirmed by measuring blood pressure. Blood work and physical assessments are necessary to monitor risk; subjective complaints are not sufficient to diagnose MS.

People with MS are twice as likely to develop heart disease and five times more likely to develop diabetes (NIH, 2016), and, according to the National Heart, Lung, and Blood Institute (2016), people with MS often have two other conditions: excessive blood clotting and constant, low-grade inflammation.

It is not known if MS causes inflammation, or if inflammation causes MS. What we do know is that inflammation is a cause of CVD (Libby, 2009). Therefore, the ability to decrease inflammatory biomarkers could potentially decrease the risk of MS and CVD. Since they tend to appear together - suggesting a common, yet multifactorial inflammatory source – it would seem

appropriate to combat them with a multi-targeted medicine that works on several pathways at once. The herbs chosen for this study, as explained later, have been shown to work on multiple inflammatory pathways.

Inflammatory Enzymes: Cyclooxygenase

Cyclooxygenase (COX) is an enzyme that promotes inflammation. COX converts arachidonic acid into prostaglandins. Some of the converted prostaglandins cause vasodilation while others produce the enzyme thromboxane A4, an aggregating agent. The vasodilation is useful in that it allows the larger white blood cell to enter the damaged area. The increased blood flow is what gives the damaged area the increased red color and warmth. Cyclooxygenase 1 (COX-1) is present in most normal healthy tissues including blood vessels, interstitial cells, platelets, mesothelial cells, and smooth muscles. Regular functions of COX-1 maintain the lining of the stomach and are involved in kidney and platelet function (Huether, 1996). Cyclooxygenase 2 (COX-2) is another enzyme found in the parenchymal cells of most tissues. COX-2 is up-regulated during inflammation and transported to the site of injury where it helps prevent thrombosis. A class of commonly used anti-inflammatory medications, the non-steroidal anti-inflammatory drugs (NSAIDS) works by inhibiting the action of COX-1 or COX-2.

Inflammatory Proteins: CRP

C-reactive protein (CRP) is synthesized primarily by the liver and is a marker for systemic inflammation. The normal level of plasma CRP for a healthy adult is 2 mg/L or less. Levels of more than 10mg/L have been associated with acute inflammation. CRP levels decrease as inflammation is resolved (Huether, 1996).

Inflammatory Cytokines: TNF-alpha and IL-6

Cytokines act like hormones, transcription factors, and bioactive lipids in that they can function in both metabolic and immune pathways. Cytokines share cellular mechanisms in the metabolic and immune systems and help regulate each other. Inflammation is dependent on metabolic support and requires a shift of energy distribution from an anabolic (building) state to a catabolic (destroying) state (Huether, 1996). There are several different cytokines activated during inflammation, including tumor necrosis factor alpha (TNF-alpha) and interleukin-6 (IL-6).

When inflammation activates the immune system, the insulin-signaling pathway, normally an anabolic process, is suppressed. TNF-alpha is the inflammatory cytokine responsible for insulin resistance. Prolonged levels of TNF-alpha lead to chronic insulin resistance, which can lead to diabetes (Popa, 2007).

Another cytokine involved in inflammation is IL-6. Increased levels of IL-6 have been associated with anemia, cancer, older age, obesity, low lipid levels, HIV replication, HAART and Hepatitis C (Borges, 2015). Chronic elevated levels of IL-6 have been strongly associated with CVD, diabetes, and dyslipidemia (Neal, 2008). Like CRP and TNA-alpha, IL-6 decreases when inflammation is resolved (Huether, 1996).

How CRP Can Increase Risk for CVD

Although multiple independent pathways lead to inflammation as a link between various risk factors for CVD, CRP is one of the most influential inflammatory biomarkers in assessing CVD risk (Libby, 2009).

There are several mechanisms by which chronic levels of CRP are thought to initiate atherosclerosis:

1. Increased levels of adhesion factors: The walls of blood vessels are lined with endothelial cells. CRP induces pro-inflammatory changes in these endothelial cells. In the presence of CRP, there is a substantial increase of vascular cell adhesion molecule-1 (Liang, 2006). Vascular cell adhesion molecule-1 (VCAM-1) is responsible for altering the cell shape to allow leukocyte binding. If chronic, the altered shape can lead to atherosclerotic plaque densely filled with inflammatory cells (Harry, 2016). The enhanced circulation of monocytes within the arterial wall is an early sign of atherosclerosis. CRP directly affects blood clotting through increasing VCAM-1.
2. Increased reactive oxygen species (ROS): Cytokines are biomolecules involved in inflammation and are activated by CRP (Wynants, 2013). When activated, cytokines cause leukocytes to release ROS which is associated with atherosclerosis by reducing levels of nitric oxide (NO) (Ritchie, 2016). NO relaxes the blood vessels and is an antioxidant that is essential for cardiovascular health.
3. Foam Cell Formation: Due to free radicals, low density lipid cholesterol (LDL) can oxidize and cause a gathering of foam cells. When lipids deposit on the wall of the blood vessel due to oxidation, macrophages are sent to the site to destroy it by endocytosis. The macrophages adhere to the wall and become filled with lipids creating a foamy appearance (Zwaka, 2001). Foam cells can accumulate, resulting in fatty streaks within the blood vessel wall. Chronic macrophage activation is not only associated with atherosclerosis, but is also seen in type 2 diabetes (Baker, 2011).

4. Increased levels of plasminogen activator inhibitor-1 (PAI-1): Tissue plasminogen activator (tPA) is a protein involved in the breakdown of clots. PAI-1 inhibits this protein, increasing the risk of thrombosis.

Due to the effects of CRP on endothelial cells, CRP levels can be used to monitor the risk of CVD and stroke (Limacher, 2010;Anderson, 2007).

CRP vs. Highly-Sensitive CRP Lab Work

In the case of an acute inflammatory response the standard CRP blood test is used to measure higher CRP levels in the range from 10 to 1,000mg/L. The standard CRP test is not able to detect low levels. The highly sensitive CRP test is necessary to detect the lower CRP levels, 0.5 to 10mg/L, associated with chronic inflammation and CVD (Calabrò, 2009).

Standard of Care Treatment for Inflammation

There are two main types of non-steroidal anti-inflammatory drugs (NSAIDS). The first including ibuprofen and naproxen, inhibit both COX-1 and COX-2 pathways. One of the main drawbacks of these drugs is that COX-1 inhibitors can cause ulcers, as the enzyme is necessary to maintain normal stomach lining. Other side effects include prolonged bleeding and possible kidney disease, and they are not intended for long term use (Bessone, 2010).

The second type of NSAIDs, including Celebrex, are selective and inhibit only COX-2. COX-2 selective inhibitors are generally easier on the stomach but also have side effects and must be prescribed (Sharma, 2005). COX-2 normally helps prevent thrombosis. When inhibited, there may be an increased risk for blood clots. The black box warning, the strictest warning from the FDA, indicates an increased risk of CVD and stroke, and prolonged use can still cause gastro-intestinal problems including ulcers and chronic bleeding.

There is no standardized medication that targets decreasing or preventing elevated CRP levels. The American Heart Association (2017) recommends people at high risk of heart attack and those who have already had a myocardial infarction take a daily, low-dose aspirin to prevent blockages. Aspirin has also been shown to decrease levels of CRP for people who are already suffering from heart disease, but was shown to be ineffective at lowering CRP levels in healthy male subjects (Feng, 2000). Long-term use of aspirin can cause gastro-intestinal bleeding and hemorrhaging (Lei, 2016).

Statins, or cholesterol-lowering drugs, have been shown to decrease levels of CRP from 13% - 50% for individuals with high cholesterol or prior MI (Prasad, 2006). In a 2005 study involving 3,745 patients with a history of a MI - people whose CRP was decreased with statins were less likely to have a recurrence of MI, regardless of whether their LDL levels decreased (Ridker, 2005). However, statins have side effects including headache, difficulty sleeping, muscle aches, nausea or vomiting, abdominal cramping, and more (Katz, 2014). If a plant compound can lower CRP levels without producing side effects, it may benefit HIV-positive patients who have elevated levels of CRP.

Diet and CRP

There is some evidence that certain diets can lower CRP levels. One study looked at a diet based on milled whole-wheat cereals with very low saturated fat and dairy versus a diet high in plant sterols, fiber, almonds, and soy protein. There was a significant drop in CRP from both diets as well as in a third group given a statin; however the changes between groups were not significant (Jenkins, 2003). Jenkins' study demonstrated that diet can reduce levels of CRP as effectively as taking cholesterol medication.

HIV/AIDS

Human Immunodeficiency Virus (HIV) attacks a specific white blood cell called CD4. Acquired Immune Deficiency Syndrome (AIDS) is defined as when the CD4 count declines to less than 200 cells/mm, Cdc.gov, 2016, which makes the host's immune system unable to fight off secondary infections or other diseases. Death does not occur from the virus itself, but from opportunistic infections such as pneumocystis or Kaposi's Sarcoma.

Highly Active Anti-Retroviral Therapy (HAART)

The side effects and damage from the first anti-retroviral therapies, beginning in the 1986, were extremely severe. However, since then, advancements in treatment have dramatically improved the life of those living with HIV. HAART is more effective, less toxic, and generally better tolerated than the earlier treatment regimens (Hall, 2011).

HAART is a combination of at least three drugs that suppress HIV replication and resistance to medication. It can reduce viral levels to an undetectable level (fewer than 45-70 copies of HIV per mm of blood), thereby preventing development into full-blown AIDS while decreasing the chance of transmission (AIDS.GOV, 2016). HAART has greatly increased the life expectancy of those who are HIV-positive. While HIV can remain dormant, preventing HAART from eliminating the virus completely, most people who adhere to the medication can expect to live a long, healthy life (Hall, 2011).

Because of HAART's success, however, a new, older generation of HIV positive people are at an increased risk of CVD. The immune system is still in a state of chronic activation even while undergoing HAART, creating chronic inflammation. The chronic immune response is most likely the driving factor behind the increased risk of CVD (Boccara, 2013). Furthermore, HAART does come with side effects, perhaps most notably diarrhea, caused by a necessary

protease inhibitor in the medication which can damage the intestinal epithelial barrier (MacArthur, 2012). Turmeric has been effective in relieving diarrhea associated with HAART (Conteas, 2009).

Side effects include:

- Bleeding
- Decrease in bone density
- Bone marrow suppression
- Diabetes
- Dyslipidemia
- Nausea
- Vomiting
- Steatosis
- Hypertension
- Esophageal varices
- Hepatotoxicity
- Rash
- Headache
- Chills
- Abdominal Pain
- Arthralgia
- Lactic acidosis
- Lipodystrophy
- Myopathy
- Psychiatric effects
- Renal dysfunction
- Kidney Disease
- Kidney Stone

(Hall, 2011)

HAART, HIV, and Inflammation

During HAART, the small amount of HIV which persists in the bloodstream, as well as the drugs themselves, are foreign stimuli that the body is exposed to daily. Daily exposure leads to daily inflammation. The exact mechanism of how HAART leads to CVD is not completely understood, although inflammation is believed to be a driving factor (Reuben, 2012) even in healthy subjects. Even when taking into consideration other possible risk factors, including age, smoking, and family history, Fichtenbaum (2011), still found the relative risk of MI was 1.26 times higher per year for those undergoing HAART. For example, ten years of undergoing HAART will increase one's risk of MI by 12.6%.

Other Comorbidities

CVD is not the only comorbidity appearing in the aging HIV population; HIV can replicate and leave viral proteins, increasing the risk of neurological conditions such as dementia and Parkinson's Disease (Green, 2005). Indeed, neuro-inflammation continues regardless of HAART; Ances et al. (2012) found through neuroimaging and neuropsychological performance exams that there is a decrease in brain volume (including the amygdala, caudate, and corpus callosum) for those with HIV even with the use of HAART.

HIV infection affects neuronal function by increasing cellular proteins in the brain, including amyloid precursor protein (APP), especially in the axons in the subcortical white matter. Local brain inflammation responds to the virus and can lead to higher APP production with β-amyloid deposition. β-amyloid may lead to the progression of Alzheimer's disease or other decreased mental functions including memory and concentration (Giunta, 2011).

Kidney damage is a possible side effect from HAART. Not only can HAART adversely affect the kidneys, but even the renal epithelial cells can become a reservoir where HIV is

transcriptionally active. Damage to the kidneys from both HAART and viral reservoirs can increase the risk for renal disease in HIV-positive patients (Ross, 2006).

It is unclear how much of the chronic inflammation seen in such patients is due to the low viral load still present or from the drugs in HAART (Blankson, 2002). We know that HIV-positive patients taking HAART are more susceptible to several comorbidities than HIV-negative persons, and it is this researcher's belief that reducing chronic inflammation could help increase longevity and reduce the risk of these comorbidities.

Limitation of Present Knowledge of Inflammation, CVD, HIV and HAART

More research is needed in monitoring the progression of CVD by measuring inflammatory biomarkers. CRP may not be the only biomarker associated with CVD and not everyone's CRP levels can be used as a risk factor. For example, people with autoimmune disorders such as rheumatoid arthritis tend to have elevated CRP levels. Because their levels are much higher than the low-level inflammation associated with CVD, CRP levels are not used to assess CVD even though the inflammation can still cause CVD (Weil, 2006). TNA-alpha and IL-6, similarly to CRP, are strongly linked but not limited to CVD (Borges, 2015; Popa, 2007). Further research may find more precise biomarkers in assessing different diseases.

Herbs Included in Herbal Anti-Inflammatory

Multiple studies have shown the efficacy of the herbs selected for the pilot study in reducing CRP levels. Moreover, many of these studies, which will be discussed in the literature synthesis, found that each herb acts on multiple inflammatory pathways, including IL-6 and TNF-alpha. If HIV and HAART, as is believed, activate multiple inflammatory pathways, employing an herbal combination that reduces multiple inflammatory biomarkers might serve as

a “shotgun” approach in reducing inflammation, CVD, and other comorbidities until a more precise approach is available.

The herbs chosen for this experiment were based not only on extensive research on their ability to lower CRP and to lower the risk of CVD, but also on their presumed safety while taking HAART, for which evidence will be detailed in the sections following. Combining these herbs, each with its multi-targeted pathways, may decrease several inflammatory biomarkers and slow down the aging process due to HIV and HAART.

Traditional Chinese Medicine and Thermal Properties

In the understanding of TCM, herbs, foods, and even pathogens have thermal properties (Bensky, 1993; Maciocia, 1989). Spicy foods or herbs, like ginger, would typically be considered warming or hot. Viruses are often diagnosed as a “heat” condition in the body; fever and sweating, manifestations of this heat, can present during initial HIV exposure.

The immune system can effectively respond to the virus and reduce the number of viral copies at first, but even with HAART the body will always have a latent, viral heat component. Many of the herbs used to treat viruses are cold in nature (Bensky, 1993), and TCM would likely say that HAART is cold in nature. For example, common side effects at the onset of HAART- loose stool, fatigue, and nausea- are usually diagnosed as a cold pathology in TCM (Maciocia, 1989). The warming properties of ginger help alleviate the GI distress that some experience with HAART (Dabaghzadeh, 2014).

Another “cold” side-effect of HAART may be in the TCM pattern called blood stagnation. Cold causes contraction and inhibits relaxation, a condition seen in the blood vessels that can be related to hypertension and circulation problems (Maciocia, 1989).

According to TCM, everyone has am inherent constitution with its attendant strengths and weaknesses (Maciocia, 1989). These relate to internal organs as well as to personality characteristics. Two general constitutions involve yin and yang. A yang-deficient constitution tends to run cold, have loose stool, frequent and clear urination, and is quick to fatigue. This theory was tested by comparing the blood of subjects who were categorized as yang-deficient to the blood of those deemed to have a balanced, healthy constitution. Interestingly, yang-deficient subjects were found to have decreased levels of thyroid hormone receptor beta as well as decreased levels of steroid receptor coactivators (Wang, 2008). Decreased thyroid hormone could lead to impaired thermogenesis, causing the individual to have a lower core temperature and to feel colder than the average person. Another study in China concluded that individuals who were undergoing HAART and were labeled yang-deficient had an increased mortality ($P<0.05$) compared to those who did not have a yang-deficient constitution (Cen, 2013). In addition, Huang et al. (2012) looked at mitochondrial mechanisms (which provide energy conversion and metabolism) and determined that yang-deficient type individuals had several impaired levels of lipids, glucose, amino acids and other metabolites in this area.

HAART is known to impact the mitochondria, a yang function; this further suggests HAART should be categorized as having a “cold” temperature. Significantly, mitochondrial health is believed to impact the aging process (Gonzalez-Freire, 2015), and HAART may damage the mitochondria by inhibiting the DNA polymerase that synthesizes the mitochondrial DNA (Reuben, 2012). Apostolova et al. (2011) suggests the adverse effects on the mitochondria go further than just DNA synthesis and that HAART acts on several pathways that negatively impact the mitochondria.

Ginger, Zingiber Officinalle, *Gan Jiang*

TCM properties.

In TCM, ginger is said to be acrid, hot, and enters the Heart, Lung, Spleen, and Stomach. It warms the digestion from a deficiency or excess cold condition (Bensky, 1993). Digestion complaints including nausea, bloating, abdominal pain, and loose stool are often treated with ginger.

Ginger and inflammation.

Diabetes.

A dose of 2g of ginger was administered twice a day to 64 subjects with type 2 diabetics in a randomized, double-blind, placebo controlled trial to evaluate its effects at lowering low-grade inflammation. The study demonstrated significantly reduced levels of TNF-alpha ($P = 0.006$), IL-6 ($P = 0.02$) and CRP ($P = 0.012$).

Another study involved 70 diabetic patients who were administered 1600mg of ginger and demonstrated a reduction in fasting plasma glucose, HbA1c, triglycerides, total cholesterol, and CRP ($P<0.05$) compared with a placebo group (Arablou, 2014).

Neurocognitive decline.

Diabetes mellitus can cause neuronal damage in the brain from increased intracellular glucose leading to oxidative stress. In one study, neurodegenerative changes in the frontal cortex, dentate gyrus, and cerebellum in diabetic-induced mice given 500mg of ginger a day were observed after week 4, 6, and 8. The study showed ginger had neuro-protective benefits on structural alterations in a diabetic brain (El-Akabawy, 2014).

Kidney function.

Ginger has also demonstrated potential to improve kidney function in a rat experiment (Yang, 2013). Renal injury was induced by a high-fructose diet. Rats given 50mg of a ginger extract showed a decrease in TNF-alpha ($P<0.05$), MCP-1 ($P<0.05$), and IL-6 ($P<0.05$).

Ginger and safety.

There are not many known side effects of ginger; Bensky, (1993), cautions the use of ginger during pregnancy and if there is heat in the blood. A TCM diagnosis of heat in the blood can cause excessive bleeding (Maciocia, 1989). It is cautioned to use ginger in combination with blood thinning medication because of the increased anticoagulants and antiplatelet action, however, there are only a few reports to support this (Chua, 2015).

Sage, Salvia Miltiorrhiza, *Dan Shen*

TCM properties.

Sage is bitter and slightly cold. It enters the Heart, Pericardium, and Liver. It is used to increase circulation of blood and helps break up blood stasis in the chest or in the lower abdomen in the case of dysmenorrhea and amenorrhea. Intravenous injections of 40-80 times the clinical dose of sage were reported to cause no toxicity or adverse changes in the kidney or liver (Bensky, 1993).

Sage and inflammation.

Sage acts on multiple inflammatory pathways as well. Sage has been shown to decrease: atherosclerosis, hypertension, platelet aggregation, anti-oxidants, and inflammation (Lin, 2015). The authors examined its prevention and treatment of cerebral infarction. Lin linked cerebral infarctions with excessive free radical damage. Because sage has been shown to enhance endogenous anti-oxidative enzymes, its use may reduce cardio and cerebral vascular risks.

Sage and metabolic syndrome.

Sage can impact a few of the risk factors for MS such as cholesterol, blood pressure, and glucose. Liu et al. (2014) reported that a lipophilic component from sage, 15,16-dihydrotanshinone I (DHTH), potently antagonized both mineralocorticoid and glucocorticoid receptors. The research suggests that such a multi-targeted pathway could inhibit COX-1 and COX-2 which may help treat MS. In a randomized, double-blind, placebo-controlled clinical trial, sage lowered blood levels of cholesterol in patients with hyperlipidemia. The researcher observed a significant decrease in total cholesterol ($p < 0.001$), triglycerides ($p = 0.001$), LDL ($p = 0.004$) and VLDL ($p = 0.001$), and a significant beneficial increase in HDL levels ($p < 0.001$) when subjects were administered 1.5g of sage per day for two months (Kianbakht, 2011). No adverse reactions or side effects were reported.

Sage has multiple effects including dilating the coronary artery, lowering blood pressure and lipids, inhibiting smooth muscle proliferation and hyperplasia, reversing myocardial hypertrophy, reducing infarct size, and protecting from ischemia-reperfusion (Chen, 2014). Because sage has multiple effects on different diseases, it has the potential to reduce the complex inflammatory pathways that HAART and HIV initiate.

Sage and neuroprotection.

In a recent meta-analysis by Lin, (2015), sage decreased the chance for a cerebral infarction by decreasing biomarkers, free radicals, and lowering high blood pressure. Sage is believed to decrease inflammation pathways in the microglia, the local macrophages of the brain and spinal cord, inhibiting the oxidative damage in neuronal cells (Wang, 2016). More research is needed but sage may serve as a neuroprotective plant compound that could decrease neurodegeneration.

Sage and safety.

No health hazards or side effects are known with proper administration. Dosages in tea form range from 3g to 15g (Brendler et al., 2007). As with ginger, it is also not advised to take sage while on blood thinners because of synergistic effects that can lead to bleeding (Chan, 2001).

Turmeric, Curcuma Domestica, *Jiang Huang*

TCM properties.

Turmeric is known in TCM for its acrid, bitter, and warm properties that enter the Spleen, Stomach, and Liver. Like sage, it increases circulation and breaks up blood stasis. It also helps circulate qi and can alleviate pain with its analgesic properties (Bensky, 1993).

Western research.

Turmeric is one of the most researched herbs with over 100 clinical trials in the literature (He, 2015). Like sage and ginger, turmeric also acts on multiple pathways. In early cell cultures and animal research, turmeric showed therapeutic potential using turmeric in treating diabetes, cancers, and auto-immune, cardiovascular, neurological and psychological diseases (Jurenka, 2009). In one trial, Meng et al. (2014) demonstrated a decrease in IL-6 and CRP in rats with atherosclerosis. Another trial involving rats with alcohol -induced liver disease showed a decrease in hepatic inflammation and levels of CRP, TNF-alpha, and IL-6 (Zhang, 2016).

Turmeric and safety.

This author found little evidence of side effects of turmeric. Bensky (1996), reports an increase in uterine contraction when tested with mice and pigs, and increased contractions of the gall bladder in dogs. Therefore, it is cautioned with pregnancy or gall bladder complications. Turmeric is used to increase circulation in TMC. Theoretically, it could increase the risk of bleeding and should be cautioned with the use of anticoagulants and antiplatelet medications.

Herb / drug interactions.

This author found no research indicating any potential harmful interactions with HAI and HAART. On the contrary, two of the herbs have been used to treat side effects of HAART: ginger did not affect HAART and was effective in reducing antiretroviral-induced nausea and vomiting (Dabaghzadeh, 2014) and turmeric did not affect HAART and was effective in reducing diarrhea from HAART's side effect (Conteas, 2009).

There is no research available for the safety of sage and HIV. The CYP3A4 enzyme found in St. John's Wort is contraindicated with HAART, but sage does not have this enzyme. The CYP3A4 enzyme increases the degradation of the drug which causes its level to drop and can make the pharmaceutical less effective (Fasinu, 2015). Grapefruit juice has the opposite effect; it slows the degradation of the drug and causes levels to rise in the blood, which can increase the drug's toxicity.

Based on the overwhelming body of evidence, the use of ginger, turmeric, or sage is highly unlikely to have any negative interaction with HAART.

Research Synthesis

The need to decrease inflammation is evident. HIV-positive people are living longer but aging faster. The current anti-inflammatories are not suggested, nor safe, for long term use. Cholesterol medication can decrease CRP but only if cholesterol is already high, and it has several possible side effects. Because of HAART's possible side effects, a plant compound that can decrease inflammation, that does not add side effects, and that can be taken daily is considered the best alternative to counter the increased risk for CVD.

Ironically, while doctors may not believe in the healing benefits of herbs to suggest them, they do seem to believe that herbs are active enough to negatively interact with medications. As

reported above, turmeric and ginger have been tested with patients undergoing HAART and have helped reduce side effects of the drugs without interfering with the drugs' efficacy. Sage is a common spice and has no reports of harmful interactions with HAART. It is believed the HAI will decrease CRP levels without any harmful interaction with HAART.

Chapter Three: Methodology

The original research was intended to support a clinical trial with the help of an HIV research department. The functional result and safety of each herb was the focus of the study to help educate and assure there is no evidence of any negative interaction between HAART and HAI. This project has turned into a report on the research that would have launched a pilot study. It is still this investigator's recommendation to perform the study and appropriate logistics of running the trial are include in the appendices.

This chapter describes the procedures used in the current study including search terms, inclusion criteria, sample procedures, and data sources.

Designation of Methodology

This study utilized a literature synthesis to establish a potential herbal formula that could decrease CRP levels and associated risk of CVD for those undergoing HAART. The primary focus is the analysis of prior published research and theory on the use of each herb and their effects on inflammation as well as their safety if combined with HAART. A quantitative literature review was chosen as the most appropriate method to integrate data from the variety of sources. The method of the synthesis involved the following steps:

- Definition of the research problem
- Examination of relevant sources
- Inclusion of reference works
- Formulation of specific search terms
- Systematic search for sources
- Summary of key points from sources

Sampling Procedures

The sources of data in this capstone were derived from various articles in both western and Chinese medicine journals as well as textbooks. The online search for existing trials on herbs and CRP were conducted at the principal investigator's computer and at the UCLA bio-medical library. Online sources included PubMed, EBSCOhost, and Google Scholar.

Search Terms

The common search words used included inflammation, HIV, HAART, CVD, CRP, ginger, turmeric, sage, and TCM.

Inclusion Criteria

To be included in the synthesis, the following inclusion criteria was created:

- Research published within the past 10 years
- Peer reviewed journals
- Preference for human trials
- Randomized, control or double-blind, randomized control trials
- Articles and resources that directly relate to HAART and herb interactions

When selecting which herbs to use, the following criteria was used:

- Fit the TCM herbal pattern of HIV and HAART side effects
- No possible herb / drug interactions
- Current research of herb and effects on CRP
- Secondary functions that may also decrease CVD

Exclusion factors included

- Trials that combined herbs not selected
- In vitro trials

- Less than twenty subjects
- Herbs that negatively impacted HAART

Chapter Four: Results

Overview

The reason for doing this research is because for the first time there is an aging HIV population that are showing signs of accelerated aging. Furthermore, western medicine does not currently have a preventative treatment to slow down the increased risk. This chapter presents the data collected from the literature review synthesis.

The first section provides a summary of the types of studies used in the synthesis. This is followed by a summary of TCM herbs and their reported effects on inflammation. The subject of herb and drug interaction is reviewed to ensure there is no harmful interactions if the herbs were taken as an adjunctive therapy to reduce chronic inflammation.

Findings

Fourteen studies on the selected herbs and their effects on CRP were reviewed, as well as six other studies indicating their safety with medication including HAART. Pertinent information from each study was recorded using a data collection form. Sample size, dosage, length of study, and effects on CRP and other CVD risks were included. The following sections summarize the findings.

Ginger and CRP.

In a meta-analysis by Mazidi et al. (2016), ginger supplementation decreased CRP levels, improved lipid profile, and lowered glucose levels. The researchers also found that the effects were not strictly dose-dependent. Effects were shown with as little as 1g per day and this did not change significantly with a dose up to 3g a day.

Atashak et al. (2010) looked at the combination of 1g of ginger a day and resistance training to decrease inflammation, weight, and cardiovascular risk. Even without exercise, the

group that was only administered ginger still had a significant reduction in CRP ($P<0.05$). The combination showed not only a decrease in CRP, but significant decreases in waist circumference, waist-to-hip ratio, body fat percentage, total cholesterol, and insulin resistance ($P<0.05$).

There were four human trials within the last two years that have shown ginger lowered CRP levels. Combing the four trials, there is a total of 158 participants with a range from a high of 70 to a low of 20 subjects. Dosages ranged from a high of 3g per day to a low of 1g per day. Trial lengths lasted either ten or twelve weeks. The analysis trials show a significant P-value of 0.024.

Figure 1: Ginger and CRP

Study	Subjects	Type	Dosage	CRP
Arablou, 2014	70	randomized double-blind	1.6g/day, 12 weeks	$P < 0.05$
Atashak, 2011	32	randomized double-blind	1g/day, 10 weeks	$P < 0.004$
Imani, 2015	36	randomized double-blind	1g/day, 10 weeks	$P < 0.04$
Shidfar, 2015	20	randomized double-blind	3g/day, 12 weeks	$P < 0.001$

Ginger and pharmaceutical interactions.

There are no presumed negative interactions between HAART and ginger. The only reported interactions with ginger are with blood thinning medication. However, one study specifically designed to test for interactions found there was no interaction with warfarin when ginger was used with the common recommended dose of 1.5g per day (Jiang, 2005). Three groups of rats were treated with different doses, as high as 2g per day, of ginger for 35 days and no side effects or organ toxicity were reported (Rong, 2009). Even though there is conflicting

evidence, the researcher still cautions the use of ginger with anticoagulant or antiplatelet medications.

Ginger was used to reduce reported nausea due to the side effects of HAART. In a trial including 102 subjects, 0.5g of ginger was taken thirty minutes before the subjects took their HAART. There was a significant ($p<0.001$) reduction in nausea compared to the placebo group (Dabaghzadeh, 2014). Since ginger has already been tested in combination with HAART, there should not be any negative interactions. Below are the researched cautions with ginger and possible medication interaction.

Figure 2: Cautions with Ginger

Main caution	increase risk of bleeding due to anticoagulant and antiplatelet properties, caution during pregnancy
Medication	cautioned with warfarin, aspirin, other blood thinners
Possible side effects	excessive bleeding
HAART interaction	tested and no documented negative interactions

Turmeric and CRP.

Turmeric is advertised as a natural anti-inflammatory and has over a 100 clinical trials. Gupta et al. (2015) reviewed completed clinical trials with turmeric and observed decreased levels of CRP, TNF-alpha, and IL-6. Three out of the five human trials that met the inclusion factors were completed in the last two years.

Guo et al., (2010) found turmeric reduces CRP levels ($p<0.01$) for patients with unstable angina pectoris. In a trial including 60 diabetic patients, CRP was reduced ($p < 0.05$) after taking two grams of turmeric per day for four weeks (Maithili, 2015). Panahi et al., (2014) found

turmeric decreased CRP levels ($p < 0.01$) in cancer patients with tumors. The study also observed a reduction in IL-6 and TNF-alpha levels.

Turmeric had a total of 352 participants with a range from a high of 100 to a low of 48. Dosages ranged from a high of 3g per day to a low of 1.8g per day. Trial lengths lasted either ten or twelve weeks. The average significance in reducing CRP was $p < 0.025$.

Figure 3: Turmeric and CRP

Study	Subjects	Type	Dosage	CRP
Guo, 2010	48	randomized, control	oral, 4 weeks	P < 0.01
Maithili, 2015	60	randomized, control	2g/day, 4 weeks	P < 0.05
Zhang, 2007	64	randomized, control	3g/day, 6 weeks	P < 0.05
Panahi, 2014	80	randomized double-blind, placebo-controlled	1.8g/day 8 weeks	P < 0.001
Pakfetrat, 2014	100	randomized double-blind		P < 0.012

Turmeric and pharmaceutical interactions.

Turmeric, like ginger, only is cautioned with the use of blood thinning medication. Also like ginger, turmeric has been used to treat side effects associated with HAART. Eight patients were given 1.9g of turmeric for 41 weeks. A rapid and complete resolution of diarrhea, substantial weight gain, and improvement in the reduction of bloating and abdominal pain were observed. There were no changes in HIV viral load during the trial. It does not appear turmeric has any negative interaction with HAART. Turmeric was also safe and effective ($p < 0.012$) at reducing CRP levels in patients with end stage renal disease and pruritus.

The suggested daily dosage for a therapeutic effect is 1.5 to 3g, two to three times a day (Brendler et al., 2007).

Figure 4: Cautions with Turmeric

Main caution	increase risk of bleeding due to anticoagulant and antiplatelet properties, caution during pregnancy
Medication	cautioned with warfarin, aspirin, other blood thinners
Possible side effects	excessive bleeding
HAART interaction	tested and no documented negative interactions (Dabaghzadeh, 2014)

Sage and CRP.

The principal investigator was unable to find sufficient human trials of sage and CRP levels. For this herb only, trials using sage to reduce CRP levels in rats were included in the research. There are human trials that have measured CRP reduction with sage but in a combination of other herbs. Xu et al., (2009) used a combination of panax notoginseng. The research has shown a consistent significant P-value of < 0.05 in the reduction of CRP levels as listed below.

Figure 8: Sage and CRP

Study	**Subjects**	**Type**	**Dosage**	**CRP**
Liang, 2013	rats	randomized, control	injections	$P < 0.05$
Meng, 2014	rats	randomized, control	injections	$P < 0.05$
Xu, 2009	Humans(160)	randomized, control	ingestion	$P < 0.05$
Zhang, 2015	rats	randomized, control	injections	$P < 0.05$

Turmeric and pharmaceutical interactions.

There were no reports supporting nor cautioning the use of sage in combination with HAART. The only cautioned, but not proven, is excessive bleeding in combination of blood

thinning medication. Doses up to 15g have shown no negative side effects or toxicity. Below are the main cautions for sage:

Figure 9: Cautions with Sage

Main caution	increase risk of bleeding due to anticoagulant and antiplatelet properties
Medication	cautioned with warfarin, aspirin, other blood thinners
Dosage	large doses have shown no toxicity
Possible side effects	no reported side effects

Secondary Measurements

The primary focus of this research is to establish each herb effectively reduces CRP therefor decreasing the risk of CVD. Majority of the trials tested multiple factors, not just CRP. The main literature synthesis is the reduction of CRP and safety of HAI. However, secondary measurements for CVD risk and/or inflammation that were tested and that had a significant ($p < 0.05$) were also noted and charted below.

Figure 7: Researched Effects of Ginger

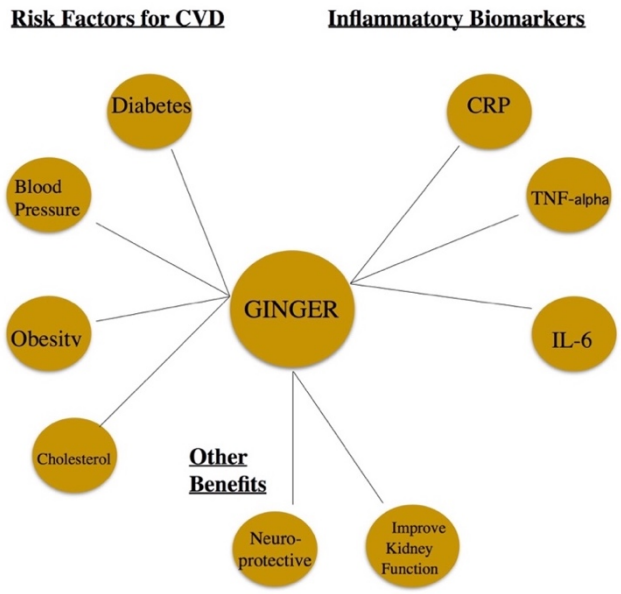


Figure 8: Researched Effects of Sage

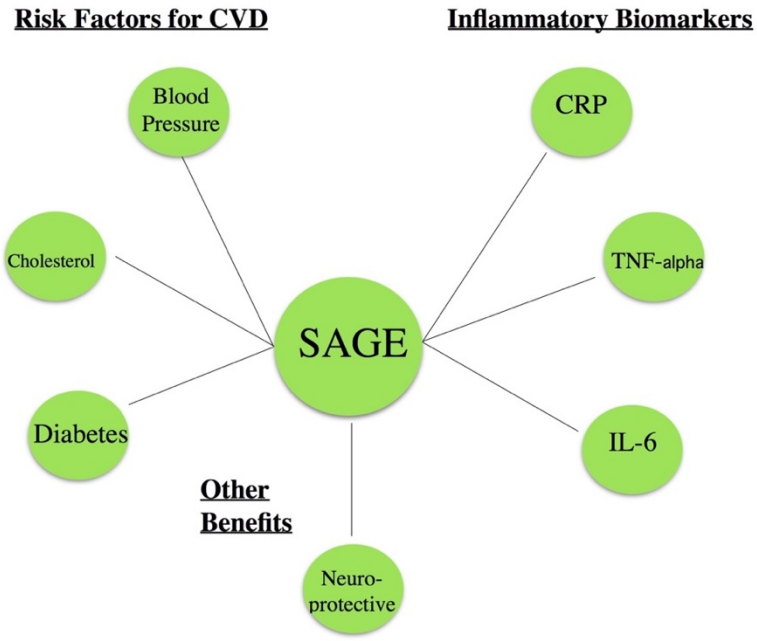
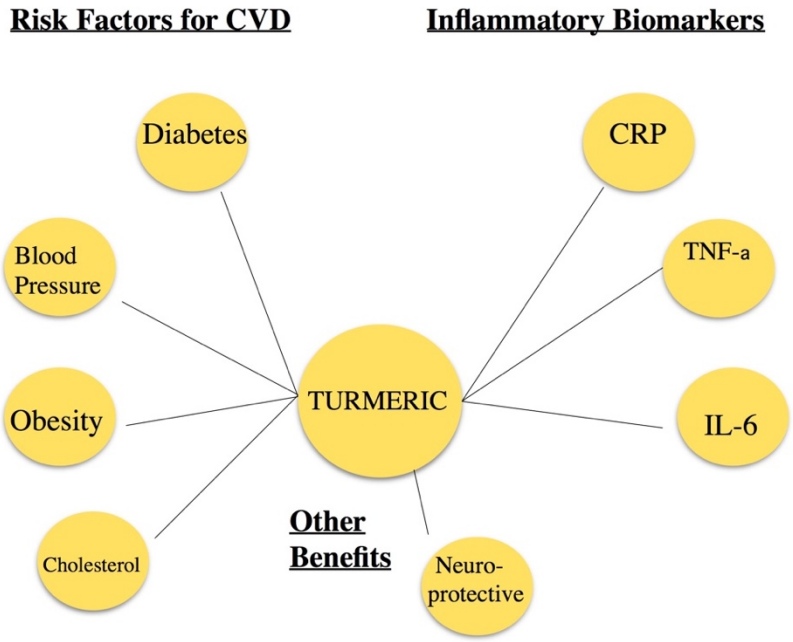


Figure 9: Researched Effects of Turmeric



Chapter Five: Discussion

Summary of Findings

There is a well-established, growing need to help control comorbidities in the aging HIV-positive population undergoing HAART. As this group of people have a 50% increased chance of MI, there is a clear need to find ways to decrease the risk for CVD. Given the large amount of research showing an association between elevated levels of CRP and risk of CVD, it would seem that reducing CRP will also reduce one's risk of CVD.

Standard treatment of inflammation by western intervention focuses on inhibiting COX-1 and COX-2 enzymes, but not CRP levels. Meanwhile, HAART patients continue to have a chronic, low-grade systemic inflammation that appears to increase the risk of CVD. Standard anti-inflammatories as well as HAART have been known to cause liver and kidney damage, especially in the case of long-term use.

The purpose of this study was to show that herbs can reduce CRP levels and do not negativity interact with HAART. Turmeric and ginger have a lot of existing research on reducing CRP levels and in many different inflammatory disease. Reviewing twenty human and animal studies, system analysis indicates that the herbs are safe and can effectively reduce CRP levels and therefore reduce the risk of CVD. It was observed that each herb was able to significantly lower CRP levels (Zhang, 2007; Naderi, 2015; Zhang, 2016). Ginger and turmeric have already been used in trials involving subjects with HAART and yielded no negative interactions (Conteas, 2009; Dabaghzadeh, 2014).

Implications for Theory

The idea of inflammation as the root of many diseases is relatively new. There is a lot of research into which biomarkers may indicate which disease, and effective ways in reducing

them. CRP levels have proven to useful in monitoring an individual's risk for CVD. Subjects undergoing HAART have statistically shown higher levels of CRP (Arnett, 2007) and significant increased chance for CVD (Fichtenbaum, 2011). It is suggested that patients undergoing HAART, especially the longer they have been taking them, should be screened for CVD at an earlier age (Boccara, 2013).

Implications for Practice

HIV subjects undergoing HAART create a unique need for a safe anti-inflammatory that can decrease their chronic inflammation from medication and small viral reservoirs. The fear of interactions between HAART and herbs has stopped many patients and doctors from combining the two. Ginger, turmeric, and sage have shown to decrease CRP levels and fit within the thermal relationships of the latent virus (heat) and HAART (cold). Ginger and turmeric are warming yet sage is cooling. As with many herbal formulas, a proper balance of temperatures is vital to prevent damage from one extreme. It is this investigator's belief the combination of the three herbs should help reduce inflammation without influencing the body's thermal balance in either direction.

As the majority of the studies tested multiple CVD risks and biomarkers, it can be concluded that the HAI may also prevent the further progression of other inflammatory diseases. Out of the twenty studies, only two were specific to CRP and CVD. CRP is not specific to heart disease so reducing CRP could have beneficial results even for those not at risk for CVD.

Challenges and Limitations

Bringing allopathic MDs on board can be a challenge when testing herbal medicines. This pilot study was proposed to a Los Angeles-based HIV clinical research group. It was passed from an interested doctor to the director of clinical research. After being fully briefed on the

research, the director expressed eagerness to help, including finding potential subjects using the group's existing database, performing the initial and exiting lab work, interviewing subjects, and storing and dispensing the HAI. However, the director later explained that the owner of the research department decided they would not be able to help due to liability and lack of resources. The lack of research into herbs in combination with HAART likely contributed to the liability concern, although there is no evidence that any of the three herbs interferes with medication.

More research is needed in monitoring the progression of CVD by measuring inflammatory biomarkers. CRP may not be the only biomarker associated with CVD and not everyone's CRP levels can be used as a risk factor. For example, people with autoimmune disorders such as rheumatoid arthritis tend to have elevated CRP levels. Because their levels are much higher than the low-level inflammation associated with CVD, CRP levels are not used to assess CVD even though the inflammation can still cause CVD (Weil, 2006). TNA-alpha and IL-6, similarly to CRP, are strongly linked but not limited to CVD (Borges, 2015; Popa, 2007). Further research may find more precise biomarkers in assessing different diseases.

Absorption of the herbs is essential and a few studies have shown that turmeric has a significant increase in absorption and efficacy when combined with pepper or fat, or if heated.

Finally, there is an overall lack of research of herbs and their functional effects on inflammation as well as interactions with HAART. With the several different biomarkers that exist, studies focusing on CRP and CVD were scarce.

Conclusion

The study never got off the ground because of the promised collaboration was not delivered. This project turned into a report on the research that would have launched this trial. It is still the investigator's recommendation to test HAI and CRP levels among HIV subjects

undergoing HAART. It is important to not be complacent in knowing that the progression of AIDS has been prevented for many of those undergoing HAART. Secondary comorbidities will continue to develop and it is important to start collaborating with western doctors showing not just the safety, but the functional efficacy of herbs.

Inflammation can be a driving factor in other diseases; therefore, the HAI could have the potential to slow the onset of diseases associated with inflammation. This would be suggested if secondary outcome measures delineated in the study were to show benefit from the HAI group. For example, decreasing glucose levels would benefit diabetes and prediabetes patients. High cholesterol alone is associated with CVD; if decreased levels of cholesterol are observed but CRP levels remain the same, there is still the possibility the HAI can still help decrease the chance of CVD. Blood pressure can lead to several life-threatening conditions including stroke or hemorrhage; if the HAI can decrease blood pressure significantly but does not decrease CRP, again, it may nonetheless decrease the risk of developing CVD. In short, any improvement would serve as evidence to continue investigating the effects of the HAI on inflammation, with potential benefit to millions of individuals with inflammation-related diseases.

References

AIDS.GOV. (2016). Viral Load. Retrieved December 17, 2016, from https://www.aids.gov/hiv-aids-basics/just-diagnosed-with-hiv-aids/understand-your-test-results/viral-load/

Ances. (2012). Independent Effects of HIV, Aging, and HAART on Brain Volumetric Measures. Retrieved December 14, 2016, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3302928/

Anderson. (2007). Prognostic Significance of the Centers for Disease Control/AHA. Retrieved March 16, 2016, from http://professional.heart.org/professional/ScienceNews/UCM_466059_Prognostic-Significance-of-the-Centers-for-Disease-ControlAHA.jsp

Arablou, T. (2014, June). The effect of ginger consumption on glycemic status, lipid profile and some inflammatory markers in patients with type 2 diabetes mellitus. - PubMed - NCBI. Retrieved August 22, 2015, from http://www.ncbi.nlm.nih.gov/pubmed/24490949

Arnett. (2007). Development and Validation of Improved Algorithms. Retrieved February 18, 2017, from http://professional.heart.org/professional/ScienceNews/UCM_465998_Development-and-Validation-of-Improved-Algorithms.jsp

Baker. (2011). NF-κB, inflammation and metabolic disease. Retrieved December 31, 2016, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3040418/#R68

Bensky. (1993). *Chinese Herbal Medicine Materia Medica*. Seattle, WA: Eastland Press, Inc.

Bessone. (2010). Non-steroidal anti-inflammatory drugs: What is the actual risk of liver damage? Retrieved October 18, 2015, from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2997980/

Blankson. (2002). The challenge of viral reservoirs in HIV-1 infection. - PubMed - NCBI. Retrieved February 25, 2017, from https://www.ncbi.nlm.nih.gov/pubmed/11818490

Boccara, F. (2013). HIV and coronary heart disease: time for a better understanding. - PubMed - NCBI. Retrieved August 26, 2016, from http://www.ncbi.nlm.nih.gov/pubmed/23369416

Borges,. (2015). Factors Associated With Plasma IL-6 Levels During HIV Infection. Retrieved December 31, 2016, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4598808/

Calabrò. (2009). CRP and the risk of atherosclerotic events. - PubMed - NCBI. Retrieved March 3, 2017, from https://www.ncbi.nlm.nih.gov/pubmed/19415283

CDC. (2016). About HIV/AIDS | HIV Basics | HIV/AIDS | CDC. Retrieved December 17, 2016, from https://www.cdc.gov/hiv/basics/whatishiv.html

Cen. (2013). The Association between Yang-Deficient Constitution and Clinical Outcome of Highly Active Antiretroviral Therapy on People Living with HIV. Retrieved January 1, 2017, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3892935/

Chan. (2001). Interaction between warfarin and danshen (Salvia miltiorrhiza). - PubMed - NCBI. Retrieved March 19, 2016, from http://www.ncbi.nlm.nih.gov/pubmed/11302416

Chen. (2014). Anti-Inflammatory and Immunomodulatory Mechanism of Tanshinone IIA for Atherosclerosis. Retrieved March 19, 2016, from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4267215/

Chua. (2015). Interaction between warfarin and Chinese herbal medicines. Retrieved March 1, 2017, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4325561/

Conteas. (2009). Treatment of HIV-associated diarrhea with curcumin. - PubMed - NCBI. Retrieved February 21, 2017, from https://www.ncbi.nlm.nih.gov/pubmed/19051018

Dabaghzadeh. (2014). Ginger for prevention of antiretroviral-induced nausea and vomiting: a randomized clinical trial. - PubMed - NCBI. Retrieved December 23, 2016, from https://www.ncbi.nlm.nih.gov/pubmed/?term=HIV+ART+Ginger

D'Ettorre, G. (2016). What happens to cardiovascular system behind the undetectable level of HIV viremia? Retrieved August 13, 2016, from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4848790/

El-Akabawy. (2014). Neuroprotective effect of ginger in the brain of streptozotocin-induced diabetic rats. - PubMed - NCBI. Retrieved August 22, 2015, from http://www.ncbi.nlm.nih.gov/pubmed/24680376

Fasinu. (2015). Clinically Relevant Pharmacokinetic Herb-drug Interactions in Antiretroviral Therapy. - PubMed - NCBI. Retrieved December 28, 2016, from https://www.ncbi.nlm.nih.gov/pubmed/26526838

Feng. (2000). Effect of Short-Term Aspirin Use on C-Reactive Protein | SpringerLink. Retrieved December 31, 2016, from http://link.springer.com/article/10.1023/A:1018644212794

Fichtenbaum. (2011). Inflammatory Markers Associated with Coronary Heart Disease in Persons with HIV Infection. Retrieved December 11, 2016, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3077066/

Giunta. (2011). Antiretroviral medications disrupt microglial phagocytosis of β-amyloid and increase its production by neurons: implications for HIV-associated neu... - PubMed - NCBI. Retrieved January 3, 2017, from https://www.ncbi.nlm.nih.gov/pubmed/21649911

Gonzalez-Freire,. (2015). Reconsidering the Role of Mitochondria in Aging. Retrieved January 1, 2017, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4612387/

Green. (2005). Brain deposition of beta-amyloid is a common pathologic feat... : AIDS. Retrieved December 14, 2016, from http://journals.lww.com/aidsonline/Abstract/2005/03040/Brain_deposition_of_beta_amyloid_is_a_common.6.aspx

Guarner. (2012). Aging, Metabolic Syndrome and the Heart. Retrieved September 26, 2015, from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3375083/

Hall, J. (2011). *HIV/AIDS in the Post-HAART Era*. Shelton, CT: People's Medical Publishing House.

Harry. (2016). Biomarkers of Metabolic Syndrome: Biochemical Background and Clinical Significance | Abstract. Retrieved March 20, 2016, from http://online.liebertpub.com/doi/abs/10.1089/met.2015.0113?src=recsys

He. (2015). Molecules | Free Full-Text | Curcumin, Inflammation, and Chronic Diseases: How Are They Linked? | HTML. Retrieved September 28, 2015, from http://www.mdpi.com/1420-3049/20/5/9183/htm

Huang. (2012). Metabolic Profiling Study of Yang Deficiency Syndrome in Hepatocellular Carcinoma by H1 NMR and Pattern Recognition. Retrieved January 1, 2017, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3463959/

Huether, S. (1996). *Understanding Pathophysiology*. St. Louis, MO: Mosby.

Jenkins. (2003). Effects of a dietary portfolio of cholesterol-lowering foods vs lovastatin on serum lipids and C-reactive protein. - PubMed - NCBI. Retrieved January 1, 2017, from https://www.ncbi.nlm.nih.gov/pubmed/12876093

Jiang. (2005). Effect of ginkgo and ginger on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. - PubMed - NCBI. Retrieved March 1, 2017, from https://www.ncbi.nlm.nih.gov/pubmed/15801937

Jurenka. (2009). Anti-inflammatory properties of curcumin, a major constituent of Curcuma longa: a review of preclinical and clinical research. - PubMed - NCBI. Retrieved February 27, 2017, from https://www.ncbi.nlm.nih.gov/pubmed/19594223

Katz. (2014). Addressing statin adverse effects in the clinic: the 5 Ms. - PubMed - NCBI. Retrieved March 2, 2017, from https://www.ncbi.nlm.nih.gov/pubmed/24770611

Kianbakht. (2011). Antihyperlipidemic effects of Salvia officinalis L. leaf extract in patients with hyperlipidemia: a randomized double-blind placebo-controlled clin... - PubMed - NCBI. Retrieved September 11, 2015, from http://www.ncbi.nlm.nih.gov/pubmed/21506190

Lei. (2016). The Benefit and Safety of Aspirin for Primary Prevention of Ischemic Stroke: A Meta-Analysis of Randomized Trials. - PubMed - NCBI. Retrieved March 2, 2017, from https://www.ncbi.nlm.nih.gov/pubmed/27917124

Liang. (2006). C-reactive protein activates the nuclear factor-kappaB pathway and induces vascular cell adhesion molecule-1 expression through CD32 in human umbil... - PubMed - NCBI. Retrieved March 20, 2016, from http://www.ncbi.nlm.nih.gov/pubmed/16430914

Libby. (2009). Inflammation in Atherosclerosis: From Pathophysiology to Practice. Retrieved December 11, 2016, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2834169/

Limacher. (2010). Screening Asymptomatic Adults for Cardiovascular Disease. Retrieved March 16, 2016, from http://professional.heart.org/professional/ScienceNews/UCM_432552_Screening-Asymptomatic-Adults-for-Cardiovascular-Disease.jsp

Lin. (2015). Pharmacological effects of Salvia miltiorrhiza (Danshen) on cerebral infarction. Retrieved March 19, 2016, from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2910010/

MacArthur. (2012). Etiology and pharmacologic management of noninfectious diarrhea in HIV-infected individuals in the highly active antiretroviral therapy era. - PubMed - NCBI. Retrieved November 28, 2016, from https://www.ncbi.nlm.nih.gov/pubmed/22700829

Maciocia. (1989). *The Foundations of Chinese Medicine*. London, UK: Churchill Livingstone.

Maithili. (2015). Efficacy of Turmeric as Adjuvant Therapy in Type 2 Diabetic Patients. - PubMed - NCBI. Retrieved September 28, 2015, from http://www.ncbi.nlm.nih.gov/pubmed/25883426

Meng. (2014). Protection of salvianolate against atherosclerosis via regulating the inflammation in rats. - PubMed - NCBI. Retrieved December 25, 2016, from https://www.ncbi.nlm.nih.gov/pubmed/25318872

Naderi. (2015). Ginger hs-crp.

Neal. (2008). Quantifying the Importance of Interleukin-6 for Coronary Heart Disease. Retrieved February 20, 2017, from http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.0050084

NIH. (2016). What Is Metabolic Syndrome? - NHLBI, NIH. Retrieved September 26, 2015, from http://www.nhlbi.nih.gov/health/health-topics/topics/ms

Popa. (2007). The role of TNF-α in chronic inflammatory conditions, intermediary metabolism, and cardiovascular risk. Retrieved September 25, 2015, from http://www.jlr.org/content/48/4/751.full

Prasad. (2006). C-reactive protein (CRP)-lowering agents. - PubMed - NCBI. Retrieved December 30, 2016, from https://www.ncbi.nlm.nih.gov/pubmed/16939632

Reuben. (2012). Premature and accelerated aging: HIV or HAART? Retrieved January 1, 2017, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3556597/#B48

Ridker. (2005). C-reactive protein levels and outcomes after statin therapy. - PubMed - NCBI. Retrieved December 31, 2016, from https://www.ncbi.nlm.nih.gov/pubmed/15635109

Ritchie. (2016). The opposing roles of NO and oxidative stress in cardiovascular disease. - PubMed - NCBI. Retrieved December 30, 2016, from https://www.ncbi.nlm.nih.gov/pubmed/27988384

Rong. (2009). A 35-day gavage safety assessment of ginger in rats. - PubMed - NCBI. Retrieved March 1, 2017, from https://www.ncbi.nlm.nih.gov/pubmed/19303040

Ross. (2006). HIV-1 Infection Initiates an Inflammatory Cascade in Human R... : JAIDS Journal of Acquired Immune Deficiency Syndromes. Retrieved December 25, 2016, from

http://journals.lww.com/jaids/Fulltext/2006/05000/HIV_1_Infection_Initiates_an_Inflammatory_Cascade.1.aspx

Sharma. (2005). Adverse effects of COX-2 inhibitors. - PubMed - NCBI. Retrieved March 2, 2017, from https://www.ncbi.nlm.nih.gov/pubmed/16113940

Triant. (2009). Association of C-reactive protein and HIV infection with acute myocardial infarction. - PubMed - NCBI. Retrieved December 21, 2016, from https://www.ncbi.nlm.nih.gov/pubmed/19387353

Wang. (2008). Molecular basis for cold-intolerant yang-deficient constitution of traditional Chinese medicine. - PubMed - NCBI. Retrieved January 1, 2017, from https://www.ncbi.nlm.nih.gov/pubmed/19051350/

Wang. (2016). Pharmacological Effects of Active Components of Chinese Herbal Medicine in the Treatment of Alzheimer's Disease: A Review. - PubMed - NCBI. Retrieved February 21, 2017, from https://www.ncbi.nlm.nih.gov/pubmed/27848250

Weil. (2006). Assessing Inflammation Levels, C-Reactive Protein? Retrieved September 25, 2015, from http://www.drweil.com/drw/u/QAA366279/Inflammation-Levels-C-Reactive-Protein.html

Wu. (2012). Metabolic syndrome among HIV-infected Taiwanese patients in the era of highly active antiretroviral therapy: prevalence and associated factors. - PubMed - NCBI. Retrieved February 20, 2017, from https://www.ncbi.nlm.nih.gov/pubmed/22232517/

Wynants. (2013). NF-κB pathway is involved in CRP-induced effects on pulmonary arterial endothelial cells in chronic thromboembolic pulmonary hypertension | Lung Cellular

and Molecular Physiology. Retrieved March 22, 2016, from http://ajplung.physiology.org/content/305/12/L934.short

Yang. (2013). [Ginger extracts improve renal injury of high fructose-fed SD rats by inhibiting the expression of proinflammatory cytokines]. - PubMed - NCBI. Retrieved August 22, 2015, from http://www.ncbi.nlm.nih.gov/pubmed/25200156

Zhang. (2007). Effect of curcumin on high-sensitivity C-reactive protein and blood-lipids in patients with coronary heart disease--《Chinese Traditional Patent Medicine》2007年02期. Retrieved February 22, 2016, from http://en.cnki.com.cn/Article_en/CJFDTOTAL-ZCYA200702002.htm

Zhang. (2016). Salvianolic acid B protects against chronic alcoholic liver injury via SIRT1-mediated inhibition of CRP and ChREBP in rats. - PubMed - NCBI. Retrieved December 25, 2016, from https://www.ncbi.nlm.nih.gov/pubmed/27989594

Zwaka. (2001). C-Reactive Protein–Mediated Low Density Lipoprotein Uptake by Macrophages | Circulation. Retrieved December 31, 2016, from http://circ.ahajournals.org/content/103/9/1194.short

Appendix A: Pilot Study Design

Design

A randomized controlled trial will be performed to compare CRP levels in subjects who took the HAI against CRP levels in the control group who didn't take the HAI. A random number generator will be used to assign subjects into the intervention or control group. Given the inclusion and exclusion criteria for the trial, it is not expected that CRP levels will change significantly with no intervention. A total of 60 subjects will be recruited, 30 of whom will be randomly assigned to the treatment group while the other 30 subjects will be in the control group.

As chronic inflammation often has no external symptoms, lab work will be used to measure results and will show whether the HAI are effective at lowering CRP. Since there is evidence of correlation between inflammation and both glucose and cholesterol – risk factors in MS – the study will include entry/exiting fasting serum glucose and cholesterol levels. Blood pressure and weight are other risk factors for CVD and entry and exiting measurements will be included. A viral load will be measured pre-administration and post-trial to confirm there is no interaction between the HAI and HAART. It is hypothesized there will be no change in viral load as the herbs in HAI are not anticipated to negatively interact with HAART.

After randomization, the trial will consist of a six-week intervention for the HAI arm, and no placebo or intervention for the control arm. No changes are expected in the control arm. At the end of six weeks, lab work will be repeated.

HAI

The HAI formula consists of single herbal powders purchased from Evergreen Herbs (Pasadena, CA). Each herb is a 5:1 extract, meaning 5lbs of raw herbs were extracted to make 1lb of final product. The herbs will be mixed and pressed into a tablet by machine. Each tablet

contains 0.25g of turmeric, 0.125g of ginger, and 0.125g of Sage. Dosage will be 3 tablets, equaling 1.5g in total, taken with one cup of water twice daily, in the morning and evening. Total daily dosage will be 3g.

Inclusion and Exclusion Factors

Only male subjects will be enrolled to rule out possible hormonal influences, as estrogen can lower inflammation and estrogen levels fluctuate through a regular cycle and even more drastically around menopause (Dworatzek, 2017). Other inclusion criteria include:

- Uninterrupted HAART medication > five years
- No change in HAART medication > three months
- Elevated levels of CRP >3.00 mg/L > six months
- Informed consent
- Ability to follow the study instruction
- English proficiency

Exclusion factors include:

- Female
- Unregulated diabetes
- Anticoagulant treatment such as warfarin, coumadin, heparin
- Gall stones or any gall bladder disease
- Starting a new medication, including HAART, within three months
- Unregulated hypertension
- Cardiovascular incident within one year
- Scheduled surgeries during study and for one week after completing
- Inability to write and speak English
- Enrollment in another clinical trial within the last three months
- Younger than the age of 21 or older than the age of 75
- Autoimmune disease such as rheumatoid arthritis, lupus, etc.

There will be no discrimination against socio-economic status, religion, or race.

Subject Recruitment and Initial Screening

Participants will be recruited from local general practitioners who have a large HIV-positive patient base; HIV research departments where subjects may be identified through a data base; local cardiologists who are more prone to test CRP levels; and local ads in the paper or online fliers posted at nonprofits for HIV. There will be an initial phone screening, followed by a visit to the clinic. The subject must bring previous lab work, within six months, that shows an elevated CRP level.

Intervention Arm

Participants in the intervention arm will be given a six-week supply of the HAI. Instructions on dosage will be verbally reviewed and printed on the bottle. Participants will be required to remain compliant with their current medications and to not introduce any new supplements, including other herbs or nutritional supplements. NSAID use, including aspirin, should be documented. The control group will not receive a placebo, but will only participate in the lab work.

Appendix B: Consent Form

INFORMED CONSENT FORM FOR SUBJECT TO PARTICIPATE IN RESEARCH

Effects of Turmeric, Sage, and Ginger on Elevated Levels of C-Reactive Protein
This study is being conducted as part of a doctoral research study. Kyle Burton, L.Ac. is the primary doctoral-candidate investigator.

Location
Original Breath Acupuncture
1106 N La Cienega Blvd. Suite 107
Los Angeles, CA 90069
Office: (310) 659-8500

Contact
Kyle Burton, L.Ac, Doctoral Candidate 2017
M:(310) 980-9764
kburton.student@yosan.edu

INTRODUCTION

My name is Kyle Burton and I am working on my doctoral capstone in Healthy Aging and Longevity at Yo San University of Traditional Chinese Medicine in Los Angeles. I am doing research on herbs and their effects on lowering elevated levels of C-Reactive Protein. The herbs may also effect blood pressure, cholesterol, and glucose levels.

The researcher will explain this study to you. **Research studies are voluntary and include only people who choose to take part.** Please take your time about deciding whether to participate in this study. Before deciding:

- You can discuss this study with friends and family.
- You can also discuss it with your health care doctor or request a second opinion.
- If you have any questions, you can ask the researchers for more information before deciding to participate.

The research team is asking you to be in this study because you have elevated levels of CRP and have expressed an interest in trying an herbal formula to potentially decrease it.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to determine if a combination of culinary herbs (ginger, turmeric, sage) can reduce high-sensitivity CRP levels, an inflammatory biomarker that is used to monitor the risk of cardiovascular disease. The herbs chosen are staple culinary spices that have been used in a variety of different cultures and have a history of being safe. In Traditional Chinese Medicine, they are known to increase blood circulation and may reduce CRP.

The research will be conducted in a six-week, randomized pilot study utilizing a formulation of herbs. A pilot study is a small-scale test of procedures and methods to examine the feasibility, time, cost, and adverse events in an attempt to predict an appropriate sample size and improve upon the study design prior to a full-scale research trial. There is no placebo formula being used.

HOW MANY PEOPLE WILL TAKE PART IN THS STUDY?

Sixty subjects will be involved in the study. A random number generator will assign subjects into a test, placebo, or control group. Thirty subjects will be given the HAI and thirty subjects will not be given anything to ingest. There is a 1 in 2 chance you will be selected for control group and 1 in 2 chance you will be selected to ingest the HAI. Lab work will still be collected for the control group.

WHAT WILL HAPPEN IF I TAKE PART IN THIS STUDY?

Once your lab work is approved by the project coordinator you will be asked to sign the Waiver of Liability, Hold Harmless Agreement and an Informed Consent Form.

Procedure during study

- You will be asked to take the herbal formula for a period of 42 days (six weeks) and maintain a daily dosing log including current medications.
- You will be asked to return to Original Breath Acupuncture for your exiting fasting* blood draw within three days of finishing HAI.
- It is expected a total of 5 hours of your time will be needed during the six-week study. The 5 hours include initial screening, interview, blood work, preparation of each dosage, and time for exiting blood draw.

  * Do not eat or drink anything (except water) for at least 8 hours before you go to the laboratory to have your blood taken.

How do I take the HAI?

- Morning Dose: Swallow three capsules with one cup of water. Drink 15-30 minutes before breakfast or 1-2 hours afterward.
- Evening Dose: Swallow three capsules with one cup of water. Drink *at least* one hour after last meal. The formula should not affect sleep.

What will they do at my final blood draw?

Your blood pressure and blood sample will be collected at Original Breath Acupuncture upon finishing the trial. Only 3-4 vials of blood (3-4 teaspoons) will be taken. The picture below is one vial:

The blood collected will be used to measure CRP, Glucose, and Cholesterol levels.
You must fast for at least eight hours before each of your blood draws!

HOW LONG WILL I BE IN THIS STUDY?
Six weeks (42 days)

WHAT KIND OF RISKS OR DISCOMFORTS COULD I EXPECT?
Known risks and discomforts:
The common risks and cautions for each of the herbs are listed below:
(**common name**, botanical and *pin y*in)

Ginger, Zingiber Officinalle, *Gan Jiang*: Cautioned with warfarin, aspirin, other blood thinners.

Sage, Salvia Miltiorrhiza, *Dan Shen*: Cautioned with warfarin, aspirin, other blood thinners.

Turmeric, Curcuma Domestica, *Jiang Huang*: Cautioned with warfarin, aspirin, other blood thinners. Individuals suffering from gallstones, or who are pregnant, are not recommended to take turmeric.

Risks of blood draw:

There may be some discomfort when blood samples are taken, and there is a small chance of bruising at the site at which the needle is inserted.

Reproductive Risks:
Due to the unknown side effects of the study on reproductive glands, if you are a male whose partner is of childbearing potential, you should use a reliable means to avoid fathering a child while taking part in this study, because the effect of the study product on sex cells and upon the development of an unborn child are not known.

Unknown risks and discomforts:
The herbs included in the formula are not expected to cause any side effects, however minor stomach or intestinal discomfort are possible anytime something new is ingested. The doses of each of the herbs are much lower than reported safety levels as published in *PDR for Herbal Medicines, Fourth Edition.* The experimental treatments may have side effects that have not been previously identified. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

ARE THERE ANY BENEFITS IF I PARTICIPATE?

Possible benefits for me:
The possible benefits you may experience from being in this study include lowered levels of CRP which possibly decreases your chance of heart disease.

Possible benefits for others:
This study will help the researchers learn more about the effectiveness of herbs in the treatment for decreasing CRP and inflammation. Hopefully this information will help in developing an herbal alternative in the treatment of inflammation and reducing a risk factor for developing heart disease.
There may not be any benefit for you but your participation is likely to help us find the answer to the research question. By participating you will be contributing to research on the use of herbs and inflammation.

WHAT OTHER CHOICES DO I HAVE IF I DON'T WANT TO PARTICIPATE?
Participation in this study is voluntary. An alternative to participate in this study is to remain under routine care of your primary care physician.

CAN THE RESEARCHER REMOVE ME FROM THIS STUDY?

The researcher may end your participation in this study for a number of reasons, such as if your safety and welfare are at risk, if you do not follow instructions or if you miss scheduled visits. The researcher might also decide to stop the study at any time.
If you decide to stop being in the study, or are removed from the study, or the study is stopped the researcher may ask you to return any unused portions of the formula and finish one last pain assessment. The data collected about you up to the point of withdrawal will remain part of the study and may not be removed from the study database.

ARE THERE ANY COSTS FOR TAKING PART IN THIS STUDY?
This study does not cost you anything other than possible expenses to travel to\from final blood draw. Possible travel expenses could include parking, gas, bus, taxi, or Uber fare. There is no fee or lab cost associated with participation in this study.

WILL I BE PAID FOR MY PARTICIPATION?
You will not be paid to participate in this study.

HOW WILL INFORMATION ABOUT ME AND MY PARTICIPATION BE KEPT CONFIDENTIAL?
The researchers will do their best to make sure that your private information is kept confidential. Information about you will be handled as confidentially as possible, but participating in research may involve a loss of privacy and the potential for a breach in confidentiality. Study data will be physically and electronically secured. As with any use of electronic means to store data, there is a risk of breach of data security

Use of personal information that can identify you:
Your identity in this study will be treated as confidential. Results of the study, including all collected data, may be published in my capstone and in possible future journal articles and professional presentations, but your name or any identifiable references to you will not be included. However, any records or data obtained as a result of your participation in this study may be inspected by persons conducting this study or Yo San University's Institutional Review Board (IRB) provided that such inspectors are legally obligated to protect any identifiable information from public disclosure, except where disclosure is otherwise required by law or a court of competent jurisdiction. These records will be kept private in so far as permitted by law. The data collected for this study will be retained in a

secured and locked location for a minimum of three years as required by the IRB and then destroyed.

WHO CAN I CONTACT IF I HAVE QUESTIONS ABOUT THIS STUDY?
The Research Team**:**
You may contact Kyle Burton at kburton.student@yosan.edu or 310-980-9764 with any questions or concerns about the research or your participation in this study.

WHAT HAPPENS IF I BELIEVE I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?
If after ingesting the formula, you experience any unforeseen discomfort, you should discontinue the herbal formula immediately. In the event that the reaction becomes serious, you should seek immediate medical help or to call 911. In this case, you should contact the researcher at the earliest convenience to report the adverse event.

Neither Kyle Burton nor Yo San University will cover any medical expenses incurred as a result from taking the formula.

Medical treatment may be provided through participant's insurance.
WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?
Taking part in this study is your choice. You can choose whether or not you want to participate. Whatever decision you make, there will be no penalty to.

- You have a right to have all of your questions answered before deciding whether to take part, and at any time during the study.
- If you decide to take part, you can leave the study at any time.
- If you decide to stop being in this study you should notify the research team right away. The researchers may ask you to complete a final pain survey as well as go to LabCorp for your final blood draw.
- If you decide not to take part, you can still get medical care from Original Breath Acupuncture or Yo San University.

HOW DO I INDICATE MY AGREEMENT TO PARTICIPATE?
If you agree to participate in this study you should sign and date below. You have been given a copy of this consent form and the Research Participant's Bill of Rights to keep. You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

SIGNATURE OF THE PARTICIPANT

_____
Name of Participant

_____ _____
Signature of Participant Date

SIGNATURE OF PERSON OBTAINING CONSENT

_____ _____
Name of Person Obtaining Consent Contact Number

_____ _____
Signature of Person Obtaining Consent Date

WITNESS

_____ _____
Signature of Witness Date

_____
Name of Witness

Appendix C: Waiver of Liability and Hold Harmless Agreement for Research Study

WAIVER OF LIABILITY AND HOLD HARMLESS AGREEMENT FOR KYLE BURTON'S RESEARCH STUDY

I,_____(write name) am over 18 years of age, fully competent, and eligible to participate in the above named research study. I recognize that I am not required to participate in this research study and choose to do so of my own free will. I recognize that inherent risk is involved in my participation in this research. I understand that this research may involve the risk of physical and/or psychological injury and death. I voluntarily assume all such risk of personal injury, including death that I may sustain as a result of participating in this research, whether caused by me, the principal investigator, Yo San University, its officers, agents or employees and/or Board of Directors for any such injury. I FURTHER AGREE AND INDEMNIFY AND HOLD HARMLESS, The principal investigator, Yo San University, its officers, agents and employees and/or Board of Directors from any loss, liability, damage or costs, including court costs, attorneys' fees and medical costs that may incur due to my participation in this research study. I intend to bind other members of my family, my heirs and assigns to this Waiver of Liability and Hold Harmless Agreement. I have read this document before signing it; I have had an opportunity to consider its meaning, and I understand the document and sign it voluntarily as my own free act and deed.

Printed Name

_____

Signature/Date

_____

Appendix D: Permission to Use Personal Health Information for Research

IRB #XXX
Yo San University
Permission to Use Personal Health Information for Research

Effects of Turmeric, Ginger, and Sage on CRP levels of Subjects Undergoing HAART

Principal Investigator Name: Kyle Burton, L.Ac, Doctoral Candidate 2017

This study will be funded Kyle Burton, L.Ac.

A. What is the purpose of this form?

State and federal privacy laws protect the use and release of your health information. Under these laws, the Yo San University or your health care provider cannot release your health information to the research team unless you give your permission. The research team includes the researchers and people hired by Yo San University to do the research. If you decide to give your permission and to participate in the study, you must sign this form as well as the Consent Form. This form describes the different ways that the researcher, research team and research sponsor may use your health information for the research study. The research team will use and protect your information as described in the attached Consent Form. However, once your health information is released it may not be protected by the privacy laws and might be shared with others. If you have questions, ask a member of the research team.

B. What Personal Health Information will be released?

If you give your permission and sign this form, you are allowing: Kyle Burton to release the following medical records containing your Personal Health Information. Your Personal Health Information includes health information in your medical records and information that can identify you. For example, Personal Health Information may include your name, address, phone number or social security number.

☒ Entire Medical Record	☐ Laboratory Reports	☐ Emergency Medicine Center Reports
☐ Outpatient Clinic Records	☐ Dental Records	☐ Health Care Billing Statements
☐ Pathology Reports	☐ Operative Reports	☐ Diagnostic Imaging Reports
☐ EKG	☐ Radiology Reports	☐ History & Physical Exams
☐ Progress Notes	☐ Radiologic & MR Scans	☐ Consultations
	☐ Discharge Summary	☐ Psychological Tests

☐ Other (describe):

Do I have to give my permission for certain specific uses?

Yes. The following information will only be released if you give your specific permission by putting your initials on the line(s).

___I agree to the release of information pertaining to drug and alcohol abuse, diagnosis or treatment.

___I agree to the release of HIV/AIDS testing information.

___I agree to the release of genetic testing information.

___I agree to the release of information pertaining to mental health diagnosis or treatment as follows:

C. How will my Personal Health Information be used?

Your Personal Health Information may be released to these people for the following purposes:

1. To the research team for the research described in the attached Consent Form;
2. To others at UC who are required by law to review the research;
3. To others who are required by law to review the quality and safety of the research, including: U.S. government agencies, such as the Food and Drug Administration, the research sponsor or the sponsor's representatives, or government agencies in other countries. These organizations and their representatives may see your Personal Health Information. They may not copy or take it from your medical records unless permitted or required by law.

D. How will my Personal Health Information be used in a research report?

If you agree to be in this study, the research team may fill out a research report. (This is sometimes called "a case report".) The research report will **not** include your name, address, or telephone or social security number. The research report may include your date of birth, initials, dates you received medical care, and a tracking code. The research report will also include information the research team collects for the study. The research team and the research sponsor may use the research report and share it with others in the following ways:

1. To perform more research;
2. Share it with researchers in the U.S. or other countries;
3. Place it into research databases;
4. Use it to improve the design of future studies;
5. Use it to publish articles or for presentations to other researchers;
6. Share it with business partners of the sponsor; or
7. File applications with U.S. or foreign government agencies to get approval for new drugs or health care products.

E. Does my permission expire?

This permission to release your Personal Health Information expires when the research ends and all required study monitoring is over. Research reports can be used forever.

Can I cancel my permission?

You can cancel your permission at any time. You can do this in two ways. You can write to the researcher or you can ask someone on the research team to give you a form to fill out to cancel your permission. If you cancel your permission, you may no longer be in the research study. You may want to ask someone on the research team if canceling will affect your medical treatment. If you cancel, information that was already collected and disclosed about you may continue to be used. Also, if the law requires it, the sponsor and government agencies may continue to look at your medical records to review the quality or safety of the study.

F. Signatures

Subject

If you agree to the use and release of your Personal Health Information, please print your name and sign below. You will be given a signed copy of this form.

_____

Subject's Name (print)--*required*

_____ _____

Subject's Signature Date

Parent or Legally Authorized Representative (where IRB approved)

If you agree to the use and release of the above named subject's Personal Health Information, please print your name and sign below.

_____ _____

Parent or Legally Authorized Representative's Name (print) Relationship to the Subject

_____ _____

Parent or Legally Authorized Representative's Signature Date

Witness

If this form is being read to the subject because s/he cannot read the form, a witness must be present and is required to print his/her name and sign here:

_____

Witness' Name (print)

_____ _____

Witness' Signature Date

Appendix E: Breakdown of Cost

PROJECTED COST OF PILOT STUDY

Cost of Lab Work

LAB TEST	PRICE		
Hs-CRP	$ 19		
Lab Visit	$ 10		
Glucose	$ 5		
Cholesterol	$ 15		
Viral Load	$139		
Sub Total	$188	X 2 (initial, exiting lab work)	$376 per subject
		TOTAL	$22,560 for 60 subjects

Cost of Herbs

Amount (in grams) of herbs needed for 30 subjects:

Dosage 1.5.g\2 x day= 3.0g\day per subject

42 days x 3.0g = 126.0g total per subject

30 subjects x 126.0g of herbs = **3,780 total grams**

Breakdown of Formula: Turmeric 50%, Ginger 25%, Sage 25%

Turmeric: 1890g Total. 19 bottles x $8.28 = $ 157.32

Ginger: 945g Total. 10 bottles x $8.28 = $ 82.80

Sage: 945g Total. 10 bottles x $10.88= $ 108.80

Total Cost of Herbs for $348.92
- Evergreen 50% Discount
= $174.46

TOTAL PROJECTED COST = $22,934.46

Appendix F: Advertisement for Study

Clinical Study on the Effects of Turmeric, Ginger, and Sage

What is the study?
Chronic, low grade inflammation could be a driving factor in the aging process. Individually, turmeric, ginger, and sage, have been shown to improve cardiovascular health and have anti-inflammatory properties. This study will test a combination of the three herbs and their synergistic effects on levels of C-Reactive Protein, a marker for inflammation.

What is C-Reactive Protein?
C-Reactive protein (CRP) is produced in the liver and increases when there is inflammation. hs-CRP (high-sensitivity c-reactive protein) is a simple blood test which measures CRP levels in the blood. Elevated hs-CRP levels have no outward appearance. Although hs-CRP is considered a "non specific" marker, it may be used to assess one's risk for cardiovascular disease because its effect on narrowing blood vessels. When levels are 3.00 mg/L or higher, you may be considered at high risk.

What does it do?
CRP produces pro-inflammatory changes in the walls of blood vessels. The changes, if chronic, can lead to atherosclerotic plaque.

What do I have to do?
Swallow 4 tablets, twice a day for six weeks. Volunteers will be randomly assigned to a test or a control group. After the six weeks, subjects will return for one more blood draw. The control group will not take the herbal formula but will have their blood drawn after six weeks.

Are there any side effects?
Although it is not expected, minor gastro-intestinal side effects are possible including indigestion and\or loose stool.

Actual Tablet

How do I know if I qualify?
Volunteers must Male between 18-75 years of age with a hs-CRP of 3.00 mg/L or higher.
If you have uncontrolled diabetes, hypertension, rheumatoid arthritis, current gall bladder stones, or are taking blood thinners, such as Warfarin (Coumadin), you do not qualify.

Will my health records be private?
Yes, all HIPAA compliancy regulations will be enforced. Only your doctor and the trial conductor will know your name.

Who is doing the study?
Doctoral candidate Kyle Burton, L.Ac. is focusing on "Healthy Aging and Longevity" and the effects of herbs and inflammation. He is conducting this study for his Capstone at Yo San University in Los Angeles. He has been in practice since 2006 and hopes to help further integrate Eastern and Western Medicine with the study of herbs using lab work to help show their safety and efficacy.

For more information: www.originalbreath.com\CRP_Trial
kburton.student@yosan.edu