Role of garlic in decreasing cardiovascular disease risk by promoting reverse-cholesterol transport

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Lifestyle and dietary changes in the last half-century have given rise to a series of nutrient-based metabolic disorders including cardiovascular disease (CVD), metabolic syndrome, obesity, and diabetes.

An alternative to pharmacological therapy is to obtain naturally occurring anti-hyperlipidemic compounds present in foods. Because of their presence in foods, these compounds can be easily incorporated into the diet at a nominal cost in comparison to common drug therapies. While dietary approaches to disease management and prevention typically exhibit more modest efficacies than drugs, they are commonly well tolerated, provide pleiotropic health benefits, and result in only negligible side effects. Thus, it is important to examine foods and their bioactive components that show promise for mitigating the negative effects of high-calorie/high-fat (especially saturated fat) diets on CVD risk. Among such foods, garlic (*Allium sativum*) has received particular attention due to its anti-hyperlipidemic and anti-cancer properties. In humans, regular garlic consumption can lead to a ~10% reduction in blood levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-c). Despite considerable evidence implicating garlic and its organosulfur compounds in reducing blood cholesterol levels, there is a paucity of data regarding the molecular mechanisms through which garlic elicits its beneficial effects on CVD risk.

The purpose of this project is to examine the extent to which bioactive components present in garlic exhibit their cardioprotective properties through an ***increase in cholesterol efflux*** and ***reduction in cholesterol synthesis*** in macrophages. Understanding the potential mechanisms through which bioactive components of garlic reduce risk of disease via enhanced RCT will provide insight into how dietary HDAC*i* may be incorporated into the diet to attenuate and even reduce the risk of developing chronic diseases. Due to the focus on the impact of dietary HDAC*i* on macrophage RCT, we will focus on examining the action of dietary HDAC*i* in primary macrophages

Our ***primary objective*** is to examine the extent to which garlic, and its bioactive components, leads to the stimulation of RCT through the enhanced release of cholesterol from macrophages. Dietary approaches or mechanisms that enhance RCT are an attractive option in reducing blood cholesterol levels and improving CVD risk at a relatively low cost with minimal side effects.

The ***central hypothesis*** is that the organosulfur compounds DADS, SAMC, and AM in garlic lead to the increased expression of genes involved in promoting RCT, enhanced macrophage cholesterol efflux, and a reduction in macrophage cholesterol biosynthesis. This hypothesis is based on observations that DADS, SAMC, and AM exhibit HDAC*i* activity leading to a de-repression (i.e., stimulation) of gene expression.

This proposal builds on preliminary research, and encompasses two specific aims:

Aim 1: *Using primary macrophages, we will examine the extent to which ogranosulfur compounds DADS, SAMC, and AM in garlic enhance the expression of genes involved in cholesterol efflux, promote increased cholesterol release, reduce cholesterol synthesis, and decrease inflammation in macrophages.*

Aim 2: *We will characterize mechanisms through which DADS, SAMC, and AM function as dietary HDACi in cultured and primary macrophages to increase cholesterol efflux and begin to define the role(s) of garlic consumption in reducing CVD risk.*