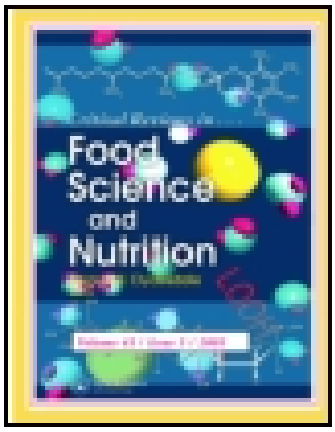

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Fruit polyphenols: A review of anti-inflammatory effects in humans

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Fruit polyphenols: a review of anti-inflammatory effects in humans

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LIST OF ABBREVIATIONS: AP-1=activator protein-1; BC=baseline controlled; BW=body weight; C=controlled; CC=comparative controlled; CAD=coronary artery disease ; CD40=CD40 protein; CHD=coronary heart disease; CVD=cardiovascular disease; DM=diabetes mellitus; FMD=flow-mediated vasodilation; HC=high carbohydrate; HF=high fat; hs-CRP=high sensitivity-C-reactive protein; IəB=inhibitors of kappa B; IKK=inhibitor of nuclear factor kappa-B kinase; IL=interleukin; iNOS=inducible nitric oxide synthase; JNK=c-Jun N-terminal kinase; LDL-C=low density lipoprotein-cholesterol; LFA-1= lymphocyte function-associated antigen-1; Lp-PLA2=lipoprotein-associated phospholipase A2; LPS=lipopolysaccharide; Mac-1=macrophage-1 antigen; MAPK=mitogen activated protein kinase; MCP-1=monocyte chemoattractant protein-1; MetS= metabolic syndrome; MIG=monokine induced by interferon-

gamma; MMP=matrix metallo proteinase; MNC=mononuclear cells; NA=not available; NAD (P) H=nicotinamide adenine dinucleotide phosphate; NAFLD=non-alcoholic fatty liver disease; NF-əB=nuclear factor kappa-light-chain-enhancer of activated B cells; NHANES=National Health and Nutrition Examination Survey; NK cells=natural killer cells; Nrf2=NF-E2 related factor 2; OX-LDL=oxidized-low density lipoprotein; PAI-1=plasminogen activator inhibitor-1; PBMC=peripheral blood mononuclear cells; PC=placebo controlled; PPAR-ɔ=peroxisome proliferator-activated receptor-gamma; ROS=reactive oxygen species; sICAM-1=soluble intercellular adhesion molecule; SOCS-3=suppressor of cytokine signaling-3; SLe^x= Syalil-Lewis; sVCAM-1=soluble vascular adhesion molecule; TLR=toll like receptor; TNF-Ŭ=tumor necrosis factor alpha; tPAI-1=tissue plasminogen activator inhibitor-1; VLA-4=very late activation antigen-4

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Abstract

Underlying etiological factors in the development of obesity-related chronic diseases are long-term imbalances of oxidative and inflammatory stress leading to tissue dysfunction, damage and ultimately failure. Poor dietary quality contributes significantly to the oxidative and inflammatory status of an individual. Conversely, various dietary approaches, including specific dietary factors can mitigate or prevent the occurrence of these risk-conferring imbalances brought about by modern lifestyle. Plant derived polyphenolic compounds are well known for their antioxidant properties. Recent evidence indicates these compounds may confer anti-inflammatory and/or inflammatory response stabilizing activities, which would have important implications in health maintenance and disease risk reduction. Commonly consumed fruits, such as grapes, berries, and oranges/orange juice, contain polyphenolic compounds that have been studied for their effects on inflammation, but the nature and extent of their effects in humans remain unclear. Therefore, this article aims to provide a comprehensive overview of human clinical trials investigating the acute and chronic (feeding) effect of polyphenols from commonly consumed fruits or their derived products on inflammation.

Introduction

Paramount to chronic disease development in modern lifestyle is inflammation. Inflammation contributes to age-related degenerative diseases of nearly every organ system peripherally and centrally, including the most well-known and globally pervasive: cardiovascular diseases (CVD), cancer, and Alzheimerôs disease (Gratchev et al., 2012, Rosenberg, 2005). Development of the obese phenotype is associated with a concomitant increase in inflammatory status. Insulin resistance, the cornerstone of the metabolic syndrome (MetS) and a major risk factor for type 2 diabetes mellitus and CVD, is fueled by heightened inflammatory states. Intake of a high energy, high fat and high carbohydrate diet/meal increases acute inflammatory stress in both healthy weight and overweight individuals (Jellema et al., 2004; Ghanim et al., 2009; Manning et al., 2008; Calder et al., 2011). Conversely, population studies indicate that diets rich in fruits and vegetables are inversely associated with inflammatory stress (Root et al., 2012; Anderson et al., 2012; Nanri et al., 2011; Calder et al., 2011). The prevalence of MetS, CVD, diabetes and Alzheimerôs disease is lower with increased fruit and vegetable intake (Dauchet et al., 2009; Hu, 2003; Dauchet et al., 2006; He et al., 2007; Fung et al., 2009; Esmaillzadeh et al.; 2007; Tortosa et al., 2007; Babio et al., 2007; Martínez-González and Sánchez-Villegas 2004; Dai et al., 2006). These effects may be attributable to increased intake of essential nutrients and fiber; however, many contend that the vitamin/mineral or fiber content alone cannot fully account for the observed protective effects of consuming fruits and vegetables (Slavin and Lloyd, 2012; Stevenson and Hurst, 2007). In addition, plant-derived foods or beverages, such as red wine, cocoa and tea have limited or no fiber or essential nutrients yet impart beneficial biological effects when consumed (Bertelli and Das, 2009; Di Castelnuovo et al., 2012). During the last few

decades these ñotherò components in plant foods/beverages have been studied for their health benefits; many of which have been chemically characterized and fall into the large family of compounds known as polyphenols.

Polyphenols are most well-known for their antioxidant properties; although early reports suggested that these compounds were anti-nutritional components of plants (Bravo, 1998). Nowadays, there is sufficient data from *in vitro* (Vauzour et al., 2010) and *in vivo* animal studies (Gonzalez-Gallego et al., 2010) to support the supposition that polyphenolic compounds have a strong potential to alter disease risk profiles in humans through their ability to modulate various biological pathways. While polyphenols have been suggested to act as antioxidants in the body; their ability to act as traditional antioxidant, free radical quenchers, is highly debated (Halliwell, 2008). Instead, evidence is accumulating showing that polyphenols are involved in modulating cell signaling pathways, which may better explain how these dietary compounds elicit biological effects when they are relatively poorly absorbed and circulate in nano molar concentrations. Pre-clinical data suggest that certain polyphenols have anti-inflammatory properties. These data combined with the significance of inflammation in disease onset, progression and complication has fueled interest and clinical research to determine whether these effects are translatable to humans.

Dietary polyphenols have been studied in a variety of clinical settings to determine whether these compounds bestow anti-inflammatory activity in humans. The effects of fruit and fruit-derived products/beverages have captured the interest of scientists, consumers and the food industry, probably due, at least in part, to early reports of wine being protective against heart

disease (also known as, ćthe French paradoxô) and then later studies revealing biological activity of wine polyphenols, grapes, among other fruits (Renaud and Gueguen, 1998; Dohadwala and Vita, 2009). Today, several fruits and fruit beverages have been studied specifically to determine if ćanti-inflammatoryô can be added to their list of beneficial attributes. Because of the broad scope of fruits, and particularly fruit-derived products (ie., extracts and nutraceutical supplements) that have been studied, the aim of the present review was to critically review and evaluate the human literature for determining anti-inflammatory effects of commonly consumed fruits and fruit products (eg., juice, wine), including apples, berries, grapes, red wine, and oranges/orange juice. Less commonly consumed fruits are included in the review if whole foods or standard food/beverage products were tested. Conclusions drawn from the collective evidence will help to provide insight about the effect of commonly consumed fruits/fruit products to modulate inflammatory processes as well as provide directions for future investigations to improve our understanding of fruit and dietary fruit polyphenols on inflammation.

An important aspect of our approach to review fruits (and beverages) that are relatively common is that these are the fruits people are choosing when deciding to eat fruit, although still well below dietary recommendations (Murphy et al., 2012). Health is a major driver of produce consumption. Hence, targeted evidenced-based messaging emphasizing the health benefits of fruits that people are already familiar with may help more people to meet daily serving recommendations for fruit, and potentially encourage intake of a variety of other fruits and produce.

Fruit (Poly) Phenolic Compounds: General Background

Phenolic compounds are widely distributed throughout the plant kingdom and range from simple molecules such as phenolic acids to complex polymerized compounds (i.e. polyphenols) (Rice-Evans et al., 1996). Flavonoids are a major subclass of polyphenols and are the most abundant polyphenols in the human diet (Rice-Evans et al., 1996; Sampson et al., 2002; Hertog and Kromhout, 1995; Hertog et al., 1997). Subclasses of flavonoids include flavonols such as quercetin and kaempferol, flavones (eg. luteolin, apigenin), flavan-3-ols (eg. catechins), flavanones (eg. hesperetin, naringenin), isoflavones (eg. genistein), the anthocyanidins (eg. pelergonidin, delphinidin) and the proanthocyanidins (eg. condensed tannins) to a name a few (Rice-Evans et al., 1996). Selected dietary sources of these compounds are listed in **Table 1**. The most commonly consumed fruit flavonoids in the diet are anthocyanins, hesperetin and quercetin (Murphy et al. 2012). Ellagic acid, delivered mostly as ellagitannin, is another commonly consumed fruit-derived phenolic compound.

Intake of fruit (poly) phenolic compounds can range several fold depending on individual dietary patterns. Various estimates suggest that Americans eat an average of 20-24 mg of flavonoids a day (Sampson et al., 2002; Vinson et al., 2001). These estimates are based predominately on flavonol and flavone intake. Reports from Finland indicate that daily consumption of fruits and berries in the Finnish diet yields ~ 38.4 mg of flavonoids/day (Hertog and Kromhout, 1995). A recent analysis of NHANES data showed that individuals meeting

dietary recommendations for fruit and vegetable consumption have a 2-4 fold higher intake of carotenoids, flavonoids and ellagic acid compared to individuals not meeting recommendations (Murphy et al., 2012). Flavonoid intake for those not meeting fruit and vegetable recommendations (which represents the majority of U.S. adults) was estimated at ~19 mg/day for men and ~17 mg/day for women. Ellagic acid intake was estimated at ~5 and 6 mg/day for men and women, respectively (Murphy et al., 2012). The main fruit contributors to polyphenol intake were strawberries, blueberries, raspberries, grapes, oranges and orange juice, apples and bananas. These data are consistent with other reports (Chun et al., 2007; Yang et al., 2011; Zamora-Ros et al., 2011).

Other important contributors of polyphenols to the human diet are tea and wine, the latter a fermentation product of grapes. Red wine is particularly rich in polyphenols and has been studied extensively for its health benefits, particularly as it relates to CVD (Natella et al., 2001; Ceriello et al., 2001; Lippi et al., 2010). Red wine is a rich source of polyphenols (up to 2-3 g/L) and contains phenolic acids/derivatives, stilbenes, anthocyanins, flavanols, flavonols and dihydroflavonols (Waterhouse, 2002). Red wine is typically consumed with food, which is a consideration for their derived health benefits. Minimizing the consequences of energy dense meals or snacks may be an important feature of dietary phenolic compoundsô effect on human health.

Fruit (Poly) Phenols: Biological Activity

Fruit phenolic compounds may provide benefit to humans via several mechanisms (Quiñones et al., 2012). The best described and most well-known mechanism is through their antioxidant properties and modulation of biological oxidative stress to prevent damage to cellular lipids, proteins and DNA. Directly, they may scavenge superoxide and other reactive oxygen species (ROS) such as hydroxyl and peroxy radicals. Indirectly, they may stimulate endogenous antioxidant defense systems, for example, NF-E2 related factor 2 (Nrf2), a transcription factor that controls the production of antioxidant enzymes such as a catalase and glutathione peroxidase (Gonzales-Gallego et al., 2007); or conversely, they may inhibit enzymes that generate large amounts of reactive oxygen species such as xanthine oxidase and NAD(P)H oxidase. Inhibiting absorption of already oxidized products, such as lipid hydroxyperoxides (Ursini et al., 1998; Hertog et al., 1995) may be another mechanism by which some phenolic compounds provide benefit. More recently, polyphenolic compounds have been studied for their action in cellular signaling, particularly in modifying pathways of inflammation. Some of these actions may be direct and others are proposed to be secondary to modifying the redox balance of the cell. More direct actions may include blocking or down regulating receptors or transcription factors leading to pro-inflammatory gene expression, such as interleukin (IL) receptors and Toll-like Receptor (TLR)-4, nuclear factor kappa B (NF-əB), activator protein (AP-1) and c-Jun-N-terminal kinases (JNK), or acting as a natural ligand for peroxisome proliferator activated receptor-gamma (PPAR-ɔ) which in turn modulate inflammatory gene expression. Activating PPAR-ɔ may also modify inflammatory stimuli for TLRs through their effects on fat redistribution in the adipose tissue (Tsai and Maeda, 2005). Less well studied is the potential prebiotic effect of polyhenols altering the composition and function of the gut microbiota, gut permeability and gut-derived

pro-inflammatory stimuli (Lee et al., 2006; Queipo-Ortuño., 2012; Roberfroid et al., 2010). Polyphenols may also beneficially increase production of anti-inflammatory molecules such as IL-4, IL-10, IL-13 and adiponectin (Crouvezier et al., 2001; Comalada et al., 2006; Cho et al., 2007; Scazzocchio et al., 2011; Nagasako-Akazome et al., 2007). Overall, phenolic compounds found in fruits have multiple paths for benefiting human health; most notably through their actions in modifying cellular events to promote balance between inflammatory state and normal state.

Inflammation: General Background

Inflammation is the normal protective response of the innate immune system to tissue injury or detrimental external stimuli such as pathogens, allergens and other irritants. During a single inflammatory event, a cascade of biochemical events propagates involving the local vascular system, the immune system, and various cells within the injured tissue (Galley and Webster, 1996). A main function of inflammation is to resolve infection and to repair the damaged tissue. Ideally, the inflammatory response should be rapid in onset, effective (destructive and efficient in clean-up) and self-limiting. Inflammation that persists due to recurrent stimuli or inefficient regulation or resolution of the inflammatory response can cause chronic inflammation. Inflammatory responses are often characterized by the production of pro-inflammatory molecules and cytokines that provide signals between immune cells to coordinate the inflammatory response. A key player in the induction of inflammation is NF-əB, a major transcription factor which stimulates the encoding of a number of genes including those responsible for production of cytokines, chemokines, immunoreceptors, cell adhesion molecules

and acute phase proteins (Pahl et al., 1999). NF-əB exists in the cytoplasm of cells in an inactive form associated with regulating proteins called inhibitors of əB (IəB), including IəBŭ, IəBɓ, and IəBů While highly complex with site and event specific responses, the most prevalent activated form of NF-əB is a heterodimer consisting of a p50 or p52 subunit and p65, which contains transactivation domains necessary for gene induction (Baldwin, 1996). IəBŭ is associated with transient NF-əB activation, whereas IəBɓ is involved in sustained activation and both bind to the p50-p65 heterodimer and the p50 homodimer, although inhibiting translocation and DNA binding activity differentially (Tak and Firestein, 2001). Activation of NF-əB requires release from the NF- əB ï IəB complex, which is mediated by inhibitor of nuclear factor kappa-B kinase (IKK). The IKK complex consists of 3 subunits of which the IKK beta (ɓ) may be most relevant in chronic inflammation. Activation of NF- əB further leads to transcription of genes that encode molecules, including cytokines, which are typically involved in the inflammatory process. Similarly, AP-1, a transcription factor involved in inflammation, is stimulated by stress factors including infections and cytokines. Other important mediators of inflammation include pattern recognition receptors such as TLRs, and kinases such as mitogen activated protein kinase (MAPK), and c-Jun N-terminal kinases (JNK). The inflammatory response can be triggered by stimuli such as endotoxin (lipopolysaccaride from bacteria), viruses, and changes in levels of reactive oxygen species, fatty acids, cytokines, growth factors, and carcinogens among others.

Inflammation, Obesity and Diet

In general, inflammation is an acute reaction to a stressor, which under proper regulation subsides with the resolution of the short-term assault. However, inflammatory stress can also be

induced by factors such as body weight and poor diet. Obesity is now well recognized as a chronic state of inflammation. Expanding adipose tissue results in morphological changes that compromise adipose tissue function. Adipose tissue is a dynamic endocrine tissue that produces a host of adipokines with well described effects on metabolism as well as the immune system. Hotamisligil et al. (1993) demonstrated early on a positive relationship between adipose mass and expression of the pro-inflammatory gene tumor necrosis factor-Ŭ (TNF-Ŭ). Adipose tissue also produces and secretes other cytokines and chemokines such as leptin, adiponectin and monocyte chemoattractant protein-1 (MCP-1), all with metabolic-/immune- modulating functions (Ouchi et al., 2011). In obesity, the secretion profile of these proteins is altered resulting in elevated pro-inflammatory proteins and reduced anti-inflammatory proteins. Hypertrophic adipocytes also promote macrophage infiltration into adipose tissue, recruited and activated by the release of MCP-1. Macrophages produce a number of pro-inflammatory proteins, such as TNFŬ, IL-6 and MCP-1, which contribute further to the pro-inflammatory state. Elevated inflammatory proteins are characteristic of obesity and provide the critical link between obesity and the development of insulin resistance, type 2 diabetes and CVD (Hummasti and Hotamisligil, 2010).

In as much as excess energy intake contributes to inflammation through obesity development, high energy diets/meals containing high amounts of fat and rapidly digestible carbohydrate, typical of western eating patterns, induce an acute inflammatory response in both obese and normal weight individuals (Patel et al., 2007; Hyson et al., 2002; Aljada et al., 2004; Aljada et al., 2006). The postprandial period is a time of active oxidative metabolism and formation of reactive oxygen species. Excess energy intake increases the production of ROS

resulting in metabolic oxidative stress. This change in a cellôs redox status activates redox sensitive signaling molecules, such as NF-kB, JNK and other stress signaling molecules, ultimately resulting in increased gene expression of a number of inflammation mediators (Calder et al., 2011). Hence, elevations in inflammatory proteins in the postprandial state are often accompanied, and likely preceded, by increases in markers of oxidative stress.

Inflammatory Biomarkers in Chronic Diseases

With the emerging role of inflammation as a major contributor to chronic disease pathologies, several biomarkers have been identified as useful tools to assess inflammatory status in humans. Circulating concentrations of inflammatory molecules, such as acute phase proteins, cytokines, adipokines and adhesion molecules are the predominant measures that are used in research as well as in clinical practice. Inflammation can also be assessed at the molecular level by studying gene expression of transcription factors, receptors and protein kinases in immune cells such as monocytes and macrophages; levels of these markers help to identify mechanisms and pathways that either stimulated or inhibited resulting in a particular inflammatory outcome. The various inflammation markers that are measured in humans are presented in **Table 2**. Inflammatory molecules that are known to be increased in frank disease conditions are also invariably observed in obesity, reinforcing the concept that obesity predisposes to disease development. Furthermore, in addition to adiposity, several environmental factors such as energy dense- and nutrient poor-diets, particularly those containing saturated fats, *trans* fats and high glycemic index foods have

been shown to stimulate inflammation (Kennedy et al., 2009; Micha and Mozzaffarian, 2008; Browning and Jebb, 2006).

Circulating high sensitivity (hs)-C-reactive protein (CRP) concentration is a common clinical biomarker used to measure inflammation. High sensitivity-CRP is an acute phase protein that increases several hundred-fold in the presence of an injury or acute infection. However, hs-CRP is chronically elevated, but to a lesser degree, in disease states that have inflammation as a component, such as CVD and cancer. Circulating hs-CRP concentration of > 3mg/L is an indicator of low grade inflammation and has been implicated in the etiology of several chronic diseases including heart disease (Ridker, 2003) and Alzheimerôs (Schmidt et al., 2002). Total fibrinogen is another acute phase protein that is gaining importance as a reliable marker of inflammation. Increased fibrinogen concentrations have been associated with thrombosis in humans (Muszbek et al., 2008). Similarly, serum amyloid A has been implicated in atherosclerosis and other inflammatory conditions such as rheumatoid arthritis (O'Brien and Chait, 2006).

Blood concentrations of several cytokines are widely used as biomarkers of inflammation. TNF-Ǔ, IL-6 and IL-1ƀ are the most widely used. TNF-Ǔwas the first cytokine to be recognized as a common factor linking obesity, inflammation and diabetes. TNF-Ǔmay also play a causal role in the development of CVD. IL-6 is mostly responsible for the acute phase response in the liver, and is significant in the progression of acute inflammation to chronic inflammation by stimulating monocyte recruitment and exerting effects on T- and B-cells (Gabay, 2006). Similar to TNF-Ǔ, circulating concentrations of IL-6 are increased in both obesity and type 2 diabetes (Bastard et al., 2007; Lazar, 2005). IL-1ƀ plays a central role in the

inflammatory response, but prolonged elevation of circulating IL-1ß concentrations has been associated with inflammatory diseases such as irritable bowel syndrome and rheumatoid arthritis, as well as implicated in CVD (Kornman, 2006). MCP-1 is a chemokine and increased concentrations in human circulation have been associated with atherosclerosis and insulin resistance (Kanda et al., 2006).

Adipokines, such as leptin and adiponectin, are white adipose tissue-derived cytokines and are reliable markers of inflammation. Leptin resistance in obesity is reflected in high concentrations of circulating leptin; and chronic elevation of circulating leptin is associated with CVD and MetS (Esteghamati et al., 2006). Conversely, adiponectin is known to play a protective role and not surprisingly circulating concentrations are known to be decreased in obesity, CVD and type 2 diabetes (Ukkola and Santaniemi, 2002).

Endothelial adhesion molecules are pro-inflammatory proteins that play a significant role in cellī cell/cellī matrix interactions. E-selectin, P-selectin, soluble vascular cell adhesion molecule-1 (sVCAM-1), and soluble intercellular adhesion molecule-1 (sICAM-1) are the major players of endothelial and leukocyte cell adhesion. These molecules maintain low concentrations in normal physiological conditions, but expressions can be enhanced when endothelium is activated due to various stimuli such as pro-inflammatory cytokines, ROS, and reactive nitrogen species. Increased circulating concentrations of these molecules present in obesity, as well as CVD and type 2 diabetes are used to evaluate disease risk (Blann et al., 2002).

Expression of inflammatory genes and the transcription factors that regulate their expression also serve as biomarkers of the inflammatory state. One such candidate is suppressor of cytokine signaling (SOCS), a family of proteins that are known to be induced by pro-

inflammatory cytokines and involved in the development of insulin resistance by inhibiting tyrosine kinase receptor signaling (Ueki et al., 2004). Similarly NF-əB activation and matrix metallo proteinase (MMP) expression are good indicators of inflammatory status in humans.

Leukocyte count is another indicator of inflammation and can be tested in a lab setting and is part of the regular battery of clinical tests. An increase in white blood cell count is a sign of inflammation and has been associated with heart disease independent of conventional risk factors (Weijenberg et al., 1996). However, it has recently been suggested that even within normal ranges leukocyte count can be an independent risk factor for developing coronary artery disease (CAD) and type 2 diabetes (Twig et al., 2012a; Twig et al., 2012b).

An important emerging area of nutrition research at present is to identify ófunctionalô foods, such as polyphenol-rich fruits and vegetables that can attenuate the increase in various inflammatory molecules and thereby reduce chronic disease risk. Clinical studies designed to investigate such potential may involve examination of changes in the abovementioned parameters subsequent to transient inflammatory challenges such as a high-fat high-carbohydrate meal, or long term intervention studies; favorable results of the former suggesting maintenance of balance and the latter indicating the resetting of homeostasis.

The clinical studies presented in this review were identified and selected based on the following online keyword search criteria: óberriesô (including names of specific berries), ófruitsô (including names of specific fruits), ópolyphenolsô, óanthocyaninsô, and óflavonoidsô, in association with the words óinflammationô, óhumansô, óclinical trialô, ólL-6ô, óTNF-Ŭô, óCRPô, óadhesion moleculesô, óchronic diseaseô, ócardiovascular diseaseô, ódiabetesô, and ópostprandialô

Studies that were published (including online-only publications) as of November 15th, 2012 have been included in the present review.

Postprandial Inflammation and the Effects of Fruit Polyphenols

The postprandial state is a dynamic period of metabolic trafficking, biosynthesis, and oxidative metabolism of absorbed substrate that requires compensatory and adaptive mechanisms to manage the short-term disturbance and restore homeostasis. In developed societies, most people eat a dietary mixture that promotes exaggerated and prolonged metabolic- and oxidative- and immune- imbalance several times a day. The consequence is chronic biological insult that over time supersedes biological defense and repair systems manifesting in cellular dysfunction and eventually chronic disease. Accordingly, a daily opportunity exists to maintain health or minimize disruptive processes that lead to chronic disease. Consumption of fruits rich in polyphenolic bioactives during these short-term dietary assaults resulting in increased inflammation has been studied in a limited number of human clinical interventions **(Table 3).** Eight of the 16 studies identified tested the effects of fruits on meal-induced inflammation (Edirisinghe et al., 2011; Ellis et al., 2011; Ghanim et al., 2010; Blanco-Colio et al., 2000; Williams et al., 2004; Huebbe et al., 2011; Lehtonen et al., 2010; Peluso et al., 2012); one study examined fruit supplementation on exercise-induced inflammation (McAnulty et al., 2011), and the remaining 6 studies examined fruit/fruit beverages alone (Deopurkar et al., 2010; Hijmering et al., 2007; Tousoulis et al., 2008; Kiviniemi et al., 2009; Kelishadi et al., 2011; Jin et al., 2011). Strawberries, orange juice, red and white wine, blueberries, grapes, blackcurrant juice, sea

buckthorn berries and pomegranate were tested over durations of approximately 1-9 hours post-consumption.

Strawberries are a widely consumed fruit and a rich source of polyphenols. The main polyphenolic compounds in strawberries are ellagic acid, ellagitannins and anthocyanins; the main anthocyanin present in strawberries is pelargonindin-3-glucoside and its major metabolite is pelargonidin-glucuronide, which peaks approximately 90 min to 2 h after strawberry consumption (Mullen et al., 2008). Ellagic acid present in strawberry metabolizes into urolithins, which have been shown *in vitro* to exert anti-inflammatory effects (Giménez-Bastida et al., 2012). Animal data have shown that polyphenolic compounds in strawberries are protective against the development of inflammatory CVD risk markers (Parelman et al., 2012). In the human context two recently published clinical trials demonstrated the ability of strawberries to offset detrimental metabolic consequences of a high-carbohydrate, moderately fat meal (Edirisinghe et al., 2011; Ellis et al., 2011). Edirisinghe et al. (2011) studied the acute postprandial effects of strawberries prepared in a beverage and consumed with a meal in twenty four overweight men and women. After a 7-day berry free, low polyphenolic run-in, subjects consumed a breakfast meal of approximately 960 kcals accompanied with either a milk-based beverage containing 10 g freeze-dried strawberry powder (providing 94.7 mg of total polyphenols) or an energy- and macronutrient- matched placebo beverage devoid of polyphenols (fiber and vitamin C differences were ~ 2 g and 8 mg respectively). Consuming the breakfast meal with the strawberry beverage attenuated meal-induced increases in specific inflammatory markers; there was a cumulative reduction in the concentrations of IL-6 and hs-CRP over the 6 hour postprandial time period. No changes were observed in circulating concentrations of TNF-

Ŭ IL-1ɓ or PAI-1. Within the same sample of subjects, postprandial evaluations of the breakfast meal (with the placebo beverage only) conducted at the end of a chronic (6 wk) intervention with the strawberry beverage compared to the placebo beverage showed a decrease in inflammatory and thrombolytic molecules [IL-1ɓ and plasminogen activator inhibitor-1 (PAI-1)] postprandially (Ellis et al., 2011). However, contrary to the results of their previous acute study there were no significant changes in either IL-6 or hs-CRP plasma concentrations as a result of 6 week strawberry supplementation compared to placebo; plasma TNF-Ŭalso remained unaffected by treatment. These data suggest that different mechanisms of action are at work related to inflammation and inflammation-associated CVD risk factors when strawberries are consumed with meals vs. in subjectsô usual diet (with unspecified times of intake, eg., with or without meals). Further studies of strawberry effects on postprandial inflammation are necessary to clarify and expand on these points of interest.

Similar to strawberries, blueberries are a rich source of anthocyanins, although with distinctive anthocyanin composition compared to strawberries (Del Rio et al., 2010). Blueberries are most well-known and touted for delivering potent dietary antioxidants; however, limited data are available about their potential anti-inflammatory effects in humans. In one study, McAnulty et al. (2011) supplemented well-trained athletes with 375 g of blueberries (n=13) within 1 hour prior to 2.5 hours of treadmill running. Exercise was used as the inflammatory challenge in this study. The control group received no blueberries (n=12). The acute study was an offshoot of a longer investigation on the chronic effects of blueberry supplementation (McAnulty et al., 2011). Subjects avoided specific foods rich in vitamins C and E during the 6 weeks chronic phase before the acute testing was conducted. One hour after the cessation of exercise, circulating pro-

inflammatory markers including total leukocyte count, IL-8, IL-6 and IL-1 receptor antagonist (ra) were measured. Results indicated no difference in these variables between the blueberry group and control groups. However, circulating concentrations of the anti-inflammatory molecule IL-10 was significantly increased in the blueberry group after exercise. Skeletal muscle NF-əB activity following exercise was not different between the 2 groups.

Oranges are a popular citrus fruit that contain the flavonoids naringenin and hesperidin. Although little is known about specific plasma metabolites of these 2 flavanones, available research indicates that hesperetin and naringenin glucuronides and sulfates are the major forms in circulation (Manach et al., 2003; Vallejo et al., 2010), which peak at approximately 4-8 hours post-ingestion of citrus fruits and fruit juices (Manach et al., 2005; Vallejo et al., 2010). Two recent studies demonstrated anti-inflammatory effects of orange juice (Deopurkar et al., 2010; Ghanim et al., 2010). Deopurkar et al. (2010) investigated the effects of 600 mL (300 kcal) of non-concentrate orange juice (alone) compared to caloric equivalents of glucose and cream on postprandial inflammatory responses in normal weight men and women. Plain water served as the control. NF-κB binding activity, protein level and mRNA expression of TLR-2 and -4, and mRNA expression of SOCS-3 were measured at baseline and after the intervention. Over the 5 hour postprandial testing period, glucose and cream induced an increase in NF-κB binding and expression of TNF-Ǔ, IL-1ƀ and SOCS-3, a protein associated with insulin resistance and induced by pro-inflammatory cytokines, in mononuclear cells (MNCs). Additionally, cream alone increased TLR-4 expression in MNCs as well as concentrations of lipopolysaccharide (LPS), which is a ligand of TLR-4. In contrast, there was no significant change in any of the pro-inflammatory markers as a result of orange juice or water intake. In a similar study, a 300 kcal

equivalent of non-concentrate orange juice consumed with a 900 kcal high-fat, high-carbohydrate meal attenuated the cumulative 5 hour postprandial increase in inflammatory markers compared to an equicaloric amount of glucose or plain water control (Ghanim et al., 2010). Specifically, the high-fat, high-carbohydrate meal with either plain water or glucose resulted in increased plasma concentrations of MMP-9 and endotoxin (LPS) as well as increased gene and/or mRNA expression products in MNCs of MMP-9, TLR-2 and TLR-4, and SOCS-3, whereas consumption of orange juice with the meal attenuated these increases. In addition, the generation of ROS was significantly lower with the addition of orange juice to the meal. These data suggest that drinking orange juice with meals may serve to minimize inflammatory responses brought about by certain meal compositions; although it is unclear the role of their inherent flavanones due to differences in their absorption profile and timing of reported anti-inflammatory effects in these studies.

Population studies have suggested that regular intake of red wine is beneficial in protecting against heart disease development (Renaud and Lorgeril, 1992). In particular, the association of red wine consumption with an improved antioxidant status has been suggested to explain the ôFrench paradoxô, i.e., the low incidence of CVD despite the intake of a high fat diet. Moreover, oxidative stress is closely tied to inflammation, suggesting that red wine components may offer additional anti-inflammatory benefits to protect against heart disease. Blanco-Colio and colleagues (2000), studied the effects of red wine on NF-əB expression in MNCs. Eight men and eight women were fed a high fat breakfast containing 602 kcals, of which 57% was comprised of fat calories. Using a crossover design, two doses of red wine were provided with the meal and postprandial blood samples were collected every 3 h for 9 hours. The 2 doses of

wine were designated as low and moderate: 12g/m^2 and 20g/m^2 for men, and 7.2 g/m^2 and 12 g/m^2 for women, respectively, which represent volumes ranging from approximately 1½ - 4½ glasses of wine, assuming average heights of 1.65 and 1.77 meters for women and men, respectively. An iso-caloric meal without wine served as the negative control and a meal with vodka served as a control for the alcohol to assess effects of the non-alcohol component of the red wine. Similar to the findings of others, the high-fat breakfast meal increased markers of inflammation. Specifically, NF-əB activation increased almost 3-fold in peripheral blood mononuclear cells (PBMCs) of subjects after the control meal starting at ~ 6 h and remained elevated until 9 h. Red wine but not vodka attenuated meal-induced activation of NF-əB, suggesting that the polyphenol component, rather than the alcohol, is responsible for the observed effects. Williams et al., (2004) investigated the protective effects of both red wine and white wine on selected inflammatory markers in males diagnosed with CAD. In a crossover design, 13 men consumed 2-3 glasses (4 mL/Kg body weight) red wine or white wine with a light meal; the meal provided 513 kcals as total energy and was low in antioxidants. Post-meal blood sampling was conducted for up to 6 hours. A non-alcoholic beverage was used as the control. Both red wine and white wine consumption resulted in a significant increase in plasma IL-6 concentrations compared to the control, with no changes in concentrations of sICAM-1 and sVCAM-1. Since IL-6 is considered to be both an anti-inflammatory as well as a pro-inflammatory molecule, the authors suggested that in the present context the increase in cytokine concentrations caused by the 2 wines may be reflective of an acute, protective effect against oxidative stress induced by the accompanying alcohol consumption. Hijmering et al. (2007) investigated the effects of binge drinking red wine to mimic effects of excess alcohol

consumption (> 5 units/day) on CVD risk. The authors were interested in determining whether the beneficial effects of the wine polyphenols would be maintained when consumed in excess amounts as is typical of the drinking habits of younger people. Binge drinking of alcohol has been associated with increased systemic inflammation and cardiovascular morbidity (Averina et al., 2006; de Lange et al., 2004). In a parallel design study, healthy male and female volunteers consumed, within 45 minutes, either 3 glasses of red wine (110 mL/glass, containing 11.4 g of alcohol/glass), or a beverage containing the same amount of alcohol, but low polyphenol content. CVD risk markers such as blood lipids, flow-mediated vasodilation (FMD) of brachial artery, and inflammatory molecules were measured following the binge drinking. The same cycle of binge drinking was repeated with the final blood samples and FMD measurements taken at the 180 min time point. Results showed no significant differences between treatment groups on either serum CRP or mannose binding lectin (an acute phase protein) concentrations (CRP increased slightly, but not significantly at 90 mins then returned to baseline values in both groups), indicating that contrary to previous studies, within the context of binge drinking red wine polyphenols do not offer any significant protection against inflammatory stress exerted by excess alcohol consumption. Similarly, Kiviniemi et al., (2009), studied the effects of a high dose of red wine (1.0 g/kg BW) consumed as a binge drink (within 1-2 hours) in 22 healthy male subjects. Effects of wine intake were compared to cognac (with matched alcohol content of 1.0 g/kg BW), and dealcoholized red wine equal in amount to the volume of the full red wine in a randomized crossover design. Red wine consumption significantly increased tissue (t) PAI-1 concentrations in circulation at the end of 2 hours when compared to baseline. There was no change in this parameter resultant of dealcoholized red wine or cognac intake. Interestingly, the

authors suggest that it may be some of the polyphenolic contents themselves of the full red wine that exert detrimental effects, since alcohol content was controlled for with the inclusion of cognac in the study design. Moreover, some of the polyphenols present in full red wine were no longer present in the dealcoholized red wine which was also used for comparison. There were no changes in any of the inflammatory markers (hs-CRP, adiponectin, MMP-9) or adhesion molecules (sVCAM-1, sICAM-1, sE-selectin) that were tested. Tousoulis et al., (2008) studied the acute effects of red wine and white wine compared to control and 2 other alcoholic beverages (beer and whiskey) in a sample population of healthy men and women (n=16-17 per group). Alcohol content of the beverages was equivalent to 30 g ethanol. Blood was sampled at baseline and at 1 hour and 4 hours after ingestion of the beverages. No changes were found in the inflammatory markers (IL-6, TNF-Ǔ, CRP, fibrinogen, PAI-1) that were tested. These data suggest that while moderate wine intake is associated with beneficial effects in humans, binge drinking of polyphenol-containing beverages may increase CVD risk factors.

A single acute study on grapes investigated the short-term effect of grape juice in humans. Kelishadi et al., (2011) supplemented purple grape juice (18 mg/Kg BW) in adolescents diagnosed with MetS. Blood was sampled at baseline and at 4 hours following juice intake. However, grape juice had no short-term effect on circulating concentrations of inflammatory markers (hs-CRP, IL-6) or adhesion molecules (sICAM-1, sVCAM-1, sE-selectin) in these subjects.

In addition to vitamin C, blackcurrants are a rich source of polyphenols, mainly anthocyanins. The dominant anthocyanins are cyanidin-3-O-glucoside, cyanidin-3-O-rutinoside,

delphinidin-3-O-glucoside, and delphinidin-3-O-rutinoside (Kapasakalidis et al., 2006), which are absorbed intact and metabolized with plasma concentrations peaking 1-2 h following ingestion (Matsumoto et al., 2001). Huebbe et al. (2011) recently investigated the postprandial effects of a blackcurrant-based juice in overweight, hyper-triglyceridemic men. In a single blind, crossover design, 11 men were asked to consume a high calorie meal containing 200 g of cream and 75 g of sucrose with either 250 g of the blackcurrant juice or a placebo beverage containing similar amounts of energy, sugars and fiber. The blackcurrant treatment beverage, which comprised purees of blackcurrant (15%), raspberry (9%) and cherry (7%) and red grape juice (39%), contained polyphenols (617 mg) and vitamin C (122.3 mg), whereas the placebo beverage contained negligible amounts of both. Postprandial blood sampling was conducted periodically up to 240 minutes. Circulating concentrations of the anthocyanin metabolite 1, 3, 5-trihydroxybenzene, but not the anthocyanins themselves, were increased postprandially between 130 and 150 min following the blackcurrant juice intake. No significant difference was found in circulating IL-6 concentrations between the two treatments; however, compared to baseline, consumption of blackcurrant-based beverage resulted in a significant increase in plasma IL-6 concentrations at the 240 minute time point. The authors concluded that the increase in IL-6 within an acute, postprandial setting may be a beneficial response for enhancing cellular glucose uptake and suppressing other pro-inflammatory cytokines that may interfere with insulin action. In addition, e*x vivo* stimulation of whole blood cultures with LPS showed that blackcurrant intake did not attenuate the production of TNF-Ŭand IL-1ɓ to the extent that was observed with the placebo and was not significantly different from baseline. Jin et al., (2011) studied the effect of a blackcurrant beverage (20% juice; containing 12.2 mg/100 mL and 8 mg/100 mL of

delphinidin and cyanidin, respectively) in healthy, normal weight men and women in a postprandial setting. Blood was sampled periodically after juice consumption for up to 8 hours. At the 3 hour time point a meal was provided. There was no difference in plasma concentrations of VCAM-1 and ICAM-1 as a result of ingesting the test juice and a placebo control. Authors suggest that the low concentration of juice used in this study with corresponding low amounts of polyphenols and vit C may explain the lack of an effect on the parameters tested.

Sea buckthorn berries are cultivated mainly in India, China and Eastern Europe and have traditionally been used in eastern medicine (Larmo et al., 2008). Sea buckthorn berries are rich in flavonol glycosides (isorhamnetin-3-rutinoside, -galactoside and -glucoside) and have been shown to favorably impact risk factors associated with CVD and diabetes, including oxidative and inflammatory stress (Mishra et al., 2008). In a crossover design study conducted by Lehtonen and colleagues (2010), healthy males (n=10) were fed a yogurt-based breakfast meal containing 50 g of glucose and 40 g of dried and crushed whole sea buckthorn berries corresponding to 200 g of fresh whole berries (containing 22.8 mg of flavonol glycosides per portion). The control meal did not contain berries. Subjects ate a meal the evening before the test day consisting of low polyphenol foods. Blood samples were collected prior to ingestion of the breakfast meal and postprandially at intervals of 30, 60 and 90 mins for 360 minutes. TNF-Ŭ concentrations were measured only at time points 0 and 60 min. The glucose-containing control meal slightly, but non-significantly increased TNF-Ŭ concentrations, whereas incorporation of the sea buckthorn berries in the yogurt meal resulted in a non-significant decrease in the cytokine compared to baseline (p=0.175). As suggested by the authors, the lack of a statistically significant effect may have been due to small sample size and high between-subject variability.

Moreover, measuring TNF-Ŭat additional time points, as well as other inflammatory biomarkers, may have been helpful in understanding postprandial inflammatory response profile in supplemented individuals.

Pomegranate is a fruit that has been used for its purported medicinal properties in some parts of the world. In recent years, the juice of this fruit has been widely touted as having one of the highest antioxidant capacities (Gil et al., 2000) with ellagitannins (mainly punicalagins) being the major polyphenol component. Kelishadi et al. (2011) examined the effects of pomegranate juice in adolescent boys and girls (12-15 years) with MetS. Subjects consumed 240 mL of pomegranate juice (not from concentrate) after a fasting baseline blood draw. Significant reductions in serum IL-6, sICAM-1 and sE-selectin were observed 4 hours after consumption of the pomegranate juice compared to baseline, but not in hs-CRP, and sVCAM-1 concentrations. No comparator was included in this study, but results support future work to better understand the utility of pomegranate juice in modifying inflammatory status of individuals characterized by low grade inflammation.

Peluso et al., (2012) studied the postprandial effects of a fruit juice drink comprised of water and 3 different fruit juices (40% pineapple, 18% blackcurrant, 5% plum) when consumed with a high-fat meal (55% fat). Fourteen men and women who were overweight but otherwise healthy were randomized to receive the fruit juice drink and a placebo drink in a crossover design. Circulating inflammatory markers, TNF-Ŭ, IL-6 and IL-17 were measured at baseline and at 30 min to 120 min intervals for up to 8 hours. The high fat diet induced postprandial increase

in plasma IL-17 concentrations which were significantly attenuated at 4 hours and 8 hours with fruit juice intake compared with the placebo drink.

Taken together, the results of these clinical interventions support the concept that polyphenol-containing fruits and fruit beverages modulate different markers of inflammation in humans. In the postprandial setting where meals reflecting compositions of Western eating patterns are stimulating inflammatory responses, red wine, strawberry and orange attenuated these responses, suggesting a relative stabilization of inflammatory-associated system responses. While all studies concluded beneficial effects, anti-inflammatory responses were not necessarily similar (i.e. differential effects on IL-6). Additionally, timing of responses differed; some occurring relatively sooner in the postprandial period (Deopurkar et al., 2010; Ghanim et al., 2010), while others later (Edirisinghe et al., 2011; Ellis et al., 2011; Blanco-colio et al., 2000). The prospect of minimizing inflammatory burden with polyphenol rich fruits/ plant foods on a day to day basis has yet to be fully described and linked to long-term clinical outcomes. However, evidence is accumulating that emphasizes the importance of the postprandial state in CVD and other metabolic disorders (type 2 diabetes, MetS), suggesting that this is an area for greater attention. Borrowing approaches from the pharmaceutical industry, understanding the pharmacokinetic-pharmacodynamic relationship of different fruit polyphenols may be incumbent on scientists to investigate and funding agencies to support if the health promoting effects of dietary polyphenols are to be elucidated.

Inflammation and Chronic Effects of Fruit Polyphenols

The number of studies investigating the anti-inflammatory effects of long term consumption of polyphenol-rich fruits in humans is relatively limited compared to the vast amounts of evidence from *in vitro* and *in vivo* animal studies. However, there are still far more chronic feeding studies compared to acute single exposure human studies. The studies examined in this section of the review include 16 interventions with berries (Basu et al., 2009, 2010; Zunino et al., 2011; Ellis et al., 2011; Basu et al., 2010; Stull et al., 2011; McAnulty et al., 2011; Riso et al., 2012; Ruel et al., 2008, 2009; Basu et al., 2011; Dohadwala et al., 2011; Karlsen et al., 2010; Lehtonen et al., 2011; Eccleston et al., 2002; Larmo et al., 2008), 8 interventions with red wine (Badia et al., 2004; Estruch et al., 2004; Hansen et al., 2005; Avellone et al., 2006; Sacanella et al., 2007; Vázquez-Agell et al., 2007; Blanco-Colio et al., 2007; Chiva-Blanch et al., 2012), and a total of 10 interventions with grapes, apples, and other fruit (Zern et al., 2005; Castilla et al., 2006, 2008; Kelishadi et al., 2011; Barona et al., 2012; Puglisi et al., 2008; Buscemi et al., 2012; Auclair et al., 2010; Chai et al., 2012; Udani et al., 2011). In addition, the subject groups studied represent different body mass categories, and range from healthy to at-risk and diseased populations. Relevant details of the clinical trials are presented in **Table 4.**

Strawberries, one of Americaôs most popular fruits, are the subject of 5 human chronic feedings studies. In these investigations, subjects who were overweight (Ellis et al., 2011), obese (Zunino et al., 2012) or who had MetS (Basu et al 2009, 2010), conditions that coincide with low-grade inflammation, were studied for 3-6 weeks to determine if daily intake of strawberries would improve fasting indices of inflammation. In an initial study by Basu and colleagues (2009), women with the MetS (n=16) consumed 50 g/day of a freeze dried strawberry powder (equivalent to ~ 500 g of fresh fruit) daily for 4 weeks. Fasting blood samples were collected

before and at the end of the intervention period. While beneficial effects on blood lipids were reported, there was no significant change in fasting concentrations of hs-CRP or adiponectin as a result of chronic strawberry intake in this population. A subsequent intervention was conducted by the same group in which the same freeze dried strawberry powder was supplemented for 8 weeks. In this study, 27 men and women with MetS consumed 50 g of the freeze dried strawberry powder (equivalent to 500 g of fresh fruit) in a water-based beverage daily. An equal amount of plain water was used as the control. At the end of the 8 week intervention period, subjects had 18% lower concentrations of sVCAM-1, but not sICAM-1, compared to controls. Circulating adhesion molecule concentrations are increased in MetS and higher concentrations are associated with CVD, suggesting that strawberry supplementation may confer a protective effect against exacerbation of risk markers in this population. Ellis et al. (2011) reported that supplementation of freeze dried strawberry powder for 6 weeks in overweight men and women resulted in significantly lower inflammatory markers; however the effect was only evident after a meal challenge. Twenty four subjects consumed 10 g/day of freeze dried strawberry powder (equivalent to ~100 g of fresh fruit) for 6 weeks in the form of a milk-based beverage in a single blinded, placebo controlled, parallel design clinical trial. Compared to consuming the placebo beverage for 6 weeks, strawberry beverage consumption daily resulted in lower cumulative postprandial concentrations of IL-1ϐ, and IL-6 concentrations tended to be lower (p=0.06) after a high fat, high carbohydrate meal challenge; however, no differences were observed in postprandial TNF-Ŭ or hs-CRP concentrations. Additionally, PAI-1 was significantly reduced after the meal challenge when subjects were consuming the strawberry beverages in their usual diets for 6 weeks compared to placebo. In contrast, no significant differences were observed in

fasting plasma concentrations of inflammatory markers following strawberry supplementation compared to placebo. It had been suggested that the lack of effect on fasting parameters at the end of the 6 weeks supplementation may be due to the lower dose (10 g vs. 50 g) used in previous studies. Additionally, the strawberry beverage contained milk, which may have influenced polyphenol bioavailability resulting in lower daily exposure than otherwise expected with the 10 g dose prepared in water alone (Le Bourvellec and Renard, 2012).

Similarly, Zunino et al. (2011) evaluated the effects of freeze dried strawberry powder (equivalent to a daily dose of 320 g frozen fruit) in 20 obese, but otherwise healthy subjects who were supplemented for 3 weeks in a diet-controlled, double-blinded, crossover study. The strawberry powder was supplemented through selected food matrices (yoghurt, cream cheese and smoothie), and corresponding foods without strawberry were used as controls. Circulating concentrations of hs-CRP, Complement C3, serum amyloid A, fibrinogen, IL-1β, IL-6, IL-8, TNF-α, leptin, sICAM-1, sVCAM-1 were measured at baseline and at the end of the supplementation periods. However, in contrast to the results of previous studies, there was no significant effect on inflammatory markers as a result of supplementation. Specifically, except for a slight, but within normal-range increase in plasma fibrinogen, no changes were observed in the concentrations of various inflammatory markers, including hs-CRP, IL-6, TNF-α and cell adhesion molecules previously reported to be modulated by strawberries intake. The discrepancy in results compared to the abovementioned studies with strawberries may be explained by the shorter duration of supplementation, as well as the lack of an appropriate washout period between the control and active treatment phases, despite being diet-controlled as opposed to the free living conditions used in the other studies. Overall, these human studies suggest that

strawberries have potential to alleviate inflammatory risk markers implicated in the etiology of CVD and diabetes. However, research to define the optimal dose, duration and delivery format is necessary to elicit meaningful physiological benefits of strawberry consumption.

Chronic human studies on blueberries and inflammation have been reported in 4 recent publications (Basu et al., 2010; Stull et al., 2011; McAnulty et al., 2011; Riso et al., 2012). A considerable amount of animal and *in vitro* data indicates that blueberries consumption may have a beneficial impact on various CVD risk factors, including inflammatory status. Basu et al. (2010) conducted a single blinded, parallel arm study in which 48 men and women with MetS consumed 50 g of freeze dried blueberry powder (equivalent to 350 g of the fresh fruit) in the form of a water-based beverage. The intervention lasted for 8 weeks, with the daily dose divided into 2 beverages/day. Compared to the plain water control, there were no significant changes in plasma hs-CRP, IL-6, adiponectin or adhesion molecules (sICAM-1 and sVCAM-1) as a result of blueberries supplementation. Similarly, no anti-inflammatory effect of blueberries intake was observed in a double-blinded, parallel arm, placebo controlled study of 32 obese, insulin resistant individuals (Stull et al., 2010). For 6 weeks, the sample population consumed a daily dose of 45 g freeze dried blueberry powder (equivalent to approximately 2 cups of fresh blueberries) in the form of yogurt plus milk-based smoothies, with relevant biomarkers (hs-CRP, TNF-Ŭ, MCP-1) assessed at the beginning and end of the intervention period. There was no significant change in the circulating concentrations of hs-CRP, TNF-Ŭ or MCP-1 when compared to control. Similar results were observed by McAnulty et al., (2011) where supplementation of trained athletes for 6 weeks with 250 g/day of blueberries did not affect inflammatory markers (IL-1ra, IL-6, IL-8 and IL-10) compared to control. However, blueberries increased natural killer (NK) cell counts in the

supplemented group. NK cells are a family of immune cells that have been shown to aid in natural cytotoxicity such as involved in the death of cancer cells (Brittenden et al., 1996). Six week supplementation with a wild blueberry drink (25 g freeze dried powder/day; providing 375 mg anthocyanins) in men with at least one CVD risk factor did not result in changes in inflammatory (IL-6, TNF-Ű, hs-CRP) or adhesion molecule (sVCAM-1) concentrations when compared to a polyphenol-free placebo drink (Riso et al., 2012). These 4 studies with blueberries demonstrating a lack of effect on pro-inflammatory markers are interesting and warrant further investigation to understand whether this is a real effect, possibly due to anthocyanin or other polyphenol composition differences (compared to strawberries for example) or an artifact of the methodology, such as doses used, delivery or study duration. Establishment of dose response in the short-term and absorption kinetics and interaction with food matrix may be an important next step before continuing forward in long-term feeding studies assessing inflammation endpoints with blueberry.

Cranberries are commonly consumed as juice, and are most well-known for the prevention of urinary tract infections (Howell, 2007). Cranberries have high antioxidant capacity due to their high content of flavonoids, including anthocyanins and pro-anthocyanidins, and ellagic acid (Basu et al., 2010). Furthermore, *in vitro* data suggest that cranberries possess specific anti-inflammatory activity in addition to scientific evidence that this fruit is able to modulate CVD risk factors (Neto, 2007). Four human studies have been published in recent years showing mixed results on selected health markers, with data from only one group (Ruel et al., 2008; Ruel et al., 2009) indicating that cranberries consumption has an impact on inflammatory status. Specifically, 30 male subjects with abdominal obesity (Ó90 cm) consumed

3 doses (125 ml, 250 ml and 500 ml/day) of low-calorie cranberry juice during 3 consecutive periods (lasting 4 weeks each), in increasing order of dosage. At the end of the intervention period, which concluded with the 500 ml of juice, both sVCAM-1 and sICAM-1 (Ruel et al., 2008) and MMP-9 (Ruel et al., 2009) concentrations in plasma were significantly lower compared to baseline. No change was observed in plasma E-selectin concentrations. In a study with MetS subjects, cranberry juice supplemented for 8 weeks at a dose of 480 mL/day had no effect on plasma hs-CRP or IL-6 (Basu et al., 2011). In keeping with these studies showing limited to no effect of cranberry supplementation on measures of inflammation, Dohadwala et al. (2011) reported that a double strength cranberry juice also supplemented at 480 mL/day to patients with coronary heart disease (CHD) did not exert significant anti-inflammatory properties (hs-CRP and sICAM-1). In this study, 44 subjects consumed daily either cranberry juice or an identical beverage devoid of polyphenols for 4 weeks in a crossover study design. At the end of the supplementation periods, no differences were observed in circulating concentrations of hs-CRP or sICAM-1 between the cranberry and placebo juice treatments. The inconsistency in results from these studies may be due to a variety of reasons, including differences in the study population, dose, or duration of supplementation. The studies by Ruel et al. (2008), the only clinical trials demonstrating a beneficial effect on inflammation markers, used a dose escalation study design. Therefore, cumulative effects or adequate adaption time may have contributed to the beneficial findings. A limitation of the study however, was the lack of a control arm and monitoring background food intake; both of which would have greatly strengthened the interpretation of the study results and conclusions about the effectiveness of the cranberry juice.

Similar to the acute studies of wine supplementation, results of chronic studies have indicated favorable anti-inflammatory effects of wine. In 2004, Badia and colleagues reported the effects of a daily dose of red wine (from merlot grapes, containing 624 mg anthocyanins/L, and 2.93 g tannins/L) consumed with dinner in a group of healthy men in a randomized, single blinded crossover trial. The dose of the test beverage was equivalent to alcohol consumption of 30 g alcohol/day. An alcohol-matched volume of gin was selected as the control beverage due to its non-detectable polyphenol content. Adhesion molecule [very late activation antigen-4 (VLA-4), lymphocyte function-associated antigen 1 (LFA-1), macrophage-1 antigen (Mac-1)] and MCP-1 expression on monocyte surface was determined at baseline and at the end of 28 days of supplementation. At the end of the intervention period, the expression of VLA-4 on monocyte surface was significantly reduced (by 18%) compared to baseline. This effect was not observed with gin intake. In addition, red wine intake attenuated monocyte adhesion to TNF-Ŭstimulated endothelial cells in culture compared to gin. Using the same study design, the research group also reported the effects of 2 glasses of red wine (320 mL; 30 g/d of ethanol) compared with gin (100 mL) in healthy men (n=40) (Estruch et al., 2004). Compared to baseline, reduction in various circulating concentrations of inflammatory (hs-CRP, fibrinogen, IL-1Ŭ) and adhesion molecules (sVCAM-1, sICAM-1) were observed at the end of the intervention. No change was observed in the concentrations of E-selectin, TNF-Ŭ and MCP-1. In addition, red wine intake elicited a reduction in surface expression of VLA-4 in both monocytes and lymphocytes, and reduction of LFA-1, Mac-1, and MCP-1 expression in monocytes. Hansen et al. (2005) compared red wine (300 mL; 38.3 g alcohol and 200 mL; 25.5 g alcohol for men and women, respectively) with a polyphenol-free placebo as well as a full-dose and half-dose of a fermented

red grape extract matched to the red wine for polyphenol content. In a parallel design study, healthy subjects consumed one of the 4 treatment beverages for 4 weeks. Red wine supplementation reduced plasma fibrinogen concentrations compared to the full-dose grape extract. No effect was observed on fibrinogen with the red grape extracts at either dose. In fact the full dose of the extract increased fibrinogen concentrations, suggesting that alcohol may be contributing to the anti-inflammatory effect of red wine. Avellone et al. (2006) supplemented the diets of 48 healthy men and women who were normally non-drinkers or rare-drinkers (< 250 ml/week) with 2 different Sicilian red wines. Subjects drank 250 ml of red wine during meals for 4 weeks (n=24 per wine tested). No wine or occasional wine consumption for 4 weeks in the same subjects served as the control phase. Wine intake resulted in lower hs-CRP and fibrinogen concentrations. Sacanella et al., (2007) reported the effects of red wine and white wine intervention (200 mL/day; 20 g of ethanol) in healthy women (n=35) for a period of 4 weeks in a crossover design. Red wine significantly lowered hs-CRP, IL-6, sICAM-1, sVCAM-1, E-selectin, P-selectin and CD40 ligand concentrations in circulation compared to baseline values. Similar anti-inflammatory effects were observed with white wine; intake lowered hs-CRP, IL-6, sICAM-1, and CD40 ligand concentrations. White wine also lowered sVCAM-1 concentrations. In addition, red wine lowered PBMC membrane expression of adhesion molecules VLA-4, MCP-1, Mac-1, and CD40, whereas white wine reduced VLA-4 and Syalil-Lewis (SLe^x). Both wines also reduced monocyte adhesion to TNF-Ŭ-stimulated cells, with red wine showing a greater lowering effect compared to white wine. Vázquez-Agell et al., (2007) studied the effect of wine with moderate polyphenol content (compared to previous studies which used polyphenol-rich wines). For 4 weeks, 20 healthy men received 30g/day of ethanol as either

Chardonnay cava (a sparkling red wine, 300 mL/day) or gin (100 mL/day) in a crossover design. Monocyte and lymphocyte surface expression of adhesion molecules LFA-1, VLA-4, SLe^x and CD40 were decreased with wine intake compared to gin. Circulating concentrations of MCP-1, ICAM-1, CD40 ligand (L) were decreased with wine compared to gin; change from baseline to endpoint, wine also reduced plasma concentrations of CD40L, VCAM-1, hs-CRP, IL-6, P-selectin, E-selectin, ICAM-1 and MCP-1. Blanco-Colio and colleagues (2007) supplemented 8 men and 8 women with 4 different ethanol-containing beverages (16 g ethanol/m^2), including red wine, in a crossover design. No ethanol served as the control. The beverages were consumed separately with a fat-enriched diet (44 % fat) for a period of 5 days each. Red wine significantly lowered plasma MCP-1 compared to baseline, and NF-əB activation in PBMC compared to control at day 5. Chiva-Blanch et al., (2012a) studied the effects of red wine supplementation in men with a high risk phenotype for developing artery disease based on either diagnosed type 2 diabetes or the presence of 3 or more CVD risk factors such as smoking, obesity and elevated plasma LDL-C concentrations. Following a 2 week run-in period in which subjects abstained from all alcoholic beverages, subjects were randomized to a 3-phase, 4-week supplementation crossover to test the effects of red wine (272 mL/day; equivalent to 30 g ethanol) compared to de-alcoholized red wine and a polyphenol-free alcoholic beverage (gin). The expression of adhesion molecules (VLA-4, LFA-1, Syalil-Lewis X (Sle^x), CD40, CD36, CCR2) on PBMCs, and serum concentrations of inflammatory and adhesion molecules (TNF-Ǔ, hs-CRP, IL-1Ǔ, IL-10, IL-16, IL-18, IL-6, MCP-1 and -2, ICAM-1, VCAM-1, E-selectin, macrophage derived chemokine (MDC), macrophage inflammatory protein (MIP)-1Ǔ, myeloid progenitor inhibitory factor 1, CD40 antigen and CD40L) were measured before and at the end of clinical intervention.

Four weeks of supplementation with red wine and dealcoholized red wine resulted in lower serum ICAM-1 and IL-6 compared to gin. Compared to baseline, serum MCP-1 and VCAM-1 were lower after all three treatments suggesting that both the polyphenolic and alcoholic components of red wine contribute towards its anti-inflammatory effect. The effects of wine supplementation on circulating adiponectin and leptin were published separately (Chiva-Blanch, et al., 2012b) showing no effect of treatment on these parameters. Overall, the results from these studies show a favorable impact on inflammatory status with relatively moderate wine intake.

Studies in animals and *in vitro* have shown that grape polyphenols may offer cardio-protective benefit by their ability to reduce oxidative stress, and particularly of markers that promote inflammation in vessel walls, such as oxidized-LDL (Yamakoshi et al., 1999; Fuhrman et al., 2005; Shafiee et al., 2003). Zern et al. (2005) conducted a single blind, placebo controlled, crossover clinical intervention with a lyophilized grape powder in 24 pre- and 20 post-menopausal women for 4 weeks. The 36 g/day dose of grape powder was equivalent to ~200 g of fresh grapes and provided 5.8 mg/kg of total phenols. At the end of the 4 week intervention period, plasma concentrations of TNF-Ŭ in both pre- and post-menopausal women were significantly lower after grape powder supplementation compared to placebo. However, there were no changes in either hs-CRP or IL-6. Similarly, in a sample of hemodialysis patients, Castilla et al. (2006) showed that daily supplementation with 100 mL of red grape juice concentrate reduced serum MCP-1 concentrations by approximately 50% after the 3-week intervention period. However, there was no change in the concentrations of measured adhesion molecules (VCAM-1, ICAM-1), complement C3 or hs-CRP. The same group subsequently examined the effects of red grape juice concentrate, vitamin E or the combination (red grape

juice and vitamin E) compared to control on lipids, inflammation and oxidation endpoints in hemodialysis patients (Castilla et al 2008). In a shorter duration study than the previous study (2 weeks vs 3 weeks), combination therapy synergistically lowered MCP-1 concentrations and significantly improved adhesion molecule status. Serum MCP-1 concentrations are consistently elevated in hemodialysis patients; increasing their risk for atherosclerosis. These data exemplify the potential clinical utility of polyphenol rich juices and even combination therapy with traditional antioxidants to lower CVD risk profile of populations at increased risk due to concomitant disease. In another relatively complicated population with elevated risk for CHD (adolescents diagnosed with MetS), Kelishadi et al., (2011) supplemented purple grape juice in adolescents diagnosed with MetS. The amount of juice consumed was 18 mL/day/Kg BW for a period of one month. Compared to baseline, daily grape juice intake resulted in significantly lower sE-selectin and IL-6 concentrations, but not sICAM-1, sVCAM-1 or hs-CRP. Similarly, in adults with MetS the intake of a grape polyphenol powder (from blue-black, red and green California grapes; equivalent to 2 servings/day of fresh grapes) for 30 days resulted in a reduction in sICAM-1 (but not sVCAM-1) concentrations compared to a sensory- and macronutrient-matched placebo (Barona et al., 2012). Raisins are essentially dehydrated grapes, suggesting that they too may impart anti-inflammatory effects. In a study of 12 men and women, 1 cup of raisins/day for 6 weeks significantly lowered plasma TNF-Ŭand sICAM-1 compared to their starting baseline concentrations, while MCP-1 was marginally decreased (p=0.078) and IL-8, tPAI-1 and sE-selectin were not impacted (Puglisi et al., 2008). The processing of grapes into raisins causes a loss in polyphenolic content (Loaiza et al., 2001); however, raisins are relatively polyphenolic-dense compared to grapes, due to the concentration of the fruitôs contents in the

dehydrated form. Therefore, losses in polyphenols from processing can be corrected relatively easily by consuming a higher amount of raisins, assuming changes in composition donôt also occur with grape-to-raisin processing.

The effects of orange juice have been evaluated in several short-term/acute studies, but only one study was found investigating the effects of orange juice consumed over a longer time frame, 7 days (Buscemi et al., 2012). In a placebo-controlled crossover study, 19 non-diabetic individuals who were at high risk for developing CVD drank 500 mL/day of an orange juice beverage which consisted of a blend of 3 different red orange varieties. Compared to starting baseline concentrations, consuming the orange juice blend for 7 days resulted in significant decreases in hs-CRP, IL-6 and TNF-Ŭconcentrations in the blood. The data are interesting and support findings after single serving interventions, but are limited due to the lack of control group.

Apples are the most commonly consumed fruit in America along with oranges and bananas (Murphy et al., 2012). Apples are a rich source of polyphenols, the main compound being quercetin (Boyer and Liu, 2004). Two clinical trials with opposing results have recently been reported (Auclair et al., 2010; Chai et al., 2012). Auclair et al. (2010) studied men with hypercholesterolemia supplemented with 40 g/day of either polyphenol-rich or polyphenol-poor apples (freeze dried powder) in a crossover design for 4 weeks each. Polyphenol-rich apple supplementation did not impact circulating CRP concentrations. In another study, post-menopausal women were randomized to receive for 1 year either 75 g of dried apple or 100 g of dried plum, which served as the comparative control. Fasting blood samples were collected at

baseline, 3, 6 and 12 months. Compared to baseline, a non-significant reduction in plasma CRP concentrations was observed after apple intake at both the 6 month (22% reduction) and the 12 month (32% reduction) evaluations (Chai et al., 2012); however, significant reductions in CRP were observed after plum intake. Since the dried plum was the comparator arm in the apple study, the amount of dried plum (100 g) was chosen to match the energy and macronutrient content of the 75 g dried apple dose. At the 3 month evaluation, circulating CRP concentrations were significantly lower with dried plum compared to dried apple supplementation. The concentrations of CRP remained constant from 3 months until 12 months, which was the end of the intervention. Collectively, the data suggest limited anti-inflammatory effects of apples and potentially favorable effects with dried plum supplementation. With both fruits, available data on this topic were inadequate to make conclusions, suggesting the need for future studies to confirm the effects observed with dried plum and explore further into potential effects of apples in healthy and at-risk populations.

In addition to the commonly consumed apples, oranges, berries and a few other fruits, there has been a recent surge in the marketing and consumption of lesser known berries such as Acai berry, bilberry, and sea buckthorn berry. Much of the interest has been generated from *in vitro* studies demonstrating their potent antioxidant properties (Schauss et al., 2006; Svobodová et al., 2008; Varshneya et al., 2012). There are, however, a few studies which have specifically investigated the effect of supplementation of these berries in humans, with a focus on their ability to impact diet-related inflammatory stress. Udani et al. (2011) conducted an open label pilot study in 10 overweight men and women in which the participants consumed 200 g/day of Açai berry puree in the form of a water-based smoothie for 4 weeks. The daily dose provided 3.5

mg/mL total phenols. Açai berry is a native South American fruit which has a high antioxidant potential due its high content of anthocyanins, particularly cyanidin (Del Pozo-Insfran et al., 2004). However, in this study there was no significant change in plasma hs-CRP concentrations in the studied population as a result of Açai intake. To date, there have been no further reports on Açai berry supplementation in humans, and therefore further studies are required to determine the value of these berries on inflammatory status. Bilberries, also known as European blueberries, are rich sources of polyphenols, with anthocyanins (mainly delphinidin, cyanidin, malvidin) comprising approximately half to 3/4 of the total polyphenol content (Määttä-Riihinen et al., 2004). As is the case with other berries, *in vitro* and animal data indicate that bilberries may be protective against CVD risk factors. Karlsen et al. (2010) conducted a parallel arm intervention in subjects who had an at-risk for CVD-phenotype based on the presence of at least one CVD risk factor such as cigarette smoking, hypertension and elevated LDL-cholesterol concentrations. Sixty two subjects consumed either 330 mL of bilberry juice or an equal amount of plain water daily. The intervention lasted for 4 weeks. Several plasma inflammatory markers [(IL-1ϐ, IL-1 Ra, IL-2, IL-2r, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-15, IL-17, TNF-ϑ, IFN-ɔ, granulocyte-macrophage colony-stimulating factor (GM-CSF), MIP-1ϑ and -1ϐ, interferon gamma-induced protein 10 (IP-10), monokine induced by interferon-gamma (MIG), eotaxin, regulated and normal T cell expressed and secreted (RANTES), MCP-1] were measured in a subset of the subject population; although hs-CRP was measured in all subjects. The authors reported a significant increase in plasma concentrations of quercetin and *p*-coumaric acid at the end of the intervention period in subjects randomized to the bilberry juice. In addition, there was a decrease in circulating IL-6, hs-CRP and MIG, compared to control. However, the bilberry

juice resulted in an increase in TNF-Ŭ which was unexpected since TNF-Ŭ stimulates increased production and secretion of IL-6 and CRP, both of which were reduced. In contrast, when whole frozen bilberries were supplemented to overweight and obese women for 33-35 days, there was a decrease in plasma TNF-Ŭ concentration (Lehtonen et al., 2011). Specifically, a randomized crossover clinical study was conducted wherein subjects (n=110) consumed an amount of frozen bilberries equivalent to approximately 100 g of fresh berries. Bilberries supplementation resulted in a decrease in plasma TNF-Ŭ, sVCAM-I and adiponectin, but did not elicit change in hs-CRP, IL-6 or sICAM-1 concentrations. A decrease in circulating adiponectin concentration is considered unfavorable. The authors suggest that the lower adiponectin concentration may have been due to insufficient observation time necessary to detect changes; adiponectin in circulation is known to respond relatively slowly to factors which modulate its circulating concentrations (Arita et al., 1999).

In addition to the short-term, postprandial investigations on sea buckthorn berries reported earlier in this review, three chronic supplementation studies on these polyphenol-rich berries have been published. Eccleston et al. (2002) studied the effect of 300 mL of a sea buckthorn berry juice (containing 1182 mg/L of flavonoids) in healthy males compared to a sensory-matched placebo drink. There was no change in sICAM-1 concentrations in plasma after 8 weeks of supplementation, which may have been due to the small sample size (n=10/group) or lower concentration of polyphenols in the test beverage compared to supra-physiological doses used in *in vitro* studies as suggested by the authors. More recently two interventions with whole sea buckthorn berries have been reported (Larmo et al., 2008; Lehtonen et al., 2011). Healthy men and women (n=233) were randomized to either a frozen sea buckthorn berry puree

(containing approximately 8.4 mg of flavonols) or a placebo for 90 days (Larmo et al, 2008). A daily dose of 28 g of the berries resulted in significantly lower serum hs-CRP concentrations. In another feeding study, the diet of 110 overweight and obese women was supplemented with air-dried whole sea buckthorn berries (~100 g fresh) for approximately 35 days (Lehtonen et al., 2011). Circulating TNF-Ŭ, hs-CRP, IL-6, sVCAM-I, adiponectin, and sICAM-1 concentrations were measured before and at the end of the intervention. Supplementation with the berries resulted in lower TNF-Ŭ concentrations in the plasma, but no change was observed in hs-CRP concentrations.

Pomegranate fruit juice has a high antioxidant capacity and has been demonstrated to reduce selected inflammatory and adhesion molecule biomarkers in an acute setting (Kelishadi et al., 2011). Two long-term pomegranate supplementation studies have been recently published. Kelishadi et al. (2011) studied 1 month supplementation of a non-concentrate pomegranate juice in adolescent boys and girls (12-15 years) diagnosed with metabolic syndrome. Subjects consumed 240 mL of pomegranate juice/day for a period of one month, at the beginning and end of which plasma concentrations of hs-CRP, IL-6, sE-selectin, sICAM-1 and sVCAM-1 were measured. At the end of the intervention period circulating concentrations IL-6, sICAM-1 and sE-selectin were significantly lower compared to baseline values. Shema-Didi et al. (2012) investigated the effect of ingesting 100 g of pomegranate juice during the 1st hour of dialysis in chronic hemodialysis patients for 1 year. Chronic kidney disease patients have increased inflammatory status which is exacerbated during the dialysis procedure. At the end of the 1 year supplementation period (at 3 drinks/week), there was a significant decrease in serum

concentrations of albumin, fibrinogen, TNF-Ŭand IL-6 when compared to hemodialysis patients who consumed a taste- and color-matched placebo beverage.

The evidence for the anti-inflammatory impact of fruits and berries in the long term in humans is encouraging; approximately two thirds of the studies reviewed support the purported ability of berries, fruits and their derived products to confer properties that favorably modify inflammatory status, suggesting protective effects from chronic disease. The clinical trials demonstrating these effects used traditional crossover or parallel study designs with varying populations, duration, delivery mode and dose of supplementation. While much has been learned, several questions remain in order to provide specific dietary recommendations, including optimal dose, delivery mode, timing and frequency of intake in different populations. Nonetheless, the data provide compelling evidence in support of regular consumption of fruits and berries and their products; however, further investigations are required to clarify, confirm, and optimize benefits.

Conclusions

The main focus of polyphenol-rich fruits in relation to health has been on their anti-oxidative activity, since many of the commonly occurring chronic diseases have an etiology based on disturbances in redox status. Recent investigations into the amelioration of these diseases have shed light on the process of inflammation, specifically an increase in inflammatory stress, as a major contributor to the development of chronic diseases. Two major facets have been

considered: inflammatory status in the fasting state and, perhaps the more significant, postprandial state.

A critical evaluation of the studies presented in this review shows that dietary polyphenols from fruits are effective in ameliorating inflammatory stress using a variety of different study designs in humans. Beneficial effects have been observed in both free living and diet-controlled studies. Most studies included a polyphenol-free run-in period to exclude potential additive effects of other polyphenol sources in the diet. An exciting aspect of the observed findings is that intake of fruit polyphenols has a significant effect on inflammatory stress shortly after consumption, highlighting the importance of encouraging intake of polyphenol-rich foods at every opportunity.

The clinical interventions that reported significant changes in inflammatory chronic diseases and particularly CVD risk factor outcomes provide the following general information: on a short-term basis, intake of strawberries, oranges, red wine and mixed fruit drinks provided protection against meal-induced increases in CVD risk via reduction of inflammatory and adhesion molecules in circulation and, at the molecular level, in immune cells. Populations that may benefit from supplementation include both normal weight and overweight men and women, as well as people with MetS, as indicated by the populations studied. Effective doses were approximately 250-600 mL of juice, 10 g of freeze dried strawberry powder (~110 g fresh fruit), and 1.5-4 glasses of red wine.

Long-term interventions of polyphenol-rich fruits and fruit products revealed that moderate wine consumption of approximately 200-300 mL/day, for a period of about 4 weeks

lowers both inflammatory and adhesion molecules in healthy and in at-risk-for-CVD populations. With respect to berries, supplementation studies ranging from 4-12 weeks elicited favorable responses in inflammatory and adhesion molecule markers in circulation. Studies showed that berries were effective in people who were generally healthy, but also in overweight and obese populations that were at risk for CVD, or exhibited features of the MetS. Effective doses were shown using fresh fruit, freeze-dried fruit powder, or juiced products consumed daily ranging in serving sizes from approximately 25-100 g of fresh or frozen berries (bilberry, sea buckthorn berry) to 50 g of freeze dried fruit (strawberry, ~ 500 g fresh weight), or 200-500 mL of bilberry and cranberry juice. Other fruits such as grapes, pomegranates and red oranges also showed reductions in disease risk markers of inflammation in healthy, at-risk and diseased populations after 1-3 weeks daily supplementation of grape or red orange juice (ranging from 100-500 mL), 4 weeks and 1 year intake of pomegranate juice (240 mL/day and 300 mL/week respectively), or 4 week supplementation of 36-46 g lyophilized grape powder (~ 180-230 g fresh weight). Overall, multiple fruit preparations have been shown to be effective in exerting beneficial effects on inflammatory biomarkers in men and women with healthy to varied CV-disease risk characteristics.

While these data are encouraging, a few practical points need to be considered, each relating to portion size of the effective doses shown to date. One concern is related to fresh fruit portion size. Some of the freeze-dried fruit powder doses used for testing translates to large fresh fruit portions (up to 500 g fresh fruit), which may not be achievable on a regular basis outside of the lab setting. Likewise, some of the large portions and beverage volumes studied could result in excess energy and specifically simple carbohydrate energy intake, which may be of concern for

weight management and other health outcomes, such as glucose and lipid metabolism in susceptible populations. While no reports indicated a significant increase in body weight, dietary counseling to help subjects maintain body weight was employed in many of the investigations. Others utilized low calorie/sugar options (Ruel et al., 2008, 2009) along with dietary monitoring to minimize issues with excess energy or sugar intake; nevertheless, a small weight loss was reported (Ruel et al., 2006). In the case of wine, excess energy intake and alcohol consumption above current U.S. guidance recommendations for people who drink alcohol (1 and 2 servings of alcohol for women and men, respectively) requires some level of attention. Overall, the data presented in this review are compelling and warrant continued investigation in this area to address questions and issues that remain. Future research should include determining the maximal effective doses/portion sizes of fruits/fruit-derived products on inflammation-associated outcomes with minimal to no adverse effects in a ñrealò life setting. Likewise, research to understand optimal delivery methods, timing of intake (consumption patterns) and polyphenols absorption patterns relative to benefits and minimal side effects would provide critical information for dietary guidance development or updating. Additionally, there are many opportunities for engagement of the food industry that would support success in this area. Regular consumption of fruits and their products long-term to achieve and maintain health will require the aforementioned knowledge along with a selection of products that meet consumer demands on price, convenience, taste and validated health benefits.

In conclusion, chronic disease development and progression is the result of long-term imbalances of oxidative and inflammatory stress leading to tissue dysfunction, damage and ultimately failure. The diet has a critical role in the contribution to and the prevention of chronic

disease through these mechanisms. Plant derived polyphenolic compounds are well known for their antioxidant properties and recent evidence indicates these compounds confer anti-inflammatory and/or inflammatory response stabilizing activities. The results of this review provide persuasive evidence that dietary polyphenols from some fruits and their products are effective in ameliorating inflammatory stress in the short- and long- term. Discrepancies in results between studies that showed beneficial effects and those that failed to do so are likely due to differences in study designs including dosage, duration, metabolic status of subjects, different ethnicities/countries with different food habits, food matrix, and methods used to monitor compliance. Overall, future research is warranted to clarify and optimize fruit-derived benefits on inflammatory endpoints. Combined with current knowledge, the results from future work will aid in the development of clear and meaningful intake recommendations that people can adopt for a life time of health benefits.

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Table 1- Major food flavonoids and their dietary sources

Flavonoid subcategory	Food flavonoids	Dietary sources
Flavan-3-ols	Catechin, Epicatechin, Gallocatechin, Epigallocatechin, Proanthocyanidins	Green tea, black tea, red grapes, red wine, cocoa
Flavanones	Naringenin, Hesperetin, Tangeritin	Citrus fruits
Flavones	Luteolin, Apigenin	Herbs, spices
Isoflavones	Genistein, Daidzein	Soybeans, soy-based foods
Flavonols	Kaempferol, Quercetin, Myrecitin	Ubiquitous in plant foods
Anthocyanidins	Pelargonidin, Cyanidin, Delphinidin	Red, blue and purple fruits and berries

Table 2- Inflammatory biomarkers in humans

Biomarker	Method	Tissue	Normal levels	Concentrations in disease and/or obesity	Reference
Acute phase proteins					
hs-CRP	ELISA, nephelometry, immuno-turbidimetry	Plasma/serum	1-3 mg/L	> 3 mg/L, (CVD, DM)	Ridker PM, (2003)
Fibrinogen	ELISA	Plasma (citrated)	150-400 mg/dL	> 400 mg/dL (arterial thrombosis)	Kratz A, (2004); Muszbek L, (2008)
Serum amyloid A	ELISA, nephelometry	Serum	~ 8-10 µg/mL	> 10 µg/mL (obesity, CVD risk)	Yang RZ, (2006)
Cytokines					
IL-6	ELISA	Plasma/serum	~ 1 pg/mL	> 5 pg/mL	DôAuria L, (1997); Roytblat L, (2000)

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IL-1ϐ	ELISA	Plasma/serum	~ 10 pg/mL	~ 20 pg/mL	Bremer AA, (2011)
TNF-Ŭ	ELISA	Plasma/serum	~ 1 pg/mL	~ 2-4 pg/mL	Illan-Gomez F, (2012); Dandona P, (1998)
MCP-1	ELISA	Plasma/serum	< 2 ng/mL, ~ 150 pg/mL	~ 3-4 ng/mL (sepsis); ~ 200-400 pg/mL (DM, CVD)	Bossink AW, (1995); Herder C, (2006); Harsimran K, (2009)
Adipokines					
Adiponectin	RIA, western blot	Plasma/serum	~ 15-17 mg/L	~ 5 mg/L (obese)	Fernández-Real JM, (2005); Illan-Gomez F, (2012)
Leptin	ELISA	Plasma/serum	~ 5ng/mL	~ 32 ng/mL	Corica F, (1999)
Adhesion molecules					

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sVCAM-1	ELISA	Plasma/serum	~ 1000 ng/mL	~ 2000 ng/mL, (obesity, atherogenesis)	Papayianni A, (2002)
sICAM-1	ELISA	Plasma/serum	~ 200 ng/mL	~ 500 ng/mL (atherogenesis, DM, obesity, hemodyalisis)	Papayianni A, (2002)
sE-selectin	ELISA	Plasma/serum	~ 30 ng/mL	~ 100 ng/mL (DM, obesity)	Pontiroli AE, (2004)
PAI-1	ELISA	Plasma/serum	~ 15ng/mL	~ 30 ng/mL (MetS, asthma)	You T, (2008)
Other					
Lp-PLA2	ELISA	Plasma/serum	~ 80 µg/L (obese)	~ 140 µg/L (obese with NAFLD)	Colak Y, (2012)
MMP-9	ELISA/zymography	Serum, monocytes	~ 250 ng/mL	~350 ng/mL (with HFHC intake)	Ghanim H, (2009)

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SOCS-3	Western blot	Monocytes		ŷ 50 % (with HFHC intake)	Ghanim H, (2009)
TLR-2, 4	Western blot/flow cytometry/ELISA	Monocytes		ŷ 30 % (with HFHC intake)	Ghanim H, (2009)
NF-əB activation	Electrophoretic mobility shift assay	Monocytes		ŷ 70 % (with HFHC intake)	Ghanim H, (2009)
OX-LDL (pro-inflammatory molecule)	ELISA	Plasma/serum	50-60 U/L	Ó80 U/L	Hulthe J, (2002); Weinbrenner T, (2006)
iNOS	Immuno-cytochemistry	Macrophages, neutrophils	10%	~ 30 %	Depalo A, (2008)
Leukocyte count	Complete blood count	Whole blood	3.5-10.5 billion cells/L	11-17 billion cells/L	Rogers K, (2011)

CVD-cardiovascular disease; DM-diabetes mellitus; HFHC-high fat high and high carbohydrate; hs-CRP-high sensitivity-C reactive protein; IL-interleukin; iNOS-inducible nitric oxide synthase; Lp-PLA2-lipoprotein-associated phospholipase A2; MCP-monocyte chemoattractant protein; MetS-metabolic syndrome; MMP-matrix metallo proteinase; NAFLD-non-alcoholic fatty liver disease; NF-əB-nuclear factor kappa B; OX-LDL-oxidized-low density lipoprotein; PAI-1-plasminogen activator

inhibitor-1; sICAM1-soluble intercellular cell adhesion molecule-1; SOCS-3-suppressor of cytokine signaling-3; sVCAM1-soluble vascular cell adhesion molecule-1; TNF-Ŭ-tumor necrosis factor-alpha; TLR-toll like receptor

Table 3- Acute studies of fruit polyphenols supplementation in humans

Fruit	Design	N[a]	Subjects	Delivery	Dose	Total phenols[b]	Biomarkers in circulation and immune cells[c,d]	Reference
Strawberry	Crossover, 2-phase, PC	24	Overweight, MF	Freeze dried powder in milk beverage with MF-HC meal	10 g	94.7 mg	↓ **IL-6, hs-CRP**	Edirisinghe I, (2011)
Strawberry	Parallel, 2-arm, PC post-6 wk-intervention[e]	24	Overweight, MF	Freeze dried powder in milk beverage with MF-HC meal			↓ **PAI-1, IL-1β**	Ellis C, (2011)
Blueberry	Parallel, 2-arm, C	25	Trained athletes, MF	Whole berries prior to exercise	375 g	NA	↑ **IL-10**	McAnulty LS, (2011)

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Orange	Parallel, 4 arm, PC, CC	12	Normal weight, MF	Juice	600 ml	NA	↓ **SOCS3, TLR-4, TNF-α, IL-1β, NF-κB binding**	Deopurkar R, (2010)
Orange	Parallel, 3-arm, PC, CC	10	Normal weight, MF	Juice with HF-HC meal	600 ml	NA	↓ **TLR-2, TLR-4, SOCS3, MMP-9**	Ghanim H, (2010)
Red wine	Crossover, 4-phase, C, PC	16/11	Healthy, MF	High dose and low dose with HF meal	20 g, 12 g (M); 12 g, 7.2 g (F)	NA	↓ **NF-κB activation**	Blanco-Colio LM, (2000)
Red wine	Crossover, 2-phase, PC	13	CAD, M	With light meal	4 ml/kg BW	1170 mg/L	↑ **IL-6**	Williams MJA, (2004)
Red wine	Parallel, 2-arm, PC	10	Normal weight, MF	Binge drink (in 45 min)	660 ml	NA	ź	Hijmering ML, (2007)
Red wine	Parallel,	16/17	Healthy,	Beverage	264 ml	NA	ź	Tousoulis D,

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	5-arm, C, CC		MF					(2008)
Red wine	Crossover,	22	Healthy,	Binge drink	810 ml	NA	ŷ **t PAI-1**	Kiviniemi
	3-phase, CC		M					TO, (2009)
White wine	Crossover,	13	CAD,	With light meal	4 ml/kg	210 mg/L	↑ **IL-6**	Williams
	2-phase, PC		M		BW			MJA, (2004)
White wine	Parallel,	16/17	Healthy,		264 ml	NA	ź	Tousoulis D,
	5-arm, C, CC		MF					(2008)
Grape	Parallel,	30	MetS	Juice	18 mL/kg	NA	↔	Kelishadi R,
	2-arm, BC		adolescents,		BW			(2011)
			MF					
Blackcurran	Crossover,	11	Overweight,	Beverage with	250 g	617 mg	↔	Huebbe P,
t based-juice	2-phase, PC		hypertriglycerid	HF-HC meal				(2011)
			emic, M					
Blackcurran	Crossover,	20	Healthy,	20% juice	250 ml	NA	↔	Jin Y,
t juice	2-phase, PC		MF					(2011)
Sea	Crossover,	10	Normal weight,	Dried and	40 g	NA	↔	Lehtonen

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buckthorn berry	2-phase, PC		M	ground; with yogurt-based meal				HM, (2010)
Pomegranate	Parallel, 2-arm, BC	30	MetS adolescents, MF	Juice	240 mL	NA	↓ **sICAM-1, sE-selectin, IL-6**	Kelishadi R, (2011)
Fruit juice drink	Crossover, 2-phase, PC	14	Overweight, MF	Juice with HF meal	500 mL	5.6 mM	↓ **IL-17**	Peluso I, (2012)

[a] Number represents ónô group in parallel design studies; [b] As reported in referenced articles, using different methods (HPLC, LC-MS/MS, Spectrophotometry, Folin Ciocalteu method) and units of expression; [c] Only biomarkers that showed statistically significant change have been specified; [d] Gene expression in mononuclear cells; [e] Postprandial test meal did not include strawberry beverage

BC-baseline controlled; BW-body weight; C-controlled; CAD-coronary artery disease; CC-comparative controlled; F-female; HC-high carbohydrate; HF-high fat; hs-CRP-high sensitivity-C reactive protein; IL-interleukin; M-male; MetS-metabolic syndrome; MF-moderate fat; MMP-matrix metallo proteinase; NA-not available; NF-əB-nuclear factor kappa B; PAI-1-

plasminogen activator inhibitor-1; PC-placebo controlled; sICAM1-soluble intercellular cell adhesion molecule-1; SOCS3-suppressor of cytokine signaling-3; TLR-4-Toll-like receptor-4; tPAI-1-tissue plasminogen activator inhibitor-1

Table 4- Chronic studies of fruit polyphenols supplementation in humans

Fruit	Design	Duration (wk)[a]	N[b]	Subjects	Delivery	Dose/day	Total phenols[c]	Biomarkers in circulation and immune cells[d, e]	Referen
Strawberry	Parallel, 1-arm, BC	4	16	MetS, F	Freeze dried powder; Water-based beverage	50 g	2006 mg	↔	Basu A, (2009)
Strawberry	Parallel, 2-arm, C	8	10/15	MetS, MF	Freeze dried powder; Water-based beverage	50 g	2006 mg	↓ **sVCAM-1**	Basu A, (2010)
Strawberry	Crossover, 2-arm, PC	3	20	Obese, MF	Freeze dried powder; Mixed into foods	å 320 g frozen berries	NA	↔	Zunino S (2011)
Strawberry	Crossover, 2-arm, PC	6	22-24	Overweight, MF	Freeze dried powder; Milk-based beverage	10 g	94.7 mg	ź	Ellis CL (2011)
Blueberry	Parallel, 2-arm, C	8	23/25	MetS, MF	Freeze dried powder; Water-based beverage	50 g	1624 mg	↔	Basu A, (2010)

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Blueberry	Parallel, 2-arm, PC	6	17/15	Insulin resistant, MF	Freeze dried powder; Yogurt-based smoothie	45 g	1462 mg	↔	Stull A, (2011)
Blueberry	Parallel, 2-arm, C	6	25	Trained athletes, MF	Whole berries	250 g	NA	↑ **NK cells**	McAnul LS, (2011)
Wild blueberry	Crossover, 2-arm, PC	6	18	CVD at risk, M	Freeze dried powder; Water-based beverage	25 g	NA	↔	Riso P, (2012)
Cranberry	Dose escalation, 3-phase, PC	12	30	Abdominal obesity, M	Juice cocktail	125, 250, 500 ml	100 mg /125ml	↓ **sICAM-1, sVCAM-1**	Ruel G, (2008)
Cranberry	Dose escalation, 3-phase, PC	12	30	Abdominal obesity, M	Juice cocktail	125, 250, 500 ml	100 mg /125ml	↓ **MMP-9**	Ruel G, (2009)
Cranberry	Parallel, 2-arm, PC	8	16/15	MetS, MF	Low-energy juice	480 ml	458 mg	↔	Basu A, (2011)

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Cranberry	Crossover, 2-phase, PC	4	44	CHD, MF	Double-strength juice	480 ml	835 mg	↔	Dohadw MM, (2011)
Red wine	Crossover, 2-phase, CC, BC	4	8	Healthy, M	Beverage	320 ml	NA	↓ **VLA-4[e], monocyte adhesion**	Badia E, (2004)
Red wine	Crossover, 2-phase, CC, BC	4	40	Healthy, M	Beverage	320 ml	NA	↓ **hs-CRP, fibrinogen, sVCAM-1, sICAM-1, IL-1α, VLA-4[e], LFA-1[e], Mac-1[e], MCP-1[e]**	Estruch (2004)
Red wine	Parallel,	4	15/17/	Healthy,	Beverage	300 ml-M;	840 mg-M;	↓ **fibrinogen**	Hansen

	4-arm, CC, PC		18/19	MF		200 ml-F	560 mg-F		(2005)
Red wine	Crossover, 2-phase, C	4	48	MF	Beverage	250 ml	NA	**↓ fibrinogen, hs-CRP**	Avellon (2006)
Red wine	Crossover, 2-phase, CC	4	35	Healthy, F	Beverage	200 ml	1945 mg/L	**↓ hs-CRP, IL-6, sICAM-1, sVCAM-1, sE-selectin, CD40L, monocyte adhesion**	Sacanell (2007)
Sparkling red wine	Crossover, 2-phase, CC, BC	4	20	Healthy, M	Beverage	300 ml	202 mg/L	**↓ VLA-4[e], LFA-1[e], CD40[e], VCAM-1,**	Vázquez Agell M (2007)

								hs-CRP, IL-6, sP-selectin, sE-selectin, ICAM-1, MCP-1	
Red wine	Crossover, 5-phase, C, CC	5 days	16	Normal weight, MF	With high-fat meal	16 g/m^2	NA	**↓ NF-κB activation[e], MCP-1**	Blanco-Colio LM (2007)
Red wine	Crossover, 3-phase, PC, CC	4	67	CAD, at risk, M	Beverage	272 mL	2933 mEqGA/L	**↓ ICAM-1, IL-6, MCP-1, sVCAM-1**	Chiva-Blanch G (2012)
White wine	Crossover, 2-phase, CC	4	35	Healthy, F	Beverage	200 ml	308 mg/L	**↓ hs-CRP, IL-6, sICAM-1, CD40L**	Sacanell (2007)

Grape	Crossover, 2-phase, PC	4	44	Pre and post MP, F	Lyophilized powder; Beverage with water	36 g	5.8 g/kg	↓ **TNF-α**	Zern TL (2005)
Grape	Parallel, 1-arm, BC	3	10	Hemodialysis, MF	Red Grape Juice concentrate	100 ml	0.64 g	↓ **MCP-1**	Castilla (2006)
Grape	Parallel, 4-arm, C	2	8	Hemodialysis, MF	Red Grape Juice concentrate + vit. E	100 ml	0.64 g	↓ **MCP-1**	Castilla (2008)
Grape	Parallel, 2-arm, BC	4	30	MetS adolescents, MF	Juice	18 mL/kg	NA	↓ **sE-selectin, IL-6**	Kelishad (2011)
Grape	Crossover, 2-phase, PC	30 days	24	MetS, M	Freeze dried grape preparation	46 g	5800 mg/kg	↓ **sICAM-1**	Barona J (2012)
Raisin	Parallel, 1-arm, BC	6	12	Obese, MF	Raisins	1 cup	NA	↓ **TNF-α, sICAM-1**	Puglisi M (2008)

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Red orange	Crossover, 2-phase, PC	1	19[f]	CVD at risk, MF	Juice	500 ml	419 mg/L	↓ **hs-CRP, IL-6, TNF-α**	Buscem (2012)
Apple	Crossover, 2-arm, PC	4	30	Hypercholesterolemic, M	Freeze-dried powder; Water-based beverage	40 g	1.43 g/d	↔	Auclair (2010)
Apple	Parallel, 2-arm, CC	1 year	45/55	Post-menopausal, F	Dried fruit	75g	NA	↔	Chai SC (2012)
Plum	Parallel, 2-arm, CC	1 year	55/45	Post-menopausal, F	Dried fruit	100 g	NA	↓ **CRP**	Chai SC (2012)
Acai berry	Parallel, 1-arm, BC	4	10	Overweight, MF	Puree; Smoothie with water	200 g	3.5 mg /mL of puree	↔	Udani JI (2011)
Bilberry	Parallel, 2-arm, C	4	31	CVD at risk, MF	Juice	330 ml	NA	↓ **IL-6, hs-CRP, IL-15, MIG,**	Karlsen (2010)

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								↑ TNF-α	
Bilberry	Crossover, 2-phase, BC[g]	33-35 days	110	Overweight and obese, F	Frozen, whole	å 100 g fresh berries	NA	**↓ TNF-α, sVCAM-1, adiponectin**	Lehtone HM, (20
Sea buckthorn berry	Parallel, 2-arm, PC	8	10	Healthy, M	Juice	300 mL	NA	↔	Eccleston (2002)
Sea buckthorn berry	Parallel, 2-arm, PC	90 days	90	Healthy, MF	Frozen puree	28 g	NA	**↓ hs-CRP**	Larmo P (2008)
Sea buckthorn berry	Crossover, 2-phase, BC[g]	33-35 days	110	Overweight and obese, F	Air dried, whole	å 100 g fresh berries	NA	**↓ TNF-α**	Lehtone HM, (20
Pomegranate	Parallel, 2-arm, BC	4	30	MetS adolescents, MF	Juice	240 mL	NA	**↓ sICAM-1, sE-selectin, IL-6**	Kelishad (2011)

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Pomegranate	Parallel, 2-arm, PC	1 year	101	Hemodialysis patients, MF	Juice	100 mL 3X/week	0.7mmol /100 ml	**↓ IL-6, TNF-α, fibrinogen**	Shema-I L, (2012

[a] Duration in weeks, unless otherwise specified; [b] Number represents ónõgroup in parallel design studies; [c] As reported in referenced articles, using different methods (HPLC, LC-MS/MS, Spectrophotometry, Folin Ciocalteu method) and units of expression; [d] Only biomarkers that showed statistically significant change have been specified; [e] Gene expression in PBMC; [f] Included healthy, non-obese controls (n=12); [g] Pre- and post-intervention washout periods were used as control

BC-baseline controlled; C-controlled; CAD-coronary artery disease; CC-comparative controlled; CD40L-CD40 ligand; CHD-coronary heart disease; DM-diabetes mellitus; F-female; GA-gallic acid; hs-CRP-high sensitivity-C reactive protein; IL-interleukin; LFA-1-lymphocyte function-associated antigen 1; M-male; MCP-monocyte chemoattractant protein; MetS-metabolic syndrome; MIG-monokine induced by IFN-ɔ; MP-menopausal; NA-not available; NF-əB-nuclear factor kappa B; PC-placebo controlled; sICAM1-soluble intercellular cell adhesion molecule-1; sVCAM1-soluble vascular cell adhesion molecule-1; TNF-Ŭ-tumor necrosis factor-alpha; VLA-4-very late activation antigen-4