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Minireview

Potential benefits of green tea polyphenol EGCG in the prevention and treatment of vascular inflammation in rheumatoid arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic inflammatory disease of the joints in which systemic overproduction of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) may accelerate cardiovascular (CV) complications. Synovial inflammation in RA spreads systemically and transforms silently into chronic inflammation manifested by increased cytokine release and abnormally high levels of acute reactive proteins (ARPs) such as C-reactive protein (CRP), suggesting inflammation as a connecting link between RA and CV dysfunction. While the treatment to improve CV function in RA patients is being validated, it is timely to propose and test two-pronged therapies that ameliorate arthritis concomitant to improving CV functions. In this review, we summarized the pre-clinical and clinical studies validating the cardiovascular and anti-rheumatic activities of epigallocatechin-3 gallate (EGCG), a potent anti-inflammatory molecule found in green tea. The review also draws many parallels that have emerged between the paradigm of cytokine-driven inflammation in the pathogenesis of RA and its CV complications. Finally, based on extensive clinical evidence of the 'synovial inflammation–systemic inflammation' link and the benefits of EGCG in regulating these two pathologies via common driving factors, authors put forward an argument that EGCG may be tested for its potential CV benefit along with anti-rheumatic activity in animal models of human RA.

Contents

Introduction

Inflammation is thought to be a major aspect of the response of the immune system to injury. The most evident physical signs of inflammation are redness, swelling, pain and heat. These symptoms are associated with increased blood flow, metabolism, vasodilatation, release of intracellular mediators, fluid leakage, and cellular influx (Ferrero-Miliani et al., 2007). Normally, the body can control this self-maintenance. Disease states develop when the constraints on inflammation are weakened, leading to chronic discomfort. The onset of inflammation occurs by the proliferation of innate immune system cells. During an acute inflammatory response, neutrophils and macrophages are primarily stimulated. In contrast, T lymphocytes and plasma cells

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are the primary propagators in chronic inflammation (Ferrero-Miliani et al., 2007). One major example of a chronic inflammatory disease is atherosclerosis, which is characterized by chronic arterial inflammation affected by immune cells including macrophages, T lymphocytes and mast cells.

Lipid-loaded cells are a significant component in early atherosclerosis. These cells form when macrophages engulf lipids lining the inner vascular membrane, creating foam cells as the basis of atherosclerotic lesions. Three lipoproteins present in lesions and considered risk factors for atherosclerosis when high in the blood include low density lipoprotein (LDL), very low density lipoproteins (VLDL) and lipoprotein (a) (LPa). Chemical modification and consequent reactions may occur as these lipids are susceptible along the vessel epithelia. T lymphocytes migrating around macrophages and foam cells also play an important role in lesion formation (Fan and Watanabe, 2003).

Inflammation as a driver of atherosclerosis and rheumatoid arthritis

While atherosclerosis was viewed for many years as a lipid-based disorder, affecting the arteries, it is now well established that inflammatory pathways play crucial roles in the development of cardiovascular diseases (CVD) in the general population. Indeed, various immune cell types are established contributors to the atherosclerotic process, including macrophages, T lymphocytes and mast cells. Cytokines involved in the disease, such as interleukin (IL)-1β, tumor necrosis factor-α (TNF-α) and IL-6, resemble immune system effector cells that eliminate foreign invaders and damage host cells (Chen et al., 2010; Hayashi et al., 2010). These cytokines promote chemokine production, which subsequently allows for monocyte recruitment (Hayashi et al., 2010). Almost all of the major types of cells that play a role in host defense have been found in either human or animal plaques (Chen et al., 2010).

Rheumatoid arthritis (RA) is another chronic inflammatory disease that affects primarily peripheral joints and contributes to significant morbidity and mortality, joint inflammation and destruction (Kaplan, 2009; Metsios et al., 2010; Semerano et al., 2011). Enhanced synovial angiogenesis is a hallmark in RA. Many pro-inflammatory cytokines, including TNF-α, IL-6, IL-1 and IL-17, are pro-angiogenic markers found elevated in RA. The CXC subfamily of chemokines, such as IL-8, express a specific amino acid sequence (ELR) that makes them pro-angiogenic, while CXC cytokines without this motif, for example, platelet factor 4 (PF4), are angiostatic. Chemokines of the subfamily CC have been shown to be either pro-angiogenic, like MCP-1 and CCL2, or angiostatic, such as CCL21 (Semerano et al., 2011). The inflammatory pathways that result in both RA and atherosclerosis involve many similar or overlapping characteristics as well, including TNF-α and IL-6. Further, these pro-inflammatory cytokines are involved in systemic inflammation associated with vascular damage (Metsios et al., 2010) (Fig. 1). Indeed, RA patients have a significantly enhanced risk of developing atherosclerotic CVD.

Treatment of atherosclerosis

Drug therapy commonly used for atherosclerosis includes fibrates and statins. Fibrates such as bezafibrate, clofibrate, ciprofibrate, fenofibrate and gemfibrozil are examples of fibrates that target nuclear peroxisome proliferator-activated receptors (PPAR), transcription factors that seem to be active participants in lipid and fatty acid metabolism. Fibrates, as well as thiazolidinediones, are effective in treating atherosclerosis, vascular inflammation, and lipid and glucose metabolism as PPAR ligands. Lowered triglyceride levels, increased cellular fatty acid uptake and oxidation, decreased fatty acid production, increased LDL catabolism, increased HDL levels and functioning, increased anti-inflammatory activity and inhibition of vascular monocyte and macrophage movement are among the intended beneficial effects of fibrates (Alagona, 2010). Statins are inhibitors of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, a key enzyme in the body's synthesis of cholesterol (Hoffman et al., 2012). Statins also decrease LDL levels and

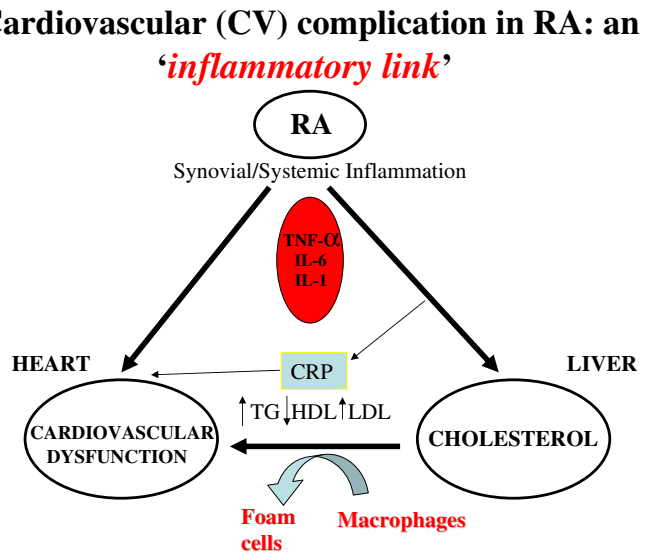

Fig. 1. Schematic diagram showing the overall mechanism of the transition of synovial inflammation to systemic inflammation that causes CV dysfunction in RA.

increase the amounts of apolipoprotein A-1 (ApoA-1) and HDL. ApoA-1 binds free plasma cholesterol and phospholipids in a process that ultimately leads to HDL formation.

Currently, many drugs are available for reducing inflammatory reactions, but these therapeutics have limitations. Nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase (COX)-2 selective inhibitors are commonly prescribed for pain and inflammation relief but could possibly promote CV complications. Several studies have noted the occurrence of acute myocardial infarction (MI) and ischemic stroke in RA or osteoarthritis (OA) patients who have taken NSAIDs or COX-2 selective inhibitors. Indeed, the COX-2 selective inhibitor rofecoxib was taken off the market in 2004 due to its increased risk for thromboembolic activity (Roth, 2012). NSAIDs have also been linked to gastrointestinal irritation and bleeding (Pirotta, 2010). Another shortcoming of these anti-inflammatory drugs may be the interference with tissue and bone healing following fractures due to their inhibitory effects on COX enzymes and subsequent prevention of prostaglandin (PG) production. PGs control osteoclast and osteoblast actions in the bone healing process (Xian and Zhou, 2009).

Complementary and alternative approaches

Another emerging approach to treat inflammation is the use of complementary and alternative medicine (CAM). This broad category includes over-the-counter drugs, vitamins and minerals, supplements, ointments, yoga and chiropractics (Callahan et al., 2009). Natural compounds found in plants have shown potential use for the treatment of inflammation (Khanna et al., 2007). In this regard, recent studies have not only analyzed the mechanisms of action, but have also characterized the active ingredient(s) key to their beneficial effects. Turmeric, an ancient Asian perennial rhizome rich in curcumin, is known for its anti-inflammatory effects through inhibition of NF-κB activation (Aggarwal and Shishodia, 2004). Resveratrol, a polyphenol in red wine, grapes and other fruits has been shown to exhibit antioxidant activity via the inhibition of IL-1β and nitric oxide (NO)-induced apoptosis in human chondrocytes (Takayama et al., 2009). Extracts from the Chinese herb *Tripterygium wilfordii* Hook F (TWHF) have shown anti-inflammatory and anti-arthritic effects in RA patients (Goldbach-Mansky et al., 2009). Triptolide is an active compound derived from TWHF extracts that acts through inhibition of IL-2 in lymphocytes by transcriptional deactivation of NF-κB (Kusunoki et al., 2004). In addition, triptolide limits vascular endothelial growth factor

expression and inhibits PGE_2 production in RA synovial fibroblasts, promoting apoptosis of the synovial tissue (Kusunoki et al., 2004). *Withania somnifera*, or ginseng, is an ancient Indian herb often formulated into supplements. Its leaves and roots are used for anti-inflammatory therapy. Some withanolides, which are components of the herb, inhibit NF-κB activation by interfering with its gene regulation and signaling pathway (Ichikawa et al., 2006).

Green tea EGCG for the treatment of inflammation

Among natural compounds of particular interest, (−)-epigallocatechin-3-gallate (EGCG) has gained significant attention in the past decade for its health benefits (Singh et al., 2011). EGCG is a major catechin present in green tea that is prepared from dried leaves of the plants *Camellia sinensis* and *Camellia assamica*, which are members of the Theaceae family (Weinreb et al., 2009). Studies have proven that the majority of beneficial effects attained through drinking green tea are attributed to the high content of EGCG, among other flavonoid-containing catechins (Wu et al., 2012). Therapeutic benefits from green tea consumption have been seen in neurodegenerative diseases, inflammatory diseases, cardiovascular diseases and several types of cancer (Clement, 2009; Khan et al., 2006).

EGCG has demonstrated its anti-inflammatory effects in numerous studies related to the pathological conditions wherein inflammation is a core driving factor. In-Bae Kim et al. found that EGCG was effective in preventing IL-8 production in airway epithelial cells, limiting the degree of respiratory inflammation. IL-8 stimulates the recruitment of neutrophils and can promote the presence of reactive oxygen species (ROS). EGCG also acts as an antioxidant by reducing IκB phosphorylation to block IL-1β-induced NF-κB activation (Kim et al., 2006). In a neuroprotection study, Orhan Aktas et al. demonstrated the ameliorative effects of EGCG on inflammation in experimental autoimmune encephalomyelitis (EAE), an animal model for the neurodegenerative disease, multiple sclerosis (MS). The therapeutic efficacy of EGCG was attributed to the inhibition of $CD4^+$ T cell production increase in the intracellular amounts of IκB-α and the prevention of ROS formation in neurons (Aktas et al., 2004). Yan Tang et al. showed that EGCG blocked $P2X_4$-receptor-mediated pro-inflammatory gene expression by IFN-γ in vascular endothelial cells via down-regulation of the $JAK_{1/2}$ tyrosine kinase pathway (Tang et al., 2008). These studies underline the ability of EGCG to distinctly target certain key signaling molecules to alleviate the downstream events associated with autoimmune diseases.

Despite the recent understanding of the in-vivo effects of EGCG, the extensive in vitro research has shown significant promise for the use of EGCG in the treatment of RA. In vitro studies have shown that EGCG has differential modulatory effects on cartilage, bone and synovial fibroblast activity (Ahmed, 2010). In the cartilage, EGCG has been found to inhibit IL-1β-induced inducible NOS (iNOS) and COX-2 expression via the inhibition of phosphorylation and proteasomal degradation of IκBα (Ahmed et al., 2002; Singh et al., 2002). EGCG also inhibits IL-1β-induced phosphorylation of c-Jun, thereby preventing activation protein-1 (AP-1) from binding to the DNA (Singh et al., 2003). A recent study by Akhtar and Haqqi analyzing the downstream effects of the inhibition of IL-1β found that when IL-1β is inhibited, IL-6, IL-8 and TNF-α are down regulated as well, due to the inhibition of NF-κB (Akhtar and Haqqi, 2011). These proteins are major components to the inflammatory response. These findings support an earlier study which suggested that the prophylactic consumption of green tea may be beneficial in ameliorating inflammation and reducing cartilage destruction associated with different forms of arthritis (Adcocks et al., 2002). Our studies in this direction laid foundation for successful testing of EGCG or green tea extract in animal models of OA and RA (Meki et al., 2009; Shen et al., 2012). However, further studies are required in this direction to determine potential interactions that EGCG, when consumed as a pure compound or in the form of green tea extract as dietary supplement, may have with current treatment modalities for RA and OA.

In relation to the bone biology, EGCG is credited with reducing the amount of osteoclast formation through the reduction of osteoblast differentiation (Kamon et al., 2010). EGCG blocks receptor activator of nuclear factor kappa-B ligand (RANKL)-mediated activation of c-Jun-N-terminal kinase (JNK) and NF-κB pathways to suppress expression of the transcription factor NFATc1, which is required for osteoclast differentiation (Lee et al., 2010). A study done in collagen induced arthritis rats showed that through the regulation of the B cell-activating factor belonging to the TNF family (BAFF)/PI3K/AKT/mTOR pathway, EGCG was able to cause the induction of apoptosis in B lymphocytes as well (Liu et al., 2012). In RA, synovial fibroblasts are resistant to apoptosis because of multiple factors including the constitutively active survival proteins like AKT and NF-κB and the over-expression of anti-apoptotic proteins such as Mcl-1 and Bcl-2. Treatment with EGCG has been shown to selectively down-regulate Mcl-1 expression, which thereby increases the synovial fibroblast's sensitivity to apoptosis (Ahmed et al., 2009). Studies also suggest that EGCG decreases the production of matrix metalloproteinase-1 (MMP-1), MMP-2, and MMP-3 by RA synovial fibroblasts to prevent further cartilage and bone destruction (Ahmed et al., 2006; Yun et al., 2008). We recently showed that EGCG selectively inhibited IL-1β-induced IL-6 synthesis in RA synovial fibroblasts and suppressed IL-6 trans-signaling via upregulation of an endogenous inhibitor, soluble gp130 receptor (Ahmed et al., 2008). This study was the first to provide novel insights into the anti-inflammatory and anti-rheumatic activity of EGCG observed in similar studies (Lin et al., 2008; Morinobu et al., 2008). Overall, these studies suggest that while EGCG is capable of neutralizing the inflammatory effects of IL-1β and IL-6, it is simultaneously effective in harnessing the presence of TNF-α to perform its essential function of regulating uncontrolled proliferation of activated synovial fibroblasts in order to improve the functional state of arthritic joints (summarized in Table 1). These findings are extremely valuable in the current treatment scenario for RA where even highly effective anti-TNF therapies face stiff challenges such as the lack of response, drug resistance, and poor clinical outcomes.

EGCG for the treatment of vascular inflammation

Vascular inflammation has been especially targeted using EGCG as a treatment modality (Shenouda and Vita, 2007). Following myocardial ischemia and subsequent reperfusion, EGCG administration has been shown to minimize ROS-mediated endothelial damage by reducing the recruitment of neutrophils and decreasing the release of IL-6 and TNF-α via inhibition of AP-1 and NF-κB pathways (Aneja et al., 2004). A study carried out by Widlansky et al. revealed the positive effects of acute EGCG consumption on brachial artery flow-mediated dilation in coronary artery disease states (Widlansky et al., 2007). Similarly, Lorenz et al. found that the post-transcriptional regulation of endothelial cell activation of endothelial nitric oxide synthase (eNOS) and vasorelaxation occurred in rat aortas following the consumption of green tea (Lorenz et al., 2004).

Because of experimental reduction in vascular inflammation by EGCG, optimism exists for its use in attenuating a number of cardiovascular diseases. In this regard, EGCG has been shown to inhibit angiotensin II and TNF-α-induced hypertrophy by suppressing ROS-induced stress in cardiomyocytes (Hao et al., 2007). In a cohort study, patients who consumed black or green tea regularly for at least one year prior to acute myocardial infarction had a greater long-term survival rate compared to the nondrinkers (Mukamal et al., 2002). EGCG's antioxidant and antithrombotic properties were attributed to the prevention of LDL oxidation, imminent macrophage accumulation, and the subsequent buildup of atheromas (Mukamal et al., 2002).

The recurring findings of EGCG as a potent antioxidant also seem crucial in the management of atherosclerosis. Apolipoprotein E-deficient mice given tea extract containing EGCG (0.8 g/L) experienced 27% plaque coverage of the aorta compared to 36% in the control group, as well as 27% and 50% reductions in cholesterol

Table 1
Summary of some in vitro and in vivo studies on the role of EGCG in RA and Cardiovascular Disease.

Disease	Description of mechanism of action	In vitro/in vivo	Citation
RA	Induced B-lymphocyte apoptosis via upregulation of BAFF/PI3K/AKT/mTOR pathway	In vivo	Liu et al. (2012)
	Reduced osteoclast differentiation	In vitro	Kamon et al. (2010)
	Increased sensitivity to synovial fibroblasts by down-regulating Mcl-1	In vitro	Ahmed et al. (2009)
	Decreased production of IL-1β-induced IL-6 production in synovial fibroblasts	In vitro	Ahmed et al. (2008)
	Suppressed osteoclast differentiation to ameliorate bone loss	In vivo	Morinobu et al. (2008)
	Diminished CCL2 expression in osteoblasts via PI3K/AKT/Raf-1 pathway	In vivo/in vitro	Lin et al. (2008)
	Decreased production of MMP-1 and MMP-3 by synovial fibroblasts	In vitro	Yun et al. (2008)
	Inhibited IL-1β-induced MMP-2 activity in synovial fibroblasts	In vitro	Ahmed et al. (2006)
	Blocked IL-1β-induced ENA-78, RANTES and GROα chemokines	In vitro	Ahmed et al. (2006)
CVD	Increased Bcl-2 and decreased Bax expression; Decreased caspase-3 activity	Ex vivo	Piao et al. (2011)
	Reduction of blood pressure	In vivo	Clement et al. (2009)
	Inhibits angiotensin II and TNFα induced hypertrophy	In vivo	Hao et al. (2007)
	Suppression of ROS-induced stress on cardiomyocytes via antioxidant effect	In vivo	Hao et al. (2007)
	Minimized ROS-mediated endothelial damage after myocardial ischemia by decreasing release of IL-6 and TNFα and reducing neutrophil recruitment	In vivo	Aneja et al. (2004)
	Induced vasorelaxation and post-transcriptional regulation of endothelial cell activation of eNOS	In vivo	Lorenz et al. (2004)
	Down-regulated VCAM-1 expression	In vitro	Ludwig et al. (2004)
	Prevented LDL oxidation and macrophage accumulation	In vivo	Mukamal et al. (2002)
	Prevented formation of atherosclerotic lesions	In vivo	Miura et al. (2001)

and triglyceride levels, respectively (Miura et al., 2001). Piao and colleagues used rat hearts to show that treatment with EGCG before ischemia and during the entire reperfusion period resulted in decreased caspase 3 activity and a recovery of superoxide dismutase and catalase activity, which results in decreased cell death and oxidative damage, respectively (Piao et al., 2011). The study also found an increase in anti-apoptotic protein Bcl-2 expression and a decrease in pro-apoptotic protein Bax expression after treatment with EGCG. In another interesting study, Ramesh and co-workers showed that EGCG administration to animals on atherogenic diet reduced the cardiovascular risk in the EGCG-treated animals by suppressing CRP, erythrocyte sedimentation rate (ESR), and platelet counts (Ramesh et al., 2010).

Adhesion molecules play an important role in atherosclerosis, and EGCG has shown some therapeutic efficacy in this regard, too. A study done by Ludwig et al. using human umbilical vein endothelial cells (HUVECs) showed that EGCG down-regulates VCAM-1 but has no effect on ICAM-1. This is clinically important because it has been shown that VCAM-1, not ICAM-1, plays a more important role in atherosclerosis (Ludwig et al., 2004). However, in a recent study using bone-marrow derived macrophages, EGCG inhibited lipopolysaccharide (LPS)-induced ICAM-1, VCAM-1, and IL-6 gene expression, suggesting the differential effect of EGCG on different cell types involved in the process of inflammation.

It is now clinically evident that RA patients have a significantly enhanced CV risk, which is comparable to the observed co-morbidity in RA patients with diabetes mellitus. RA patients, especially those over age 50, have been found to have a greater than 10% higher risk of cardiovascular disease within the first 10 years of the disease onset (Gupta and Fomberstein, 2009). Importantly, RA patients frequently do not have symptoms associated with CVD and are more likely to suffer silent MI and sudden cardiac failure (Gabriel, 2010). While the exact mechanisms leading to this enhanced risk are unclear, it is considered that the inflammatory burden characteristic of RA plays a prominent role in this increased risk for CVD. In particular, patients who are seropositive for RA-specific autoantibodies and who have longer disease duration are at an enhanced risk (Kumeda et al., 2002).

RA patients also have an enhanced risk for developing systemic hypertension. The results from a recent study showed that there was about a 10% increase in hypertension in patients with RA versus healthy volunteers (Panoulas et al., 2008). While this is likely multifactorial, systemic inflammation may set a foundation in the development of hypertension in RA patients. In addition, patients with RA have increased CRP levels, a factor known to inhibit NO synthesis, thereby leading to platelet activation and thrombosis (Panoulas et al., 2008).

Unfortunately, some of the medications administered to RA patients can further contribute to increasing their CV risk. In a clinical study, RA patients treated with the non-selective NSAIDs ibuprofen and indomethacin showed an increase in blood pressure within 4 weeks of treatment when compared to the placebo group (Morrison et al., 2007). Consequently, RA patients at a higher risk for gastrointestinal toxicity and genetically predisposed to cardiovascular complications are advised to avoid their long-term use (Panoulas et al., 2008). Conversely, there is evidence that drugs such as methotrexate and anti-TNF biologics may have vasculoprotective effects in RA (Atzeni et al., 2010; Zhang et al., 2009).

Can EGCG regulate CV complications in RA?

Whether anti-rheumatic drugs themselves increase CV risk is controversial and heavily confounded by indications and contraindications to treatment. While some studies provide evidence that methotrexate is protective against CV events and mortality (Choi et al., 2002; van Halm et al., 2006), others showed that anti-TNF therapies did not decrease the risk of CV events in the therapy responders (Listing et al., 2008). Interestingly, studies using EGCG have shown positive effects in both RA and CVD, independently. However, the benefit of EGCG in regulating systemic inflammation that evolves from the synovial inflammation in RA remains to be tested. Importantly, these protective actions give EGCG an additional advantage to be tested for the prevention of unwanted CV remodeling that leads to an accelerated vascular damage in RA. This notion is further supported by recent pre-clinical and clinical studies showing that statins may be a useful addition for the treatment of vascular dysfunction in RA (Haruna et al., 2007; Ridker and Solomon, 2009). In addition to the studies discussed in the early part of this review, Fig. 2 provides accumulating evidence of the clinical efficacy of EGCG in regulating the symptoms that exist as the traditional risk factors or mediators for CV damage in RA including age, gender, smoking, hypertension, hypercholesterolemia, diabetes, and acute-phase proteins in independent studies. Overall health benefits in the clinical and pre-clinical testing of EGCG in the present scenario outweighs any minor adverse effects. Recent studies from our and other labs have proven IL-6 as a key mediator in the transition of synovial inflammation to systemic inflammation in RA. Developing EGCG or its analogs as IL-6 inhibitors may be one of the potential ways of 'killing two birds (vascular dysfunction in RA) with one stone'.

Although epidemiological evidence has made a case for the pathological role of some of the key players involved in cardiovascular insult in RA, certain limitations in this area of research need to be recognized for clearer understanding of the cardiovascular complications in RA. In

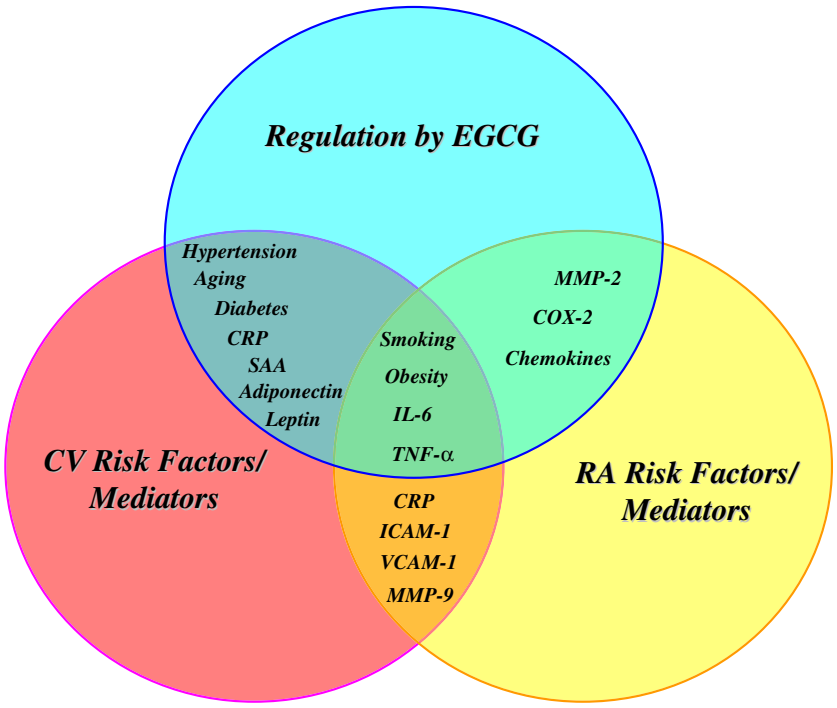

Fig. 2. Summary of the overlapping risk factors/mediators in CV and RA: regulation by EGCG.

RA, a systemic inflammatory milieu generated by high levels of pro-inflammatory cytokines, IL-6 and TNF-α in particular, contributes to the enhanced risk of myocardial infarction and higher mortality rates. Despite an established role of IL-6 and IL-6-induced CRP in propagating CV complications in RA patients, the lack of understanding of the detrimental cardiac remodeling as RA establishes has restricted our approach to predict and treat CV complications in RA. Hence, evaluation of the heart remodeling using an animal model of inflammatory RA may serve as an important tool to track the onset, the role of key signaling pathways, and the consequent pathological events.

Conclusions

EGCG found in green tea has been shown to possess CV benefits and anti-rheumatic activity in independent studies using in vitro and pre-clinical models of these pathologies. Some of these benefits of EGCG are achieved via inhibition of markers/mediators such as IL-6, CRP, TNF-α, MMPs, and obesity that play important role in the initiation and propagation stages of both CVD and RA. Unfortunately, there is no clearer understanding of the CV events that govern vascular dysfunction in RA and no current therapy for RA is capable of managing CV complications. Given the fact that EGCG is safer, natural, and readily available natural product that could be easily incorporated in the diet, testing of this hypothesis may have exponential benefit in the management of CV co-morbidity, even possibly mortality, in RA. Further pre-clinical studies are warranted to validate this concept so that these findings may be tested for their rapid clinical impact.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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