Phytomedicine xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Phytomedicine

journal homepage: www.elsevier.com/locate/phymed

Inflammaging and cardiovascular disease: Management by medicinal plants

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ARTICLE INFO

Article history:
Received 23 August 2015
Revised 6 November 2015
Accepted 10 November 2015
Available online xxx

Keywords:
Aging
Anti-inflammatory drugs
Cardiovascular disease
Inflammation
Inflammaging
Medicinal plants

ABSTRACT

Background: In aging, a host of molecular and cellular changes occur which accelerate alteration and progression of inflammatory diseases. These conditions in the elderly people cause appearance of a phenomenon which has been denoted as "inflammaging". Understanding the pathogenesis and finding new methods for management of inflammaging are essential.
Purpose: In this paper we tried not only to explain inflammaging and its treatments with concentrating on medical plants but to collect a sufficient collection of anti-inflammatory plants with focusing on their mechanism of action.
Method: In this review paper, by searching in indexing cites, desired articles were obtained since 1995 by using keywords of inflammation, inflammaging, inflammation pathophysiology, free radicals and inflammation, aging inflammation, inflammatory disease, and plants or herbal medicine in inflammation.
Sections: In advanced age the generation of free radicals increases in cardiovascular system. Pathological inflammation is also associated with production of excess free radicals More importantly, chronic inflammation makes aged people susceptible to age-related diseases. Some medicinal plants have been shown promising results in inhibition of inflammaging. Some other sections such as inflammation and inflammaging in cardiovascular diseases, oxidative stress in cardiovascular complications, prevention and treatment strategies are presented.
Conclusion: The results of published papers show that the symptoms of several inflammatory diseases can be inhibited or treated by active ingredients from medicinal plants.

Introduction

The world's population age is increasing and the aging population is a risk factor for cardiovascular diseases (CVD). Aging generally causes some changes which, even in absence of usual risk factors, render the cardiovascular system prone to some diseases (Lakatta 2000).

The progressive degeneration of the heart in elderly makes it more vulnerable to stress and causes an increase in cardiovascular morbidity and mortality (Brodsky et al. 2004). Cardiovascular diseases are also fuelled by some other risk factors such as diabetes (Baradaran et al. 2013; Behradmanesh et al. 2013), hypertension (Asgary et al. 2013; Ghorbani et al. 2013), and obesity (Nasri and rafieian-kopaei 2013; Rabiei et al. 2013a; Favarato et al. 2014). Aging is a phenomenon resulted from genetic, epigenetic stochastic, and environmental events in different cells and tissues. In fact in aging, a host of molecular and cellular changes occur which accelerate these alterations and implicate in the progression of arterial diseases (Rabiei et al. 2013b; Favarato et al. 2014). Pathological inflammation is also associated with production of excess free radicals arising predominantly from mitochondria (Beller 2010; Rafieian-kopaei et al. 2012). There are also evidences showing that in advanced age the generation of free radicals increase in cardiovascular system (Judge et al. 2005; Asadbeigi et al. 2014). More importantly, chronic inflammation makes aged people susceptible to age-related diseases (Franceschi et al. 2000).

A wide variety of diseases including diabetes (Asadbeigi et al. 2014) cancer (Azadmehr et al. 2011; Nasri and rafieian-kopaei 2014), infection (Bagheri 2013; Bagheri 2013), atherosclerosis (Rafieian-Kopaei et al. 2011; Rafieian-Kopaei et al. 2014a), cardiovascular diseases (Khosravi-Boroujeni et al., 2013; Sarrafzadegan et al. 2013), Alzheimer (Rabiei et al. 2013c, 2014) and other degenerative diseases

Abbreviations: CVD, Cardiovascular diseases; NOS, Nitric oxide synthase; eNOS, Endothelial nitric oxide synthase; LDLox, Oxidized low density lipoprotein; NSAIDs, Non-steroidal anti-inflammatory drugs; DMARDs, Disease-modifying agents of rheumatoid diseases; NF-kβ, Nuclear factor- kb.

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http://dx.doi.org/10.1016/j.phymed.2015.11.004
0944-7113/

(Mardani et al. 2014; Rafieian-Kopaei et al. 2014b) are associated with increased oxidative stress and inflammatory conditions and are degraded in aging. Moreover, the process of inflammation is involved in initiation and development of a wide variety of chronic diseases (Paolisso et al. 1998).

In aging the normal balance between the oxidative stress and antioxidant system culminates in cardiovascular complications. These conditions in the elderly people cause appearance of a phenomenon which has been denoted as "inflammaging". In fact, the word inflammaging is used to show inflammatory state in the aged individuals (Franceschi et al. 2000).

Chronic inflammation in aging tissues "Inflammaging" is a pervasive feature of aging and most age-related diseases are associated with inflammation. In fact inflammaging is described as systemic, low-grade chronic inflammation in aged people, in absence of infection. It is a great risk factor for mortality and morbidity in the elderly people (Zhang et al. 2010).

A mild inflammation is predictive of, and is associated with many aging phenotypes. The etiology of inflammation in aging people and its contribution in adverse health events is unknown. The pathways that make us able to control inflammation are not fully established. Hence, understanding the pathogenesis and finding new methods for management of inflammation are beneficial. This paper, therefore, aimed to present the recently published papers regarding inflammation in cardiovascular diseases, focusing on the role of oxidative stress. and to summarize the herbal medicines which have had promising results in prevention and treatment of this phenomenon.

Inflammation and cardiovascular disease

Inflammation participates to the pathophysiology of a wide variety of chronic diseases particularly injury and infectious diseases. Interaction of various cells in the adaptive and innate immune systems with inflammatory mediators modulates the acute and chronic inflammation causing various diseases. This coordination in inflammatory mechanisms triggers remodeling of the extracellular matrix, oxidative stress, tissue injury, angiogenesis and fibrosis in various tissues. These inflammatory mechanisms are involved in most of cardiovascular complications, including coronary artery disease, ischemia, rheumatic disease, rheumatoid arthritis, plaque disruption, thrombosis and atherosclerosis. The mastery of the inflammatory responses necessitates the development of new approaches to the prevention and treatment of chronic diseases associated with aging, such as atherosclerosis (Libby, 2007).

Although inflammation was previously considered as being a response to development of atheromatous vascular damage, it is now considered as the main causing factor in atherosclerosis rather than being its result. In this regard, a dramatically increased risk of cardiovascular disease has been reported in patients with pre-existing inflammatory diseases. Also, patients with autoimmune disorders including lupus erythematous and rheumatoid arthritis have higher rates of cardiovascular diseases such as atherosclerosis (Franceschi et al. 2000). Untreated infections such as periodontal disease which cause inflammation are associated with increased risk of cardiovascular complications (Candore et al. 2010).

The inflammation mediators have been shown to participate in atheromatous changes and vascular insults. Secretion of a host of inflammatory factors might contribute to the increased cardiovascular risks. The cardio-protective effects of many of drugs are mediated through improvement of systemic inflammation. The targeted suppression of various pro-inflammatory cascades in adipocytes specifically represents an exciting new therapeutic opportunity for the cardiovascular disease area (Berg and Scherer 2005).

The mechanisms underlying cardiovascular complications by systemic inflammation are not established. Type 2 diabetes mellitus, hypercholesterolemia, atherosclerosis, hypercoagulability, and metabolic syndrome are associated with coronary vasculopathy, and with circulating serum factors which mediate the connections between these disease conditions. These circulating mediators are mostly participated in systemic inflammation. Therefore, these factors may show the evidence for their connections with cardiovascular pathology (Berg and Scherer 2005; Rafieian-Kopaei 2014).

Inflammaging and cardiovascular diseases

The association between systemic inflammation and increase in the risk of cardiovascular diseases has stimulated basic and clinical investigators to research for precise nature and the differences in the nature of traditional inflammation and inflammaging in relation to cardiovascular diseases. In this regard, although their different roles in accelerating atherogenesis remain unresolved, however, it is known that inflammatory response in elderly is not as fast as younger individuals. Inflammation can be beneficial facilitating the adaptation, turnover and repair of many tissues. However, this inflammatory response might be impaired during aging which increase the susceptibility to pathogens (Griendling and FitzGerald 2003).

More importantly, in aging period, a host of molecular and cellular changes including genetic, epigenetic and environmental events occur which increase the progression of arterial diseases.

In aged people, the tissues are mostly in a chronically inflamed state, with no sign of infection. The generation of free radicals also increases, and makes aged people susceptible to cardiovascular diseases (Asadbeigi et al. 2014).

Inflammaging is associated with increased levels of IL-1, IL-6, TNF and CRP which are independent risk factors for mortality and morbidity. In aging process interference occurs with anabolic signaling, IL-6 and tumor necrosis factor-a increase, down-regulating insulin and insulin-like growth factor-1, as well as erythropoietin signaling and protein synthesis. Inflammaging can be due to the accumulation of damaged macromolecules and cells which increases with age due to increased production and/or inadequate elimination. Inflammaging might also be due to increase in harmful agents produced by microorganisms of the human body, including gut microbiota. In aging period, the gut microbiota may change and the capability of the gut to sequester these microbes and their products declines, leading to chronic inflammation (Pawelec, 1999).

Increase in inflammation in aging also might be due to high level of cellular response to stress and damage (cellular senescence). Senescent cells likely fuel age-related diseases such as cardiovascular disease, because they secrete numerous proinflammatory cytokines, modifying the tissue microenvironment and altering the function of nearby normal cells. Immunosenescence also contributes to inflammaging. In aging the adaptive immunity decreases and the innate immunity increases resulting in mild hyperactivity, which may lead to local inflammatory reactions in elderly people. Coagulation is considered as a part of the inflammation system. Increase in activation of the coagulation system in age people also can increase the inflammation. The higher incidence of thrombosis in the elderly has been attributed to hypercoagulable state in elderly people (Belge et al. 2002).

Oxidative stress in cardiovascular complications

Reactive oxygen species induced oxidative stress play a crucial role in development of vasculopathies, such as hypertension, atherosclerosis and restenosis after angioplasty. Although atherosclerosis was initially suggested to be the result of an injury to endothelial cells and subsequent macrophage infiltration, however, LDL oxidation and its implication in formation of fatty streaks are very important in process of atherogenesis (Griendling and FitzGerald 2003).

Various free radicals are produced in cardiovascular system and play a crucial role in vascular physiology as well as pathophysiology;

the most important of them are superoxide ($O_2^{\cdot -}$), hydrogen peroxide (H_2O_2), peroxynitrite ($ONOO^{\cdot -}$) and nitric oxide ($NO^{\cdot}$). In vasculature, superoxide reacts with nitric oxide to form the highly reactive molecule of peroxynitrite (ONOO.-) which has an important role in protein nitration and lipid peroxidation. One of the most important productions of lipid peroxidation is LDLox (Oxidized low density lipoprotein) which has crucial role in atherogenesis (Madihi 2013a,b).

Nitric oxide is produced normally by endothelial nitric oxide synthase (eNOS), but in process of inflammation, inducible NOS can also be expressed in smooth muscle cells and macrophages (Asgary et al. 2014).

Nitric oxide plays an important role in platelet aggregation. Nitric oxide which is an important mediator of endothelium-dependent vasodilation also has a crucial role in maintaining smooth muscle cell growth and function (Rafieian-Kopaei et al. 2014c).

The function of most of free radicals including superoxide and hydrogen peroxide on cardiovascular system is critically dependent on the amounts produced (Rafieian-Kopaei et al. 2013; Nasri and Rafieian-Kopaei 2014). In low concentrations, they modulate the function of biochemical pathways mediating the responses such as growth of vascular smooth muscle cells (Rafieian-Kopaei et al. 2013; Rafieian-Kopae et al. 2014d) . However, in high concentrations, free radicals can cause DNA damage and apoptosis as demonstrated in smooth muscle and endothelial cells (Rafieian-Kopaei 2014; Baradaran et al. 2014). Pathological inflammation is generally associated with excess free radicals and in advanced age the generation of free radicals increases, especially in cardiovascular system. More importantly, chronic inflammation makes aged people susceptible to age-related diseases, including cardiovascular complications (Franceschi et al. 2000).

Prevention and treatment strategies

Anti-inflammatory drugs

When the inflammatory response is no longer needed, it should be terminated to prevent unnecessary bystander damage to tissues. The most important anti-inflammatory drugs include nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and disease-modifying agents of rheumatoid diseases (DMARDs) (Singh 2012). NSAIDs and glucocorticoids are used in order to relieve symptoms, while, DMARDs are used with the aim of reducing or preventing tissue damage which are caused by inflammatory attack. Unfortunately, all of these have unacceptable side effects. Moreover, it is necessary to find out drugs for very long period of times in order to design a successful anti-inflammatory therapy for chronic disease. However, more potent anti-inflammatory therapy, usually has greater chance for adverse effects to host defense. For example, increased risk for infections are more observed in patients taking anti-TNFα therapy (Tabas et al. 2013). Nowadays, more attention has been paid to medicinal plants with antioxidant activity.

Potential role of antioxidants

Although free radicals are able to damage cells or its components by oxidizing proteins or DNA or causing lipid peroxidation, but they also possess crucial useful physiological functions. The useful function of antioxidant systems should not be removal of free radicals entirely, but instead keeping oxidative stress at a level below which they would trigger the inflammatory cascade, a series of intra-nuclear and intra-cellular signaling which results in the release of destructive inflammatory cytokines (Valko et al. 2007).

Progress has been made regarding the role of the signaling cascades in inflammatory process and early studies have also suggested that antioxidants might be useful in the treatment of vascular diseases (Hall Ratclife 1949). Studies on the effects of vegetables and fruits with antioxidant activity, less or more, have suggested reduction in cardiovascular morbidity and mortality (Verlangieri et al. 1985), particularly in regard to ischemic heart disease (Gey and Puska 1989; Emmert and Kirchner 1999).

Some studies on combinations of antioxidant drugs and vitamins have also had positive results. Consumption of 800 IU/day vitamin E in patients with prevalent cardiovascular disease showed reduction in the myocardial infarction (Boaz et al. 2000).

In another study in India, combined consumption of vitamins A, C, E, and beta-carotene were protective against oxidative stress and cardiac necrosis. They also were useful in reduction of the cardiac events and in preventing complications (Singh et al. 1996).

Combined supplementation with vitamins C and E reduced the progression of carotid atherosclerosis (Salonen et al. 2000). Probucol alone or in combination with antioxidant vitamins seems to be effective in reduction of subsequent restenosis rates (Tardif et al. 1997; Yokoi et al. 1997).

Most of the above mentioned studies are modest in size and involved subgroups where more than one antioxidant (combinations therapy) was used. However, in large randomized clinical trials the results were not all consistent with results of the above mentioned studies. Pooled data from over 77,000 subjects and randomized trials of vitamin E as well as 6 trials of ß-carotene with over 131,000 participants revealed that the vitamin E was not effective and ß-carotene consumption was associated with a worse outcome ($P = 0.003$).

A large, long-term trial, on women at high risk for cardiovascular diseases reported that vitamin C, vitamin E or ß carotene had no significant effect on cardiovascular events (Cook et al. 2007). Another large trial in Cambridge on the effects of vitamin C or vitamin E also revealed no significant reduction on the risk of major cardiovascular events (Sesso et al. 2008) . Although the statistical analyses have suggested overall significance of antioxidant therapy in some studies, only those trials using probucol with or without antioxidant vitamins showed significant effect (Tardif et al. 1997). N-Acetylcysteine, in a trial on acute coronary syndrome, also produced significant improvement in cardiac index in patients treated with streptokinase (Arstall et al. 1995).

Hence, there it is necessary to search for more scientific evidence of the relative contribution of antioxidant constituents in inhibition and progression of cardiovascular events (Badimon et al. 2010).

Anti-inflammatory plants

Targeting the desired pathway through treating inflammation is not easy because of a wide range of changes in pathology as a consequence of existence of many inflammatory mediators and pathways in inflammation (Qiuhong et al. 2013).

Cyclooxygenase and lipoxygenase pathways and possibly some other mechanisms of initiation of inflammation can be efficiently stopped by some of the phytochemicals found in certain plants as well as aspirin (Lavet et al. 2013). NSAIDs and corticosteroids have an extensive use in the current treatment of inflammatory disorders in Western medicine. Lately, phytochemicals and their anti-inflammatory efficacies have attracted more attention in treatment of inflammation. Therefore; we tried to list and introduce some of these kinds of herbal drugs in this study (Xu et al. 2007).

Symptoms of several inflammatory diseases can be inhibited by Chinese Material Medica, such as Qijie Granule including the root of Astragalus membranaceus, the resin of Dranaena cochinchinensis (Lour.) S.C. Chen, the root of Angelica sinensis (Oliv.), Diels, the dried twig of Cinnamomum cassia Presl (Zhang et al. 2004), the dried rattan of Sargentodoxa cuneata (Oliv.) Rehd. etwils, the root of Rheum palmatum L., the resin of Commiphora myrrha Engl., the root of Paeonia lactiflora Pall., and the root of Glycyrrhiza uralensis Fisch, which are proven to have acceptable curative effects in treating chronic pelvic inflammation through improving the blood viscosity and regulating

Table 1
Anti-inflammatory compounds of plant origin.

Compounds	Uses	Mechanism of action	reference
Seeds of *Phaseolus angularis Wight*	*Anti-inflammation*	Dercreases NO, PGE2, iNOS, COX2, NF-$\kappa\beta$	(Yu et al. 2011)
Bark of *Cinnamomum cassia Blume*	"	Decreases NO iNOS, COX2, NF-$\kappa\beta$	(Yu et al. 2012)
Dried roots *Asparagus cochinchinensis* Merrill	"	Decreases MPO	(Lee et al. 2009)
Aerial of Houttuynia cordata Thunb	"	Decreases NO, COX2	(Li et al. 2011c)
Roots of *Scutellaria baicalensis* Georgi	"	Decreases IL2, IL6, IL12, IL1β, TNF-α, NF-$\kappa\beta$, I$\kappa\beta$	(Kim et al. 2009a)
Aerial part of *Andrographis paniculata*	"	Decreases IL6, COX2, IL1β, TNF-α	(Parichatikanond et al. 2010)
The fruits of *Forsythia koreana Nakai*	"	Decreases NO, iNOS, COX-2	(Lim et al. 2008)
Dried heart wood of *Caesalpinia sappan* L.	"	Decreases NO, PGE2, iNOS, COX2, *IL-6*, IL1β, TNF-α, and increases IL10	(Wang et al. 2011)
Corolla of *Carthamus tinctorius* L.	"	Decreases NO,PGE2,iNOS, COX2, NO, iNOS TNF-α, NF-$\kappa\beta$	(Jun et al. 2011)
Inflorescence of *Chrysanthemum indicum* Linne	"	Decreases NO,PGE2,iNOS, COX2	(Wu et al. 2011c)
Ripe fruit of *Evodia rutaecarpa*	"	Decreases NO, iNOS	(Ko et al. 2007)
Roots of *Glycyrrhiza uralensis* Fisch.	"	Decreases NO, iNOS,IL-6, NO, NF-$\kappa\beta$, IL1β, I$\kappa\beta$	(Yu et al. 2012)
Roots of *Polygala tenuifolia* Willd.	"	Decreases NO, PGE2, iNOS, COX2,IL1β, TNF-α	(Cheng et al. 2005)
Dried bark of *Phellodendron chinense* Schneid.	"	Decreases COX-2, IL-6	(Xian et al. 2011)
Fruit of *Vitex trifolia* L.	"	Decreases iNOS, IL-6, IL-1β, TNF-α and increases IL-10	(Matsui et al. 2009)
Pericarp *of Zanthoxylum schinifolium* Sieb. et Zucc	"	Decreases IL-8, TNF-α, NF-$\kappa\beta$, I$\kappa\beta$	(Cheong et al. 2011)
Roots of *Angelica sinensis* (Oliv.) Diels	"	Decreases iNOS, COX-2, *IL1β*, TNF-α	(Cao et al. 2009)
Roots of *Clematis chinensis Osbeck*	"	Decreases COX-2, *IL1β*, TNF-α, NF-$\kappa\beta$	(Peng et al. 2011)
Leaves of *Plectranthus amboinicus* (Lour.) Spreng	"	Decreases COX-2, TNF-α, NF-$\kappa\beta$, I$\kappa\beta$	(Deng et al. 2011)
Branches and leaves of *Taxillus liquidambaricola Hosokawa*	"	Decreases NO, iNOS, COX-2, TNF-α	(Deng et al. 2011)
Aerial part of *Pogostemon cablin* (Blanco) Benth	"	Decreases, *IL1β*, TNFα, NO, PGE2, iNOS, COX2, NF-$\kappa\beta$	(Li et al. 2011)
Young shoot of *Aralia elata Seemann*	"	Decreases *IL1β*, TNFα, NO, PGE2, NF-$\kappa\beta$, I$\kappa\beta$	(Suh et al. 2007)
Flower of *Glossogyne tenuifolia Cass*	"	Decreases PGE2, iNOS, COX-2, IL-6, IL-12, *IL1β*, TNF-α, NF-$\kappa\beta$	(Wu et al. 2004)
Dried roots of *Alpinia conchigera Griff*	"	Decreases NO, iNOS, *IL1β*, TNF-α, NF-$\kappa\beta$	(Lee et al. 2006)
Roots of *Sophora alopecuroides* L.	"	Decreases IL-6, *IL1β*	(Wang et al. 2012c)
Leaves of *Cistus Lourifolius* Linn. (Cistaceae)	Inflammatory ailments such as rheumatism and renal inflammation	Inhibits activity of IL-1α and PGs	(Kupeli and Yesilada 2007)
Roots of *Daphne pontica* Linn. (Thymelaeceae)	Anti-tumor	Inhibits production of PGE2 and IL-1β	(Kupeli and Yesilada 2007)
Fruit rinds of *Garcinia mangostana* Linn. (Guttiferas; Clusiaceae)	Treatment of trauma and skin infections	Block production of iNOS and COX-2	(Chen et al. 2008)
Fruit of *Gardenia jasminoides* Ellis (Rubiaceae)	Treatment of inflammation	Block production of COX-2, NF- $\kappa\beta$ and I $\kappa\beta$	(Koo et al. 2006)
Leaves of *Piper ovatum* Vahl (Piperaceae)	Treatment of inflammation	Inhibitory effecr on production of COX-1	(Siva et al. 2008)
Hydroethanolic (70%) extract of *Macrosiphonia longiflora*	"	Decreases IL-1β, IL-10 and NO release, and possibly the PGs.	(Alberto et al. 2009)
B. incarum, Baccharis boliviensis, Ch. atacamensis and *P. lucida* ethanolic extracts	"	Inhibit COX-1 and COX-2 activities	(Calle et al. 2012)
J. seriphioides and *P. lepidophylla* extracts	"	Effect on COX-2 activity but not on the enzyme expression,	(Torres Carro et al. 2007)
Essential oil of *Eugenia caryophyllata*	Nasal obstruction, musculoskeletal pain, inflammation	Inhibitory effect	
on COX-2 activity	(Ozturk and Ozbek 2005)		
Ethanol extracted of *Desmodium pauciflorum, Mangifera indica* and *Andrographis paniculata*	Injuries	Inhibition of prostoglandin synthesis	(Shirani et al. 2011)
Curcumin (a naturally-occuring yellow pigment present in the rhizomes of the plant *curcuma Longa L. (Zingiberaceae))*	Atherosclerosis, Alzheimer´s disease, Arthrits and Pancreases	Inhibition of lipooxigenase and COX-2	(Song et al. 2001)
Resveratol (phytoalexin polyphenol) present in grape skin, red wines and other plants	Anticarcinogenic and anti-platelet activity	Inhibition of COX-1 and COX-2	(Jangand Pezzutto 1999)
Flavonoids baicalein (isolated from roots of *scutellaria baicalensis Georgi* (Lamiaceae)	Anticancer agent	Inhibition of 5-LO and LTC4 and PGE2	(Middelton et al. 2000)

(*continued on next page*)

Table 1 (*continued*)

Compounds	Uses	Mechanism of action	reference
Cirsilio (isolated from *achillea fragrantissima Forssk* (Asteraceae)), Luteolin, morin	Leuchemia	Inhibits production of COX-2 activity	(Lindolfi et al. 1984)
Chrysin, apigenin and pheloretin	Anti-inflammatory activity	Inhibits COX-2 expression and platelet aggregation	(Raso et al. 2001)
Silbin, silydian and silychristin, (*from silybum marianum L.* (Milk thistle) (Asteraceae)	Anti-inflammatory activity	Inhibit both LO and COX activity	(Gupta et al. 2000)
Biflavon(from *ginkgo biloba L.* (ginkgoaceae)	Arthtitic inflammation	Inhibit PLA2	(Kim et al. 1999)
Tectorigenin and tectoridin (isolated from rhizomes of *belomcanda chinensis L.* (Iridaceae))	Anti-inflammatory activity	Inhibits production of COX-2	(Yamki et al. 2002)
Platycodin D (isolated from roots of *platycodon grandiflorum* A. (campanulaceae)	"	Inhibits production of COX-2	(Kim et al. 2001)
Ursolic acid and oleanic acid isomers (extracted from *plantago major* L. (plantaginaceae)	"	Inhibit production of COX-2	(Suh et al. 1998)
B-tumerone and artumeron (sesquiterpens from *Curcuma zedoaria* L. (Zingiberaceae)	Respiratory problems	Inhibit LPS-induced PGE2 production	(Hong et al. 2002)
Fatty acids extracted from *Plantago major* L. (Plantaginaceae)	Anti-inflammatory activity	Inhibit both COX-A and COX-2	(Ringbom et al. 2001)
CAPE (Caffeic acid phenetyl ester, a cpumpond produced by honeybees from the gum of various plants)	Anti –inflammatory, anticarcinogenic, anti-mitogenic and immunomedulator	Inhibits both COX-A and COX-2	(Michaluat et al. 1999)
Quinazolinocarboline alkaloid rutacarpine (from *Evodia rutaecarpa* Bentham (Rutaceae))	Antithrombotic effect	Inhibit LPS-induced PGE2 production, inhibition of TXA2	(Woo et al. 2001)
Aqueous and alcholic extract of *Achillea millefolium Linn.* (Asteraceae)	Treatment of gastro-intestinal andhepato-biliary disorders, skin inflammasion	Inhibition of arachidonic acid	(Benedik et al. 2007)
Aspilia africina (Pars.) (Asteraceae)	Stops blood flow from fresh wounds, traditional treatment of malaria	Inhibit action of mediators like histamine, 5-HT, kinins and prostanoieds	(Okoli et al. 2007)
Ethanolic extract of *Bacopa monnieri* (Linn.) penn (scrophulariacceae)	Treatment of bronchitis, asthma and rhumatism	Suppres PGE1, bradykinin and serotonin	(Channa et al. 2006)
Chloroform extract of *Bryonopsis Laciniosa* (Linn.) (Cucurbitaceae)	Anti-inflammatory activity in chronic and acute disease	Inhibits increasing of fibroblasts and synthesis of mucopolysacharids during formation of granuloma	(Gupta et al. 2003)
Neptin (isolated from dichloromethane extract of arial parts of *Eupatorium arnottianum* Grieseb. (Asteraceae)	Hepatoprotective and against fever and rheumatism	Inhibits NF-$\kappa\beta$ activity	(Okoli et al. 2007)

T-lymphocytic sub groups (Zhao et al. 2010). Contrasting with western drugs; boiling, steaming, treating with salt or vinegar, frying, or charring as some specific treatments are subjecting before use of these plants in decoctions or in the manufacture of herbal products (Aggarwal and Shishodia 2006).

It has been shown that active ingredients from medicinal plants play a significant part in the prevention and treatment of inflammatory diseases (Schepetkin and Quinn 2006). A characteristic of medicinal plants is their unique structural diversity and wide-ranging of pharmacological effects in contrast with common synthetic anti-inflammatory drugs (Qiuhong et al. 2013).

Recently, polysaccharides, which are widely used in the biomedical field as a result of their therapeutic effects and relatively low toxicity (He et al. 2012), are screened for their anti-inflammatory activities based on their unique structures in herbal plants. For example, it has been revealed that the main component of Astragalus membranaceus Bunge and Astragalus polysaccharides, have anti-inflammatory ability involving the inhibition of TNF-α and IL-1β and reduction of nuclear factor- kb (NF-kβ) activity (Quang et al. 2012). The challenging part of using the polysaccharide drugs is the difficulty of targeting a specific location not only because of their large molecular weight but also due to their easy digestion and oral degradation by oral delivery. Hence, it seems that it is essential to set up the smallest effective parts of the structure and a useful form of direction for anti-inflammatory polysaccharides in further studies (Mendes et al. 2012).

It has been reported that essential oils of some medicinal plants have significant anti-inflammatory activities (Dunga et al. 2009). For example, secretion of pro-inflammatory cytokines such as TNF-α, IL-1β, and NF-$\kappa\beta$ in RAW264.7 cells, a mouse macrophage-like cell line, that are induced by lipopolysaccharide (LPS) can be obviously prevented by applying the essential oil of the buds of Cleistocalyx operculatus (Roxb.) Merret Perry. Additionally, this oil can suppress the nuclear translocation of the p65 subunit and has the ability of inhibiting a phorbolester- induced which caused ear swelling and the water content of the skin in BALB/c mice (Lin et al. 1997). All together, these results suggest the anti-inflammatory effect of these essential oil extracts by suppressing the expression of pro-inflammatory cytokines.

It is proven that alkaloids are the main bioactive components in anti-inflammatory treatments, such as matrine. Matrine is extracted from the root of Sophora flavescens Ait, in order to use in treatment of some inflammatory diseases, such as enteritis, hepatitis and atopic dermatitis by inhibiting the activation of inflammatory signal and also, expression of pro-inflammatory mediators in human skin

keratinocytes, fibroblasts, Kupffer cells, and rat intestinal microvascular endothelial cells (Liu et al. 2007; Zhang et al. 2008; Cheng et al. 2009; Zhang et al. 2011). Moreover, it has been found that the alkaloid, matrine, can reduce the increased levels of TNF-α, IL-6 and HMGβ1 induced by LPS, in both in vivo and in vitro situations (Havsteen 1983) (see the table).

Citrus fruits, tea and wine are good sources for a wide range of bioflavonoids, with the ability of reducing inflammation by inhibiting cyclooxygenase and lipoxygenase pathways (Heim et al. 2002). Flavonoids, are one of the important members in anti-inflammatory components category, with a large family of compounds which represent varied biological properties and having the ability of suppressing the expression of inflammatory proteins and cytokines (Hu and Kitts 2003; Kim et al. 2004). Flavanoieds have been used in the form of crude plant extracts for their anti-inflammatory effects. For example, it has been confirmed that flavonoids are the major bioactive flavones in Radix Scutellariae (the root of Scutellariae baicalensis Georgi.), existing in the forms of aglycones (baicalein, wogonin, oroxylin A) and glycosides, which are used for the treatment of inflammatory diseases.

Luteolin, 3′,4′-dihydroxyflavone, galangin, morin and apigenin as some examples of flavonoieds are proven to be inhibitors of COX, whereas some flavones/ flavonols/isoflavones, mainly flavones, significantly inhibit production of NO, as well (Abad-Martinez et al. 2005). Some of these compounds have been previously isolated and identified in B. incarum, B. boliviensis and P. lucida (Zampini et al. 2008; Calle et al. 2012; D'Almeida et al. 2013). D'Almeida et al. demonstrated that P. lucida extract inhibits arachidonic acid metabolism via several enzymes (COX, LOX and phospholipase A2).

Steroidal saponins are naturally found in the roots and barks of various Chinese herbs, which possess anti- inflammatory effects, such as: anemar saponin B, a steroidal saponin which are isolated from the rhizomes of Anemarrhena asphodeloides Bge by decreasing the protein and mRNA levels of iNOS and COX-2. Similar to flavonoids, steroidal saponins decrease the expression and production of pro-inflammatory cytokines, as well as TNF-α and IL-6. Additionally, the p65 subunit of NF-kB is obviously inhibited by phosphorylation of inhibitory kappa β-a (Qiuhong et al. 2013).

Phenyl-propanoids are important components of the anti-inflammatory plants. Honokiol, as a member of phenyl propanoid component can be isolated from the herb Magnolia officinalis Rehd. etwils. (Qiuhong et al. 2013). It seems that saponins act as therapeutic agents on atherosclerosis by their anti-inflammatory activity, involving NF-kβ signaling pathway (Qiuhong et al. 2013). Table 1 shows the anti-inflammatory compounds of plant origin with their mechanisms actions.

Conclusion

Inflammation is an acute or chronic process and a defense response to injury, autoimmune response, tissue ischemia or infectious agents. Acute inflammation is a primary defense against injury or infection and a suitable stimulus factor in the healing process. It is usually beneficial, starts quickly, and then becomes severe. Chronic inflammation, occurring after acute inflammation, is not favorable to the system. Chronic inflammation has significant role in most of the chronic disease such as diabetes mellitus, atherosclerosis, Crohn's disease, cancer, ulcerative colitis and CNS disorders, which have briefly discussed in the present study.

Obviously, chronic diseases involve very suffering ones, so that it has been tried to find drugs with low side effects in order to design a successful anti-inflammatory therapy for. Medical plants can be applied because of their structural diversity and wide-ranging of pharmacological effects in contrast with common synthetic anti-inflammatory drugs. One of the good strategies that can be sufficiently used is extracting or isolating components from medical plants in order to develop anti-inflammatory drugs. It should be note that the pathological inflammation is associated with production of excess free radicals and medicinal plants mostly counteract oxidative stress by reducing free radicals (Asadi-Samani et al. 2014; Bahmani et al. 2014). Therefore, isolation of anti-inflammatory compounds may not be associated with antioxidant activity.

At the present study, we tried to not only explain inflammation, disease and its treatments with concentration on medical plants but collected a sufficient collection of anti-inflammatory plants with focusing on their mechanism of action. But as far as the huge number of existent herbs around the world collecting all together seems to be impossible.

Conflict of interest

The authors declare that there is not any conflict of interest.

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Please cite this article as: E. Shayganni et al., Inflammaging and cardiovascular disease: Management by medicinal plants, Phytomedicine (2015), http://dx.doi.org/10.1016/j.phymed.2015.11.004

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Please cite this article as: E. Shayganni et al., Inflammaging and cardiovascular disease: Management by medicinal plants, Phytomedicine (2015), http://dx.doi.org/10.1016/j.phymed.2015.11.004