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TARGETING CRUCIAL INFLAMMATORY SIGNALING MOLECULES WITH PLANT NATURAL PRODUCTS IN INFLAMMATORY DISEASES

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ABSTRACT

The majority of recent studies in anti-inflammatory therapeutics is focused on the discovery of agents that target key inflammatory factors in the fight against chronic inflammatory diseases (CIDs). Increasing body of evidence from research on a large number of plant secondary metabolites have demonstrated that these natural plant agents have potent anti-inflammatory as well as antioxidant abilities. Current progress in metabolomics and genomics have capacitated researchers to adequately evaluate the prospective use of natural anti-inflammatory agents for the prevention and treatment of a variety of CIDs. The prophylactic actions of many anti-inflammatory Plant natural agents rest on their actions on cellular protection such as antioxidant enzyme systems and the stimulation of inflammatory reactions, usually through targeting particular key inflammatory mediators like cytokine, transcription factors, adhesion molecules, inflammatory enzymes among others. This present review discusses current discoveries and hypotheses on the molecular mechanisms through which a variety of inflammatory actions are linked to disease processes and the particular natural agents that may inhibit inflammation and the associated disease progression both in vitro and in vivo.

KEYWORDS: Plant natural product, Inflammation, key cell signaling inhibition, chronic inflammatory disorders.

INTRODUCTION

Inflammation involves a series of complicated steps stimulated by many factors ranging from microbial infection and chemical injury to environmental factors that lead to cell damage or death.[1] Trauma as a result of tissue injury damage may lead to the expression of inflammatory factors such as proinflammatory cytokines (TNF-α, IL) from leukocytes, monocytes, and macrophages.[2] Stimulated proinflammatory cytokines further promote the production of other cytokines and chemokines, immunoglobulins, and also upregulate the expression of several cellular adhesion molecules (CAMs).[3] Also, the phagocytosis of microorganisms or foreign agents by neutrophils will result in a rise in oxygen uptake, and this will culminate in the production of the substantial amount of reactive oxygen species (ROS-) like superoxide anion (O2-), hydroxyl radical (HO·), and hydrogen peroxide (H2O2) are produced.[4] Furthermore, there is an up-regulation of the production of cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), phospholipase A2 and 5-lipoxygenase (5-LOX).[5] Additionally, there are activation nuclear factors (NF-κB, STAT3, AP1 and HIF3) which play a significant role in the modulation of inflammatory enzymes, inflammatory cytokines, growth factors, CAMs, and other factors that promote inflammatory process. Deregulated inflammatory response contributes significantly to the pathogenesis of several diseases. The actual molecular mechanism(s) that lead to inflammatory related diseases is not entirely understood owing to the complex cross-talk that exist between pro-inflammatory mediators such as cytokines, chemokines, enzymes, transcription factors and immune cells. These molecular factors have demonstrated to be critical links between inflammation and several diseases, and their activation and deactivation have resulted in the alteration of the initiation, development, and progression of inflammatory diseases. Therefore, studies connected to targeting inflammation in chronic diseases has received overwhelming attention from researchers.

Epidemiological studies have demonstrated the parallel decline of incidences of particular chronic diseases such as cancer, atherosclerosis, arthritis, type 2 diabetes, asthma, degenerative and cardiovascular diseases with the usual eating of fruits and vegetables.[6] An avalanche of experimental animal studies has also demonstrated the biological effects of many naturally occurring constituents from plants on several chronic diseases. Most of these

plants products with anti-inflammatory activity have been shown to play a vital role in disease prevention and therapy in CID.[7] Natural compounds have emerged as novel therapies that contribute significantly to drug discovery process.[8, 9] These natural products usually display multi-targeted actions and can affect several molecular targets such as transcription factors, cytokines, chemokines, adhesion, molecules, growth factor, receptors, and inflammatory enzymes.[10] It appears that there is increasing interest in the anti-inflammatory activity of plant extracts by Pharmaceutical companies as well as the herbal industry. Because of their important role in providing a lead for new drug discovery, majority of United States Food and Drug Administration (US FDA) approved entities shows that natural products and their derivatives account for one-third of all novel drugs.[11, 12] The present review outlines the various molecular and cellular inflammatory mediators implicated in the initiation, progression, and development of chronic inflammatory with a particular focus on cancer, type 2 diabetes and atherosclerosis.

From Acute to Chronic Inflammation

Inflammation is the normal physiological and immune response of the tissues to harmful stimuli like allergens, microbial infections, mechanical injuries burns, and other noxious stimuli, intended to remove the causative agent and repair the damaged tissue ultimately resulting in regeneration and returning to homeostasis.[1] Inflammation can be classified as either acute or chronic. Acute inflammation is the primary immune response that arises in the first few hours following tissue injury. This stage is characterized by up surging in blood flow through vasodilatation induce a structural alteration in the microvasculature resulting in vascular permeability in which plasma fluid and proteins and leukocytes leave the circulation into the injured region.[13] At the very initial recognition of infection, neutrophils are the first cells to migrate to the inflammatory sites under the control of molecules produced by rapidly responding macrophages and mast cells prepositioned in tissues.[14] As the inflammation advances, different types of leukocytes, lymphocytes, and other inflammatory cells are stimulated and drawn towards the inflamed site through a signaling network associated with a myriad of inflammatory mediators, including chemokines, cytokines, vasoactive amines, eicosanoids, products of proteolytic cascades and growth factors.[15] Neutrophils become activated on arrival the damaged tissue site through either primary contact with a causative factor or due to the activities of cytokines produced by tissue-resident cells. The neutrophils function by releasing the toxic constituents within their granules, like proteinase 3, ROS and reactive nitrogen species, cathepsin G and elastase.[16] All cells directed to the inflammatory

site promotes tissue breakdown and are useful through enhancing and controlling the protection against infection.[17] A favorable acute inflammatory reaction leads to eradication of the causative agents followed by also mechanisms to inhibitory inflammation response from lasting too long.[14] A shift from tissue damage resolution and repair takes place, including the concerted effort of proinflammatory as well as anti-inflammatory agents. Resolution and repair are mediated chiefly by tissue-resident and recruited macrophages including Prostaglandin E2[18], transforming growth factor-h[19], and reactive oxygen and nitrogen intermediates.[20] During resolution of inflammation, there is the rapid, organized removal of inflammatory cells by neighboring macrophages, dendritic cells, and backup phagocytes through induction of apoptosis and conducting phagocytosis.[21] The phagocytosis of apoptotic cells can enhance anti-inflammatory activity, like promoting the production of lipid mediators like resolvins and protectins, as well as transforming growth factor-β and growth factors produced by macrophages.[22] The shift in lipid mediators from pro-inflammatory prostaglandins to lipoxins, which are anti-inflammatory, is critical for the progression from inflammation to resolution. Lipoxins prevent the release of neutrophils and, rather, enhance the recruitment of monocytes, which eliminate dead cells and promote tissue remodeling.[23] However, if the acute inflammatory activity does not eradicate the causative agent successfully, there will be persistence of the inflammatory process and this new assumed inflammatory state is characterized by replacement of neutrophil infiltrates with macrophages and T cells. If the collective effect of these cells is not enough to resolve the inflammation, the cellular reaction changes to the pattern of chronic inflammation, including the development of granulomas and tertiary lymphoid tissues. The link between excessive and chronic inflammation and various disorders link cancer, type 2 diabetes, autoimmune diseases, cardiovascular diseases, and degenerative neurological diseases is well-established.[24] Regulation of inflammatory response is recognized to be crucial to reduce or prevent these diseases, and also to relieve painful conditions. Although targeting inflammation is a new therapeutic goal, the incidence of certain inflammatory diseases, such as asthma, cancer, type 2 diabetes, cardiovascular diseases, and allergies, has not been brought under control over the past few decades, and inflammation continues to be a major therapeutic target.[25]

Chronic inflammatory disease (CID): An Overview

Chronic inflammatory disease (CID) is a health status associated with chronic inflammation that arises from prolonged and persistent proinflammatory state characterized by infiltration

of immune cells like macrophages, lymphocytes, and plasma cells that lead to tissue damage, and fibrosis.[26] Moreover, the upregulation of proinflammatory molecules such as cytokines, Inducible nitric oxide synthase (iNOS), reactive oxygen species (ROS), nuclear factor kappa (NF-κB) is parallel to CID progression.[27] Diseases such as cancer, cardiovascular diseases (atherosclerosis, stroke, heart failure, and cerebrovascular disease), metabolic diseases (diabetes and metabolic syndrome), neurodegenerative diseases (Parkinson's disease, Alzheimer's disease, epilepsy and dementia), chronic inflammatory bowel disease, Chronic obstructive pulmonary disease pulmonary(COPD), rheumatoid arthritis, osteoarthritis, muscular dystrophy and chronic fatigue syndrome are linked with persistent and dysregulated inflammation processes. A substantial increase in some people suffering from CIDs over the last three decades has been observed. From an epidemiologic point of view, CIDs are amongst the largest cause of mortality worldwide. In 2015, the leading chronic diseases (Ischemic heart diseases, stroke, chronic obstructive pulmonary disease, lung cancer, Diabetes mellitus and Alzheimer's diseases) ranked amongst the top 7 and caused 22.99 million deaths worldwide.[96] Worldwide the annual death from CID is anticipated to rise by 2030; it has been hypothesized that 171 million people will be affected by CID in the United States.[28] A great number of studies have been carried to unravel the pathogenesis associated with CID like cardiovascular diseases[29],cancer[30, 31], type 2 diabetes[32], neurodegenerative diseases[33], chronic inflammatory bowel disease[34, 35],COPD[36],rheumatoid arthritis[37], osteoarthritis[38, 39],muscular dystrophy and chronic fatigue.[40] There are several possible mechanisms through chronic inflammation causes diseases: (1) Prolong production of reactive agents by infiltrating leukocytes tailored to eliminate pathogens, consequently causing destruction to the structural and cellular constituents of tissues; (2) destroy nonimmune cells and activated immune cells promote the production of cytokines that escalate or regulate the inflammatory reaction and modify the phenotypes of neighboring cells, usually to the disadvantage to the traditional tissue activity.(3) The intrusion with "anabolic signaling"; for instance, IL-6 and tumor necrosis factor-α repress Insulin-like growth factor-1, insulin, and erythropoietin signaling and protein synthesis after a meal.Circulating proinflammatory molecules are strong determinants of morbidity and mortality associated with chronic disease.[41] Nonetheless, it is unclear to what extent these systemic factors contributes towards CID in humans. Contrarily, there is increasing evidence in humans that the local production of inflammatory cytokines can drive phenotypes and pathologies associated with inflammation.[41] Therefore, upregulated levels of inflammatory mediators in the blood may be due to spillage from local origin. The potential causal role of

chronic inflammation in promoting diseases remains largely unknown. Therefore the discovery of pathways that modulate inflammation across various CID is crucial to understanding whether treatments that control chronic or dysregulated inflammation may be useful in the treatment and prevention of associated inflammation diseases.

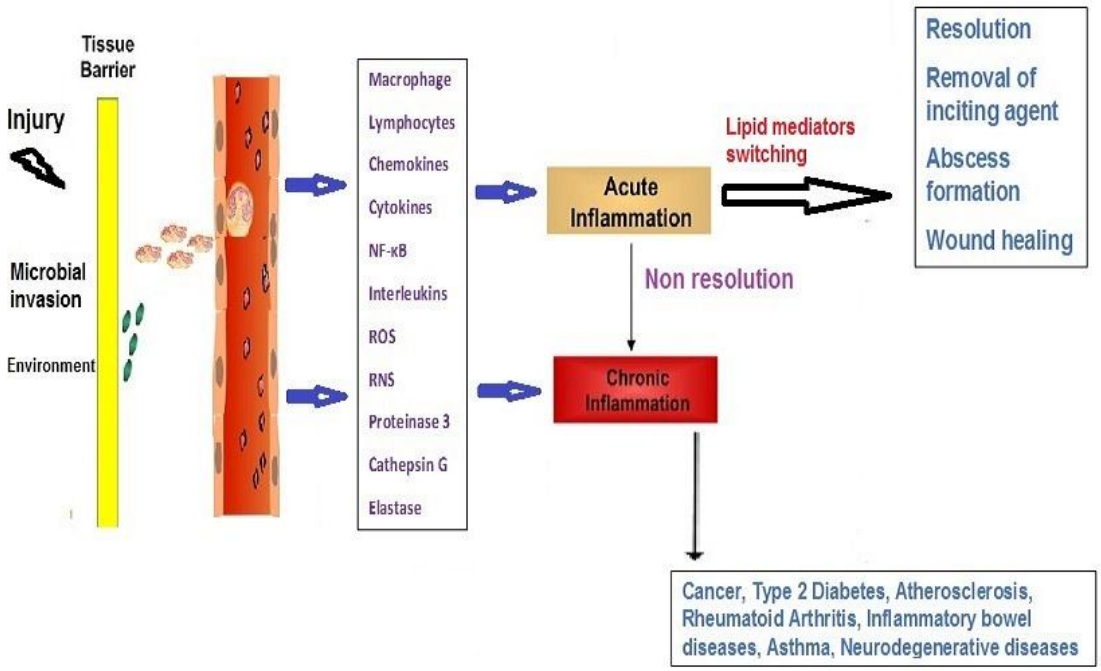

Figure 1: Pathway describing the change from acute to chronic inflammation.

Table 1: Expression of Major Inflammatory mediators in chronic inflammatory diseases.

Chronic inflammatory disorders	Major Inflammatory Mediators	References
Type 2 Diabetes	(IL)-1β, IL-6, TNF-α, and MAPK	[32, 42]
Cancer	TNF-α, IL-1, IL-6, NFκB, STAT, IKK, p38 MAPK, JNK1/2, ERK1/2, AP-1,iNOS, COX-2, and CXCR3/CXCR4	[43, 44]
Atherosclerosis	TNF, IL-6, IL-1, MCP-1, CRP, NF-κB,ICAM-1, VCAM-1, P-selectin, PECAM-1, Integrin α2/β3, MyD88, TLR4, TLR2, MMP1, MMP2, MMP3, MMP9 and MMP12,	[45, 46]
muscular dystrophy and chronic fatigue	NF-κB, MAPK, IL-6 and TNF-α	[47-50]
osteoarthritis	ROS, RNS, iNOS, NF-κB and IL-6	[51, 52]
Asthma	IL-2, IL-6, IL-10, CD40, HIF-1α JNK-, PAK-, p38-, ERK-, Jak/ Stat and NF-κB	[53, 54]
Congestive Heart Failure	TGF-β, MMPs, MCP-1, TNF-α, IL-1 and IL-6	[55, 56]
Alzheimer's Disease	TNF-α, superoxide, nitric oxide NO, ROS, IL-1β, and IL-6	[57, 58]

Multiple Sclerosis	IFN-γ, IL-17, and CCL2	[59, 60]
Rheumatoid Arthritis	JAK2, STAT3, TNF-α, IL-1β, IL-6 and NF-κB	[61, 62]
Peptic Ulcer	NF-κB, IL-8, P-selectin, ICAM-1, IL-1β, TNF-α, IL-6, p38 MAPK and ERKs	[63, 64]
Crohn's Disease	NF-κB, JAK, TNF-α, IL-6, IL-12, IL-23 and integrin/MAdCAM-1	[65, 66]
Acute Infection	IFN-γ, TNF, NO, iNOS, IL-6, and IL-12	[67, 68]
Stress	TNF-α, Akt, ERK, IL-6 and NF-κB	[69, 70]
Depression	VEGF, TNF-α, PI3K-Akt and MAPK-ERK, IL-1β, IL-6 and NF-κB	[69, 70]

Abbreviation. IL: interleukin, TNF: tumor necrosis factor-alpha, MAPK: mitogen-activated protein kinase, STAT: signal transducer and activator of transcription-3, IKK: IkB kinase, JNK: c-Jun NH2-terminal kinase, ERK: extracellular signal-regulated kinases, AP-1: activator protein-1, COX: cyclooxygenase, CXCR: chemokine receptor, MCP-1: monocyte chemotactic protein-1, CRP: C-reactive protein, ICAM-1: Intercellular Adhesion Molecule 1, VCAM-1: vascular cell adhesion molecule-1, PECAM-1: Platelet endothelial cell adhesion molecule, MyD88: Myeloid differentiation primary response gene 88, TLR: Toll-like receptor, MMP: Matrix metalloproteinases, NOS: nitric oxide synthase, CD40: Cluster of differentiation 40, Jak: Janus kinase, MAdCAM-1: mucosal vascular addressin cell adhesion molecule 1, HIF-1α: hypoxia-inducible factor 1α, PAK: p21-activated kinase, IFN-γ: Interferon gamma, CCL2: chemokine (C-C motif) ligand 2, Akt: Protein kinase B, PI3K: phosphoinositide 3-kinase.

Therapeutic Interventions that can change the actions of Inflammation and Prevent/treat Chronic Disease using natural plant products

Cancer

The first step that provides evidence of a possible relationship between Inflammation and cancer started in 1828 when Jean Nickolas Marjolin, a French surgeon accounted for the existence of squamous carcinoma in a post-traumatic chronically inflamed wound. Later in 1863, Dr. Rudolf Virchow proposed that cancer can originate from inflammation because he detected the presence of leukocytes in neoplastic tissues. Over the past decades, abundance studies have provided evidence to support cancer and inflammation hypothesis, and now it is established that inflammation is a hallmark of cancer.[71] Since time immemorial natural product has been the basis for drug discovery, as they can be useful as bioactive phytochemicals. Even when some phytochemicals are less or not biologically active, they can serve as a guideline to medicinal chemist and biochemists who modifies the structures to

induce various Pharmacological activities. Recently, six analogs of long chain fatty acid/ester of diosgenin-7- ketoxime (Diosgenin is a phytosteroid sapogenin found mainly in *Dioscorea* spp) exhibited significant anticancer activity against a panel of human cancer cell lines. (22, 25R)- 3_-hydroxy-spirost-5-en-7-iminoxy-heptanoic acid, an important representative of the series exerted S phase arrest in DU145 prostate cancer cells and induced apoptosis through caspase pathway. Additionally, these analogs inhibited lipopolysaccharide-induced proinflammatory cytokines (TNF-α and IL-6).[72] Studies have shown how inhibition of TNF-α and IL-6 have led to the suppression tumor proliferation.[73] Therefore, it can be said that the anticancer activities demonstrated by these analogs match up with their anti-inflammatory properties. The anticancer and anti-inflammatory properties of (22_,25R)- 3_-hydroxy-spirost-5-en-7-iminoxy-heptanoic acid are essential and can further be improved for an excellent anti-prostate cancer candidate.[72] A natural flavonol glycoside, quercetin-3-O-b-D-galactopyranoside (hyperoxide) isolated from the genus Hypericum, have shown a remarkable anticancer property by promoting apoptosis and repressing proliferation of lung cancer in-vitro.[74] The induction of apoptosis by hyperoxide could be as a result of the inhibition of NF-kB transcriptional activity; as NF-kB has been reported to be involved in apoptosis via the Akt-regulated pathways.[75, 76] Other phytochemicals that have the ability to modulate inflammation in cancer includes Mangiferin and Ginsenoside Rc. These two have shown the significant inhibitory effect on various inflammatory markers such as TNF-α, IL-1β, IL-6, AP-1, NF-kB and COX-2[77, 78], which a known to be critical involved in promoting tumor cell proliferation, transformation, invasion, metastasis, and angiogenesis.

Type 2 diabetes

Over the last decades, recognition of the role of inflammation in type 2 (T2D) has escalated. Although the main known pathological causes are insulin resistance (IR) and β- cell dysfunction, substantial advances in basic and experimental science have to a greater extent reveal the role of inflammation and the possible cellular and molecular mechanisms that contribute to initiation and progression of T2D. Compelling evidence for the significance of inflammation and T2D at both the basic and clinical level has evolved in parallel. Also, insights gained from the link between inflammation and T2D can yield predictive and prognostic information of considerable clinical utility. A great body of evidence have demonstrated the connection between chronic low-grade inflammation with the pathogenesis of T2DM.[79] The plant product, Bamboo *Phyllostachys edulis* Extract (BEX) have proven to be a cost-effective antiinflammation nutraceutical by Suppressing lipotoxicity-induced IL-6

in T2D.[80] However, the Safety and Efficacy of BEX for human consumption is still undergoing investigation. Therefore, more studies are needed to identify the compound(s) in BEX that is responsible for its anti-inflammatory property, to ascertain its potency of becoming a drug candidate. The Ethyl acetate (EtOAc) fraction of *Brucea javanica* seeds demonstrated an inhibitory effect on TNF-α, IL-6, and IL-1β, making it valuable for the treatment of T2D.[81] A streptozotocin-nicotin- amide model has been used to determine the therapeutic effect of the EtOAc of *Clerodendrum volubile* leaves, wherein the expression levels of α –glucosidase and TNF- α were suppressed.[82] Also, a bioactive compound, a protocatechuic acid which can be a possible drug candidate for the treatment of T2D was isolated from *Clerodendrum volubile.*[82] Diabetea tea TM (DT) a black tea obtained from *Camellia sinensis* including 12 other medicinal plant supplements, may provide a beneficial adjunctive therapy for T2D. DT constitute of flavonoids, triterpenes, and phytosterol which could be synergically responsible for its anti-inflammatory action of suppressing CD4+ T cell expression of IL-1β and IL-8.[83] Evidence from numerous experimental studies has identified quercetin (one of the most abundant of plant flavonoids) to be highly valuable for the treatment of T2D.[84] As a matter of fact, quercetin has shown to suppress a broad range of inflammatory markers such as cyclooxygenase (COX), NF-*κ*B, NO, iNOS, IL-6, TNF-*α*[85], lipoxygenase (LOX)[86] and IL-1β.[87] More recently, quercetin and ascorbic acid inhibited fructose-induced NOD-like receptor protein 3 (NLRP3) inflammasome activation and decreased the gene expressions of IL-1β, IL-18, and caspase-1 in human macrophages.[88] Also, the production of reactive oxygen species (ROS) was significantly reduced by the administration of quercetin.[88]

Atherosclerosis

Atherosclerosis is a progressive disease beginning with aggregation of lipids, lipoproteins, and immune cells in the arterial wall. Movement of inflammatory cells towards atherosclerotic lesion sites plays a pivotal role in atherogenesis. Abundance proofs support the presence of monocyte-containing cytokines and macrophage. Secretion of growth factors, cytokines, and inflammatory mediators influence the growth of different cell types residing inside the atherosclerotic lesion. Cytokines like interleukin (IL)-1, tumor necrosis factor-α (TNF-α), and IL-6 are produced by endothelial cells (ECs), SMCs, T cells, monocytes, macrophages, and platelets in response to inflammation and other stimuli. An increased production of pro-inflammatory cytokines is related to disease progression and promotes atherosclerosis.[89] *Plantago lanceolata*, a plant that has been traditionally used for the

treatment of inflammatory disorders such as skin diseases[90] have recently demonstrated the ability to be useful as an anti- atherosclerosis agent. n-Hexane Insoluble Fraction of *Plantago lanceolate* was able to suppress the expression of the proinflammatory enzyme, COX-2, reduced the level of chemokines, Interleukine-8 (IL-8) and Monocyte chemoattractant protein-1 (MCP-1), and consequently inhibited the migration of leukocytes.[91] Moreover, A phenanthrene derivative, 5, 7-dimethoxy-1,4-phenanthrenequinone (DMPQ) markedly decreased tumor necrosis factor-α (TNF-α)-induced intercellular adhesion molecule and vascular CAM expression in endothelial cells (ECs). Also, DMPQ ameliorated the activities of TNF-α-induced IκB activation, nuclear factor kappaB (NF-κB) translocation, NF-κB-DNA complex formation and reactive oxygen species production. All of these effects of DMPQ contributed to its anti-inflammatory and anti-migratory bioactivity toward vascular ECs and Smooth Muscle Cells (SMCs).[92] Making it attractive for use in the treatment of atherosclerosis. Based on available evidence that have implicated Advanced glycation end products (AGEs) to be involved in atherosclerotic cardiovascular disease, Yuji *et al*. went further investigate the effects of n-butanol extracts of *Morinda citrifolia* (noni) on reactive oxygen species (ROS) generation and inflammatory reactions on AGE-exposed human umbilical vein ECs (HUVECs). Noni exerted an inhibitory effect on AGE-induced ROS production, the receptor for AGEs (RAGE), intercellular adhesion molecule-1 and plasminogen activator inhibitor-1 gene expressions.[93] Furthermore, an experimental study carried out to evaluate the ability of quercetin to inhibit high fructose feeding- or LPS-induced atherosclerosis through regulating oxidative stress, apoptosis and inflammation response, revealed the ability of quercetin to attenuated LPS-induced ROS production and inflammatory response via the suppression of the activities and expression of PI3K/AKT-regulated Caspase-3 and NF-kB pathways.[94] This finding suggests the anti-atherosclerotic therapeutic potential of quercetin.

CONCLUSION AND FUTURE DIRECTION

One of the principal mechanism by which chronic inflammation promotes disease is via aberrant activation of intracellular signaling molecules. The increasing knowledge on how chronic inflammation influence the outcomes of several disease conditions provides a solid foundation for the targeting of key molecules of inflammation like cytokines, inflammatory enzymes(iNOS, COX-2), transcription factors(NFkB) and growth factors for disease prevention as well as therapeutics. Evidence obtained from several experimental and clinical studies have highlighted the importance of targeting the altered cell signaling transduction

pathways to block the transmitted signals to downstream transcription factors and co-activators culminating in carcinogenesis. Despite the promising results with the use nonsteroidal anti-inflammatory agents in clinical practice to modify the process of inflammatory diseases, a significant number of patients have shown poor outcomes, and because of this, the attempt to discover new therapies with improved efficacy and reduce side effects continue. Plant extracts and their associated phytochemicals have been extensively studied for their anti-inflammatory properties, antioxidant activities, and activation or inhibition of signal transduction pathways. A great variety of anti-inflammatory plant natural products has been isolated from fruits, vegetables, spices and traditional herbal compounds. These natural products have gained overwhelming interest over the past three decades for application as preventive or therapeutic agents in chronic inflammatory diseases. Progress in cellular, biochemical and molecular biology practice and experimental strides have offered useful new insights into therapeutics, such as the uncovering of different plant secondary metabolites as natural products to treat immune imbalances and inflammation-related abnormalities. These plant secondary metabolites may display substantial benefits over synthetic drug as they provide a less costly, nontoxic, handy and accessible health-care approach for prevention, control, and management of these diseases. However, the correct use of these natural agents as medicines requires concerted future systematic research, particularly in line with translational study rather than the present mechanistic path and there is increasing enthusiasm about their future. The increasing development of novel evidence for the precise anti-inflammatory actions of these natural plant agents on cell signaling and molecular target pathways has added much incentive for a prospective study into their mechanism of action and their use preventive and therapeutic agents. There exist a major problem for researchers on how to make excellent use of these anti-inflammatory plant natural agent for prevention of CID in diverse populations. The use of individualized medicines (as prescribed in traditional Chinese medicine practice), a knowledge of the fluctuating nutritional requirements for distinct races or individuals are all considerations for choosing anti-inflammatory treatment. Furthermore, additional improvement of these effective natural agents is required to boost the potency of intended therapeutic design to tackle inflammatory diseases in the future. Moreover, further consideration is required for combinational approaches utilizing fractionated or crude plant extracts and various plant formulations amidst the few ongoing clinical trials including single anti-inflammatory plant natural products with multiple activities.[95] Prospectively, continuing systematic and epidemiological studies of human clinical trials of plants with specific anti-inflammatory

activities will be vital to providing possible insight of their anti-inflammatory potential. Our increase in knowledge of the novel inflammatory signaling pathways, transcription factors and molecular target genes modulated by anti-inflammatory plant agents offers great promise as preventive and therapeutic improve the quality of life for all. Although many of the natural products appear to be very promising, the should be precisely isolated and adequately characterized for strong actions over a range of disease phenotypes. Moreover, to translate the above discussed natural products into clinical use, their toxicity and their bioavailability should be properly scrutinized either alone or in combination with existing therapy. Finally, studies have shown that majority of inflammatory diseases exhibit high genetic heterogeneity and the trend of resurgence associated with several treatments are as a result of the emergence of resistance to therapy. Therefore, plant anti-inflammatory treatments along this path should be linked with other related methods that target precise pathways which have significance across the range of disease phenotypes, and this will serve as a good recipe to tackle the challenge of heterogeneity. Although this approach is encouraging, extensive studies needs to be carried out to ascertain further the methodological effectiveness.

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