Extended|Longevity

Scientific White Paper

Inflasolve Formula reduces systemic "Inflammaging". Includes phytotherapeutic extracts of: *Curcuma longa*, *Boswellia sacra, Salix alba, Camellia sinensis and Cinnamomum verum*. Bioavailability, Biological Actions, Molecular Mechanisms, and Their Effects.

Steven M Schorr
***Extended Longevity, Inc**., Department of Scientific Research. P.O. Box 448 Puunene, HI 96784 USA*

Inflasolve Formula is formulated to reduce systemic inflammation that is a root cause of aging called "Inflammaging". It contains phytotherapeutic extracts of: ***Curcuma longa Boswellia sacra, Salix alba, Camellia sinensis and Cinnamomum verum.*** This formula is a synergistic herbal analog providing anti-inflammation support for all human cells and organ functions.

Turmeric Extract

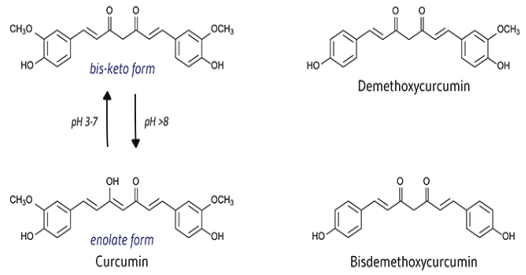
Turmeric is a spice derived from the rhizomes of the tropical plant Curcuma longa, which is a member of the ginger family (Zingiberaceae). Turmeric is a plant that has a very long history of medicinal use, dating back nearly 4000 years. The bright yellow-orange color of turmeric comes mainly from fat-soluble, polyphenolic pigments known as curcuminoids. Curcumin, the principal curcuminoid found in turmeric, is generally considered its most active constituent. Turmeric and curcumin are non-mutagenic and non-genotoxic. Turmeric root and its curcuminoid constituents have demonstrated properties consistent with decreases in inflammatory stress signaling and increases in protective signaling. Curcumin is known to have anti-aging, anti-oxidant, anti-inflammatory, anti-arthritic, and anti-cancer effects and increases BDNF while having a positive effect on Alzheimer's disease and depression. Turmeric can play an important role in the prevention and treatment of various illnesses ranging from cancer to autoimmune, neurological, cardiovascular diseases, and the effects of aging.

Turmeric Overview

Turmeric contains bioactive compounds with powerful medicinal properties**.** Turmeric contains curcumin, a substance with powerful anti-inflammatory and antioxidant properties. Curcumin (1,7-bis [4-hydroxy-3-methoxyphenyl]-1,6 heptadiene-3,5-dione), the yellow pigment occurring as the most active component in turmeric obtained from *Curcuma longa*, has emerged as the newest "nutraceutical" agent that is efficacious against colon cancer and other disorders, including correcting cystic fibrosis (CF) defects. In addition to inhibiting tumorigenesis, metastasis, platelet aggregation, inflammatory cytokine production, cataract formation, inflammatory bowel disease, and myocardial infarction, curcumin has been shown to lower cholesterol, suppress diabetes, enhance wound healing, modulate multiple sclerosis and Alzheimer's disease,

and block human immunodeficiency virus replication. More than 100 components have been isolated from turmeric. The main component of the root is a volatile oil, containing turmerone, and there are other coloring agents called curcuminoids in turmeric.

Figure 1. Major Turmeric-derived Curcuminoids



Curcuminoids in turmeric roots are a mixture of three main compounds: curcumin (~77%), demethoxycurcumin (~17%), and bisdemethoxycurcumin (~3%). Curcumin exists in two molecular configurations (known as tautomers): the bis-keto form is predominantly found in neutral and acidic conditions and in a solid phase, while the enolate form is predominately found in alkaline conditions.

Curcuminoids

Curcuminoids, occurring in Turmeric root, have been demonstrated to exert beneficial effects in a large array of disease states, including cancer, cardiovascular disease, and neurodegenerative disorders. Many of the biological effects of curcuminoids have been attributed to their antioxidant properties, either through their reducing capacities or through their influences on intracellular redox status. Curcuminoids may protect cell constituents against oxidative damage and have been reported to limit the risk of various degenerative diseases associated with oxidative stress, including cardiovascular diseases, and cancer.

Bioavailability

Clinical trials in humans indicate that the systemic bioavailability of orally administered curcumin is relatively low. Metabolites of curcumin are detected in plasma or serum following oral consumption. In the intestine and liver, curcumin is readily conjugated to form curcumin glucuronide and curcumin sulfate or reduced to tetra-hydrocurcumin, hexa-hydrocurcumin, and octahydrocurcumin. Increasing bioavailability requires innovative strategies including alcohol extraction using heat, without degrading the bioactivity of the extracted constituents. Research papers show that curcumin content for alcohol extract of turmeric is 10.23% whereas it is 3.5% in average turmeric powders. For a given dose or equal amounts of the two, alcoholic turmeric extract will provide you with more curcumin. Research has also shown increased solubility of curcumin (12 fold or 1,200%) and turmeric (3 fold) by the use of heat. Spectrophotometric (400-700 nm) and mass spectrometric profiling of the heat-extracted curcumin displays no significant heat-mediated disintegration of curcumin. The treatment with heat did not destroy curcumin's biological activity. The treatment with heat, however, appears to protect curcumin from breaking down faster.

Anti-inflammatory Properties of Curcumin

Curcumin is a natural anti-inflammatory compound. Inflammation helps your body fight foreign invaders and also has a role in repairing damage. Without inflammation, pathogens like bacteria could easily take over your body. Short-term inflammation is beneficial, but it can become a problem when it becomes chronic and attacks your body's tissues. Chronic, low-level inflammation plays a major role in almost every Western disease. This includes heart disease, cancer, metabolic syndrome,

Alzheimer's and various degenerative conditions. Anything that can help fight chronic inflammation is of potential importance in preventing and even treating these diseases. Curcumin matches the effectiveness of some anti-inflammatory drugs, without the side effects. It blocks NF-kB, a molecule that travels into the nuclei of your cells and turns on genes related to inflammation. NF-kB is believed to play a major role in many chronic diseases. Curcumin is a bioactive substance that fights inflammation at the molecular level.

Curcumin has been shown to inhibit mediators of the inflammatory response, including cytokines, chemokines, adhesion molecules, growth factors, and enzymes like cyclooxygenase (COX), lipoxygenase (LOX), and inducible nitric oxide synthase

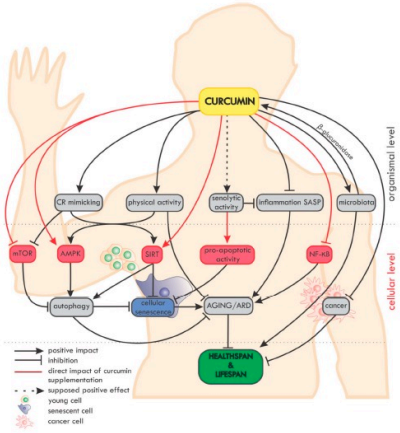


Figure 2. Overview of the impact of curcumin on ageing and age-related diseases (ARD) at the organismal and cellular level. On the organismal level, curcumin mimics caloric restriction (CR) and improves the effectiveness of physical activity (which in fact mimics CR). The potential senolytic activity of curcumin is still unclear, but curcumin can reduce inflammation and SASP, which are also considered as elements of senotherapy. Moreover, curcumin maintains the diversity of the microbiome and, in turn, the microbiota secrete β-glucuronidase, an enzyme, which, by deglucuronisation increases the level of curcumin in tissues. Curcumin is able to protect against cancer and to reduce the progression of already existing tumors. On the cellular level, curcumin elevates the level/activity of some anti-ageing proteins (e.g., sirtuins, AMPK) and inhibits pro-ageing ones (e.g., NF-κB, mTOR). Autophagy, considered as an anti-ageing mechanism, is modulated by curcumin, with the effect of preventing cell senescence. Altogether, by delaying ageing and ARD, curcumin can elongate the healthspan and probably also the lifespan.

iNOS). Nuclear factor-kappa B (NF-ϰB) is a transcription factor that binds DNA and induces the transcription of the COX-2 gene, other pro-inflammatory genes, and genes involved in cell proliferation, adhesion, survival, and differentiation. The anti-inflammatory effects of curcumin result from its ability to inhibit the NF-ϰB pathway, as well as other pro-inflammatory pathways like the mitogen-activated protein kinase (MAPK)- and the Janus kinase (JAK)/Signal transducer and activator of transcription (STAT)-dependent signaling pathways. Curcumin has also been found to reduce the secretion of TNF-α and IL-1β and the production of COX-2-induced prostaglandin G2.

Rheumatoid arthritis

A preliminary intervention trial that compared curcumin with a nonsteroidal anti-inflammatory drug (NSAID) in 18 patients with rheumatoid arthritis (RA) found that improvements in morning stiffness, walking time, and joint swelling after two weeks of curcumin supplementation (1.2 g/day) were comparable to those experienced after two weeks of phenylbutazone (NSAID) therapy (300 mg/day). In a more recent randomized, open-label study in 45 RA patients, supplementation with a mixture of all three major curcuminoids (0.5 g/day for eight weeks) was found to be as effective as diclofenac (NSAID; 50 mg/day) in reducing measures of disease activity, tenderness, and swelling joints. Larger randomized controlled trials are needed to determine whether oral curcumin supplementation is effective in the treatment of RA.

Ulcerative colitis

Ulcerative colitis (UC) is a long-term condition characterized by diffuse and superficial inflammation of the colonic mucosa. Disease activity may

fluctuate between periods of remission and periods of relapse. Preliminary evidence suggests that curcumin might be useful as an add-on therapy to control disease activity. Larger trials are needed to ensure that curcumin can be safely used with conventional UC treatments and to further support its potential therapeutic benefits for relapsing-remitting UC.

Turmeric as an Antioxidant

Turmeric dramatically increases the antioxidant capacity of the body. Oxidative damage is believed to be one of the mechanisms behind aging and many diseases. It involves free radicals, highly reactive molecules with unpaired electrons. Free radicals tend to react with important organic substances, such as fatty acids, proteins or DNA. The main reason antioxidants are so beneficial is that they protect your body from free radicals. Curcumin is a potent antioxidant that can neutralize free radicals due to its chemical structure. Curcumin boosts the activity of your body's antioxidant enzymes. Curcumin works against free radicals. It blocks them directly, then stimulates your body's antioxidant defenses.

Curcumin and Brain-Derived Neurotrophic Factor (BDNF)

Curcumin boosts brain-derived neurotrophic factor linked to improved brain function and a lower risk of brain diseases. Neurons are capable of forming new connections, but in certain areas of the brain, they can also multiply and increase in number. One of the main drivers of this process is brain-derived neurotrophic factor (BDNF), which is a type of growth hormone that functions in your brain. Many common brain disorders have been linked to decreased levels of this hormone, including depression and Alzheimer's disease. Curcumin can increase brain levels of BDNF. It may be effective in delaying or even reversing many brain diseases and age-related decreases in brain function. It may also improve memory and make you smarter, which seems logical given its effects on BDNF levels. Curcumin boosts levels of the brain hormone BDNF, which increases the growth of new neurons and fights various degenerative processes in your brain.

Curcumin and Heart Disease

Curcumin may help reverse many steps in the heart disease process. The main benefit of curcumin when it comes to heart disease is improving the function of the endothelium, which is the lining of your blood vessels. Endothelial dysfunction is a major driver of heart disease and involves an inability of your endothelium to regulate blood pressure, blood clotting and various other factors. Curcumin has beneficial effects on several factors known to play a role in heart disease. It improves the function of the endothelium and is a potent anti-inflammatory agent and antioxidant.

Turmeric and Cancer

Turmeric may help prevent cancer. There are many different forms of cancer. Some of them appear to be affected by curcumin. Curcumin has been studied as a beneficial herb in cancer treatment and been found to affect cancer growth, development and spread at the molecular level. Studies have shown that it can contribute to the death of cancerous cells and reduce angiogenesis (growth of new blood vessels in tumors) and metastasis (spread of cancer). There is evidence that it may prevent cancer from occurring in the first place, especially cancers of the digestive system like

colorectal cancer. Curcumin leads to several changes on the molecular level that may help prevent and perhaps even treat cancer. "While the chemotherapeutic effect of curcumin, one of three major curcuminoids derived from turmeric, has been reported, largely unexplored are the effects of complex turmeric extracts more analogous to traditional medicinal preparations, as well as the relative importance of the three curcuminoids and their metabolites as anticancer agents. These studies emphasize the structural and biological importance of curcuminoids in the anti-breast cancer effects of turmeric and contradict recent assertions that certain of the curcuminoid metabolites studied here mediate these anticancer effects." Ethanolic turmeric extract was found to have opposing actions on murine lymphocytes and on Ehlrich ascitic carcinoma cells. Turmeric enhances lymphocyte viability and blastogenesis but induces the formation of cytoplasmic blebs and plasma membrane disintegration of tumor cells. Thus, it is suggested that turmeric is a conducive agent for lymphocytes and inhibitory as well as apoptosis-inducing for tumor cells.

Inhibition of proliferation and induction of apoptosis

Following DNA damage, the cell cycle can be transiently arrested to allow for DNA repair or for activation of pathways leading to programmed cell death (apoptosis) if the damage is irreparable. Defective cell-cycle regulation may result in the propagation of mutations that contribute to the development of cancer. Unlike normal cells, cancer cells proliferate rapidly and are unable to respond to cell death signals that initiate apoptosis. Curcumin has been found to induce cell-cycle arrest and apoptosis by regulating a variety of cell-signaling pathways. For example, the inhibition of cell proliferation by curcumin has been associated with the Nrf2-dependent downregulation of DNA repair-specific flap endonuclease 1 (Fen1) in breast cancer cells in culture. Curcumin has been shown to induce p53-dependent or -independent apoptosis depending on the cancer cell type. In a panel of cancer cell lines, p53-independent apoptosis induced by curcumin was mediated by the rapid increase of ROS and the activation of MAPK and c-jun kinase (JNK) signaling cascades. Inhibition of NF-κB signaling by curcumin also suppresses proliferation and induces apoptosis in cancer cells.

Curcumin and Alzheimer's disease.

Curcumin may be useful in preventing and treating Alzheimer's disease. Alzheimer's disease is the most common neurodegenerative disease in the world and a leading cause of dementia. Curcumin has been shown to cross the blood-brain barrier. It's known that inflammation and oxidative damage play a role in Alzheimer's disease, and curcumin has beneficial effects on both. A key feature of Alzheimer's disease is a buildup of protein tangles called amyloid plaques. Studies show that curcumin can help clear these plaques. Alzheimer's disease (AD) is a form of dementia characterized by extracellular deposition of β-amyloid plaques, the intracellular formation of neurofibrillary tangles, and neuronal loss, brain atrophy and cognitive impairment in affected individuals. When injected into the carotid artery, curcumin was found to cross the blood-brain barrier in an animal model of AD, though it is not known whether curcumin taken orally can reach the blood-brain barrier at sufficient concentrations and impede cognitive

decline in humans. A randomized, double-blind, placebo-controlled trial in 60 healthy older adults (mean age, 68.5 years) investigated whether acute (80 mg) or chronic (80 mg/day for 4 weeks) oral intake of curcumin could improve their ability to cope with the mental stress and change in mood usually associated with undergoing a battery of cognitive tests. A significant reduction in mental fatigue and higher levels of calmness and contentedness following cognitive test sessions were observed in individuals who consumed curcumin (either acutely or chronically) compared to the placebo group. Additionally, the results of cognitive ability tests suggested that curcumin treatment had limited benefits on cognitive function, as shown by better scores in measures of sustained attention and working memory compared to placebo. The results of a six-month trial in 27 patients with AD found that oral supplementation with up to 4 g/day of curcumin — containing all three major curcuminoids — was safe.

Curcumin and Arthritis

Arthritis can be treated with Curcumin. Arthritis is a common problem. There are several different types, most of which involve inflammation in the joints. In a study in people with rheumatoid arthritis, curcumin was even more effective than an anti-inflammatory drug. Many other studies have looked at the effects of curcumin on arthritis and noted improvements in various symptoms. The antiarthritic effects of turmeric include inhibition of joint inflammation and periarticular joint destruction. In vivo treatment with turmeric extract prevented local activation of NF-κB and the subsequent expression of NF-κB-regulated genes mediating joint inflammation and destruction, including chemokines, COX-2, and the receptor activator of NF-κB ligand. It also inhibited inflammatory cell influx, joint levels of PGE2, and periarticular osteoclast formation in rats. Turmeric extract, when given intraperitoneally, was found to be more active than hydrocortisone. The yellow powder of turmeric is known to have potent vasorelaxant activity and to decrease the atherogenic properties of cholesterol. A study showed that supplementation of turmeric in the diet-controlled arterial blood pressure in animals and enhanced vasorelaxant responses to adenosine, acetylcholine, and isoproterenol. Turmeric's anti-atherosclerotic effect is associated with inhibition of low-density lipoprotein oxidation, prevention of lipoperoxidation, and reduction in levels of cholesterol. A study showed that feeding an ethanolic extract of turmeric to rats elevated the high-density lipoprotein (HDL)-cholesterol/total cholesterol ratio. The extract also caused a significant decrease in the ratio of total cholesterol/phospholipids.

Curcumin and Depression

Turmeric is also useful against depression (Yu, Kong, and Chen 2002; Xia et al. 2006; Xia et al. 2007). Its ethanolic extract markedly attenuated swim stress-induced decreases in serotonin, 5-hydroxyindoleacetic acid, and noradrenaline and dopamine concentrations, as well as increases in serotonin turnover. Also, this extract significantly reversed swim stress-induced increases in serum corticotropin-releasing factor and cortisol levels and thus regulated neurochemical and neuroendocrine systems in mice (Xia et al. 2007). The extracts significantly inhibited brain monoamine oxidase (MAO)-A activity at a

low dose, but at a higher dose, they inhibited brain MAO-B activity. In comparison, fluoxetine showed only a tendency to inhibit MAO-A and -B activity in animal brains. These results demonstrate that turmeric has specific antidepressant effects in vivo.

Curcumin and Aging

Curcumin fights age-related chronic diseases. By preventing heart disease, cancer and Alzheimer's, Curcumin has obvious benefits for longevity. Given that oxidation and inflammation are believed to play a role in aging, curcumin's effects go beyond just preventing disease. Lifespan is regulated by genes controlling the activity of metabolism, antioxidant systems, DNA repair, cellular senescence, and cell death. Their functions gradually decline due to random errors in DNA replication and damage to macromolecules, which leads to the accumulation of senescent cells and damaged tissue with age. However, diverse tissues building various organs may show different patterns of senescence. A key in the aging of an organism is immune-senescence which may play a part in the age-related immunological changes. Lifelong exposure to a plethora of antigens (bacterial, viral, exogenous, auto, which can be considered as stressors) leads to a gradual decline of naive T cells. In turn, there is an accumulation of memory T and effector CD8+CD28- T cells that secrete increased amounts of pro-inflammatory cytokines. Cellular participants in low-grade inflammatory status not only include cells of the immune system but also other ones which have undergone genotoxic stress-induced senescence and secrete many inflammatory cytokines, to the so-called senescence-associated secretory phenotype (SASP). Curcumin can counteract the pro-inflammatory state which is believed to participate in many age-related diseases. It seems that curcumin directly affects a few major targets, just like ROS scavenging and production and the NF-B signaling pathways, which can, in turn, suppresses the pro-inflammatory state involved in the etiology of aging and age-related diseases.

Curcumin and Diabetes

Oxidative stress and inflammation have been implicated in the pathogenesis of type 2 diabetes mellitus and related vascular complications. A large body of preclinical evidence suggests that the antioxidant, anti-inflammatory, and glucose-lowering activities of curcumin and its analogs may be useful in the prevention and/or treatment of type 2 diabetes.

Curcumin supplementation was shown to reduce insulin resistance and improve measures of pancreatic β-cell function and glucose tolerance. Supplemental curcumin was found to be as effective as lipid-lowering drug atorvastatin (10 mg/day) in reducing circulating markers of oxidative stress (malondialdehyde) and inflammation (endothelin-1, TNFα, IL-6) and in improving endothelial function. Larger trials are needed to assess whether curcumin could be useful in the prevention or management of type 2 diabetes and vascular complications.

Efficacy of Boswellia

The herbal extracts prepared from the Boswellia are found to be novel, potent, specific useful biological properties such as anti-inflammatory, anti-arthritic, antirheumatic, anti-diarrheal, anti-hyperlipidemic, anti-asthmatic, anti-cancer, anti-microbial, anti-fungal, anti-complementary and analgesic activity

agents due to non-redox inhibition of 5-lipoxygenase (5-LO) enzyme. The other important targets of Boswellic acids also include topoisomerases, angiogenesis, and cytochrome p450 enzymes. It is considered as the potential pharmacophoric molecule of natural origin that can play a vital role in drug discovery of anti-inflammatory and chemotherapeutic agents. Boswellia serrata extract use in patients with osteoarthritis has been substantiated; dramatic alleviation in the frequency of joint swelling and pain and augmentation in joint flexibility and walking distance have been observed at the end of treatment period. Likewise, a significant reduction in erythrocyte sedimentation rate (ESR), morning stiffness, and NSAID administration requirement during therapy has occurred in rheumatoid arthritis patients within another clinical trial. In one pilot study which has been carried out on patients with chronic polyarthritis, no significant remission has been observed in patient's manifestations after 12 weeks of therapy with extract of B. serrata ; just minor attenuation in NSAIDs requirement has been recorded. Collagenous colitis is an inflammatory bowel disease (IBD) and B. serrata has been clinically effective in the process of ameliorating this disease in target therapy group compared to the placebo group [48]. The combination of B. serrata with C. longa has been effective on improvement of asthmatic patient's symptoms and has demonstrated significant diminishing in plasma level of leukotriene C4. Modulating in inflammatory mediators (TNF-α , IL-1β , IL-6, IFN-γ , and PGE2) by B. serrata extract has been proved in in vivo and in vitro studies. Boswellic acid is the main component of this gum which can inhibit C3 convertase and suppressed classic pathway of complement system. It has had topical anti-inflammatory impress as well as systemic effects.

Efficacy of Salix alba

Bark from the Salix alba tree is one of the oldest herbal remedies for pain and inflammation, dating back to ancient Egyptian, Roman, Greek, and Indian civilizations, as an analgesic and antipyretic agent. Because of the gastric side effects of aspirin, there has been a resurgence in the use of white willow bark for the treatment of inflammatory syndromes. The mechanism of action of Salix alba is similar to that of aspirin which is a nonselective inhibitor of COX-1 and COX-2, used to block inflammatory prostaglandins. Various randomized, placebo-controlled studies comparing white willow bark with nonsteroidal agents have shown an efficacy comparable to these agents and aspirin. Salicin from Salix alba bark is converted to salicylic acid by the liver and is considered to have fewer side effects than aspirin.

Efficacy of Camellia sinensis

Camellia sinensis has long been recognized to have cardiovascular and cancer preventative characteristics due to its antioxidant properties. Its use in the treatment of arthritic disease as an anti-inflammatory agent has been recognized more recently. The constituents of Camellia sinensis are polyphenolic compounds called catechins, and epigallocatechin-3 galate is the most abundant catechin in Camellia sinensis. Epigallocatechin-3 galate inhibits IL-1–induced proteoglycan release and type 2 collagen degradation in cartilage explants. In human *in vitro* models, it also suppresses IL-1b and attenuates activation of the transcription factor NF-kB.

Active Herbal Ingredients

Curcuma longa, or Turmeric root, and its curcuminoid constituents have demonstrated properties consistent with decreases in inflammatory stress signaling and increases in protective signaling. Curcumin is known to have anti-aging, anti-oxidant, anti-inflammatory, anti-arthritic, and anti-cancer effects and increases BDNF while having a positive effect on Alzheimer's disease and depression. It is also anti-rheumatic, and anti-microbial.

Boswellia sacra, is anti-inflammatory, anti-arthritic, anti-rheumatic, anti-diarrheal, anti-hyperlipidemic, anti-asthmatic, anti-cancer, anti-microbial, anti-fungal, anti-complementary and analgesic activity.

Salix alba. The mechanism of action of Salix alba is similar to that of aspirin which is a nonselective inhibitor of COX-1 and COX-2, used to block inflammatory prostaglandins. Salicin from Salix alba bark is converted to salicylic acid by the liver and is considered to have fewer side effects than aspirin. A research group screened 37 different plant extracts to see what effect they might have on slowing aging and extending life. Salix alba was found to be the most potent life extension substance ever found. A specific extract of white Salix alba is the most potent longevity - extending pharmacological intervention ever described in the scientific literature.

Camellia sinensis, has diverse pharmacological activities, including anti-hyperglycemia, antioxidative, anti-obesity and antitumor activities. the major theaflavins in black tea are theaflavin (TF1), theaflavin-3-gallate (TF2A), theaflavin-3'-gallate (TF2B) and theaflavin-3,3'-digallate (TF3). The polyphenolic compounds in Camellia sinensis demonstrate potential antitumor and anti-oxidant effects in various cancer cell lines, including gastric, colon, and lung. Its use in the treatment of arthritic disease as an anti-inflammatory agent has been recognized. The constituents of Camellia sinensis are polyphenolic compounds called catechins, and epigallocatechin-3 galate is the most abundant catechin in Camellia sinensis. Epigallocatechin-3 galate inhibits IL-1–induced proteoglycan release and type 2 collagen degradation in cartilage explants. It also suppresses IL-1b and attenuates activation of the transcription factor NF-kB.

Cinnamomum verum, Cinnamon health benefits are attributed to its content of a few specific types of antioxidants, including polyphenols, phenolic acid and flavonoids. These compounds work to fight oxidative stress in the body and aid in the prevention of chronic disease. The effects of cinnamon on life span implicated major longevity pathways. These include the DAF-16 transcription factor in the insulin signaling pathway, which promotes expression of stress resistance and the longevity genes. Cinnamon activates the insulin signaling pathway, anti-oxidative pathway and serotonin signaling for its lifespan prolonging effect.

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Review Article

Natural anti-inflammatory agents for pain relief

Joseph C. Maroon, Jeffrey W. Bost, Adara Maroon[1]

Department of Neurosurgery, University of Pittsburgh Medical Center, Pittsburgh, PA, [1]Vanderbilt University, Nashville, TN, USA

E-mail: Joseph C. Maroon - maroonjc@upmc.edu; *Jeffrey W. Bost - bostj@upmc.edu; Adara Maroon - amaroon@sewickley.org
*Corresponding author

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Abstract

The use of both over-the-counter and prescription nonsteroidal medications is frequently recommended in a typical neurosurgical practice. But persistent long-term use safety concerns must be considered when prescribing these medications for chronic and degenerative pain conditions. This article is a literature review of the biochemical pathways of inflammatory pain, the potentially serious side effects of nonsteroidal drugs and commonly used and clinically studied natural alternative anti-inflammatory supplements. Although nonsteroidal medications can be effective, herbs and dietary supplements may offer a safer, and often an effective, alternative treatment for pain relief, especially for long-term use.

Key Words: Alternative treatments, inflammation, natural anti-inflammatories, pain

INTRODUCTION

Pain, heat, redness, and swelling (dolor, calor, rubor, tumor) are the classic manifestations of the inflammatory process. Abnormalities of the joints of the spine, associated muscles, tendons, ligaments and bone structural abnormalities can all result in pain and need for neurosurgical consultations. Typically, patients will not require immediate surgical intervention, and therefore require treatments to reduce pain and enhance quality of life activities.[71]

In most cases, the genesis of pain is inflammatory, regardless of the etiology. With the elucidation of the role of inflammatory cytokines, there is now a clear understanding of the pathways by which many anti-inflammatory drugs can alleviate inflammation and relieve pain.

The use of non-steroidal anti-inflammatory drug (NSAID) medication is still the mainstay of most classically taught clinicians for joint and spine related inflammatory pain, despite their commonly known side effects [Table 1].

Table 1: The commonly known and documented side effects of steroid-based medications[106]

Side effects of steroid-based medications	
Increased risk of infection	Impaired wound healing
Dermatitis	Increased appetite
Fluid retention edema	Weight gain
Fat deposits in face, chest, upper back and stomach	Worsening of previously acquired medical conditions
Mood change	Depression
Hypertension	Hyperglycemia
Cushingoid-like state	Adrenal suppression and crisis
Stomach ulcers	Cataracts
Osteoporosis	

NSAID mechanisms are primarily through interaction with proinflammatory cytokines interleukin (IL)-1a, IL-1b, IL-6 and tumor necrosis factor (TNF-α). Increased concentrations of TNF-α are believed to cause the cardinal signs of inflammation to occur.[44]

These proinflammatory cytokines result in

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Review

The Role of Curcumin in the Modulation of Ageing

Anna Bielak-Zmijewska *, Wioleta Grabowska, Agata Ciolko, Agnieszka Bojko, Grażyna Mosieniak, Łukasz Bijoch and Ewa Sikora *

Nencki Institute of Experimental Biology, Polish Academy of Sciences, 3 Pasteur St., 02-093 Warsaw, Poland; w.grabowska@nencki.gov.pl (W.G.); a.ciolko@nencki.gov.pl (A.C.); a.bojko@nencki.gov.pl (A.B.); g.mosieniak@nencki.gov.pl (G.M.); l.bijoch@nencki.gov.pl (Ł.B.)

* Correspondence: a.bielak@nencki.gov.pl (A.B.-Z.); e.sikora@nencki.gov.pl (E.S.); Tel.: +48-22-589-2250 (A.B.-Z. & E.S.)

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Abstract: It is believed that postponing ageing is more effective and less expensive than the treatment of particular age-related diseases. Compounds which could delay symptoms of ageing, especially natural products present in a daily diet, are intensively studied. One of them is curcumin. It causes the elongation of the lifespan of model organisms, alleviates ageing symptoms and postpones the progression of age-related diseases in which cellular senescence is directly involved. It has been demonstrated that the elimination of senescent cells significantly improves the quality of life of mice. There is a continuous search for compounds, named senolytic drugs, that selectively eliminate senescent cells from organisms. In this paper, we endeavor to review the current knowledge about the anti-ageing role of curcumin and discuss its senolytic potential.

Keywords: ageing; anti-cancer; autophagy; microbiota; senescence; senolytics

1. Introduction

Demographic data unquestionably show that the population of elderly and very elderly people is continuously increasing. The population of people aged 65 and above represents 8.7% of the total population. However, this percentage differs between continents and is around 15–16% in North America, Europe and Central Asia, but only about 5% in the Middle East, North Africa and South Asia [1]. The increase of lifespan is not really satisfactory without an improvement of healthspan. We would like to live longer, but in good health, which is necessary to enjoy the world around us. Actually, there is a great deal of evidence that the ageing process is malleable and the rate and quality of ageing can be modulated [2]. In order to be able to postpone ageing, it is urgent to reveal the mechanisms of ageing.

It is commonly accepted that cellular senescence plays a very important role in organismal ageing and age-related diseases [3]. Namely, it has been observed that senescent cells accumulate in the tissues and organs of old animals and humans, and that proliferation potential differs among cells derived from individuals of different age [4–8]. Even though the actual number of senescent cells seems not to be very high and fluctuates between a few and a dozen percent, changes in the extracellular milieu caused by the increased production of cytokines by senescent cells, and the senescence-associated impairment of regenerative processes, can lead to spectacular organismal dysfunctions. Moreover, senescent cells contribute to the onset and progression of diseases, the frequency of which increases with age. The accumulation of senescent cells has been observed in the course of almost all age-related disorders [9]. Breakthrough experiments, which have definitely proved the involvement of cell senescence in the progression of ageing and age-related diseases, came from animal studies. It has been clearly shown that the elimination of senescent cells alleviated the symptoms of ageing and age-related

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Review Article

Review of Anti-Inflammatory Herbal Medicines

Mona Ghasemian,[1] Sina Owlia,[2] and Mohammad Bagher Owlia[2]

[1]*School of Pharmacy, Shahid Sadoughi University of Medical Sciences, Yazd, Iran*
[2]*School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran*

Correspondence should be addressed to Mohammad Bagher Owlia; bagherowlia@gmail.com

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Medicinal plants and their secondary metabolites are progressively used in the treatment of diseases as a complementary medicine. Inflammation is a pathologic condition that includes a wide range of diseases such as rheumatic and immune-mediated conditions, diabetes, cardiovascular accident, and etcetera. We introduce some herbs which their anti-inflammatory effects have been evaluated in clinical and experimental studies. *Curcuma longa*, *Zingiber officinale*, *Rosmarinus officinalis*, *Borago officinalis*, evening primrose, and Devil's claw are some of the introduced medicinal herbs in this review. Since the treatment of inflammation is not a one-dimensional remedy, this review tries to reach a multidimensional therapeutic approach to inflammation with the help of herbal medicine and modification in lifestyle.

1. Introduction

Inflammation is a defense response of our body to hazardous stimuli such as allergens and/or injury to the tissues; on the other hand, uncontrolled inflammatory response is the main cause of a vast continuum of disorders including allergies, cardiovascular dysfunctions, metabolic syndrome, cancer, and autoimmune diseases imposing a huge economic burden on individuals and consequently on the society [1]. There are various medicines for controlling and suppressing inflammatory crisis; steroids, nonsteroid anti-inflammatory drugs, and immunosuppressant are the practical examples of these medications which are associated with adverse effects while in practice our goal is to apply minimum effective dose by the highest efficacy with the least adverse effects. Thus, we need to apply natural anti-inflammatory factors within medication therapy to achieve increased pharmacological response and the lowest degree of unwanted side effects [1, 2]. Herbal medicines are promoting subjects in medicine and, of course, we have to increase our knowledge about them. Complementary, alternative, and traditional medicines are the pivotal source of herbal medication guidance, but surely modern medicine must prove these guidelines through scientific methods before using them in practice. In this review, we have endeavored to assess the plants and the most clinical evidence of their anti-inflammatory effects.

2. Methods

In this study, all the data were gathered from search engines as follows: PubMed, ScienceDirect, and Google Scholar.

We have used these keywords "anti-inflammatory", "plant", "herb", and "herbal medicine" for searching in these databases.

All the references which were used to publish this review article were written in English and from the standpoint of the time interval, they belonged to 1980 to the present. The entire articles relating to our goal were collected and classified based on the level of evidence, where systematic reviews and randomized control trials (RCT) have possessed the highest values. Open-label, cohort, case-control, case series, preclinical, in vivo, ex vivo, and in vitro studies have less importance than the first two, respectively.

It is obvious that each subject that we have found which has higher valuable studies, such as RCT in association

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Anti-inflammatory Properties of Curcumin, a Major Constituent of *Curcuma longa*: A Review of Preclinical and Clinical Research

Julie S. Jurenka, MT(ASCP)

Abstract

Curcuma longa (turmeric) has a long history of use in Ayurvedic medicine as a treatment for inflammatory conditions. Turmeric constituents include the three curcuminoids: curcumin (diferuloylmethane; the primary constituent and the one responsible for its vibrant yellow color), demethoxycurcumin, and bisdemethoxycurcumin, as well as volatile oils (tumerone, atlantone, and zingiberone), sugars, proteins, and resins. While numerous pharmacological activities, including antioxidant and antimicrobial properties, have been attributed to curcumin, this article focuses on curcumin's anti-inflammatory properties and its use for inflammatory conditions. Curcumin's effect on cancer (from an anti-inflammatory perspective) will also be discussed; however, an exhaustive review of its many anticancer mechanisms is outside the scope of this article. Research has shown curcumin to be a highly pleiotropic molecule capable of interacting with numerous molecular targets involved in inflammation. Based on early cell culture and animal research, clinical trials indicate curcumin may have potential as a therapeutic agent in diseases such as inflammatory bowel disease, pancreatitis, arthritis, and chronic anterior uveitis, as well as certain types of cancer. Because of curcumin's rapid plasma clearance and conjugation, its therapeutic usefulness has been somewhat limited, leading researchers to investigate the benefits of complexing curcumin with other substances to increase systemic bioavailability. Numerous in-progress clinical trials should provide an even deeper understanding of the mechanisms and therapeutic potential of curcumin. (*Altern Med Rev* 2009;14(2):141-153)

Introduction

Turmeric (the common name for *Curcuma longa*) is an Indian spice derived from the rhizomes of the plant and has a long history of use in Ayurvedic medicine as a treatment for inflammatory conditions. C. *longa* is a perennial member of the Zingiberaceae family and is cultivated in India and other parts of Southeast Asia.[1] The primary active constituent of turmeric and the one responsible for its vibrant yellow color is curcumin, first identified in 1910 by Lampe and Milobedzka.[2] While curcumin has been attributed numerous pharmacological activities, including antioxidant[3] and antimicrobial properties,[4] this article focuses on one of the best-explored actions, the anti-inflammatory effects of curcumin. Curcumin's effect on cancer (from an anti-inflammatory perspective) is also discussed; however, an exhaustive review of its many anticancer mechanisms is outside the scope of this article. Based on early research conducted with cell cultures and animal models, pilot and clinical trials indicate curcumin may have potential as a therapeutic agent in diseases such as inflammatory bowel disease, pancreatitis, arthritis, and chronic anterior uveitis, as well as certain types of cancer. Numerous clinical trials are currently in progress that, over the next few years, will provide an even deeper understanding of the therapeutic potential of curcumin.

Julie Jurenka, MT (ASCP) – Associate Editor, Alternative Medicine Review; technical assistant, Thorne Research, Inc. – the manufacturer of Meriva Curcumin Phytosome
Correspondence address: Thorne Research, Inc, PO Box 25, Dover, ID 83825
Email: juliej@thorne.com

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The effect of curcumin (turmeric) on Alzheimer's disease: An overview

Shrikant Mishra and Kalpana Palanivelu

Department of Neurology, VA/USC 16111, Sepulveda, CA, USA
For correspondence: Shrikant Mishra, Department of Neurology, VA/USC 16111, Plummer Street, Sepulveda, CA, 91343 USA. E-mail: smishra@usc.edu

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Abstract

This paper discusses the effects of curcumin on patients with Alzheimer's disease (AD). Curcumin (Turmeric), an ancient Indian herb used in curry powder, has been extensively studied in modern medicine and Indian systems of medicine for the treatment of various medical conditions, including cystic fibrosis, haemorrhoids, gastric ulcer, colon cancer, breast cancer, atherosclerosis, liver diseases and arthritis. It has been used in various types of treatments for dementia and traumatic brain injury. Curcumin also has a potential role in the prevention and treatment of AD. Curcumin as an antioxidant, anti-inflammatory and lipophilic action improves the cognitive functions in patients with AD. A growing body of evidence indicates that oxidative stress, free radicals, beta amyloid, cerebral deregulation caused by bio-metal toxicity and abnormal inflammatory reactions contribute to the key event in Alzheimer's disease pathology. Due to various effects of curcumin, such as decreased Beta-amyloid plaques, delayed degradation of neurons, metal-chelation, anti-inflammatory, antioxidant and decreased microglia formation, the overall memory in patients with AD has improved. This paper reviews the various mechanisms of actions of curcumin in AD and pathology.

Keywords: Alternative approach to Alzheimer's, beta amyloid plaques, curcumin, curcumin and dementia, epidemiology, turmeric

Introduction

Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disease. It is characterized by progressive cognitive deterioration together with declining activities of daily living and behavioral changes. It is the most common type of pre-senile and senile dementia. According to the World Health Organization (WHO), 5% of men and 6% of woman of above the age of 60 years are affected with Alzheimer's type dementia worldwide.[1] In India, the total prevalence of dementia per 1000 people is 33.6%, of which AD constitutes approximately 54% and vascular dementia constitutes approximately 39%. AD affects

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Targeting Inflammation-Induced Obesity and Metabolic Diseases by Curcumin and Other Nutraceuticals

Bharat B. Aggarwal
Cytokine Research Laboratory, Department of Experimental Therapeutics, The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030

Bharat B. Aggarwal: aggarwal@mdanderson.org

Abstract

Extensive research within the past two decades has revealed that obesity, a major risk factor for type 2 diabetes, atherosclerosis, cancer, and other chronic diseases, is a proinflammatory disease. Several spices have been shown to exhibit activity against obesity through antioxidant and anti-inflammatory mechanisms. Among them, curcumin, a yellow pigment derived from the spice turmeric (an essential component of curry powder), has been investigated most extensively as a treatment for obesity and obesity-related metabolic diseases. Curcumin directly interacts with adipocytes, pancreatic cells, hepatic stellate cells, macrophages, and muscle cells. There, it suppresses the proinflammatory transcription factors nuclear factor-kappa B, signal transducer and activators of transcription-3, and Wnt/β-catenin, and it activates peroxisome proliferator-activated receptor-γ and Nrf2 cell-signaling pathways, thus leading to the downregulation of adipokines, including tumor necrosis factor, interleukin-6, resistin, leptin, and monocyte chemotactic protein-1, and the upregulation of adiponectin and other gene products. These curcumin-induced alterations reverse insulin resistance, hyperglycemia, hyperlipidemia, and other symptoms linked to obesity. Other structurally homologous nutraceuticals, derived from red chili, cinnamon, cloves, black pepper, and ginger, also exhibit effects against obesity and insulin resistance.

Keywords

inflammation; obesity; diabetes; insulin; cancer; NF-κB; curcumin; nutraceuticals

INTRODUCTION

According to Centers for Disease Control and Prevention (CDC), America is a home to the largest population of obese people in the world (http://www.cdc.gov/obesity/index.html). Thirty-three percent of adult Americans are obese, obesity has increased 60% within the past 20 years, 66% of American adults are overweight, one in six children are obese (http://www.cdc.gov/obesity/data/index.html), and obesity-related deaths have climbed to more than 300,000 a year, second only to tobacco-related deaths (191).The CDC indicated that American society has become obesogenic, characterized by environments that promote increased food intake, nonhealthful foods, and physical inactivity. According to the National Institute of Diabetes and Digestive and Kidney Diseases, approximately two-thirds of U.S. adults—nearly 167 million—are overweight, and nearly one-third (31.4%) are obese

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Oral administration of heat-solubilized curcumin for potentially increasing curcumin bioavailability in experimental animals

Biji T. Kurien[*,†] and **R. Hal Scofield**[†,ð,§]

[†]Arthritis and Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma, OK 73104, USA

[ð]Department of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, OK 73104, USA

[§]Department of Veterans Affairs Medical Center, Oklahoma City, Oklahoma, OK 73104, USA

Sir,

The paper by Narayanan *et al*., 20091 demonstrating the protective effect of curcumin and resveratrol in prostate cancer gives an interesting insight regarding the use of phytochemical combination therapy. It is of interest to note that liposome encapsulated curcumin was used for in vivo experimental animal use in this study to resolve the bioavailability issue of curcumin, resulting from poor absorption.1

It is very likely that poor absorption is a consequence of the fact that curcumin is practically insoluble in water. Therefore, solubility is an important issue in *in vitro* and *in vivo* experiments. Here, we would like to point out that we have shown increased solubility of curcumin (12-fold) and turmeric (3-fold) by the use of heat.2

The treatment with heat did not destroy curcumin's biological activity, as shown by its inhibition of 4-hydroxy-2-nonenal (HNE) mediated modification (80% inhibition of HNE-modification) of a multiple antigenic peptide3 substrate in an enzyme-linked immunosorbent assay4 that employed HNE-modification of a solid-phase antigen substrate. Mass-spectrometric (matrix assisted laser desorption ionization time of flight) and spectrophotometric (400-700 nm) analysis of curcumin solubilized by heat did not demonstrate any heat-mediated disintegration of curcumin.3›5 In addition, we have also shown that curcumin solubilized in mild alkali (pH 7.6, 130 μM) also significantly inhibited HNE-antigen modification.6 It has been shown that most of the curcumin (90%) in phosphate buffered sulfate and serum free media (pH 7.2, at 37°C) was broken down in 30 min.7 The treatment with heat, however, appears to protect curcumin from breaking down faster. Heat-solubilized curcumin amounts decreased 47% in 12 h compared to starting levels, and 67% in 72 h compared to starting levels.2

Curcumin (1,7-bis[4-hydroxy-3-methoxyphenyl]-1,6-heptadiene-3,5-dione) is the most active ingredient of turmeric obtained from the rhizome *Curcuma longa*.7 This yellow pigment is a polyphenol that has been shown to be efficaceous against a variety of diseases, including cancer.2›7–9

Several vehicles have been employed to deliver curcumin *in vivo* or topically. DMSO (dimethyl sulfoxide) has been used for curcumin administration *in vivo*.10 A combination of

[*]To whom correspondence should be addressed: Oklahoma Medical Research Foundation, 825 NE 13th Street, OKC, OK 73104, Tel: (405) 271-7394, Fax: (405) 271-7063, biji-kurien@omrf.org

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Phytochemistry and potential therapeutic actions of Boswellic acids: A mini-review

Farah Iram[1], Shah Alam Khan[2*], Asif Husain[1*]

[1]*Department of Pharmaceutical Chemistry, School of Pharmaceutical Sciences, Jamia Hamdard (Hamdard University), New Delhi 110062, India*

[2]*Department of Pharmacy, Oman Medical College, PO Box 620, PC 130, Muscat, Oman*

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ABSTRACT

The pentacyclic triterpenic acids isolated from the oleo gum resin of various Boswellia species are collectively called as Boswellic acids (BA). The oleo gum resin obtained from Indian variety i.e. *Boswellia serrata* (Family – Burseraceae) is commonly known as Salai guggal. The resin fraction of Salai guggal is rich in Boswellic acids and its essential oil is composed of a mixture of mono, di and sesquiterpenes while gum fraction chiefly contains pentose and hexose sugars. This oleo-gum resin is quite popular among traditional practitioners of traditional Chinese and Indian Systems of medicine owing to their wide range of useful biological properties such as anti-inflammatory, anti-arthritic, anti-rheumatic, anti-diarrheal, anti-hyperlipidemic, anti-asthmatic, anti-cancer, anti-microbial anti-fungal, anti-complementary and analgesic activity, etc. It has been used as a herbal medicine since the prehistoric time to cure acute and chronic ailments including inflammatory diseases. Phytochemical investigation of this herbal medicine lead to identification of Boswellic acids which are found to be novel, potent, specific anti-inflammatory agents due to non-redox inhibition of 5-lipoxygenase (5-LO) enzyme. However, the other important targets of Boswellic acids also include topoisomerases, angiogenesis, and cytochrome p450 enzymes. This review is a sincere attempt to discuss and present the current status of therapeutic potential, phytochemical as well as pharmacological profile of Boswellic acids primarily obtained from *B. serrata*.

1. Introduction

The herbal extracts prepared from various species of Boswellia (family Burseraaceae) tree have been used for couple of centuries in traditional medicine worldwide for the treatment of several diseases [1]. Boswellia genus comprises of nearly 25 distinct species and some of the important species of this genus include *Boswellia serrata*, *Boswellia sacra*, *Boswellia carterii*, *Boswellia papyrifera*, *Boswellia neglecta*, *Boswellia rivae*, *Boswellia frereana*, and *Boswellia ovalifoliolata*, *etc* [2–5]. The tree is commonly grown in gulf countries *viz.* Oman, Yemen and Southern Saudi Arabia, in East Africa (Somalia and Ethiopia), South Asia and abundantly grows in dry hilly tracts of India [6–9]. The Indian states where it is grown widely include Rajasthan, Gujarat, Maharashtra, Madhya Pradesh, Bihar, Orissa and some parts of Western Himalayas [10]. The dried exudate from the bark of *B. serrata* tree is an oleo-gum-resin which is commonly known as Indian Frankincense, Indian olibanum, Incense or Salai guggal. The dried gum appears in form of lumps or tears which are white-yellow in color. The word frankincense meaning "pure incense" is derived from the ancient French name [11]. In Arabic language, frankincense is also known as "al-luban," which means "white" or "cream and is a basis for its other name, olibanum [10,12–15]. It is known by the name of Ru Xiang in Chinese [16]. In Ayurveda, an Indian traditional system of medicine, the gum is used to treat a number of inflammatory diseases affecting skin, eye, gums, gastrointestinal tract (GIT) in addition to the respiratory inflammatory disorders such as asthma, bronchitis, laryngitis *etc* [15].

Salai guggal or oleo gum resin is a mixture of essential oil, gum and resin. The essential oil is chiefly a mixture of monoterpenes, diterpenes and sesquiterpenes. Its essential oil also contains

*Corresponding authors: Shah Alam Khan, Deparment of Pharmacy, Oman Medical College, PO Box 620, PC 130, Muscat, Sultanate of Oman.
Asif Husain, Department of Pharmaceutical Chemistry, Jamia Hamdard (Hamdard University), New Delhi-110062, India.
Tels: +968 24504608 (173) (S.A. Khan); +91 11 26059681, 26059688, ext. 5647, +91 989 1116086 (A. Husain)
E-mails: shahalamkhan@yahoo.com, sakhan@omc.edu.om (S.A. Khan), drasifhusain@yahoo.com, ahusain@jamiahamdard.ac.in (A. Husain).
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Boswellia serrata extract attenuates inflammatory mediators and oxidative stress in collagen induced arthritis

Sadiq Umar [a, g, 1] ✉, Khalid Umar [b], Abu Hasnath Md. Golam Sarwar [c], Altaf Khan [d], Niyaz Ahmad [e], Sayeed Ahmad [e], Chandra Kant Katiyar [f], Syed Akhtar Husain [g], Haider A. Khan [a] ✉

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Abstract

Rheumatoid arthritis (RA) is a chronic inflammatory disease which leads to destruction of joints. Current treatment modalities for RA either produce symptomatic relief (NSAIDs) or modify the disease process (DMARDs). Though effective, their use is also limited by their side effects. As a result, the interest in alternative, well tolerated anti-inflammatory remedies has re-emerged. Our aim was to evaluate the antioxidant and antiarthritic activity of *Boswellia serrata* gum resin extract (BSE) in collagen induced arthritis. Arthritis was induced in male Wistar rats by collagen induced arthritis (CIA) method. BSE was administered at doses of 100 and 200 mg/kg body weight once daily for 21 days. The effects of treatment in the rats were assessed by biochemical (articular elastase, MPO, LPO, GSH, catalase, SOD and NO), inflammatory mediators (IL-1β, IL-6, TNF-α, IL-10, IFN-γ and PGE_2), and histological studies in joints. BSE was effective in bringing significant changes on all the parameters (articular elastase, MPO, LPO, GSH, catalase, SOD and NO) studied. Oral administration of BSE resulted in significantly reduced levels of inflammatory mediators (IL-1β, IL-6, TNF-α, IFN-γ and PGE_2), and increased level of IL-10. The protective effects of BSE against RA were also evident from the decrease in arthritis scoring and bone histology. The abilities to inhibit proinflammatory cytokines and modulation of antioxidant status suggest that the

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