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Natural Therapies for Rheumatoid Arthritis and Other Chronic Inflammatory Conditions

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ABSTRACT: *Rheumatoid arthritis and other chronic inflammatory conditions are affecting increasing numbers of Americans. Due to the complex nature and etiology of these disorders, the focus of conventional treatments has been unsatisfactory in bringing true, principle-centered relief to sufferers. Substantial scientific evidence supports common underlying mechanisms at work in these disease processes—namely intestinal health and function. Systemic manifestations of poor intestinal health and compromised function are not new; however, their implication in growing numbers of chronic inflammatory diseases, such as rheumatoid arthritis, has opened a new avenue for treatment. A natural, multi-faceted approach can now be utilized that addresses: 1.) reduction of the antigenic burden in the patient and improved detoxification, 2.) safe modulation of the inflammatory response, 3.) control of oxidative tissue damage, 4.) improved gut ecology, and 5.) improved mucosal tissue health. By incorporating this new approach, health care practitioners can now offer their patients a broad-based, integrated program for the management of chronic inflammatory conditions.*

Autoimmune disorders with associated chronic inflammation present with varying symptomology; however, recent scientific evidence indicates some commonality in etiology. When the gut-associated lymphoid tissue (GALT) and immunologic-secreting cells that line the intestines are overstimulated by antigenic material, or the integrity of the mucosal barrier compromised, disease processes that involve immune and inflammatory responses (e.g., rheumatoid arthritis) can result via complex antigen/immune interactions—especially in individuals with genetic susceptibility.[1-4] While this paper will focus on rheumatoid arthritis, bear in mind that the underlying mechanisms of disease and the therapies discussed herein may apply to other autoimmune/inflammatory disorders as well.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is the second most common form of arthritis affecting approximately 2.5 million Americans, over 60% of them women. It can occur at any age, but usually appears between the ages of 20 and 50.[5] RA is a chronic autoimmune disorder characterized by inflammation of the synovial membranes (synovium) of multiple joints, leading to varying degrees of destruction.[6] Though the disease primarily involves the synovial joints, virtually every tissue in the body can be affected by the inflammatory process. Continuous inflammation of the synovium gradually destroys cartilage, narrowing the joint space and eventually damaging bone. In progressive RA, destruction of cartilage accelerates when the fluid and inflammatory cells accumulate in the synovium to produce a *pannus*—a growth composed of thickened synovial tissue. Enzymes produced by the pannus destroy cartilage, which further propagates the inflammatory process.[5-7]

Symptoms

The hallmark symptom of RA is morning stiffness that lasts for at least an hour, with associated pain and tenderness.[8] Symptoms such as fatigue, weight loss, and fever may also occur. The inflamed joints are usually swollen and often feel warm and spongy when palpated. RA is typically symmetric (both left and right joints are affected) and almost always initially develops in the wrists and knuckles.[7,8]

Etiology

The most prevalent theory regarding the etiology of RA is a combination of factors including genetic susceptibility, infection, and an abnormal autoimmune response.[1-9] Blood tests may reveal the presence of an antibody called rheumatoid factor (RF), which is found in at least 85% of those with RA. Some research suggests that the source antigen for some RFs may well be peptidoglycans, or cellular proteins, of enteric (intestinal) origin bacteria.[1,3,8,9] Researchers have also identified a gene factor called HLA-DR4, which is present in many patients with autoimmune conditions. In people who have this genetic susceptibility, the immune system may attack collagen protein because of its resemblance (molecular mimicry) to a foreign antigen. HLA-DR4, however, is also present in many people who do not contract RA, and many experts believe that more than one gene must be involved in order for the disease to develop.[5-7] Growing research indicates that the underlying trigger for such chronic inflammatory and autoimmune responses may well be reactions to antigens originating from the intestinal tract.[1-4,9-17] [For more information on treating disease resulting from an enteric infection, please refer to the ANSR article entitled *Herbal Antimicrobials for Intestinal Infections*.]

The Link to the Intestinal Tract

Approximately 25% of the intestinal mucosa is lymphoid tissue and 70% to 80% of all immunologic-secreting cells are located within the intestines.[2] Lumenal exposure to potent, nonspecific antigens—of endogenous or exogenous origin—can markedly up-regulate the intestinal immune system and mucosal inflammatory pathways.[11] This "altered" gut-associated mucosal activity causes an imbalance in cellular inflammatory mediators (e.g., eicosanoids, tumor necrosis factor-alpha, etc.), resulting in cellular signaling that not only produces localized gastrointestinal inflammatory disorders, but perpetuates systemic inflammatory messages associated with a variety of chronic diseases.[1,3,4,11,12] The antigenic activation of T-cells in the GALT further propagates the inflammatory cascade through secretion of either interleukin-2 or interferon-gamma, or through direct cellular interaction with macrophages and synoviocytes (synovial intimal cells).

Adding insult to injury, hyperresponsive immune and inflammatory activity is recognized as a contributing factor in intestinal tissue destruction and mucosal barrier dysfunction.[3,13,14] Normally, various molecules cross the epithelium by active and passive mechanisms; however, when the integrity of the intestinal mucosa has been compromised, the crossing of material (antigens) into systemic circulation (translocation) is increased, and thus antigenic burden in the host amplified. Abnormal bowel permeability has been observed in RA, as well as other inflammatory conditions such as ankylosing spondylitis.[1,10,15]

The presence of circulating immune complexes—possibly a reflection of systemically absorbed enteric antigens—suggests continuous antigenic challenge in patients with chronic inflammatory disorders.[3] In RA, the deposition of these immune complexes in joints leads to tissue damage and a subsequent expansion of the immune reaction resulting in joint inflammation. According to a study cited in the *Scandinavian Journal of Rheumatology*, the joints have a predisposition for rheumatoid inflammation because of the settlement and persistence of antigens and joint tissue capacity for antigen capture.[9] Furthermore, primed T-cells interacting with synovial endothelium recognize intestinal-derived antigens and expand the immune reaction.[9] This destructive overstimulation of T-cells by antigens (sometimes termed "superantigens") has a substantial role in the progression of joint destruction.[6,12,16]

The cyclic and interrelated events of antigen hyperresponsivity, inflammation, and intestinal tissue destruction must all be addressed in order to gain control of the complex mechanisms at work in chronic inflammatory disorders.

Conventional Treatments—Narrow Focus

Several drugs are used to treat RA, along with adjunctive physical therapy and corrective surgery. Common drug treatments include NSAIDs, COX-2 (cyclooxygenase-2) inhibitors, and second line disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate, hydroxychloroquine, and gold. In addition, newer genetically engineered medications (e.g., Enbrel, Remicade), termed biological response modifiers, interfere with the autoimmune response in RA by targeting cytokines, specifically tumor necrosis factor (TNF) and certain interleukins.[5] Unfortunately, all of these drugs can lose effectiveness over time and produce side effects like increased intestinal permeability, and even more serious, life-threatening problems like sepsis and lowered immunity.[5,17]

Plainly, conventional treatments have serious limitations.

In a search for safe, yet effective, therapies for RA and other chronic inflammatory conditions, scientists have identified dietary measures to reduce antigenicity and support detoxification, as well as natural substances to control dysregulated inflammation, reduce the associated free radical damage, and support the integrity of the intestinal tract.

Dietary Considerations

In some patients, food antigens may be involved in the production of the circulating immune complexes that deposit in synovium. As the concept of antigenicity in RA has evolved, methods of dietary manipulation have been investigated. Elimination, elemental (a hypoallergenic, protein-free artificial diet consisting of amino acids, glucose, trace elements, and vitamins), vegetarian, and vegan diets, as well as fasting, decrease the antigenic burden in patients and thus immune reactions.[15,18-22] According to a review published in the *British Journal of Rheumatology*, "There are now sufficient good scientific studies, from the UK and abroad, to suggest that, at least in some patients with RA, dietary therapy may influence at least some of the symptoms and possibly the progression of the disease."[15]

Due to the increased likelihood of macromolecular absorption of antigens in RA, providing these patients with a low-allergy potential medical food that suppresses inflammation and supports gut health may be a critical step in gaining control of dietary issues that propagate the disease. Such a dietary intervention should also address the excessive free radical production associated with inflammation by supplying a broad spectrum of antioxidants and detoxifying substances including vitamins A, C, and E, mixed carotenoids, and zinc.[23]

In addition, lack of proper nutrition taxes both metabolic and detoxification processes, and can therefore exacerbate any disease process. Nutritional imbalances are common in patients with RA, with studies indicating inadequate levels of multiple nutrients.[24,25] For example, a study on 48 patients with RA showed that only 23% met the RDI for calcium, 46% for folic acid, 29% for vitamin E, 10% for zinc, and only 6% for selenium.[24] In another study it was determined that patients with RA ingest too much total fat and too little polyunsaturated fats and fiber, as well as inadequate levels of pyridoxine, zinc, and magnesium.[25] These observations suggest that daily supplementation with micronutrients, as well as a well-balanced diet, are appropriate recommendations in this population.

Modulating the Inflammatory Response Naturally

Safe methods of controlling inflammation have become a primary focus of research in chronic autoimmune/inflammatory conditions, largely due to their necessity and the serious side effects associated with prescription and over-the-counter medications. Essential fatty acids, various herbs, bioflavonoids, niacinamide, and N-acetylcysteine may serve as favorable alternatives to medications due to their effective, yet safe, actions.[26-63]

Essential Fatty Acids

A balanced consumption of omega-3 and omega-6 fatty acids is necessary to maintain an appropriate production of both pro-inflammatory and anti-inflammatory cellular mediators (i.e.,

eicosanoids, cytokines).[26,27] Unfortunately, Westerners typically consume diets high in omega-6 fatty acids, such as arachidonic acid (AA). Most omega-6 fatty acids perpetuate the production of pro-inflammatory mediators and thus intensify chronic inflammatory conditions.[26-29] On the other hand, omega-3 fatty acids—such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)—found primarily in fresh, cold water fish, leafy green vegetables, and flax and canola oils, promote the production of anti-inflammatory mediators.[27,30]

The omega-3 fatty acid EPA acts as a competitive inhibitor of AA conversion to pro-inflammatory eicosanoids. In RA patients specifically, supplementation with fish oils has resulted in a reduction of pro-inflammatory cytokines approaching 90%, and at least 11 double-blind, placebo-controlled studies have shown beneficial clinical effects.[30] In fact, some RA patients who take fish oil are able to discontinue NSAIDs without experiencing a disease flare.[31] Furthermore, research also indicates that enhancement of omega-3 status improves pain tolerance.[31] It should be noted that the omega-6 fatty acid, gamma-linoleic acid (GLA), found in hemp, borage, black currant, and evening primrose oils, has an almost identical chemical structure to alpha-linoleic acid (omega-3) and is therefore beneficial for many of the same purposes.[27] In one study, treatment with 1.4 g/d GLA resulted in a 36% reduction in tender joints and a 28% reduction in swollen joints in active RA.[32]

Numerous research articles and clinical studies have demonstrated the efficacy of omega-3 fatty acids and GLA as anti-inflammatory agents.[28,31-34] Their dual ability to suppress the production of pro-inflammatory mediators while enhancing the production of anti-inflammatory mediators is uniquely beneficial. Thus, balancing a typically omega-6-rich diet with GLA and omega-3 fatty acids, such as EPA and DHA, is an effective way to shift the balance toward anti-inflammatory mediator production—a very necessary change in chronic inflammatory disorders.[29] Furthermore, new research indicates that essential fatty acids may exert beneficial effects on autoimmune disease through regulation of gene expression, suppression of autoantibody and T lymphocyte proliferation, and apoptosis of autoreactive lymphocytes.[34,35]

It is important to be aware that supplementation with essential fatty acids may require additional vitamin E intake to prevent increased peroxidation of membrane lipids.[36]

Herbs

Chemical compounds (phytochemicals) found in herbs including ginger, turmeric, cayenne, and boswellia demonstrate pain and inflammation-reducing properties.[37-49] Bioflavonoids, a broad class of phytochemicals found largely in citrus fruits, tea, and wine, reduce inflammation as well.[41] These compounds work primarily through inhibition of the formation of pro-inflammatory eicosanoids by inactivating enzymes (cyclooxygenase, lipoxygenase) in the inflammatory cascade.

Ginger & Turmeric

Ginger (*Zingiber officinale*) and turmeric (*Curcuma longa*) have long been used in the east Indian system of medicine known as Ayurveda and have application in a variety of inflammatory conditions.[40,42] Animal and in vitro studies suggest that these herbs may block cyclooxygenase and lipoxygenase activity, as well as inhibit the incorporation and hydrolysis of AA into cell phospholipids, resulting in the reduced formation of pro-inflammatory mediators.[37-39,43]

Curcumin, the principal compound in turmeric, was studied in comparison to phenylbutazone (an anti-inflammatory drug) in a double-blind clinical trial of 49 patients with RA. Those receiving 1,200 mg/d of curcumin for 5 to 6 weeks had significant improvements, with relief of morning stiffness and joint swelling comparable to those receiving phenylbutazone.[46] In an investigation that evaluated the effects of ginger on patients with osteoarthritis, RA, and muscular discomfort, more than 75% of arthritic patients reported improvements in pain and swelling, while all patients who experienced muscle discomfort reported relief.[38]

Boswellia

Boswellia (*Boswellia serrata*) is another Ayurvedic herb that demonstrates potent anti-inflammatory properties.[44,47] The effectiveness of boswellia extract was studied on 260 RA patients; compared to placebo, it produced a significant reduction in joint pain and swelling, as well as morning stiffness, while improving general health and well-being.[47] In addition, boswellic acids have also been shown in vitro to inhibit the complement system, a set of enzymes that work with antibodies to attack foreign antigens.[48] Pathologically prolonged and sustained activation of the complement system is implicated in a variety of inflammatory disorders.[48]

Cayenne

Capsaicin, the main constituent of cayenne pepper (*Capsicum annuum*), also suppresses inflammation through enzyme inhibition.[37,40] Not only is capsaicin useful in reducing inflammation, it also reduces pain by selectively depleting a neuropeptide called substance P in the nerves that transmit pain (substance P is thought to be the principle neurotransmitter of pain impulse from the periphery to the central nervous system).[40,49]

Bioflavonoids

Bioflavonoids are an extensive group of phytochemicals ubiquitous in the plant kingdom. Their activities include inhibition of enzymes involved in AA metabolism, inhibition of leukocyte infiltration into the site of inflammation, and protection of collagen and hyaluronan in connective tissue.[41,50] Quercetin, a flavonoid of high biological activity, is an effective inhibitor of lipoxygenases.[51] It also prevents the overproduction of tumor necrosis factor-alpha (TNF-alpha) and nitric oxide (NO), which can induce several pathophysiological conditions during acute and chronic inflammation.[52]

Niacinamide

During inflammatory states, activated immune cells (e.g., neutrophils and monocytes) of patients suffering from various inflammatory and autoimmune rheumatic diseases can produce up to tenfold the normal levels of reactive oxygen species (ROS) than do immune cells of healthy subjects.[53] These ROS induce DNA strand breaks, which stimulate the activation of the nuclear repair enzyme poly (ADP-ribose) synthetase (PARS). Rapid PARS activation triggers a futile energy-consuming cycle, resulting in depletion of its substrate NAD+ and eventual cell death. Recent data demonstrates that this PARS suicide pathway plays a crucial role during the inflammatory process and is involved in the pathogenesis of several inflammatory diseases.[54,55]

Niacinamide has been shown to be effective in relieving symptoms of RA and osteoarthritis in both human and animal models.[53,56-58] The primary mechanism of action of niacinamide appears to be related to its ability to inhibit cytokine-mediated NO synthesis and PARS activation.[53,59] NO reacts with superoxide to form peroxynitrite, a potent trigger of the DNA damage that activates PARS.[55] Furthermore, niacinamide inhibits the synthesis of TNF-alpha, a pro-inflammatory cytokine that plays a decisive role during the development of RA.

N-acetylcysteine (NAC)

NAC stimulates the synthesis of glutathione (GSH), a principal defense within the body against free radicals.[60] NAC appears to support the synthesis of GSH primarily under conditions when the demand for GSH is increased, such as during oxidative stress associated with inflammatory conditions. NAC has been shown to inhibit the synthesis of TNF-alpha and the activation of PARS, as well as having an inhibitory effect upon experimentally-induced arthritis in mice.[53,61,62] Furthermore, a recent study demonstrated that combining NAC with niacinamide results in a marked potentiation of their individual effects on PARS inhibition and suppression of arthritis in mice.[63]

The Role of Free Radicals and Antioxidants

The excessive free radical production associated with immune/inflammatory hyperresponsitivity is an area of concern in RA and similar conditions.[64] The migration of activated immune cells into synovial fluid and periarticular tissue is characteristic of RA. ROS and other mediating substances produced by these activated immune cells exacerbate and perpetuate the rheumatoid condition.[51,65] For instance, increases in oxidative substances in synovium are associated with depolymerization of hyaluronic acid (HA) with subsequent losses in its lubricating properties.[66-68] These findings support the hypothesis that free radical damage is responsible for the accelerated degradation in the rheumatoid joint.[66] Free radical scavengers, therefore, may be beneficial in supporting antioxidant enzyme systems and reducing free radical injury to HA, synovial fluid, and articular tissues.[51,66,67]

Vitamin E

Free radicals predominantly react with the polyunsaturated fatty acids that compose the lipid portion of cell membranes, leading to the eventual destruction of the cell. In fact, a single free radical can destroy an entire membrane through a self-propagating chain reaction. Free radicals oxidize lipids in the synovial fluid, thus reducing its viscosity. Hence, joint movement is further impeded and the disease process aggravated.[51,69] Vitamin E, which is an important fat-soluble antioxidant, provides chain-breaking free radical protection to these lipids. Furthermore, vitamin E supplementation at levels from 200 IU to 600 IU/d can also produce significant pain relief in RA patients.[51,70]

Recently, the benefit of mixed tocopherol vitamin E has been examined.[71-73] Studies have demonstrated that although alpha-tocopherol is an effective antioxidant in and of itself, gamma-tocopherol is required to more effectively remove specific free radical species (peroxynitrite-derived nitrating species) and prevent lipid hydroperoxide formation.[71-73] Additionally, large doses of alpha tocopherol can displace gamma-tocopherol in plasma and other tissues by as much as 20-fold.[73] The complementary action of these two tocopherols provides a greater level of protection against oxidative damage, and better reflects the ratios found in a healthy diet.

Vitamin C

Vitamin C, or ascorbic acid, functions as a very important water-soluble antioxidant and is capable of regenerating other antioxidants—especially vitamin E.[74,75] Vitamin C levels are suboptimal in patients with RA despite normal absorption, which is likely a reflection of increased free radical scavenging activity in these individuals, as well as increased consumption of vitamin C for vitamin E regeneration.[26,64] Furthermore, vitamin C is required for the synthesis of collagen, an important structural component of joint cartilage, and a deficiency in vitamin C is associated with poor collagen formation.[76,77] Animal research shows that vitamin C supplementation increases cartilage weight and appears to protect against erosion of articular cartilage.[77]

Endogenous Antioxidant Enzymes

Superoxide dismutase (SOD) is an endogenous antioxidant enzyme that interferes with free radical generation and is a primary scavenger of ROS in synovial fluid. There are two forms of SOD: copper-zinc SOD (Cu-Zn SOD) and manganese SOD (Mn-SOD). Both forms protect tissues by converting damaging ROS into hydrogen peroxide, which is in turn reduced to water and oxygen by peroxidase glutathione and catalase enzymes.[64]

An adequate dietary supply of copper, zinc, and manganese is required for SOD enzymes to function. Research suggests that raising the intake of minerals needed for SOD induction may improve SOD activity.[78,79] One study reported a significant increase in Mn-SOD activity in women who received 15 mg of manganese daily for 119 days, compared to women who received placebos.[78] Another study reported increased Cu-Zn SOD activity in RA patients an average of 21% who supplemented with 2 mg of copper daily for 4 weeks.[79]

Glutathione peroxidase, which requires selenium, is another important antioxidant enzyme that interferes with the propagation of free radicals by decomposing hydrogen peroxides and lipid peroxides.[64]

In addition to gaining control of inflammation and reducing the associated free radical activity, supplying nutritional factors that directly influence the health and integrity of the intestinal tract, as well as protect and nourish its tissues, serves to promote local and systemic well-being.

Nutritional Support of Gut Ecology

Small intestine bacterial overgrowth, or dysbiosis, is thought to be an initiating factor in some immune-related disorders due to its negative effect on the condition of the mucosal barrier, and is associated with a more pronounced disease activity in RA patients, as indicated by clinical and biochemical parameters.[9,17] Furthermore, dysbiosis has also been postulated to cause enterometabolic disorders resulting in food intolerance, translocation of antigenic material, and allergic reactions.[4,17,80] Motility disorders, IgA deficiency, digestive secretions, diet, antibiotic use, and epithelial turnover represent some common factors known to influence the ecology of the small intestines.[17] Substances that support a balanced bacterial ecology of the gut, and therefore enhance the health and proper function of the mucosal barrier,

include beneficial microorganisms (probiotics) and substances that support the growth of beneficial microorganisms and local immunity (prebiotics).

Probiotics

Bifidobacterium infantis and *Lactobacillus acidophilus* are two common species of "friendly" bacteria that reside in the intestinal tract. They have multiple functions, with their primary benefit being their promotion of healthful gut ecology and their ability to keep undesirable bacteria in check.[81-83] The *L. acidophilus* NCFM® strain is perhaps the most extensively researched *L. acidophilus* strain available. It demonstrates a multitude of beneficial properties, including bacteriocidin effects and an ability to reduce levels of toxic amines created in a dysbiotic environment.[84-86] [For more information on the beneficial effects of probiotics, please refer to the CNI article entitled *Intestinal Health.*]

Prebiotics

Fructooligosaccharides are complex carbohydrates found in a variety of foods such as honey, onions, asparagus, bananas, oats, chicory, and Jerusalem artichoke. They are fiber-like in that human digestive enzymes have little or no effect on them, but they do act as a food supply for the indigenous healthful microflora.[87,88] Consumption of fructooligosaccharides has been shown to increase the number of beneficial organisms in the intestinal tract.[87]

Lactoferrin and immunoglobulins are a class of supportive substances that beneficially affect intestinal microbial balance by directly inhibiting the growth of harmful bacteria and providing passive immunity.[89,90] In addition, lactoperoxidase (the second most prominent enzyme in bovine milk) forms, with hydrogen peroxide and thiocyanate, a potent natural antibacterial system known as the LP-system. The antimicrobial activity of the LP-system has been studied extensively, with a wide range of microorganisms being inhibited such as *Staphylococcus aureus, Campylobacter* species, *Streptococcus* species, *Bacillus* species, *E. coli, Salmonella* species, and *Pseudomonas* species.[91]

A healthy intestinal microbial environment participates in a wide range of host supportive roles, from formation and absorption of nutrients (e.g., vitamin B_{12}) to detoxification and systemic protection from antigens and pathogens.[4,9,17,81-91] With these facts in mind, promoting a symbiotic intestinal microbial environment may have a crucial role in the attenuation of RA and other inflammatory and immune hyperresponsivity disorders.

Nutritional Support of Gut Integrity

Above and beyond sustaining healthy gut ecology, supporting the morphology (form and structure) and function of the intestinal mucosa is critical for proper barrier function and intestinal health. Tissue injury and increased intestinal permeability may be critical propagating factors in RA and other chronic inflammatory diseases, as discussed earlier. Various nutrients and herbs have been scientifically and empirically recognized for their beneficial effects on epithelial tissue, mucous membranes, and overall intestinal condition.[92-102]

L-Glutamine

Glutamine is the most abundant amino acid in the human body and plays a central role in numerous metabolic processes. It serves as a primary fuel for the rapidly dividing cells of the intestinal mucosa and immune system, enhances the function of the intestinal barrier, and transports as much as 35% of whole blood amino acid nitrogen.[92-94] These properties make glutamine essential for maintaining the integrity of the intestinal mucosa and for promoting an optimal immune response. Studies measuring intestinal permeability before and after glutamine administration showed that supplementation maintained intestinal mucosal morphology and barrier function and reduced the translocation of antigenic molecules.[92,94,95] In fact, because of the increased intestinal permeability caused by long-term NSAID use, glutamine administration with NSAID-dosing was studied in healthy volunteers. The results showed that glutamine administration with NSAID-dosing significantly lowered permeability as compared to NSAID-dosing without glutamine.[96]

Deglycyrrhizinized Licorice (DGL)

DGL is an extract of licorice (*Glycyrrhiza glabra*) from which glycyrrhizinic acid has been removed to prevent potential adverse side effects associated with fluid and electrolyte balance. It enhances the resistance of the gastric mucosa against the eroding action of bile, promotes proliferation of gastric epithelial cells, and enhances mucous production and secretion.[97] DGL has been shown to reduce aspirin-induced gastric mucosal damage and accelerate gastric ulcer healing, benefits especially important for those patients experiencing gastrointestinal side effects from NSAID use.[98,99] (It is important to note that the bitter principles found in licorice should also be removed to prevent a laxative effect.)

Aloe Vera

Aloe (*Aloe barbadensis*) is a complex plant that supplies biologically active substances (polysaccharrides) including acemannan and mannose. Aloe works in two main areas: epithelial tissues (which line the intestinal tract), where it promotes faster healing, and the immune system, where it promotes immunomodulation by influencing the cytokine system.[100] Furthermore, aloe has been shown to inhibit enzyme activity in the inflammatory cascade, thereby reducing inflammation, and to enhance the phagocytic action of macrophages, thereby supporting a healthy intestinal microbial balance.[101,102] (Aloe-emodin anthrone should be removed to prevent a laxative effect.)

Systemic manifestations of intestinal dysfunction continue to be revealed as scientific knowledge of the body's cellular communication and interconnected systems is gained. RA must be viewed as a multi-faceted condition that requires a comprehensive approach to treatment. Hallmark studies and reviews have established, beyond a reasonable doubt, that the root of the problem may lie in the health and function of the intestines. Beyond management of symptoms alone, today's health care professional can take a step-wise, integrated approach to treating RA that reduces external antigen loading and supports detoxification, utilizes safe and natural substances to control pain and inflammation, addresses free radical stress, and supports a symbiotic gut ecology as well as healthy mucosal tissues.

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