Inflammation is the body’s immediate response to damage to its tissues and cells by pathogens, noxious stimuli such as chemicals, or physical injury. Acute inflammation is a short-term response that usually results in healing: leukocytes infiltrate the damaged region, removing the stimulus and repairing the tissue. Chronic inflammation, by contrast, is a prolonged, dysregulated and maladaptive response that involves active inflammation, tissue destruction and attempts at tissue repair. Such persistent inflammation is associated with many chronic human conditions and diseases, including allergy, atherosclerosis, cancer, arthritis and autoimmune diseases.

The processes by which acute inflammation is initiated and develops are well defined, but much less is known about the causes of chronic inflammation and the associated molecular and cellular pathways. This Insight highlights recent advances in our knowledge of the exogenous and endogenous inducers of chronic inflammation, as well as the inflammatory mediators and cells that are involved. We hope that these articles will contribute to a better understanding of inflammatory responses, and ultimately result in the design of more effective therapies for the numerous debilitating diseases with a chronic inflammatory component.

Ursula Weiss, Senior Editor
Inflammation has been found to be an underlying cause in many diseases, making it a hot topic in the health media. But what do we really know about chronic inflammation and its effects on the body?

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Illustration ANNA & ELENA BALBUSSO
As scientists have searched for the mysteries behind the diseases most likely to afflict us, they have alighted on one factor common to virtually all of them: inflammation. Chronic inflammation, headlines now regularly state, has a role in a host of common and often deadly diseases, including Alzheimer’s, arthritis, cancer, diabetes, heart disease, and possibly even depression.

Unsurprisingly, this news brings with it a raft of self-proclaimed remedies purporting to fight inflammation. Diets, herbs, supplements, and exercise regimens have flooded the market with promises to keep inflammation in check and improve overall health.

But is there evidence that over-the-counter products or sweeping lifestyle changes will reduce inflammation’s damaging effects? Scientists caution that despite its current high profile, inflammation remains a mystery. “Basic science hasn’t yet answered the major questions about inflammation,” says Michelle Petri, a rheumatologist and a director of the Johns Hopkins Lupus Center. Researchers like Petri have been studying low-level inflammation as a culprit in a number of diseases for decades. What they have discovered has led to an emerging understanding of how lifestyle choices—like diet, dental health, and exercise—may influence inflammation and its potentially damaging downsides.
Inflammation is a vital part of the human immune system. When harmful bacteria or viruses enter your body, when you scrape or twist your knee, the body’s defense system kicks into high gear. Chemicals ramp up the body to fight, bathing the damaged area with blood, fluid, and proteins; creating swelling and heat to protect and repair damaged tissue; and setting the stage for healing.

Sentinel cells first alert the immune system to the presence of invaders. Another set of cells releases chemicals that signal the capillaries to leak blood plasma, which surrounds and slows down trespassers. Another group of sentinels, called macrophages, releases cytokines, which are specialized germ fighters. Immunizing B- and T-cells join in, destroying both the pathogens and the tissues they have damaged. Finally, a last wave of cytokines is released to end the job and signal the immune system that its work is done. Its mission completed, the immune system calls off its dogs.

When our body’s powers of correction go wrong, however, they can work against us. Think of the acute heat and swelling that protect us during a normal immune response—a fever, or the redness and pain that surround a new injury, for example—and you can get a hint of what chronic inflammation is. Unlike the inflammation that follows a sudden infection or injury, the chronic kind produces a steady, low level of inflammation within the body that can contribute to the development of disease. It’s the result, in part, of an overfiring immune system. Low levels of inflammation can get triggered in the body even when there’s no disease to fight or injury to heal, and sometimes the system can’t shut itself off. Arteries and organs break down under the pressure, leading to other diseases, including cancer and diabetes.

Scientists don’t fully understand how the immune system becomes short-circuited, but they have long known that some diseases, such as lupus and rheumatoid arthritis, emerge after the immune system has gone awry and attacked healthy tissue. Increasingly, as Americans and other Westerners live longer and get larger (35 percent of Americans are obese), researchers have also found that low-level immune responses triggered by extra weight and a lack of exercise can contribute to the development of other illnesses.

“For a long time, we had the idea that inflammation was involved in certain autoimmune diseases, but now we’re seeing this lower level of inflammation in people who are obese and people who are sedentary,” says Kimberly Gudzune, a
physician at Johns Hopkins and a clinical researcher who focuses on obesity. “We see a link between obesity and some diagnostic markers for inflammation, but we don’t know what causes them. We worry that there’s something brewing for these people, that they are at higher risk for heart disease, cancer, and diabetes.”

Researchers have discovered that fat cells can trigger the release of a steady, low hum of cytokines that, in lieu of an invader to attack, go after healthy nerves, organs, or tissues. As we gain weight, the release becomes prolific, affecting our body’s ability to use insulin, sometimes leading to type 2 diabetes.

They have also learned that inflammatory cells can have an effect elsewhere in the body—for example, chronically infected and inflamed gums in the mouth can cause damage that leads to heart attack and stroke. And they know that inflammation contributes to congestive heart failure and uncontrolled hypertension, and that it somehow has a role in the tangled cells that are the hallmarks of Alzheimer’s disease.

Researchers continue to find answers about how inflammation contributes to cancer. Inflammatory cells produce free radicals that destroy genetic material, including DNA, leading to mutations that cause cells to endlessly grow and divide. More immune cells are then called in, creating inflammation that feeds the growth of tumors.

The link between inflammation and cancer can sometimes be direct. When too much stomach acid—a feature of the immune system that evolved to fight foodborne bacteria—creeps up the esophagus, it causes inflammation and chronic heartburn. Extended exposure to this acid changes the nature of the cells lining the esophagus, increasing the risk of cancer.

In colon cancer patients, certain communities of bacteria associated with diarrhea can create cancer with help from inflammatory cytokines. Cells protected by mucus can become inflamed when that mucus wall is breached by bacteria, says Cynthia Sears, a doctor who specializes in infectious disease research at Johns Hopkins. “The lining in the colon makes peptides”—short chains of amino acids that act to protect the lining of the organ—“to thwart bacteria. If there aren’t enough peptides, bacteria can get a foothold, which means even more bacteria,” Sears says. As inflammation ramps up to fight it, so does the risk of cancer.
If inflammation is the behind-the-curtain factor in so many diseases, what can we do to keep it at bay? Researchers admit that they’re still figuring this out.

Petri has studied lupus for more than three decades and has been investigating the effects of chronic inflammation. “Lupus is basically friendly fire,” Petri explains. “We can’t get the immune system to calm itself down.”

Treating chronic inflammation, whether for lupus or other chronic ailments, is a challenge. Researchers have an idea that inflammation exists as part of a self-reinforcing loop system. If they could figure out how to interrupt or reverse one stage in that loop, then they might be able to develop drugs to stop it. But how do you tone down the immune response enough to control the inflammation but not so much that a body can’t fight disease? “We’ve done 20 to 25 years of clinical trials on lupus drugs,” Petri says, by way of example. “We’ve had maybe one success and 30 failures.”

Currently, there are no prescription drugs that specifically target chronic inflammation. (There are, of course, over-the-counter medications that treat the minor and temporary inflammation and accompanying pain caused by injuries or procedures, such as surgery. These are not meant to treat chronic inflammation.) Some drugs, such as hydroxychloroquine, once used to battle malaria, are useful in treating some lupus patients, but they don’t cure the disease. Aspirin and statins have shown promise in reducing inflammation in some people, but researchers aren’t sure how broadly useful such drugs are in that role. With the exception of far-from-perfect anti-inflammatory drugs, such as prednisone, a corticosteroid that brings with it a slew of side effects, scientists are still researching how best to contain inflammation. “We need something that can work broadly and quickly, and without a lot of side effects,” says Petri.

Finding a drug that both interrupts the immune cycle and maintains a healthy immune response is important not just for people battling illness but for all of us, because as we age, inflammation increases in the body. Scientists aren’t sure how and why, but interestingly, the study of HIV is offering some insight.

HIV triggers chronic inflammation in the body, even after medications have
rendered levels of the virus undetectable in blood tests. Certain cytokines involved in that inflammation process can profoundly decrease testosterone levels, leading to muscle loss. “It’s possible that the chronic inflammation in people with HIV is similar to the chronic inflammation we see in aging,” says Todd Brown, an endocrinologist who researches the link between bodily markers for inflammation and chronic diseases found in people with HIV. If researchers can understand that process and create treatments to disrupt it in people with HIV, they could potentially translate their findings into treatments for similar muscle loss in aging.

Jeremy Walston is a Johns Hopkins geriatrician who investigates immune system response and muscle function in the elderly. He has been searching for markers that highlight the early signs of inflammation. Some blood tests for inflammation markers exist, but the researchers have uncovered two new markers that they believe may predict mortality and mark signs of late-in-life decline. “These are powerful inflammatory molecules that, when chronically expressed, lead to declines in stem cells and a remodulation of the immune system,” says Walston. “They also contribute to cell death,” particularly in the elderly, he says.

Finding a drug that both interrupts the immune cycle and maintains a healthy immune response is important not just for people battling illness but for all of us as we age.

As the quest for diagnostic measures and therapies continues, researchers point to simple lifestyle measures we can all take to help prevent chronic inflammation. Scientists are skeptical of cure-all claims found in the new crop of anti-inflammation diet books, but they do recommend dropping pounds (and the harmful fat cells that come with obesity) and avoiding the now common American diet high in fats and sugars.

“Losing weight can have profound effects on lowering inflammation,” says Brown, who adds that eating a diet rich
in fruits and vegetables and low in fats, processed foods, and sugars is generally a good idea, though more study needs to be done to determine how it might affect inflammation. Exercising, which causes an acute inflammatory response in the short term, but an anti-inflammatory one when we regularly get moving, is another strong step to take, he adds.

Other researchers advise getting plenty of sleep, lowering stress levels, and seeking out treatment for inflammation-inducing culprits, such as gum disease and high cholesterol levels. Avoid contact with heavy metals such as mercury, which is found in dangerous amounts in some large fish, and limit exposure to substances, such as diesel exhaust and cigarette smoke, that can set off the immune system. Additional studies by Brown and his colleagues have also shown some advantage in increasing our intake of omega-3 fatty acids and vitamin D, though more research is needed.

Walston and others caution against popping dietary supplements touted as anti-inflammatory cures. Some so-called remedies, such as turmeric, taken in large amounts, may actually be toxic to the liver and other organs.

For most of us, keeping inflammation in check comes down to common sense basics: eat well, don’t smoke, get moving, get more rest, and see your doctor for regular physicals, which could help stop chronic inflammation before it becomes rampant. “All of the things our grandmothers told us were good for us are actually good for us,” says Brown. “Until we have a more nuanced understanding of what inflammation does, that’s what we have to fall back on.”
What is an inflammation?


When a wound swells up, turns red and hurts, it may be a sign of inflammation. Inflammation is – very generally speaking – the body's immune system's response to stimulus. This can be bacteria colonizing a wound or a splinter piercing your finger, for example. Inflammation happens when the immune system fights against something that may turn out to be harmful.

Causes of an inflammation

Inflammation may have many different causes. These are the most common:

- Pathogens (germs) like bacteria, viruses or fungi
- External injuries like scrapes or foreign objects (for example a thorn in your finger)
- Effects of chemicals or radiation

Diseases or conditions that cause inflammation often have a name ending in “-itis.” For example:

- Cystitis, an inflammation of the bladder
- Bronchitis, an inflammation of the bronchi
- Otitis media, a middle ear infection
- Dermatitis, a disease where the skin is inflamed

Signs of an inflammation

There are five signs that may indicate an acute inflammation:

- Redness
- Heat
- Swelling
- Pain
- Loss of function

There is a loss of function, for example, when the inflamed limb can no longer be moved properly or when the sense of smell is worse during a cold, or when it is more difficult to breathe when you have bronchitis.

This means that an inflammation does not start when a wound has been infected by bacteria, festers, or heals poorly, but already as the body is trying to fight against the harmful stimulus or a viral infection.

Not all five signs occur in every inflammation. Some inflammations occur “silently” and do not cause any symptoms.

The body’s general response

If the inflammation is severe, it may cause general reactions in the body. This may include the following signs and symptoms:

- General symptoms of feeling sick, exhaustion and fever: These symptoms are a sign that the immune defense is very active and needs a lot of energy, which may be lacking for other activities. If the rate of metabolism is higher due to a fever, more defense substances and cells can be produced.
- Changes in the blood such as an increased number of defense cells.

A very rare but dangerous complication of an inflammation is called sepsis. Sepsis may occur if bacteria multiply quickly in a certain part of the body and then suddenly enter the bloodstream in large quantities. This can happen if the body does not succeed in fighting the inflammation locally, the pathogens are very aggressive, or the immune system is severely weakened.

Chills, feeling very ill, and very high fever can also be signs of blood poisoning. If blood poisoning is suspected, medical assistance is urgently needed.

What happens when you have an inflammation

Many different immune cells can take part in an inflammation. They release different substances, the inflammatory mediators. These include the tissue hormones bradykinin and histamine. They cause the narrow blood vessels in the tissue to expand,
allowing more blood to reach the injured tissue. For this reason the inflamed area turns red and becomes hot.

More defense cells are also brought along with the blood to the injured tissue, to help with the healing process. Both hormones can also irritate nerves and cause pain signals to be sent to the brain. If the inflammation hurts, you usually favor the affected part of the body.

The inflammatory mediators have yet another function: they increase the permeability of the narrow vessels, so that more defense cells can enter the affected tissue. The defense cells also carry more fluid into the inflamed tissue, which is why it often swells up. After this fluid is transported out of the tissue once again a while later and the swelling disappears again.

The mucous membranes also release more fluid during inflammation. This happens for example when you have a stuffy nose and the nasal mucous membranes are inflamed. Then the nasal secretions can help to quickly flush the viruses out of the body.

**Inflammations can also cause chronic diseases**

An inflammation is not always a helpful response of the body. In certain diseases the immune system fights against its own cells by mistake, causing harmful inflammatory responses. These include, for example:

- Rheumatoid arthritis, where many joints throughout the entire body are permanently inflamed
- Psoriasis, a chronic skin disease
- Inflammations of the bowel like Crohn’s disease or ulcerative colitis

These diseases are called chronic inflammatory diseases, and can last for years or even a lifetime in varying degrees of severity and activity.

**Sources**


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Chronic Diseases Caused by Chronic Inflammation Require Chronic Treatment: Anti-inflammatory Role of Dietary Spices

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Abstract

Noncommunicable chronic diseases such as inflammatory bowel diseases, cancer, diabetes, obesity, and pulmonary, cardiovascular, and neurodegenerative diseases are becoming the leading cause of death throughout the world. Unhealthy diet, smoking, lack of exercise, stress, radiation exposure, and environmental pollution are among the common causes of chronic diseases. Most of these risk factors are closely linked to chronic inflammation, which leads to the development of various chronic diseases. Diets high in fruits, vegetables, legumes, fiber, and certain spices have been shown to suppress chronic inflammation and prevent the development of chronic diseases. In this review we discuss the evidence for the molecular basis of inflammation and how inflammation mediates most chronic diseases. We also present clinical and experimental models showing the molecular effects of selected spices and spice-derived nutraceuticals such as cardamonin, curcumin, capsacin, gingerol, thymoquinone, and piperine on these inflammatory pathways and the potential role of nutraceuticals in preventing chronic diseases.

Keywords: Inflammation; Chronic diseases, Spices; Inflammatory pathways; Nutraceuticals

Introduction

Chronic diseases, defined as diseases of long duration and slow progression, include inflammatory bowel disease (IBD), heart disease, stroke, cancer, chronic respiratory diseases, neurological diseases, obesity, and diabetes. According to the U.S. Centers for Disease Control and Prevention, together these diseases account for 63% of all deaths worldwide and about 70% of all deaths (1.7 million each year) in the United States. The chief causes of these diseases are the changes in diet and lifestyle brought about by industrialization, economic development, urbanization, and market globalization, all of which have accelerated over the past 10 years. Most chronic diseases are preventable because they are linked to lifestyle. A modified diet, daily exercise, and avoiding tobacco can prolong life by preventing the occurrence of chronic diseases or improving the management of illnesses that do occur. Among these modifiable determinants of chronic diseases, nutrition may be the most influential, and scientific evidence increasingly supports the view that alterations in diet have strong effects on health throughout life [1].

Over the past few decades, studies have investigated the possible protective role of plant foods against chronic diseases. Several epidemiological studies have revealed that greater consumption of fruits and vegetables is associated with a lower risk of chronic diseases such as cancer. [2]. The World Health Organization stated that diets high in fruits and vegetables may have a protective effect against many cancers. More specifically, intake of fruits and vegetables probably reduce the risk for colorectal, pancreatic, lung, oral, esophageal, and stomach cancers. Conversely, obesity, excess consumption of red and preserved meat, alcohol may be associated with an increased risk of cancer. (http://www.who.int/dietphysicalactivity).

Among the foods containing beneficial active compounds, spices have their own particular importance. Some common spices and their bioactive components are shown in Figure 1. In general, spices are consumed in the form of dried seed, fruit, root, bark, or vegetative substance. Spices usually are used in nutritionally insignificant quantities as a food additive for flavor or color or as a preservative. Spices also are sometimes eaten as vegetables or used for other purposes, such as medicine, religious rituals, cosmetics, or perfumery. In this review, we will discuss the link between inflammation and chronic diseases, the anti-inflammatory activities of some spices and spice-derived nutraceuticals, and the use of spices and spice-derived nutraceuticals in the prevention and treatment of chronic diseases.

Role of Inflammation in Chronic Disease

Inflammation is a response of the immune system to injury, irritation, or infection caused by invading pathogens, radiation exposure, very high or low temperatures, or autoimmune processes. Therefore, inflammation is a mechanism for removing damaged cells, irritants, or pathogens. Inflammation is considered to be beneficial when it is short term and under control within the immune system (acute inflammation). Inflammation that persists longer is known as chronic inflammation. This inflammation is characterized by the simultaneous destruction and healing of tissue [3].

The various factors known to induce chronic inflammatory responses also cause numerous chronic diseases. These factors include bacterial, viral, and parasitic infections (eg, Helicobacter pylori, Epstein-Barr virus, human immunodeficiency virus, flukes, schistosomes); chemical irritants (eg, tumor promoters such as phorbol ester 12-O-tetradecanoylphorbol-13-acetate, also known as phorbolmyristate acetate); and nondigestible particles (eg, asbestos, silica) [4,5]. Inflammation produces reactive oxygen species and reactive nitrogen species, which cause oxidative damage and further lead to chronic diseases [6]. Inflammation also recruits leukocytes that...
secrete inflammatory cytokines and angiogenic factors to the site of tissue insult. These cytokines are required for proper wound healing and to stimulate epithelial cell proliferation; however, if uncontrolled these cytokines can lead to inflammatory disorders. All these inflammatory products have shown to be regulated by the nuclear transcription factor NF-κB, which is considered the master molecule of inflammation.

Figure 1: Anti-inflammatory spices and their bioactive molecules.
The transcription factor NF-xB is activated in response to a wide variety of stimuli such as stress (physical, psychological, mechanical, or chemical), tobacco, radiation, asbestos, dietary agents, environmental pollutants, obesity, and various infectious agents. NF-xB is activated by at least two separate pathways “canonical or classical” and “non-canonical or alternate”. Canonical pathway is triggered by microbial products and proinflammatory cytokines such as TNF-α and IL-1, usually leading to activation of RelA (p65) or cRel (p50/p105)-containing complexes while non-canonical or alternative pathway is activated by lymphotixin β, CD40 ligand, B cell activating factor, and receptor activator of NF-xB ligand, resulting in activation of RelB/p52 complexes [7]. The NF-xB activation pathway typically involves activation of NF-xB inhibitor α (IκBa) kinase (known as IKK), leading to phosphorylation, ubiquitination, and degradation of IκBa, nuclear translocation of the p50 and p65 subunits of NF-xB, DNA binding and transcription of NF-xB target gene. Although canonical NF-xB activation is mediated through the activation of IKK, noncanonical activation involves IKKα [8]. Binding of NF-xB on target gene results in transcription of over 500 genes involved in inflammation, immunoregulation, growth regulation, carcinogenesis, and apoptosis [7]. The activation of NF-xB in various immune cells, including T cells, B cells, macrophages, dendritic cells, and neutrophils, leads to expression of proinflammatory cytokines. The activation of NF-xB has also been shown to production of proinflammatory cytokine and chemokine in disease tissue from patients [9]. Another study also showed that proinflammatory cytokine production in human atherosclerotic plaques is NF-xB-dependent [10]. Thus, NF-xB plays a crucial role in inflammation.

Besides NF-xB, STAT3 pathway is also known to contribute to the inflammatory microenvironment. STAT3 is activated by many cytokines and growth factors, including epidermal growth factor, platelet-derived growth factor, and IL-6, oncogenic proteins, such as Src and Ras as well as by numerous carcinogens, such as cigarette smoke and tumor promoters [11]. The activation of STAT3 is regulated by phosphorylation at its tyrosine residue at 705 by receptor and nonreceptor protein tyrosine kinases. The phosphorylation of STAT3 in the cytoplasm leads to its dimerization, translocation into the nucleus, and DNA binding which result in transcription of genes that regulate inflammation, cell proliferation, differentiation, and apoptosis [11]. In addition, phosphorylation at serine 727 has been implicated in the activation of STAT3 [12]. STAT3 promote inflammatory environment by regulating the expression of cytokines, chemokines and other mediators [13,14]. STAT3 is highly interconnected with NF-xB signaling and interacts with NF-xB. For example the pro-inflammatory cytokine IL-6, encoded by NF-xB target genes, is important for STAT3 activation. STAT3 and NF-xB also co-regulate numerous oncogenic and inflammatory genes [15]. These indicate that NF-xB and STAT3 alone or in combination produce inflammation and inflammatory microenvironment.

There is a strong association between chronic inflammatory conditions and chronic diseases. Chronic inflammation damages the cells of the brain, heart, arterial walls, and other anatomic structures; this damage leads to various inflammatory chronic diseases. Studies on the causes of inflammation at the molecular level showed that numerous biomarkers are involved in the process of inflammation. Many of these biomarkers—transcription factors such as NF-xB and STAT3; inflammatory cytokines and chemokines such as tumor necrosis factor-alpha (TNF)-α, interleukin (IL)-1, IL-6, IL-8, and MCP-1; inflammatory enzymes such as cyclooxygenase (COX)-2, 5-lipoxygenase (LOX), 12-LOX, and matrix metalloproteinases (MMPs); and other factors such as prostate-specific antigen (PSA), C-reactive protein (CRP), adhesion molecules, vascular endothelial growth factor (VEGF), and TWIST are found common in most chronic diseases [16].

IBD is a group of inflammatory conditions of the colon and small intestine comprising in Crohn disease (CD) and ulcerative colitis (UC). IBD causes inflammation anywhere along the lining of digestive tract and often spreads deep into affected tissues. A number of cytokines/chemokines and their receptors have shown to be upregulated in patients with IBD. For example, the overproduction of various cytokines such as IL-2, IL-12, IL-18, IFN-γ, and TNF-α has been well documented in patients with CD [17,18]. A pilot study of 33 IBD patients (19 with CD and 14 with UC) and 33 matched healthy controls showed that cytokine and chemokine levels increased with disease severity [19]. Kader et al. [20] identified IBD serum biomarkers such as cytokines, growth factors, and soluble receptors in 65 patients with CD and 23 with UC; the researchers found that the levels of 4 cytokines [placental growth factor (PLGF), IL-7, IL-12p40, and TGF-β1] were significantly higher in patients with clinical remission than in those with active disease. Besides these, increased levels of NF-xB, myeloperoxidase, and fecal calprotectin were reported in healthy twins with IBD [21]. The association of STAT3 in IBD was also described in CD and UC populations [22]. These studies indicate that inflammatory transcription factors and cytokines are integral to IBD.

Epidemiological evidence points to a connection between inflammation and a predisposition for the development of cancer, ie, long-term inflammation leads to the development of dysplasia. Various pro-inflammatory biomarkers have been found to be elevated in several cancers. The pro-inflammatory biomarker STAT3 was found to be activated in 82% of patients with late-stage prostate cancer [23-25]. Another inflammatory transcription factor, NF-xB, was found in 60% of colorectal cancer patients [26]. Also, the overproduction of cytokines has shown to be associated with cancer-related fatigue [27].

Inflammation has also been shown to mediate cardiovascular diseases [28,29]. CRP, an acute-phase protein produced by the liver during bacterial infections and inflammation, was found to be a common marker for detecting cardiovascular and atherosclerotic diseases [30]. Inflammation is also a cause of autoimmune diseases such as rheumatoid arthritis, in which excess levels of cytokines such as TNF-α, IL-6, IL-1β, and IL-8 are often found [31]. Multiple sclerosis, another autoimmune disease, is caused by chronic inflammation in the central nervous system. Activated NF-xB is found in patients with multiple sclerosis [32]. Elevated levels of other cytokines such as IL-1α, IL-2, IL-4, IL-6, IL-10, IFN-γ, TGF-β1, TGF-β2, and TNF-α have also been found in frozen sections of central nervous system tissue from multiple sclerosis patients [33]. Similarly, cerebrospinal fluid samples from patients with Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, multiple sclerosis, and schizophrenia have been shown to exhibit the overexpression of cytokines and NF-xB [34]. Likewise, in patients with diabetes, high levels of CRP, IL-6, IL-1, and TNF-α—along with abnormal expression of NF-xB—have been observed [35-37]. The studies listed above indicate mounting evidence of a stronger association between inflammation and chronic diseases than was once believed.

Role of Spices in Regulation of Inflammation

For centuries, spices available in nature have been used as medicines against inflammation. Numerous studies have shown that
some spices have great potential to inhibit chronic inflammation. Turmeric, one of the common spices used in daily life in Asian countries, has been used as a medicine against inflammation. The active component of turmeric, curcumin, is a potent inhibitor of inflammation. Studies on animal models have shown that curcumin is effective in preventing UC and inflammation. Over the past few decades, curcumin has been shown to inhibit myeloperoxidase, COX-1, COX-2, LOX, TNF-α, IFN-γ, iNOS, and NF-xB in patients with IBD [38].

Curcumin at concentrations of 0.5 and 20 μM inhibited pro-inflammatory cytokine (TNF-α, IL-1β, and IL-8) production induced by lipopolysaccharide (LPS) in lung inflammatory cells ex vivo [39]. Treatment with curcumin also inhibited the upregulation of COX-2 in ultraviolet B-irradiated HaCaT cells [40]. In one study, curcumin was found to inhibit the NF-xB activation induced by TNF in human myeloid ML-1a cells. Specifically, curcumin blocked phorbol ester- and hydrogen peroxide-mediated activation of NF-xB [41], indicating that curcumin inhibits free radical–induced inflammation. Another study found that the constitutive phosphorylation of STAT3 transcription factors was inhibited by curcumin treatment. In multiple myeloma cells, curcumin suppressed both constitutive and IL-6-induced STAT3 activation [42]. Treatment with curcumin also was shown to block the activation of AP-1 and NF-xB induced by IL-1α and TNF-α cytokines [43]. This study indicated that curcumin inhibits cytokine-induced inflammation by suppressing inflammatory pathways.

Capsaicin, a major ingredient of pepper, has been shown to inhibit NF-xB activation. Phorbol ester-induced activation of AP-1 was also abolished by capsaicin pretreatment [44]. Capsaicin inhibited constitutive and IL-6-induced STAT3 activation. The activation of JAK1 and c-Src, which are implicated in STAT3 activation, were also inhibited by capsaicin [45]. Capsaicin treatment in HepG2 cells resulted in a transient increase in the nuclear translocation of Nrf2, enhancing the binding of Nrf2 to the antioxidant response element (ARE) [46]. Thus, capsaicin inhibits inflammation by inhibiting different inflammatory pathways.

*Nigella sativa* (also known as black cumin), a plant commonly used in Ayurvedic medicine for more than 2,000 years, exhibits anticancer activity through its inhibition of the inflammatory pathway. The predominant bioactive component of *N. sativa*, thymoquinone, suppressed NF-xB activation, which was correlated with the inhibition of IκBa kinase activation and the direct binding of nuclear p65 to the DNA [47]. Thymoquinone also inhibited both constitutive and IL-6-induced STAT3 phosphorylation, which correlated with the inhibition of c-Src and JAK2 activation, in multiple myeloma cells [48]. This inhibition of inflammatory transcription factors indicates that thymoquinone has anti-inflammatory activities.

Cardamom, a chalcone, has shown potent anti-inflammatory effects in *vitro* and *in vivo*. In a cellular model of inflammation, cardamom inhibited the production of nitric oxide (NO) and prostaglandin E2 (PGE2) and attenuated the expression of TNF-α, IL-6, IL-1β, inducible NO synthase (iNOS), and COX-2. Cardamom also prevented the nuclear translocation of NF-xB. In a mouse model of endotoxic shock, cardamom suppressed TNF-α, IL-6, and IL-1β secretion in LPS-induced mouse blood serum [49].

Piperine, an alkaloid found in black pepper, inhibited cerebral ischemia-induced inflammation in Wistar rats. In same study, piperine also reduced the levels of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α in the ischemic rats and lowered the expression of COX-2, NOx-2, and NF-xB. Both cytosolic and nuclear NF-xB were downregulated in the ischemic rats [50]. Thus, piperine exhibits anti-inflammatory activities by suppressing cytokines and inflammatory transcription factors.

Ginger is known for its ethnobotanical applications as an anti-inflammatory agent. It has been found that *6* gingerol, an active component of ginger, inhibited the production of TNF-α, IL-1β, and IL-12 from LPS-stimulated macrophages [51]. In an *in vitro* study [6], gingerol and 6-shogaol, another active compound of ginger, inhibited MAPK and PI3K/Akt phosphorylation and NF-xB and STAT3 translocation [52].

Dietary zerumbone, a sesquiterpene phytochemical present in Asian ginger, can prevent inflammation, as observed in a mouse model of ultraviolet B–induced corneal damage. In the mice given dietary zerumbone, corneal damage was ameliorated by the inhibition of NF-xB activation and nuclear translocation; concomitant decreases in iNOS and TNF-α expression were also seen in these mice [53]. However, another report suggested that zerumbone induces the expression of IL-1α, IL-1β, IL-6, and tumor TNF-α in colorectal carcinoma cell lines, which implies that zerumbone increases the production of pro-inflammatory cytokines in cancerous tissues in the colon and that this biochemical property may cause side-effects [54].

Taken together, these reports from animal and *in vitro* studies have revealed that spices have a strong potential to inhibit inflammation. Spices and spice-derived nutraceuticals suppressed most, if not all, inflammatory biomarkers. The major biomarker of inflammation is NF-xB, which is inhibited by spice-derived nutraceuticals. The inhibition of inflammatory transcription factors is not restricted to NF-xB. Spice-derived nutraceuticals also inhibited cytokines and inflammatory enzymes. Some active components of spices also suppressed constitutive and inducible STAT3. Thus, the studies collectively suggest that spices could be used for targeting inflammatory molecules in the prevention and treatment of chronic diseases.

**Clinical Aspects of Dietary Spices Against Chronic Diseases**

Extensive preclinical studies over the past 3 decades have indicated curcumin’s therapeutic potential against a wide range of human diseases [12]. These preclinical studies have formed a solid basis for evaluating curcumin’s efficacy in clinical trials. Clinical studies have shown that co-administration of curcumin with conventional drugs is effective against IBD and well tolerated [38]. In one study of patients with ulcerative proctitis and CD, curcumin decreased the symptoms and inflammatory markers in all patients [55]. In another study of IBD patients, curcumin (360 mg 3 or 4 times/day for 3 months) significantly reduced clinical relapse. Curcumin inhibited major inflammatory mechanisms such as COX-2, LOX, TNF-α, IFN-γ, and NF-xB [56]; and thus it opens bright prospects for the treatment of IBD. In addition, curcumin has shown to be effective in maintenance therapy in patients with quiescent UC. In a randomized, double-blind study with 89 patients, those treated with curcumin (1 g twice daily) plus sulphasalazine or mesalazine for 6 months had a lower relapse rate than those treated with placebo plus sulphasalazine or mesalazine [57]. In a study of cultured *ex vivo* colonic mucosal biopsies and colonic myofibroblasts from children and adults with active IBD, curcumin reduced p38 MAPK activation, enhanced IL-10, and...
Curcumin has shown effectiveness in patients with other chronic inflammatory diseases. The signs and symptoms of osteoarthritis were decreased in patients who received 200 mg of curcumin (present in Meriva). Curcumin inhibited serum inflammatory biomarkers such as IL-1β, IL-6, soluble CD40 ligand, soluble vascular cell adhesion molecule-1, and erythrocyte sedimentation [67]. In a randomized, double-blind, placebo-controlled clinical trial, curcumin delayed the development of type 2 diabetes in a prediabetes population [68]. A total of 240 participants received curcumin (1.5 g/day) or placebo. After 9 months of treatment, 16.4% of participants in the placebo group were diagnosed with diabetes, but no participants treated with curcumin developed diabetes. The authors of this study concluded that the curcumin might be beneficial in a prediabetes population [68].

Fenugreek seeds (Trigonella foenum-graecum) have been shown to improve blood glucose and the serum lipid profile in insulin-dependent (type 1) diabetic patients. In patients who ate a fenugreek diet, fasting blood sugar was significantly reduced, glucose tolerance improved, and 24-hour urinary glucose excretion was reduced by 54%. Also, levels of total cholesterol, LDL and VLDL cholesterol, and triglycerides in the serum were significantly reduced [69]. An inverse relationship between the risk of gallbladder cancer and the amount of vegetables (including fenugreek) consumed was observed in 153 patients with gallbladder cancer and 153 controls with gallstone disease [70]. In a double-blind, placebo-controlled study conducted in 50 patients with Parkinson disease, fenugreek capsules (300 mg, twice daily) had an excellent safety and tolerability profile. Thus, it has been concluded that fenugreek can be useful in the management of Parkinson disease [71].

Curcumin has demonstrated potential against colorectal cancer in numerous clinical trials. In 1 study, in 15 patients with advanced, treatment-refractory colorectal cancer received 440 mg of Curcuma extract containing 36 mg of curcumin for 29 days, resulting in a 59% decrease in lymphocytic glutathione S-transferase activity. Leukocytic DNA damage was constant within each patient and unaffected by treatment. The researchers observed no dose-limiting toxicities and reported that the Curcuma extract was well tolerated [61]. In a study of 15 patients with advanced, treatment-refractory colorectal cancer, a daily dose of 3.6 g of curcumin caused 62% and 57% decreases in inducible prostaglandin E2 production in blood samples taken 1 hour after the dose administered on days 1 and 29, respectively [62]. Curcumin in combination with quercetin suppresses adenosin in patients with familial adenomatous polyposis [63]. Five patients with familial adenomatous polyposis received curcumin (480 mg) and quercetin (20 mg) orally 3 times a day. After 6 months of treatment, the number and size of the patients’ polyps were reduced with no significant toxicity [63].

In patients with breast or prostate cancer, curcumin was found to be well tolerated. The maximum tolerated dose of curcumin was found to be 8 g per day, whereas the recommended dose was 6 g per day for 7 consecutive days every 3 weeks when combined with a standard dose of docetaxel [64]. In a randomized, double-blind, controlled study, 85 men who underwent prostate biopsies were given soy isoflavones and curcumin. In the patient group with baseline PSA values greater than 10ng/mL, PSA levels decreased among those who were receiving isoflavones and curcumin [65]. Another study investigated the safety, tolerability, and clinical efficacy of curcumin in 29 patients with asymptomatic, relapsed, or plateau-phase multiple myeloma. Oral curcumin (2, 4, 6, 8, or 12 g/day in 2 divided doses) was well tolerated and significantly downregulated the constitutive activation of NF-κB and STAT3; curcumin also inhibited the expression of COX-2 in most patients [66].

Ginger has also great potential against inflammatory diseases. In a pilot trial, 20 people at increased risk for colorectal cancer were given ginger (2 g) or placebo daily for 28 days. Differences between the 2 groups in levels of biomarkers for cell proliferation, apoptosis, and differentiation in colorectal epithelial cells with normal appearance indicated that ginger may reduce proliferation, increase apoptosis, and increase differentiation [78]. Another study in patients with acute respiratory distress syndrome, diet enriched with ginger showed lower serum levels of inflammatory cytokines IL-1, IL-6, and TNF-α [79].
Cinnamon’s effects on blood glucose were identified in a meta-analysis of clinical trials, which found that consuming whole cinnamon or as cinnamon extract significantly reduced fasting blood glucose levels in people with type 2 diabetes or prediabetes [80]. The studies described above show than various spices act against inflammation in vitro, in animal models, and in patients.

Role of Dietary Spices in Preventing Chronic Diseases

Because spices have chemical properties that reduce inflammation, the occurrence of some chronic diseases can be prevented by increasing the consumption of spices (Figure 2). For example, differences in spice consumption could be the reason the occurrence of cancer in India, where spices are used routinely, is much lower than in the United States [81].

Curcumin has displayed a protective role in mouse models of IBD and in human UC by reducing neutrophil infiltration and levels of inflammatory molecules. In rat model of IBD, treatment with curcumin decreased levels of inflammatory molecules indicating, curcumin could be effective in the prevention and treatment of IBD [82]. Another preclinical study showed that curcumin interfered with inflammation in colonic epithelial cells by inhibiting chemokine expression neutrophil chemotaxis and chemokinesis, which results in the prevention of IBD [83]. Besides these, curcumin as well as cyclodextrin-conjugated curcumin decreased the degree of colitis caused by the administration of dextran sodium sulfate (DSS) [84,85]. In primary cultures of human intestinal microvascular endothelial cells, curcumin inhibited the expression of VCAM-1, Akt, p38 MAPK, and NF-κB and thus may have a therapeutic role against endothelial activation in IBD [86].

Curcumin may have therapeutic potential, as it was found to be associated with the suppression of inflammatory cytokines and enzymes, transcription factors, and gene products linked with cell survival, proliferation, invasion, and angiogenesis. Curcumin exhibited anticancer activities in in vitro and in animal models of cancer. Several phase I and phase II clinical trials have indicated that curcumin is safe [87].

Numerous lines of evidence suggest that curcumin mediates cardioprotective effects through diverse mechanisms. Several studies have suggested that curcumin protects the heart from ischemia/reperfusion injury [88,89]. Venkatesan [90] showed that curcumin also decreased acute adriamycin-induced myocardial toxicity in rats. In preclinical studies of diabetes, curcumin can lower levels of blood glucose, raise pancreatic β-cells’ antioxidant status, and facilitate PPAR-γ activation [91]. Curcumin can also induce hypoglycemia in rats with streptozotocin-induced diabetes [92]. The most likely mechanism for this action is that curcumin inhibits cholesterol, induces antioxidant and scavange free radicals.

Capsaicin also has shown chemopreventive and chemoprotective effects [93]. In a mouse model, topical capsaicin was shown to inhibit skin tumors induced by phorbol 12-myristate 13-acetate [44]. In a study of 29 normotensive and 13 hypertensive people with alopecia, capsaicin and isoflavone reduced arterial blood pressure; this likely resulted from elevated levels of serum IGF-I [94]. Capsaicin has also been found to be protective against stress-induced neurological impairment. In an animal model, capsaicin administered at 10 mg/kg 1 hour before the introduction of stress mitigated stress-induced cognitive and Alzheimer disease-like pathological alterations [95]. In other animal studies, capsaicin had preventive effects against neonatal hypoxic-ischemic brain injury [95], epileptogenesis [96], and diabetic neuropathy [97]; it also reduced toxin-induced neuroaparalytic effects in neuromuscular junctions [98].

Cardamonin has shown potential against several cancer types, such as colorectal and gastric cancers, sarcoma, and multiple myeloma. Cardamonin inhibited the proliferation, invasion, and angiogenesis of cancer cells [99,100]. Cardamonin also suppressed bone loss, which often occurs in multiple myeloma, breast cancer, and prostate cancer patients [101]. Cardamonin also enhances cell death of colorectal cancer cells induced by TRAIL through induction of ROS-CHOP-mediated death receptor as well as suppression of decoy receptor and cell survival proteins [102]. Beside this, cardamonin exhibits cardioprotective effects. It induced relaxation of phenylephrine-preconstricted mesenteric arteries in a rat model [103]. In a study of fructose-induced diabetes in rats, cardamonin reduced insulin.
resistance and smooth muscle hyperplasia of the major vessels [104].
Cardamonin has been shown to act against systemic hypertension by
inhibiting I(Ca(L)) and stimulating K(Ca)L1 current [105]. Recently,
thymoquinone was shown to protect and ameliorate colonic
inflammation in a mouse model of IBD. Treatment of mice with
thymoquinone ameliorated of DSS-induced colitis by lowering colonic
myeloperoxidase activity and malondialdehyde levels and raising
glutathione levels [106]. A rat model showed that pretreatment for 3
days with 10 mg/kg of thymoquinone completely prevented acetate
duced colitis, while 500 mg/kg of sultasalazine provided less
protection [107].

Thymoquinone has been shown to inhibit proliferation in several
cancer cell lines and to inhibit angiogenesis and tumor growth in vitro
and in vivo [47,108]. Thymoquinone also reduced diabetes-related
inflammation and protected β cells [109]. In a study of rats with
streptozotocin-induced diabetes, thymoquinone protected the kidneys
against oxidative stress [110]. Thymoquinone may protect neurons
against toxicity and apoptosis. In a rat study, thymoquinone
ameliorated ethanol-induced neurotoxicity in the primary cortical
neurons, indicating its potential as a treatment against neonatal
alcohol exposure [111]. Cinnamaldehyde, a compound in cinnamom,
has shown activity against several chronic diseases. For example,
cinnamaldehyde inhibits proliferation and induces apoptosis in cancer
cells [112]. The compound also exhibits antiadiabetic, antioxidant, and
hypolipidemic activity [113] and acts as a vasorelaxant on isolated rat
aorta [114].
Piperine has been found to be effective against IBD alone or in
combination with other natural products. In one study, piperine
combination with tea polyphenol inhibited DSS-induced colitis. Mice
treated with the combination had reduced levels of histological
damage to the colon and lipid peroxidation; the colon tissue had a
decreased level of myeloperoxidase (a marker for neutrophil
accumulation) and higher levels of superoxide dismutase and
glutathione peroxidase (antioxidant enzymes) [115]. Piperine
combined with a hydroalcoholic extract of Amaranthus roxburghianus
and piperine had effects against UC that were comparable to those of
prednisolone [116]. Recently, a combination of the polyphenols,
zerumbetin and piperine, which was encapsulated into reconstituted oil
bodies, was shown to protect against DSS-induced colitis and weight
loss [117].
Piperine inhibited the growth of 4T1 mammary carcinoma cells in
vitro and lung metastases in mice [118]. Co-administration of piperine
also improved the antitumor efficacy of the chemotherapeutic agent
doctaxel in a mouse xenograft model of castration-resistant prostate
cancer [119] and of 5-fluorouracil in in vitro and in vivo models [120].
In mice with alloxan-induced diabetes, piperine lowered blood glucose
levels at subacute doses but raised blood glucose levels at high doses
[121]. Piperine was also shown protection against corticosterone-
induced neurotoxicity in cultured rat pheochromocytoma cells [122].
In another study, piperine was shown to protect against epilepsy-
associated depression; this antidepressant activity was likely due to
piperine’s activity as a monoamine oxidase inhibitor and its
neuroprotective properties [123].

Ginger has been shown to ameliorate UC. In a rat model, ginger
extract reduced the effects of acetic acid-induced UC [124]. In support,
Hsiang et al. [125] showed that ginger extract and gingerone reduced
the effects of 2,4,6-trinitrobenzene sulphonic acid-induced colitis by
inhibiting NF-kB activity and IL-1β signaling. Furthermore, ginger
volatile oil found to reduce colitis symptoms in a rat model by
decreasing the colon weight/length ratio, ulcer severity, ulcer area, and
ulcer index with a concomitant decrease in the inflammation induced
by acetic acid [126]. 6-Gingerol has demonstrated antioxidant, anti-
inflammatory, and anticancer properties. In a preclinical study of
hepatocellular carcinoma, 6-Gingerol and 6-shogaol inhibited
invasion and metastasis through multiple molecular mechanisms [52].
The antitumor potential of 6-gingerol was demonstrated when it
prevented skin tumor growth and induced apoptosis in a mouse model
[127]. It has also been shown that crude ginger extract and gingerol
each reduced joint swelling in an animal model of rheumatoid arthritis
[128]. The neuroprotective effect of 6-gingerol was demonstrated in
SH-SYSY cells when pretreatment with the compound protected
against cytotoxicity and apoptosis [129]. In a study of arsenic-
toxicated mice, 6-gingerol had an anti-hyperglycemic effect and
improved insulin signaling [130].
Zerumbone has been found to be effective against colitis. In a study
mouse model, oral zerumbone lowered the DSS-induced levels of
IL-1β, TNF-α and PGE(2) and suppressed colitis [131]. Zerumbone
was also shown to suppress tumor growth and induce apoptosis in various cancer cell lines. In a mouse model of skin cancer,
zerumbone inhibited both tumor initiation and promotion through its
antioxidant inducing nature and activation of phase II drug
metabolizing enzymes along with attenuation of proinflammatory
molecules [132]. A mouse model of colon cancer demonstrated that
zerumbone prevented tumorigenesis and that this effect was mediated
through its modulation of antiproliferative mechanisms, apoptosis,
and inflammatory molecules [133]. These studies indicate
zerumbone’s potential against chronic diseases such as cancer.

Conclusion

Spices have been used as traditional medicine against chronic
diseases for thousands of years. Numerous preclinical study results
suggest that spices and spice-derived nutraceuticals are associated
with a decreased risk of inflammation-regulated chronic diseases. More
clinical trials are needed to strengthen this preclinical evidence.
Because chronic diseases require a long time to manifest, structuring
such clinical trials will be difficult. However, to validate the
importance of spices in daily life, long-term prospective epidemiology
studies and well-controlled clinical trials of spices are needed. The
Dietary Approaches to Stop Hypertension (DASH) diet, which
features high intakes of spices, fruits, vegetables, legumes, and nuts;
moderate amounts of low-fat dairy products; low amounts of animal
protein and sweets; and sodium reduction, is recommended because
the DASH diet diet has a potential to prevent cancer. Until further
evidence is available, we recommend increasing the amount of
inexpensive, nontoxic nutraceuticals such as spices in the daily diet to
help prevent the occurrence of chronic diseases.

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Chemical and in vitro assessment of Alaskan coastal vegetation antioxidant capacity.
Kellogg J¹, Lila MA.

Abstract
Alaska Native (AN) communities have utilized tidal plants and marine seaweeds as food and medicine for generations, yet the bioactive potential of these resources has not been widely examined. This study screened six species of Alaskan seaweed (Fucus distichus, Saccharina latissima, Saccharina groenlandica, Alaria marginata, Pyropia fallax, and Ulva lactuca) and one tidal plant (Plantago maritima) for antioxidant activity. Total polyphenolic content (TPC) was determined, and chemical antioxidant capacity was assessed by 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging, ferrous ion chelating, and nitric oxide (NO) inhibition assays. In vitro inhibition of radical oxygen species (ROS) generation and NO synthesis was evaluated in a RAW 264.7 macrophage culture. Greatest TPC (557.2 μg phloroglucinol equivalents (PGE)/mg extract) was discovered in the ethyl acetate fraction of F. distichus, and highest DDPH scavenging activity was exhibited by F. distichus and S. groenlandica fractions (IC50 = 4.29-5.12 μg/mL). These results support the potential of Alaskan coastal vegetation, especially the brown algae, as natural sources of antioxidants for preventing oxidative degeneration and maintaining human health.

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Chemopreventive Activity of Polyphenolics from Black Jamapa Bean (Phaseolus vulgaris L.) on HeLa and HaCaT Cells

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Abstract

The antiproliferative effects of 100% methanol crude extract and of Toyopearl and silica gel fractions from the seed coats of black Jamapa beans (Phaseolus vulgaris L.) were evaluated using HeLa, human adenocarcinoma cells, and HaCaT, human premalignant keratinocytes. The 100% methanol crude extract [172.2 μM equiv of (+)-catechin] increased adhesion of HeLa cells; however, 3- and 5-fold higher concentrations decreased the number of cells attached as a function of the treatment time. The highest concentration tested diminished the cell adhesion until 40% (after 24 h) to almost 80% (after 72 h). The IC₅₀ values showed that the 100% methanol crude extract was the most effective inhibitor of HeLa cell proliferation, even when it was dissolved in dimethylsulfoxide (DMSO) [34.5 μM equiv of (+)-catechin] or in medium [97.7 μM equiv of (+)-catechin]. The Toyopearl 5 (TP5) fraction and silica gel 2 (SG2) fraction inhibited 60% of the HeLa cell proliferation. The IC₅₀ was 154 μM equiv of (+)-catechin of the 100% methanol crude extract on HaCaT cells. Toyopearl fractions TP4 and TP6 significantly inhibited HaCaT cell proliferation, but the silica gel fractions did not have a significant effect. The 100% methanol crude extract (35 μg of dry material/mL) decreased the number of HeLa cells in the G₂/G₃ phase from 68.9% (for control cells) to 51.4% (for treated cells) and increased apoptosis (2.9 and 21.2% for control and treated cells, respectively). The results indicated that black Jamapa beans could be a source of polyphenolic compounds, which have an inhibitory effect toward HeLa cancer cells but are less aggressive on HaCaT premalignant cells.

Keywords: Phaseolus vulgaris; polyphenolic compounds; cytotoxicity; HeLa cells; HaCaT cells

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Impact of Cranberries on Gut Microbiota and Cardiometabolic Health: Proceedings of the Cranberry Health Research Conference 2015\(^1,2,3\)

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Abstract

Recent advances in cranberry research have expanded the evidence for the role of this Vaccinium berry fruit in modulating gut microbiota function and cardiometabolic risk factors. The A-type structure of cranberry proanthocyanidins seems to be responsible for much of this fruit’s efficacy as a natural antimicrobial. Cranberry proanthocyanidins interfere with colonization of the gut by extraintestinal pathogenic Escherichia coli in vitro and attenuate gut barrier dysfunction caused by dietary insults in vivo. Furthermore, new studies indicate synergy between these proanthocyanidins, other cranberry components such as isoprenoids and xyl稿lucans, and gut microbiota. Together, cranberry constituents and their bioactive catabolites have been found to contribute to mechanisms affecting bacterial adhesion, coaggregation, and biofilm formation that may underlie potential clinical benefits on gastrointestinal and urinary tract infections, as well as on systemic anti-inflammatory actions mediated via the gut microbiome. A limited but growing body of evidence from randomized clinical trials reveals favorable effects of cranberry consumption on measures of cardiometabolic health, including serum lipid profiles, blood pressure, endothelial function, glucose regulation, and a variety of biomarkers of inflammation and oxidative stress. These results warrant further research, particularly studies dedicated to the elucidation of dose-response relations, pharmacokinetic/metabolomics profiles, and relevant biomarkers of action with the use of fully characterized cranberry products. Freeze-dried whole cranberry powder and a matched placebo were recently made available to investigators to facilitate such work, including interlaboratory comparability.

Keywords:

cranberry, proanthocyanidins, microbiome, cardiometabolic, antimicrobial

Introduction

Dietary guidance is consistent in recommending greater consumption of fruit and vegetables to promote health. Indeed, the 2015 Dietary Guidelines Advisory Committee report noted that greater fruit and vegetable intake was the only characteristic of dietary patterns that was consistently identified in their report in every conclusion statement across health outcomes (1). Although the report does not recommend specific types of fruit, there has been a growing body of evidence that the phytochemical composition of berry fruit may differentiate them from other fruits and underlie some of their putative benefits. Recent advances in analytical methods have improved the characterization of polyphenols in berry fruit and subsequently the data in food-composition and metabolomics databases that are essential for observational studies. Furthermore, the development of a standard reference material (SRM)\(^14\) and matched placebos for use in clinical trials has provided an important and innovative component for the design and conduct of new randomized clinical trials. This review, prepared from the proceedings of the Cranberry Health Research Conference held in conjunction with the Berry Health Benefits Symposium in Madison, Wisconsin, 12–15 October 2015, focuses particularly on advances in the field during the last 5 y with regard to the gut microbiota and cardiometabolic health.

Cranberries and the Gut Microbiota

Molecular mechanisms.
Much of the attention regarding the impact of cranberries on the gut microbiota has been directed to studies of the effect of cranberry extracts or juice on uropathogens and urinary tract infections (UTIs) (2, 3). However, this focus has expanded to encompass a broader range of the cranberry’s antimicrobial, antifungal, and antiviral actions against Helicobacter pylori (4–6), Streptococcus mutans (7), Porphyromonas gingivalis (8), Staphylococcus aureus (9), Pseudomonas aeruginosa (10), Cryptococcus neoformans (6), Haemophilus influenzae (11), Candida albicans (12, 13), and extraintestinal pathogenic Escherichia coli (ExPEC) (14). Cranberry constituents, particularly the proanthocyanidins, flavonols, and hydroxycinnamic acids, may act against these pathogens by preventing bacterial adhesion and coaggregation, decreasing biofilm formation and/or reducing inflammation rather than via bactericidal activity. This expanding body of research includes in vitro, ex vivo, and animal studies that have suggested potential clinical effects and have helped to elucidate mechanisms of action as well as human studies that have shown physiologic effects (3–5, 14).

The antimicrobial properties of cranberry proanthocyanidins have been generally associated with their degree of polymerization (DP) and ratio of A- to B-type linkages. For example, by using an in vitro broth microdilution assay for growth inhibition of several yeast species, treatment of cultures with cranberry fractions of varying composition showed that cranberry proanthocyanidin fractions with a larger DP were found to be more effective than those with a smaller DP at inhibiting the growth of Candida spp. (12). In comparing primarily A-type proanthocyanidins from cranberries with primarily B-type proanthocyanidins from apples, Feliciano et al. (15) found that, although both increased agglutination and reduced epithelial cell invasion by ExPEC, the strongest effects were associated with a higher percentage of A-type linkages. This observation is consistent with other research that showed that A-type proanthocyanidins interact most strongly with bacterial virulence factors and more effectively decrease bacterial motility (16, 17).

**Microbiota biofilm.**

The prevention of biofilm formation, an early step in the development of infection, through interference in the coaggregation of bacteria is a well-documented antimicrobial mechanism of cranberry proanthocyanidins. The extensively hydroxylated structure of proanthocyanidins encourages intermolecular hydrogen bonding, allowing smaller molecules to aggregate and interact with receptors on cell surfaces. Thus, many studies of high-molecular-weight nondialyzable material from cranberry juice concentrate reveal potent antiahesion activity with microbial species, including those found in the oral cavity, stomach, small intestine, and colon (6, 11, 14, 18, 19). However, although purified cranberry proanthocyanidins are more effective in some antimicrobial assays than are crude or mixed extracts, several studies suggest that other compounds in cranberry possess antibacterial properties that alone or in combination with proanthocyanidins may enhance overall protection against infection. For example, Pinzn´-Arango et al. (20) exposed E. coli to cranberry juice cocktail (CJC) or cranberry proanthocyanidins over 48 h and found that the proanthocyanidins reduced whereas the CJC completely eliminated biofilm formation. Candidate CJC constituents may include nonphenolic compounds such as isoprenoids like ursoic acid and xyloglucans, hemicellulose oligosaccharides found in high-molecular-weight nondialyzable fractions (21). Hotchkiss et al. (22) found that arabinoxyloglucans isolated from pectinase-treated cranberry hulls prevented the adhesion of E. coli strains to bladder and colonic epithelial cells in vitro.

Bacterial adhesion to cells and other surfaces involves basic physical forces such as electrostatic and steric interactions, van der Waals forces, and surface charge, as well as both specific and nonspecific interactions of surface proteins and carbohydrates such as glucans, adhesins, and sugar-specific lectins (23–25). Using atomic force microscopy, Liu et al. (26) found that exposure to cranberry juice decreased the adhesion forces of P-fimbriated E. coli (HB101pDC1) and altered the conformation and length of the P-fimbriae. Pinzn´-Arango et al. (24) found that these fimbral changes were reversible, even for cultures grown in the presence of cranberry juice. de Liano et al. (27) showed the efficacy of colonic metabolites of cranberry polyphenols, including hydroxylated benzoic and phenylacetic acids, in inhibiting the adhesion and biofilm formation of uropathogenic E. coli to bladder epithelial cells, a relation that underscores the critical need to elucidate the role of the gut microbiota in transforming cranberry polyphenols to bioactive and bioavailable compounds.

**Gut microbiota metabolism and function.**

The gut microbiota is now appreciated as a critical factor in nutrition and health, influencing the bioavailability and metabolism of food components and affecting body systems, including brain and immune functions. The integrity of the gut mucosal barrier is essential
for maintaining a chemical and physical barrier against food, environmental antigens, and microbes (28, 29). Goblet cells migrate up the villi after differentiating from crypt stem cells and turn over with the epithelial layer every 3–5 d. Goblet cells secrete mucins, particularly mucin 2 (Muc-2), that contribute substantially to the maintenance of mucosal integrity (30). Mucin secretion is regulated by a complex network of cholinergic stimulation and T-helper 2 (Th2) cytokines IL-4 and IL-13 (31–35).

Dysfunction of the gut barrier and dysbiosis have been associated with typical Western diets high in saturated fat and low in fiber and phytochemicals, patterns that may lead to increased permeability of bacterial LPS and a pathogen-associated molecular pattern that stimulates innate immune responses in macrophages, neutrophils, endothelial cells, and adipocytes. LPS plays a role in acute infection-related inflammatory responses and is found in blood and tissues with both postprandial and chronic inflammation (36–39). With the use of mice (CEABAC10) that express human carcinoembryonic antigen-related cell adhesion molecules (CEACAMs), Martinez-Medina et al. (37) found that a high-fat, high-sugar diet increased intestinal permeability and TNF-α secretion, which resulted in a greater ability of adherent-invasive E. coli (AIEC) to colonize gut mucosa and induce inflammation. This diet also induced gut barrier dysfunction reflected by reduced levels of Muc-2 mRNA, increased permeability of 4-kDa fluorescein isothiocyanate-dextran, and decreased numbers of goblet cells. It is worth noting that AIEC may contribute substantially to the etiology of Crohn disease, an inflammatory bowel disease in which CEACAM6 is overexpressed on the apical surface of ileum epithelium (40). Furthermore, variant AIEC type 1 pil adhes to CEACAM6, a key step in the colonization of the ileum and chronic inflammation present in Crohn disease. In addition, after feeding mice a high-fat, high-sugar diet, Anhê et al. (41) reported that the addition of a cranberry extract attenuated the consequent chronic inflammation associated with gut barrier dysfunction, including reductions in plasma LPS, cyclooxygenase-2, and TNF-α. Furthermore, the ratio of NF-xB to inhibitor xB was significantly lower in the jejunal tissue of the mice fed cranberry extract relative to the mice fed the high-fat, high-sugar diet. Also suggesting the capacity of cranberry polyphenols to reduce intestinal oxidative stress and inflammation, in vitro experiments with Caco-2/15 intestinal cells by Denis et al. (42) revealed positive but differential effects of low-, medium-, and high-molecular-mass polyphenols from cranberries on oxidative stress, proinflammatory cytokines, NF-xB activation, and nuclear factor E2-related factor 2 (Nrf2) downregulation, as well as PPAR-y coactivator 1a.

Interestingly, the effects of high-fat, high-sugar diets on gut barrier function in mice are similar to those observed in animal models of parenteral nutrition and elemental enteral nutrition (EEN) (43, 44). EEN induces dysfunction of gut-associated lymphoid tissue, including decreased lymphocytes in Peyer’s patch and reduced tissue Th2 cytokines, and suppresses mucosal barrier function when compared with normal nutrition (43, 45–48). The addition of cranberry proanthocyanidins to EEN was found to increase ileal tissue IL-4 and IL-13 concentrations, goblet cell number and size, and the secretion of intestinal Muc-2, attenuating the impairment of the mucosal barrier integrity after EEN alone (44). Pierre et al. (43) reported that the addition of cranberry proanthocyanidins significantly supported other indexes of gut-associated lymphoid tissue function impaired by EEN in mice, indicated in part by decreased Peyer’s patch lymphocytes and lower concentrations of tissue Th2 cytokines. Cranberry proanthocyanidins also helped to restore the EEN-induced decreases in polymeric Ig receptor, a transport protein involved in enterocyte transcytosis of secretory IgA (sIgA) from B cells in the lamina propria into the intestinal lumen. EEN decreases in luminal concentrations of sIgA were attenuated by cranberry proanthocyanidins; intestinal sIgA opsonizes bacterial antigens such as the virulence factors of pathogenic E. coli, rendering them less viable and more susceptible to killing by lymphocytes. The addition of cranberry proanthocyanidins also significantly prevented EEN-induced decreases in tissue IL-4 and phosphorylated signal transducers and activators of transcription 6 (STAT6).

Clinical studies are necessary to determine whether the results from these mouse models can be translated to the capacity of cranberry phytochemicals to reduce diet-induced intestinal inflammation in humans. Interestingly, there is limited evidence suggesting an effect of cranberry on systemic immune function in humans, which may be partly mediated via gut metabolism of cranberry polyphenols. For example, a randomized, double-blind placebo-controlled study documented increased ex vivo proliferation of γδ-T cells, immune cells located within the epithelium of the gastrointestinal and reproductive tracts, after the consumption of a cranberry beverage for 10 wk (49).

*ExPEC in the gut.*
Although ExPEC generally do not cause acute enteric disease, their colonization in the gut increases the risk of subsequent extraintestinal infection, including UTIs, septicemia, surgical wound infections, and neonatal meningitis (50, 51). ExPEC attach to and invade epithelial cells through adhesins expressed on type I pili (protein FimH) and P fimbriae (fimbrial adhesin PapG) and persist inside the host cell in vacuoles where they may evade immune detection. ExPEC, uropathogenic E. coli, and the AIEC associated with Crohn disease have similar virulence factors and are within the same E. coli phylogroups (B2 and D) (40). These phylogroups differ from enteropathogenic E. coli and Shiga toxin–producing E. coli, such as O157:H7, because enteropathogenic E. coli and Shiga toxin–producing E. coli cause acute intestinal disease and produce attaching and effacing lesions of the intestinal epithelium. Gut colonization by ExPEC is a likely cause of a chronic inflammatory state because ExPEC may evade immune detection and colonize enterocytes. The continuous presence of E. coli LPS in the gut mucosa may cause chronic intestinal inflammation. Although ExPEC have a meaningful impact on public health via their consequences on morbidity and mortality, they have not received concordant attention because they have been highly susceptible to antibiotics. However, 20–45% of ExPEC have become resistant to first-line antibiotics such as cephalosporins, fluoroquinolones, and trimethoprim-sulfamethoxazole (52, 53). Thus, it is becoming critical to appreciate and further investigate the potential role for dietary bioactive components in reducing such infections.

Recently, Feliciano et al. (15) showed that A-type proanthocyanidins have greater bioactivity than B-type proanthocyanidins for increasing ExPEC agglutination and decreasing their invasion (and subsequent colonization) of gut epithelial cells, an important observation for the elucidation of the effect of cranberry proanthocyanidins on UTIs. As suggested by Feliciano et al. (15) and other studies described above, decreasing intestinal colonization and associated inflammation may be achieved by usual serving sizes of cranberry juice without the requirement for absorption of its constituent proanthocyanidins into the circulation or their appearance in the urine. It is important to note that recent randomized clinical trials have confirmed and extended the body of evidence showing cranberry’s bacterial antiadhesion activity in urine ex vivo (3, 54), its capacity to reduce the recurrence of UTIs (55), and its therapeutic efficacy in preventing UTIs in gynecologic surgery patients after catheter removal (56). Nonetheless, additional research that uses similarly relevant ex vivo and in vivo models can be used to substantiate the structure-function relation of A-type proanthocyanidins to intestinal and extraintestinal infections and to develop preventive and therapeutic strategies against increasingly antibiotic-resistant classes of pathogens (57, 58). Such an effort could be advanced by the availability of a cranberry SRM as discussed below.

Cranberries and Cardiometabolic Health

A limited but growing number of clinical research studies (59–72) have focused on cardiometabolic health (Tables 1 and 2). The most commonly examined risk factors for cardiometabolic conditions in these studies have included serum lipid profiles, blood pressure (BP), endothelial function, glucoregulation, and a variety of biomarkers of inflammation and oxidative stress. Although the results of this research have generally been promising, a clear and consistent picture of this emerging area is confounded by sometimes marked differences in the cranberry products (cranberry juices, dried cranberries, and cranberry extracts) and doses used, as well as the characteristics of the study populations (2, 73). Although few animal model studies have examined this topic, Kim et al. (74–76) reported that 5% cranberry powder added to atherogenic diets with or without intraperitoneal LPS administration produced positive effects on serum lipids, proinflammatory cytokines, oxidative stress, and antioxidant capacity in rodents.

| TABLE 1 | Summary of randomized placebo-controlled trials on the cardiometabolic effects of cranberry1 |
| TABLE 2 | Summary of open-label trials on the effects of cranberry on cardiometabolic markers1 |

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Lipid profile.

Early reports by Ruel et al. (66–68) found that interventions with low-calorie cranberry juice were associated with increases in plasma HDL cholesterol as well as with reductions in plasma oxidized LDL cholesterol, adhesion molecules, and matrix metalloproteinase 9. Lee et al. (69) showed a reduction in both LDL cholesterol and total cholesterol in a trial in 30 patients with type 2 diabetes (T2D) who consumed cranberry extract supplements daily for 12 wk. In a double-blind, placebo-controlled trial, Shitifar et al. (60) reported that 58 men with T2D who consumed 1 cup cranberry juice/d for 12 wk experienced decreases in apoB and increases in apo A-1 and paraoxonase-1, although data on LDL, HDL, and total cholesterol were not reported. In an 8-wk randomized clinical trial of low-calorie cranberry juice consumption by 56 healthy adults, Novotny et al. (61) found that TGs were significantly decreased in the cranberry group whereas other elements of the lipid profile were unchanged.

BP.

Previous studies of the effect of cranberry juice on BP suggested a potential benefit on BP (67, 69). More recent studies also examined changes in BP after cranberry intake (60, 61–65). The durations of these studies ranged from 1 to 4 mo and tested intakes of total polyphenols ranging from 346 to 835 mg/d; and study populations were heterogeneous, including subjects with obesity, metabolic syndrome, T2D, coronary artery disease (CAD), and risk factors for cardiovascular disease (CVD), as well as healthy volunteers. With daily doses of CJC increasing every 4 wk from 0–125 to 250–500 mL, systolic BP decreased by 3 mm Hg with the 500-mL intervention compared with baseline in obese men (67). Of the more recent studies, only the study performed in healthy individuals and with the lowest dose of polyphenols showed an improvement in BP, with a reduction of 4.7 mm Hg in diastolic BP achieved after 8 wk of daily supplementation (61).

Endothelial function.

Endothelial dysfunction, often characterized by a decrease in nitric oxide production and impaired flow-mediated vasodilation (FMD), is a critical factor underlying the development and progression of atherosclerosis (77). In a randomized controlled trial with a crossover design, Dohadwala et al. (63) found that daily supplementation with cranberry juice for 4 wk did not improve FMD or peripheral artery tonometry in 44 patients with CAD, although an uncontrolled pilot study in a subset of the same population showed a modest improvement in FMD 4 h after an acute dose of cranberry juice. In a 4-wk trial with a cranberry juice drink, Flammer et al. (84) found no significant changes in peripheral artery tonometry in individuals with endothelial dysfunction and other CVD risk factors. Further research on the effect of cranberries on measures of vascular reactivity is required in healthy individuals examining both the dose-response and time course of the intervention.

Recently, in a clinical study of 10 healthy adults, Feliciano et al. (78) identified and quantified by ultra-performance liquid chromatography/quadrupole-time-of-flight mass spectrometry analysis a total of 68 cranberry-derived phenolic metabolites in plasma and urine after the acute ingestion of cranberry juice containing 787 mg polyphenols. These metabolites included sulfates of pyrogallol, valerolactone, benzoic acids, phenylacetic acids, and glucuronides of flavonols, as well as sulfates and glucuronides of cinnamic acids. Their concentrations ranged from in the low nanomolars to the high micromolars depending on the compound. Among these 60 phenolic metabolites, 12 were found to be independent predictors of time- (0–6 h) dependent increases in FMD after an acute dose (range: 409–1909 mg total polyphenols) (79). These results indicate that cranberry polyphenols can acutely increase endothelial function in healthy individuals. Arterial stiffness, commonly assessed by pulse-wave velocity or the augmentation index (a measure of the enhancement of central aortic pressure by a reflected pulse wave), is an established risk factor for CVD (80–82). In their randomized clinical trial of patients with CAD, Dohadwala et al. (63) found that a 4-wk intervention with cranberry juice significantly reduced the carotid-femoral pulse-wave velocity. However, no changes in the augmentation index were observed by Ruel et al. (65) after 4 wk of supplementation with cranberry juice in 35 volunteers presenting with obesity and other cardiovascular risk factors.

Glucoregulation.

Berry fruit polyphenols have been shown by in vitro experiments and animal models to inhibit carbohydrate digestion and glucose absorption in the intestine, stimulate insulin secretion from β cells in the pancreas, regulate glucose release from the liver, and activate insulin receptors and glucose uptake in insulin-sensitive tissues (83–85). Emerging clinical evidence suggests that dietary modification to increase polyphenol intakes from whole-food
sources can lead to improved glycemic control in T2D (86, 87). While exploring the antidiabetic effects of a cranberry extract in high-fat, high-sugar–fed mice, Anhê et al. (41) found a decrease in glucose-induced hyperinsulinemia and improved insulin sensitivity along with a reduction in weight gain and visceral obesity. As noted above, along with these improvements, the cranberry extract also altered the gut microbiome by increasing mucus-degrading bacteria. In light of the evolving link between the gut microbiota and diabetes, these findings provide an important connection between the studies documenting the effects of cranberry on gut barrier function and the potential to reverse the dysbiosis and metabolic inflammation underlying diabetes (88).

Human studies testing low-calorie cranberry juice and unsweetened dried cranberries were shown to produce favorable acute postprandial glycemic responses in adults with T2D (70, 71). However, the limited number of longer-term studies in patients with T2D generated discordant outcomes. Shidfar et al. (60) reported that daily cranberry juice consumed for 12 wk by 58 male patients with T2D induced significant decreases in fasting blood glucose when compared with the placebo group. In contrast, in a trial of 30 patients with T2D, Lee et al. (59) found no impact of daily supplementation with cranberry extracts for 12 wk on fasting blood glucose or glycated hemoglobin. In a diet therapy intervention in 27 adults with T2D, Chambers and Camire (89) found no significant effect of treatment with cranberry extract on measures of glycemia. However, in 12 healthy volunteers in a randomized crossover trial, Törönen et al. (90) found that a berry puree containing cranberries was able to delay the postprandial plasma response to sucrose. Clinical trials in patients with metabolic syndrome have suggested some benefit associated with cranberry intervention but not specifically on outcomes of glycemic control (62, 72, 91).

**Biomarkers of inflammation.**

In their analysis of observational data collected from NHANES, Duffey and Sutherland (92, 93) found inverse associations of popular polyphenol-containing beverages, such as cranberry juice, with obesity and inflammation. In their 8-wk randomized clinical trial, Novotny et al. (81) showed a reduction in C-reactive protein (CRP) after daily consumption of cranberry juice. In a clinical trial of 56 subjects with metabolic syndrome, Simão et al. (72) reported that daily intake of low-calorie cranberry juice for 8 wk had no significant effect on proinflammatory cytokines IL-1, IL-6, and TNF-α but did reduce biomarkers of lipid peroxidation and advanced oxidation protein products. Similarly, in an 8-wk study of 36 patients with metabolic syndrome, Basu et al. (62) observed increases in plasma biomarkers of antioxidant capacity and decreases in lipid peroxidation after the daily consumption of low-calorie cranberry juice. These results are consistent with in vitro experiments showing that cranberry polyphenols decreased the generation of reactive oxygen species and lipid peroxides and increased glutathione peroxidase activity and phospho-c-Jun N-terminal kinase (94).

**Cranberries and Health: Knowledge Gaps**

The recent growing body of research on cranberries and health is a part of the emerging evidence from in vitro, animal model, and human studies of plant polyphenols as protective dietary agents that act both directly and indirectly via their metabolites and/or interactions with the gut microbiota. Improvements in these research approaches, particularly in analytical methods as diverse as MS and gene-sequencing methods for microbial communities, are making important contributions to our understanding of polyphenol mechanisms and functions.

However, an important need in cranberry health research is the consistent use of a fully characterized SRM to help promote the generation of more readily comparable and replicable research protocols. SRMs have been available for some other polyphenol-rich foods, including highbush blueberries (95) and California table grapes (96), for in vitro, animal, and human studies. Although SRMs for cranberries have been developed by the National Institute of Standards and Technology and the Office of Dietary Supplements of the NIH, these materials are intended for the validation of analytical methods and quality assurance for in-house control materials. Furthermore, these SRMs are not accompanied by matching placebos for use in research studies. Wide availability of cranberry SRMs in sufficient quantities to conduct in vivo human health research remained lacking until recently. Because concerns for study accuracy and quality were raised because of the diversity of cranberry products available commercially and in research protocols (97), the Cranberry Institute undertook the development of a cranberry reference material in 2014 to ensure the authenticity and consistency of cranberry products used in research on human health.

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The first question to be answered was whether the SRM would be developed from whole fruit or one of the many processed forms in which cranberry is consumed. The impact of processing, particularly juicing, on the phytochemical content and profile of fresh cranberries has been characterized \(96, 99\). Grace et al. \(100\) compared fresh and freeze-dried cranberries to cranberry-containing commercial products including juices (from concentrate and not from concentrate), sweetened dried cranberries, and cranberry sauces (homemade and commercially canned). Cranberry skins and flesh were cross-compared for anthocyanin and proanthocyanidin content. Proanthocyanidins were typically higher in skins than in flesh with the exception of the proanthocyanidin A-2 dimer. Anthocyanin and proanthocyanidin concentrations were lower in juice reconstituted from concentrate. In general, the retention of proanthocyanidins in processed cranberries was found to be robust, whereas anthocyanins were sensitive to degradation. Grace et al. \(101\) explored ways to better concentrate and stabilize cranberry bioactive compounds via complexing concentrated juices with proteins isolated from soy, hemp, peanuts, and peas for formulation into beverages and solid-food products. By using an in vitro model to simulate digestion, Ribnicky et al. \(102\) were able to show that protein complexes with blueberry polyphenols remained more intact and bioaccessible than the free bioactive compounds.

To retain and encourage the study of the complete phytochemical profile of cranberry, the SRM is a freeze-dried whole-cranberry powder (FWCP). It is produced from a blend of cranberry varieties grown in Wisconsin and approximating the proportion available in the marketplace (i.e., 56% Stevens plus 11% each of Ben Lear, Grygleski, Pilgrim, and HyRed varieties for the first batch produced in 2015). The berries are individually frozen after harvest, freeze-dried, and ground into powder form. Silicon dioxide (3% total volume of powder) is added as an anticaking agent. The production process is fully documented from harvest to storage. Each 50 g (0.5 cup) of whole cranberries produces ~4.5 g FWCP.

Complete specifications for each nutrient and phytochemical ingredient were prepared by using a series of assays, including matrix-assisted laser desorption/ionization time-of-flight MS for authentication of proanthocyanidins \(103, 104\), 4-(dimethylamino)cinnamaldehyde assay for quantification of soluble proanthocyanidins \(105, 106\), and butanol-hydrochloric acid for quantification of insoluble proanthocyanidins as well as characterization of efficacy via an established in vitro antiadhesion assay and microbiological testing.

Accurate quantification of proanthocyanidins for health research is essential but also problematic because proanthocyanidins are complex polydispersed hetero-oligomers \(107\). Previously, the procyanidin A2 (ProA2) dimer was recommended as the standard of choice for proanthocyanidin analysis in the 4-(dimethylamino)cinnamaldehyde assay because cranberry proanthocyanidins contain 1 “A-type” interflavan bonds \(108\). However, current evidence shows that the use of the ProA2 dimer as a standard for quantification of complex proanthocyanidin oligomers results in a serious underestimation of proanthocyanidins \(109\). To address this problem, a cranberry proanthocyanidin standard (c-PAC), reflective of the structural heterogeneity of proanthocyanidins found in fresh cranberry (i.e., DP, hydroxylation pattern, and ratio of A- to B-type interflavan bonds), was developed. The use of the c-PAC to quantify proanthocyanidin content in FWCP resulted in values that were 3.6 times those determined by ProA2. Thus, adoption of this c-PAC standard reflects an improvement over the use of ProA2 for the accurate quantification of cranberry proanthocyanidins \(105\). Because these findings were only recently published, the soluble proanthocyanidin content of the FWCP is reported as both c-PAC and ProA2 equivalents, allowing researchers time to adopt the new methodology. The c-PAC was also used to quantify the FWCP insoluble proanthocyanidins by the butanol-hydrochloric acid method.

The polyphenol content of the FWCP includes the following: 28.35 mg total polyphenols (gallic acid equivalents)/g, 31.20 mg total soluble proanthocyanidins (c-PACs)/g, 8.77 mg soluble proanthocyanidins (ProA2)/g, 10.38 mg insoluble proanthocyanidins (c-PACs)/g, 5.98 mg anthocyanins (cyanidin-3-galactoside equivalents)/g, 9.01 mg flavonols (quercetin-3-rhamnoside equivalents)/g, and 1.81-mg hydroxycinnamic acids (cafeic acid equivalents)/g \(108\). The FWCP processing and packaging facilities are compliant with FDA regulations. A suitable placebo was created from a blend of maltodextrin, citric acid, artificial flavoring, fructose, and food-grade coloring agents \(109\). Calcium silicate is added to the FWCP and placebo as a flow agent.

The use of the FWCP should help overcome some of the critical limitations associated with past studies that used uncharacterized or only partly characterized cranberry foods or extracts. Recipes for the administration of FWCP and placebo in human studies have been developed and are made freely available to researchers. Like other studies of whole foods, it is recommended that protocols that use the FWCP not apply this material directly to
target tissues, with some possible exceptions such as oral and gastrointestinal cells. In vitro and ex vivo research approaches should consider the use of metabolite(s) on the basis of their likely bioavailability to these tissues, an approach not often followed in early studies of polyphenol-rich foods and extracts. The design of clinical trials that use the FWCP should also be informed by human bioavailability data generated from studies of other cranberry foods and extracts (Table 3) (110–114), although some consideration should be directed to results from animal models (115). However, because the product matrices and pharmacokinetic characteristics of these other products will undoubtedly differ, new studies on the absorption, metabolism, and elimination of the bioactive compounds in the FWCP must be undertaken. Although the availability of the FWCP as an SRM for clinical research may help ensure the consistency and full characterization of the cranberry intervention, the need to perform reasonable dose-response and time-course studies for each health-related outcome remains an important priority, as does the need to develop biomarkers of compliance to the intervention.

### Table 3

Summary of human trials investigating the bioavailability and pharmacokinetic variables of cranberry

**Summary**

Cranberry juice, dried cranberries, and various cranberry extracts have been shown via in vitro, animal model, and human studies to possess an array of biochemical and physiologic activities mediated by their phytochemical constituents. Although the greatest research focus has been reasonably placed on their rich content of polyphenols, emerging evidence of their actions on the gut microbiota and cardiometabolic functions suggests that attention is also warranted on their synergy with cranberry phenolic acids, isoprenoids, and oligosaccharides. Acting in high concentrations within the gastrointestinal lumen, these cranberry compounds may act to quench reactive oxygen species, modulate inflammatory pathways, adhere to carbohydrates and proteins on bacterial surfaces, exert prebiotic effects, and alter the dynamic cross-talk between intestinal epithelial cells and the gut microbiota. These actions may underlie not only the antimicrobial effects of cranberries but their role in the complex pathogenesis of UTIs and inflammatory bowel diseases. The importance of these relations beyond the gastrointestinal tract has grown substantially with the recognition of the broad role that the gut microbiota plays in regulating energy homeostasis, glucose and lipid metabolism, and systemic inflammation, all factors associated with the maintenance of cardiometabolic health.

Further substantiating the actions and mechanisms of cranberry constituents can best be accomplished by taking advantage of recent advances in cranberry research. For example, efforts to identify biomarkers of compliance to clinical protocols, as well as their relation to physiologic and health outcomes, may evolve from improved understanding of cranberry constituents (e.g., the specific nature of proanthocyanidin interflavan bonds and DP, as well as a more robust phytochemical profile) and the numerous active catabolites arising from the biotransformation of cranberry constituents by the gut microbiota and phase I, II, and III metabolism pathways. Furthermore, a greater degree of accuracy, consistency, and quality of new studies has become possible with the availability of a fully characterized FWCP and matched placebo as SRMs.

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**Footnotes**
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3 This is a free access article, distributed under terms (http://www.nutrition.org/publications/guidelines-and-policies/license/) that permit unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

14 Abbreviations used: AIEC, adherent-invasive Escherichia coli; BP, blood pressure; CAD, coronary artery disease; CEACAM, carinoembryonic antigen-related cell adhesion molecule; CJC, cranberry juice cocktail; c-PAC, cranberry proanthocyanidin standard; CRP, C-reactive protein; CVD, cardiovascular disease; DP, degree of polymerization; EEN, elemental enteral nutrition; ExPEC, extraintestinal pathogenic Escherichia coli; FimH, protein FimH; FMD, flow-mediated vasodilation; FWCP, freeze-dried whole-cranberry powder; Muc-2, mucin 2; NrF2, nuclear factor E2-related factor 2; PapG, fimbrial adhesin PapG; ProA2, procyandin A2; sIgA, secretory IgA; SM, standard reference material; STAT6, signal transducers and activators of transcription 6; Th2, T-helper 2; T2D, type 2 diabetes; UTI, urinary tract infection.

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