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REPORT

Novel Method Combats Chronic Inflammation

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For the past 16 years, green tea polyphenols have grabbed the headlines,¹ but a related family of black tea compounds called theaflavins is capturing the attention of longevity researchers.²

Theaflavins possess a unique ability to favorably influence human health by regulating genes that produce inflammatory cytokines and other toxic factors implicated in degenerative disease and aging. By modulating inflammation at its earliest stages, theaflavins represent a new tool in the fight against inflammation-related pathologies such as cancer, heart disease, senility, and arthritis.

TEA EXTRACTS AND THEAFLAVINS

The past decade has seen a veritable explosion of data on the active components of tea.³ The flavonoid *epigallocatechin gallate* (EGCG) found in green tea is widely known for its disease-preventing capabilities,⁴ and now its sister molecules, the theaflavins, are beginning to share the spotlight. What has researchers particularly excited is how theaflavins exert their health-promoting benefits by favorably altering our genes. This phenomenon, known as “*nutrigenomics*,” will be fully explained in this article.



THEAFLAVIN INHIBITS INFLAMMATION

Much of the misery of age-related conditions such as cardiovascular disease, diabetes, chronic pain, and even cancer can be laid at the feet of inflammatory processes that presumably originally evolved for the preservation of our health. A lifetime of exposure to oxidation and inflammatory stimuli leaves us awash in molecules known as *cytokines* and *chemokines*, which are used by immune system cells to signal each other and react to potential threats.

Long-term effects of these cytokines include increased tissue oxidation and further inflammation, which perpetuates the cycle and increases our risk for a myriad of chronic conditions. These inflammatory signaling molecules, of course, are the protein products of specific genes, and their production is regulated by *transcription factors*, as is all genetic activity in the body. Many nutrients help prevent or mitigate chronic disease either “upstream” in the process by preventing oxidation or “downstream” by inhibiting the effects of cytokines once produced. The remarkable ability of theaflavins to target specific gene *transcription factors* may allow for exquisite control of inflammation exactly when and where it starts—when inflammation-producing genes are “switched on” to start manufacturing cytokines.



Children’s health researchers at the University of Cincinnati described theaflavin’s novel anti-inflammatory characteristics in a 2004 paper,⁵ in which they identified the effect of varying concentrations of theaflavin on cells in a laboratory culture dish. The researchers were specifically interested in the gene that produces the inflammatory cytokine interleukin-8 (IL-8), which is responsible for much of the acute inflammation seen in conditions such as asthma, gum disease, and inflammatory bowel disease.^{6,7} Remarkably, theaflavin inhibited IL-8 production, even at very low concentrations. Even more remarkably, the effect was traced to theaflavin’s ability to inhibit the transcription of the IL-8 gene—in other words; theaflavin blocked the gene from actually expressing its product, the inflammatory cytokine.⁵ This pinpoint accuracy opens the door to many specific applications of theaflavin as an anti-inflammatory nutrigenomic agent.

THEAFLAVINS—WORKING AT THE GENETIC LEVEL TO CONTROL AGE-RELATED DISEASE

The first studies of theaflavins as modulators of genetic transcription began to appear at the turn of the present century, with recognition that theaflavins could control the expression of genes involved in cancer production, and a possible role in cancer chemoprevention as a result.^{8,9} (remember that cancer, like heart disease, has direct connections with inflammation, particularly

in its earliest stages).

By 2006, biologists in Iowa were already able to review the multiple sites at which theaflavins exert their gene-regulating effects: they (along with other polyphenols) up- or down-regulated production of enzymes involved in cancer production, they inhibited metastasis by blocking the effects of genes that produce enzymes making tissues more permeable to malignant cells, and they reduced the formation of new blood vessel growth needed for tumors to spread by blocking production of *vascular endothelial growth* factor, or VEGF. The review article concluded that **“green and black tea polyphenols act at numerous points regulating cancer cell growth, survival, and metastasis, including effects at the DNA, RNA, and protein levels.”**¹



Further studies have supported and expanded upon this work, progressively building the case for a specific group of theaflavin extracts from black tea.¹⁰ In 1999, biochemists in Taiwan investigated the effects of various tea components, including theaflavins, on induction of inflammatory molecules in mouse cells in culture.¹¹ A group of four theaflavins was found to potently inhibit production of those inflammatory molecules.

In 2000, other scientists in the same group were able to demonstrate that these theaflavin extracts could reduce inflammatory cytokine production even in the face of stimulation by one of the most powerful inducers of inflammation known, a bacterial molecule called *lipopolysaccharide* (LPS).¹² Importantly, this group also began the process of identifying the specific fractions, or groups of factors, in the theaflavin extracts that were the most powerfully active in blocking production of the inflammatory cytokines.

By 2002, these productive researchers had further extended their findings, demonstrating that the most active fractions of the theaflavin extracts could prevent inflammation on the skin and paws of mice that was induced experimentally with a toxic substance.¹³ Another Taiwanese researcher also published a 2002 report showing that the most active fraction of theaflavins was a potent cancer chemopreventive, chiefly through suppressing genes involved in tumor promotion and inflammation.¹⁴ In 2004, Japanese researchers were able to pin down platelet anti-aggregating effect to those same highly active fractions of theaflavins.¹⁵

Since 2005, the number of scholarly papers describing the powerful anti-inflammatory, anticancer, and longevity-enhancing qualities of these highly active theaflavin fractions has blossomed to several dozen studies, each providing more high-resolution details about just how these molecules act,¹⁶⁻²⁰ and broadening their beneficial effects to prevention of ischemia-reperfusion injury following strokes,^{16,21} alcohol-induced pancreatitis,²² colitis,²³ cigarette smoke-induced lung damage and cancers,²⁴⁻²⁶ cardiovascular disease,²⁷ and even parasitic infection.²⁸

WHAT YOU NEED TO KNOW: THEAFLAVINS

- Inflammation is intimately involved in aging and the manifestations of age-related diseases—in fact, the two processes are so closely intertwined they have recently been dubbed inflammaging by an internationally recognized expert.
- Many dietary approaches to countering the effects of inflammation are effective, but the emerging science of nutrigenomics offers insight into highly targeted nutritional supplements such as the theaflavin family of molecules extracted from black tea.
- Theaflavins, like other nutrigenomically active molecules, exert their powerful effects by promoting activity of genes involved in controlling inflammation, and suppressing activity of genes involved in promoting inflammation.
- Highly purified theaflavin extracts have been shown to reduce damage caused by inflammation-based diseases such as cancer, cardiovascular disease, diabetes, and other age-related conditions.
- A human study of purified theaflavin extracts produced dramatic reduction in disease-causing mediators of inflammation, including levels of CRP. This effect has been directly associated with longevity.

PROTECTING AGAINST VASCULAR DISEASES

Evidence that tea confers health benefits is millennia-old, but the mechanisms by which it works have only recently been revealed. It is known from epidemiologic studies, for example, that drinking multiple cups of tea per day reduces *low-density lipoprotein* (LDL). Cardiologists at Vanderbilt University studied the impact of a theaflavin-enriched green tea extract on lipid profiles of subjects with mild-to-moderately elevated cholesterol.²⁹ Studying 240 men and women in China, the researchers randomly assigned patients to receive either placebo or a theaflavin-enriched green tea extract (375 mg) daily for 12 weeks. At

the end of the study, the theaflavin-supplemented patients experienced decreases in their total cholesterol by 11% and LDL by 16%. Placebo recipients had no change at all. No significant adverse effects were observed, and the researchers concluded that this theaflavin-enriched extract was **“an effective adjunct to a low-saturated-fat diet.”**

Boston cardiologists studied the impact of black tea and its theaflavin components supplementation on *endothelial dysfunction*³⁰ in a study that randomly assigned 66 patients with coronary artery disease to consume either black tea or water. The study was designed in a “cross-over” fashion so that all subjects got both the tea and the water at different times (this allows comparisons within individuals as well as between subjects). The findings were dramatic: both short- and long-term tea consumption significantly improved blood flow in arteries, as detected by ultrasound measurements. This flow is controlled by endothelial cells and is typically decreased in patients with cardiovascular diseases. The researchers concluded that, **“short- and long-term black tea consumption reverses endothelial vasomotor dysfunction in patients with coronary artery disease.”**

In a British study of healthy men aged 18-55 years, subjects were given black tea or placebo for four weeks, and the effects on their *platelet activation* were measured. By the end of the study, the tea-drinking group had significantly fewer platelet “clumps,” or aggregates, than the placebo group.³¹

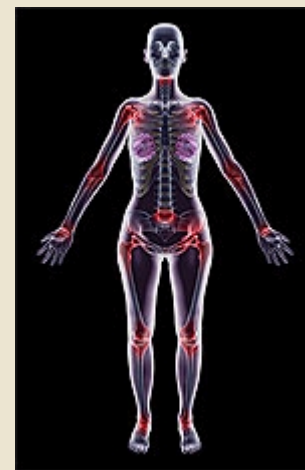
NUTRIGENOMICS: DIETARY CONTROL OF GENETIC EXPRESSION

The laws of genetic inheritance were first described in the mid-19th century, and from that time practically until the present we’ve tended to think of specific genes as permanent fixtures of each individual—we get our genes from our parents and they define our traits, such as hair and eye color, etc. By the early 20th century it was clear that genes could specify, or “code for,” unhealthy traits as well, and we all learned about inherited diseases such as sickle cell anemia and cystic fibrosis in high school biology. But it has only been within the past two decades that we have come to understand just how dynamic our genes really are.

We now understand that while individual genes may be the simple equivalents of “blueprints” on our chromosomes that tell cells how to make the specific enzymes and other proteins that define us, those genes are under exquisite control by a host of complex and interrelated systems collectively called *transcription factors*. Transcription factors may be thought of as the general contractors that, depending on the body’s needs, “order” production of necessary products built according to the genetic blueprints. And *transcription factors*, it turns out, are themselves controlled by a host of molecular influences—including a growing number of specific nutrients.

The study of how these nutrients work to control the genes’ production levels is called nutrigenomics.⁴⁴ Well-known nutrigenomics molecules include, for example, the *omega-3 fatty acids*, which regulate lipid profiles,⁴⁵ insulin responses,⁴⁶ and inflammatory mediators,⁴⁷ and the spice-derived curcumin molecule that shuts down transcription factors involved in inflammation and cancer production.⁴⁸

In fact, according to acclaimed scientist Peter J. Gillies, PhD, *“Nutrigenomics may provide the nutritional sciences with a molecular basis for positioning nutritional bioactives, functional foods, and designer diets to preemptively offset chronic disease.”*⁴⁴ Dr. Gillies goes on to note that, “With the expansion of research and the development of shared nutrigenomic databases, it may well become possible to define and track the influence of targeted nutrition on inflammation and the aging process.” In just the past two years, a host of other prestigious scientists have weighed in, supporting the pursuit of nutrigenomics as a vital framework for better understanding human biology and our relationship with our diets and our environments.^{2,43,49-56}



Why was this study so significant? This study represented an important first step in understanding how tea components actually influence gene transcription, and therefore in understanding the role of tea components in nutrigenomic influences on health. Here’s how: platelets, the tiny cell fragments involved in blood clotting, stick together (aggregate) when activated in an important step in the cardiovascular disease process. The triggers for platelet activation include oxidative stress and inflammation, which cause transcription factors to increase the activity of genes making proteins involved in the aggregation process, acutely increasing cardiovascular disease risk.³²⁻³⁴

In other words, the British researchers had found that tea components must act as nutrigenomic factors, modulating production of these potentially lethal proteins. This groundbreaking finding led the way for further research investigating which tea components were responsible for its nutrigenomic activity and how to utilize theaflavin consumption to influence health and longevity.

BREAKING NEWS: HUMAN STUDY WITH HIGHLY ACTIVE THEAFLAVIN EXTRACTS

The studies listed above only begin to tell the theaflavin story—a similarly overwhelming body of literature supports their effectiveness in switching off the genes involved in virtually every cancer type,^{1,35,36} for example, as well as in modifying the way

liver cells handle cholesterol and other fats.³⁷ Of course, the most exciting news always has to do with human studies, and how any given supplement might benefit human health and preventing human disease. While there are numerous studies of the impact of tea drinking on the health of large human populations (epidemiologic studies), there are still no published studies on the effects of the specially purified, highly active theaflavin extracts we have been discussing. But late-breaking news is about to change that—with data too recent to have yet been published, a private company has revealed the outlines of a compelling human trial using just one such extract. Let us review what the company was able to share with us about this exciting, still-proprietary information, in advance of publication in a peer-reviewed journal.

The study was conducted in 2007 with 12 human volunteers. Eight of the subjects were supplemented with the highly purified theaflavin extract for one week, while four received placebo. At the end of the week, the subjects received injections of a bacterial cell membrane component called LPS, one of the most powerful stimulators of inflammation known to science. LPS in modest doses can induce shock, coma, and even death, so naturally these were only minute and safe doses, but clearly the volunteers were expected to show some evidence of acute inflammatory reactions. In addition to clinical monitoring, the investigators drew blood samples to monitor for early signs of inflammation, particularly those involving the “inducible” cytokines such as TNF-alpha, IL-6, IL-8, and C-reactive protein (CRP).^{38,39}



Astonishingly, the supplemented subjects had a 56% reduction in levels of these cytokines even before they received the inflammatory challenge! Equally importantly, supplemented subjects experienced a 52% increase in levels of the protective, anti-inflammatory cytokine called IL-10,³⁹ which is involved in prevention of viral respiratory infections, for example.⁴⁰ The supplemented patients also demonstrated lower rates of production of the inflammation-generating transcription factor NF-kB (71%), the cytokine-generating enzyme COX -2 (72%), and the adhesion molecule ICAM-1.³⁹

C-reactive protein rose dramatically as expected in the placebo recipients—this protein is a sensitive marker of acute inflammation, and chronically elevated levels of CRP are known to be a risk factor for advanced atherosclerosis. Remarkably, that elevation was 75% greater in the placebo group than in the theaflavin supplemented group.³⁹

The ability of this highly active theaflavin extract to offset inflammatory cytokines points to a broad range of applications in human health in inflammatory conditions such as joint stiffness, muscle soreness, arthritis, osteoporosis, cardiovascular problems, diabetes, periodontal disease, and age-related immune dysfunction.

PULLING IT ALL TOGETHER—HOW THEAFLAVINS PROMOTE HEALTH AND LONGEVITY

There is a plethora of solid data on theaflavins' nutrigenomic effects—modulating the activity of genes involved in the inflammatory cascade that leads to cancer, heart disease, diabetes, and other age-related conditions. But these are more than just numbers—reduction or control of those powerful genetic functions is likely to produce measurable results in individual humans. In fact, the term “inflammaging” has recently been coined by Professor Claudio Franceschi, a researcher in aging at the University of Bologna, to describe the inevitable accumulation of products of inflammation associated with advancing age.⁴¹ Modern risk-screening protocols aimed at identifying those at highest risk for early demise now routinely incorporate at least one measure of inflammation,⁴² and Professor Jose Ordovas of the Tufts University School of Graduate Biomedical Sciences has observed that “studies have established a ‘diet/genetic interaction’ that further modulates markers of inflammation, producing both positive and negative effects, depending on the net changes in gene expression.”⁴³ Taken together, these researchers' comments suggest that dietary interventions to reduce inflammation will enhance health, prevent disease, and ultimately promote longevity and quality of life. The highly purified theaflavins now available as supplements, with their targeted, nutrigenomics mechanisms of action, certainly deserve a place in any responsible, scientifically based program of preventive health maintenance.



If you have any questions on the scientific content of this article, please call a Life Extension Health Advisor at 1-800-226-2370.

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