



Contents lists available at ScienceDirect

Journal of Traditional and Complementary Medicine

journal homepage: <http://www.elsevier.com/locate/jtcme>

Review article

Understanding nutrition and immunity in disease management



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ARTICLE INFO

Article history:

Received 29 April 2016

Received in revised form

6 December 2016

Accepted 8 December 2016

Available online 16 January 2017

Keywords:

Nutrition

Immunity

Supplements

Phytochemicals

eCAM

ABSTRACT

As we search for answers to modern medicine's most prevalent and challenging problems, the relationship between nutrition, immunity, and biological function of various natural compounds are pre-imminent. Nutritional research involving genomics provides rational capabilities for preventing disease. Scientific advances in genomic sequencing reveal opportunities for exploring diet-health relationships and potential for individual, genotype based dietary recommendations. Utilizing molecular and genetic technology to analyze impact of nutrition on genomics and metabolism reveals that nutrients may influence certain innate and/or acquired immune functions. By analyzing immune mechanisms including their cells and complex molecules, animal models have offered relevant insight that clarifies interrelations between immunity and nutrition. Plant products also provide numerous resources through bioengineering for designing novel pharmaceuticals. Having long been employed successfully in traditional and folk medicines, plant compounds exhibit anti-inflammatory, antimicrobial, and angiogenic activity. As a result, we now have a promising arsenal for successful application of bioactive compounds.

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1. Nutrition and clinical practice

The impact of diet on human health has long been a topic of research, from its effects on human evolution during the Paleolithic times to its role in causing illness such as diabetes and heart disease, fueled by recent scientific advances in genomic sequencing, exploring diet-health relationships have expanded, revealing potential for genotype based dietary recommendations. Although double edged nutritional research and genomics reveal clues for preventing disease and promoting optimal health, these opportunities have not been enthusiastically utilized nor given necessary importance during discussions of national health care.¹ New technology presents novel approaches for advancing nutritional genomics and tools for analyzing biochemical mechanisms involved in disease. As nutrition is an important environmental factor that could affect disease, genome based diets potentially improve overall public health. Through nutritional guidelines based on

individual genetics, we are then equipped to prevent and treat disease based on variations in the human genome.²

With recent progress in nutritional genomics and promotion of customized, genome based diets, individual guidelines for optimal health are more prevalent in Western medicine. Yet this approach also corresponds with patient centered philosophy of Eastern medicine focusing on the whole individual. Many nutritional concepts of Eastern medicine have not been adopted by systems of Western nutrition. However, while both Eastern and Western medicine possess varying strengths and weaknesses with respect to techniques, as well as interpretation of an integrated approach to nutrition could be achieved by selecting advantages of both systems based on knowledge and practice. Combining both systems may therefore create an inclusive, all-encompassing concept of medicine, providing holistic methods and improved care from each individual system.³

While western medicine tends to be reductionist, eastern complementary and alternative medicine (CAM) is inclusive. Understanding CAM and how it meshes with western practices and biological processes will help construct a workable framework for application of CAM in public health and clinical practice.⁴ As nutrition has a profound effect on multiple body systems, clearly analysis of nutrition should seek to obtain a broad understanding of food. Food and its beneficial properties possesses the capability to provide answers and the potential to be utilized in preventing,

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Peer review under responsibility of The Center for Food and Biomolecules, National Taiwan University.

treating, and even developing pharmaceuticals for the most perplexing and problematic diseases known to medicine.

2. Evolution of immunity and digestion

Investigating relationships between nutrition and immunity from an evolutionary perspective has revealed ancient connections in development and function. Historically, the digestive and immune systems have been viewed and analyzed as separate entities. However newly interpreted evidence demonstrates that both systems share essential similarities and common functions, both in nutrient acquisition and host defense with origins common to both systems. This provides a new and perhaps novel way to envision the emergence and evolution of host defense mechanisms.⁵ Unicellular invertebrates phagocytose for food and defense, and phagocytosis represents the most ancient and ubiquitous form of food acquisition and defense against foreign insult. Multicellular invertebrates and vertebrates possess phagocytic cells for defense and have evolved more complex functions attributed to immunodefense cells that became specialized for effecting cellular and humoral immune responses. From the oral cavity through terminus of the intestine, our tubular digestive system is amply equipped with cells, tissues, and organs that coevolved and remain forever together. Digestive and immune systems are inextricable.⁶

Host responses against invading pathogens are basic physiological reactions of all living organisms. Since appearance of first eukaryotic cells, a series of defense mechanisms have evolved to secure cellular integrity, homeostasis, and host survival. Invertebrates, ranging from protozoans to metazoans, possess cellular receptors, which bind to foreign antigens and therefore differentiate self from non-self. This rudimentary ability in multicellular animals is associated with phagocytes, bearing different names (e.g. amoebocytes, hemocytes, coelomocytes) in various groups species such as sponges, round worms, cnidarians, mollusks, crustaceans, chelicerates, insects, annelid worms and echinoderms. The cells, macrophage-like in appearance, function, and associated repair are prominent even at the earliest evolutionary stage, and possess well conserved molecular structures such as pathogen recognizing receptors (PRRs) and pathogen-associated molecular patterns (PAMPs). Scavenger receptors, Toll-like receptors, and Nod-like receptors (NLRs) are also prominent members within this group of host receptors. Following receptor-ligand binding, signal transduction initiates a complex cellular reaction cascade, which leads to production of diverse effector molecules. As examples, cytokines participate in this response evoking orchestration even in “lower” invertebrates, which eventually may result in intruder elimination or inactivation. Important innate effector molecules are antimicrobial peptides, lectins, fibrinogen-related peptides, leucine rich repeats (LRRs), pentraxins, and complement-related proteins.⁷

3. Nutrition and immunity in relation to an animal model: the earthworm

Analysis of nutrition and immunity in animals other than humans, especially invertebrates, has introduced newer discoveries and insights. As a rich source of macromolecules and nutrients, earthworms have long been used as food among various indigenous cultures.⁸ The nutritional and medicinal value of earthworms has been utilized for centuries among traditional and complementary practices such as Ayurveda, Traditional Chinese Medicine, Kampo, and Traditional Korean Medicine, the foundation from which current knowledge of the healing properties of earthworms stems. Earthworms and their nutritional products exhibit anti-inflammatory properties, and promise in treating human disorders of blood coagulation.^{8,9} Their ability to regenerate lost

appendages has prompted further research in mammalian applications, specifically by extending this ability in order to regenerate damaged nerves. Analyzing earthworms and invertebrates is advantageous since we can bypass ethical restrictions and financial constraints that normally more than ever impede research using vertebrates, especially mammals. Newer non-vertebrate models allow for generation of vast amounts of useful research surrounding biomedical capabilities and potential. Nutritional and therapeutic benefits of earthworms and their impact on chronic human conditions are closely tied to understanding evolution of innate immunity.¹⁰

Earthworm innate immunity has recently been analyzed through gene profiling of earthworm coelomic cells (leukocytes) which play an important role in immune function. Analysis of expressed sequence tags leads to identification of immune-related and cell defense genes, providing valuable knowledge for future research that focuses on earthworm immune systems.¹¹ Compounds derived from earthworms have the potential to provide groundbreaking treatments for conditions such as thrombosis. For example, analysis of the earthworm compound Lumbrokinase has revealed its efficacy as an extremely potent treatment of blood-clots, with the purification of a single Lumbrokinase increasing its antithrombotic activity and in turn improving the general use of Lumbrokinase.¹² Despite other available pharmaceuticals and drugs, thrombosis remains one of the main causes of death among Americans, making Lumbrokinase and its antithrombotic effects a valuable alternative treatment.⁹ Development of molecular and genetic resources may help achieve a more complete understanding of earthworms as a genetic model that may facilitate research of the immune system.¹³

In general, animal products provide a wealth of resources for utilization in creating novel pharmaceuticals and in bioengineering. Historically, animal models have been successful subjects that offer insight into biological processes, and have long been used in various traditional and folk medicines. Animals are a valuable source of biological compounds, exhibiting extensive drug applications including anti-cancer, antimicrobial, and angiogenic activity. Recent discoveries and successful applications demonstrate great potential that will impact modern medicine, improving and revealing new treatments and methods of prevention.^{14,15}

4. Nutritional models for disease treatment

Analysis utilizing molecular and genetic technology measuring impacts of foods on genomics and metabolism reveal how nutrients may influence certain immune functions.¹⁶ Innate immunity and nutrient metabolism are complex biological systems that must work in concert to sustain and preserve life. Effector cells of the innate immune system rely on essential nutrients to generate energy, produce metabolic precursors for biosynthesis of macromolecules and tune their responses to infectious agents. Thus disruptions to nutritional status exert a substantial impact on immune competence and can result in increased susceptibility to infection during nutrient deficiency, or chronic inflammation associated with over-nutrition.¹⁷

Research concerning modulation of immune function by foods in persons varying from healthy to those with compromised immune systems have supported the general conclusion that foods are capable of influencing innate or even acquired immunity. Demonstrating capabilities for treating disease in compromised individuals, preventing disease in those who are healthy, and analyzing nutrition and its complex effects on immunity have contributed to an emerging discipline known as immunonutrition.¹⁸ Immunonutrition is multidisciplinary, involving definition of relationships between nutrition, immunity, infection,

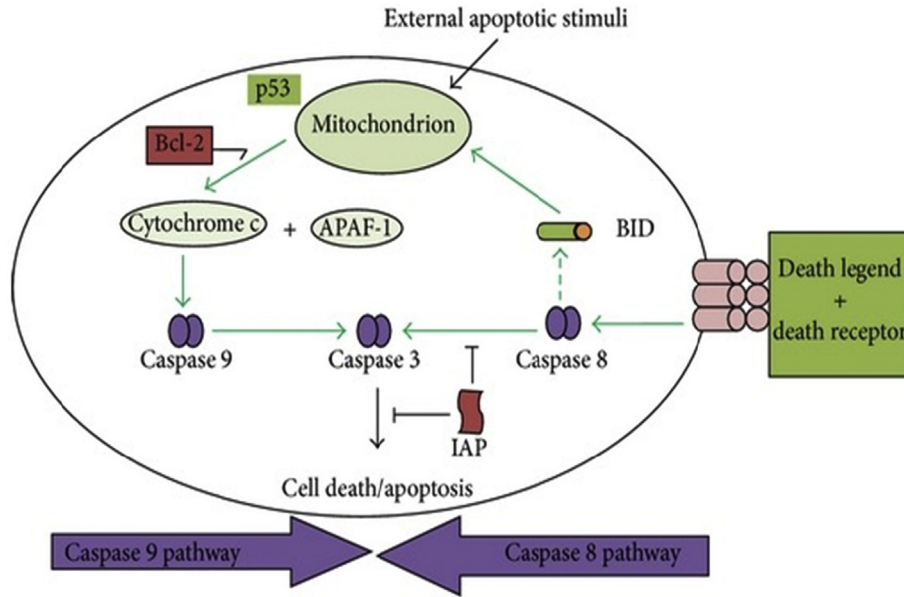


Fig. 1. Honey and its apoptotic activity, following caspase 8 and caspase 9 pathways.²³

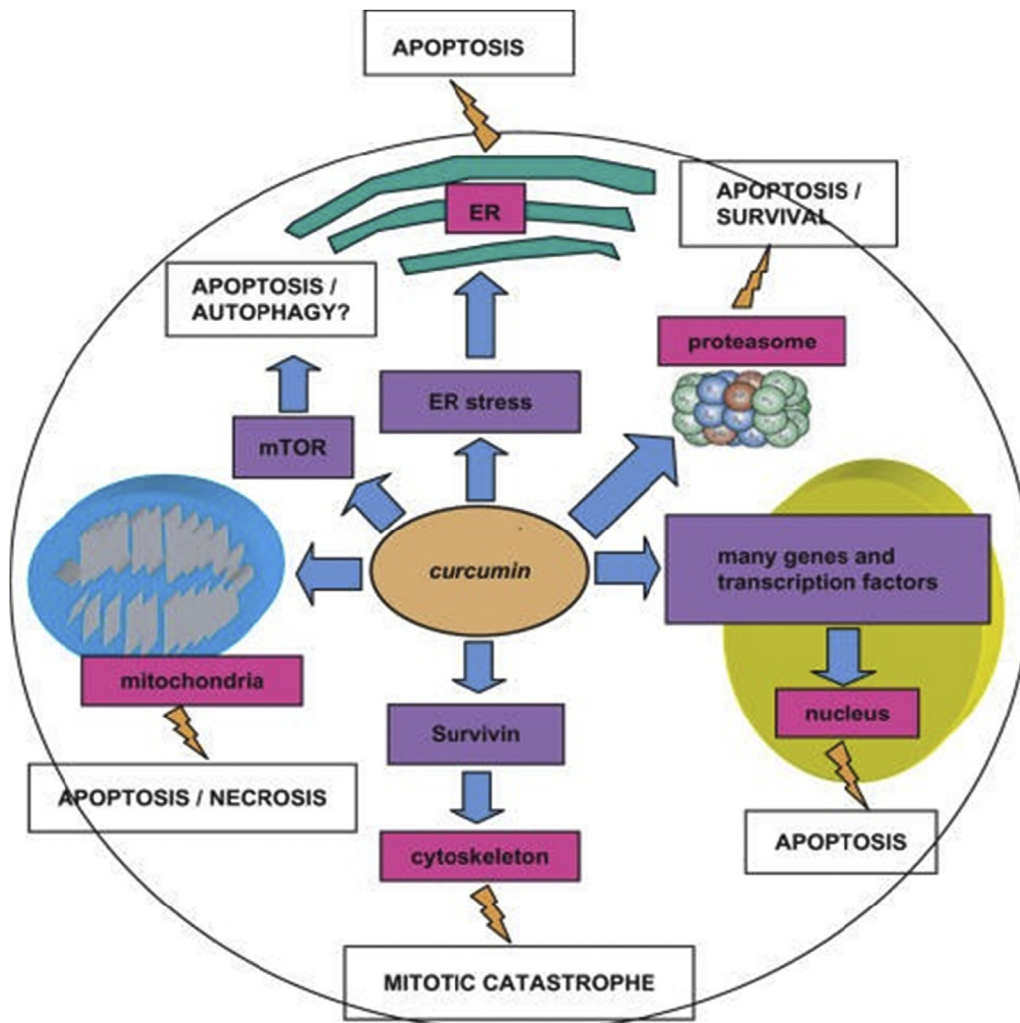


Fig. 2. Main molecular targets of curcumin that lead to different types of cell death.²⁴

inflammation, and injury or damage.¹⁹ For example, immunonutrition plays a role in immune function, modulating gene expression in immune cells in neck and esophageal cancer patients treated by radiochemotherapy. This enhancement of immune function has also allowed patients to adapt to inflammation and oxidative stress caused by chemotherapy. Such a promising result highlights a potential practical application of immunonutrition in treating disease.²⁰

Numerous studies demonstrate the beneficial effects of plant-derived bioactive compounds using invertebrate models. The active ingredients in nutraceuticals help plants overcome stressful conditions, promote longevity, improve life-span, and reduce oxidative damage. Thus, nutrition plays an important preventative role, especially among aging populations that exhibit decreased immunity and greater susceptibility for diseases such as hypertension, cancer, type 2 diabetes, and cognitive impairments.²¹ Green tea has been shown to increase lifespan and stress resistance, protecting against angiogenesis and tumor formation. Containing polyphenolic catechins, green tea may exhibit health benefits including the prevention of neurodegenerative and heart diseases. Green tea contains a unique amino acid, l-theanine, reported to promote longevity through its antioxidant properties.²¹

Phytochemicals in cranberries are well known to affect anti-oxidative and antimicrobial activities, increasing host innate immunity and resistance to infection. Using the tiny nematode worm *Caenorhabditis elegans* as an animal model to demonstrate effects of water soluble cranberry extract, proanthocyanidins, a bioactive

compound within cranberries upregulated expression of *C. elegans* innate immune genes, enhancing host immune response. With its immunity promoting activity, cranberry phytochemicals may thus have potential benefits that promote healthy aging.²²

Abundant research of natural compounds such as honey and pomegranate as sources of palliative and preventative care for patients is gaining momentum. The damaging and toxic effects of chemotherapy and radiotherapy to human cells have stimulated an interest in nontoxic, natural anticancer agents that may improve a patient's overall health and even prevent the incidence of cancer. Honey has been extensively researched as natural anticancer agent. Although we still do not fully understand its varied and numerous chemopreventive mechanisms, many of its beneficial properties are related to its apoptotic, antiproliferative, antitumor, antioxidant, anti-inflammatory, estrogenic and immunomodulatory activities (Fig. 1).²³

Curcumin, an anti-inflammatory and anti-oxidative phytochemical, has also been well studied as a potential natural anticancer agent. As inflammation and oxidative stress are tied to a variety of diseases as well as the process of aging, curcumin has many potential biomedical applications (Fig. 2).²⁴

Pomegranate is an abundant source of various bioactive compounds with numerous beneficial health effects, especially in treating chronic inflammatory diseases. Numerous studies reveal the beneficial effects of pomegranate constituents, associated with the components: ellagic acid, ellagitannins, punicalic acid and other fatty acids, flavonoids, anthocyanidins, anthocyanins, estrogenic

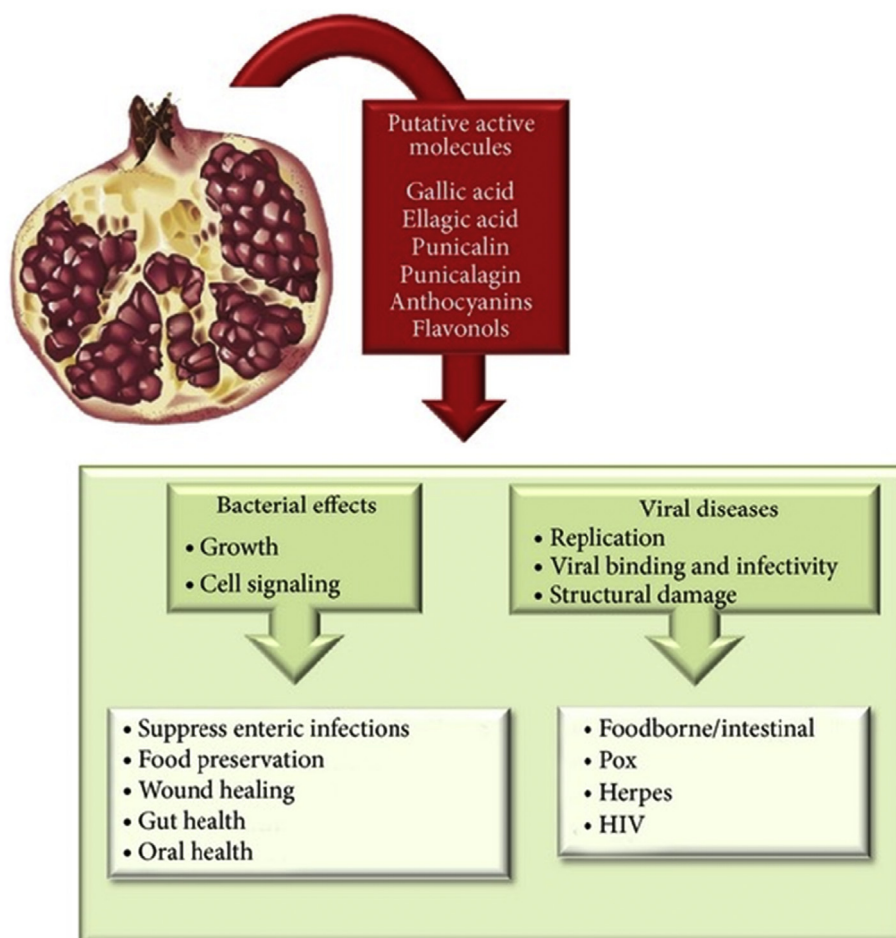


Fig. 3. Pomegranate extracts and their effects on bacteria infecting humans.²⁵

flavonols, and flavones. These compounds seem to have the strongest therapeutic effects.²⁵ The potent healing properties of pomegranates include antioxidant, antiobesity, anti-inflammatory, and anti-tumoral effects (Fig. 3).²⁶ Application of pomegranate to treat diseases e.g. obesity, insulin resistance, intestinal inflammation, and cancer have yielded promising results, prompting the development of pharmaceuticals and certain applicable treatments. Interestingly, the medicinal properties of pomegranate constituents seem to be most effective in conjunction with one another rather than in isolation, a discovery to be considered for the most effective application of pomegranate's benefits.²⁶

Although natural products have long been used as remedies, recent advances in molecular biotechnology allow analysis of their molecular effects on gene expression. Certain plant polyphenols demonstrate ability to modify microRNA expression, impacting gene expression and initiating effects on inflammatory response. The mechanisms by which such natural products act is not clear, but some plant polyphenols such as resveratrol exhibit anti-inflammatory, anti-aging and health promoting properties.^{27,28} Resveratrol is a polyphenol that occurs naturally in plants species such as grapevines and berries, and antioxidants such as resveratrol possess significant therapeutic potential for treating inflammatory disorders. Treating peripheral blood mononuclear cells with resveratrol inhibited inflammatory mediator production by innately-activated leukocytes, thus characterizing and supporting its potent anti-inflammatory effects.²⁸ Dietary intake of resveratrol among aged rats induced a significant increase in T helper cells, enhancing adaptive immunity and suggesting a capability to counteract immunosenescence. Overall, resveratrol is a multi-functional bioactive substance shown to have an array of inhibiting activity: carcinogenic, inflammatory, microbial, viral, antioxidant, and aging properties. This suggests a useful role in generating stronger humoral and cell-mediated immune responses.²⁹

5. Beneficial applications of nutrition and immunity

Exploring and analyzing origins of immunity reveals evolutionary and developmental ties to diet and nutrition, ancient connections in function and development. Foods are capable of influencing immune function. Recently expanded knowledge of invertebrate immune mechanisms and their essential complex molecules offer an opportunity to utilize this information for designing therapeutic treatment. As an increasing number of diseases and health conditions lack a cure, modern biomedicine is obliged to explore all potential options that promise patient care. Recent discoveries and successful application of animal products and bioactive compounds reveal potential to impact modern medicine. With beneficial outcomes that include avoiding toxic effects of chemotherapy, slowing senescence, and reducing oxidative damage and inflammation, there is a new threat. The challenge now remains in integrating alternative treatments into national health care. Finding effective compounds with practical applications provide enormous opportunities for medical advancement if utilized and incorporated judiciously.

Conflict of interest

There are no conflicts of interest.

Acknowledgements

Expressions of appreciation to Hillary Brown for assistance in preparing the manuscript, and to Melody Ma for assistance in the revision process.

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