

REVIEW ARTICLE

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Nutraceutical potentials of synergic foods: a systematic review



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Abstract

Food synergy is a concept of linking foods to health. Food consists of mixtures of nutrients, serving as a fuel for the body. When synergistic foods are put together, the evidence for potential health benefits becomes stronger than individual foods. Nutrient deficiency is a known phenomenon in many individuals, and synergy plays a very important role in combating the nutritional deficiency. Today's consumer expresses high interest to build knowledge on the active role of food in their well-being, as well as in the prevention of non-transmissible chronic diseases. Functional foods and their active compounds play a vital role in preventing chronic diseases, improving immunity, and decreasing infections. The concept of synergy is an overthinking in nutrition research which can enhance effective dietary planning value added to the forthcoming nutrition research. This paper gives an overview of various synergic combinations of food components and their interactions within the food and with the human system to attain ideal health benefits.

Keywords: Food synergy, Functional foods, Interactive nutrients, Synergic foods, Bioavailability

Introduction

Food synergy is a concept of understanding the interaction between nutrients, its absorption, and bioavailability in human body which can be either positive or negative. The sole idea of food synergy is interaction between nutrients in many foods rather than single food component [1–3]. Interactions within the food and combination of food components need to be addressed within the human system for potential health benefits. Evidence-based studies are available for certain active components in the food we eat, its functional property in preventing diseases and betterment of health. This perception on nutrition is called food synergy.

Although food and nutrition have been studied for centuries, modern nutritional science is surprisingly young. Research on the role of nutrition in complex non-communicable chronic diseases, such as cardiovascular disease, diabetes, obesity, and cancers, is even more recent, accelerating over the past two or three decades and especially after 2000. Historical summaries of nutrition science and synergic combinations of foods have

been published, focusing on dietary guidelines, general scientific advances, or particular nutritional therapies. Most research has focused on studying single substances: macronutrients and micronutrients, as well as the many other bioactive substances present in food, either beneficial or harmful to the human system.

The first half of the twentieth century witnessed the identification and synthesis of many of the known essential vitamins and minerals and their use to prevent and treat nutritional deficiency related diseases. By the mid-twentieth century, all major vitamins had been isolated and synthesized. Their identification in animal and human studies proved the nutritional basis of serious deficiency diseases and initially led to dietary strategies to tackle diseases through food synergy.

The phenomena of multicultural reality created by globalization, immigration, food processing, food availability, and global needs within any given country needs deeper understanding on the cultural and subcultural realities to comprehend individual's eating habits. Among the cultural dimensions connected to food preparations, food preferences and ethnicity, consumption of food choices play a central role with relevant implications in terms of better food choices. A major trend in (un)sustainable and (un)healthy food

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production and consumption is occurring at the global level, across different cultural contexts. The food production and consumption systems have serious and intertwined implications for both public health and environmental quality, worldwide. Indeed, cultural or country differences might not fully account for the variations in diet styles, food intake, and health outcomes that many studies outlined understanding food consumption and its related health outcomes across different cultures and subcultures has to be studied.

Food possesses the essential nutrient with specific active compound having functional properties in preventing diseases. Various epidemiological *in vivo* and *in vitro* studies have proved the same. Today's consumer expresses high interest to build knowledge on the active role of food in their well-being, as well as in the prevention of non-transmissible chronic diseases. In the human system, food components must undergo digestion to attain mutual effects of the different components and its active role. Right combination of food is health conscious approach in consumption. Our body undergoes three processes, digestion, synthesis of new compounds, and metabolism. We consider on what we consume, how much we consume, how we consume, and which have a better impact on health [4].

Functional foods and their active compounds play a vital role in preventing chronic diseases, improving immunity, and preventing infections. One important strategy to augment good health is increased consumption of fruits, vegetables, and whole grains which reduce the risk of various chronic diseases and cancer. Phytochemicals present in the functional foods play an important role in maintaining balance between health and disease. Thousands of phytochemicals which have been identified interfere with multiple cellular pathways [5].

It is extremely difficult to scientifically meet the demands of a human being irrespective of the individual and living environment. Thus, this paper explores and reveals the scientific evidences behind nutrient-nutrient interactions within the food in the human system to attain ideal health benefits.

Significance of synergic foods

Synergistic foods as immune boosters

Immunity, infection, and malnutrition have been always interlinked. Malnutrition and nutritional alterations, common complications of human immunodeficiency virus infection, include disorders of food intake, nutrient absorption, and intermediary metabolism which play a significant and independent role in morbidity and mortality. The immune system is a complex network of focused tissues, cells, organs, proteins, and chemicals. Hence, immune competence can be regarded as a measure of adequate nutrition. Interindividual variations in

many immune functions existing within the normal healthy population are due to age, genetics, gender, ethnic background, socioeconomic situation, diet, stress, habitual levels of exercise, alcohol consumption, smoking habits, etc. Human cells are continuously exposed to diverse oxidizing agents of which few are necessary for life. The imbalance in the production of oxidants may lead to oxidative stress, including viral, bacterial, and parasitic infections in the human system [6]. Intake of certain foods may help to keep our immune system strong. A balanced mix of vitamins and minerals over time reflects a healthy immune system.

Foods like *green tea* and *black pepper* works in a synergistic way and enhances the bioavailability of epigallocatechin gallate (EGCG) which is present in green tea. Lambert et al. [7] conducted an *in vivo* study which reveals piperine present in black pepper inhibits the glucuronidation of EGCG, thereby lowering the transit rate of EGCG in the gastrointestinal (GI) tract. The reduced transit rate in turn reduces the resident time of EGCG in GI tract which allows maximum absorption. High amount of catechin present in green tea is associated with improved immune tolerance thereby leading to lower incidences of cancer, cardiovascular diseases, high cholesterol, and many more. Also, *lemon along with green tea* enhances the absorption of EGCG ten times more when compared to the absorption when green tea is drunk alone [8]. A study published in *Food Chemistry* ensured that vitamin C promotes the absorption and utilization of antioxidant in green tea five times more when compared to green tea consumed alone. The catechins and vitamin C act synergistically for better absorption of antioxidants [9, 10]. *Raspberries and chocolates* show a better synergistic effect for their antioxidant capacity. Todorovic et al. [11] discovered significant increase in antioxidant capacity in cocoa, polyphenol, proanthocyanidin, and flavonoids.

Synergistic foods to prevent infections

Malnutrition is the primary cause of immunodeficiency and infections worldwide, with infants, children, adolescents, and the elderly most affected. There is a strong relationship between malnutrition and infection and infant mortality, because poor nutrition leaves children underweight, weakened, and vulnerable to infections, primarily because of epithelial integrity and inflammation. In our understanding of this interaction between infection and malnutrition, it is important to remember that a decreased immune function is not always a defective one, and many indicators of nutritional status are not reliable during infection. Food synergy plays a vital role in preventing infections.

Healing was more rapid in the skin of those rats treated with *curcumin and ginger* extract which was

found to be a novel approach improving the structure of skin in rats [12]. Through multiple signaling of proteins, curcumin inhibits cell proliferation, metastasis, invasion, and angiogenesis in different types of cancers.

An intervention study on interaction between *turmeric and fish* revealed that curcumin and polyunsaturated fatty acids (PUFA) or docosahexaenoic acid (DHA) or eicosapentaenoic acid (EPA) are potent anti-inflammatory agents acting synergistically, decreasing the production of inflammatory eicosanoids and reactive oxygen species (ROS) to relieve oxidative stress [13].

Turmeric has its own potential anti-inflammatory effects, anticancer properties, and tumor-fighting properties. The active component in the turmeric is curcumin. Black pepper has its own hot and active component called piperine. While adding *black pepper to turmeric* or turmeric-based foods, piperine increases the bioavailability of curcumin to 1000 times [14]. Piperine inhibits the metabolic breakdown of curcumin compounds in the gut and liver. This increases the bioavailability of curcumin compounds in the body.

A significant contribution for the antibacterial activity is proved in *garlic and honey* with phenols and fatty acids which act synergistically in higher growth reduction of bacteria, enhancing the killing activity. This also helps to improve the shelf life of each other [15]. Both are powerful antibiotics that preserve our immune system.

Synergistic foods to increase bioavailability of nutrients

Plant foods are enriched with micronutrients, but a common understanding on the bioavailability of nutrients is primarily very essential. When we consume a food or drink, certain nutrients are absorbed into the bloodstream and transported to their respective target tissues. The nutrient supply in the human body depends mainly on the bioavailability of the particular nutrient rather than the quantity consumed. The bioavailability of the nutrient is based on various factors like its reacting medium, promoters and inhibitors, and the host environment. Understanding nutrient bioavailability helps in setting appropriate dietary recommendations.

Garlic and honey have a good synergistic effect; when garlic reaches the stomach, it promotes the production of gastric juices which are essential for absorption of iron and enrich the bloodstream [14].

Flavonoids with *almond skin* predominantly benefit health and act synergistically with vitamin C and vitamin E to protect LDL oxidation [16].

The carotenoids found in the salads include lycopene, lutein, beta-carotene, alpha-carotene, and zeaxanthin. The egg yolk also contains zeaxanthin and lutein. Eating *boiled eggs with the salad* of tomatoes, carrots, and green leafy vegetables increased absorption of carotenoids 3–9-fold [17].

Lemon and green leafy vegetables address iron deficiency anemia by increasing hemoglobin. It helps in improving the bioavailability of iron in the blood volume. Ascorbic acid or vitamin C enhances the dietary absorption of non-heme iron. First, it forms non-absorbable iron, and later, ferric iron is converted to ferrous iron which helps in better absorption of iron into the mucosal cells [18].

Yoghurt and banana play a significant role in mutual benefits of probiotic and prebiotic. Probiotics introduce good bacteria into the gut, whereas prebiotics act as a fertilizer for the good bacteria. So, consumption of probiotics along with prebiotics is good for the gut bacteria which improves gastrointestinal digestion [18]. Inulin present in bananas energizes the growth of good bacteria in yoghurt, which helps to improve immunity and regulate digestion. Inulin with probiotics (good bacteria) found in yoghurt helps to increase the level of calcium in our body [19].

The key concept of attaining balanced nutrition in a plant-based diet is food synergy. In the context of micronutrients, the concept of food synergy relies heavily on bioavailability. Keeping bioavailability of micronutrients as a center point and designing intelligent food synergy have the advantage of being close to population psyche but require efforts to create them as national missions. Therefore, the available evidence with respect to foods and measurement of their additive effects on bioavailability of these micronutrients would help to improve the nutrition status of the population.

Synergistic foods to reduce chronic diseases

Prospective epidemiological studies, some randomized prevention trials, and many short-term studies of intermediate endpoints such as blood pressure and lipids have revealed a good deal about the specific dietary and lifestyle determinants of major chronic diseases. Most of these studies were in part with the historical importance of these diseases. A general opinion is that reducing identified, modifiable dietary and lifestyle risk factors could prevent most cases of chronic diseases like coronary artery disease, stroke, diabetes, and many cancers among high-income populations. The essential bioactive compounds present in the foods help in preventing diseases and betterment of health. Studies have shown that synergistic combination of foods plays an important role in the prevention of chronic diseases.

Cardiovascular diseases

Combination of *honey and garlic* potentially reduces the blood cholesterol and triglyceride levels and helps in improving cardiovascular problems [15]. Studies prove the good synergistic roles of honey with garlic to regulate LDL levels [16].

Garlic and fish synergistically boost immunity and improve cardiovascular health. Effects of fish oil and omega-3 fatty acids are modulated by the inhibition of hepatic very-low-density lipoprotein (VLDL)-triglyceride synthesis and an increase in the fractional catabolic rate of VLDL. Various co-factors like selenium, copper, zinc, iron, and iodine works better with EPA and DHA for their anti-inflammatory and cholesterol-reducing properties [20].

For *tomatoes and olive oil*, tomatoes contain carotenoids which are fat soluble, and hence, absorption is increased with a fat medium like olive oil. Lycopenes as carotenoids as an antioxidant reduce the risk of cardiovascular diseases by improving the serum lipid profile in high-fat diet when compared to low-fat lycopene-rich diet. Lycopene content increases by 5–6 times on cooking rather than eating them raw [21–23].

Onion and grape combination resulted in a synergistic anti-proliferative effect (APE) rather than consuming onion or grape alone. Black grapes are rich in polyphenol antioxidant catechin, which helps to prevent cardiovascular disease, cancer, and neurological disorders and in weight management. Together, onion and grapes inhibit blood clots and boost cardiovascular health. Studies have shown that this combination helps to relieve allergy symptoms and improve cardiovascular protection by improving circulation [24].

Diabetes mellitus

An in vitro study by Agustinah et al. [25] reveals that a combination of 80% *apple cider* and 20% whole *blueberry juice* has potential anti-hypertensive and anti-hyperglycemic properties. Increased blueberry juice proportion increases the total phenol content in apples with the inhibitory activity of angiotensin-1-converting enzyme (ACE), α -amylase, and α -glucosidase; the ACE inhibitory activity is decreased.

Onion and garlic contain active components like methiin and *S*-allyl cysteine sulphoxide (SACS), which stimulates the insulin production from the pancreas and reduces the blood glucose level. This interference with dietary glucose absorption by the insulin helps to control diabetes mellitus [26, 27].

Vitamin D and vitamin K supplements help to upregulate the insulin receptor genes and promote secretion of insulin from pancreatic cell, thus improving blood glucose metabolism [28, 29]. Interaction of vitamin D and K supplements can also upregulate vascular smooth muscle cells [30].

Anthocyanin-rich *black currant* combined with *rowanberry* enriched in chlorogenic acids is a synergistic combination to improve diabetes mellitus. As a synergistic combination, both black currant and rowanberry extracts could replace the inhibition lost by reducing the

acarbose dose and help to maintain glycemic level for type 2 diabetes [31].

Cancer

Whole foods, such as *broccoli and tomatoes*, have anti-tumorogenesis property by themselves which may lower the growth of cancer cells. Prostate tumors grew much less in rats that were fed with tomatoes and broccoli [32, 33].

Apples contain a number of phytochemicals, like phloridzin, quercetin, chlorogenic acid, and catechin; the peel of apple has potential phytochemical with anticancer properties. Eating *apple with skin* inhibits cancer cell proliferation, reduces lipid oxidation, and lowers cholesterol in cancer patients [34, 35]. *Almonds with skin* rich in antioxidants also benefits in the reduction of cancer and cardiovascular risks [36].

Apple and berry juices potentially benefit colon cancer in the presence of dietary compounds such as vitamins, minerals, phytochemicals, and fiber. They are consumed among various ethnic groups widely based on their dual nutritional value. Adequate intake of these phytochemicals may hinder the growth of cancer cells by enhancing DNA repair, thereby reducing the DNA damage by oxidative stress [37].

People consuming red meat frequently are more exposed to carcinogens and cancer-causing agents (HCAs). These agents are formed when meat is cooked at very high temperatures (grilling). Research studies by Tsen et al. [38] have found that certain phenolic compounds and antioxidants in the *rosemary spice* can when added with *red meat* could hinder the formation of carcinogenic compounds.

Synergic foods to improve mental and reproductive health

Diverse symptoms, including changes in mood, behavior, fluid retention, and certain aspects of mental or physical functioning, are common among women in the luteal phase of the menstrual cycle. Various reports, many of a preliminary nature, or based on clinical experience suggest that these symptoms are related to diet, in particular to high intakes of sugar or to deficiency of certain vitamins and minerals or to both. Several studies have been reported since the 1970s on the effect of high-dose vitamin B6 supplementation on the relief of premenstrual symptoms. Several studies were carried out to find the effect of synergic foods on mental and reproductive health.

Blueberries and strawberries have potential protective effects of antioxidant on neuronal functioning. Antioxidant-rich blueberries and strawberries reduce oxidative stress and inflammation and thus improve neuronal signal processing [39]. Apples are rich in flavonoids, and green leafy vegetables are rich in dietary nitrate. Studies reveal that combination of

Table 1 List of synergic food supplements and its benefits of human health

S. number	Combination of nutrient supplements	Effects on human health
1	Calcium and vitamin D	Prevention of colorectal neoplasia [42], lowered risk of fracture [43]
2	Vitamin A, vitamin A plus zinc, and multiple micronutrients	Improves anemia [44]
3	Extra virgin olive oil and apple-enriched dark chocolate	Improves endothelial function [45]
4	Vitamins D and K	Increased bone mineral density, improves cardiovascular health, beneficial effects on endocrine and oxidative stress [46]
	Calcium and selenium	Reduces risk of prostate, lung, and colorectal cancer [47]
5	Zinc and vitamin A	Improves vitamin A status [48], decrease the risk of non-ardia stomach cancer [48]
6	Magnesium and vitamin B ₆	Relieves anxiety-related problems in premenopausal women [42]
7	Vitamins C and D and zinc	Improves immune functions and prevents infections [49]
8	Vitamin A and vitamin E	Enhances vitamin A intestinal absorption, increased antioxidant capabilities, protect against some forms of cancer, and support a healthier gut [50, 51]
9	Vitamin A and iron	Increases the bioavailability of pro-vitamin A carotenoids, including alpha-carotene, beta-carotene, and beta-cryptoxanthin [52]; increases iron absorption, especially non-heme iron [53]; reverse iron deficiency anemia [54]

flavonoids and nitrate could increase nitrous oxide production. The increase in nitrous oxide following consumption of flavonoids and dietary nitrate could improve cognitive function and mood [40].

Ethnic post-partum care nutritional practices act synergistically on rejuvenating post-partum needs and addressing the nutritional support for delivered mother like improving lactation, smooth bowel movement, immunity, better nourishment, preventing excess bleeding, preventing infections, wound healing, and strengthening of bones and muscles. Synergic combinations of foods would better help in relieving post-partum symptoms [41]. *Chick pea and beetroot* relieve anxiety-related menstrual symptoms. Vitamin B₆ is required for maintaining normal intracellular magnesium concentrations as vitamin B₆ helps in transport of magnesium across the cell membranes [42].

Synergic nutri-supplements on human health

The concept of food synergy is based on the proposition that the interrelations between constituents in foods are significant. This significance is dependent on the balance between constituents within the food, how well the constituents survive digestion, and the extent to which they appear biologically active at the cellular level. Many examples are provided on the superior effects of whole foods over their isolated constituents. The food synergy concept supports the idea of dietary variety and of selecting nutrient-rich foods. The viability of the food synergy concept is bolstered by the lack of effect of many isolated compounds shown in clinical trials (Table 1).

Nevertheless, to attain ideal health benefits, the combination of food components needs to address their

Table 2 An overview of synergistic combinations of foods

Synergistic combinations of foods	Functional properties of foods	Synergistic nutri-supplements
Yoghurt and banana	Increases bioavailability	Vitamin A and vitamin E
Almond with skin		Vitamin A and vitamin C
Lemon and green leafy vegetables		Vitamin A and zinc Vitamin C and iron
Garlic and honey	Acts as immune boosters	Vitamin C, vitamin D, and zinc
Green tea and black pepper		
Lemon and green tea		
Raspberry and chocolate		
Garlic and honey	Prevents infections	Vitamin C, vitamin D, and zinc
Turmeric and fish		
Black pepper and turmeric		
Curcumin and ginger	Reduces chronic diseases	Vitamins D and K Calcium and selenium Zinc and vitamin A
Honey and garlic		
Garlic and fish		
Tomatoes and olive oil		
Onion and grape		
Broccoli and tomatoes		
Apple with skin	Improves reproductive health	Magnesium and vitamin B ₆
Apple and berry		
Rosemary and meat		
Beetroot and chick pea		

A review of dietary supplementation suggests that although supplements may be beneficial in states of insufficiency, the safe middle ground for consumption likely is food. Also, food provides a buffer during absorption. The more we understand about our own biology and that of plants and animal, the better we will be able to discern the combinations of foods, rather than supplements, which best promote health

interactions within the food and with the human system. Food components must survive digestion to arrive in the human system in such a way that the mutual effects of the different components can be realized by the eater.

An overview of food synergy

Constituents delivered by foods taken directly from their biological environment may have different effects from those formulated through technologic processing, but either way health benefits are likely to be determined by the total diet (Table 2).

Conclusion

Synergic foods reveal that components in single food and components in different foods, when eaten together, equally benefit our health. Positive nutrient synergic food choices holistically improve one's health, by increasing the immunity and bioavailability of nutrients, decreasing infections, improving wound healing and preventing chronic diseases which also attributes to reproductive and mental health needs. Available research findings including in vivo and in vitro studies are handful to collect further understanding on the good or bad synergic combination of foods, nutrients, and their impact on health. All the above synergic examples clarify the complex nutritional relationships.

There are still hidden truths either to the common man or to the scientific community about how the components in food work together. Throwing research light on the interactive synergic foods, nutrients, and their significance on health and disease prevention would help a common man to lead a better quality and healthy life.

Abbreviations

ACE: Angiotensin-1-converting enzyme; APE: Anti-proliferative effect; DHA: Docosahexaenoic acid; EGCG: Epigallocatechin gallate; EPA: Eicosapentaenoic acid; GI: Gastrointestinal; LDL-C: Low-density lipoprotein cholesterol; ROS: Reactive oxygen species; SACS: S-Allyl cysteine sulphoxide; VLDL-C: Very-low-density lipoprotein cholesterol

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