Derleme/Review

T.C SAĞLIK BAKANLIĞI
Sağlık Hizmetleri Genel Müdürlüğü
GETAT Daire Başkanlığı

Anadolu Tıbbı Dergisi

ISSN: 2822-3373 https:// anadolutibbidergisi.saglik.gov.tr Yıl/Year: 2022 Eylül/September Sayı/Issue:2 Bakanlık Yayın No:1230

FUNCTIONAL FOODS: CAPCAISIN AND RECEPTOR-INDEPENDENT WAYS

FONKSİYONEL GIDALAR: KAPSAİSİN VE ALICIDAN BAĞIMSIZ YOLLAR

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ÖZET

Biber, Solanaceae ailesinin bir üyesidir. Dünyada her yıl 2 milyon hektardan fazla arazide 36.000 milyon kilodan fazla biber üretiliyor. Bu fonksiyonel gıdanın üretim miktarı 50 yıl öncesine göre 40 kat daha fazladır. Etkin Madde Kapsaisin (trans-8-metil-N-vanilil-6-noneamid), biber ve biber ekstraktlarında bol miktarda bulunan hidrofobik, lipofilik bir vanilloid fitokimyasaldır. Aslında kırmızı biberde bulunan kapsaisinoidlerin yaklaşık %80-90'ı kapsaisin ve dihidrokapsaisin'den oluşur. Geri kalanı nordihidrokapsaisin, homodihidrokapsaisin, homokapsaisin, norkapsaisin ve nornorkapsaisin'den oluşur. Fonksiyonel bir gıda olarak hem kapsaisin hem de analogları yüzyıllardır kullanılmaktadır, ancak son zamanlarda analjezik, antioksidan, anti-inflamatuar, anti-aterosklerotik ve anti-obezite özellikleri ve son zamanlarda çeşitli kanserlere karşı antikanser aktivitesi için kapsamlı bir şekilde çalışılmıştır. Kanser türleri. Kapsaisin etki mekaniz

ABSTRACT

Pepper is a member of the Solanaceae family. More than 36,000 million kilos of pepper are produced on more than 2 million hectares of land in the world every year. The production amount of this functional food is 40 times higher than 50 years ago. Active Ingredient Capsaicin (trans-8-methyl-N-vanilyl-6-noneamide) is a hydrophobic, lipophilic vanilloid phytochemical found in abundance in pepper and pepper extracts. In factaround 80%–90% of capsaicinoids present in capsicum consist of capsaicin and dihydrocapsaicin. The rest is comprised of nordihydrocapsaicin, homodihydrocapsaicin, homocapsaicin, norcapsaicin and nornorcapsaicin. As a functional food, both capsaicin and its analogs have been used for centuries, but recently it has been extensively studied for its analgesic, antioxidant,anti-inflammatory,anti-atherosclerotic and anti-obesity properties, and recently for its anticancer activity against various types of cancer.

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Geliş Tarihi/Received: 22/08/2022 Kabul Tarihi/Accepted: 30/09/2022

maları en çok çalışılan reseptör aracılığıyla ortaya çıkan etkidir. Kapsaisin, geçici reseptör potansiyeli vanilloid kanal 1 (TRPV1) üzerinde bir agonisttir. Bununla birlikte, TRPV1'in aktivasyon yolu dışındaki Kapsaisin'in reseptör olmayan etkileri, klinik kullanımını garanti eder.

Anahtar Kelimeler; Fonksiyonel gıdalar, Biber, Kapsaisin, geçici reseptör potansiyeli vanilloid kanal 1, Kanser, Nutrasötikler.

Among the mechanisms of action of capsaicin, it is the effect revealed through the most studied receptor. Capsaicin is an agonist on the transient receptor potential vanilloid channel 1 (TRPV1). However, the non-receptor effects of Capsaicin other than the activation pathway of TRPV1 warrant its clinical use.

Keywords: Functional foods, Pepper, Capsaicin, transient receptor potential vanilloid channel 1, Cancer, Nutraceuticals.

Introduction

Pepper

With the increase in health literacy, the consumption of pepper, whose high nutritional value is better understood, continues to increase. In fact, functional food hot pepper is a rich source of vitamins C and E, as well as provitamin A and carotenoids, which are well-known compounds with antioxidant properties.

The origin of functional food pepper is the continent of South America. Capsaicin, the active ingredient of functional food pepper, was first described two hundred years ago, and its chemical composition 8-methyl-N-vanilyl-6-nonenamide was shown 100 years ago.Although pepper has spread from the Americas to the world, the largest production and consumption is in the Asian continent. For example, China, one of the largest pepper producing countries, meets about half of the world's pepper production; Mexico; Indonesia and Turkey are other major producers. Pepper species are Capsicum(C) annuum, C. baccatum, C. chinense, C. frutescens and C. pubescens. Among these species, the most widely used is C. chinense (1-4).

Functional Foods

The concept of functional food, which is widely used today, first emerged in Japan in the 1980s. However, the effects of these foods, which have been consumed by humanity for thousands of years, on protecting public health are better understood today and have begun to take place in the health policies of states. Because functional foods are foods that have a potentially positive impact on health beyond basic nutrition(5,6). Functional foods can be defined as “similar in appearance to a conventional food, consumed as part of a normal diet, having proven physiological benefits and/or reducing the risk of chronic disease beyond basic nutritional functions”.An example that is widely used today will be shown. For example, examples of functional foods; Oatmeal contains soluble fiber, which may help lower cholesterol levels.

In accordance with government policies, sometimes additional additives can be made to foods. Thus, some foods are modified to have health benefits. For example, adding vitamins to bread, adding vitamins and minerals to milk, or producing calcium-fortified orange juice for bone health has become widespread. Sometimes unprocessed food consumption is essential for food function. For example, oats contain a type of fiber called beta glucan, which has been shown to reduce inflammation, improve immune function, and improve heart health (5,6).

Pepper, which is the subject of this article, is actually a good example of functional food. Capsaicin, a bitter alkaloid of pepper, which is widely consumed in the world, has been extensively studied in the medical literature due to its biological effects with pharmacological importance. Especially in recent years, the main biological effects of capsaicin, including its anti-cancer, cardioprotective and metabolic modulation effects, have been reported in the literature(7,8).

Nutraceuticals

There has been an increasing interest in nutraceuticals in recent years. Whereas, nutraceuticals are derived from the words pharmaceutical, which means nutrition and medicine/pharmacy. nowadays mostly the term Nutraceutical is widely used for anything consumed for health reasons. In fact, they are industrial products, and nutraceuticals are products prepared from food, but sold in pill or powder form in specially packaged packages. Nutraceuticals has become a multi-billion dollar industry in the global market. Because the world population is aging. In addition, obesity is now recognized as a global problem in terms of incidence. In addition, Heart disease continues to be the primary cause of death in the world. Today's people are more knowledgeable and interested in health-related issues than ever before. Today, many journals in the field of medicine give wide coverage to research in this field(9-11).

Capcaisin and receptor-independent ways

As is well known, capsaicin is an agonist on its receptor TRPV1. Appropriate administration of capsaicin at an effective dose ensures its clinical use through activation of TRPV1.However, as it is now better understood, capsaicin can exert its effects not only in a receptor-dependent manner, but also in a receptor-independent manner.

Among the examples of non-receptor capsaicin activity, its effect on inflammation is important. Because inflammation and inflammatory molecules, which play a role in the development of many diseases, can be reduced by the use of capsaicin.Capsaicin at adequate doses is also known to activate PPARγ via TRPV-independent mechanisms by activating liver X receptors, which inhibits activation of the NF-κB pathway (12).

Thanks to the regulation of the synthesis pathway of cellular proinflammatory molecules with pepper consumption and non-receptor function, it may be possible to maintain a healthier life. Because Capsaicin's ability to block NF-kB activation inhibits the production of inflammatory cytokines such as IL-1β, IL-6 and TNFα (12). Studies during the pandemic have shown that functional food consumption can help reduce the impact of the pandemic. For example, the ability of capsaicin to reduce proinflammatory cytokines suggests that it may be effective in the treatment of COVID-19 disease (13, 14).

As a result, cancer continues to be a worldwide problem that is not only the cause of death, but also has a negative impact on the economy of countries. Like proinflammatory molecular structures, capsaicin can also regulate mechanisms that may occur. It has been reported recently that capsaicin suppresses hepatocarcinogenesis by inhibiting the stemness of HPCs via SIRT1/SOX2 signaling. Thus, pepper consumption may serve as a promising therapeutic candidate for liver cancer. Similarly, long-term consumption of capsaicin reduces inflammation, which plays a role in tumorigenesis, may causes depletion of the tumor promoter substance –P (15).

In addition, in a study, acyl-CoA synthetase long chain family member 4(ACSL4) mRNA and protein levels increased, while glutathione peroxidase 4(GPx4) mRNA and protein levels decreased in glioblastoma cells treated with capsaicin. Capsaicin contained in the functional food pepper can be considered as a potential anticancer agent with ferroptosis-induced anti-proliferative effects in the treatment of human glioblastoma (16). Capsaicin can suppress the proliferation of cancer cells and inhibit many biochemical pathways associated with tumorigenesis and metastasis. Another study shows that the increase in oxidative stress with pepper consumption can suppress tumor development. Because it shows that capsaicin can effectively cause higher oxidative, apoptotic and DNA damage in cancer cells by acting on cellular pathways (17). Similarly, Hypoxia-inducible factor (HIF)-1α is an important transcription factor regulating cancer metabolism in hypoxic environment. Functional food pepper has long been known to inhibit hypoxia-induced HIF activity in lung cancer (18). In addition, capsaicin can increase intracellular oxygen levels by suppressing mitochondrial respiration, resulting in decreased HIF-1α accumulation. Consumption of functional food chili has a potential anticancer therapeutic effect in lung cancer under hypoxic conditions.

Literatur data show that the capsaicin exhibits anticancer proterties, favoring it to act as a nutraceutical agent. Functional food, whether through nutraceutical or natural consumption, can regulate the cellular pathways necessary for the growth of melanoma cancer cells. Of these pathways, tumor-associated NADH oxidase (tNOX) can bind to capsaicin and showed that its inhibition contributes to the induction of ROS-dependent autophagy in melanoma cells(19).In both sexes, lung cancer is the most frequently diagnosed cancer and the leading cause of cancer deaths, closely followed by female breast cancer (20) . In another study, it was reported that capsaicin sensitized cancer cells to anticancer drugs in a synergetic way through up-regulation of autophagy and down-regulation of ribophorin II. Thus, induction of necroptosis may be important in the anti-cancer effect mediated by capsaicin (21).

The synergetic effect of functional foods can be demonstrated by another natural compound S-allyl cysteine (SAC) and capsaicin, the less pungent capsaicin analogue Nonivamide (NOV), which is found in various Capsicum species. The synergistic effect of NOV-SAC may be with therapeutic target proteins for cancer treatment: human estrogen receptor α, tumor protein negative regulator mouse double min 2, B-cell lymphoma 2, and cyclin-dependent kinase 2(22). Moreover, Capsaicin potently suppresses the growth of prostate carcinoma cells *in vitro* and *in vivo*. Antiproliferative activity in prostate cancer cells is associated with oxidative stress induction and apoptosis. In addition, capsaicin induces intracellular ceramide accumulation and endoplasmic reticulum stress in prostate cells (23).

The association between poor nutrition and cancer is increasingly evident, and following a healthy diet is a key lifestyle change to reduce its role as a cancer risk factor(24). According to the information in the literature, capsaicin can show anti-cancer effects through many cellular molecules and pathways, except for the TRPV1 receptor. In addition, capsaicin has regulatory roles on enzymes as a functional food or nutraceutical.

For example, Capsaicin can reduce the activation of carcinogens by inhibiting microsomal phase-I xenobiotic metabolizing enzymes. Pepper can be recommended as a functional food in the diet, especially for smokers, because capsaicin can reduce the mutagenicity of the smoking-associated carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone through microsomal enzymes (25). Capsaicin is also another multifunctional food antioxidant. In recent studies, capsaicin has anti-carcinogenic effects as well as anti-atherosclerotic properties. Capsaicin may cause a decrease in lipid peroxidation through the restoration of some antioxidant enzymes (26).

Despite advances in diagnosis, medication and treatment approach, cancer is one of the leading causes of death today. Therefore, there is a need to increase the number of functional foods or nuraceuticals among existing approaches. In particular, synergistic strategies may represent an intriguing approach, combining natural compounds with classical chemotherapeutic drugs to increase therapeutic efficacy and reduce required drug concentrations. A good example for the synergetic property of nutraceuticals is the inhibition of capsaicin, the drug efflux pump P-Glycoprotein (P-gp) and ATP binding cassette transporter G2 (ABCG2) protein, which can cause chemoresistance. Thus, the cancer patient can regain chemosensitivity (27). At the same time, nutritive or functional foods, such as capsaicin, can increase autophagy in cancer cells, while increasing the chemosensitivity of chemotherapeutic agents (28). As a result, thanks to the capsaicin in pepper, it can inhibit tumor initiation, development, progression and metastasis formation. Moreover, capsaicin may be thought to modulate genes involved in cancer cell survival, angiogenesis, and metastasis. Anticarcinogenic pathways related to capsicin also include cell cycle arrest and apoptosis.

Moreover, non-receptor effects such as ROS production, c-Jun N-terminal Kinase activation, mitochondrial membrane functional changes, cytosolic cytochrome C release and caspase cascade stimulation are important to the activity of capsaicin.

Capsaicin and diseases

Capsaicin exerts its main activity by binding to the TRPV1 transient receptor potential channel located in the A and C-delta fibers of the nociceptive sensory pathway. The capsaicin receptor ultimately leads to desensitization of afferent nerve fibers (29). Capsasin and its derivatives can be used in many clinical situations with their analgesic, antioxidant, anti-inflammatory, anti-carcinogenic, weight-regulating, cardio-protective, anti-lithogenic and circadian-modulatory effects. Therefore, capsaicin has been used as a therapeutic agent in neuropathies, various painful chronic conditions such as temporo-mandibular joint disorder, burning mouth syndrome, postherpetic neuralgia, osteoarthritis or rheumatoid arthritis.

However, although there are few in the literature, there are data showing that the use of capsaicin at very high doses can increase the development of gastrointestinal and urogenital cancer and induce peptic ulcers in active helico bacter pylori infection (30, 31). Even though few adverse effects have been identified in judicious consumption of pepper and appropriate doses of capsaicin, there are only a few relative contraindications such as asthma (32). Currently, the antidote of capsisin and its derivatives is still unknown, but no adverse events related to excessive consumption of pepper have been reported.

Perhaps most importantly, a prospective study noted that subjects who consumed spicy food almost daily had a 14% lower risk of death, although no causal relationship could be established (33).

Intestinal microbiota

The biodiversity of the intestinal flora has been associated with many autoimmune and chronic diseases. Thus, re-diversifying the population's gut microbiome with dietary supplements of functional foods or nutraceuticals may represent a contemporary therapeutic strategy against chronic diseases (33,34). Because capsaicin can eliminate disease-causing enteric pathogens and promote the growth of beneficial bacteria (34). Consumption of pepper as a functional food may have positive effects in diabetic patients. Because capsaicin has a significant effect on glucose homeostasis through the TRPV1 channel. So, Capsaicin increases the influx and secretion of glucagon-like peptide-1 calcium from intestinal cells (35). In addition, consumption of pepper can regulate blood glucose level by increasing gastric inhibitory polypeptide, insulin secretion and inhibiting glucagon release. Thus, capsaicin can reduce impaired glucose tolerance and insulin resistance (36).

Functional foods have a great impact on the intestinal microbiota. As expected, intestinal microorganisms are in constant interaction with foods. So many microorganisms live, the weight of the microbiota is up to two kilograms (37). Functional foods such as peppers may contribute to immune system maturation. . Because the microbiota can shape the immune system, an altered gut microenvironment may contribute to immune-related diseases such as allergies and autoimmune disorders (38, 39). Many scientists point to the importance of personalized nutritional guidance with dietary capsaicin due to the stratification of the gut microbiota (40,41). In fact, the effect of capsaicin on the gut microbiota can be divided into direct (TRPV1-dependent) and indirect (TRPV1-independent effects). The gut is richly innervated by afferent sensory nerves expressing TRPV1 channels, and their activation has revealed an important role in the regulation of gut function or capsaicin-stimulated

neuropeptides can regulate gut microbiota composition by altering inflammatory and immune conditions in the gut environment (41,42). There is evidence that capsaicin reduces weight gain by inducing thermogenesis, increasing lipid oxidation and inhibiting white adipose tissue adipogenesis, and suppressing appetite in the hypothalamus (42-44).

In addition to its adipose tissue effect, capsaicin regulates the energy balance and may have an anti-obesity effect with more than one mechanism. In many studies, it has been shown that the use of pepper exhibits a feeling of satiety. In addition, capsaicin reduces food intake, can suppress food cravings and hunger (44-46). Ultimately, the positive effects on the gut microbiota, thanks to the functional food pepper capsaicin, are mediated by both dependent and independent mechanisms of TRPV1 channel activation.

The information in the literature suggests that combined treatments are much more effective than treatments based on a single drug. Therefore, a combination of functional foods can be used to treat not only neoplasms but also other diseases such as infections, inflammatory diseases. As a result, synergy is the most favorable feature of combined therapies, including in neutraceuticals. Capsaicin, a pungent component of pepper, has been reported to lower blood pressure (BP) and cause vascular relaxation through nitric oxide (NO) production (47). Topical application of capsaicin has been proven to relieve pain in arthritis, postoperative neuralgia, diabetic neuropathy and, psoriasis (48,49).

Gastrointestinal system

Contrary to popular belief, Capsaicin in Pepper can inhibit gastric acid secretion, further stimulate alkaline and mucus secretion and gastric mucosal blood flow, which helps to prevent and heal stomach ulcers in particular (50).

On the contrary, during active *Helicobacter pylori* infection, capsaicin may not be beneficial for the stomach but may be harmful. Because H. pylori infection may promote gastric mucosal injury in the early phase of high-dose capsaicin exposure. This relationship may contribute to H. pylori infection and capsaicin inflammation and gastric cancer formation (51). While consuming functional foods, personal conditions and diseases must be taken into consideration. Capsaicin consumption may have an effect on liver functions. With regular consumption of pepper, capsaicin may be protective against alcoholic liver disease and non-alcoholic fatty liver disease. The protective role of capsaicin may be thought to be related to its anti-steatotic, anti-oxidant, anti-inflammatory and anti-fibrotic effects. In addition, with the positive effect of capsaicin on gastro-hepatic circulation, intestinal dysbiosis and increased bile acid production play a positive role against liver fattening (52). The hypocholesterolemic effect of capsaicin has other effects, such as the prevention of cholesterol gallstones under conditions of hypercholesterolemia (53). Preclinical studies show that low-dose dietary capsaicin may improve metabolic disorders and liver function (54).

The inclusion of pepper in the diet may be beneficial in reducing the risk of transmission of *Salmonella* enteritis, which is common in hot climates. Because *Salmonella* does not develop any resistance to the use of capsaicin and the gastroenteritis and hemolytic activity of *Salmonella* resulting from adhesion to monolayer cells can be significantly reduced (55).

As a result, pepper and its active ingredient capsaicin, which is an important member of functional foods, will be more prominent in the future with its beneficial effects on health.

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