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Abstract

Members of the genus *Capsicum* (Family: Solanaceae), which belongs to a dicotyledonous group of flowering plants, show fluctuating degrees of spiciness that mirror the relative concentrations of capsaicin, dihydrocapsaicin, and other analogs (nordihydrocapsaicin, homocapsaicin, and homodihydrocapsaicin) collectively known as capsaicinoids present in the fruit placenta. Pungent Chili varieties are grown for their food value, health-promoting properties and as a source of capsaicinoids that have a variety of medicinal uses. Accessions of the cultivated species (*Capsicum annuum*, *C. baccatum*, *C. chinense*, *C. frutescens*, and *C. pubescens*) have not all been analyzed for their capsaicinoids content. Identifying *Capsicum* species and accessions (genotypes) within species with high levels of antioxidants and bioactive compounds (capsaicin, dihydrocapsaicin, vitamin C, vitamin E, phenols, and β-carotene) that contribute to human disease therapy is the focus of this investigation. The main objectives of this chapter are to compile an overview of most recent achievements of the pharmacological properties of hot pepper compounds and provide a rationale for their use as analgesics and to present an evidence that supports the use of capsaicinoids in the treatment of neuropathic pain and other top leading death of worldwide human diseases.

Keywords: capsaicin, dihydrocapsaicin, pungency, cancer, anti-obesity, diabetes, osteoarthritis, pharmacology

1. Introduction

Understanding the nutritional content in human diet could aid in prevention of diseases and malnutrition. Nutritional deficiencies, and their appearing diseases, remain widespread in both the developed and developing world. The enhancement of compounds in foods that
have health promoting attributes, such as antioxidant properties is the current focus of agricultural practices and the search for healthy food. In consideration of the enormous worldwide consumption of fruits of various Capsicum spp. and the utilization of capsaicinoids as food additives and their current medicinal application in humans warrant a world-wide screening of hot pepper fruits. Identifying Capsicum spp. and accessions (genotypes) within species with high levels of antioxidants (capsaicin, dihydrocapsaicin, vitamin C, vitamin E, phenols, and β-carotene) is a unique way to explore phytochemicals in medicinal plants such as hot peppers. Capsaicinoids (capsaicin, dihydrocapsaicin, nor-dihydrocapsaicin, homocapsaicin, and homodihydrocapsaicin) are a group of phenolic alkaloids specific to the genus Capsicum [1] and are comprised of a vanillylamine head and a fatty acid tail. Capsaicin is the active ingredient in Chili peppers and the most abundant irritant compound in hot pepper that cause a burning sensation in humans. Dihydrocapsaicin constitutes 22% of total capsaicinoids and is almost similar to capsaicin pungency. Capsaicin (N-vanillyl-8-methyl-6-nonanamide) and dihydrocapsaicin (Figure 1) accounted for about 80–90% of the naturally occurring capsaicinoids in hot peppers [2]. Nordihydrocapsaicin is about 7% of the total capsaicinoids mixture. About 1% of total capsaicinoids is homocapsaicin that has about half the capsaicin pungency. Homodihydrocapsaicin represents about 1% of total capsaicinoids and its pungency is about half of capsaicin pungency. The ratio of capsaicin/dihydrocapsaicin can be 1:1 or 2:1 [3]. The chemical structure of each individual capsaicinoid contains a vanilloid group (an aromatic ring with a hydroxyl and a methyl group), attached a long hydrocarbon chain and a polar amide group [3, 4]. Capsaicinoids show antioxidant properties, potent antimutagenic and anticarcinogenic possessions [5].

The cultivation practices of Capsicum spp., for food production with nutritional composition cover a wide range of natural sciences (physiology, pharmacology, nutrition, agriculture, food industry, and medicine) that support both healthy food and human existence. Among the various plant metabolites that can help protect against free radical damage are phenols (including flavonoids and capsaicinoids), ascorbic acid (vitamin C), carotenoids such as β-carotene (vitamin A), and tocopherol (vitamin E) that are the major antioxidants produced in Capsicum spp. The field of pepper metabolites is rapidly expanding as interest in enhancing plant quality and nutritional composition rises. Several research studies have elucidated how levels of these compounds vary among pepper genotypes and species [6, 7]. The vanilloid group is common among other natural compounds of the so-called vanilloid family, such as vanillin, eugenol, and zingerone that determines the biological activity [3]. Capsaicin and dihydrocapsaicin are the predominant capsaicinoids in the crude pepper fruit extracts, although concentrations of each varied among genotypes. Nordihydrocapsaicin is always present at very low concentrations when compared to capsaicin and dihydrocapsaicin. Concentrations of nordihydrocapsaicin in fruits of C. frutescens averaged 0.1 μg g⁻¹ fresh fruit. Because of this low concentration, few studies and efforts were made by many investigators to quantify nordihydrocapsaicin and other capsaicin analogs in pepper fruit extracts which, in turns directed the screening of pepper genotypes to the two noticeable capsaicinoids, capsaicin and dihydrocapsaicin.
Pepper fruits have antioxidant activity. Antioxidant compounds protect macromolecules from dangerous free radicals, such as reactive oxygen species (ROS). Free radicals are unstable, highly reactive compounds created as the result of normal aerobic metabolism. Reactive species can damage nucleic acids, proteins and lipids, which can hasten aging and the onset of diseases including cancer, heart disease, atherosclerosis, and cataracts [8], if not deactivated. Pepper is an excellent source of antioxidants including flavonoids, capsaicinoids, vitamin C, vitamin E, and carotenoids such as β-carotene. When peppers compared with other vegetables, pepper ranks high for antioxidant activity. Using the ferric reducing antioxidant power assay, researchers found that Chili and red peppers ranked in the top when compared with other common

Figure 1. Molecular structures of five capsaicinoids detected in hot pepper fruit extracts. Note that a double bond (two hydrogen atoms) differentiates capsaicin from dihydrocapsaicin molecule.
vegetables [9, 10]. When antioxidant activity was measured in terms of total radical-trapping antioxidant parameter, Chili and red pepper were two of the top ten sources of antioxidant capacity [10]. Antioxidant capacity variation was also apparent at the genotypic level [11–13]. Pepper usually ranks first or second in terms of phenolic content with levels greater than other high-phenolic vegetables including spinach, broccoli and garlic [14, 15]. Pungent types of peppers have more phenolic compounds than sweet types, an expected result given that pungency is due to capsaicinoids, important phenolic compounds in pepper [13]. Hot pepper can be successfully grown in Kentucky. On a trial basis, several field studies were conducted at Kentucky State University (KSU) College of Agriculture and at the University of Kentucky (Figure 2) to produce hot pepper for industrial uses and as a cash crop for limited resource farmers. Results revealed that yield was sufficient so that we (KSU) are confident that we can produce and develop a hot pepper niche market in Kentucky. Capsicum spp. can provide an entrepreneurial niche market for small farmers because these species can be explored as a cash crop and also as a new industry in Kentucky and may provide an opportunity to collaborate with various well known food and pharmaceutical companies for producing hot pepper and extracting capsaicin at low costs.

There is a direct correlation between total capsaicinoids level and pepper pungency. Five levels of pungency are classified using the Scoville Heat Units (SHU). The SHU scale is a measurement of the pungency (spicy heat) of Chili peppers, or other spicy foods, as a function of capsaicin and dihydrocapsaicin concentrations. The SHU can be categorized into: (1) non-pungent (0–700 SHU), (2) mildly pungent (700–3000 SHU), (3) moderately pungent (3000–25,000 SHU), (4) highly pungent (25,000–70,000 SHU) and (5) very highly pungent (>80,000 SHU) [16]. Nordihydrocapsaicin which is a lipophilic colorless odorless crystalline to waxy compound has 9,100,000 SHU (Scoville heat units). Today, the SHU organoleptic test has been replaced by chromatographic methods which are found to be more consistent and accurate compared to the SHU scale that depends on subjective bases (sensory organs). Capsaicinoids content is a major quality factor in spice (Chile and paprika) peppers. Accordingly, variability in the content of capsaicinoids greatly impacts pepper pungency and other quality peppers characteristics of interest such as yield, fruit size, fruit color, and shape [17]. The public interest and consumption of pepper is increasing [18]. In addition, growers and food producers have become more interested in developing new crops to meet the increasing demands of trades perceiving food with health promoting properties. There are thousands of different pepper varieties around the world, making the documentation of their variability in composition, plant, and fruit variations challenging.

1.1. Role of capsaicin in disease therapy

Pepper has been described for centuries as a source of compounds with therapeutic properties. In the past decade, many articles reported that capsaicin and dihydrocapsaicin exhibit considerable antioxygenic activity [19]. Studies carried out using mixtures of 64.5% capsaicin and 32.6% dihydrocapsaicin revealed that capsaicinoids are not carcinogenic in mice experiments [20]. Capsaicin is exempt from the requirement of a tolerance in or on all food commodities when used in accordance with approved label rates and good agricultural practice (USEPA) [21]. The evidence of painkilling properties of capsaicin has led to the discovery of its pharmacological target, the transient receptor potential cation channel subfamily V member 1 (TrpV1), also known as the capsaicin receptor or polymodal receptor of pain. TrpV1, also
known as and the vanilloid receptor 1. Capsaicin has been shown, in vitro and in vivo, to have different biological effects, in addition to its analgesic ones, including anticancer, antiobesity, cardiovascular, urinary, and gastrointestinal effects, due to the large distribution of the target receptors; that is currently representing an active field of research [22].

1.2. Capsaicin and Parkinson’s disease

Parkinson’s disease (PD) is described by the progressive degeneration of nigrostriatal dopamine (DA) neurons, which is associated with motor dysfunctions such as slowness of movement, resting tremor and rigidity. Stimulations by capsaicin rescued nigrostriatal DA neurons, enhanced striatal DA functions and improved behavioral recovery in treated mice.
Capsaicin neuroprotection was associated with reduced expression of proinflammatory cytokines (signaling proteins) and reactive oxygen species/reactive nitrogen species from activated microglia-derived nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. These results suggest that capsaicin and its analogs may be beneficial therapeutic agents for the treatment of PD and other neurodegenerative disorders that are associated with neuroinflammation and glial activation-derived oxidative damage [23].

1.3. Capsaicin and renal disease pain relief

Effective pain relief can be difficult to achieve in patients with end stage renal disease (ESRD), which is the last stage of kidney disease. The active metabolites of most opiates are renal excreted and side effects, such as confusion and drowsiness, are common in patients with renal disease. Qutenza® (8% capsaicin patch) treatment has been presented to be effective and well-tolerated to treat neuropathic pain from critical ischemia (restriction of blood flow to tissues) in patients with ESRD. Qutenza® is an advanced dermal application system designed for rapid delivery of capsaicin through the patient skin. The high concentration of capsaicin results in reversible desensitization of the transient receptor potential channel subfamily V member 1 (TRPV-1), which is involved in detection and regulation of body temperature, expressing cutaneous sensory nerve endings and reduction in nerve fiber density in the epidermis. The resulting pain relief is long-lasting (12 weeks after a single application) [24].

Capsaicin topical route consists of the direct application to the skin, mainly in the form of creams and patches applied on the affected area. After application capsaicin is rapidly absorbed into the epidermis and derma in humans. Management of acute and chronic pain has been recognized and currently constitutes a promising approach for the peripheral neuropathic pain. The oral consumption of capsaicin with food is also safe, but it does not have pharmacologic effects on pain. For these reasons, the majority of studies on the pharmacokinetics of capsaicin in humans have been concerned with topical administration [4].

1.4. Capsaicin and heart disease

Heart disease is the top cause of death in the U.S. due in some cases to blood cholesterol level. HDL stands for high-density lipoproteins known as the “good” cholesterol because it carries cholesterol from all parts of human body back to your liver. The liver then removes the cholesterol from human body. Hart disease inflammation is related to high-density lipoprotein (HDL) cholesterol metabolism. Low levels of HDL cholesterol is associated with an increased risk of coronary heart disease (CHD). Taking 4 mg of capsaicin capsules orally considerably increased fasting serum HDL cholesterol levels and reasonably decreased levels of triglycerides and cholesterol-reactive protein and phospholipid transfer protein activity. In addition, other lipids like apolipoproteins, glucose levels, and other parameters did not significantly change in the human body cycle. In conclusion, capsaicin improved risk factors of CHD in individuals with low HDL-cholesterol and may contribute to the prevention and treatment of CHD [25].
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