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Capsaicin and its Human Therapeutic Development

Edited by Gyula Mózsik

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Notice

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Meet the editor

Gyula Mózsik, MD, PhD, ScD (Med) is an emeritus professor of Medicine at the First Department of Medicine, University of Pécs, Hungary. He was the head of the department from 1993 to 2003. His specializations are medicine, gastroenterology, clinical pharmacology, and clinical nutrition. His research fields are biochemical and molecular pharmacological studies in the gastrointestinal tract, clinical pharmacological and clinical nutritional studies, clinical genetic studies, and innovative pharmacological and nutritional (dietary) research in new drug production and food production. He published around 360 peer-reviewed papers, 196 book chapters, 692 abstracts, 19 monographs, and 32 edited books. He organized 38 national and international (in Croatia, France, Romania, Italy, U.S.A., and Japan) congresses/symposiums. He received the Andre Robert Award from the International Union of Pharmacology, Gastrointestinal Section (2014). Fourteen of his students have been appointed as full professors in Cuba, Egypt, and Hungary.

Contents

Preface

The enormous field of this topic is clearly shown by the following facts: during the last ten years (2007-2016) around 500 scientific papers/year and 523 review articles are listed in the PubMed database on capsaicin, and over 200/year are under keywords of "capsaicin human".

Recently, two major studies on the mortality of consumers of spicy food containing capsaicin and nonconsumers showed a significant reduction of death in favor of capsaicin consumption in China (14%) and in the USA (13%). These observations strongly supported the theorem that capsaicin or its other active derivatives have significant beneficial effects on the human life (emphasizing the key role of "nutritional prevention" in humans).

Recently, the book series "Progress in Drug Research" the 68th volume dealt for the first time on "Capsaicin as a Therapeutic Molecule" (Springer, Basel, 2014).

These facts, together with the new results of very active research, indicated to IntechOpen Limited, London, the need for a summarized account of the actual (updated) position of capsaicin research.

Besides introductory chapter, five excellent chapters are found in this book dealing with procedures of capsaicin from capsicum plants, emerging technologies to improve capsaicin delivery, correlations between capsaicinoid diversity and its human food preference, correlation between the capsaicin and lipid metabolism, and predictors that can be used in treatment responses to capsaicin in humans. The results of these observations clearly indicate that the capsaicin research has changed direction to include human medical treatment with capsaicin. This is why the editor has emphasized the key roles of international laws and necessary permissions.

The book provides a cross section of updated capsaicin research and the importance of scientifically monitored human observations in this field.

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Introduction

Chapter 1

Introductory Chapter: The General Problems of Human Clinical Nutritional and Pharmacological Observations of Capsaicin in Human Beings and Patients

Gyula Mozsik

Additional information is available at the end of the chapter

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1. Introduction

The enormous field of this topic is clearly shown by the following facts: during the last 10 years (2007–2016), around 500 scientific papers/year and 523 review articles were listed in the PubMed database on capsaicin, and over 200/year are under keywords of "capsaicin human."

Recently, two major studies on the mortality of subpopulations consuming spicy food containing capsaicin and nonconsumers showed a significant reduction of death in favor of capsaicin consumption. The two cohort studies were made in China [1] and in the USA [2]. In the study on Chinese population over 350,000 men and women aged 30–79 with heart disease, cancer and stroke at baseline over 3.5 million person-years (2004–2013) the relative risk in total mortality was reduced significantly by 14% in the population who ate spice food 6–7 days/week as compared to those who ate only once/week. The population enrolled was in 10 diverse geographic areas of China.

In the USA more recently the effect of consumption of hot chili pepper of apparently healthy population mortality was surveyed in 16,179 participants during over 270,000 person year (follow up median 18.9 years). Out of a total nearly 5000 deaths, the hazard rate was significantly reduced by 13% in the population which consumed regularly hot red chili pepper. Although in this study published few weeks ago, the mechanism by which hot chili peppers reduced mortality was not analyzed. The beneficial effect of chili pepper of the diet (raised already much earlier) has been strongly supported.

The spicy hot ingredient of chili pepper is capsaicin, and its similarly active derivatives are called capsaicinoids. The site of action of capsaicin on sensory nerve terminals has been

identified and the membrane protein of "capsaicin receptor" being a cation channel was cloned in 1997 and is now denoted also on structural ground TRPV1.

Recently, within the book series of Progress in Drug Research, the 68th volume deals for the first time on "Capsaicin as a Therapeutic Molecule" [3].

Meta-analysis of human studies suggests that capsaicin could be a new approach in treatment obesity promoting negative energy balance, increasing fat oxidation and the reduction of ad libitum energy intake [4]. This conclusion is strongly supported over a decade. However, we have to notify that 627 papers were collected, but only 9 studies offered scientifically important data.

Capsaicin consumption in concentrations equivalent to that which can be detected in moderately spicy foods enhances gastric mucosal blood flow by releasing neuropeptide calcitonin gene-related peptide (CGRP) from the sensory receptors of the stomach. It elicits pronounced gastroprotective effects both in rats and in humans. Testing in healthy subjects under Good Clinical Practice (GCP) condition, the capsaicin (in the range of 200–800 μg/100 ml) dose range inhibited gastric basal acid output, decreased the COX-inhibitor indomethacin and induced gastric microbleeding or ethanol-induced mucosal damage in healthy human beings.

The beneficial effects of capsaicin have been observed on (1) cardiovascular functions; (2) stroke; (3) metabolic homeostasis; (4) autoimmune diseases; (5) obesity; (6) tumor; (7) Alzheimer disease; (8) prevention of gastrointestinal mucosal damage produced by nonsteroidal anti-inflammatory compounds; and many other diseases.

The capsaicin actions are dose-dependent, because of small doses (400–1200 ug/day) produce preventing actions; however, in higher doses (after desensitization), the beneficial effects disappear. This phenomenon is also well detectable in the pain of humans.

The capsaicin research in animals (*in vivo*) and in *in vitro* circumstances (conditions) was in extreme progress in the last decades; however, the human observations followed relatively slowly than the animal observations.

Of course, the human observations can be carried out on the dependence of respecting many (ethical permissions, human rights, laws of human clinical nutrition and human clinical pharmacology, clinical conditions, education and practice of clinicians, etc.) factors.

It is, however, important that the capsaicin (capsaicinoids) can be used as a modifying substance on the capsaicin-sensitive afferent nerves during the food consumption and drug application; consequently capsaicin (capsaicinoids) is (are) involved in human nutrition and human medical drug therapy.

We have been working with capsaicin from the 1980s, involved in both clinical nutrition and human drug therapy. The prospective, randomized and multiclinical studies have been carried out (respecting the Good Clinical Practice (GPC) and Helsinki Declaration and its modifications – from the years of 1997. We had to learn many problems of capsaicin therapy from that time. Therefore, the editor wants to demonstrate some general problems of capsaicin application in human beings or in patients.

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2. Some general problems of human medical therapy with capsaicin

Extremely big extend of reference list dealing with capsaicin in humans. Furthermore, it is impossible to clear up the applied doses of capsaicin and the different preparations used in these examinations (different extractions, different species, stabilities, many other factors in time of plant cultivations, environmental circumstances, applied chemicals, punctual chemical compositions of capsaicinoids, pesticide residues, fungal residues, etc.).

A new issue of this research started in the last decade when the so-called pure capsaicin (obtained from different international trade firms [Sigma-Aldrich and other well-known firms]) was used in human observations: by this step the chemical composition of capsaicin became clear. Later on, we have to learn that these preparations can be used in classical human therapy (from the points of human clinical pharmacology).

3. Drug Master File (DMF)

To receive permission for human use of capsaicin preparations from the National and International Regulatory Authorities, we have to present the following details: (1) specification of the capsicum species; (2) climatic regulations in places of capsicum cultivation; (3) chemical treatments of capsicum plants during their cultivation; (4) detailed treatment of capsicum plants (their collection, drying, extractions storages, etc.); (5) analytical results supporting the chemical composition of the plant origin of capsaicinoids extract; (6) chemical stability of natural capsaicin (capsaicinoids); (7) analytical results showing the (possible) contamination of natural compounds with organic phosphates, pesticides, fusarium, aflatoxins; (8) international certification (including the Food and Drug Administration, FDA) on the capsaicin (capsaicinoids) content of the natural preparation. Data of abovementioned facts need to be given by internationally accredited laboratories. These data are collected in the Drug Master File (DMF).

The leading chemical trading firms—concerning capsaicin supply—had no DMF for their capsaicin preparations. Independently, several trading firms keep the natural capsaicin (capsaicinoids) preparation in the market without the exact knowledge on the circumstances of cultivation, details of extraction and stability of the product. They have no exact information on the quantities of residues of organic phosphates, pesticides, fusariums and aflatoxins in the capsaicin (proved by certifications of various internationally accredited laboratories).

According to the observations of Foodnews Environmental Working Group (food-news.org://www.drgreene.org/body.cfm?xyzpdqabc=21&detail& ref. = 1920), the most sweet peppers are contaminated with more than one pesticide. Pesticides were not found, detected only in 32%, and seven pesticides were observed in 1% of tested samples. The samples of sweet bell peppers contain acephate, dicophar, dimethoate, diphenylamine, fenvalerate, metalaxyl, methamidophos, methomyl, permethrin, malathion, endosulfates, azinophosmethyl and o-phenylphenol, which may produce animal carcinogens, birth defects, brain and nervous damage as well as the damage of immune system and endocrine system (Report Card www.ewg.org).

In our case, we found only one capsaicin preparation with the Drug Master File (DMF) from India, which was signed by the Food and Drug Administration, USA for orally applicable capsaicin (capsaicum) in humans. Along with this preparation, we could not extract exact information from the manufacturer on abovementioned data to be incorporated into the DMF.

The National Institute of Pharmacy in Hungary requested additional examinations with this natural capsaicin (Capsaicin Natural USP 27) obtained from India on geno- and other toxicological studies due to limited knowledge of circumstances on cultivation, collection, storage, stability and preparation. In the literature, some data are provided, supporting the genotoxic property of some natural preparations by different researchers. Some positivities were indicated with natural capsaicin on the genotoxicity, and the different researchers suggested that these mostly depend on various environmental factors of natural capsaicin, since these were negative with synthetic capsaicin.

These requested studies with natural capsaicin obtained from India were: (1) the testing of natural capsaicin with reverse mutation assay; (2) the testing of mutagenic effects of natural capsaicin by the mouse micronucleus test; (3) a 14-day oral average dose range finding study with natural capsaicin (30, 60 and 120 mg/kg b.w. or orally 14 days); (4) oral dose range including the toxicity study of natural capsaicin in Beagle dogs (0.3–0.6–0.9 mg/kg b.w./day orally given for 14 days); (5) a 28-day oral toxicity study of natural capsaicin in rats (placebo, 5, 15 and 30 mg/kg b.w orally for 28 days); and (6) a 28-day oral toxicity study test in Beagle dogs (placebo, 0.1–0.3–0.9 mg/kg b.w. orally for 28 days) (together with capsaicin kinetics) [5].

It needs to be mentioned that the time period of the planned human clinical pharmacological study was also 1 month. We had to give the results in the DMF for authorities. These toxicological studies were accepted by the authorities because the studies were done by internationally accredited toxicological institutes. However, if the application of capsaicin is planned for a longer time (chronically) then new animal toxicological studies are needed for a longer time (generally these studies are done in rats and in Beagle dogs together at least for 6 months).

Sorry to say that no correct chronic toxicological studies exist neither in animals nor in humans. It's true that the capsaicin used in the human nutrition for ages of years of 7000s–9000s (used in different forms and in different doses or portions). Furthermore, we have no any concrete knowledge on the environments, chemical contaminations, storages, chemical stabilities, chemical components of capsaicin and toxicological aspects of these different capsaicin-containing plants.

Although we participated in clinical pharmacological studies, however, the principle laws of capsaicin application are the same in human clinical nutritional studies.

The name of "capsaicin" is generally used in agricultural, medical, physiological and pharmacological researches; however, this material does not contain uniform chemical entities; the name of capsaicin correctly is "capsaicinoids." The name of "capsaicinoids" covers five analogue (capsaicin, dihydrocapsaicin, nordihydrocapsaicin, homocapsaicin) and two homolog (nonanoic acid vanillylamide, decanoic acid vanillylamide) compounds.

The United States Pharmacopeia (USP) describes the list of capsaicins (similar to other pharmacopeia in different countries) and their definitions, identification, melting range and the content of capsaicin, dihydrocapsaicin and other capsaicinoids as follows (USP30-NF25 2006 Edition,

pp. 1609); capsaicin contains not less than 90% and more than 110.0% of the labeled percentage of total capsaicinoids. The content of capsaicin is not less than 55%, and the sum of content of capsaicin plus dihydrocapsaicin should not be less than 15%, all calculated on the dried basis [5].

For the human application of capsaicinoids, we received permission from the National Institute of Pharmacy; we had to give the following documentations to the National Institute of Pharmacy: (1) expert's opinion; (2) results of all toxicological studies; (3) chemical stability of the natural capsaicin preparation; (4) results of pharmaceutical industrial formulation from the natural capsaicin; (5) various permissions from our university; (6) the documentation of health insurance of volunteers; (7) preclinical dossiers; (8) documented valid permission on the accreditation of the clinical pharmacological unit for human phase I and II examinations (accreditation controlled by the National Institute of Pharmacy); (9) exact protocols for human clinical pharmacological studies; (10) written information on the planned examinations for the volunteers; (11) request for authorization of a clinical trial on medical products for human use to the competent authorities and ethical committees in the community; and (12) lists of investigators together with their CV and qualifications and data of involved institutes (departments participating in this study) [6].

After taking an overview of the different human observations with capsaicin, then practically, we are not able to see these criteria abovementioned.

The different book chapters cover some parts from current observations and the classical studies dealing with the details of mechanisms of actions of capsaicin are dominant in the preclinical studies.

We can see new results on the cultivation procedures of capsaicin from capsicum plants, emerging technologies to improve capsaicin delivery, correlations between the capsaicinoid diversability and its human food preference, new results on correlation between beneficial effects of capsaicin in metabolic diseases (lipid metabolism) and predictors used in treatment response to capsaicin. The results of these observations clearly indicate that the capsaicin research forwarded to the direction of human medical treatment with capsaicin in the last decade.

The evaluation of effectiveness and safety of chemically produced compound(s) are very strictly regulated testing programs both in animals and humans.

After a very careful and critical overview of plant origin compounds, it was very surprisingly to see health and scientific requirements differ so much in regard to their application as dietary components (Response to EMEA Document CPMP/QWP/2819/00 REV 1 AKA EMEA/CVMP/814/00 REV 1. Guideline on Quality of Herbal Medical Products/Traditional Medicinal Products [Released 21 July 2001/Consultation Date 30 September 2005]) and as a drug therapy (this Notice to Applicants [NTA] prepared by the European Commission consultation with the authorities of the member states, the European Medicines Agency and interested parties in order to fulfill the Commission's obligations with respect to Article 6 of Regulation [EC] No. 726/ 2004, and with respect to the Annex 1 to obligations amendment [Directive 2003/63/EC as amendment. Directive 2003/63/EC, 0 J L 159 27.6.2003 p.46 NTA, Vol 2B-CTD, foreword & introduction, edition June 2006]).

I, as the author of this introductory chapter, could not understand the extremely high number of applications of plant origin compounds needed for foods, food additive agents, health modification compounds and classical drugs (especially orally applicable preparations). A lot of

chemical compounds are used during the cultivations of different plants (as capsicum spices), which are used as sources of various compounds of food and drug preparations. Furthermore, during the preparation of the cultivated plants are treated with different chemicals to result aimed chemical compounds (we can use "Drug Mas Master File, DMF", surprisingly up to now no "Food Master File, FMF" These aspects are now under the discussion in our days.).

The primary aims of this book were to give an actual cross-sectional research in the field of human capsaicin treatments with capsaicin. We hope very much that we gave a good cross section from this field in our days.

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Section 2

Cultivation Procedures of Capsaicin from Capsicum Plants

Chapter 2

Capsaicinoids and Vitamins in Hot Pepper and Their Role in Disease Therapy

George F. Antonious

Additional information is available at the end of the chapter

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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, nordihydrocapsaicin, 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-nonenamide) 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.

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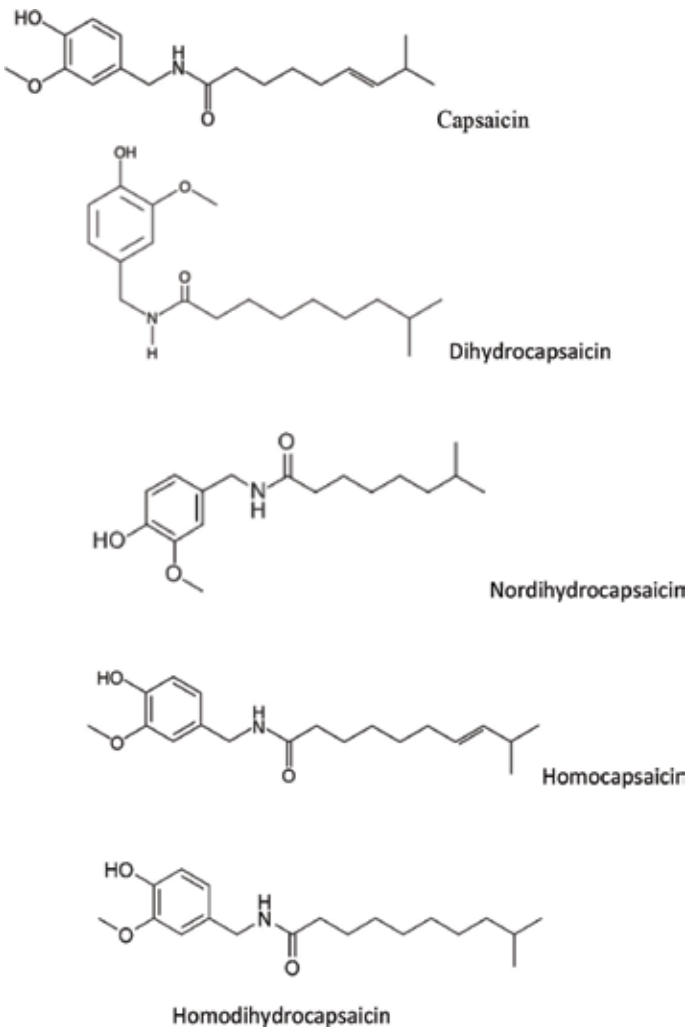

Figure 1. Molecular structures of five capsaicinoids detected in hot pepper fruit extracts. Note that a double bond (two hydrogen atoms) differentiates capsaicin from dihydrocapsaicin molecule.

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

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

Figure 2. Growing hot pepper of the world at Kentucky State University (KSU) HR Benson Research and Demonstration Farm (Franklin County, Kentucky, USA) and screening hot pepper genotypes at KSU Environmental Quality Laboratories for capsaicin content.

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].

1.5. Capsaicin and cancer

Cancer is still the second leading cause of death in the U.S. and a major cause of illness and mortality worldwide. Cancer cells acquire unique capabilities that most healthy cells do not possess. Cancer cells become resistant to growth-inhibitory signals, proliferate without dependence on growth-stimulatory factors, replicate without limit, escape apoptosis (breakdown of cells) and acquire invasive and angiogenic (creation of new blood vessels) properties. Capsaicin has been shown to alter the expression of several genes involved in cancer cell survival, growth arrest, angiogenesis, and metastasis (spread throughout the body). Recently, it was found that capsaicin targets multiple signaling pathways, oncogenes (genes that contribute to cancerous changes in cells), and tumor suppressor genes in various types of cancer models. Anticancer mechanisms of capsaicin include activation of apoptosis in many different cancer cell lines, while leaving normal cells unharmed. Capsaicin interacts with other cancer preventive agents synergistically, providing the possibility for the potential use of capsaicin in cancer therapy with other chemotherapeutic agents [26].

1.6. Anti-obesity of capsaicin

For individuals suffering from obesity, ingestion of capsaicin or other capsaicinoids increased energy expenditure and decreased respiratory quotient, indicating a rise in fat oxidation. Studies with mean body mass indexes (BMI) gives an indication of person's nutritional status. While BMI of individuals below 25 kg m^{-2} failed to report any effect of capsaicin or capsaicinoids on the energy expenditure or on the respiratory quotient, studies with mean BMI patients exceeding 25 kg m^{-2} demonstrated an increase in energy expenditure and a marked decrease in respiratory quotient. Data clearly suggest that capsaicin or capsiate could be a new therapeutic approach in obesity promoting an increased fat oxidation [27]. Recent laboratory studies support a role of capsaicin as an anti-obesity agent. Studies in obese/diabetic mice revealed that dietary capsaicin reduced mice metabolic dysregulation by enhancing expression of adiponectin and its receptor. In addition, the effects of capsaicin in fat and liver tissues are related to its dual action on peroxisome proliferator-activated receptor alpha and transient receptor potential vanilloid-1 expression/activation. Capsaicin encourages apoptosis and prevents adipogenesis in adipocytes. Gastrointestinal exposure to capsaicin reduces energy and fat intake. This effect is stronger with oral exposure to capsaicin which indicates a sensory effect of capsaicin. Diets containing capsaicin enhance body weight maintenance following a high caloric diet. Consumption of capsaicin before low intensity exercise has been recommended as a valuable supplement for the treatment of patients with hyperlipidemia and/or obesity due to improvements in lipolysis [28].

1.7. Anti-diabetic effect of capsaicin

Diabetes is a condition in which the body is either impaired or unable to regulate blood glucose levels and involves either improper or an inappropriate reaction to the hormone insulin. Capsaicin in human diets reduces glucose levels and increases insulin levels following its oral administration in glucose tolerance test. Studies determined that capsaicin could be detected in

the blood as early as 10 min after ingestion at levels maintained for up to 90 min. It was found that capsaicin levels is related to the lower blood glucose levels and preservation of the high insulin levels [29]. Gestational diabetes mellitus (GDM), is a case when a hormone made by the placenta prevents the body from using insulin successfully. This cause glucose level to build up in the blood instead of being absorbed by the cells. GDM may increase the future health risks of women and their offspring. Many women with GDM experience pregnancy-related complications including high blood pressure, large birth weight babies and obstructed labor. The effect of capsaicin supplementation on blood glucose, lipid metabolism and pregnancy outcomes in women with GDM was investigated. Capsaicin-containing Chili supplementation regularly improved postprandial hyperglycemia and hyperinsulinemia as well as fasting lipid metabolic disorders in women with GDM, and decreased the incidence of large-for-gestational-age newborns [30]. Capsaicin may inhibit glucose tolerance by inhibiting adipose tissue (body fat) inflammatory responses in obesity. Ingestion of capsaicin in human diets may reduce obesity due to induced glucose intolerance and enhance fatty acid oxidation in adipose and liver tissues that are important peripheral tissues affecting insulin resistance [31].

1.8. Use of vanilloids in urologic disorders

Urologic disorders are diseases of the kidneys and urinary tract. Neurogenic bladder (NGB) or bladder dysfunction can result from any neurological insult that interferes with the normal functioning of the lower urinary tract which requires intact pathways involving the central and peripheral neurological systems. There are many causes of NGB, but most commonly include spinal cord injury, multiple sclerosis, spina bifida, degenerative spinal disease, cerebrovascular accident and as a result of surgical extirpative procedures that affect peripheral bladder innervation. Vanilloids are compounds that contain vanillyl group such as vanillyl alcohol, vanillin, vanillic acid, homovanillic acid, capsaicin, and capsaicinoids (**Figure 1**), etc. Vanilloids bind to the transient receptor potential vanilloid type 1 (TRPV1) receptor (an ion channel which respond naturally to noxious stimuli such as high temperature and acidic pH). Capsaicin reduced the number of daily urinary incontinence episodes by 3.8 episodes when compared to a placebo. A noticeable reduction in the use of pads was achieved daily from 10 to 4. Studies conducted to compare capsaicin to a chemical called resiniferatoxin or RTX (the best-known vanilloid from *Euphorbia resinifera)* showed no difference between treatments with capsaicin and RTX and both compounds decreased the urinary incontinence episodes. The human pelvis include bowel, bladder, womb (uterus) and ovaries. When a person suffers from pelvic pain it is usually means pain that starts from one of the pelvis organs. MacDonald et al. [32] and Foster and Lake [33] reported that, while the use of capsaicin is promising at this time, it appears that RTX is a better treatment.

Urinary frequency or overactive bladder (OAB) is caused by assemblage of symptoms that can be summarized into urinary tract infection, bladder outlet obstruction, bladder cancer, or disorder of the neurologic system (i.e., cerebrovascular accident, spina bifida, Parkinson's disease, etc.) which can result in a similar clinical presentation. Soontrapa et al. [34] published a report on 25 patients with either OAB or what they described as either a hypersensitive bladder or primary detrusor instability, who were treated with 1 mM of capsaicin diluted in 100 mL of 30% ethanol solution. In those with OAB, it was found that daytime urinary frequency

(16.5–8.6), incontinence episodes per day (9.7–2.4), bladder capacity (160.1–236.9 mL), and detrusor contraction pressure (71.1–57.3 cm H_2O) improved following treatment with capsaicin. Vanilloids have been found to be useful in patients with OAB for reasoning similar to that of neurogenic bladder. Although efficacy has been shown in some studies, currently the use of vanilloids cannot be recommended for routine use in patients with overactive bladder (OAB) [33]. Bladder pain syndrome (BPS) is a condition that falls under a larger category of genitourinary pain syndromes, hypersensitivity, or sensory disorders of the urinary tract. Vanilloid receptors in the bladder modulate activity of sensory neurons. RTX and capsaicin act at this receptor and may potentially offer a viable treatment modality for BPS, though at this time more research is required in this area.

1.9. Capsaicin for osteoarthritis pain

Osteoarthritis (OA) sometimes called degenerative joint disease is the most common joint disorder. It is commonly due to aging. Topical capsaicin treatment four times daily is moderately effective in reducing pain intensity up to 20 weeks regardless of site of application and dose inpatients with at least moderate pain. Capsaicin treatment is also generally well tolerated, suggesting that capsaicin should be used early in the OA treatment process, especially for superficial joints such as the hand and knee that is well tolerated [35].

Research suggests OA is a complex collection of heterogeneous pathologies which result in a common outcome [36], rather than a single disease entity. Most existing treatments focus on relieving pain, with a few examples of improving function. Capsaicin is found to be active in reducing osteoarthritis pain. However, it is unclear whether this activity has a dose response consistent across joints, or this effect changes over time. The most common adverse effect is contained burning sensations of slight to modest intensity associated with capsaicin use, but this burning weakens with ongoing use.

1.10. Research conducted on separation and identification of capsaicinoids in hot pepper genotypes at Kentucky State University (KSU), College of Agriculture (Franklin County, Kentucky, USA)

Studies on screening hot pepper, *Capsicum* spp. genotypes were started in summer 2006 at Kentucky State University Research and Demonstration Farm. Seeds of 63 previously uncharacterized genotypes of hot pepper were selected from the USDA/Agricultural Research Service (Griffin, GA, USA) to represent the main cultivated species of pepper (*Capsicum annuum*, *C. baccatum*, *C. chinense*, *C. frutescens*, and *C. pubescens*) from a world-genotypes collection. Seeds were germinated in the greenhouse and transplanted into the field. At harvest, pepper fruits were collected and transported from the field experiment, in coolers, to the KSU Environmental Toxicology Laboratories. Fruits were analyzed and screened for their composition of capsaicin and dihydrocapsaicin using spectrophotometric methods [37]. After 2 years of growing hot pepper, top twenty-nine genotypes (**Figure 3**) were selected based on their disease tolerance, fruit yield, and fruit size characteristics under Kentucky environmental conditions for further investigation on quantification of capsaicinoids and other phytochemicals having antioxidant properties.

Figure 3. Hot pepper genotypes grown at Kentucky State University HR Benson Research and Demonstration Farm (Franklin County, Kentucky, USA).

1.11. Quantification of capsaicin, dihydrocapsaicin, ascorbic acid, β-carotene, and phenols in hot pepper

As described earlier, pepper pungency is measured in Scoville units, a subjective scale based on the ratio and capsaicinoids content. It is about 200,000–300,000 Scoville units for habanero and 16 million units for pure capsaicin. The content and the hotness of capsaicin increase during the process of fruit ripening. In general, dried forms of Chili pepper are spicier than fresh fruits, because the lower water content concentrates capsaicinoids. Capsaicinoids were extracted by blending 10 fresh fruit of comparable size in methanol for 1 min. The extracts were then decanted through 55 mm Whatman 934-AH glass microfiber filter discs (Fisher Scientific) and concentrated in a rotary vacuum evaporator (Buchi Rotavapor) at 35°C, chased with nitrogen gas (N_2), and reconstituted in 10 mL of methanol. Each extract of the genotypes tested was subsequently passed through a 0.45 μm GD/X disposable syringe filter. One μL of this filtrate was injected into a gas chromatograph (GC) equipped with a nitrogen phosphorus detector (NPD). GC separations were accomplished using a 25 m × 0.20 mm ID capillary column with 0.33 μm film thickness (HP-1). Operating conditions were 230, 250, and 280°C for injector, oven, and detector, respectively, and a carrier gas (He) flow rate at 5.2 mL min^{-1}. Peak areas were determined using a Hewlett-Packard (HP) model 3396 series II integrator. Quantifications were based on average peak areas of 1 μL injections obtained from external standard solutions of capsaicinoids (capsaicin and dihydrocapsaicin) prepared in methanol. Peak identities were confirmed by consistent retention time and co-elution with standards under the conditions described above. A HP gas chromatograph model 5890A equipped with a mass chromatograph operated in total ion monitoring (GC/MS) with electron impact ionization (EI) mode and

70-eV electron energy was also used for identification and confirmation of individual peaks. Standards of capsaicin (N-vanillyl-8-methyl-6-nonenamide) and dihydrocapsaicin were purchased from Sigma-Aldrich Inc. in Saint Louis, MO, USA and used to prepare standard curves using regression lines. To determine the recovery of the extraction, cleanup, and quantification procedure, concentrations of capsaicin and dihydrocapsaicin in the range of 20–200 μg g^{-1} fresh fruit were added to 20 g of non-pungent bell pepper (*C. annuum*) fruits. Linearity over the range of concentrations were determined using regression analysis.

Mass spectrometry of the fruit crude extracts (**Figure 4**) indicated that the molecular ions at m/z 305, 307, and 293 that correspond to capsaicin, dihydrocapsaicin, and nordihydrocapsaicin, respectively, have a common benzyl fragment at m/z 137 that is a fingerprint for monitoring capsaicinoids in pepper fruit extracts. The two capsaicinoids, capsaicin and dihydrocapsaicin, were the main capsaicinoids found in the fruit extracts. However, their concentrations varied among pepper genotypes tested. Nordihydrocapsaicin was present at very low concentrations when compared to capsaicin and dihydrocapsaicin. Capsaicin concentrations were typically greater than dihydrocapsaicin. Concentrations of total capsaicinoids in the 29 genotypes tested varied from not detectable to 11.2 mg $fruit^{-1}$. Statistical analysis revealed that accession PI-441624 (*Capsicum chinense*) had the highest capsaicin content (2.9 mg g^{-1} fresh fruit) and accession PI-497984 (*C. frutescens*) had the highest dihydrocapsaicin content (2.3 mg g^{-1} fresh fruit). Other characteristic fragment ion peaks were consistent with the assignment of the molecular formulae of capsaicin ($C_{18}H_{27}NO_3$), dihydrocapsaicin ($C_{18}H_{29}NO_3$), and nordihydrocapsaicin ($C_{17}H_{27}NO_3$), respectively. These capsaicinoids had a common benzyl cation fragment ($C_8H_9O_2$, m/z 137) that was observed in all hot pepper extracts. The retention time and mass spectra of capsaicinoids isolated from the fruits of *Capsicum* genotypes matched those of their standards.

1.12. Quantification of other antioxidants in hot pepper fruits

Capsicum spp. also contain other medicinal agents, such as vitamins and antioxidants (flavonoids, carotenoids, vitamin C, and vitamin E), that have biological activity as well, such as the role of vitamin C and β-carotene in inflammation and cancer prevention, respectively. Pepper fruits of the twenty-nine genotypes selected, after 2 years of field screening, were cut into small pieces and 30 g representative subsamples were blended in a household blender at high speed with 100 mL of acetone for 2 min in dim light to extract β-carotene [38]. The homogentate were filtered with suction through a Buchner funnel containing Whatman filter paper No.1 (Fisher Scientific, Pittsburg, PA). The resulting thick paste were extracted twice with acetone until the extract is colorless. The filtrates were combined, transferred to separatory funnel containing 50 mL of 4% aqueous NaCl and 100 mL of petroleum ether (BP 40–60°C). Absorption of the petroleum ether layer were measured at 450 nm in dim light. β-carotene was quantified using a high performance liquid chromatograph (HPLC) for confirmation purposes. A calibration curve was also prepared using 99% pure β-carotene in the range of 10–100 μg mL^{-1}. Representative fruit samples (20 g) were also blended with 150 mL of ethanol to extract phenols. Homogenates were filtered through Whatman No. 1 filter paper and 1 mL aliquots of filtrate were used for determination of total phenols [39, 40] using a standard calibration curve (1–16 μg mL^{-1}) of chlorogenic acid. Ascorbic acid (vitamin C) was extracted by blending 20 g of fruit with 100 mL of 0.4% (w/v) oxalic acid solution and determined by the

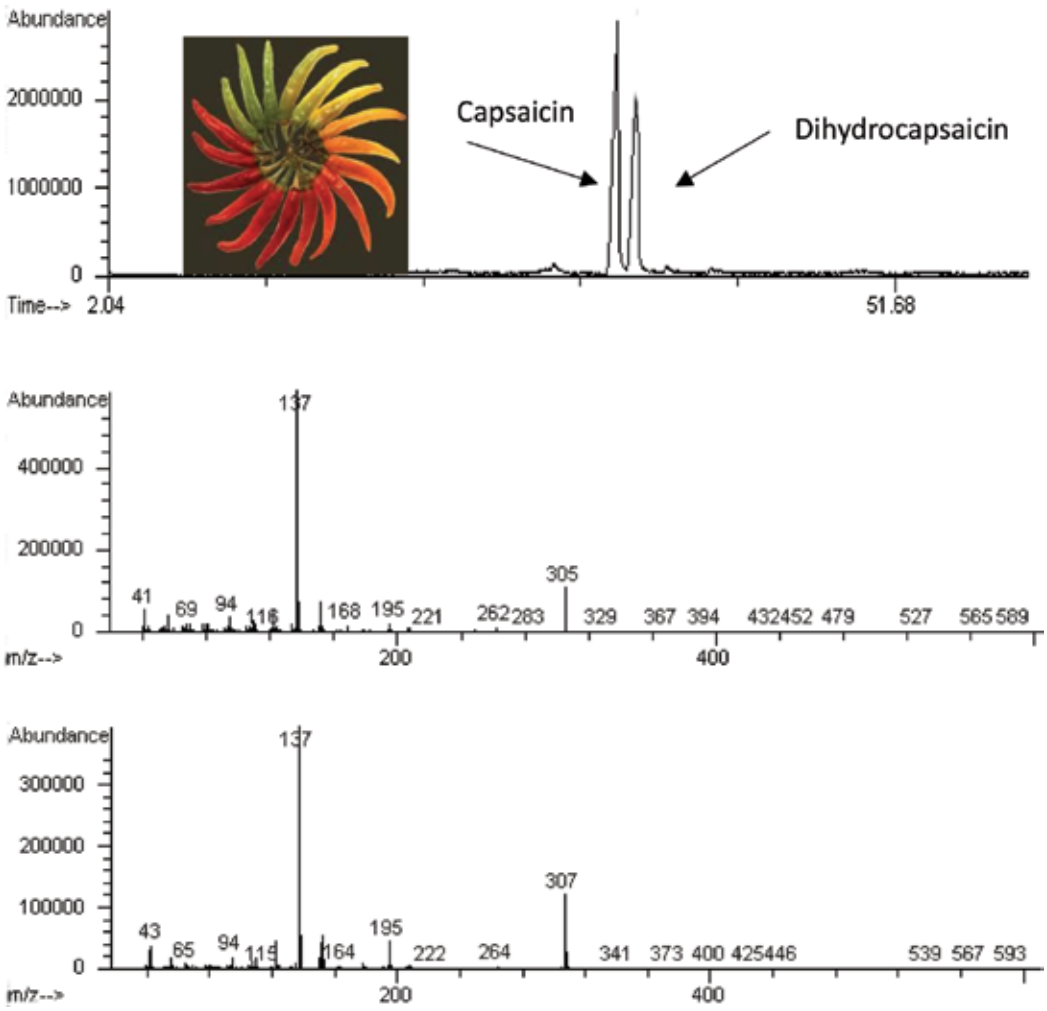

Figure 4. Gas liquid chromatographic peaks of capsaicin and dihydrocapsaicin (upper graph), capsaicin ion fragments (middle graph), and dihydrocapsaicin ion fragments (lower graph).

dichlorophenolindo-phenol method [41]. Purified standards of β-carotene, ascorbic acid, and chlorogenic acid were purchased from Sigma-Aldrich Inc. (Saint Louis, MO, USA) and used to obtain calibration curves. Concentrations of each compound, expressed on a fresh weight basis, was calculated and statistically analyzed using ANOVA procedure. Means were compared using Duncan's multiple range test [42]. Quantification of the level of capsaicinoids and other antioxidants in the selected genotypes allowed the identification of accessions having high levels of health-promoting phytochemicals and provided a mass balance information for each accession tested in relation to countries of seeds origin (**Figure 5**). Results of fruit analysis revealed that the concentrations of individual capsaicinoid and the proportion of capsaicin/dihydrocapsaicin fluctuated within and among species and even among genotypes of the same species. Absolute capsaicinoids concentrations are subject to a variety of environmental,

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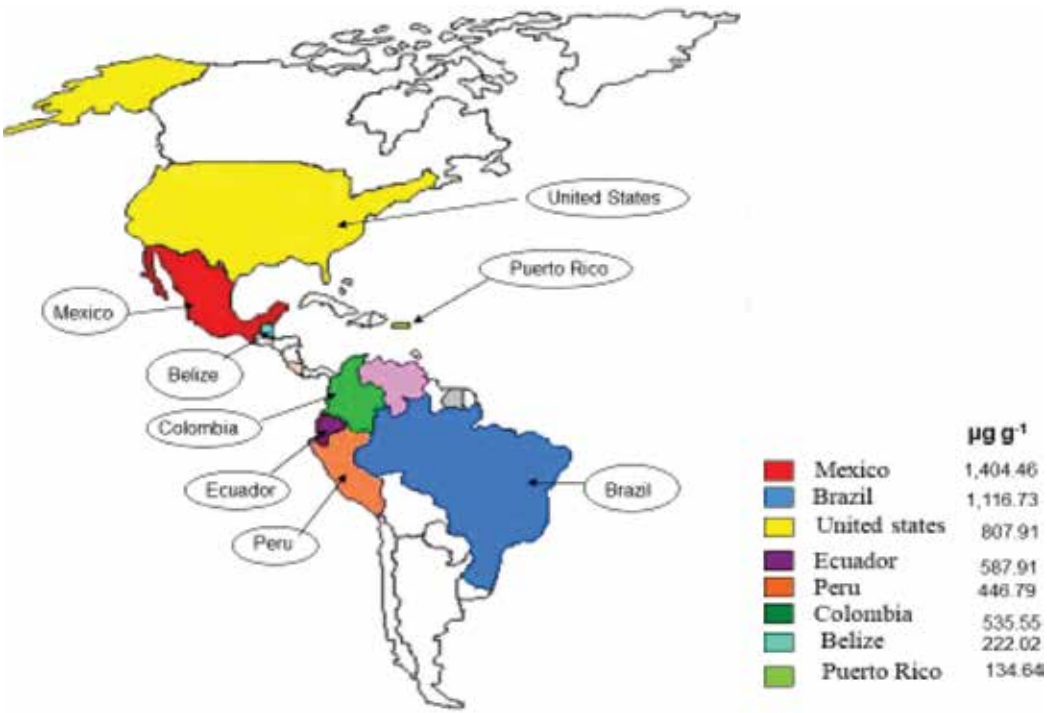

Figure 5. Eight top hot pepper (*Capsicum* spp.) generating countries of the world indicating 1404 μg capsaicinoids g^{-1} fresh fruits in fruits of seeds obtained from Mexico and 135 μg g^{-1} fresh fruit in fruits of plants grown from seeds obtained from Puerto Rico.

cultural, and other factors. The greatest concentrations of capsaicinoids (1405 μg/g fresh fruits) were found in pepper seeds obtained from Mexico [43]. Among the 63 accessions analyzed, concentrations of total phenols were significantly higher in PI 438648, PI 159248, and PI 360900. Seeds of these accessions are originated in Mexico and the US, respectively. While, total phenols concentration was generally low in fruits of genotypes from Belize.

Statistical analyses of 63 genotypes obtained from the USDA/ARS (Griffin, GA) revealed that the greatest concentrations of β-carotene were found in fruits of accessions obtained from Ecuador. Fruits of *C. chinense* accessions PI-152452 (Brazil) and PI-360726 (Ecuador) contained the greatest concentrations of vitamin C (1.2 and 1.1 mg g^{-1} fresh fruit, respectively), while PI-438648 (Mexico) contained the greatest concentration of total phenols content (349 μg g^{-1} fresh fruit) among the other 63 accessions tested. Accession PI-355817 from Ecuador contained the greatest concentrations of β-carotene (8 mg g^{-1} fresh fruit). These accessions were identified as potential candidates for mass production of antioxidants with health-promoting properties. When different colored pepper fruits (green, yellow, orange, and red) were analyzed, orange and red contained the greatest β-carotene and sugar contents; whereas, green fruits contained the greatest concentrations of total phenols and vitamin C. Capsaicinoids (capsaicin plus dihydrocapsaicin) were higher in orange and red compared to green and yellow colors [17].

In a similar study carried out by Antonious 2017 [44] at the University of Kentucky South Farm (Fayette County, KY), seeds of 29 genotypes were obtained from the USDA/ARS (Griffin, GA, USA). The selected genotypes were: from *Capsicum annuum* (PI 123474, PI 127442, PI 138565, PI 159256, PI 164271; PI 169129, PI 200725, PI 210980, PI 215743, PI 241670, PI 246331, PI 257048); *Capsicum baccatum* (PI 260539, PI 260571, PI 439409); *Capsicum chinense* (PI 209028, PI 224443, PI 238047, PI 238051, PI 257136, PI 439464, PI 594139, PI 485593, PI 439420, PI 281443); and *Capsicum frutescens* (PI 631144). These selected genotypes represented cultivars originally acquired from world-wide different locations. Results of capsaicinoids analysis revealed that PI 631144 of *C. frutescens* contained the greatest concentrations of capsaicin compared to other genotypes tested (**Table 1**). Concentration of capsaicin and dihydrocapsaicin varied among genotypes and no one genotype contained the greatest concentration of both. Total capsaicinoids varied from 1 μg g^{-1} (PI 169129; *C. annuum*) to 465 μg g^{-1} fresh fruit (PI 631144; *C. frutescens*, the greatest capsaicinoids content in the 2017 study. PI 631144 (*C. frutescens*) from Guatemala) was identified as potential candidate for the mass production of total capsaicinoids. Concentration of dihydrocapsaicin also varied among genotypes and was lowest in PI 169129 and greatest in PI 123474 and PI 127442 (**Table 1** and **Figure 6**). In most cases, capsaicin concentrations were greater than dihydrocapsaicin as shown in the chromatogram (**Figure 4**). Concentration of total capsaicinoids (capsaicin and dihydrocapsaicin) was greatest (465 μg g^{-1} fresh fruits) in PI 631144 and lowest in (1.2 μg g^{-1} fresh fruits) in PI 169129 compared to all genotypes analyzed. Accordingly, integration of nutrient rich pepper types into diets could help combat nutrient deficiencies by providing a significant portion of recommended daily nutrients [45].

1.13. Other pharmacological properties of chili pepper, *Capsicum* spp. fruits

The enhancement of compounds in foods, such as antioxidants in hot pepper (*Capsicum* spp.) is due to the presence of capsaicin, dihydrocapsaicin, vitamin C, vitamin A, vitamin E, and total phenols content. Peppers, an important component of the human diet in many regions of the world, protect macromolecules from dangerous free radicals, i.e., reactive oxygen species (ROS). Free radicals are unstable, highly reactive compounds produced as the result of normal aerobic metabolism. They can damage nucleic acids, proteins and lipids, which can hasten aging and the onset of diseases including cancer, heart disease, atherosclerosis, and cataracts. 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]. Pepper usually ranks first or second in terms of phenolic content with levels greater than other high-phenolic vegetables including spinach, broccoli and garlic [15, 46]. Pungent types had more phenolic compounds than sweet types, an expected result given that pungency is due to capsaicinoids, important phenolic compounds in pepper.

Chili pepper constitutes one of most consumed spices in the world. Capsaicin and vitamin C content in hot pepper determine chili pepper quality on the international market [47] as two important antioxidants in food. Antioxidants could be organic or inorganic compounds, either present naturally or synthesized industrially. When antioxidants added to a formulation even in minute amounts, they tend to neutralize free radicals, preventing the cells from potential damage which in turn cure numerous diseases [48]. Antioxidants are also useful as dietary supplements for sustaining health, prevention of diseases reducing the adverse effects of chemo-and radio-therapy [49]. Antioxidants can be classified on the basis of their

		μg g^{-1} fresh fruit*	
PI	**Capsaicin (A)**	**Dihydrocapsaicin (B)**	**Total (A + B)**
PI123474	170.61 ± 23	203.41 ± 25	374.02 ± 45
PI127442	172.73 ± 15	68.1 ± 11	240.83 ± 22
PI138565	55.62 ± 10	42.86 ± 8	98.48 ± 16
PI159256	15.57 ± 2.3	10.29 ± 2.3	25.86 ± 4.2
PI164271	95.53 ± 16	39.1 ± 9.2	134.63 ± 33
PI169129	0.61 ± 0.2	0.61 ± 0.12	1.22 ± 0.22
PI200725	29.31 ± 5	1.417.08 ±	46.38 ± 12
PI210980	100.69 ± 16	32.21 ± 12	132.91 ± 24
PI215743	1.3 ± 04	1.22 ± 52	2.52 ± 0.8
PI241670	110.46 ± 14	142.77 ± 22	253.23 ± 33
PI246331	146.19 ± 22	85.47 ± 15	231.66 ± 25
PI257048	87.55 ± 12	56.57 ± 11	144.12 ± 16
PI260539	8.64 ± 2.1	8.39 ± 3	17.03 ± 2.5
PI260571	3.35 ± 1.3	1.04 ± 0.3	4.39 ± 1.7
PI439409	14.19 ± 2.5	2.18 ± 0.4	16.37 ± 6
PI209028	40.11 ± 4.2	6.85 ± 1.2	46.96 ± 11
PI224443	3.17 ± 1.3	3.09 ± 0.8	6.26 ± 1.2
PI238047	129.64 ± 13	95.94 ± 12	225.58 ± 27
PI238051	62.96 ± 12	25.98 ± 4.6	88.95 ± 11
PI257136	87.23 ± 8.8	30.1 ± 12	117.33 ± 15
PI281443	93.51 ± 12	36.62 ± 6.6	130.13 ± 17
PI439420	154.26 ± 18	44.94 ± 13	199.2 ± 22
PI439464	61.29 ± 13	36.3 ± 9.5	97.59 ± 13
PI485593	15.98 ± 2.6	10.62 ± 2.4	26.6 ± 3.2
PI594139	222.76 ± 26	60.25 ± 11	283.01 ± 29
PI631144	323.31 ± 35	142.15 ± 32	465.46 ± 43
GRIF 9213	66.4 ± 16	38.94 ± 13	103 ± 22
PI241676	33.29 ± 13	16.3 ± 9.5	49.59 ± 17
PI639661	18.28 ± 2.6	10.62 ± 2.4	28.9 ± 4.2

*Each value in the table is an average of three replicates ± std. error.

Table 1. Capsaicin and dihydrocapsaicin in hot pepper genotypes of twenty-nine ***Capsicum*** spp. grown at Kentucky State University South Farm (Fayette County, Kentucky).

origin, solubility (i.e., aqueous or lipid). Ascorbic acid (vitamin C), α-tocopherol (vitamin E), β-carotene (vitamin A) and capsaicin have been documented in hot pepper as natural antioxidants [50, 51]. Recent findings have demonstrated the antibacterial, anti-inflammatory, anticancer, antimutagenic properties, and blood glucose regulation [52] of various natural antioxidants. In addition to their natural resources, antioxidants can be synthesized and

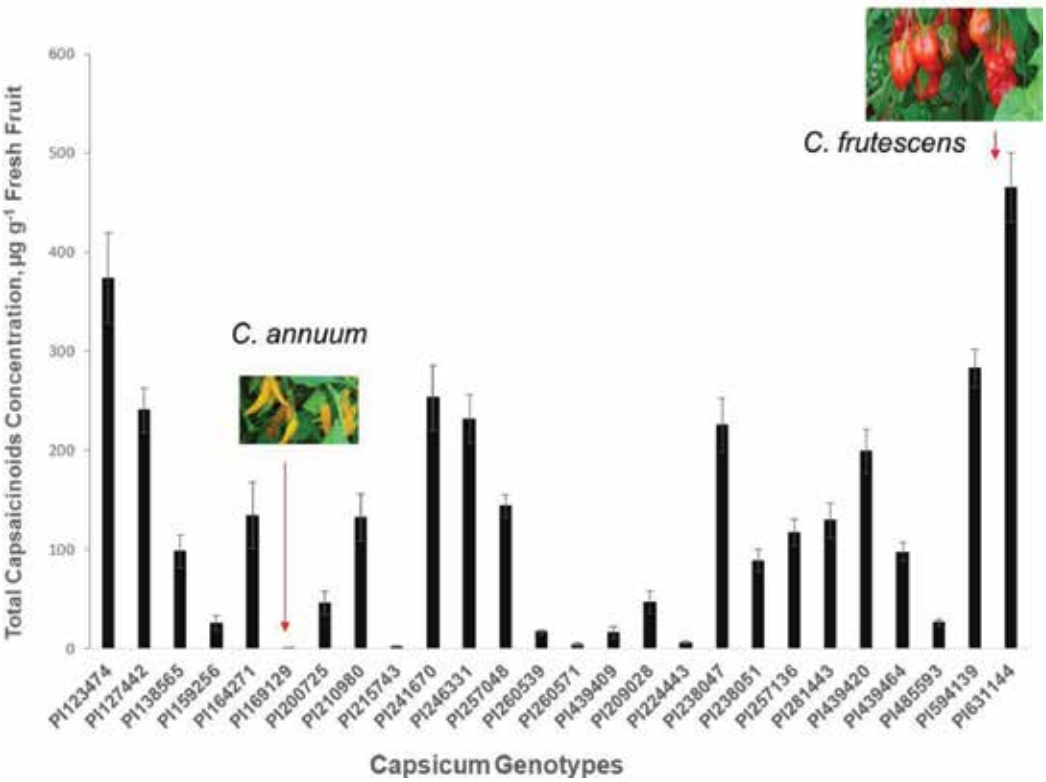

Figure 6. Fluctuations in total concentrations of capsaicinoids (capsaicin and dihydrocapsaicin) in fresh fruits of *Capsicum* spp. grown at Kentucky State University HR Benson Research and Demonstration Farm (Franklin County, Kentucky).

added to food and pharmaceutical products to improve the shelf-life of therapeutic agents that are susceptible to chemical degradation by oxidation. However, preclinical and clinical reports suggest that synthetic antioxidants cannot afford appropriate protection against oxidative stress [53].

1.14. Role of β-carotene (vitamin A) in hot pepper in disease therapy

Vitamin A deficiency is a serious and widespread public health problem and the leading cause of preventable blindness in young children. Deficiency of vitamin A can lead to a series of ocular symptoms, anemia, and weak resistance to infection, which can increase the severity of infectious diseases and the risk of death [54]. Deficiency of vitamin-A impacts hundreds of millions of pre-school age children in low income countries. Fruits of pepper (*C. annuum* L.) can be a major dietary source of precursors to vitamin A biosynthesis, such as β-carotene [55]. Antioxidants such as β-carotene are suggested to decrease risk of type 2 diabetes by preventing progressive impairment of pancreatic β-cell and endothelial function. A study was conducted to investigate the relationship between dietary antioxidants and risk of type 2 diabetes in 24,377 adults (19–74 years old) [56]. Men in the highest quartile of β-carotene intake showed lower risk of type 2 diabetes. Peppers are an important source of nutrients in human diet. *C. annuum*

is characterized by its high levels of vitamin C (ascorbic acid), and provitamin A (carotene). Ingestion of 50–100 g fresh pepper fruits can provide about 100 and 60% of the recommended daily amounts of vitamin C and A, respectively. Ripe fruits of pepper are also rich in compounds with antioxidant and anticancer action [57]. In addition, vitamin A deficiency was associated with a 10-fold increase in risk of tuberculosis [58].

1.15. Role of ascorbic acid (vitamin C) in disease therapy

The presence of pus-forming bacteria or their toxins in the blood or tissues is known as "sepsis" due to the body response to an infection by harmful bacteria and their toxins that enter the body through a wound. Without appropriate treatment, sepsis can rapidly damage human tissue, cause organ failure, and sometimes death. Sepsis is affecting approximately 26 million people worldwide every year [59]. Vitamin C is found effective in mediating inflammation through its antioxidant properties and is also important in the synthesis of cortisol, catecholamines, and vasopressin, that are all key mediators in the disease development. Investigators provided data that revealed the effect of vitamin C therapy to ameliorate the effects of inflammation and improve hemodynamic stability in patients with sepsis. However, further evidence is needed to support this practice. According to Teng et al. [59], vitamin C is a cost-effective therapy that can be used to ameliorate the effects of inflammation and oxidative stress in sepsis. Although classical vitamin C deficiency marked by scurvy is rare in most parts of the world, some research has shown variable heart disease risks on plasma vitamin C concentration, even within the normal range. Studies have also proposed possible heart-related assistances when vitamin C is taken. It is well established that vitamin C inhibits oxidation of LDL-protein, thereby reducing atherosclerosis [60]. Vitamin C has been found effective in enhancements in lipid contours such as, arterial stiffness and endothelial function. Research findings indicated vitamin C deficiency is linked with a higher risk of cardiovascular diseases and mortality and that vitamin C may slightly improve endothelial function and lipid profiles in some patients, particularly patients with low plasma vitamin C levels.

At Kentucky State University Environmental Toxicology Laboratories, screening 63 hot pepper genotypes of worldwide collection revealed that hot pepper is a rich source of vitamin C. Concentrations of the analyzed phytochemicals in hot pepper genotypes varied significantly among accessions from the same country of origin, and between countries of origin. Concentrations of vitamin C in two accessions, PI 152452 (Brazil) and PI 360726 (Ecuador), were significantly higher (1224 and 1139 $\mu g\ g^{-1}$ fresh fruit, respectively) compared to other genotypes analyzed. These two genotypes may be useful as parents in hybridization programs to produce high vitamin C containing varieties. On the contrary, PI 281424 from Peru contained the lowest vitamin C concentration (266 $\mu g\ g^{-1}$ fresh fruit) [43].

1.16. Role of tocopherols (vitamin E) in hot pepper in disease therapy

Tocopherols are among the most important lipid-soluble antioxidants in food and in human and animal tissues. There are different types of vitamin E (tocopherol), the most found are α, β, γ, δ, ε, ξ, and η, tocopherols. α-Tocopherol in Capsicum spp. is mainly found in the pericarp and γ-tocopherol is a specific constituent in the pepper seeds [18]. All studied

C. pubescens pepper accessions contained α-tocopherol at levels between 6.8 and 18.4 mg 100 g^{-1}. β-Tocopherol was found in only a few pepper accessions at trace levels reaching 0.2 mg 100 g^{-1} at maximum [18]. Peppers are rich in antioxidants, including carotenoids, capsaicinoids, and tocopherols [61].

Waniek et al. [62] reported that vitamin E levels in foods might protect from gallstone disease (gallstone disease is defined as gallbladder stones visualized at the ultrasound examination). Participants with gallstones had lower circulating α-tocopherol and α-tocopherol/cholesterol ratio levels compared to participants without gallstones. A total of 44 participants (7.6%) of a study were taking vitamin E supplements. The results revealed that higher levels of the antioxidant α-tocopherol may protect against gallstone disease. More investigation in this important disease is needed to prevent the incidence of gallstone. Nonalcoholic fatty liver disease (NAFLD) is defined as the accumulation of excessive fat in the liver. NAFLD is strongly associated with obesity and related metabolic disorders such as insulin resistance and dyslipidemia. Like other fat-soluble vitamins, the bioavailability of vitamin E depends on pancreatic function, biliary secretion, micellar formation, and penetration across intestinal membranes. In the last decades, adult and childhood obesity has reached epidemic levels, and as a consequence the global incidence of NAFLD has increased significantly. According to a recent report, prevalence estimates in the general population of Europe and the Middle East are 20–30%, with higher prevalence in Western countries' populations with obesity or diabetes (75%) and with morbid obesity (90–95%) [63]. Oxidative stress is defined as the imbalance between the generation of reactive species and antioxidant defense, and leads to the damage of DNA and disturbances in cellular biology. The antioxidant property of vitamin E is attributed to the hydroxyl group from the aromatic ring of tocochromanols, which donates hydrogen to neutralize free radicals or reactive oxygen species (ROS). Vitamin E is widely accepted as one of the most potent antioxidants in nature [64]. Vitamin E biological activity is not limited to antioxidant properties. In fact, vitamin E forms are involved in the regulation of inflammatory response, gene expression, membrane-bound enzymes, modulation of cellular signaling, and cell proliferation.

1.17. Role of total phenols in hot pepper in disease therapy

About 8000 different classes of polyphenols are found as secondary products in plants. The most important are flavonols, flavones, flavan-3-ols, flavanones and anthocyanins and the most commonly occurring polyphenols in food include flavonoids and phenolic acids. Dietary polyphenols have shown a substantial evidence in vitro that they can affect numerous cellular processes like, gene expression, apoptosis, platelet aggregation, intercellular signaling, causing anticarcinogenic and antiatherogenic implication [65]. Polyphenols in *Capsicum* spp. also possess antioxidant, anti-inflammatory, anti-microbial, cardioprotective activities and play a role in the prevention of neurodegenerative diseases and diabetes mellitus [66]. Polyphenols are mostly acknowledged for their antioxidant activities on the basis of their structural chemistry. They have been recognized as more effective antioxidants in vitro than vitamins E and C on a molar basis. Recent research reveals that dietary spices in minute quantities has an immense influence on the human health by their antioxidative, chemopreventive,

antimutagenic, anti-inflammatory, immune modulatory effects on cells and a wide range of beneficial effects on human health by the action of gastrointestinal, cardiovascular, respiratory, metabolic, reproductive, neural and other systems [67].

1.18. FDA regulations regarding capsaicin in human therapeutic application and development

The repurposing of existing drugs that have been permitted by the Food and Drug Administration (FDA) for human therapy is a continuous strategy for drug development [68]. Drugs that are likely to have low risks and known mechanisms of action after methodically and extensively screened for safety, are usually FDA approved. This is because many pharmaceuticals have much broader ranges of action and application than their certificates recommend. Accordingly, chemicals in the FDA inventory of approved drugs can be used again and again in different purposes when the safety of these drugs in humans is well-known. Phytochemicals found in various plants are frequently included in the human diet that are commonly assumed to be safe for consumption since they are created naturally. However, there are some exceptions and in fact many natural compounds found in several commonly consumed plants can be toxic and may cause cancer or can be tumor promoters and should be evaded. In the United States most phytochemicals are not under regulation by the FDA and their possible toxicity is understudied [69]. One of the most controversial phytochemical is capsaicin. In spite of being a well-studied phytochemical, capsaicin epidemiologic studies revealed that ingesting of hot peppers, which contain variable levels of capsaicin, might be connected with cancer, mostly of the gallbladder [70]. Thus, a complete consensus as to whether the primary effect of capsaicin is cancer anticipation or elevation has not yet been reached with complete evidence.

Conflicting epidemiologic and basic research studies propose that capsaicin could have a role in either preventing cancer or causing cancer. Hundreds of basic research studies show that capsaicin suppresses growth of numerous types of cancer cell, suggesting that it has chemo preventive activities and these studies have been well reviewed [69]. Capsaicin formulations in the form of creams have been in use for many years to relieve painful conditions such as arthritis, osteoarthritis, and diabetic neuropathy. Results of the effectiveness and safety of capsaicin use in pain relief is controversial. Prolonged use of capsaicin in topical treatment in patients exposed to sunlight and its ultraviolet radiation should be more investigated. Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage [71]. There are two common types of pain, acute pain and chronic pain. Basically, acute pain is crucial in alerting an individual to withdraw from a harmful situation while chronic pain could constitute of serious, separate disease entity. Formulations of capsaicin in the form of patches containing capsaicin in the range of 0.025–0.1% by weight are currently available in many countries around the world in drug stores out of the counter, without the requirement of a prescription, for the controlling neuropathic and musculoskeletal pain. Clinical studies involving 3–5 topical skin applications per day for periods of 2–6 weeks have been recommended for use against various pain syndromes, including osteoarthritis, postherpetic neuralgia, and painful diabetic neuropathy [72]. Accordingly, with the FDA and

European Medicines Agency (EMA) approvals of Qutenza®, a single-use high concentration topical capsaicin formulation for the management of peripheral neuropathic pain is approved on the basis of safety and effectiveness by FDA under sections 505 of the Federal Food, Drug, and Cosmetic Act in 2016 [73]. However, published articles from case studies revealed that a high dose of capsicum can cause tissue inflammation, which can trigger an inflammatory response such as anaphylactic shock defined as an allergic reaction to an antigen to which the body has become hypersensitive [74] and gastrointestinal tract irritation that occur when people overeat Chili peppers [74, 75]. Symptoms caused by ingesting too much capsaicin also include severe burning mouth sensation, mouth pain, itchiness, vomiting, nausea and diarrhea [76]. It could be concluded that customers of Chili pepper are at higher risk for gastric cancer, anticarcinogenic, and antimutagenic. Capsaicin in pepper fruits has dual effects. When consumed at minute amounts, capsaicin shows few or no poisonous effects, but substantial ingestion of capsaicin has been linked with necrosis, ulceration and carcinogenesis. This is why some scientists in 2011 [77] called the capsaicin molecule "two-faces-molecule" Capsaicin has elicited enormous interest for several centuries due to its conspicuous culinary and clinical applications. Despite its adverse effects, capsaicin is still being used as an active principle in several pharmaceutical formulations for treating various human ailments [78].

1.19. Pepper cultivation, pesticide application, and fruit storage

In Kentucky, peppers are grown primarily for the fresh market. Lying pepper fields close to creeks and rivers is subject to high humidity and moisture conditions that result in serious disease risks such as bacterial leaf-spot disease. Poorly drained soils and some herbicides such as atrazine that may have been used in previous seasons should be avoided. This is because herbicide carryover can cause serious injury to pepper plants. Soils high in N content should also be avoided to prevent pepper plants from producing excessive foliage at the expense of fruit production. Growers should also plow (rototill) the soil 8–10 inches (20.5–25.4 cm) deep several weeks in advance of the transplanting date. Seed should be treated with chlorine bleach by the grower to help reduce seed transmission of bacterial leaf spot. Two rows of peppers spaced 15 inches (38 cm) apart are planted on each bed; plants are spaced 12–15 inches (about 20–25 cm) apart within each row. The beds are usually 5–6 feet (1.5–1.8 m) from center to center (approximately 14,500 plants $acre^{-1}$) considering that 1 acre is equal to 0.405 hectare) using trickle irrigation and plastic mulch cover. Several pesticides are permitted for use in growing peppers for commercial crop production in Kentucky agriculture. The most common are the insecticide dimethoate 4E formulation that requires 48 re-entry hours following spraying to reach safe residue levels, the fungicide chlorothalonil that requires 12 re-entry hours after spraying, and the herbicide command 3ME [79]. After harvest, pepper fruits should be stored at 45–50°F in cooler as soon as possible, cool rooms with forced-air equipment will extend fruit shelf life. Once fruits are precooled, growers hold them at 45–50°F with 90–95% relative humidity. When pepper fruits are stored at temperatures below 40°F, chilling fruit injury symptoms appear. Chilling injury are browning at the calyx end and surface pitting. Fungal and bacterial diseases are common in pepper production, and most spraying programs target bacterial leaf spot, anthracnose, and *Phytophthora* blight. Mefenoxam (the active ingredient in the fungicide Ridomil Gold®) should be repeated 30–60 days after transplanting [79, 80].

1.20. Capsaicin toxicological data

In environmental toxicology, a general measure of acute toxicity of a chemical is its lethal dose (LD_{50}) or lethal concentration (LC_{50}) of that chemical that causes significant toxicity or death to 50% of that living organism resulted from a single or limited exposure of the treated animals. LD_{50} is generally expressed as the dose of a chemical in milligrams (mg) kilogram (kg) of body weight. Whereas, LC_{50} is often expressed as mg of chemical per volume e.g. liter (L) of air or water that the living organism is exposed to. Toxicological studies revealed that capsaicin acute oral LD_{50} values are in the range of 97.4 mg kg^{-1} and 118.8 mg kg^{-1} in female and male mice, respectively. LC_{50} values of capsaicin are in the range of 148.1 mg kg^{-1} and 161.2 mg kg^{-1} in female and male rats, respectively [81]. Male mice exposed to capsaicin in their stomach, revealed an average lethal dose (LD_{50}) of 68 mg kg^{-1} [82]. Exposure to capsaicin can cause several dose-dependent acute physical responses such as feeling of burning and pain, respiratory depression, and occasionally death [83]. Cytochrome P_{450} is a group of enzymes found mainly in the liver cells and also in other cells in the animal body. These enzymes are responsible for drug metabolism. Metabolism of capsaicin by cytochrome P_{450} decreased its toxicity to lung and liver cells. When the metabolism of two capsaicinoids, capsaicin and nonivamide (a capsaicin analogue) was investigated, the results demonstrated similar pathways in the cytochrome P_{450} dependent metabolism. Cytotoxicity was enhanced 5 and 40% for both compounds by 1-ABT in BEAS-2B (human lung epithelial cell line) and HepG2 (human liver cancer cell line), respectively [83]. These observed results proposed that metabolism of capsaicinoids by cytochrome P_{450} in cells denoted a detoxification mode of action. Generally, when the LD_{50}/LC_{50} ratio is small, the toxicity of a chemical is high and when this ratio is high, it indicates that a chemical might be practically slightly toxic or non-toxic. It is also important to mention here that LD_{50}/LC_{50} ratio could not be used to predict an organism long-term exposure to diseases, such as cancer [84].

2. Conclusion

Capsaicin, and its analogs, is an affordable inexpensive and effective therapeutic molecule present in fresh and dry fruits of *Capsicum* spp. The addition of this compound to human diet at minute amounts has the potential of curing several diseases. Natural capsaicinoids in hot peppers could be obtained by growing pepper in home gardens on small-scale and could be produced on large-scale (**Figure 7**) for industrial purposes. Some pepper fruit types were found to have high levels of antioxidants such as vitamin A, phenols, and vitamin C [50]. Information and correlation between pepper nutrient content, species, genotypes of the same species, cultivation practices, and geographic regions are limited. Selecting pepper genotypes for plant breeding programs provide a management tool to produce fruits with high levels of nutrient content. Incorporation of nutrient rich pepper genotypes that contain high levels on antioxidants into human diets could help combat nutrient deficiencies by providing the needs of recommended daily nutrients [45]. Capsaicin, the main pungent ingredient in 'hot' Chili peppers, causes a sensation of burning pain, mechanical or thermal stimuli by selectively activating sensory neurons in humans that transport information about harmful stimuli to

Figure 7. Preparation of hot pepper powder from *Capsicum* spp. for use of its unique bioactive therapeutic molecules as dietary medicine.

the central nervous system. When consuming peppers that contain capsaicin, capsaicin binds with the pain receptors in the mouth and throat releasing the pain sensation. In spite of all the out mentioned medicinal positive and negative properties of capsaicin, the efficacy of capsaicin in the treatment of chronic pain disorders is still indefinite. In topical capsaicin application, capsaicin employs its therapeutic action by the desensitization process and continued usage of topical capsaicin may lead to persistent desensitization [85]. According to the FDA Qutenza patch, a pure synthetic capsaicin-containing prescription drug, may cause a significant rise in blood pressure [86]. Capsaicin is associated with some severe side effects such as capsaicin-induced dermal pain and contact dermatitis [77]. In addition, there is a lack of information on the effectiveness of capsaicin on post herpetic neuralgia (PHN) that affects nerve fibers and skin, causing burning pain that lasts long after the rash and blisters of shingles disappear [85]. Capsaicin might be associated with an increased risk of cancer, especially gallbladder [70] and stomach cancer [87].

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Section 3

Emerging Technologies to Improve Capsicum Delivery

Chapter 3

Emerging Technologies to Improve Capsaicin Delivery and its Therapeutic Efficacy

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Additional information is available at the end of the chapter

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Abstract

Capsaicin, a pungent alkaloid of chili pepper (*Capsicum annuum*) is responsible for the "hot and spicy" taste of chili. Also, Capsaicin is a pharmaceutical agent with broad therapeutic applications in controlling different diseases like diabetes, obesity, cancer, pain, and other inflammatory diseases. Capsaicin therapeutic effect is dependent on various factors like the concentration of capsaicin, delivery to different cell types, route of administration, and their metabolism. Improvement in the delivery of capsaicin will increase its therapeutic efficacy. Recent advancement in various technologies had provided numerous strategies to deliver capsaicin. This chapter outlines different strategies for using multiple new materials, formulations for the capsaicin delivery and improve their therapeutic efficacy as well their advantages and disadvantages.

Keywords: capsaicin, drug delivery, micro and nanotechnology tools, pharmaceutical formulations

1. Introduction

Capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide), one of the active ingredient of chili peppers, possess pungent flavor, was first isolated in 1816 in partially purified crystalline form by Bucholz and in a pure crystalline form in 1876 by Thresh [1], who named it capsaicin. Nelson partially solved the structure of capsaicin in 1919 [2], and the compound has initially been synthesized in 1930 by Späth and Darling [3]. Capsaicin is one of the member of capsaicinoids family and other members of capsaicinoids are shown in **Figure 1**. Capsaicin biosynthesis in

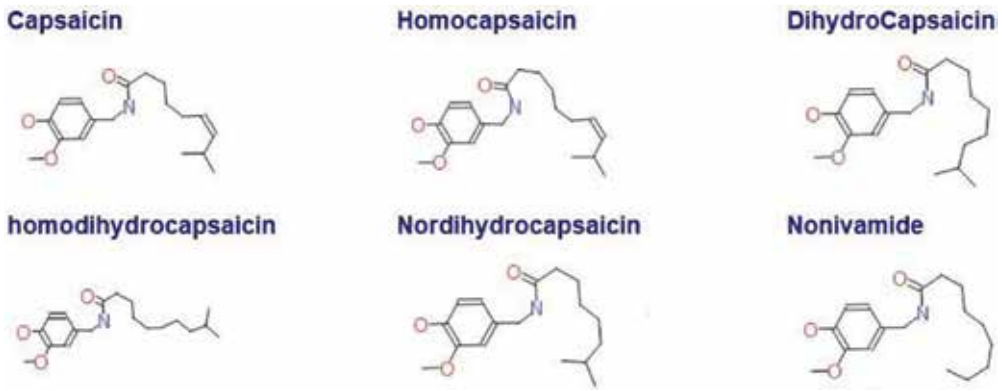

Figure 1. Three-dimensional structure representation of capsaicin and their derivatives present in chili pepper, were retrieved from PubChem database.

plants is defined by two pathways: phenylpropanoid, which determines phenolic structure; and fatty acid metabolism, which determines the molecule's fatty acids [3]. Capsaicin concentration increases gradually during fruit development reaching maximum levels at 40–50 days. Level of capsaicin increases by the increase in the activity of the enzymes phenylalanine ammonia-lyase (PAL), cinnamic acid-4-hydroxylase (C4H) and capsaicin synthase enzyme (CS), all involved in capsaicin biosynthesis [4]. Capsaicin is an odorless fat-soluble compound which is used to spice up cuisines, especially in Mexico and South America. Europeans introduced chili peppers to Asia and Africa, and they are now an essential ingredient of cuisines in Ethiopia, India, China, Sri Lanka, Thailand, Korea and Malaysia [5]. The Scoville heat units are used to measure the 'hotness' of chili peppers, which represents the number dilution required with water for it to lose its heat. Capsaicin scores about 16,000,000 units. The "heat

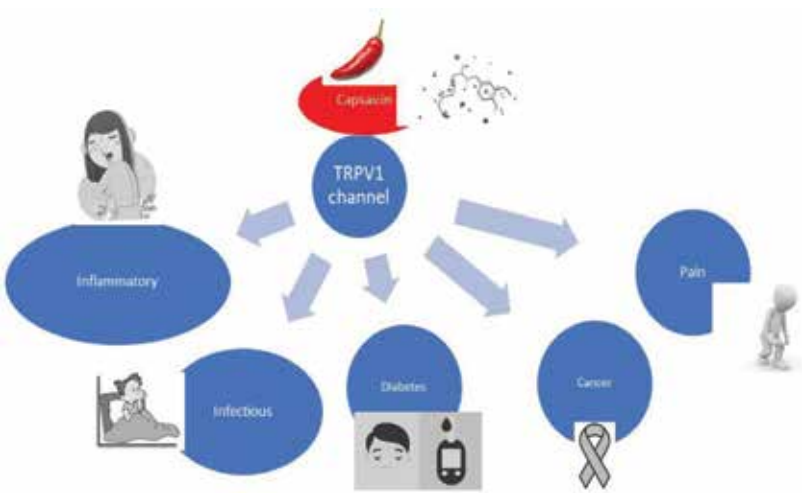

Figure 2. Pathological mechanisms involved when capsaicin modulates TRPV1 channel.

sensation" of capsaicin arises due to the binding of capsaicin to transient receptor potential vanilloid subfamily member 1 (TRPV1) ion-channel receptors. Capsaicin also is known as a modulator of TRPV1 [6]. A unique feature called as defunctionalization is responsible for capsaicin to use as therapeutic use. Capsaicin is proven to be beneficial in many physiological systems and can be used to treat diseases like pain, cancer, diabetes, obesity, infectious diseases, and inflammatory diseases (as shown in **Figure 2**). Many pharmacological and pain research studies have shown the multiple effects of capsaicin in a variety of physiological systems (cardiovascular, respiratory, and urinary) [7].

2. Mechanism of action

The device of action of capsaicin has been studied widely from the past decades. Nearly 20 years ago, it was demonstrated that capsaicin releases substance P from afferent nociceptive neurons. Capsaicin activates afferent nociceptive neurons and evokes sensations ranging from hotness to burning. The depletion of substance P mediates the analgesic properties of capsaicin that leads to the desensitization of small afferent sensory neurons [8]. Capsaicin binds to a specific nerve membrane receptor, the Transient Receptor Potential V1 receptor (previously known as vanilloid receptor, VR1 or TRPV1) encoded by gene TRPV1 gene. Capsaicin plays an essential role in the transmembrane signaling receptor. The TRPV1 receptors also respond to temperature, acidosis, painful stimuli, and osmolarity. TRPV1 has a central role in thermal nociception and inflammatory hyperalgesia [9]. The human and rodent TRPV1 receptor which consists of 838 amino acids (molecular weight of 95 kDa) was identified and cloned in rats in 1997 by Caterina [10]. The distribution of TRPV1 is there in other tissues such as the brain [11], bladder [12], kidney, and bowel [13]. Endovanilloids may regulate and activate the channels. TRPV1 is expressed not only on cellular membranes but also on

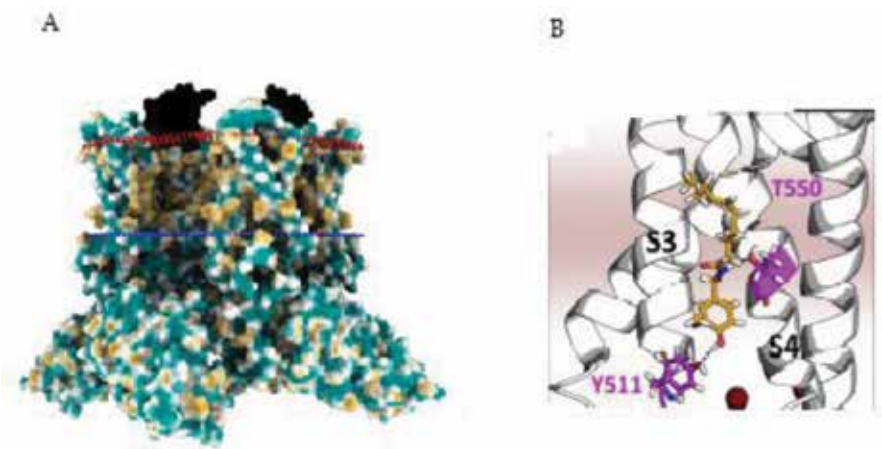

Figure 3. A represents the three dimensional structure of TRPV1 (adopted from PDB ID 3J5Q) and B represents TRPV1-capsaicin complex especially S3 and S4 domain interacting residues adopted from [17].

the endoplasmic reticulum [14]. Endoplasmic reticulum expression of regulates intracellular calcium levels, reverses the phosphorylation by involvement of kinases and phosphatases, role in formation of heteromers and regulate gene expression as well. Recently structural biology researchers, investigate the binding pose of capsaicin bound to TRPV1 channel, and it was resolved using cryo-EM. This study revealed that Capsaicin stabilizes TRPV1's open state by 'pull-and-contact' interactions between the vanillyl group and the S4-S5 linker. The interacting residues involved in capsaicin-TRPV1 channels are TYR 511, M547, and T550(as shown in **Figure 3**) [15]. Once, the agonists like capsaicin activate TRPV1 channels, many intracellular proteins containing Ankyrin repeats (AR) initiate signaling pathways, NFkB pathways, Apoptosis, degrade ubiquitin ligase, p38 -MAPK signaling pathway, controlling calcium ion concentration, regulating ATP metabolism, PIP2 hydrolysis, inhibiting CDk2, CDK4, and CDK6, and controlling cell cycle progression. Hence, Capsaicin-treated cells were proven to be anticancer, antidiabetic, and anti-inflammatory [16].

3. Metabolism of capsaicin

Metabolism of capsaicin is very rapid in the human stratum corneum, and it is dependent on the solubility of capsaicin in non-polar viscous solvents [18]. Oral administration of capsaicin is rapidly metabolized in liver, kidney, intestine, and in blood peak concentration is observed in 1 h [19]. In human studies, oral administration of 5 g of capsaicin and capsaicinoids to healthy volunteers had resulted in significant reduction in plasma glucose levels and also, increase in plasma insulin levels (Observed pharmacokinetics in this study are C(max), T(max), AUC(0-t), T1/2 are 2.47 ± 0.13 ng/ml, 47.08 ± 1.99 min, 103.6 ± 11.3 ng × min/ml, and 24.87 ± 4.97 min, respectively.) [20]. Topical administration of capsaicin [(640 μg/cm^2) like capsaicin patch, also called as NGX-4010] to different diseased patients, had resulted in quantifiable amounts of capsaicin. The amount of capsaicin detected in plasma is 31% for postherpetic neuralgia (PHN), 7% for painful human immunodeficiency virus-associated neuropathy (HIV-AN), and 3% for painful diabetic neuropathy (PDN) [21]. Intravenous administration of capsaicin leads to the rapid entry of capsaicin in the central nervous system, and their metabolism is low when compared to liver and kidney [22]. Bioavailability and half-life of capsaicin are low and is independent of the route of administration. This leads to investigate in the areas to design and develop new strategies to improve drug-delivery of capsaicin, to enhance their bioavailability and half-life.

4. General strategies for capsaicin delivery and their clinical challenges

To date, capsaicin formulations on the market include Capzasin-HP (Topical Analgesic Cream), Qutenza patches, LEADER CAPSAICIN (cream). The current administration of commercial capsaicin comprises topical delivery. Challenges in the clinical application of capsaicin are its short half-life, low bioavailability, produces burning sensation and side effects are dependent

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on the concentration of capsaicin, skin irritation, burning and others. Alternative approaches have been extensively explored, to improve the delivery of capsaicin, including oral, gastrointestinal, intraperitoneal, subcutaneous, topical, and ocular. Emerging micro and nanotechnologies have attracted and lead to a general idea to encapsulate capsaicin to various carriers like lipid-based carriers (liposomes, microemulsion, solid-lipid nanoparticle), polymeric carriers (micelle, dendrimer, and polymersome), Inorganic carriers (metal nanoparticles, carbon spheres). The primary objective of chosen carriers is: (1) improve bioavailability; (2) enhance delivery to different cell types; (3) improve pharmacokinetics; (4) improve half-life of capsaicin.

5. Micro and nanotechnology tools to deliver capsaicin

Topical administration is the only method used in clinical use and as well to deliver capsaicin for pain treatment. Certain drawbacks observed by patients are, the short half-life of capsaicin, bioavailability is low, burning sensation of capsaicin had resulted in patient discomfort. In this study, we report different strategies proven to be successful at research level to improve the bioavailability, increase the half-life, reduce irritation, different routes of administration, use of micro and nanotechnology tools to improve the drug delivery and overcome the drawbacks of capsaicin treatment. Micro and nanotechnology tools were classified into three categories: lipid-based carriers, polymeric carriers, and inorganic nanocarriers.

5.1. Lipid based carriers

Liposome, microemulsions and solid lipid nanoparticles are chosen to be considered in the category of lipid-based carriers (as shown in **Figure 4**). Briefly, Liposomes (20 nm to several microns) can be used to encapsulate hydrophilic and hydrophobic compounds. Lipid constituent, surface charge, the physical state of the phospholipid bilayer plays a vital role in the enhancement of therapeutic efficacy of encapsulated pharmaceutical ingredients [23]. General methods used to encapsulate capsaicin are thin film hydration method, modified film method, film dispersion method [24]. Distinct advantages of using liposomes are high entrapment efficiency, non-toxic, biodegradable, active ingredients encapsulated in liposomes are protected

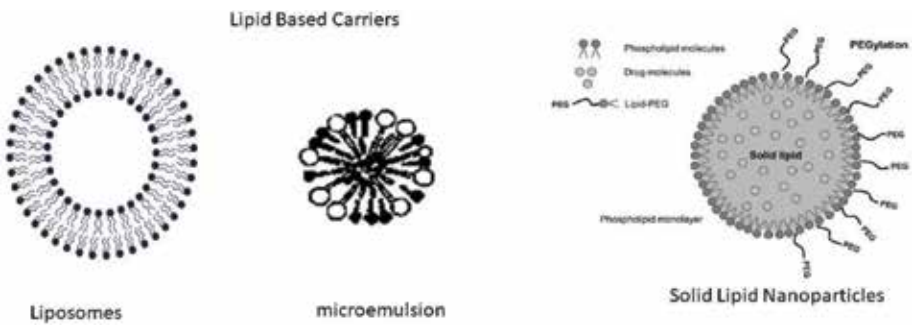

Figure 4. Lipid based carrier classification.

from immediate dilution or degradation. A microemulsion is defined as a system of water, oil, and amphiphile which is single optically isotropic and thermodynamically stable liquid solution [25]. Solid lipid nanoparticles are a new generation of colloidal drug carrier systems and consist of surfactant-stabilized lipids that are solid both at room and body temperatures [26].

5.1.1. Examples

Oral administration of Capsaicin Liposomes of mean size 52.2 ± 1.3 nm, had resulted in the encapsulation of Capsaicin with encapsulation efficiency 81.9 ± 2.43%, resulting in a 3.34-fold increase in bioavailability, as well the formulation reduces inflammation in gastric mucosa model [27]. Cather administration of phosphatidylcholine (PC) liposomes of the mean size smaller than 100 nm, were proven to benefit bladder irritation [28]. Oral administration of microemulsion consisting of Cremophor EL, ethanol, medium-chain triglycerides (oil phase) and water (external phase) of mean size 53.5 ± 1.6 nm with encapsulation efficiency 85.3 ± 1.1%, had resulted in the 2.64-fold increase in bioavailability, safe and effective [29]. Transdermal delivery of capsaicin, encapsulated in microemulsions based on non-ionic surfactants consisting of isopropyl myristate as the oil phase, Comperlan® KD as the surfactant, ethanol as cosurfactant, and reverse osmosis water as aqueous phase resulted in use of low dose capsaicin [0.15% (w/w)] as effective delivery when compared to current clinical products [30]. Solid lipid nanoparticles were used to encapsulate capsaicin with mean size 100 nm, prolonged release of the drug is observed for a duration of 14 h, encapsulation efficiency found to be 90%, and further studies are needed to understand PK and PD studies [31].

5.2. Polymeric carriers

Micelles and dendrimers are chosen under the category of polymeric carriers (as shown in **Figure 5**).Briefly, micelles are defined as nanoscopic core/shell structures formed by amphiphilic copolymers. These have a high potential to deliver compounds that are hydrophobic

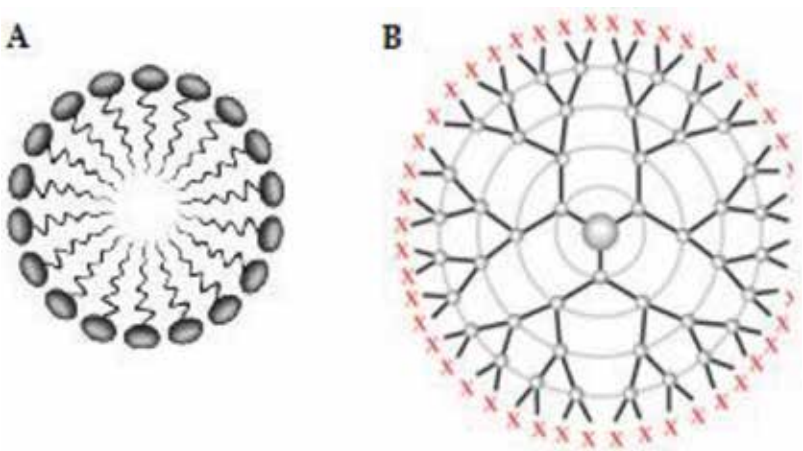

Figure 5. A represents micelle and B represents dendrimer.

and exhibit bioavailability. Dialysis method (organic-solvent free method) and solvent-switch method (direct dissolution method) are used for self-assembly of AB or ABA polymers into micelles in solutions. These are used primarily to incorporate water-soluble drugs. Direct dissolution and dialysis methods are used to synthesize polymeric micelles.

5.2.1. Examples

Oral administration of capsaicin with polyvinylpyrrolidone (PVP)/sodium cholate/phospholipid mixed micellar system was synthesized with mean size below 50 nm, with the 2.42-fold increase in bioavailability, as well reduced irritation on gastric mucosa [32]. Oral delivery of capsaicin using methoxy poly(ethylene glycol)-poly(ε-caprolactone) (called as MPEG-PCl) nanoparticles of mean size 82.54 ± 0.51 nm, acquired sustained release for 60 h. Pharmacokinetics revealed 6-fold increase and reduced gastric mucosa irritation is observed [33].

5.3. Polymeric dendrimers

Dendrimers consists of tree-like branches with many functional terminals ends also considered as monodisperse macromolecules. These are prepared using convergent or diverge methods and growth is dependent on cascade regions.

5.3.1. Examples

The oleoyl chloride, Polyethylene glycol (PEG) 400, and triethylamine were used to synthesize dendrimers using esterification process and bound with capsaicin. The resulting formulation possesses mean size 143.1 nm and resulting formulation was found to be cytotoxic to MCF-7 cells and Hep2 cells [34]and not toxic in case of zebrafish model [35].

5.4. Inorganic nanocarriers (metal nanoparticles, carbon spheres)

Inorganic nanocarriers are classified as metal nanoparticles and carbon spheres. Physical and chemical methods can be used to prepare metal nanoparticles, and they can exhibit multifunctional properties, size-dependent metal to non-transition. Functionalized with groups like thiols are responsible for bioconjugate chemistry application, fluorescent particles [36]. Till date, few applications support the use of inorganic nanocarriers. Use of copper sulfide (CuS) nanoparticles, when functionalized with antibodies targeting TRPV1, the complex acted as a photothermal switch, and results were found to be significant and can be used in future as a therapeutic tool, to attenuate atherosclerosis [37]. Another application revealed that capsaicin as bioreductant of silver nitrate to form silver nanoparticles and the resulting capsaicin-capped silver nanoparticles (mean size 20–30 nm) were found to be compatible with blood groups, and no further studies on this nanomaterial complex [38]. High sensitivity assay was developed when glass carbon electrodes are coated with carbon nanotubes, resulted in excellent detection of capsaicin in various pepper samples [39]. Based on the literature, it is evident that use of metal nanoparticles and carbon nanotubes to improve the bioavailability, increase the half-life and improve pharmacokinetic (PK) and Pharmacodynamic (PD) of capsaicin, is the new area to be explored to enhance the efficacy of capsaicin therapeutic.

6. Conclusion

Strategies to use micro-nanotechnology tools to deliver capsaicin have exhibited tremendous therapeutic potency for treating pain, cancer and other diseases at a research level. More studies are required at the basic and clinical stage to demonstrate their efficacy. The tools described in this study can also be used to deliver capsaicin through different routes of administration. Of course, potential challenges like delivery of the exact dose, maintain physicochemical properties of materials and capsaicin, the biodegradability of materials used to encapsulate capsaicin.

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Conflict of interest

The authors declare no conflict of interest.

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Section 4

Capsaicinoid Deversibility and its Human Food Preference

Chapter 4

A Matter of Taste: Capsaicinoid Diversity in Chile Peppers and the Importance to Human Food Preference

Ivette Guzmán and Paul W. Bosland

Additional information is available at the end of the chapter

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Abstract

Chile peppers are valued worldwide for their distinct capsaicinoid compounds that have been used traditionally in medicine and culinary practices. With 32 known species, five of them domesticated, they provide unique chemical profiles, when consumed by humans. Capsaicinoids, the spicy compounds, are alkaloids used to deter herbivory in the wild, offering protection to the chile pepper fruit seeds. Among the 22 known capsaicinoid structures, capsaicin and dihydrocapsaicin are normally the most abundant. In humans, capsaicin binds to nociceptor TRPV1 that generates a heat sensation. Capsaicin also mitigates inflammation responses in the digestive tract and has the potential to aid in nutrient absorption. Distinct heat profiles were recently described for the five domesticated *Capsicum* species showing a difference in heat sensations specific to species and pod type. Due to the many capsaicinoid structures, we explore the implications and opportunities of having a diverse array of heat profiles in genetically diverse *Capsicum* species.

Keywords: TRPV1 receptors, pain, heat sensitization, desensitization, capsaicinoid, *Capsicum*, capsaicin, inflammation, peppers, chile peppers

1. Introduction

Chile peppers (*Capsicum* sp.) are one of the most important vegetable and spice crops in the world. *Capsicum* species are members of the Solanaceae, a large tropical family that includes tomato, potato, tobacco, and petunia. They are not related to *Piper nigrum*, the source of black pepper, nor is it related to the Guinea pepper or grains of paradise, *Aframomum melegueta*. They are one of the first crops domesticated in the Western Hemisphere about 10,000 B.C.E. [1]. In

fact, the genus *Capsicum* was so important to humans that when they came in contact with it, five different *Capsicum* species in separate regions of the Americas were independently domesticated. One possible reason for such an early domestication is that chile peppers are well known as medicinal plants by indigenous peoples [2].

Capsicum originated in South America in an area near Bolivia and southeast Brazil. *Capsicum* then spread to North and Central America by bird dispersal. Currently, there are 32 known species with five domesticated species being *Capsicum annuum var. annuum*, *C. baccatum* var. *pendulum*, *C. chinense*, *C. frutescens*, and *C. pubescens* (**Figure 1**) [3]. There are an estimated 3000 different chile pepper types worldwide [4]. Many of these varieties are selected by cultures for their specific heat profile [5–7]. In their native habitats, *Capsicum* grows as tender perennials. In many parts of the world, however, they are grown as annuals. Being members of the Solanaceae family, they share morphology similar to that of tomatoes. However, there are significant differences between the two crops. Domesticated chile peppers have shiny glabrous simple leaves, and in general are more compact and erect than tomato. Cultivars vary from the "normal" description, so intraspecific as well as interspecific variation must be taken into account. Since domestication, many mutants have been saved by humans, for example, yellow or orange mature fruit color, unusual fruit shapes, and the mutation that causes fruit to not taste hot when consumed.

There is extensive diversity in fruit shapes, sizes and color. Among different pod types fruit length can vary from less than 1 cm to 32.5 cm., the Guinness Record for the world's largest *Capsicum* fruit [8]. Fruit growth is dependent on ovule growth, whether it is fertilized or not. The fruit is usually seeded, but seedless, parthenocarpic forms do exist. Seed number affects the fruit's growth rate rather than its growing period. When seed number increases in a fruit there

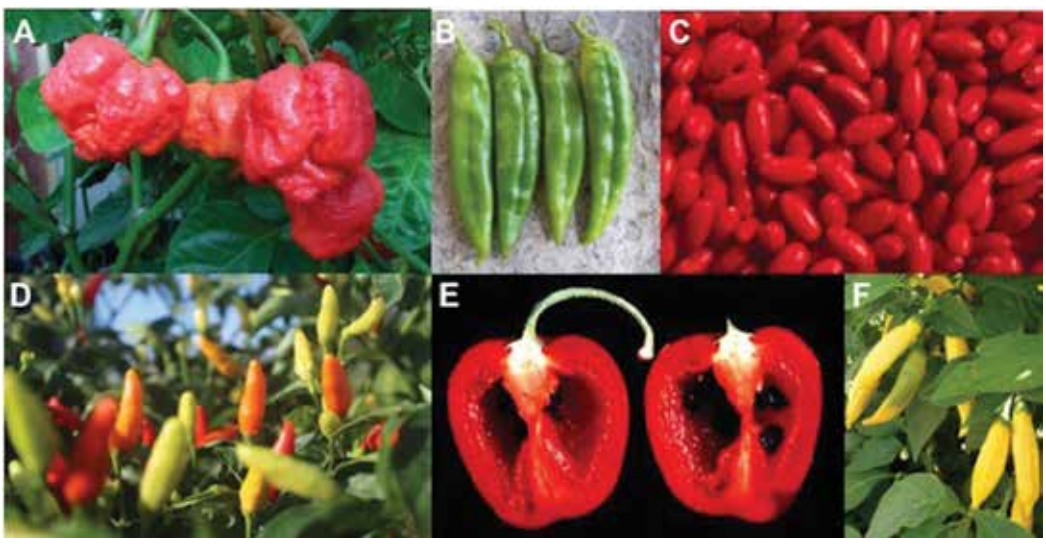

Figure 1. Selected varieties for (A) *Capsicum chinense* 'Trinidad Moruga Scorpion', (B) *Capsicum annuum* 'NuMex Heritage Big Jim', (C) *Capsicum chacoense* (wild), (D) *Capsicum frutescens* 'Tabasco', (E) *Capsicum pubescens* 'Rocoto', and (F) *Capsicum baccatum var. pendulum* 'Aji Limon'.

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is an inhibitory effect on fruit set and growth of later-developing fruits [8]. The pod may have two or more locules each divided by a central placenta. The placenta is the location of oleoresin and capsaicinoid production and storage vesicles. Recently, a mutation was discovered that allows the 'walls' or pericarp of the pod to produce vesicles increasing the heat level [9].

It is the capsaicinoids, alkaloids, that cause the heat sensation when consumed by mammals, that distinguishes this genus in the Solanaceae family. The primary function of capsaicinoids is to discourage mammalian feeding of the spicy chile pepper fruit, which results in destroying the seeds, while remaining attractive to birds who disperse the seeds [10]. Most Solanaceous plants have sufficiently high levels of alkaloids in their leaves that are known to be toxic to many mammals. Oddly, chile peppers do not contain alkaloids in their leaves. In fact, in the Philippines, chile pepper leaves are eaten as a leafy vegetable. Without these alkaloids, chile peppers evolved another strategy for partial protection by deterring the wrong herbivores and attracting to the desired ones, the capsaicinoids. Capsaicinoids are not toxic per se, but are ferocious enough to discourage mammalian herbivory. Birds, on the other hand, are attracted to the small red fruit on wild plants and have digestive tracts that chemically and physically soften the seed coats without damaging the seeds, thus encouraging germination. In fact, some seeds will suffer retarded germination if they do not pass through a bird's digestion system. It is suggested that capsaicinoids are the cause of slow germination of *Capsicum* seed [11]. Because birds lack the receptors in their mouth for detecting capsaicinoids, they do not taste any heat when eating very hot chile peppers. Wild chiltepins are so strongly associated with birds that a common name for them is bird pepper. Recently, it has been shown that the capsaicinoids also protect the seeds from microbial infections [12].

Capsaicinoids are used in food, and are equally important in pharmaceutical applications, as a repellent in self-defense sprays, as a rodent repellent, as an anti-inflammatory agent, as a pain reliever, and as an antimicrobial agent [2, 10, 13–21].

2. Capsaicinoid biogenesis

2.1. Capsaicinoid chemistry

Capsaicinoids consist of compounds that belong to the vanilloid group and differ in the structure of branched fatty acid (acyl) moieties attached to the benzene ring of vanillylamine [18]. The chemical structures contain three important regions; an aromatic head, an amide linkage, and a hydrophobic tail. Any variation in the chemical structure of the capsaicinoids, mainly the structure of the fatty acid chain, affects the heat profile and their pharmacological activities (**Figure 2**). Studies indicate that the aromatic head and the amide structures provide the excitation of sensory neurons while the hydrophobic tail is responsible for maximal potency [22, 23]. Currently, a total of 22 distinct capsaicinoids are found occurring naturally, each with a different hydrophobic fatty acid tail. Capsaicin (8-methyl-N-vanillyl-trans-6-nonenamide) and dihydrocapsaicin (*N*-(4-hydroxy-3-methoxybenzyl)-8-methylnonanamide) are considered the two major capsaicinoids found in chile peppers, whereas the others, e.g., nordihydrocapsaicin, homodihydrocapsaicin, homocapsaicin, etc., are considered minor capsaicinoids.

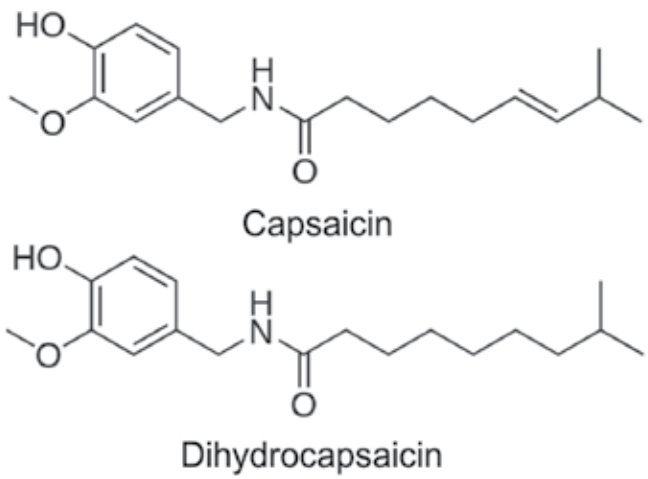

Figure 2. Chemical structures of capsaicin and dihydrocapsaicin illustrating the difference in fatty acid moiety.

Due to the slight variations in structure, each capsaicinoid creates a different heat sensation effect in the mouth [5, 24]. The variability of amount and type of capsaicinoids within *Capsicum* is enormous. For example, the wild species *C. chacoense* does not contain nordihydrocapsaicin, while other species such as *C. pubescens* can have only small amounts of capsaicin, but large amounts of the "minor" capsaicinoid, isomer of dihydrocapsaicin (**Figures 1** and **2**). The diversity of capsaicinoids has created a cultural context to eating chile peppers.

Normally in food and processing industries, the level of total capsaicinoids is converted to Scoville Heat Units (SHU), a measurement for heat level developed by Wilbur Scoville [25]. Scoville Heat Units are based on a dilution formula with the approximate number of times a standardized chile pepper extract is diluted to be imperceptible to a set of trained tasters. A modern method of calculation is to use analytical instrumentation that produces part per million (ppm) readings, followed by conversion of the ppm amounts to SHU by multiplying the ppm by 16 [26]. The hottest chile pepper cultivar, as determined by the Chile Pepper Institute is the 'Trinidad Moruga Scorpion', that has been documented to have fruits surpassing two million SHU (**Figure 1**) [27].

2.2. Capsaicinoid location in chile pepper fruits

For most *Capsicum* fruits, capsaicinoids are synthesized and accumulated in the epidermal cells of the fruit placenta within structures know as vesicles, also called "blisters." Seeds do not produce capsaicinoids but can be tainted with the capsaicinoids from the surrounding tissue containing the vesicles. Capsaicinoids are always associated with the oil producing vesicles. Even though, most chile pepper fruits are hot, there are numerous varieties that produce no heat fruit [28–30]. The *Pun1* locus, formerly known as the *C* locus, found on chromosome 2 encodes a putative acyltransferase that theoretically condenses the fatty acid (acyl) moieties to the vanillylamine benzene ring. Chile pepper varieties with heat have a functional allele, while the no heat varieties have a non-functional allele. A novel mechanism for having no heat chile pepper fruits is to lose the ability to make the vesicle structures. This locus is

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known as the loss-of-vesicle (lov) gene [8]. With this mutation, the plant has a functional *Pun-1* gene, but cannot express capsaicinoids because of the lack of vesicles.

The level of heat, i.e., capsaicinoid production, is genetic with a high genotype by environment interaction component. The environment can increase or decrease significantly the heat level of a given cultivar [31–36]. The capsaicinoid content can be affected by weather conditions, growing conditions and fruit age. Plant breeders selectively develop cultivars within certain ranges of heat, e.g., mild, medium, hot, superhot. Because heat level is augmented with increased environmental stress, growers can moderate heat level by the amount of stress to which they subject their plants [31, 32]. A few hot days can increase the capsaicinoid content significantly. Anthropopathically, the plant has sensed the stress, and has increased the capsaicinoid level in its fruit. If the same cultivar is grown in both a hot semi-arid region and a cool coastal region, the fruit harvested from the hot semi-arid region will be higher in capsaicinoid amounts than that the fruits harvested in the cool coastal climate. Capsaicinoids start to accumulate when fruits begin to ripen and reach their highest content when fruits reach their maximum size. Variation in capsaicinoid content has been observed in wild *Capsicum* accessions. Even *Capsicum* plants with no capsaicinoid production have been documented in the wild [12, 37].

Though Bennett and Kirby considered capsaicin and dihydrocapsaicin as the major capsaicinoids, this generalization is not true for all chile pepper varieties [38]. Collins et al. reported a capsaicinoid profile in *C. pubescens* accessions, where dihydrocapsaicin is the largest proportion, i.e., 35% dihydrocapsaicin, 29% capsaicin, 21% nordihydrocapsaicin, 8% unidentified capsaicinoid, 4% isomer of dihydrocapsaicin, 2% unidentified capsaicinoid and 1% homodihydrocapsaicin [26]. Zewdie et al. reported an unusual capsaicinoid profile in two *C. pubescens* accessions, where the isomer of dihydrocapsaicin is the largest proportion, i.e., 39% isomer of dihydrocapsaicin, 17% homodihydrocapsaicin, 13% capsaicin, 13% dihydrocapsaicin, 13% nordihydrocapsaicin, and 5% nornordihydrocapsaicin [39]. Other anomalies were found where a *C. chacoense* accession had 30% nordihydrocapsaicin, and a *C. pubescens* accession had 42% isomer of dihydrocapsaicin and 23% homodihydrocapsaicin [39].

It has been shown organoleptically that humans not only note the intensity of hotness, but perceive each capsaicinoid differently [5, 24]. The investigations of Krajewska and Powers revealed that nordihydrocapsaicin was the least irritating, and the burning was located in the front of the mouth and palate. It caused a "mellow warming effect" [24]. The heat sensation developed immediately after swallowing and receded rapidly. In comparison, capsaicin and dihydrocapsaicin were more irritating, and were described as having a "typical" heat sensation. Both compounds produced the heat in the mid-mouth and mid-palate as well as the throat and the back of the tongue. In contrast, homodihydrocapsaicin was very irritating, harsh and very shape. The heat did not develop immediately and it affected the throat, back of the tongue, and the palate for a prolonged period. After ingestion, the heat sensation can last up to 12 hours in some individuals. Different combinations of these capsaicinoids produce the chile pepper heat profile [5]. Capsaicinoids are valuable pharmacological compounds that have been studied for pain relief, weight management, cholesterol management, anti-inflammation, anti-cancer, and anti-oxidant activity.

Because of the natural variation of capsaicinoid content occurring in chile peppers, it is necessary to find their bioactivity differences in the digestive tract and afferent sensory neurons.

3. Capsaicinoid pharmacology

3.1. Capsaicinoids role in pain

Due to the prevalence of capsaicin in *Capsicum* species, most capsaicinoid pharmacological studies have focused on capsaicin. Capsaicin is used orally or as intradermal and topical applications to treat pain. Sensations of stimuli like temperature, touch, pain, taste, originate in transient receptor potential (TRP) ion channels found on afferent neurons. There are six TRP heat dependent channel families; one of which is the vanilloid type (TRPV), a group of nociceptors [40]. Capsaicin acts by binding to the TRPV1 receptor located on nociceptor neurons resulting in an influx of cytosolic calcium ions [41, 42]. This activation of TRPV1 receptors by capsaicin or temperatures above 52°C induces "hot" pain-like sensations. Other TRP receptors are sensitive to lower temperatures as well as other compounds, i.e., menthol, isothiocyanates [40, 43].

In 1968, Jancso was the first to discover that repeated doses of capsaicin induced pain initially followed by analgesia [44]. This was noticed in response to thermal, mechanical, and chemical noxious stimuli. Inhibition of the receptor function is called desensitization. Topical application of 8% capsaicin produces desensitization by decreasing pain for 12 weeks [42, 45]. Pain relieving effects of an 8% capsaicin patch lasting up to 18 months have been shown in post-traumatic patients suffering with neuropathic pain [46]. In addition, oral capsaicin has been used to treat cough because inflammation of the airways can be caused by noxious stimuli on nociceptors [47].

Even though capsaicinoids have been used for thousands of years as a medicinal compound and scientific work has proven the efficacy as a pain attenuator, the problematic issue is estimating the correct dosage for the desired response. One method to moderate response is to use different known amounts of capsaicin. For example, topical creams, lotions and patches available on the market, some even over the counter, contain different concentrations of predominantly capsaicin (0.025–0.1% wt/wt) [42]. Another method would be to use a mixture of capsaicinoids to induce a desired effect. Structural studies indicate that the aromatic benzene ring hydrogen bonds to the TRPV1 domains while the fatty acid tail uses van der Waals interactions to bind [48]. This parallels the fact that the capsaicinoid aromatic head provides the excitation of sensory neurons while the hydrophobic tail is responsible for maximal potency. Therefore, we can expect to see differences in overall effects from one capsaicinoid to another. Considering that the 22 capsaicinoids have the aromatic benzene ring in common but differ in the fatty acid tails, the possibility of each one exerting a slightly different response from the TRPV1 is possible. As mentioned previously, capsaicinoid profiles are unique in each chile pepper type and species and the unique profiles exert unique heat sensations from short lasting to long lasting [5]. Not only can different concentrations of capsaicin provide desensitization, but the other capsaicinoids could also provide varying levels pain relief.

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3.2. Capsaicinoids, inflammation and the digestive tract

There is more than one mode of action for the capsaicin induced anti-inflammation response. One is by binding to TRPV1, and the other is by regulating pro-inflammatory cytokine production pathways in neurons. By targeting capsaicin-triggered TRPV1 receptors, a select group of compounds have been shown to reduce inflammatory pain. These compounds are flavonoids like naringenin, vitexin, hesperidin methyl chalcone [42, 49]. In the stomach, binding of capsaicin to TRPV1 produces increased mucosal blood flow, mucus secretion and bicarbonate secretion [40, 50]. Employing a capsaicin blocker (capsazepine) on TRPV1, evidence confirmed that there was an increase in blood flow, hyperemia, generated by capsaicin binding to TRPV1 [50, 51]. Just like the topical applications of capsaicin, capsaicin desensitization is used with patients suffering from stomach pain associated with gastric acid, irritable bowel syndrome or irritable bladder [40, 52–54]. However, there could be a different response in the small intestine, pancreas and colon because their environments and digestive roles are different than the stomach's environment.

In the mouth, salivary gland epithelial cells (SGEC) release cytokines, such as TNFα and IL-6, both of which are associated with inflammation of salivary glands [55]. If the inflammation response is triggered too often by the cytokines, the result could lead to cancer. The same phenomena exist in the gastrointestinal tract. Striking evidence shows that capsaicin's inflammation inhibitory action in SGEC is through inhibition of the IkB-α/NF-kB signaling pathway and not TRPV1 [55]. The transcription factor NF-kB regulates the expression of cytokines TNFα and IL-6, two pro-inflammatory signals [56, 57]. Therefore, capsaicin inactivates the transcription factor associated with a pro-inflammatory response [58]. Due to the elevated risk of developing cancers from chronic inflammation, the capsaicin NF-kB interaction has been studied to suppress inflammation associated with cholangiocarcinoma, bile duct cancer, making capsaicin a potential anti-tumor compound [58, 59].

Capsaicin is also able to reduce production of inflammatory cytokines produced as a response to bacterial lipopolysaccharide (LPS) infection in human microphages [17]. After bacterial infection, LPS serves as stimuli promoting NF-kB induced pro-inflammatory cytokine production [60]. This effect is interrupted by capsaicin signaling the expressing Liver X Receptor (LXRα) that inhibits NF-kB, therefore inhibiting inflammatory cytokine production. Capsaicin's anti-inflammatory response in the gastric epithelial cells extends to inhibiting *Helicobacter pylori* bacteria cytokine production in the gut, thus reducing inflammation generated from *H. pylori* infections, a common cause of ulcers [61]. It was previously thought that spicy food caused ulcers, however, these results prove the opposite and could potentially help patients suffering from *H. pylori*-induced ulcers. The novel role of capsaicin opens up opportunities to study the influence of other capsaicinoids in the inhibition of cytokine induced inflammation.

Not only does chronic digestive tract inflammation increase the risk of cancer, but it is correlated to decreased gut nutrient absorption. A group of chronic diseases are commonly referred to as inflammatory bowel disease (IBD). Causes are sometimes unknown or could be brought on by pathogenic bacteria. All of these diseases however trigger certain factors that give rise to chronic inflammation [62]. Inflammation causes poor absorption of nutrients by altering the structure, physiology, bile amounts and microbiota of the digestive tract [63].

Patients with an IBD are deficient in minerals and vitamins like folic acid, zinc, iron, selenium, and fat-soluble vitamins like beta-carotene (pro-vitamin A) due to malabsorption [63].

Additionally, studies show that capsaicin alters the structure of the intestines promoting absorption. Small intestine segments isolated from rats who were fed with capsaicin for 8 weeks were able to absorb higher amounts of iron, zinc and calcium [64]. Veda and Srinivasan also reported an *in vivo* study where higher amounts of beta-carotene were absorbed by rats being fed beta-carotene and capsaicin [65]. With the recent work correlating capsaicin to decreased inflammatory signals and increased nutrient absorption, further work is needed to observe improved nutrient absorption with an intake of more capsaicinoids.

3.3. Capsaicinoids and absorption of chile pepper carotenoids

Due to the impact capsaicinoids, particularly capsaicin, have on nutrient absorption in the gut, other chile pepper compounds ingested simultaneously are more bioaccessible for absorption. As mentioned, beta-carotene consumed with capsaicin increased the beta-carotene amounts in rats [65]. Besides capsaicinoids, *Capsicum* species are a rich source of anthocyanins, organic acids, phenolic acids, carotenoids, tocopherols, and ascorbic acid [66]. In particular, chile peppers produce a large number of carotenoids, some of which are unique to *Capsicum* species like capsanthin and capsorubin [18]. A number of conditions and diseases (i.e., poor cardiovascular health, macular degeneration, Alzheimer's disease and dementia) may be linked to effects of malnutrition and low consumption of carotenoids like lutein and zeaxanthin [67–70]. Both lutein and zeaxanthin act as antioxidants and anti-inflammatory agents by reducing oxidative stress [71]. Macular degeneration, an age-related eye disease, is clearly associated with insufficient dietary lutein and zeaxanthin [72, 73]. Additionally, recent work found higher human serum levels of these two carotenoids in older populations showing no symptoms of Alzheimer's while lower amounts were found in a population exhibiting dementia and Alzheimer's symptoms [67, 74]. By the year 2050, there will be 106 million cases of Alzheimer's disease and dementia in the US [68]. Access to foods rich in health promoting carotenoids, such as lutein and zeaxanthin, that are bioavailable are key to prevention of age-related chronic diseases [67–70].

Chile peppers, *Capsicum* spp., are among one of the few fruits and vegetables, that produce both lutein and zeaxanthin [75, 76]. They may contain amounts up to 10.76 mg/g dry weight of total carotenoids. Two classes exist, the carotenes and the xanthophylls [18]. Carotenes include nutritionally important carotenoids like alpha-carotene and beta-carotene, all of which are provitamin A. In the mammalian stomach, carotenes are converted to vitamin A [77]. Xanthophylls such as lutein and zeaxanthin, are among the few plant compounds that are known to be absorbed by the human digestive tract [78]. They can also be passed on from the mother's diet to her breast milk and subsequently to the infant's digestive tract and blood stream [78]. Once they enter the blood stream, they reach the human retina where they make up the macular pigment [72]. Lutein and zeaxanthin are found throughout the eye tissues but are in high concentrations near the retina. Our eyes are constantly exposed to light, therefore, lutein and zeaxanthin act as a shield by filtering the sun's blue light, the most harmful wavelength responsible for creating dangerous oxidative compounds that damage our DNA, proteins and cell membranes [67, 72, 79].

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Currently, there is no recommended daily allowance (RDA) for lutein, however 6–10 mg/day have been reported to decrease macular degeneration risks [80]. Normally, a typical diet will include about 1–3 mg/day of lutein. As a result of capsaicinoids' anti-inflammation properties, beta-carotene absorption has already been shown to increase when eaten with capsaicin [65]. If a typical diet includes *Capsicum* species high in capsaicin, humans could absorb more carotenes and xanthophylls already present in chile peppers.

4. Conclusions

When reviewing capsaicinoid nutritional and medicinal properties, it is clear why over so many years, people have been saving chile pepper seeds and using them in traditional medicines and culinary practices. As we have shown, their properties go beyond adding heat and flavor to a culinary dish. Capsaicinoids have pharmacological activities that help the human body reduce pain. It also serves as an anti-inflammatory agent which not only aids in pain reduction, but also has the potential to be used to promote absorption of other essential nutrients like beta-carotene, lutein and zeaxanthin. The diversity of *Capsicum* species, each with their own diverse capsaicinoid profile, increases their versatility in pharmacology.

These approaches to reducing pain and inflammation using capsaicin and knowing that there are 21 other capsaicinoids that have yet to be characterized pharmacologically, offers new opportunities to explore *Capsicum* species diversity. Because most of the research has been done with capsaicin, and initial capsaicin treatments result in pain and burning sensations, researchers could attempt to circumvent the initial capsaicin burn by using other "not so spicy" capsaicinoids. In view of the fact that studies indicate that the capsaicinoid aromatic head provides the excitation of sensory neurons while the hydrophobic tail is responsible for maximal potency, one can expect to see differences in overall effects from one capsaicinoid to another. However, more work is needed to show the specific bioactivity of the remaining 21 capsaicinoids found in diverse *Capsicum* species and their physiological effects on cytokine pro-inflammatory mechanisms and TRPV1 induction. Each capsaicinoid could have different chemical binding properties to receptors and therefore, different *Capsicum* species could provide novel capsaicinoid formulas for specific health related treatments.

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Section 5

Capsaicin and Metabolic Diseases

Chapter 5

CAP and Metabolic Diseases: A Mini Review on Preclinical Mechanisms and Clinical Efficacy

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Additional information is available at the end of the chapter

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Abstract

Capsaicin (CAP) is the chief active ingredient of natural chili peppers. It has culinary and medicinal benefits. CAP activates its receptor, transient receptor potential vanilloid subfamily 1 (TRPV1), which is expressed in the sensory and motor neurons, adipocytes, liver, vascular smooth muscle cells, neuromuscular junction, skeletal muscle, heart and brain. The specificity of CAP to activate TRPV1 is the fundamental mechanism for its medicinal benefits to treat pain, obesity, hypertension, and other diseases. Preclinical data from rodent model of high fat diet-induced obesity collectively suggest that CAP exerts its effects by activating TRPV1 signaling pathway, which stimulates thermogenic mechanisms in the white and brown adipose tissues to induce browning of white adipose tissues and brown adipose tissue thermogenesis. This leads to enhancement of metabolic activity and thermogenesis to counter obesity. Although CAP and its pungent and non-pungent analogs are used in human clinical studies, their effects on satiety and energy expenditure have been the highlights of such studies. The precise mechanism of action of CAP has not been evaluated in humans. This article summarizes these data and suggests that long-term safety and tolerance studies are important for advancing CAP to treat human obesity.

Keywords: capsaicin, TRPV1, weight gain, obesity, adipose tissue, browning, brite, chili peppers, satiety, energy expenditure

1. Introduction

Capsaicin (CAP) is the most commonly occurring capsaicinoids in chili peppers. It is enriched in the pith and ribs of the pepper. The pungency and heat of CAP give a prominent place

as a chief spice ingredient in food industry. Chili peppers contain both pungent CAPoids and non-pungent capsinoids (**Figure 1**). CAP and dihydrocapsaicin belong to the group of pungent capsaicinoids, while non-pungent capsinoids like capsiate, dihydrocapsiate and nordihydrocapsiate have also been shown in preclinical studies to be beneficial against metabolic diseases. Chemically, CAP is known as 8-Methyl-N-vanillyl-trans-6-nonenamide. Biologically, CAP binds to and activates its receptor transient receptor potential vanilloid subfamily 1 (TRPV1) predominately expressed at the sensory nerve endings. Activation of TRPV1 by CAP is responsible for the intense heat and burning. CAP desensitizes TRPV1 and exerts its analgesic activity.

1.1. TRPV1: capsaicin receptor

TRPV1 is the first member of the vanilloid subfamily of the TRP superfamily of proteins. It is a non-selective cation channel protein discovered by Michael Caterina [1]. TRPV1 consists of six transmembrane domains, with intracellular N and C termini. The ion channel pore region is situated between the fifth and sixth transmembrane domains. Although CAP and resiniferatoxin are exogenous activators of TRPV1, it is endogenous activation is regulated by heat (~43°C), acidic pH (~5.5) and by inflammation mediators. Primarily, the expression of TRPV1 is recognized in sensory neurons. Published literature suggests that TRPV1 is also expressed in various other tissues such as the neuromuscular junction [2–4], adipose tissue [5–7], liver [8, 9], skeletal muscle [10, 11], vascular smooth muscle [12], etc. Also, published work suggests that TRPV1 in the brain. TRPV1 is involved in experimental model of temporal lobe epilepsy (TLE) [13]. Although TRPV1 expression has been reported in some brain areas [14], it is still

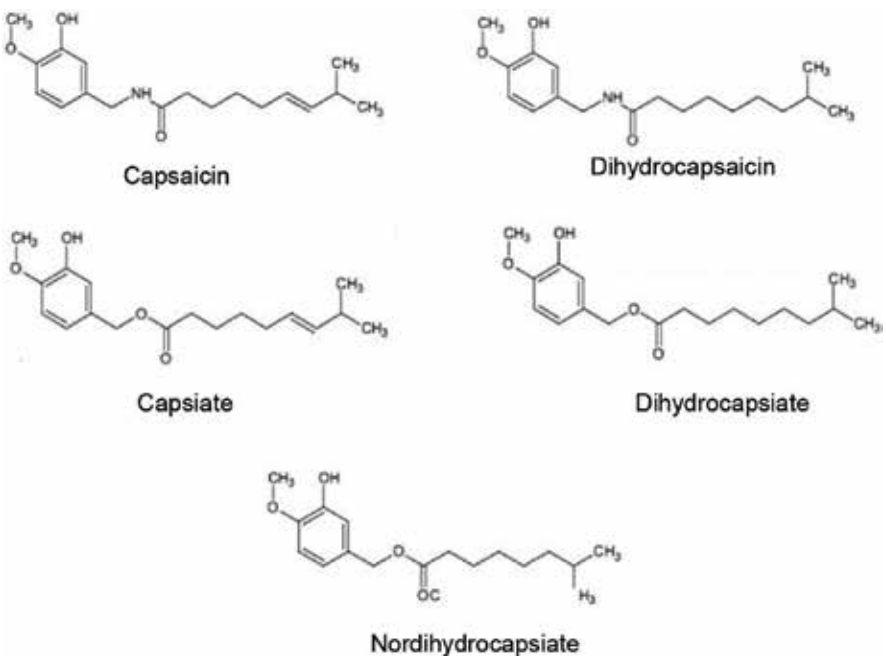

Figure 1. Structure of capsinoids and capsaicinoids.

Topical cream 0.01 or 0.025% for 6 weeks [15]	Psoriasis vulgaris	Beneficial
Topical cream 0.075% for 8 weeks [16]	Painful diabetic neuropathy	Beneficial
Topical cream 0.05% for several days [17]	Idiopathic trigeminal neuralgia	Beneficial
Topical cream: 0.075% [18] or 0.025% for 2 months [19]	Post mastectomy pain syndrome	Beneficial
Topical cream 0.025% for 7 days [20]	Cluster headaches	Beneficial
Topical cream 0.025% for 3 weeks [21]	Solar (brachioradial) pruritus	Beneficial
Oral candy (taffy): 5–9 ppm [22]	Oral mucositis pain	Beneficial
Topical cream 0.075% for 4, 8 and 12 weeks [23]	Chronic distal painful polyneuropathy	No beneficial effects
Intravesical injection 2 mM [24]	Chronic traumatic spinal detrusor hyperreflexia	Beneficial
Intravesical injection 10 μM for 1 month (twice weekly) [25]	Severe bladder pain	No Beneficial effects
Intranasal solution (0.1 mMol/L) every 2 or 3 days. Seven total treatments [26]	Non-allergic, non-infectious perennial rhinitis	No beneficial effects
Topical cream: 0.075% for 8 weeks [27] or 0.025% for 4 weeks [28]	Neuropathic pain	Beneficial
Intravesical solution: 100 ml of 2 mM for 30 min. [29]	Refractory detrusor hyperreflexia	Beneficial
Topical: 0.025% for 4 weeks [30]	Atypical odontalgia	Beneficial
Topical cream: 5–10% [31]	Refractory pain	Beneficial
Topical cream: 0.075% for 4 weeks (four times a day) [32]	HIV-associated distal symmetrical peripheral neuropathy	No beneficial effects
Intravesical solution (Pelargonic acid vanillamide): 0.5 ml of 0.1 mmol/L solution per administration. Seven times in 14 days [33]	Perennial allergic rhinitis	No beneficial effects
Topical cream 0.025% for 6 weeks [34]	Painful osteoarthritis	Beneficial
Topical cream: 0.025–0.3% for 2 weeks to 4 months [35]	Prurigo nodularis	Beneficial
Oral red pepper powder 5 g/day for 5 weeks [36]	Functional dyspepsia	Beneficial
Topical liniment 0.05% for 5 days (three times a day) [37]	Hemodialysis-related pruritus	Beneficial
Topical ointment 0.006% for 4 weeks [38]	Intractable pruritus ani	Beneficial
Oral capsaicin 0.25% [39]	Burning mouth syndrome	Beneficial

Transdermal oleic capsaicin: containing patches 3 g per patch on 2 days with a 2-day interval between trials [40]	Stable coronary disease (to improve ischemic threshold)	Beneficial
Oral troche: 1.5 μg per troche. One troche per meal for 4 weeks [41]	Swallowing dysfunction	Beneficial
Topical cream 0.075% [42]	UV induced immunosuppression	Beneficial
Transdermal dermal patch: 640 μg/cm^2, 8% w/w for 60 min [43]	HIV-associated peripheral neuropathy	Beneficial
Intraoperative wound instillation of ultra purified CAP instillation 1000 μg—single instillation [44]	Post herniotomy pain	Beneficial
Topical ointment: 0.03% for 4 weeks (four times a day) [45]	Uremic pruritus	Beneficial
CAP dermal patch: 8 or 0.04% for 30, 60 and 90 min [46]	Post herpetic neuralgia	Beneficial
Topical capsaicin cream 0.05% for 3 weeks (thrice a day) [47]	Chronic soft tissue pain	Beneficial
Topical civamide cream: 0.075% for 12 weeks (thrice a day) [48]	Osteoarthritis of the knee	Beneficial
CAP hydrogel patch: 0.1% for 4 weeks (12 h a day) [49]	Myofascial neck pain	No beneficial effects
CAP cutaneous patch: 8% for 30 to 60 min [50]	Peripheral neuropathic pain	Beneficial
CAP Cutaneous patch 8% for 60 min [51]	Persistent inguinal postherniorrhaphy pain	No beneficial effects
Topical CAPoid cream 0.01% nonivamide for 30 min a day for 21 days [52]	Chronic low back pain	Beneficial
Oral capsules 0.4 mg per capsule (once daily for 2 weeks followed by twice daily for 2 weeks) [53]	Chronic cough	Beneficial
Oral Yanjiao 425 chili peppers containing 4 mg/g of CAP 1.25 g per day for 4 weeks [54]	Gestational diabetes mellitus	Beneficial
Topical liposomal CAP 0.025% for two 6-week blocks with a gap of 2 weeks [55]	Post-herpetic neuralgia	No beneficial effect
CAP cutaneous patch 8% for 60 min [56]	Lumbosacral pain	Beneficial
CAP cutaneous patch 8% for 30 min [57, 58]	Neuropathy and painful diabetic peripheral neuropathy	Beneficial
Topical CAP gel: 0.01% or 0.025% for 14 days (thrice a day) [59]	Burning mouth syndrome	Beneficial

Table 1. Capsaicin (type and dose) target disease effect.

highly controversial. Nonetheless, the activation of TRPV1 and its ability to sense pain signaling mechanism make it a valuable target for treating pain in humans.

Recent research has dramatically advanced TRPV1 as a target for treating various human diseases. **Table 1** describes a list of preclinical and clinical studies for the beneficial effects of CAP against diseases.

Also, several preclinical and clinical studies have indicated that either capsiate alone or in combination with CAP is beneficial to counteract obesity and increase energy utilization [60–64]. However, the mechanisms behind such effect of CAP or capsiate still remain elusive.

2. Obesity and metabolic dysfunction

Obesity is a major health care issue in the world. About one third of the world's population is either obese or overweight. When energy intake exceeds energy expenditure, the excess energy is stored as triglycerides in the white adipose tissues. This leads to increase in adiposity, which presents glucose intolerance, insulin resistance, dyslipidemia and metabolic dysfunctions. Thus, diet-induced obesity progressively leads to type 2 diabetes, hypertension, hypercholesterolemia, and cardiovascular diseases. Although diet restriction and exercise are good strategies to combat obesity, lack of consistent motivation to stick to healthy diet and regular exercise regimen leads to rebound weight gain when such interventions are stopped. Further, the pharmacotherapy for weight loss is associated with toxicities and side effects [65–68]. Bariatric surgeries are invasive procedures, not easily reversible but associated with high cost and potentials for adverse events.

2.1. CAP for obesity

There are overwhelming evidences for the effectiveness of CAP, its analogs and the whole chili pepper to ameliorate diet-induced obesity in rodents and humans [5, 69–72]. Majority of these research studies have been directed to analyze broader outcome in terms of increase in energy expenditure, metabolic activity or measurement of weight loss. Scientific research unambiguously supports the concept that activation of CAP receptor is important for the effect of CAP to counter diet-induce obesity [5–7, 73]. However, it still remains unclear whether TRPV1 expressed on adipose tissues or on the nerves that innervate the adipose tissues. Further, there is no direct evidence to either support or disregard the role of TRPV1 expressed in central nervous system in this process. Although further research is warranted to clarify these mechanisms, published research works unambiguously support the benefits of CAP in abating obesity and metabolic syndrome in rodent models and humans. This article will discuss mechanisms emerging from studies focused on rodent models of obesity, which have translational value and help to interpret such mechanisms relevance to humans.

2.2. CAP and satiety

Since CAP is a pungent principle in chili peppers, its pungency has been regarded to satiety. Published work suggests that decreased appetite and increased energy expenditure were observed in humans who received red pepper in diet [74]. However, the ability of nonivamide,

a less pungent analog of CAP to reduce appetite [75] suggests that the pungency of CAP may not be directly related to the appetite regulation. **Table 2** below summarizes the clinical data that on the appetite regulation of CAP in the form of chili pepper powder or analog.

One important point to remember is the form of CAP that is used for human studies that have yielded contradictory data on the effect of CAP on energy intake. The discrepancy in the quality and type of CAP and variability in the duration of exposure of CAP to participants make interpretation difficult. These studies also lack validations on the ability of the form or type of CAP to activate TRPV1. This must be addressed in future studies. Nonetheless, important questions regarding how CAP mediates satiety or enhances energy expenditure in humans still remain unclear. Research studies focusing the effect of CAP on animal models of obesity will be invaluable to analyze such mechanism(s).

2.3. Adipose depots, functions and TRPV1 expression

Obesity is characterized by increased adiposity. White adipose tissue (WAT) primarily performs the function of insulation and protection in the body, and is regarded as the store for fat as triglycerides. Brown adipose tissue (BAT) plays a critical role in expending energy as it burns the stored energy into heat by a process called thermogenesis. These adipocytes were classified based on their functions and they significantly differ in their mitochondrial content, expression of genes/proteins that regulate thermogenic mechanisms and their localization in the body. BAT represents a small portion depot located throughout the human body at numerous distinct places, especially within the chest (perivascular-around the aorta, common carotid artery, cardiac veins and brachiocephalic artery), visceral cavity and subcutaneous region. BAT occurs along hollowed tissues (heart, trachea, lungs and esophagus), and in the visceral region, it is present around colon pancreas, kidneys, adrenal, liver and spleen [83–87]. Recently, a third type of adipose tissue called beige tissue or brite (brown in white) has been recognized, which are derived from WAT but express BAT specific thermogenic genes and proteins. In mammals, the beige-able adipose tissue locations haven identified as subcutaneous, inguinal and visceral [88] in rodents and supraclavicular [88], perirenal, visceral and subcutaneous depots [89] in humans.

Recent research has also characterized the expression of TRPV1 in these tissues. TRPV1 expression has been shown on cultured adipocytes [90–92] and epididymal, subcutaneous and brown adipocytes [6, 7, 93]. The validation of expression of TRPV1 on adipose tissues suggests a plausible role of TRPV1 in the recruitment of BAT activity and thermogenesis and the induction of the molecular conversion of WAT to beige like cells.

2.4. CAP and browning of white adipose tissue

Beige adipose tissue is characterized by the enhanced expression of thermogenic genes and proteins that are not usually expressed at a higher level in WAT. They show enhanced expression of mitochondrial uncoupling protein-1 (UCP-1), bone morphogenetic protein 8b (BMP8b), and central metabolic sensor, sirtuin-1 (SIRT-1), peroxisome proliferator activated receptor gamma (PPARγ) and PR domain 16 containing protein (PRDM-16) and PPARγ coactivator 1α (PGC-1α), which are recognized as factors regulating the beiging of WAT [94, 95]. Further, published literature suggests that Cd137 [96], Shox2 [97], Cited 1 [88], Tmem26 [96], Tbx1 [96, 98], Bmp8b [99–101], ucp-1 [102, 103], SIRT-1-dependent mechanisms [6, 104], are considered

Intraduodenal infusion of CAP 1.5 mg [76]	Promoted satiety
Oral red chili peppers 1.03 g [77]	Increase satiety
Oral red pepper 10 g [78, 79]	Decreases appetite—Desire to consume fatty, salty, and sweet foods were decreased
Oral chili 30 g/day chili blend [80]	No effect on energy intake
Oral CAP 135 mg/day [81]	No effect on satiety and hunger
Oral CAP 1.03 mg [82]	No effect on satiety

Table 2. CAP (type and dose) effect on appetite.

as markers for browning of WAT. Research work suggests that posttranslational modification, such as deacetylation, of PPARγ and PRDM-16 by SIRT-1 is involved in the beiging of WAT [6]. The deacetylation and stabilization of PPARγ and PRDM-16 by SiRT-1 been shown to induce browning of WAT in rodents [6, 7, 104]. CAP has been shown to induce browning of WAT in vitro [105] and in vivo [6] by activating SiRT-1 [6].

SiRT-1 plays a pivotal role in the regulation of cellular energy homeostasis. The phosphorylation and activation of SiRT-1 by cellular protein kinases like Ca^{2+}/calmodulin-dependent protein kinase kinase β {CaMKKβ [106]}, CaMKIIα [6] and 5′-adenosine monophosphate-activated protein kinase {AMPK [6, 107–109]} has been shown to be important for the effect of CAP in browning of WAT. Preclinical data in mouse model of obesity suggests that feeding a high fat diet inhibits the expression and activity of TRPV1 in WAT and dietary CAP reversed it. CAP stimulates a robust Ca^{2+} influx via TRPV1, which stimulates CaMKII/AMPK-mediated SiRT-1 phosphorylation. This subsequently deacetylates PPARγ and PRDM-16 and promotes their stabilization. **Figure 2** describes SiRT-1-dependent mechanisms by which CAP enhances the deacetylation of PPARalha and PGC-1alpha to enhance fatty acid oxidation and mitochondrial biogenesis to promote the browning of WAT and counter obesity. However, such a mechanism has not been shown in humans and future studies are needed to address this.

2.5. CAP and BAT thermogenesis

Recognition of expression of TRPV1 in BAT poses important questions on the ability of CAP to enhance thermogenesis. Research approaches have aimed at activation of SiRT-1 [110–112], β3 adrenergic receptors [113–115], thyroid hormone, irisin [116, 117] and FGF21 [118] induction in BAT. Studies also suggest that secretory signaling mechanisms from muscle and liver, such as irisin and Fgf21 are also recognized humans [119]. In rodent model, TRPV1 activation protects against high fat diet-induced obesity by stimulating the expression of thermogenic genes and proteins in BAT [7, 105, 120–122]. Further, CAP enhances SiRT-1-depenent deacetylation and interaction of PPARγ and PRDM-16 in BAT [7].

The crosstalk between TRPV1 and beta-adrenergic action (possible mechanism illustrated in **Figure 3**) has been reported in the literature [123], which could influence an additive effect on the thermogenic mechanisms in BAT. Also, there are data suggesting that TRPV1 expressed on vagal afferents or intestinal mucosal afferents are important for the anti-obesity effect of CAP [124, 125]. Further studies are required to address these mechanisms.

Research studies are now beginning to address the physiological functions of TRPV1 in adipose tissues. TRPV1 activation has been suggested to regulate adipogenesis and thermogenic pathways. It is also possible that along with the expression of TRPV1 on adipose tissue membranes, the expression of TRPV1 on the nerves that innervate adipose tissues may contribute for the browning of WAT and BAT thermogenic mechanisms. This necessitates the development of mouse strains that lack TRPV1 in specific tissues. Such a tool will be invaluable to delineate the precise role of TRPV1 signaling in metabolic tissues.

2.6. Safety and toxicological analyses of CAP

Studies have also addressed to evaluate the short-term and long-term effects of CAP in rodents and humans. In mice, oral administration of semisynthetic powdered CAP at a dose of 0.3125% caused benign tumors in cecum [126], Chili pepper extract-fed orally at a dose of 800 mg/kg per day in male and 200 mg/kg/day in female showed no toxicity in mice [127]. Mice received CAP at a dose of 1.46 or 1.94 mg/kg by *intraperitoneal* injection showed increase in gastric cancer [128], while oral gavage of 2 and 10 mg/kg of CAP showed chemoprevention against tumorigenesis [129]. Studies have also demonstrated the oral LD50 of CAP for mouse and rat were 161.2 and 118.8 mg/kg, respectively, [130]. Studies in humans suggest that feeding CAP in Women with gestational diabetes mellitus improved postprandial hyperglycemia,

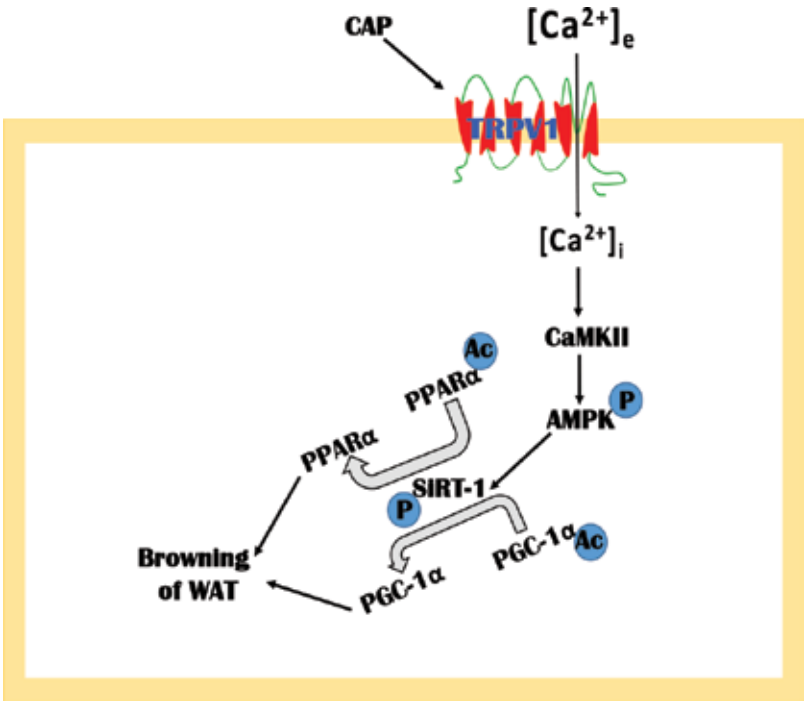

Figure 2. Mechanism by which CAP induces browning of WAT. CAP (CAP)-stimulated Ca^{2+} influx via TRPV1. Activates CaMKII/AMPK-dependent SiRT-1 activation. SiRT-1 deacetylates PPARalpha and PGC-1alpha. This increases fatty acid oxidation and mitochondrial biogenesis to promote browning of WAT, and counters diet-induced obesity.

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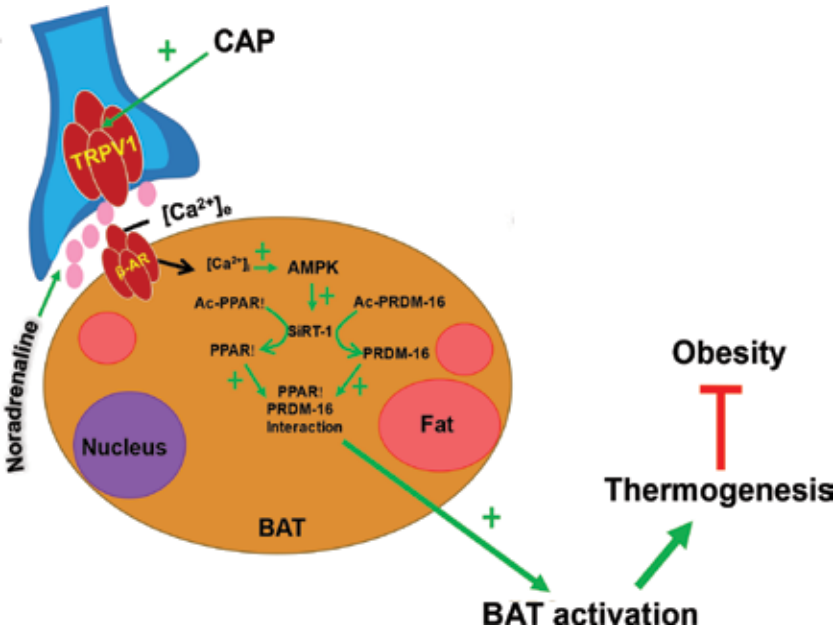

Figure 3. Model describing the neuronal effect of TRPV1. CAP (CAP) activates TRPV1 expressed in the innervating nerve of iWAT. This increases noradrenaline release, which activates β adrenergic receptors. The resultant Ca^{2+} influx enhances AMPK-dependent SiRT-1 activation. SiRT-1 deacetylates PPAR**γ** and PRDM-16. This causes PPAR**γ**-PRDM-16 interaction leading to BAT activation, which stimulates thermogenesis to ameliorate diet-induced obesity.

hyperinsulinemia, and fasting lipid disorders [54]. Also, CAP inhalation for cough challenge test had no single serious adverse event associated with CAP [131]. Further, a study in humans suggests that oral administration of 2.56 mg of CAP with every meal increased satiety and fullness and prevented over eating [77]. However, recent studies show that when along with a high fat diet CAP did not alter energy intake in mouse [6, 7]. However, there is still lack of clear evidence for the long-term effectiveness and safety of CAP in humans. Further studies are required to address this.

3. Conclusions and future perspectives

This article summarizes the preclinical and clinical data, which collectively suggest the anti-obesity effect of CAP. However, the long-term efficacy and safety of TRPV1 agonist remain to be established. Although CAP is a natural product, its pungency is considered as a limitation for oral use. Therefore, research should be geared to develop approaches to mask the pungency of CAP by coating it with polymers of agents, which decrease its burst release in the oral cavity and in the gastrointestinal tract. Since non-pungent analogs have been shown to be effective, efforts should be made to enhance their bioavailability and stability in the body. For example, capsiate, a non-pungent analog of CAP, is effective [62, 64, 132, 133] but issues exist on its stability [134], which requires attention. Recently, a site-specific delivery

system for CAP magnetic nanoparticles for obesity management has been reported [135, 136]. Such approaches should help in advancing the therapeutic efficacy of CAP. Further, efforts to deliver CAP at specific sites in the gastrointestinal tract through formulations such as enteric coated tablets and capsules will be beneficial to prevent its burst release in the stomach. Since human clinical study meta-analyses suggest that both CAPoids and capsinoids are beneficial in enhancing energy expenditure [64], dose products to combine them to counter obesity could be more effective.

Preclinical toxicological studies should be performed to demonstrate the safety and tolerance of CAP. These studies are important to clarify the perceptions that CAP could cause gastrointestinal disturbances and gastric ulcers [137–142]. However, such studies should use quality controlled pure CAP instead of chili pepper powder since the quality of CAP in those powders depends on the source of the peppers. Further, establishing the proof of concept for the anti-obesity effect of CAP using a proper dose and delivery system and validation of its bioavailability and pharmacokinetics are important for advancing its use in humans to treat obesity and associated metabolic complications.

Conflict of interest

The authors declare that there are no conflicts of interest.

Abbreviations

CAP	Capsaicin
TRP	transient receptor potential
TRPV1	transient receptor potential vanilloid subfamily 1
SiRT-1	sirtuin-1
PPAR	peroxisome proliferator activated receptor
PGC-1α	PPARγ coactivator 1α
PRDM-16	PR domain 16 containing protein
BMP8b	bone morphogenetic protein 8b
UCP-1	uncoupling protein 1
CaMKKβ	Ca^{2+}/calmodulin-dependent protein kinase kinase β
CaMKII	Ca^{2+}/calmodulin dependent protein kinase II
AMPK	5′-adenosine monophosphate activated kinase
WAT	white adipose tissue

BAT	brown adipose tissue
LD50	lethal dose 50

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Section 6

Predictors in Treatment Responses to Capsaicin in Humans

Chapter 6

Predictors of Treatment Response to Capsaicin Patch

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Additional information is available at the end of the chapter

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Abstract

Neuropathic pain is a very difficult to treat chronic condition. One of the most promising treatments developed in recent years is the capsaicin 8% patch. But given the high cost of treatment, the patch should be applied only to those most likely to benefit from improvement. There have been several studies that have tried to look for predictors of treatment response. Three of them found correlation with pain and response to treatment. The predictors found were: baseline pain scores, variability of pain prior to treatment, pain response for lidocaine pretreatment, and time with preexisting pain. Four studies found that sensory abnormalities used for prediction of response to treatment seems to be useful as well. Though the correct sensory sensations are not clear there seems to be a tendency for the burning or heat-pain sensations and the pressure-pain sensations to be taken into account. From this findings, it seems that patients with exclusively peripheral damage and with no central plastic changes are the most suitable for treatment. There must be some more research to be done, where a combination of the predictors already found could give a very high predictability of treatment response, lowering de NNT to almost 1.

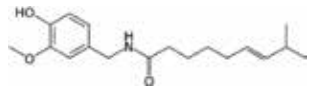
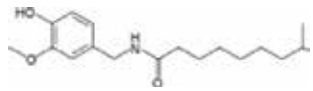
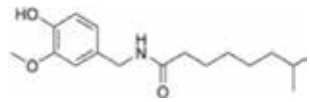
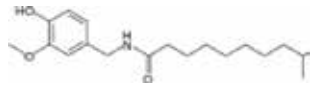
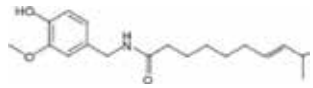
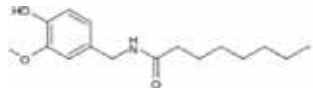
Keywords: capsaicin patch, QST, QTT, sensory symptoms, response to treatment, pain scores

1. Introduction

Neuropathic pain (NP) is a very difficult to treat chronic condition [1]. Additionally, managing NP involves selecting the appropriate treatment for each patient, since not all patients respond to the same treatments. Currently, there is little to no information regarding the prognostic factors associated with positive treatment outcomes for clinicians who treat patients with NP to decide which is the better course of action with each patient. One of the most promising treatments developed in recent years is the capsaicin 8% patch (CP8%) (QutenzaTM) [2] which delivers capsaicin into the skin providing up to 12 weeks of relief with a single topical patch

application [3–5]. CP8% delivers up to 179 mg of capsaicin to the skin in a pharmacokinetic linear administration. Capsaicin (8-methyl-N-vanillyl-6-nonenamide) is the most frequently found capsaicinoid, and a well-known exogenous activator of transient receptor potential vanilloid 1 (TRPV1) [6]. Other capsaicinoids have been described [7]. See **Table 1** for the other capsaicinoids. Especial interest may be given to Nonivamide, also called pelargonic acid vanillylamide (PAVA), which is used as the active ingredient in most pepper spray. Even though, the most studied has been capsaicin, being the active component of CP8%. Capsaicin, up to date, is the only capsaicinoid used for clinical treatment in humans.

Capsaicin in CP8% works by directly targeting the TRPV1 receptor (present in C-fibers and in some Aδ-fibers) The largest group of nociceptors found in the skin is the family of channels of the transient receptor potential [8]. There are four different molecules (TRPV1, TRPV2, TRPV3 and TRPV4) that respond to different degrees of temperature increase, ranging from the perception of heat all the way up to harmful levels [9–11]. TRPV1 is a non-selective, ligand-dependent cationic channel that can be activated by a series of exogenous and endogenous physical and chemical stimuli, [12, 13], allowing the passage of different monovalent or divalent cations [14, 15], such as sodium and calcium. This triggers the release of various peptides, causing the transmission of nociceptive information to the brain, which is interpreted

Common name	Chemical name	Chemical structure	Freq.	Heat units
Capsaicin	*8-methyl-N-vanillyl-6-nonenamide*		69	16
Dihydrocapsaicin	*N-(4-Hydroxy-3-methoxybenzyl)-8-methylnonanamide*		22	15
Nordihydrocapsaicin	*N-(4-Hydroxy-3-methoxybenzyl)-7-methyloctanamide*		7	9.1
Homodihydrocapsaicin	*N-(4-Hydroxy-3-methoxybenzyl)-9-methyldecanamide*		1	8.6
Homocapsaicin	*(6E)-N-(4-Hydroxy-3-methoxybenzyl)-8-methyldec-6-enamide*		1	8.6
Nonivamide	*N-[(4-Hydroxy-3-methoxyphenyl) methyl]nonanamide*			9.2

Freq. stands for percentage (%) of the capsaicinoid found in nature.
*Nonivamide can be found in less frequency, but is mostly synthetically manufactured. Heat Units stands for the pungency, which is measured with the Scoville scale. Numbers for the Heat Units are in millions.

Table 1. Description of most common capsaicinoids.

as a burning pain or an itch. Its pain relief effect is believed to be due to the activation of small diameter afferent nerve fibers and specialized dorsal root ganglia neurons after high dose application of capsaicin, resulting in the defunctionalization of the nociceptor nerve fibers. After defunctionalization, patients perceive a decrease in pain [16–18], which is frequently referred to as "desensitization". This desensitization allows the use of capsaicin as an analgesic [19]. Long term treatment have been studied along several prospective cohort studies [20–22] CP8% treatment have been studied up to 52 weeks of follow-up, with repeated patch application. In these studies no sensory changes in the skin was found after repeated treatment. Also, skin biopsy reports in these studies showed that intraepidermal nerve fiber density change was only temporary. Adverse effects reported were all topical and localized to the site of application. All of them were temporal and reversed to normal after some time.

The European Medical Agency (EMA) has recommended that CP8% be applied by a doctor, or other healthcare professional under the supervision of a doctor. Treatment is to be done for no more than 60 minutes, as the pharmacodynamic studies showed no increase in benefit [23]. This recommendation limits treatment options and also makes treatment more expensive. In addition, the indirect costs of personnel and other materials must be added to the direct cost of CP8% [24]. While many patients with peripheral NP (PeNP) respond positively to treatment with the capsaicin 8% patch, others do not. Given the aforementioned high cost of treatment and adding to it that the number-needed-to-treat (NNT) for CP8% is high [25], the patch should be applied only to those most likely to benefit from improvement. At present, there are no reliable predictors of response to treatment with capsaicin for analgesia. There have been several studies that have tried to look for predictors of treatment response [26–31]. In this chapter we are going to comment on them trying to give more light into this issue.

2. Pain as a predictor of response to treatment

Three studies have found correlation with pain and response to treatment [26–28]. Although, the correlation is not the same, and the quality of pain investigated was different too. The predictors found were: baseline pain scores, variability of pain prior to treatment, pain response for lidocaine pretreatment, and time with preexisting pain.

One investigated data from 4 double-blind, randomized controlled trials (RCT) [26]. All trials were done on the efficacy of the capsaicin 8% patch versus capsaicin 0.04% patch in patients suffering from post-herpetic neuralgia (PHN). For the purpose of analyzing old data in this new study, the investigators used a Bateman function for a non-linear mixed effect. For such extent they used a longitudinal model. The overall number of patients was 1248. Treatment outcomes, or responders was to be identified at week 12. So it is a meta-analysis with revised data from different studies.

The procedure resulted in five distinct response populations:

- Subgroup 1. worsening of pain during treatment (i.e., pain increases)
- Subgroup 2. no response to treatment

- Subgroup 3. (partial or full) analgesic response with return to pretreatment pain levels within 12 weeks
- Subgroup 4. partial analgesic response at week 1 that remained constant during the study period
- Subgroup 5. ongoing decline in pain rating during the 12 weeks.

Analyzing the treatment outcomes in this groups and the data extracted from them, some predictors could be found.

1. Pain scores following lidocaine pretreatment over the skin on numeric pain rating scale (NPRS) score predicted the efficacy of the capsaicin 8% patch. In contrast, when pain scores were elevated after lidocaine pretreatment (NPRS = 10), the probability of capsaicin 8% treatment success decreased. High variability in pain rating scores could be due to a more recent development of chronic pain status.
2. The variability of pain reporting in the 14 days prior to treatment also had a significant impact on treatment efficacy. When variability was high, the probability of full response to treatment was almost 80%. Possibly the low variability NRPSs are an indication of a rigid and fully manifested long-term chronic pain process with severe central plastic changes unresponsive to therapy. Although not as potential predictors as the above, it was also found that concomitant opioid use and high baseline pain scores reduce the probability of a full analgesic response.

Maihöfner et al. [27] studied A total of 1063 patients receiving a single treatment of the CP8% were evaluated. The highest treatment response to the CP8% was observed in patients with a history of pre-existing peripheral neuropathic pain of less than 6 months, suggesting that early initiation of topical treatment might be indicated. Responder rates of 30 and 50% in patients with pain duration of <6 months were significantly higher than in patients with pain duration of 6 months to 2 years, >2–10 years or > 10 years ($p \leq 0.001$; chi-square test) (**Table 2**).

Patients with a pain history of less than 6 months had the highest pain reduction with an average of −2.7 points (n = 105; 0.3 standard error of the mean (SEM); $p \leq 0.001$) and improvement of 36.6% (4.6 SEM). This difference was significantly higher compared to patients with pre-existing pain for more than 6 months. Patients with a pain history of more than 10 years experienced the lowest absolute and relative change of pain intensity, with a mean value of −1.2 points (n = 99; 0.2 SEM; $p \leq 0.001$) and 19.2% improvement. Thus, Patients with preexisting pain of less than 6 months seem to benefit to an even greater extent from treatment than those with a longer history of pain.

Katz et al. [28] conducted meta-analyses out of 6 completed randomized and controlled Qutenza studies evaluating the capsaicin patch efficacy, and used individual data patient data from capsaicin patch–treated patients only to identify which types of patients have the greatest response to capsaicin patch treatment. Logistic regression was used to identify predictors of response and Complete Response, and subgroups of patients who respond best to the capsaicin patch. The potential predictors of response selected were the baseline patient characteristics that can easily be measured by physicians during office visits and for which data were

	Responder rates (% patients)	
Pain duration	**>30%**	**>50%**
<6 months	61.7*	39.3**
6 months-2 years	42.3	23.3***
>2-10 years	40.8	21.6
>10 years	32.3	14.1
No data	41.8	24.6
Total	42.7	23.6

From Maihöfner et al. [27].
*p < 0.001 versus 6 months-2 years, >2–10 years, >10 years (chi-square test).
**p < 0.001 versus 6 months-2 years, >2–10 years, >10 years (chi-square test).
***p = 0.042 versus >10 years (chi-square test).

Table 2. Responder rates: Pain relief of at least 30 and 50% at day 7–14 to week 12 versus baseline for subgroups of duration of pre-existing peripheral neuropathic pain.

collected in the trials. This is another meta-analysis with data obtained from different studies done before. Treatment outcomes and response rate was to be compared to week 12. Baseline characteristics with X2 P-value ≤0.15 were considered as potential predictors of the respective efficacy outcomes.

Characteristics associated with the highest chance of responding to the capsaicin patch were, for PHN, baseline pain intensity score (BPIS) ≤ 4, McGill Pain Questionnaire (MPQ) sensory score ≤ 22, absence of allodynia, and presence of hypoesthesia; for human immunodeficiency virus associated neuropathy (HIV-AN), they were female sex and BPIS ≤ 4.

- Absence of allodynia on examination was associated with better outcome in the PHN-Sustained Response group;
- Absence of allodynia and presence of hypoesthesia on examination, and absence of allodynia and presence of hypoesthesia on the Neurological/Sensory Assessment (NSA; a questionnaire), was associated with better outcome in the PHN Complete Response group;
- MPQ sensory scores were associated with better outcome for PHN patients;
- Better physical and mental health (SF-36) was associated with better outcome across disease and efficacy response categories;
- Female sex and absence of use of concomitant analgesics were associated with better outcome in HIV-AN patients;
- Higher body mass index (BMI) was associated with better outcome in PHN patients;
- Decreased sensation on the baseline sensory examination was associated with better outcome in PHN patients.

They found that baseline pain intensity was a consistent predictor of response. Patients with a Mean baseline pain intensity ≤4 had a significantly better response than when they reported >7. But they also found that sensory symptoms could be useful for response to treatment too.

3. Sensory symptoms and response to treatment

As stated above, Katz et al. found not only predictability with pain scores. They also found sensory abnormalities which, at baseline visit, could be useful predictors. Patients without allodynia and with hypoesthesia, on both the physical examination and the NSA, had better outcomes. This seems to be a robust finding as it is consistent across clinical examination and patient self-report methods of capturing these phenomena.

Another study evaluated sensory neuropathic abnormalities (painDETECT questionnaire), collected from a multi-center, prospective, non-interventional study 1044 patients [29]. Treatment outcomes or response rate was to be compared to week 12. In this paper, only weak associations were found: Short disease duration predicted an improved treatment effect. High painDETECT score, presence of burning and pressure-evoked pain were weak predictors of treatment response.

Patients with a positive painDETECT score showed an average overall pain reduction of 24% following treatment, whereas patients with a negative score had a mean reduction of 13%. At single symptom level a weak association was found between burning and pressure-evoked pain at baseline and response. However, for the majority of symptoms the extent was greater in patients with a short duration of pain (**Table 3**).

Thermal hyperalgesia is difficult to interpret, which could be due to the fact that the painDETECT questionnaire does not distinguish between cold and heat-evoked pain. Since the burning quality (data on heat-evoked pain) is frequently associated with the presence of

Pain duration	**<6 m [57]**	**6 m–2 y [166]**	**>2 y–10 y [225]**	**>10 y [54]**
Symptoms				
Burning	43.1 (5.6)	23.4 (3.5)	15.9 (2.6)	12.1 (10.8)
Prickling	21.6 (8.3)	21.9 (3.7)	12.9 (3.4)	18.6 (5.0)
Allodynia	36.9 (6.8)	20.9 (4.0)	18.9 (3.6)	8.5 (4.5)
Pain attacks	35.9 (7.4)	23.5 (4.4)	15.3 (3.5)	10.6 (5.3)
Thermal hyperalgesia	24.1 (10.8)	24.9 (4.6)	20.5 (4.1)	15.7 (6.9)
Numbness	35.9 (6.5)	15.7 (3.5)	16.2 (3.6)	5.2 (9.7)
Pressure-evoked pain	30.7 (10.2)	18.1 (4.2)	11.9 (3.8)	12.2 (6.1)

Modified from Hoeper et al. [29] Pain duration. m = months. y = years. In brackets, [] number of patients in each subgroup with different duration of preexisting pain. Reduction in symptom intensity. Numbers are % of reduction and in parenthesis () the standard error of the mean is shown.

Table 3. Reduction in sensory symptom intensity depending on duration of preexisting pain.

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TRPV1 receptors on nociceptors, this association is in line with the proposed mechanism of action of capsaicin.

The previous two studies found sensory profiles in clinical examination or in self-reported questionnaires. Two attempts have been made to find predictability for capsaicin treatment response with quantitative sensory profiles. Given that capsaicin affects unmyelinated or, slightly myelinated fibers, and studies have shown that the CP8% patch involves heat sensation [7], a retrospective study of clinical records was performed to see if that quantitative thermal testing (QTT) could be a potential predictor of treatment response [30]. The QTT profiles at the target localized PeNP (PeLNP) area were compared to the corresponding QTT profile at the contralateral area. There were no baseline differences between responders and nonresponders in terms of gender, age, Douleur Neuropathique 4 scores, etiological diagnosis (PHN, chronic post-surgical pain, chronic post-traumatic pain, complex regional pain syndrome) or NPRS scores. QTT could not be compared to already published normalized data due to slight simple heterogeneity, which made subgroup analysis impossible. Heterogeneity was due to the following: concomitant medication, pain localization, and time elapsed from injury to treatment. Thus, QTT was compared between the treatment area and the asymptomatic contralateral healthy area, used as a control. Differences between the values in the target and control areas were considered not significant when there was a crossover between mean results (±1.96SD) for the measurement on both areas; when this occurred, the painful area was considered to present normal thermal sensations.

Two distinct groups were identified (**Figure 1**):

- Homogenous profile group: defined as either the presence of significant differences in the same direction (both high or both low) in warm sensation threshold (WST) and heat pain

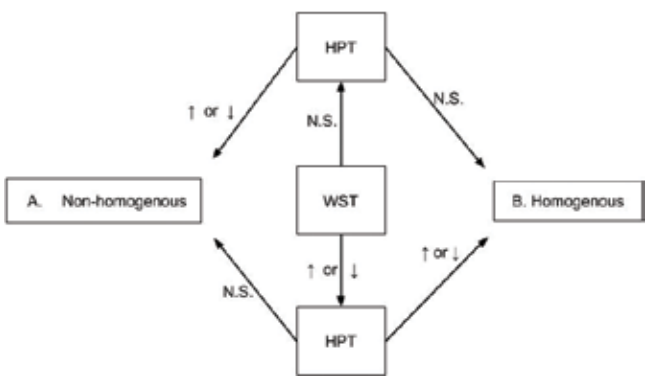

Figure 1. QTT profile flow diagram. From Serrano et al. [27] QTT profile groups identified after matching responder and non-responders to treatment with capsaicin patch. WST: Warm sensation threshold. HPT: Heat pain threshold. N.S. Stands for no significant difference between pain site and asymptomatic contralateral area for the thermal test. ↑ stands for a significantly higher result for the thermal test on the painful area versus the asymptomatic contralateral area. ↓ stands for a significantly lower result for the thermal test on the painful area versus the asymptomatic contralateral area. For the arrow coming from the HPT box to the homogenous box, the painful area was significantly higher when WST was significantly higher or significantly lower when WST was significantly lower than the asymptomatic contralateral area, being both QTT test in the same direction.

threshold (HPT) values between the PeLNP region and the asymptomatic contralateral area; or no significant difference in these measures (both the treatment and control sites normal).

- Non-homogenous group: defined as the presence of significant differences between the PeLNP area and the contralateral site in only one (either WST or HPT) measure but not the other.

For instance, a significantly differently low HPT (i.e., heat hyperalgesia) with no significant difference in WST was considered non-homogeneous. By contrast, if the WST was also significantly different between the control and treatment areas, then the QTT profile was considered homogenous.

Most patients (27/31, 87.1%) with a homogenous profile were non-responders. By contrast, more than half of the patients (13/24, 54.2%) with a nonhomogeneous profile were responders ($p = 0.0028$). The clinical effects of CP8% were better in patients with non-homogenous QTT profiles. These patients showed a significantly higher response rate than patients with homogenous QTT profiles. It appears that patients who show a non-homogenous profile in terms of WST and HPT values are significantly more likely to respond to capsaicin treatment, probably due to the presence of incomplete nerve damage. This nociceptors are giving imbalanced inputs to second order neurons. So, patients with this non-homogeneous profile seem to have purely peripheral pain, with no central plastic changes. Treating them with CP8% could have removed such imbalance through desensitization, giving pain relief. By contrast, an homogeneous QTT profile is to be expected in patients with either no peripheral damage at all, with peripheral nociceptors working properly; or either in patients with complete peripheral nerve damage. When there is no peripheral nerve damage there should be no differences to be expected in WST/HPT values between painful and contralateral asymptomatic area. And when there is complete damage, the loss of peripheral nociceptors should give differences in both warm and heat pain sensations between both areas. Being this the neurophysiological reasoning for patients with an homogeneous profile to have Little or no clinical improvement.

Another study [31] used quantitative sensory testing (QST) to determine whether any patient characteristics can predict response to treatment with the capsaicin 8% patch where a total of 57 patients were treated. Responders to treatment were defined as those with ≥30% reduction in pain score at Day 7/10 post-treatment compared with baseline. They identified potential differences in the sensory profiles—particularly the pressure pain threshold and degree of allodynia—of patients with PeNP who responded to CP8% and those who did not. The authors found similar QTT profiles at baseline for both responders and nonresponders. There was no difference in temperature perception or heat and cold thresholds, and did not identify warm hyperaesthesia or heat hyperalgesia in responders.

Responders showed a trend towards a reduction in warm perception and also appeared to show normalization of the pinprick hyperalgesia at some stimulus levels. They also had a significant reduction in the size of the painful area at Day 28. (**Table 4**). At baseline the PNeP area in responders was found to have a significantly lower pressure pain threshold compared with the control area.

Stimulus (units)	Non-responders			Responders		
	n	PNeP site	Control area	n	PNeP site	Control area
MPT (mN)	12	32.2 (14.0–92.9)	34.3 (21.2–46.9)	9	58.7 (22.5–134.5)	90.5 (41.9–115.4)
PPT (kPa)	6	380 (250–500)	510 (300–630)	7	320 (290–800)	480 (410–1000)*
PS (mN)	14			9		
8		3.4 (1.3–13.3)	1.5 (.0–3.5)		4.6 (.0–10.4)	1.2 8.0–4.4)
16		5.2 (.0–15.4)	1.6 (.4–7.0)		6.6 (1.8–11.7)	2.3 (.0–6.3)**
32		14.5 (1.9–21.3)	3.5 (1.3–12.5)[1]		10.0 (1.5–17.5)	4.0 (1.1–9.1)**
64		10.0 (2.9–35.0)	5.0 (2.8–21.5)		12.0 (1.3–26.7)	7.9 (3.9–11.9)
128		16.3 (3.0–36.3)	8.9 (2.9–23.0)		10.0 (3.6–25.0)	10.0 (7.2–19.8)
256		32.5 (4.7–48.8)	11.0 (3.2–28.8)		16.6 (7.1–31.0)	12.1 (9.1–25.4)
512		38.5 (5.8–71.3)	14.0 (5.1–44.8)		19.4 89.9–38.8)	20.0 (11.5–43.0)

Modified from Gustorff et al. [31] PNeP, peripheral neuropathic pain. MPT = Mechanical pain threshold. PPT = Pressure pain threshold. PS = pinprick stimuli, in a stimulus–response function, using a numerical pain rating scale (0–100). For non-responders and responders, numbers represent the median, with the interquartile range in parenthesis (). When comparing PNeP site vs. control area: * $p < 0.01$, ** $p < 0.05$, [1] $p = 0.51$.

Table 4. Sensory thresholds in PNeP sites compared with control areas at baseline, for non-responders and responders to capsaicin 8% patch treatment, as determined by quantitative sensory testing (QST).

Non-responders had approximately three times greater degree of allodynia at baseline compared with responders. At baseline in non-responders, there was a trend towards greater sensitivity to painful pinprick stimuli at most intensities (8–512 mN) in areas of PNeP compared with control areas (**Table 4**). Non-responders appeared to display a generally higher mechanical pain sensitivity in the painful area than in the control area and three times higher allodynia than in responders.

4. Overall, predictors and limitations

From the published studies so far, several predictors have been already been found to be useful in clinical practice. But comparing published studies is not possible due to methodological differences (**Table 5**). However, from them, it can be hypothesized that patients characteristics are important for treatment response, and a careful selection will be more efficient in cost-effectiveness.

Pain have been found to be a good predictor of response. Both, high variability and less than 6 months of preexisting pain suggest the importance of treating patients when no central plastic changes are organized. Other predictors as lidocaine pretreatment response or low basal pain rating have do not have a certain neurophysiological assumption. There is even some contradiction within high variability in pain scores previous to treatment and low

	N	Study type	Timeline	NP type	Response definition	Control	Predictor
Martini [26]	1248	DB re-analyses	retrospective	PHN	Week 12 subgroups	Capsaicin 0.04%	1) Pain scores after lidocaine 2) Pain scores variability
Hoeper [29]	1044	Cohort	prospective	PeNP (excluding DM or head)	Week 12	None	painDETECT sensory symptoms
Gustorf [31]	57	Cohort	prospective	PeNP	Day 7–10	None	QST: PPT/PS
Katz [28]	1299	DB re-analyses	Retrospective	PHN HIV-AN	Week 12	Capsaicin 0.04%	1) Baseline pain score 2) allodynia hypoesthesia
Maihöfner [27]	1063	Cohort	Prospective	PeNP (excluding DM or head)	Days 7–14 Week 12	None	Time with preexisting pain
Serrano [30]	55	Cohort	Retrospective	PeLNP	Week 6 Week 12	None	QTT profile

Description of main variables of the different studies published with predictors of response to capsaicin patch.
N = number of patients in study. NP = Neuropathic Pain. DB = Data Base, PHN = Postherpetic Neuralgia. PeNP = Peripheral Neuropathic Pain. DM = Diabetes Mellitus. QST = Quantitative Sensory Testing. PPT = Pressure Pain Threshold. PS = Pinprick Stimulation. HIV-AN = Human Immunodeficiency Virus Associated Neuralgia. PeLNP = Peripheral Localized Neuropathic Pain. QTT = Quantitative Thermal Test.

Table 5. Published studies characteristics with predictors for response to capsaicin patch.

baseline pain score. Both are meta-analyses done with several RCT, where one only was done with PHN patients. The time with preexisting pain was found within a cohort prospective study, where any kind of PeNP was included, except for DM or pain in the head.

Sensory abnormalities used for prediction of response to treatment seems to be useful as well. Though the correct sensory sensations are not clear. Whereas burning and pressure evoked-pain symptoms where potential predictors in painDETECT questionnaire in a cohort study, These findings support the hypothesis developed by Malmberg et al. [17], who argued that the foremost psychophysical manifestation of topical capsaicin treatment is a reduced sensitivity to heat stimuli. This is the expression of an elevated-warmth detection threshold, corresponding to a loss of cutaneous sensory nerve fibers. QTT homogeneity profiles between WST and HPT was found to be useful. But, thermal sensations could not be found when applying QST in another cohort. However, response definition was not the same in neither of the studies. Also, it has to be taken into account that QST/QTT is time consuming. This is a big limitation for the number of patients to be studied with. This can be seen in **Table 5** where the QST studies have a big difference in number of patients, where both studies had a relatively small number of patients, which precluded the use of subgroup analysis, compared with the other studies.

From the predictors that have been found it already seems that patients with exclusively peripheral damage and with no central plastic changes are the most suitable for treatment. Patients with a partial loss of cutaneous nerve fibers or receptors are more likely to respond to

treatment. By contrast, when severe nerve damage or normal cutaneous sensations are present, responsive to capsaicin treatment is not so good. This difference may be due to incomplete nerve damage in these patients, leading to an imbalance in the sensitive inputs to second order neurons from peripheral receptors, and to the presence of ectopic discharges on nerve endings. If so, pain in these patients may be purely peripheral, with no additional central sensitizaion (CS) mechanisms. Capsaicin application in these patients could eliminate the factor resulting in dysaesthesia when they activate the remaining TRPV1 receptors, desensitizing the nerve terminals of nociceptors by destroying the remaining axons and nociceptors. Pain in non-responders could be due to CS mechanisms, with inputs multiplied at the DH, that is, the origin of the pain in these patients is probably less peripheral and more central. For this reason, the capsaicin is less effective in providing pain relief. Nevertheless, these findings need to be confirmed in a prospective controlled blinded study, preferably with a large sample to enable subgroup analysis to better identify the different pain scores found since far, and the QTT profile of responders.

5. Conclusion

Although there are no clear predictors for response to treatment with capsaicin patch, several attempts have been made. It is clear that there is a relationship between pain scores and response to treatment. The most probable patients to benefit from capsaicin patch treatment should be the ones with less than 6 month to 1 year of preexisting pain and high variability with pain scores, thus with a recent chronic pain problem, where no central sensitization has developed, or yet organized. It also seems clear that sensory symptoms can be useful to predict treatment response. But here there must be some more research to be done, as the number of patients under investigation is low, and studies have found different sensory abnormalities. Studies could not be compared as the methods were different too. Even though, there seems to be a tendency for the burning-heat sensations and the pressure sensations to be useful as predictors of treatment response. Also, a combination of the 4 mentioned above (recent chronic pain development with high variability in pain scores previous to treatment and with burning/heat-pain and/or pressure-pain sensory symptoms) could give a very high predictability of treatment response, lowering de NNT to almost 1.

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Nomenclature

BMI	body mass index
BPIS	baseline pain intensity score
CP8%	capsaicin patch
CS	central sensitizaion
EMA	European Medical Agency
HIV-AN	human immunodeficiency virus associated neuropathy
HPT	heat pain threshold
MPQ	McGill pain questionnaire
NNT	number needed to treat
NP	neuropathic pain
NPRS	numeric pain rating scale
NSA	neurological/sensory assessment
PeNP	peripheral neuropathic pain
PeLNP	localized PeNP
PHN	post-herpetic neuralgia
QTT	quantitative thermal testing
QST	quantitative sensory testing
RCT	randomized controlled trials
SEM	standard error of the mean
TRPV1	transient receptor potential vanilloid 1
WST	warm sensation threshold

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The enormous field of this topic is clearly shown by the following facts: during the last ten years (2007-2016) around 500 papers/ year and 523 review articles are listed in the PubMed database on capsaicin, and over 200/year are under keywords of "capsaicin human". Recently, two major studies on the mortality of consumers of spicy food containing capsaicin and nonconsumers (over 350000 men and women aged 30–79 with heart disease, cancer, and stroke at baseline over 3.5 million person-years, 2004–2013) showed that the relative risk in total mortality was reduced by 14% in 10 diverse geographic areas of China (2015). Similarly, in the USA, (16,179 participants during over 2,70,000 person/year with the median of 18.9 years) the total mortality was reduced by 13% in populations consuming hot chili (2017). Recently, the book series "Progress in Drug Research" the 68th volume dealt for the first time on "Capsaicin as a Therapeutic Molecule" (Springer, Basel, 2014).

Five excellent chapters are found in this book dealing with procedures of capsaicin from capsicum plants, emerging technologies to improve capsaicin delivery, capsaicinoid diversity and its human food preference, capsaicin and lipid metabolism, and predictors in treatment response to capsaicin. The results of these observations clearly indicate that the capsaicin research has changed direction to include human medical treatment with capsaicin.

The book gathers knowledge from experts in basic and clinical sciences, pharmacologists, in the nutrition and food industry, in the drug industry, technologists, plant cultivators, as well as experts across a wide scale of medical branches.

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