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

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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 µg/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 (GCP) 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.

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 (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 diversity 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, O 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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