REVIEW PAPER

Health-promoting properties of compounds derived from *Capsicum* sp.
A review

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Summary

This article presents multidirectional effects of capsaicin and its natural derivatives as well as natural and synthetic analogs in term of their therapeutic properties. Active agents present in various *Capsicum* genus plants exert analgesic, anti-inflammatory, antibacterial, antioxidant and gastroprotective effects. Furthermore, capsaicin positively influences the metabolism of lipids. Numerous research show that capsaicinoids inhibit proliferation and migration process of cancer cells, what makes them molecules of high interest in oncology. Among broad range of positive activities, we have focused only on those properties that have already found application in medicine or seemed to be the most probably used in the near future. Even if in low or single doses this compound has been reported successful in numerous therapies, the negative consequences of high doses or prolonged administration is also discussed in the review.

Key words: *capsaicin, capsaicinoids, capsaicin derivatives, capsaicin analogs, multidirectional activity, toxicity*

INTRODUCTION

Capsaicin (CAP, 8-methyl-N-vanillyl-6-nonenamide) is responsible for hot and spicy flavor of various types of chili peppers – plants which represent *Capsicum* L. genus and belong to *Solanaceae* family. The most common among all wild and domesticated

species are *Capsicum annuum* L., *Capsicum baccatum* L., *Capsicum chinense* Jacq., *Capsicum frutescens* L., and *Capsicum pubescens* Ruiz & Pav. Average content of capsaicin comprises about 0.1 to 1% of total weight of peppers. The highest amount was reported in representatives of *Carolina Reaper* species (Ed Currie) (a cultivar of chili peeper of the *C. chinense* species, originally named HP22B) which has on average 1 569 3000 SHU (*Scoville hotness unit*), reaching records of over 2 000 000 SHU.

Capsaicin is a chemical compound belonging to phenylalkylamines, called capsaicinoids – one of alkaloids [1]. It has a form of white or red-orange crystal substance of molar mass 305.40 g/mol. Due to its chemical structure (tab. 1) capsaicin does not dissolve in water, but is soluble in alcohol and fats [2]. Pure capsaicin in crystal form was isolated by American scientist John Clough Thresh in 1876 [3, 4] but chemical structure of this compound was proposed for the first time in 1919 by E.K. Nelson and L.E. Dawson. To obtain 2.13 g of pure, crystal form of capsaicin 1.5 kg of African pepper was extracted at 64.5°C by Micko method [5]. The first successful attempt to obtain a synthetic form of this compound was taken by E. Späth and S.F. Darling in 1930 [6].

Table 1.

Names and chemical structures of natural capsaicin molecule, with marked similarities in structure for the whole group of capsaicinoids, as well as its natural derivatives and natural and synthetic analogs [8]

<p style="text-align: center;">natural capsaicin N-(4-Hydroxy-3-methoxybenzyl)-8-methyl-6-nonenamide</p>	
Natural derivatives
<p style="text-align: center;">dihydrocapsaicin N-(4-Hydroxy-3-methoxybenzyl)-8-methylnonanamide</p>	<p style="text-align: center;">homodihydrocapsaicin N-(4-Hydroxy-3-methoxybenzyl)-9-methyldecenamide</p>
Natural analogs
<p style="text-align: center;">nordihydrocapsaicin N-(4-Hydroxy-3-methoxybenzyl)-7-methyloctenamide</p>	<p style="text-align: center;">capsiate 4-Hydroxy-3-methoxybenzyl (E)-8-methyl-6-nonenolate</p>

Synthetic analogs

synthetic capsaicin, nonivamide
N-(4-Hydroxy-3-methoxybenzyl)-nonanamide

palvanil
N-(4-Hydroxy-3-methoxybenzyl)-hexadecanamide

arvanil
N-(4-Hydroxy-3-methoxybenzyl)-5,8,11,14-eicosatetraenamide

olvanil
N-(4-Hydroxy-3-methoxybenzyl)-9-oleamide

phenylacetylirinvanil
N-(4-Hydroxy-3-methoxybenzyl)-12-(phenylacetyl)-octadec-9-enamide

All capsaicinoids, in terms of the chemical structure, are quite similar to capsaicin, because they preserve the aromatic catechol ring and the amide bond, but they differ in the fatty acid side chain and variable number of carbon-carbon double bonds (tab. 1). For this reason, compounds are diversified in terms of pungency level and biological activity. Among other natural capsaicinoids which have very similar features to CAP, dihydrocapsaicin (8-methyl-N-vanillyl-nonamide), homodihydrocapsaicin (9-methyl-N-vanillyl-decamide), and nordihydrocapsaicin (7-methyl-N-vanillyl-octamides) are noteworthy [7, 8]. Capsaicin and dihydrocapsaicin pose the greatest content, as about 90% of all capsaicinoids naturally occurring in peppers with the highest pungency level [9]. Significantly lower content of capsicum cultivars are the capsinoids such as capsiate, which are novel, natural, non-pungent and easily dissolving in the aqueous conditions capsaicin analogs. Besides, capsinoids have an ester bond as compared with the amide bond presented in capsaicin structure, which makes the differences in the pharmacological effects of these two groups of substances [10]. Nowadays, more and more attention is also paid to the use of synthetic CAP analogs such as nonivamide, palvanil, arvanil, olvanil or phenylacetylirinvanil in medical practice, mainly due to lower costs of their production and increased safety in clinical application [8]. The names and chemical structures of capsaicin molecule as well

as its natural derivatives and natural and synthetic analogs are summarized in table 1.

Capsaicin as a plant origin compound exerts multidirectional influence on human organism. Observations of the last decades prove that active compounds present in plants may become an alternative therapeutic strategy for many diseases which cannot be treated by contemporary medicine. One of the increasingly developing branches of healthcare is chemoprevention. It uses substances of natural origin in order to decrease the risk of cancer development or to inhibit the process of carcinogenesis [11]. Capsaicin is also extensively studied in terms of use in gastroenterology (gastroesophageal reflux, peptic ulcer) as well as treatment of pain (especially occurring in the course of chronic diseases), obesity and infections [12].

Moreover, stimulating effect of CAP on the cardiovascular system by improving the heart rate, vasodilatation, alleviating hypertension and improving glucose metabolism has been revealed [13]. Clinical study results also indicate the potential use of this compound in patients with rhinitis and particularly its idiopathic form [14,15].

A systematic review of the literature published mainly in 2010–2016 and closely related to the given keywords was performed and analyzed. This article summarizes a broad spectrum of biological activities of capsaicin and its potential use in clinical medicine such as analgesic, anti-inflammatory and antibacterial properties. In addition, we discuss the latest scientific reports on the impact of CAP and its analogs on lipid metabolism as well as anti-cancer activity. Noteworthy, this compound for many years has not only brought a hope, but also controversies, especially within the context of dose and the duration of treatment (tab. 2).

Table 2.

Potential therapeutical use of capsaicin and its doses with regard to the selection of the study (the effective dose in case of each study is bold)

Medical properties	Potential clinical use	Mechanism of action	Dose	Selection of the study	Reference
Analgesic effect	to avoid inflammatory hyperalgesia	inactivation of TRPV1 receptor	10 µg; i.p.	<i>in vivo</i> (mice)	25
	diabetic peripheral neuropathy (DPN)		0.75% cream		26
	chronic pain arising from postherpetic neuralgia (PHN) or HIV-neuropathy		8% topical capsaicin	clinical trials	28
	osteoarthritis pain		0.025 to 0.075% topical capsaicin		30
Gastro-protective influence	GERD symptoms, gastric ulcer, chronic gastritis, eradication of <i>H. pylori</i>	activation of TRPV1 receptors, secretion of CGRP, neurokinin A, somatostatin, nitric oxide	0,1 µg/kg	<i>in vivo</i> (rats)	40
			> 10 µg/ml		43
			100 ppm		46

Medical properties	Potential clinical use	Mechanism of action	Dose	Selection of the study	Reference
Anti-obesity effect	obesity	upregulate PGC-1 α mRNA in liver, enhance mitochondrial β -oxidation activating PPAR α transcription	0.015% dietary capsaicin	<i>in vivo</i> (mice)	54
		increase levels of HMG-CoA reductase, CPT-1, FAT/CD36, GLUT4, promote the lipid metabolism in liver and adipose tissue	5% capsaicin	<i>in vivo</i> (mice)	55
		up-regulation of Cx43 by TRPV-1 activation	0.01%	<i>in vivo</i> (mice)	57
Anticancer properties	colorectal cancer	increase ROS production, activation of caspase 3	0.1, 0.2, 0.3, 0.4, 0.5 mM		69
	pancreatic cancer	increase ROS generation, expression of Bax, down-regulation of bcl-2	150 μ M		70
	bladder tumor	induce apoptosis by activating DCs <i>via</i> CD9, increase ROS production, inhibit of CDK2, CDK4 and CDK6	50, 100, 150, 200 μ mol/L		71, 72
	gastric cancer	decrease at mitochondrial and increase at cytosolic level of cytochrome c	25, 50, 100 μ M	<i>in vitro</i>	73
	breast cancer	increase the expression level of E-cadherin and decrease the secretion of MMP-2 and 9	10, 25, 50 μ g/ml		78
	hepatocellular carcinoma	increase CL-PARP and Bcl-2 levels, inhibiting ROS-STAT3-dependent autophagy	50, 100 and 200 μ mol/L		79
	melanoma	down-regulation the Bcl-2	200 μ M		80
	pancreatic cancer	activation of JNK, increase the expression of Bax, cytochrome c, AIF and caspase-3	2.5 mg capsaicin/kg b.w. p.os. and 5.0 mg/kg b.w.		70
	lung cancer	inhibit MMP-2 and 9 expression, decrease the amount of ECM components	10 mg/kg b.w. dissolved in olive oil i.p.	<i>in vivo</i> (mice)	74, 75
	prostate cancer	reduction in proliferation and NFkB expression, increase in DNA damage	5 mg/kg b.w. (0,2M ethanol solution) p.os.		76, 77

Analgesic and anti-inflammatory activities

As a result of the latest research conducted in past decades, capsaicin has revealed strong analgesic properties. Mechanism of relieving pain is closely connected with CAP influence on TRPV1 receptors (*transient receptor potential vanilloid type 1*) located in nociceptors of peripheral neurons [16]. The TRPV1, also known

as capsaicin receptor, was discovered in 1997 by Caterin *et al.* [17, 18]. It is one of the earliest studied receptor among all 6 receptors which belong to a family of nonselective TRP ion channels activated by temperature. It is characterized by especially high permeability for Ca^{2+} ions. The highest expression is observed in endings of peripheral nociceptors and other sensory neurons. Moreover, TRPV1 is also located in cells of vascular endothelium, epithelium, hepatocytes, adipocytes, cells of smooth muscles, mast cells, fibroblasts, and also in astrocytes of brain and the spinal cord [19].

TRPV1 differs from other receptors of this group by its polymodality, so that can be activated not only by exogenous, but also endogenous physical and chemical stimuli. Among physical factors, the most important for organism's homeostasis are stimulation of those receptors by high temperature (higher than 43°C), low pH values and the presence of other cations as well as endogenous vanilloids including 15-hydroperoxyeicosa-(5Z,8Z,11Z,13E)-tetraenoic acid (15(S)-HPETE) produced by lipoxygenase [20-23].

Activation of TRPV1 by pain stimuli causes immediate opening of ion channel and inflow of calcium ions to synaptic vesicle. In turn, it facilitates migration of presynaptic vesicles which are released to synaptic cleft in exocytosis. It results in activation of postsynaptic membrane and generation of mediators which have proinflammatory properties such as CGRP (calcitonin gene related peptide) or P substance [24]. As it may seem, there is an internal contradiction. How may capsaicin cause analgesic effect when it is an antagonist of TRPV1 which aim is to activate pain sensation? It turned out that long-term stimulation of TRPV1 by capsaicin causes a change of its spatial conformation and leads to the inactivation of this receptor, thus making sensation of pain imperceptible. Furthermore, analgesic activity of CAP is significantly increased during inflammation, what may become extremely important in the avoidance of hyperalgesia (which occurs in acute inflammations). Currently, capsaicin is used in patients with peripheral neuropathy, especially diabetic, postherpetic neuralgia caused by zoster, muscle and joints pains, rheumatoid arthritis, osteoarthritis and in case of sciatica and brachialgia. Usually, it is administered as an ointment but due to poor absorption through the skin it is more and more often advised to use in a form of sticking plaster in concentration of 0.025% or 0.075% [25-31]. Moreover, the use of high-doses of capsaicin might rapidly provide therapeutic effects for brachioradial pruritus and notalgia paraesthetica patients with almost no side-effects [32].

Anti-inflammatory properties of capsaicin have been widely confirmed. According to latest reports, CAP may inhibit the development of inflammation in the area of joints and gastric mucosa when etiology leads to increased intake of ethanol or aspirine (acetylsalicylic acid, ASA). It turns out that this compound in TRPV1 receptors dependent way decreases expression of induced nitric oxide synthase (iNOS), reduces activity of cyclooxygenase type 2 (COX-2), and it disrupts NF- κ B signaling pathway (nuclear factor kappa-light-chain-enhancer of activated B cells) in macrophages [33-35]. Special role in inhibiting inflammatory process

generated by bacterial LPS (lipopolysaccharide) has LXR α (liver X receptor alpha). Capsaicin as an agonist of LXR α significantly disturbs NF- κ B, which is responsible for the production of cytokines regulating cell response such as TNF- α , IL-1, IL-6, IL-8, and adhesive molecules, which final effect is the migration of leukocytes to places of ongoing inflammation [36]. Research on experimental animal model proves that CAP exerts anti-inflammatory properties during inhibition of PGE₂ production (prostaglandin type 2), which is a mediator of inflammatory process and has strong chemotactic influence on leukocytes [37]. Moreover, anti-inflammatory effects of capsaicin are comparable to activity of diclofenac, which is a nonsteroidal anti-inflammatory drug (NSAID). Conclusions were based on systematic measurement of leukocytes, corticosterone and CRP (C-reactive protein) in serum as biomarkers of ongoing inflammatory process [38]. To sum up, capsaicin turns out to be not only an analgetic, but also useful natural drug able to stop or limit inflammatory process.

Gastroprotective activity

Diseases of digestive system are currently one of the major health problems. Fast pace of life, stress and inadequate nutrition may cause gastrointestinal afflictions. The latest epidemiological data report that one of the most frequent digestive diseases is peptic ulcer disease involving stomach and/or duodenum. In 60% of cases it involves first part of small intestine. It is commonly believed that one of the main etiological factors of the disease is chronic use of nonsteroidal anti-inflammatory drugs such as piroxicam, indometacin, ketoprofen, ibuprofen, and nabumetone. These drugs cause not only systemic, but also local changes. Pharmacological effects are based mainly on inhibiting activity of cyclooxygenase type 1 (COX-1). It leads to decrease in production of prostaglandins (PGE₁, PGE₂) and prostacyclin (PGI₂), which in physiological conditions have a protective influence on gastric membrane. Prolonged use of these drugs causes a decrease in production of mucus by goblet cells of gastric mucosa and secretion of bicarbonates, thus the natural barrier of this organ is disturbed. This condition significantly contributes to irritations and increases the risk of gastric ulcers. A totally new view on CAP influence on digestive system is presented by the latest results of research which prove that regular intake of small doses of capsaicin in amounts of about 0.1 μ g/kg of rat's body weight has a protective influence on gastric mucosa subjected to activity of aspirin, 96% concentrated ethanol or 0.6 molar solution of hydrochloric acid [39-41]. Moreover, capsaicin may inhibit processes of mucosa damage induced by indometacin. Gastroprotective influence of capsaicin is based on affecting TRPV1 receptors located in endings of sensory nerves in the area of gastric mucosa [42, 43]. Effect of their activation is secretion of CGRP, neurokinin A, somatostatin, or nitric oxide which have vasodilatative influence and significantly contribute to improvement of blood flow through gastric mucosa.

The attention should be also paid to the safety of co-administration therapy of NSAIDs, such as aspirin, with capsaicin. Clinical studies indicate that CAP administered orally at the dose of 400 μg and 800 μg in combination with 500 mg ASA does not affect the anti-aggregation effect caused by ASA. As a result, capsaicin appears to be a useful therapeutic agent in the prevention of gastrointestinal mucosa injury during chronic treatment with the acetylsalicylic acid, especially in patients with coronary artery disease [44].

In turn, other research on potential gastroprotective activity of capsaicin confirm that CAP (in doses higher than 10 $\mu\text{g}/\text{ml}$) causes growth inhibition of *Helicobacter pylori* – bacteria which is the main factor of peptic ulcer disease. However, further research in order to determine precise therapeutic dose regarding pharmacological features are necessary as too high doses of capsaicin may have the opposite effect and even pathological changes in gastric mucosa and liver [45-47].

On the basis of profound and long-term observations of culinary customs of Malaysia and India residents, who due to climatic conditions eat small doses of capsaicin for a long time, it was established that they develop peptic ulcer disease of stomach or duodenum less frequently [47]. Broad application of capsaicin, the major pungent ingredient of various species of red-chili pepper, in gastronomy is a perfect chance to use it as a natural chemopreventive and healing drug.

Antibacterial activity

Human organism is colonized by several thousands of microorganism species. It is estimated that their number exceeds almost ten times the number of our body cells. Some of the microbes may have protective influence on human organism but still, the most of them are opportunistic – they become pathogenic in case of immunodeficiency.

Struggle with the world of microorganisms is still a great challenge for scientists, especially in time of increasing resistance to antibiotics. Capsaicin, as well as its derivative – dihydrocapsaicin, present in extract from *C. annum*, *C. baccatum*, *C. chinense*, *C. frutescens* and *C. pubescens* have bacteriostatic effect towards different species of bacteria, both Gram-positive and Gram-negative [48]. The minimum inhibitory concentration at which the ethyl acetate extract prevented the growth of *Streptococcus mutans* (γ -hemolytic species which is responsible mainly for tooth decay, bacteremia, and infective endocarditis) was 2.5 mg/mL [49]. It was also proved that CAP and its derivative are growth inhibitors of *Salmonella typhimurium*, *Pseudomonas aeruginosa*, *Bacillus cereus*, *B. subtilis*, *Clostridium tetani*, and also *Streptococcus pyogenes* [50, 51]. Mechanisms in which capsaicinoids inhibit bacteria growth are not completely known yet, however it is more and more often said that it is the osmotic stress caused by capsaicin and disorders in expression of genes responsible for cell growth and proper structure of cell membrane.

Antiobesity activity

Struggle with obesity and endeavor to have a slim figure is a problem of not only contemporary, but also ancient medicine. It engages work of doctors of various specialties and among them there are groups of endocrinologists, diabetologists, and cardiologists. Diabetes and obesity are an important issue because of many reports that prove they are growing to a scale of 21st century epidemic. From a medical point of view it is important that insulin resistance develops in the course of both, obesity and NIDDM (non-insulin-dependent diabetes mellitus). Research conducted over many years worldwide show that capsaicin may become a perfect remedy to combat with those afflictions because it has multidirectional influence on lipids metabolism. CAP as well as dihydrocapsaicin and capsiate, as strong agonists of TRPV1 receptor cause significant increase in amount of proteins engaged in thermogenesis processes in the area of brown adipose tissue and they contribute to inhibition of transformation of preadipocytes to adipocytes of white adipose tissue [52, 53]. Therefore, these natural compounds seem to be promising dietary supplement, which not only help to prevent obesity, but also help to fight it by activation of fatty acid oxidation in adipose tissue and/or in liver [54]. In the theme of slimming activity of capsaicinoids, they significantly speed up lipids metabolism not only in brown adipose tissue (BAT), but also in the liver [19]. Level of changes activity was assessed on the basis of measurement of expression of genes responsible for coding of reductase HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A – an enzyme taking part in transformations of mevalonic acid and engaged in production of cholesterol and other isoprenoids), CPT-1 (carnitine palmitoyltransferase I; enzyme of β -oxidation of long chain fatty acids), FAT/CD36 (integral membrane protein taking part in an uptake of long chain fatty acids) and GLUT4 (glucose transporter type 4 which is responsible for the transport of glucose to a cell in insulin-dependent mechanism), which amounts increased noticeably. Additionally, decreased accumulation of fats in adipocytes was observed. Many research confirm also other mechanisms of metabolism regulation by capsaicin. CAP increases adrenaline and nor-adrenaline secretion from adrenal medulla and thus it contributes to loss of body weight. Moreover, stimulation of UCP1 (uncoupling protein 1) expression in brown adipose tissue and adrenaline concentration in the serum leads to reduction of significant amount of perirenal adipose tissue [55]. Mice feed with high-fat diet (HFD), in which TRPV1 receptor was blocked and simultaneously capsaicin was administered, developed higher index of insulin resistance than mice with properly functioning receptor. Universal biomarkers of insulin and lectin resistance were measured on the basis of genes which code them. CAP, by activating TRPV1 located in the endings of nerves cause initiation of afferent impulsation through vagus nerve which, in turn, by central regulation leads to increase the activity of sympathetic system in a selective ways towards adipose tissue. It does not cause any adverse effects to other organs, for example to heart [56, 57]. Capsaicin also regulates the appetite. The research show that it reduces appetite on fatty, salty, and sweet foods

and it increases feeling of satiety after meal. Furthermore, capsaicin has been found to influence on condition of women with gestational diabetes mellitus (GDM) and frequency of large-for-gestational-age (LGA) in children, whose mothers were subjected to capsaicin supplementation [58]. CAP contributed to regulation of postprandial hyperglycemia, hiperinsulinemia, and metabolism of lipids on an empty stomach, and also it significantly decreased the number of infants with LGA.

The results of scientific research show that analogs of CAP have also potential anti-obesity properties. One of these natural compounds with similar properties to capsaicin is capsiate. Its supplementation in daily dose of 6 mg for 12 weeks causes decrease of abdominal adipose tissue [59]. Studies on animal experimental model confirmed that administration of 5 ml/kg b.w. of capsiate solution led to up-regulation of UCPs in skeletal muscle and BAT. Moreover, *in vivo* studies have shown that body weight was equal in case of mice which have an administration of capsiate solution (6.48 mmol/l) and the group of mice which exercised in the pool three times a week for two weeks [60].

Among the non-pungent, synthetic capsaicin analogs obtained by enzymatic synthesis, only nonivamide demonstrated capability for regulating lipid metabolism. Recent scientific reports indicate that probably also olvanil improves lipolysis and interferes in the process of maturation of preadipocytes into adipocytes by changes in PPAR γ activity. Other compounds such as palvanil, arvanil or phenylacetylrlinvanil have not exerted any effects on the lipid metabolism [8, 61].

Current results of the research unambiguously stress important role of capsaicin in combating with obesity [62]. While many previous *in vitro* and on the animal experimental model studies have proved the impact of dietary supplements containing capsaicinoids on weight/fat loss, the number of clinical trials is still insufficient. One of them is a randomized, placebo controlled, double-blind, cross-over study involving 20 participants (male: $n=10$, female: $n=10$) which were administered orally with low dose (2 mg) of capsaicinoids in a microencapsulated matrix (CapsimaxTM, containing 2% capsaicinoids of which 1.2–1.35% was capsaicin, 0.6–0.8% was dihydrocapsaicin and 0.1–0.2% was nordihydrocapsaicin) [63]. The study indicates that in contrast to previous research that have reported increased lipolysis after administration capsaicinoids in doses ranging from 3 mg to over 150 mg, elevated level of free fatty acids (FFA) (2 h and 2.5 h) and glycerol (4 h) concentrations in blood samples were noted in response to low dose of capsaicinoids intake, without side effects, especially gastric upset and discomfort. However, in order to ensure safety of capsaicin administration to patients further research are needed and the effective therapeutic dose based on kilogram body weight rather than a standard dosage should be determined as in two cases (41-year-old male patient with no cardiovascular risk factors and 25-year-old men who denied using stimulants e.g., alcohol, butane, cigarettes, cocaine, amphetamines and marijuana, had no cardiac risk factors for coronary artery disease and history of recent emotional or physical stress was excluded) regular intake of Cayenne pepper (a cultivar of *C. annuum*) in order to reduce body mass led to a heart attack [64–65].

Chemopreventive properties and anticancer activity

Cancers are one of the main causes of morbidity and mortality. It is estimated that the number of new cases will increase by about 70% in the course of the nearest two decades [66]. Despite many years of efforts of scientists all over the world, there is still no effective medication for this disease and treatment of oncologic patients, especially in case of cancers with metastases. That is why the use of capsaicin in chemoprevention and cancer therapies is a great hope in oncology.

Properties of capsaicin as an anticancer agent are widely discussed. Scientific research from the last few years give indisputable evidences of its anticarcinogenic and antioxidant activity, what makes capsaicin the best of natural remedies which in the nearest future may be widely used in chemoprevention [67]. So far, inhibiting effect of CAP on development of lung cancer, colorectal cancer, stomach cancer, pancreatic cancer, skin and bladder cancer was confirmed [68]. Also there are ongoing research on influence of CAP on cells of melanoma, glioma, prostate cancer, breast cancer and hepatocellular carcinoma in order to precisely determine mechanisms and effects of this substance on carcinogenesis process.

Currently, one of the best described mechanisms of capsaicinoids influence on cancerous process was devised on the basis of human cell line of colorectal cancer [69]. Influence of capsaicin on apoptosis process induction was studied on cancerous cell line Colo320DM and LoVo. Treatment of colorectal cancer with capsaicin at concentration range from 0.1 to 0.5 mM for 24 hours caused noticeable apoptosis and inhibition of cancerous process. Significant decrease in cell viability was observed (morphological changes, fragmentation and decrease of DNA content in cells, and translocation of phosphatidylserine). Apoptosis process may be induced not only by intracellular, but also extracellular mechanisms which final effect is activation of specific endonucleases able to fragmentation of genetic material and consequently to the so-called programmed cell death (PCD). Capsaicin leads to cell death by induction of increased production of reactive oxygen species (ROS), disturbance of values of mitochondrial intermembrane potential, ATP production and activation of caspase 3 – a key enzyme of intrinsic and extrinsic apoptosis path which lead to degradation of structural and enzymatic proteins in cells.

Anticancer properties of capsaicin have been confirmed in a study on human pancreatic cancer cell lines AsPC-1 and BxPC-3. Induction of apoptosis through capsaicin (in a dose-dependent manner with an IC_{50} of about 150 μ M) takes place not only by ROS generation, but also through down-regulation of Bcl-2, significantly increasing expression of Bax which is a protein from Bcl-2 family accelerating death process of cancerous cells by creating pores in external mitochondrial membrane thus increasing its permeability. Moreover, it also increases secretion of cytochrome c and AIF (Apoptosis Inducing Factor) to cytosol. In addition, capsaicin leads to down-regulation of survivin – a novel inhibitor of apoptosis (IAP) acting by inhibiting of caspases. These effects were not noticed in normal human acinar cells. Furthermore, the efficacy of *in vitro* capsaicin-treatment study was proved by preclinical *in vivo* research on AsPC-1 pancreatic tumor xenografts in

athymic nude mice which have given capsaicin, dissolved in ethanol and then diluted in PBS, orally. It turns out that capsaicin significantly suppresses the growth of tumor xenografts both in the dose of 2.5 mg capsaicin/kg (5 days a week) or 5 mg capsaicin/kg (3 days a week). The mechanisms of induction of apoptosis demonstrated in animal models is in agreement with *in vitro* observations. Results of research unambiguously indicate that capsaicin is an effective inhibitor of pancreatic cancer growth and at the same time it does not cause side effect to normal cells both in *in vivo* and *in vitro* conditions [70].

The role of this alkaloid in bladder cancer and stomach cancer therapies also seems to be very promising [71-73]. Regarding the fact that bladder cancer often entails high risk of recurrence and necessity of use inter-bladder chemotherapy after transurethral resection, and is characterized by high mortality, the use of capsaicin as a natural chemopreventive drug may help to decrease prevalence and even open a new therapeutic strategy to fight with this type of cancer.

Lung cancer is currently the most often cause of death among oncologic patients and holds second place in frequency classification of cancer prevalence. Key role in the process of carcinogenesis of this type of tumor has an extracellular matrix (ECM). Its components are currently considered as important modulators of cell growth and development, inflammatory process, angiogenesis, cellular migration, and tissue repair and diversification.

Special attention should be paid to collagen and elastine, which are the main proteins of connective tissue. Their amount significantly increases in microenvironment of lung cancer in comparison with healthy cells. Animals with benzopyrene induced lung cancer subjected to capsaicin showed significant decrease in collagen and elastine amount and changes in quality and quantity of other components of ECM such as uronic acid, hexosamines, glycosaminoglycans (hyaluronate, chondroitin sulphate, keratan sulfate, dermatan sulfate). Furthermore, capsaicin as one of MMP-2 and 9 (metalloproteinase-2, 9) inhibitor significantly contributes to suppression of lung cancer metastases to other organs [74, 75].

Influence of capsaicin and its structural analogs on prostate cancer and prostate adenocarcinoma, breast cancer, hepatocellular cancer, and melanoma already gives high hopes. Although, there is still a need for further research in order to determine paths and destination of capsaicin influence on cells of these cancers. Due to these findings, capsaicin will be indexed as chemopreventive drugs and it will be widely used in treatment of oncologic disease in the nearest future [76-80].

Toxicity of capsaicin

Despite broad range of beneficial influence of capsaicin on human organism, its toxicity should be taken into consideration because CAP, as every natural origin chemical substance used in therapy, may exert toxic effects after exceeding the safe dose.

Single dose toxicity

The oral LD₅₀ of capsaicin (solution with propylene glycol) in mice was determined to be 97.4 mg/kg b.w. for female and 118.8 mg/kg b.w. for male. Slightly higher values of LD₅₀ were noted in female and male rats and were 148.1 mg/kg b.w. and 161.2 mg/kg b.w., respectively [81, 82]. The major observed symptoms after administration above-mentioned doses were salivation, convulsion, erythema of skin and bradypnoea in both animals and the death occurred within 26 minutes after administration of capsaicin. The lethal dose of CAP is diversified according to the route of administration. Significantly higher doses appear to be toxic for topical administration (>512 mg/kg b.w., mice) compared to rectal administration (>218 mg/kg b.w., mice), intratracheal (1.03–2.48 mg/kg b.w., mice) or intravenous (0.36–0.87 mg/kg b.w., mice) [82].

Repeated dose toxicity

Safety of long-term intake of capsaicin are confirmed by results of one of the few research in which capsaicin was administered intragastrically to rats for 28 days (daily doses: a low dose 0.025 g d.m. Habanero fruit/kg b.w., a medium dose: 0.05 g d.m. Habanero fruit/kg b.w., a high dose: 0.08 g d.m. Habanero fruit/kg b.w.). In the experiment no changes in hematologic parameters and histopathologic post-mortem examination of organs were stated. Moreover, parameters of kidneys and liver functions were also undisturbed [83]. The results of another study demonstrate that chronic (60 days) orally administration of capsaicin derived from *C. baccatum* extract at the dose of 200 mg/kg b.w./day, revealed no significant side effects without eosinophilia in day 29 of administration. However, it is underlined that this changes might be caused by the allergic reaction on peanut oil in which the tested substance was suspended [84].

Contraindications, interactions with other drugs

Contraindications in the use of capsaicin and interactions with other drugs are not well known. It is worth mentioning that capsaicin as the cytochrome P450 (CYP) enzymes inhibitor can increase the metabolism of drugs that are CYP substrates and at the same time modify their pharmacokinetic profiles [85]. The study revealed CAP is the most potent inhibitor of CYP3A4, subsequently CYP1A2, CYP2C9 and it presents weak activity towards CYP2D6. Researches on animal model (rats) showed that orally administration of high doses of capsaicin (3, 8 or 25 mg/kg for seven days and on the seventh day 80 mg/kg) significantly reduces bioavailability of simvastatin, one of the most common lipid-lowering clinically used drug, metabolized by CYP3A4 [86, 87]. It has also been demonstrated that capsaicin influences the pharmacokinetics of galantamine, a competitive and reversible cholinesterase inhibitor, mainly metabolized by CYP3A4 and CYP2D6 [88].

Topical application of capsaicin is contraindicated in the case of irritated, damaged skin and hypersensitivity to capsaicin. It should not be applied on skin of the face, the area above the hairline of the skull and the mucosal membrane. Interactions with other drugs during external use are not full-understood due to small and short systemic absorption. However, there is a case of 53-year-old female patient receiving angiotensin converting enzyme inhibitor (ACEI) with recurrent cough appearing only after application of topical capsaicin 0.075% cream which suggests that capsaicin may cause or exacerbate ACE inhibitor-induced cough [89].

The date on the use of capsaicin during pregnancy and lactation are incomplete [81]. It is recommended to stop breast-feeding on the day of applying the patches containing capsaicin.

Side effects

Currently, only short-term side effects of capsaicin influence are known. However, there are no sufficient scientific evidence which would confirm side effects occurring after long-term of use. Regarding special physico-chemical properties of capsaicinoids, cases of poisoning are extremely rare. It is because high doses of this compound cause extreme spiciness and hotness of food and that is why its consumption is impossible for the most of people. Consequently, intake of dose which would be close to lethal is unreachable in practice. Basic symptoms of capsaicin overdose are problems with breathing, gray-blue skin and convulsions. These symptoms are mainly a reason of TRPV1 receptor activation by capsaicin. Inhalation of high doses of this substance causes increase in activity of parasympathetic nervous system. In turn, it initiates cough reflex, bronchospasm, mucus secretion, dilation of blood vessels, and shortness of breath. Short-term exposition to high doses may be a high risk for asthmatics [90].

For centuries, there was a myth that intake of hot and spicy foods, including compounds found in chili peppers, Habanero (*C. chinense*), and other spices, contributes to development of mouth cancer, laryngeal cancer, tracheal cancer, esophageal cancer, and stomach cancer. Furthermore, the latest research show that capsaicin applied topically on skin may act as carcinogen or co-carcinogen. However, its influence on skin cancers development in case of its oral administration has not been unambiguously determined yet [91]. In the light of conducted research it is thought that whether capsaicin has properties of carcinogen or anti-cancerous is determined by quantity of administered dose and the route of intake.

Dosage and administration

External use

Capsaicin is available for topical application as the active compound of patches and ointments. Most frequently, patches containing dense extract of *C. annuum*

in a quantity corresponding to the content of 6–8 $\mu\text{g}/\text{cm}^2$ capsaicinoids (0.025%, 0.075%; low-dose formulations) as well as 0.64 mg/cm^2 of pure capsaicin (8%; high-dose formulations) are applied on the skin for 30 minutes to one hour. The treatment can be repeated at least 90 days after the previous therapy, particularly in the cases of relapsed pain [92]. Synthetic capsaicin (nonivamide) is used extensively in the form of ointment (0.025–0.05%) as a warming agent to alleviate muscular pain as well as associated with arthritis and neuralgia *ad hoc*, usually 1–2 times a day for no longer than two days. A break before re-application for the same place must be at least 14 days [93, 94].

Internal use

Internal administration of capsaicinoids still raises many controversies, mainly due to the fact that their pharmacokinetics in humans have been still not precisely defined. Nevertheless, scientific observations, in the countries which are known from the spicy dishes, revealed that the daily dose of capsaicin in consumed species range from 25–200 $\text{mg}/\text{person}/\text{day}$ or in the case of a person with 50 kg body weight will be 0.5–4 mg/kg b.w./day. Significantly lower doses was reported for the USA or Europe reaching 0.025 mg/kg b.w./day [70]. Currently, research on the use of the lipid-based formulations of capsaicin, to enhance the bioavailability, to decrease the hot and spicy flavor of that compound and the risk of side effects on gastrointestinal mucosa are conducted. The novel method for the oral administration of nutraceuticals such as capsaicin will be organogel-based nanoemulsion systems (content of CAP: 80.4 mg/ml) which are in the phase of *in vivo* animal studies [95].

CONCLUSIONS

Capsaicin, as well as its natural derivatives, natural and synthetic analogs exert multidirectional influence on human organism engaging various molecular mechanisms and metabolic pathways. Anti-inflammatory and analgesic properties of capsaicinoids, mediated mainly through TRPV1 receptor, are studied extensively and used in clinical practice. Researches on gastroprotective activity of CAP suggest that TRPV1 receptor may be a promising target for the management of peptic ulcer disease, chronic gastritis and eradication of *Helicobacter pylori*. Antibacterial mechanisms of capsaicinoids are not completely known yet. Furthermore, capsaicin is involved in regulation of lipid metabolism, thermogenesis, adipogenesis, and cancer therapy. Therefore, special hopes are put in the use of capsaicin as potential agent in chemoprevention of cancers which therapy is still a huge problem for contemporary oncology. Despite broad range of biological activities of capsaicin, its toxicity should be taken into consideration and the appropriate dose and term of its application should be recommended.

Ethical approval: The conducted research is not related to either human or animal use.

Conflict of interest: Authors declare no conflict of interest.

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PROZDROWOTNE WŁAŚCIWOŚCI SKŁADNIKÓW POCHODZĄCYCH Z *CAPSICUM* SP. PRZEGLĄD

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Streszczenie

Opracowanie przedstawia wielokierunkowe działanie kapsaicyny, jak również jej naturalnych pochodnych oraz naturalnych i syntetycznych analogów pod względem właściwości prozdrowotnych. Związki aktywne obecne w różnych gatunkach roślin z rodzaju *Capsicum* wykazują działanie przeciwbólowe, przeciwzapalne, przeciwbakteryjne, antyoksydacyjne i gastroprotekcyjne. Ponadto, kapsaicyna wpływa korzystnie na metabolizm lipidów. Liczne badania donoszą, że kapsaicynoidy hamują proces proliferacji i migracji komórek nowotworowych, co sprawia, że budzi ona duże zainteresowanie w onkologii. Pośród szerokiego spektrum pozytywnych aktywności, skupiliśmy się tylko na tych właściwościach, które już znalazły zastosowanie w medycynie bądź prawdopodobnie zostaną wykorzystane w najbliższej przyszłości. Nawet jeśli niskie lub pojedyncze dawki tego związku okazały się skuteczne w wielu terapiach, negatywne konsekwencje wynikające z aplikowania wysokich dawek lub długotrwałego stosowania również zostały omówione w przeglądzie.

Słowa kluczowe: kapsaicyna, kapsaicynoidy, pochodne kapsaicyny, analogi kapsaicyny, wielokierunkowe działanie, toksyczność