REVIEW ARTICLE

Capsaicin: Current Understanding in Therapeutic Effects, Drug Interaction, and Bioavailability

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ABSTRACT

Capsaicin (N-vanillyl-8-methyl-6-(E)-none amide) is a unique and significant compound from group component of capsaicinoids. This component can only be found in the plants from the Capsicum genus. It is the primary source of pungency or spiciness of chilli pepper. Traditionally, capsaicin has been used to alleviate pain. Recently, some studies showed significant therapeutic effects of capsaicin in many diseases such as diabetes, hypertension, cancer and obesity. Determination of the most effective dosage used and underlying working mechanism of capsaicin are still in progress. Currently, capsaicin research, especially in drug interaction and encapsulation technologies, has not been reviewed. We aim to report current experimental evidence of capsaicin research focusing on its pharmacological properties, interaction with drugs and ways to improve the bioavailability of capsaicin. It is essential to provide a general orientation for further investigation that can discover more potency of capsaicin usage as a medicinal supplement to treat various diseases.

Keywords: Anti-obesity, Antioxidant, Capsaicin, Capsicum, Chronic disease

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INTRODUCTION

Chillies belong to the genus Capsicum, the most prominent genus in the family of *Solanaceae*. Chillies fruits are botanically berries. The fruits vary in shapes and depend on different species and varieties (1).

The extreme variability in fruit characters has caused insufficient diagnostic features in chillies crops. For commercial purposes, classification of chilli products is based on the variations in pungency, colour, flavour, their uses, the size and shape of the fruits (2). Despite the unstable taxonomy and the lack of a general agreement upon nomenclature, only some 38 species are recognized, of which five species have been domesticated (2). The domesticated species are divided into *Capsicum annuum* L., *C. chinense* Jacq., *C. frustescens* L., *C. baccatum* L. and *C. pubescens* (1).

Capsaicinoids consist of a group of related alkaloid compounds that only exists in the Capsicum genus. This group of a compound is produced as secondary metabolites by chillies. According to Thiele et al. (3), the biosynthesis of capsaicinoids starts by condensation of fatty acids and vanillylamine where the placenta of pepper is the primary site for capsaicinoids biosynthesis. It is the variation in the acyl group that determines the quantity of the burning sensation of chillies (4). The group of capsaicinoids includes unique components such as capsaicin, dihydrocapsaicin, nordihydrocapsaicin, and nonivamide that are found in the raw form of chillies. The total capsaicinoids level in the extract of fresh chillies was reflective of the relative 'hotness' of the chilli (5).

N-vanillyl-8-methyl-6-(E)-noneamide, or capsaicin, is the primary active component from the group component of capsaicinoids. It is also a unique component that existed in the Capsicum genus (5). A dominant gene determines the presence of capsaicin in chilli, but it is the action of polygenes acting in a cumulative manner that determines the various degrees of pungency. Fattori et al. (6) stated that the absorption of capsaicin reaching up to 94% of absorption due to its chemical structure when administered topically or orally. The structure of capsaicin is shown in Fig. 1.

Chilli peppers were probably first used as a medicinal plant before its usage for cooking. The Mayans used

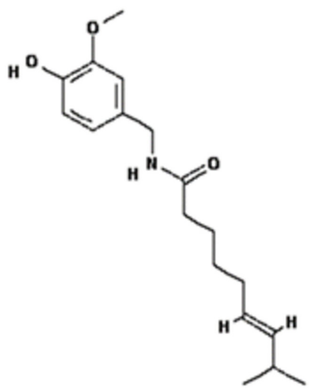

Figure 1: Structure of capsaicin

chillies to treats asthma, coughs and sore throats (8). In Columbia, the Tukano group use chilli peppers to relieve a hangover (9). According to Bosland et al. (10), the Aztecs and Mayan mixed pepper with maize flour to produce chillatolli as the remedy for the common cold. The Teenek (Huastec) Indian of Mexico used chilli peppers to cure infected wounds. Some other uses include putting red crushed fruits on feet to cure athlete's foot fungus, and to cure snakebite by making a drink from boiled green fruit. Medicinally, capsaicin is being used to alleviate pain (11). A cream containing capsaicin is used to reduce the pain associated with the post-operative pain for mastectomy patient (10). The potency of capsaicin usage is then slowly discovered and widened in the medical field.

This review summarizes recent 10 years of studies on therapeutic effects of capsaicin, interaction with drugs and improved capsaicin's bioavailability by using novel encapsulation technologies (Table I).

THERAPEUTIC EFFECT

Antioxidant

According to Gangabhagirathi and Joshi (31), capsaicin

Table I: Summary table for capsaicin research on animal, human and in-vitro studies

Types of Study	Reference No.	Year	Property	Subjects	Form of capsaicin	Dosage	Treatment Duration	Result
Animal studies	12	2005	Anti-hypertensive	dogs	Pure capsaicin (IV injection)	0 – 0.3 mg/kg	14 days	- High dose of capsaicin does not alter duration of cardiac action potential. - Maximum dosage of capsaicin used only caused very minimal organ toxicity. - Capsaicin is rapidly eliminated from body system.
	14	2007	Drug interaction	Rats intestinal tissue	Pure capsaicin	10 – 400 µM	-	- Capsaicin affect intestinal cephalexin absorption.
	15	2010	Anti-hypertensive	Human umbilical vein endothelial cells (HUVEC)	- *Capsicum* spp. extract - Pure capsaicin	1000 µg/ml (extract) 25 µM (pure capsaicin)	-	- Did not induce cytotoxicity in HUVEC - Improved endothelial function - Protected against LPS-induced apoptosis
	16	2010	Anti-obesity	Obese mice	- Pure capsaicin	0.015% in diet	10 weeks	- Dietary capsaicin suppress inflammatory response, reduce obesity-induced diabetes
	17	2010	Encapsulation technologies	Rats	- Cylcodextrin complexion formulation capsaicin - Pure capsaicin	1 g (complexion injection) 10 mg/kg (dorsal subcutaneous tissue injection)	-	- Permeability of capsaicin through subcutaneous tissues was enhanced
	18	2013	Anti-cancer	Mice	- Pure capsaicin	10 mg/kg BW	15 weeks	- Capsaicin inhibit development of mice lung carcinogenesis through apoptosis
	20	2013	Antioxidant	Microorganism	- Microemulsion of capsaicin	1 – 50 µg/ml	-	- Microemulsion of capsaicin has higher antioxidant activity than synthetic antioxidant BHT - effective inhibition for *S. aureus, Salmonella enteric* & *E. coli.*
	21	2013	Drug interaction	Rats	- Pure capsaicin	0.3 – 3 mg/kg	1 week pretreatment before administration of drug	- High dose of capsaicin significantly increase bioavailability of CyA in rats. - Mechanism of capsaicin reaction to drugs due to modulation of P-gp and CYP3A gene expression
	22	2014	Anti-hypertensive	Wild type & TRPV-/- mouse model, M1-CCD cells from mouse renal	- Pure capsaicin	1 µM/L	-	- TRPV1 activation by dietary capsaicin increased urinary sodium excretion through sodium reabsorption in wild-type mice
	24	2014	Anti-obesity	Wild type & TRPV-/- mouse model, preadipocytes & fat pad from mice	Pure capsaicin	0.01% in normal and high fat diet	- 26 weeks	- Activation of TRPV1 by dietary capsaicin triggered browning of white adipose tissue (WAT)
	25	2014	Anti-obesity	Bovine bone marrow mesenchymal stem cells (BMSC)	- Pure capsacin	0 – 10 µM	6 days	- Capsaicin inhibits fat deposition by triggered apoptosis of cells. - Capsaicin decreased mRNA expression of adipogenesis-related genes.
	27	2014	Anti-tumor	Rat hind paw	- Ethyl acetate extract of *C. frutescens* - Pure capsaicin	2.5 – 10 mg/kg (extract) 8 mg/kg (pure capsaicin)	2 weeks	- Both chili extract and capsaicin reduce thromboembolism

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Table I: Summary table for capsaicin research on animal, human and in-vitro studies (Continued)

Types of Study	Reference No.	Year	Property	Subjects	Form of capsaicin	Dosage	Treatment Duration	Result
Animal studies	28	2014	Encapsulation technologies	Rats	Capsaicinoid-loaded poly-microparticles	30 mg/kg (orally)	15 days	- Microencapsulation increased gastric tolerability because it prevented inflammatory process in rats' stomach.
	29	2014	Encapsulation technologies	Rats	- Capsaicin-loaded micelle - Pure capsaicin	90 mg/kg (oral administration)	2 hours	- Exhibited prolonged plasma circulation with improved oral bioavailability - Reduced irritation on gastric mucosa - Solubility of capsaicin significantly improved - Absorption of capsaicin in micelle was facilitated.
	31	2015	Antioxidant	Rat liver mitochondrial membrane	Pure capsaicin	5 – 50 µM	Up to 10 µs	- Inhibit gamma radiation-induced lipid peroxidation and protein oxidation
	32	2015	Antioxidant	High-fat diet fed mice	Pure capsaicin	5 mg/kg	4 weeks (intragastcal)	- Reduce high fat diet-induced oxidative stress & organ damage markers. - Combination of capsaicin and vitamin E decrease weight, fat pad and inflammation
	33	2015	Drug interaction	Rats	Pure capsaicin	3 -25 mg/kg	1 week pretreatment	- Chronic ingestion (start from 8 mg/kg) of capsaicin increases the bioavailability of pitavastatin in rats - Oatplb2 gene expression in rat liver is little affected by capsaicin
	34	2016	Anti-inflammation	Mice's bladder	Capsaicin from chili extract	3mM (capsaicin) 30mM (capsaicin-loaded liposome)	24 hours	- Capsaicin-loaded liposome provide protective effect to irritative action of capsaicin to bladder.
	36	2016	Encapsulation technologies	Rats' stomach	Pure capsaicin	9 0mg/kg (oral gavage)	6 hours	- Reduced rat gastric mucosa irritation by reducing direct contact between capsaicin and surface of gastric mucosa.
	37	2017	Anti-diabetic	Type 1 diabetes mice	Pure capsaicin and capsiate	6 mg/kg	28 days	- Capsaicin reduce blood glucose level through elevated insulin level - reduce weight gain and food intake
Human studies	13	2006	Anti-diabetic	36 subjects (mid-age, overweight)	Chili-containing meal	30 g/day	4 weeks	- Regular consumption of chili may attenuate postprandial hyperinsulinemia.
	19	2013	Anti-obesity	24 young, overweight, normal body fat participants	Diet with added capsaicin	80% capsaicin of diet	-	- During energy restriction, combination of protein and capsaicin treatment promote negative protein balance
	26	2014	Anti-obesity	15 subjects (overweight, mid-age)	Red chilli pepper from Capsicum frustescen and Capsicum annuum	1.03 g red chilli pepper in every meal	3 weeks	- In energy balance, addition of capsaicin to diet increases satiety and fullness, prevent overeating. - Effect of capsaicin depends on the dosage, energy intake, macronutrient composition of meal and maximum tolerable dose of the subject.
In-vitro studies	23	2014	Anti-obesity	3T3-L1 preadipocytes Leptin, adiponectin, anti-inflammatory molecule, pro-inflammatory factors, LACA mice	Pure capsaicin	0.1– 100 µM (preadipocytes) 2 mg/kg body weight (mice)	12 weeks	- Capsaicin, inhibits adipogenesis in 3T3-L1 preadipocytes via TRPV1 activation and induces brown like phenotype
	25	2014	Anti-obesity	Bovine bone marrow mesenchymal stem cells (BMSC)	Pure capsacin	0 – 10 µM	6 days	- Capsaicin inhibits fat deposition by triggered apoptosis of cells. - Capsaicin decreased mRNA expression of adipogenesis-related genes
	30	2015	Anti-obesity	3T3-L1 preadipocytes	Pure capsaicin	0 - 250µM	72 hours	- Capsaicin treatment inhibit adipocyte differentiation through downregulation of transcription factors
	35	2016	Encapsulation technologies	Liver hepatic cells in rats	Nanoliposome of pure capsaicin	1 mg/kg (injection)	30 mk	- liposomal capsaicin provide significant protection from ROS reaction on hepatic cells. - Adverse drug reactions reduced and maximal therapeutic efficacy can be achieved.

has been found to efficiently inhibit radiation-induced biochemical alterations, namely lipid peroxidation, and protein oxidation in rat liver mitochondrial (RLM) membrane (p. 163-171). At a concentration of 40 µm capsaicin, gamma radiation-induced depletion of protein thiols are restored to a reasonable level while the reduced radiation-induced formation of protein carbonyl and inhibit activity loss in mitochondrial marker enzyme, SDH. Besides, capsaicin at a concentration range of 5-50µm can protect from oxidative damage. Therefore, the study suggested that capsaicin can act as a potential antioxidant and radio-protector in physiological systems through free radical scavenging activity (31).

In an intervention study of capsaicin micro-emulsions, it showed that both pure capsaicin and capsaicin micro-emulsions manifest higher inhibitory capacity than synthetic antioxidant BHT. This formulation can be used as a natural preservative in meat products preparation (20). The application of capsaicin (5 mg/kg) intragastrically to high-fat diet-fed mice results in significant antioxidant protection that reduced high fat diet-induced oxidative stress. Damage to organs was also improved based on markers such as urea, creatine, creatine kinase–MB (CK-MB) lactate dehydrogenase (LDH). At the same time, elevated MDA, an indicator of lipid peroxidation and protein content by high-fat diet in mice were normalized after 4 weeks of capsaicin consumption (32). To further proven and understand antioxidant mechanisms of capsaicin, follow-up studies with cell system or in-vivo system can be carried out in the future.

Anti-tumour and anti-cancer

Capsaicin has been found to inhibit the growth of different cancer cell system in recent studies. In several studies, capsaicin is believed to have an anti-thrombotic and anti-cancer effect. According to Ezekiel (2014), capsaicin at the dose of 2.5-10 mg/kg is suggested to be a potential blood thinner due to its ability to reduce thromboembolism without causing an alteration to blood platelets (27).

As reviewed by Cao et al. (2015) and Al-snafi (2015), capsaicin provided significant anti-cancer effects towards various cancer cells, such as breast cancer, prostatic cancer, colorectal cancer, lung cancer, gastric cancer, and pancreatic cancer (38). Its anti-cancer pathways are different for each type of cancer cells. Most of its working mechanisms showed that capsaicin compound interrupts cell cycle of the cancer cells, which leads to cell apoptosis, and inhibited further cell division. It is also reported that capsaicin selectively inhibits the growth of malignant cells, but not the healthy cells (39). The illustration of capsaicin's anti-tumor mechanism is showed in Fig. 2.

The anti-cancer property of capsaicin was further justified by Oyagbemi et al. in the year 2010. In this

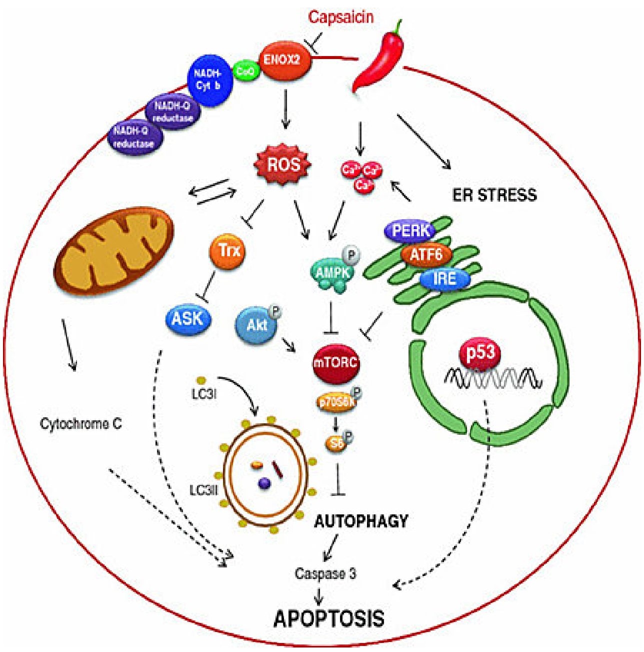

Figure 2: Cell apoptosis pathway of capsaicin

study, it showed that capsaicin blocks the translocation of nuclear factor-kappa β (NF-kβ), activator protein-1 (AP-1), signal transducer and activator of transcription (STAT 3) signalling pathway that is required for carcinogenesis. Capsaicin induces apoptosis and cell cycle arrest of cancer cells due to generation of reactive oxygen species (ROS) (40).

Cholangiocarcinoma (CCA) is cancer, which has multi-drugs resistant that lower the effectiveness of radiotherapy and chemotherapy (41). Application of 40 μM capsaicin is found to provide significant synergy effect with 5-fluorouracil (5-FU), a drug that is widely used in cancer treatment. The combination of capsaicin and 5-FU significantly increase drug sensitivity of CCA, thus lead to reduce the viability of cancer cell (42). As reported by Anandakumar et al., mice were treated with capsaicin with (10 mg/kg BW) for 15 weeks, showed that capsaicin significantly inhibited the development of mice lung carcinogenesis through activating early and late apoptosis of the cancer cells (18).

Further studies are necessary to evaluate the efficiency of capsaicin in anti-cancer effect. Although the growth of various cancer cells can be inhibited by capsaicin, the pharmacokinetic and pharmacodynamics mechanisms of capsaicin remained unknown. Besides, the various used concentration in cancer-preventing or treatment purpose should also be further studied to determine the most effective concentration of capsaicin that bring maximum therapeutic effect without causing discomfort to patients. Applying same concentration of capsaicin should be applied to both cancer cells and healthy cells and compare the viability of both cells may help to discover the beneficial dosage that protects the healthy cells and target on cancer cells at the same time. Attention should be given to cancer patients who consume capsaicin-containing food during chemical treatments, to appropriately adjust the dosage of chemical syntheses to reduce harmful side effect and maximize the therapeutic effect of capsaicin. Interaction between capsaicin and anticoagulant or anti-hypertensive drugs should also be further clarified to prevent from causing toxicity to patients. Capsaicin may be a potential agent to tackle multi-drug resistant (MDR) for cancer cells. Therefore, further investigation can be carried out to several cancer cells with MDR properties.

Anti-obesity

Capsaicin exerts many pathways that contribute to weight control and anti-obesity effect43. However, the exact anti-obesity mechanism for capsaicin is not yet confirmed. Capsaicin is found to significantly decrease the amount of intracellular triglyceride and glycerol-3-phosphate dehydrogenase (GDPH) activity in 3T3-L1 adipocytes. The component also inhibited the expression of obesity-related proteins such as peroxisome proliferator-activated receptor-gamma (PPARy), enhancer-binding protein alpha (C/EBPa), and leptin (30, 44).

Transient receptor potential cation channel subfamily V member 1 (TRPV1) receptor binds explicitly to vanilloid and capsaicin molecules. It is commonly found in the nociceptive neuron of the peripheral nervous system. It is an ion channel for calcium (Ca2+) ion into sensory cells during activation (45). In recent studies, it is found that the activation of the TRPV1 receptor by capsaicin initiates anti-obesity mechanisms (23, 24).

Capsaicin compound extracted from Capsicum annuum is proved to contribute to thermogenesis significantly. By activating TRPV1 receptor, it increases the energy expenditure. Activation of TRPV1 receptor by 1 μM of capsaicin is reported to significantly increased the body's metabolic activity through up regulation of thermogenic and 'browning' gene expression (23) which was further proven by Baskaran et al. (24). Their results showed that capsaicin reduced high-fat diet-induced obesity; produce more heat energy, provided higher locomotors and ambulatory activity in mice. The suggested anti-obesity mechanism of capsaicin in the study is the activation of TRPV1 by capsaicin involved brown fat thermogenic effect, which helps to elevate metabolic activity and energy expenditure (24).

As reported by Kang et al., dietary capsaicin reduces metabolic dysregulation in obese/diabetic KKAy mice by enhancing the expression of adiponectin and its receptor (16). Besides, capsaicin also exerts an anti-proliferative effect that prevents the 3T3-L1 preadipocytes from differentiating into mature adipocytes. In the same study, it is also reported that capsaicin significantly down-regulated the transcription factors, especially PPARγ. Hence, the capsaicin content in chilli may contribute to the maintenance of body weight (BW) and prevent the development of obesity. Similarly, findings by Berkuz et al. and Jeong et al., reported that the addition of capsaicin into adipocytes altered the transcription factors, hence significantly reduced adipocytes differentiation, induced adipocytes apoptosis, and hydrolyzed lipid (25,30).

In a human study which investigated the 24-hours effect of protein and capsaicin combination on fullness and energy expenditure (EE) during 20% energy intake restriction, the formulation increased energy expenditure and provided satiety in overweight human subjects. The result showed that protein and capsaicin mixture from 80% of subjects' daily energy requirement has higher efficiency in fat lowering and preserves protein balance; hence it does not affect existed muscle cells (19). Another human study involving 15 overweight subjects reported by Janssens et al., where the addition of 2.56 mg capsaicin in the daily diet increased satiety, stimulate negative fat balance and the fullness and prevent negative protein balance. However, individual tolerability to the pungency of capsaicin may affect the anti-obesity effect of capsaicin (26).

Fat balance is defined as the total amount of metabolizable fat remained in the body after the process of whole-body fat oxidation. The negative fat balance may lead to weight loss. A chronic positive fat balance is one of the contributing factors that cause obesity (46). Protein balance is the dynamic equilibrium between proteins synthesis and breakdown. Negative protein balance may cause loss of lean body mass (47), which is not favourable in weight loss.

There are some limitations found in all studies mentioned above. First, the role of TRPV1 channel agonist as potential anti-obesity should be further justified. Next, the interrelationship between capsaicin and PPARγ expression and induction of 'browning' effect should further be clarified. Although capsaicin does significantly reduced population of adipocytes, the actual underlying mechanisms remained unclear. For clinical studies, more extended study period and well-designed weight loss studies in overweight and obese individuals are necessary to further proven capsaicin's anti-obesity effect. Besides, the application of capsaicin on positive energy intake is also necessary to be tested, since positive energy intake is one of the causes that lead to obesity. In clinical studies, the dosage of capsaicin used in clinical studies should be carefully adjusted as population's maximum tolerable dose varies from a different country or food culture.

Anti-diabetic and anti-hypertensive

Application of capsaicin in a human diet has also been studied. The results showed that it gives favourable effect to control the blood sugar level by enhancing the sensitivity of insulin in mid-age, overweight patients (13).

In a recent animal study, Zhang et al. reported that application of capsaicin (6 mg/kg BW) to type 1 diabetes mice for 28 days, significantly reduce blood glucose level of mice. It is suggested that capsaicin elevated insulin level through improving glucose metabolism (37).

Besides, capsaicin also has anti-hypertensive effect without interruption to the function of the cardiac system (14). However, the dosage used (0.3 mg/kg) in this study is higher than human dietary exposure to capsaicin. Therefore a further study is needed to confirm its effect further. The study by Chularojmontri et al. showed that treatment of capsaicin compound has cardioprotective effect by inducing vasodilation in the blood vessel when lower dosage (25 μM) is used in human umbilical vein endothelial cells (HUVEC) (15). Another study conducted by Li et al. showed that dietary capsaicin (1 μM/L) significantly promotes urinary sodium excretion. Thus it can control the concentration of sodium in the body system, bring beneficial effect to hypertension (22). However, further study on the effective and safe dose of capsaicin used for human consumption is necessary.

Synergistic effects of Capsaicin with drugs
The dose of some drugs should be carefully adjusted as the application of capsaicin can interact with them, causing undesired toxicity to patients. Komori et al. discovered that consumption of capsaicin at a concentration of 400 μM inhibited intestinal absorption of cephalexin, an antibiotic which is used to treat infections caused by bacteria (14).

Kitahara and Kawai (45) stated that cyclosporin (CyA) is a drug with a narrow therapeutic window, which is widely used in transplant patients as an immunosuppressant (p.238-245). CyA is metabolism substrate for CYP3A and P-gp, which is a multi-drug efflux transporter (49, 50). In a study conducted by Zhai et al., it is found that capsaicin does inhibit the activity of CYP3A, thus decreased CyA metabolism rate. Besides, capsaicin also reduced the efflux action of P-gp; thus, the higher concentration remains in the blood of mice (21).

The dosage of pitavastatin, blood cholesterol-lowering medication used also should be carefully adjusted when consumption of capsaicin is involved (33). Based on the obtained result, it is found that the capsaicin compound increased the bioavailability of the drug. This condition is not favourable for the patient as it can cause a higher risk of medication side effect or toxicity. It is suggested that the dosage of pitavastatin should be decreased if the patient consumed food containing capsaicin more than 8 mg/kg.

Further investigations through in-vitro and in-vivo studies are necessary to clarify the underlying mechanisms responsible for the changes in drugs' membrane permeability in the presence of capsaicin. Besides, consumption of capsaicin can be tested with other narrow therapeutic window drugs to prevent undesirable toxicity or adverse effect to patients.

Novel encapsulation formulas to improve bioavailability
Although capsaicin does provide various therapeutic effects to humans, its effect cannot be maximized due to its low oral bioavailability and poor aqueous solubility (10.3 mg/L at 25°C) (35, 51). Hence, nanotechnology in encapsulation for capsaicin has been applied to solve this problem. The general type of nano-encapsulation used is shown as in Fig.3. In the year of 2010, Chen et al. suggested that cyclodextrin (CD) complexion can be used in encapsulation of capsaicin. CD complexion can effectively trap lipophilic capsaicin, thus can enhance capsaicin's solubility and dissolution rate. In this study, hydroxypropyl-β-cyclodextrin (HP-β-CD) is used due to its higher water solubility, greater solubilizing capacity and safe for consumption. The results showed that utilization of HP-β-CD significantly increases solubility, cell permeability, dissolution rate and subcutaneous absorption rate of capsaicin (17).

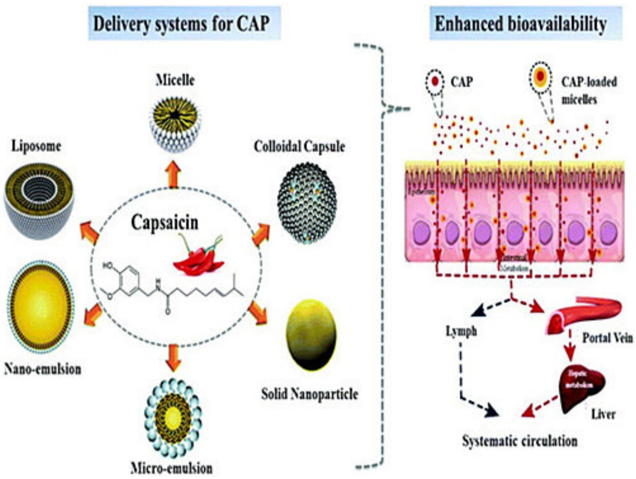

Figure 3: Types of delivery system of capsaicin for bioavailability enhancement

In the year of 2014, a few novel encapsulation methods have been studied. Almeida et al. reported that microencapsulation of capsaicin with PCL-microparticles by simple emulsion/solvent evaporation method is a potential oral carrier for prolonged consumption (28). The method reduced the pungency of capsaicinoids, decreased the irritation to the gastric mucosa and enhanced gastric mucosa tolerability to the compound. Besides, PCL-microparticles were able to control the dissolution rate of capsaicinoids into plasma, to maintain the effective concentration of drug for a long time without changing its release model, which help to maximize the therapeutic effect of capsaicinoids.

Polymeric micelle using thin-film hydration method is suggested to be another potential oral carrier of capsaicin (29). In the process of encapsulation, capsaicin is solubilized in the micelle. Due to its nano- and uniform size, it has increased oral bioavailability and absorption rate of capsaicin. Although its maximum concentration of capsaicin-loaded micelle is less than free capsaicin in rats, the micelle has longer circulation time, which means that it has longer reaction time and higher therapeutic rate.

Capsaicin-loaded liposome and oil-water-emulsion are also reported as a potential carrier for capsaicin consumption (52, 53). Both formulations enhanced capsaicin bioavailability, membrane permeability, and absorption rate in the body system. These formulations also prolonged dispersal time of capsaicin. Thus the maximum release of capsaicin is targeted at colon instead of the stomach, which is believed as the best absorption site of capsaicin (54), which reduced the risk of gastric irritation. The formulation was proven by an in-vivo test conducted by Zhu et al., showing no significant gastric irritation sign in mice after consumption of capsaicin in oil-water-emulsion (52).

To further maximize the solubility and absorption rate of capsaicin, there are two modified formulations, namely nano-liposome (35) and organogel-derived capsaicin nanoemulsion (36) used in rats' liver hepatic cells. Formulation of nanoliposome and capsaicin by the formation of a thin film followed by a hydration method efficiently reduced free radicals and provided a significant protective effect of liver damage compared to the free form of capsaicin.

In organogel-derived capsaicin nanoemulsion, capsaicin reacted synergistically with medium-chain triacylglycerol to act as a potential anti-obesity agent (36). This formulation can prolonged drug dispersal time, hence provided the gastroprotective effect. Cirino et al. also demonstrated that 30 mM of capsaicin-loaded liposome provides a significant protective effect on the irritative action of pure capsaicin to the mice bladder (34).

Further studies are necessary to discover more compatible encapsulation materials for enhancement of bioavailability and pharmacological effect of capsaicin. Besides, to determine the chemical interaction and its mechanisms, the application of novel encapsulated capsaicin together with other drugs or supplements should be further clarified.

CONCLUSION

Capsaicin exerts significant therapeutic effects such as antioxidant, anti-obesity and anti-cancer properties. However, there is no evidence to prove the actual mechanism of capsaicin that presents these functions. Thus, more in-vivo, in-vitro and clinical studies are required to understand the working mechanisms of capsaicin further. Consumption of drugs such as cephalexin, pitavastatin, and cyclosporin (CyA) should be given more attention if consumed together with food containing capsaicin as these drugs are from a narrow therapeutic window, which possibly causes toxicity to patients. Besides, the low solubility and bioavailability of capsaicin also can be solved by novel encapsulation technologies.

REFERENCES

1. Lim TK. Edible medicinal and non-medicinal plants: 2013; 6.
2. Bosland PW, Votava EJ. Peppers: vegetable and species Capsicum. CABI Publishing, Wallingford, UK. 2000.
3. Thiele R, Mueller-Seitz E, Petz M. Chili pepper fruits: presumed precursors of fatty acids characteristic for capsaicinoids. J Agric Food Chem. 2008;56(11):4219-4224.
4. Russo VM. Peppers: botany, production and uses. Wallingford, Oxfordshire: CABI; 2012.
5. Meghvansi M, Siddiqui S, Khan MH, Gupta V, Vairale M, Gogoi H, Singh L. Naga chilli: A potential source of capsaicinoids with broad-spectrum ethnopharmacological applications. J Ethnopharmacol. 2010;132(1):1-14.
6. Fattori V, Hohmann M, Rossaneis A, Pinho-Ribeiro F, Verri W. Capsaicin: current understanding of its mechanisms and therapy of pain and other pre-clinical and clinical uses. Molecules. 2016;21(7):844.
7. National Center for Biotechnology Information. PubChem Compound Database; CID=1548943, https://pubchem.ncbi.nlm.nih.gov/compound/1548943 (accessed Sept. 28, 2017).
8. Parthasarathy VA, Chempakam B, Zachariah TJ. Chemistry of spices. Wallingford, UK: CABI Pub; 2008.
9. Randall JJ, Bosland P, Hanson SF. A new phytoplasm associated disease of Chile peppers. Phytopatology. 2008;98(6):S130
10. Bosland PW,Votava EJ, Votava EM. Peppers: vegetable and spice capsicums. Cabi. CABI Publishing, Wallingford, UK; 2012:1-16.
11. Rashid MH, Inoue M, Bakoshi S, Ueda H. Increased expression of vanilloid receptor 1 on myelinated primary afferent neurons contributes to the anti-hyperalgesic effect of capsaicin cream in diabetic neuropathic pain in mice. J Pharmacol Experiment Therap. 2003;306(2):709-717.
12. Chanda S, Mould A, Esmail A, Bley K. Toxicity studies with pure trans-capsaicin delivered to dogs via intravenous administration. Regul Toxicol Pharmacol. 2005;43(1):66-75.
13. Ahuja KDK, Robertson IK, Geraghty DP, Ball MJ. Effects of chili consumption on postprandial glucose, insulin, and energy metabolism. Am J Clin Nutr. 2006;84(1):63-69.
14. Komori Y, Aiba, T, Sugiyama R, Nakai C, Kawasaki H, Kurosaki Y. Effects of capsaicin on intestinal cephalexin absorption in rats. Biol Pharm Bull. 2007;30(3):547-551.
15. Chularojmontri L, Suwatronnakorn M, Wattanapitayakul SK. Influence of capsicum extract and capsaicin on endothelial health. J Med Assoc Thail. 2010;93(2):92-101.
16. Kang JH, Goto T, Han IS, Kawada T, Kim YM, Yu R. Dietary capsaicin reduces obesity-induced insulin resistance and hepatic steatosis in obese mice fed a high-fat diet. Obesity (Silver Spring). 2010;18(4):780-787.
17. Chen X, Sun X, Ren K, Zhang X, Zhang Z, Gong T. Enhanced aqueous solubility and bioavailability of capsaicin by the preparation of an inclusion complex. Arzneimittel-Forschung. 2010;60(9):571-574.
18. Anandakumar P, Kamaraj S, Jagan S, Ramakrishnan G, Devaki T. Capsaicin provokes apoptosis and restricts benzo(a) pyrene-induced lung tumorigenesis in Swiss albino mice. Int Immunopharmacol. 2013;17(2):254-259.
19. Smeets AJ, Janssens PLHR, Westerterp-Plantenga MS. Addition of capsaicin and exchange of

carbohydrate with protein counteract energy intake restriction effects on fullness and energy expenditure. J Nutr. 2013;143(4):442-447.
20. Dima C, Coman G, Cotвrlet M, Alexe P, Dima S. Antioxidant and antibacterial properties of capsaicin microemulsions. Annals University Dunarea de Jos Galati. Fascicle VI. Food Technology. 2013;37(1):39.
21. Zhai XJ, Shi F, Chen F, Lu YN. Capsaicin pretreatment increased the bioavailability of cyclosporin in rats: Involvement of P-glycoprotein and CYP 3A inhibition. Food Chem Toxicol. 2013;62:323-328.
22. Li L, Wang F, Wei X, Liang Y, Cui Y, Gao F. et al. Transient receptor potential vanilloid 1 activation by dietary capsaicin promotes urinary sodium excretion by inhibiting epithelial sodium channel α subunit-mediated sodium reabsorption. Hypertension. 2014. Hypertensionaha-114.
23. Baboota RK, Singh DP, Sarma SM, et al. Capsaicin induces "Brite" phenotype in differentiating 3T3-L1 preadipocytes. PloS One. 2014;9(7):1-12.
24. Baskaran P, Krishnan V, Ren J, Thyagarajan B. Capsaicin induces browning of white adipose tissue and counters obesity by activating TRPV1 channel-dependent mechanisms. Br J Pharmacol. 2016;173(15):2369-2389.
25. Jeong JY, Suresh S, Park MN. et al. Effects of capsaicin on adipogenic differentiation in bovine bone marrow mesenchymal stem cell. Asian-Aust J Anim Sci. 2014;27(12):1783.
26. Janssens PLHR, Hursel R, Martens EAP, Westerterp-Plantenga MS. Acute effects of capsaicin on energy expenditure and fat oxidation in negative energy balance. PloS One. 2013;8(7):1-7.
27. Ezekiel JAT. Effects of capsaicin on coagulation: will this be the new blood thinner. Clin Med Res. 2014;3(5):145.
28. Almeida MA, Nadal JM, Grassiolli S, et al. Enhanced gastric tolerability and improved anti-obesity effect of capsaicinoids-loaded PCL microparticles. Mater Sci Eng C. 2014;40:345-356.
29. Zhu Y, Peng W, Zhang J, et al. Enhanced oral bioavailability of capsaicin in mixed polymeric micelles: Preparation, in vitro and in vivo evaluation. J Funct Foods. 2014;8(1):358-366.
30. Berkuz M, Yildirim M, Arvas G, Turkmen O, Allahyerdiyev O. Effect of capsaicin on transcription factors in 3T3-L1 cell line. East J Med. 2015;20(1):34-45.
31. Gangabhagirathi R, Joshi R. et al. Antioxidant activity of capsaicin on radiation-induced oxidation of murine hepatic mitochondrial membrane preparation. Res Rep Biochem. 2015;5:163-171.
32. Aydin B. The effects of capsaicin and vitamin e on high fat diet induced obesity, hyperlipidemia and oxidative stress in different organs of mice. J Food Nutr Res. 2015;3(6):357-364.
33. Chen F, Zhai X, Zhu C, Lu Y. Effects of capsaicin on pharmacokinetics of pitavastatin in rats. Xenobiotica. 2015;45(2):171-176.
34. Cirino L, Vergne D, Santana PF, Almeida ED, Costa LP, et al. Decreased inflammatory response in rat bladder after intravesical administration of capsaicin-loaded liposomes. Anais da Academia Brasileira de Ciкncias. 2016;88(3):1539-1547.
35. Giri TK, Mukherjee P, Barman TK, Maity S. Nano-encapsulation of capsaicin on lipid vesicle and evaluation of their hepatocellular protective effect. Int J Biol Macromol. 2016;88:236-243.
36. Lu M, Cao Y, Ho CT, Huang Q. Development of organogel-derived capsaicin nanoemulsion with improved bioaccessibility and reduced gastric mucosa irritation. J Agric Food Chem. 2016;64(23):4735-4741.
37. Zhang S, Ma X, Zhang L, Sun H, Liu X. Capsaicin reduces blood glucose by increasing insulin levels and glycogen content better than capsiate in streptozotocin-induced diabetic rats. J Agric Food Chem. 2017;65(11):2323-2330.
38. Cao S, Chen H, Xiang S, Hong J, Weng L, Zhu H. Anti-cancer effects and mechanisms of capsaicin in chili peppers. Am J Plant Sci. 2015;6(19):3075-3081.
39. Chamikara MDM, Dissanayake DRRP, Ishan M, Sooriyapathirana SDSS. Dietary, anticancer and medicinal properties of the phytochemicals in chili pepper (Capsicum spp.). Ceylon J Sci. 2016;45(3):5.
40. Oyagbemi AA, Saba AB, & Azeez OI. Capsaicin: a novelchemopreventive molecule and its underlying molecular mechanisms of action. Ind J Cancer. 2010;47(1):53.
41. Fava G, Lorenzini I. Molecular pathogenesis of cholangiocarcinoma. Int J Hepatol. 2011;2012.
42. Hong Z, Zhao W, Yin Z, Xie C, Xu Y, et al. Capsaicin enhances the drug sensitivity of cholangiocarcinoma through the inhibition of chemotherapeutic-induced autophagy. PloS One, 2015;10(5):1-11.
43. Varghese S, Kubatka P, Rodrigo L, Gazdikova K, Caprnda M, Fedotova J, et al.. Chili pepper as a body weight-loss food. Int J Food Sci Nutr. 2017;68(4):392-401.
44. Hsu CL, Yen GC. Effects of capsaicin on induction of apoptosis and inhibition of adipogenesis in 3T3-L1 cells. J Agric Food Chem. 2007;55(5):1730-1736.
45. Smutzer G, Devassy RK. Integrating TRPV1 receptor function with capsaicin psychophysics. Adv Pharmacol Sci. 2016;2016.
46. Schutz Y. Concept of fat balance in human obesity revisited with particular reference to de novo lipogenesis. Int J Obesity, 2004;28:3-11.
47. Christopher SF, Blake BR. Skeletal muscle protein balance and metabolism in the elderly. Curr Aging Sci. 2011;4(3):260-268.
48. Kitahara K, Kawai S. Cyclosporine and tacrolimus for the treatment of rheumatoid arthritis. Curr Opin

Rheumatol. 2007;19(3):238-245
49. Hou YC, Lin SP, Chao PDL. Liquorice reduced cyclosporine bioavailability by activating P-glycoprotein and CYP 3A. Food Chem. 2012;135(4):2307-2312.
50. Hsiao P, Unadkat JD. P-Glycoprotein-based loperamide–cyclosporine drug interaction at the rat blood–brain barrier: prediction from in vitro studies and extrapolation to humans. Mol Pharm. 2012;9(3):629-633.
51. Al-snafi AE. The pharmacological importance of Capsicum species (Capsicum annuum and Capsicum frutescens) grown in Iraq. J Pharm Biol. 2015;5(3):124-142.
52. Zhu Y, Wang M, Zhang J, et al. Improved oral bioavailability of capsaicin via liposomal nanoformulation: preparation, in vitro drug release and pharmacokinetics in rats. Arch Pharm Res. 2015;38(4):512-521.
53. Zhu Y, Zhang J, Zheng Q, et al. In vitro and in vivo evaluation of capsaicin-loaded microemulsion for enhanced oral bioavailability. J Sci Food Agric. 2015;95(13):2678-2685.
54. Duan L, Yan Y, Sun Y, Zhao B, Hu W, Li G. Contribution of TRPV1 and multidrug resistance proteins in the permeation of capsaicin across different intestinal regions. Int J Pharm. 2013;445(1):134-140
55. Díaz-Laviada, I., & Rodríguez-Henche, N. (2014). The potential antitumor effects of capsaicin. In Capsaicin as a Therapeutic Molecule (pp. 181-208). Springer, Basel.
56. Lu, M., Chen, C., Lan, Y., Xiao, J., Li, R., Huang, J., ... & Ho, C. T. (2020). Capsaicin-the Major Bioactive Ingredient of Chili Peppers: Bio-efficacy and Delivery Systems. Food & Function.