Medicinal chemistry

Morales-Martínez et al., Med chem (Los Angeles) 2016, 6:5
http://dx.doi.org/10.4172/2161-0444.1000371

Review Article Open Access

The Prospective Antiobesity Effect of Capsaicin Synthetic Analogs: A Matter of Weight

Claudia E Morales-Martínez[1], Ana L Márquez-Aguirre[1], Emmanuel Díaz-Martínez[1], Jorge A Rodríguez-González[2], Juan C Mateos-Díaz[2], Hugo Esquivel-Solís[1], Carlos Alvarez-Moya[3] and Alejandro A Canales-Aguirre[1]*

[1]Medical and Pharmaceutical Biotechnology, Centro de Investigación y Asistencia en Tecnología y Diseño del Estado de Jalisco (CIATEJ), Guadalajara 44270, Jalisco, Mexico
[2]Industrial Biotechnology, Centro de Investigación y Asistencia en Tecnología y Diseño del Estado de Jalisco (CIATEJ), Guadalajara 44270, Jalisco, Mexico
[3]Environmental Laboratory Mutagenesis, Cellular and Molecular Department, CUCBA University of Guadalajara, Carr. a Nogales Km 15.5, Zapopan,45020, México

Abstract

Capsaicin, the major component of chili peppers, has shown potential therapeutic effect against metabolic disease inducing weight loss. Its effect is exerted by a particular molecular mechanism and pharmacodynamics, distinct to current obesity treatments. However, its high irritating taste or pungency has limited its use to some clinical trials. Capsaicin-like molecules, known as capsaicin synthetic analogs, contain the majority of capsaicin domains but without those of pungency. Recently, they have received much attention by their potent antiobesity effect. The study of their structure-activity relationship would unravel the mechanisms responsible of this effect. This review summarizes much of the current experimental evidence of the potential effect in metabolism regulation of natural and synthetic capsaicin analogs discovered to date.

Keywords: *Capsicum annum*; Capsaicinoids; Capsaicin; Capsaicin analogs; Antiobesity; Olvanil; TRPV-1

Introduction

Obesity is caused by an increased intake of highly caloric foods and by a sedentary lifestyle. Therefore, it is important to search for new strategies or therapies that prevent weight gain or are helpful to lose weight. Pharmacological therapy is a complementary strategy to low-caloric diet and physical activity for weight loss and weight maintenance. There are many drugs approved by the Food and Drug Administration indicated for weight loss in obesity, which can be classified by their mechanism of action: 1) appetite suppression, 2) lipase inhibitors and 3) increased energy expenditure. Nevertheless, such drugs might have many side effects [1].

It has been demonstrated that numerous foods have beneficial effects in body-weight management [2,3] but only a few bioactive elements have been discovered and studied, such as resveratrol from grapes, genistein from soy and quercetin from onion [4,5]. Capsaicin, the bioactive component of red pepper, has been shown potent effects as lipid metabolism modulator [6]. However, its therapeutic use has been limited due to its high pungency. For this reason, the synthesis of capsaicin analogue molecules without pungency, may be an excellent alternative strategy for treating obesity and its associated health complications.

In this review we addressed the compilation and analysis of the most recent studies about the pharmacological effects of natural and synthetic capsaicin analogs in energy balance and adipocyte biology. The scientific data of its possible mechanisms of action is also discussed.

Pathogeny of Obesity

The abnormal increase of adipose tissue in the body is the cause of overweight and obesity. Despite the complexity of their etiology, the low energy expenditure due to less physical activity and the intake of a High-Caloric Diet, are advised the major causes. Excess in energy balance (blood stream), induces adipocytes to accumulate energy as triglycerides that leads to hypertrophic adipose tissue. The free fatty acid (FFA) flux from adipocyte lysis, together with the metabolic abnormalities of cholesterol in hypertrophied adipocytes cause the obesity-related dyslipidemias, exacerbating the problem. The well-known lipid master regulators, members of the PPAR (Peroxisome Proliferator-Activated Receptor) family, principally PPAR-gamma, participate in lipid homeostasis abnormalities throughout the body and specifically in adipose tissue during obesity. When PPAR-gamma is over activated it promotes the activation of adipogenic genes and the blockade of anti-adipogenic genes [7]. Thus blocking of PPAR-gamma in obesity is one of the most important drug targets.

Capsaicinoids

Capsaicinoids are bioactive components than can be found in the fruits of the plant genus *Capsicum*, better known as chilli peppers. They are produced as secondary metabolites that deter consumption by vertebrates and discourage predators without deterring more effective seed dispersers [8]. Currently, capsaicinoids are known as chemicals responsible for the fruit's peppery heat, burning sensation and the hot or spicy flavor they confer [9]. There have been identified nine naturally occurring capsaicinoids in peppers which differences are centered on carbon-carbon double bonds and pungency levels according to Scoville´s heat unit scale [10,11].

An aromatic ring integrates the chemical structure of capsaicinoids, named catechol or vaniloid ring which contains two substituents in the positions 3 and 4. Moreover, capsaicinoids also have a fatty acid hydrophobic side chain linked by an amide bond (Figure 1) [12]. Natural capsaicinoids are *N-vanillylamides* of fatty acids and their structural conformations depend on the number of lateral chain carbons or the presence/absence of unsaturations. In comparison, capsaicin synthetic analogs may have other modifications as addition/deletion of one or more functional groups [11].

***Corresponding author:** Alejandro A Canales-Aguirre, Medical and Pharmaceutical Biotechnology, Centro de Investigación y Asistencia en Tecnología y Diseño del Estado de Jalisco (CIATEJ), Guadalajara 44270, Jalisco, Mexico, Tel: +5213333455200 extn. 1303; E-mail: acanales@ciatej.mx

Received May 18, 2016; **Accepted** May 23, 2016; **Published** May 30, 2016

Citation: Morales-Martínez CE, Márquez-Aguirre AL, Díaz-Martínez E, Rodríguez-González JA, Mateos-Díaz JC, et al. (2016) The Prospective Antiobesity Effect of Capsaicin Synthetic Analogs: A Matter of Weight. Med chem (Los Angeles) 6: 365-371. doi:10.4172/2161-0444.1000371

All these molecules have shown a wide variety of biological and pharmacological properties, as antiobesity on which relies their therapeutic values. On this regard, capsaicin has gained the most scientific interest.

Capsaicin

Capsaicin (*trans-8-methyl-N-vanillyl-6-nonenamide*) is the most abundant capsaicinoid in peppers comprising the 50-60% [13]. It was discovered by Tresh in 1846 and its chemical structure was determined by Nelson in 1919. Following years of study, it has been demonstrated that capsaicin is one of the most promissory constituents because its important pharmacological effects of which antinociception was the first evidenced [14]. Capsaicin is currently used for treatment of several pain syndromes, including diabetic neuropathy [15]. Moreover, capsaicin has also demonstrated beneficial effect on osteoarthritis pain relief due to its high capacity to inhibit P substance release, a powerful neuropeptide pain neuromodulator from the sensory nerves to the central nervous system [16].

Capsaicin has also shown potential effects as anti-obesity drug [6]. There is plenty of evidence that capsaicin can induce body weight reduction, [17] increases energy expenditure, [18] improves lipolysis in adipocytes [19] (Table 1). Additionally, some clinical studies support that capsaicin ingestion increased satiety and reduced energy and fat intake during negative energy balance [20]. Similar studies have shown that capsaicin increases the sensation of fullness and decreases the desire to eat [21-27].

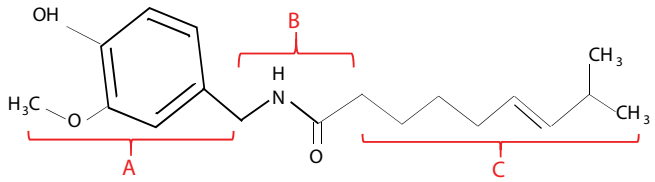

Figure 1: Capsaicin chemical structure. All capsaicinoids are quite similar to capsaicin, they preserve the catechol/vaniloid ring (A) and the amide bond (B), while they differ on the fatty acid side chain (C).

Despite the wide evidence of the favorable capsaicin effects in metabolism regulation, applications of this molecule are limited by its pungency. For the same reason, the doses employed in clinical trials are lower than those reported *in vitro* and *in vivo* preclinical tests. Thus it has been difficult to achieve similar effects in clinical research until date.

Mechanism of action

Binding of capsaicin to its receptor TRPV1: Capsaicin is a potent agonist of the transient receptor potential cation channel subfamily V member 1 (TRPV1), better known as vanilloid receptor 1. This receptor is a nonselective cation channel that allows the transient influx of Ca^{2+} when is activated during the detection and transduction of nociceptive stimuli [28]. Its structure and topology have been well characterized [29]. This receptor was initially found on key sensory afferents neurons and it has recently been shown expressed in hepatocytes, kidney cells and adipocytes [30]. Several studies have focused on elucidating how capsaicin interacts and regulates TRP channels. Such may help as model of the capsaicin-channel complex for pharmacological applications and would potentially guide further developments of capsaicin analogs. These experimental reports have shown that capsaicin binds to a pocket of TRPV1 in a conformation where the vanillyl ring points toward the S4-S5 linker, while the lipid tail points upward in the direction of the S4 helix, [31] where Tyr511 was critical for vanilloid sensitivity [32] Yang et al. proposed that, though matching with the 'tail-up, head-down' model, the specificity for ligand binding is bestowed by hydrogen bonds that formed between its vanillyl head with residues E571 and Tyr511 of the TRPV1 channel [33].

Capsaicin molecular target in adipocyte: It has not yet been clarified in detail the mechanism by which capsaicin exerts its anti-adipogenic effect, however, some findings suggest the possible signaling pathways, which are described in Figure 2.

Because capsaicin and its analogues are lipophilic, they pass through the cell membrane and act on binding site located in the intracellular portion of the TRPV1 receptor. The interaction of vanillyl head of capsaicin with residue Tyr 511 (located between the second and third transmembrane domain) of the TRPV1 receptor leads to a

CAPSAICIN		
2011	Exerts lipolytic action by increasing the mRNA levels of HSL, CPTI-α, UCP2 genes in 3T3-L1 cells	[19]
2013	Inhibit the LPL mRNA expression level in 3T3-L1 cells	[22]
2013	Topical application reduces weight gain and visceral fat and decreases the expression of TNF-α and IL-6 in high-fat-induced obese mice	[17]
2014	Inhibits proliferation and differentiation 3T3-L1 preadipocytes by decreasing the protein expression of LPL, leptin, PPARγ and C/EBPα	[23]
2014	Decreases the serum levels of TG, LDL and HDL and UPC2, PPARγ, leptin gene expression in high- fat induced obese rats	[24]
2014	Increases satiety and sensation of fullness in healthy humans	[21]
2015	Inhibits the adipogenic differentiation of mesenchymal stem cells by repressing PPARγ, C/ EBPα, FABP4 and SCD-1 gene expression	[25]
SYNTHETIC ANALOGS		
Nonivamide		
2014	Reduces feelings of hunger and carbohydrates intakes in moderately overweight men	[26]
2015	Reduces fatty acid uptake and increases the acetyl-coenzyme A synthetase activity by Caco-2 cells	[27]
2015	Decreases lipid accumulation in 3T3-L1 cells by reducing the PPARγ protein levels	[73]
Olvanil		
2015	Improves lipolysis process while decreases the intracellular triglycerides in 3T3-L1 cells	[*]
2015	Inhibits adipogenesis by reducing the PPARγ activity in 3T3-L1 cells	[*]
Phenylacetylrinvanil		
	Induces apoptosis and inhibits *in vitro* cell proliferation of carcinogenic cell lines HeLa, J774, CasKi, ViBo and P388.	[79,80]

*Data send for publication

Table 1: Antiobesity effect of capsaicin and their synthetic analogs.

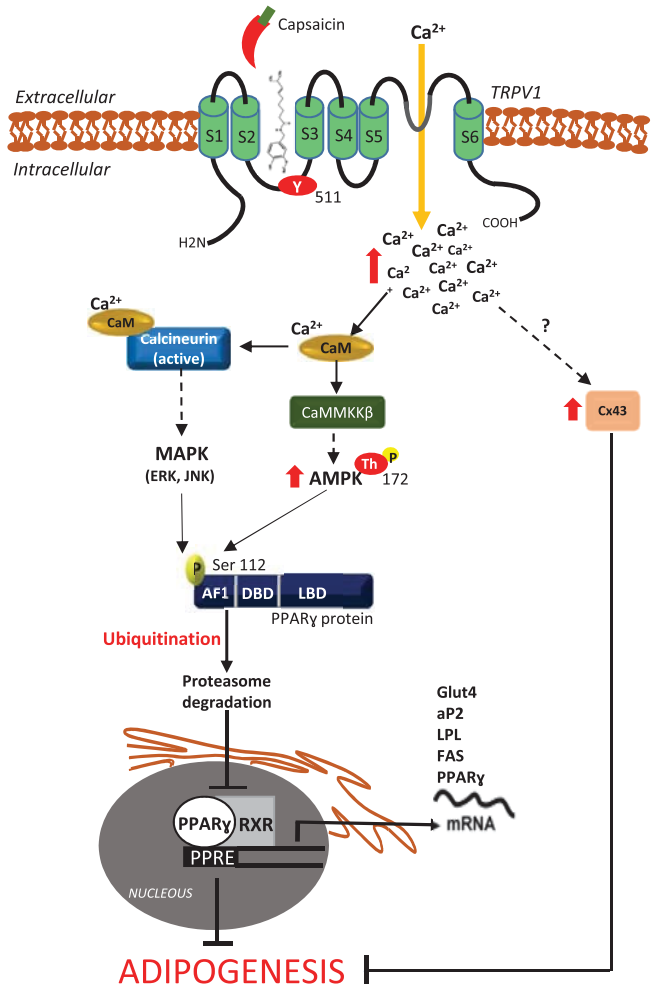

Figure 2: Putative signaling pathways of capsaicin in the adipocyte. It has been described that capsaicin and its analogs bind the Transient Receptor Potential Vanilloid 1 (TRPV1), a non-specific cation channel located in the cellular membrane which comprises six putative transmembrane segments (S1-S6), intracellular N- and C-termini, and a cation-selective pore-forming reentrant loop between S5 and S6 with high permeability to calcium. Capsaicin and its analogues pass through the cell membrane by their lipophilic properties and bind their vanilloid ring to the residue Tyr511 located on the intracellular loop between S2 and S3 of TRPV1 leading to a conformational change that opens the cation-selective pore. This triggers an influx of extracellular Ca^{2+} resulting in a high cytosolic concentration. As it is well known that Ca^{2+} is one of the most versatile second messengers that can activate several Ca^{2+}-binding proteins, we suggest that capsaicin and its analogues might activate calmodulin-calcineurin and then the MAPK pathway, which this has been reported to blockade PPARγ- and C/EBPα-dependent adipogenesis by PPARγ-phosphorylation, ubiquitination and degrading. In addition, since AMP-activated protein kinase (AMPK), a metabolic regulator that reduces the PPARγ-mediated transcriptional activity, can be activated by calmodulin-dependent protein kinase kinase-β (CaMMKKβ) through elevated intracellular Ca^{2+} levels, we propose this as an additional signaling pathway of capsaicin and its analogues. Furthermore, it has been found that the increase of intracellular Ca^{2+} activates connexin43 (Cx43), a major gap junction protein that should be degraded through the phosphorylation-ubiquitination course to allow the differentiation of adipocytes. We suggest that Cx43 is up-regulated by the Ca^{2+} influx after capsaicin and its analogues bound TRPV1, thus preventing adipogenesis by an unknown mechanism.

conformational change that opens the channel by the pore-forming S5–S6 transmembrane helix. Because TRPV1 is a Ca^{2+} channel with high permeability its activation triggers an influx of Ca^{2+}, resulting in increased cytosolic concentration [34]. It is known that calcium in the cell is one of the most versatile second messengers in numerous intracellular signaling pathways, and a change in the intracellular Ca^{2+} levels, actives a number of intracellular Ca^{2+}-binding proteins, including calmodulin (CaM), calcineurin B, protein kinase A (PKA), S100B and DREAM [35]. Calcineurin mediates the calcium-dependent inhibition of adipogenesis in 3T3-L1 cells by preventing the expression of the pro-adipogenic transcription factors peroxisome proliferator-activated receptor gamma (PPARɣ) and CCAAT/enhancer-binding protein alpha (C/EBPα) by a still unknown mechanism [36]. These results were tested again and found that the increase of extracellular Ca^{2+} influx activates connexin43 (Cx43) [37], a major gap junctions protein that should be phosphorylated and degraded to allow the differentiation of adipocytes [38]. Therefore, calcium influx induced by the action of capsaicin might probably act on the maintaining of Cx43 thus interrupting the adipocyte differentiation and adipogenesis. Additional work suggests that activation of AMP-activated protein kinase (AMPK), a regulator pathway of metabolism, reduces the PPARɣ- mediated transcriptional activity [39,40]. Reports supported that AMPK can be activated by an elevated intracellular Ca^{2+} level mediated by calmodulin-dependent protein kinase kinase-β (CaMMKKβ) [41].

Despite these investigations, there are still some questions about the intracellular downstream signaling targets of capsaicin in adipocytes and thus the real mechanism is still unknown.

Capsaicin Analogs

Capsaicin analogs are molecules that preserve all or part of the aromatic catechol ring in its chemical structure, which are clearly demonstrated to be TRPV1 receptor agonists [42]. Nevertheless, they may or may not have similar effects due to different functional groups and variable number of carbon-carbon double bonds located in different positions along the chain, which may modify its pungency level and biological activity [43]. Here we present the current knowledge of some of the most studied.

Natural analogs

Capsiate: It was the first natural capsaicin analogue characterized in the CH-19 sweet pepper variety (*Capsicum annum* L.) [44]. Similar to capsaicin, is the most abundant capsinoid in peppers of this variety. The main difference between capsiate and capsaicin is the pungency level; capsiate is a non-pungent capsinoid. Capsiate is structurally identical to capsaicin, except that it has an ester bond rather than an amide bond between the vanilloid ring and the fatty acid chain (Figure 3). It is known that this molecule exerts some of the same effects as capsaicin, such as the increase in swimming endurance capacity of mice by raising fat oxidation, thus improving carbohydrate utilization [45] and glucose homeostasis while, decreasing fat accumulation in diabetic rats [46] and suppressing fat accumulation in adipocytes 3T3-L1 [47]. Capsiate, also increases energy expenditure and enhances fat oxidation at high doses in humans [48]. Additionally, recent research has shown that capsiate also activates TRPV1 and other TRP channels by an as yet unknown mechanism by which evokes its action [49].

Resiniferatoxin (RTX): RTX is also a natural ultra-pungent capsaicin analogue found in the latex of *Euphorbia resinifera*, a cactus-like plant and is ten times as pungent as capsaicin. This molecule preserves the aromatic catechol ring and contains an ester bond rather than an amide bond in its chemical structure (Figure 3). It has been shown that unlike the capsaicin-induced adrenaline increase, RTX produced only a slowly initiated adrenaline reaction [50]. However, it preserves the analgesic effect because it diminishes thermal pain sensitivity but increases the sensitivity to tactile stimulation in adult rats [51]. Studies on the potential role of RTX in the regulation of lipid metabolism are limited.

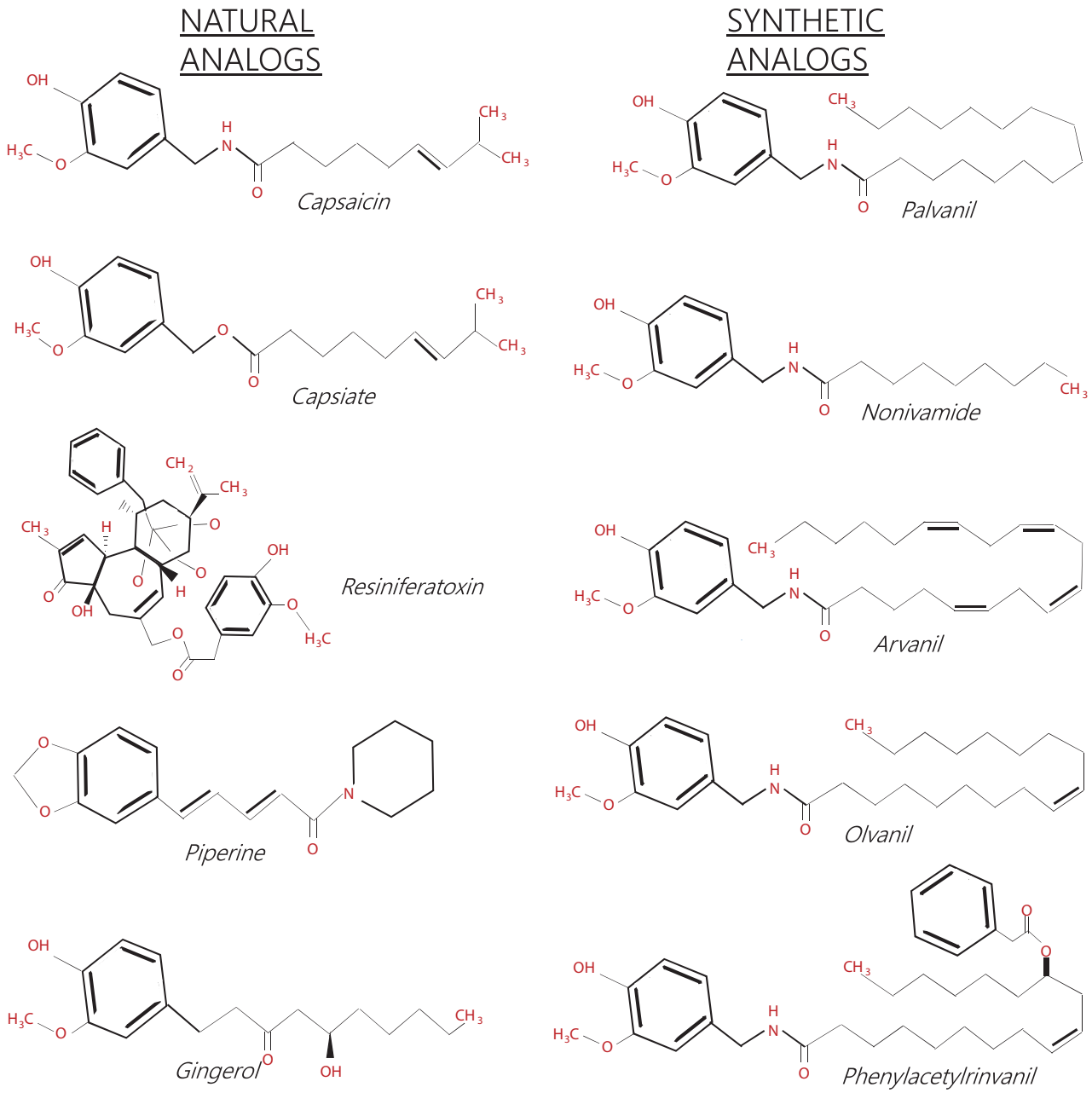

Figure 3: Names and chemical structure of natural and synthetic analogs of capsaicin.

Piperine: Piperine is the molecule responsible for the pungency of black pepper and is also considered a capsaicin analogue due to its capacity to produce a clear agonist activity at the TRPV1 receptor [52]. Nevertheless, piperine contains a benzodioxole ring rather than an aromatic catechol ring present in capsaicin (Figure 3), it is considered a capsaicin analogue due to its high TRPV1 affinity [53]. A number of studies have been addressed to elucidate the biological roles and physiological effects of piperine, such as the enhancement of the digestive capacity, the reduction of the gastrointestinal transit time for food, its ability to protect against oxidative damage and increasing the bioavailability of a number of therapeutic drugs, and some anti-tumoral effects as well [54]. To date, piperine has been reported to exhibit similar biological activities as capsaicin, including inhibition of adipogenesis by antagonizing PPARγ activity in 3T3-L1 cells [55], reduction of HFD-induced hepatic steatosis by decreasing triglycerides, free fatty acids and cholesterol in liver, as well decrease of hepatic lipogenic markers such as LXR, SREBP1c, Leptina, aP2 y CD36 in mice [56]. Nevertheless, other *in vivo* studies reported that piperine consumption does not amplify beneficial effects of caloric restriction in obese mice [57].

Gingerol: 6-gingerol is the bioactive constituent of the rhizome of fresh ginger (*Zingiber officinale*). Chemically, gingerol contains the characteristic vanilloid ring without the amide bond and the double bond in the carbon chain. It has an insertion of a hydroxyl group at C-5 (Figure 3) and has been used as a medicinal plant since ancient times because it possesses several pharmacological activities, including the effect on lipid metabolism [58]. Previous research has shown that

6-gingerol may reduce adiposity by promoting the catabolism of lipid through the increase of acetyl-coenzyme A acyl-transferase in high-fat diet mice [59]. It has also been shown a decrease in glucose levels, body weight, leptin, insulin and tissue lipids in high-fat diet-induced obese rats treated with 6-gingerol [60,61]. Furthermore, gingerol prevents adipogenesis in 3T3-L1 through the significant down-regulation of PPARɣ and C/EBPα [62,63].

Synthetic analogs

Since the discovery of multiple capsaicinoid effects, a number of researchers have focused in the chemical characterization of these molecules [64,65]. However, the development of additional potential of capsaicinoids as drugs has been restricted by their limited natural availability and low structural variability. At the moment, chemical synthesis has been an alternative tool to discover new capsaicin analogs without the inherent and undesirable effects [66,67]. In this section, we described the knowledge on synthetic analogs molecules that have shown similar effects to capsaicin, emphasizing the effect on lipid metabolism and energy balance.

Palvanil: *N-Palmitoyl-vanillamide* is a non-pungent capsaicin analogue, which is currently obtained by enzymatic synthesis [68]. It contains the aromatic catechol ring linked to a palmitic acid ($CH_3(CH_2)_{14}COOH$) by an amide bond in its chemical structure (Figure 3). Recent studies have shown that Palvanil is an antinociceptive agent because it inhibits inflammatory and neuropathic pain by activating TRPV1 receptor, besides, it has been demonstrated that this molecule produced significantly less side effects such as hypothermia and bronchoconstriction than capsaicin [69]. The use of Palvanil in the treatment of pathologies such as inflammatory and neuropathic hyperalgesia and other types of pain has been protected for commercial purposes [70]. However, there is a lack of studies regarding the potential effects of Palvanil in the regulation of lipid metabolism.

Nonivamide (VAMC9): The chemical name of Nonivamide is *N-vanillylamide of nonanoic* acid and is also obtained by enzymatic synthesis through a direct lipase-catalyzed reaction [71]. It contains the aromatic catechol ring linked to a pelargonic acid ($CH_3(CH_2)_{14}COOH$) by an amide bond (Figure 3). Nonivamide is a capsaicin analogue with two times less pungency than capsaicin (9,200,000 SHU compared to 16,100,000 SHU for capsaicin). It has been reported to exhibit similar biological activities as capsaicin, including the increase in intracellular Ca^{2+} levels via the activation of vanilloid receptors in some cell types [72], the reduction of lipid accumulation in adipocytes by decreasing PPARɣ protein levels in a similar way than capsaicin [73]. In the report of the only clinical trial performed with Nonivamide to our knowledge, is been shown that the addition of nonivamide to a glucose solution *ad libitum*, reduced the energy intake from a standardized breakfast in moderately overweight men [26]. This suggests that Nonivamide has a therapeutic potential as anti-obesity drug with better efficacy than capsaicin but without the undesirable effects of pungency.

Arvanil: The Arvanil´s chemical name is *N-Vanillylarachidonamide*. It contains the aromatic catechol ring linked to an arachidonic acid by an amide bond in its structure (Figure 3). It is also obtained by enzymatic synthesis and it has been demonstrated that only one modification in its chemical structure changes its biological activity. For example, methylation of the amide group decreases the affinity to TRPV1, and the substitution of the 3-methoxy group with a chlorine atom on the aromatic ring, increases its capacity to inhibit fatty acid amide hydrolase [74]. It has been shown that Arvanil has a beneficial effect in a rat model of Huntington´s disease, reducing ambulatory and stereotypic activity, and increasing the activity [75]. Moreover, it has been demonstrated the beneficial potential of Arvanil in neuronal affectations such as astrocytomas and mild cognitive impairment [76]. However, there is a lack of evidence about the Arvanil effects on the regulation of lipid metabolism.

Olvanil: Olvanil is a non-pungent capsaicin analogue that is also obtained by enzymatic synthesis through a direct lipase-catalyzed reaction [66,77]. It contains the aromatic catechol ring linked to an oleic acid by an amide bond (Figure 3).

Although its antinociceptive effect was discovered in 1990, no more studies on its potentially actions have been published to date. In our group, we found that olvanil treatment improves lipolysis while decreases the amount of intracellular triglycerides in 3T3-L1 cells in a similar manner to capsaicin. We also found that olvanil inhibits adipogenesis by reducing the activity of PPARɣ and preventing the maturation of 3T3-L1 preadipocytes (data send for publication).

Phenylacetylrinvanil (PhAR): PhAR is a capsaicin analogue, without pungency but with one thousand more affinity to TRPV1 receptors than capsaicin [78]. It contains an insertion of a hydroxyl group at C-12 of the chemical structure of olvanil and the presence of an additional functional group (Figure 3). About the potentials of this molecule, only the anti-carcinogenic effect has been evidenced. Recent studies have proven that PhAR induces apoptosis in leukaemia cell lines, such as P388, J774 and WEHI-3 [79] and it also inhibits *in vitro* cell proliferation of carcinogenic cells such as HeLa, CasKi and ViBo [80]. However, no evidence was found of its possible role in energy metabolism regulation.

Conclusions

Synthesis of capsaicin analogs and its chemical variants are a very useful alternative tool for drug therapy of obesity. Besides, their study might be helpful to understand the structural-activity relationship of molecules that have shown a highly medicinal value but with undesirable side effects, like capsaicin. Information found in scientific literature about the biological activity on metabolic disease of capsaicin analogs synthetized until now, adds knowledge about the plausible molecular mechanisms and possible portion of the capsaicin chemical structure responsible for its effect that is not completely understood.

Vanillyl structure was considered very important for activation of the TRPV1 receptors, however, as can be seen in the available data, it has been recently found that molecules lacking the vanillyl structure can also activate the TRPV1 receptors and in some cases magnify the affinity to these receptors, higher than capsaicin itself. This could lead to the conclusion that there are other structural moieties or functional groups than can activate TRPV1 receptors, inducing the same or enhanced biological effects, therefore, the concept "capsaicin analogue" can be difficult to define. Another important subject is the fact that many capsaicin analogs, despite having different pungency levels, have the same receptor affinity and different antinociception capacity but some preserve, and in some cases increase, their potential benefits in the regulation of metabolism, like nonivamide and olvanil compared to capsaicin. The majority of evidence provided suggest that the pungency level of these molecules does not determine the biological effect discussed here. Additional work should be conducted on synthetizing different analog molecules with some structural modifications, based in previous research to obtain a better molecule

with the highest potential therapeutic effect but with less inherent undesirable side effects.

References

1. Yanovski SZ, Yanovski JA (2014) Long-term drug treatment for obesity: a systematic and clinical review. JAMA 311: 74-86.
2. Yun JW (2010) Possible anti-obesity therapeutics from nature--a review. Phytochemistry 71: 1625-1641.
3. Kim KH, Park Y (2011) Food components with anti-obesity effect. Annu Rev Food Sci Technol 2: 237-257.
4. Behloul N, Wu G (2013) Genistein: a promising therapeutic agent for obesity and diabetes treatment. Eur J Pharmacol 698: 31-38.
5. Rayalam S, Della-Fera MA, Yang JY, Park HJ, Ambati S, et al. (2007) Resveratrol potentiates genistein's antiadipogenic and proapoptotic effects in 3T3-L1 adipocytes. J. Nutr. 137: 2668-2673.
6. Leung FW (2014) Capsaicin as an anti-obesity drug. Prog Drug Res 68: 171-179.
7. Lefterova MI, Haakonsson AK, Lazar MA, Mandrup S (2014) PPARγ and the global map of adipogenesis and beyond. Trends Endocrinol Metab 25: 293-302.
8. Tewksbury JJ, Nabhan GP (2001) Seed dispersal. Directed deterrence by capsaicin in chilies. Nature 412: 403-404.
9. Chinn MS, Sharma-Shivappa RR, Cotter JL (2011) Solvent extraction and quantification of capsaicinoids from Capsicum chinense. Food Bioprod Process 89: 340-345.
10. Ishimov UZ, Ziyavitdinov ZF, Sagdiev NZ (2011) Minor constituents of total capsaicinoids from Capsicum annuum. Chem Nat Compd 46: 1006-1007.
11. González-Zamora A, Sierra-Campos E, Luna-Ortega JG, Pérez-Morales R, Rodríguez Ortiz JC, et al. (2013) Characterization of different capsicum varieties by evaluation of their capsaicinoids content by high performance liquid chromatography, determination of pungency and effect of high temperature. Molecules 18: 13471-13486.
12. Reyes-Escogido Mde L, Gonzalez-Mondragon EG, Vazquez-Tzompantzi E (2011) Chemical and pharmacological aspects of capsaicin. Molecules 16: 1253-1270.
13. Othman ZAA, Ahmed YBH, Habila MA, Ghafar AA (2011) Determination of capsaicin and dihydrocapsaicin in Capsicum fruit samples using high performance liquid chromatography. Molecules 16: 8919-8929.
14. Hayman M, Kam PC (2008) Capsaicin: a review of its pharmacology and clinical applications. Curr Anaesth Crit Care 19: 338-343.
15. Anand P, Bley K (2011) Topical capsaicin for pain management: therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8% patch. Br J Anaesth 107: 490-502.
16. De Silva V, El-Metwally A, Ernst E, Lewith G, Macfarlane GJ (2011) Evidence for the efficacy of complementary and alternative medicines in the management of osteoarthritis: a systematic review. Rheumatology 50: 911-920.
17. Lee GR, Shin MK, Yoon DJ, Kim AR, Yu R, et al. (2013) Topical application of capsaicin reduces visceral adipose fat by affecting adipokine levels in high-fat diet-induced obese mice. Obesity 21: 115-122.
18. Janssens PL, Hursel R, Martens EA, Westerterp-Plantenga MS (2013) Acute effects of capsaicin on energy expenditure and fat oxidation in negative energy balance. PLoS One 8: e67786.
19. Lee MS, Kim CT, Kim IH, Kim Y (2011) Effects of capsaicin on lipid catabolism in 3T3-L1 adipocytes. Phytother Res 25: 935-939.
20. Reinbach HC, Smeets A, Martinussen T, Møller P, Westerterp-Plantenga MS (2009) Effects of capsaicin, green tea and CH-19 sweet pepper on appetite and energy intake in humans in negative and positive energy balance. Clin Nutr 28: 260-265.
21. Janssens PL, Hursel R, Westerterp-Plantenga MS (2014) Capsaicin increases sensation of fullness in energy balance, and decreases desire to eat after dinner in negative energy balance. Appetite 77: 46-51.
22. Baek J, Lee J, Kim K, Kim T, Kim D, et al. (2013) Inhibitory effects of Capsicum annuum L. water extracts on lipoprotein lipase activity in 3T3-L1 cells. Nutr Res Pract 7: 96-102.
23. Feng Z, Hai-ning Y, Xiao-man C, Zun-chen W, Sheng-rong S, et al. (2014) Effect of yellow capsicum extract on proliferation and differentiation of 3T3-L1 preadipocytes. Nutrition 30: 319-325.
24. Tan S, Gao B, Tao Y, Guo J, Su ZQ (2014) Antiobese effects of capsaicin-chitosan microsphere (CCMS) in obese rats induced by high fat diet. J Agric Food Chem 62: 1866-1874.
25. Ibrahim M, Jang M, Park M, Gobianand K, You S, et al. (2015) Capsaicin inhibits the adipogenic differentiation of bone marrow mesenchymal stem cells by regulating cell proliferation, apoptosis, oxidative and nitrosative stress. Food Funct 6: 2165-2178.
26. Hochkogler CM, Rohm B, Hojdar K, Pignitter M, Widder S, et al. (2014) The capsaicin analog nonivamide decreases total energy intake from a standardized breakfast and enhances plasma serotonin levels in moderately overweight men after administered in an oral glucose tolerance test: A randomized, crossover trial. Mol Nutr Food Res 58: 1282-1290.
27. Rohm B, Riedel A, Ley JP, Widder S, Krammer GE, et al. (2015) Capsaicin, nonivamide and trans-pellitorine decrease free fatty acid uptake without TRPV1 activation and increase acetyl-coenzyme A synthetase activity in Caco-2 cells. Food Funct 6: 173-185.
28. Palazzo E, Luongo L, de Novellis V, Rossi F, Marabese I, et al. (2012) Transient receptor potential vanilloid type 1 and pain development. Curr Opin Pharmacol 12: 9-17.
29. Liao M, Cao E, Julius D, Cheng Y (2013) Structure of the TRPV1 ion channel determined by electron cryo-microscopy. Nature 504: 107-112.
30. Bishnoi M, Kondepudi KK, Gupta A, Karmase A, Boparai RK (2013) Expression of multiple Transient Receptor Potential channel genes in murine 3T3-L1 cell lines and adipose tissue. Pharmacol Rep 65: 751-755.
31. Darré L, Domene C (2015) Binding of Capsaicin to the TRPV1 Ion Channel. Mol Pharm 12: 4454-4465.
32. Feng Z, Pearce LV, Xu X, Yang X, Yang P, et al. (2015) Structural insight into tetrameric hTRPV1 from homology modeling, molecular docking, molecular dynamics simulation, virtual screening, and bioassay validations. J. Chem. Inf. Model 55: 572-588.
33. Yang F, Xiao X, Cheng W, Yang W, Yu P, et al. (2015) Structural mechanism underlying capsaicin binding and activation of the TRPV1 ion channel. Nat. Chem. Biol 11: 518-524.
34. Zhang LL, Yan Liu D, Ma LQ, Luo ZD, Cao TB, et al. (2007) Activation of transient receptor potential vanilloid type-1 channel prevents adipogenesis and obesity. Cir. Res 100: 1063-1070.
35. Ikura M, Osawa M, Ames JB (2002) The role of calcium-binding proteins in the control of transcription: structure to function. Bioessays 24: 625-636.
36. Neal JW, Clipstone NA (2002) Calcineurin mediates the calcium-dependent inhibition of adipocyte differentiation in 3T3-L1 cells. J. Biol. Chem 277: 49776-49781.
37. Chen J, Li L, Li Y, Liang X, Sun Q, et al. (2015) Activation of TRPV1 channel by dietary capsaicin improves visceral fat remodeling through connexin43-mediated Ca2+ Influx. Cardiovasc Diabetol 14: 1-14.
38. Yeganeh A, Stelmack GL, Fandrich RR, Halayko AJ, Kardami E, et al. (2012) Connexin 43 phosphorylation and degradation are required for adipogenesis. Biochim Biophys Acta 1823: 1731-1744.
39. Leff T (2003) AMP-activated protein kinase regulates gene expression by direct phosphorylation of nuclear proteins. Biochem Soc Trans 31: 224-227.
40. Burns KA, Vanden Heuvel JP (2007) Modulation of PPAR activity via phosphorylation. Biochim Biophys Acta 1771: 952-960.
41. Carling D, Sanders MJ, Woods A (2008) The regulation of AMP-activated protein kinase by upstream kinases. Int J Obes (Lond) 32 Suppl 4: S55-59.
42. Ursu D, Knopp K, Beattie RE, Liu B, Sher E (2010) Pungency of TRPV1 agonists is directly correlated with kinetics of receptor activation and lipophilicity. Eur. J. Pharmacol 641: 114-122.
43. Wang J, Peng Z, Zhou S, Zhang J, Zhang S, et al. (2011) A study of pungency of capsaicinoid as affected by their molecular structure alteration. Pharmacol Pharm 2: 109-115.
44. Sasahara I, Furuhata Y, Iwasaki Y, Inoue N, Sato H, et al. (2010) Assessment of the biological similarity of three capsaicin analogs (Capsinoids) found in non-pungent chili pepper (CH-19 Sweet) fruits. Biosci Biotechnol Biochem 74: 274-278.

45. Haramizu S, Mizunoya W, Masuda Y, Ohnuki K, Watanabe T, et al. (2006) Capsiate, a nonpungent capsaicin analog, increases endurance swimming capacity of mice by stimulation of vanilloid receptors. Biosci Biotechnol Biochem 70: 774-781.

46. Kwon DY, Kim YS, Ryu SY, Cha MR, Yon GH, et al. (2013) Capsiate improves glucose metabolism by improving insulin sensitivity better than capsaicin in diabetic rats. J Nutr Biochem 24: 1078-1085.

47. Hong Q, Xia C, Xiangying H, Quan Y (2015) Capsinoids suppress fat accumulation via lipid metabolism. Mol Med Rep 11: 1669-1674.

48. Ludy MJ, Moore GE, Mattes RD (2012) The effects of capsaicin and capsiate on energy balance: critical review and meta-analyses of studies in humans. Chem Senses 37: 103-121.

49. Shintaku K, Uchida K, Suzuki Y, Zhou Y, Fushiki T, et al. (2012) Activation of transient receptor potential A1 by a non-pungent capsaicin-like compound, capsiate. Br J Pharmacol 165: 1476-1486.

50. Watanabe T, Sakurada N, Kobata K (2001) Capsaicin-, resiniferatoxin-, and olvanil-induced adrenaline secretions in rats via the vanilloid receptor. Biosci Biotechnol Biochem 65: 2443-2447.

51. Pan HL, Khan GM, Alloway KD, Chen SR (2003) Resiniferatoxin induces paradoxical changes in thermal and mechanical sensitivities in rats: mechanism of action. J Neurosci 23: 2911-2919.

52. McNamara FN, Randall A, Gunthorpe MJ (2005) Effects of piperine, the pungent component of black pepper, at the human vanilloid receptor (TRPV1). Br. J. Pharmacol 144: 781-790.

53. Damião MC, Pasqualoto KF, Ferreira AK, Teixeira SF, Azevedo RA, et al. (2014) Novel capsaicin analogues as potential anticancer agents: synthesis, biological evaluation, and in silico approach. Archiv der Pharmazie 347: 885-895.

54. Srinivasan K (2007) Black pepper and its pungent principle-piperine: a review of diverse physiological effects. Crit Rev Food Sci Nutr 47: 735-748.

55. Park UH, Jeong HS, Jo EY, Park T, Yoon SK, et al. (2012) Piperine, a component of black pepper, inhibits adipogenesis by antagonizing PPAR? activity in 3T3-L1 cells. J. Agric. Food Chem 60: 3853-3860.

56. Choi S, Choi Y, Choi Y, Kim S, Jang J, et al. (2013) Piperine reverses high fat diet-induced hepatic steatosis and insulin resistance in mice. Food Chem 141: 3627-3635.

57. Wang J, Vanegas SM, Du X, Noble T, Zingg JM, et al. (2013) Caloric restriction favorably impacts metabolic and immune/inflammatory profiles in obese mice but curcumin/piperine consumption adds no further benefit. Nutr Metab 10: 29.

58. Wang S, Zhang C, Yang G, Yang Y (2014) Biological properties of 6-gingerol: a brief review. Nat Prod Commun 9: 1027-1030.

59. Beattie JH, Nicol F, Gordon MJ, Reid MD, Cantlay L, et al. (2011) Ginger phytochemicals mitigate the obesogenic effects of a high-fat diet in mice: a proteomic and biomarker network analysis. Mol Nutr Food Res 55 Suppl 2: S203-213.

60. Saravanan G, Ponmurugan P, Deepa MA, Senthilkumar B (2014) Anti-obesity action of gingerol: effect on lipid profile, insulin, leptin, amylase and lipase in male obese rats induced by a high-fat diet. J Sci Food Agric 94: 2972-2977.

61. Brahma Naidu P, Uddandrao VV, Ravindar Naik R, Suresh P, Meriga B, et al. (2016) Ameliorative potential of gingerol: Promising modulation of inflammatory factors and lipid marker enzymes expressions in HFD induced obesity in rats. Mol. Cell. End 419: 139-147.

62. Tzeng TF, Liu IM (2013) 6-gingerol prevents adipogenesis and the accumulation of cytoplasmic lipid droplets in 3T3-L1 cells. Phytomedicine 20: 481-487.

63. Tzeng TF, Chang CJ, Liu IM (2014) 6-Gingerol Inhibits Rosiglitazone-Induced Adipogenesis in 3T3-L1 Adipocytes. Phytother Res 28: 187-192.

64. Wang B, Yang F, Shan YF, Qiu WW, Tang J (2009) Highly efficient synthesis of capsaicin analogues by condensation of vanillylamine and acyl chlorides in a biphase H2O/CHCl3 system. Tetrahedron 65: 5409-5412.

65. Ishihara K, Kwon SI, Masuoka N, Nakajima N, Hamada H (2010) One-procedure synthesis of capsiate from capsaicin by lipase-catalyzed dynamic transacylation. World J Microbiol Biotechnol 26: 1337-1340.

66. Castillo E, Torres A, Severiano P, Arturo N, López A (2007) Lipase-catalyzed synthesis of pungent capsaicin analogues. Food Chem 100: 1202-1208.

67. Peng B, Wang J, Peng Z, Zhou S, Wang F, et al. (2012) Studies on the synthesis, pungency and anti-biofouling performance of capsaicin analogues. Sci China Chem 55: 435-442.

68. Liu KJ, Liu KM, Chang HM (2007) Biocatalytic synthesis of palmitoyl vanillylamide in supercritical carbon dioxide through amidation of vanillylamine hydrochloride and palmitic anhydride by lipase. Food chem 102: 1020-1026.

69. Luongo L, Costa B, D'Agostino B, Guida F, Comelli F, et al. (2012) Palvanil, a non-pungent capsaicin analogue, inhibits inflammatory and neuropathic pain with little effects on bronchopulmonary function and body temperature. Pharmacol Res 66: 243-250.

70. De Petrocellis L, Guida F, Moriello AS, De Chiaro M, Piscitelli F, et al. (2011) N-palmitoyl-vanillamide (palvanil) is a non-pungent analogue of capsaicin with stronger desensitizing capability against the TRPV1 receptor and anti-hyperalgesic activity. Pharmacoll Res 63: 294-299.

71. Castillo E, López-González I, De Regil-Hernández R, Reyes-Duarte D, Sánchez-Herrera D, et al. (2007) Enzymatic synthesis of capsaicin analogs and their effect on the T-type Ca2+ channels. Biochem Biophys Res Commun 356: 424-430.

72. Saitoh S, Fukunaga E, Honda S, Kanemaru K, Satoh M, et al. (2014) Nonivamide, a natural analog of capsaicin, affects intracellular Ca2+ level in rat thymic lymphocytes. Natural Science Research, The University of Tokushima 28: 15-19.

73. Rohm B, Holik AK, Kretschy N, Somoza MM, Ley JP, et al. (2015) Nonivamide Enhances miRNA let-7d Expression and Decreases Adipogenesis PPAR? Expression in 3T3-L1 Cells. J. Cell Biochem 116: 1153-1163.

74. Di Marzo V, Griffin G, De Petrocellis L, Brandi I, Bisogno T, et al. (2002) A structure/activity relationship study on arvanil, an endocannabinoid and vanilloid hybrid. J Pharmacol Exp Ther 300: 984-991.

75. de Lago E, Urbani P, Ramos JA, Di Marzo V, Fernández-Ruiz J (2005) Arvanil, a hybrid endocannabinoid and vanilloid compound, behaves as an antihyperkinetic agent in a rat model of Huntington's disease. Brain Res 1050: 210-216.

76. Stock K, Kumar J, Synowitz M, Petrosino S, Imperatore R, et al. (2012) Neural precursor cells induce cell death of high-grade astrocytomas through stimulation of TRPV1. Nat. Med 18: 1232-1238.

77. Reyes D, Castillo E, Martínez R, López A (2002) Lipase-catalysed synthesis of olvanil in organic solvents. Biotechnol Lett 24: 2057-2061.

78. Appendino G, De Petrocellis L, Trevisani M, Minassi A, Daddario N, et al. (2005) Development of the first ultra-potent "capsaicinoid" agonist at transient receptor potential vanilloid type 1 (TRPV1) channels and its therapeutic potential. J Pharmacol Exp Ther 312: 561-570.

79. Luviano A, Aguiñiga-Sánchez I, Demare P, Tiburcio R, Ledesma-Martínez E, et al. (2014) Antineoplastic activity of rinvanil and phenylacetylrinvanil in leukaemia cell lines. Oncol Lett 7: 1651-1656.

80. Sánchez-Sánchez L, Alvarado-Sansininea JJ, Escobar ML, López-Muñoz H, Hernández-Vázquez JM, et al. (2015) Evaluation of the antitumour activity of Rinvanil and Phenylacetylrinvanil on the cervical cancer tumour cell lines HeLa, CaSKi and ViBo. Eur J Pharmacol 758: 129-136.

Citation: Morales-Martínez CE, Márquez-Aguirre AL, Díaz-Martínez E, Rodríguez-González JA, Mateos-Díaz JC, et al. (2016) The Prospective Antiobesity Effect of Capsaicin Synthetic Analogs: A Matter of Weight. Med chem (Los Angeles) 6: 365-371. doi:10.4172/2161-0444.1000371