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CAPSAICIN, A MILESTONE IN PHARMACEUTICAL FIELD: A PROSPECTIVE REVIEW

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Abstract

Uses of natural plant extract or fruits and vegetables for well-being of life and as a medicine is the latest trend of current scientific community. Nature is the best and safest source for medicine as the chemically synthesized drugs have lots of side effects. This review will cover the medicinal properties of Capsaicin in different types of diseases and in other fields. Capsaicin is the main component of the Capsicum which is one of the common food ingredients across the world. It signifies that the development of drugs which will be easily available and cheap with least number of side effects. In this review, we have systematically discussed about the potential drug molecule Capsaicin. We have discussed in detail about the physicochemical properties of the Capsaicin and how that affects its therapeutic behavior. We have discussed its pharmaceutical properties in elaborated ways and in separated paragraph discussing about its antifungal, antibacterial and pain relief properties. So, reading this article will develop an intense interest in readers about the Capsaicin molecule which may encourage for further drug development using Capsaicin.

1. INTRODUCTION

Capsaicin (8-methyl-N-vanilly-6-nonenamide): a compound which is active component of chili peppers and are mainly present in the placenta of chili fruits of the genus Capsicum. Means it is not equally distributed in all parts of the chili fruit, but its concentration is higher

in the area surrounding the seeds (placental tissue) and this localization is related directly in the increased germination of seeds [1]. It is basically pungent in nature and it produces burning sensation in any tissues of humans which comes into contact[2]. Capsaicin is an intriguing molecule, and its consumption evokes opposing sensation (pleasant and unpleasant) depending upon the individual's experience and chili peppers consumption habits. The effects of capsaicin go well beyond the taste and its role in plants health, protecting from parasites and further that help us to understand how its use can improve for human health [3]. And human have been using this property to treat infectious diseases and to preserve food [4, 5]. It has to be seen that rodents and mammals don't use these types of plants as food material and this is the reason behind to increase the germination of seeds [6]. And chili plants are easy to grow in topical region for such a main spices ingredient in our food. Now a days researchers are interested about its prosperous pharmacological properties and have not any severe side effects.

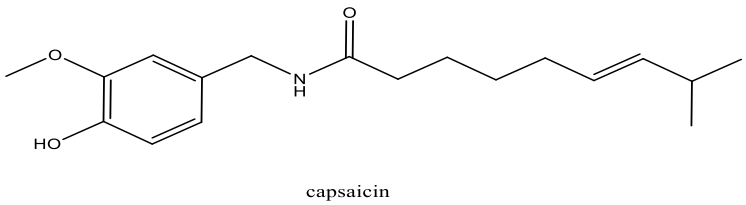
The chemical composition of Capsaicin was first introduced in 1919 by E. K. Nelson [7], and it was first synthesized in 1930 by Ernst Spath and S. F. Darling [8]. Plants belong to Capsicum genus produce varied amount of Capsaicin, except Capsicum annum, and all of them mainly used as a spice ingredient and consumed by human for over 6000 years [9]. Even we know that from ancient era chili have been used probably as spices in the food ingredients. But much research shows that it has not only the spices properties but also has some therapeutic properties. It has been used in topical creams and patches to treat chronic pain syndrome such as post herpetic neuralgia [10, 11], musculoskeletal pain, diabetic neuropathy [12, 13], osteoarthritis, rheumatoid arthritis [14]. Many recent studies have confirmed that Capsaicin can also be used to relieve pain (scientifically what was already known by some cultures) [15]. And many clinical trials shows that it is also effective in gastrointestinal tract, alzheimer, parkinson like diseases [16, 17]. In particular, Capsaicin has a wide variety of biological activities which provide its functions as anti-carcinogens [18], antifungal, antioxidants, anti-inflammatories, suppression of fat accumulation, promotion of energy metabolism, anti- obesity, analgesic, neuroprotective [19, 20], etc. In this review, we will highlight the biological and therapeutic importance and applications of Capsaicin. Furthermore, we know that the different variety of chilies, which are generally spicy in taste,

are easily available and very cheap in the Indian sub-continent therefore, people from different financial background can use the chilies very easily and get somehow a healthy and disease-free life. In these contexts, we will study the physicochemical and biological activities of capsaicin.

2. PHYSICOCHEMICAL PROPERTIES OF CAPSAICIN

Capsaicin is a natural proto-alkaloid and the major pungent component of chili peppers. It can also found in fruits of other plants belonging to the genus Capsicum [1, 21]. Capsicum fruits contain about 0.1 to 1.0% 0f capsaicin [22]. Also known as 8-methyl-N-vanilly-6-nonenamide, its empirical formula is C18H27O3N and its molecular weight is 305.40 Daltons. It is crystalline, off white solid, lipophilic, colorless, and odorless. It has a melting point of 62-65oC and it is sparingly soluble in cold water and more soluble in hot water, it is readily soluble in alcohol, ether, glacial acetic acid, acetone and fatty oils[23].

Capsaicin displays both cis- and trans- isomerism but generally found as the trans-isomerism, because in the cis-form, the -CH(CH3)2 and the longer chain on the other side of the double bond will be close together and it causes repel to each other slightly, this steric hindrance does not exist in the trans isomer which is a more stable arrangement than cis-isomer. Capsaicin belongs to the vanilloid family of compounds such as vanillin (derived from vanilla), eugenol (extracted from bay leaves and cloves), and zingerone (encountered in zinger) [24]. Capsaicin structure has an aromatic ring and a long hydrophobic chain with a polar amide group (fig. 1).

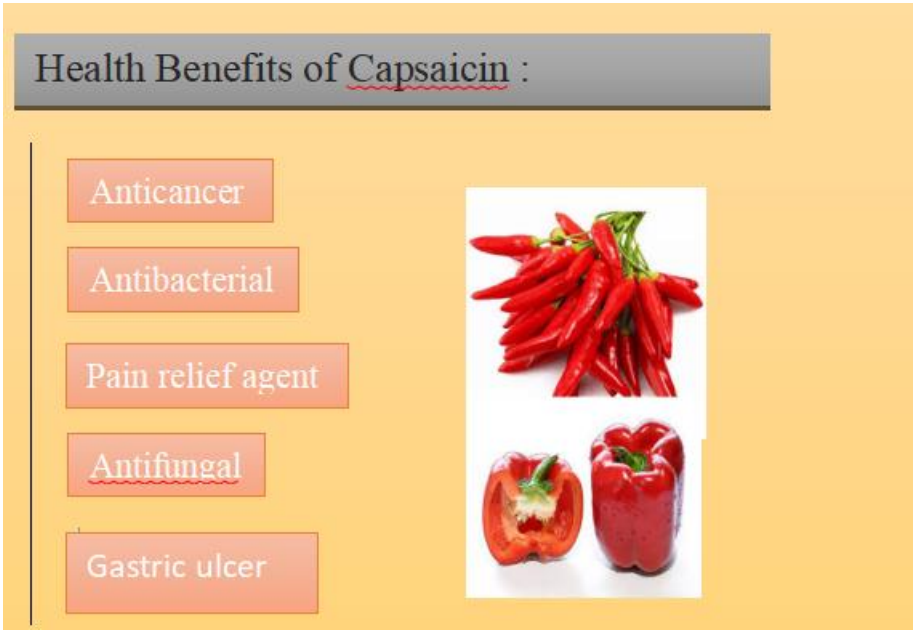


capsaicin

Figure 1: Chemical structure of Capsaicin

3. BIOLOGICAL IMPORTANT PROPERTIES OF CAPSAICIN IN PHARMACEUTICALS

Capsaicin is very effective in the treatment of different types of painful conditions such as complex regional pain syndromes and neuropathic pain [25, 26], post- herpetic neuralgia [11]; and painful diabetic peripheral neuropathy [12]. Plants are the primarily source of about 25% of global therapeutic drugs [27]. Capsaicin inhibits acid secretion, stimulates alkali and mucus secretion and particularly gastric mucosal blood flow which helps in prevention and healing of gastric ulcers. Some studies are shows that repeated use of nasal capsaicin prevents cluster headache attacks [28] and others we have been already discussed above. Now further, we will discuss about the impact of capsaicin in different biological perspective.



4. ANTICANCER PROPERTIES

As we know that cancer is a non-communicable disease and present day many studies have shown that capsaicin possesses chemotherapeutic and chemo preventive effects [29-32] because of it has the property to induce apoptosis in many different types of cancer cell lines including pancreatic [33], lung [34], liver[35], bladder [36], skin [37], leukemia [38], prostatic [39], endothelial cells and unharmed to normal leaving cells [40]. Apoptosis is an essential barrier against cancer cell development and progression [41]. In the gastrointestinal tract, capsaicin shows anti-tumoral effects in gastric cancer [42,43]. Now, cancer is considered as an increasing public health concern, its impact on quality of life and burden on healthcare

system [44] that devastates the economy in a major perspective and make the family helpless economically [45]. Because of growing and aging population, about 29 million cancer cases are expected by 2040 [46]. So, it is very important to study all the things related to cure the cancer which is mostly the fatal disease when patient don't know about this at initial stage.

As we discussed above that plants are the most important resource in the production of therapeutic drugs. For instance, anticancer agents such as vinblastine and paclitaxel were derived from Catharanthus Roseus (L.) G. Don (syn. Vinca rosea L.) and Taxusbrevifolia Nutt. respectively [47]. Thus, natural therapeutic agent are the major contributor in drugs discovery for various diseases, as they are cheap and gas least health hazards including cancer [48]. Capsaicin, a homo vanillic acid derivative, is one of such dietary phytochemical agents which have ability to ameliorate cancer at various levels [49,50]. Apoptosis is the process of programmed cell death then it is an essential barrier aganist cancer development and a recent review by Bley et al. noted that Capsaicin appears to induce apoptosis in over 40 distinct cancer cell lines [18]. Capsaicin has also pro-aptotic activity which is mediated via TRPV1 in many types of cancers [51-55] and via TRPV6 [56,57]. A well-known anticancer mechanism is the p53 tumor suppressor that is frequently mutated in many carcinomas [58]. From decades, the role of p53 in apoptosis has been intensely studied [59]. It has been also studied that Capsaicin reversed the activity of 5- fluorouracil in cholangio-carcinoma that is resistant to chemotherapeutic agent [60].

5. ANTIFUNGAL PROPERTIES

Capsaicinoids (the derivative of capsaicin) has antifungal activities, this is because of the presence of the polar moiety (the hydroxyl group of the vanilly ring) and mainly due to the lipophilic part of their chemical structure (e.g., acyl chain) [4]. Also the numbers of carbon atoms and double bonds present in the capsaicinoid side chain can affects with the fungal lipid bilayers [61,62]. This antifungal property makes capsaicinoids used as a pesticide and interestingly, it has very low toxicity to non-target organisms [63,64]. and the other applications of capsaicin is to discourage the growth of living organisms (like fungi), particularly for underwater covering objects such as boat hulls or water intake pipes (United States Patent No.5226380 ; Fischer ,1993) [65].

In fungi, the addition of pure capsaicin inhibits the growth of Aspergillus section Nigri strains (ATHUM 6997, 6998, 6999, 7000), as well as the biosynthesis of ochratoxin-A production. So, capsaicin emerges as a natural preservative agent for foods and crops that have ochratoxin-A and Aspergillus section Nigri contamination problems [66].

6. ANTIBACTERIAL PROPERTIES

Capsaicin and its derivatives has antibacterial effects, this were supported by many experimental results, with a mixture comprised of 74.6% capsaicin, 15.8% di-hydro capsaicin, 4.4% norhydro capsaicin and nonivamide which were analyzed against both Gram-negative and Gram-positive bacteria including E. coli, Pseudomonas solanacearum, and Bacillius subtilis, respectively [67].Various results revealed that the mixture could only hinder the growth of the E. coli strain when applied at the highest concentration and given that growth was reduced by approximately 20% at the same concentration [68]. Furthermore, in future the antibacterial properties of the natural compounds will help us to develop an important tool to combat against the bacterial infections in human and the veterinary medicine [69].

A comprehensive study investigated that the capsaicinoids and capsinoids have antibacterial, efflux pump inhibitory and resistant-modulatory properties against Mycobacteria such as Mycobacterium smegmatis [70].

7. PAIN RELIEF PROPERTIES

In chronic pain, Capsaicin has a slight analgesic action, where topical usage promotes to relief in pain after recurrent applications [71]. A significant pain reduction of 33 and 57% was reported by the topical use of a 0.025% capsaicin cream for treating rheumatoid arthritis and osteoarthritis in patients, respectively [72]. Hence, capsaicin has played an important role in treating burning pain like medicine [73]. Capsaicin initially is being used in creams, lotions and patches generally in the range of 0.025-0.1% by weight and are now being used for the management of neuropathic pain and musculoskeletal pain [74, 75]

Further, through some experimental study it is already reported that capsaicin has selective action on C-polymodal nociceptors to obtain the response of C-fibers in the cat saphenous nerve. It has observed that after the injection of capsaicin it reduces the thermal threshold in both rats and humans [76]. Thus, Capsaicin has the selective effect on C-

polymodal nociceptors and the thermo dependency sensory effects on humans and animals [76]. Capsaicin has helped us to aware of the chronic abdominal pain and the mechanisms related to the patients with irritable bowel syndrome (IBS). It induces pain related behaviors such as abdominal pain in a morphine sensitive manner, this shows its nociceptive nature [77]. The abdominal mechanical hyperalgesia and allodynia present in IBS patients [78]. Nociceptive fibers present in the colon respond to TRPV1 (transient receptor potential vanilloid -1) receptors, these receptors as potential target for abdominal pain [79]. And in many studies have shown that TRPV1 pathway is an attractive pharmacological approach to treat visceral pain [80] and it also modulates the emotional components of visceral pain [81]. Injection of capsaicin in wild rats activates putative pain neutral circuit and TRPV1 receptors deficiency reduces the activation in these same brain regions in response to capsaicin [82].

Further, many studies suggests it may be very useful in treating scaling, redness, inflammation and pain from psoriasis (skin disorder due to cell multiplication ten times faster in comparison of normal cell). It may also useful in relieving pain from nerve damage disease like:

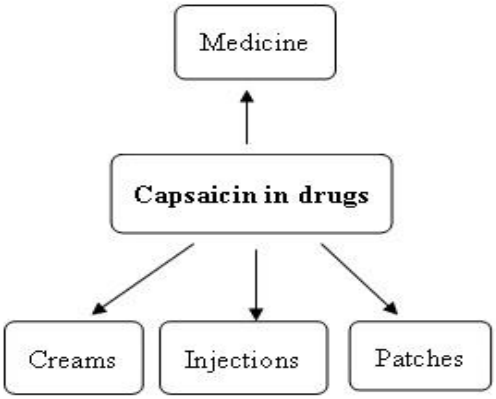
- HIV
- Shingles
- Peripheral diabetic neuropathy
- Postherpetic neuralgia

And in ancient era capsaicin was to be used as natural medicine in its raw form (chili powder) because it helps block pain messages to nerves and also mixed with other components to enhance its therapeutic properties. It is also an important component of ayurvedic sect. According to many research studies capsaicin creams and patches may help relieve pain due to:

- Surgery
- Migraines and other severe headaches
- Muscle strains

- Fibromyalgia: pain in muscles, by itself doesn't raise chance of getting COVID-19(disease caused by corona virus) but if patient live with fibromyalgia, COVID-19 can cause worries and create a long-term pain [83].

Now we can't ignore that capsaicin has many more useful effects in the treatment of human health issues. Basically, it is used as oral intake and the outer surface of the affected area of skin too. The below diagram clearly shows that Capsaicin is used in the main component in pharmaceutical drugs in the form of medicine, creams, injection, patches, etc., but we can't ignore the futuristic research approach of this drugs in other areas like for example in animal.



We know about its many more useful properties on human disease diagnostics. But a little bit of side effects on human body which is not very serious. That have discussed in the next paragraph, clearly.

8. SIDE EFFECTS OF CAPSAICIN

It doesn't give any severe side effects, but its creams and patches necessarily irritate the skin and can cause some problems like:

(a) Burning and itching

(b) Redness and swelling

(c) Dryness

(d) Soreness, etc.

9. CONCLUSION

The Capsaicin has enormous importance in different fields which some have discussed in above paragraph and here our interest is basically due to its conspicuous biological role in clinical applications. Despite of its some adverse effects, capsaicin is used as an active component of many pharmaceutical formulations for treating human ailments [84]. Many research have revealed that the potency of Capsaicin for managing human cancer and other therapeutics for several health concerns makes this a suitable drug molecule of interest. The last two decades have witnessed that the researchers are more interested in the field of capsaicin that's where capsaicin is potentially active. The futuristic research approach may be based on how Capsaicin interacts with DNA molecule and its specific binding with nucleic acid? And due the binding property, we will be able to know about not only its properties but also its disadvantages of more or less intake. This will contribute significantly to drug discovery in the times to come. As we have discussed above that capsaicin is important due to its medicinal property but it is also important due to its property like anti-inflammatory, anti-oxidant, anti-mutagenic, etc. Overall this review will attract the attentions of researchers for low-cost drug development using Capsaicin, which is one of the most common food ingredients across the globe. This article will not only be beneficial for the scientific community but also for the common reader. The easy and simple language of this article will attract the attention of readers from different disciplines and encourage them for including the fruits and vegetables in their dietary habits.

10. CONFLICT OF INTEREST

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article**.**

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