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Guest Editorial

Health with hotness

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A decreased prevalence of obesity, type 2 diabetes, and cardiovascular illnesses is linked to eating spicy spices in food. Hot peppers contain the active ingredient capsaicin. It is a naturally occurring compound found in peppers of the *Capsicum* genus, which includes varieties like jalapeno, habanero, and cayenne. It is responsible for the spicy or hot taste that these peppers are known for. Capsicums are long recognised for their great nutritional contents, such as the chilli pepper (Munjuluri et al., 2022). Human health benefits of capsaicin have been the subject of extensive research (López Pacheco et al., 2021). Numerous advantages of capsaicin, including cardio protective influence, anti-lithogenic effect, anti-inflammatory, analgesic, thermogenic influence and advantageous effects on gastrointestinal system, have been described in various studies (Srinivasan, 2016). It has been found to help with weight loss by increasing metabolism and reducing appetite. There have also been reports of capsaicin's positive benefits on cancer and cardiovascular diseases.

Hotness and pain

For the treatment of conditions involving pain and inflammation, capsaicin has been employed as a therapeutic option (Braga Ferreira et al., 2020). In comparison to oral NSAIDs, topical NSAIDs are often used to treat pain and inflammation since they have less systemic adverse effects and medication interactions. Diclofenac alone had effectiveness equivalent to a placebo, and when combined with capsaicin, there was no additional pain alleviation above only capsaicin (Predel et al., 2020).

Topical capsaicin reduces pain and cutaneous hypersensitivity by "defunctionalizing" nociceptor fibres, which is the best way to describe how it works on the skin. According to Anand and Bley (2011), defunctionalisation is caused by a variety of mechanisms, including a brief loss of membrane potential and an inability to transfer neurotrophic substances, which causes the terminals of epidermal and dermal nerve fibres to retract. The pain associated with osteoarthritis, one of the most prevalent joint disorders globally, was also found to be effectively and safely treated with topical capsaicin instead of paracetamol (Guedes et al., 2018). Additionally, long-lasting analgesia for trigeminal neuropathic pain has been successfully treated with capsaicin (Wang et al., 2020). The therapeutic effectiveness of capsaicin injection in patients with Morton's neuroma, a painful foot ailment brought on by compression of one of the digital nerves, has also been demonstrated. In this instance, pain was reduced without affecting tactile sensitivity (Chung and Campbell, 2016). In a different investigation, it was shown that long-lasting analgesia in a mouse model of neuropathic pain required capsaicin-induced Ca^{2+}/calpain-mediated ablation of axonal terminals (Arora et al., 2021).

CVDs

Cardiovascular diseases and metabolic syndrome has become widespread due to sedentary lifestyles, excessive food consumption, and insufficient exercise. Metabolic syndrome is a significant risk factor for type 2 diabetes and cardiovascular disease. It has been seen that regular chilli pepper eaters appear to maintain better health and outlive non-chili pepper eaters. According to studies, capsaicin dramatically modifies cardiovascular functions and the contractility and automaticity of the heart (Isaev et al., 2022). Thus, it has been discovered that a diet high in chilli peppers is linked to a lower risk of passing away from cardiovascular disease. However, there is no conclusive link between dietary capsaicin and lipid or blood glucose profiles (Szallasi, 2022). According to a recent study, capsaicin influences cardiac electrophysiology by influencing a variety of ion channels (Isaev et al., 2022). According to a different research, capsaicin and TRPV1

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may be useful therapeutic targets for the treatment of cardiometabolic vascular disorders and the dysfunction of their associated target organs (Sun et al., 2016). Capsaicin has also been discovered to lessen the infarct area in animal stroke models (Pasierski and Szulczyk, 2022).

Role of TRPV1

The transient receptor potential vanilloid type 1 (TRPV1) channel is strongly agonistic to capsaicin. Structure of TRP

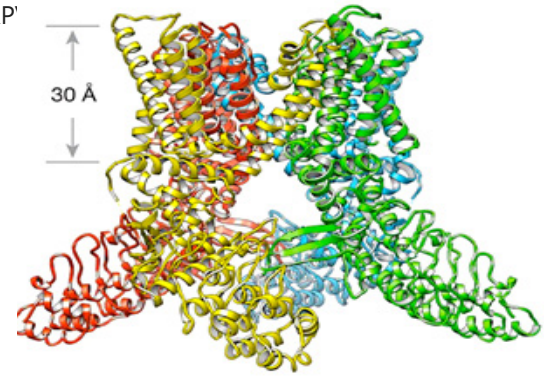

Fig. 1. Structure of the TRPV1 ion channel determined by electron cryo-microscopy (Reprinted from Liao et al. (2013)).

Capsaicin works by binding to TRPV1, which is found on the surface of various cells types including nerve cells. This receptor is responsible for detecting heat and pain. When capsaicin binds to it, it triggers a series of events that lead to the sensation of heat and pain. This is why capsaicin is often used in pain-relieving creams and ointments which act by overloading the TRPV1 receptors with capsaicin and desensitizing them to other forms of pain. According to Sun et al. (2016), TRPV1 plays important role in oxidative stress, inflammation, and pain perception. TRPV1 is a promising target for metabolic therapies since it is found on many metabolically active organs, including the brain, sensory neurons, dorsal root ganglia, bladder, stomach, and blood vessels (Panchal et al., 2018). Since the TRPV1 ion channel was identified, a wide range of experimental methods have been used to investigate how capsaicin activates this channel, including mutagenesis, patch-clamp recording, crystallography, cryo-electron microscopy, computational docking, and molecular dynamic simulation (Yang and Zheng, 2017). Moving further with mechanistic approach, TRPV1 activation has been shown to boost intracellular calcium signalling, which has a variety of physiological implications (Sun et al., 2016). TRPV1 and neuropeptides have been discovered to have a role in controlling visceral pain and immunological response, which in turn influences the levels of oxidative stress (Xiang et al., 2021). A growing body of research suggests that capsaicin has the potential to constrict blood vessels by acting on the vascular TRPV1 channel, raising the possibility that excessive consumption of the spice could lead to myocardial infarction and vasospasm in people with underlying inflammatory conditions. Additionally, some studies suggest that capsaicin may alter membrane fluidity, ion flux, and reactive oxygen species levels without relying on the TRPV1 channel (Braga Ferreira et al., 2020).

Inflammation

The body's natural response to injury or infection is inflammation. In extreme circumstances, if the inflammatory cells remain at the infection site for an extended period of time, chronic inflammation may develop. It has been discovered that capsaicin reduces inflammation by preventing the PKM2-LDHA-mediated Warburg effect. Researchers have shown that capsaicin efficiently decreases sepsis-related inflammation *in-vivo* in addition to suppressing inflammation in lipopolysaccharide generated macrophages (Zhang et al., 2022). In a different investigation, it was shown that delivering capsaicin epicutaneously to imiquimod-treated mouse skin greatly reduced the production of a number of inflammatory cytokines. Capsaicin's advantageous impact strengthens its neuroimmune role in psoriasiform inflammation (Chan et al., 2021).

Neurological disorders

Influence on TRPV1 channels in nociceptive sensory neurons is one of the key mechanisms by which capsaicin exerts its effects. Numerous recent publications demonstrate how capsaicin helps animal models of brain disorders. Capsaicin has been shown to lessen neurodegeneration and cognitive loss in Alzheimer's patients. There have also been written accounts of how capsaicin helps people with depression and Parkinson's disease.

Skin health

Reactive oxygen species (ROS), which have a harmful effect on cellular structures, are formed in the body as a result of a variety of external causes (Singh et al., 2014). Additionally, UV exposure causes a reduction in collagen synthesis, an increase in ROS production, and phosphorylation of Erk and c-Jun, all of which contribute to skin damage. It has been discovered that pre-treating with capsaicin in a dose-dependent way can counteract UV-mediated damages. By lowering ROS production in dermal fibroblasts, capsaicin protected the skin from injury and prevented UV-mediated collagen formation (Wu et al., 2022).

Concluding remarks

Overall, capsaicin is a fascinating compound with a wide range of potential benefits. From pain relief, reducing inflammation, cardiovascular health to skin health, it has been the subject of numerous studies and continues to be a popular ingredient in many natural health remedies. However, it is important to use capsaicin safely and responsibly, as it can be quite potent and

may not be suitable for everyone. Further studies are recommended using capsaicin as the core compound for exploring underlying action mechanisms.

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