

Red Pepper: from the Kitchen to the Pharmacy

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Some plants, including red pepper, ginger, black pepper, garlic, etc. have developed chemical substances as secondary metabolites that can be considered vegetable toxins with the purpose of dissuading their predators from eating them because of the unpleasant taste [1, 2]. The main target of the strategy of these plants are mammals [2], whereas birds are spared being devoid of the receptor for these toxins [3], likely for a finalistic reason, because birds, once they have ingested the fruit, sow the seeds with their faeces in a larger territory than mammals, helping the possibility of this plant species survival. Although these substances were created for plant defence and have an obnoxious taste, humans started to add them to food, because it was discovered that they helped to preserve the food from decomposition, also noting the fact that they alleviated the smells. Up to the Middle Ages the principal preserving additive in Europe was black pepper (*Piper nigrum*), but, when its import from India was hampered by the conquest of Constantinople in 1453 by the Turkish army, it became rare and extremely expensive. Fortunately, the discovery of America by Christopher Columbus focussed attention on the red pepper (*Capsicum annum*), that had been used as a food preserving

substance from 5500 B.C. by Mexicans. Thus this spice began to be imported from 1493 to Spain, and this spread across all of Europe and was cultivated around the Mediterranean sea, Africa and Asia, replacing more and more the use of black pepper, until it reached second in the world after black pepper in trade, both in volume and value.

The use of red pepper became very soon worldwide and today is present in the kitchens of every country with thousand of recipes, where its particular taste is exploited using dozens of *Capsicum* varieties more or less piquant. The piquancy is due to a particular component of red pepper, capsaicin that stimulates particular receptors of the oral mucosa giving the sensation of pain-burning, whereas mucosal blood flow and temperature are increased [4]. The sensory experience ranges from pleasant, for some persons, to painful, for others, and explains why some people love and others abhor red pepper [5]. The excess of the burning sensation may be attenuated by means of alcoholic drinks, fatty meals or bread crumb, that are able to remove the water insoluble pungent substance.

Very soon people realized that this addiction not only improves food taste and gives gustatory and olfactory pleasures, but also may offer new curative possibilities that were included in popular and ethnical medicine. Its use as medical remedy started most likely in the kitchen of hot countries, where it was used not only to preserve food from decay, but also to avoid the risk of intestinal infections, because of its antiputrefactive action. Now we know that this property is due to its antimicrobial and antimycotic activity [6-8]. Moreover, the inhabitants of these countries ate food with red pepper also as a remedy against the heat, because they realized that its property of vasodilating cutaneous vessels together with the increase of perspiration (known as „gustatory sweating”) was able to disperse the heat of the body. In addition, this vasodilating property was also considered effective to increase sexual performances, giving red pepper the reputation of an aphrodisiac drug. However, the folk healers very soon discovered that the most interesting property of red pepper is its analgesic activity. In fact from the beginning of time native Americans have rubbed their gems with pepper to alleviate tooth ache, whereas Indians made pepper tea to relieve the same kind of pain [9]. In Europe, red pepper was also used from the 19th century up to present times for relieving osteoarticular [10, 11], cutaneous

[12] and neuropathic [13-16] pain with ointments, creams, sticking plasters and patches with various concentrations of capsaicin, representing a valid alternative to NSAIDs and other analgesics burdened by sometimes noxious side effects [17]. The substances of red pepper responsible for analgesic activity are capsaicin (8-methyl-N-vanillyl-6-nonenamide) [18] and other capsaicinoids [19], that act on a specific receptor of pain, also activated by protons, noxious heat (>42°C) and endogenous stimuli, such as acids (pH<6) ammonia (pH>8), and arachidonic acid metabolites [20, 21]. This polymodal receptor is named VR1 (vanilloid receptor) or TRPV1 (transient receptor potential vanilloid-1) hypothesized by Jancsó et al 1977 [22] and identified in 1997 by Caterina et al [23].

The mechanism of the analgesic activity of capsaicin has been elucidated in these last decades and was attributed to a sensitization followed by a desensitization of this receptor TRPV1. This receptor is expressed by primary nociceptive neurons, that transfer the pain sensations to CNS, and is activated by proalgesic and inflammatory mediators giving rise to pain. The analgesic action is explained as follows. Capsaicin first binds the TRPV1 changing the membrane permeability to Ca²⁺ of the primary nociceptive neurons with consequent depolarization, which releases many neuropeptides including substance P and calcitonin gene related peptide. Afterwards it locks the neuronal membrane in a depolarized state that prevents subsequent depolarization and the release of neuropeptides, so that the fibres become unresponsive to nociceptive stimuli [24]. These effects are reversible, except when the treatment is applied during the neonatal period, leading in this case to complete ablation of these nociceptive neurons [25].

Until about ten years ago the analgesic effect of capsaicin was exploited only through cutaneous applications acting on somatic nociceptive nerves, the TRPV1 of which was reached by capsaicin absorbed through the epidermis. However, an important step forward in the utilization of the analgesic properties of capsaicin was taken when the TRPV1 of visceral nociceptive nerves was picked on and desensitized.

The novel idea was to reach the mucosal endings of the gastrointestinal nociceptive fibers by ingesting red pepper and this was realized for the first time in a study of the effect of red pepper on painful symptoms of functional dyspepsia in 2002 [26]. In fact, the epigastric pain of patients affected by functional dyspepsia, who ingested a daily amount of 2.5 gr of red pepper containing 0.7 mg/g of capsaicin for five weeks, after an initial period of worsening, decreased significantly with respect to that of a basal period and that of patients who received placebo randomly and in a double blind manner. This paper represented the first clinical application of TRPV1 channels to treat visceral pain, giving rise to the first real „visceral analgesic“, that stimulated a remarkable increase of studies in this field.

The favourable clinical results obtained desensitizing gastric TRPV1 receptors in functional dyspepsia drove the attention on other gut areas where TRPV1 receptors are involved in the pathophysiology of functional intestinal diseases with hyperalgesia, such as irritable bowel syndrome (IBS)[27], where TRPV1 nerve fibers are found increased and this increase is correlated with pain [28]. A double blind controlled study on

the effect of red pepper on IBS symptoms demonstrated that capsaicin contained in red pepper administered with enteric-coated pills for six weeks is able to significantly improve at the end of treatment abdominal pain in IBS patients instead of placebo [29]. This result suggested a novel way of dealing with this frequent and distressing functional disease, that to date does not have yet an effective pathophysiological treatment.

Another utilization of the visceral analgesic effect of capsaicin was suggested for GERD symptoms, because TRPV1 is found to play a key role in the pathogenesis of symptoms associated with reflux [30], and because capsaicin instillation induces symptoms of heartburn in healthy volunteers [31]. In fact, in a clinical study 31 GERD patients were treated with a chronic intraesophageal infusion of capsaicin that induced, after a period of sensitization, a desensitization with a significant decrease of GERD symptoms [32]. These results suggest that the capsaicin analgesic treatment could become an attractive new therapy for patients with NERD and „irritable esophagus“.

Rectal pain and urgency, due to rectal hypersensitivity and characterized by an increase of TRPV1 positive nerve fibers in muscle and mucosal layer [33], could also benefit from a desensitization of TRPV1 receptors in a manner similar to that used for IBS patients[29] or, alternatively, with enemas containing red pepper or capsaicin.

However, the analgesic effect of red pepper is obtained at the expense of an initial, although temporary, exacerbation of pain in the first weeks of treatment, as was observed in patients with functional dyspepsia [26] and in patients with IBS [29]. This problem may be obviated with the use of non pungent capsaicin-like compounds, such as resiniferatoxin (*Euphorbia resinifera*), that, on the other hand, is markedly superior to capsaicin in terms not only of tolerability, but also of effectiveness [34], and other capsaicin analogues, such as olvanil (*Capsicum* genus)[35] and palvanil [36], both more potent than capsaicin. Unfortunately the capsate and capsinoids, that are less pungent than capsaicin [37], are likely less able to produce a similar analgesic effect, because their interaction with TRPV1 could not last enough to desensitize the sensory neurons [38].

The necessity of reaching and deactivating the nociceptive fibres of internal organs, avoiding the first period of sensitization that characterize the desensitizing treatment of capsaicin, pushed the investigators to look for another way of neutralizing the activation of TRPV1 receptors. To date at least six pharmaceutical Companies have discovered various TRPV1 antagonists that were submitted to animal experimentation [39]. Instead of desensitize TRPV1 receptors, these antagonists block the activation of TRPV1 nocisensors [40] obtaining a good analgesic effect.

This way is certainly effective for treating the pain from various origins and especially from internal organs, but it is also more risky, because it does not take into consideration that these receptors are expressed not only in these neurons, but also in other neurons and non-neuronal cells and are involved in many other important physiological functions of the body [41-44]. The appearance in animal experimentation of more or less serious side effects with all these TRPV1 antagonists, such as hyperthermia and insensitivity to noxious heat [45, 46]

has prevented their human experimentation. The investigators would like to find a second generation of modality-specific TRPV1 antagonists that are devoid of undesirable effects on body temperature and can still provide a good analgesic activity, but to date none are available for clinical use [39]. Whereas the main advantage of TRPV1 antagonists is the possibility of reaching other internal organs besides the gastrointestinal tract, the main advantage of desensitization of TRPV1 receptor through capsaicin administration lies in the fact that this method is surely less dangerous than TRPV1 blockers. This conviction rises from the consideration that not only red pepper is recognized as safe by the U.S. Food and Drug Administration for oral use, but also that millions of persons in the world, especially in the South-East Asia, assume large quantities of capsaicin with red pepper (about 2.5-8 g/person) [47] every day for life without evident adverse consequences. On the contrary, a beneficial effect on functional gut diseases may be inferred, considering that these functional diseases, and in particular IBS, have a prevalence markedly less in these countries in comparison to western countries [48, 49]. In addition, red pepper seems to display a protective effect on gastric mucosa against HCl, ammonia, ethanol, aspirin and indomethacin [50-52], by increasing both basal gastric mucosal blood flow as well as mucus-bicarbonate secretion and facilitating epithelial restitution [53, 54]. Another advantage of using capsaicin or non pungent capsaicin-like compounds to obtain a gastro-intestinal analgesic activity, is represented by the fact that this method is seen by patients as more „natural”, and consequently more appreciated than the pharmaceutical one.

For all the above mentioned reasons a revival of capsaicin in the clinical management of pain has been predicted and auspicated by some investigators [55], at least until the TRPV1 antagonists reach a level of safety warranting the lack of interferences with other body functions.

Conflicts of interest: None to declare.

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