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The key role of vitamin C and zinc in throat health and the benefits of regular fortified lozenge use in counteracting discomfort

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Abstract
The throat is an area of the body which undergoes constant strain, experiencing the stress of numerous normal activities, such as shouting, snoring, smoking, or drinking alcohol. Frequent exposure to these stressors alongside chemical and environmental factors (e.g., pollution, temperature, humidity) have a detrimental impact on the integrity of the mucosal barrier and cellular function resulting in throat irritation or dryness, ultimately leading to the development of inflammation if left unchecked.
This review considers the important role vitamin C and zinc play in processes integral to throat health and how their supplementation is key in maintaining the primary defences of this passage and preventing more serious symptoms. The consequences of deficiency in these micronutrients lead to myriad conditions relating to impaired control of inflammation, poorer control of ROS and their effects, in addition to the inability to properly build, repair and maintain vital cell structures.
Supplementation of these micronutrients at higher doses has yielded health benefits in numerous studies centred around symptom and disease management. Therefore, the implications of long-term low dose supplementation of vitamin C and zinc on throat health, which has been seldom studied, are promising. To achieve effective delivery of such supplementation; lozenges present as an optimal delivery system. Their direct and prolonged contact with the mouth and throat potentially increases bioavailability of the dosage and their flavour profile beneficially increases the salivary response and hence demulcent effect of this fortified lozenge while masking the unpleasant flavour of zinc. As this locally supplied supplemental intervention in lozenge form is unstudied in regard to throat health in a preventative capacity, further studies to demonstrate this value would be useful.

Keywords: throat health, lozenges, vitamin c, zinc, mucosal integrity, ROS

Introduction

The throat is a soft and vulnerable structure which undergoes constant use due to its inherent physiological functions, not only as a passage for food and drink but also coordinating breathing and swallowing, additionally housing the vocal cords, which produce sound through powerful and frequent vibration. These regular and crucial functions occur alongside the throat's inevitable exposure to an array of harmful external influences via the nasal and oral passages.

Some everyday activities can cause more exposure to these influences than others; recreational habits such as smoking and drinking alcohol, or unconscious actions such as inhaling pollutants [1] expose the throat to high levels of irritants, whilst other everyday actions such as speaking, shouting, snoring, eating or simply breathing result in constant exertion of the muscular soft tissue structures and mucosal surface. While these actions represent normal activity for the throat as a functional passage, the repeated strain alongside exposure to chemical and environmental factors (e.g., pollution, temperature, humidity) [1] have a detrimental impact on the mucosal barrier's cellular integrity and function.

This impact is often perceived as throat irritation or dryness which, if left unaddressed, will eventually develop into more substantial inflammation, with recent investigations showing a significant connection between sore throat and increased levels of air pollution [2].

Safeguarding the throat's muscular, cartilaginous, and mucosal surfaces is crucial as their exposure to environmental factors cannot be prevented, with this passage experiencing constant use, it is justifiable to say it requires regular and even daily care. One such measure of throat-care is to minimise strenuous use of the throat or use face masks to limit exposure to factors associated with irritation. Additionally, sufficient vitamin and mineral uptake is essential for general wellbeing and plays an important role in maintaining healthy mucous membranes [3] including those in the throat.

Scientific and epidemiological data suggest a synergy between diet, nutrition, and integrity of the mucosal surfaces in the human body, in health and disease. Nutritional deficiencies are known to occur when there is an imbalance in the intake of vitamins and minerals versus their consumption through physiological processes in the human body [3]. The oral manifestations of nutritional deficiencies include non-specific signs and symptoms that involve the mucous membrane, the salivary glands, and other body structures. The rapid rate of cell turnover in the mucous membrane, typically 3 to 7 days, means the oral cavity may

exhibit early signs and symptoms of systemic disease or nutritional deficiencies [4]. The many functions of the throat and the normal microbiome of the oropharyngeal cavity can increase stress on its mucous membrane [4].

While it is possible for the recommended level of nutrients to support good health to be attained through diet, this can be difficult to achieve through diet alone. This is well recognised by food authorities including EFSA and US FDA who advocate for the use of dietary supplements to maintain an adequate intake of certain nutrients, or to support specific physiological functions.

Some water-soluble micronutrients, such as vitamin C, are significantly involved in mucosal integrity and soft tissue functioning [5] but are not usually stored in the body in large quantities, so ideally, they must be consumed on a daily basis to maintain optimal quantities. Minerals, such as zinc, are also heavily involved in these functions and must also be consumed daily to maintain good throat health.

Due to it being difficult to attain optimal levels of micronutrients through di*et al*one, many of the world's population may have deficiencies in integral nutrients without realizing, with a study by Zofkova *et al*. suggesting as much as one-quarter of the world's population is deficient in zinc [6], with 800,000 children dying annually from zinc deficiency related conditions, mostly affecting the respiratory and gastrointestinal systems. Instances of zinc deficiency are more common in the developing world, with 2.5 billion children estimated to be deficient [7], this is largely due to respiratory or diarrhoea-related conditions increasing the body's demand for this essential micronutrient [8].

There are many food supplements delivered via fortification, topical preparations, and oral forms, including lozenges, but the taste of these supplements can be unpalatable and therefore patient adherence to daily consumption can be limited [9]. A suitable lozenge could potentially overcome this issue if well flavoured to mask any unpleasant tastes from supplements and increase the prospect of their daily use, especially for those with a preference for this format, such as people with difficulty swallowing.

Despite the throat being such a resilient passage, it requires support, thus practicing proper throat care alongside an awareness of one's general health should not be overlooked but rather considered an integral part of wellbeing. While there are many factors to consider when reviewing nutritional supplementation and its benefits on general and throat health, this review will focus on the latter. The role regularly consumed vitamin C and zinc plays in maintaining the throat's protective homeostasis, as well as delivery of these nutrients via lozenges for targeted supplementation using a simple and appealing format. This is a novel intervention; hence this review is the first to consider long-term supplementation of vitamin C and zinc using fortified lozenges to bolster throat health, serving to both reduce discomfort and aid natural defences.

Factors affecting throat health

Non-infectious stressors on the throat passage typically fall under two general categories: environmental and physico-chemical. Environmental stressors include air pollution, humidity, and temperature, while physico-chemical factors may arise from habits like smoking, which introduce harmful chemicals into the throat, or behaviours such as shouting and snoring, which physically damage tissues through strong vibration [1]. The intensity and quantity of stressors one is exposed to is closely linked to lifestyle and location; with those living in highly urbanised areas typically experiencing increased inhalation of toxic air pollutants such as nitrogen dioxide, sulphur dioxide and volatile organic compounds such as toluene and benzene. These are just a few of the many airborne compounds which are known to cause irritation in the throat [10], with numerous studies linking poor air quality to increased levels of sore throat in urban areas [1].

Food products can also expose people to heightened levels of toxicity, such as herbal teas containing pyrrolizidine alkaloids, several of which have been identified as having detrimental effects on the body [11], or more severe cases such as harmful Spanish rapeseed oil, which caused an epidemic of respiratory illness in the 1980s [12]. Regardless of their origin these stressors can all lead to disruption of the delicate epithelial layers of the throat over time, with avoiding them altogether being difficult for most, this being especially true for those living in areas with poor air quality.

While there are an abundance of toxic airborne compounds present in many urban areas today, their toxicity varies depending on the method through which they cause irritation and eventually cellular damage. Many contain reactive oxygen species (ROS), highly reactive chemicals formed from diatomic oxygen, which are also produced by the body to combat foreign entities. These ROS can cause damage through a process known as oxidative stress (OS) to delicate cell structures such as carbohydrates, lipids, and proteins, such as those found in the delicate epithelium and mucous membrane of the throat, changing, or diminishing their function [13].

The body naturally produces these oxidising compounds as a part of its basic immune response, subsequently producing antioxidants to prevent ROS levels becoming too high, limiting any unintended damage to cellular structures [5]. But with the high levels of ROS introduced by air pollutants, either directly or by the body in response to these toxic compounds, it becomes difficult for sufficient levels of antioxidants to be produced, at which point the signs of OS can begin to show. This will initially present as irritation and if unmitigated will ultimately lead to inflammation of affected areas, especially those more frequently exposed to external sources of ROS, including air pollution, such as the nose and throat [14].

While excess interaction with ROS can lead to irritation and inflammation, this can also be caused directly by various airborne stressors that stimulate the body's inflammatory response, these inflammatory mediators (IM) come in many forms and are even produced by the primary immune system in response to perceived threats [15].

In response to stress from external stimuli, epithelial tissues counter foreign entities with several systems, one of which is the primary inflammatory response, causing increased blood flow to the area in question, as well as the production of ROS.

The impetus for this inflammation typically comes in the form of IM which act as chemical signals for tissues to elicit a cascade of additional signalling molecules to bring on inflammation [15]. These IM are both produced by tissues themselves in response to stress-inducing external stimuli, as well as having external sources, with many components of polluted air acting as IM which directly elicit an inflammatory response in our bodies [16].

These airborne IM can cause activation of chemoreceptors, if the interaction involves those present on afferent nerve fibres this may also trigger symptoms of irritation [17], with it being possible for the health of sensitive and susceptible individuals to be impacted even on low air pollution days.

While the throat is irritated by the introduction of IM, with irritation and discomfort being a precursor of inflammation, irritation is also directly caused by ROS which act on sensory nerves in the throat. These ROS can cause changes to the chemical composition of the protective layer of saliva and mucous as the antioxidants present in this layer continuously neutralise these stressors [18, 19].

Air pollution, from both natural and human-made sources, can take a considerable toll on the delicate airway epithelium due to typically high ROS content. This delicate layer utilizes a layer of mucous and saliva, known as the mucous membrane (MM) as a primary form of defence, which traps and displaces harmful foreign substances as this fluid layer is constantly moving down through the airway, replenished from salivary and mucosal glands above. But once this outer MM is breached, ROS are naturally dispelled by extracellular antioxidants and those that manage to reach underlying epithelial cells are neutralised by intracellular antioxidants, although the levels of both are quickly depleted when under continuous exposure to ROS sources [20]. At this point, the epithelial cells are forced to adapt through the translation of cytoprotective genes, disrupting their normal behaviour, with further oxidative stress leading to inflammation and ultimately apoptosis. This effect, which leads to irritation of the airways and inflammation in more serious cases, scales with the level of pollutants and toxins that manage to bypass the MM [20]. Hence the primary method of preventing the negative effects of ROS on the throat, regardless of their origin, is to frequently replenish antioxidant levels at both a local and systemic scale, as well as maintain a healthy MM. This maintenance of ROS homeostasis is essential to avoid the diverse consequences of OS, which can lead to many diseases due to redox signalling interference and molecular damage [21], especially in areas such as the throat which are constantly under the influence of harmful external factors which can cause such damage.

In addition to direct chemical means, temperature and humidity also cause irritation of the throat; poor air quality and specifically cold, dry air has been linked with increased incidence of throat irritation and increased production of saliva is required to sooth this sensation [22]. This irritant effect was shown by an international survey of relative humidity levels in office buildings which found that a 10% increase in relative humidity when original levels were low or intermediate reduced the odds of female participants reporting a dry or sore throat by 40% [23].

A survey of throat discomfort over four countries found that 42% of respondents attributed throat discomfort over the last 12 months to ‘sudden change in temperature’, the most frequently chosen non-infectious cause, with next most frequent being ‘hot and dry indoor conditions’ and ‘dust and outdoor conditions’ which both came to 34% [24].

While it is clear that dry or irritating air conditions can lead to throat discomfort, drying of the vocal folds has also been reported to increase vulnerability to the effects of air pollution, with sustained insults from environmental sources disrupting the structure of the vocal fold epithelial barrier [25].

A study of 26 healthy volunteers, identified that dry mouth was experienced due to various conditions such as smoking, climate, and dehydration due to low fluid intake, and that their mouth dryness was reduced considerably by sucking flavoured pastilles. This led to significant improvement in their mouth dryness scores as compared to an unflavoured pastille [26]. The authors consider alleviation of dry feeling due to the flavoured pastille stimulating an increased flow rate of saliva and that this saliva became less viscous and more adhesive resulting in more effective moisturising of the oral cavity as compared to unflavoured pastille. Low surface tension of saliva is thought to be a favourable quality to promote proper moisturisation of the oral mucosa in patients with dry mouth, a quality that is facilitated by well-flavoured consumables. Overall saliva functions include moisturizing and dilution, both of which facilitate maintenance of mucosal integrity [22].

Due to saliva production taking place in the buccal cavity, the throat relies on the production of saliva transferred through swallowing to maintain its moisture levels and subsequently the integrity of its MM. Hence, given the many factors that can increase the need for lubrication and moisturisation from saliva to replenish the mucous layer, support of the structures which serve to produce saliva is necessary to prevent increased incidence of dry mouth and ultimately dry throat. An effective form of support for this process is supplementation, through which healthy saliva production can be facilitated, with gustatory stimulation of saliva having been reported to be mediated via Vitamin C tablets [27]. Similarly low salivary gland secretary ratio values were found in patients with zinc deficiency and its supplementation over 6 months showed relief from dry mouth [28].

Importance of nutrition

There are many studies that clarify the relationship between the intake of sufficient nutrition and oral health [29], with this nutrition coming primarily from dietary sources. Adequate nutritional health requires a balance of macronutrients and micronutrients, including vitamins and minerals, to maintain cellular balance between supply of nutrients and energy, in addition to the body’s demand for growth, maintenance, and specific functions [30]. However, nutrition obtained from diet is not always easily absorbed, for example even though the dietary intake of zinc may be adequate via diet, it may not be absorbed if it taken alongside fibres and phytates which inhibit its natural absorption, resulting in its reduced availability [8], but this limitation may be overcome by consuming additional zinc supplementally.

Considering proper nutrition can be difficult to attain, many utilise such nutritional supplements, these concentrated sources of nutrients are marketed in dose forms and are intended to be used to bolster the user’s diet, which may have been deficient in certain aspects beforehand [31]. These doses are typically designed with recommended dietary allowances (RDA) [32] in mind, these are predetermined by governmental bodies as a guide for healthy consumption, with many supplements offering doses in substantial excess of these values to accommodate partial absorption, or losses before full absorption as in the case of zinc [8].

Making efforts to ensure proper intake of micronutrients is essential, as the negative effects of malnutrition are well known and it is a common practice to actively change one’s diet to improve general health, but some micronutrients are

difficult to attain through natural sources, especially when dietary restrictions are a factor. There are numerous micronutrients necessary for healthy functioning of the body that are exclusively attained through dietary means, vitamin C for example, which is potent antioxidant, is not synthesised in humans due to the lack of the L-gluconolactone oxidase enzyme, which is possessed by many other vertebrates, from a key biosynthetic pathway [33, 32]. Zinc, like vitamin C, is necessary for proper physical barrier function [5] but must be consumed in sufficient doses to maintain healthy levels in the body.

These micronutrients are essential in building and maintaining the structural and functional integrity of physical and biochemical barriers throughout the body, in the throat this mainly consists of the airway epithelial cells [5]. These cells rely on an array of micronutrients gained dietarily to maintain their structures, including those meant to defend against environmental stressors, such as tight- and adherens-junctions which help to hold the cells in this delicate layer together and prevent external entities slipping through the intercellular gaps, while allowing the movement of beneficial macromolecules through this layer [34]. Micronutrients such as vitamin C not only serve as direct ROS scavengers in the MM and within epithelial cells, but also to ensure the proper function of these key subcellular structures [35].

Essentially, cells in more exposed parts of our body such the throat, require proper nutrition in the form of adequate levels of micronutrients to maintain regular processes and structures, allowing them to mitigate the more harmful effects of external stressors. In the event that these effects do take place; adequate resources are required by the body to repair itself. For example, good intracellular vitamin C levels promote collagen synthesis and prevent ROS damage to cell membranes, which is particularly useful in maintaining epithelial cells. While adequate intake of zinc is associated with proper structural and functional integrity of skin and mucosal cells [5].

Proper nutrition serves a dual purpose in terms of healthy inflammation levels, as micronutrients found in one's diet can both support the body in mounting an inflammatory response, as well as preventing this response from becoming overpowered and causing damage to healthy structures [29]. There are many micronutrients involved in this maintenance of inflammatory homeostasis, such as vitamin C which maintains a delicate healthy balance of ROS by directly scavenging excess free radicals within cells during an inflammatory response. While copper gathers at the site of inflammation and forms an important enzyme, together with zinc, that also works to inhibit the generation of harmful levels of ROS. Zinc also directly acts as an anti-inflammatory both directly and by reducing the production of inflammatory cells that serve to produce IM such as cytokines [5]. Therefore, without an adequate intake of the micronutrients that make our body's initiation and mitigation of the inflammatory response possible, these processes become unbalanced and can quickly lead to irritation, this effect is exasperated when our diet not only fails to offer supportive nutrition, but actively contributes to the levels of stressors introduced by our environment.

Recently certain studies have shown an intrinsic link to diet and the mitigation of harmful ROS levels, one such study investigated the capacity for saliva to control the levels of ROS in the buccal cavity, which ultimately effects the oxidative environment of the throat. It was found that antioxidant levels in saliva are meticulously controlled to prevent damage to sensitive structures by oxidative stress, and that the level of antioxidant compounds present in one's diet, as well as the level of ROS generating compounds, have a direct influence on these levels, leading to effects on the overall health of the mouth and ultimately throat due to saliva composition [36].

Deficiency in Vitamin C and Zinc

Numerous studies have found sufficient vitamin C and Zinc levels are frequently not met, with it being estimated that around 2 billion people globally are affected by zinc deficiency [37]. While in the UK, a study focusing on the low-income/materially deprived population estimated that 25% of men and 16% of women suffer from vitamin C deficiency, after testing the levels of this micronutrient in the plasma of participants [38]. These two micronutrients are typically under-consumed due to the inability to synthesise them naturally as well as dietary limitations. Sufficient intake of vitamin C and zinc relies on adequate consumption of fresh fruit and vegetables [33] and of red meat or oysters [37], respectively, which may not be an option for many, especially for those with limited access to fresh and healthy foods. Counterintuitively zinc is also readily absorbed by substances known as phytates, which are strong zinc-chelating agents and are found in unrefined cereals, legumes and plant parts, the consumption of which will decrease the body's store of zinc [37].

Deficiency in vitamin C has numerous effects on the body; due to its active role as an antioxidant even short-term deficiency can quickly lead to this role being stunted. It has been shown that vitamin C is one of the variety of compounds found in saliva, acting as a ROS scavenger and preventing damage to tissues that come into contact with this complex secretion [39]. A well-known side effect of serious vitamin C deficiency is bleeding or swollen gums, partly due to the micronutrient being essential for collagen synthesis [40], hence deficiency local to the buccal cavity can lead to lower levels in the saliva and subsequently an impaired ability to maintain the delicate epithelial layers of the mouth and throat.

In addition to vitamin C's antioxidant properties, it also plays a role in mitigating inflammation; plasma concentrations of this compound have also been closely linked to general health and resistance to certain disorders, specifically conditions related to chronic inflammation [41]. While it has been suggested in multiple studies that regular, high doses of supplemental vitamin C can relieve levels of inflammation caused by diseases such as the common cold [42], there have also been studies showing significantly decreased levels blood plasma levels of vitamin C in those suffering from various inflammatory conditions such as gastritis and lung inflammation [41]. This is suggestive of vitamin C's role as an anti-inflammatory agent, with this micronutrient having been shown to play a role in reducing the severity of inflammatory response in those suffering from coeliac disease [43].

The prevalence of inflammatory disorders due to dietary deficiency also extends to zinc; in a trial measuring the levels of micronutrients in the blood of children with chronic rhinosinusitis, which causes inflammation of tissues in the upper respiratory tract, found that the levels of both vitamin C and zinc were significantly lower in the chronic

sinusitis group when compared to the healthy control group [44]. Interestingly this difference was not seen in the levels of other micronutrients measured, such as vitamin A or magnesium, implying vitamin C and zinc play a key role in regulating healthy levels of inflammation.

Zinc deficiency in humans has many negative consequences, such as increased oxidative stress and a heightened inflammatory immune response [37], with researchers having connected zinc deficiency with increased incidence of gingivitis and potentially the onset of inflammatory bone-loss disease [29]. This is particularly prevalent in the geriatric portion of the population as it is estimated that as much as 30% of the elderly population are zinc deficient, with age related conditions such as macular degeneration thought to be linked [37].

Another study, which focused on patients with zinc deficiencies, showed salivary gland function relied on zinc supplementation as dryness or reduced salivary secretion was correlated with zinc deficiency. Salivary flow rates of patients with confirmed or suspected zinc deficiency were less than those of controls in both the parotid and especially the submandibular glands [28]. This finding was substantiated by animal studies where chronic zinc deficiency led to morphological changes in the glandular ducts and dependence of the enzyme carbonic anhydrase for salivary secretion, decreased zinc in the body resulted in reduced concentrations in salivary glands and as a result saliva secretion function was negatively affected [45, 46].

Vitamin C: benefits concerning cell integrity and inflammation

The RDA for vitamin C (ascorbic acid) is 75-90 mg/day for adults [47] this micronutrient has been shown to be necessary for the promotion of collagen synthesis in epithelial tissue [48] with adequate levels helping the soft tissues lining and mucosal membrane of respiratory system to recover from damage. Endogenous Vitamin C concentration falls rapidly with the onset of infection and tends to return to normal once damaging foreign entities are dispelled, suggesting that its administration may be beneficial for recovery [48, 42].

Ascorbic acid's role in recovery does not lie solely in the repair of epithelial barriers through reducing oxidative stress but also through its ability to increase collagen synthesis, in addition to enhancing keratinocyte and fibroblast function [32]. Even relatively low doses have been shown to lead to significantly increased collagen and elastin biosynthesis, when applied to human skin cells *in vitro* [49].

The demulcent and reparative qualities of vitamin C can also be connected to saliva, in which high levels of the micronutrient can be found, having adequate levels of vitamin C present in the buccal cavity can aid in maintaining cellular structures and soothing irritation, both in the mouth and the throat as both are affected by saliva content [39].

Certain cells reap a greater benefit from this restorative action, for example those containing high levels of polyunsaturated fatty acids in their plasma membranes, including airway epithelial cells [34], are particularly sensitive to oxidation from ROS, accordingly these cells have shown increased motility after introduction of additional vitamin C [32].

As vitamin C is a powerful water-soluble antioxidant, it protects the inflammatory cells involved in the inflammatory response from the damaging effects of excessive ROS which are produced by these cells to combat foreign entities. Hence it keeps the body's natural defence mechanisms in check by allowing these destructive ROS to act on their intended targets, while keeping them from affecting key cell structures, and assist in containing the resultant pro-inflammatory signalling cascade produced by this surge of ROS [47].

Ascorbic acid not only contributes to maintaining epithelial barrier integrity through reducing oxidative stress but has been shown to increase collagen synthesis, in addition to enhancing keratinocyte and fibroblast function [32]. Even relatively low doses have been shown to lead to significantly increased collagen and elastin biosynthesis, when applied to human skin cells *in vitro* [49, 50].

Zinc: benefits concerning cell integrity and inflammation

The RDA of zinc is 8-11mg/day [5], this metallic chemical element is required for the function of numerous enzymes and transcription factors [51], accordingly zinc is present all over the body, but is considered of particular importance in oral health. The measurement of zinc levels in saliva is used to gauge the quality of oral health and ultimately low zinc levels in this secretion can be a sign of potential illness [52].

While being omnipresent in saliva [29], zinc also stimulates healthy salivation and has been directly linked to the process through research that showed the dependence of human salivary glands on the presence of the metalloenzyme carbonic anhydrase, a protein containing zinc [45, 46]. These findings are supported by a previous animal study in which rats suffering from zinc deficiency were found to have inhibited growth of cells associated with salivary glands, implying zinc and zinc-containing proteins are essential for the healthy function of salivary structures [53]. Another study found that patients with dry mouth who were supplemented with zinc recovered from their symptoms and regained proper secretary function of their salivary glands after continuous, daily intake of the mineral [28].

While zinc plays a role in salivation itself, its presence in saliva also serves numerous other purposes, such as mitigating the effects of inflammation in the mouth and upper airway. Maintaining healthy levels of zinc allows for the proper control of the inflammatory response, as this mineral can assist in reducing the effect of pro-inflammatory cells and by forming an integral part of the anti-inflammatory zinc-finger protein A20 [37]. Through this action, having an excess of zinc locally available in the mouth and throat may act to diminish the potential inflammatory action of IM and other irritating compounds, allowing the epithelial tissue to deal with the insult quickly and safely before it can escalate into an uncomfortable sensation, while also preventing an overreaction from the inflammatory system.

This shepherding of the inflammatory response also extends to handling the effects of ROS produced in the process, as zinc can directly act as an antioxidant and prevent oxidative stress from damaging delicate cellular structures. This mineral is also essential for inflammatory cells to mount a protective oxidative burst of ROS, and to modulate the activity of antioxidant proteins. In addition to protecting cells from damage, zinc is also integral in the process of maintaining epithelia and MMs as it acts a cofactor for metalloenzymes which facilitate the repair of cell membranes [5].

In addition to facilitating the repair of cells, zinc is also integral to cell division and the synthesis of DNA and subsequently proteins, as it is required for the function of over 300 of the enzymes found in the human body. As a result, everything from connective tissue growth and maintenance, to wound healing rely on adequate levels of zinc [54]. This role as an essential building block makes zinc a key player in maintaining proper cellular health and function in exposed areas such as the throat which are subject to constant attrition from external influences, hence levels of this vital micronutrient rapidly deplete in these areas.

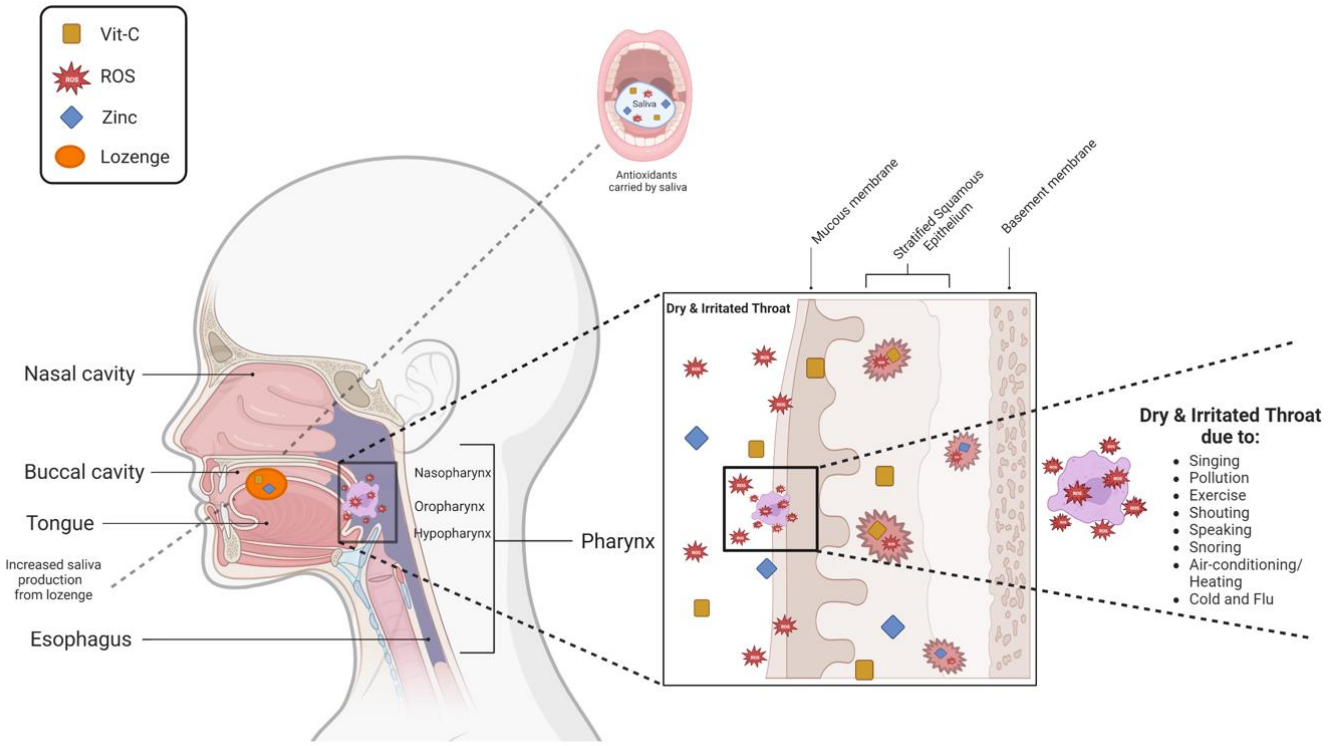

Fig. 1: Vitamin C and Zinc delivered through fortified lozenges promote a healthy throat, while preventing dryness and irritation from everyday activities *(Created with BioRender.com)*

Lozenges

Lozenges are a solid dosage form that can contain flavouring or sweetening agents in addition to active ingredients and are intended to dissolve slowly in the mouth or pharynx. Their use as a delivery system, specifically for therapies meant to treat symptoms localised in the throat, is preferable. As the lozenge breaks down in the mouth, it is slowly and evenly carried by saliva, administering the product to the affected area in the throat. This increases retention time and therefore bioavailability, while reducing gastric irritation [55], when compared to other delivery methods such as pills or syrups. Lozenges allow for the incorporation of myriad active ingredients, many of which benefit from this local application.

The action of sucking lozenges is necessary to release their composite ingredients and stimulate the salivary gland, increasing saliva volume, ultimately inducing a lubricating and soothing effect on tissues in the throat. Lozenges increase retention time of the active ingredients in the oral cavity, enhance the salivary response and provide a longer period of contact of the throat with the contained dosage than other forms of administration [55].

One of the more obvious benefits to lozenges is that their usage is easy and preferable, especially with paediatric patients, as they are typically palatable, require a low dose and are not perceived negatively by those wary of taking unnecessary medicines, leading to generally good patient compliance [55]. They also hold advantages with geriatric patients as they can deliver medication to the throats of those who find it difficult to swallow [56], with studies having even shown sour-flavoured lozenges to induce a heightened swallowing reflex [57], further allowing for moisturisation and lubrication of a dry throat.

This demulcent effect is achieved both directly through salivary stimulation and through a strong placebo effect. It has been shown that a perceived effectiveness of a treatment, even when no active ingredients are present, can have therapeutic effects and lead to improvement in clinical symptoms [58], with sweetness, viscosity and a cooling/warming effect (e.g., menthol) influencing the intensity of this placebo response [59]. By typically being quite sweet and pleasant in flavour, masking the noticeable taste of additives such as zinc, lozenges can utilize this quality to improve usage outcomes for sore throat therapies, allowing for regular topical application of supplements that may otherwise be unpleasant in flavour or sensation. This

effect is actively utilised by manufacturers of lozenges containing zinc acetate dihydrate, who effectively mask its bitter flavour using the sweet base of the lozenge [60].

As lozenges typically have a sweet base from sugars or synthetic sweeteners, which becomes smooth upon dissolution, as well as an acidic flavouring, a great deal of salivation occurs upon their consumption [61] leading to a subsequent production of mucous, renewing the vital MMs of the throat. This natural response further aids in the demulcent action of lozenges, as the tissues of the oral cavity are lubricated by saliva and mucous, as well as soothed by anti-inflammatory properties that are naturally present in saliva [62].

In addition to simply sweet (e.g. sugar) or sour (e.g. vitamin C) flavours, more complex and noticeably flavoured additives such as botanical extracts are often used, even in low doses many botanicals still possess a strong flavour and when applied in lozenge form, which elicits a further increased salivary flow rate [63] and can serve to improve the flavour profile of the lozenge and therefore attitude of the patient towards the intervention. It has been established in previous studies that people prefer natural ingredients and feel they have greater benefits [64, 65], therefore the addition of botanical flavourings, which are easy to identify by taste as being of natural origin, serves to improve the patient's perception and response to the lozenge. This addition of herbal or botanical flavourings to improve patient uptake of lozenges is well documented and is rising in popularity in various parts of the world [66], not simply due to the potential health benefits of the additives, but also due to the familiarity and trust these flavours elicit in users over more artificial and generic tastes.

Discussion

While nutritional supplements are well known for their holistic benefits for various organ systems in the body, their importance in throat health has not been sufficiently explored. A constantly changing environment and the delicate nature of the throat results in this area being particularly exposed and therefore one of the most susceptible structures to external conditions in the body, hence there being such rapid and uncomfortable consequences due to environmental changes such as temperature or humidity shifts [1]. Historically, there has been ample study on pharyngitis, altered immunity and the role of nutritional supplements in mitigating or supporting these factors. But despite this focus, there has been little review on the effects of nutritional supplementation of vitamin C and zinc, particularly on mucosal integrity and subsequent benefits in preventing throat irritation and dryness, despite these being natural precursors to their more serious symptoms such as pharyngitis or infection.

Studies on the effects of supplementation of zinc and vitamin C in the throat typically use high concentrations of these micronutrients and demonstrate marked improvements in the conditions being studied [37, 42], namely mitigation of inflammatory responses and recovery from ailments. This clearly demonstrates the active roles these micronutrients play in controlling inflammation and ROS levels, both of which are integral to the defending against external threats and limiting cellular damage.

Hence it stands to reason that the regular supplementation using lower concentrations, while still in line with RDA values, of these vital micronutrients could offer many of the same benefits that are demonstrated with studies using higher doses, but with long term benefits due to continued replenishment of these nutritional resources.

The mouth and throat are physiological targets that could likely benefit from such regular supplementation, considering their constant use and exposure to particularly high levels of stress inducing factors, which can be particularly high in those with certain habits, lifestyles, or environments [23].

Such long-term supplementation can be achieved using lozenges, partly due to the nature of the format allowing for elongated contact of the supplement with the target area, allowing for better uptake of the dosage into the tissue. This is beneficial considering some formulations of zinc or vitamin C can have limited rates of uptake into tissues [8, 67], with an extended absorption time curbing this limitation. The lozenge itself can also improve the condition of the throat as its pleasant flavour stimulates a demulcent effect through salivation, further lubricating and rejuvenating the hydration of the tissues, while in some cases this flavouring can also effectively mask the unpleasant tase of some supplements. Careful design has led to the creation of complimentary formulations with naturally acceptable flavours such as cherry, lemon, or honey [60] which modulate the taste profile of supplements to notably improve patient uptake. This has additional value as paediatric users may be more sensitive to stronger tastes and benefit from this flavour masking, while members of the geriatric population may have a hard time swallowing, a process which can be facilitated by well perceived flavours [57].

It then stands to reason that the daily supplementation of vitamin C and zinc through a lozenge format may be an effective solution to maintaining good throat health, which acts as a shield to minimize the effects of constant exposure to non-infectious factors on the throat's physiology, ultimately preventing irritants from causing dryness and irritation, which in turn reduces the likelihood of inflammation occurring. Due to the novel nature of this intervention, further studies are required to demonstrate effectivity of this form of supplementation, on both improving structural mucosal integrity and reducing the initiation of dryness and irritation. These benefits could prevent the development of inflammatory symptoms, which can provoke a cyclical reaction as the area is more susceptible to infection and subsequent worsening inflammation. This research could entail a long-term study in which a diverse group can report the effects of regular supplementation on throat health, investigating the possibility of regular low-concentrations of locally administered micronutrients providing significant benefits.

Conclusion

The aim of this review is to demonstrate the wealth of evidence that exists to support the importance of micronutrients in the maintenance of throat health, a subject that has previously only been approached from the perspective of high dose supplementation and its effect on illness prevention and treatment. By considering the benefits of regular lower doses of supplementation on the maintenance of a comfortable throat, avoiding dryness or irritation, the idea of a preventative intervention can be evaluated, one which maintains user comfort while preventing the development of inflammation.

The throat is an area of the body under constant exertion, one which is regularly exposed through constant use, including influences from air pollution to normal behaviours such as talking, shouting and snoring. This leads to the attrition of the mucosal tissues making up the most exposed portions of the throat, which the body responds to through constant defence and repair. These homeostatic processes heavily rely on the integrity of epithelial cells, the mucous membrane, and the inflammatory response, which need to balance their defensive activities to not incur excessive damage to healthy structures. To effectively manage this response, the body utilizes a great deal of resources gathered from dietary sources, many of which can only be attained through external sources, such as vitamin C and zinc. Therefore, additional supplementation of these micronutrients is common, with this becoming increasingly common as the extent of deficiency in most populations becomes more apparent.

To maintain mucosal integrity, and to prevent irritation and dryness, vitamin C and zinc remain fundamental, hence the benefits of providing a surplus of these micronutrients to offset the effects of harmful external influences are clear. An effective and direct method of providing this supplementation is through the daily use of fortified lozenges, as this allows for direct contact with the throat tissues. This format can also deliver an additional benefit to the throat by stimulating a salivary response in the mouth, leading to increased production of saliva, which acts as a carrier of beneficial micronutrients, in addition to having demulcent and moisturising properties of its own. Hence a daily supplementation of vitamin C and zinc through fortified lozenges presents as a promising method to promote a healthy throat, while preventing environmental and physiological factors from causing dryness and irritation, which if ignored could ultimately lead to subclinical inflammation. This review is the first to consider this intervention as a method of maintaining a healthy throat and protecting this passage from the stresses of everyday activities. Further consumer studies on benefits of daily use of fortified lozenges preventing dryness and irritation from everyday life, while preventing the onset of more severe symptoms and inflammation, would demonstrate the true efficacy of the intervention proposed in this review.

Author contributions

All authors: contributed to the article and approved the submitted version.

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