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Casein tryptic hydrolysate and its role in oral cancer – A review

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Abstract

Casein-derived peptides are shown to possess radical scavenging and metal chelating properties. It is well-recognized that food-derived peptides can exert beneficial biological activities in addition to their basic nutritional role.

These bioactive peptides are relatively short (typically 2–20 amino acids) and may possess antioxidant, anti-inflammatory, antihypertensive, antimicrobial, and anticancer properties that have a potential role in maintaining or promoting human health.

Both anti-inflammatory and antioxidant properties are two of the main topics considered for preventing chronic diseases such as cardiovascular disease and cancer due to oxidative stress, as well as abnormal inflammatory responses.

The intake of natural food-derived peptides may delay the onset of diseases by reducing the oxidative damage and pro-inflammatory responses.

Casein-derived peptides possess strong radical scavenging and metal chelating properties. The successful control of oral cancer will depend on its prevention. Main Prevention measures are discontinuing tobacco use and the use of various nutritional agents containing antioxidants. Casein tryptic hydrolysate a powerful antioxidant can be endogenous or obtained exogenously as a part of a diet or as dietary supplements are molecules that inhibit oxidation of other molecules, thereby preventing the formation of free radicals.

Thus the literature review aims at the evaluation of novel anti-inflammatory properties of casein tryptic hydrolysates.

Keywords: Caesin, Cancer, Oral Squamous Cell Carcinoma.

Introduction

It is well-recognized that food-derived peptides can exert beneficial biological activities in addition to their basic nutritional role[1]. These bioactive peptides are relatively short (typically 2–20 amino acids) and may possess antioxidant, anti-inflammatory, antihypertensive, antimicrobial, and anticancer properties that have a potential role in maintaining or promoting human health[2]. Both anti-inflammatory and antioxidant properties are two of the main topics considered for preventing chronic diseases such as cardiovascular

disease and cancer due to oxidative stress, as well as abnormal inflammatory responses[3].

The intake of natural food-derived peptides may delay the onset of diseases by reducing the oxidative damage and pro-inflammatory responses[4]. Among other animal-derived food sources, milk proteins are considered as a highly nutritious food component with a well-balanced essential amino acid composition, and have also been reported as a good source of bioactive components[5].

Approximately, casein accounts for 80% of the total milk proteins, which are mainly composed of αS1 (~40% of total casein), αS2 (~10% of total casein), β (~35% of total casein), and κ (~15% of total casein) casein sub-units[6].

Accordingly, casein phosphopeptide derived from gastrointestinal and commercial proteases may act as multifunctional bioactive peptides with radical scavenging and metal chelating properties, and may play a role in enhancing mineral bioavailability[7].

As mentioned above, casein-derived peptides possess strong radical scavenging and metal chelating properties. Thus the literature review aims at the evaluation of novel anti-inflammatory and anti-oxidant properties of casein tryptic hydrolysates.

Oral cancer

Oral cavity cancer is one of the ten most frequent cancers in the world as to 25% of all malignancies are found in the oral cavity[8]. Tobacco is the predominant cause of this cancer. About 48.2% of cancers in men and 20.5% in women are related to tobacco, a major proportion of which is in the oral cavity, pharynx, larynx, oesophagus (74.7%), while lung cancers account only for 15%2.

Alcohol use is a risk factor that acts synergistically with tobacco. Thus, the major risk factor for oral cancer is the same as that of some other common diseases. E.g.: emphysema, lung cancer and heart disease. Oral cancers have a poor 5-year survival rate of 50% or less. Consequently, prevention strategies for oral cancer, such as discontinuing tobacco use, can affect many life-threatening diseases; other prevention modalities, such as nutritional agents, may similarly be beneficial for several chronic diseases. The successful control of oral cavity cancer will depend on its prevention[9].

Anti-oxidants in oral cancer

The role of antioxidants in cancer chemoprevention can be summarized as:

1. Inhibits oral cavity carcinogenesis
2. Reduces the risk of developing oral cancer.
3. Causes reversal of premalignant lesion like oral leukoplakia.

Oxidative damage is recognized as playing a role in the pathogenesis of cancer which could arise from incorrect nutritional habits and lifestyle practices. This process can cause DNA damage, which is a basic mechanism in cancer induction. Sufficient anti-oxidative status is crucial in free radical defence[10].

To reduce the risk of oral and pharyngeal cancer, especially oral cell carcinoma, diet must be optimized, primarily to reduce calorie intake, monosaturated fat and red or processed meat. The important dietary micronutrients that are antioxidant in action include vitamin A, β-carotene, lycopene, Vitamin C, vitamin E (alpha- tocopherol), Zinc and Selenium. Considerable evidence exists suggesting a role for nutrients, particularly the so-called antioxidants vitamin A, β-carotene, vitamin C, vitamin E, lipoic acid, zinc, selenium and spirulina in the prevention of this disease[11].

Antioxidants are group of chemical compounds that can deactivate the free radicals and prevent their formation.

Free radicals are oxidants which are single unpaired electron that bombard and destroy cells and other molecules in their search for another electron[12].

A recent study has suggested that these anti-oxidant nutrients act to inhibit the development of cancer cells and to destroy them through apoptosis (programmed cell death), by their stimulation of cytotoxic cytokines, by their action on gene expression, by preventing the development of tumor's necessary blood supply or by cellular differentiation. A report has also shown a reduction in adverse effects of chemotherapy when given concurrently with antioxidants[13].

Casein tryptic hydrolysates - an anti-oxidant

Milk is a heterogeneous lacteal secretion mixture of numerous components (carbohydrates as oligosaccharides, lipids as long-chain polyunsaturated fatty acid, milk-specific microbiota, etc.) that exhibit a wide variety of chemical and functional activities. Milk is considered to be a functional food with direct and measurable influences on the health of the recipient, and it is now widely accepted that components of milk can influence and direct the physiological development of offspring.

There are solid data indicating that caseins are linked to the immune system and to the generation of blood cells in mouse and rat models. Studies in vitro suggest that casein tryptic hydrolysate, and the peptides resulting from the enzymatic hydrolysis of casein, have anti tumour activity[14].

Casein tryptic hydrolysate as regulators of hematopoiesis and the immune system

Casein tryptic hydrolysate a bovine casein salt soluble in water with 65% proteins[15], provided the first evidence that milk proteins are linked to the biology of the immune system. Casein tryptic hydrolysate used as a pro-inflammatory molecule induces chemotaxis of granulocytes and macrophages in the peritoneal cavity of mice[16,17]and induces the accumulation of myeloid progenitor cells in mouse bone marrow[18].

Over time, it has been shown that Casein tryptic hydrolysate accelerates the transition of band cells from bone marrow to polymorphonuclear cells, thus inducing macrophage colony stimulating factor (M-CSF)[19]

Evidence has shown that caseins in vivo, through the production of cytokines, could be involved in the development of the mucosal immune system in neonatal mice[20], in erythropoiesis of mice[21], and in the restoration of hematopoiesis in rat models of myelosuppression[22].

Casein tryptic hydrolysate in regulation of cancer and oral cancer

A wide variety of bioactivities for milk protein components has been reported, with one component having more than one type of biological activity, but here, we present only examples in which caseins tryptic hydrolysate and casein peptides have effects on different cancer cell lines or animal models. we focus on the anti-leukemic activities of these casein tryptic hydrolysate proteins all inhibit the migration in vitro of murine mammary tumour cells of the Met-1 cell line, the human breast cancer cell line MCF10A-H-Ras (G12V), and MDA-MB-231 cells, with α-casein being the most effective[23].

Casein tryptic hydrolysates generated using different commercially available food-grade enzyme preparations from mammalian, bacterial, and plant sources have an inhibitory effect on the viability and growth of both human leukemia T-cells and human epithelial colorectal adeno carcinoma Caco-2 cells lines, but casein tryptic hydrolysates had no significant effect on the viability and growth of Caco-2 cells[24].

Casein tryptic hydrolysate peptides derived from αs1-casein and β-casein digested by lactic acid bacteria inhibit the enzymatic activities of purified recombinant matrix metalloprotease (MMP)-2, MMP-7, and MMP-9 in human HT-29 and SW480 colon carcinoma cells[25]. Lactaptin, the proteolytic fragment (f57 ± 134) of human κ-casein, induces apoptosis of MCF-7 adenocarcinoma cells snd oral squamous cell carcinoma cells[26].

Casein tryptic hydrolysate in prevention of cancer and oral cancer

The first evidence of the anti tumour activity of protein milks was shown in vitro by casein tryptic hydrolysate inhibiting the proliferation of oral squamous cell carcinoma in mouse cells, such as those from the WEHI-3, J774, and P388 cell lines, even inducing apoptosis in one of them: the WEHI-3 oral squamous cell carcinoma cell line.

However, in mononuclear normal cells from BALB/c mice (MNCs) bone marrow, casein tryptic hydrolysate induces a marked proliferation stimulus.

The evidence showed that normal tissues could be less sensitive to the biological effects of new molecules with potential anti tumour properties[27,28].

These data are significant since the usefulness of a potential anticancer compound depends not only on its ability to induce cytotoxicity in malignant cells but also on its relative lack of ability to induce toxicity in normal tissues and, in the case of casein tryptic hydrolysate, its ability to suppress the proliferation and induce the death of cancer cells.

However, in addition to exerting no cytotoxicity, casein tryptic hydrolysate induces their proliferation, which is a rare property among most drugs tested for use in the treatment of early oral cancer, and it became clear that not only caseins but also casein peptides had an inhibitory effect on the proliferation of cancer cells when the casein tryptic hydrolysate inhibited the proliferation of the J774 and P388 oral squamous cell carcinoma macrophage-like cell lines, although only in the latter was cytotoxicity confirmed[29].

Other evidence suggest that κ-casein f25-34 and f35-41 inhibit the proliferation of 32D normal cells and WEHI-3 oral cancer cells and induce the differentiation of cells in the monocyte-macrophage and granulocyte-neutrophil lineages. κ-casein f35-41 reduces the proliferation of cells in both cell lines and induces 32D differentiation towards the monocyte-macrophage lineage, and WEHI-3 cell differentiation towards the granulocyte neutrophil lineage, whereas κ-casein f58-61 has no effect on the proliferation of any of the cells but induces their differentiation towards becoming granulocytes in both cell lines.

Additionally, casein tryptic hydrolysate can activate mechanisms other that those associated with a simple inflammatory process because, although other agents, such as zymosan or thioglycolate, increase the levels of pro-inflammatory cytokines (IL-1β, TNF-α, MIP-2, and MCP-1/ CCL2), they have no inhibitory effect on the proliferation of hematopoietic cells[30,31,32].

The available evidence for caseins, both in their complete form and in fragments resulting from their enzymatic degradation, reveal an enhancement of different aspects of the immune system, but their potential as anti tumour agents has been scarcely explored.

The use of caseins or their peptides to enhance the immune system to fight cancer is a rational strategy, as the immune system constantly works to keep us free of tumours. However, it is, of course, not always successful, with an estimated 19,520 new cases of oral

cancer diagnosed in the United States in 2018, accounting for approximately one-third of all new leukemia cases. Nevertheless, enhancing the immune system to eradicate cancer remains a valid and widely explored strategy against cancer[32].

There are elements that suggest that caseins or casein peptides could eradicate cancer and oral cancer by functioning as enhancers of the immune system and inducing cell death of malignant cells. As we noted above, the mechanisms of the anti tumour action of casein tryptic hydrolysate in vivo are unknown, but all these data on casomorphins, added to the fact that both granulocytes and macrophages are capable of hydrolysing caseins to release biologically active peptides, suggest to us that these opioid peptides may be responsible for the anti tumour effects observed for caseins [33].

Future perspective

It is undeniable that cancer cells over express TLRs and opioid receptors that bind caseins and casomorphins, respectively. In both cases, the interaction leads to a reduction in the pro-inflammatory microenvironment prevalent in the development of tumours, so it would be interesting to evaluate whether by effectively reducing the oxidative stress, the production of anti-inflammatory cytokines is favoured over the production of pro-inflammatory cytokines; such information would support the potential antioncogenic use of caseins and casomorphins.

Caseins and some casomorphins inhibit proliferation and induce the differentiation of cancerous cells, and caseins promote proliferation and differentiation of cells and even prolong the survival of cancer mice.

Given the relevance of the physiological effect of the peptides derived from casein, it is reasonable to consider that they can have a relevant role as micronutrients and that their absence can cause the development of not only leukemia but also of another types of cancers. It should not be overlooked that αS1-casein is expressed in cells distinct from the mammary gland, mainly in patients with autoimmune diseases, which makes it necessary to analyse with caution the role of this compound as an anti-neoplastic agent.

Conclusion

There is evidence that caseins, both in their complete form and in fragments produced by their enzymatic degradation, enhance different aspects of the immune system, such as the proliferation of lymphocytes and generation of antibodies.

They can also regulate normal hematopoiesis in vitro and in vivo via the secretion of cytokines, thereby inducing differentiation and enhancing proliferation. In cancer cells, however, they induce apoptosis and negatively regulate proliferation.

This phenomenon highlights the potential of milk proteins as anti tumour agents, but further research is needed to fully understand the mechanisms underlying the effects of the bioactive peptides of milk. Although humans consume milk over a much longer period than other mammals, we do not yet understand the complete scope of the administration of casein or its peptides as an anti-cancerous agent.

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