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BENEFITS OF TRANSGLUTAMINASE IN THE FOOD INDUSTRY

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ABSTRACT

The present study aimed to present an overview of the literature addressing the characteristics and applications of Transglutaminase, analyzing its benefits for the food industry. Studies on the application of MTGase in several products were reported, showing the importance of this technology adjuvant for scientific research and industrial application in the area of food production. Therefore, the methodology applied for the development of the present study was the bibliographic review in scientific databases. The approach used in the present research was qualitative. It has been observed that Transglutaminase, due to its unique properties, is an enzyme widely used in various branches of the food industry. It has been recognized as safe by an independent panel of scientific experts. The discovery that it has a cheap source of its biosynthesis, that is, by microorganisms, has provided an opportunity for a broader and more practical application of this enzyme.

Keywords: Benefits, Food Industry, Transglutaminase.

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INTRODUCTION

The transglutaminase secreted by bacteria is called microbial transglutaminase (mTG). Evolutionarily, it is an important survival factor for prokaryotes such as bacteria, fungi, and actinomycetes. In humans and animals, transglutaminase plays a role in various bodily processes, including blood clotting and sperm production. Also, it is vital for the growth and development of plants. Transglutaminase used in food is manufactured from blood clotting factors of animals, such as cows and pigs, or bacteria derived from plant extracts (XIA *et al.,* 2019).

Due to its avidity for primary amine-containing substrates and its strict specificity for high-glutamine-containing proteins or peptides, the enzyme has become a very practical tool for enzymatically forming iso-peptide bonds between protein and small protein molecule conjugates. What's more, the production, consumption, and applications of mTG have increased enormously in recent decades (DOTI *et al.,* 2020).

In fact, its application has spread to the processed food and textile industries, biomedical engineering, diagnostics, and even to biomedical therapies. Several reviews have evaluated the potential health risks of mTG used in food industries. Also, mTG has come to be suspected of being a new environmental factor in gluten-dependent conditions and neurodegenerative diseases (LERNER; MATTHIAS, 2019).

As a problem with the research, it is observed that the extremely high costs of manufacturing transglutaminase of animal origin have led scientists to search for new sources of this enzyme. Interdisciplinary efforts have been directed to the production of enzymes synthesized by microorganisms that may have a broader scope of use.

However, its characterization indicated that this isoform can be extremely useful as a biotechnological tool in the food industry. Thus, enzymatic preparations can be used in almost all industrial branches due to their wide variety and low costs associated with their biotechnical production processes.

As a justification for the development of the present study, it is observed that many studies have been carried out to find microbial sources capable of secreting the enzyme due to their excellent ability to cross-link proteins or peptides.

Thus, the present study aimed to present an overview of the literature addressing the characteristics and applications of Transglutaminase, analyzing its benefits for the food industry.

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PATHOGENIC MICROBIAL TRANSGLUTAMINASE CROSS-LINKED COMPLEXES

Initially, it is worth mentioning here that mTG is a widely used food additive and its use of industrial transamide complexes is increasing rapidly. Despite the manufacturers' claims, mTG – or its cross-linked compounds – are immunogenic, pathogenic, pro-inflammatory, allergenic, and toxic, thus posing a risk to public health. Thus, the pathogenic pathways and mechanisms of mTG, as well as its transamidate complexes, can be summarized as follows (SZONDY *et al.,* 2017).

Labeling with gliadin gold and mTG allowed the monitoring of the two molecules by electron microscopy. Both can be detected while transcycled through early-late endosomes in the endoplasmic reticulum, to be deposited below the basolateral membrane of the enterocytic monolayer. The strong localization of mTG in the basolateral membrane and lamina propria may also indicate a potential antigenic interaction with immune cells (STRICKER *et al.,* 2019).

In the face of active subepithelial immune systems, most likely, mTG-neo antibodies are the result of this compartmental interaction. Notably, mTG transamidated gliadins create stable covalent isopeptide bonds, which are known to be resistant to local peptidases, luminal bile acids, and pH variations, further challenging local immune cells (LERNER; MATTHIAS, 2019).

Multiple mechanisms can be suggested by which mTG itself or its gliadin cross-linked complexes may increase enteric permeability. Zonuline, claudins, F-actin, occludins, myosin, F-cadherin, keratin and catenin present good substrates for mTG, as they contain acyl donors and acceptors. Being essential for tight junction performance, their mTG transamidation will open the enterocytic gap (LERNER; MATTHIAS, 2020).

Emulsifiers are performance disruptors of the narrow junctions of the intestine, and mTG has emulsifying activity. What's more, the nanoparticles were designed to increase intestinal permeability to drugs and nutrients. However, they have the potential to compromise human health. On the other hand, neo-nanoparticles designed with mTG are increasingly used. Therefore, both increase intestinal permeability (LERNER; AMINOV; MATTHIAS, 2017).

Pathogenic prokaryotes are powerful disruptors of human intestinal permeability. Since mTG presents a survival factor for luminal microbes, and since mTG compromises some basic physical and enteric immune protection mechanisms, it can support luminal and mucosal pathobiont activities (SANDERS *et al.,* 2021).

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Gliadins and gluten are known to open the tight junction gap by stimulating the release of zonulin. As an integral part of the mTG-gliadin neocomplex, the gluten/gliadin part of the complex can drive intestinal permeability. Histones are substrates of mTG, and their cross-linking can result in free histone deprivation. What's more, nutritional deficiency can induce a leaky gut. Glutamine and zinc deprivations are an example (CARDOSO-SILVA *et al.,* 2019).

Leaky gut can allow bacteria and their metabolome, toxins, or many small molecules to "leak" into the bloodstream. Even gliadins/gluten can be detected in the blood or urine in celiac disease, for example. Since leaky gut/brain are associated, these factors can affect brain activity and be involved in neurodegenerative diseases and neurological/psychiatric presentations (LERNER; NEIDHÖFER; MATTHIAS, 2017).

In fact, processed food additives, cross-reactive nutrients, alpha enolase and potentially mTG, are suspected of leading to several chronic neurodegenerative diseases. However, some issues deserve further study. Because mTG crosslinks its substrate, the differential part of the enzyme in the integrity of the tight junction is unclear. One may wonder how mTG works when mixed with various nutrients during the meal and what the bioavailability of the enzyme would be within the gut (VOJDANI; LERNER; VOJDANI, 2021).

Apical-basal transfer of various gliadin peptides is aided by secretory IgA and apical transferrin receptor when tissue transglutaminase (tTG) is applied to epithelial cells. Moreover, gliadin uptake is increased when tTG is applied to a cell line *in vitro*. Since mTG functionally mimics its family member – tTG, it is logical to assume that mTG may also facilitate the uptake of gliadins from the mucosa, thereby increasing celiac disease. However, the effects of mTG on the blood-brain barrier are not known (LERNER; MATTHIAS, 2020).

An intact and functional mucus layer is a primordial protective intestinal barrier to prevent damaging luminal factors and pathobionts from approaching the brush edge of enterocytes. The main structural compound of mucus is mucin MUC2, and, due to its high glutamine and lysine content, it represents an ideal substrate for tTG. In reality, the enzyme transamides the MUC2 CysD2 domain, thereby enhancing its protective function (XIA *et al.,* 2019).

By adding the resistant isopeptide bond, mTG can disturb the stability and fluidity of mucin, resulting in the harmful binding of pathogenic luminal factors to epithelial receptors.

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At the immune level, mTG suppresses mucosal immune functions. *Streptococcus suis* mTG exerts antiphagocytic activity, thereby suppressing an important immune protection mechanism (XU *et al.,* 2017).

As a survival factor for microbes and a suppressant of intestinal immunity, mTG is a protective and growth factor for prokaryotes. When the *Streptoverticillium mobaraense mTG* gene was cloned in *Lactococcus lactis*, the bacterial mass increased significantly. The most recent cloning of mTG by bioengineering is successful in producing a higher yield and a more active form of the enzyme for a more cost-effective industrial application (ZHANG *et al.,* 2020).

Intestinal, intra or subepithelial dendritic cells with their elongations can detect, process and present luminal antigens. It appears that tTG derived from monocytes and macrophages is clearly involved in several inflammatory conditions. Macrophages derived from tTG and dendritic cells are capable of endocytosis the enzyme (CHROBOK *et al.,* 2017).

In fact, the lumen is rich in mTG and digested gluten juxtaposed to the intestinal apical brush edge. This novel dendritic cell-assisted tTG transcytosis may represent a new gateway for mTG and gliadins or cross-linked complexes to confront subepithelial immune cells (LERNER; MATTHIAS, 2020).

MTG AS ACTIVE IN THE LUMEN OF THE HUMAN GUT

A substantial amount of mTG resides in the human enteric lumen. There is no doubt that the mTG secreted by luminal microbes is active. The question arises whether the contaminated food products or the mTG added to process the food is active within the intestinal lumen. In view of this, several points were raised and should be clarified (LERNER; MATTHIAS, 2019).

mTG is temperature-dependent and is active up to 60°C. In reality, many food products are not boiled before consumption or during processing, and some populations prefer to eat raw meat. Just as a reminder, analyzing the meat and meat products on supermarket shelves, many contain Transglutaminase (LERNER; RAMESH; MATTHIAS, 2020).

Interestingly, the anchored complexes of mTG gliadin become more immunogenic when heated to 90°C. It is logical to speculate that during denaturation, epitopes are externalized and exposed to the immune system. Regarding mTG activity and temperature,

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the newly identified Atlantic cold cod transglutaminase opens up a new application area of thermostable mTG for the manufacture of boiled/heated/cooked food products (STRICKER *et al.,* 2019).

mTG is active at pH-4.0 and above. However, gastric physiology and pathophysiology show that when eating or postprandial, gastric acidity is neutralized. Paediatric people, adults and the elderly are chronically consuming acid-suppressing medications; Infants and the elderly have higher gastric pH, and alkaline reflux is not uncommon. Notably, the pH of the stomach is differentially distributed and some areas are less acidic (LERNER; MATTHIAS, 2019).

In summary, it is suggested that active mTG can perform its functions in the duodenum, small and large intestine. The cross-linked complexes are created *ex-vivo*, and during food processing, they are resistant to the passage of the stomach and are immunogenic (SZONDY *et al.,* 2017).

APPLICATIONS OF TRANSGLUTAMINASE

Preparations containing transglutaminase have a potentially wide range of applications. They often attract interest because they are used in the food industry for the cross-linking of proteins. Transglutaminase is also used to produce, for example, edible films of protein or compounds (CHAN; LIM, 2019).

Transglutaminase is an enzyme that catalyzes the formation of cross-links both within a protein molecule and between molecules of different proteins. This characteristic has an impact on changes in the functionalities of proteins: solubility, emulsifying capacity, foaming properties and gelling (TOKAY *et al.,* 2017).

In this context, studies have shown that the enzymatic cross-linking of β-casein is more resistant to digestion by pepsin than is the case of non-cross-linked β-casein. These results can have a considerable impact on the development of new types of foods with better structural characteristics (DUARTE *et al.,* 2020).

The polymerization of milk proteins with transglutaminase results in the formation of a protein film that improves the functional properties of dairy products. Thus, cross-linking is a predominant process that leads to the formation of specific bonds, for example. ε-(γ-glutamyl) lysine bonds within and between isopeptide chains (FATIMA; KHARE, 2018).

In the baking industry, for example, Transglutaminase is used to improve the quality of flour, the texture and volume of bread, and the texture of dough after baking. From a

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nutritional standpoint, rice flour contains many valuable nutrients, such as protein, fiber, and vitamins E and B; however, its use is limited to unfermented baked goods. Research has shown that the addition of Transglutaminase to rice flour improved the rheological properties of the dough, increasing the triglyceride content (ALVAREZ *et al.,* 2020).

Transglutaminase is also widely used in the meat industry, particularly in the manufacture of restructured meats. In addition to having a positive impact on the texture of the final product, the use of Transglutaminase preparations facilitates the strong cohesion of a block of meat without the need for thermal processing or the addition of salt or phosphates. The use of Transglutaminase in meat processing significantly improves the texture of the final product, which results, for example, in an increase in its hardness (CHAN; LIM, 2019).

In addition, it reinforces the texture of homogenized pork, beef or poultry sausages. The addition of Transglutaminase allows the use of lower quality raw materials, such as collagen, blood proteins, and mechanically deboned meat, in the manufacture of meat products with higher nutritional value, supplementing it with amino acids in which it is deficient (e.g., exogenous lysine) (AGARDH *et al.,* 2019).

The application of Transglutaminase has created new technological opportunities for the production of fine and ground sausages, Vienna sausages and smoked meat. Instead of high-quality meat, lower-quality raw materials and additives such as skim milk powder, soy flour, or wheat flour can now be used to manufacture these products. The enzyme's impact on the proteins of these raw materials produces products that do not differ in appearance, texture, odor, taste, and nutritional value from analog products made exclusively from high-quality meat (DUARTE *et al.,* 2020).

In this way, the use of Transglutaminase allows the production of some types of processed meats with lower fat content; in this case, the sodium casein treated with Transglutaminase replaces the previously extracted animal fat. Products with fillers do not differ in their organoleptic properties from conventionally processed meat (CHAN; LIM, 2019).

In the dairy industry, Transglutaminase has been introduced in the production of various products, such as yogurt, for example, in order to prevent syneresis or make its texture firmer and softer. Transglutaminase-modified casein makes it possible to manufacture dairy products with better structure and consistency (ALVAREZ *et al.,* 2020).

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This method is used to produce yogurts from milk incubated with Transglutaminase; they have a homogeneous, firm and creamy consistency, as well as a smooth, dry curd surface. This results from a reduction in syneresis. These yogurts serve as the basis for the production of creams, frozen desserts, ice cream, dairy drinks, and sauces (AGARDH *et al.,* 2019).

Transglutaminase is also used in cheese making and the curd yield is increased by the use of Transglutaminase in the manufacturing process. Three production patterns of natural cheese with Transglutaminase are proposed: addition of Transglutaminase to milk, heating of the milk for pasteurization and deactivation of the enzyme, and then addition of rennet to the milk; addition of rennet to milk and then addition of Transglutaminase; addition of transglutaminase to milk at the same time as rennet (TOKAY *et al.,* 2017).

Studies proposed to improve the yield and properties of cheese have shown that the addition of transglutaminase before the addition of rennet prevented milk coagulation; while the simultaneous addition of the enzyme and rennet significantly reduced the strength and hardness of cheese, protein content, and fat content in whey (AGARDH *et al.,* 2019).

Currently, transglutaminases are being used in baking technologies to form bonds between polypeptide prolamin chains. The first data on the cooking of pasta with the addition of Transglutaminase were provided in 1992. Thus, it was found that Transglutaminase has a positive impact on the stability and volume of the dough, as well as on improving the baking quality of poor flours and, consequently, on the texture of the bread (ALVAREZ *et al.,* 2020).

Other studies have also reported that Transglutaminase improved the rheological properties of the dough and ensured the proper pore size and elasticity of the bread after baking. In addition, transglutaminases have been shown to improve the adsorption of water by the mass. Modifying the proteins of wheat flour with Transglutaminase increases the elasticity and resilience of the dough as well as the volume of the bread by 14% compared to the dough made with traditionally prepared dough (CHAN; LIM, 2019).

Transglutaminase enables the development of entirely new products, for example, protein films used to coat fresh vegetables and fruits, and processed food products to extend their shelf life and freshness. Transglutaminase-modified whey protein is used to produce such films. These films are edible and can be consumed along with food products. In addition, depending on the technology, they have different water permeabilities, elasticity, resilience, resistance to tension, and mechanical damage (TOKAY *et al.,* 2017).

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More and more frequently, transglutaminase is being used in many branches of industry as a protein modifier. There is optimism about the potential use of transglutaminase to improve the nutritional values of deficient proteins by inserting the desired amino acids and peptides. It has been suggested that this enzyme could be used to block allergenic and proteolysis-resistant peptides in soy proteins. Numerous protein modification products with Transglutaminase are being used in the leather, cosmetics, and pharmaceutical industries (FATIMA; KHARE, 2018).

Transglutaminases may in the future be used to rebuild bonds between polypeptide prolamin chains. The formation of *isobonds* with the support of glutamine probably inhibits the process of recognition of this peptide fragment by T cells and, therefore, blocks the mechanism that leads to the development of Celiac Disease (DUARTE *et al.,* 2020).

THE USE OF MTG BEING LABELED AND DECLARED ON FOOD PRODUCTS

For decades, American regulatory authorities, such as the *Food and Drug Administration* (FDA), have classified mTG in the *Generally Recognized As Safe* (GRAS) category. They followed the manufacturers' statements about mTG being non-toxic, safe, non-allergenic, non-immunogenic, and non-pathogenic to public health. In addition, the issue of industrial production of enzymes, use and safety of genetically modified microorganisms is the subject of intense debate, while the discrepancies are wide (HANLON; FRESTEDT; MAGURANY, 2017).

Several questions are raised and the antibiotic resistance gene is a cause for concern. In view of ongoing efforts to bioengineer mTG more cost-effectively for industrial applications, and in view of all the detrimental effects of mTG and its complex transamidates used for food processing, public health against the side effects of mTG should be a priority (LERNER; RAMESH; MATTHIAS, 2020).

Thus, the world's food and industrial safety regulatory authorities should re-evaluate the updated observations; therefore, consideration should be given to easing the GRAS status and enforce labeling of this much-used processed food additive (ZHANG *et al.,* 2020).

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COMMUNICATING TO CUSTOMERS FOR POTENTIAL HEALTH RISK IN MTG CONSUMPTION

The FDA's GRAS category has evolved over the past few decades and has attracted quite a bit of attention from scientists, regulators, policymakers, practitioners and social media, as well as nongovernmental organizations. Critical opinions have been expressed, including a recent one on the lack of a master list of all GRAS chemicals used in food (FAUSTMAN *et al.,* 2021).

Furthermore, it is suggested that an inadequate scientifically sound, rigorous and transparent application of the "GRAS" concept is suggested. This reinforces the need for international evaluations related to GRAS determinations. Independent review of GRAS determinations is not mandatory, raising questions about the integrity of the assessment (SANDER *et al.,* 2020).

The fundamental issue of the conflict of interest between the FDA and food manufacturers poses real concerns. Above all, without knowing the substance's characteristics, activities, metabolism, physicochemical characterization, or the optimal amounts in the food product, FDA cannot meet its statutory obligation to ensure the chemical safety of the United States food supply. On the other hand, despite carefully observing GRAS warnings, grades are clearly defined, efficient, and cost-effective (SEWALT *et al.,* 2017).

Safety concerns have been raised in the pediatric field, even to the extent of retesting all previously approved chemicals and labeling direct additives with limited or no toxicity data. The classification of mTG in the GRAS category can be an example for the aforementioned criticisms (SANDER *et al.,* 2020).

The declaration of the manufacturers of the enzyme as non-toxic, safe, non-allergenic, non-immunogenic, and non-pathogenic for public health is not consistent with what is known in the literature. It appears that in butcher shops and bakeries, mTG induces allergic reactions that manifest themselves by respiratory symptoms and unflatteringly categorized as occupational allergens. The enzyme or its cross-linked complexes can be toxic, unsafe, immunogenic, and pathogenic, being pro-inflammatory, increasing intestinal permeability, and even autoimmunogenic (OLIVEIRA *et al.,* 2021).

Based on the widely criticized GRAS category, the harmful effects of mTG and its cross-linked complexes, as well as the updated scientific literature, national and international food regulatory authorities should re-evaluate the enzyme's processing aid

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classification. Thus, mTG must be labeled as a food ingredient and meet the standards that require the maintenance of public health (LERNER *et al.,* 2017).

WARNINGS FOR THE USE OF MICROBIAL TRANSGLUTAMINASE

Regulatory bodies, academic experts, and social media opinion leaders are warning about the use of mTG in the processed food industries. Several arguments have been raised against the mTG of unlabeled "processed help." It is known that the use of Transglutaminase as a food additive is allowed in some countries. However, their use must be declared to ensure transparency for consumers (KUMAR *et al.,* 2020).

Therefore, mTg may increase the immunogenicity of gluten and should not be used in food products intended for consumption by patients with Celiac Disease. In fact, concerns and warnings about the safe use of the industrial enzyme exist in several publications (SZONDY *et al.,* 2017).

Notably, in some European countries, such as Switzerland and Germany, or in Canada, the public is notified of potential public safety concerns and labeling of the enzyme on the final product is recommended. According to European Union (EU) Regulation No. 1169/2011, reconstituted meat or fish products must include the word "formed" or "restructured" on the label. Unlike European legislation, Transglutaminase is not considered a processing aid that would be exempt from labeling by the FDA (KUMAR *et al.,* 2020).

Therefore, it is a dynamic process, and regulatory policies on food enzymes produced by microbes and food additives are still evolving, and must follow and respond to new mTG biosynthetic methodologies and their expanding application in the food chain (KOCABAŞ; GRUMET, 2019).

CONCLUSION

It was concluded that Transglutaminase, due to its unique properties, is an enzyme widely used in several branches of the food industry. It has been recognized as safe (GRAS) by an independent panel of scientific experts. The discovery that it has a cheap source of its biosynthesis, that is, by microorganisms, has provided an opportunity for a broader and more practical application of this enzyme.

It has been observed that further research and development for the cost-effective production of Transglutaminase by microorganisms may result in the development of more affordable products with a wider scope of use. A mechanistic approach aims to identify new

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and promising areas of use of Transglutaminase that will lead to its safe use in the food industry. The great applicability of microbial transglutaminases has led to the search for new strains capable of synthesizing substantial amounts of enzymes with high activity from the cheapest possible substrates.

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