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Bioactive peptides with the inhibitory activity that are produced by lactic acid bacteria; their importance and mechanism

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Abstract: The inhibitory action of peptides refers to a group of microorganisms that peptides can influence and inhibit. Most peptides have limited inhibitory action, as their effect is limited to bacteria which close to the bacteria that produce them, especially lactic acid peptides. As most of them are characterized by a broad inhibitory action extending to include unrelated bacteria from Gram-positive bacteria and pathogenic or food spoilage bacteria, and in some cases, they include lactose-negative bacteria too. The main application of lactic acid bacteria is to use it as priorities, as it contributes to strengthening the flavor, feeling, and nutritional value of the different fermentation through three main paths, which are the fermentation of sugars, fats analysis, and the main path to manufacture and develop the flavor which is the protein analysis. In order to develop new functional foods that provide a beneficial health effect, many tests are carried out for lactic acid bacteria strains. To be used in food production, taking into consideration the economic feasibility, required sensory characteristics, and consumer acceptance. In addition, testing it on the living body to know its effect on the digestive system using analytical methods. Bioactive peptides are considered valuable nutritional components that have biological properties and many therapeutic effects for many health disorders, especially heart diseases and cancer, in addition to many chronic diseases. And because it has a functional factor that has beneficial effects on the health of the consumer, it has been studied extensively, as it can be absorbed in the intestine without digestion, it is preferable to be used over free amino acids, as it is transmitted at the same level as the transport of free amino acids by the cell. Moreover, free amino acids make foods hyperactive and may cause diarrhea, while some bioactive peptides may cause allergic reactions, as the allergenic effects disappear with partial weight reduction. However, the use of peptides remains a matter of great importance in food preservation in terms of providing food safety, ensuring the quality of the food supply, and prolonging the shelf life.

Keywords: Bioactive Peptides, Inhibitory, Lactic Acid

Introduction

Foodborne Diseases (FBDs) remain cause many illnesses and deaths worldwide according to the 2017 US Food and Drug Administration (USFDA) (Wasey and Salen, 2019; Gasu *et al*. 2018). Studies confirm the persistent risks which could be existed by foodborne pathogens (Hoffmann *et al*., 2017 Li *et al*., 2019;). Besides, rapid detection of foodborne pathogens is essential to avoid many chronic diseases (Kaden *et al*., 2018; Sidari and Caridi 2011). Gut microbes are an example of a wide range complex of microorganisms that play a vital role in maintaining internal homeostasis. Tens of trillions of microbes have significant effects on host metabolism, physiology, and immune function (Semenkovich, 2017).

Biologically active peptides

Recent scientific evidence indicates that dietary proteins not only act as nutrients, they can also regulate physiological functions primarily by means of some peptides encoded in the original protein sequence. These bioactive peptides can exert health-beneficial properties, thus considered a key compound for the development of functional foods (Solak and Akin, 2012). In the past few decades, a wide variety of food-derived bioactive peptides have been identified. However, commercial application of these peptides has been delayed due to a lack of suitable and scalable production methods, proper exploration of action mechanisms, high digestibility, variable absorption rate, as well as a lack of well-designed clinical trials to provide concrete evidence of potential health claims (Chakrabarti *et al*., 2018). Studies have confirmed the important physical and chemical

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role of food proteins that occur naturally by peptide sequences encoded within the parent protein, and which exert their activity when released either enzymatically during food processing or through microbial fermentation (Daliri *et al*., 2017; Korhonen *et al*., 2006).

Biologically active peptides are peptide chains within a protein that have a beneficial effect on body functions and positively affect human health, in addition to their well-known nutritional value (Wang *et al*., 2018), It can regulate important body functions through its many activities including lower blood pressure, antimicrobial, anticoagulant, immunity, and antioxidant, as well as mineral binding (Wang *et al*., 2018; Sánchez and Vázquez, 2017; k Rutherfurd-Mar, 2012). Bioactive peptides are produced from dietary proteins either by enzymatic hydrolysis (using proteolytic enzymes from plants or microbes), hydrolysis using digestive enzymes (gastrointestinal digestion), or by fermentation using starter cultures. Some studies have also confirmed the use of a combination of these methods for the production of biologically active peptides (Korhonen *et al*. 2006) and bioactive peptides can also be synthesized biochemically, since the amount of these peptides found in nature is very low, and there is a continuing growing commercial interest in commercial bioactive peptide production. (Perez Espitia *et al*., 2012) However, it is doubtful that purely synthetic peptides would be considered a nutrient.

Chemical structure of peptides

Active peptides can be defined as a small protein with a short chain of amino acids. These amino acids are linked by a strong chemical bond in the protein structure called Bond Peptides, and a water molecule is produced at each bond. There are three kinds of these chains؛ short peptides which consist of up to ten amino acids, long peptides which consist of amino acids more than short peptides, up to more than 50 amino acids, and protein which consists of more than 100 amino acids, so we can differentiate between peptides and proteins (Schirwitz, 2013). The chemical bond between carbon and nitrogen atoms for each amide group is called a peptide bond, and some or all peptide bonds can be broken through partial or complete hydrolysis of the compound. This reaction is used to form smaller peptides and finally individual amino acids (Guichard, 2006), and there are several kinds of peptides according to the amino acid sequence, including a dipeptide, where one amino acid is linked to another amino acid to produce it, this occurs through the linkage of the carboxyl (COOH) of the first amino acid and the amine (NH_2) of the second amino acid through the formation of the peptide bond between them, and as a result of this process one molecule of water is excreted. (Mine *et al*., 2010). A tripeptide, which results from the association of three amino acids together and liberation of two water molecules, and so on with all peptides, there are tetrapeptides, pentapeptides, and so on, depending on the number of amino acids. Bioactive peptides also undergo amino acid sequences, where they interact with other proteins and regulate natural processes in the body (Fields *et al*., 2009). Examples of peptide compounds include vasopressin consisting of nine amino acids, oxytoxin, a cyclopeptide consisting of nine amino acids, glutathione, a tripeptide found in most plant and animal tissues, and gramicidin, a cyclopeptide that is used as an antibiotic, and it is a tetrapeptide (Abdul-Saadawi and Issa, 2009). To understand peptides more, we have to know the structure of amino acids. An amino acid is a small molecule containing a center carbon with an amino group (NH_2) positive, a carboxyl group (COOH) negative and a hydrogen atom in addition to a side chain known as the R group.

The antagonistic activity of lactic acid bacteria

The most important inhibitory substances produced by lactic acid bacteria can be explained as follows:

1- organic acid

Lactic acid bacteria produce lactic and acetic acid through their metabolic pathways, which have an inhibitory effect on the growth of microorganisms. Acetic acid is more effective than lactic acid. The quantity produced from acids depends on the genus of bacteria and the components of the nutrient medium in addition to the type of fermentation of bacteria. Homogeneous fermentation produces lactic acid as a final product through the Embden-Meyerhof pathway. Lactic acid is produced from pyruvate through the enzyme Lactic acid dehydrogenase inside the cell. The accumulation of acid produced leads to a decrease in the PH, Thus, it affects the activity of internal enzymes and hinders the synthesis of ATP, which leads to the manifestation of the inhibitory effects of pathogenic microorganisms (Cubas-Cano *et al*., 2018; Martinez *et al*., 2013). Lactic acid bacteria is produced in heterogeneous fermentation, while lactic acid, acetic acid, and probiotics are

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through the phosphatase pathway. (Eş *et al.*, 2018) and due to a decrease in the pH, which leads to an increase in the acidity inside the cytoplasm of the cell, thus the inhibitory activity of lactic acid bacteria increases.

The Lactic acid in its ionized form in aqueous solutions is either dissociated or undissociated, and the latter has a stronger effect about (10-100) times in the inhibitory process, as the undissociated lactic acid diffuses freely through the cell membrane to the cytoplasm depending on the PH, then moves to the dissociated form inside the cell leads to the release of hydrogen ions H^+, which in turn increases the acidity in the cytoplasm. Moreover, the acid molecule of the undissociated form exerts another antagonistic activity by destroying the chemical-electrical mechanism of transporting proteins across the membrane, which causes a change in the permeability of the membrane. Mutagenesis of cellular proteins and enzymes, in addition to their ability to dissolve in fats, which helps them to penetrate the plasma membrane of the cell and spread rapidly to the cytoplasm, which leads to impeding the transfer of nutrients across the membrane (Martinez *et al*., 2013; Delgado *et al*. 2001).

2- Carbon dioxide

Lactic acid bacteria produce heterogeneous fermentation carbon dioxide, which works to inhibit the growth of microorganisms through the availability of anaerobic conditions in addition to the negative effect on the carboxylic enzymes of microscopic cells, as the amount of gas produced varies according to the type of microorganism that produces it.

3- Hydrogen peroxide

Lactic acid bacteria produce hydrogen peroxide in the presence of oxygen, which contributes to the inhibitory effect of both gram-negative and gram-positive bacteria, according to what was mentioned (Lu *et al*., 2012; Gilliland, 1985). The inhibitory effect of hydrogen peroxide is due to the molecule of the same compound or other compounds resulting from its interaction with food. It also produces intermediate compounds when interacting with peroxidase and thiocyanate that have an inhibitory effect on other microorganisms, in addition to its ability to denature proteins through oxidation of the sulphonyl group and thus destroying the molecular structure of cell proteins also oxidizes fats and inhibits enzymatic reactions, which leads to an increase in the permeability of the components of the cell wall, and it works to capture free radicals with a lethal effect. In addition to what was mentioned above, hydrogen peroxide works to break the phosphate bonds and causes mutations in the DNA strand, liberating the nitrogenous bases and thus preventing the chromosome from replicating (Bjorck, 1978).

4- Aromatic compounds

4-1- Diacetyl

Homogeneous lactic acid bacteria produce the compound (Diacetyl 2,3-butanedione) in the presence of citrate and pyruvate during the fermentation process of carbohydrates, but heterogeneous lactic acid bacteria do not produce this compound, which is characterized by its high inhibitory activity against molds, yeasts and gram-negative bacteria (Simova *et al*., 2009; Adams and Nicolaides, 1997), as it inhibits pathogenic bacteria such as S. aureus and Bacillus spp. Through the interaction of diacetyls with proteins bound to the amino acid arginine in microorganisms, which affects the consumption and manufacture of arginine (Lavermicocca *et al*., 2000; Naidu *et al.*, 1999).

4-2- Acetaldehyde

Some types of homogenous lactic acid bacteria produce acetaldehyde fermentation in the presence of the enzyme Threonine aldolase, which in turn breaks down the amino acid Threonine into acetaldehyde and glycine. When acetaldehyde is collected, its inhibitory effect begins at a concentration of (10-100) ppm towards E. coli, S. aureus and Salmonella typhimurium (Flynn *et al.*, 2002; Messens and De Vuyst, 2002).

5 Bacteriocins

Bacteriocins are protein bio-compounds produced by bacteria that may be combined with fats or carbohydrates and may be toxic to strains of the same species or genetically related species. Its toxicity is due to its association with the receptors of the sensitive cell to it. It creates bacteriocins in the ribosome and is considered a peptide complex with positively charged ions that are not affected by disinfectants with a negative charge. These biological substances work to disturb the cytoplasmic membrane of sensitive cells. (Saranya and

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Hemashenpagam, 2011) and contains less than 60 amino acids produced by microorganisms, especially bacteriocins produced by lactic acid bacteria, which are known as low molecular weight peptides and possess high antibacterial activity, and their inhibitory range often extends to include other types of non-lactating bacteria. Species related to the producing bacteria (Richard *et al*., 2006; Eijsink *et al*., 2002). Most bacteriocins are thermally stable, non-toxic and degradable by proteolytic enzymes present in the gastrointestinal tract (Abriouel *et al*., 2003). Bacteriocins are characterized by having a hydrophilic and a hydrophobic end, and they increase the permeability of the cytoplasmic membrane, denature proteins and inhibit nucleic acids (Walsh *et al*., 2015; Rahayu *et al*., 2013; Georgalaki *et al*., 2013).

Classification of bacteriocins from Gram-positive bacteria

Bacteriocins are produced by Gram-positive and Gram-negative bacteria, and bacteriocins inactivate microorganisms that may or may not be related to the strain Which is produced by them and may be small peptides less than 10 kDa or may reach greater than 30 kDa. Bacteria have been classified in different ways, they have been classified on the basis of their tolerance and resistance to different temperatures, Simoes, (2010) (Alvarez-Sieiro *et al*., 2016). There is another classification that includes lactic acid bacteria from among the bacteriocins which are produced from positive bacteria. On this basis, it was classified into four groups (Jack *et al*., 1995). Klaenhammer, (1993) suggested classifying them into four main groups, depending on the presence of modified amino acids, molecular weight, sensitivity to enzymes, thermal stability, and their mechanism of action. This classification includes the following four main categories:

Class I - called antibiotics: It includes small peptides with molecular weights less than 5 kDa, containing modified amino acids such as Lanthionine (Lan) and Beta-methyl-Lanthionine (Melan)-3 or amino acids with double unsaturated bonds such as Dehydrobutyrine (Dhb), 3,-Dehydroalanine (Dha) that all types are synthesize in ribosomes. This class is divided into three types: A, B and C. The first type A, is in the form of a long straight chain of positively charged amino acids, and it consists of two groups, Al and All, and it represents Nisin A and Nisin U. But type B, a protein with a small molecular weight, negative or neutral charge, spherical shape and works to inhibit some special enzymes inside the cell. While bacteriocin C, contains two modified amino acids and has less inhibitory activity than other types.

Class II: This class includes all bacteriocins with molecular weights less than 10 kDa, including heat-stable peptides, they do not contain modified or spherical amino acids (Non-antibiotics), They contain disulfide bonds and each bacteriocin contains more than 40 amino acids. Its mechanism of action depends on the disruption of the function of the cell membrane. This class contains about 50 types of bacteriocins and is divided into three subsections:

II a: It is called Pediocin-like bacteriocins and contains more than 20 bacteriocins which are anti-Listeria monocytogenes peptides found in foods, because of this inhibitory property prompted many researchers to study this group for the purpose of using them as preservatives. This type is a positive charge, its electrical neutralization is between (8-10), and its amine end is a hydrophilic type with a β-sheet structure. As a result of the presence of disulfuric bonds that link the amino acid molecules Cysteine, this type gives a broad inhibitory spectrum towards other microorganisms, while the C-terminal carboxyl terminal is either hydrophobic or heterophilic and includes 1 and 2 α-helices. This type consists of 37-48 amino acids and all of them contain the YGNGV sequence of amino acids at the amino end of the peptide which are called Pediocin Box.

II b: The bacteriocins in this type consist of two peptide chains that work synergistically to produce the inhibitory effect (Synergistic) such as (β and α) Lactococccin G.

II c: It includes all bacteria of class II that do not fall into subdivisions II a and II b. This type includes two subtypes of bacteriocins, the first containing one cysteine molecule, called thiolbiotics, or two cysteine molecules called cystibiotics, such as Lactococcin B, and the other type includes bacteriocins that do not contain cysteine, such as Acidocin A.

Class III: This class of bacteriocins includes heat-sensitive proteins, with molecular weights greater than 10 kDa, most of which are produced by the genus Lactobacillus such as Lacticin B.

Class IV: This class includes cyclic bacteriocins which are created in ribosomes. The first amino acid of the peptide chain is linked to the last amino acid through a covalent bond, this linkage is called head-to-tail linkage. It contains a protein with fat molecules and carbohydrates that help in antimicrobial activity.

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The mechanism of action of peptides

Studied Zhang *et al*. (2021) the mechanism of the inhibitory action of peptides based on the study done by Nomura in 1967 on colicin, as he focused on two points, the first showed that the binding of peptides to cells leads to openings or holes in the walls of bacteria cells, the second point shows the strength of the interaction between peptides and components of sensitive cells, and the biological and chemical damage that occurs in the affected cells. In order to explain the interaction between peptides and sensitive cells, an accepted theory was found that states there are two phases, the first phase involves the physical adsorption of peptide molecules on receptors located in the cell walls. Most likely, this step is reversible and does not cause physiological damage to the cells, the second phase leads to the occurrence of chemical and biological injuries in the affected cells (Tagg, 1976). In line with what was mentioned, peptides cause openings or holes in the cytoplasm membrane of cells, and their size varies according to the peptides, it also effectively affects the production of ATP by stopping the stimulation of protons and the exit of some nutrients from the cell (Chikindas *et al*., 1993).

The study explained to researchers (Chen *et al*. 1997) peptides are small, electrically stable, positively charged proteins that interact with the negatively charged phosphate group found in phospholipids in the cell walls, peptides may infect intracellular targets such as RNA, DNA, enzymes, and other sites, causing cell death. There are three factors that contribute to the formation of openings and holes, which are the types and structures of phospholipids present in the cytoplasm membrane, the acidity function of the medium, and the effect of peptides' minimum concentration values to inhibit susceptible bacteria (Breukink *et al*., 1999).

Methods for detecting peptides in bacteria

Due to the tremendous development and the emergence of modern technologies in this field, the methods used to detect peptides and the bacteria that produce them varied, among these multiple methods were divided into the following groups, according to what the researchers mentioned. (Settanni and Corsetti, 2008; Wahlstrom and Saris, 1999; Martinez *et al*, 1998; Waterworth, 1978; Pucci *et al*., 1988).

1- Methods based on inhibitory activity such as diffusion in solid media.
2- Methods based on measuring the density of bacterial growth in liquid media: Detection of bacteriocin liquid media.
3- Immunological modalities such as Competitive Sandwich Type ELISA, Direct ELISA, and Immunoblot.
4- Genetic methods such as colony hybridization and cloning of genes responsible for the production of peptides.
5- Bioluminescence methods.

It is noted that the methods of diffusion in solid media are the most widely used, despite the diversity in the methods of detection of peptide-producing bacteria. These methods are summarized by developing the bacteria whose ability to produce peptides is detected on the surface of the solid medium, which is then vaccinated with the test bacteria, the inhibition can be observed around the producing bacteria colonies and it is called the indirect method. There are direct methods, such as the method of diffusion in the pits. (Gasu *et al*., 2018; Balasubramanyam and Varadaraji, 1998), Disc distribution method (Ferreira and Gilliland,1988), and the staining method on the surface of the growth layer (Ko and Ahn, 2000).

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