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Opinion Paper

Save the Food: Antimicrobial Peptide Surrogates for Food Preservation

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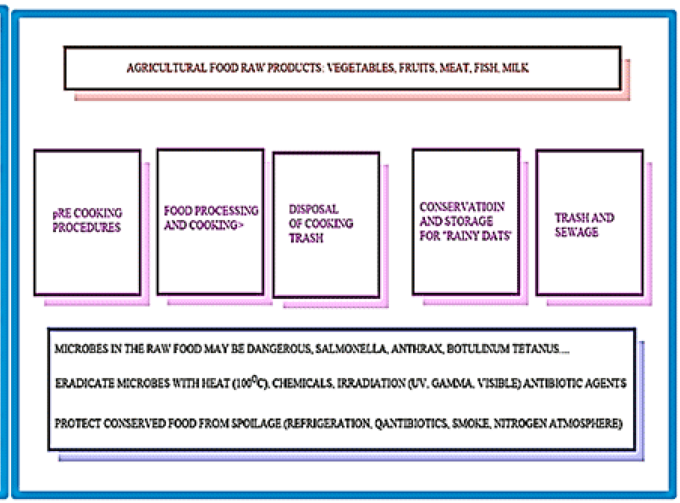
Abstract

Food contamination is a serious problem related to public health as it causes great morbidity. For that reason, there is a need to develop alternative preservation methods able to provide a better and safer quality of food from a microbiological and toxicology point of view. Thus, natural conservatives will have an important role shortly. Faced with this reality, the investigation of antimicrobial peptides which have activity against important pathogenic microorganisms in food remains promising and is the focus of ongoing research. Although there is some knowledge about these peptides, many aspects related to structure and function, biosynthesis and mode of action remain unknown.

Foreword and Guidelines



Food Trash *Preservation of food*

Microbes are living organisms, such as bacteria, fungi, and parasites, which are the critical sources of infections [1]. Infectious diseases result from pathogenic microbes and kill more people than any other single cause. An antimicrobial is an agent used to kill microbes or inhibit their growth. Although numerous antimicrobial drugs have been developed to kill or inhibit microbes, many infectious diseases remain difficult to treat. Tens of millions of tons of food get trashed every year in the USA, often because people buy too much or cook meals that are too big. Here are six ways to stop wasting so much by making your grocery trips more efficient, keeping your pantry organized and sharing what you can't manage to eat yourself. 40% of

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the food in America is wasted [2]. Grill it, Cook it, and Store it. Share it. Altering consumer awareness and perception around the issue of food waste could have significant environmental, social and economic impact on our country. By taking just a few simple steps around food storage, preservation, and use, the home cook has an incredible opportunity to reduce waste and minimize their environmental footprint. Improved conservation, packaging and distributing ways can save this trashing of food from demise. Food comes in a wide variety of packaging. That's not all just for show. Food packaging helps to protect it from the air and light.

Temperature Effects on Microbes

There are versatile effects of temperature on microbes, depending on the race of the bacteria. The Arrhenius low governs the biochemical reactions that are involved in bacterial growth. Microbes can be roughly classified according to the range of temperature at which they can grow. The growth rates are the highest at the optimum growth temperature for the organism. The lowest temperature at which the organism can survive and replicate is its minimum growth temperature. The highest temperature at which growth can occur is its maximum growth temperature. The following ranges of permissive growth temperatures are approximate only and can vary according to other environmental factors. Organisms categorized as mesophiles ("middle loving") are adapted to moderate temperatures, with optimal growth temperatures ranging from room temperature (about 20 °C) to about 45 °C. As would be expected from the core temperature of the human body, 37 °C (98.6 °F), normal human microbiota and pathogens (e.g., E. coli, Salmonella spp., and Lactobacillus spp.) are mesophiles. Controlling temperature by and freezing foods also helps to slow down chemical reactions. Organisms called psychrotrophs, also known as psychrotolerant, prefer cooler environments, from a high temperature of 25°C to refrigeration temperature about 4°C. They are found in many natural environments in temperate climates. They are also responsible for the spoilage of refrigerated food. Finally, the against microorganisms is often fought by adding chemicals known as preservatives to food. These chemicals help to the chemical reactions that allow microorganisms to break down food for energy. Temperature Refrigerating battle inhibit the effort is the latest step in an American national trend to examine and reduce food practices that result in waste. This past September, the Obama Administration announced the nation's first-ever food waste reduction goal, calling for a 50 percent cut by 2030; days later the U.N. set a similar target internationally. A report released last month by ReFED – a collaboration of over 30 business, government, investor, foundation and nonprofit leaders – identified consumer education campaigns as one of the best ways to cut U.S. food waste and put the country on track to its reduction target.

Food Preservatives

Food preservation [3] the term food preservation refers to any one of several techniques used to prevent food from spoiling. It includes methods such as canning, pickling, drying and freeze-drying, irradiation, pasteurization, smoking, and the addition of chemical additives. Food preservation has become an increasingly important component of the food industry as fewer people eat foods produced on their own lands, and as consumers expect to be able to purchase and consume foods that are out of season. The vast majority of instances of food spoilage can be attributed to one of two major causes: (1) the attack by pathogens (disease-causing microorganisms) such as bacteria and molds, or (2) oxidation that destroys essential biochemical compounds and the destruction of plant and animal cells. The various methods that have been devised for preserving foods are all designed to reduce or eliminate one or the other (or both) of these causative agents [4]. Foods contamination leading to spoilage and growth of pathogenic microorganisms can happen when exposed to the environment during slaughtering, processing, packaging [5] and shipping. Food preservation prevents the growth of microorganisms (such as yeasts), or other microorganisms (although some methods work by introducing benign bacteria or fungi to the food), as well as slowing the oxidation of fats that cause rancidity. Food preservation may also include processes that inhibit visual deterioration, such as the enzymatic browning reaction in apples after they are cut during food preparation. Surprisingly, despite the considerable length of time that food antimicrobials and equipment sanitizers have been used in the food industry, there is little data about the development of microbial resistance to these compounds. Many processes designed to preserve food involve more than one food preservation method. Preserving fruit by turning it into jam, for example, involves boiling (to reduce the fruit's moisture content and to kill bacteria, etc.), sugaring (to prevent their re-growth) and sealing within an airtight jar (to prevent recontamination). Some traditional methods of preserving food have been shown to have a lower energy input and carbon footprint when compared to modern methods [6]. Substances which, under certain conditions, either delay the growth of microorganisms without necessarily destroying them or prevent deterioration of quality during manufacture and distribution. Can be naturally occurring or synthetic substance that is added to products such as foods, pharmaceuticals, paints, biological samples, wood, etc. to prevent decomposition by microbial growth or by undesirable chemical changes. These substances are added in very low quantities (up to 0.2%) which do not alter the organoleptic and physicochemical properties of the foods at or only very little. This method is usually based on the combined or synergistic activity of several additives, intrinsic product parameters, and extrinsic factors. Food preservatives, spices, and flavoring agents have been added to foods for thousands of years. These compounds which are added to foods are termed as food additives

Chemical food preservatives are applied to foods as direct additives during processing, or develop by themselves during processes such as fermentation. The frequent failure of antibiotic treatment is an acute public health problem. The most apparent reason is that the development of bacterial resistance compromises the successful use of any therapeutic agent. An example is amino glycoside antibiotics, such as gentamicin and kanamycin, directly target the ribosome, yet the mechanisms by which these bactericidal drugs induce cell death are not fully understood. The majority of the antibiotic agents in use today are aiming at the genetic materials (DNA, RNA) but a great portion is effective at the cell membrane domain. The mechanisms [7] of action of today'sagentare clarified to a great extent after the elucidation of the structure of the ribosome [8]. The era of antibiotics based on such (nucleic acids for example) intracellular target components seem to end. Also, the era of antibiotics that hinder cell wall synthesis is losing momentum. The long list of antibiotic drugs to its families is becoming insufficient since it hardly answers the common bacterial infections acquired nonsocial or otherwise. It seems, that exploitation of the Antimicrobial Peptides. AMPs: Examples include cecropins from insects, magainins from amphibians and cathelicidins from mammals. Their way to eradicate bacteria by cell wall disruption is one of the few clues to the problem of microbe's resistance. The eradication of persister cells, dormant cells and mutants may become a real option and bring remedy to those who suffer the incurable infection caused by those killer bacteria. The ability of nisin, synthetic temporin analogs, magainins, defensins, and cecropins to inhibit Bacillus anthracis, Bacillus cereus, Bacillus thuringiensis, Bacillus mycoides, and Bacillus subtilis growth from spore inocula was determined using well diffusion assays. Nisin, magainin II amide, and defensins were inhibitory in screening against B. anthracis Sterne or B. cereus ATCC 7004, but the only nisin inhibited virulent B. anthracis strains. The MICs (minimum inhibitory concentrations [9]) of nisin against the 10 Bacillus strains examined were 0.70 to 13.51 _g/ml. Synthetic temporin analogs also inhibited B. anthracis but were not as potent as nisin. None of the strains examined were appropriate B. anthracis surrogates for testing sensitivity to antimicrobial peptides [10]. The antimicrobial peptides are nature's weapon to combat the invasion of microbes as host defense agents, the first line of defense. However, the natural peptides suffer from serious drawbacks the first in the list is their being peptides and sensitive to enzymatic digestion. The approach of peptidomimetics [11] bears many advantages over the gift of nature and that is:

1. Stability in the enzymatic world.
2. The option of human design.
3. Use of un-natural components to the construction of the mimetic architecture [12].

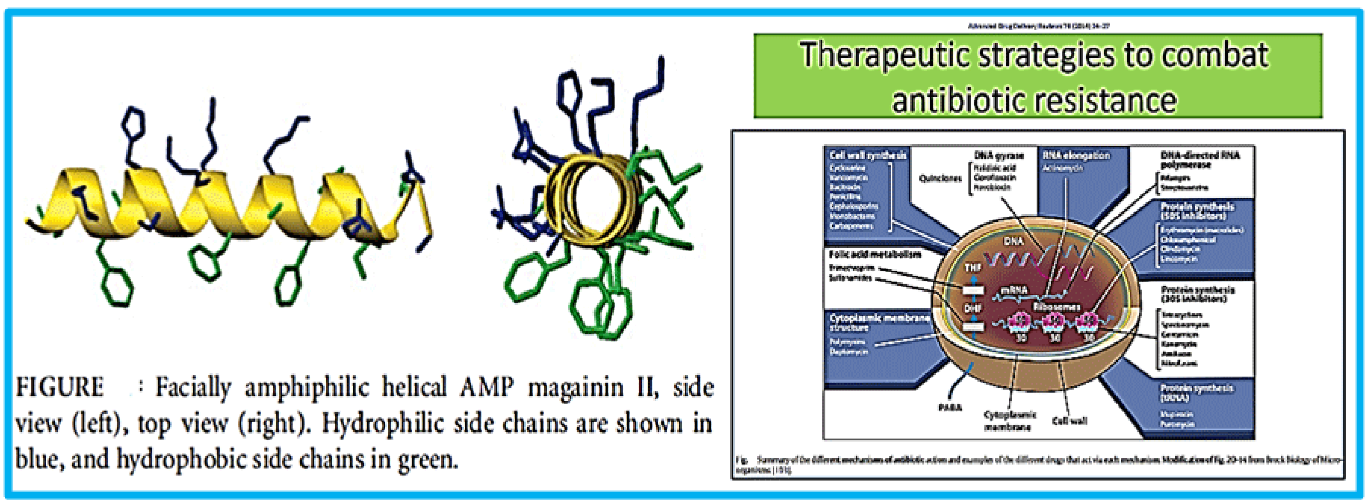


FIGURE : Facially amphiphilic helical AMP magainin II, side view (left), top view (right). Hydrophilic side chains are shown in blue, and hydrophobic side chains in green.

A B

Antimicrobial peptide amphipathic structure (Panel A), cellular targets and strategies for microbe eradication (panel B)

Nowadays, the grim situation is taking a toll [13] of hundreds that pass away every day [14]. There is no doubt, a new approach to the novel design of antimicrobial active and selective drug is needed [15]. The antimicrobial peptides (AMP), amphipathic structures [16] composed of amino acids, the natural first line of the innate immune system, may provide the clue based on the novel mechanism of microbial eradication in which the operate in the microbes [17]. Disruption of the cell membranes [18,19]. The compounds eradicate microbes efficiently. These are broad bands lytic biocides. The agents eradicate all sorts of bacteria: Gram positive, Gram negative and mycobacteria in a similar effectivity.

Food Additives [20]

Currently, traditionally applied chemicals and handling procedures are applied. The following are mainly resistance to antibiotics used for therapeutic purposes in human and animal medicine. A second concern is an increasing reliance on antimicrobials and sanitizers as primary tools for controlling the outgrowth of pathogens in foods. A third concern is an evidence, indicating that tolerance to antimicrobials, sanitizers, and other preservation processes may be generated within microorganisms exposed to certain stresses used in food preservation. One concern is the increasing incidence of microorganisms exhibiting Substance or mixture of substance, other than a basic foodstuff which is present in food as result of any aspect of production, processing, storage or packaging. This definition does not include any chemicals that are contaminants pesticides, color additives or new animal drugs.

Common Chemicals Currently Applied for Food Preservation

Table 1—Traditional and naturally occurring food antimicrobials approved by the Food and Drug Administration. From Davidson and Branen (1993) and CFR (2001)

Compound(s)	Microbial target	Primary food applications	Title 21 CFR designation[a]
Acetic acid, acetates, diacetates, dehydroacetic acid	Yeasts, bacteria	Baked goods, condiments, confections, dairy products, fats/oils, meats, sauces	184.1005, 182.6197, 184.1754, 184.1185, 184.1721, 172.130
Benzoic acid, benzoates	Yeasts, molds	Beverages, fruit products, margarine	184.1021, 184.1733
Dimethyl dicarbonate	Yeasts	Beverages	172.133
Lactic acid, lactates	Bacteria	Meats, fermented foods	184.1061, 184.1207, 184.1639, 184.1768
Lactoferrin	Bacteria	Meats	—[b]
Lysozyme	*Clostridium botulinum*, other bacteria	Cheese, frankfurters, cooked meat and poultry products	184.1550[c]
Natamycin	Molds	Cheese	172.155
Nisin	*Clostridium botulinum*, other bacteria	Cheese, other products	184.1538[d]
Nitrite, nitrate	*Clostridium botulinum*	Cured meats	172.160, 172.170, 172.175, 172.177
Parabens (alkyl esters (propyl, methyl, heptyl) of *p*-hydroxybenzoic acid)	Yeasts, molds, bacteria (Gram-positive)	Beverages, baked goods, syrups	184.1490, 184.1670, 172.145
Propionic acid, propionates	Molds	Bakery products, dairy products	184.1081, 184.1221, 184.1784
Sorbic acid, sorbates	Yeasts, molds, bacteria	Most foods, beverages, wines	182.3089, 182.3225, 182.3640, 182.3795
Sulfites	Yeasts, molds	Fruits, fruit products, potato products, wines	Various

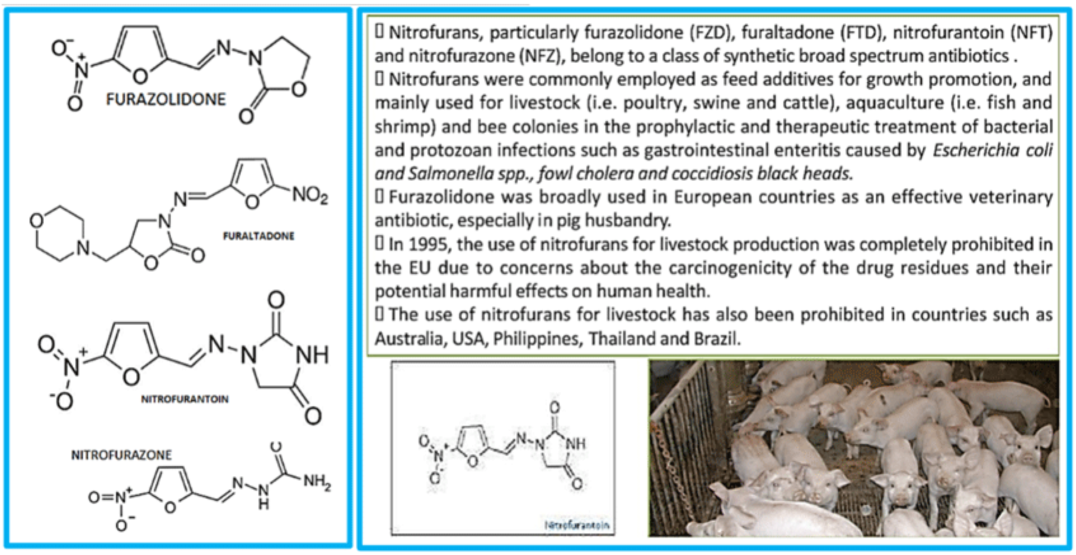
[a]These are the Food and Drug Administration's designations in Title 21 of the *Code of Federal Regulations*. Food antimicrobials approved by the U.S. Dept. of Agriculture's Food Safety and Inspection Service for use in meat products are listed in Sections 424.21 and 424.22 of Title 9 of the CFR.
[b]FDA/CFSAN (2001a)
[c]FDA/ CFSAN (2001b)
[d]FDA/CFSAN (2001c)

Preservatives	*Maximum Tolerance*	*Organisms Affected*	*Foods*
Ethyl formate	15-120 ppm	Yeasts and molds	Dried fruits, nuts
Caprylic acid	—	Molds	Cheese wraps
Sodium nitrite	120 ppm	Clostridia	Meat-curing preparations
Dehydroacetic acid	65 ppm	Insects	Pesticide on strawberries, Squash
Nisin	1%	Lactics, clostridia	Certain pasteurized cheese spreads
Sodium diacetate	0.32%	Molds	Bread
Ethylene/ propylene oxides	700 ppm	Yeasts, molds,	vermin Fumigant for spices, nuts
SO2/ sulfites	200-300 ppm	Insects, microorganisms	Molasses, dried fruits, wine making, lemon juice (not to be used in meats or other foods recognized as sources of thiamine)
Parabens	0.1 %f	Yeasts and molds	Bakery products, soft drinks, pickles, salad dressings
Benzoic acid/ benzoates	0.1 %	Yeasts and molds	Margarine, pickle relishes, apple cider, soft drinks, tomato ketchup, salad dressings
Sorbic acid/ sorbates	0.2%	Molds	Hard cheeses, figs, syrups, salad dressings, jellies, cakes
Propionic acid/ propionates	0.32%	Molds	Bread, cakes, some cheeses, rope inhibitor in bread dough

Sugar, Salt, Sugar preserving action is determined by the ration between the total sugar quantity in the finished product and the total sugar concentration in the liquid phase. The concentrations of 60% in the finished product assures food preservation The food preserved with sugar; the water activity cannot reduce below 0.845; this value is sufficient for bacteria and neosmophile yeast inhibition, other technique should be employed to prevent mold growth Benzoic acid, the Benzoic acid in the form of its sodium salt, constitutes one of the most common chemical food preservatives. Sodium benzoate is a common preservative in acid or acidified foods such as fruit juices, syrups, jams and jellies, sauerkraut, pickles, preserves, fruit cocktails, etc. Yeasts are inhibited by benzoate than are molds and bacteria Sorbic acid and its salts are practically tasteless and odorless in foods when used at reasonable levels (< 0.3%) and their antimicrobial activity is generally adequate. It is considered nontoxic and is metabolized; among other common food preservatives the WHO has set the highest acceptable daily intake (25 mg/kg body weight) for sorbic acid. Sorbates are used for mold and yeast inhibition in a variety of foods including fruits and vegetables, fruit juices, pickles, sauerkraut, syrups, jellies, jams, preserves, high moisture dehydrated fruits, etc.

Lactic acid, this acid is the main product of many food fermentations; it is formed by microbial degradation of sugars in products such as sauerkraut and pickles. The acid produced in such fermentations decreases the pH to levels unfavorable for the growth of spoilage organisms such as putrefactive anaerobes and butyric-acid-producing bacteria. Yeasts and molds that can grow at such pH levels can be controlled by the inclusion of other preservatives such as sorbate and benzoate.

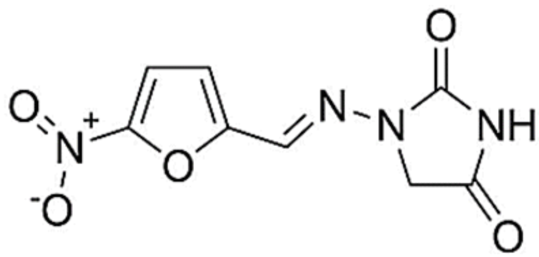
Sulfur dioxide and sulfites, SO2 and sulfites may be added to such foods as dived fruits, fruit pulp and juices, and molasses. They conserve color, act as antioxidants and control microbial growth. Sulfur dioxide and its various sulfites dissolve in water, and at low pH levels yield sulfurous acid, bisulfate and sulfite ions. The various sulfite salts contain 50-68% active sulfur dioxide. A pH-dependent equilibrium is formed in water,and the proportion of SO2 ions increases with decreasing pH values. At pH values, less than 4.0 the antimicrobial activity reaches its maximum Carbon dioxide, In the controlled/ modified environment storage of fruit and vegetables, the correct combination of O2 and CO2 delays respiration and ripening as well as retarding mold and yeast growth. The final result is extended storage of the products for transportation and for consumption during the off-season. The amount of CO2 (5-10%) is determined by factors such as nature of product, variety, climate and extent of storage Nitrates and Nitrites have been used as preservatives for meats for centuries especially in hams, bacon, bologna hotdogs, and sausages.



Their use produces a cured meat flavor and helps stabilize the pink color. Nitrites prevent the growth Clostridium botulinum, micro organisms that secrete a deadly toxin these micro organisms grow in anaerobic condition readily found in the interior of ham or in meat that has been vacuum package. However, it has been found that nitrite can react with amino acids (found in proteins of meat) to form nitrosamines. These compounds have been reported to include livers cancers in animals. **Nitrofurans** are a class of drugs typically used as antibiotics or antimicrobials. The defining structural component is a furan ring with a nitro group. Nitrofurans are synthetic [21] chemotherapeutic agents with a broad antimicrobial spectrum; they are active against both gram-positive and gram-negative bacteria, including *Salmonella and Giardia spp*, trichomonads, amebae, and some coccidial species. However, when compared with other antimicrobial chemotherapeutic agents, their potency is not of particular note. The nitrofurans appear to inhibit several microbial enzyme systems, including those involved in carbohydrate metabolism, and they also block the initiation of translation. However, their basic mechanism of action has not yet been clarified. Their primary action is bacteriostatic, but at high doses they are also bactericidal. They are much more active in acidic environments (pH 5.5 is optimal for nitrofurantoin activity). Resistant mutants are rare, and clinical resistance emerges slowly. Among themselves, nitrofurans show complete cross-resistance, but there is no cross-resistance with any other antibacterial agents.

Nitrofurantoin The mechanism of action of nitrofurantoin is unique. It is reduced by bacterial flavoproteins to reactive intermediates that inhibit bacterial ribosomes and other macromolecules. Protein synthesis, aerobic energy metabolism, DNA and RNA synthesis, and cell wall synthesis are inhibited. Nitrofurantoin is bactericidal in urine at therapeutic doses. Resistance is rare. Nitrofurantoin is used to treat urinary tract infections caused by susceptible bacteria, such as Escherichia coli, Staphylococcus aureus, Streptococcus pyogenes, and Aerobacter aerogenes. Proteus spp, Pseudomonas aeruginosa, and Streptococcus faecalis are usually resistant.

Without a doubt, literatures claim that the sole use of the drug is in the treatment of Urinary Tract Infection (UTI), as after oral or intravenous (i.v.) administration, therapeutically active concentrations are attained only in urine. Nitrofurantoin can be adminsitered i.v. but this is rarely used and and the parenteral preparation is not generally available. Intravenous nitrofurantoin is unsuitable for the treatment of systemic infections of any kind because of poor serum levels.



Following absorption, concentrations of nitrofurantoin in blood and body tissues are low because of rapid elimination and therefore, antibacterial concentrations are not achieved. Nitrofurantoin should not be administered when the possibility of bacteremia exists, as the drug does not achieve therapeutic serum levels when administered orally.

Because of very slight water solubility, the nitrofurans are used either PO or topically. No nitrofuran is effective systemically. They are either not absorbed at all from the GI tract or are so rapidly eliminated that they reach inhibitory concentrations only in the urine. Toxic signs seen with excessive doses of nitrofurans derivatives include CNS involvement (excitement, tremors, convulsions, and peripheral neuritis), GI disturbances, poor weight gain, and depression of spermatogenesis. Various hypersensitivity reactions can also be seen. Some nitrofurans are carcinogenic, and their future use is in doubt. Nitrofurans are among the drugs for which extra-label use is prohibited in food animals in the USA. Antioxidants, Antioxidants are beneficial in preventing rancidity in fats and foods containing fats. Fats exposed to light, moisture, heat or heavy metal ions become activated and oxidize (reach with available oxygen) to peroxides. The most used antioxidants are Butylated Hydroxy Anisole (BHA), Butylated Hydroxy Toluene (BHT), Propyl Gallate, Natural/Synthetic Tocopherols (Vitamin E)

Improving [22] Food Preservation

Most antimicrobials used in food manufacture have been in use for about 50 to 100 years. A few antimicrobials, e.g., sulfites and nitrites, have been in use for an even longer period. Similarly, sanitizing agents, used to reduce microorganisms on processing equipment, have been in use for nearly 100 years. Concern has been recently raised, however, about the potential for target pathogenic microorganisms to develop resistance to these compounds.

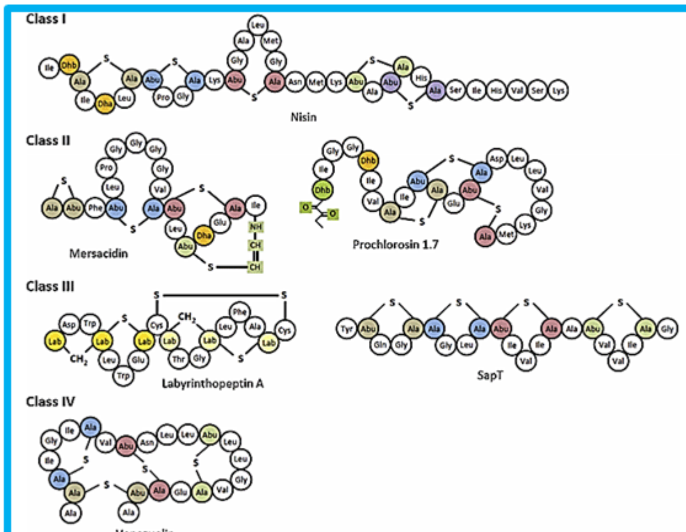


Fig. . Structures of different lanthipeptides. (Me)Lan and labionin rings are highlighted by color and residues contributing to the same thioether amino acids are marked in same color. Didehydro amino acids are designated in orange.

Introduction -Antimicrobial Peptides

In addition to antimicrobial action, AMPs have other less known properties. There are evidences that indicate some AMPs have mitogenic characteristics or are involved in particular signaling pathways as signaling molecules. Some of them have proven role in promotion of adaptive immune response by direct or indirect effects on immune cells. The food situation worldwide will become critical as the vulnerability of modern agriculture to diseases and pests increases. Annually, high amounts of pesticides are used to inhibit the loss of yield imposed by plant diseases and pest insects. However, chemical pesticides cause other problems due to their risks for the environment and consumers' health, mainly because of untimely or excessive use of them. Therefore, in agriculture, there is a common trend to find and exploit elements that present sustainable resistance to a broad range of pests and pathogens and are safe for the host organisms with no side effects for the environment, animals or the people that consume the products. Due to the above-mentioned concerns and expectations, AMPs are suitable candidates to be used in various fields of agriculture. They are ubiquitous in nature, they have high selectivity against target organisms and resistance against them is rarely observed. Food industry depends on chemicals for the preservation of foodstuff and to increase the shelf life of food. The use of chemical preservatives such as nitrites and sulfur dioxide may cause adverse effects on human health and also on the nutrition level of food. Due to the traditional food preservation practices, the safety and standard quality of food are inadequate for the consumers, because of the excess use of chemical preservatives, bacteria have developed resistance [23]. Hence, there is a pressing need to search new natural preservatives for the preservation of food. The major benefit of using antimicrobial peptides is that it preserves the food without changing its quality and it is not harmful [24]. Considering the problem of food-spoilage, food products can be preserved by using microbes and their antimicrobial products as bio-preservatives, which improve the shelf-life of food and enhance the food safety [25]. Alternatively, antimicrobial peptides are also referred to as cationic host defense peptides anionic peptides/proteins [26], cationic antimicrobial peptides, and a-helical antimicrobial peptide [27]. Antimicrobial peptides may be synthesized ribosomally or non-ribosomally.In eukaryotes and prokaryotes, antimicrobial peptides are synthesized in the ribosome, and hence known as ribosomally synthesized peptides. Non-ribosomal peptides are synthesized in the cytosol of fungi or bacteria [28]. For example, lipopeptide is a nonribosomally synthesized peptide, which possesses broad-spectrum activity against multidrug-resistant microorganisms [29]. Regardless of the challenges noted above with developing AMPs for clinical use, the rise of resistant bacteria has prompted the continual search for new AMPs, and this interest has never waned [30]. The purpose of this paper is to describe the newer functional classes of modified AMPs that have the potential to overcome these hurdles and become an important class of available antibiotics. Here we present some of the contemporary strategies proposed to design and engineer AMPs for unique and specific applications. These applications are not all designed solely for preventing or treating microbial infections in humans or animals, but have expanded applications as slow delivery systems, wound dressings, food preservation systems, and coatings for implants, catheters and toys. Even when immobilized or in complex environments, AMPs still retain their antimicrobial activity, which questions earlier work on their mechanisms of action, particularly for AMPs known to form well-structured pores. The descriptions, potential and mechanisms of action of these new groups of modified AMPs have served as the topics of many excellent and recent reviews. The foodborne diseases (FBDs) are one of the most common problems of public health in the contemporary world. Etiological agents cause the FBDs, mainly microorganisms and their toxins through ingestion of contaminated water and food, resulting in disorders to the health and well-being of affected individuals, as well as serious economic consequences for the country. Thus, the microbiological safety of foods is becoming increasingly relevant, and governments around the world are giving great importance in actions to ensure safe food production in response to the increasing number of FBDs [31]. The epidemiological profile of diseases transmitted by food has changed in the last decade due to: expansion of consumer markets; economic globalization; changes in dietary habits; increased consumption of processed or manufactured foods outside the home; intensification of production, which makes the control of FBDs by public health authorities and the intensive rearing of livestock. According to the Ministry of Health in 2013 called mixed food prevailed as the main cause of the occurrence of FBDs. There were eight cases with this type of food, totaling 1,529 outbreaks. This is probably due to the increase of manipulation and transport of food, which offers new doors for bacteriological contamination and the spread and proliferation of bacteria from the slaughter and marketing process. Examples of microorganism that cause Foodborne infections in humans are bacteria of the genus Salmonella which remains a major problem for the poultry industry. Food intake and water containing viable cells of the bacterium is the most common route of infection for the host [32]. Other bacteria frequently involved in human food infections are members of the *genus Listeria spp*. Listeria monocytogenes is the only species of the genus Listeria that is pathogenic to humans. Listeriosis leads the post of diseases associated with foods that cause more deaths and hospitalizations (91%), mainly involving pregnant women, new born and immunocompromised persons [33]. Although listeriosis causes more complications, the main microorganisms responsible for FBDs, between the years 2000-2013, continue to be *Salmonella spp,* Staphylococcus aureus and Escherichia coli [34].

Gallidermin	
Identifiers	
Symbol	Gallidermin
Pfam	PF02052
InterPro	IPR006079
SCOP	1mqy
SUPERFAMILY	1mqy
TCDB	1.C.20
OPM superfamily	170
OPM protein	1mqy
[show]**Available protein structures:**	

Lantibiotics are a class of peptide antibiotics that contain the characteristic polycyclic thioether amino acids lanthionine or methyllanthionine, as well as the unsaturated amino acids dehydroalanine and 2-aminoisobutyric acid. Lanthionine is composed of two alanine residues that are cross linked on their β-carbon atoms by a thioether (monosulfide) linkage. Lantibiotics are produced by a large number of Gram-positive bacteria such as Streptococcus and Streptomyces to attack other Gram-positive bacteria, and as such, they are considered a member of the bacteriocins. Bacteriocins are classified according to their extent of posttranslational modification. The lantibiotics are a class of more extensively modified bacteriocins, also called Class I bacteriocins. (Bacteriocins for which disulfide bonds are the only modification to the peptide are Class II bacteriocins.) Lantibiotics are well studied because of the commercial use of these bacteria in the food industry for making dairy products such as cheese.

Nisin

- Nisin was discovered in 1928 by Rogers and his workgroup.
- *N*isin is a lantibiotic (contains the rare amino acids, meso-lanthionine and 3-methyl-lanthionine instead of cysteine and methionine), it is a bacteriocin.
- Nisin has approved bactericidal effect against most *LAB*; *S. aureus*; *L. monocytogenes*, *Bacillus* and *Clostridium* vegetative forms.
- Nisin ihibits synthesis of peptidoglycan: Inhibition of cell wall synthesis

Nisin – E234

Nisaplin (Danisco)

GRAS status

1969 WHO and FDA

1983 EU

1988 US Food and Drug Agency

- The first food use of nisin was by Hurst to prevent the spoilage of Swiss cheese by *Clostridium butyricum.*
- *Most* widely used compound for food preservation, with around 50 countries.
- Approved in 1988 for food use in the United States.
- The compound is effective against gram-positive bacteria, primarily spore formers, and is ineffective against fungi and gram-negative bacteria.
- Among some of its desirable properties as a food preservative are the following:
  - It is nontoxic.
  - It is produced naturally by *Lactococcus lactis strains.*
  - It is heat stable and has excellent storage stability.
  - It is destroyed by digestive enzymes.
- Nisin as a heat adjunct in canned foods or as an inhibitor of heat-shocked spores of *Bacillus* and *Clostridium strains.* Nisin, however, is used most widely in cheeses.
- Usable levels are in the range of about 2.5-100 ppm.
- Nisin is most often employed in dairy products—processed cheeses, condensed milk, pasteurized milk, and so on. Some countries permit its use in processed tomato products and canned fruits and vegetables. It is most stable

NISIN (ref. [14])

Milk and dairy products are largely consumed by humans worldwide because they are considered as balanced and nutritive foods (Pereira 2014), but if consumed unpasteurized, they pose risks to human health as they could be contaminated by food-associated pathogenic bacteria, such as Listeria monocytogenes and *Staphylococcus aureus*, among others (Zhao et al. m 2014). L. monocytogenes is the aetiological agent of a disease called listeriosis with associated high mortality (Freitag et al. 2009). Therefore, a zero tolerance policy is implemented in many countries concerning L. monocytogenes presence in food (Iseppiet al. 2008). On the other hand, *Staph. aureus* strains can produce enterotoxins (SE) or enterotoxin-like toxins (Sel) which cause food poisoning (Otto 2014). Nisin and epidermin are members of a family of lantibiotics that bind to lipid II, a cell wall precursor lipid component of target bacteria and disrupt cell wall production. The duramycin family of lantibiotics binds phosphoethanolamine in the membranes of its target cells and seem to disrupt several physiological functions. In general, lantibiotics, the mostly used is NISIN in the food industry [35], exhibit activity against Gram-positive bacteria. Due to its naturally selective spectrum of activity, it is also employed as a selective agent in microbiological media for the isolation of gram-negative bacteria, yeast, and molds. Only a few naturally occurring antimicrobials, such as Nisin, natamycin, lactoferrin and lysozyme, have regulatory approval for application to foods. The Nisin molecule is acidic in nature and exhibits greatest stability under acid, conditions. In the pH range 3 to 7, the nisin molecule becomes increasingly more vulnerable to the effect of heat with the rise in pH value Nisin has proved to be a most effective preservative in processed cheese and processed cheese spreads. The fact that nisin is produced by lactic streptococci which occur naturally in raw milk supplies is an indication of its harmless nature by virtue of its intake by humans and animals over past centuries. Nisin producing streptococci (*LactococcusLudacris*) are abundantly present in nature. This was shown by a worldwide survey of raw milk samples carried out by Aplin and Barrett (unpublished).

Figure 2. Covalent structure of some representative peptide-bacteriocins. A: nisin, B: microcin B17, C: pediocin PA-1, D patellamide A.

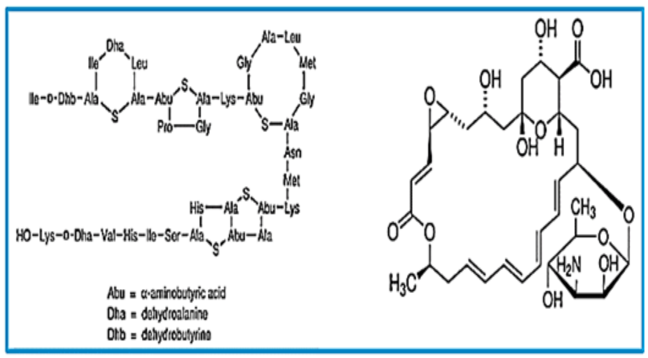


Figure : nisin and natamycin

Only a few naturally occurring antimicrobials, such as the mostly applied antibiotic agent (bacteriocins) from natural source, nisin for example, the macrolide-glycoside natamycin, and the protein lactoferrin and the enzyme lysozyme, have regulatory approval for application to foods. Many additional antimicrobials, especially those derived from microorganisms, hold the potential for regulatory approval in the future [36] .The bacteriocins [37], a class of AMPs, are being employed in bio preservation of food with the aim of controlling the growth of pathogenic and spoilage microorganisms. For this reason, there is growing interest in the food industry for the potential use thereof. Being described as a natural preservative, its use in food is very promising, since the chemical additives have been seen as villains in the food industry, because of poisoning risks that constant intake of these substances can cause. Also, chemical preservatives, has reduced its inhibitory action due to the continuous emergence of multidrug-resistant microbial strains and are potentially toxic to the human body [38]. Despite a variety of compounds as subtilin, cerein, turicina, plantaricin, pediocin, among others, nisin is the only one so far that has FDA GRAS status (United States) [39]. The use of AMPs as an alternative to conventional agents to combat microorganisms of interest for human and animal health has been an interesting alternative. In the unseen world of microbes, the search for nutrients and overpopulation formed by different bodies, leads to several strategies to ensure the survival of a species and its dominion over others. Thus, it is of vital importance, the search for substances that exhibit antimicrobial activity and, above all, that carry through alternative mechanisms of action available to the chemical preservatives. Bacteriocins are synthesized in ribosome of most bacteria that have the ability to eliminate bacteria closely related [40]. They have various chemical structures and their role in innate immunity is essential. These are usually composed of small peptides (3-10 kD), and are inactivated by proteolytic enzymes. It is also known that in a single bacterium, various peptides with these characteristics can be produced. The study of bacteriocins began in 1925 with the discovery of colicins produced by Escherichia coli [41]. Because of their potential application as a natural preservative, a large number of substances have been identified and characterized, particularly those produced by lactic acid bacteria [42]. There is great interest in the study of these peptides due to its therapeutic potential as antimicrobial and antitumor agents. Because of natural production of bacteriocins by lactic bacteria in fermented foods the addition of antimicrobial peptides as food additives will be more easily accepted by health authorities and consumers. GÁLVEZ et al. [43] emphasize that the bacteriocin can be used in the development of bioactive food packaging. Moreover, GÁLVEZ et al. [22] emphasized that many bacteriocins showed synergistic effects in combination with other antimicrobial agents, including chemical preservatives, natural phenolic compounds and other antimicrobial proteins, which is relevant when microbial resistance is emphasized. Consequently, the possibility of application of these antimicrobial peptides becomes of great interest to the scientific community, because they are considered safe for either human animal health [44]. The activity of bacteriocins varies according to the bacterial species and the environment, in which they are being divided into different classifications [45,46]. Only a few naturally occurring antimicrobials, such as the mostly applied antibiotic agent (bacteriocins) from a natural source, nisin, for example, the macrolide-glycoside natamycin, and the protein lactoferrin and the enzyme lysozyme, have regulatory approval for application to foods. Many additional antimicrobials, especially those derived from microorganisms; hold the potential for regulatory approval in the future. Antibiotics could be medical and nonmedical. Nonmedical antibiotics, such as natamycin and nisin, produced either by microbes or synthetically, inhibit microbes at very low concentration. Organisms present in food can become resistant to antibiotics and colonize the gut of animals and man. Antibiotics used therapeutically may then become ineffective. Also, antibiotics are used in growth enhancement and disease control in healthy animals. However, the increasing incidence of antibiotic resistance is of great concern and is becoming a complicated issue [47]. Accumulating evidence [48] suggests that bacteriocin production represents a probiotic trait for intestinal strains to promote dominance, fight infection, and even signal the immune system. Purified nisin H inhibits a wide range of Gram-positive bacteria, including staphylococci, streptococci, Listeria spp., bacilli, and enterococci. It represents the first example of a natural nisin variant produced by an intestinal isolate of streptococcal origin.

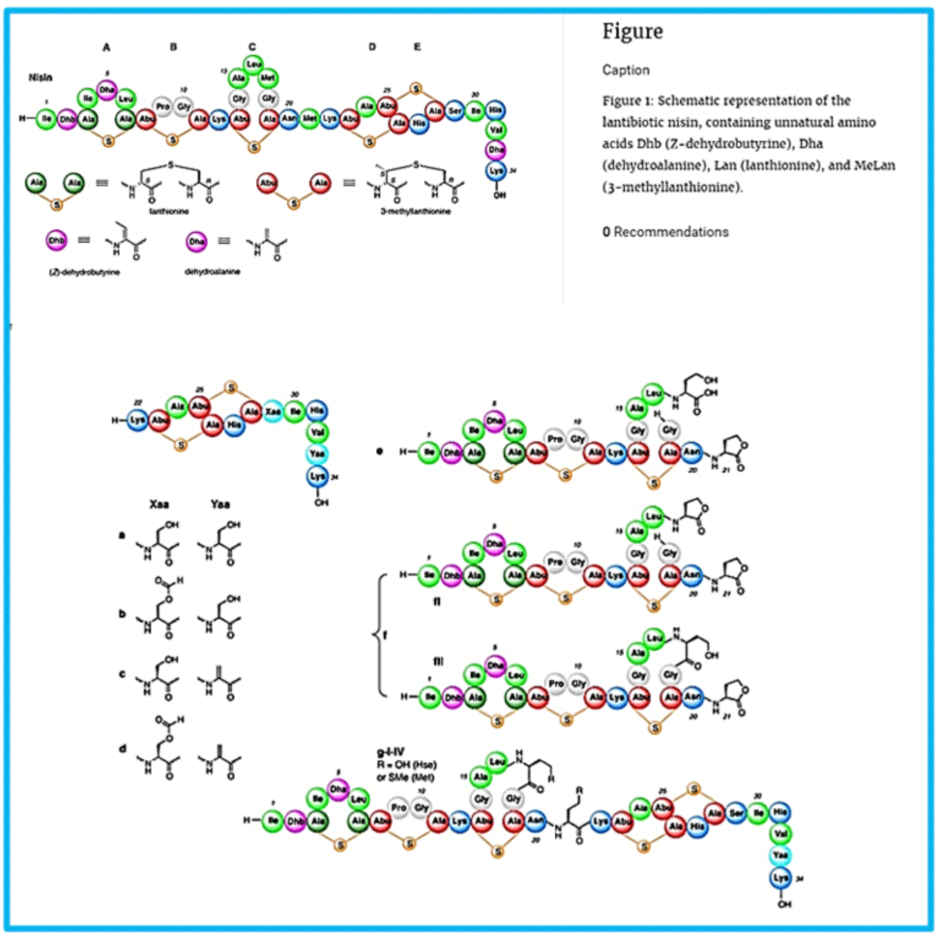
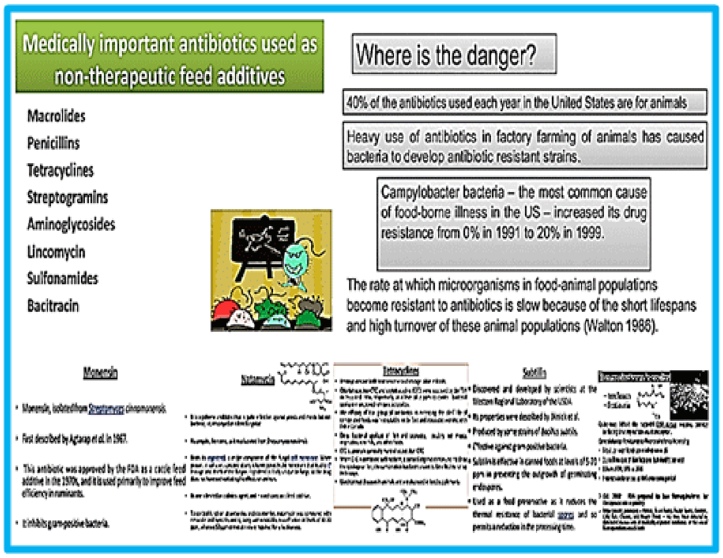
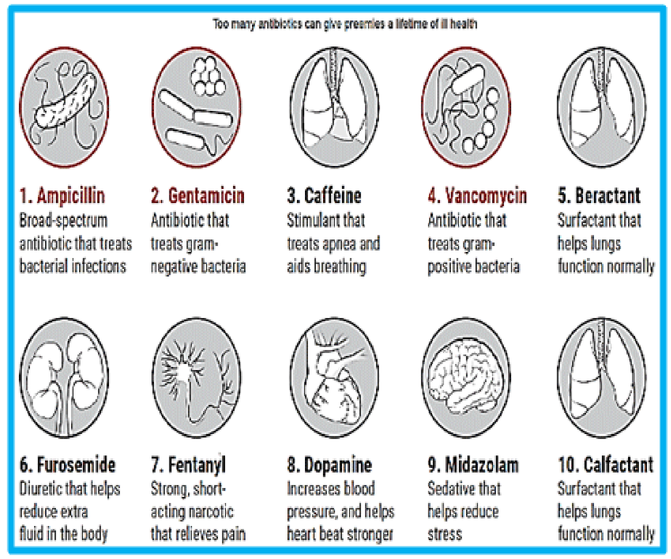


Figure 1: Schematic representation of the lantibiotic nisin, containing unnatural amino acids Dhb (Z-dehydrobutyrine), Dha (dehydroalanine), Lan (lanthionine), and MeLan (3-methyllanthionine).

Nisin H peptides of different size were isolated and purified and were tested for their antibacterial activities. Many fragments of molecular weight below 100 were shown to be antibacterial offering low molecular weight polypeptides for considerations regarding the design and synthesis of such analogs to the higher molecular weight nisin as antimicrobial conservation chemicals [49]. Biopreservation systems in foods are of increasing interest for industry and consumers. Bacteriocinogenic lactic acid bacteria and/or their isolated bacteriocins are considered safe additives (GRAS), useful to control the frequent development of pathogens and spoiling microorganisms in foods and feed. The spreading of bacterial antibiotic resistance and the demand for products with fewer chemicals create the necessity of exploring new alternatives, in order to reduce the abusive use of therapeutic antibiotics. In this context, bacteriocins are indicated to prevent the growth of undesirable bacteria in a food-grade and more natural way, which is convenient for health and accepted by the community. According to their properties, structure, molecular weight (MW), and antimicrobial spectrum, bacteriocins are classified in three different groups: lantibiotics and non-lantibiotics of low MW, and those of higher MW. Several strategies for isolation and purification of bacteriocins from complex cultivation broths to final products were described. Biotechnological procedures including salting-out, solvent extraction, ultra filtration, adsorption desortion, ion-exchange, and size exclusion chromatography are among the most usual methods. Peptide structure-function studies of bacteriocins and bacterial genetic advances will help to understand the molecular basis of their specificity and mode of action. Nisin is a good example of commercial success, and a good perspective is open to continue the study and development of new bacteriocins and their biotechnological applications. These substances in appropriate concentrations may be used in veterinary medicine and as animal growth promoter instead usual antibiotics, as well as an additional hurdle factor for increasing the shelf life of minimal processed foods. Lactic Acid Bacteria The addition of living cultures of lactic acid bacteria is used to control pathogen growth in fish. L. monocytogenes is difficult to control in lightly salted (6% NaCl in aqueous phase) fish products, pH 5, and storage temperature ~5°C. Wessels and Huss [64] noted that L. monocytogenes in lightly preserved fish products can be controlled using food-grade lactic bacteria. The effect was not due to lactic acid inhibition, but because of the production of the natural preservative nisin by the lactic acid bacteria. Sodium Postharvest Handling and Preservation of Fresh Fish and Seafood 167 TABLE 6.9 Approximate Shelf Life of Selected Types of Raw Fish at Different Temperatures Fish Temperature (°C) Shelf Life (Days) [50] Cod 0 16 57 10 4 16 1 Herring 0 10 54 Salmon 0 2 10 5 Plaice 0 18 10 8 Meat Concern on the toxicological safety of nitrite in cured meat has led various workers to consider alternative preservative systems, and these have incuded nisin (Taylor et al, 1985; Taylor & Somers, 1985; Caldcroner al, 1985). Results have been vaned and indicate further work is required before a case can be proposed for its use as a partial replacement for nitrite. Reasons proposed for poor preservative effect include the binding of nisin onto meat pe rticles and surfaces, uneven distribution, poor solubility in meat systems and possible interference with the mode of action l'rom phospholipids (Henning etal, 1986a).Red meat [51] has a limited shelf-life at refrigerated temperatures, where spoilage is mainly due to the proliferation of bacteria, yeast and moulds, acquired during the dressing process. In addition, almost a fifth of food-borne disease outbreaks, caused by microorganisms such as Escherichia coli 0157:H7, Listeria monocytogenes and Staphylococcus aureus are associated with red meat. To improve the microbiological quality of red meat, systems such as HACCP, GHP and GMP are currently practiced; however, these practices are not able to extend the shelf-life of these products. At present suitable food-grade preservatives are recommended, but the use of some of these preservatives is increasingly being questioned with regard to their impact on human health. Additionally, food service customers demand high quality products that have a relatively long shelf-life, but still prefer the appearance of minimally processed food. All these factors challenge the food manufacturing industry to consider more natural means of preservation. Antimicrobial metabolites of food grade bacteria, especially lactic acid bacteria, are attracting increasing attention as food preservatives. Bacteriocins are antimicrobial peptides (3 to 10 kDa) with variable activity spectra, mode of action, molecular weight, genetic origin and biochemical properties that are bacteriostatic or bactericidal to bacteria closely related and bacteria confined within the same ecological niche. Micro-organisms were isolated from beef, lamb and pork, obtained from four commercial retailers. The number of viable cells three days after the sell-by date at 4°C ranged from 80 cfu.g-1 to 1.4 × 108 cfu.g-1. Fifty-three percent were Gram-negative bacteria, 35% Gram-positive and 12% yeast. The microbial population of the meat was greatly influenced by the origin, i.e. the retailer. Bacteriocins produced by *Enterococcus faecalis* BFE 1071, *Lactobacillus curvatus* DF 38, Lb. plantarum 423, Lb. casei LHS, Lb. salivarius 241 and *Pediococcus pentosaceus* ATCC 43201 were screened for activity against bacteria isolated from the different meat samples. Sixteen to 21% of the isolates, identified as members of *Klebsiella, Shigella, Staphylococcus, Lactobacillus, Lactococcus, Leuconostoc, Enterococcus, Pediococcus, Streptococcus and Bacillus* were sensitive to the bacteriocins.

Veterinary antibiotic and drugs [52] used in food production





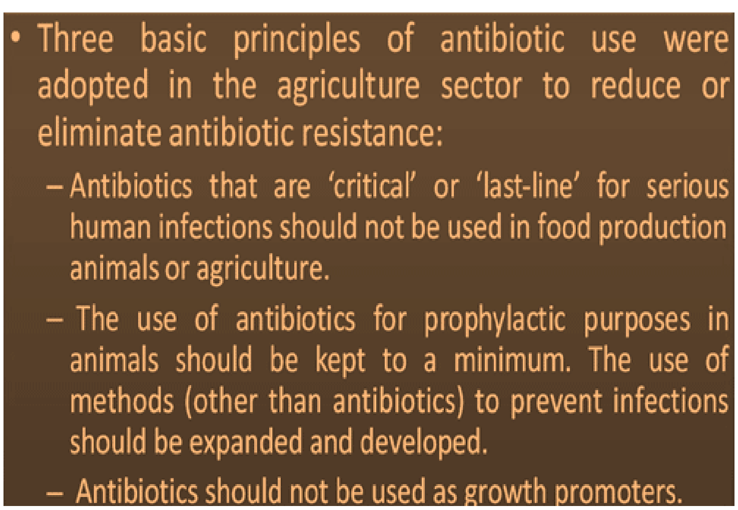
Consequences of Agricultural Antibiotic Use - Microbial Resistance

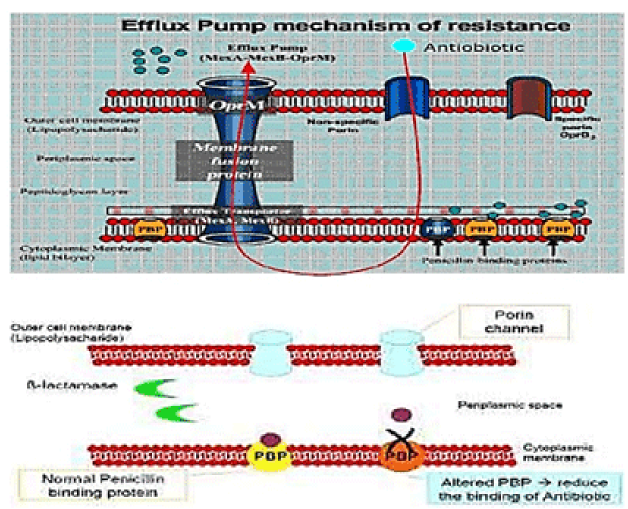
a. Campylobacter fluoroquinolines resistance

b. VREF (Vancomycin-resistant Enterococcus faecium, an antibiotic-resistant microorganism due to avoparcinuse in chickens)

c. MRSA in pork, chickens

d. Gentamycin-and Cipro-resistant E. coli in chickens





Drawbacks - Antibiotic Uses in Food

RESISTANCE TO ANTIBIOTIC DRUGS

- Use of drugs in food animals - Microorganisms can mutate to develop or acquire resistance to antibiotic drugs.
- Is the microorganism zoonotic; that is, can it cause a human disease by moving from the animal to a human, more virulent, treatable with other antibiotics?
- Passage of antibiotic-resistant bacteria from animals to humans occurs from
  - direct contact with animals or their manure,
  - through indirect exposure to food contaminated with animal-derived bacteria,
  - from person-to-person contact after a primary exposure of nonfarm persons.
- The resistance of microorganisms arising from subtherapeutic use of penicillin, tetracyclines, and sulfa drugs in agriculture is suggested by WHO (WHO 1997) to be a high- priority issue.
- World Health Organization in 1997- "The use of any antimicrobial agent for growth promotion in animals should be terminated if it is used in human therapeutics or known to select for cross-resistance to antimicrobials used in human medicine."
- *zoonotic pathogens:*
  - *Salmonella* DT-104 and
  - *Campylobacter jejuni*

- **Vancomycin and Ciprofloxacin resistance is linked to antibiotic use in animals.**
- In Europe there is strong evidence that one type of the vancomycin-resistant enterococci (VRE - vanA) developed in animals fed an antibiotic called avoparcin (a glycopeptide or vancomycin-like antibiotic).
- Vancomycin-resistance genes can spread from VRE to bacteria that are much more common and aggressive such as the multi-resistant strains of *Staphylococcus aureus (MRSA)*.
- Use of enrofloxacin has resulted in the development of ciprofloxacin-resistant strains of *Salmonella spp and Campylobacter spp. These resistant bacteria* have subsequently caused human infections.
- When the glycopeptide, avoparcin, was used as a growth promoter in food animals in Europe this resulted in the development and amplification of vancomycin resistant enterococcus (VRE) and subsequent colonisation by a significant percentage of the human population via the food chain (between 2 and 17%).

Antibiotic-Resistant Bacteria Have Been Transferred from Animals to Humans (statistical data)

- Epidemiologic studies suggest transference of antibiotic-resistant *E. coli* and campylobacter bacteria
- Examples:
  - Chickens on farm fed tetracycline-supplemented feed and within 2 weeks 90% were excreting all tetracycline-resistant *E. coli*. Within 6 months, 7 of 11 people living on or near farm were excreting high numbers of resistant *E coli*.
  - Percentage of *Campylobacter jejuni* resistant to quinolone in human isolates increased from 0.8% in 1996 to ~3% in 1998. FDA approved the use of fluoroquinolones in 1995.
- Epidemiologic studies with molecular subtyping show transference of antibiotic-resistant campylobacter and salmonella bacteria
  - Fluoroquinolone-resistant *Campylobacter jejuni* was isolated from 14% of 91 chicken products obtained from retail markets in 1997.
  - In 1998, salmonella bacteria resistant to ceftriaxone were isolated from a 12-year-old boy who lived on a cattle farm.

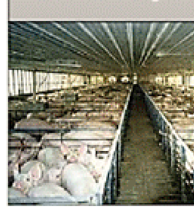
- Enrofloxacin is administered to flocks of poultry through their water to control mortality from *E. coli* and *Pasteurella multocida* organisms
- New evidence that enrofloxacin use in poultry has not been shown safe for humans
  - FDA determined that the use of enrofloxacin in poultry causes the development of a fluoroquinolone-resistant strain of campylobacter in poultry, which, when transferred to humans, is a significant cause of fluoroquinolone-resistant campylobacter infections in humans

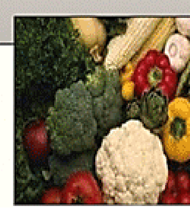
The use of antibiotics in livestock production for increased feed efficiency is widespread. Such use may indirectly access human food in the form of residuals in products such as meat and milk. For years, scientists and health officials have warned of the risk of developing resistant pathogens from feeding antibiotics to livestock. Recently, this concern was fueled by a fatal case of salmonellosis caused by an antibiotic resistant strain linked to meat.

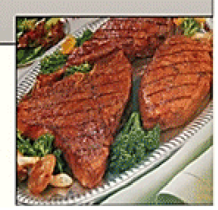
- Use of antibiotics in the treatment of mastitis has created problems for the milk processor and consumer. Following treatment of mastitis with antibiotics, they may be found in the milk in sufficient concentrations to inhibit dairy starter microorganisms and cause economic losses to the cheese and fermented milk industries.
- Penicillin in very small concentrations found in milk may cause reactions in highly sensitive individuals.
- When antibiotics are used to treat mastitis, dairymen should follow the prescribed recommendations for withholding milk for human use following treatment.
- When adulterated milk leaves the farm, it is subjected to various processes in the milk plant. Antibiotics in milk are relatively stable to pasteurization temperatures and above, as well as to low temperatures (0–10° F.). Under refrigeration temperatures up to seven days of storage, in raw and pasteurized milk there tends to be a loss in antibiotic activity.
- The presence of antibiotics in milk constitutes an adulteration under the Federal Food, Drug and Cosmetic Act.

Findings on antibiotic resistance for food animals are as follows:

- Increases the risk of emergence of microorganisms that are resistant to specific, and perhaps other, antibiotics.
- Resistance emergence should be classified with regard to each antibiotic used, the concentration and dosage administered, the blood and tissue concentrations attained, the bacterial species or strain affected, and the animal species in which the drug is used.
- Zoonotic spread of pathogens to humans is very low. Postfarm food processing, storage, and improper handling and cooking are major contributors to the chain of events that allows the pathogen to contaminate the product, proliferate on or in the food, and attain the large numbers that cause disease.

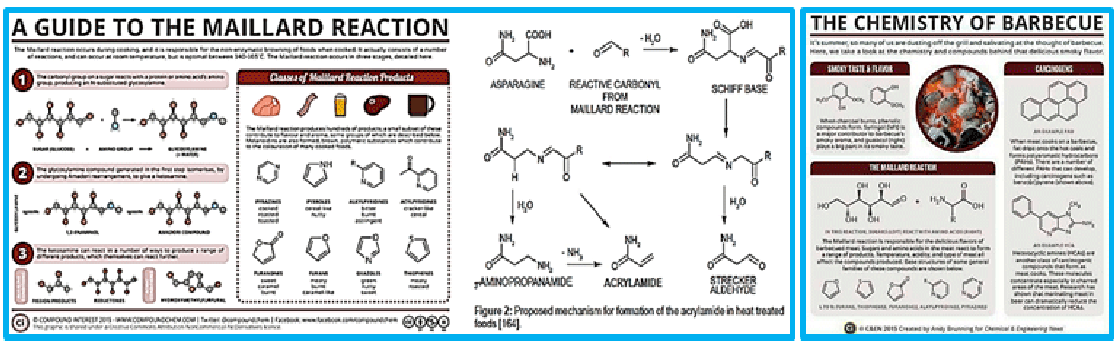






Preserving Food at Home

Involves cooking food, sealing it in sterilized cans or jars, and boiling the containers to kill or weaken any remaining bacteria as a form of sterilization. It was invented by the French confectioner Nicolas Appert. By 1806, this process was used by the French Navy to preserve meat, fruit, vegetables, and even milk. Although Appert had discovered a new way of preservation, it wasn't understood until 1864 when Louis Pasteur found the relationship between microorganisms, food spoilage, and illness. Food Browning (Roasting, Grilling, Baking): Acryl amide or 2-propenamide an industrial chemical formed in some foods particularly starchy foods during heating process such as baking, frying and roasting. The major limiting factors responsible for the formation of acryl amide in potato and cereal products are reducing sugars (glucose and fructose) and free asparagines (amino acids) respectively. For commercial production of potato products, select cultivars with low levels of reducing sugars taking into account seasonal and regional variability for high temperature processes such as frying and baking. Acryl amide is proven to be carcinogenic in animals and a probable human carcinogen mainly formed in foods by the reaction of asparagines (free amino acid) with reducing sugars (glucose and fructose) as part of the Maillard reaction during heating under high temperature and low moisture conditions. The main aim of this review is to summarize the results of academic and industrial research on occurrence, dietary exposure, formation mechanism and mitigation measures of acrylamide in bakery, cereal and potato food products [53].



Carcinogenic Chemicals Formed In Food On High Temperature Cooking (Grill, Baking, Roasting...)

Foods have varying degrees of natural protection against spoilage and may require that the final step occur in a pressure cooker. High-acid fruits like strawberries require no preservatives to can and only a short boiling cycle, whereas marginal vegetables such as carrots require longer boiling and addition of other acidic elements. Low-acid foods, such as vegetables and meats, require pressure canning. Food preserved by canning or bottling is at immediate risk of spoilage once the can or bottle has been opened. Lack of quality control in the canning process may allow ingress of water or micro-organisms. Most such failures are rapidly detected as decomposition within the can causes gas production and the can will swell or burst. However, there have been examples of poor manufacture (under processing) and poor hygiene allowing contamination of canned food by the obligate anaerobe Clostridium botulinum, which produces an acute toxin within the food, leading to severe illness or death. This organism produces no gas or obvious taste and remains undetected by taste or smell. Its toxin is denatured by cooking, however. Cooked mushrooms, handled poorly and then canned, can support the growth of Staphylococcus aureus, which produces a toxin that is not destroyed by canning or subsequent reheating. A pressure canner is essential for canning low acid foods such as vegetables, meats, ash, and poultry. Temperatures inside pressure canners reach higher than boiling water canners (for example, 240°F and above as compared to about 212°F). This is necessary to follow the tested processes available to be sure and kill the toxin–producing spores of the bacteria Clostridium botulinum. If not killed, these spores can grow out and produce a deadly toxin (poison) in room-temperature stored jars of the low-acid foods mentioned.

Growing your own? You may be lucky enough to have previously started keeping garden records so you remember the name of that great tomato or pepper variety you have liked this past year. If not, think about planning to keep records this year. A garden journal might include variety, seed source, date planted, date harvested, notes on how it grew and resisted disease, and your personal evaluation of the crop. m A final must is reliable, up-to-date canning and other food preservation instructions. Specific kitchen equipment or ingredients could be needed to follow directions as they are written for food preservation. And in the case of canning especially, very significant food safety risks by following unsound recommendations. Reliable, up-to-date canning instructions are available at the NCHFP website, the USDA Complete Guide to Home Canning, So Easy to Preserve, or the county or.

Clostridium and Listeria [54]

These micro-organisms belong to groups of bacteria that can be major health hazards through contamination of food. C. sporogenes is a non-toxic analogue of C. botulinum (which causes botulism) and C. perfringens. Whereas the principal hazard from clostridia is the toxins that are produced in the food, Listeria monocytogenes causes an infection, listeriosis.

Clostridia

Clostridia are strictly anaerobic (except for a few aerotolerant species), proteolytic catalase-negative rod-shaped organisms, which produce heat-resistant spores [56]. The primary source of clostridia is soil. Some are free-living nitrogen-¢xing organisms, such as C. pasteurianum; others, such as C. acetobutylicum, are used to produce commercial chemicals such as butyric acid, butanol, acetone and enzymes. Other clostridia cause serious infections such as tetanus and gas gangrene.

Botulinum

Botulinum neurotoxins (BoNT) are the most toxic substances known, with a lethal dose (LD50) value of B1ngkg Seven distinct serotypes of BoNTs (A-G) exist. Because of their extreme toxicity, they are one of the top potential bioterrorism agents. However, members of the BoNTs (BoNT/A and B) are also extensively used therapeutically to treat numerous medical conditions, such as cervical dystonia, cerebral palsy, strabismus, hemifacial spasm and myofascial pain, as well as for cosmetic purposes [55].

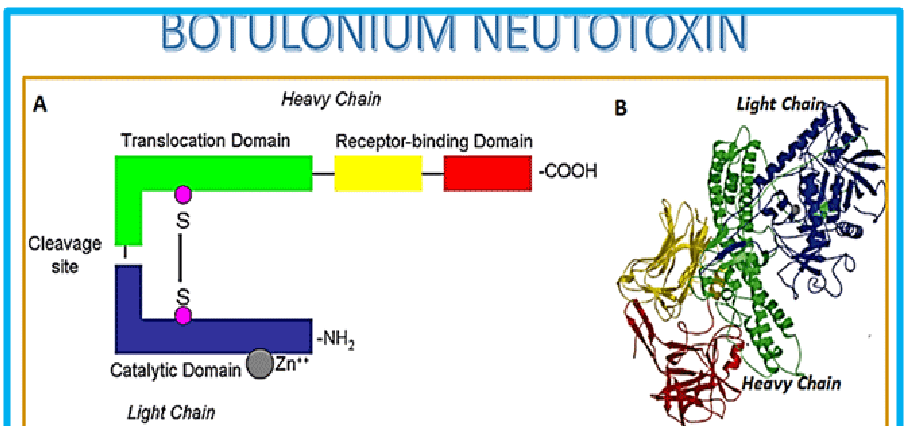


Figure : Botulinum toxin structure A) schematic representation of BoNT, B) Crystal structure of BoNT/A - PDBcode:3BTA. Figure B - taken from [1]. The Light chain catalytic domain is coloured in blue. The heavy chain translocation domain is coloured in green, N-terminal and the C-terminal receptor binding domains are coloured in yellow and red respectively. The catalytic zinc is represented as a ball in gray. The colour code is same for Figures 1A and 1B.

The toxin produced by C. botulinum is described as the most poisonous and deadliest substance known to science. It's earned the status of a Select Agent, which means serious criminal prosecution for anyone violating the strict federal guidelines on obtaining, handing, and documenting it [3]. As previously mentioned, a single gram of the crystalline toxin would kill over a million people if evenly dispersed and inhaled and 8.3 million people if split into injections. For a 70 kg human, the lethal dose of the crystalline toxin is estimated to be 0.09-0.15 µg intravenously, 0.7-0.9 µg through inhalation, and 70 µg orally (1 microgram (µg) = 0.000001 grams (g); in other words, very tiny amounts will kill you). It is tasteless, odorless, and colorless. Luckily, the toxin cannot penetrate human skin and it is easily destroyed; heating it to 85°C (185°F) will detoxify it and it will inactivate 2 days after being aerosolized. The deadly naturally occurring neurotoxin, Botulinum neurotoxin (BoNT) produced by an anaerobic and spore forming bacterium Clostridium botulinum (and rarely by other Clostridium species such as C. butyricum, C. baratii and C. argentinense), induces a potentially fatal paralysis known as botulism. Botulism is characterized by symmetric, descending, flaccid paralysis of motor and autonomic nerves, usually beginning with the cranial nerves. Blurred vision, dysphagia, and dysarthria are common initial complaints. C. botulinum produces seven antigenically and serologically distint but structurally similar toxins (A to G) that are found in soil and ocean sediment. Human botulism is mainly caused by types A, B, E and F. Types C, D and G cause toxicity in birds, horses, cattle and primates. BoNT enters through 1) Ingestion of preformed toxin, 2) Inhalation of preformed toxin, 3) Local production of toxin by C botulinum organisms in the gastrointestinal tract, 4) Local production of toxin by C botulinum organisms in devitalized tissue at the site of a wound.

Tetanus

Tetanus [56], also called lockjaw, is a serious illness caused by tetanospasmin, a powerful nerve toxin produced by Clostridium tetani. The bacterium Clostridium tetani is an organism capable of living many years in the soil as a spore. Tetanus occurs when a wound becomes contaminated with bacterial spores. Infection follows when spores become active, multiply, and produce a very powerful poison that affects the muscles. Tetanus spores are found throughout the environment, usually in soil, dust, and animal waste (such as manure). Clostridium may enter the body through a deep cut, such as cuts acquired when stepping on a nail, from splinters, insect bites, burns, injection-drug sites, or puncturing the skin with a sharp object. Deep wounds or those with devitalized (dead) tissue are particularly prone to tetanus infection. Tetanus is not transmitted from person to person. An individual usually becomes infected with tetanus when dirt enters a wound or cut. The infection causes a painful tightening of the muscles, usually all over the body. It can lead to "locking" of the jaw, which makes it impossible to open the mouth or swallow. If this occurs, the individual may suffocate. Due to symptoms, tetanus is frequently a fatal infectious disease. If an individual gets tetanus, there is usually a long course of treatment. Drugs that increase immunity to fight infection and decrease muscle spasms are used. Tetanus is curable but depending on the severity and number of symptoms up to 50% of individuals with tetanus may die. The tetanus vaccine is effective, but its protection does not last forever. Adults should get a tetanus shot, or booster, every ten years. There are four types of tetanus: generalized, local, cephalic, and neonatal. In generalized tetanus, all skeletal muscles can be affected. Generalized tetanus is the most common, as well as the most severe form of tetanus. Death is usually due to respiratory failure or disturbance of heart rhythm. Local tetanus causes muscle spasms at or near the wound that has been infected with the bacteria. Cephalic tetanus primarily affects one or more muscles in the face. No muscles elsewhere are involved, unless the disease progresses to generalized tetanus. Neonatal tetanus is a common and serious tetanus infection found in newborn babies. Most infants who get the disease die. Neonatal tetanus is particularly common in rural areas where most deliveries are at home without adequate sterile procedures. In 2000, WHO estimates that neonatal tetanus killed about 200,000 infants. Before World War II, when the vaccine came into widespread use, about 600 cases of tetanus and 180 deaths were reported annually in the United States. Now there are about 70 cases per year and 15 deaths, most of them in elderly adults. Overall, the mortality rate is approximately 45%.

Handling of Foods

Food Trash

Between 33-50% of all food produced globally is never eaten, and the value of this wasted food is worth over $1 trillion. To put that in perspective, in the USA food waste represents 1.3% of the total GDP. Food waste is a massive market indecency, the kind of which does not persist in other industries. Microscopic bacteria cause food to spoil. These tiny organisms, called spoilage bacteria, consume unprotected foods and produce waste products. As long as nutrition and water are present, bacteria will multiply, sometimes rapidly. Bacterial waste is the cause of the foul smell and rotten appearance of spoiled food. Surprisingly, rotten food will not necessarily cause illness if consumed. Instead, other bacteria species called pathogenic bacteria are the cause of foodborne illnesses like salmonella and E. coli. It's possible for food to look and smell safe, but still contain dangerous levels of pathogenic bacteria. Keep your food fresh! So Yummy - 7 Super easy ways to keep your food fresher [57].

Refrigeration and Freezing

Refrigerators set below 40 F will prevent pathogenic bacteria from growing freely. However, refrigerators generally aren't cold enough to stop all bacterial growth. Monitor foods for signs of spoilage, especially meats. Freezers are ideal for long-term storage. To properly store foods in the freezer, remove as much air as possible from the container. Ensure that the temperature is set at or below 0 F. If you experience a power outage, leave refrigerator and freezer doors closed. An external thermometer will let you keep tabs on the fridge or freezer temperatures without opening the doors.

Dehydration

Bacteria need moisture, oxygen and the proper temperature range in order to multiply. Dehydration is the process of removing moisture from foods, thereby slowing or stopping the growth of spoilage bacteria. To dehydrate food properly, you need low humidity and a source of heat. You can use a conventional oven set to warm with the door open or an actual food dehydrator. The food needs to be heated to about 140 F. Dry, circulating air helps draw moisture out of the food. Dehydration also makes foods lighter, smaller and easier to store and transport.

Canning

You can preserve high-acid foods using a traditional process called canning. Apples, berries, peaches and tomatoes are just a few foods that may be canned safely. Boiling water kills spoilage bacteria and creates a vacuum seal around the jar lid. Canned food items must be cooked for a minimum amount of time to ensure that all bacteria are killed. Botulism, a deadly bacterial toxin, grows quickly in canned goods that have been improperly processed. The Virginia Cooperative Extension Office recommends closed-kettle boiling with heat-tempered jars and lids. Food waste is really, bad for the environment. It takes a land mass larger than China to grow the food each year that is ultimately never eaten land that has been deforested, species that have been driven to extinction, indigenous populations that have been moved, soil that has been degraded – all to produce food that we then just throw away. In addition, food that is never eaten accounts for 25% of all fresh water consumption globally. In the United States, 40 percent of edible food is wasted about 1,200 calories per person every single day [58]. Not only do we waste more than the global average, but the amount of food we waste has tripled over the past 50 years, increasing at a faster rate than our population. Every year $218 billion worth of food in the United States is simply thrown away, at a steep cost to wildlife, the environment and the 1 in 7 Americans who don't get enough to eat. Agriculture is responsible for enormous amounts of habitat loss, greenhouse gas emissions, water use and pollution, making it one of the biggest threats to biodiversity worldwide. When food is wasted, so are the natural resources and wildlife sacrificed to our food system and we waste a lot of food. Although food is the growing nutrition problem for the living on this earth, only France has taken a stand against the enormous amount of food wastage and is the first country to pass this great law on supermarket food [59]. Trashed food can nourish millions, provides a safe method of preservation is available.

Food waste

The World Food Program said the crisis put a heavy burden on the world's 1 billion very poor, who spend between 50 and 70 percent of their income on food. Some said the crisis increased the number of worlds's poorest poor from 1 billion to 2 billion. In developing countries food was scarce then it was available but too expensive for most people to buy. The cost of a 50 percent price rise on basic food stuffs can be devastating to the very poor, who often live on $1 or $2 a day. A doubling or tripling of prices can be catastrophic. Plastic-wrap produce such as cucumbers and bananas now often come wrapped in plastic at the grocery store. It's not a thoughtless ploy to create more garbage, industry experts say. The plastic keeps fruits and veggies from ripening too quickly by slowing the intake of oxygen and the release of ethylene gas, says Gina Jones, vice president of research and development at the Produce Marketing Association. So, seek out these plastic-swaddled items, especially if you don't plan to use the produce for a while. Leave food in its packaging [5c,60] and rewrap it if you have leftovers after opening. Often the plastic is recyclable, too, if not in curbside collection than with plastic recycling collection some grocery chains offer.

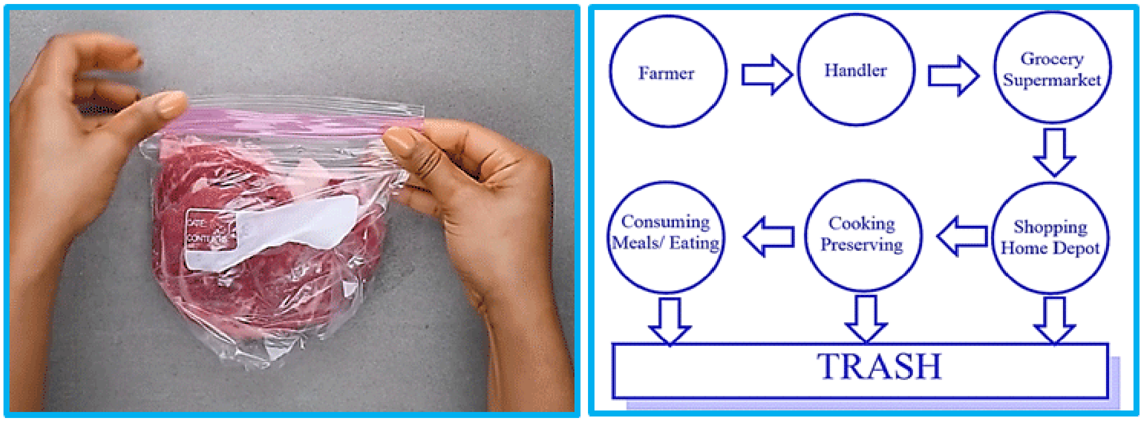


Figure: Packaging [57] and handling food and trashing stations

Wasted! Successfully creates awareness by giving concrete evidence and inspires action. Some suggestions provided include making a grocery list, preparing meals, and creatively utilizing leftovers. The biggest lesson is to start caring because relating to the food we eat can help us take back responsibility for our food chain. Recent spikes in food prices have led to increasing concern about global food shortages and the apparent need to increase agricultural production .Surprisingly little discussion has been devoted to the issue of food waste. Quantifying food waste at a national level is difficult because traditional methods rely on structured interviews, measurement of plate waste, direct examination of garbage, and application of inferential methods using waste factors measured in sample populations and applied across the food system. In contrast, national agricultural production, utilization, and net external trade are tracked and codified in detailed food balance sheets published by the Food and Agriculture Organization of the United Nations (FAO). The food balance sheets provide a comprehensive assessment of the national food supply, including alcohol and beverages, adjusted for any change of food stocks over the reference period. Since 1974, there has been a progressive increase in the per capita US food supply. Over the same period, there has also been an increase of body weight as manifested by the US obesity epidemic. We sought to estimate the energy content of food waste by comparing the US food supply data with the calculated food consumed by the US population [61]. In the wild, leftovers of the hunted game kept for further consumption. An example is the behavior of the Lynx, a member of the "BIG CATS" clan. Other examples of more food handling by animals are available. The short life of food was the reason that medieval armies "lived off the land" by scavenging, but in 1809 a Frenchman named Nicholas Appert won a prize offered by his government for a process for preserving food. He showed that food sealed inside a container to exclude air and then cooked to a high enough temperature to kill microbes such as Clostridium botulinum kept for a long time. Keeping fresh and cooked food be isolated from the germs of the atmosphere, helped in conserving. Usually, humans use technology for keeping food eatable. Invented the refrigerator and the deep freeze cooler to keep food and raw component for a longer period. It is only the stat of the needed. These technologies do not stop humans from destroying almost a half of the consumable nourishing food by disposal; to trash.

1. Why does food rot?

2. What is photo degradation?

3. How can you prevent food from spoiling?

It seems that wasting of food is a result of many impulses characteristic to humans. The habits and guidance by the parents, within the family, the history of the society in which the infant grows up, the lack of suitable technology for the re-use of the meals leftovers, the preservation of the bulk and tastes of food. The aesthetic aspect of leftovers uses. The fevers of food tend to become infected with microbes that are present everywhere, even in the surrounding air. This might be a fundamental course for the rejection of freshly cooked food to waste after is used for nourishment. Old food may be dangerous by the accumulation of pathogens that may cause the "rotting" of the food. Back in the 19th century, Louis Pasteur invented the process that bears his name. Pasteurisation kills the bacteria that make food go off, and today this is applied mainly to milk. Milk that has been pasteurized by heating to just over 70°C will keep for two to three weeks when refrigerated, while UHT milk, made by heating to 140°C, will keep in airtight, sterile containers for up to nine months. Raw milk left in the fridge would last only a few days. Guidance for "no food wasting" in the human educational level (it is a moral guideline: as we teach the children 'THOUGH SHALL NOT KILL" we can also teach not to waste food). This and home conservation of food and cooking by applying the leftover. This together with the finding of novel antimicrobial agent that will prevent the spoilage of the leftovers. It may bring great relief in the food shortage of most of the humans on earth and ease the environmental stress resulting from the current need for producing more agricultural nutrition products, livestock, vegetables and fruits. A guidance for "no food wasting" in the human educational level (it is a moral guideline: as we teach the children 'THOUGH SHALL NOT KILL" we can also teach not to waste food). This and home conservation of food and cooking by applying the leftover. This together with the finding of novel antimicrobial agent that will prevent the spoilage of the leftovers. It may bring great relief in the food shortage of most of the humans on earth and ease the environmental stress resulting from the current need for producing more agricultural nutrition products, livestock, vegetables, and fruits. When food is harvested, either in the form of vegetables, fruits, or meats (from animals), it becomes detached from the sources that gave it life. In other words, once you pick an apple, it begins to die immediately. Some foods, such as fruits and vegetables, have thick cell walls that keep the food in an edible state for several days or even weeks. Over time, though, those cell walls begin to break down. When this happens, you can feel these fruits and vegetables become less solid. They may also begin to turn colors, smell bad, and taste even worse! What causes these changes within foods? Some of the primary culprits are air, moisture, light, temperature, and microbial growth. When two or more of these culprits get together, they can accelerate the spoiling process even further. When food is exposed to air, microorganisms can land on the food and begin their work of breaking down the food for their own uses. The presence of oxygen enhances the growth of microorganisms, such as molds and yeasts, and contributes directly to deterioration of fats, vitamins, flavors, and colors within foods through the work of enzymes. All food is made up of a certain percentage of water. Over time, microorganisms use the water within food to fuel the chemical reactions they need to dissolve the food for energy and growth. Moisture on the outside of food also allows molds and other microorganisms to grow on the outside of food, as well as within any cracks or holes in the surface of the food, further contributing to increased decay. When food is exposed to light, its outer layers can begin to spoil in a process known as photo degradation. Photo degradation can result in discoloration, as well as loss of flavor, vitamins, and proteins. Temperature also plays a role in food spoilage. As temperature increases, the chemical reactions that drive the spoiling process accelerate. That's why putting foods in the refrigerator or freezer helps to slow down the rotting process. The agriculture provides the many food ingredients, but the methods of bulk production suffer from drawbacks:

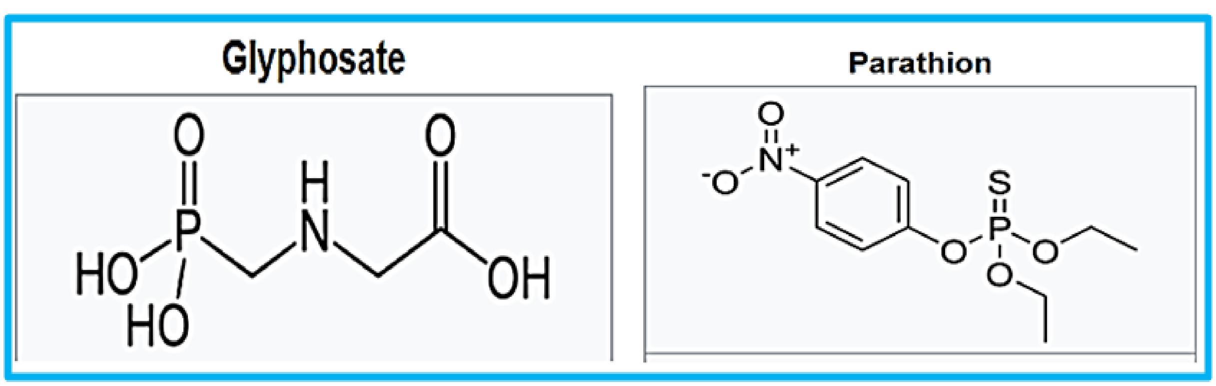
1. The contamination of the product with a variety of chemicals, as pollutants

2. Contamination by microorganisms and parasites.

3. The use of veterinary drugs to enhance food production. Such is characteristic of livestock.

4. Irrigation with braking, black or grey waters, introduces compounds into the agricultural product of novel activity which is not yet fully known.

The need of the farmers to aid the plants and animals in their struggle with natural pests forces the embarkation on the hazardous vehicle of chemicals that enable the eradication of the microbes and insects and parasites damaging the crops in the fields, stables, and plantations. The leftovers of the treatments are present in the products consumed by users, harming in many cases the physiology of the human, as phosphorous based insecticides examples: Parathion, an acetylcholinesterase inhibitoror the systemic herbicide Glyphosate (Roundup) are.

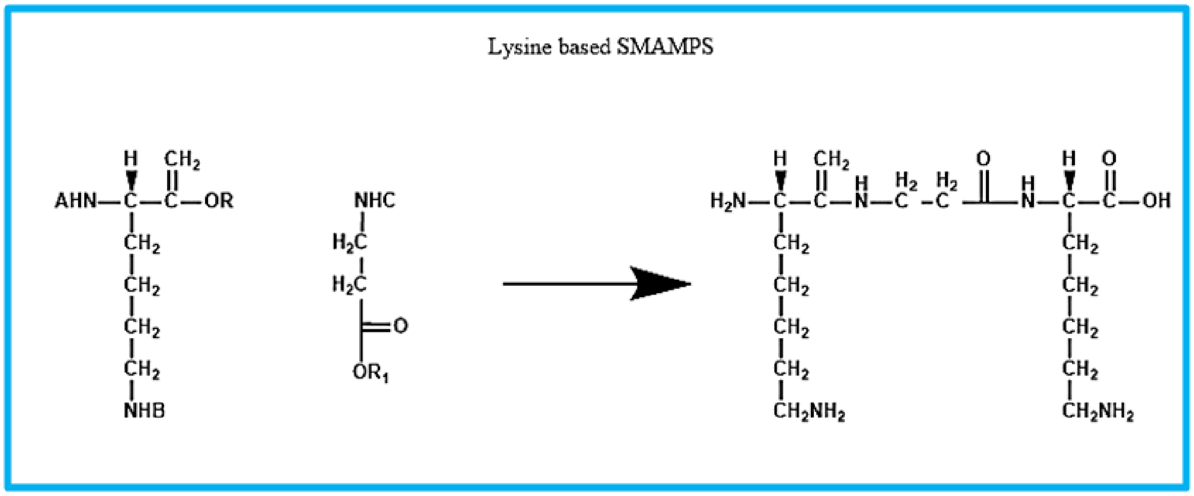


The antibiotics, in particular NISIN have established themselves as efficient, un-harming to humans, conservation agent. The antimicrobial peptide Nissan is mainly applies in the milk sector in cheese reservation. Recent reports indicate that ultra short peptide surrogates od antimicrobial peptides (AMPs) agents, "small" molecule may replace the AMP, the Synthetic mimics of AMPs, (SMAMPs). These low molecular weight compounds that are easy to access synthetically, poses two main biologic related features:

a. They eradicate very efficiently broad-spectrum of microbes

b. They are harmless to humans. Do not hemolyze red human blood cells (RBCs).

These SMAMPs will take care and stop an important factor in the decay and rotting of food. The microbe-culprit.



Since most of us do not grow our food today, we must take steps to prevent food spoilage, so that food will last long enough for it to be transported to a store where we can buy it and bring it home to cook and eat. More effective handling which includes the "leftovers" and the "old ingredients", the vegetables, meats, fruits that were purchased in the store a few days ago. Delaying the rotting of the foods is possible by applying better antimicrobial agent based on natural lantibiotics and other AMPs, their surrogates for coating containers, coating the ingredients and the films applied for the wrappings and refrigerated storage. Scientists and researchers have helped develop many tactics over the years to fight against the main causes of spoilage, such as air, chemical reactions, and microorganisms. The frames of the needed technologies exist and utilized. However, the need to save the trashed food, those means must be upgraded and simplified as to make them available to all with reasonable effort.

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58. So Yummy - 7 Super easy ways to keep your food fresher, longer!

How to Keep Food Fresh in the Kitchen Sometimes, with the best of intentions and even with a tight budget, we end up throwing out food because it is no longer fresh One way to get around this is to keep kitchen storage well organized and well rotated. This article provides some easy suggestions to help you put a system in place in your kitchen.

1. Keep your purchasing quantities for perishable foodstuffs small. Buying larger quantities of food that you don't eat quickly is not usually good economy, and you risk losing the food to spoilage if not used in time. Except for items eaten quickly in your household, only purchase small quantities of perishable food and refresh as needed.

2. Rotate ingredients. Make sure that when you buy a new food item, you pull the unfinished one forward in the pantry cupboard or refrigerator so that the older item is finished first. Now and then do a sweep of the food to bring forward all items that are getting near their use-by date.

3 .Throw out old spices and dried herbs. These items lose their flavor over time, and the use-by date is there for a reason. Only purchase new ones when you are going to use them.

4. Keep expensive food items at the front. Resist the temptation to not eat or use them in cooking or you may end up finding you waited too long. Enjoy them quickly so that you make the most of them. Don't let such items get stuck at the back of the fridge!

5. Keep the pantry storage area away from heat sources. Food stored next to the oven will deteriorate more quickly than food kept in a cooler environment. Move your food items that are stored next to the oven if necessary.

6. Read the use-by dates. Read them even before you buy and look for the freshest item to bring home.Once home, always be very careful to use refrigerated and frozen foods by their use-by date. Expired use by dates on pantry items are often less urgent within a short period but remember that even food in tins and dried food loses its taste and appeal with too much storage.

7. Store items correctly. Maintaining freshness is dependent on knowing how the food should be stored. For many items, you can find the information on the packaging. There are also numerous articles on wikiHow about storing fruit, vegetables, meat, etc. Freezers often indicate on the door how food should be stored. Following the food storage guidelines will help to prolong the freshness of your food.

8. Make it easy to find your food. Pantries and food cupboards should be well lit; refrigerators and freezers should not be crammed so full that you can't bear to rummage through them. Use shelves, rolling wire storage drawers, and other helpful storage elements to make arranging food at eye level possible. A small outlay on good kitchen storage can pay its way to less spoiled food.

9. Use containers to prolong the freshness of foods. Plastic, glass and tin containers all work well and canbe purchased in a wide variety of shapes and sizes suited to your needs

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a. http://www.takeextinctionoffyourplate.com/waste/

b. Hall KD, Guo J, Dore M, Chow CC (2009) "The Progressive Increase of Food Waste in America and Its Environmental Impact". Plos One 4(11): e7940.

60.https://www.carbonated.tv/news/frances-law-bans-supermarkets-throw-waste-food-donate-charity

61. Franklin NB, Cooksey KD, Getty K (2004)" Inhibition of Listeria monocytogenes on the Surface of Individually Packaged Hot Dogs with a Packaging Film Coating Containing Nisin"; Journal of Food Protection 67(3): 480–485.

62. Hall KD, Guo J, Dore M, Chow CC (2009) "The Progressive Increase of Food Waste in America and Its Environmental Impact". PLoS ONE 4(11): e7940.