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# A general overview of the genetic effects of extracellular polymers For *Enterococcus faecium* in cancer cells

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ABSTRACT

Tumour cells continue to grow and multiply to form a mass or a tumour called tumour, which causes growth to develop pressure on neighbouring tissue and remove it and can invade and destroy normal cells to pass through to other tissue and vital organs. Smoking is one of the most important chemical causes of cancer. Tobacco smoke causes lung and respiratory diseases. Cigarette smoke contains many types of Mutagenic substances, including Nitrogen oxides, which cause damage to DNA (DNA) Some epidemiological studies have also pointed to the relationship of alcohol to prostate cancer. Alcoholic beverages also play an important role in the incidence of breast cancer by altering the level of estrogen in the blood. Alcoholic beverages also play an important role in the incidence of breast cancer by altering the level of estrogen in the blood. The process of DNA repair and then breast cancer also found that benzene and its derivatives cause a mutation in the p53 gene, and it was noted that they damage the DNA of lymphocytes in the surrounding human blood.

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## INTRODUCTION

Cancerous tumours: Is an abnormal tissue block with asymmetric growth that begins to expand at the expense of natural tissue cells and goes beyond normal tissues and continues to grow itself even after the stimulus that led to this growth change has stopped (Beniston *et al.,* 2001).

Tumour cells continue to grow and multiply to form a mass or a tumour called tumour, which causes growth to develop pressure on neighbouring tissue and remove it, and can invade and destroy normal cells to pass through to other tissue and vital organs. The tumours are on two types: a Benign tumour, this tumour consists of cells possessing the characteristics of normal cells but do not respond to long-term natural growth regulators, and these cells are unable to invade natural tissues or spread to distant sites, but the growth rate is incorrect and most Benign tumours do not cause real problems and can be removed by surgery. The other type of tumours is malignant tumours (Malignant tumours), which is the most dangerous to the life of the patient as they are fast growing and have a mass and a malignant tumour does not resemble (Whitfield *et al.,* 1995). The original cell has the ability to spread metastasis (metastasis) to the rest of the body Cancer tumours are classified into three main types: Carcinomas, which account for about 95% of cancers in humans, such as skin cancer, colon, breast, prostate, and lung. Sarcomas are a very small percentage of human cancers. These are solid tumours that affect muscles, bones, cartilages, and fibrous tissue. And Hematopoietic tissue, i.e., blood cells and bone marrow, called soft tumours.

### Cancer aetiology Etiology of Cancer

**Chemical causes:** Smoking is one of the most important chemical causes of cancer. Tobacco smoke causes lung and respiratory diseases. Cigarette

smoke contains many types of Mutagenic substances, including Nitrogen oxides, which cause damage to DNA (DNA) Some epidemiological studies have also pointed to the relationship of alcohol to prostate cancer. Alcoholic beverages also play an important role in the incidence of breast cancer by altering the level of estrogen in the blood. The process of DNA repair and then breast cancer also found that benzene and its derivatives cause a mutation in the p53 gene, and it was noted that they damage the DNA of lymphocytes in the surrounding human blood. Contaminated polycyclic hydrocarbons (polycyclohydrocarbons) are carcinogenic substances that lead to events Ryan skin cancer and respiratory exposure site as the exposure to arsenic causes chromosomal variations and induces cancer events (Vineis, 2005).

**Physical causes:** Ionizing radiation is one of the most important physical factors causing cancer, where fractures occur in the DNA, resulting in chromosomal variations. The effect of radiation such as kama rays depends on the amount of dose and duration of exposure, which causes a significant increase in the incidence of cancers of the gastrointestinal tract, kidney cancers, adrenal cancer

UV rays also play a role in skin cancer events in humans. These rays are found to disrupt the DNA by forming links between the pyrimidines and the DNA itself Which prevents them from correlating with purines of the purines on the opposite tape, which occurs as a result of exposure to long and long direct sunlight and then the occurrence of skin cancer. Asbestos and silica fibres are hazardous to human health if they enter the bodies of workers in the factories by inhalation, causing the lung cancer.

**Biological causes:** Viruses are among the most important causes of life that lead to cancer, including the virus Hepatitis C has been linked to the events of liver cancer by the mutations in many somatic genes and the events of fractures in the second strips of DNA (DNA). The hepatitis B virus causes cancer by expressing the X (Xgene) gene, which encodes the production of X protein, which in turn causes disruption of cell division Mediated by chronic damage. In the liver causes the continuous division of cells. The human papillomavirus, which causes sexually transmitted cervical cancer, contributes to the transformation of transformation cells by gene expression of proteins that negatively affect the activity of tumour suppressor genes such as P53 and stimulate the activity of telomerase. On the other hand, I have returned mycotoxins, which are secondary metabolites (Atlas *et al.,* 2005).

Secondary Metabolites are severe causes of leukaemia including the fungal toxin Aflatoxin B1, which is extracted from Aspergillus flavus. Bacteria and cancer are closely linked to the cause of chronic exposure to antigens and the production of carcinogenic products including Helicobacter pylori, which causes gastric cancer. It has been found to affect the lining of the inner wall of the stomach by ulcerative events and gastric ulcers (Adenocarcinomas). The incidence of syphilis (Trepanoma pallidum) increases the susceptibility to oral and tongue cancer. Parasites Studies have shown that the infection of Schistosoma haematobium parasites causes Bladder Cancer, which irritates Chronic inflammation of the bladder and hyperplasia (Wessels *et al.,* 1990).

**Treatment of Cancer**

There are several types of treatment for cancer as follows;

**Surgical treatment**

The ability to eradicate a tumour is often dependent on early detection before it is spread (Metastasis). The survival of a single cancer cell can cause tumour resurgence after years. Excision may not include a whole tumour, either the difficulty of the place or the complete removal of a tumour leads to the loss of a certain physiological function in the body. Chemotherapy or radiotherapy is used to kill the cancer cell after surgery (Holt *et al.,* 1994).

**Radiotherapy**

Radiation therapy is used against local cancers where it affects the genetic material (DNA) by cracking the snail or by interfering with DNA and chromosome proteins. Radiation helps to form free radicals that are toxic to the cell and cause death (Mather). Radiation directly affects the process of the formation of new blood vessels of cancer, as the radiation to break the blood vessels of cancer cells and blood clotting in them and there are many side effects that appear during the course of treatment such as anorexia, nausea, Nausea, hair loss Hair loss, osteoporosis, lung fibrosis, renal insufficiency, and long-term use (Vincent *et al.,* 1999).

**Chemotherapy**

Useful chemotherapy in cases of widespread tumors such as leukemia (Leukemia) chemotherapy occurs malfunction in one or more of the metabolic processes such as inhibition of protein manufacturing process (Protein Synthesis) and transport within the cell (Intracellular transport) and increasing the permeability of the plasma membrane, and includes chemotherapy substances Various antimetabolites inhibit the pathways of nucleic acid synthesis and mitotic inhibitors. Chemotherapy may affect high-replication or high-divisional cells such as bone marrow cells, epithelial cells, and hair follicles. (Hair follicle) And Sperm

forming cells. But the causes of chemotherapy failure in the treatment of some tumors may be due to the resistance of cancer cells to chemical treatments through excessive expression (Overexpression) to Keiko protein found in cell membranes called glycoprotein p as this Alkleikoprutin works to pump anti-cancer outside the cancer cell drugs, and turn cancer cells to change the antigens on the surface, such as: loss of receptor programmed death (apoptosis receptors) and so the cancer cell can escape or resist treatment.

**Complementary and Alternative Medicine**

Several studies have been conducted to investigate the contribution of plant extracts to the treatment Cancer Cancers There are also a lot of definitions that have been developed to describe this term. In general, complementary or alternative medicine refers to methods of using natural products (Natural products) that individuals resort to protect themselves from some life-threatening diseases, including cancer. Al-Jeraisy 2007 conducted a study on the effect of raw extracts of fruits and fruits of phoenix day life cultivar zahdi in inhibiting the growth of certain cancer cell lines such as AMN-3 and Hep-2 and in the treatment of lacto blastic carcinoma of white mice. The toxic effect of the raw extract of Lactuca serriola stems in cancer cells outside the vivo. The reasons that lead many cancer patients to resort to these methods are the collateral damage caused by chemotherapy and radiation treatments and the adverse effects associated with these treatments. The complementary and alternative medicine methods are highly effective in multiple locations of the body with ease of oral intake, and their low cost as well as acceptable by all, where plants secrete many metabolic products as defensive means to prevent their invasion from other neighbourhoods. Regularly handling natural chemicals enables the individual to resist many serious diseases such as cancer.

**Immunotherapy**

Despite all the results and achievements in this area, they did not enter the field of application to have new effective immunotherapy. Immunogenic activity is the mainstay of the host's host defense mechanism, either by stimulating its natural immune system or by giving natural substances prepared from other living organisms. The tumour cell is taken and grown outside the body by adding different growth factors. It has been found to have immunogenic activity, High against the same species, and was able to stimulate toxic T cells to act against them and kill them. These cells interact with special proteins on the surface of tumour cells that cause tumour decay and weakness by making holes in the membranes of these cells or stimulating programmed death. The removal of part of a tumour and injecting it with certain non-pathogenic viruses may produce superficial antigens that enable immune cells to recognise them when they are returned to them and thus generate immunity against a tumour itself. The researchers used immunosuppressants produced by bacteria in the treatment of patients with different Oncology such as Pseudomonas and Salmonella enterica And Klebsiella pneumonia.

**Genus: Enterococcus**

The genus of intestinal bacteria is a group of lactic acid bacteria (Lactic acid bacterium), which includes the genus Streptococcus, Lactobacillus, where the members of this group produce lactic acid as a result of the fermentation of sugars and endemic intestinal tract genetics and gastrointestinal tract is found in food and feed. The classification of the genus of gastrointestinal intestines is not constant, as new species are continuously added to it as a result of the development of isolation and diagnostic methods, especially genetic studies, and this species currently includes 28 different species, divided into seven main groups depending on the genetic affinity between them.

The genus of the intestinal genus is relatively modern. It was part of the sex of spherical pools until the mid-1980s when both S. faecium and S. faecalis were transferred to a separate species called the Enterococcus genus based on studies of acid hybridisation DNA-DNA and DNA-RNA. In 1919, Oral-Jensen used a new label for bacterial species when describing two isolates: S. faecalis; S. faecium, while the view was that these two isolates were S. faecalis.

The world of Jones and his group 1972 laid the boundary between the bacteria S. faecalis and S. faecium, where the latter is a separate species depending on the genetic and biochemical characteristics, notably Potassium tellurite (K2TeO3) and its inability to reduce (Tetrazolium) to Formazan and other fermentation reactions.

The two species, S. faecalis S. faecium, were transferred to a new and independent species called Enterococcus and thus named E. faecalis and E. based on the use of DNA-DNA hybridisation techniques (DAN-RNA) and a new classification system, Lansfield 1933 where *Enterococcus spp*. with the serological D group, the species were transferred *S. avium, S. caseliflavus, S. gallinarium, S. durans, S. maldoratus* respectively.

**Diagnostic characteristics of gastrointestinal**

The cells of the genus intestinal tracts are positive to the gram-spherical shape of the pelvis with di-

mensions of 2.6 x 2.50 micrometres showing in single or double cells when preparing the swab from a solid medium and in short chains when preparing the swab from a fluid medium, are non-moving in most species except E. casseliflavus, E. gallinarium, which possesses polarity. Gastrointestinal colonies are characterised by being small white or milky circular round with alpha, beta, or kamma decomposition in pests with 5% sheep blood or human blood. The intestinal genus is characterised by the ability to grow at high concentrations of 6.5% NaCl, 9.6% and 10-45°C. It also resists 60°C for 30 minutes and has the ability to grow by High concentrations of bile salts are up to 40% as they are an analyte of ascolin.

E. faecium is characterized by other types of intestinal tracts with the ability to grow at 50°C, the inability to consume pyruvate, the production of acid from arabinose and clisrol, the fermentation of sorbitol, sorbose, adonitol, its consumption of arginine, its inability to grow in 0.04% potassium potassium Tolerates and its inability to grow in 0.01% of Tetrazolium. Gastrointestinal tracts and swimming pools were subdivided into serotypes based on the polycrystalline antigen of the cell wall. Intestinal tracts were placed within the Streptococci D group because they contained the Glycerol teichoic acid antigen, giving a systemic interaction with the antibodies prepared for this group.

**Multi-Screed Extracellular Exopolysaccharide (EPS)**

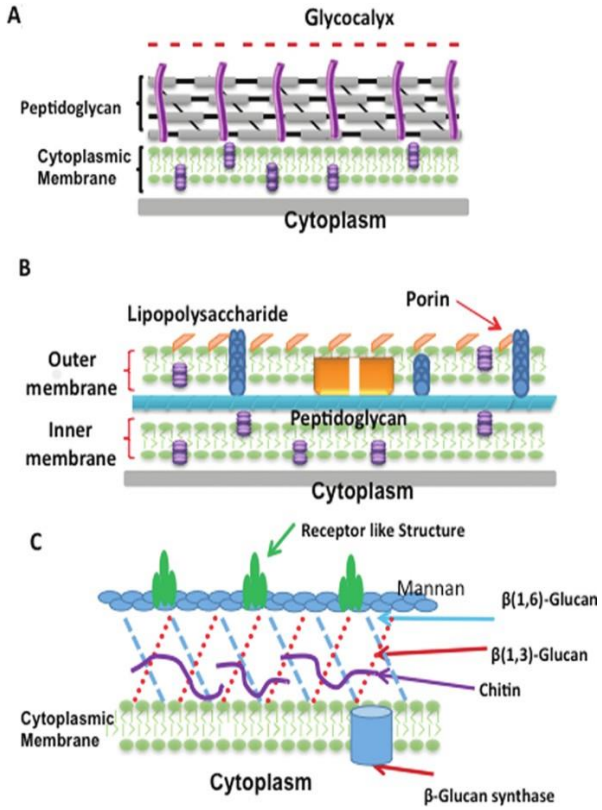


**Figure 1: Cell wall of gram-positive bacteria**

Most types of Lactic Acid Bacteria (LAB) Lactic acid bacterium are produced from the extracellular matrix. EPS are two types depending on its association with the bacterial cell or in the form of a portfolio Capsular polysaccharide (CPS) which is strongly attached to the bacterial cell wall, or It is in the form of a mucous mucus produced by the bacteria outside, EPS may be associated with protein and is similar to CPS in relation to the bacterial wall and is then called glycocalyx.

There are two types of EPS depending on the quality of monomers and the method of arrangement of these repeating units in the polymer. Homopolysaccharides (HOPS), which consist of one type of monocrystalline sugars and Heteropolysaccharides (HePS) of two or more monosaccharides. Sugar constituents of HOPS may be called glucose

The glucan is composed of fructose and is called fructan or mannose sugar (Mannan). Heps consists of different sugary units in type, number, and repeating units, Glucose, galactose, Or Ramenos and Fucose, or Glucosamine, and Clactosamine in the order of binary, triple, quadrilateral etc. Sugar units are related to one another and arranged in different proportions: 1: 1 or 2: 1: 1 depending on the nature of sugar and the type of bacteria produced. Sugar units are associated with different bonds (β1,3, α1,6 and α1,4) The quality of these bonds, their ratio to each other, their length in sugar, And its other phenotypic characteristics of viscosity, solubility and density. Other bonds lead to the production of a compound with a high fork ratio, as ratios (A1,3) is responsible for the nature of the water-insoluble sugar. The molecular weight of the bacterium EPS is 10-160 kg, and it contains (50-50.000) polymerised polycrystalline units.

In general, Heps productivity is relatively lower than HOPS where it ranges (10-160) mg / l, while the HOPS yield exceeds 100 mg / l. (CPS) Or polysaccharide into the extracellular medium (Slime) in different species of Lactobacillus (LAB) varies depending on the type of breeds produced and incubation conditions, and the heat-loving bacterial strains. Thermophilic produces Heps higher than medium-temperature breeds (Devuyst and Degeest, 1999; Devuyst and Vaningelgeem, 2004). Enterococcus faecium bacteria belong to medium temperature-loving bacteria and are also produced for both CPS and Slime EPS and high molecular weight mass.

**Importance of extracellular polysaccharide**

Antitumoral and Immunological Importance of Exopolysaccharide (EPS) Interest in the EPS produced from the new Lactic Acid (LAB) has increased significantly depending on its physiological, structural and genetic importance. Many types

of MB are used in the dairy industry using starter cultures and food additives to add Cremoris texture), Food stabilisers and natural preservatives for antimicrobial properties (Kleerebezem *et al.,* 1999; Duboc and Mollet, 2001; Ruas-Madiedo and Reyes-Gavilan, 2005).

Lactic acid bacteria are important in their use as Probiotic bacteria because they are part of Generic Recognized as Safe (GRAS). These bacteria have the ability to tolerate high acidity, bile salts and the production of antibacterial compounds against bacteria.

Pathogenic and carcinogenic bacteria, as well as its ability to adhere to the colonisation of the intestine due to the adhesion nature of EPS and its formation of biofilm. EPS is also used as Prebiotics, which stimulates beneficial bacterial strains, which is naturally present in the intestines such as Bifidobacterium where it is used by a carbonic source and an environment.

Suitable for settlement, stimulates growth, activity and reproduction, as EPS is resistant to digestion by digestive enzymes. EPS is of human health importance through its ability to lower cholesterol where the immunomodulators are known to be the compounds capable of interacting with the organ (immunomodulator), as well as its antitumoral importance (Fujimiya *et al.,* 1998). Immune system to increase the host's immune response depending on the amount of dosage, the dosage method, and the mechanics of the mediator's work.

EPS affects both the initiation and progression of cancer through the stimulation of the body's immunity against detoxification of mutagenic compounds. Or the direct effect of cytotoxicity Against cancer cells. The newly available information indicates the EPS characteristics Is in its direct effect on the number and function of cells Macrophages, Nk cell, T-cell. Experiments showed that daily intraperitoneal injection of carcinogenic mice with EPS extract for 19 days reduced a tumour by 82% compared to control mice with an increase in productivity (Araya *et al.,* 2005).

TNF and IFN from spleen and NK cells. The addition of the same extract to Macrophage cells outside the vivo in a range of 500-1000 µg / mL resulted in increased IL-1 production, which plays an important role in the cytotoxicity of cells.

The stimulation of EPS to increase immune T cells and stimulate increased secretion of TNF, IL-1, IL-2 and IL-6 has recently gained significant importance because of its extensive uses in immunotherapy for cancer. EPS stimulates the production of TNF and IL-1 by the macrophage macrophages, which attract PMN cells, infiltrate and pool them in the injury area, as well as stimulate the production of cytokines and chemokines. There are two groups of cytokines

In stimulating their production both inside and outside the organism, the first group includes IL-1, IL-2 and IFN The second group was 13,10,6,5, IL-4 Although EPS does not stimulate CD4 + T-cell cells, although the mechanism of action of this stimulus is not known, CD4 + T-Cell receptors are CD25 found on T-Cell). There was an increase in the number of cytotoxic T-Cell cells in the cancerous tumour area at different concentrations of EPS and an increase in the production of Superoxide dismutase (SOD). It appears to protect cells from the mutagenic and carcinogenic effects of free radicals. (1) Glucan receptor on the surfaces of NK Neutrophils cells, and the effect of the immune response on EPS, by its effect on the receptor type on the surfaces of the immune cells and the molecular interaction between EPS and these receptors, has been the focus of many researchers in recent years. Human Monocyte is called Complement receptor Type3 (CR3) and is located in the C-terminal area of the CR3. The greater the difference in the quality of the bonds between EPS units such as bonds (1.3 β) and (3), the difference in the quality of the sugar groups, the degree of division, the molecular weight and the polymer charge determines the future and the future quality of the EPS (1,4α) and branching bonds (α1,6) leads to the diversity of receptors on the immune cell surfaces of these complexes, which may provide a more inhibitory effect on the tumour. The gene responsible for regulating the apoptosis of cells primarily bcl2, which encodes protein production, inhibits apoptosis genes, including the gene Bax (Shamran *et al.,* 2018).

**Bioproduction of extracellular polymers**

The EPS processing capability of the LAB is directly dependent on the quality of the breeds, the nature of the medium and the incubation conditions. The composition of the component crystalline sugars of the EPS significantly differentiates the nature of EPS by partial weight and phenotypic tissue.

Sugar nucleotide is manufactured and polymerised on the cytoplasmic membrane of the bacterial cell. Sugar nucleotide is used as a precursor in the manufacture and polymerisation of sugar units (Roberts, 1996). Once these units are made, they are transported through the membrane by isoprenoid lipid carriers to the extracellular Bacteria, where they are polymerised or covalently linked to the surface of the cell to be a capsule or released freely in the middle space in the form of slime. The Galactosyl-1-phosphate transferase binds the monosaccharide galactosylphosphate with lipid carriers P. Three enzymes within the glycosyltransferases group that add and polymerise sugary units to the

 

basic unit are: EPSF, EPSI, EPSG. The polymerisation process needs energy derived from breaking the phosphoric bonds in the nucleotide sugars, turning UDP into UMP (Devriese *et al.,* 1995).

Lipid carriers are also involved in the manufacture of peptidoglycan, Teichoic acid and lipoteichoic acid, so the scarcity of this component is a specific component of EPS manufacturing. Incubation conditions that stimulate growth and cellular division reduce EPS productivity. Glucosamine polysaccharides are also a specific factor in the manufacture of EPS because they are involved in the metabolic pathways of sugars and the manufacture of peptidocleicanes as well as other sugary polymers.

**Genes responsible for EPS manufacturing**

Five gene clusters are responsible for EPS manufacturing and are symbolised by EPS. The region for each gene group chellebrutin participates in the process of EPS manufacturing and identification. The length of the chain and this region follows the region of the encoded genes of the sugary enzymes glycosyl-1-phosphate transverse & glycosyltransferase, which are incorporated into the manufacture of a glycosylated base and polymerised units (DeJong, 2003).

The end of the genomes contains additional genes for the production of proteins involved in membrane transport, as well as the manufacture of nucleotide sugars. The first gene in the EPS genotype is epsA, which encodes proteins that regulate the work of the three other genes: epsB, espC, and epsD. It may inhibit the process of cloning the proteins of these genes. The epsB gene co-regulates the manufacture of EPS, but in collaboration with epsC and espD, inhibiting the action of the last two gene proteins reduces the length of the EPS chain, adversely affecting the molecular weight of the polymer. The proteins of these genes bind the amino and carboxylic endings in the multicrystalline chain. The maximum EPS yield is a complex complication involving epsA epsB espC proteins plus ATP, so any deletion of one of the components of this complex leads to reduced productivity.

The fifth gene of the gene group is epsE, which encodes the enzyme Glycosyl-1-phosphate transferase, where the enzyme polymerises the basic repeating unit and also binds the sugary units to the fatty transport (Compton, 1992).

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