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Anticancer Compounds from Bacterial Origin (A Review)

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Abstract

This review aims to boost the creation and delivery of anticancer drugs to tumor tissues, which helps make cancer treatment safer and more effective while reducing damage to healthy cells. Environmental microorganisms can alter or degrade anticancer medications, contributing to the enzymatic inactivation of antineoplastic agents by bacterial derived. The extensive range of chemical modification capabilities available in our soil isolate library, which can be utilized to alter or decompose medicinal medicines, can be evaluated for novel activity on various therapeutic agents. The selective detoxification of medicines in non-malignant tissues may enhance the quality of life for chemotherapy patients. The utilization of bacteria and bacteria-derived membrane vesicles (MVs) holds significant promise for advancing controllable targeted medication delivery in the figureht against cancer. In comparison to conventional drug delivery systems, bacteria and their membrane vesicles possess distinctive attributes as medication carriers for cancer therapy. They can be changed through genetic and chemical methods to surmount physical obstacles to localize and aggregate in tumor tissues, thereby initiating anticancer immune responses.

Keywords: Bacteria, Cancer, Anti-cancer Compounds.

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Introduction

Investigate a collection of environmental isolates for their capacity to accelerate the detoxification of antineoplastic agents, understanding how environmental microorganisms can break down anticancer agents could provide many benefits, the sale of pharmaceutical waste, which includes spill remediation, could be life-saving in cases of accidental overdose by eliminating excess medication, additionally, accurately targeting the inactivation of drugs in healthy tissues could help reduce side effects for patients receiving chemotherapy while still keeping the treatment effective (1).

The primary obstacles in managing infections and malignancies are treatment resistance and the scarcity of novel antibacterial or anticancer pharmaceuticals. Microorganisms have proven to be the most abundant source of antibiotics and anticancer agents., antibacterial and anticancer agents can come from bacteria in nature or our gut microbiome, with some medicines like actinomycin D and bleomycin showing both antibacterial and anticancer properties. Such as Bacteria Streptomyces verticillus: Produces bleomycin, a glycopeptide antibiotic used to treat various cancers, Streptomyces peucetius: Produces anthracyclines like doxorubicin and daunorubicin, Streptomyces caespitosus: Produces mitomycin C, Lactococcus lactis: Produces nisin A and bacteriocin, Lactobacillus species: Known to have anticancer effects, Klebsiella pneumoniae: Produces Microcin E492, which is cytotoxic to certain cancer cells, Actinomycetes is known for producing dactinomycin, one of the first antibiotics found to have anticancer properties (2).

Dual activity from bacterial proteins and peptides

Bacteriocins are types of proteins and peptides made by bacteria, including colicin, pyocin, nisin, microcin, laterosporulin, pediocin, plantaricin, and duramycin, among others. The special proteins and peptides made by Gram-positive bacteria (like Lactococcus lactis and Lactobacillus plantarum) and Gram-negative bacteria (like Escherichia coli and Pseudomonas aeruginosa) show abilities to fight bacteria and cancer. These properties make bacteriocins of significant interest in both medical and food preservation applications. Researchers are exploring their potential to combat antibiotic resistance and to serve as natural preservatives in various food products (3). Bacteria employ both indirect and direct methods for competition and survival. Host bacteria can demonstrate antimicrobial properties indirectly by altering the host immune system (4). Alternatively, host bacteria may produce proteins and peptides that are secreted into the

extracellular milieu to target other bacteria (5). Proteins and peptides display varied structures linked to their functions, confounding their classification (6,7). Figure 1, Bacteriocins such as colicin and pyocin, as well as peptides like nisin, pediocin, and plantaricin, are different types of antimicrobial agents (Figure 1). These substances are crucial for microbial survival in competitive environments and have potential uses in food preservation and therapeutic applications. Understanding their mechanisms of action can lead to the development of novel strategies for combating antibiotic resistance and enhancing human health. These peptides possess antibacterial characteristics that are essential for food preservation and safety. Comprehending their structures can facilitate the creation of novel antibacterial drugs to address resistant bacterial strains (2).

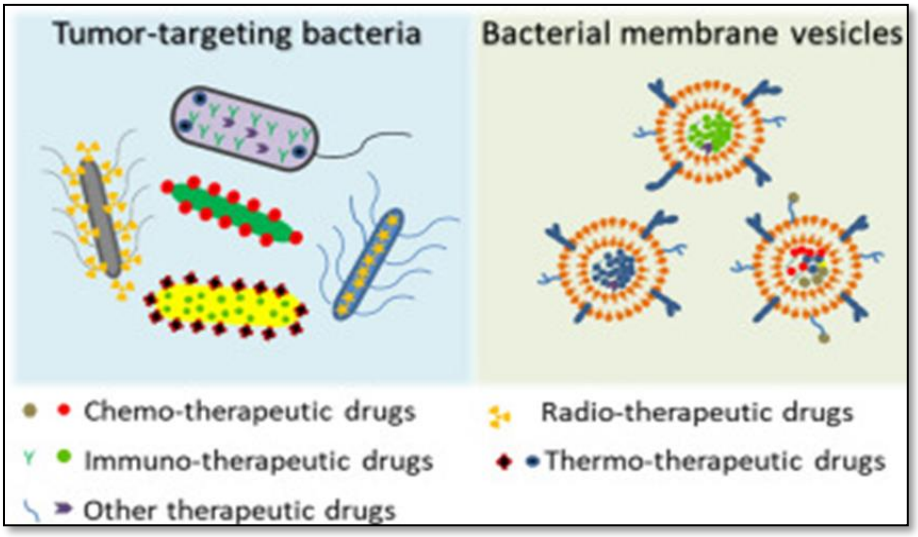

Figure 1. Two applications of bacteria in cancer chemotherapy (8).

Types of bacterial Anti-Cancer toxins

Colicins have three parts: the N-terminal helps them through membranes, the middle region facilitates receptor attachment, while the C-terminal region governs their activity (5). How well these domains work is essential for pyocin to effectively target and kill competing bacteria. Understanding these structural components can aid in the development of novel antibacterial strategies and therapeutic applications. These insights could lead to innovative approaches in combating antibiotic resistance and enhancing the efficacy of existing treatments. By using the special features of pyocins, researchers might create treatments that specifically kill harmful bacteria without harming the good bacteria (7).

Types of bacterial Anti-Cancer peptides

Nisin exists in two forms, A and Z, distinguished mainly by the substitution of His27 with Asparagine; they interact with the membrane surface in the C-terminal region (9).

Pediocins interact with the target cell surface in the N-terminal domain, whereas the C-terminal domain penetrates the membrane. In medicine, the domain functions as the principal factor influencing specificity (10).

Plantaricin has three types: one with a 26-residue peptide and two N-terminal types with 23 and 22 residues, all coming from a 48-residue precursor made by the Plantaricin A (plnA) gene. The amphiphilic characteristics of plnA can facilitate the formation of pores in the cell membrane (11). Additionally, many methods may be devised to combat antimicrobial infections and enhance cancer treatment through the use of proteins and peptides (12).

Proteins and peptides can be used with conventional medications for cancer therapy (13), They can serve as an alternative chemical composition when combined with other proteins or peptides to precisely target certain regions. Proteins and peptides may be coated or conjugated with polymers such as polyethylene glycol (PEG) (14,15), Another approach involves carefully creating these molecules so that natural amino acids can be swapped out for synthetic ones. These chemicals have exhibited many applications and methods of action against antimicrobial infections and cancer, as previously illustrated in (Figurers 2, 3 and 4). (16).

Antimicrobials and anticancer agents of Bacterial Origins

Primary chemical compounds produced by gut microbiota that may impede bacterial reproduction or diminish microbial survival. The significance of microcin. Tiny peptides synthesized by Gram-negative bacteria (mostly Enterobacteriaceae) that can inhibit other bacterial species have been emphasized as mediators of antimicrobial interactions. Fernando Baquero and his team (18). Thoroughly researched the background. Types, how microcin's work, and how bacteria that produce them defend against them, as well as how non-producing bacteria resist them. Shafiee examined the specific application of diphtheria toxin, a widely researched immunotoxin in cancer treatment. Strategies employing cancer-specific ligands and gene treatments were examined.

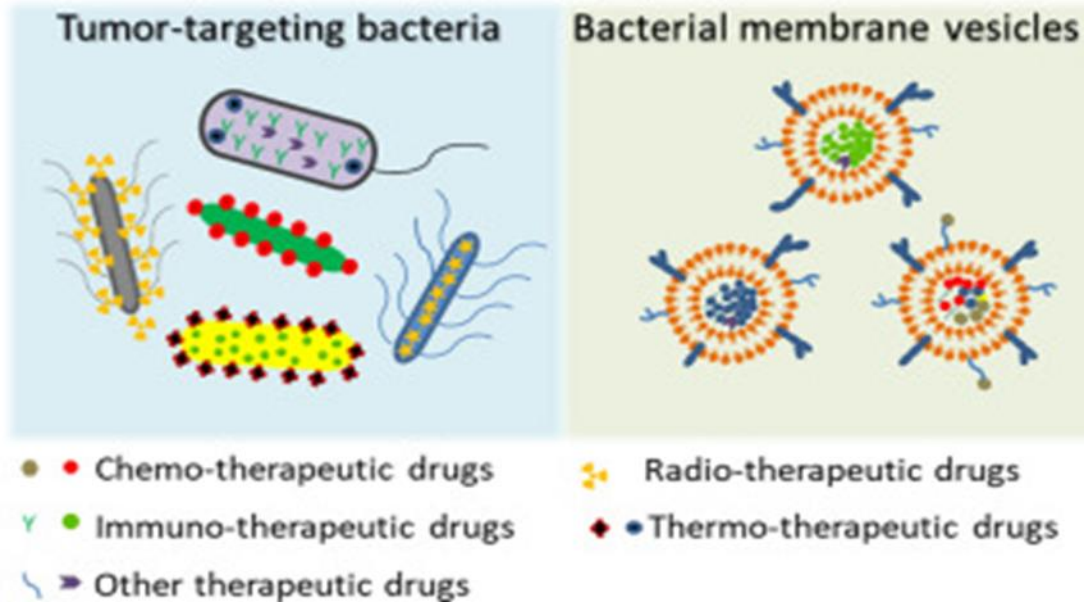

Figure 2. The diverse architectures of bacteriocins, such as colicin and pyocin, as well as peptides like nisin, pediocin, and plantaricin. With dual anticancer and antimicrobial activity (17).

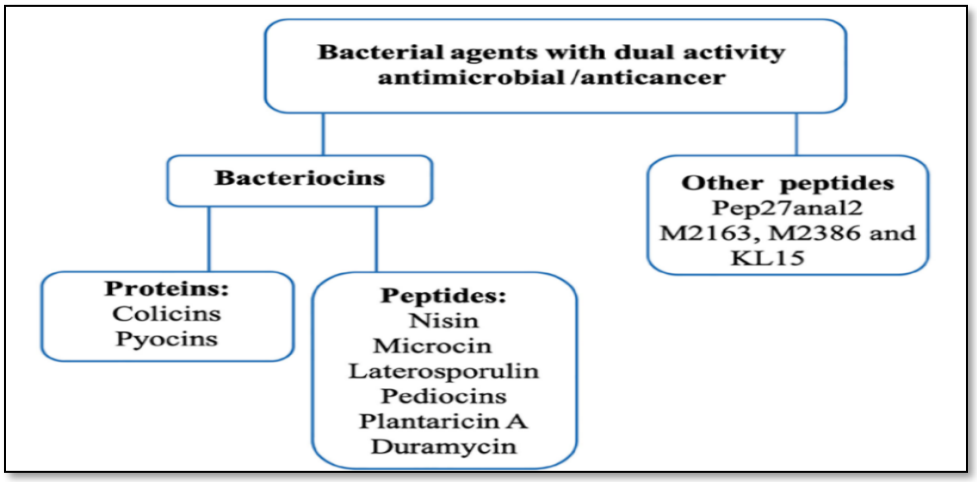

Figure 3. Distribution of characterized anticancer and antibacterial proteins and peptides (17).

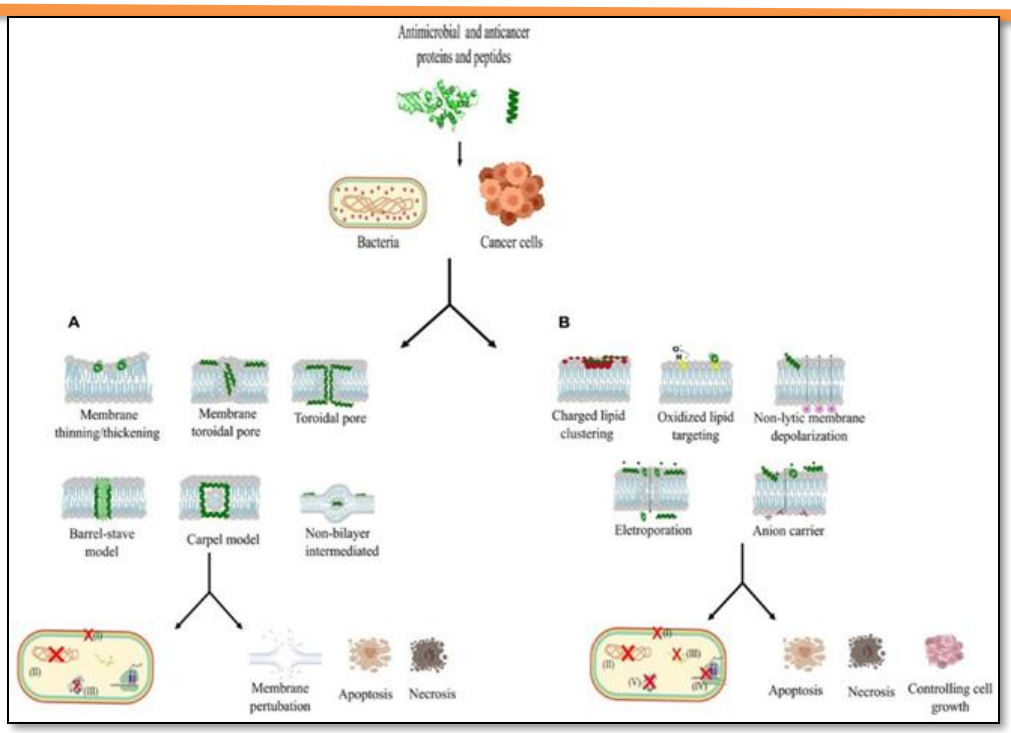

Figure 4. Different mechanisms of action of proteins and peptides with anticancer and antibacterial activity. (A) This section represents the protein and peptide interaction with the carpet model, barrel-stave model, toroidal pore, disorder toroidal pore, non-bilayer intermediate and membrane (17).

The researchers found that targeted diphtheria toxin-based therapy for cancer shows promising results through two main strategies: immunotoxins, which use fusion proteins to target cancer cells, and gene therapy, which delivers the gene for the toxin's a-fragment directly to tumor cells. While these approaches have shown efficacy, the study also highlighted significant challenges, including off-target toxicity to healthy cells and the potential for pre-existing patient immunity to reduce treatment effectiveness. The findings recommend continued efforts to improve targeting strategies and delivery methods for more effective elimination of cancer cells (19). The study by Marcolefas involved the collection of several materials from high Arctic ecosystems, distinguished by elevated salinity and extended subzero temperatures, which were subsequently evaluated for their antibacterial characteristics. Two kinds of Arctic microbes were found to be effective against harmful bacteria that cause food poisoning and serious infections like Staphylococcus aureus, Enterococcus faecium, and Acinetobacter baumannii, even in very cold temperatures. This finding suggests that the variety of microbes found in the Arctic could be an important source of medicines that work well against bacteria at low temperatures (20).

Qin found a new bacteriocin called subtilin L-Q11 from a Bacillus subtilis strain L-Q11, which was taken from orchard soil in Beijing, China. This new bacteriocin showed impressive features, such as being stable at high temperatures, working well in different pH levels, resisting chemicals, and being affected by certain human enzymes, while successfully stopping the growth of harmful bacteria like Staphylococcus aureus and Enterococcus faecalis, as well as bacteria that spoil food like Bacillus cereus, the most notable reliable inhibitory activity was shown against Staphylococcus aureus. Subtilin L-Q11 may serve as a prospective antibacterial agent for food preservation (21).

Zhao studied the genome of a Pseudomonas spp. 11K1 bacterium, which was collected from the root area of plants in China, using computer analysis and genetic research to explore possible groups of genes that make secondary metabolites. This strain was previously recognized for its potent inhibitory effects against plant pathogenic fungus and bacteria. Two possible new groups of genes that help make cyclic lipopeptides (brasmycin and braspeptin) have been discovered to play a role in fighting fungi by affecting how biofilms form and the shape of colonies (22).

The research by Cebrián focused on finding, designing, and creating new antibiotics, which are a type of antibiotic made of peptides that work better against Clostridium difficile. They used a method that included searching through genomes, producing the peptides in different organisms, creating new types of antibiotics, and copying and producing the modified peptides in Lactococcus lactis. A peptide showed higher production levels in different systems and worked well against clostridial species, making it a potential substitute for traditional antibiotics in treating Clostridium difficile infections (23).

Pérez Navarro studied how well fluopsin C, a type of metalloantibiotic made by Pseudomonas spp., works against important bacterial species that are resistant to many drugs, like Staphylococcus aureus, Enterococcus faecium, and Klebsiella pneumoniae, using both in vitro and vivo evaluations. More studies are needed to understand how fluopsin C works in the body and its safety; however, fluopsin C and its related compounds show promise as treatments for infections caused by bacteria that are resistant to multiple drugs. Various antimicrobial agents, such as antimicrobial peptides, were evaluated for their potential anticancer effects. For instance, the antimicrobial peptide microcin E492, which comes from the Gram-negative bacterium Klebsiella pneumoniae, showed cancer-fighting abilities in lab tests and in living organisms against colorectal cancer cells.

Zebrafish-based models have been established and may be effective for screening preclinical anticancer pharmaceuticals. Domalaon says that some common cancer drugs, including mitomycin C, etoposide, camptothecin, doxorubicin, 5-fluorouracil, and cisplatin, have been used again to fight bacteria. Mitomycin C, when used with tobramycin-ciprofloxacin combinations, showed it can effectively fight against tough bacteria like Pseudomonas aeruginosa, Acinetobacter baumannii, Escherichia coli, Klebsiella pneumoniae, and Enterobacter cloacae exhibiting multidrug resistance. As a result, many drugs can work as both antibacterial and anticancer agents, and using FDA-approved drugs in new ways could save time and money in finding new treatments for infections or cancer. These data collectively illustrate the adaptability of bioactive compounds from natural sources and suggest the need for enhanced methods to improve the development of new antibacterial and anticancer medicines (24).

Clinically established anticancer microbial metabolites

By 1990, biologically active natural compounds constituted a substantial segment of the medications accessible; this segment encompassed many microbial metabolites identified to possess antineoplastic properties (25). These chemicals, recognized for their potent cytotoxic properties, have proven essential in the treatment of numerous cancer forms in contemporary medicine. This section comprehensively elucidates the mechanisms of action of DNA intercalators (such as actinomycin D and inotuzumab ozogamicin), topoisomerase II inhibitors (such as doxorubicin), and DNA cross-links (such as mitomycin C). Proteasome inhibitors (such as carfilzomib), nucleoside analogues (such as pentostatin), and DNA free radical inducers (such as bleomycins), along with their potential toxicological effects. The anticancer signalling pathways of these pharmaceuticals are elucidated in (figurer 5). (26).

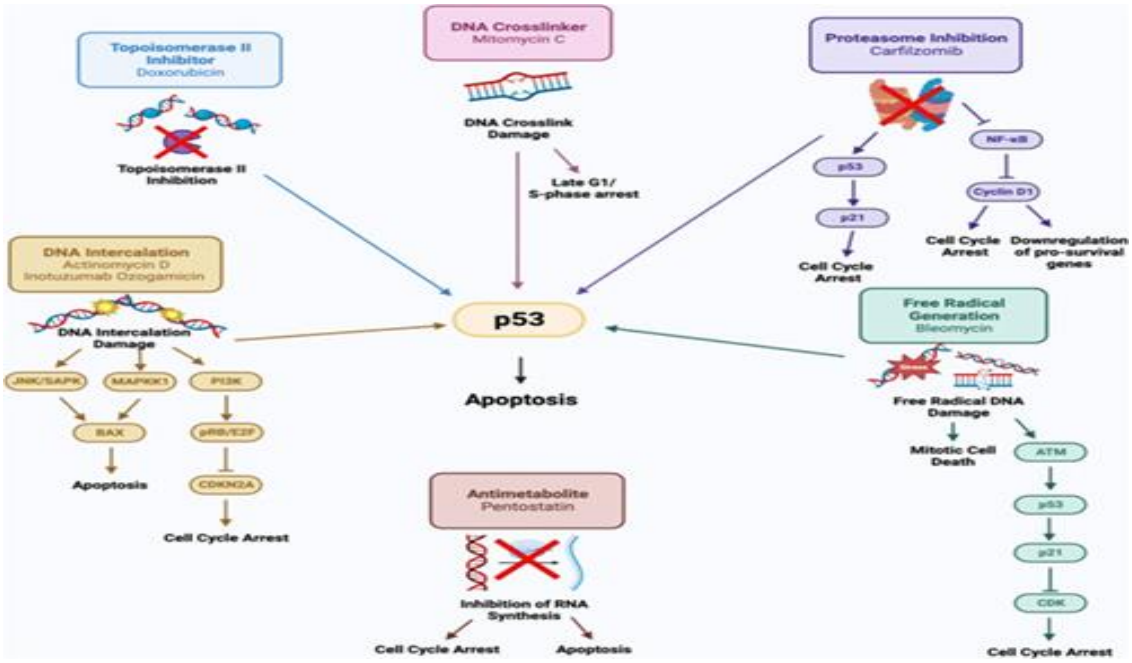

Figure 5. The topoisomerase II inhibitor doxorubicin activates p53, leading to death in cancer cells. Mitomycin C causes damage to DNA by linking strands together, stopping the cell cycle in the late G1/S-phase and activating p53 to start cell death. The proteasome inhibitor carfilzomib helps p53 work better and stay active, causing the cell cycle to stop and leading to cell death. Carfilzomib also blocks the NF-κB pathway, which stops cyclin D1 from working, causing the cell cycle to pause and reducing the activity of genes that help cells survive. Bleomycin causes damage to DNA, which leads to stopping the cell cycle, cell death during mitosis, and the activation of apoptosis through p53. Pentostatin impedes RNA synthesis, leading to apoptosis and cell cycle halt. Actinomycin D and the calicheamicin component of inotuzumab ozogamicin integrate into DNA, inducing cellular apoptosis via the p53, c-Jun N-terminal kinase/stress-activated protein (JNK/SAPK) and Mitogen-Activated Protein Kinase Kinase1 (MAPKK1) signalling pathways while simultaneously halting the cell cycle by inhibiting CDKN2A (26).

Emerging anticancer agents from microbial metabolites

Figure 6 illustrates the mechanisms of action for these drugs. The varied collection of metabolites offers several distinct strategies for cancer treatment. These compounds can start processes that lead to cell death, like apoptosis or necrosis (azurin-p28, butyrate, cordycepin, nisin), boost the activity of tumour-fighting T-cells (butyrate, inosine, propionate), or help keep p53 levels high by stopping its breakdown (azurin-p28). Additionally, these compounds have the capacity to modulate signalling pathways commonly disrupted in cancer. Including the Phosphoinositide 3-kinase - protein kinase B(PI3K-Akt) and Nuclear Factor-kappa (BNF-κB) pathways (cordycepin), inhibit histone deacetylases (HDACs), butyrate, and obstruct tumor associated angiogenesis (nisin) (26).

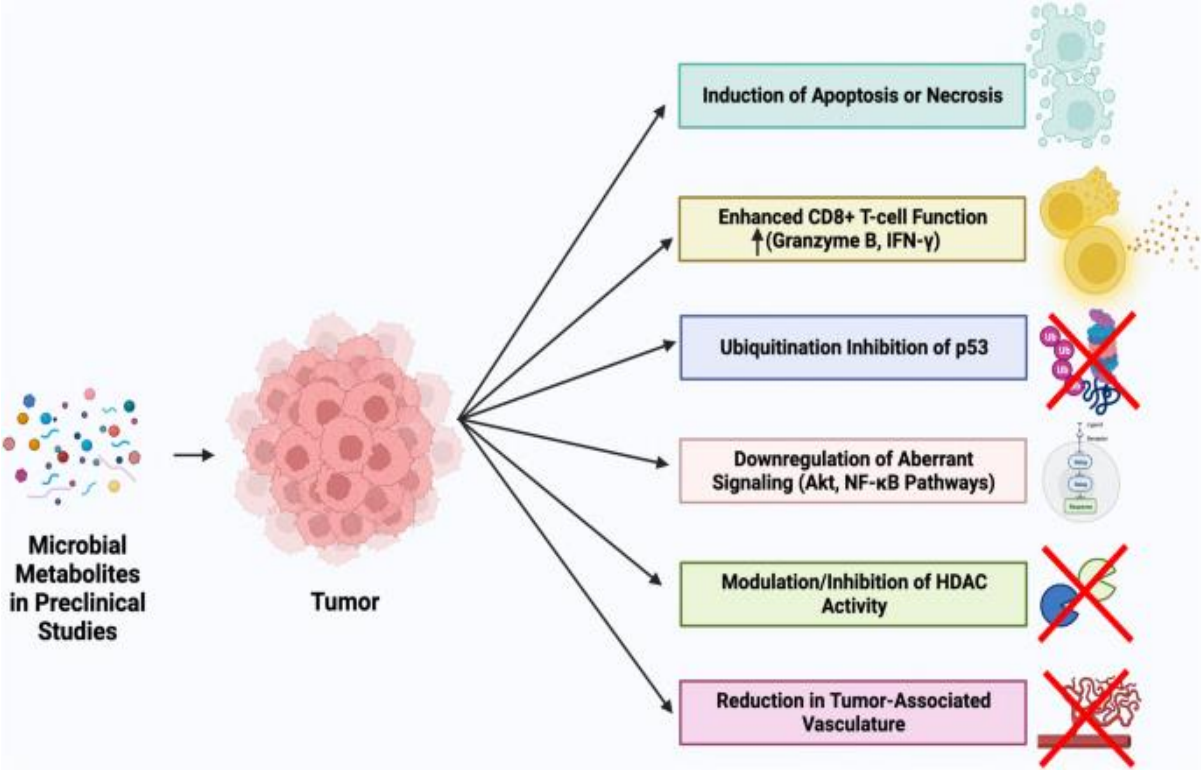

Figure 6. Mechanisms of action of anticancer agents generated from microbial metabolites under evaluation in preclinical investigations (26).

Microbial metabolites as immune modulatory agents

The immune system's primary function is to differentiate between "self" and "non-self." The immune system initiates a strong inflammatory response upon identifying alien or "non-self" antigens to eliminate foreign agents. Researchers are examining the potential of microbial compounds to bolster the immune system in the fight against cancer. Recent studies indicate that gut and tumor microbiome metabolites can modulate the immune system. In lab tests, pentanoate, a fatty acid produced by the gut bacteria *Megasphaera massiliensis*, significantly boosted the number of active IFN-γ+ and TNF-α+ CD8+ T cells. Pentanoate significantly reducing tumor growth. The mice that received T cells grown with pentanoate had more active IFN-γ+ and TNF-α+ CD8+ T cells in their tumors, along with higher levels of CD25. Giving pentanoate to T cells could help in treatment, as human Chimeric Antigen Receptor cells treated with pentanoate showed higher CD25 levels and produced more IL-2 (Figure 7). (27).

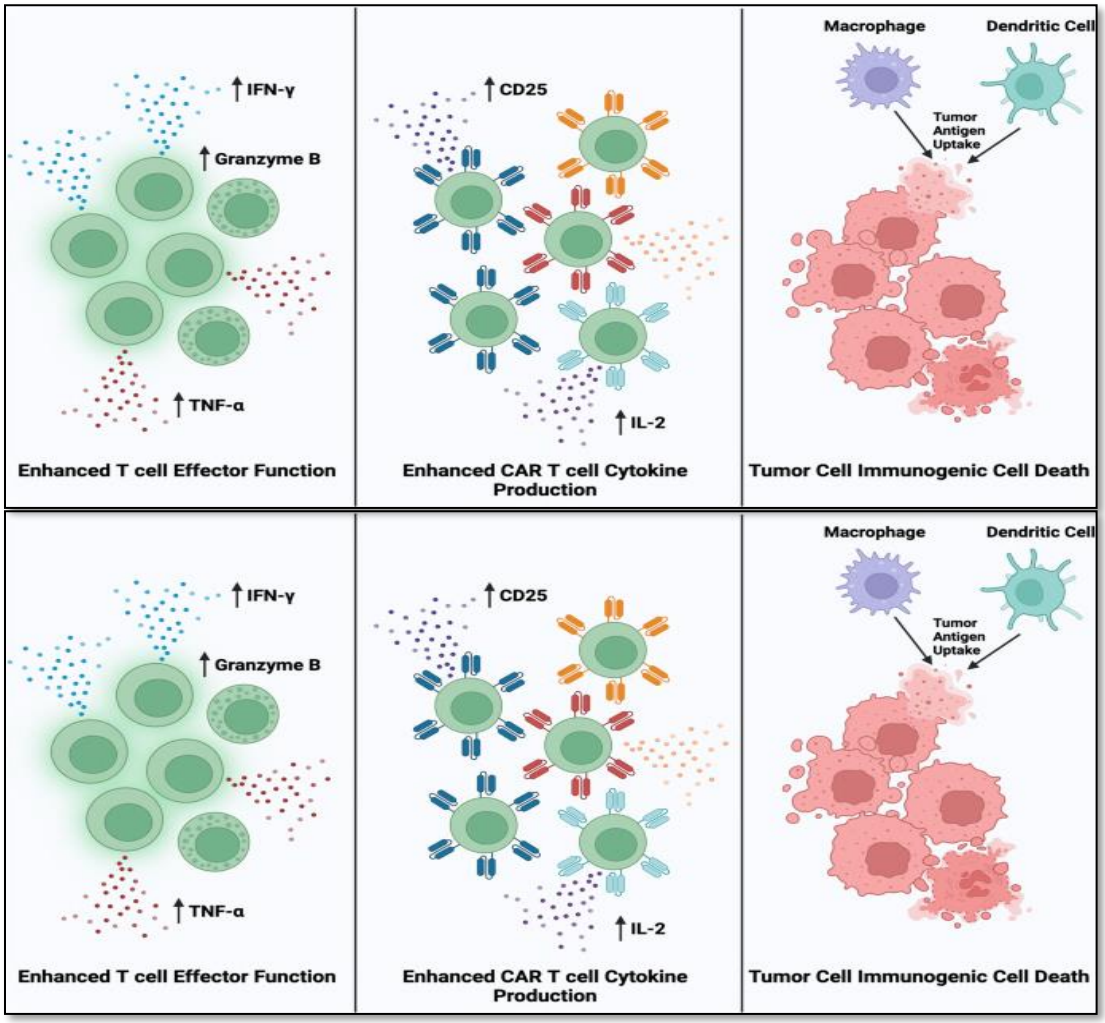

Figure 7. The diverse range of metabolites provides multiple strategies for cancer treatment (28).

These compounds can kill cancer cells in different ways, such as causing them to die naturally (apoptosis) or through cell injury (necrosis) (azurin-p28, butyrate, cordycepin, nisin); help the immune system by activating T-cells that attack tumors (butyrate, inosine, propionate); or keep p53 levels high by stopping it from breaking down (azurin-p28). These drugs can also target specific communication routes in cancer cells that are often altered, such as the PI3K-Akt and NF-κB pathways (cordycepin), stop enzymes that change how DNA is packaged (butyrate), and reduce the formation of blood vessels that supply tumors (nisin). By targeting these pathways, these compounds inhibit tumor growth and enhance the overall efficacy of existing cancer therapies.

Continued research into these mechanisms may further unveil innovative strategies for cancer treatment and prevention (27).

Tumor suppression and microenvironmental changes

Bacterial overgrowth in tumors promotes tumor regression through various mechanisms (Figure 8). Bacteria decrease tumors in the tumor microenvironment in different ways (29). Toxin generation and nutritional deprivation by Salmonella spp. Cause tumor cell death and autophagy (30). Salmonella infection also increases tumor cell Connexin 43 (Cx43). Which helps tumor cells attach to dendritic cells. The connections link tumor markers to dendritic cells, which reduces T cell indoleamine 2,3-dioxygenase (IDO) and activates CD8+ T cells (31,32). In the interactions between the host and pathogens, parts of bacteria like lipopolysaccharides (LPS) and flagellin, along with the growth of bacteria in tumor areas, cause macrophages, dendritic cells (DC), and neutrophils to move towards the tumors. Inflammasome activation leads to significant IL-1β production by macrophages and dendritic cells through two mechanisms: direct activation by Salmonella LPS interaction with TLR4 and indirect activation by tumor cells influenced by Salmonella. LPS can increase TNF-α release via CD14, TLR4, and myeloid differentiation main response 88. Additionally, flagellin and TLR5 signaling directly inhibit tumor cell proliferation and CD4+ and CD25+ regulatory T cell numbers. In cells, Salmonella flagellin activates the NLRC4 inflammasome, releasing IL-1β and IL-18. Cytokines can trigger cytotoxic T cells to produce IFN-γ and activate NK cells, and research indicates that Salmonella spp can complexly modulate these immune cells throughout a cancer response. This modulation boosts the anti-tumor immune response, improving cancer treatments. Understanding these systems may lead to new methods for using the immune system to fight cancer (33,34).

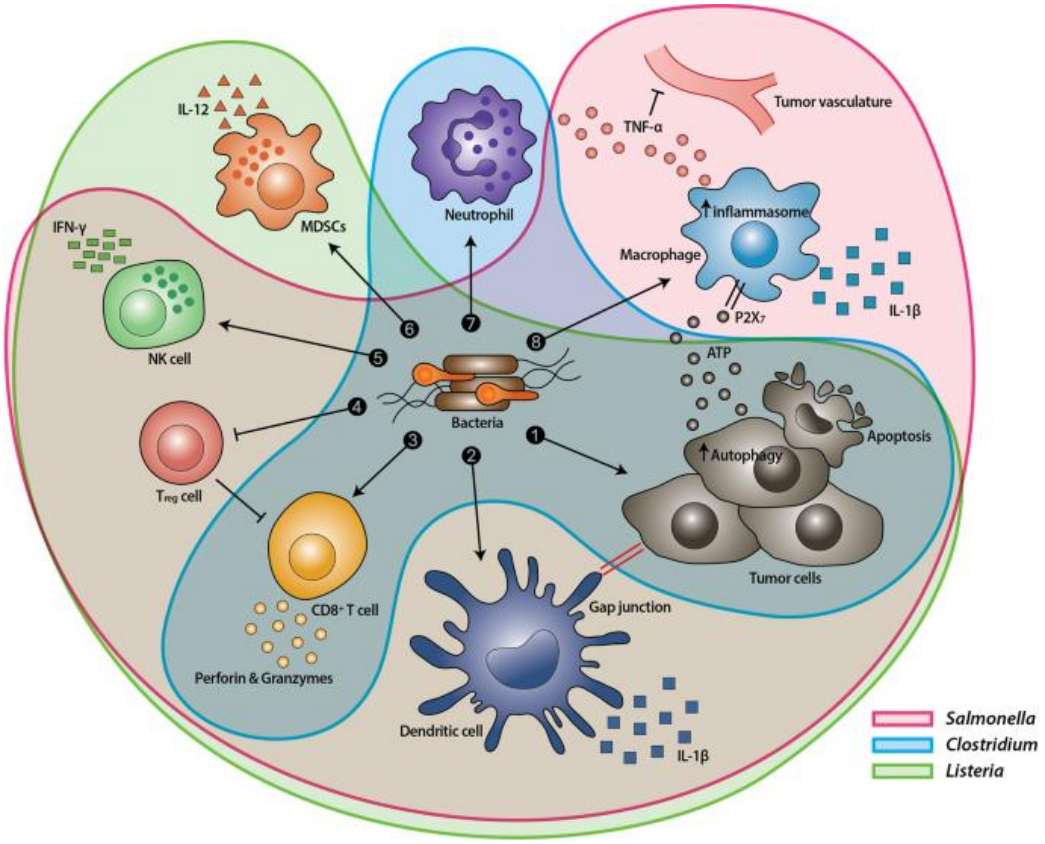

Figure 8. Mechanisms by which bacteria target tumors (35).

The process of systemically injecting bacteria leads them to gather within a tumor's microenvironment, where their interactions with cancer cells and surrounding elements can modify the body's immune response to cause tumor regression. *S. Typhimurium*, *Listeria*, and *Clostridium* toxins can induce apoptosis or autophagy in tumor cells (36,37). Salmonella toxins increase Connexin 43 (Cx43), which links tumor cells and dendritic cells (DCs). Helping DCs send tumor signals to the immune system, when dendritic cells (DCs) come into contact with tumor antigens and microorganisms. They produce IL-1β, which helps activate CD8+ T lymphocytes, by activating TLR5; bacterial flagellin boosts activated CD8+ T cells' antitumor response. Activated CD8+ T lymphocytes release proteins called perforin and granzyme that destroy tumor cells in both primary and spread-out cancers. Flagellin and TLR5 signaling diminish CD4+ CD25+ regulatory T (Treg) cells.

Improving activated CD8+ T cell antitumor response (38). S. Typhimurium flagellin causes NK cells to produce IFN-γ, an important protein for quick and lasting immune reactions. Listeria-infected MDSCs produce higher IL-12. Which improves CD8+ T and NK cell response (39). *S. Typhimurium* and Clostridium infections boost neutrophils. TNF- and TRAIL increase (40). Apoptosis by neutrophils boosts immunity and kills cancer cells. Macrophage inflammasome activation occurs when Salmonella-damaged cancer cells and bacteria (e.g., LPS and flagellin) interact, resulting in increased IL-1β and TNF-α production around the tumor NK: natural killer, regulatory T cells (also called Tregs) are regulatory T lymphocytes. These are myeloid suppressors. P2X7: extracellular ATP purinergic receptor 7 Lipopolysaccharide (41).

Conclusion

Microbially derived anticancer drugs like doxorubicin are effective but often cause severe side effects that limit their use. To address this, newer microbial-based therapies focus on higher cancer selectivity and immune system modulation. Microbial metabolites can activate innate immunity, enhance antigen presentation, and stimulate cytokine production, allowing more precise targeting of tumors. These immune-activating properties also support targeted treatments such as antibody–drug conjugates, where a toxic microbial molecule is delivered specifically to cancer cells via a monoclonal antibody. Such therapies have shown clinical success and are expected to improve further as new targets and stronger microbial compounds are developed. Microbial secondary metabolites remain a promising but largely untapped source for future cancer treatments.

Conflicts of interest

The authors declare that there is no conflict of interest.

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مركبات مضادة للسرطان من أصل بكتيري (مراجعة بحثية)

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الخلاصة

يمكن للكائنات الحية الدقيقة البيئية أن تُغيّر أو تُفكّك أدوية السرطان، مما يُسهم في التعطيل الإنزيمي للعوامل المضادة للأورام بواسطة الفطريات. ويمكن تقييم المجموعة الواسعة من قدرات التعديل الكيميائي المتاحة في مكتبة عينات التربة لدينا، والتي يُمكن استخدامها لتعديل أو تحليل الأدوية الطبية، لاكتشاف فعاليتها الجديدة على مختلف العوامل العلاجية. وقد يُحسّن الإزالة الانتقائية للسموم من الأدوية في الأنسجة غير الخبيثة جودة حياة مرضى العلاج الكيميائي. ويُعدّ استخدام البكتيريا والحويصلات الغشائية المشتقة منها (MVs) واعدًا للغاية في تطوير توصيل الأدوية المُوجّهة والقابلة للتحكم في مكافحة السرطان. وبالمقارنة مع أنظمة توصيل الأدوية التقليدية، تتميز البكتيريا وحويصلاتها الغشائية بخصائص مميزة كحاملات للأدوية لعلاج السرطان. فهي قادرة على تجاوز العوائق المادية للتمركز والتجمع في أنسجة الورم، مما يُحفّز الاستجابات المناعية المضادة للسرطان. بالإضافة إلى ذلك، يمكن تغييرها من خلال الأساليب الجينية والكيميائية لتعزيز إنشاء وتوصيل الأدوية المضادة للسرطان إلى أنسجة الورم، مما يساعد على جعل علاج السرطان أكثر أمانا وفعالية مع تقليل الضرر للخلايا السليمة.

الكلمات المفتاحية: جودة اللحوم، جسيمات أكسيد السيريوم النانوية، جسيمات أكسيد الزنك النانوية، الحيوانات المنوية البربخية، الكبش.