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Recent Updates and Advancement Related to Bacteria as DDS in Cancer Therapy.

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ABSTRACT:

Drug delivery systems (DDS) refer to techniques utilized to transport medications to specific tissues, organs, cells, and even subcellular compartments for effective drug release and absorption. These systems employ diverse drug carriers with the primary aim of enhancing the therapeutic effects of drugs and addressing challenges like restricted solubility, drug aggregation, diminished bioavailability, inadequate biodistribution, lack of specificity, or minimizing the adverse effects associated with therapeutic drugs.

Cancer stands as a prominent contributor to mortality and morbidity, characterized by a multifaceted pathophysiology. Conventional approaches to cancer treatment encompass chemotherapy, radiation therapy, targeted therapy, and immunotherapy. Nonetheless, obstacles like non-specificity, cytotoxicity, and the emergence of multi-drug resistance present significant hurdles in achieving effective cancer management. Bacteria and bacteria-derived membrane vesicles (MVs) offer exciting potential for advancing controllable targeted drug delivery in the fight against cancer. Compared to conventional drug delivery systems, these agents possess unique attributes that make them particularly promising as carriers for cancer treatment. They have the capability to overcome physical obstacles, allowing them to target and gather within tumour tissues and initiate anti-tumour immune reactions. Moreover, they can undergo genetic and chemical modifications to generate and transport anti-cancer agents into tumour tissues, enhancing the safety and effectiveness of cancer treatment while diminishing cytotoxic impacts on healthy cells.

KEYWORDS: Antitumour Response, Bacteria-Mediated Therapy, Cancer Therapy.

I. INTRODUCTION:

Cancer refers to a group of illnesses marked by uncontrolled and randomised cell division, along with invasive tendencies. Substantial efforts spanning numerous years have been dedicated to identifying various cancer risk factors. Unhealthy lifestyle choices have also been significantly associated with the development of certain cancers, alongside specific environmental factors like radiation and pollution, an imbalanced diet, smoking, stress, and sedentary behaviour, significantly influences the determination of cancer risk.[1]Globally, cancer poses a substantial public health challenge, ranking as the second leading cause of death. Research conducted by the American Cancer Society indicates that by the end of 2021, there were estimated to be 1.9 million new cases[2].

Bacteriotherapy has been proposed to progress and raise the effectiveness of current conventional cancer therapy.The idea of using microorganisms in cancer therapy originate in the late 19th century, but recent advancements in molecular biology have significantly propelled research in this area.[3] Numerous studies have demonstrated that bacteria, whether acting independently or in conjunction with conventional treatments, hold potential as potent anti-tumour agents. In response to the limitations of standard therapies, researchers have successfully developed bacteria-mediated tumour therapy, notably utilizing probiotic Escherichia coli Nissle 1917 (EcN) for targeted delivery of cytotoxic proteins against colorectal cancer. Additionally, investigations have

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focused on optimizing therapeutic effectiveness. Bacteria can exert anticancer effects by bolstering human immunity through inflammasome pathway activation, functioning either as immune-stimulating vaccines or carriers for delivering antitumour agents.[4]

Probiotic bacteria and gut microbiota play integral roles in cancer prevention and treatment by modulating levels of anti-inflammatory cytokines, thereby reducing the risk of carcinogenesis. Moreover, early-stage cancers may be targeted through phagocyte activation and dairy product consumption has been linked to decreased colon cancer risk. Consequently, probiotic bacteria hold promise as a valuable tool in cancer prevention and diagnosis. However, the implementation of bacteria in cancer treatment presents notable challenges.[5]

BACTERIA IN CANCER THERAPY:

Cancer presents a formidable challenge, demanding a comprehensive treatment approach. The historical significance of bacteria in combating cancer traces back more than a century, with early clinicians employing live bacteria like Streptococci and Clostridia for treatment showed in figure 1. Today, genetically modified bacteria are the primary focus for such endeavours. Various strategies harness bacteria for cancer therapy, including utilizing their inherent toxicity, combining them with other treatments, controlling the expression of anticancer agents, expressing tumour-specific antigens, facilitating gene transfer, employing RNA interference, and catalysing pro-drug activation. These approaches may involve the use of whole live bacteria, attenuated strains, or genetically engineered variants, either individually or in conjunction with standard treatments[6].

Various experimental cancer models have been tested with bacterial interventions. The most common bacterial genera used in these studies include Salmonella, Lactobacillus, Escherichia, Pseudomonasand Streptococcus[7]. These investigations have explored the potential of certain bacterial species like Clostridia, Bifidobacteria, and Salmonellae as vectors for delivering or expressing genes associated with tumour suppression, anti-angiogenesis, suicide, or tumour-associated antigens in animal models harbouring different types of tumours. Clinical trials have demonstrated partial responses, warranting further exploration in human subjects. Additionally, modified bacteria have shown promise for theragnostic applications, as they can be detected using imaging techniques like magnetic resonance imaging (MRI) or positron emission tomography (PET), serving as both therapeutic and diagnostic agents[8].

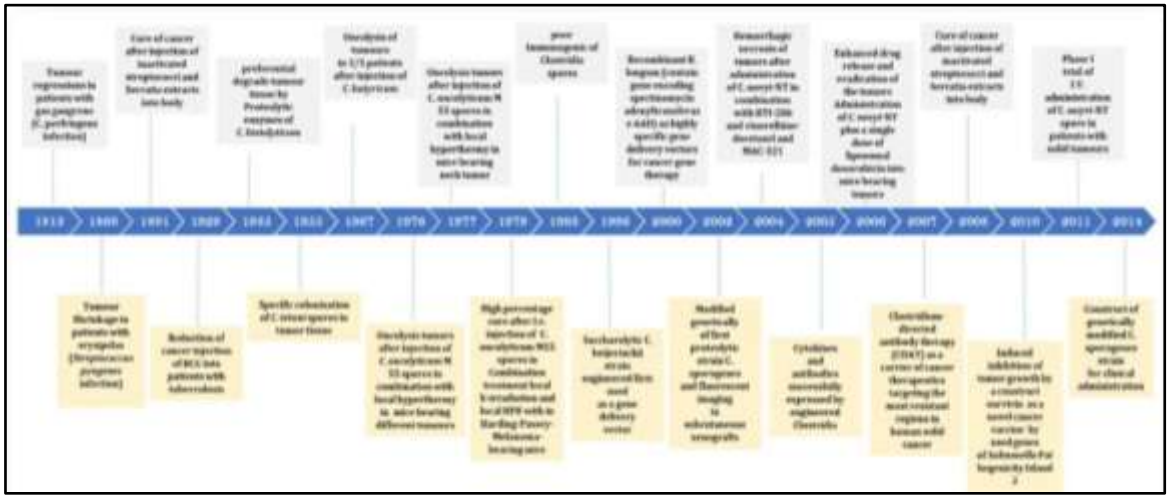

Figure 1. Therapeutic bacteriauses history in oncology.

MECHANISM OF DRUG DELIVERY THROUGH BACTERIA:

Bacterial therapeutics for cancer treatment focus on selecting non-pathogenic species that colonize tumour regions, benefiting from the supportive tumour microenvironment and host cell protection. While the exact mechanisms are unclear, four potential mechanisms for tumour suppression have been proposed (Fig. 2). Recent literature highlights successful cancer treatment using bacteria-mediated drug delivery, demonstrating promising advancements in targeted therapy within the cancer micro environment.[9]

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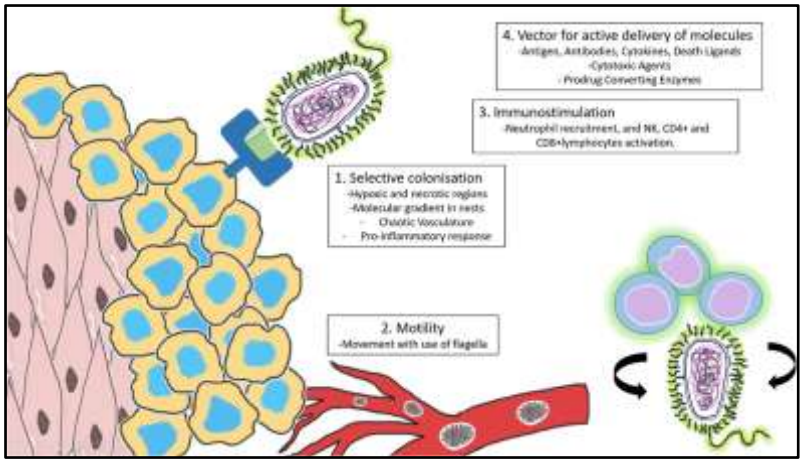

Fig. 2Bacterial Mode of Action in Anti-Cancer Therapy.

ENDOGENOUS CELL DEATH- INDUCING AGENTS:

Utilizing endogenous cell-death-inducing molecules, like TNF-related apoptosis presents a localized and controlled approach for cancer therapy. However, challenges arise due to the natural tumour tropism of bacteria like S. typhimurium.[10] TRAIL, activating extrinsic apoptosis, selectively induces tumour cell death via death receptors 4 and 5, without harming normal cells. Clinical trials employing recombinant human TRAIL highlight its promising potential as a targeted therapeutic agent for cancer treatment.[11]

IMMUNE EFFECTORS:

The immune system of host plays a crucial role in controlling malignant cell formation through organized cytokine signalling. While many cytokines pose systemic toxicity risks in cancer therapy, S. typhimurium-mediated delivery of select cytokines like IL-4and TNFSF14 has demonstrated significant tumour growth reduction via localized synthesis, triggering juxta-tumoral immune responses. IL-4 and IL-18 activation boosts IFN-γ levels, inhibiting stromal fibroblast growth and angiogenesis, while TNFSF14 causes proliferation of T cell, dendritic cell growth, and cancer cell apoptosis.[12]

TUMOUR IMMUNIZATION:

Stimulating the immune system is a viable strategy to control tumour growth. Recent research highlights the importance of an active immune system to support an effective immune response. Tumours undergo a process known as 'immunoediting,' involving three phases: elimination, equilibrium, and escape. In elimination, immunogenic tumours are aggressively eradicated, followed by an equilibrium phase where tumour growth is restrained. However, some tumour cells develop resistance, aided by immune suppressor cells, leading to the escape phase where tumours evade immune attack through mutation. S. typhimurium has been implicated in CD8 formation, aiding in this immunoediting process.[13]

ANTICANCER DRUG DELIVERY THROUGH BACTERIA:

Since the late 1800s, bacteria and bacterial spores have been utilized in the treatment of tumours to transport a range of therapeutic compounds, such as poisonous proteins and low molecular-weight medications. Researchers observed that bacteria could infiltrate tumour tissues and impede their growth. Several anaerobic bacterial species have demonstrated the ability to surmount physiological barriers that hinder conventional chemotherapy and thrive selectively in tumours, owing to the hypoxic environment within tumours. It helps to precise local targeting of tumour. Challenges such as side effects like dose-dependent from bacteria and minimum therapeutic efficacy due to bacterial clearance by the reticuloendothelial system before reaching specific targets have been observed. Consequently, significant efforts have been devoted to reducing systemic toxicity through chemical and genetic modifications of bacteria.[14]

BACTOFECTION:

Bactofection is a method which involves inserting genes directly into the desired organism, tissue and organ using bacteria; this fundamental idea was initially presented thirty years ago. When it comes to cancer therapy, bacteria transfer

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plasmids containing the therapeutic (like anticancer) gene into tumour cells while a eukaryotic promoter controls the gene's expression. The host cell's transcription and translation machinery express the therapeutic gene when the plasmid has entered the target cell and been released into the cytoplasm and cell nucleus. The plasmid DNA transferby bacteria into mammalian cells offers a powerful method for producing heterologous proteins encoded by plasmids in a various cell types.

In cancer therapy, therapeutic proteins typically act as cytotoxic agents towards target cells and surrounding ones by initiating suicide pathways. Engineered bacteria used in this therapy undergo lysis upon entering target cells and releases plasmids in the cytoplasm to prevent long bacterial survival in the host. Bacterial lysis products may serve as foreign antigens, stimulating cellular immune responses, potentially enhancing tumour-ablating effects, although severe immune reactions, like cytokine storms, must be avoided. Genetically attenuated bacterial strains are commonly used to prevent adverse effects, although their efficacy in clinical trials remains uncertain. Salmonella strains are extensively studied for bactofection-mediated cancer therapy, showing promise in inhibiting tumour growth and reducing microvessel density. For instance, Salmonella cholerae Suis carrying plasmids encoding endostatin selectively inhibited tumour growth with decreased microvessel density. Additionally, bactofection using auxotrophic Salmonella carrying plasmids encoding cytokines and antiangiogenic molecules has shown effectiveness in experimental tumour models, highlighting its potential in cancer therapy.[15]

DNA VACCINATION:

DNA vaccination, facilitated through bactofection, utilizes plasmids encoding tumour-specific antigens to induce humoral and cellular immune responses, offering protection against tumours. Preclinical studies primarily employ attenuated-strain Salmonella Typhimurium due to its proven efficacy. Oral Salmonella-based DNA vaccines targeting antigens like VEGFR-2, IL-18, surviving and others have shown effectiveness in suppressing tumour growth across various cancer models. T-cell epitopes from tumour antigens are key targets, suggesting a breakdown of immunological tolerance to self-antigens. Though the molecular mechanisms remain unclear, further research is crucial, especially considering the overlap between DNA vaccination and bactofection. While as an undesired side effect in bacterial gene therapy causes immune activation, it's pivotal for the therapeutic effect of DNA vaccination. The oral administration potential of therapeutic bacterial strains underscores the promise of bacterial mediated DNA vaccination as a strategy in treatment of cancer, necessitating comprehensive mechanistic understanding before advancing to clinical trials.[16-17]

BACTERIALLY MEDIATED DELIVERY OF RNAI:

A promising advancement in anticancer therapy combines bacteriotherapy with RNA interference (RNAi), leveraging bacteria as efficient gene delivery vectors. Two approaches, transkingdom RNAi (tkRNAi) and bacterially mediated RNAi (bmRNAi), have been developed for this purpose. In tkRNAi, genetically modified bacteria produce and deliver short hairpin RNA (shRNA) against oncogenes or tumour-expressed factors into tumour cells, inducing gene silencing via the RNAi pathway. This system, exemplified by invasive E. coli, has shown efficacy in delivering shRNA against cancer-associated genes in mouse models. Companies like Cequent Pharmaceuticals and ViThera Laboratories are developing tkRNAi for various human and veterinary applications, including colon cancer treatment. In contrast, the bmRNAi system relies on carrier bacteria to transfer shRNA expression plasmids to host cells, utilizing the host cell's transcriptional machinery for shRNA production, akin to bactofection. Attenuated Salmonella Typhimurium has been used to deliver shRNA expression plasmids against cancer-related genes in mouse models of various cancers. While bacterially mediated RNAi presents a promising avenue for cancer therapy, further research is needed to explore its full potential and applications.[18-19]

BACTERIAL COMPONENTS OF ANTITUMOUR TREATMENT:

Bacterial toxins such as Coley toxin, diphtheria toxin, and Clostridium perfringens enterotoxin, as well as enzymes like L-asparaginase and arginine deaminase, impede tumour growth by inducing cell-cycle arrest and interrupting signal pathways. Biosurfactants such as surface and prodigiosin-like pigments also aid in this process. Additionally, bacterial components such as the outer surface, membrane, wall, and biofilm

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stimulate the immune response to selectively eliminate tumour cells.

BACTERIAL TOXINS:

In 1891, by administering a mixture of live bacteria and heat-inactivated bacteria, Dr. Coley achieved successful cancer remission in patients. The bacteria known as "Coley toxin," derived from Bacillus mirabilis and Streptococcus pyogenes, marking the inception of bacterial cancer treatment.[20-21] Further research exotoxins encompass from Streptococcus pyogenes and Serratia marcescens. Additionally, S. pyogenes produces pyrogenic exotoxins SpeA, SpeB, and SpeC, which non-specifically activate CD4+ lymphocytes, enhancing cytokine secretion. Likewise, prodigiosin, a small molecular weightand heterocyclic tripyrrole toxin with red pigment from S. marcescens, exhibits antitumour properties, inducing potential antitumour effectin combination with other constituents.[22]

BACTERIAL ENZYMES:

L-asparaginase is a bacterial enzyme which is sourced from E. coli. It serves as potential therapeutic agent against cancer. It slows down the growth of malignant cells by catalyzing hydrolysis. of asparagine, leading to a reduction in its blood concentration and inducing toxicity in cell lines like MCF-7, HepG2, and SK-LU-1. Asparaginase which is derived from bacteria has gained approval for treating non-Hodgkin's lymphoma and acute lymphoblastic leukemia. Furthermore, research by Fiedler et al. revealed that arginine deaminase produced by Streptococcus pyogenes, which depletes arginine within tumour cells, thereby Decreasing the growth of arginine-deficient glioblastoma multiforme tumours .[23-24]

BIOSURFACTANT:

Biosurfactants, such as cyclic lipopeptides from Bacillus subtilis natto TK-1 and surfactin, demonstrate significant antitumour activities by inducing apoptosis, cell-cycle arrest, and inhibiting cancer cell proliferation. For instance, cyclic lipopeptides induce apoptosis and cell-cycle arrest in human breast cancer cells, while surfactin increases calcium ions and tumour suppressors, leading to apoptosis and cell-cycle arrest.[25-26] Epsilon-poly-L-lysine from Marine Bacillus subtilis sp. exhibits cytotoxicity against cervical and liver cancer cells. Additionally, cyclic lipopeptides like viscosin from Pseudomonas libanensis m9-3 inhibit breast and prostate cancer cell proliferation and migration. Apoptosis in B-cell chronic lymphocytic leukemia induced by Serratamolide from Serratia marcescens. Prodigiosin-like fragments and roseophilin from Streptomyces sp. demonstrate cytotoxic activity against various cancer. Biosurfactants also show promise in microemulsion-based drug formulations and can enhance cellular delivery of liposome siRNA, enhancing antitumour effectiveness. Overall, biosurfactants offer potential for broad-spectrum antitumour treatments and safe utilization in drug-delivery systems.

Table 1. Some Biosurfactants having antitumour activity against tumour cells.[27]

Biosurfactant	Cancer Type	
Cyclic lipopeptide	Bacillus subtilis natto TK-1	Breast cancer
Surfactin	Bacillus subtilis natto T-2	Breast cancer
L-lysine biopolymer	Marine Bacillus	Liver carcinoma
Epsilon-poly-L-lysine	subtilis sp.	Cervix adenocarcinoma
Viscosin	Pseudomonas libanensis m9-3	Breast cancer
Roseophilin	Streptomyces sp.	Hematologic cancer, Colon cancer

II. CONCLUSIONS AND FUTURE PROSPECTS:

It is critical to find efficient and secure delivery systems for the controlled release of novel cancer treatments as they are created and tested in clinical trials. The development of anticancer drug delivery strategies has advanced significantly in recent studies, but there are still major challenges that must be solved immediately. These challenges include decreasing the cytotoxic effects on healthy cells by drugs, increasing drug accumulation attumour sites, and improving the effectiveness forelimination of tumour.

We have briefly reviewed the present state of development on the use of bacteria and their vesicles as carrier of drugin cancer treatment in this study. The properties of bacteria and their derivatives include the ability to target tumours,

modify them easily with an infinite capacity for genepacking, and trigger an immune response. Because of these benefits, tumour-targeting bacteria and their MVs are perfect for the targeted release of immunotherapeutic, photothermal, radiotherapeutic, and chemotherapeutic drugs. With the rapid progress of advanced modification techniques for creating bacterial MVs and tumour-targeting bacteria, these drug carriers have a lot of potential for use in the fight against cancer expected to be another potent tool in therapeutic settings soon.

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