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Insights into Bacteriotherapy: Harnessing Bacteria for the Greater Good

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ABSTRACT

Bacteriotherapy, the process of using bacteria or bacterial products for therapeutic purposes, is gaining more popularity over the years. It has been used for the prevention and treatment of a wide variety of ailments and has been used as either the primary mode of therapy or in conjunction with other therapies. Bacteriotherapy has employed live bacteria, bacterial products, probiotics, prebiotics, synbiotics, and engineered organisms. There have been significant advancements over the years but there are still challenges that need to be addressed. In this article, we review bacteriotherapy in the context of infectious diseases, inflammatory diseases, and cancers.

Keywords: Bacteriotherapy; Probiotics; Prebiotics; Synbiotics; Fecal Microbiota Transplantation

Abbreviations: FMT: Fecal Microbiota Transplantation; IBD: Inflammatory Bowel Disease; CDIs: *C. difficile* Infections; UTIs: Urinary Tract Infections; TURBT: Transurethral Resection of Bladder Tumor; BCG: Bacillus Calmette-Guerin

Introduction

The concept of using bacteria to treat ailments is ancient. There are records that fecal slurries in the form of 'yellow soup' were consumed in the 4th century for treating food poisoning and diarrhea (Stripling C, et al. [1]). Since then, many advancements have been made to use bacteria and bacterial products as therapeutics, referred to as bacteriotherapy, for treating a variety of ailments (Huovinen, et al. [2]). Bacteriotherapy has been successfully employed for the prevention and treatment of different conditions (Otto [3]). From using live naturally occurring bacteria, bacterial compounds and metabolites, to synthetic compounds and engineered bacteria, bacteriotherapy has come a long way (Figure 1). In the current minireview, we will summarize different bacteriotherapy-based strategies that have been used for the prevention or treatment of infectious diseases, inflammatory diseases, and cancer.

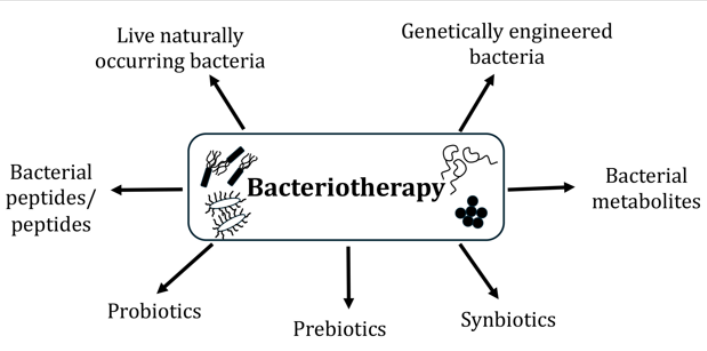

Figure 1: Bacteriotherapy involves the use of bacteria and their products for different therapeutic purposes. The image created by J. K. Iyer is under the CC0 license.

Bacteriotherapy and Infectious Diseases

Bacteriotherapy has been used to treat different types of diseases caused by pathogens. It is most popularly known for its therapeutic potential in treating gastrointestinal infections caused by *Clostridioides difficile* (*C. difficile*). *C. difficile* infections (CDIs) are treated with antibiotics and immunotherapy but bacteriotherapy has also been proven to be an effective strategy, especially for recurrent infections caused by *C. difficile* (Al Jashaami, et al. [4,5]). CDIs are associated with dysbiosis of the gut microbiome due to factors such as antibiotic use, genetic predisposition, weakened immune systems, and others. Fecal microbiota transplantation (FMT), also known as fecal bacteriotherapy, involves addressing this dysbiosis by introducing normal fecal microflora associated with healthy individuals into a patient (Bakken, et al. [6,7]). Fecal transplants are effective against primary and recurrent CDIs but are used more commonly to treat recurrent CDIs (Kaakoush, et al. [8]). Fecal microflora can be introduced in the form of feces from healthy donors or mixtures of specific bacterial strains that are found in the gut and can be administered through enemas, colonoscopy, or oral capsules (Rode, et al. [9-11]). Due to the efficacy of FMT and relatively low risks associated with the therapy, the FDA (Food and Drug Administration) has approved microbiome-based therapies for the treatment of CDIs (Cold, et al. [11,12]).

In addition to FMT, probiotics and prebiotics also show promise in the treatment of infectious diseases, especially those associated with the gastrointestinal and urogenital tract (Li, et al. [13,14]). Probiotics are live microorganisms that provide health benefits when administered in adequate amounts. The most commonly used probiotics to treat gastrointestinal ailments belong to the genera *Lactobacillus* and *Bifidobacterium* (Patel, et al. [14]). When *Lactobacillus rhamnosus* was administered to children diagnosed with rotaviral infections, there was a significant decrease in the duration of diarrhea (Szyman´ski, et al. [15]). Probiotics can also be used to prevent and treat diarrhea caused by other agents in children and adults (Newberry, et al. [16,17]). Different systematic reviews have demonstrated that when probiotics are included in standard therapies, there is higher eradication of *Helicobacter pylori* along with lower adverse events (Mestre, et al. [18-20]). In addition to gastrointestinal infections, probiotics have also shown promise in the treatment and prevention of respiratory tract infections (Bellussi, et al. [21]). In clinical trials as well as in vivo animal models, probiotics that include different species of *Lactobacillus* and *Bifidobacterium* have aided in the reduction of incidence and duration of respiratory tract infections caused by different viruses and bacteria (Darbandi, et al. [22,23]). Probiotics have also been used in the prevention and treatment of urogenital diseases, including urinary tract infections (UTIs) (Kenneally, et al. [24]). UTIs are commonly caused by bacteria and routinely treated with antibiotics (Flores-Mireles, et al. [25,26]). This has resulted in a dramatic increase of antimicrobial resistance among uropathogens and the need for different treatment strategies (Gupta, et al. [27,28]). Probiotics can directly influence the vaginal flora when administered orally or in the form of vaginal suppositories (Patel, et al. [14]). A non-inferiority study comparing orally administered probiotic treatment with a trimethoprim-sulfamethoxazole treatment regimen in women with recurrent UTIs demonstrated that, while probiotic treatment did not meet the non-inferiority criteria in the prevention of UTIs, the probiotic group did not show an increase in antibiotic resistance (Beerepoot, et al. [29]). A recent study compared the effect of orally and vaginally administered probiotics on the prevention of recurrent UTIs and found that prophylactic supplementation of vaginal probiotics in the presence or absence of oral probiotics resulted in significantly lesser incidences of UTIs (Gupta, et al. [30]).

In addition to probiotics, prebiotics and synbiotics can also aid in the prevention or treatment of some infectious diseases (Markowiak, et al. [31]). Prebiotics are non-digestible oligosaccharides (Figure 2) that can stimulate the growth of selective and beneficial gut bacteria, thus promoting gut microbiota homeostasis (You, et al. [32]). Most prebiotics are oligosaccharides like fructo-oligosaccharides, galacto-oligosaccharides, polydextrose, etc., and are fermented to form short chain fatty acids (Davani-Davari, et al. [33]). These short chain fatty acids influence different physiological processes in the body and improve immune responses (Fusco, et al. [34]). Prebiotic administration of fructo-oligosaccharides in patients with CDIs resulted in lesser incidence of relapse in diarrhea (34% in placebo vs 8.3% in treatment group) demonstrating the therapeutic effect of the prebiotic (Lewis, et al. [35]). Prebiotics are not effective in the treatment of other infections by themselves (van Stuijvenberg, et al. [36]) but in combination with probiotics, the resulting synbiotics are usually more effective. When infants were provided with a mixture of *Lactobacillus rhamnosus* GG and LC705, *Bifidobacterium breve* Bb99, and *Propionibacterium freudenreichii* ssp *shermanii* along with galacto- oligosaccharide for 6 months, they had fewer respiratory tract infections than the placebo group (Kukkonen, et al. [37]). As more clinical trials are performed, the effects of probiotics, prebiotics, and synbiotics on the prevention and treatment of infectious diseases will become clearer.

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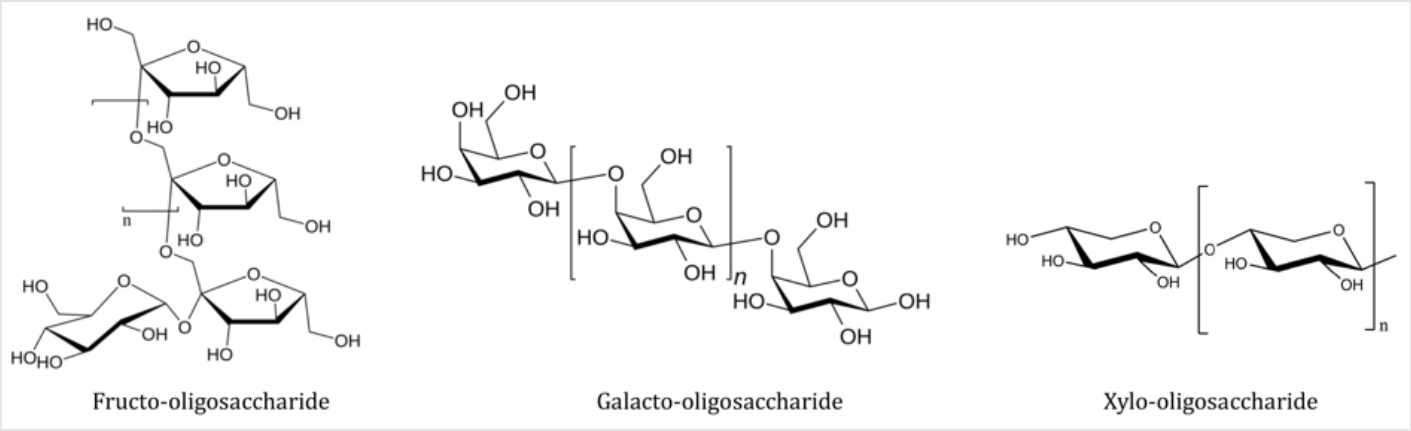

Figure 2: Different prebiotics that have been commonly used.

The use of antimicrobial agents, such as antibiotics, is also a form of bacteriotherapy because many antibiotics are metabolites obtained from bacteria. Since Sir Alexander Fleming discovered penicillin from the fungus *Penicillium* in 1928, there have been many classes of antibiotics that have been identified and made available as therapeutics (Hutchings, et al. [38]). Many classes of antibiotics were isolated from actinomycetes, especially from the genus *Streptomyces* (de Lima Procopio, et al. [39]). In fact, antibiotics obtained from *Streptomyces* are some of the most widely prescribed therapeutics to treat bacterial infections (Quinn, et al. [40]). Some common classes of antibiotics obtained from *Streptomyces* (Figure 3) include aminoglycosides, macrolides, glycopeptides, 'and tetracyclines (Alam, et al. [41]). Due to an increase in antimicrobial resistance among pathogens, there is an urgent need for finding novel antimicrobial agents and other therapeutics (De Kraker, et al. [42]). The novel antibiotics can be in the form of newly discovered molecules or chemical modifications of existing molecules to increase their potency and efficacy. By using innovative culturing methods like iChip technology, researchers can identify antibiotics produced by bacteria that are not easy to culture using traditional methods (Chabib, et al. [43,44]). iChip technology has led to the discovery of novel antibiotics such as teixobactin and clovibactin among others (Chabib, et al. [43-46]). Chemical synthesis approaches that aid in changing the structure of existing antibiotics has led to the creation of antibiotics like iboxamycin and cresomycin that display broad spectrum antimicrobial properties (Brodiazhenko, et al. [47-49]).

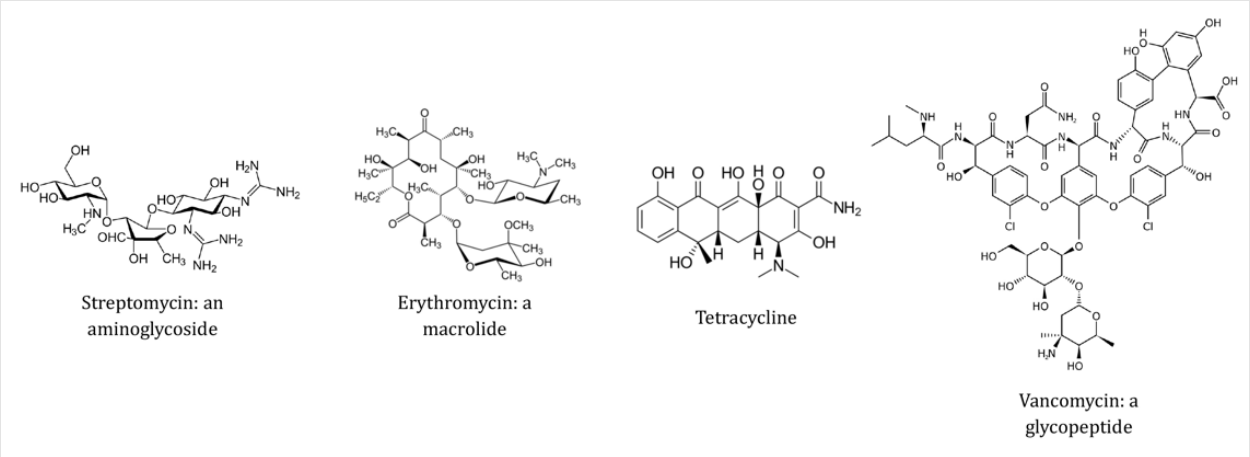

Figure 3: Different classes of antibiotics obtained from *Streptomyces* spp.

In addition to antibiotics, bacteria can make antimicrobial compounds that negatively affect growth of other bacteria (Danquah, et al. [50]). These compounds include bacteriocins, rhamnolipids, siderophores, and polyketides, which can be used for treatment of infections themselves or in conjunction with other therapeutics (Figure 4). Bacteriocins are ribosomally synthesized antimicrobial peptides produced by Gram-positive and Gram-negative bacteria (Darbandi, et al. [51]). Bacteriocins produced by lactic acid bacteria like *Lactococcus lactis* and *Bacillus* species can inhibit the growth of different types of bacteria including those that are multidrug resistant (Aunpad, et al. [52,53]). Rhamnolipids are another class of antimicrobial molecules that are produced by different bacteria and the rhamnolipids synthesized by *Pseudomonas* and *Burkholderia* species have been well characterized (Kumar, et al. [54,55]). These molecules are glycosurfactants that can disrupt bacterial cell membranes (Herzog, et al. [56]). Rhamnolipids isolated from *Pseudomonas aeruginosa* have demonstrated antimicrobial activity towards Gram-positive organisms like *Staphylococcus aureus* and *Enterococcus faecium*, Gram-negative organisms like *Acinetobacter baumannii*, and viruses like respiratory syncytial virus and coronavirus (Cerqueira dos Santos, et al. [57,58]). Siderophores are antimicrobial molecules that aid with iron acquisition and are produced by Gram-positive and Gram-negative bacteria in iron deficient conditions (Kramer, et al. [59]). Some siderophores inhibit the growth of pathogenic protists like *Plasmodium falciparum* and *Trypanosoma cruzi* while some are being tested to be used as 'Trojan horses' in the effort to make drug delivery more efficient (Khasheii, et al. [60]). By linking antimicrobial compounds with siderophores, these compounds can be introduced into the pathogenic bacteria when it transports the siderophore and thereby interfere with cellular processes (Peukert, et al. [61]).

In addition to the antimicrobial molecules mentioned above, there are other naturally occurring molecules that are used as therapeutics. There is also a lot of interest in designing novel molecules to treat infectious diseases. For this purpose, researchers are using more and more in silico methods such as quantitative Structure-Activity Relationship analysis, molecular docking, and structure-based virtual screening, to design novel molecules to treat infectious diseases (Filipić, et al. [62]).

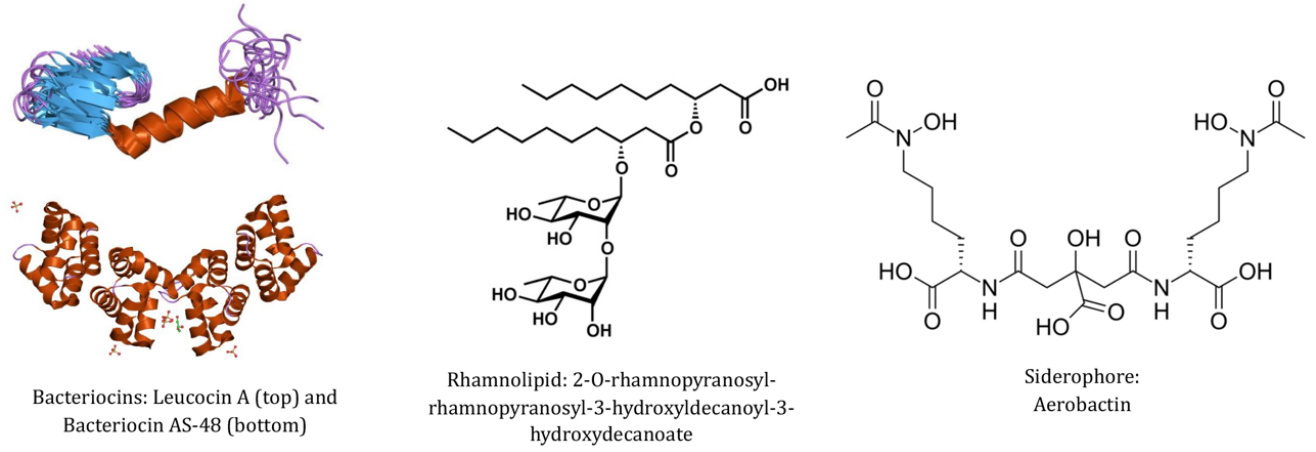

Figure 4: Examples of bacteriocins, rhamnolipids, and siderophores that exhibit antibacterial properties.

Bacteriotherapy and Inflammatory Diseases

Bacteriotherapy has been successfully used in the treatment of different diseases that arise due to inflammatory responses including inflammatory bowel disease, cystic fibrosis, and dermatitis. Inflammatory bowel disease (IBD), which comprises Crohn's disease and ulcerative colitis, is caused by different factors such as genetic predisposition, aberrant immune responses, and gut microbiome dysbiosis. It can be treated by different bacteriotherapeutics like antibiotics, probiotics, synbiotics, and fecal transplants (Hu, et al. [63]). The efficacy of the antibiotics, ciprofloxacin, metronidazole, rifaximin, and clarithromycin, have been tested in different randomized clinical trials and rifaximin was found to be the most effective among them (Nitzan, et al. [64]). In one study, patients with moderately active Crohn's disease who received 800 mg of an extended intestinal release rifaximin twice a day over a span of 12 weeks, showed 62% remission compared to 43% who received the placebo (Prantera, et al. [65]).

Probiotic therapy has also shown promise in the treatment of IBD. Patients with mild to moderate ulcerative colitis showed a significant decrease in their ulcerative colitis disease activity index and Rachmilewitz endoscopic index when they were treated with *Bifidobacterium longum* 536 (Tamaki, et al. [66]). Another study demonstrated

that 42.7% of patients that were provided with VSL#3, a probiotic preparation comprising of four *Lactobacillus* species, three *Bifidobacterium* species, and *Streptococcus thermophilus*, achieved remission compared to 15.7% of patients who were given the placebo (Sood, et al. [67]). There is not much evidence to support that prebiotics can be used for the treatment of IBD but synbiotics-based therapy has shown to alleviate symptoms in ulcerative colitis patients and improvement in clinical activity (Dhaneshwar, et al. [68]). In addition to antibiotics, probiotics and synbiotics, FMT has also been used in the treatment of IBD (Hu, et al. [63]). A study that involved patients with refractory Crohn's disease found that 86.7% of the patients showed clinical improvement and 76.7% of the patients showed remission upon FMT treatment (Cui, et al. [69]). Similarly, 87.5% patients with ulcerative colitis achieved a clinical response to FMT and had reduced levels of different cytokines in the serum, indicating that immune responses can be modulated by FMT (Wang, et al. [70]).

In addition to IBD, bacteriotherapy has been utilized to treat skin conditions like atopic dermatitis. A phase 1 randomized clinical trial involving patients with atopic dermatitis caused by *Staphylococcus aureus* showed that topical application of *Staphylococcus hominis* A9 resulted in fewer adverse events associated with atopic dermatitis (Nakatsuji, et al. [71]). In addition to *Staphylococcus hominis*, other bacteria such as *Roseomonas mucosa* have shown therapeutic activity against atopic dermatitis (Myles, et al. [72]). A meta-analysis of studies involving the use of probiotics for the treatment of atopic dermatitis found that probiotics decreased the Scoring Atopic Dermatitis (SCORAD) and improved quality of life (Umborowati, et al. [73]) in patients. More clinical studies need to be performed to gain more insight into the molecular mechanisms of action of bacteriotherapy in inflammatory diseases.

Bacteriotherapy and Cancer

Cancers are normally treated using multi-pronged approaches like chemotherapy, surgery, and radiotherapy. Each one of these has significant risks and adverse side effects associated with it; hence, more alternative and targeted therapies are needed. The concept of using bacteria to treat cancer was used by William B. Covey, a bone sarcoma surgeon, who used a mixture of heat-killed *Streptococcus pyogenes* and *Serratia marcescens* to treat malignant tumors (Nguyen, et al. [74,75]). Since then, different bacteria and bacterial products have been tested for their anti-cancer potential. Studies have demonstrated that colonization of instilled bacteria in the tumor environment interferes with tumor metabolic and proliferation characteristics and promotes host immune responses towards the cancerous cells in the tumor (Soleimanpour, et al. [76]). There have been reports that some bacterial strains belonging to the genera of *Escherichia, Salmonella, Bifidobacterium, Clostridioides* etc., can kill tumor cells by colonizing in hypoxic regions of the tumor (Kang, et al. [77,78]). They show anti-tumor activities in animal models but more clinical trials are needed to evaluate their efficacy in humans. A study involving administering a *Pseudomonas aeruginosa* preparation (PAP) in conjunction with chemotherapy in patients with advanced non-small-cell lung cancer found that these patients had a higher objective response rate of 46.88% compared to 23.53% of patients who received only the chemotherapeutic (Chang, et al. [79]).

A bacteriotherapy strategy approved by the FDA involves the use of Bacillus Calmette-Guerin (BCG) for the treatment of non-muscle invasive bladder cancer. BCG utilizes a strain of *Mycobacterium bovis*, which was isolated from a cow infected with bovine tuberculosis. The strain was continuously cultured from 1908 to 1921 before it was weakened enough to be used in humans (Mukherjee, et al. [80]). BCG is delivered intravesically and relies on the host's own immune responses to eliminate remaining bladder cancer cells after a surgical procedure involving transurethral resection of the bladder tumor, also known as TURBT (Jiang, et al. [81]). BCG is equally or more effective than some chemotherapeutics. According to a study by Lamm DL, the probability of being disease-free at five years' survival among patients with carcinoma in situ (CIS) was 45% after treatment with BCG compared to 18% percent following treatment with doxorubicin (Lamm, et al. [82]). Delaying BCG treatment for more than 15 weeks post TURBT as compared to 6 weeks, increases the risk of recurrence by 50% and disease progression by 200% for every week of delay (Krajewski, et al. [83]). Another study found that patients with less than 6 instillations of BCG showed a recurrence rate of 59% compared to 13% shown by patients who had ~18 instillations of BCG (Alhogbani, et al. [84]). BCG therapy aids in activating immune responses that result in killing cancer cells. A study using a rat model of bladder cancer found that BCG therapy resulted in a transient increase of helper T-cells in the urothelial lining of the bladder (Kates, et al. [85]). A recent study demonstrated that BCG therapy resulted in the secretion of Fms-related receptor tyrosine kinase 3 ligand (FLT3LG) that can activate cytotoxic T-cells (Zhang, et al. [86]). Thus, BCG therapy is an effective therapeutic for the treatment of bladder cancer. While BCG has its benefits, it can also cause adverse side effects in some patients and hence patients should be monitored closely.

In addition to bacteria, bacterial toxins have been investigated as therapeutic agents for treatment of cancers in different cell lines and animal models (Trivanovic´, et al. [87,88]). A study from Michl et al., showed that the *Clostridium perfringens* enterotoxin promoted necrosis in tumor cells along with significant reduction of tumor growth in a mouse xenograft model (Michl, et al. [89]). Studies with botulinum toxin demonstrated that it improved radio- and chemotherapy outcomes in a mouse model by increasing tumor oxygenation and perfusion and is being considered for other cancer-related therapies (Ansiaux, et al. [90,91]). There is also interest in conjugating bacterial toxins to cell proteins that allow the toxins to be targeted to cancers. Many different conjugates have been made with diphtheria toxin, and the conjugate of IL-2 and diphtheria toxin is used for treatment of patients with T-cell lymphoma (Shafiee, et al. [92]).

Currently, genetically engineered bacteria that can express different types of genes that aid in the identification and/or destruction of cancer cells have been created (Nguyen, et al. [74]). These genes can code for a variety of molecules including cytotoxic proteins, tumor specific antigens, immunomodulators, and small interfering RNA (Nguyen, et al. [74,75]). A study that used engineered attenuated *Salmonella typhimurium* expressing the flagellin of *Vibrio vulnificus* demonstrated increased infiltration of immune cells and activation of intratumoral macrophages in tumors generated in mouse models (Zheng, et al. [93]). Similarly, engineered attenuated *Salmonella typhimurium* VNP20009 expressing the eukaryotic apoptosis-inducing factor triggered an anti-tumor effect in in vitro and in vivo models (Wang, et al. [94]). In another study, *Escherichia coli* that was engineered to express the toxin cytolysin A, significantly reduced tumor growth in primary and metastatic tumor mouse models when used in combination with radiotherapy. It should be noted that radiotherapy or treatment with the engineered *E. coli* by itself was not sufficient to rid the mice of tumors (Jiang, et al. [95]). There are more examples of genetically engineered bacteria that can deliver therapeutics to a variety of cancers in vivo models, thereby allowing them to function as potential therapeutics in the treatment of cancers (Liu, et al. [96]). The clinical efficacy of these agents in treating cancers remains to be observed in patients.

Conclusion

Bacteriotherapy has proven to be an effective therapeutic and in many cases shows little to no adverse effects. It can be used not only to treat ailments but also improve the general health of patients. There are challenges associated with bacteriotherapy that are being addressed but it is clear that ongoing research will lead to improvements that will create innovative and effective treatment strategies that harness the power of bacteria and bacterial products.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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