Chapter-8

Microbial Metabolites and its Ameliorative Role in Cancer Treatment

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Abstract

Microbial metabolites are compounds that have various regulatory, inhibitory, agonistic, and antagonistic activities. These microbial metabolites show antitumor and anticancer properties and can cause assembly of tubulin, induction of interferon, damage to DNA, induction of apoptosis, inhibition of angiogenesis, and antimitogenic activities. Many researchers are performing studies on these microbial metabolites which have a role as medication for cancer. Some of these include Short Chain Fatty Acids, Bacteriocin, Phenylpropanoids, Prenylflavonoids, Ellagitannins, Indole related compounds. In this paper, we will discuss the various types of microbial metabolites used for inhibiting or killing cancer cells.

Keywords: Bacteriocin; Cancer; Ellagitannins; Indole; Short chain fatty acids

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1. INTRODUCTION

Microorganisms are all organisms that are not visible to the naked eye which includes bacteria, fungi, algae, and protozoa. Microorganisms play a vital role in recycling nutrition to the environment as decomposers. Microorganisms are present in all habitats from a wide range of temperature to a wide variety of pH. They are found in deep oceans, volcanos, and glaciers. To avoid and persist in such inimical situations, microorganisms become highly active metabolically and produce certain chemical compounds termed metabolites which have a role in trans kingdom signaling with host and other competing microorganisms[1]. These metabolites can be divided into two categories., Primary Metabolites and Secondary Metabolites. Primary Metabolites are those chemical compounds that are mandatory for the proper development of those microorganisms. Primary Metabolites may include amino acids and other fermentation products. Secondary Metabolites are those compounds that do not have a direct role in growth and development. They have a lower molecular mass (MW <3000), have particular functions, and are produced at the stationary phase of growth or the end of growth by only some specific organisms[2]. Secondary Metabolites have a role in human and animal health[3] and can be utilized in various ways as antimicrobial agents, antiparasitic agents, antitumors, immunosuppressants enzyme inhibitors, etc. Secondary metabolites are responsible for the inhibition, regulation, and stimulation of the life cycle of the organisms. Secondary Metabolites can be generated by almost all organisms, prokaryotic as well as eukaryotic. Some unicellular bacteria such as *Bacillus, Pseudomonas, Streptomyces Myxobacteria,* and *Cyanobacteria* species are commonly considered the producers of secondary metabolites. Members of Deuteromycetes, Ascomycetes, Basidiomycetes, and some other endophytic fungi are responsible for the production of 38% of all known microbial products. Some members of microscopic algae such as diatoms, dinoflagellates, Rhodophyta, Phaeophyta, and Chlorophyta were responsible for the production of 1700 varieties of secondary metabolites [2].

2. TYPES OF MICROBIAL METABOLITES

The microbes produce various microbial metabolites which include primary as well as secondary metabolites. Primary metabolites are responsible for primary activities such as growth and reproduction which is essential for the microbes. Secondary Metabolites play supporting role and can be divided into various groups on the basis of source, mode of action, chemical nature, etc. They can be produced from various sources such as bacteria, fungi, algae, etc., and can have various modes of action such as antifungal, antibacterial, antiviral, etc. On the basis of their chemical nature, they can be divided into groups that produce Peptides, Phenazines, Pyrrols, etc. These microbes have a great potency

for producing various secondary metabolites, examples of such groups include Pyrroles, glycosides, oligopeptides, benzene derivatives, propanoids, terpenes, terpenoids, alkaloids, pyrrolidones, phenazines, Fatty acids, Indole group, etc [4].

Amino acids and vitamins are essential microbial metabolites that cannot be made or are deficient in the body, so are taken as dietary and feed supplements [5]. Enzymes, secreted from microbes are used in food, chemical, and healthcare industries. Many enzymes such as Lipase, amylase, Protease, Cellulase, and Laccase are extracted from different sources of microbes and can be utilised in various industries [6]. Organic Acids, a type of primary metabolite are used in food, beverages, detergents, textiles, dyes, rubber, plastic, perfume, and pharmaceutical industries [7]. After the discovery of penicillin, antibiotics showed their reign, becoming "The miracle drug". Antibiotics can obstruct many pathways such as nucleic acid synthesis, protein synthesis, cell wall formation, and electron transport pathway. They are also known as lifesaving drugs and are exploited by healthcare facilities and pharmaceutical industries. Antibiotics are also used for preserving food, chemotherapy, and in research laboratories. Actinomycin, the first anticancer drug was first discovered by Wakesman and Woodruff [8]. Genus *Streptomyces* is majorly responsible for the production of secondary metabolites which are used as anticancer agents and antineoplastic agents. After the fortuitous discovery of Penicillin by Alexander Fleming in 1929, secondary metabolites were seen as a compound that could have a significant therapeutic role and since then many microorganisms have been isolated from soil, and aquatic environments that can be used in pharmaceutical and healthcare industries [9].

3. THERAPEUTIC ROLE OF MICROBIAL METABOLITES

Microbial metabolites are compounds that have various regulatory, inhibitory, agonistic, and antagonistic activities which include anti-inflammatory, antioxidative, and various toxic actions. They can cause the assembly of tubulin, induction of interferon, damage to DNA, induction of apoptosis, inhibition of angiogenesis, and antimitogenic activities. Around 60% of all known microbial metabolites have antimicrobial roles whereas approx. 20% of the microbial metabolites show antitumor and anticancer properties [2]. Tryptophan, an essential amino acid via fermentation by *Vibrio cholera*, *Escherichia coli*, *Acinetobacter species*, *Pseudomonas species*, etc. can produce various metabolites such as indole, indole acetic acid [10]. Indole-related compounds have a role as an anti-inflammatory compound, protect against colitis, cause reduction of oxidative stress in the intestine, and have role in cancer [11]. Short Chain fatty acids (SCFAs) can be produced by microbial fermentation of carbohydrates which could not be digested by glycolytic pathway and pentose phosphate pathways [11]. SCFAs are one of the most studied

microbial metabolites and have many therapeutic roles. They have a role in maintaining host metabolic homeostasis. They also have roles in decreasing fierceness of many metabolic and inflammatory diseases such as Type 2 diabetes, colorectal cancer, irritable bowel syndrome and influences metabolic diseases related to insulin resistance and glucose metabolism positively. They also inhibit histone deacetylases [12]. Ellagitannins, a type of non-flavonoids tannins gets transformed into urolithins which shows anti-inflammatory and anticancer properties. Equol, a group of isoflavonoids activates signalling in pancreatic cells that prevents Type 2 diabetes. S-equol is a natural anticancer compound attached to estrogen receptors found in cancer cell lines and downregulate their gene expression. Indole, another important microbial metabolite formed from tryptophan could regulate glucagon-like peptides, maintains integrity of gut cell wall and has anti-inflammatory properties. Protocatechuic Acid also lessens inflammation and protects cells from cancer. Prenylnaringenin throttles proliferation of colon cancer and inhibits breast cancer [12]. Phenylpropanoids derived metabolites such as phenylacetic acid is the byproduct of fermentation of proteins containing Phenylalanine, Tyrosine, Tryptophan within the colon [13].

4. CANCER

In the current scenario, many researchers are studying to find a cure to cancer. Cancer has become most important area of research in biomedical sciences. Cancer is uncontrolled growth of malignant cells in any part of the body. Cancer can happen due to various reason, some of which are mutation, exposure to UV rays, radiation, stress etc. Indication of cancer can be observed as six signs which are cells getting differentiated in an uncontrolled manner, immense replica formation of the cells, Angiogenesis, Infinite cell proliferation due to increase in signalling, resistance to apoptosis, invasion of metastasis [14]. Cancer can be treated by obstructing these indications. Cancer is being treated by using various technologies such as chemotherapy, radiotherapy, modern medicines. Alternate to these medications can be found in microbial metabolites. Many researchers are performing study on these microbial metabolites which has role as medication for cancer.

5. MICROBIAL METABOLITES AND CANCER

Many Secondary metabolites isolated from various microbial source has been studied for role in cancer as showed in table 1. Some common examples of drugs or compounds isolated from microbial source are available in the market and used to treat cancer, these drugs are Actinomycin D, Bleomycin, Doxorubicin, Carfilzomib, Mitomycin C, Pentostatin, etc.

Table 1: Microbial Metabolites, their Sources and mode of Action against Cancer

Metabolites	Source	Mode of Action against Cancer	References
Actinomycin D	*Streptomyces Parvulus*	Blocks RNA polymerase, Inhibits synthesis of RNA	15,16
Bleomycin	*Streptomyces Verticullis*	Causes DNA breakage, Prevents DNA Synthesis	15
Carfilzomib	*Actinomyces Sp.*	Proteasome Inhibition, Activation of Bak and Bax, Activation of Caspase, Apoptosis	17,18
Doxorubicin	*Streptomyces Peucetius*	Attaches to DNA after double stranded breaks and stops from re-ligating, Causes Chromatin Damage, inhibits DNA damage repairing machineries	19,20
Mitomycin C	*Streptomyces Caespitosis*	Damages DNA synthesis machinery, inhibits RNA synthesis and Protein translation, causes cell cycle arrest and cell death	15,21
Pentostatin	*Streptomyces Antibioticus*	Inhibition of ADA, obstruction of DNA synthesis, Cell cycle arrest in S-phase, Cell death	15,22
Nisin	*Lactococcus Lactis Streptococcus Uberis*	Increase Apoptotic Index, Induction of intrinsic apoptotic pathway,	23
Enterocin	*Enterococcus Faecalis, Enterococcus Faecium*	Inhibition of cell growth	24
Epidermicin	*Staphylococcus Epidermidis*	Exhibit cytotoxic activity	25
Bovicin	*Streptococcus Bovis*	Induction of cell death	15

Colicin	*Escherichia Coli*	Cell cycle arrest at G1 phase, upregulation of p53, downregulation of bcl-2, Induction of cell apoptosis	26
Laterosporulin	*Brevibacillus Sp.*	Induction of apoptosis	27
Pediocin	*Pediococcus Acidilactici K2a2-3*	Induction of cell death	28
Plantaricin	*Lactobacillus Plantarum*	Induction of apoptosis	29,30
Butyrate	*Faecalibacterium Prausnitzii*, *Clostridium Leptum*, *Eubacterium Rectale*	Inhibition of cell proliferation, Induction of apoptosis, Differentiation of cells by initiating hyperacetylation of histone of cancer cells, Damage of DNA synthesis machinery	24
Propionate	*Veillonella Parvula*, *Bacteroides Eggerthii*, *Bacteroides Fragilis*, *Ruminococcus Bromii*, *Eubacterium Dolichum*	Reduction of tumour development by inhibition of ROS generation and JAK-2-STAT3 signalling	31
Phenylacetic acid	***Bacteroidetes*** (*Bacteroides Thetaiotaomicron*, *Bacteroides Eggerthii*, *Bacteroides Ovatus*, *Bacteroides Fragilis*, *Parabacteroides Distasonis*), ***Firmicutes*** *(Eubacterium*	Induction of apoptosis	32

	Hallii And *Clostridium Bartlettii*)		
4-hydroxy-phenylacetic acid	*Lactobacillus Rhamnosus*	Induction of mitochondrial regulated apoptosis	33
Urolithins	Gordonibacter Pamelaeae, Gordonibacter Urolithinfaciens	Inhibit formation of neoplastic cells formations, Inhibits cell proliferation, Induction of cell cycle arrest at G_2/M and S-phase	34
Indole 3-Lactic Acid	*Lactobacillus Plantarum Lactobacillus Gallinarum*	Induction of apoptosis	35
Rebaccamycin	*Saccharothrix Aerocolonigenes*	Inhibition of cell proliferation	36

Actinomycin D, also called Dactinomycin isolated from *Streptomyces parvulus* has an antineoplastic role. They are proven as a potent anticancer drug. Actinomycin D gets intercalated to DNA minor groove by forming stable hydrogen bonds with guanine residues, thus preventing attachment and blocking of RNA polymerase. RNA Polymerase does not read the template DNA, thus stopping elongation of RNA strands [15]. Bleomycin is an antineoplastic antibiotic, derived from *Streptomyces verticullis,* contains four domains metal-binding domain, a DNA-binding domain, 4-amino-3 hydroxy-2-methylpentanoic acid connectivity domain, and a carbo hydrate domain which has cytotoxic effect. Different forms of Bleomycin have been used in combination to treat ovarian cancer, testicular cancer, Hodgkin's and non-Hodgkin's lymphoma, and squamous cell carcinomas of the head and neck. Bleomycin forms Bleomycin-Cu (II) complex, gets into nucleus, then exchanges Cu to Fe and forms Bleomycin-Fe (II) complex which binds with O_2 and forms Bleomycin-Fe (III)-OOH complex. This leads to DNA breakage in single or double stranded forms leading to prevention of DNA synthesis [15]. Carfilzomib, an analog of epoxomicin is isolated from *Actinomyces* which has a role as a proteasome inhibitor. Proteasome inhibition results in accumulation and stabilization of protein that is degraded during cancer. They also stabilise and activate Bak and Bax forms apoptosome, leading to activation of caspase and apoptosis. They cause stable expression of p53 (tumour suppressor) and also results in cell cycle arrest in G_1 phase which causes cell death [15].

Doxorubicin is one of most potent anticancer compounds derived from *Streptomyces peucetius.* Doxorubicin is responsible for treating breast, lung, gastric, ovarian, thyroid, Hodgkin's and non-Hodgkin's lymphoma, multiple myeloma, sarcoma, and paediatric cancers. They form proteosomal complex, enters the nucleus and then intercalate to DNA on which causes double stranded breaks. These double stranded breaks are due to Topoisomerase II, as DNA binds to doxorubicin and forms a stable complex, which stops the DNA from re-ligating. Doxorubicin also causes chromatin damage, by competing for space with H4 histone. The nucleosome without histone causes epigenetic and transcriptomic alterations and also reduces capabilities of DNA damage mechanisms. Mitomycin C (MMC), is a potent antibiotic metabolite isolated from *Streptomyces caespitosis* which has role as an anticancer drug. MMC interfere in DNA synthesis machinery, causes cell cycle arrest and cell death. A high dosage of MMC also inhibits RNA synthesis and protein translation. MMCs are selective to cancerous cells and remains inactive in non-cancerous cells. Thus, MMCs are used as a treatment technique for bladder, breast, anal and gastrointestinal cancer. Pentostatin, also referred to as 2'-deoxycoformycin is produced by *Streptomyces antibioticus.* Pentostatin is analogous to nucleoside adenosine and enters through the nucleoside transporters hENT1 and hENT2. Pentostatin attaches itself and stops the enzyme adenosine adeaminase (ADA) which converts adenosine and deoxyadenosine into inosine and deoxyinosine respectively. Due to inactivation of ADA, nucleotides could not be catabolised, thus leading to increase in concentration of deoxyadenosine. Deoxyadenosine gets converted into deoxyadenosine triphosphate (dATP), which increases its concentration and then results in inhibition of ribonucleotide reductase activity inhibiting production of other nucleotides. The lack of other nucleotides causes obstruction in synthesis of DNA and RNA, then leading to cell death. Pentostatin also has role in arrest of cell cycle in S-phase [15]. Microbial metabolites can be classified into various groups according to chemical composition into Short Chain Fatty Acids, Bacteriocin, Phenylpropanoids, Prenylflavonoids, Ellagitannins, Indole derived metabolites.

6. BACTERIOCINS

Bacteriocins, cationic peptide are biodegradable and non-immunogenic, is extracted from various probiotic bacteria by performing ribosomal activity and considered as a good candidate for exhibiting antimicrobial activities [37]. These bacteriocins have shown immense cytotoxicity towards various cancer cells. They target the cancer cells by causing formation of negatively charged molecules which leads to change in cell permeability thus, encouraging induction of apoptosis and cytotoxicity [38]. The basic mode of action of bacteriocin is dependent on amphiphilic nature of these compounds and the ability of interaction of these cationic peptides negatively charged parts of cell

membrane, thus causing depolarization and disruption of the cell membrane[39]. One of the most investigated bacteriocin is Nisin. Four variants of Nisin-Nisin A, Z, Q, U is well known and was produced via bacterial fermentation by *Lactococcus lactis* and *Streptococcus uberis* [40].Nisin develops pores in the cell membrane and resulted in depolarization of cytoplasmic membranes [41]. Nisin prevents expression of some metastatic gene such as MMP2, MMP9, cytolethal distending toxins (CDTs) and the cycle inhibiting factor (Cif) and leads to expression of genes such as LS-180, HT-29, SW480, and Caco-2 which inhibits CRC cell lines [42]. Nisin is responsible for increasing apoptotic index via inducing intrinsic apoptotic pathway [23]. Nisin is also responsible for apoptotic death and cause cytotoxicity to head and neck cancer cells [43]. Fusion protein acquired by fusing three bacteriocin- Nisin, Enterocin, Epidermicin is tested for utilisation against gastric cancer [25]. Nisin supresses the proliferation of breast, liver, skin, blood, gastrointestinal cancer by induction of apoptosis [38]. Nisin and 5-Fluorouracil when used combinedly shows synergism against 7,12-dimethylbenz(a)anthracene in skin cancer cells [44]. Nisin in combination with doxorubicin caused sudden increase in rate of apoptosis. Bovicin HC5 isolated from *Streptococcus bovis* could be responsible for induction of cell death. Colicin extracted from *Escherichia coli* caused G_1 phase arrest of cell cycle, upregulated p53, downregulated bcl-2 and induced cell apoptosis. Colicin work by forming pores, a non-specified DNase activity, RNase activity, and by inhibiting murein biosynthesis[45]. Laterosporulin isolated from microbial source *Brevibacillus* sp. when experimented on HeLa cells and MCF-7 breast cancer cells was found to cause induction of apoptosis by causing membrane permeabilization. Pediocin and Plantaricin extracted respectively from *Pediococcus acidilactici K2a2-3* and *Lactobacillus plantarum* could cause induction of cell death and apoptosis [15].

7. SHORT CHAIN FATTY ACIDS (SCFA)

Short Chain Fatty Acids (SCFA), group of metabolites is the product of fermentation of non-digestible carbohydrate by certain bacteria such as *Faecalibacterium prausnitzii*, *Clostridium leptum*, *Eubacterium rectale*, and *Roseburia* species, as well as lactate-utilising species [46]. The mode of action of SCFA can be explained both intracellularly and extracellularly. Extracellularly, they interact via specific G-protein coupled receptors (GPCRs) such as GPR41 (also known as free fatty acid receptor 3 [*FFAR3*]), GPR43 (*FFAR2*), and GPR109a (PUMA-G). These SCFA-specific GPCRs ionize SCFA and modulate signal to the nucleus.[47]. Intracellularly SCFA are responsible for inhibition of histone deacetylases (HDACs) [48]. Many SCFAs such as butyrate, acetate, propionate showed protection towards colon carcinogenesis [49]. Butyrate has showed a great efficiency in inhibition of cell proliferation, induction of apoptosis, differentiation of cells by initiating hyperacetylation of histone of

cancer cells [50]. Expression of GRP3 receptor in human adenocarcinoma cells, activation of which is mediated by SCFA (butyrate, propionate) showed G_0/G_1 cell cycle arrest and an induced cell apoptosis [51]. As per, 'butyrate paradox' higher concentration of butyrate inhibited tumour whereas a lower concentration promoted tumour [52]. Butyrate when used in combination with 5-Fluorouracil has a higher efficacy of increased damage to DNA synthesis and works against colon cancer [53].SCFAs when used in combination with standard chemotherapeutic drugs such as doxorubicin could inhibit drug resistance, thus more efficiently works against cancer [54]. Butyrate showed agonistic effect on cancer cell of human colonic adenocarcinomic cells by expressing G- protein coupled receptor 3 (GPR43) which inactivated procaspase 3 which activated caspase, thus inducing apoptosis and inhibiting cell proliferation [13]. Histone deacetylases regulate epigenetic gene expression. Butyrate inhibit only type 1 and type 2 HDACs. Butyrate molecules could inhibit by attaching itself to the hydrophobic binding cleft of the active site of the enzyme. Butyrate can be recognized as the most potential HDAC inhibitor [4855]. Propionate, extracted from gut microbiota such as *Veillonella parvula, Bacteroides eggerthii, Bacteroides fragilis, Ruminococcus bromii, Eubacterium dolichum* etc. has an obscure role in cancer treatment. Propionate regulate certain SCFA-specific such as GPR41, GPR43 which influences downstream signal to the nucleus [47]. The right amount of propionate when administered orally showed great efficiency in reducing tumour development by inhibiting ROS generations and JAK2- STAT3 signalling whereas high propionate level causes resistance to cancer therapy [15]. Tributyrin, compound consisting of butyrate and glycerol showed ameliorative effect on various cell lines. Acetate and butyrate causes a decrease in single stranded DNA fracture and a increased apoptosis in colon cancer cells [56].

8. PHENYLPROPANOID

Phenylpropanoid-derived metabolites such as phenylacetic acid (PAA), 4-hydroxyphenylacetic acid (4-hydroxy PAA) etc. can be synthesized from microbial fermentation of Aromatic amino acids (Tryptophan, Phenylalanine, tyrosine) by *Bacteroidetes* (*Bacteroides thetaiotaomicron*, *Bacteroides eggerthii*, *Bacteroides ovatus*, *Bacteroides fragilis*, *Parabacteroides distasonis*), and *Firmicutes (Eubacterium hallii* and *Clostridium bartlettii*) [57]. 4-hydroxy PAA produced from *Lactobacillus rhamnosus* has the capability to induce mitochondrial-regulated apoptosis against HepG2 liver cancer cells [58]. A Zn(II) Complex, a combination of Phenylacetic acid and the 4,4'-bipyridine ligand has a role in the induction of apoptosis in the HeLa cervical cancer cell line[59]. Verbascoside, a phenylpropanoid compound shows great antimicrobial and antioxidant properties. They were found to seize sub-G1 and G_2/M phases of the cell cycle of gastric epithelial cancer cell [60 61]. Eugenol, ferulic acids, and caffeic

acids when combined with 5-fluorouracil showed synergistic effect against HeLa cervical cancer cells [62].

9. PRENYLFLAVONOIDS

Xanthohumol (XN) is a type of prenylated flavonoid which is metabolised by gut microbiota into 8-prenylnaringenin (8-PN) which shows great efficiency against cancer of various cell lines[63]. 8-PN shows anticancer activity by inhibiting HDAC against SK-MEL-28 and BLM human metastatic melanoma cells[64]. Induction of apoptosis which inhibited the proliferation of MCF7 human breast cancer cells was an effect of 8-PN. Other derivatives of prenylflavonones when compared to potential of 8-PN was able to show great efficiency of targeting multi-drug resistant leukemia cells and induce apoptosis [65]. 8-PN showed inhibition of proliferation by inducing intrinsic and extrinsic pathways of apoptosis [66].

10. ELLAGITANNINS

Ellagitannins are converted into urolithins via microbial fermentations which has shown anti-inflammatory and anticancer properties [12]. Urolithins have role in targeting specific pathways of tumorigenesis in prostate cancer. They inhibit formation of neoplastic cells formations by fixing tumorigenic pathways in prostate cancer such as obstruction of cytochrome P450 enzyme expression, Phosphorylation of kinases and by stopping formation of neoplastic cells by arresting p21 pathway [67]. In Caco-2, HT-29, and SW480 human colon cancer cells, urolithins inhibited cell proliferation by inducing cell cycle arrest at G_2/M and S phase[68].

11. INDOLE DERIVED METABOLITES

Tryptophan goes through microbial fermentation for formation of Indole and its derivatives such as Indole Acetic acid (IAA), Indole-3 Lactic acid (ILA), etc. A derivative of tryptophan Indole-3 Lactic acid is isolated from *Lactobacillus gallinarum* and *Lactobacillus plantarum* and has shown great success as an anticancer bioactive compound. When experimented on mice, ILA stopped sudden colon cancer formation and reduced the size of pre-existing ones. ILA also caused the induction of apoptosis in colorectal cancer cells[15]. Rebaccamycin is an indolocarbazol alkaloid that is extracted from *Saccharothrix aerocolonigenes* are efficiently used as a drug against cancer. Rebaccamycin and some of their analogs could inhibit the proliferation of cancer cell lines. They affect the mechanism of type 2 topoisomerase, which in turn leads to apoptosis. They showed anticancer activities and suppressed tumors in cases with soft tissue sarcoma and ovarian cancer[56].

12. CONCLUSIONS

Microbial metabolites have gained considerable attention in the field of cancer research and treatment. Several microbial metabolites have been shown effective results against various types of cancer cell lines as they regulate metabolic pathways related to cancer and tumor growth. Scientists are exploring microbial metabolites for cancer treatment as an alternative to conventional therapies. Increasing research for the discovery of new microbial metabolites that have the least side effects on normal cells is very useful in the future for cancer treatment. The branch of genetic engineering also plays an important role in the development of genetically engineered microbial strains. These engineered microbial strains release metabolites that have the potential to be used as antitumor agents with minimum side effects in vivo and in vitro. By producing these microbes on a large scale through fermenters, we can meet the world's demand by creating the desired compounds for cancer treatment.

Conflict of Interest: The authors declare no conflict of interest

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