ABSTRACT
Microorganisms are the part of the living world. They are the main causes of various infections such as polio, rabies, small pox, influenza, typhoid and many others. They are also proved for commercial loss such as spoilage of food, beverage and many valuable materials. The outlook of human to microbes had been totally changed after the publication of the germ theory. But all microorganisms are not harmful. They have opened a new era of treatment in medical science. They are used in various therapeutic purposes such as production of vaccines of rabies, influenza, polio, small pox, hepatitis B etc. and production of antibiotics such as penicillin, cephalosporin, chloramphenicol, tetracycline etc. without which many human lives will have to be lost from the world. A wonder microbe, M. Vaccum, had been shown to have anti-depression and mood elevating property which may be a very cheap therapeutic source of anti depression therapy. Microorganisms have also increased the therapeutic acceptability of medicine such as insulin which formerly came from pig. The most wonderful usage of microorganisms is in cancer treatment.

KEYWORDS: Microorganisms, vaccine, anti-depression, cancer, toxin, treatment.

1. INTRODUCTION
Microorganisms the small bacteria and fungi which inhabit just about every environment on Earth have become a large focus of the medical community in recent years. Though small (they can range from .15 micrometers to 700 micrometers), their impact and their potential impact is tremendous. Microbes first came to human attention due to the work of the Dutch scientist Anton Van Leeuwenhoek. In 1676 using one of his homemade single-lens
microscopes, Van Leeuwenhoek discovered what he called “animalcules,” and which are now what the science community currently refers to as bacteria.[49] The advent of microorganisms in medicine, though seemingly a modern day application, actually began in the mid-19th century with the work of Louis Pasteur. However, a majority of civilization believed that disease was spontaneously generated.

So before microbes could be used to benefit mankind, mankind had to prove they existed. Pasteur, through experiments with nutrient broths, rejected the common thought that microbes appeared spontaneously and that they traveled through the air causing diseases in silkworms as well as spoiling beverages such as wine, beer, and milk. Though not the first to propose germ theory of disease, Pasteur accepted the hypothesis of germ theory scientifically and was able to persuade much of Europe of the validity of his findings.[51] This understanding began to explain many historical phenomena, notably instances in India and China where people were vaccinated against the smallpox disease using powdered scabs of patients infected with smallpox. [50] Over time, the development of vaccinations was used to help protect against a wide array of diseases such as measles, mumps, and hepatitis. Microbes consist of bacteria, fungi, archaea, protists, plants which are invisible to the naked eye, and plankton.[42]

2. Polio Vaccine
Polio vaccines are vaccines used to prevent poliomyelitis (polio). One type uses inactivated poliovirus and is given by injection (IPV), while the other type uses weakened poliovirus and is given by mouth (OPV). The World Health Organization recommends all children be vaccinated against polio. Both are generally safe to give during pregnancy and in those who have HIV/AIDS but are otherwise well. The first polio vaccine was the inactivated polio vaccine. It was developed by Jonas Salk and came into use in 1955. The oral polio vaccine was developed by Albert Sabin and came into commercial use in 1961.[1] They are on the World Health Organization's List of Essential Medicines.[2]

3. Rabies Vaccine
Rabies vaccine is a vaccine used to prevent rabies. They can be used to prevent rabies before and for a period of time after exposure to the virus such as by a dog or bat bite. Doses are usually given by injection into the skin or muscle. After exposure vaccination is typically used along with rabies immunoglobulin. It is recommended that those who are at high risk of exposure be vaccinated before potential exposure. Vaccines are effective in humans and other
animals. Vaccinating dogs is very effective in preventing the spread of rabies to humans.\(^3\)
The first rabies vaccine was introduced in 1885, which was followed by an improved version in 1908.\(^4\) Millions of people globally have been vaccinated and it is estimated that this saves more than 250,000 people a year.\(^3\) It is on the World Health Organization's List of Essential Medicines, the most important medication recommended for a basic health system.\(^2\)

4. **Influenza Vaccine, Chicken Pox Vaccine**

Vaccination against influenza began in the 1930s.\(^5\)[6]\(^7\) The vaccines come in both inactive and weakened viral forms. The inactive version should be used for those who are pregnant. They come in forms that are injected into a muscle, sprayed into the nose, or injected into the middle layer of the skin.\(^7\)

Varicella vaccine, also known as chickenpox vaccine, is a vaccine that protects against chickenpox.\(^8\) The chickenpox vaccine first became commercially available in 1984. It is made from weakened virus.\(^9\)

5. **Small Pox Vaccines**

Smallpox vaccine, the first successful vaccine to be developed, was introduced by Edward Jenner in 1798. He followed up his observation that milkmaids who had previously caught cowpox did not later catch smallpox by showing that inoculated cowpox protected against inoculated smallpox. The word vaccine is derived from Variolae vaccinae.\(^10\) Vaccination, the term which soon replaced cowpox inoculation and vaccine inoculation, was first used in print by Jenner's friend, Richard Dunning in 1800. Initially, the terms vaccine/vaccination referred only to smallpox, but in 1881 Louis Pasteur proposed that to honor Jenner the terms be widened to cover the new protective inoculations being introduced.\(^11\)

6. **Different Types of Microbes Derived Vaccines Used for Immunization.**\(^12\)

<table>
<thead>
<tr>
<th>Vaccine type</th>
<th>Vaccines of this type on U.S. Recommended Childhood (ages 0-6) Immunization Schedule</th>
</tr>
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<tbody>
<tr>
<td>Live, attenuated</td>
<td>Measles, mumps, rubella (MMR combined vaccine), Varicella (chickenpox), Influenza (nasal spray), Rotavirus, Zoster (shingles), Yellow fever.</td>
</tr>
<tr>
<td>Inactivated/Killed</td>
<td>Polio (IPV), Hepatitis A, Rabies.</td>
</tr>
<tr>
<td>Toxoid (inactivated toxin)</td>
<td>Diphtheria, tetanus (part of DTaP combined immunization)</td>
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7. Microorganisms with Anti-depression and Mood Elevating Property

The hypothesis Chris Lowry, of Bristol University, and his colleagues has indicated the use of bacteria in Neuroscience. They think a particular sort of bacterium might alleviate clinical depression. Dr O’Brien, an oncologist at Royal Marsden Hospital in London, surprisingly observed an improvement of her patient’s emotional health while undergoing an experimental treatment for lung cancer that involved inoculating patients with *Mycobacterium vaccae* which is a harmless relative of the bugs that cause tuberculosis and leprosy that had, in this case, been rendered even more harmless by killing it. This effect was further reviewed by Chris Lowry, of Bristol University, and his colleagues on mice. His hypothesis was that the immune response to *M. Vaccae* induces the brain to produce serotonin. This molecule is a neurotransmitter (a chemical messenger between nerve cells) and one symptom of depression is low levels of it. Dr Lowry and his team injected their mice with *M. Vaccae* and examined them to find out what was going on. First, they looked for a rise in the level of cytokines, which are molecules produced by the immune system that trigger responses in the brain. As expected, cytokine levels rose. They then looked directly in their animals’ brains for the effect of those cytokines. Cytokines actually act on sensory nerves that run to the brain reprints from organs such as the heart and the lungs. That action stimulates a brain structure called the dorsal raphe nucleus. He found a group of cells within it that connect directly to the limbic system, the brain’s emotion-generating area. These cells release serotonin into the limbic system in response to sensory-nerve stimulation. The consequence of that release is stress-free mice. Dr Lowry was able to measure their stress by dropping them into a tiny swimming pool. Previous research has shown that unstressed mice enjoy swimming, while stressed ones do not. His mice swam around enthusiastically. This result is intriguing for two reasons. First, it offers the possibility of treating clinical depression with what is, in effect, a vaccination. Indeed, *M. Vaccae* is considered a bit of a wonder-bug in this context. Besides cancer, and now depression, it is being looked at as a way of treating Crohn’s disease (an inflammation of the gut) and rheumatoid arthritis.\[13\]
8. Insulin, Human Growth Hormone and Sweetener from Bacteria

Not long ago, if one’s were diabetic, the insulin doctor prescribed would have come from a pig. If one’s required human growth hormone, it would have come from human cadavers, a source that is costly, not to mention a little creepy. Now, these and other medicines can be made by specially-modified bacteria, called transgenic bacteria. These single-celled organisms have foreign genes alongside their own DNA. They live and reproduce like ordinary bacteria, but they also do a bit of extra duty, and produce human proteins for medicines and vaccines. The sweetener in most diet soda sp phenylalanine is made by transgenic bacteria.\(^{[14]}\)

9. Microorganisms in Cancer Therapy

Cancer is characterized by uncontrolled and invasive growth of cells. These cells may spread to other parts of the body and this is called metastasis. In 2002, 10.9 million new cancer cases (excluding skin cancer) were diagnosed, and the number of deaths caused by this disease reached 6.7 million (GLOBOCAN). In Europe, cancer has become a major public health problem with an estimated prevalence of about 3%, increasing to 15% at old age.\(^{[15]}\) Although conventional anticancer therapies, consisting of surgical resection, radiotherapy and chemotherapy, are effective in the management of many patients but for about half of cancer sufferers these are ineffective, so alternative techniques are being developed to target their tumors.\(^{[16]}\)

The use of bacteria or their extracts in the treatment of cancer goes back more than 100 years. The most cited case is that by the physician and surgeon William B. Coley of the then Memorial Hospital in New York City, now called Memorial Sloan-Kettering Hospital, who observed that many of his patients with various forms of cancer had their tumors regress when they were infected with bacterial pathogens. Treatment to eliminate the infections allowed the cancer to come back. He developed a treatment modality by making extracts of some of these bacteria, later described as Coley’s toxin, which he used to help shrink the tumors in his patients. Subsequently, many bacteria have been used in an effort to reduce the growth rate or size of tumors.\(^{[17]}\)

Novel strategies also include the use of bacterial products such as proteins, enzymes, immunotoxins and secondary metabolites, which specifically target cancer cells and cause tumor regression through growth inhibition, cell cycle arrest or apoptosis induction.\(^{[15]}\)
9.1. Antitumor Effect of Clostridia Strains

In the middle of the last decade, the use of engineered Clostridial strains to increase anti-tumor effects gathered more attention. Saccharolytic, non-pathogenic strains were reevaluated and it was seen that spores of *C. beijerinckii* NCIMB 8052 germinated in EMT6 tumor-bearing mice and spores of *C. beijerinckii* ATCC 17778, *C. limosum* DSM1400, *C. acetobutylicum* ATCC 824 and NI-4082 germinated in WAG/Rij rats with syngeneic rhabdomyosarcomas. In all cases, vegetative bacteria were only present in tumor regions but not in healthy tissues. *C. beijerinckii* NCIMB 8052 was also used to clone *Escherichia coli* cytosine deaminase (CD) and nitroreductase (NTR) genes, and in the presence of the correct prodrug, these enzymes were present in sufficient amount to induce EMT6 cell death. However, the studies showed that only intratumoral administration of the spores, but not intravenous, was able to produce a therapeutic effect. Genetically saccharolytic *C. acetobutylicum* strains containing cloned murine tumor necrosis factor α (mTNFα) or rat interleukin 2 (rIL2) were also constructed. The engineered strains gained the ability to produce significant amounts of these antitumor factors, but upon injection of the spores in rhabdomyosarcoma-bearing rats, tumor regression was not successful, even in combination with radiotherapy. This is likely to be due to the less ability of saccharolytic clostridia to colonize tumors when compared to proteolytic bacteria.

Though proteolytic clostridia presented higher ability to colonize tumors, they were more difficult to manipulate. After a systemic administration of spores from both Clostridia types, tumor colonization from proteolytic Clostridia was about 1,000-fold higher than that of saccharolytic Clostridia. The proteolytic strain *C. oncolyticum* M-55 was transformed with a plasmid containing the CD gene and injected intravenously together with the prodrug 5-fluorocytosine (5-FC). The results demonstrated higher antitumor activity than with other drugs tested, but failed to maintain the effect for more than one week, even though the bacteria remained in the tumor. More recently, this strain has been genetically engineered to over express the enzyme nitroreductase from *Haemophilus influenza*, producing better antitumor results.\[15\]

9.2. *Mycobacterium bovis* BCG and Bladder Cancer

*Mycobacterium bovis* BCG, the vaccine strain, is used in the treatment of bladder cancer. Several well-coordinated studies have shown a clear relationship between the use of *M. bovis* BCG immunoprophylaxis after surgical removal of the tumor and the decreased recurrence
rate or the delayed period during which recurrence could occur. The mode of action of BCG to exert its antineoplastic effect is believed to be due to its effect on the immune system, with CD4 and CD8 T lymphocytes playing a major role, although the intravesical instillation of BCG is thought to result in nonspecific cystitis, which is likely accompanied by the local production of cytokines and the accumulation of inflammatory cells that are more damaging to the malignant rather than normal cells. Positive effects have also been reported to be seen with immunoadjuvants such as tumor necrosis factor alpha. Using a human in vitro system to analyze the role of NK cells in BCG induced cellular cytotoxicity, Brandau ET al. treated mononuclear cells with BCG for 7 days and demonstrated the ability of the BCG-activated killer cells to significantly destroy bladder tumor cells. Similarly, using C57BL/6 wild-type mice, NK deficient beige mice, and mice treated with anti-NK1.1 monoclonal antibody, these authors noticed that viable BCG cells significantly prolonged survival in wild-type mice compared with control non treated mice while BCG therapy was completely ineffective in NK-deficient beige mice or in mice treated with anti-NK1.1 monoclonal antibody.[17][18]

9.3. C. novyi as Antitumor Agent

C. novyi, the α-toxin was removed through heating (it was located in a phage) and the strain became non-toxic and was renamed as C. novyi-NT. This strain is very sensitive to oxygen and, thus, grows only in the core hypoxic region of the tumors. For this reason when it reached the well oxygenated rim area of the tumors, bacteria didn’t survive thus tumor recurrence remained a concern. Resembling the other strains, alternative therapeutics were tested, combining the C. novyi-NT treatment with conventional chemotherapeutics (a strategy named COBALT—combined bacteriological therapy). As example, the simultaneous use of the C. novyi-NT spores with a DNA-damaging drug and an anti-vascular agent, mitomycin C and dolastin-10, respectively, resulted in very satisfactory tumor shrinking, however it was always accompanied by severe toxicity. Combinations of C. novyi-NT with radiotherapy were evaluated which showed positive effects in several tumor models. Interestingly, this combination acts in distinct cell components. In solid tumors, radiation hits the rapidly proliferating and highly oxygen-exposed cells, and C. novyi-NT hits those cells resistant to radiation. The key advantage of this therapy is that the doses of radiotherapy can be much smaller than the ones used now, not damaging healthy tissues and with obvious advantages for patients’ welfare.[15]
9.4. Tumor Regression Property of Parasite

It was previously demonstrated that a protozoan parasite, *Toxoplasma gondii*, when injected into melanoma-bearing mice, caused tumor regression by blocking angiogenesis (formation of blood vessels). It was thought that inhibition of angiogenesis in the tumor was due to the production of infection-induced antiangiogenic soluble factor(s) that created hypoxic conditions in the tumors, leading to their necrosis.\(^\text{[19]}\)

9.5. Bifidobacterium as Anti-cancer Agent

Another genus with promising results in anticancer treatment is Bifidobacterium. These are anaerobic bacteria, non-motile, and, unlike the Clostridium genus, non-sporulating. This is the most abundant genus inhabiting human colon and it has been used as a probiotic for many years.\(^\text{[20]}\) In the 1980s, it was shown that Bifidobacteria selectively grow in the hypoxic areas of solid mouse tumors upon intravenous injection of 5 x 10^6 cfu (colony forming units), and 96 hours after injection, virtually no bacteria were found in other tissues.\(^\text{[21]}\) Bifidobacterium not only inhibit cancer progression in mice but have also shown the ability to induce a powerful immune response, enhancing the killing activity of NK cells and recruiting the activity of IL-2, INFγ and INFα.\(^\text{[22]}\)

9.6. Salmonella Species and Cancer

Salmonella species are facultative anaerobes known to selectively colonize tumoral cells of solid tumors showing a replication ratio between tumor and healthy tissues of 1,000:1.34 However, most strains are pathogenic, causing significant immunostimulation due to the presence of lipopolysaccharide (LPS) and other virulence factors.\(^\text{[23]}\) To solve this problem, *Salmonella thyphimurium* was genetically modified in order to attenuate its virulence, disrupting the msbB gene, responsible for the terminal myristalization of lipid A, and purI, which introduced the need of an external adenine source. After showing the lower toxicity in several animal models, Pawelek and colleagues injected it into tumor-bearing mice and showed its specificity to tumors. Additionally, Salmonella strains were engineered to produce several proteins and toxins with anticancer activity: CD, TNFα, mitomycin C, herpes simplex virus thymidine kinase (HSV-tk) and colicin E3. More recently, reports have appeared of attenuated strains with the ability to delay tumor growth, including metastasis, in several models.\(^\text{[23]}\) A vaccine strain of *Salmonella choleraesuis* was developed and used both as a single anticancer agent and in combination with low-dose cisplatin (a platinum-based chemotherapy drug) in lung tumor and hepatocarcinoma in mice models.\(^\text{[15]}\)
9.7. *Listeria monocytogenes* in Cancer Treatment

In the specific area of increased immune responses, *Listeria monocytogenes* is another example of bacteria that can be used to treat cancer. It is an intracellular bacterium, capable of infecting phagocytic and non-phagocytic cells. Upon infection with Listeria, a significant immune response is elicited to clear the organism. A variety of live attenuated *L. monocytogenes* strains expressing viral and tumor antigens as fusion proteins have been produced during the last several years: HPV-16 E7, Her-2/neu, HMW-MAA, influenza NP and PSA. These recombinant strains cause specific CD4+ and CD8+ T cell responses in mice. In this bacterium, Listeriolysin O (LLO), a pore forming hemolysin, is the major virulence factor. Fusion of the antigens to a non-hemolytic truncated form of LLO resulted in enhanced immunogenicity and anti-tumor efficacy. It had the ability to induce inflammatory cytokines and an active strong immune response.\(^{15}\)

10. Microbe’s Derived Anticancer Agents

10.1. Azurin, a Novel and Promising Anticancer Agent Derived From Microbes

It has now been demonstrated that *Pseudomonas aeruginosa* produces at least two cytotoxic proteins against cancer cells. One protein, interestingly, is not known as a virulence factor or an enzyme but a water soluble low molecular weight copper-containing redox protein named azurin (128 aa–14 kDa) involved in the electron transport chain.\(^{15}\)

Purified redox proteins such as azurin have been shown to allow cancer regression in nude mice harboring human melanoma.\(^{24}\) Azurin is a copper-containing oxidoreductase that is normally involved in denitrification in *P. aeruginosa*. Yamada et al.\(^{24}\) demonstrated that azurin enters into the cytosol of a human melanoma cell line (UISO-Mel-2), is transported to the nucleus, and forms a complex with the tumor suppressor protein p53, thereby stabilizing it. Stabilization of p53 allows the significant generation of reactive oxygen species, which is a potent inducer of apoptosis.\(^{25}\)\(^{26}\) Indeed antioxidants that scavenge reactive oxygen species significantly reduce azurin-mediated cytotoxicity.\(^{25}\) p53 is normally a labile protein with a half-life of a few minutes. It acts primarily as a transcriptional regulator within the cell, although its role in nontranscriptional processes and various instances of cell networking is also well known. The two primary functions of p53 within the cell are to allow growth arrest and to induce apoptosis in cells. Stabilization of p53 in azurin-treated cells enhances the level of intracellular p53, which triggers apoptosis in the melanoma cells xenotransplanted in nude mice, leading to their in vivo regression.\(^{27}\)
10.2. Staphylococcal Superantigens-like (SSL) Proteins

It a class of bacterial proteins produced by *Staphylococcus aureus* capable of binding several eukaryotic receptors over expressed in cancer cells. SSL10 binds CXCR4; a GPCR expressed on human T-ALL lymphoma and cervical carcinoma cells. The natural ligand for CXCR4 is CXCL12, but SSL10’s action clearly inhibited the chemotactic response of HeLa (cervical carcinoma) cells towards the natural ligand.[28]

The class of bacterial protein SSL5 has been demonstrated to bind to the receptor for P-selectin glycoprotein-1 (PSGL-1), inhibiting rolling of neutrophils on a surface by acting as a decoy and thus hampering the interaction with its natural ligand, the P-selectin. The inhibitory action of SSL5, without any observed toxicity, was demonstrated in HL-60 leukemia cells since these cells express the receptor P-selectin glycoprotein-1 (PSGL-1). Besides the novel therapeutic action towards hematological malignancies, the bacterial protein SSL5 also binds epithelial cells that circulate in the blood stream during metastasis and thus can be a very interesting therapeutic tool for metastatic carcinoma.[29]

10.3. Arginine Deiminase

This is the case of the amino acid-degrading enzyme arginine deiminase of *Mycoplasma arginini* (Ma-ADI), a tumor growth inhibitor and potentially a therapeutic agent for the treatment of in vitro and in vivo tumors, such as hepatocellular carcinoma, melanoma, leukemia, renal cell carcinoma and prostate cancer.[30] Such inhibition of cancer cell growth by ADI is believed to be due to depletion of arginine.[31] Interestingly Ma-ADI has not only anticancer activity, but also has been implicated in inhibiting the growth of viruses such as HIV-1 and hepatitis C. These pleiotropic effects appear to suggest that the enzymatic activity of ADI, leading to arginine depletion. Two enzymes are required for the synthesis of arginine from citrulline: first, argininosuccinate synthetase (ASS) converts citrulline to argininosuccinate and then, this is converted to arginine by argininosuccinate lyase (ASL). Conversely, ADI converts arginine to citrulline and ammonia. While arginine is a non-essential amino acid in humans, certain cancers such as hepatocellular carcinoma, melanoma or renal cell carcinomas do not express ASS in vivo, making them sensitive to arginine deprivation due to ADI action.[31][15]

10.4. Immunotoxins

Recombinant immunotoxins based on *Pseudomonas aeruginosa* exotoxin A (PE) are also promising anticancer agents. These chimeric proteins contain the Exotoxin A (a toxic domain
for cytotoxicity) fused either to monoclonal antibodies or antibody fragments or physiologically important ligands like cytokines and growth factors. Exotoxin A from *P. aeruginosa* is a potent virulence factor that catalyzes the ADP-ribosylation of the eukaryotic elongation factor 2 (eEF-2) in host cells, affecting protein synthesis and cell viability. It shares an A-B structure with other bacterial toxins. The B-domain is responsible for the interaction with eukaryotic host cell receptors, after which the A-domain translocates to the cytoplasma and exerts its action. Recombinant Exotoxin A-immunotoxins kill cancer cells by binding specifically to overexpressed cell-surface receptors, which carries them into the cell interior, where they arrest protein synthesis and induce apoptosis.

10.5. Obatoclax (GX15-070)

It is a synthetic derivative of natural prodiginines developed at Gemin X Pharmaceuticals. This compound was designed to antagonize the effects of Bcl-2 anti-apoptotic proteins family, through binding and sequestering Bcl-2 proteins, releasing the pro-apoptotic Bax and Bak proteins. Obatoclax is the leading prodiginine candidate to be applied in clinics. This new drug is now undergoing multiple phase I and phase II clinical trials against several forms of cancer both as a single agent and in combined therapies.

10.6. Epothilones

They were discovered as cytotoxic metabolites in the myxobacterium *Sorangium cellulosum*. They show anti-tumor activity in cancer cell lines, many of those multidrug-resistant or paclitaxel-resistant. Epitholones bind to the α, β-tubulin dimer of microtubules, inducing its polymerization and stabilization which causes cell cycle arrest at the G2/M transition and apoptosis. The first studies on the mechanism of binding seemed to indicate that these natural drugs shared pharmacophores with taxanes; however, recent crystallography results with epothilones indicated a unique tubulin-binding pocket that is not common to taxanes.

10.7. The Anthracycline Antibiotics

They are fermentation products of *Streptomyces peucetius*. Daunorubicin is used to treat acute leukemias, while its structural analogue; doxorubicin is extensively employed against a broad spectrum of cancers. Although the two drugs have similar pharmacological and toxicological properties, doxorubicin is more potent against most animal and human tumors. Doxorubicin binds tightly to DNA by its ability to intercalate between base pairs and therefore is preferred concentrated in nuclear structures. Intercalation results in steric hindrance, hence production of single-strand breaks in DNA and inhibition of DNA synthesis.
and DNA-dependent RNA synthesis. The enzyme topoisomerase II is thought to be involved in the generation of DNA strand breaks by the anthracyclines. Cells in S-phase are most sensitive to doxorubicin, although cytotoxicity also occurs in other phases of the cell cycle. In addition to the intercalation mechanism described, the anthracycline ring of doxorubicin can undergo a one-electron reduction to form free radicals and participate in further electron transfer.\[38\]

10.8. L-Asparaginase

The form of the enzyme used chemotherapeutically is derived from bacteria Escherichia coli and Erwinia carotovora. L-Asparaginase catalyzes the deamination of asparagine to aspartic acid and ammonia. Its mechanism of action is based on the fact that some neoplastic cells require an external source of asparagine because of their limited capacity to synthesize sufficient amounts of that amino acid to support growth and function. L-Asparaginase hydrolyzes blood asparagine and, thus, deprives the tumor cells of this amino acid, which is needed for protein synthesis.\[38\]

10.9. Camptothecin

It is a modified monoterpene indole alkaloid produced by certain plants (angiosperms). It also is produced by the endophytic fungus, Entrophospora infrequens, from the plant Nathapodytes foetida. In view of the low concentration of camptothecin in tree roots and poor yield from chemical synthesis, the fungal fermentation is very promising for industrial production. Camptothecin is used for recurrent colon cancer and has unusual activity against lung, ovarian, and uterine cancer. Colon cancer is the second leading cause of cancer fatalities in the USA and the third most common cancer among US citizens. Camptothecin is known commercially as Camptosar and Campto and achieved sales of $1 billion in 2003. Camptothecin's water-soluble derivatives irinotecan and topotecan are also used clinically.

The cellular target of camptothecin is type I DNA topoisomerase. When patients become resistant to irinotecan, its use can be prolonged by combining it with the monoclonal antibody Erbitux (Cetuximab). Erbitux blocks a protein that stimulates tumour growth and the combination helps metastatic colorectal cancer patients expressing epidermal growth factor receptor (EGFR). This protein is expressed in 80% of advanced metastatic colorectal cancers. The drug combination reduces invasion of normal tissues by tumour cells and the spread of tumours to new areas.\[39\]
10.10. Carfilzomib
In 1992, Bristol-Myers Squibb scientists from Tokyo reported the structure of epoxomicin, a microbial tetrapeptide appended with an electrophilic epoxy ketone group. This compound displayed potent in vivo antitumor activity against murine B16 melanoma tumors. However, because the mechanism of action could not be established, its investigation was abandoned, thereby leading to the publication of the initial discovery. Eventually, BMS closed the research center in Tokyo. It was a common practice during that period for big pharmaceutical companies to close their departments of natural product chemistry.

In 1999, the potent anticancer activity of epoxomicin attracted the attention of Craig Crews at Yale University, who designed the first synthesis of epoxomicin. In the course of this endeavor, he established the absolute configuration of the epoxide stereocenter and synthesized also a biotinylated probe, which was used to identify the proteasome as the molecular target of epoxomicin. The proteasome is a multiprotein complex that degrades unneeded or damaged proteins by proteolysis. Importantly, epoxomicin does not display any cross-inhibition with proteases, which is a major problem encountered with other anti-cancer proteasome inhibitors, such as bortezomib (Velcade®). The source of this selectivity was elucidated by a crystallographic approach. The crystal structure of the proteasome bound to epoxomicin revealed the formation of a morpholino ring between the amino terminal threonine of the proteasome and the electrophilic moiety of epoxomicin, probably through the mechanism.

The specificity of epoxomicin toward proteasome prompted Crews to associate with Caltech professor Raymond Deshaies to establish a start-up company, Proteolix, dedicated to the development of a clinical candidate. During this process, they identified YU-101, which had better inhibitory activity than bortezomib. Addition of a morpholine moiety to YU-101 improved its solubility, thereby creating carfilzomib, which rapidly entered Phase I and II clinical trials. Importantly, the peripheral neuropathy that was observed with bortezomib did not occur with carfilzomib. In 2009, Onyx Pharmaceuticals acquired Proteolix and this compound was approved for the treatment of multiple myeloma in 2012.\textsuperscript{[40]}

10.11. Paclitaxel
The drug paclitaxel is produced by the fungi \textit{Nodulisporium sylviforme}, and is used as a means of disrupting the mechanism of reproduction in ovarian, breast, and lung cancers. Paclitaxel acts by stabilizing the microtubule of the mitotic spindle and prevents the
movement of chromosomes to the metaphase plate which occurs in normal mitosis.\textsuperscript{[41]}  The mitotic block caused by Paclitaxel eventually leads to the apoptosis of the cell and thus the eradication of cancer cells.\textsuperscript{[42]}

10.12. Polysaccharide-K
The mushroom \textit{Trametes versicolor} produces a polysaccharide called polysaccharide-K and is known to act in a variety of anti-cancer mechanisms.\textsuperscript{[43]} Polysaccharide-K acts by a variety of mechanisms including the suppression of tumor detachment, cell matrix degrading enzymes, tumor growth by inhibition of angiogenesis, expression of oncogenes, and the reduction of free radicals. Animal research conducted with polysaccharide-K has shown that it has the ability to increase the survival time in test subjects with spontaneous metastasis lung cancer, and it suppresses lesion growth of liver cancer in test subjects.\textsuperscript{[42]}

11. Microbes in Other Usages

11.1. Botulinum Toxin
One bacterial protein which is of use to the medical community is the Botulinum toxin. Produced by the bacterium \textit{Clostridium Botulinum}, the neurotoxin is commonly used by physicians in Botox treatments for cosmetic procedure. Botulinum toxin type A, the first microbial toxin ever used for human medical treatment, serves as a treatment for a variety of strabismus (lazy-eye), blepharospasm (eyelid spasm) and hemifacial spasm. By injecting the neurotoxin directly into the muscle, Botulinum toxin type A blocks the release of the neurotransmitter acetylcholine at myoneural junctions chemically suppressing hyperactive muscle disorders.\textsuperscript{[42]}

11.2. Penicillin
Everyone has heard of penicillin, the fungal mold which can treat all sorts of infections, but this is simply a snowflake on the tip of the iceberg that is the modern day use of fungi in medicine.\textsuperscript{[42]} Penicillin (PCN or pen) is a group of antibiotics which include penicillin G (intravenous use), penicillin V (oral use), procaine penicillin and benzathine penicillin (intramuscular use). They are derived from Penicillium fungi. Penicillin antibiotics were among the first medications to be effective against many bacterial infections caused by staphylococci and streptococci. Penicillin was discovered in 1928 by Scottish scientist Alexander Fleming.\textsuperscript{[44]}
11.3. Lovastatin
One derivative, known as lovastatin, is naturally created by oyster mushrooms which act to lower LDL cholesterol levels through inhibition of the enzyme HMG-CoA reductase. HMG-CoA reductase is an important enzyme in the liver and is a central role in the production of cholesterol in the organ. Statins, the family of drugs which lovastatin is a member of, act to lower LDL cholesterol and has been shown to decrease the number of heart attacks and sudden cardiac death by 60% and reducing the risk of stroke of 17%.\[45\]

11.4. Fingolimod from Myriocin
*Isaria Sincliarii*, is a fungi which produces the compound myriocin. Through chemical synthesis researchers were able to produce the immunosuppressive drug fingolimod. Fingolimod was a milestone drug because it was the first disease modifying drug designed to be taken orally which was approved by the Food and Drug Administration.\[46\] Fingolimod is used to reduce relapse and delay the progression of relapsing multiple sclerosis. The synthetic drug acts by building up stores of lymphocytes in lymph nodes and preventing the lymphocytes from interacting with the central nervous system and causing the autoimmune responses present in patients with multiple sclerosis. Patients taking Fingolimod was found to reduce patient relapse rates to less than 50% of those taking the placebo.\[42\]

11.5. *Boletus Edulis*, an Inhibitor of HIV-1
*Boletus Edulis*, a mushroom found throughout the northern hemisphere shows promise in inhibiting the spread of the human immunodeficiency virus-1.\[47\] The mushroom produces a lectin (a sugar binding protein), which has a large impact on the activity of the HIV-1 reverse transcriptase. Since the first step of retroviral infection following the injection and uncoating of viral nucleic RNA into the host cell is the action of reverse transcriptase in reading the RNA and writing a complimentary DNA sequence, the best place to halt HIV-1 infection other than preventing the entrance into the host would be at the reverse transcriptase. Researchers at the China Agricultural University in Beijing were able to show that through a protein-protein interaction, the lectin produced by *Boletus Edulis* inhibited HIV-1 reverse transcriptase activity in a level of potency higher than that of other natural products. The mechanism whereby *Boletus Edulis* works may be very useful in the fight against HIV. For both recently infected patients and long-term patients the reverse transcriptase inhibition will inhibit the spread of the infection providing a means of early treatment of the infection.\[42\]
11.6. Erinacin E
The comb tooth mushroom *Hericium coralloides* is a colorless fungus which grows on dead hardwood trees and creates a substance which erinacin E can be isolated from. At the department of Neuropsychopharmacology and Hospital Pharmacy at Nagoya University School of Medicine, research shows that erinacin E acts as an effective nerve growth factor stimulator. This ability is especially useful as a potential suppressor of the effects of degenerative diseases such as Alzheimer’s disease. Patients suffering from Alzheimer’s have degenerating cholinergic neurons in their central nervous system. Cholinergic neurons are those which have acetylcholine neurotransmitters, and include neuromuscular junctions, preganglionic neurons, and brain stem complexes. By increasing the amount of nerve growth factors in the patients’ circulatory system, researchers restored the amount of nerve growth factors in the frontal cortex and the parietal cortex using erinacin E.

12. CONCLUSION
Microorganisms have a great contribution in medical history. At present some are commercially used as probiotics e.g. lactobacillus. Many microbes’ derived products are in various clinical trials. Microorganisms can be used to treat various fatal diseases such as HIV, cancer etc. by effective manipulation in near future.

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