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Therapeutic Potentials of Cyclic Peptides as Promising Anticancer Drugs

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Abstract

This review focuses on studying the pharmacological effect of cyclic peptides as anti-cancer drugs. There are many examples which are already used to treat cancer, either directly or in the treatment of episodes associated with cancer tumors. Goserelin acetate; is an anti-cancer drug, trade name Zoladex, is an injectable gonadotropin releasing hormone superagonist. Leuprolide acetate; is a gonadotropin-releasing hormone or luteinizing-hormone-releasing hormone analog used in the treatment of hormone-responsive cancers such as prostate cancer or breast cancer. Somatostatin, (SST), is a peptide hormone; the peptide hormone somatostatin regulates the endocrine system, affects neurotransmission and cell proliferation via interaction with G protein-coupled somatostatin receptors and inhibits the release of numerous secondary hormones. Octreotide: is a somatostatin mimic, trade name sandostatin, Octreotide is also a more potent inhibitor of growth hormone, glucagon, and insulin than the natural hormone. On the other hand there are many natural bioactive peptides: derived from different foods represent another source of health-enhancing or cancer fighting compounds. Different studies indicate that it is possible that many of these peptides may be released during digestion in the human stomach or during food processing from various plant and animal proteins, especially milk, soy, and fish proteins, for examples Depsipeptides and Argyrins.

Keywords: Amino Acids, Cyclic Peptide Derivatives, Anticancer Activities**,** Therapeutic Peptides**.**

1. Introduction

Cancer (medical term: malignant neoplasm), can be defined as a disease in which a group of abnormal cells grow uncontrollably by disregarding the normal rules of cell division. Invasion (intrusion on and destruction of adjacent tissues) and metastasis, which means the spread to other locations in the body via lymph or blood, are subsequent steps [1]. These three malignant properties of cancers differentiate them from benign tumors, which are self-limited and do not invade or metastasize. Nearly all cancers are caused by abnormalities in the genetic material of the transformed cells [2]. In the late stages of cancer, metastatic tumors are common. The spread of metastasis may occur via the blood or the lymphatics or through both routes. The most common places for the metastases to occur are the lungs, liver, brain, and the bones [3]. In fact, almost 90% of cancers-related deaths are due to metastasis process. The distinct classification of cancer revealed more than 150 currently known types of cancer [4]. The worldwide distribution of new cases for each sex in 1998 estimated 23% lung cancer) as the most predominated in males, followed by prostate (15%), colorectal (13%), stomach (10%) and bladder (7%) cancer. Breast cancer (28%) had the highest frequency in females, followed by colorectal (15%), lung (9%), stomach (7%) and ovarian (5%) [5], for many cancer types, early diagnosis could reduce mortality. Current diagnosis techniques include imaging such as X-ray imaging and MRI, and biopsy [6]. There are many methods for treating cancer as surgery, chemotherapy, radiation therapy, immunotherapy, monoclonal antibody therapy; finding the best type of therapy depends on the location and level of the tumor and the stage of the disease, beside the general state of the patient (performance status). At present, available therapies cure a little more than half cancer patients. Surgery is considered as an efficient treatment, possibly because it is used to cure very small tumors, which are rarely accompanied by

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metastasis. Chemotherapy appears to be more efficient, possibly because it's spreading nature all over the body [7]. When treating cancer with a cytotoxic agent, the pharmacological goal must deliver as much active drug as possible to the molecular target in the cancer cells; causing more molecular damage leading to cell death [8]. The most common type of cancer is Breast cancer and the second cause of death from cancer in US women [9].

2. Anticancer Medications and their side effects:

Anticancer, or antineoplastic, drugs are used to treat malignancies, or cancerous growths. Drug therapy may be used alone, or in combination with other treatments such as surgery or radiation therapy [10]. There many derivatives of current peptide drugs available in the market for treating cancer and also peptide candidates in clinical and preclinical stages of development. Peptides can be utilized in a number of different ways in treating cancer [11-14]. This includes using peptides directly as drugs (e.g., as angiogenesis inhibitors), tumor targeting agents that carry cytotoxic drugs and radionuclides (targeted chemotherapy and radiation therapy). Out of these different possibilities, peptide drugs currently available in the market come from peptide hormone therapy and tumor targeting agents carrying radionuclides (peptide-receptor radio nuclide therapy and imaging). Exceptions to these are two short chain peptide-related drugs, bortezomib and mifamurtide [15-17].

3. A brief summary of the beginning cancer drugs:

The first use of drugs to treat cancer was in the early 20th century, although it was not originally intended for that purpose. Mustard gas was used as a chemical warfare agent during World War I and was discovered to be a potent suppressor of hematopoiesis (blood production) [18]. A similar family of compounds known as nitrogen mustards was studied further during World War II at Yale University [19]. It was reasoned that an agent that damaged the rapidly growing white blood cells might have a similar effect on cancer. Therefore, in December 1942, several patients with advanced lymphomas (cancers of certain white blood cells) were given the drug by vein, rather than by breathing the irritating gas [19], their improvement, although temporary, was remarkable [20, 21].

4. Cancer cells resistant to drugs:

Generally the resistance to drugs; is a major cause of treatment failure in any chemotherapeutic drugs. Currently, 90% of failures in the chemotherapy are during the invasion and metastasis of cancers related to drug resistance. Anticancer drugs resistance is a complex process that arises from altering in the drug targets [22].

5. Side effects of chemotherapy:

Side effects of chemotherapy differ greatly and do not depend on cancer type only. But they depend on many factors as type of cancer, dose of chemotherapeutic drug, health status of the patient and stage of cancer. Though there are many types of cancer treatments available now, but all of them have some associated side effects. Chemotherapy is more effective and always use in treatment of most types of malignancies [23]. Unfortunately, chemotherapy drugs does not kill the cancer cells only but it also damages the normal cells, result in more damage to normal cell and more side effects such as fatigue, nausea, hair loss vomiting, etc. and even death may occurs in severe cases [24]. According to a study on 2014, the most frequently reported side effects were weakness (95%), fatigue (90%), nausea (77%), hair loss (76%) and vomiting (75%). Each of these side effects was experienced by more than 70% of the patients. The below graph showing the prevalence of different side effects of chemotherapeutic drugs among cancer patients having multiple carcinomas [25].

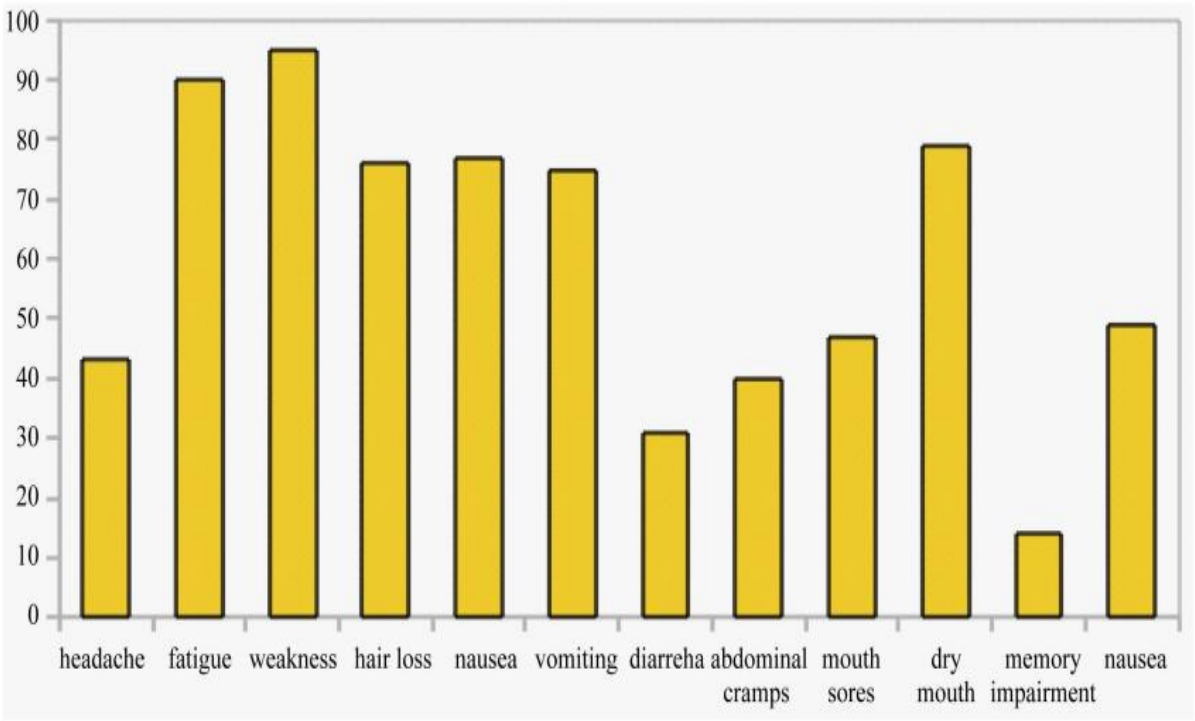


Figure 1: the prevalence of different side effects of chemotherapeutic drugs among cancer patients having multiple carcinomas

5. 1. Specific side effects:

Specific chemotherapeutic agents; are associated with organ-specific toxicities, including cardiovascular disease, Doxorubicin®), interstitial lung disease, Bleomycin®, and occasionally secondary neoplasm, MOPP therapy for Hodgkin's disease. MOPP is a combination chemotherapy regimen used to treat Hodgkin's disease, Mustargen (mechlorethamine) - Oncovin (Vincristine) -Procarbazine (Matulane) Prednisone (Deltasone).

5. 2. Chemotherapy's Effects on Organs and Body Systems:

5. 2. 1. Chemotherapy's potential effects on the Heart:

Heart, Cardiotoxicity, heart damage, is especially prominent with the use of anthracycline drugs (Doxorubicin®, Epirubicin®, Idarubicin®, and Liposomal Doxorubicin®). The cause is, most likely, due to the production of free radicals in the cell and subsequent DNA damage. Other chemotherapeutic agents that cause cardiotoxicity, but at a lower incidence, are Cyclophosphamide®, Docetaxel® and Clofarabine® [26].

5. 2. 2. Chemotherapy's potential effects on the Liver:

Liver plays a central role in transforming and clearing chemicals and is susceptible to toxicity from chemotherapy drugs [27, 28]. In chemotherapy, less than 10% of available drugs are moved to tumor tissues, and more than 60% concentrate in the liver [29]. Hepatotoxicity (liver damage) can be caused by many cytotoxic drugs. The susceptibility of an individual to liver damage can be altered by other factors such as the cancer itself, viral hepatitis, immunosuppression and nutritional deficiency [30, 31].

5. 2. 3. Chemotherapy's potential effects on the Kidney

Kidney, Nephrotoxicity (kidney damage) can be caused by tumor lysis syndrome and also due direct effects of drug clearance by the kidneys [32, 33].

5. 2. 4. Chemotherapy's potential effects on the Inner ear

Inner ear, Ototoxicity (damage to the inner ear) is a common side effect of platinum based drugs that can produce symptoms such as dizziness and vertigo [34, 35].

5.2.5. Minimization of chemotherapy side effects:

Experimental studies on tumored animals, showed that chemotherapy drug dose can be decreased when combined with nanoparticles and heterocyclic compounds. Such combinations which will allow reduction of recommended dose by ten- or even hundredfold – with preserved effectiveness. The main advantage of this is t there is no increase of cytostatic drugs' effect by additional antitumor activity of nanoparticles and heterocycles. Nanoparticles and heterocyclic compounds which have neither antitumor effect nor side effects [36, 37].

6. Therapeutic Peptides for Treating Cancer

In our previous studies of peptide candidates, we observed that the peptide derivatives have distinct biological properties such as, anticancer activities, anti-inflammatory, analgesic agents and good antimicrobial properties [38-61]. Peptides, either natural or synthetic, have seen increased application as therapeutic agents in recent years. In 2012, in addition to almost 80 peptides on the market, approximately 200 more have been reported to be in clinical phases and 400 are in advanced preclinical stages. Recently, peptide drugs targeting disorders of metabolic pathways or cancer are also demonstrating potential applications in other clinical fields, such as cardiovascular, CNS, gastrointestinal and autoimmune diseases. This development marks a noticeable trend because towards the end of the previous century the use of peptides for the treatment of diseases was very limited. The hope is that the development of new improved peptide based therapeutics may change this in the future.

6. 1. Some examples of therapeutic peptides

There are many examples which are already used to treat cancer, either directly or in the treatment of episodes associated with cancer tumors.

6. 1. 1. Goserelin acetate:-

Goserelin is an anti-cancer drug, trade name Zoladex, the salt of a decapeptide, is an injectable gonadotropin releasing hormone superagonist, also known as a luteinizing hormone releasing hormone agonist. A superagonist is a compound that can bind to a receptor and activate it more strongly than the naturally produced activating molecule. Goserelin is used to suppress production of the sex hormones in the treatment of breast and prostate cancer and to treat hormone-sensitive cancers of the breast and prostate [62-65].

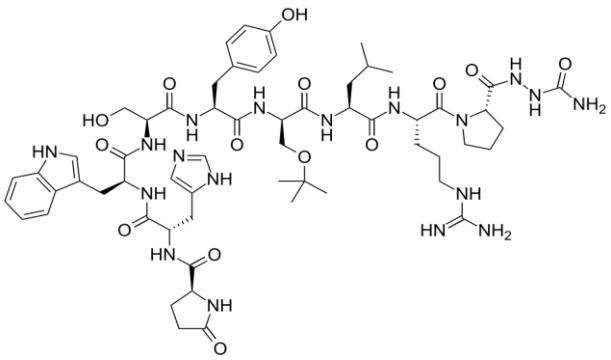


Figure 2; structure of Goserelin

6. 1. 2. Leuprolide acetate:-

Leuprolide is a gonadotropin-releasing hormone or luteinizing-hormone-releasing hormone analog used in the treatment of hormone-responsive cancers such as prostate cancer or breast cancer, estrogen-dependent conditions, precocious puberty, and to control ovarian stimulation in In-Vitro Fertilization. Lupron is the brand name for leuprolide acetate. This drug is a type of hormone therapy that doctors typically use in combination with other treatments to treat people with prostate cancer [66].

Figure 3; structure of Leuprolide

6. 1. 3. Somatostatin, (SST),

Somatostatin also known as growth hormone-inhibiting hormone (GHIH) or by several other names, is a peptide hormone, the peptide hormone somatostatin regulates the endocrine system, affects neurotransmission and cell proliferation via interaction with G protein-coupled somatostatin receptors and inhibits the release of numerous secondary hormones [67].

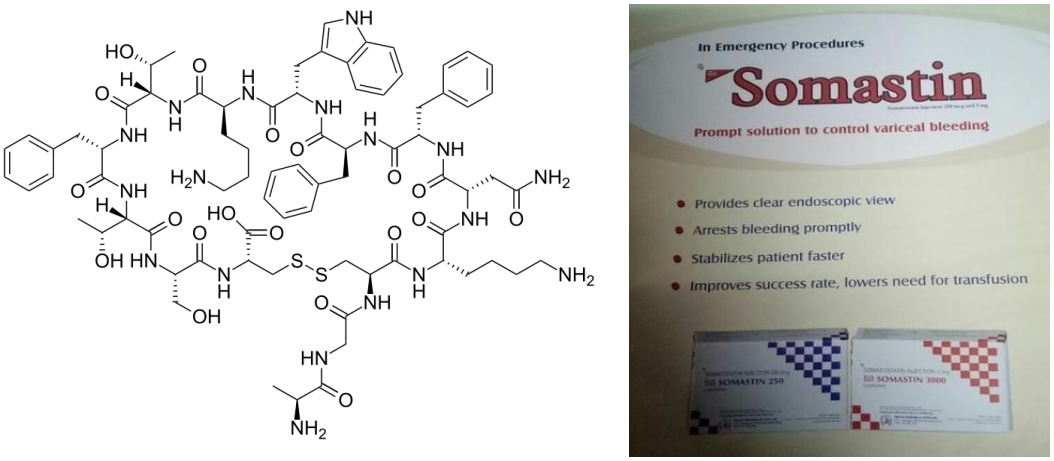


Figure 4; structure of Somatostatin

6. 1. 4. Octreotide:

Octreotide is a somatostatin mimic, trade name sandostatin, Octreotide is also a more potent inhibitor of growth hormone, glucagon, and insulin than the natural hormone. The salt form of the peptide, octreotide acetate, is approved by the Food and Drug Administration (FDA) to be used as an injectable depot formulation for the treatment of growth hormone producing tumors, pituitary tumors that secrete thyroid stimulating hormone, diarrhea and flushing episodes associated with carcinoid syndrome, and diarrhea in patients with vasoactive intestinal peptide-secreting tumors [68].

Figure 5; structure of Octreotide

6. 2. Natural bioactive peptides:

Natural bioactive peptides derived from different foods represent another source of health-enhancing or cancer fighting compounds. Different studies indicate that it is possible that many of these peptides may be released during digestion in the human stomach or during food processing from various plant and animal proteins, especially milk, soy, and fish proteins.

6. 2. 1. Some examples of Natural bioactive therapeutic peptides

6. 2. 1. 1. Depsipeptides:

These types of peptides been extracted from various marine animals like tunicates, sponges, soft corals, sea hares, nudibranchs, bryozoans, sea slugs, and other marine organisms [69-72]. A depsipeptide is a peptide in which one or more of its amide, -C (O) NHR-, groups are replaced by the corresponding ester, -C(O)OR, Many depsipeptides have both peptide and ester linkages. They are mainly found in marine and microbial natural products. Several depsipeptides have been found to exhibit anti-cancer properties [73-75].

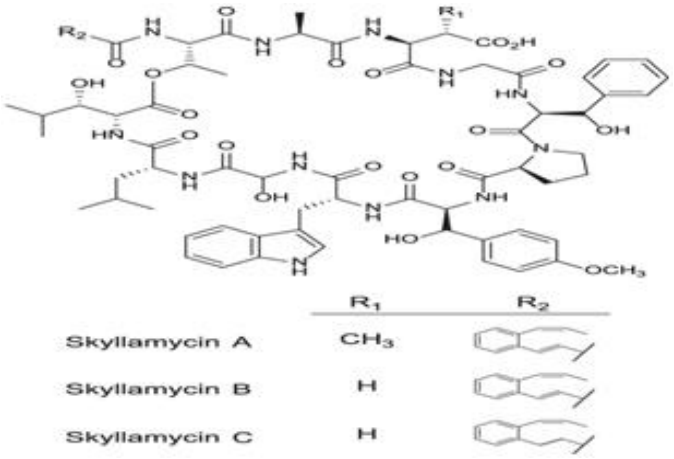
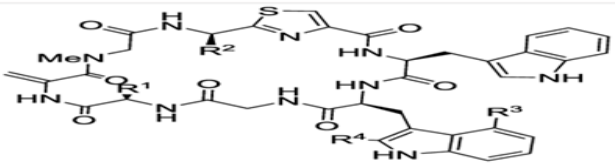


Figure 6; General structure of a depsipeptides

6. 2. 1. 2. Argyrins:

Argyrins were known for some time to inhibit bacterial protein synthesis and were also shown to have activity against eukaryotic cells. They were reported to be immunosuppressive and antitumorigenic, and it was suggested that argyrin A inhibits the proteasome, induces apoptosis, and blocks angiogenesis by a p27-dependent mechanism [76-78]. Argyrin A, a cyclical peptide derived from the myxobacterium Archangium gephyra, as a potent antitumoral drug [76].



Argyrin		R^1	R^2	R^3	R^4	IC_{50} [µg/mL]
A	1	CH_3	CH_3	OCH_3	H	0.12
B	2	C_2H_5	CH_3	OCH_3	H	0.08
C	3	CH_3	CH_3	OCH_3	CH_3	0.1
D	4	C_2H_5	CH_3	OCH_3	CH_3	0.14
E	5	CH_3	CH_3	H	H	1.4
F	6	CH_3	CH_2OH	OCH_3	H	5
G	7	C_2H_5	CH_2OH	OCH_3	H	4
H	8	CH_3	H	OCH_3	H	0.8

Figure 7; chemical structure of naturally occurring argyrins with potent antipseudomonal activity

6. 2. 1. 3.Jaspamides:

Jaspamides are cytotoxic peptides that disrupt the proper function of actin [79]. Jaspamide is a cyclodepsipeptide that has antitumor activity. A narrow margin of safety was observed between doses required for efficacy in mouse tumor models and doses that caused severe acute toxicity in rats and dogs [80].

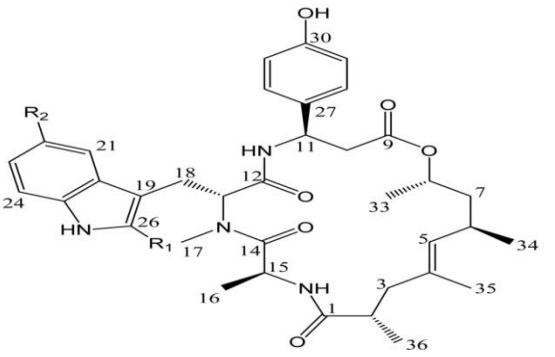


Figure 8; chemical structure of Jaspamides

6. 2. 1. 4. phallotoxins:

The phallotoxins, such as Phalloidin are toxic peptides isolated from the poisonous mushroom Amanita phalloides. Phalloidin, like the later-detected phallotoxins, consists of a cyclic heptapeptide backbone, the ring being crosslinked by a 2'-indolylthioether moiety (tryptathionine). phallotoxins, damage the liver specifically, presumably in consequence of its very tight binding to F-actin preventing its dissociation. This affinity can be utilized for a sensitive visual identification of F-actin by using fluorescent derivatives [81, 82].

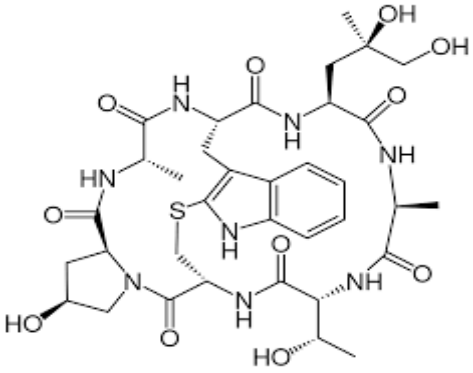
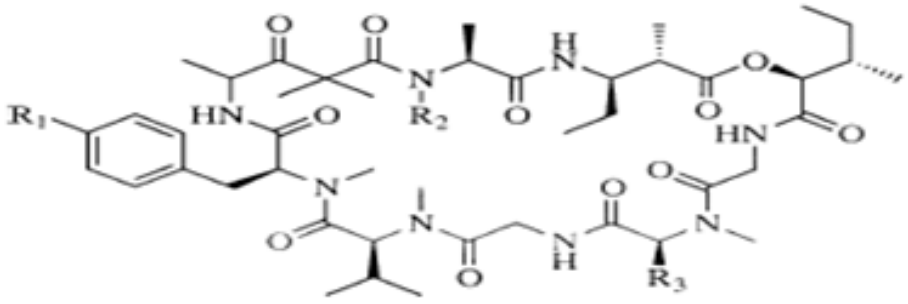


Figure 9; chemical structure of phallotoxins

6. 2. 1. 5. Dolastatin:

Dolastatin 11 and the structurally related Majusculamide C, Lyngbyastatin and Dolastatin 12 induce hyperpolymerization of purified actin. Dolastatin 11 is the most cytotoxic of the peptides that induces the assembly of actin *in vitro*. The successful synthesis of dolastatin 11, a depsipeptide originally isolated from the mollusk Dolabella auricularia, permitted us to study its effects on cells. The compound arrested cells at cytokinesis by causing a rapid and massive rearrangement of the cellular actin filament network. In a dose-and time-dependent manner, F-actin was rearranged into aggregates, and subsequently the cells displayed dramatic cytoplasmic retraction. The effects of dolastatin 11 were most similar to those of the sponge-derived depsipeptide jasplakinolide [83].

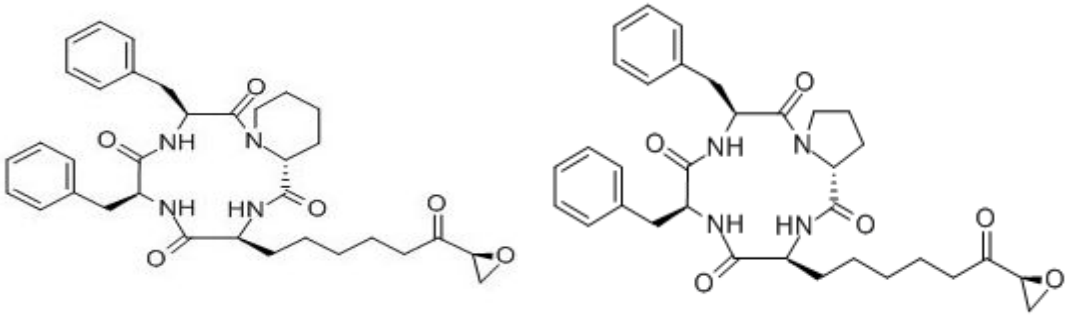


Dolastatin 10: R_1 = OMe, R_2 = H, R_3 = CH_2: Pr, Dolastatin 12: R_1 = H, R_2 = CH_3, R_3 = CH_2: Pr, Lyngbyastatin 1: R_1 = OMe, R_2 = CH_3, R_3 = CH_2: Pr, Majusculamide C : R_1 = OMe, R_2 = H, R_3 = (S) CH_2Bu

Figure 10; chemical structure of Dolastatin

6. 2. 1. 6. Trapoxins:

Trapoxin (cyclo-(L-phenylalanyl-L-phenylalanyl-D-pipecolinyl-L-2-amino-8-oxo-9, 10-epoxy-decanoyl)), Trapoxins are a cyclotetrapeptide histone deacetylase (HDAC) inhibitor [84]. The two tetrapeptides Trapoxins A and B, containing an epoxyde moiety, are isolated from Helicoma ambiens. A homodetic cyclic tetrapeptide constructed from L-phenylalanyl (x2), D-pipecolinyl and L-2-amino-8-oxo-9, 10-epoxydecanoyl residues [85]. Trapoxins are a fungal product that induces morphological reversion from transformed to normal in cis-transformed NIH_3T_3 fibroblasts. Trapoxins were found to cause accumulation of highly acetylated core histones in a variety of mammalian cell lines. *In vitro* experiments using partially purified mouse histone deacetylase showed that a low concentration of trapoxin irreversibly inhibited deacetylation of acetylated histone molecules [84].



Trapoxins A Trapoxins B

Figure 11; chemical structure of Trapoxins

7. Conclusions

In this review, reports of many previous literature concluded that cyclic peptides showed great activity as anti-cancer drugs, which led to the existence of many different efforts that focus on studying the composition and studying the biological activity of them, and many of these cyclic peptide products have been made exclusively by Natural organisms as well as by chemical synthesis, and thus continued to present new industrial challenges as anti-cancers.

8. Conflicts of interest

There are no conflicts to declare.

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