Journalof Pharmaceutical Sciences and Emerging Drugs

Research A SCITECHNOL JOURNAL

Biological significance of natural cyclic peptides: A review.

Renu Saharan, Suresh Kumar*, Sukhbir Lal Khokra, Randhir Singh

Department of Pharmaceutical Chemistry, Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra, (Haryana), India

***Corresponding author:** Suresh Kumar, Department of Pharmaceutical Chemistry, Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra,(Haryana), India, E-mail: sureshmpharma@rediffmail.com

Received date: 27 April, 2022, Manuscript No. JPSED-22-24261;

Editor assigned date: 29 April, 2022, PreQC No. JPSED-22-24261 (PQ);

Reviewed date: 13 May, 2022, QC No. JPSED-22-24261;

Revised date: 20 May, 2022, Manuscript No. JPSED-22-24261 (R);

Published date: 27 May, 2022, DOI: 10.4172/2380-9477.1000124

Abstract

Background: Natural sources like plants, fungi, marine organisms, algae and bacteria are the most abundant sources of cyclic peptides of therapeutic use. Numerous novel cyclic peptides isolated from natural sources and successfully developed in to bioactive products. Recently, cyclic peptides derived from natural resources have attracted attention to explore their numerous beneficial effects. Moreover, literature review have reported that natural cyclic peptides exhibit various biological activities like anti-microbial, cyto-toxic, anthelmentic activity, immune-suppressive activity, anti-inflammatory activity, anti-HIV activity, repellent (anti-fouling) activity, anti-tubercular activity and anti-viral activity. In this review, we will present the structures and biological activities of cyclic peptides isolated from various natural sources.

Objective: The purpose of this review is to summarize the biological potentials associated with naturally occurring cyclic peptides.

Conclusion: The natural cyclic peptides possess a wide spectrum of biological activities and can be become drug of future for replacing the existing drugs which developed resistance.

Keywords: Cyclic peptides, bioactive, biological potential, cyto-toxic, anthelmentic activity, anti-viral activity.

Introduction

The novel therapeutic compounds are present in abundant amount in natural sources. Drug molecules which are produced by micro-organisms play a vital role in field of drug discovery. Among natural sources of new therapeutic compounds, the marine organisms are recognized as unique sources of natural therapeutic agents having wide spectrum of biological activities. Among them, peptides are the bio-molecules which are involved in complex biological processes and targeted as future drugs. Hence, they are identified as unique therapeutic agents used in pharmaceutical field.

In comparison to linear peptides, cyclic peptides possess better biological activities due to the conformational rigidity. The entropy gets decreased due to rigidity which increased binding towards receptor. Cyclic structure also prevents hydrolysis of peptides by peptidases. Cyclosporine A, having cyclic peptide structure can cross the blood brain barrier very easily, better than the linear peptides.

Cyclic peptides have good binding affinity, selectivity for target and low level of toxicity which promote them as therapeutics. So many drugs containing cyclic peptide structure are present in market for clinical use. Every year, one new cyclic peptide drug enters in market having natural origin. Due to variations in structure and function they are used as neurotransmitters or as signaling molecules.

Microbial chemical templates of cyclic peptides are used in pharmaceutical industry as a target to modify them as a lead molecule exhibits numerous pharmacological activities like cyto-toxic, anti-microbial, anti-parasitic, anti-inflammation, anti-proliferative and anti-hypertensive. Cyanobacteria also possess broad range of pharmacological activities due to presence of diverse cyclic peptide structure. The marine peptides and their analogues have high commercial value, hence used in market as nutraceuticals while some others are in different stages of clinical trials. Examples of recently isolated cyclic are Gymnopeptides A and B from the mushroom G. fusipes, pseudoxylallemycins A-F from Pseudoxylaria sp. X802 (anti-bacterial), a cyclic hexapeptide - ASP2397 from A. persicinum (anti-fungal), a cyclic pentapeptide (Malformin-E) isolated from fungus A. Tamarii [3].

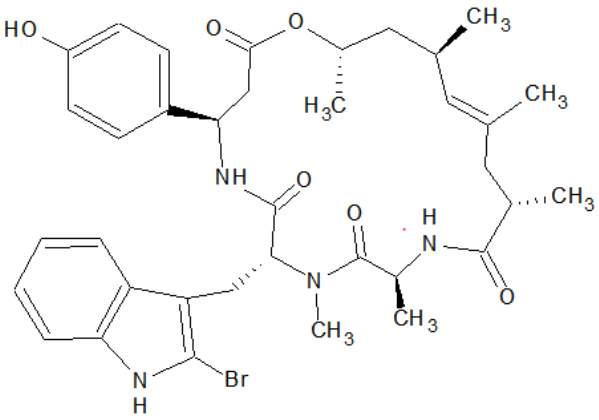
Other examples include Endolides A-B from fungus Stachylidium sp. (affinity for vasopressin receptor 1A and serotonin receptor 5HT2b) and Psychrophilins E-H, from the marine-derived fungus Aspergillus versicolor ZLN-60 (anti-fungal). To isolate more cyclic peptides from natural sources need new dereplication procedures and biotechnological screening [3].

Animals and plants from marine origin such as fungi, higher plants, marine sponges, tunicates and Cyanobacteria provide various natural products with unusual structures and potent biological activities. Out of them, cyclopeptides reflects activities like anti-microbial, cyto-toxic, anthelmentic activity, immune-suppressive activity, anti-inflammatory activity, anti-HIV activity, repellent (anti-fouling) activity, anti-tubercular activity and anti-viral activity. Because of such versatile and potent biological properties and unique structure of cyclic peptides a lot of research work has been carried out through worldwide. The extensive literature review study concluded the following biological activities of cyclic peptides:

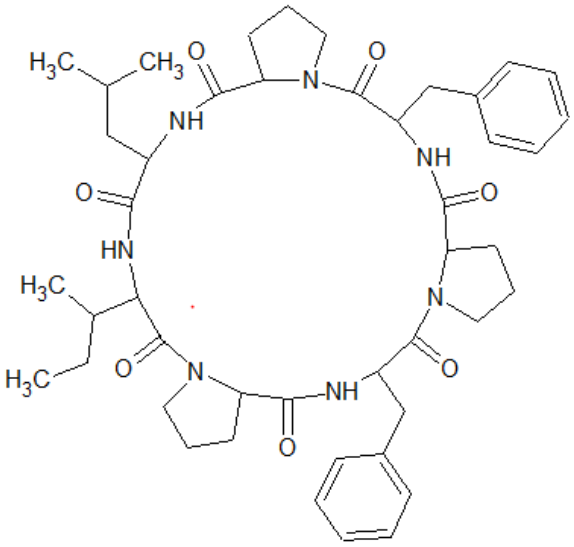
Biological Activities:

Anthelmintic activity

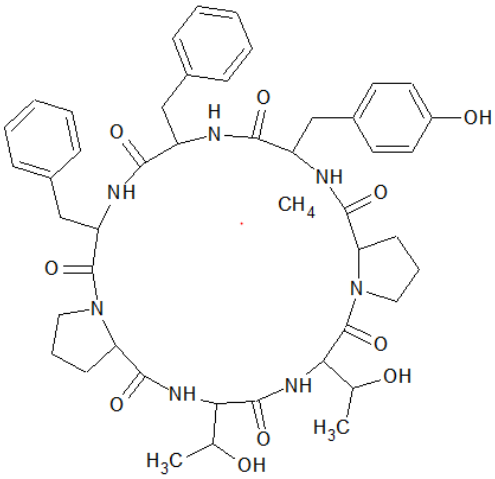
The following three cyclic peptides were found to be potent Anthelmintic agents. A cyclic depsipeptide, Jaspamide (Jasplakinolide) (1) was isolated from a south pacific marine sponge Jaspis johnstoni by Zabriskie et al., (1986). Conformational analysis of jasplakinolide was carried out by Inman and Crews (1989) followed by its stereoselective synthesis by Imaeda et al., (1994). In addition to the potent cyto-toxic and anti-fungal activity against yeast, jasplakinolide was found to exhibit insecticidal and anthelmintic activities against *E. histolytica* and *E. invadens.*



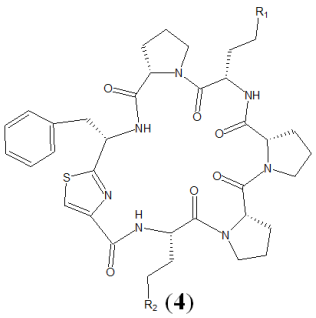
Stylissamide G (2), was synthesized first time by Dahiya et al., (2016) which was isolated from a sponge of marine origin Stylissa caribica. It was found to be a potent Anthelmintic agent againt earth worms like *P. corethruses, M. konkanensis* and *E. eugeniea*.



A cyclic heptapeptide, Hymenamide E (3) was synthesized first time by Dahiya et al., (2006) and previously extracted from marine sponge of genus Hymeniacidon by Tsuda et al., (1993). Synthesized, Hymenamide E was found to be a potent Anthelmintic agent against *M. konkanensis* and *Eudrilus* species.



Cyto-toxic Activity: The following cyclic peptides were found to be potent cyto-toxic agents: Geodiamolides A-B (depsipeptides) (4d, e) were isolated by Chan et al., (1987) from marine sponge Geodia sp. while Geodiamolides C-F (4a-c, 4f) by de Silva et al. (1990) from papua new guinean sponge Pseudaxinyssa sp. Grieco and Perez-Medrano (1988) reported the total synthesis of geodiamolides but their stereoselective synthesis was achieved by Imaeda et al., (1994). These all depsipeptides possessed cyto-toxic activity.



(**4**)

(**4a**) R = H, X = I

(**4b**) R = H, X = Br

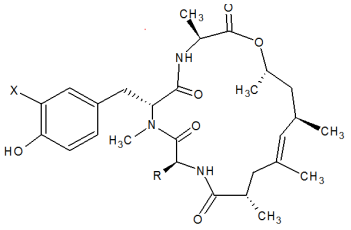
(**4c**) R = H, X = Cl

(**4d**) R = Me, X = I

(**4e**) R = Me, X = Br

(**4f**) R = Me, X = Cl

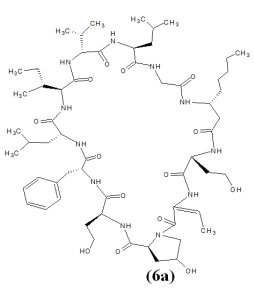
Two novel cyclohexapeptides i.e., Haligramides A and B (5a, b) were isolated by bioassay-guided fractionation of a cyto-toxic aqueous extract of marine sponge Haliclona nigra by Rashid et al., (2000). These cyclopeptides exhibited potent cyto-toxic activity against A-549 (lung), HCT-15 (colon), SF-539 (CNS) and SNB-19 (CNS) human tumor cell lines.



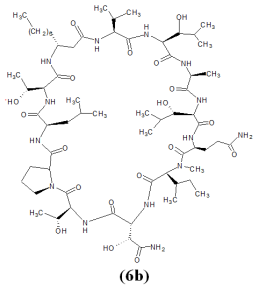
(**5a**) $R_1 = R_2$ = S-Me

(**5b**) R_1 = S-Me, R2 = S-OMe

Two cyclopeptides, Laxaphycin A and B (6a, b) were isolated from the terrestrial blue-green algae Anabaena laxa by Frankmolle et al., (1992). Total stereostructure and biological properties of these cyclic undeca and dodecapeptides were established by Bonnard et al., (1997). These peptides were found to possess anti-fungal as well as cyto-toxic activities.

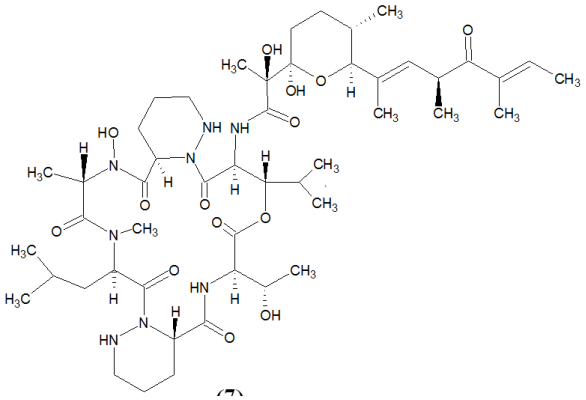


(6a)

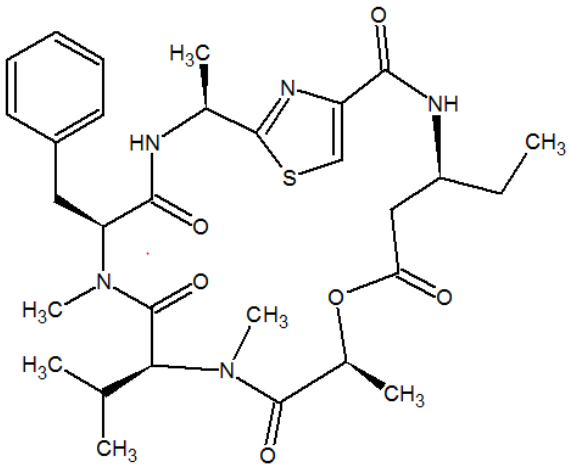


(6b)

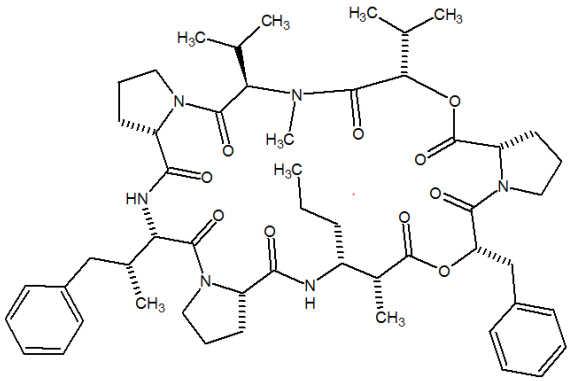
A cyclic hexadepsipeptide, anti-tumor antibiotic, GE3 (7) was isolated from Streptomyces sp. by Sakai et al., (1997). Its structure was established by Agatsuma et al., (1997). GE3 possessed moderate anti-bacterial profile against S. aureus, E. hirae, B. subtilis and P. aeruginosa and potent cyto-toxic activity against human tumors both in vitro and in vivo especially against pancreatic carcinoma PSN-1.



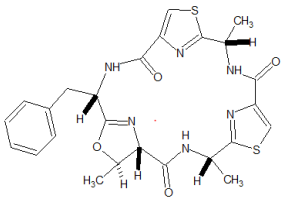
A novel cyclic depsipeptide, Obyanamide (8) was isolated by Williams et al., (2002) from marine cyano-bacterium Lyngbya confervoides. Obyanamide was found to show moderate cyto-toxic activity.



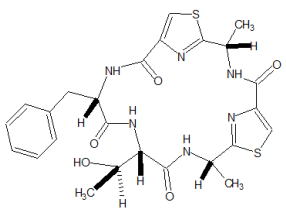
A cyto-toxic depsipeptide, Kulokekahilide-1 (9) was isolated from the cephalospidean mollusk Philinopsis speciosa by Kimura et al., (2002). This isolated depsipeptide possessed cyto-toxic activity at CTC50 value of 2.1 µg/ml against P-388 murine leukemia cells.



Didmolamide A and B (10a, b), cyclo hexapeptides were confined from the marine ascidian Didemnum molle by Rudi et al., (2003). Both Didmolamides were exhibited moderate cyto-toxic activity against A549, HT29 & MEL28 cell lines with IC50 values of 10-20 µg/ml.

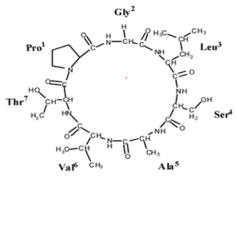


(10a)

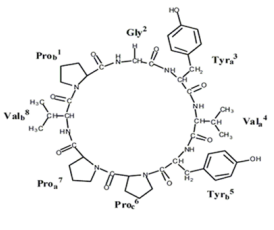


(10b)

Cyclosenegalin A (11) and cyclosenegalin B (12) have been isolated by Alassane et al., (2002) from the seeds of Annona senegalensis pers., by using methanol extract. Their structures were established by spectral methods. Cyclosenegalin A produced moderate cyto-toxic effects on DU-145 cell lines of human prostate cancer.

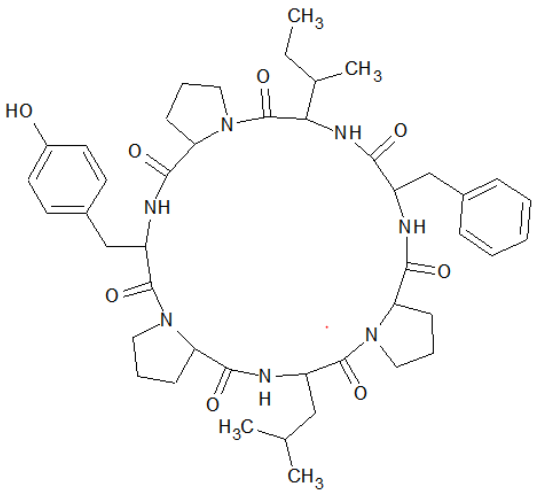


(11)

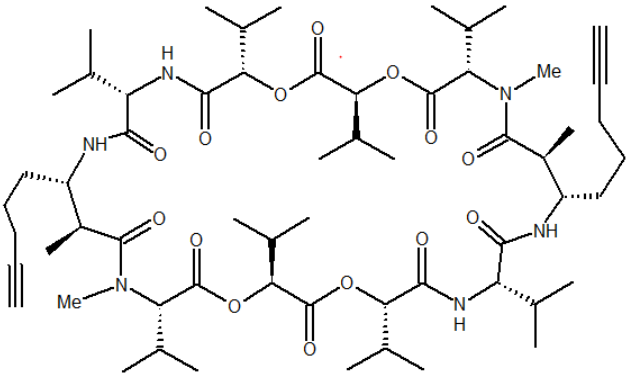


(12)

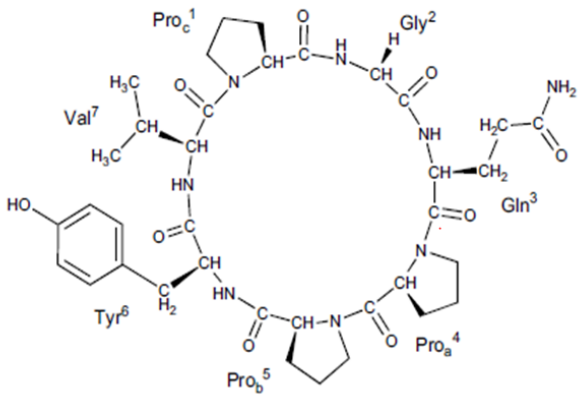
A cyclic heptapeptide, Stylisin-1 (13) was synthesized first time by Dahiya et al., (2009) which was previously isolated from a marine sponge Stylissa caribica by Mohammad et al., (2006). Stylisin-1 possessed moderate cyto-toxicity against EAC and DLA cell lines.



The total synthesis of Onchidin (14), a C2-symmetric cyclic decadepsipeptide was synthesized by Kobayashi et al., (2007) using efficient solid-phase method and was previously isolated from the pulmonate mollusc Onchidium sp. by Rodriguez et al., (1994) and was found to be potent cyto-toxic agent.

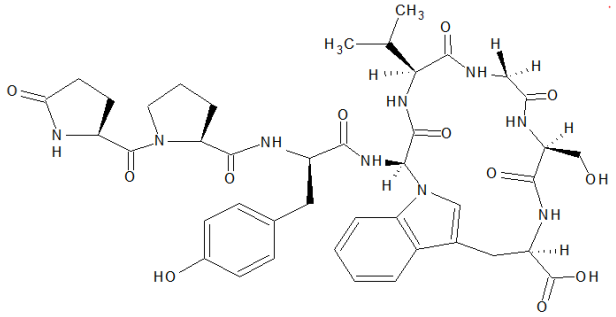


The cyclohexapeptide, Glabrin A (15), was extracted from Annona reticulate by Alassane et al., (2009) by using methanol extract. Its structure was confirmed by mass spectroscopy and NMR. The isolated cyclic peptide was found to be potent anti-cancer agent.



ACE Inhibitory Activity

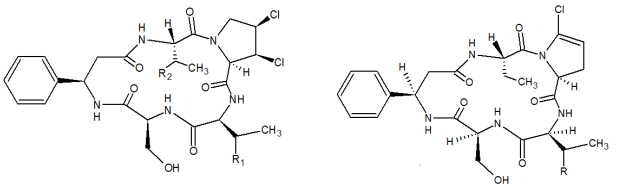
The following octapeptide showed ACE Inhibitory activity: LyciuminsA-B (octapeptides) were isolated by Yahara et al., (1989) from roots of Lycium chinense MILL. Synthesis of Lyciumins A-B was firstly carried out by Schmidt and Stabler (1992) while elucidation of the complete stereostructure and conformational analysis of



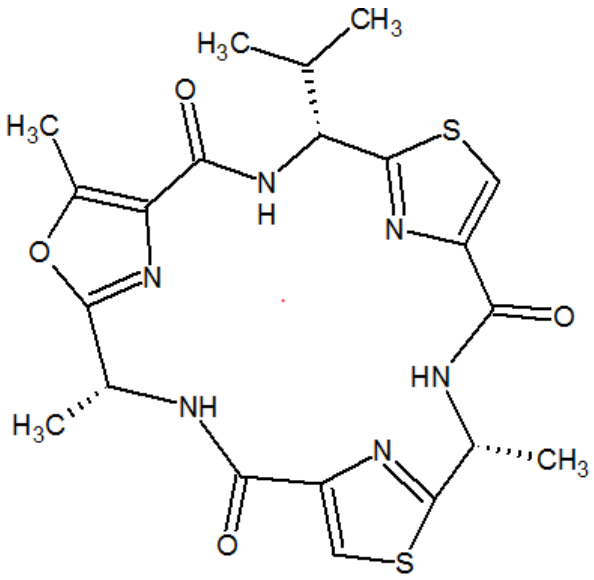
Lyciumin A (16) was done by Morita et al., (1996). This cyclic octapeptide (16) showed inhibitory activity on angiotensin converting enzyme.

4. Anti-tumor Activity: The following cyclic peptides were found to be potent anti-tumor agents:

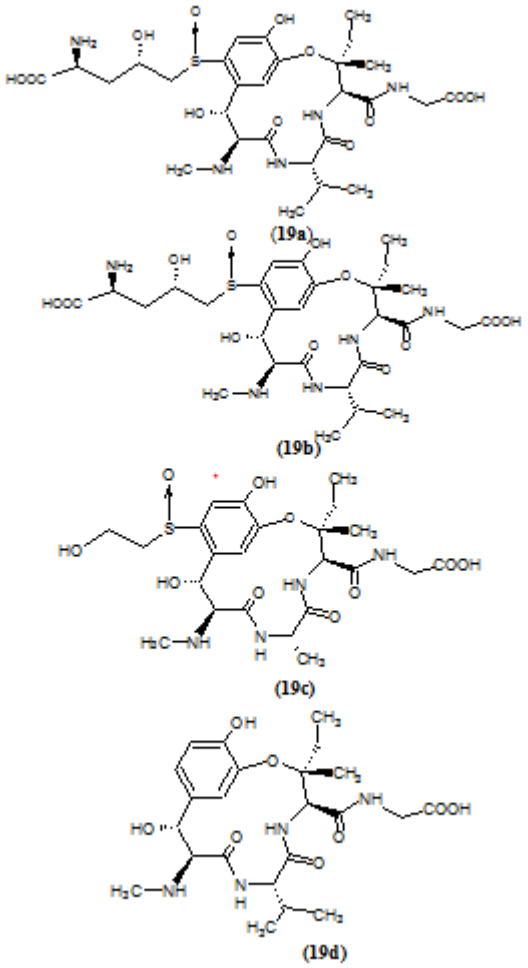
Two novel monochlorinated cyclic pentapeptides, Astin-D and E (17a, b) were isolated by Morita et al., (1993) along with related cyclic peptide, Astin-G from roots of Aster tataricus (compositae). Total synthesis of Astin-G was reported by Schumacher et al., (1999). Astin-D and E were found to possess potent anti-tumor activity.



A cyclic hexapeptide, Dendroamide A (18) which was isolated from the cyanobacterium Stigonema dendroideum fremy by Ogino et al., (1996) and synthesized by Xia and Smith (2001). This synthesized cyclopeptide exhibited significant ability to antagonize transport proteins viz. Pgp and MRP1 which can also used against resistant tumors.



Microtubule Inhibitors: The following cyclic peptides were found to be microtubule inhibitors: Anti-mitotic cyclic peptides, Ustiloxins A-D (19a-d) were isolated from fungus Ustilaginoidea virens by Koiso et al., (1994). Later, Ustiloxin F was isolated and its structure was determined by spectroscopic analysis and chemical interrelation with Ustiloxin B by Koiso et al., (1998). Synthesis of Ustiloxin analogs was reported by Takahashi et al., (1998). Ustiloxins were found to be effective microtubule assembly inhibitor.



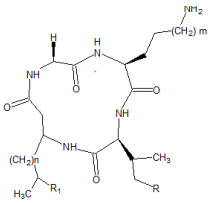
(19a)

(19b)

(19c)

(19d)

Anti-fungal Activity: The following cyclic peptides were found to be potent anti-fungal agents: Rhodopeptins C1 to B5 (20a-e), novel cyclotetrapeptides were confined from Rhodococcus sp. by Chiba et al., (1999). Synthetic studies on rhodopeptins were reported by the Chiba et al., (1999). Rhodopeptins exhibited potent anti-fungal efficacy against C. albicans and C. neoformans.



(20a) n = 6, m = 1, R = H, $R_1 = C_2H_5$

(20b) n = 6, m = 1, R = CH_3, $R_1 = C_2H_5$

(20c) n = 8, m = 1, R = H, $R_1 = CH_3$

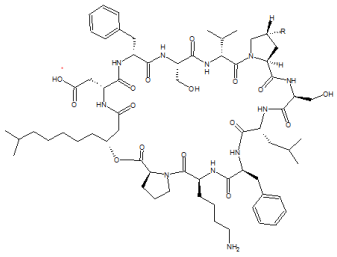
(20d) n = 8, m = 1, R = H, $R_1 = C_2H_5$

(20e) n = 9, m = 2, R = H, $R_1 = CH_3$

Anti-malarial Activity: The following cyclic peptides were found to be potent anti-malarial agents:

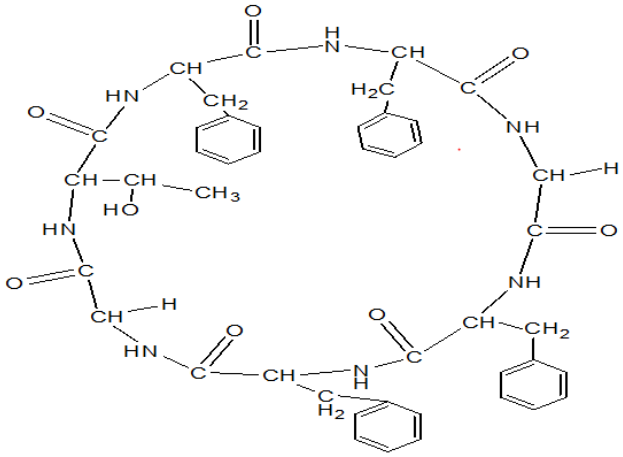
Kahalalides P and Q (21a, b) were confined from the green algae Bryopsis sp. by Dmitrenok et al., (2006) . Both cyclopeptides were found to inhibit HL-60 cancer cell lines with IC50 value of 100 µg/ml. Kahalalides A-F were previously isolated from sacoglossan mollusk Elysia rufescens and its green algae Bryopsis sp. by Hamann et al., (1996). Kahalalide A was found to show moderate anti-malarial

activity against P. falciparum.

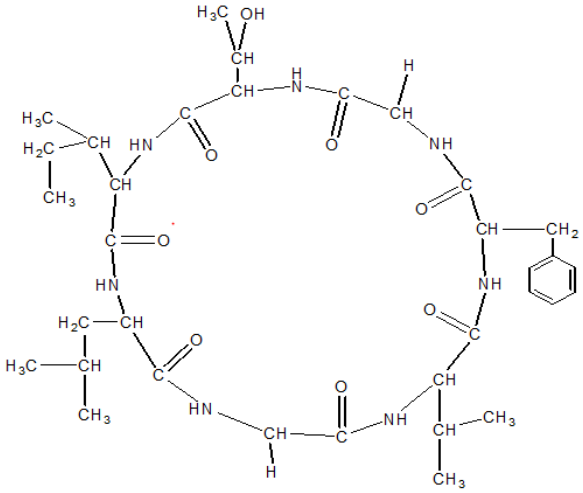


(**21a**) R = OH
(**21b**) R = H

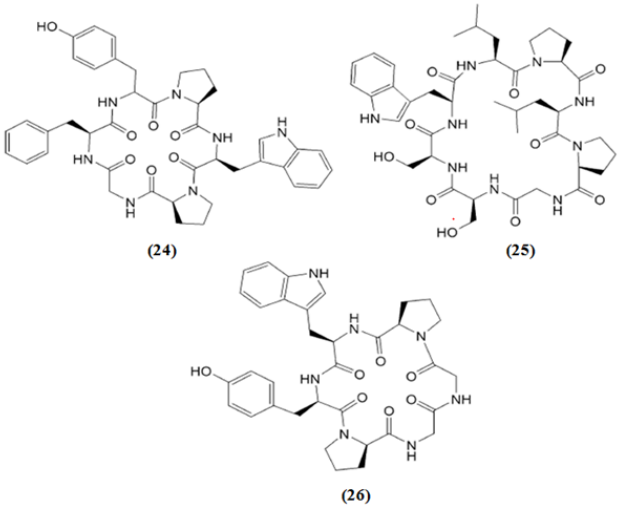
A cyclic heptapeptide, Mahafacyclin B (22) was isolated by using latex of Jatropha mahafalensis by Carine et al., (2001). The structure was established by spectral methods. The synthesized cyclic peptide was found to be potent anti-malarial agent.



A cyclic heptapeptide, Mahafacyclin A (23) was isolated from the latex of Jatropha mahafalensis by Carine et al., (2000). The structure was confirmed by using spectral methods like NMR and Mass spectroscopy. The synthesized cyclic peptide was found to be potent anti-malarial agent.



Platelet Aggregation Inhibitors: The following cyclic peptides found to inhibit the platelet aggregation: Three cyclopeptide, Diandrine A-C (24-26), were isolated from the Drymaria Diandrine by Hsieh et al., (2004). Chemical and spectroscopic methods were used to confirm their structures. Compound (26) has stable conformation. Cyclopeptide (24) was found to inhibit platelet aggregation among all isolated cyclopeptides.



(24) (25) (26)

Conclusion and Future Prospective

In this review, many cyclic peptides possessing different biological activities have been overviewed. As can be seen, the area is flourishing and many research as well as knowledgeable works is reported time to time regarding cyclic peptides. The cyclic peptides have a promising perspective as good therapeutic agents in the field of large molecules as well as small molecules. Due to unique structure which is easily modifiable, cyclic peptides are the area of interest for researchers. In addition, the most medicinally valuable cyclic peptides containing compounds have entered in to preclinical, clinical studies and market also possessing a wide spectrum of biological activities. Hopefully, the information brought here will be helpful to medicinal chemists to carry on the research on cyclic peptides to develop and to synthesize some new cyclic peptides and their derivatives for new biological activities.

Conflicts of Interest

The authors declare no conflict of interest.

Acknowledgement

Declared none.

References

1. Ramakrishnaiah G, Hariprasad T (2012) In vitro antimicrobial activity of leaves and bark extracts of Ficus religiosa (Linn.). Int Res J Pharm 3: 178-79.
2. Dipasquale R (2005) The aboca museum: Displaying the history of herbal medicine in Italy and Europe. J Am Botani Council 65: 50-57.
3. Manimozhi DM, Sankaranarayanan S, Kumar GS (2012) Effect of different extracts of stem bark of Ficus sp. on multidrug resistant pathogenic bacteria. Int J Pharm Sci Res 3: 2122-29.

4. Preethi R, Devanathan VV, Loganathan M (2010) Antimicrobial and antioxidant efficacy of some medicinal plants against food borne pathogens. Adv Biol Res 4: 122-25.
5. Nair R, Chanda SV (2007) Antibacterial activities of some medicinal plants of the western region of India. Turk J Biol 31: 231-36.
6. Uma B, Prabhakar K, Rajendran S (2009) In-vitro antimicrobial activity and phytochemical analysis of Ficusr eligiosa L. and Ficus bengalensis L. against diarrhoeal enterotoxigenic E. Coli. Ethnobotanical Leaflets 13: 472-74.