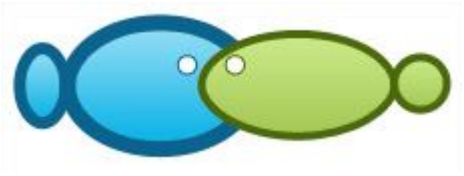

Aquatic peptides: prospects and limitations in developing them as therapeutic products

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Abstract. In the present scenario, there is a great demand for targeted treatment to cure various diseases; researchers are searching for an efficient drug to treat pathologies. Aquatic peptides identified from various bio-resources of the aquatic environment such as aquatic plants, microbes and animals are one of the important therapeutic molecules. The aquatic organisms are native to innate immune system that exclusively synthesis numerous immune protein and bioactive peptides to protect the organisms from a variety of life-threatening environmental factors and subsequent pathogenic attack. Aquatic peptides from both freshwater and marine aquatic ecosystems have promising active molecules against pathogenic infection. Each peptide has unique properties to treat the disease. Meanwhile, peptide-based drug development is not an easy task; it requires overcoming various hurdles even in the current advanced techniques available today. This review discusses the potential of aquatic peptides and the limitations in developing them as drug and the current techniques and strategies to achieve a successful peptide-based drug development.

Key Words: aquaculture environment, aquatic peptides, freshwater ecosystem, innate immunity, marine resources, peptide-based drugs.

Introduction. The aquatic system surrounds 70% of the earth's environment; from the past decades' novel bioactive peptides derived from various aquatic resources with potential pharmaceutical activities and utilized as therapeutic agents (Raja et al 2013). When compared with the terrestrial environment, aquatic living organisms have severe threats to survive in the marine as well as freshwater aquatic ecosystems, because the aquatic environment is subsequently exposed to a wide variety of chemical and other environmental contaminants that affect life and biodiversity (Sable et al 2017). To overcome and survive in such an aquatic environment, the organisms in the aquatic sources secrete several kinds of proteins, peptides, and other compounds to improve their immune system and fight against pathogens. Currently, aquatic peptides garnered attention due to their remarkable properties including antibacterial, antifungal, antiviral, anti-parasitic, anticoagulant, anti-aging, anti-tuberculosis, and anti-diabetic. Altogether, these properties make them auspicious therapeutic agents, to treat a variety of diseases (Vlieghe et al 2010; Anjum et al 2017). The main reserves of peptides and other secondary metabolites are marine sources because they occupy the major portion of the aquatic ecosystems (Sable et al 2017).

The current advancement in the synthesis of peptides depends on the size of the peptide and it was achieved by biochemical synthesis, enzymatic synthesis, recombinant DNA technology, cell-free expression, and transgenic animal or plant species. The peptide size is ranged between 5 and 50 amino acid residues. The large-scale production of the peptides is done mostly through chemical synthesis, since it is a sustainable technology for the production of small and medium-sized peptides (Vlieghe et al 2010). The unique structures of many aquatic peptides are more resistant to proteolysis enzymes like gastrointestinal protease (Shinnar et al 2003). Even though the peptide-based drugs have several limitations that need to be addressed, there is much recent advancement to

improve the quantity and quality of peptide synthesis, short half-life of the peptide drugs, techniques involved in the peptide-based drug delivery system, computational tools involved in the therapeutic approaches, etc. Overall, peptide-based research is an important discipline that recently has attained considerable growth and development in therapeutic applications. This review was focused on the recent development strategies in clinical and therapeutical approaches of peptides-based drugs derived from the various aquatic sources as well as the limiting parameters which hinder them to develop as pharmaceutical agents.

Sources of aquatic peptides and classification. Nature offers a wide range of peptides that are reported from most species on this planet. As evolutionary advantage and natural selection have developed and evolved, these peptides have high affinity, binding ability and biochemical properties, thus need to be explored. These peptides provide an abundance of chemical space to be explored in peptide-based pharmaceutical research (Pukala et al 2006). Based on the aquatic environment and the bio reserve, they were classified as freshwater recourse-derived peptides and marine recourse-derived peptides. Biologically active peptides from aquatic sources may have different configurations in the side chain structure compared with peptides from humans due to variations in the environmental structure. They are, therefore, desirable as substrates for drug development as well as provide the stability against various thermal fluctuations (Jo et al 2017).

Peptides are categorized based on various aspects such as protein nature, source, peptide synthesis techniques, and biological functions. Each peptide has unique features on its activity and function that depends on the physicochemical properties and amino acid composition. Aquatic peptides from the various resources have diversified class, bio-functional activities and therapeutical applications including antimicrobial (Raju et al 2020), anti-diabetic (Zhu et al 2010), anti-inflammatory (Gao et al 2021), antihypertensive (Ngo et al 2014), immunomodulatory (Vo et al 2014), antioxidant (Sannasimuthu et al 2020) and anticancer (Prabha et al 2020). Not only the living organisms of aquatic resource from marine source but its waste also can be utilized as a source for peptide synthesis with proven antioxidant, angiotensin-converting enzyme (ACE) inhibitor and immunomodulatory activities (Gajanan et al 2016). Numerous studies have reported that peptides obtained from aquatic resources have been grouped into a wide category based on a different aspect as reported earlier (Raju et al 2021).

The marine resource is the major contributor when compared to the freshwater system because it covers more than 70% of the total water system and has a wide range of species from different taxa such as Porifera, Cnidarian, Mollusca, Chordata, Echinodermata, Arthropods, etc. (Cheung et al 2015; Sable et al 2017). Table 1 gives the information of peptides derived from the various aquatic resources and listed based on their taxonomic phyla. The domain of marine resources became the hotspot for drug discovery research. But still, a diverse number of untouched components are available in the aquatic organisms, it is a challenging task to screen essential elements for drug development (Wu et al 2015). The structural configuration of marine bioactive peptides is highly specified based on source, similar to peptides extracted and purified from plant and animal resources (Mayer et al 2017; Blunt et al 2018).

Table 1

List of peptides derived from various aquatic resources

Taxa	*Source*	*Peptide*	*Application*	*References*
Porifera	*Callipelta* sp. (Marine Lithistida sponge)	Callipeltins	Anti-HIV	Kikuchi & Konno (2016)
	Callyspongia aerizusa (Cladochalina)	Callyaerins A-G, I-M	Antimicrobial, anti-tuberculosis and antiviral	Daletos et al (2015)
	Theonella swinhoei (Red Sea sponge)	Theonellamide A-E, G	Antifungal	Youssef et al (2014); Espiritu et al (2016)
	Pipestela candelabra (Bob Marley sponge)	Milnamide A	Anti proliferative and antitumor	Tran et al (2014)
	Geodia barretti (Deep sponge)	Barrettides A and B	Antifouling effect with barnacle larvae	Carstens et al (2015)
Cnidaria	*Chiropsalmus quadrigatus* (four-handed box jellyfish)	Peptide Ala-Cys-Pro-Gly-Pro-Asn-Pro-Gly-Arg-Pro	Anti-hypertensive	So et al (2016)
	Anemonia viridis (Snakelocks anemone)	Neurotoxin AV3	Modulation of voltage gated sodium channel	Gur Barzilai et al (2014)
	Palythoa caribaeorum (Zoanthid)	Toxin of *P. caribaeorum*	Neuronal function modulation	Lazcano-Pérez et al (2016)
Mollusca	*Cenchritis muricatus* (Marine snail)	Cm-p1 and Cm-p5	Antifungal	López-Abarrategui et al (2015)
	Conus araneosus (cobweb cone)	Crude peptide extract	Sleep inductive	Franklin & Rajesh (2015)
	Conus geographus (geography cone)	Neurotensin (NT) and Contulakin-G	Analgesic	Lee et al (2015)
Chordata	*Styela clava* (Asian tunicate)	Peptide (Ala-His-Ile-Ile-Ile, MW: 565.3 Da)	Antihypertensive, antioxidant, cytotoxic, hepatoprotective	Ko et al (2016)
	Pseudosciaena crocea (large yellow croaker)	PC-1, PC-2 and PC-3	Antioxidant	Chi et al (2015a)
	Katsuwonus pelamis (skipjack tuna)	Hydrolysate fractions FrA3 and FrB2	Antioxidant	Chi et al (2015a)
Echinodermata	*Acanthaster planci* (Spine of crown of thorns starfish)	Plancitoxin I	Apoptotic	Chi et al (2015b)
Arthropoda	*Scylla paramamosain* (green mud crab)	Histone H2A derivative Sp histin, Sp histatin	Antimicrobial	Chen et al (2015); Shan et al (2016)
	Penaeus monodon (giant tiger prawn)	Shrimp anti-lipopolysaccharide factor (SALF)	Adjuvant in cancer vaccine, antibacterial	Huang et al (2015)
Rhodophyta	*Pyropia yezoensis* (seaweed)	PPY1	Anti-inflammatory	Lee et al (2015)
Microorganism	*Streptomyces* sp. (identified from coastal wetlands)	Hormaomycins B and C	Antibacterial	Bae et al (2015)
	Aspergillus terreus (marine-derived fungus)	Terrelumamides A and B	Antidiabetic	You et al (2015)

Isolation and synthesis of aquatic peptides. The synthesis of aquatic peptides was achieved from various aquatic resources such as microbes, animals and plants through direct extraction, enzymatic digestion of protein and bioprocess technique (Sable et al 2017; Pavlicevic et al 2020). Direct extraction method is usually considered as conventional technique for the identification and isolation of linear or cyclic bioactive peptides. These peptides are being prepared from the crude protein extract followed by the screening for functional properties including antimicrobial, antioxidant or other functions (Du et al 2014). The first step of cyclic and linear peptide extraction is generally performed with organic solvents such as methanol or ethyl acetate, then it was further processed with the solvents such as dichloromethane, carbon tetrachloride or hexane. To isolate the cyclic peptide, extract were subjected to size exclusion chromatography or silica gel for increasing the polarity through solvents elution and further it was purified in the C18 column of reverse-phase high performance liquid chromatography (RP-HPLC). In linear peptide isolation, the extracted fractions are applied in ion-exchange chromatography; based on the peptide basicity the fractions were purified in the C18 column of RP-HPLC, and a further step of rechromatography on the same column for final purification (Lebbe et al 2014).

Enzymatic digestion of protein is another wildly used technique; in this method, the peptide was isolated from the aquatic organism and it was digested with commercial enzyme cocktails or other proteolytic enzymes such as trypsin, pepsin, protease, α-chymotrypsin and papain (Qian et al 2007). The digested peptide fragment was subjected to ultrafiltration to segregate the molecules based on size and further, it was analyzed for bio-functional activity (Jeon et al 1999). The final process of sequence identification and purification in RP-HPLC was performed according to the results of the bioactivity of the fraction (Iijima et al 2003).

Bioprocess techniques otherwise known as microbial fermentation method, industrial-scale production of peptides were synthesized by an advanced technique such as enzyme-assisted extraction, supercritical fluid extraction, ultrasound-assisted extraction, pressurized solvent extraction, pulsed electric field-assisted extraction and microwave-assisted extraction (Grosso et al 2015). To identify the amino acid sequence of peptides, it was analyzed through Matrix-Assisted Laser Desorption Ionization Time of Flight Mass Spectrometry (MALDI-TOF-MS/MS) or NMR spectroscopy (Li et al 2016). Angiotensin-converting enzyme (ACE) inhibitor peptide synthesized from *Acetes chinensis* (marine shrimp) with *Lactobacillus* fermentum (Wang et al 2008). This method was cost-effective when compared with the other methods like enzymatic hydrolysis of protein (protease degradation) and direct extraction. Enzymatic hydrolysis was the most preferred process in the biopharmaceutical industries despite the loss of expected chemical residues in byproducts such as peptides (Fan et al 2014). Aquatic peptide synthesis needs to overcome some challenges such as extraction or enzymatic digestion standardization, determination of bioactivity by utilizing the whole extract, structural variation and composition of the peptide from the different organisms and purification techniques (Pavlicevic et al 2020).

Functional properties of aquatic peptides. Oxidative stress is otherwise known as reactive oxygen species (ROS) that cause severe health effects such as diabetes, cancer, Alzheimer's disease and cardiovascular disease. In type II diabetes, ROS plays a vital role to damage the pancreatic β-cells and reduce insulin production or develop the insulin resistance condition by alternating cell-signaling mechanisms (Maiese et al 2007; Siti et al 2015). The precise function of marine peptides' anti-oxidative activity was unknown. Regrettably, numerous mechanisms for elucidating their properties have been proposed (Zhou & Decker 1999). Peptides, PC-1, 2 and 3 from *Pseudosciaena crocea* (croceine croaker) through enzymatic hydrolysis (pepsin and alcalase) showed potential antioxidant activity (Chi et al 2015a). Marine salmon skin-derived oligopeptide reduces ROS, inflammation and blood glucose levels during fasting, which was established in treating type 2 diabetes mellitus induced rat model proven with increased superoxide dismutase activity and reduce malondialdehyde, interferon-gamma and serum tumor necrosis factor-α (Zhu et al 2010). Bioactive peptides of various aquatic sources such as Pacific

oyster *Crassostrea gigas* (Wang et al 2010), Asian tunicate *Styela clava* (Jumeri & Kim 2011), tuna dark muscle (Hsu et al 2011) and squid gelatin hydrolysates (Alemán et al 2011) were exhibit to the toxic effect on cancer cell lines.

Antimicrobial peptides (AMPs) are host defense peptides that play a vital role in innate immunity. AMPs are generally amphiphilic, rich in cysteine content and positively charged in their active forms. Since AMPs can prevent hosts from a wide range of pathogenic infections they are used as therapeutic agents (da Costa et al 2015). They are commonly isolated from a variety of aquatic organisms, particularly sponges (Onishi et al 2000) and epinecidin-1 peptide from *Epinephelus coioides* (orange-spotted grouper) shown strong antibacterial activity against *Staphylococcus aureus, Vibrio vulnificus, Streptococcus pyogenes* and *Pseudomonas aeruginosa* (Jheng et al 2015). Marine peptides prevent neurodegenerative disorders such as multiple sclerosis, Parkinson's and Alzheimer's. Their neuroprotective activity is caused by the direct association of peptide targets with cellular molecules and the enzymes or ion channels (Pangestuti et al 2013). HTP-1 peptide from *Hippocampus trimaculatus* (seahorse) demonstrated neuroprotective activity that prevents amyloid β42 (pathogenesis of Alzheimer's disease) damage on PC12 cells, validated through the Bcl-2 gene expression and enhancement of cell viability (Pangestuti et al 2013).

Peptides as drugs and their mechanism of action. The Food and Drug Administration (FDA) of the U.S has approved fifteen peptide drugs, which is an impressive number. Moreover, 7% of the total amount of drugs which was approved during the past five years are peptide-based drugs (de la Torre & Albericio 2020). Diabetes mellitus was a widespread metabolic disorder that affects millions of people by the increase in blood glucose levels. According to the International Diabetes Federation (Acquah et al 2020), Nearly 463 million adults were affected by diabetes for the past 20 years, and it was anticipated to reach 700 million by 2045 as per 2019 data. Peptides are promising candidates to treat many metabolic disorders like type 2 diabetes mellitus (Zhu et al 2010). To treat type II diabetes some specific enzymes were targeted such as dipeptidyl peptidase-4 (DPP-IV), α-glucosidase and α-amylase (Hu et al 2019). Targeting DPP-IV inhibition was a unique therapeutic approach for the treatment of diabetes. Harnedy et al (2018) reported that the bioactive peptides from Atlantic salmon, *Salmo salar* (skin gelatin and trimmings) enzymatic hydrolysis by alcalase and flavorsome have been shown to exhibit strong DPP-IV inhibitory activity, insulin and GLP-1 secretory activities. Inhibitors of dipeptidyl-peptidase-IV (DPP-IV) enzymes degraded incretins like GLP-1 and glucose-dependent insulinotropic polypeptides (gastric inhibitory polypeptide and GIP including sitagliptin and saxagliptin. These incretins reduce blood glucose levels by inhibiting glucagon activity, inducing insulin release and slowing gastric emptying (Acquah et al 2020). Hu et al (2019) reported that peptides synthesized through protein extraction and chromatographic fractionation from *Spirulina platensis* have inhibition activities against α-amylase, α-glucosidase and DPP-IV. It is reported that the peptides isolated from wild Chum salmon, *Oncorhynchus keta* skin have anti-diabetic property which reduces the glucose level and the pancreatic apoptosis of islet cells (Zhu et al 2010).

Dolastatin 10 peptide derivatives such as Enfortumab vedotin-ejfv and Polatuzumab Vedotin-Piiq can be used as antibody-drug conjugate (ADCs) which was recently approved by the FDA; those were initially isolated from marine organism, *Dolabella auricularia* (de la Torre & Albericio 2020). There are several numbers of natural and synthetic bioactive peptides isolated from the aquatic origin but only a few amounts of compounds were entering into drug development research and a very few were only passed and gets approval (Table 2).

Table 2

Current status of the aquatic peptide in drug development process

Current status	*Peptide*	*Source*	*Therapeutic applications*	*References*
Preclinical study	HTI-286	Derivative of hemiasterlin; Sponge, *Hemiasterella minor*	Metastatic prostate cancer	Rawat et al (2006); Hadaschik et al (2008)
	Curacin A (lipopeptide)	*Lyngbya majuscula*	Inhibits microtubuleassembly and tubulin	Swain et al (2015)
	Desmethoxymajusculamide C (DMMC)	*L. majuscula*	Tubulin	Schmitt et al (1998)
	Dolastatin 15	*Lyngbya* sp.	Microtubule assembly	Ennaas et al (2016)
Clinical study, Phase III	Tasidotin (ILX-651)	Dolastatin 15 synthetic analogues	Solid tumors, microtubule assembly, lung cancer	Simmons et al (2005); Rawat et al (2006)
	Soblidotin (TZT 1027)	Dolastatin 10 synthetic analogues	Microtubule assembly and breast cancer	Simmons et al (2009)
Clinical study, Phase II	XEN-2174	Derivative of ziconotide; marine cone snail, *Conus magus*	Analgesic	Newman & Cragg (2014); Okkerse et al (2017)
	Cematodin (LU-103793)	Dolastatin 15 synthetic analogues	Microtubule assembly	Huang et al (2010); Bayala et al (2014)
	Plitidepsin	Ascidian, *Aplidium albicans*	Anticancer	Ribrag et al (2013); van Andel et al (2017)
	Glembatumumabvedotin	Dolastatin 10 from *Dolabella auricularia*	Cancer treatment	Cheung et al (2015); Venkatesan et al (2017)
Clinical study, Phase I	E7974	Derivative of hemiasterlin; sponge, *Hemiasterella minor*	Cancer treatment	Rocha-Lima et al (2012)
	Dolastatin 10	*Lyngbya* sp.	Tubulin	Rawat et al (2006)
	Kahalalide F	Mollusc, *Elysia rufescens* and its diet green algae *Bryopsis* sp.	Anticancer	Martín-Algarra et al (2009); Cheung et al (2015)
	Elisidepsin (PM02734)	Synthetic analogue of kahalalide F	Malignant solid tumors	Ratain et al (2015)
FDA-approved	Ziconotide	Marine cone snail, *C. magus*	Analgesic drug	Pope & Deer (2013)
	Brentuximabvedotin	Dolastatin 10 from *D. auricularia*	Cancer treatment	Cheung et al (2015)

Many glucosidase inhibitory peptides were obtained from a marine sponge, *Aka coralliphaga* and those peptides may be used to treat weight loss, hypertension, hyperglycemia and dyslipidemia condition (de Mello-Sampayo et al 2013; Pandey et al 2013). The anti-diabetic mechanism of peptide drug from aquatic resources is reported by many researchers (Nauck 2016; Xia et al 2017). Bioactive peptides from the aquatic resource especially marine peptides play a key role in various mechanisms such as protecting pancreatic β-cells, enhance the glucose-stimulated insulin secretion, regulate the insulin-signaling pathways, regulating glucose uptake and lipid accumulation on the insulin-regulated glucose metabolism (Xia et al 2017). The aquatic peptides showed a significant protective effect on pancreatic cells against high glucose stress (Fernández-Millán et al 2015).

Each peptide drug has a specific mechanism on its function that depends on the physiological properties of the peptide. For example, anticancer drugs can inhibit or up-regulate any of the following biochemical pathways such as cell cycle regulation, signal transduction pathways, and apoptotic pathways (Raucher et al 2009). Wei et al (2020) reported the mechanism of brentuximab vedotin anticancer drug involves in the NF-κB pathway responsiveness and resistance mechanism in Hodgkin lymphoma (HL). According to the Database of Antimicrobial Activity and Structure of Peptides (DBAASP), 16,180 peptides were reported from various resources such as microbes, plants and animals. In which, 80% of antimicrobial peptides were synthesized by synthetic methods and 90% are monomer and multimer-peptide. Due to the limited information or experimental evidences on the properties of the isolated/derived aquatic peptides including potency of bio-function, stability, viability and toxicity only a few peptides were developed as therapeutic drugs; others are yet to explore. The health care industries are focused on developing software for AMPs that prevent and treat several diseases (Cheung et al 2015). Almost more than thirty peptide drugs have been approved worldwide in the past twenty years. The anticipated use of such drugs is most predominantly focused to cure cancer and metabolic disorders. A global industry analysis on peptide therapeutics predicted a compound annual growth rate (CAGR) of 9.1% from 2016 to 2024 and sales of peptide drugs to exceed 70 billion USD in 2021 (Lee et al 2019).

Limitations and strategies to improve the drug development. The aquatic source-derived peptide has so many advantages in broad-spectrum on their activity but still, it has comparatively less chance and also has some limitations in the field of pharmacology to develop drugs. Stability, toxicity, pharmacokinetics, pharmacodynamic properties of ADME, and efficacy were the factors involved in the development of peptide-based drugs (Seo et al 2012). From the literature, it is observed that numerous peptides were discovered from the aquatic as well as other resources. However, only 38% of these peptides have entered into the clinical trial study at phase I, based on the bioavailability and efficacy factors, 63% of drugs can pass the clinical trial at phase II. Nearly 40% of drugs failed in a clinical trial at phase III and 23% of the peptide-based drugs are not approved by the European Medicines Agency (EMEA) or the Food and Drug Administration (FDA) (Lee et al 2019). Peptide-based drugs face major issues of poor bioavailability due to shorter half-life and physical barriers to transport across the biological membranes. Some peptides are quickly eliminated from the liver and kidneys even if administrated through intravenous injection (Haggag 2018). In some cases, the peptide drug has very poor bio-distribution owing to its structural sensitivity, often this results in loss of receptor specificity and up-regulation of various target receptors, altogether it is contributing to various side effects.

The extensive administration of peptide drugs degrades the existing gut microbiome, which leads to other severe symptoms attributed to the microflora absence. Different host elements, such as host cell membrane, extracellular surfaces, and extracellular matrix may also be attached to an AMP that altogether leads to adverse effects (Dathe & Wieprecht 1999). Another disadvantage of peptides was their structural stability. AMPs have electrostatic interaction with the microbial cells and the receptors attached to the surface of the plasma membrane. Sometimes peptides are damaged in the drug solution due to their ionic strength, and also due to various physiological

conditions such as pH, enzymes that are present in the digestive tract (protease), and biological fluids like a serum (Matsuzaki et al 1995). Production cost was the most important factor; when compared with the other chemical synthesized drugs and pure compound-based drugs, peptide-based drug production is expensive. Apart from this, peptide-based drugs have various other technical challenges including synthesis and purification process during development (Hancock & Sahl 2006).

Improving bioavailability via extending the short half-life. Half-life extension was achieved by various techniques such as improve circulation plasma half-life. The first-line strategy is to restrict the enzymatic hydrolysis of peptides by defining potential molecular targets accompanied by the replacement of necessary amino acids. Researchers and biotechnology industries are focused on such areas namely Aileron Therapeutics, Pepscan, lactam bridges, cyclization, and structure inducing probe (SIP)-tail approaches to modify the secondary structure of the peptides that prevent the enzyme degradation (Sim et al 2012). Peptide elimination can be protected by inserting albumin-binding components in the peptide sequence. The albumin-binding components are foundation as a backbone of peptide. This insertion leads to the production of albumin-binding antibody fragments. Moreover, albumin can be utilized as a carrier vehicle to extent the half-life of peptide (Bao et al 2013). Also, polyethylene glycol (PEG)-ylation is often used to reduce peptide elimination and globular filtration (Xia et al 2017).

Computational tools in therapeutic approaches. Recent advancements in various bioinformatics platforms are available to predict solubility, hydrophobicity, net charges, membrane permeability, and cell-penetration of peptides (Dietrich et al 1999). Support-vector machine (SVM), machine-learning bioinformatics, and ccSOL omics are the bioinformatics tools utilized to calculate the solubility of the peptide (Agostini et al 2014). Another tool PROSO II is an online tool that can predict physicochemical properties and secondary structural properties (Smialowski et al 2012). HADDOCK and ClusPro are the top-ranked servers that are utilized to predict rigid-body docking methods on the basics of root mean square deviation (RMSD) to yield free energy association and embedded surface region with the greatest optimism (Lensink et al 2016; Van Zundert et al 2016). Researchers described the detailed information on the various computational tools, which have the potency to improve the drug development process (Lee et al 2019).

Enhancement of *in vitro* and *in vivo* stability of peptides. To enrich the stability of the peptide-based drug various strategies have been followed through chemical modifications such as modification of side-chain length, D-enantiomer, N-methylation residues, bulky residues, terminal capping, and cross-link containing peptides. The most common strategy was the modification of side-chain length, which improved the vulnerability particularly against proteolytic enzyme digestions (Wang et al 2019). D-amino acids were utilized to enhance peptide activity and stability towards proteolytic digestion known as D-enantiomer (Zaet et al 2017). The peptides cyclization, which means joining the carboxyl and amino terminals of the peptide was a known strategy to enhance the stability and activity of the linear peptide (Giuliani et al 2007). The effects of cyclic and linear forms of an indolicidin analog CP-11 have proved that head-to-tail cyclization significantly enhances the resistance against proteolysis and stability (Rozek et al 2003). The modification in either the C-terminal or the N-terminal region of the peptide is known as acetylation or amidation. This terminal modification of the peptides slightly increases hydrophobicity, thus improved stability against proteases (Dennison et al 2015). Amphipathic balance in this modification improves the helicity which leads to enhance its stability (Nguyen et al 2005). Bulky residues are modifying the short peptides with the non-genetically encoded amino acids that enhance the pharmaceutical activity (Solanas et al 2010). The optimization of the secondary structure of peptides was achieved by cross-linking the peptide which is termed macrocyclic peptides (Gaillard et al 2017). Lactam-bridge, modification of disulfide bonds, and all hydrocarbon stapling systems were three methods utilized for the construction of cross-link peptides (Kale et al 2018). The cross-linking of short peptides improved the affinity of cell membrane binding

efficiency and also enhances the stability against the enzymatic degradation (Bagheri et al 2018). Other studies stated that modification of acidic and basic residues enhanced the stability and the activity of the peptides (Kang et al 2009). EeCentrocin 1 HC antimicrobial peptide from *Echinus esculentus*, modification of its structure in carboxyl-terminal amidation results the peptide potent antifungal activity as well as low hemolytic and cytotoxic activity altogether rendering its potential lead for further drug production (Solstad et al 2020). Peptide IE13 synthesized from *Channa striata*, the glutamic acid in IE13 peptide at position 13 was replaced by tryptophan at the C-terminal (IW13) which results the peptide potent anticancer activity against human lung cancer cells and human cervical carcinoma cells (Prabha et al 2020).

Approaches towards reducing cytotoxicity. In some cases, the peptide drugs have potential activity but, it shows some adverse side effects which are known as toxicity. Preliminary screening of the peptide toxicity was detected based on the hemolytic assay, the higher hemolytic activity was depended on the hydrophobicity and charge of the amino acid sequence present in the peptide (Yeaman & Yount 2003). Increased hydrophobicity and charge of the peptide showed higher hemolytic activity. The AMP derived from frog brevinin-1EMa prepared with slight modifications like amino acid Leu residues were replaced with Ala that leads to the reduction of hydrophobicity and charge, thus enhance the therapeutic property and reduce the toxicity against human erythrocyte (Won et al 2011). Some other strategies such as drug delivery system and molecular targeting also improve the efficiency of the peptides against toxicity, the bioavailability of the drug, and extend the half-life of the drug.

Strategies on drug delivery system. The drug delivery system is the most important area to be focused on in the process of new drug development. Various factors were concerned to improve the stability and bioavailability of drugs such as route of administration, elimination of the drug, membrane permeabilization, site of drug absorption, and stability towards the biological fluids such as serum, enzymes protease, etc. (Malik et al 2007). AMP-based drugs were required to reach the gastro-intestinal tract with its stability because there were a lot of barriers like bile salts, protease, gastric acids, and intestinal mucus membrane (Cone 2009). AMPs were encapsulated with nanoparticles, hydrogels, and other technical devices like intestinal patches and microneedles were utilized to overcome the challenges (Choonara et al 2014). The nasal or inhalation route administration of the drug was the second widely used technique in the system, where the drug molecules were delivered to the lungs. The practical difficulties in the peptide drug optimization were focused on the structural properties (Bosquillon et al 2001). The other drug route system such as transdermal and subcutaneous delivery systems was also utilized to improve the bioavailability and activity. The drug delivery system has improved through the techniques such as lipid encapsulations, metal nanoparticles, and natural biomolecules. The goal of delivery vehicles is to reach the targeted site. It improves the circulation time, solubility, stability, biocompatibility, and pharmacokinetics of the drug (Czaplewski et al 2016). Comparing the free peptide with nanostructured lipid carriers (NLCs), the nanoencapsulation LL37 demonstrated to have improved efficiency such as wound healing, antimicrobial and immunomodulatory activity (Garcia-Orue et al 2016). It is reported that Anderson-Y1 antimicrobial peptide encapsulated with the silver nanoparticles (AgNPs) with the addition of cysteine amino acid residues in both the amino and carboxyl terminals, peptide resulted in increased biocompatibility (Strauss et al 2019). SMAP28 antimicrobial peptide was conjugated with rabbit immunoglobulin (IgG) antibodies (antibody-AMP conjugate) established high activity against the targeted strain (Peschen et al 2004).

Molecular targeting of drug peptides. Molecular targeting is the process of delivering a drug in a specific target region to improve bioavailability, stability, and pharmacokinetics. The term is generally classified into endogenous targeting and exogenous targeting (Ekladious et al 2019). The drug is released in the infection site, which is known as endogenous targeting. The intercellular targeting antimicrobial

peptide, LL-37 was used as a potent drug against *S. aureus* (Noore et al 2013). Spatiotemporal release of AMP drug is a good example for exogenous targeting. The hybrid AMP cecropin melittin conjugated with gold-coated superparamagnetic iron oxide nanoparticles is a potential material for site-specific targeting (Maleki et al 2016).

Production cost. As far as the industry is concerned about manufacturing peptide-based drugs with adequate stability, the main problem is associated with the cost of production. In addition, there are other various issues such as size reduction, *de novo* synthesis, a new expression system, and cost-effective purification e.g. Gaegurin 5 (Won et al 2006). A group of cationic peptides with different sizes and physicochemical properties were developed by Faccone et al (2014). For example, Faccone et al (2014) find out the smallest peptide retaining biological activity and proved that the P5 peptide exhibited the strongest antimicrobial activity and low hemolytic activity (Won et al 2006). Fusion expression system is a potent technique to synthesize peptide in a reduced production cost with significant solubility (Giuliani et al 2007). Butt et al (2005) reported that thioredoxin and little ubiquitin-related modifiers are used for rising the solubility of peptides and produced high yields of peptides. A cost-effective purification process can be implemented using the intent system, which reduces the cost of production (Ram, K. Seetha, et al. 2014).

Conclusions. The aquatic peptides have the potency to develop as therapeutic drugs while the limitations have to be resolved with relatively inexpensive techniques. Numerous peptides have been demonstrated in various biological functions such as antimicrobial, anti-diabetic, antioxidant, anti-tumor, and various other immunological properties. Each peptide has unique features and specific properties and mechanisms, so it requires more specific research towards its domain in various aspects like pharmacodynamics, pharmacokinetics, and toxicity. Due to the limiting factors such as stability, drug delivery, and production cost, only a very few peptides reached the market as therapeutic drugs. The future direction of peptide-based drugs has to be utilized with the recent advancement in techniques like *insilco* tools, various drug delivery systems, and encapsulation techniques that can improve the quality of bioavailability and improve drug performance. Moreover, the cost-effectiveness in synthesis, characterization, and purification has also need to be overcome.

Conflict of interest. The authors declare that there is no conflict of interest.

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