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The Updated Review on Plant Peptides and Their Applications in Human Health

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Abstract

Biologically active plant peptides, consisting of secondary metabolites, are compounds (amino acids) utilized by plants in their defense arsenal. Enzymatic processes and metabolic pathways secrete these plant peptides. They are also known for their medicinal value and have been incorporated in therapeutics of major human diseases. Nevertheless, its limitations (low bioavailability, high cytotoxicity, poor absorption, low abundance, improper metabolism, etc.) have demanded a need to explore further and discover other new plant compounds that overcome these limitations. Keeping this in mind, therapeutic plant proteins can be excellent remedial substitutes for bodily affliction. A multitude of these peptides demonstrates anti-carcinogenic, anti-microbial, anti-HIV, and neuro-regulating properties. This article's main aim is to list out and report the status of various therapeutic plant peptides and their prospective status as peptide-based drugs for multiple diseases (infectious and non-infectious). The feasibility of these compounds in the imminent future has also been discussed.

Keywords Therapeutic plant peptides · Peptide-based drugs · Anti-carcinogenic · Anti-HIV · Antifungal · Ribosomal-Inactivating Proteins (RIPs)

Introduction

Plants can be exploited as a bioreactor for many therapeutic proteins, the majority of which are secondary metabolites and their derivatives. Nephroblastoma lymphoma and acute lymphoblastic leukemia are treated with paclitaxel and vincristine which are derived from *Taxus brevifolia Nutt* and *Catharanthus roseus,* respectively (Seca and Pinto 2018). Furthermore, ingenol mebutate and curcumin extracted from *Euphorbia peplus* L and *Curcuma longa* L. being were tested in clinical trials for pancreatic, colorectal (Pan et al. 2012), and non-melanoma skin cancers (Seca and Pinto 2018). Notwithstanding, these peptide-based drugs are accompanied by unquestionable impediments, including toxicity, low abundance, complex multi-step synthesis, developmental stage-specific production, improper metabolism, poor absorption, poor systemic bioavailability, development of multi-drug resistance, and associated adverse health issues (Seca and Pinto 2018). These preordained constraints have compelled the scientific community to explore plants for other medicinal peptides.

In contrast to metabolite-based drugs, protein-based drugs have high therapeutic efficiency due to: (i) High specificity ergo fewer chances of interference with biological processes, thereby alleviating the toxicity, (ii) Performance of complex functions, (iii) High tolerance (Leader et al. 2008) and (iv) Varying charging of proteins/peptides due to existence of numerous functional groups thereby targeting different tissues of our body with varying pH (Reddy and Yang 2011). Although a multitude of therapeutic plant peptides has been identified, only a small number of them have found their way into databases i.e., research on the characterization of plant peptides has been left halfway or indeterminate (Leader et al. 2008 and references therein). This is due to: (i) the absence of high-throughput techniques, (ii) expensive and arduous, (iii) problems associated with protein stability. Nevertheless, therapeutic plant peptides appear propitious in

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peptide-based drugs for many diseases and are brought to the scientific community. This review article encapsulates therapeutic plant proteins and their implementation focusing on infectious and non-infectious diseases in light of this situation.

Infectious diseases encompass diseases caused by organisms (bacteria, viruses, fungi, parasites, nematodes). In contrast, non-infectious diseases constitute metabolic disorders (diabetes, obesity, cancer, cardiovascular, genetic disorders, neuroregulatory, and much more). This review might guide to development of peptide drugs for the treatment of various diseases and disorders (Fig. 1).

Infectious Diseases

Anti-microbial activity of plant peptides/proteins

Microbes are one of the leading causes of various infectious diseases like common cough, cold, influenza, etc. Owing to their ubiquitous nature, infectious diseases can be transmitted easily from anywhere. To protect our bodies from such conditions, antibiotics have been used. However, the consumption of many antibiotics has given rise to the problem of anti-microbial resistance and has rendered present anti-microbial drugs fruitless (Kaur et al. 2012). Therefore, the scientific community has taken a keen interest in identifying prospective anti-microbial agents from native sources, particularly plants. Plants produce an extensive range of Anti-microbial Peptides/Proteins (AMP) since these peptides act as the first line of defense against pathogens, hence dubbed as Pathogen Response/Pathogenesis-Related (P.R.) Proteins. Plant AMPs are tissue-specific and are expressed constitutively, having both polar and non-polar groups and positive charges. They are cysteine-rich residues, and they generate multiple (2–6) disulfide bonds, thereby granting them stability and resistance against proteases and chemicals (Hernández-Ledesma et al. 2009; Hernández-Ledesma and Hsieh 2017). In addition to this, plant AMPs are small, have high target specificity, simple configuration (structure), various modes of administration, quick modifications can be performed, and negligible antigenicity (Yadav and Batra 2015). Considering the characteristics mentioned above and advantages, plant AMPs have been used to develop novel, highly efficient drugs to resolve multi-drug resistance infections. The main drawback is that only a few (not more than thousands) have been structurally and functionally characterized. In this article, we will consider three main classes of microbes: Bacteria, Fungi and Viruses. This review also deals with the Pathogenesis—Related (PR) proteins from plants and their therapeutic applications.

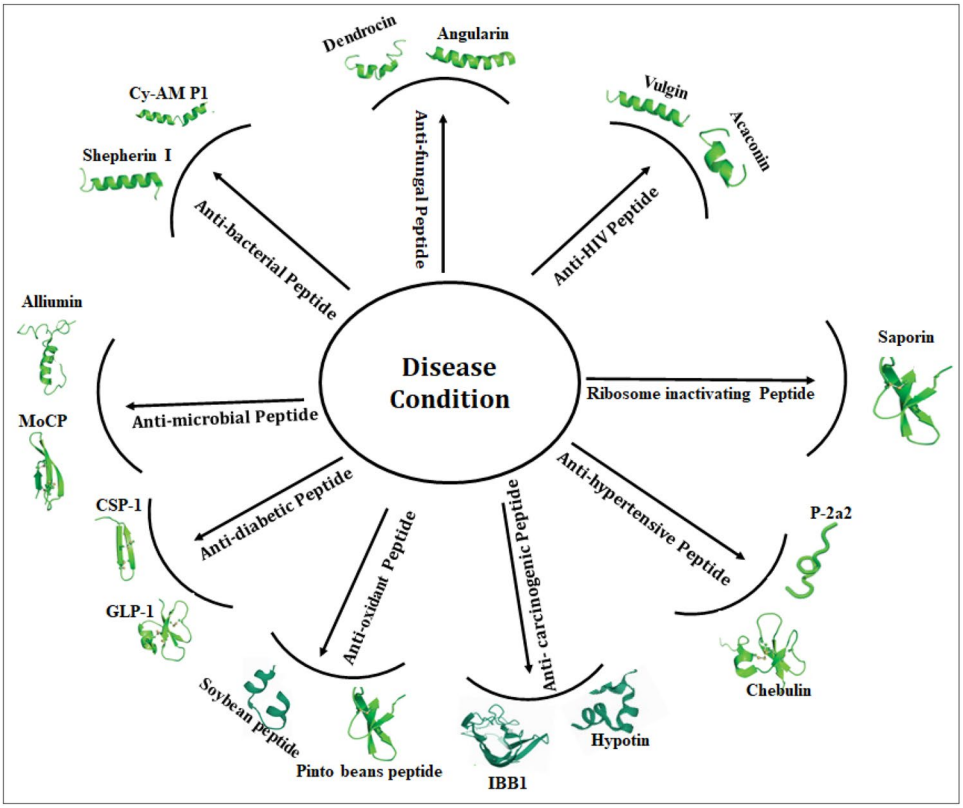

Fig. 1 Schematic representation of plants peptides displaying various therapeutic properties

Anti-bacterial activity

Plant ABPs (Anti-Bacterial Proteins) had emerged as potential alternative for a new class of antibiotics, tackling the obstacle of multi-drug resistance pathogens. Purothionin, the introductory ABP, was extracted from *Triticum aestivum* to inhibit a multitude of bacteria, including *Xanthomonas campestris, Corynebacterium michiganens,* and *Pseudomonas solanacearum* (Naider and Anglister 2009). The majority of these plant ABPs are positively charged (Kaur et al. 2012). They are highly antagonistic against a multitude of bacteria, even in lower concentrations. In contrast, some of them are highly specific. Nevertheless, though promising, only a few have been identified and characterized structurally and functionally (Naider and Anglister 2009). The amino acid sequence, location and number of cysteine residues are the key classification criteria for ABPs. There are several families such as defensins, thionins, lipid transfer proteins (LTR), snakins, cyclotides, thaumatins, etc.

Talking about the mechanism of action of ABPs, the most established notion is that ABPs will cause the breakage of bacteria when they come in contact with the negatively charged membrane (Pan et al. 2012). The strong selectivity of ABPs towards bacterial cells is due to the intrinsic negative charge of the bacterial cell membrane which protects the host cell against infection. Once the ABPs associate with the cell membrane, the ABP concentration builds until it reaches its threshold value (Girish et al. 2006). Upon attaining the threshold value ABP oligomers were generated to enter the membrane perpendicularly forming micelle-like structures (Barrel-Stave Model). Owing to the electrostatic interactions, ABPs assemble on bacterial membrane, manifesting like a carpet generating tension in the lipid membrane and subsequent phospholipids rearrangement. This results in varied membrane fluidity and membrane disruption (Carpet Model); ABPs, upon interacting with the polar head groups of the phospholipids, manifest into a transmembrane pore that provokes bends in the membrane, causing the adjacent layers of the pore to merge. Pore formation causes ion and metabolite efflux, membrane depolarization, deranging the respiratory mechanism, preventing cell wall formation, disrupting the membrane, ultimately leading to cell death (Toroidal Pore Model) (Girish et al. 2006). One of the primary purposes for producing ABPs is to overcome the challenge of antibiotic resistance. ABP drugs are multifarious and have a high potential of forming a new class of antibiotics with lower odds of bacterial resistance. Many proteins have been extracted from plants with high antibacterial activity having low IC_{50} value (Half Maximal Inhibitory Concentration) and Minimal Inhibitory Concentration (MIC). Shepherin I and II, two glycine-histidine-containing peptides isolated from *Capsella bursa-pastoris* inhibits several gram-negative bacteria. Circulin A and B, macrocyclic peptides (Cyclotides) extracted from *Chassalia parviflora* inhibits a multitude of gram-positive and gram-negative bacteria, with Circulin B inhibiting both (Park et al. 2004). In *Chromobacterium violaceum*, the amino acid lysine had anti-QS and anti-biofilm properties. It was documented that at a concentration of 0.684 mM, lysine decreased biofilm development by 16%, chitinolytic activity by 88.3%, and EPS production by 12.5% after 24 hours. It might also be used as a key component in the synthesis of peptides/proteins and tested for use in the treatment of bacterial infections, perhaps lowering the need for traditional antibiotics (Champalal et al. 2018).

The chitin-binding peptides isolated from *Tulipa gesneriana* Tu-AMP-1 and Tu-AMP-2, affect a wide variety of bacteria, including *Agrobacterium rhizogenes, Curtobacterium flaccumfaciens, Erwinia carotovora,* and *Agrobacterium radiobacter,* having an IC_{50} value of 11–20 µg/ml (Walsh et al. 2013). The ABPs mentioned above are some of the examples that have been structurally and functionally defined. A variety of ABPs with superior specificity and other novel properties is yet to be explored. Additionally, research should be focused on identifying novel ABPs having low toxicity, rapid mode of action and reported antibacterial peptides as shown in Table 1.

Anti-fungal activity of plant peptides/proteins

There have been high incidences of patients with threatening fungal infections, particularly those with a compromised immune system like AIDS, organ transplants, cancer, etc. The prolonged use of medicines they take for their therapy makes them vulnerable to potent fungal infections that can ultimately lead to death. The main challenge is that not many drugs are available for many conditions and, worst case, the absence of drugs for the treatment. Furthermore, another obstacle of drug resistance originates from extended drug utilization, rendering the current drug unusable. Correspondingly, we have to hunt for novel drugs, especially from natural sources like plants. Antifungal Proteins/Peptides (AFP) are low molecular weight compounds that act as the first line of defense against fungal pathogens. These proteins include defensins, thionins, lipid-transfer proteins (LTR), chitinase-like proteins, lectins, etc. (Lee-Huang et al. 1991a). The majority of AFPs work by lysis of fungal cell wall or by targeting components like sphingolipids and chitin, thereupon inhibiting cell wall synthesis. One of the instances is that certain AFPs result in pore formation or membrane polarization upon binding of chitin on its conserve domain, causing an efflux of K^+ and influx of Ca^{2+}, ultimately cell lysis (Lee-Huang et al. 1991b). Some other examples of AFPs mechanism of action are of defensins. They follow receptor-mediated activation (Leader et al. 2008). Subsequent binding to this receptor causes ion

Table 1 List of anti-bacterial and anti-microbial peptides/proteins from plants

S. No	Plant and its part	Protein	Nature	M. Wt (kDa)	N-terminal sequence	Bacterial species (Tested)	*IC_{50}	References
1	*Vigna sesqui- pedalis* (Seeds)	Sesquin	Peptide	7	KTCENLADTY	*M. phlei*	87 ± 5 µM	Wong and Ng (2005b)
						B. megaterium	105 ± 5 µM	
						B. subtilis	98 ± 2 µM	
						P. vulgaris	75 ± 6 µM	
2	*Phaseolus lunatus L.* (Seeds)	Lunatusin	Peptide	7	KTCENLADTFRGPCFATSNC	*M. phlei*	96 ± 9 µM	Wong and Ng (2005a)
						B. megaterium	115 ± 6 µM	
						B. subtilis	98 ± 5 µM	
						P. vulgaris	81 ± 6 µM	
3	*Cycas revoluta* (Seeds)	Cy-AM P1	Peptide	4.58	KGAPCAKKPCCGPLGHYKVD	*C. michiganensi*	7.3 µg/ml	Yokoyama et al. (2008)
						C. flaccumfaciens	8.9 µg/ml	
						A. radiobacter	8.3 µg/ml	
						A. rhizogenes	8.5 µg/ml	
						E. carobora	8.0 µg/ml	
		Cy-AMP2	Peptide	4.57	KGAPCAKKPCCGPLGHYKVD	*C. michiganensi*	7.6 µg/ml	
						C. flaccumfaciens	8.3 µg/ml	
						A. radiobacter	7.8 µg/ml	
						A. rhizogenes	8.2 µg/ml	
						E. carobora	8.1 µg/ml	
		Cy-AMP3	Peptide	9.27	AVTCNTVTSSLAPCVPFFA	*C. michiganensi*	235 µg/ml	
						C. flaccumfaciens	195 µg/ml	
						A. radiobacter	260 µg/ml	
						A. rhizogenes	235 µg/ml	
						E. carobora	230 µg/ml	
4	*Phytolacca americana* (Seeds)	Pa-AMP-1	Protein	3.94	–	*B. megaterium*	8 µg/ml	Liu et al. (2000)
						Staphylococcus. sp.	11 µg/ml	
						E. coli	> 300 µg/ml	
5	*Impatiens balsamina* (Seeds)	Ib-AMP1	Peptide	2.46	QWGRRCCGWGPGRRYCVRWC	*B. subtilis*	10 µg/ml	Tailor et al. (1997)
						M. luteus	10 µg/ml	
						S. aureus	30 µg/ml	
						S. faecalis	6 µg/ml	
		Ib-AMP4	Peptide	2.52	QYGRRCCNWGPGRRYCKRWC	*B. subtilis*	5 µg/ml	
						M. luteus	5 µg/ml	
						S. aureus	20 µg/ml	
						S. faecalis	5 µg/ml	
						X. campestris	6 µg/ml	
						X. oryzae	15 µg/ml	

Table 1 (continued)

S. No	Plant and its part	Protein	Nature	M. Wt (kDa)	N-terminal sequence	Bacterial species (Tested)	*IC_{50}	References
6	*Capsella bursapastoris* (Roots)	Shepherin I	Peptide	2.36		*E. coli*	< 2.5 µg/ml	Park et al. (2000)
						P. putida	< 2.5 µg/ml	
						P. syringae	< 2.5 µg/ml	
						S. typhimurium	< 2.5 µg/ml	
						Serratia sp.	8 µg/ml	
7	*Mirabilis jalapa* (Seeds)	Mj-AMP1	Homodimeric peptide	8	–	*B. megaterium*	6 µg/ml	Cammue et al. (1992)
						S. lutea	100 µg/ml	
		Mj-AMP2	Homodimeric peptide	7	–	*B. megaterium*	2 µg/ml	
						S. lutea	50 µg/ml	
8	*Psidium guajava* (Seeds)	Pg-AMP1	Peptide	6.0	–	*Klebsiella sp.*	ND	Pelegrini et al. (2008)
						E. coli		
						Proteus sp.		
9	*Withania somnifera* (Root tubers)	WSG	Glycoprotein	28	–	*B. subtilis*	ND	Girish et al. (2006)
						P. fluorescens		
						C. michiganensis sub. sp, michiganensis		
						X. oryzae pv. oryzae		
						X. axanopodis pv. malva-cearum		
10	*Ficus glomerata* (Leaves)	NA	Protein	35	–	*S. entrica*	ND	Thapliyal et al. (2016)
						P. aeruginosa		
						E. coli		
						B. subtilis		

Table 1 (continued)

S. No	Plant and its part	Protein	Nature	M. Wt (kDa)	N-terminal sequence	Bacterial species (Tested)	*IC_{50}	References
11	*Foeniculum vulgare* Mill. (Seeds)	Elute1	Protein mixture		–	*S. aureus*	27.64 µg/ml	al Akeel et al. (2017)
						E. coli	67.56 µg/ml	
						P. aeruginosa	28.01 µg/ml	
						P. vulgaris	59.68 µg/ml	
		Elute2	Protein mixture	34.4–48	–	*S. aureus*	25.91 µg/ml	
						E. coli	64.12 µg/ml	
						P. aeruginosa	68.33 µg/ml	
						P. vulgaris	57.83 µg/ml	
		Elute3	Protein mixture		–	*S. aureus*	21.27 µg/ml	
						E. coli	60.52 µg/ml	
						P. aeruginosa	25.02 µg/ml	
						P. vulgaris	41.24 µg/ml	
		Elute4	Protein mixture		–	*S. aureus*	20.8 µg/ml	
						E. coli	41.06 µg/ml	
						P. aeruginosa	26.67 µg/ml	
						P. vulgaris	35.67 µg/ml	
12	*Murraya koenigii* L. (Leaves)	APC	Protein	35	–	*S. aureus*	ND	Ningappa et al. (2010)
						B. subtilis		
						E. coli		
						S. typhi		
						V. cholerae		
						K. pneumoniae		
						S. paratyphi		
13	*Chassalia parviflora* (Whole Plant)	Circulin A	Macrocyclic peptides	3.17	–	*S. aureus*	ND	Tam et al. (1999)
						C. kefyr		
						C. tropicalis		
		Circulin B	Macrocyclic peptides	3.30	–	*E. coli*	ND	
						P. vulgaris		
						K. oxytoca		
						S. aureus		

Table 1 (continued)

S. No	Plant and its part	Protein	Nature	M. Wt (kDa)	N-terminal sequence	Bacterial species (Tested)	*IC_{50}	References
14	*Spinacia oleracea* (Leaves)	So-D1	Peptide	2.29	–	*C. michiganensis*	1 µM	Segura et al. (1998)
						R. solanacearum	15 µM	
		So-D2		5.80		*C. michiganensis*	1 µM	
						R. solanacearum	2 µM	
		So-D6		2.55		*C. michiganensis*	1 µM	
						R. solanacearum	6 µM	
		So-D7		4.23		*C. michiganensis*	0.1 µM	
						R. solanacearum	1 µM	
15	*Oldenlandia affinis* (Whole Plant)	Kalata B2	Macrocyclic peptides	2.9	–	*S. aureus* (DA7127)	ND	Pränting et al. (2010)
						E. coli (DA4201)		
						S. enterica (DA6192)		
		Kalata B1		2.89	–	*S. aureus* (DA7127)	ND	
						E. coli (DA4201)		
						S. enterica (DA6192)		
16	*Vigna unguiculata* (Seeds)	Cp-thionin II	Peptide	5.2	–	*S. aureus* (ATTC 25923)	ND	Franco et al. (2006)
						E. coli (ATTC25922)		
						P. syringae		
17	*Pharbitis nil* (Seeds)	Pn-AMP1	Peptide	4.3		*B. subtilis*	38 µg/ml	Koo et al. (1998)
		Pn-AMP2	Peptide	4.2		*B. subtilis*	20 µg/ml	
18	*Vigna angularis* (Seeds)	VaD1	Peptide	5.0	–	*S. epidermidis*	36.6 µg/ml	Chen et al. (2005b)
						X. campestris pv. vesicatoria	40.8 µg/ml	
						S. typhimurium	143.4 µg/ml	
						B. cereus	> 500 µg/ml	
						E. coli	> 500 µg/ml	
						E. carotovora pv.carotovora	1000 µg/ml	
						P. vulgaris	> 1000 µg/ml	
						S. enteritidis	> 1000 µg/ml	
						P. syringae pv. syringae	> 1000 µg/ml	
19	*Phaseolus vulgaris* (Seeds)	Vulgarinin	Seeds	7	–	*M. phlei*	87 ± 5 µM	Wong and Ng (2005c)
						B. megaterium	105 ± 5 µM	
						B. subtilis	98 ± 2 µM	
						P. vulgaris	75 ± 6 M µM	

Table 1 (continued)

S. No	Plant and its part	Protein	Nature	M. Wt (kDa)	N-terminal sequence	Bacterial species (Tested)	*IC_{50}	References
20	*Tulipa gesneriana* (Tulip Bulbs)	Tu-AMP-1	Peptide	4.9	–	*E. carotovora*	11 µg/ml	Fujimura et al. (2004)
						A. radiobacter	15 µg/ml	
						A. rhizogenes	20 µg/ml	
						C. michiganensis	14 µg/ml	
						C. flaccumfaciens	13 µg/ml	
		Tu-AMP 2	Heterodimeric Peptide	5	–	*E. carotovora*	15 µg/ml	
						A. radiobacter	17 µg/ml	
						A. rhizogenes	20 µg/ml	
						C. michiganensis	17 µg/ml	
						C. flaccumfaciens	15 µg/ml	
21	*Solanum tuberosum* (Tubers)	Snakin-1	Peptide	6.9	M	*C. michiganensis*	4 µM	Berrocal-Lobo et al. (2002)
		Snakin-2	Peptide	7.0	MAISKALFAS LLLSLLLLEQ	*C. michiganensis*	1 µM	
						R. meliloti	8 µM	
22	*Triticum aestivum* L. (Endosperm)	α-Purothionin	Polypeptide	6	MKSCCRSTLG RNCYNLCRAR	*P. solanacearum*	ND	de Caleya et al. (1972)
						X. phaseoli		
		β-Purothionin	Polypeptide	6	MGSKGLKGVM VCLLILGLVL	*P. solanacearum*	ND	
						X. phaseoli		
23	*Viola odorata* (Whole Plant)	Cycloviolacin O2	Macrocyclic peptides	3.14	GIPCGESCVW IPCISSAIGC SCKSKVCYRN	*S. enterica* (DA6192)	ND	
						E. coli (DA4201)		
						S. aureus (DA7127)		
24	*Viola abyssinica* (Whole Plant)	Vaby A	Macrocyclic peptides	2.86	–	*S. enterica* (DA6192)	ND	Pränting et al. (2010)
						E. coli (DA4201)		
						S. aureus (DA7127)		
		Vaby D	Macrocyclic peptides	3.06	–	*S. enterica* (DA6192)	ND	
						E. coli (DA4201)		
						S. aureus (DA7127)		
25	*Beta vulgaris* (Leaves)	AX 1	Peptides	5.0	AICKKPSKFF KGACGRDADC EKACDQENWP GGVCVPFLRC ECQRSC	*C. beticola*	0.4–0.8 µM	Kragh et al. (1995)
		AX2	Peptides	5.1	ATCRKPSMYF SGACFSDTNC QKACNREDWP NGKCLVG-FKC ECQRPC			

Table 1 (continued)

S. No	Plant and its part	Protein	Nature	M. Wt (kDa)	N-terminal sequence	Bacterial species (Tested)	*IC_{50}	References
26	*Mirabilis expansa* (Roots)	ME1	Protein	27	METMRLLFLL LTIWTTVVGS	*P. syringae B* *A. tumefaciens* C58 *A. rhizogenes ATCC15834* *B. subtilis G13R* *F. carotovora ATCC15713* *X. campestris pv vesicatoria* *R. leguminosarum* *S. marcescens*	ND	Vivanco et al. (1999)
		ME2	Protein	27.5	–	*P. syringae* *A. tumefaciens* *A. rhizogenes* (ATCC15834) *B. subtilis G13R* *F. carotovora* *X. campestris pv vesicatoria* *R. leguminosarum* *S. marcescens*		
27	*Benincasa hispida* (Seeds)	Hispidalin	Peptide	5.7	–	*E. coli* *P. aeruginosa* *S. enterica* *S. aureus*	ND	Sharma et al. (2014)
28	*Zizyphus jujuba* (Fruit)	Snakin-Z	Peptide	3.3	–	*E. coli* *K. pneumoniae* *B. subtilis* *S. aureus*	ND	Daneshmand et al. (2013)

Table 1 (continued)

S. No	Plant and its part	Protein	Nature	M. Wt (kDa)	N-terminal sequence	Bacterial species (Tested)	*IC_{50}	References
29	*Fagopyrum esculentum Moench.* (Seeds)	Fa-AMP1	Peptide	3.8	AQCGAQGGGA TCPGGLCCSQ WGWCGSTPKY CGAGCQSNCK	*E. carotovora*	11 µg/ml	Fujimura et al. (2003)
						A. radiobacter	24 µg/ml	
						A. rhizogenes	20 µg/ml	
						C. michiganensis	14 µg/ml	
						C. flaccumfaciens	13 µg/ml	
		Fa-AMP2	Peptide	3.9	AQCGAQGGGA TCPGGLCCSQ WGWCGSTPKY CGAGCQSNCR	*E. carotovora*	15 µg/ml	
						A. radiobacter	17 µg/ml	
						A. rhizogenes	24 µg/ml	
						C. michiganensis	17 µg/ml	
						C. flaccumfaciens	15 µg/ml	
30	*Allium sativum* (Bulbs)	Alliumin	Protein	13	DDFLCAGGCL	*P. fluorescens*	ND	Xia and Ng (2005)
31	*Vicia faba* (Flower)	Fabatin-1	Peptide	5.2	LLGRCKVKSN RFHGPCLTDT HCSTVCRGEG YKGGDCHGLR RRCMCLC	*E. coli*	ND	Zhang and Lewis (1997)
						P. aeruginosa		
						E. hirae		
		Fabatin-2	Peptide	5.20	LLGRCKVKSN RFNGPCLTDT HCSTVCRGEG YKGGDCHGLR RRCMCLC	*E. coli*	ND	
						P. aeruginosa		
						E. hirae		
32	*Moringa Oleifera* (Seeds)	MoCP	Dimeric protein	13		*E. coli*	ND	Shebek et al. (2015)
33	*Zea mays* (Kernel)	MBP-1	Peptide	4.1	RSGRGECRRQ CLRRHEGQPW	*C. michiganense* ssp. *Nebraskense*	ND	Duvick et al. (1992)
34	*Vigna radiate* (Seeds)	VrD1	Peptide	5.1	MERKTFSFLF LLLLVLASDV	*E. coli*	ND	Lin et al. (2007)

*IC_{50} Concentration of protein required for 50% growth inhibition, *NA* Not available, *ND* Not determined, *Cy-AMP* Cycad antimicrobial peptide, *Pa-AMP-1 Phytolacca americana* antimicrobial protein, *Ib-AMP1 Impatiens balsamina* antimicrobial peptides, *Pg-AMP Psidium guajava*-antimicrobial peptide, *WSG Withania somnifera* glycoprotein, *APC* antioxidant protein from curry leaves, *VaD1 Vigna angularis* defensing, *M.E. Mirabilis expansa*, *MoCP Moringa oleifera* cationic protein, *MBP-1* Maize Basic Peptide 1, *VrD1 Vigna radiate* defensing-1, *Mj-AMP Mirabilis jalapa* antimicrobial peptide

permeability and pore formation. Other AFPs cause various modifications in host cell signaling processes, leading to ROS generation (Reactive Oxygen Species), eventually leading to apoptosis. AX1 and AX2, thionin-like peptides that are cationic, interact with anionic phospholipids causing fungal membrane permeabilization (Lee-Huang et al. 1991a; b). Thaumatin-like proteins, a class of AFPs, inhibit the fungal spore formation, leading to lysis. Pn-AMP-1 and Pn-AMP-2 (extracted from *Pharbitis nil*) hinder the hyphal growth, causing the tips to be shattered upon insertion of hyphae, ultimately leading to rupture of fungal membrane and cytoplasmic leakage (Leader et al. 2008). Like other plant peptides, AFPs are diverse, having inert anti-cancer and anti-HIV activity. Mungin, sesquin, lunatusin, and PHP (Peganum harmala protein) are examples (Lee-Huang et al. 1991a; b; Liu et al. 2000; Mazalovska and Kouokam 2018).

The non-specific lipid transfer protein (nLTP) PHP, isolated from *Peganum harmala* have been shown to inhibit various fungal species with an IC_{50} value ranging 1.5–12.19 µM (Yokoyama et al. 2008). Hypotin (extracted from *Arachis hypogaea*) has been shown to inhibit the activity of species like *Pythium aphanidermatum*, *Fusarium solani*, *Physalospora piricola*, *Alternaria alternata*, *Botrytis cinerea*, *Fusarium oxysporum,* and *Pythium aphanidermatum* (Stirpe et al. 1986). Vulgin inhibits the fungal activity of a wide variety of species, combined with potent anti-HIV activity by inhibiting HIV reverse transcriptase (Ye and Ng 2003). It was reported that a proteinaceous α-amylase inhibitor extracted from rhizome of *Cheilocostus speciosus* and purified employing anion exchange chromatography and column gel filtration had an activity on fungal α -amylase. The fungal activity was reduced by this 31.18 kDa protein from *C. speciosus* by 71% using ion-exchange chromatography and 96% using gel filtration (Balasubramanian et al. 2018). It was documented that *Ferula asafoetida* root was used to extract three major proteins with molecular weights of 14 kDa, 27 kDa, and 39 kDa. The 39-kDa protein significantly improved chymotrypsin activity, while the 14-kDa protein had antibacterial action towards *Pseudomonas aeruginosa*. All three pure proteins were also reported to have significantly increased antioxidant activity (Chandran et al. 2017). Quorum-sensing inhibitors from Solanaceae family were also reported to possess anti-bacterial action against *Pseudomonas aeruginosa* (Singh et al. 2015).

Until now, hundreds of AFPs have been identified as having negligible toxicity. Tu-AMP-1 and Tu-AMP-2 are highly potent AFPs inhibiting *Fusarium oxysporum* and *Geotrichum candidum* (Wong and Ng 2005). Ginkbilobin (extracted from *Ginkgo biloba*) strongly affects the activity of *B. cinerea* (Wang and Ng 2000). Sesquin (extracted from *Vigna sesquipedalis*) is a highly active AFP with an IC_{50} value of 0.15 µM and 1.4 µM for *Mycosphaerella arachidicola* and *F. oxysporium,* respectively (Wani et al. 2020). Despite all of these studies showing the therapeutic effects of AFPs, not many have reached clinical trials. Most of these peptides have been ignored due to a lack of proper classification and structural and functional diversity. Efforts in this direction are required so that the therapeutic potential of AFPs can be used to a full extent and the available AFPs are tabulated (Table 2).

Anti-viral Activity of plant peptides and proteins

Anti-HIV Activity

Acquired Immunodeficiency Syndrome (AIDS) is the fourth leading cause of death triggered by the Human immunodeficiency virus (HIV) (Irvin and Uckun 1992). Two variants of HIV are HIV-1 and HIV-2, each being etiologically and genetically different. Medically, these types vary with the disease's pace of progression, with HIV-1 being faster than HIV-2 (Irvin and Uckun 1992). The mode of action of HIV-1 involves host and viral membrane interaction through binding of the envelope glycoproteins (g120 and gp41) to CD4, CCR5 and CXCR4 receptors of the host cell. Subsequently, the virus enters the cell along with the integration of the viral genome into the host genome (Wang 2012). Preventing protein maturation and viral RNA replication to DNA are some of the treatment options available to enhance the infected's survivability. Nevertheless, no proper vaccine is available yet due to: (i) Advent of viral strains that are highly resistant to current anti-HIV drugs, (ii) Incapability to annihilate latent viruses, (iii) Toxicity, (iv) Lack of proper route of administration (Irvin and Uckun 1992). Hence, as mentioned earlier, the scientific community is probing novel drug molecules to curb the obstacle. Within this framework, therapeutic plant peptides are seen as prospective contestants. As an alternative, plant peptides can be used as an excellent medication due to their highly specific nature, increased bioactivity, non accumulated in our organs and less to negligible toxicity (Barbieri et al. 1982; Barbosa Pelegrini et al. 2011). Many antiviral plant proteins belong to the family of cyclotides endowed with a highly stable peptide framework. Cyclotides are cyclic structures that are 28–37 amino acid residues long. They consist of a cyclic cysteine knot motif (CCK) made up of highly conserved cysteine residues linked together by three disulfide bonds. Surface-exposed hydrophobic patches formed by the CCK motif and its cyclicity are some of the reasons for its anti-HIV activity (Gerlach and Mondal 2012). Some other plant proteins including RIPs (Ribosome Inactivating Proteins) such as TCS (Trichosanthin) and PAP (Pokeweed antiviral Protein-N-glycosidase that exhibits antiviral activity against several viruses) have strong anti-HIV potential with some present in clinical trials. TCS has

Table 2 List of anti-fungal peptides/proteins from different parts of plants

S. No	Plant and its part	Protein	Nature	M.Wt. (kDa)	Peptide sequence	Fungal species (Tested)	*IC_{50}	References
1	*Momordica charantia* (Leaves)	MCha-Pr	Protein	25.5	VEYTITGNAGNTPGG	*A. brassicae*	33 µM	Zhang et al. (2015)
						C. personata	42 µM	
						F. oxysporum	37 µM	
						Mucor sp.,	40 µM	
						R. solani	48 µM	
2	*Arachis hypogaea* (Seeds)	Hypotin	Protein	30.4	CDVGSVISASLFE-ALQKHRN	*P. aphanider-matum*	18.9 µM	Wang et al. (2007)
						B. cinerea	NA	
						A. alternate		
						S. rolfsii		
						F. oxysporum		
						F. solani		
3	*Phaseolus coccineus* cv. 'Major' (Seeds)	Coccinin	Peptide	7	KQTENLADTY	*M. arachidicola*	75 ± 5 µM	Ngai and Ng (2004)
						F. oxysporum	81 ± 7 µM	
						P. piricola	89 ± 4 µM	
						B. cinerea,	109 ± 5 µM	
						C. comatus	122 ± 7 µM	
						R. solani	134 ± 2 µM	
4	*Phaseolus vulgaris* (Seeds)	Vulgin	Polypep-tide	5	VDVGTVLTAT-FIEQFFKHRNDQAPEGK-GFYTYNAFISAAR	*B. cinerea*	7 µM	Ye and Ng (2003)
						M. arachidicola	NA	
						C. comatus		
						F. oxysporum,		
		Fraction PTA2c	Peptide	5	KTCENLVDTYRGPCFT	*M. arachidicola*	NA	Ye and Ng (2001)
						B. cinerea	1 µM	
						F. oxysporum	NA	
5	*Chrysanthemum coronarium* (Seeds)	Chrysan-corin	Protein	13.4	RVDQKAQNLKCCQQHR-FNCHCERVCVFQDQ	*B. cinerea*	11 µM	Wang et al. (2001)
						M. arachidicola	17.4 µM	
						P. piricola	14.6 µM	
6	*Phaseolus lunatus L.* (Seeds)	Lunatusin	Peptide	7	KTCENLADTFRGPC-FATSNC	*F. oxysporum*	1.9 µM	Wong and Ng (2005a)
						B. cinerea	2.6 µM	
						M. arachidicola	0.32 µM	
7	*Brassica junceavar. integrifolia* (Seeds)	Juncin	Protein	18.9	GVEVTRELRSERPSGKIVTI	*F. oxysporum*	13.5 µM	Ye and Ng (2009)
						H. maydis	27 µM	
						M. arachidicola	10 µM	
8	*Vigna angularis* (Seeds)	Angularin	Peptide	8	–	*B. cinerea*	14.3 µM	Ye and Ng (2002b)
						M. arachidicola	NA	
9	*Ginkgo biloba*	Ginkbilobin (Seeds)	Protein	13		*B. cinerea*	0.25 µM	Wang and Ng (2000)
						M. arachidicola	6.5 µM	
						F. oxysporum	3.6 µM	
						R. solani	8.7 µM	
						C. comatus	3.4 µM	
		GAFP (Leaves)	Peptide	4.24		*P. sasakii Ito*	ND	Huang et al. (2000)
						A. alternate (Fries) Keissler		
10	*Dendrocalamus latiflora* Munro (Shoot)	Dendrocin	Protein	20		*B. cinerea*	1.8 µM	Wang and Ng (2003)
						F. oxysporium	1.4 µM	
						M. arachidicola	5.1 µM	

Table 2 (continued)

S. No	Plant and its part	Protein	Nature	M.Wt. (kDa)	Peptide sequence	Fungal species (Tested)	*IC_{50}	References
11	*Vigna sesquipedalis* (Seeds)	Sesquin	Peptide	7		*B. cinerea*	2.5 µM	Wong and Ng (2005b)
						F. oxysporum	1.4 µM	
						M. arachidicola	0.15 µM	
12	*Withania somnifera* (Root tubers)	WSG	Glyco-protein	28		*A. flavus*	ND	Girish et al. (2006)
						A. niger		
						A. nidulans		
						A. flaviceps		
						A. alternate		
						A. carthami		
						F. oxysporum		
						F. verticilloides		
13	*Allium sativum* (Bulbs)	Alliumin	Protein	13		*M. arachidicola*	1.3 µM	Xia and Ng (2005)
14	*Pharbitis nil* (Seeds)	Pn-AMP1	Peptides	4.29		*B. cinerea*	16 µg/ml	Koo et al. (1998)
						C. langenarium	10 µg/ml	
						S. sclerotiorum	11 µg/ml	
						F. oxysporum	10 µg/ml	
						R. solani	26 µg/ml	
						P. capsici	5 µg/ml	
						P. parasitica	3 µg/ml	
						Pythium spp.	N.A	
						S. cerevisiae	14 µg/ml	
		Pn-AMP2	Peptides	4.21		*B. cinerea*	2 µg/ml	
						C. langenarium	4 µg/ml	
						S. sclerotiorum	3 µg/ml	
						F. oxysporum	2.5 µg/ml	
						R. solani	75 µg/ml	
						P. capsici	0.6 µg/ml	
						P. parasitica	2 µg/ml	
						Pythium spp.	2.5 µg/ml	
						S. cerevisiae	8 µg/ml	
15	*Beta vulgaris* L. (Leaves)	IWF4	Dimeric protein	4.5		C. *beticola*	≤2 µg/ml (0.7 µM)	Nielsen et al. (1997)
16	*Eucommia ulmoides* Oliv (Bark)	EAFP1	Peptides	4.20		*A. lycopersici*	155 µg/ml	Huang et al. (2002)
						F. moniliforme	56 µg/ml	
						F. oxysporum	46 µg/ml	
						C. gossypii	35 µg/ml	
		EAFP2	Peptides	4.15		*A. lycopersici*	109 µg/ml	
						F. moniliforme	18 µg/ml	
						F. oxysporum	94 µg/ml	
						C. gossypii	56 µg/ml	

Table 2 (continued)

S. No	Plant and its part	Protein	Nature	M.Wt. (kDa)	Peptide sequence	Fungal species (Tested)	*IC_{50}	References
17	*Capsella bursa-pastoris* (Roots)	Shepherin I	Peptide	2.36		*C. albicans*	8 µg/ml	Park et al. (2000)
						C. neoformans	< 2.5 µg/ml	
						S. cerevisiae	7 µg/ml	
						A. alternate	7 µg/ml	
						A. flavus	65 µg/ml	
						A. fumigatus	> 100 µg/ml	
						F. culmorum	72 µg/ml	
		Shepherin II	Peptide	3.26		*C. albicans*	5 µg/ml	
						C. neoformans	< 2.5 µg/ml	
						S. cerevisiae	3 µg/ml	
						A. alternate	> 100 µg/ml	
						A. flavus	60 µg/ml	
						A. fumigatus	> 100 µg/ml	
						F. culmorum	68 µg/ml	
18	*Hevea brasiliensis* (Latex)	Hevein	Protein	4.7		*B. cinerea*	500 µg/ml	van Parijs et al. (1991)
						F. culmorum	600 µg/ml	
						F. oxysporum	1.25 mg/ml	
						P. blakesleeanus	300 µg/ml	
						P. triticirepentis	350 µg/ml	
						P. oryzae	500 µg/ml	
						S. nodorum	500 µg/ml	
						T. hamatum	90 µg/ml	
19	*Gentiana triflora* (Leaves)	GtAFP1	Protein	20		*A. alternate*	51 µg /ml	Kiba et al. (2005)
						B. cinerea	61 µg /ml	
						F. solani	99 µg /ml	
20	*Acacia confusa* (Seeds)	Acaconin	Protein	32		*R. solani*	30 ± 4 µM	Lam and Ng (2010)
21	*Tulipa gesnerian* (Tulip Bulbs)	Tu-AMP1	Peptide	4.9		*F. oxysporum*	2 µg /ml	Fujimura et al. (2004)
						G. candidum	2 µg /ml	
						F. oxysporum	2 µg /ml	
		Tu-AMP2	Dimeric peptide	2.259		*G. candidum*	2 µg /ml	
22	*Cicer arietinum* (Seeds)	CLAP	Protein	18		*M. arachidicola*	5.5 µM	Ye and Ng (2002b)
						B. cinerea	1.3 µM	
		C-25	Lectin protein	25		*C. krusei*, *C. tropicalis*, *C. parapsilosis*	1.56–12.5 µg/ml	Kumar et al. (2014)
23	*Gymnocladus chinensis* Baill (Beans)	Gymnin	Peptide	6.5		*F. oxysporum*	2 µM	Wong and Ng (2003a)
						M. arachidicola	10 µM	
24	*Adzuckia angularia* (Seeds)	Fraction AB2	Peptide	5		*B. cinerea*	3.5 µM	Ye and Ng (2001)
						M. arachidicola	NA	
						F. oxysporum		

Table 2 (continued)

S. No	Plant and its part	Protein	Nature	M.Wt. (kDa)	Peptide sequence	Fungal species (Tested)	*IC_{50}	References
25	*Macadamia integrifolia* (Seeds)	MiAMP1	Peptide	5.9		*C. michiganensis*	50 µg/ml	Marcus et al. (1999)
26	*Vigna angularis* (Seeds)	VaD1	Peptide	5.0		*F. oxysporum*	30 µg/ml	Chen et al. (2005b)
						F. oxysporumf. sp. pisi	53.2 µg/ml	
						T. rubrum	> 500 µg/ml	
27	*Phaseolus vulgaris* (Seeds)	Vulgarinin	Peptide	7	KTCENLADTYKGP CFTSGGD	*B. cinerea*	2.9 µM	Wong and Ng (2005c)
						F. oxysporum	1.7 µM	
						P. piricola	2.2 µM	
						M. arachidicola	0.21 µM	
						C. albicans	cc	
						P. azadirachtae		
						P. ultimum		
						G. candidum		
28	*Spinacia oleracea* (Leaves)	So- D2	Peptide	5.80		*F. culmorum*	0.2 µM	Segura et al. (1998)
						F. solani	11 µM	
		So-D6	Peptide	2.55		*F. culmorum*	NA	
						F. solani	11 µM	
		So-D7	Peptide	4.23		*F. culmorum*	N.A	
						F. solani	9 µM	
29	*Actinidia chinensis* (Fruit)	Kiwi TLP	Protein	21		*B. cinerea*	0.43 µM	Wang and Ng (2002)
						M. arachidicola	8 µM	
						P. piricola	NA	
30	*Benincasa hispida* (Seeds)	Hispidalin	Peptide	5.7		*A. flavus*	ND	Sharma et al. (2014)
						F. solani		
						C. geniculata		
						P. chrysogenum		
						C. gloeosporioides		
31	*Peganum harmala* (Seeds)	PHP	Homodimeric protein	18		*A. alternate*	1.5 µM	Ma et al. (2013)
						P. degitatum	7.5 µM	
						R. stuolonifer	8.44 µM	
						M. grisea	2.19 µM	
32	*Cycas revoluta* (Seeds)	Cy-AMP1	Peptide	4.58		*F. oxysporum*	6.0 µg/ml	Yokoyama et al. (2008)
						G. candidum	7.4 µg/ml	
		Cy-AMP2	Peptide	4.56		*F. oxysporum*	7.1 µg/ml	
						G. candidum	7.0 µg/ml	
		Cy-AMP3	Peptide	9.27		*F. oxysporum*	250 µg/ml	
						G. candidum	200 µg/ml	
33	*Allium tuberosum* (Shoot)	Fraction MS3	Protein	36		*R. solani*	NA	Lam et al. (2000)
						F. oxysporum	0.2 µM	
						C. comatus		
						M. arachidicola		
						B. cinerea		
34	*Dolichos lablab* (Seeds)	Dolichin	Protein	28		*F. oxysporum*	ND	Ye et al. (2000)
						R. solani		
						C. comatus		

Table 2 (continued)

S. No	Plant and its part	Protein	Nature	M.Wt. (kDa)	Peptide sequence	Fungal species (Tested)	*IC_{50}	References
35	*Panax ginseng* (Roots)	Panaxagin	Homodimeric protein	53	–	*F. oxysporum* *C. comatus* *R. solani*	ND	Ng and Wang (2001)
36	*Phaseolus mungo* (Seeds)	Mungin	Protein	18	–	*R. solani* *C. comatus* *M. arachidicola* *B. cinerea* *F. oxysporum*	ND	Ye and Ng (2000)
37	*Zea mays* (Kernels)	MBP-1	Peptide	4.13	–	*F. graminearum* *F. moniliforme* *A. flavus* *F. oxysporum* *A. solani* *T. reesei* *T. harzianum*	ND	Duvick et al. (1992)
38	*Raphanus sativus* (Seeds)	RsAFP1	Tetrameric polypeptide	20	–	*A. brassicola* *Ascochyta pis* *B. cinerea* *C. beticola* *C. lindemuthianum* *F. culmorum* *T. hamatum* *P. oryzae*	ND	Terras et al. (1992)
		RsAFP2	Trimeric polypeptide	15		*A. brassicola* *Ascochyta pis* *B. cinerea* *C. beticola* *C. lindemuthianum* *F. culmorum* *T. hamatum* *P. oryzae*	ND	
39	*Zingiber officinalis* (Rhizome)	G-24	Protein	24	–	*F. oxysporium* *C. albicans*	4.6 µM 8.0 µM	Terras et al. (1992)
40	*Trichosanthes dioica* (Seeds)	TDSC	Glycoprotein	39 ± 1	EING GGA	*A. niger and Trichoderma sp.*	ND	Kabir et al. (2016)

**IC_{50}* Concentration of protein required for 50% growth inhibition, *ND* Not determined, *NA* Not available, as these proteins have been claimed to exhibit the activity, but no activity parameters have been mentioned, *Kiwi TLP* Kiwi fruit thaumatin-like protein, *MCha-Pr Momordica charantia* pathogenesis-related protein, *Fraction PTA2c* Pinto bean antifungal peptide, *WSG Withania somnifera* glycoprotein, *IWF4* Intercellular washing fluid, *EAFP* Eucommia antifungal peptide, *GtAFP Gentiana triflora* antifungal protein, *MBP-1* Maize basic peptide, *CLAP* Chickpea cyclophilin-like antifungal protein, *VaD1 Vigna angularis* variegate 1, *TDSC Trichosanthes dioica* seed chitinase

been shown to lower HIV-1 p24 antigen levels in AIDS patients (Leader et al. 2008). MAP30 (Momordica anti-human immunodeficiency virus protein) is a highly potent anti-HIV agent and a type-I RIP, with an IC_{50} of only 0.33 nM (Lee-Huang et al. 1990). Due to the strong IC_{50} value of PAP, the conjugation of PAP and immunoconjugates have been used as inhibitors for HIV infection (Irvin and Uckun 1992). An example of this is TXU-PAP, wherein

PAP has been conjugated with TXU and attacks the CD7 antigen of HIV-infected cells, thereby inhibiting the infection (Lee-Huang et al. 1990).

Being prone to microbial infections, the combined activity of both anti-HIV and anti-microbial peptides could create new opportunities for HIV therapy. Aforementioned proteins have properly recorded structures, but not much research has been done to understand their mode of action. The most widely accepted hypothesis is attacking the viral envelope (Bokesch et al. 2004). The cyclotides work by viral membrane disruption leading to the formation of the pore (Gerlach and Mondal 2012). These cyclotides (Kalata 1) get bound to the phospholipid-rich viral coat with the help of its hydrophobic patches, resulting in an oligomeric form that penetrates the viral coat. This leads to the formation of discrete pores, thereby causing the coat to collapse (Wang 2012). As viral coat has glycoproteins in it, plant peptides like ricin and con A, possessing carbohydrate-binding sites in them, have been considered as potential candidates for inhibiting HIV at initial stages (Mazalovska and Kouokam 2018). RIPs like PAP, MAP30, TCS stop HIV-1 replication through depurination of long terminal repeats (LTRs) present in the DNA (Kaur et al. 2012). Another RIP saporin impedes the activity of HIV1 integrase for processing the 3' end of the viral DNA disintegrating genome and its mRNA (Yadav and Batra 2015). If we can decipher the role of such proteins at different phases of the viral infection, anti-HIV activity can be exploited. Steps are to be taken to extract and characterize much more powerful anti-HIV agents that are less toxic. The available anti-HIV peptides are reported in Table 3.

Anti-SARS-CoV-2 activity

SARS-CoV-2, also called COVID-19 (Coronavirus Disease 2019), has more than 130 million reported cases worldwide and has taken the lives of more than 2.8 million people since its onset in late 2019 (Zhou et al. 2020) and successive pandemic declarations by the WHO on 11 March 2020 (WHO 2021). Since the virus outbreak, a monumental effort has been made by researchers and drug companies worldwide to discover a vaccine. Multiple candidates were chosen from varied sources, most of them being in clinical trials. But so far, no definite cure has been developed. Only a few vaccines have been engineered as a contingency plan against the virus. Plant peptides have also been tested for vaccine production to broaden the range of candidates. Lectin extracted from red marine alga *Griffithsia* sp. (GRFT) have been shown to inhibit the cytopathic effect of SARS-CoV, enhancing the mortality of cells (O'Keefe et al. 2010). In the case of MERS-CoV (Middle East respiratory syndrome-CoV: Strain of SARS-CoV in the Middle East), GRFT acts by preventing its entry into the host cell through spike protein inhibition. Thus, GRFT serves as an effective inhibitor of MERS-CoV infection (Millet et al. 2016). In-silico methods using plant proteins have also been utilized to identify the potential lead compounds for COVID-19 vaccine design. Avenin from oats, α/β-gliadin from wheat, and ribulose bisphosphate carboxylase small chain from multiple sources have been utilized to generate effective binders to SARS-CoV-2 spike receptor-binding protein (RBD). When combined with certain oligopeptides (VQVVN, PISCR), these plant peptides / proteins might be employed as lead compounds in developing potent entry inhibitors (Luo et al. 2020). A wide variety of therapeutic plant peptides exist, out of which only a few have been explored (Mammari et al. 2021). Future research should focus on other plant-derived peptides, their mode of action, and their side effects in order to engineer a proper peptide vaccine for COVID-19.

Non-infectious Diseases

The diseases which are mainly caused due to environmental or genetic factors and not by pathogens are termed non-infectious diseases. Examples of non-infectious diseases include diabetes mellitus, most cancers, and cardiovascular diseases. These could be cured using therapeutic peptides obtained from various plant sources. Peptides are essential molecules that can attach to multiple cell surface receptors. The plant peptides used as drugs are increasing day by day. This review is majorly discuss the plant peptides with anti-diabetic, anti-cancer, and anti-hypertensive properties. When treated with proteolytic enzymes of plant proteins form protein hydrolysates and yield peptides. These therapeutic peptides could be used to treat various non-infectious diseases. Nineteen percent of the medicinal plant peptides are used to cure metabolic disorders, twelve percent are used to cure cancer, and almost three percent to cure cardiac related problems (Patil et al. 2020). The peptides obtained from various plant sources such as common bean, rice, pinto bean, hemp seeds, and mulberry have anti-diabetic properties. Peptides obtained from soybean, wheat, barley, and walnut have anti-cancer properties. Anti-hypertensive activity is observed in peptides purified from rice and walnut. This review focuses on the various peptides, their origins, sequences, and how they prevent non-infectious diseases (Table 4).

Anti-diabetic activity of plant peptides/proteins

Diabetes mellitus is widespread, and it is one of the most prevalent non-infectious diseases and its treatment is challenging. A study conducted in India, reports 80 million diabetic cases, and projected to be 140 million cases by 2037 (Deepthi et al. 2018). The increasing number of cases shows diabetic prevalence in India and the need

Table 3 List of anti-HIV peptides/proteins from plants

S. No	Plant and its part	Protein	Nature	M. Wt. (kDa)	Peptide Sequence	Mode of action	*IC_{50}	References
1	*Phaseolus lunatus* (Seeds)	Lunatusin	Peptide	7	KTCENLADTFRGPC-FATSNC	HIV-1 reverse transcriptase inhibition	120 µM	Wong and Ng (2005a)
2	*Phaseolus vulgaris* (Seeds)	Vulgin	Polypeptide	5	VDVGTVLTAT-FIEQFFKHRNDQAPEG-KGFYTYNAFISAAR	HIV-1 reverse transcriptase inhibition	58 µM	Ye and Ng (2003)
		Fraction PTA2c	Peptide				258 µM	Ye and Ng (2001)
3	*Lens culinaris* (Seeds)	LTI	Protein	16	GDKKQAYTDTYLSTR-SQPP	HIV-1 reverse transcriptase inhibition	30 mM	Cheung and Ng (2007)
4	*Vigna sesquipedalis* (Ground Beans)	Sesquin	Peptide	7	KTCENLADTY	HIV-1 reverse transcriptase inhibition	ND	Wong and Ng (2005b)
		N.A	Heterodimeric lectin	60	–		73 µM	Wong and Ng (2003b)
5	*Acacia confusa* (Seeds)	Acaconin	Protein	32	–	HIV-1 reverse transcriptase inhibition	10 ± 2.3 µM	Lam and Ng (2010)
6	*Gelonium multiflorum* (Seeds)	GAP 31	Protein	31	–	HIV-1 reverse transcriptase inhibition	0.32 nM	Lee-Huang et al. (1991b)
						Inhibition of syncytium formation	0.28 nM	
						Viral core protein p24 inhibition	0.23 nM	
7	*Dianthus caryophyllus* (Leaves)	DAPs 30	Protein	30	ATAYLNLAPSASQYSXF	HIV-1 reverse transcriptase inhibition	0.88 nM	Lee-Huang et al. (1991b)
						Inhibition of syncytium formation	0.76 nM	
						Viral core protein p24 inhibition	0.85 nM	
		DAPs 32	Protein	32	AVKTILNLVSPSANRY-ATF	HIV-1 reverse transcriptase inhibition	0.76 nM	
						Inhibition of syncytium formation	0.76 nM	
						Viral core protein p24 inhibition	0.71 nM	
8	*Momordica charantia* (Seeds)	MAP 30	Protein	30	DVNFDLSTATAKTYT-FIEDFRATLPF	HIV-1 reverse transcriptase inhibition	0.33 nM	Lee-Huang et al. (1990)
						Inhibition of viral core protein p24 expression	0.22 nM	
						Inhibition on syncytium formation	0.83 nM	

Table 3 (continued)

S. No	Plant and its part	Protein	Nature	M. Wt. (kDa)	Peptide Sequence	Mode of action	*IC_{50}	References
9	*Trichosanthes kirilowii* (Root tubers)	TAP 29	Protein	29	–	Inhibition of syncytium formation	0.34 nM	Lee-Huang, et al. (1991a)
						Inhibition of viral core protein p24 expression	0.37 nM	
						Inhibition of viral-associated reverse transcriptase activity	0.46 nM	
10	*Dorstenia contrajerva* (Leaves)	Contrajervin	Peptide	5	ERDDHRCGPDYGNPSCS-GDRCCSIYNWCGGGS-SYCSGGSCRYQCWY	HIV-1 inhibition by binding to gp120 and gp41	> 4.9 µM	Bokesch et al. (2004)
11	*Treculia obovoidea* (Bark)	Treculavirin	Dimeric peptide	10	PGCEERPDHQCGPDYG-NPGCGAGRCCSIHG-WCGSSADYCSGTSC-QYQCSC	HIV-1 inhibition by binding to gp120 and gp41	> 2.5 µM	Bokesch et al. (2004)
12	*Dolichos lablab* (Seeds)	Dolichin	Protein	28	GAVGSVINA-SLFEQLLKHRNDQD-PEGKG	HIV-1 reverse transcriptase inhibition	< 180 µM	Ye et al. (2000)
13	*Oldenlandia affinis*	Kalata B1 (Whole Plant)	Macrocyclic Peptides	2.89	GLPVCGETCVGGTC-NTPG	HIV inhibition by cell envelope disruption	3.5 µM	Daly et al. (2004)
		Kalata B8 (Aerial Parts)	Macrocyclic Peptides	3.28	GSVLNCGETCLLGTC YTTG		11 µM	Daly et al. (2006)
14	*Chassalia parvifolia*	Circulin A (Crude Extract)	Macrocyclic Peptides	3.17	GIPCGESCVW IPCISAALGC SCKNKV-CYRN	HIV replication inhibition	0.05 µM	Gustafson et al. (1994)
		Circulins B (Crude Extract)	Macrocyclic Peptides	3.3	GVIPCGESCV FIP-CISTLLG CSCKNKV-CYR N		0.05 µM	
		Circulins C (Stems)	Macrocyclic Peptides	3.1		NA	NA	Gustafson et al. (2000)
		Circulins D (Stems)	Macrocyclic peptides	3.39			NA	
		Circulins E (Stems)	Macrocyclic peptides	3.39			NA	
		Circulins F (Stems)	Macrocyclic peptides	3.05			NA	
15	*Peganum harmala* (Seeds)	PHP	Homodimeric protein	18	–	HIV-1-RT inhibition	1.26 µM	Ma et al. (2013)
16	*Palicourea condensata* (Bark)	Palicourein	Polypeptide	3.9	RNGDPTFCGETCRVI-PVCTYSAALGCTCD-DRSDGLCK	HIV-1 replication inhibition	1.5 µM	Bokesch et al. (2001)
17	*Trichosanthes kirilowii* (Root tubers)	TCS or (GLQ 223)	Protein	26	–	HIV-1 replication inhibition	0.46 nM	Shu et al. (2009)

Table 3 (continued)

S. No	Plant and its part	Protein	Nature	M. Wt. (kDa)	Peptide Sequence	Mode of action	*IC_{50}	References
18	*Leonia cymosa* (Bark)	Cycloviolin A	Macrocyclic peptides	3.2	SCVFIPCISAAIGC-SCKNKVCY	NA	0.56 µM	Hallock et al. (2000)
		Cycloviolin B		2.8	SCYVLPCFTVGCTCTT SSQ			
		Cycloviolin C		3.1	SCVFIPCLTTVAGC-SCKNK			
		Cycloviolin D		3.1	SCVFIPCISAAIGC-SCKNKCY			
19	*Viola odorata*	Cycloviolacin O2 (Whole Plant)	Macrocyclic peptides	3.1		HIV inhibition by cell membrane disruption	NA	Gerlach et al. (2010)
		Cycloviolacin O13 (Aerial Parts)		3.12			6.4 µM	Ireland et al. (2008)
		Cycloviolacin O14 (Aerial Parts)		3.17			4.8 µM	
		Cycloviolacin O24 (Aerial Parts)		3.04			6.17 µM	
20	*Viola yedoensis* (Whole Plant)	Cycloviolin Y1	Macrocyclic peptides	3		NA	4.47 µM	Wang et al. (2008)
		Cycloviolin Y4					1.72 µM	
		Cycloviolin Y5					1.76 µM	
21	*Viola tricolor* (Whole Plant)	Varv E	Macrocyclic peptides	2.99		NA	3.98 µM	Wang et al. (2008)
22	*Viola hederacea* (Leaves)	Vhl-1	Macrocyclic peptides	3.33		NA	0.87 µM	Chen et al. (2005a)
23	*Vicia faba* cv. Giza 843 (Seeds)	VFTI-G1	Protein	15		HIV-1-RT inhibition	0.76 µM	Dia and Krishnan (2016)
24	*Gymnocladus chinensis* Baill (Beans)	Gymnin	Peptide	6.5		HIV-1-RT inhibition	200 µM	Wong and Ng (2003b)
25	*Adzuckia angularia* (Seeds)	Fraction AB2	Peptide	5		HIV-1-RT inhibition	280 µM	Ye and Ng (2001)
26	*Bauhinia variegate* (Seeds)	Fraction BG2	Homodimeric lectin	64		HIV-1-RT inhibition	1.02 µM	Chan and Ng (2015)
27	*Momordica balsamina* (Seeds)	Balsamin	Protein	28		HIV-1 replication inhibition	10.2 nM	Kaur et al. (2012)
28	*Phaseolus vulgaris* (Seeds)	Vulgarinin	Peptide	7	KTCENLADTYKGP-CFTSGGD	HIV-1-RT inhibition	130 µM	Wong and Ng (2005c)

Table 3 (continued)

S. No	Plant and its part	Protein	Nature	M. Wt. (kDa)	Peptide Sequence	Mode of action	*IC_{50}	References
29	*Phytolacca americana* (Leaves)	PAP	Protein	29 -30	–	Inhibited p24 production in HIV	0.5 nM	Irvin and Uckun (1992)
		PAP-I		29	–	HIV-1-RT inhibition	14 ± 2.1 nM	Rajamohan et al. (1999)
		PAP-II		30	–		26 ± 2.5 nM	
		PAP-III		30	–		17 ± 2.0 nM	
30	*Momordica charantia* (Seeds)	MRK29	Protein	28.6	Asp Val Asn Phe Arg Leu Ser Gly Ala Asp	HIV-1-RT inhibition	18 µg/ml	Jiratchariyakul et al. (2001)
31	*Brassica juncea var. integrifolia* (Seeds)	Juncin	Protein	18.9	–	HIV-1-RT inhibition	4.5 µM	Ye and Ng (2009)
32	*Panax ginseng* (Roots)	Panaxagin	Homodimeric protein	53	–	HIV-1-RT inhibition	NA	Ng and Wang (2001)
33	*Allium tuberosum* (Shoot)	Fraction MS3	Protein	36	EQHGSQAGGALH-PGXLHYSKYGGYGG TTPDYYGDGQQ	HIV-1-RT inhibition	NA	Lam et al. (2000)

*IC_{50} Concentration causing 50% inhibition, *ND* Not determined, *NA* Not available, as these proteins have been claimed to exhibit activity, but no activity parameters have been mentioned. *LTI* Lentil trypsin-chymotrypsin inhibitor, *TAP 29* *Trichosanthes* anti-HIV protein, *MAP 30* *Momordica* anti-HIV protein, *Vhl-1* *Viola hederaceae* leaf cyclotide-1, *MRK29* Thai bitter gourd protein, *HIV-1-RT* Human immunodeficiency virus-1 reverse transcriptase

for developing new strategy in controlling the disease. Several peptides in plants are reported to possess anti-diabetic property by controlling/inhibiting the enzymes and transporters associated with glucose metabolism (α-glucosidase inhibitors, α-amylase inhibitors, DPP-1V inhibitors, GLUT and SLUT) (Patil et al. 2020).

α-Glucosidase Peptide Inhibitors

The outcome of Ren et al. (2016) study reported that *Cannabis sativa L.* (hemp seeds) peptide (Leucine-Arginine and Proline-Leucine-Methionine-Leucine-Proline) has α-glucosidase inhibitory activity. The hydrophobic nature of the amino acids proline and leucine has shown to have α-glucosidase inhibitory activity, which can be incorporated in therapeutic peptide for further development of effective anti-diabetics. Similarity, 14 amino acids (Tryptophan-glycine-valine-glutamate-asparagine-alanine-alanine-threonine-tyrosine-phenylalanine-tryptophan-glutamine-threonine-valine) long peptide from *Morus alba L.* (Mulberry) and a peptide (Threonine-threonine-glycine-glycine-lysine-glycine-glycine-lysine) from *Phaseolus vulgaris L.* (black bean) were shown to have α-glucosidase inhibitory activity (Jha et al. 2018; Mojica and de Mejia 2016).

α-Amylase Peptide Inhibitors

The peptide CSP-1 (cumin seed peptide) obtained from *Cuminum cyminum L.,* has shown 25 % of α-amylase inhibition property (Patil et al. 2020), whereas the peptide from *Phaseolus vulgaris cv. Pinto* (pinto beans) showed 62.10 % of inhibition. Seven peptides from pinto beans are reported to have α-amylase inhibition property and each of which are in 6–16 amino acids in length. One among the seven peptides which had higher inhibition activity is composed of proline-proline-histidine-methionine-leucine-proline (Ngoh and Gan 2016).

Dipeptidyl Peptidase-IV (DPP-IV) Peptide Inhibitors

DPP-IV facilitates the degradation of Glucagon-like peptide-1 (GLP-1), hence DPP-IV inhibitors are the prime molecules in controlling diabetics. The proteases Umamizyme G and Bioprase SP containing Leucine-Proline and Isoleucine-Proline amino acids from *Oryza sativa* were having inhibitory activity against DPP-IV. Among which, Isoleucine-Proline was the most potent DPP-IV enzyme inhibitor with the IC_{50} value of 2.5 mg/ml (Hatanaka et al. 2015).

Table 4 List of plant peptides/proteins used for non-infectious diseases

S. No	Plant and its part	M. Wt	Sequence	Inhibitor target	Property	References
1	*Cannabis sativa L.* (Seeds)	287.2 Da 568.4 Da	LR PLMLP	Alpha-glucosidase inhibition	Anti-diabetic	Ren et al. (2016)
2	*Morus alba L.* (Leaves)	0.3–5 KDa	WGVENAATY-FWQTV	Alpha-glucosidase inhibition	Anti-diabetic	Jha et al. (2018)
3	*Phaseolus vulgaris L.* (Fruit)	–	–	Alpha-glucosidase inhibition	Anti-diabetic	Mojica and de Mejia (2016)
4	*Phaseolus vulgaris L.* (Fruit)	> 3 kDa	–	Alpha-amylase inhibition	Anti-diabetic	Ngoh and Gan (2016)
5	*Oryza sativa L.* (Seeds)	–	–	DPP-IV enzyme inhibitor	Anti-diabetic	Hatanaka et al. (2015)
6	*Phaseolus vulgaris L.* (Fruit)	–	–	GLUT2 and SLUT1 inhibitor	Anti-diabetic	Patil et al. (2020)
7	Walnut (Fruit)	1033.42 Da	WPERPPEIP	ACE inhibitor	Anti-hypertensive	Liu et al. (2013)
8	*Oryza sativa* (Husk)	–		ACE inhibitor	Anti-hypertensive	Shobako and Ohinata (2020)
9	*Terminalia chebula Retz* (Fruit)	1033 Da	DENSKF	ACE inhibitor	Anti-hypertensive	Sornwatana et al. (2015)
10	*Oryza sativa* (Husk)	–		–	Anti-proliferative	Kannan et al. (2010)
11	*Glycine max* *Triticum aestivum* *Hordeum vulgare* *Amaranthus- hypochondriacs* (Fruit)	–		–	Anti-mitotic, anti-cancer	Hernandez-Ledesma et al. (2009)
12	*Juglans regia L* (Fruit)	621.2795 Da	CTLEW	–	Causes apoptosis and autophagy	Ma et al. (2015)

GLUT and SLUT Plant-Based Peptide Inhibitors

GLUT and SLUT are to be inhibited during hyperglycemic condition where the blood glucose levels are highly elevated. Patil et al. 2020 reported that the peptides in black beans (*Phaseolus vulgaris L.*) have the ability to block the glucose transporters (GLUT-2 and SLUT-1) in order to control the elevated blood glucose level.

Anti-hypertensive activity of plant peptides/proteins

Hypertension, an elevated pressure in the blood vessels and it is one of the major causes of cardiovascular diseases. Renin-Angiotensinogen System (RAS) is mainly involved in the management of blood pressure. The inhibitors of these enzymes (renin and Angiotensin-I-Converting Enzyme (ACE) of RAS) inhibits the elevated vasodilators to control the blood pressure level. Daskaya-Dikmen et al. 2017 reported several plant-based peptides showing inhibitory activity against ACE towards the development of novel anti-hypertensive therapeutics.

Peptide Inhibitors of ACE

The peptide P-2a2 (Tryptophan-proline-glutamate-arginine-proline-proline-glutamine-isoleucine-proline) from walnut has the molecular weight of 1034 Da and it has shown higher level of inhibition profile with an IC_{50} value of 23.67 µg/ml against ACE, which prevents the breakdown of vasodilator, bradykinin (Liu et al. 2013). The peptide (Leucine–Arginine–Alanine) obtained from *Oryza sativa* and chebulin (Aspartate–Glutamate–Asparagine-Serine–Lysine–Phenylalanine) from *Terminalia chebula Retz* has shown anti-hypertension activity by inhibiting ACE. The walnut and the fruit of *Terminalia chebula Retz* have been used as a food supplement in the control the hypertension (Shobako and Ohinata 2020; Sornwatana et al. 2015).

Anti-oxidant activity of plant peptide/proteins

The reactive oxygen species (ROS) during metabolism are controlled by host antioxidant enzymes, however, excessive amount of ROS cause severe oxidative stress leads to cell damage which facilitate other diseases including cardiovascular, cancer and diabetes. Zou et al. 2016 reported that the antioxidant peptides possess higher level of hydrophobic amino acids than hydrophilic amino acids and contains 33.7 % of Glycine, Proline and Leucine, 18.7 % of Alanine, Tyrosine and Valine, 4.9 % of Methionine and Glutamine, 2 % of Cysteine and 40.7 % of other amino acids in its composition. Comparative study conducted by Nath et al. 2019 showed that papain-treated soybean milk peptide has higher

antioxidant property than native soybean peptide. Similarly, Zhang et al. 2018 study shows the antioxidant peptides, valine-leucine-tyrosine-isoleucine-tryptophan (MW 673.1 Da) and serine-valine-proline-tyrosine-glutamate (MW 566.9 Da) were having potential antioxidant activity. Six peptides obtained from Pinto beans by Ngoh and Gan (2016) shown highest antioxidant activity.

Ribosome Inactivating proteins and peptides from plants

Ribosome-Inactivating Proteins (RIPs) are a category of proteins whose principal function is to impair ribosomes in an irreparable manner modifying rapidly through enzymatic pathways (Stirpe 2004). Considering their discovery in the last few decades, RIPs investigation and inculcation in therapeutics have garnered tremendous scientific attention. RIPs are present in bacteria and plants, yet many plant RIPs have been well-characterized and have been traced to their functions compared to bacterial RIPs (Walsh et al. 2013). By hydrolyzing a specific N-C glycosidic bond of the eukaryotic 28S rRNA (belonging to the large 60S ribosomal subunit), the integral N-glycosidase activity of RIPs liberates the adenine residue from the 3' end of its conserved GAGA tetraloop (sarcin/ricin loop), thereby impeding protein synthesis and irreversibly inactivating the ribosome (Walsh et al. 2013). RIPs have also been shown to exhibit RNase, DNase, polynucleotide adenosine glycosidase, superoxide dismutase activity (Park et al. 2006). RIPs have been classified into three subclasses, two of them being most prominently exploited for research purposes (Girish et al. 2006). The highly ubiquitous RIP-I is the most widely used RIP with a 26–35 kDa molecular weight. RIP-I launches itself into the cell by attaching to the LDL (Low-Density Lipoprotein) receptors (Walsh et al. 2013).

The example of Saporin (Type I RIP extracted from *Saponaria officinalis*) can be used to understand the mechanism of protein synthesis inhibition by RIP-I. Internalization of saporin takes place through endocytosis by binding to the member of the LDL receptor family, α2-macroglobulin/LPR1(low-density lipoprotein receptor-related protein1) existent in the host cell membrane (Vago et al. 2005). Saporin sets foot on cytoplasm through golgi independent pathway, thereby steering clear of low pH conditions of intracellular compartments. Once inside the cytoplasm, saporin inhibits protein synthesis by excising the adenine residue from the 3' end of the particular site of the ribosome (Walsh et al. 2013). Another example of RIP-I, TCS (Trichosanthin-extracted from *Trichosanthes kirilowii*), associated with negatively charged phospholipid containing monolayer through electrostatic, hydrophobic interactions under acidic conditions (low pH), altering the charge of some residues, which is accompanied by salt-bridge breakage and charge to charge repulsion. This is followed by partial denaturation of TCS into a molten globular state, thus entering the host cell (Puri et al. 2012).

The process of protein synthesis inhibition is similar to that of any Type-I RIP. The RIP-II, is group of proteins is highly toxic. It is a heterodimeric carbohydrate-binding protein composed of 2 chains, A and B, held together by a disulfide bond. It has a molecular weight of 56–69 kDa, with each chain having a molecular weight of about 30 kDa (Girish et al. 2006). The A-chain exhibits vital N-glycosidase activity. The B-chain enables RIP-II to attach to the particular carbohydrate-containing cell receptors, as it has a strong affinity for carbohydrate moieties. This, in turn, leads to the migration of chain A across the cell membrane (Stirpe 2004). The entry process into cells for RIP-II is highly different from RIP-I because the latter lacks B-chain, which plays a vital role in its internalization process. Ricin (extracted from *Ricinus communis*) as almost all the Type-II RIPs are analogous to ricin, which has a well-identified for their mode of action (Puri et al. 2012). Binding to a particular receptor on the host cell membrane through the B-chain, ricin enters the cell either by clathrin-dependent or clathrin-independent endocytosis resulting in the origin of ricin containing endosomal vacuole (Puri et al. 2012). Eventually, ricin enters the trans-golgi network in COP-I vesicles. It is delivered to the early endosomes, either recycled by returning it to the cell surface or undergoes proteolytic degradation by the lysosome, finally reaching the E.R. lumen (Fujimura et al. 2004; Gustafson et al. 2000). The disulfide bond joining the two chains is degraded within the E.R. lumen, letting the remaining ricin transported by Endoplasmic Reticulum Associated Degradation (ERAD-Pathway for degradation of misfolded proteins) to the cytoplasm (Fujimura et al. 2004; Gustafson et al. 2000). Almost most of the toxin is degraded by 26s proteasome, leaving behind only a small portion that influences protein synthesis (Puri et al. 2012). Additionally, another class of RIP is not universal-Type-III RIPs. They show similar enzymatic activity to RIP-I as they have an identical N-terminal domain bound to the carboxyl domain with an unestablished function. Moreover, they are always synthesized in an inactive form (Girish et al. 2006). In the present scenario, in-depth research on RIPs has been encouraged due to their miscellaneous biological involvement in viral, HIV, and microbial infections (Pizzo and di Maro 2016).

RIPs have been coupled to specific antibodies to generate immunoconjugates in cancer and HIV therapy by targeting a specific cell due to their ability to hydrolyze N-glycosidase bond (Pizzo and di Maro 2016). Anti CD4-PAP is an immunoconjugate created by combining PAP with an antibody that targets HIV-infected CD4 T-cells and prevents HIV infection (Irvin and Uckun 1992). Another example is B43-PAP (anti-CD19 pokeweed antiviral protein), an

immunotoxin made by combining B43 [an antibody-targeting CD19 antigen found on B-lineage acute lymphoblastic leukemia (ALL) cells] and PAP (Irvin and Uckun 1992). Alpha-momorcharin (0.12 nM), beta-momorcharin (0.11 nM), MAP30, balsamin, isomers of luffin (a—1.64 ng/ml and b—0.84 ng/ml), ricin (814 pM), abrin (500 pM), and other plant RIPs with extremely low IC_{50} values have been isolated. Cell-Free Protein Synthesis (CFPS-growing in vitro) has been demonstrated to be inhibited by these RIPs (Puri et al. 2012). Despite having many RIPs, only a minority have been fully identified. Therefore, the main challenge arises in exploring and identifying some potent plant RIPs with high therapeutic efficiency and less toxicity. The available ribosome-inactivating peptides are listed in Table 5.

Anti-carcinogenic activity of plant peptides/proteins

One of the causes of death in recent times is the various types of cancer. Cancer caused due to genetic effects is 5-10%, but almost 90-95 % of the cancers are caused due to the environment and lifestyle changes. Bioactive plant peptides can be used to cure cancer. Plant peptides prevent the proliferation of cancerous cells and cause their death-apoptosis (Hernandez-Ledesma and Hsieh 2017). A study conducted by Kannan et al. (2010) on *Oryza sativa*—heat stabilized defatted rice bran showed that when treated with alcalase (protease), peptide hydrolysates were produced, which are less than 5 kDa. This peptide hydrolysate was subjected to ion-exchange chromatography followed by an MTS assay. The peptide at 1000 µg/ml could show the highest inhibition for the colon and liver cancer cells for up to 84 %. This study further analysed for the amino acid composition from the peptide, and it was found that the peptide contains arginine, proline, and glutamic acid. The peptide chain was found to be glutamate-glutamine-arginine-proline-arginine, a short pentapeptide sequence. The peptide showed anti-proliferative effects on cancer cells. A peptide that prevents cancer is found in *Glycine max* (soybean), *Triticum aestivum* (wheat), *Hordeum vulgare* (barley) is called lunasin. Lunasin is an effective anticancer agent consisting of 43 amino acids. It has a presence of 8 aspartate residues in the C terminal; they are responsible for opposing mitosis, they play a role in the attachment of lunasin to chromatin. The amino acids arginine-glycine-aspartate are called cell adhesion motif they internalize lunasin into the cell's nucleus. The amino acids 23–31 target the lunasin to H3–H4 histones in DNA.

In vivo mouse models were used to check the effects of lunasin on cancer cells. Lunasin was also found in *Amaranthus hypochondriacs*. Lunasin obtained from soybean could be taken orally as it is resistant to enzymes present in our body like pepsin and pancreatin. This property of lunasin makes it an ideal plant peptide that could cure the cancer. The amount of lunasin found was 4.4–70.5 mg lunasin/g of protein in *Glycine max*, the highest among the other plants like wheat and barley (Hernandez-Ledesma *et al*. 2009). A study was conducted by Ma et al. (2015) on *Juglans regia L* (walnut). The walnut protein was treated with different proteases, followed by purification steps to obtain the pure peptide. The peptide was further subjected to its anti-cancer activity on cells. The walnut protein hydrolyzed with papain exhibited inhibitory actions on the MCF-7 cell line (human breast cancer cell line). The peptide was found to be cysteine-threonine-leucine-glutamate-tryptophan. This peptide CTLEW induces the process of apoptosis and autophagy. The reported anti-carcinogenic proteins are listed in Table 6.

Plant Peptides for Drug Design

Rational drug design is the process of designing drug molecules that bind to a target. Cyclotides are a new type of microproteins with a unique topology that includes a head-to-tail cyclized backbone structure that is further stabilised by three disulfide bonds that form a cystine knot. They are disulphide rich peptides and their basic function is plant defence. When compared to linear peptides of equal size, they have a unique molecular architecture that renders them extremely resistant to physical, chemical, and biological destruction. Apart from the conserved regions composing the cystine knot, the cyclotides are orally accessible and able to traverse cellular membranes to alter intracellular protein–protein interactions (PPIs) in vitro and in vivo. They are ideal scaffolds for numerous biotechnological applications, including drug development, because to their unique characteristics (Camarero and Campbell 2019). It does not involve trial and error like traditional drug design. The cyclotide sequences are updated on Cybase regularly. The example, plant cyclotide used is Kalakata B1, the peptide sequence is converted to cyclotide scaffold because of the cysteine knot. Grafting of sequences from myelin oligodendrocyte glycoprotein (MOG) into kalakata B1 has been used to design drugs for multiple sclerosis (Craik and Du 2017). By applying molecular grafting of bioactive epitopes or even molecular evolution methods, it is possible to create cyclotides with unique biological properties. Cyclotides which can target a wide range of protein targets have been developed and evaluated using these methods, largely in vitro but also in animal models. Despite the early success of using the cyclotide scaffold to target specific proteins and modify their biological activity, no cyclotides have yet been tested in humans. Potential immunogenicity and oral bioavailability are two obstacles that bioactive cyclotides must overcome before entering the clinic. More research into the biopharmaceutical properties of these fascinating new micro-proteins

Table 5 List of ribosome-inactivating proteins from plants

S. No	Plant and its part	Protein	Nature	M. Wt. (kDa)	Class of RIP	Mode of action	*IC_{50}	References
1	*Momordica balsamina* (Seeds)	Balsamin	Protein	28	RIP-I	28S rRNA depurination with the liberation of RNA fragment of about 400 nucleotides	90.6 ng/ml	Kaur et al. (2012)
2	*Cucurbita foetidissima* (Root)	Foetidissimin	Protein	63	RIP-II	28S rRNA depurination with the liberation of RNA fragment of about 550 nucleotides	25.9 nM	Zhang and Halaweish (2003)
		Foetidissimin II		61		28S rRNA depurination with the liberation of RNA fragment of about 450 nucleotides	0.251 µM	Zhang and Halaweish (2007)
3	*Cucurbita texana*	Texanin (Fruit)	Protein	29.7	RIP-I	28S rRNA depurination	NA	Zhang and Halaweish (2007)
		ME2 (Roots)	Protein	27.5		NA		Vivanco et al. (1999)
4	*Abrus precatorius* (Seeds)	AGG	Heterodimeric lectin	134	RIP-II	28S rRNA depurination	0.469 µg/ml	Bhutia et al. (2016)
		Abrin	Homotetrameric protein	260			500 pM	Ferreras et al. (2011)
5	*Viscum album* L. (Green Parts)	Viscum	Heterodimeric protein	60	RIP-II	28S rRNA depurination	NA	Olsnes et al. (1982)
6	*Amaranthus viridis* L. (Leaves)	Amaranthin	Protein	30	RIP-I	28S rRNA depurination	25 pM	Kwon et al. (1997)
7	*Beta vulgaris L.* (Leaves)	Beetin-27	Protein	27.59	RIP I	28S rRNA depurination	1.15 ng/ml	Iglesias et al. (2005)
8	*Citrullus colocynthis* (L.) Schrad (Seeds)	Colocin 1	Protein	26.3	RIP-I	28S rRNA depurination	0.04 nM	Bolognesi et al. (1990)
		Colocin 2					0.13 nM	
9	*Marah oreganus* (Seeds)	MOR-I	Protein	27.98	RIP-I	28S rRNA depurination	0.063 nM	Remi Shih et al. (1998)
		MOR-II		27.63			0.071 nM	
10	*Momordica charantia* L. (Seeds)	MCL	Heterotetrameric lectin	115	RIP-II	28S rRNA depurination	5 µg/ml	Puri et al. (2012)
		α-momorcharin	Protein	28	RIP-I		0.12 nM	
		β-momorcharin		29	RIP-I		0.11 nM	
		MAP30		30	RIP-I		3.3 nM	
		γ-momorcharin		11.5	sRIP-I		55 nM	
		δ-momorcharin		30	RIP-I		0.15 nM	
11	*Trichosanthes kirilowii* Maxim	TCS(GLQ223) (Seeds)	Protein	26	RIP-I	28S rRNA depurination	0.36 ng/ml (3.7 nM)	Lee-Huang et al. (1991a); Schrot et al. (2015)

Table 5 (continued)

S. No	Plant and its part	Protein	Nature	M. Wt. (kDa)	Class of RIP	Mode of action	*IC_{50}	References
		TAP 29 (Root tubers)		29	RIP-I		3.7 nM	Lee-Huang et al. (1991a)
		Trichosanthrip (Seeds)		10.96	sRIP-I		1.6 ng/ml	Shu et al. (2009)
		α-kirilowin (Seeds)		28.8	RIP-I	NA	1.2–1.8 ng/ml	Wong et al. (1996)
		β-kirilowin (Seeds)		27.5	RIP-I		1.8 ng/ml	
12	*Basella rubra L.* (Seeds)	*Basella* RIP 2a protein fraction	Protein	30.6	RIP-I	NA	1.70 ng/ml	Bolognesi et al. (1997)
		Basella RIP 2b protein fraction		31.2			1.70 ng/ml	
		Basella RIP 3		31.2			1.66 ng/ml	
13	*Saponaria ocymoides L.* (Seeds)	Ocymoidin	Protein	30.2	RIP-I	28S rRNA depurination	46 pM; 4.8 ng/ml	Bolognesi et al. (1995), di Massimo et al. (1997)
14	*Secale cereale* (Seeds)	RPSI (Seeds)	Protein	30.1	RIP-I	NA	0.42 µg/ml	Minami et al. (1998)
15	*Phytolacca americana* L	PAP (Leaves)	Protein	29–30	RIP-I	28S rRNA depurination	0.29 nM	Irvin and Uckun (1992), Poyet and Hoeveler (1997)
		PAP-I (Leaves)		29			3 ± 0.2 pM	Rajamohan et al. (1999)
		PAP-II (Leaves)		30			4 ± 0.2 pM	
		PAP-III (Leaves)		30			3 ± 0.2 pM	
		PAP-S (Seeds)		30			36–83 nM; 1.09 -2.5 ng/ml	Barbieri et al. (1982)
		PAP-R (Roots)		25.0			0.05 nM	Stirpe et al. (1986)
16	*Trichosanthes lepiniate* (Root tuber)	Trichomaglin	Protein	24.6	RIP-I	28S rRNA depurination	10.1 nM	Chen et al. (1999)
17	*Iris hollandica* var. Professor Blaauw (Bulbs)	IrisRIP	Protein	28	RIP-I	28S rRNA depurination	0.1–0.16 nM	Desmyter et al. (2003)
		IrisRIP.A1		29			0.16 nM	van Damme et al. (1997)
		IrisRIP.A2		29			0.12 nM	
		IrisRIP.A3		29			0.10 nM	
18	*Viscum album* L. (Leaves)	ML-I	Heterodimeric lectin	115	RIP-II	NA	2.6 µg/mL	Stirpe et al. (1980)
19	*Momordica grosvenorii* (Seeds)	Momorgrosvin	Glycoprotein	27.7	RIP-I	NA	0.3 nM	Tsang and Ng (2001)
20	*Pisum sativum var. arvense Poir* (Seeds)	α pisavins	Protein	20.5	RIP-I	NA	0.5 nM	Lam et al. (1998)
		β pisavins		18.7				
21	*Vaccaria pyramidata* (Seeds)	Pyramidatine	Protein	28.0	RIP-I	28S rRNA depurination	3.6 ng/ml	di Massimo et al. (1997)

Table 5 (continued)

S. No	Plant and its part	Protein	Nature	M. Wt. (kDa)	Class of RIP	Mode of action	*IC_{50}	References
22	*Cinnamomum porrectum* (Seeds)	Porrectin	Glycoproteins	64.5	RIP-II	28S rRNA depurination	0.11 µM	Li et al. (1996)
23	*Cicer arietinum* (Seeds)	CLAP	Protein	18	–	NA	20 µM	Ye and Ng (2002a)
24	*Phaseolus mungo* (Seeds)	Mungin	Protein	18	–	NA	24 µM	Ye and Ng (2000)
25	*Adzuckia angularia* (Seeds)	Fraction AB2	Peptide	5	–	NA	11 µM	Ye and Ng (2001)
26	*Phaseolus vulgaris* (Seeds)	Fraction PTA2c	Peptide	5	–	NA	9 µM	Ye and Ng (2001)
27	*Dianthus caryophyllus* (Leaves)	DAPs 30	Protein	30	RIP-I	28S rRNAdepurination	3.4 nM	Lee-Huang et al. (1991b)
		DAPs 32		32			2.3 nM	
28	*Gelonium multiflorum* (Seeds)	GAP 31	Protein	31	RIP-I	28S rRNAdepurination	4.1 nM	Lee-Huang et al. (1991b)
29	*Asparagus officinali* (Seeds)	Asparin 1	Protein	30.5	RIP-I	NA	0.27 nM	Bolognesi et al. (1990)
		Asparin 2		29.8			0.15 nM	
30	*Luffa cylindria*Roem (Seeds)	Luffin	Protein	26	RIP-I	NA	0.42 ng/ml	Kishida et al. (1983)
		Luffin a		28			1.64 ng/ml	Ng et al. (1992b); Schrot et al. (2015)
		Luffin b		29			0.84 ng/ml	
31	*Lychnis chalcedonica* (Seeds)	Lychnin	Protein	26.6	RIP-I	NA	0.17 nM	Bolognesi et al. (1990)
32	*Manihot palmata* (Seeds)	Mapalmin	Protein	32.3	RIP-I	NA	0.05 nM	Bolognesi et al. (1990)
33	*Bryonia dioica*	Bryodin-L (Leaves)	Protein	28.8	RIP-I	NA	0.09 nM	Bolognesi et al. (1990)
		Bryodin (Roots)		30			0.12 nM	Stirpe et al. (1986)
34	*Ricinus communis*.L (Seeds)	Ricin D = Ricin	Glycoprotein	62.8	RIP-II	28S rRNAdepurination	5.5 ng/ml; 814 pM	Battelli et al. (1997), Endo and Tsurugi (1987), Schrot et al. (2015), Wei and Koh (1978)
		Ricin E		64			NA	Schrot et al. (2015)
		RCA		118–130			NA	
35	*Ricinus commnis*.L USA (Seeds)	Ricin 1	Glycoprotein	66	RIP-II	28S rRNAdepurination	NA	
		Ricin 2						
		Ricin 3						

Table 5 (continued)

S. No	Plant and its part	Protein	Nature	M. Wt. (kDa)	Class of RIP	Mode of action	*IC_{50}	References
36	*Ricinus communis*, India (Seeds)	Ricin I	Glycoprotein	64	RIP-II	28S rRNAdepurination	NA	
		Ricin II						
		Ricin III						
37	*Trichosanthes cucumeroides* (Ser.) Maxim (Root tubers)	β-TCS	Protein	28	RIP-I	28S rRNAdepurination	2.8 ng/ml; 0.1 nM	Ng et al. (1992a); No et al. (1991); Yeung and Li (1987)
38	*Saponaria officinalis* L	Saporin-L1 (Leaves)	Protein	31.6	RIP-I	28S rRNAdepurination	0.25 nM	Ferreras et al. (1993)
		Saporin-L2 (Leaves)		31.6			0.54 nM	
		Saporin-R1 (Roots)		30.2			0.86 nM	
		Saporin-R2 (Roots)		30.9			0.47 nM	
		Saporin-R3 (Roots)		30.9			0.48 nM	
		Saporin-S5 (Seeds)		30.9			0.05 nM	
		Saporin-S6 (Seeds)		31.6			0.06 nM	
39	*Phaseolus vulgaris* (Seeds)	Vulgarinin	Peptide	7	–	NA	13 µM	Wong and Ng (2005c)
40	*Adenia digitata* (Roots)	Modeccin	Protein	57–63	RIP-II	28S rRNAdepurination	4 µg/ml	Olsnes et al. (1978); Schrot et al. (2015)
		Modeccin 6B		57			0.31 µg/ml	Barbieri et al. (1980)
41	*Panax ginseng* (Roots)	Panaxagin	Homodimeric protein	53	–	NA	0.28 nM	Ng and Wang (2001)
42	*Allium tuberosum* (Shoot)	Fraction MS3	Protein	36	–	NA	850 nM	Lam et al. (2000)

IC_{50} Concentration causing 50% inhibition, *ND* Not determined, *NA* Not available, *CAP30 Chenopodium album* antiviral RIP, *RPSI* Rye protein synthesis inhibitor, *PAP* Pokeweed antiviral protein, *IrisRIP = IRIP* Type-1 ribosome-inactivating protein from iris bulbs, *CLAP* Chickpea cyclophilin-like antifungal protein, *Fraction AB2* Red bean antifungal peptide, *Fraction PTA2c* Pinto bean antifungal peptide, *DAPs 30* Dianthus anti-HIV proteins, *GAP 31* Gelonium anti-HIV protein, *RCA* *Ricinus communis* agglutinin, *TAP 29* Trichosanthes anti-HIV protein, *β-TCS* β-trichosanthin

Table 6 List of anti-carcinogenic peptides/proteins from plants

S. No	Plant and its part	Protein	Nature	Sequence	Mode of action	M. Wt. (kDa)	*IC_{50}	References
1	*Acacia confuse* (Seeds)	Acaconin	Protein			32	128 ± 9 µM	Lam and Ng (2010)
2	*Clausena lansium* (Lour) (Seeds)	CLTI	Homodimeric protein	DPLLDFPGNEVEAS-RAYYVVSVIRGAG	Prevents the growth of human hepatoma cells and leukemia cells	54	100 µM	Ng et al. (2003)
							NA	
3	*Momordica charantia* (Seeds)	BG-4	Peptide	RDSDCLAQCICVDGHCG	Apoptosis of human colon cancer cells	4	134.4 µg/ml	Dia and Krishnan (2016)
							217.0 µg/ml	
		MAP 30	RIP-I	–	Apoptosis in liver cancer cells	30	28.6 µM	Fang et al. (2012b)
		MCL	Lectin (RIP-II)	–	Antitumor activity toward human nasopharyngeal carcinoma cells	115	6.9 µM	Fang et al. (2012a)
							7.4 µM	
		α-MMC	RIP-I	–	–	28	NA	Fan et al. (2015)
4	*Castanopsis chinensis* (Seeds)	CCL	Homotetrameric lectin	NFEETILGSK	Prevents growth of HepG2 cells	120	NA	Wong et al. (2008)
5	*Phaseolus lunatus* (Seeds)	Lunatusin	Peptide	KTCENLADTFRGPC-FATSNC	Inhibits growth of MCF-7, breast cancer cell line	7	5.71 µM	Wong and Ng (2005a)
6	*Vigna sesquipedalis* (Seeds)	Sesquin	Peptide	KTCENLADTY	Anti tumour activity	7	NA	Wong and Ng (2005b)
7	*Phaseolus coccineus cv. 'Major'* (Seeds)	Coccinin	Peptide	KQTENLADTY	Prevents proliferation in leukemia cell lines	7	30 µM	Ngai and Ng (2004)
							40 µM	
8	*Arachis hypogaea* (Seeds)	Hypotin	Protein	CDVGSVISASLFE-ALQKHRN	Anti-proliferative activity	30.4	296 µg/ml	Wang et al. (2007)
9	*Cicer arietinum* (Seeds)	C-25	Lectin	TKTGYINAAF	Anti-proliferative activity	25	37.5 µg/ml	Kumar et al. (2014)
10	*Corydalis cava* (Tubers)	Fraction 18	Protein	–	Prevents the growth of human carcinoma cells	30	NA	Nawrot et al. (2010)
11	*Arisaema tortuosum Schott* (Tubers)	ATL	Homotetrameric lectin	–	–	54	NA	Dhuna et al. (2005)

Table 6 (continued)

S. No	Plant and its part	Protein	Nature	Sequence	Mode of action	M. Wt. (kDa)	*IC_{50}	References
12	*Phaseolus vulgaris cv.* Blue tiger king (Seeds)	BTKL	Dimeric lectin	–	–	60	35.2 ± 2.7 µM	Fang et al. (2011b)
							347.9 ± 24.5 µM	
							494.6 ± 70.4 µM	
13	*Canavalia ensiformis* (Seeds)	Con A	Homotetraeric lectin	–	Anti-hepatoma effect	104	5 µg/ml	Lei and Chang (2009), Liu et al. (2009)
							10 µg/ml	
							10 µg/ml	
							20 µg/ml	
							NA	
14	*Withania somnifera* (Fruit)	Asparginase	Homodimeric protein	–	Anti-tumour activity	72 ± 0.5	1.45 ± 0.05 IU/ml	Oza et al. (2010)
15	*Glycine max* (Seeds)	BBI	Peptide	–	Colorectal chemopreventive agents	8	32 to 73 µM	Clemente and del Carmen Arques (2014); Kennedy (1998)
							NA	
							NA	
		IBB1	Protein	DDESSKPCCDQCACTKSNPPQCRCSDMRLNSCHSACKSCICALSYPAQCFCVDITDFCYEPCKPSEDDKEN	Colorectal chemopreventive agents	10–12	39.9 ± 2.3 µM	Clemente et al. (2010)
		IBBD2	Protein	SDQSSSYDDDEYSKPCCDLCMCTRSMPPQCSCEDIRLNSCHSDCKSCMCTRSQPGQCRCLDTNDFCYKPCKSRDD	colorectal chemopreventive agents	10–12	48.3 ± 3.5 µM	
16	*Abrus precatorius* (Seeds)	Abrin	Homotetrameric protein			260	3.70 pM	Lin et al. (1971); Olsnes and Pihl (1973)
		AGG	Heterodimeric glycoprotein			134	NA	Bhutia et al. (2016); Mukhopadhyay et al. (2014)
17	*Trichosanthes* kirilowi*i* (Root Tuber)	TCS	Protein			26–27	31.6 µM	Fang et al. (2012c)
							20.5 µM	
							130 µM	
							28.6 µM	

Table 6 (continued)

S. No	Plant and its part	Protein	Nature	Sequence	Mode of action	M. Wt. (kDa)	*IC_{50}	References
							NA	Tsao et al. (1986)
18	*Gynura procumbens (Lour.)* Merr. (Leaves)	SN-F11/12	Mixture of proteins			25	3.8 µg/ml	Hew et al. (2013)
19	*Allium sativum* (Bulbs)	Alliumin	Protein			13	8.33 µM	Xia and Ng (2005)
20	*Cucurbita foetidissima* (Roots)	Foetidissimin II	Proteins			61	70 nM	Zhang and Halaweish (2007)
							70 nM	
21	*Viola arvensis* (Whole plant)	Varv A	Macrocyclic peptides			2.87	3.56 µM	Lindholm et al. (2002)
							1.34 µM	
							4.88 µM	
							11.03 µM	
							3.24 µM	
							3.19 µM	
							6.35 µM	
		Varv F	Macrocyclic peptides			2.95	7.13 µM	
							7.49 µM	
							7.07 µM	
							5.90 µM	
							6.31 µM	
							NA	
22	*Viola odorata* (Whole plant)	Cycloviolacin O2	Macrocyclic peptides			3.14	0.11 µM	Lindholm et al. (2002)
							0.12 µM	
							0.26 µM	
							0.12 µM	
							0.12 µM	
							0.10 µM	
							1.32 µM	
23	*Viola biflora* (Aerial parts)	Vibi D	Macrocyclic peptides			2.9	> 30 µM	Herrmann et al. (2008)
		Vibi E				3.08	3.2 µM	
		Vibi G				3.2	0.96 µM	
		Vibi H				3.27	1.6 µM	

Table 6 (continued)

S. No	Plant and its part	Protein	Nature	Sequence	Mode of action	M. Wt. (kDa)	*IC_{50}	References
24	*Viola philippica* (Whole plant)	Viphi A	Macrocyclic peptides			3.17	4.91 ± 0.04 µM	He et al. (2011)
							15.5 ± 0.06 µM	
							1.75 ± 0.05 µM	
		Viphi B				2.98	NA	
		Viphi C				3.05	NA	
		Viphi D				3.08	2.51 ± 0.03 µM	
							5.24 ± 0.40 µM	
							NA	
		Viphi E				3.15	2.51 ± 0.03 µM	
							5.24 ± 0.40 µM	
							NA	
		Viphi F				3.14	1.03 ± 0.03 µM	
							6.35 ± 0.31 µM	
							2.91 ± 0.06 µM	
		Viphi G				3.17	1.03 ± 0.03 µM	
							6.35 ± 0.31 µM	
							2.91 ± 0.06 µM	
		Viphi H				3.09	NA	
		Viba 15				2.86	1.32 ± 0.15 µM	
							10.2 ± 0.43 µM	
							3.10 ± 0.06 µM	
		Viba17				2.84	1.32 ± 0.15 µM	
							10.2 ± 0.43 µM	
							3.10 ± 0.06 µM	
		Varv A				2.87	1.32 ± 0.15 µM	
							10.2 ± 0.43 µM	
							3.10 ± 0.06 µM	
		Kalata B1				2.89	1.32 ± 0.15 µM	
							10.2 ± 0.43 µM	
							3.10 ± 0.06 µM	
25	*Viola labridorica* (Whole Plant)	Vila A	Macrocyclic peptides			3.16	7.08 µg/ml	Tang et al. (2010a)
							5.13 µg/ml	
							> 10 µg/ml	
							5.08 µg/ml	

Table 6 (continued)

S. No	Plant and its part	Protein	Nature	Sequence	Mode of action	M. Wt. (kDa)	*IC_{50}	References
							5.80 µg/ml	
							> 10 µg/ml	
		Vila B	Macrocyclic peptides			3.16	34.65 µg/ml	
							8.25 µg/ml	
							> 10 µg/ml	
							6.34 µg/ml	
							6.25 µg/ml	
							> 10 µg/ml	
		Vila D	Macrocyclic peptides			2.94	49.59 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
		Varv D	Macrocyclic peptides			2.87	46.62 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
26	*Psychotria leptothyrsa* (Whole Plant)	Psyle A	Macrocyclic peptides			2.91	26 µM	Gerlach et al. (2010)
							NA	
		Psyle B	Macrocyclic peptides			.01	NA	
		Psyle C	Linear cyclotide			2.84	3.5 µM	
							NA	
		Psyle D	Macrocyclic peptides			3.25	NA	
		Psyle E	Macrocyclic peptides			3.25	0.76 µM	
							NA	
		Psyle F	Macrocyclic peptides			3.21	NA	
27	*Viola abyssinica* (Whole Plant)	Vaby A	Macrocyclic peptides			2.86	7.6 µM	Yeshak et al. (2011)
		Vaby D	Macrocyclic peptides			3.06	2.8 µM	
28	*Viola tricolor* (Whole Plant)	Varv A	Macrocyclic peptides			2.87	3 µM	Tang et al. (2010b)
							6 µM	

Table 6 (continued)

S. No	Plant and its part	Protein	Nature	Sequence	Mode of action	M. Wt. (kDa)	*IC_{50}	References
							37.18 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
		Varv D	Macrocyclic peptides			2.87	NA	
							46.62 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
		Varv E	Macrocyclic peptides			2.99	4 µM	
							4 µM	
							38.84 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
		Varv F	Macrocyclic peptides			2.95	6 µM	
							7 µM	
							44.49 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
		Varv H	Macrocyclic peptides			3.05	NA	
							44.70 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
		Varv He	Macrocyclic peptides			3.08	NA	
							55.43 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	

Table 6 (continued)

S. No	Plant and its part	Protein	Nature	Sequence	Mode of action	M. Wt. (kDa)	*IC_{50}	References
							> 10 µg/ml	
		Varv Hm	Macrocyclic peptides			3.06	NA	
							74.39 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
		Vitri A	Macrocyclic peptides			3.15	3.90 µg/ml	
							4.94 µg/ml	
							3.07 µg/ml	
							3.69 µg/ml	
							NA	
							6.03 µg/ml	
							NA	
		Vitri B	Macrocyclic peptides			2.87	> 10 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
							NA	
							45.21 µg/ml	
							NA	
		Vitri C	Macrocyclic peptides			2.96	> 10 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
							NA	
							46.96 µg/ml	
							NA	
		Vitri D	Macrocyclic peptides			3.04	> 10 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
							NA	
							51.65 µg/ml	
							NA	
		Vitri E	Macrocyclic peptides			2.92	> 10 µg/ml	

Table 6 (continued)

S. No	Plant and its part	Protein	Nature	Sequence	Mode of action	M. Wt. (kDa)	*IC_{50}	References
							> 10 µg/ml	
							> 10 µg/ml	
							> 10 µg/ml	
							NA	
							54.39 µg/ml	
							NA	
		Vitri F	Macrocyclic peptides			3.21	3.58 µg/ml	
							5.36 µg/ml	
							3.44 µg/ml	
							2.74 µg/ml	
							6.31 µg/ml	
29	*Vicia faba cv. Giza 843* (Seeds)	VFTI-G1	Protein			15	30 µM	Fang et al. (2011a)
30	*Asparagus officinalis* (Seeds)	Asparin 1	Protein			29.7	> 3.33 µM	Bolognesi et al. (1990)
							0.61 µM	
							0.18 µM	
							> 3.33 µM	
							NA	
		Asparin 2	Protein			28.1	> 3.33 µM	
							0.21 µM	
							0.18 µM	
							> 3.33 µM	
							NA	
31	*Citrullus colocynthis* (Seeds)	Colocin 1	Glycoprotein			20.4	> 3.33 µM	
							0.54 µM	
							0.01 µM	
							0.32 µM	
							0.23 µM	
		Colocin 2	Glycoprotein			19.5	1.41 µM	
							0.25 µM	
							0.004 µM	
							0.14 µM	
							0.10 µM	
32	*Lychnis chalcedonica* (Seeds)	Lychnin	Glycoprotein			20.0	> 3.33 µM	

Table 6 (continued)

S. No	Plant and its part	Protein	Nature	Sequence	Mode of action	M. Wt. (kDa)	*IC_{50}	References
							2.11 µM	
							0.03 µM	
							1.53 µM	
							0.33 µM	
33	*Manihot palmata* (Seeds)	Mapalmin	Glycoprotein			26.9	> 3.33 µM	
							1.68 µM	
							0.03 µM	
							1.64 µM	
							0.08 µM	
34	*Bryonia dioica*	Bryodin-L (Leaves)	Glycoprotein			27.3	> 3.33 µM	
							0.77 µM	
							0.05 µM	
							> 3.33 µM	
							NA	
		Bryodin (Roots)	Glycoprotein			30	0.86 µM	Stirpe et al. (1986)
							0.90 µM	
							0.15 µM	
							2.24 µM	
							1.01 µM	
35	*Bauhinia variegate var. variegate* (Seeds)	BvvL	Homodimeric lectin			64	12.8 µM	Chan and Ng (2015)
	Bauhinia variegate (Seeds)	BG2	Homodimeric lectin				1.4 µM	Lin and Ng (2008)
							0.18 µM	
36	*Dioclea lasiocarpa* (Seeds)	DlasiL	Homotetrameric lectin				52 ± 2 nM	Gondim et al. (2017)
							224 ± 10 nM	
							275 ± 4 nM	
							167 ± 1 nM	
37	*Lens culinaris* (Seeds)	Bowman-Birk Isoinhibitor	Peptide			7.5	32 ± 2 µM	Caccialupi et al. (2010)
38	*Pisum Sativum* (Seeds)	TI1B	Peptide			7.9	31 µM	Clemente et al. (2012)
39	*Canavalia brasiliensis* (Seeds)	ConBr	Lectin			30	108 ± 14 nM	Grangeiro et al. (1997)

Table 6 (continued)

S. No	Plant and its part	Protein	Nature	Sequence	Mode of action	M. Wt. (kDa)	*IC_{50}	References
							95 ± 14 nM	
							1146 ± 24 nM	
							529 ± 8 nM	
40	*Canavalia maritima* (Seeds)	ConM	Tetrameric lectin			102	67 ± 2 nM	Delatorre et al. (2006)
							62 ± 4 nM	
							1382 ± 17 nM	
							176 ± 2 nM	
41	*Dioclea sclerocarpa* (Seeds)	DsclerL	Lectin		Anti-cancer	50.8	64 ± 4 nM	Gondim et al. (2017)
							102 ± 8 nM	
							1250 ± 9 nM	
							264 ± 1 nM	
42	*Aspidistra elatior Blume* (Rhizomes)	AEL	Heterotetramer lectin			56	NA	Xu et al. (2007)
43	*Soybean* (Cotyledon)	Lunasin	Peptide	MTKFTILLIS LLFCI-AHTCS		5.5	181 µM	Hernandez-Ledesma et al. (2013)
							14 µM	
							62 µM	
44	*Saponaria officinalis* L	Saporin-L1 (Leaves)	Protein	MKSWIMLVVT WLIILQT-TVT	–	31.6	> 3300 nM	Ferreras et al. (1993)
							120 nM	
							13 nM	
		Saporin-L2 (Leaves)	Protein	–		31.6	> 3300 nM	
							160 nM	
							25 nM	
		Saporin-R1 (Roots)	Protein	–		30.2	340 nM	
							490 nM	
							76 nM	
		Saporin-R2 (Roots)	Protein	–		30.9	170 nM	
							230 nM	
							33 nM	
		Saporin-R3 (Roots)	Protein	–		30.9	3200 nM	
							84 nM	
							34 nM	
		Saporin-S5 (Seeds)	Protein	–		30.9	420 nM	
							7 nM	

Table 6 (continued)

S. No	Plant and its part	Protein	Nature	Sequence	Mode of action	M. Wt. (kDa)	*IC_{50}	References
							2 nM	
		Saporin-S6 (Seeds)	Protein	–		31.6	310 nM	
							18 nM	
							6 nM	
45	*Ricinus communis* (Seeds)	Ricin	Protein			64	34.1 ng/ml	Trung et al. (2016)
46	*Basella rubra L.* (Seeds)	Basella RIP 2	Mixture of two proteins			30.6–31.2	63.7 ± 15.6 nM	Bolognesi et al. (1997)
							166 ± 24 nM	
							16.6 ± 3.7 nM	
							169 ± 87 nM	
							353 ± 5.7 nM	
		Basella RIP 3	Protein			31.2	43.8 ± 9.2 nM	
							315 ± 25 nM	
							9.3 ± 0 nM	
							110 ± 75 nM	
							700 ± 369 nM	
47	*Vaccaria pyramidata* (Seeds)	Pyramidatine	Protein			28.0	6.3 nM	Bolognesi et al. (1995)
							179 nM	
							142 nM	
							5.7 nM	
							4.3 nM	
48	*Saponaria ocymoides* L. (Seeds)	Ocymoidin	Protein			30.2	11.7 nM	
							493 nM	
							> 3330 nM	
							9.3 nM	
							8.7 nM	
49	*Viscum album* L. var. coloratum (Arial parts)	VCA	Heterodimeric lectin	–	Anti-tumour	60	125 ng/ml	Han et al. (2015)
							125 ng/ml	
50	*Viscum album* L. (N.A.)	ML-I	Heterodimeric lectin			115	NA	Franz et al. (1981)
							7 ng/ml	
		ML-II	Heterodimeric lectin			60	NA	

Table 6 (continued)

S. No	Plant and its part	Protein	Nature	Sequence	Mode of action	M. Wt. (kDa)	*IC_{50}	References
		ML-III	Heterodimeric lectin			50	NA	
51	*Dianthus superbus*-var longicalycinus (Whole Plant)	Longicalycinin A	Cyclic peptide	Cyclo(Gly1–Phe2–Tyr3–Pro4–Phe5–	Cytotoxic to HepG2 cancer cell line	0.611	13.52 µg/ml	Hsieh et al. (2005)
52	*Phaseolus vulgaris* (Seeds)	Vulgarinin	Peptide	K T CENLADTYKGP CFTS G GD	Inhibition of proliferation in leukemia cell lines	7	NA	Wong and Ng (2005c)
53	*Brassica juncea* var. *Integrifolia* (Seeds)	Juncin	Protein	–	–	18.9	5.6 µM	Kwon et al. (1997)
							6.4 µM	
54	*Peganum harmala*(Seeds)	PHP	Homodimeric protein	ITCPQVTQSLAP-CVPYLISG	Anti-proliferative activity against cancer cells	18	0.7 µM	Ma et al. (2013)
							2.74 µM	
							3.13 µM	
							1.47 µM	
55	*Allium tuberosum* (Shoot)	Fraction MS3	Protein	–	–	36	NA	Lam et al. (2000)
56	*Zingiber officinalis* (Rhizome)	G-24	Protein	–	Inhibition of human oral cancer cell line	24	NA	Gill et al. (2012)

*IC_{50} Concentration causing 50% inhibition, *ND* Not determined, *NA* Not available, *CLTI* *Clausena lansium* trypsin inhibitor, *VFTI-G1* Bowman birk type trypsin inhibitor, *BG-4* Bitter gourd-4, *MAP 30* Momordica anti-human immunodeficiency virus protein, *MCL* *Momordica charantia* lectin, *α-MMC* α-Momorcharin, *CCL* *Castanopsis chinensis* lectin, *ATL Arisaema tortuosum* lectin, *BTKL* Blue Tiger King Lectin, *Con A* Concanavalin A, *BBI* Bowmans birk inhibitor, *IBB1* and *IBB2* Bowmans birk isoinhibitors, *TCS* Trichosanthin or Tin Hua Fen or GLQ223, *BvvL* Bauhinia variegate var variegata lectin, *DlasiL* Dioclea lasiocarpa lectin, *TI1B* Bowman birk isoinhibitor, *ConBr Canavalia brasiliensis L*ectin, *ConM* Canavalia maritime lectin, *DsclerL* Dioclea sclerocarpa lectin, *VCA* *Viscum album* L. var coloratum agglutinin, *ML-I,II,III* Mistletoe lectin-I,II,III, *PHP* Peganum harmala protein, *AEL* Aspidistra elatior Blume lectin, *AGG* Abrus agglutinin

is expected to be released soon (Camarero and Campbell 2019).

Conclusion

Finally, this review encapsulates the therapeutic plant peptides and their prospective applications. They can serve as future treatments that are both unique and effective. Although many plant peptides have been explored for therapeutic applications, only a handful have progressed to the next stages. Usually, drug development constitutes in vitro examinations, in vivo corroboration and clinical trial review. Regrettably, almost all the research involving protein therapies reaches a dead-end in vitro, with only a handful of them being marketed as medicine. Various strategies have been applied to overcome such disadvantages (low bioavailability, high toxicity). One such strategy is bioconjugation and it has improved target selectivity, lower toxicity, and enhanced retention time with a regulated release in the target tissue. As these intricate component systems become more ubiquitous, research into bioconjugate treatments should become more focused due to their peculiarity in contrast to single-molecule drug organization. New formulation strategies have to be developed to design new drug candidates and bring out the peptide's full potential. To summarise, substantial research into medicinal plant proteome could identify novel plant-based peptide drugs. Many therapies involving proteins could be discovered due to research in this approach. Plant-derived peptide therapeutics is still the primary source of bioactive compounds worldwide.

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