Balgir and Sharma et al., J Proteomics Bioinform 2017, 10:7
DOI: 10.4172/jpb.1000437

Journal of
Proteomics & Bioinformatics

Research Article Open Access

Biopharmaceutical Potential of ACE-Inhibitory Peptides

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Abstract

Bioactive peptides are defined as peptides with hormone or drug like activity that bind to specific receptors leading to induction of physiological responses with a positive impact on body functions and health. Though pharmaceuticals are available, the responses to these drugs show variability and outright toxicity in some patients. Peptides of food origin have been reported to play an important role in the prevention and treatment of hypertension therefore researchers are extensively exploring food based strategies to produce functional food products with antihypertensive properties. These peptides act by intervening in different biochemical pathways that control blood pressure, fluid and electrolyte balance. Some targeted pathways are the renin-angiotensin system, kinin-kallikrein system, sympathetic nervous system, ion regulation system, sodium-transport system and the endothelin-converting enzyme system. These peptides are more reactive than their native proteins and have been produced by fermentation and enzymatic hydrolysis of food sources. Recombinant DNA technology has opened more avenues of production of antihypertensive peptides. In the present work antihypertensive Angiotensin-Converting-Enzyme (ACE) inhibitor peptides (2-5 in length and from food source) were selected from BIOPEP database and validated *in silico* for anti-hypertensive activity using web-based software Molsoft and Molinspiration. An overall drug-likeness score for the selected peptides was calculated using Molsoft. The more positive the value of drug-likeness scores the more active the peptide is. The molecular properties like hydrophobicity, electron distribution, hydrogen bonding characteristics and molecular size of active peptides were predicted using Molinspiration. In comparison with others only eight peptides WP, PLW, YPR, LPP, FP, LW, YW, RW showed positive drug-likeness score and bioactivity score (not violating Lipinski's rule).

Keywords: Hypertension; ACE: Angiotensin-converting enzyme; *In silico*; Bioactive peptides; Drug likeness score; Lipinski's rule

Introduction

Bioactive peptides

Proteins play the major role in body functioning and are a good source of biologically active (bioactive peptides) as these peptides are specific protein fragments. According to Fitzgerald and Murray [1], bioactive peptides are defined as peptides with hormone or drug like activity that bind to specific receptors leading to induction of physiological responses [2]. The bioactive peptides as drugs have advantages such as small size, low cost and low price, oral availability, membrane-penetrating ability and stability in the physiological milieu [3]. According to their functional properties, bioactive peptides may be classified as antimicrobial, antioxidative, antihypertensive, mineral binding and opioid. Similar to the antihypertensive drugs, different classes of anti-hypertensive peptides are Angiotensin Converting Enzyme (ACE) inhibitory peptides, Renin Inhibitory peptides, Calcium channel blocking peptides, vaso-relaxative peptides, Endothelin-1 and Endothelin Converting Enzyme (ECE) inhibitory peptides [4]. The main group of the antihypertensive peptides corresponds to the inhibitors of ACE as playing an important role in the regulation of blood pressure as well as fluid and salt balance in mammals (Figure 1).

ACE: Structural analysis and ACE-inhibitor pharmacokinetics

ACE is a zinc- dependent dipeptide carboxypeptidase. The resolution of the 3D structure of somatic form of ACE contains two metalloproteinase domains (N- and C-terminal domains). Each of these domains has Zn binding motif. In spite of the structural and protease activity similarity of both the domains, the C-Domain has crucial role in blood pressure regulation and is strongly activated by chloride ion (http://www.proteopedia.org/wiki/index.php/ACE). Important structural features of ACE are given in Table 1.

Further, Molecular docking studies by He et al. [5] confirm that the ACE activity is through binding of peptide to enzyme active site, leading to formation of extensive hydrogen bonds. Lisinopril is a competitive inhibitor, since it has a similar structure to angiotensin I and binds to the active site of ACE (Figure 2). Molecular docking of peptides TF, LY, RALP to the active site of ACE demonstrates that these peptides bind to the hydrophobic pocket, via hydrophobic interactions with Ala354, Glu384, Tyr523, Gln281, Tyr520, Lys511, His513 and His353 residues. Peptides RALP and LY had higher ACE-Inhibition than TF because of the 4 Hydrogen bonds with the enzyme's active site residues (Table 2).

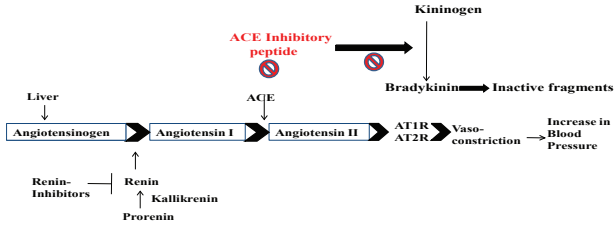

Figure 1: Pathophysiology of hypertension: As a result of its dual functionality ACE is a prominent target for developing anti-hypertensive therapeutics.

Different sources of anti-hypertensive peptides

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Received June 26, 2017; **Accepted** July 27, 2017; **Published** July 31, 2017

Citation: Balgir PP, Sharma M (2017) Biopharmaceutical Potential of ACE-Inhibitory Peptides. J Proteomics Bioinform 10: 171-177. doi: 10.4172/jpb.1000437

Annotations	Details	References
Domain Assignment:	ACE: 575 residues	SCOP Database
Secondary Structure:	61% helical (31 helices; 364 residues) 3% beta sheet (7 strands; 19 residues)	DSSP databank
Structural Feature:	BINDING SITE FOR RESIDUE LPR A 702 BINDING SITE FOR RESIDUE CL A 703 BINDING SITE FOR RESIDUE CL A 704 BINDING SITE FOR RESIDUE ZN A 701 BINDING SITE FOR RESIDUE GLY A2000	Site Record
Structural Feature:	L-cystine (cross-link) A protein modification that effectively cross-links two L-cysteine residues to form L-cystine.	Protein Modification Database: PSI-MOD RESID Database

Table 1: Features of Angiotensin-converting enzyme.

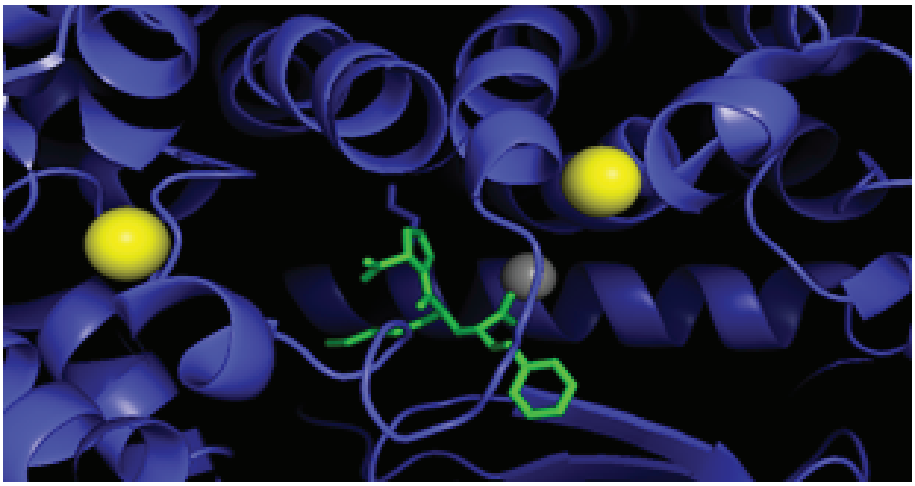

Figure 2: ACE in complex with inhibitor Lisinopril, zinc cation shown in grey, chloride anions in yellow (PDB: 1O86).

S. No.	ACE residues in H-bonds	Number of H-bonds			
		TF	LY	RALP	LISINOPRIL
1.	Glu162				1
2.	Gln281		1	2	2
3.	Ala354	1	1		2
4.	Glu384	1	2		1
5.	Asp415			1	
6.	Lys511				1
7.	Tyr520			1	1
8.	Tyr523				1
Total		2	4	4	9

Table 2: Hydrogen bonds observed between ACE (PDB: 1O86) and the docked peptides [5].

During the last two decades it has been found that milk proteins (human caseins, bovine and whey proteins) are a source of biologically active peptides [6]. Recent identification and characterization of bioactive peptides (in the size range of 2-20 amino acids and molecular masses of less than 6000 Da) have been obtained from cereal grains, particularly wheat, oat, barley, rice, rye, oat, millet, sorghum, corn and mushroom, algae protein waste etc. has been an emerging area [7].

Production of anti-hypertensive peptides

Biological active peptides have been produced from precursor milk proteins in the following ways:

a) Enzymatic hydrolysis.

b) Fermentation of milk with proteolytic starter cultures.

c) Genetic recombination in bacteria.

In many studies, combination of (a) and (b) or (a) and (c), has proven effective in generation of short functional peptides [8,9].

ACE-inhibitory peptides: *In-silico* approach

Recent trends in bio-active peptides includes designing of novel peptide sequences with potential applications in the prevention and mitigation of ill health, which has tremendous significance to the scientific community, pharmaceutical corporations and consumers. As bioactive peptides play important roles in physiological functions as signalling molecules. The fast development of bioinformatics, have

led to rapid accumulation of large amount of peptide data organized in numerous biological databases such as ACEpep, AHTP, BIOPEP, EROP etc. [10]. Further, the bioinformatic tools can be used to analyze the potency of different anti-hypertensive peptides. The objective of this research work was to compare different peptides which are isolated from different food sources on the basis of physiological interpretation by Molsoft and Molinspiration software.

Materials and Methods

A total of 90 peptides (2-5 amino acids in size and from food source) were selected from BIOPEP database and analysed using Molsoft and Molinspiration.

BIOPEP database

BIOPEP (www.uwm.edu.pl/biochemia) was developed in the Chair of Food Biochemistry of Warmia and Mazury University in Olsztyn (Poland). The database provides comprehensive information on 2123 peptides representing 48 types of bioactivities, their EC_{50} values and source of origin. BIOPEP thus provides the useful techniques to obtain the information and classification of bioactive peptides in a quick and simple way.

Drug-likeness score using Molsoft

MolSoft provides services and software tools which leads to cheminformatics, modelling, discovery, bioinformatics, and forms with pharmaceutical companies and bioinformatics. It was founded by Ruben Abagyan in 1994. It provides tools and software's for rational drug designing, structure prediction, bioinformatics, molecular visualization and animation, proteomics (http://molsoft.com/mprop/).

Features of MolSoft: It helps in validating and building structural models for protein targets. It gives access to identify biological ligand binding sites or new sites for allosteric regulation of interest protein. It provides molecule visualizing and data sharing. It also helps in finding out amino acid positions in protein-protein interaction. It aids in designing proteins with desired properties. It assists screening virtual libraries of millions of compounds by using the revolutionary MolSoft flexible docking and scoring procedure.

It helps in evaluating and ranking drug targets. It provides a feature of docking flexible peptides to proteins and designing peptides that blocks protein-protein interactions. It assists in predicting properties of a compound, building its QSAR models. It also helps in conversion of 2-D structure to 3-D and its clustering of large compound libraries and its analysis.

Tools and softwares of MolSoft: It provides us various free online tools are as following:

- PDB (protein databank) which is used for determining 3-D structures of biological macromolecules. This also contains bibliographic citations, 1-D 2-D structure information, atomic coordinates as well as NMR data and crystallographic structure factors.
- 2-D to 3-D convertor allows the user in construction of ICM molecular objects from 2-D drawing and promotes optimized 3-D structures using MMFF atom type assignment and force field optimization. It can be used to convert the chemical structure and view it by using iMolveiw app for mobile users and Activelcm.
- **Chemical search:** This tool is used to check out similarity between the structures.
- **Drug-likeness** is defined as a complex balance of various molecular properties and structure features (mainly hydrophobicity, electronic distribution, hydrogen bonding characteristics and molecule size) which determine whether particular molecule is similar to the known drug. For a peptide to act as drug the score should fall within the range -2.0 to 2.0 [11,12]. MolSoft uses chemical fingerprints for the prediction of drug likeness score. It was founded in 1994. It also helps in conversion of 2-D structure to 3-D and its clustering of large compound libraries and its analysis.
- **Protein-protein interaction:** It is used for predicting protein-protein interaction sites on a protein by the process known as Optimal Docking Areas (ODA). It helps in identifying optimal surface patches with lowest docking desolvation energy values as calculated by ASP (atomic salvation parameters) which are derived from octanol/water transfer experiments and adapted for protein-protein docking.
- **Green chemistry prediction engine:** It is chemical test engine. In this we can find out the chemical that interferes biological pathway.

Softwares that are provided by MolSoft are

- **ICM-browser:** It is used for desktop molecule viewer.
- **Active ICM:** It displays fully interactive 3-D structures.
- **HTML5 molecular editor:** It is a molecular editor based on Java Script that is fast and lightweight.
- **XPDB:** It consists of fully annotated protein structure files.

KNIME nodes: It is a comprehensive licensed user-friendly data integration, processing and exploration platform (http://www.MolSoft.com).

Calculation of properties using Molinspiration

It is created by Peter Ertl and Bruno Beinfait at Novartis. It offers a wide range of cheminformatics software tools. These softwares supports molecule manipulation and processing that includes SD files and SMILES conversion, generation of tautomers, normalization of molecules, molecule fragmentation, molecular modelling and drug designing, high quality molecule depiction. Molecular database tools also support similarity and substructure searches. All the Molinspiration tools are written in JAVA. Molinspiration is now also available on ipads, smart phones. There are 434 citations in Molinspiration till 2016 and are still in count (http://www.MolInspiration.com/).

Tools and softwares of Molinspiration

- **Calculation of molecular properties and bioactivity score:** We can draw structures in this tool for predicting its properties. We can also paste SMILES in the SMILE box and then it will show us the whole bioactivity and molecular properties.
- **Galaxy 3-D generator:** In this tool we can 3-D structures of organic macromolecules.
- Molecular database-substructure and similarity search: It allows us to find similarities of our query to other structures and it also allows finding out substructures.

Molinspiration molecular viewer: With the help of this tool one can do visualization of collection of molecules in form of SD files or SMILES. It is an automatic system that transforms the SMILES into 2-D

structures with the help of depiction engine (http://wiki.bkslab.org/index.php/MolInspiration) (http://www.MolInspiration.com/).

Molinspiration Parameters

- **Topological molecular surface area:** TPSA is defined as the surface of polar atoms. It helps in determining drug transport, intestinal absorption, drug permeability, and drug absorption. It is sum of fragments present in bimolecules such as oxygen, nitrogen etc.
- **Volume:** Volume of bimolecules can be calculated by s method based upon group contributions by adjusting total fragment into real 3-D volume.
- **MiLogP:** Log P is used for the determination of hydrophobicity. It is the octanol-water coefficient. Drug toxicity is affected by the hydrophobicity as its interaction with receptors, drug absorption and their metabolism.
- **Nrotb:** It is useful in determining the flexibility of molecule by measuring the no of rotatable bonds. Amide bonds are not considered because of their high rotational barrier. Rotatable bonds can be defined as any single non-ring bond, bounded to non terminal heavy atom that is non-hydrogen.
- **Lipinski rule of five:** this rule states that most "drug like" molecules have molecular weight less than 500, no of hydrogen bond acceptors less than or equal to 10, Log P value less than or equal to 5, no of hydrogen bond donors less than or equal to 5. Molecules that do not follow more than one of these rules may have problem with bioavailability. The rule of five determines the permeability across the cell membrane.
- Through drug likeness and molecular properties data of molecule, the bioactivity can be checked in respect to known drugs.

Results and Discussion

Drug likeness calculation of the selected peptides was done to examine that weather the peptides are bioactive based on their drug-likeness score using Drug-Likeness and molecular property prediction tool of Molsoft. The input is 2-D structure of the peptide in SMILES format, which is converted to 3-D structure and the Drug-Likeness Score is calculated as summarized in Table 3.

Out of 90 analysed peptides 13 PQR, GWAP, KW, LW, LPP, YW, FWN, FP, PLW, YPR, RW, DW, WP were found to have a positive drug likeness score. Although as shown in Figure 3 the green color indicates non drug-like behaviour and those fall under blue color are considered as drug-like but if the drug-likeness score is (>0), then it is active, if (-2.0-0.0) then the peptide is moderately active. Hence peptides having more positive values should be considered as active drug-like. Maximum drug-likeness score was found out to be 0.72 for compound WP [13,14].

S. No.	Peptide Sequence	Food Source	Molecular Weight	IC_{50} Value(μM)	Drug Likeness Score
1	YLLF	Whey protein (Beta Lacto globulin)	554.69	172	-0.47
2	FQP	Fish	390.425	0	-0.32
3	GPA	Milk	243.26	405	-0.46
4	ALPHA	Fish	507.59	10	-0.17
5	IWHHT	Fish	692.78	5.8	-0.22
6	IKP	Fish	356.47	6.9	-1.06
7	LKL	Fish	372.494	188	-0.77
8	HGLF	α-lactalbumin and alpha-lactoglobulin	472.53	0	-0.76
9	AVP	Milk	285.34	340	-1.01
10	AVPYP	Casein	545.616	80	-0.47
11	PYP	Milk	375.42	220	-0.24
12	PQR	Casein	399.437	401	0.20
13	PFPE	Casein	488.52	1000	-0.22
14	AAP	Casein	257.27	0	-0.79
15	FGK	Casein	350	160	-1.21
16	GRP	Fish	328.35	19.9	-0.88
17	AKK	Fish	345.42	3.2	-0.79
18	RY	Fish	337.3	10.5	-0.79
19	LY	Fish	294.3	18	-0.47
20	GWAP	Fish	429.48	3.85	0.33
21	IY	Fish	294.33	2.1	-0.69
22	VF	Fish	264.31	9.2	-0.78
23	MF	Fish	296.37	45	-0.53
24	KW	Fish	332.38	1.63	0.06
25	RFH	Fish	458.5	331	-0.79
26	MY	Fish	312.38	193	-0.53
27	LW	Milk casein	317.3	50	0.27
28	LPP	Casein	325.3	9.6	0.53
29	FAP	Casein	333.37	3.8	-0.13
30	VRP	Casein	370.43	2.2	-1.12

31	TAP	Milk	287.3	3.5	-1.00
32	MYY	Casein	475.53	9.6	-0.53
33	ALPP	Casein	396.47	0.0	-0.58
34	LALPP	Casein	509.63	0.0	-0.62
35	LVL	Porcine plasma	343.45	12.3	-0.77
36	GDAP	Cuttlefish muscle	358.33	22.5	-0.61
37	VW	Sake and sake lees	303.34	1.4	-0.03
38	VWY	Sake and sake lees	466.5	9.4	0.00
39	YW	Sake and sake lees	367.38	10.5	0.24
40	RF	Sake and sake lees	321.36	93	-0.79
41	FWN	Sake and sake lees	465.49	18.3	0.37
42	IYPRY	Sake and sake lees	710.8	4.1	-0.68
43	VY	Sake and sake lees	280.30	7.1	-0.78
44	YGGY	Sake and sake lees	458.44	3.4	-0.96
45	HY	Sake	318.3	26.1	-0.62
46	FP	Whey Protein	262.29	315	0.53
47	VYP	Whey Protein	377.4	288	-0.44
48	GKP	Whey Protein	300.34	352	-0.84
49	IPA	Whey Protein	299.35	141	-0.68
50	GGY	Sake and sake lees	295.27	1.3	-0.87
51	IRAQQ	A-zein hydrolysate	614.68	4.2	-0.64
52	VAA	A-zein	259.29	13	-1.58
53	AYFYP	A-casein	659.71	1001	-0.19
54	VAP	A-casein	285.32	2	-1.01
55	IPP	Sour Milk	325.39	5	-0.69
56	LYPVK	Fig	618.75	4.5	-0.71
57	VPP	Sour Milk	311.36	9	-1.07
58	VHIPP	Cereals	561.66	10	-0.38
59	VHLPP	Cereals	561.66	18	-0.39
60	PLW	A-casein	414.49	36	0.70
61	YPRY	Sake and sake lees	597.64	17.4	-0.62
62	YPR	Sake and sake lees	434.47	16.5	0.53
63	PRY	Sake and sake lees	434.47	2.5	-0.43
64	PR	Sake and sake lees	271.30	4.1	-0.19
65	VSP	Alpha-zein	301.33	10	-0.80
66	LAA	Alpha-zein	273.31	13	-1.20
67	IYPR	Sake and sake lees	547.63	10	-0.68
68	LSP	Cereals	315.35	1.7	-0.67
69	LQP	Alpha-zein	356.40	1.9	-0.38
70	LRP	Cereals	384.46	1	-0.98
71	LNP	Alpha-zein	342.38	43	-0.38
72	VHLAP	Cereals	535.63	4.5	-0.49
73	ILP	Egg	341.45	46	-0.72
74	FK	Sweet potato	293.37	265.43	-0.95
75	RW SVR	Flaxseed protein	360.42 360.41	0.4	0.09 -1.12
76	IVF	Egg yolk	377.48	260	-0.74
77	LQP LLP	Rye malt sourdough	356.42 341.45	2.0 57.0	-0.38 -0.50
78	LSA IVY LKY	Sesame	289.16 393.48 422.52	7.8 14.7 0.78	-1.21 -0.74 -0.78
79	DW	Fish	319.32	13	0.18
80	WP	Cheese	301.35	217.27	0.72
81	YPYY	Milk	604.66	90.9	-0.21
82	SKVYP	Casein	592.69	NOT Determined (ND)	-1.01
83	FGRCVSP	ND	ND	6.2	-1.40
84	FCF	ND	415.51	ND	-0.67
85	NIFYCP	ND	755.89	15	-0.29

86	LRP	Cereals (Maize alpha-zein)	384.48	0.29	-0.98
87	ALEP	ND	428.49	ND	-0.64
88	VIKP	Amaranthus globulin	455.6	ND	-1.10
89	LVR LYPVK	Fig Sap	386.49 618.77	<20 4.5	-1.06 -0.71
90	IAP	Wheat Gliadin	299.37	2.7	-0.71

Table 3: Drug-likeness score of ACE-inhibitory peptides using Molsoft.

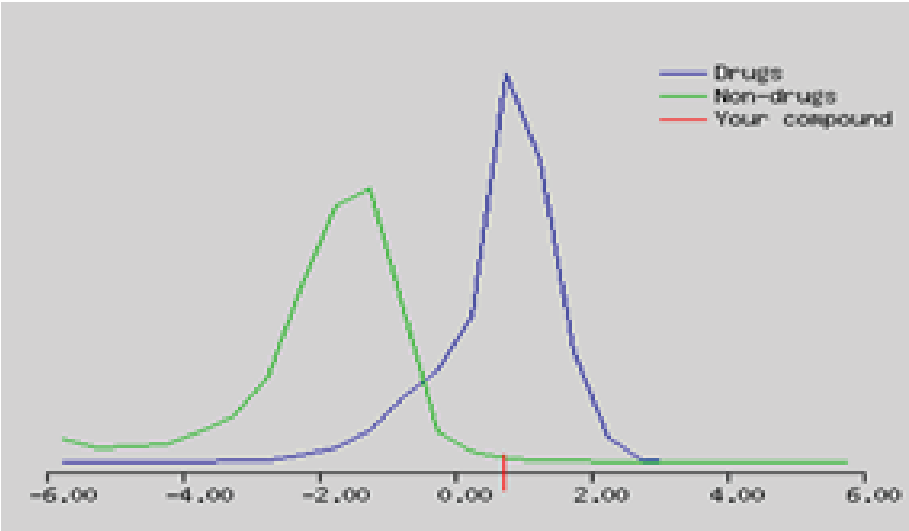

Figure 3: Graph showing peptide WP to have maximum drug-likeness model score using MolSoft.

Peptide	TPSA	NROTB	HBA	HBD	Log P	MW	Lipinski's violations
RULE	≥60 A²	≤10	≤10	≤5	≤5	≤500	≤1
PQR	162.98	12	10	6	-3.84	369.42	2
GWAP	157.62	9	10	6	-2.61	421.5	1
KW	134.2	10	7	7	-2.38	324.4	1
LW	108.21	8	6	5	-0.58	309.4	0
LPP	103.94	5	7	3	-1.90	325.41	0
YW	108.21	8	6	5	-0.43	343.43	0
FWN	180.40	12	10	8	-1.11	457.53	2
FP	83.36	4	5	3	-1.49	262.31	0
PLW	123.31	10	8	5	-0.17	406.53	0
YPR	125.09	10	8	4	-1.98	388.47	0
RW	120.58	10	7	5	-1.81	322.41	0
DW	145.51	8	8	6	-2.71	311.34	1
WP	99.42	5	6	4	-1.58	293.37	0

Table 4: Molinspiration calculations for pharmacokinetic parameters important for bioavailability of peptides.

Calculation of pharmacokinetic parameters using Molinspiration

Various parameters like log P (partition coefficient), molecular weight, number of hydrogen donor, number of hydrogen acceptor and number of violation, number of rotatable bonds, molecular polar surface area TPSA were calculated for the peptides that showed positive drug-likeness score (Table 4).

TPSA, topological polar surface area; NROTB, number of rotatable bonds; MW, molecular weight; LogP, logarithm of compound partition coefficient between n-octanol and water; HBA, number of hydrogen bond donors; HBD, number of hydrogen bond acceptors.

These parameters of above 13 peptides are also calculated on the basis of Lipinski rule of five [15] gave "the rule of five" according to which orally active drugs should have a molecular weight under 500 Daltons, a maximum number of 5 hydrogen bond donors [expressed as the sum of OH and NH groups], and a maximum number of 10 hydrogen bond acceptors [expressed as the sum of N and O atoms]. The best descriptor to differentiate poorly absorbed drugs at an early stage of the drug discovery process is TPSA i.e., total polar surface area and drugs that are completely absorbed have PSA greater than or equal to 60 A^2 [16]. For the calculation of drug transport properties PSA parameter is used. It is also used for the estimation of absorbance percentage. Nrotb depicts the conformational changes of a molecule

which decides binding of channels or receptors. It should be equal to or less than 10 to have good oral bioavailability. Log P (lipophilicity) should have value equal to or less than 5 to fall under the range of good intestinal permeability. Out of 13 analyzed peptides 8 peptides are not violating the rule of five.

Conclusion

Although there is availability of multiple pharmacotherapies and the known preventative effects of lifestyle modification, hypertension remains a highly prevalent disorder worldwide. Due to various disadvantages of pharmaceutical antihypertensive drugs such as high fever, cough, dizziness, chills, sweating, blurred vision, hypoglycaemia, depression etc., antihypertensive bioactive peptides are used for the treatment of hypertension. ACE Inhibitors are the first-line drug of choice and these can be derived from various food sources like milk, curd, spinach, shark meat, pork, chicken, rice hydrolysate, corn, wheat, soy proteins etc.

The *In-silico* analysis of food protein-derived peptides is a cost- and time-effective, method to select peptides with therapeutic potential. From the 90 analysed peptides, 13 peptides had positive drug-likeness score. These peptides were further taken for calculation of Pharmacokinetic Parameters. Eight peptides WP, PLW, YPR, LPP, FP, LW, YW, RW have logP not greater than 5, molecular weight less than 500 Daltons, No. hydrogen bond donors ≤5, No. hydrogen bond acceptor ≤ 10 and does not violate Lipinski's rule. So these programs are highly useful for predicting the various properties of peptides and the results are relatable to QSAR studies.

Acknowledgements

This work was supported by the grant from DBT-Punjabi University Patiala Interdisciplinary Life Science Programme for Advance Research and Education (DBT-IPLS PROJECT) (No. BT/PR4548/INF/22/146/2012).

Web links

http://www.molsoft.com/mprop/

http://www.molinspiration.com/cgi-bin/properties

http://vina.scripps.edu/

http://crdd.osdd.net/raghava/ahtpdb/

http://www.uwm.edu.pl/biochemia/index.php/en/biopep

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