Biointerface Research in Applied Chemistry

Original Review Article   **Open Access Journal**

Protein structure from the essential amino acids to the 3D structure

Diaa Atta [1,*], Abd Elaziz Mahmoud [1], Ahmed Fakhry [1]

[1]Spectroscopy Department, National Research Centre, Giza, Egypt.

*corresponding author e-mail address:**Diaalolo2004@yahoo.com**

ABSTRACT

Protein structure is a hot topic, not only to the specialist, but with others like the physicists. So this review is targeting those who are not biologists and have to deal with the protein in their research. In this review we travel with the protein structures from the amino acids and its classifications, and how the polypeptide chain is formed from these building blocks up to the final 3D structure. We introduced the secondary structure species like helices with its different types and how it is formed; also the beta sheet formation and types are explained briefly. Finally the tertiary and quaternary structures are presented. The approaches of molecular modeling as well as other important computational methods present significant contribution to studying proteins.

Keywords: *Protein structure- Amino acid-Primary structure- Secondary structure- tertiary structure-quaternary structure.*

1. INTRODUCTION

One from the most important and used class of molecules is the proteins class. It is engineered to incorporate any molecule that one can imagine, and convert it from the ion structure into a large complex such as, sugar molecules, Fats and many other forms [1,2]. Protein different forms are the catalysis of a vast range of biological and chemical reactions which controls all the live cell reactions such as providing the cell membrane permeability for the different important fluids, cell toughness, and one from the most important process which is the metabolic molecules concentrations, as well as many other cell reactions [3-7]. Regardlessof its effect on the substance properties, the molecular 3D structure in the protein molecule has a great effect on its functionality [8-11]. Understanding the 3D structure of any protein molecule is the way to realize its role and function through the biological reactions that took place inside and outside the biological cell and how it works even on the cell membrane itself. From the facts mentioned before and the more known about the proteins, this class of molecules is a very rich class with its different types of the molecular structures, for example one class of proteins is the Enzymes, the known enzymes are around 75000 different molecules [12, 13].

In the protein structure there is very strange information that any protein is constructed from only 20 different amino acids (the standard amino acids) [8]. This makes protein structure and conformation a hot topic for many of the biological research groups. Simply proteins could be explained as biological polymers, it is a non-branched single chain of amino acids. As polymers are constructed by a polymerization process for such monomer, the amino acids are regarded as the monomers of the protein which polymerized in different arrangements. This arrangement produces the protein polypeptide chain, this chain did not last for a long time but it went in folding process by covalent bonds producing what so called secondary structure, which directly went also in the folding process producing the tertiary structure, than the quaternary structure which gives the protein its functionality and unique 3D structure.

The aim of this mini-review is to help the non-biologists researchers especially the physicists to understand the protein structure and how it is built without going too much into sophisticated details.

2. AMINO ACIDS

Now after the previous introduction one should ask, what are these amino acids? How it is constructed?

Amino acids are more than 100 different structures, but what we mean are the 20 standards alpha amino acids. As is clear from figure 1, alpha amino acids are constructed in common from an alpha Carbon (αC) atom [14-17] (the term alpha) connected with an amid (NH2) group (the term amino) and carboxyl (COOH) group (the term acids) and Hydrogen (H) atom then an alkyl (R) group. Hence the major difference is the alkyl group as in figure 2. As it is presented in figure 2 the simplest alpha amino acid is the Glycine which has only a hydrogen atom instead of the alkyl, while the largest side chain comes in both leucine and iso-leucine which contains 4 carbon side-chains. Any polypeptide chain is

constructed from a special arrangement of the mentioned alpha amino acids connected from the amino and carboxyl groups via peptide bonds. The polypeptide chain starts with the amino (NH2) group -called N terminal- and ends with the carboxyl group -called C terminal- (COO-)[18,19]. Normally the proteins molecular weight evaluated by what so called Dalton (D) every Dalton is the MW of the H atom. Despite the alpha amino acids are the building blocks of any protein, the human body could not produce all of them, for examplephe, val, Thr, Met, Trp, Ilu, Leu, His and Lys did not self-produced by the human body. This class of amino acids is called the essential amino acids[20-23] that should be essentially found in the human daily food, while there are others that could be produced in the human body (but it happen) under

certain conditions like Arg, Tyr, Pro, Glu, CysandGly are called conditional essential amino acids [24,25]. The rest amino acids are produced regularly in the human body. The easiest and straight forward way to supply your body with the essential amino acids is the mammalian meat, but vegetarians depend only on plants in their diet so they have to complement their food by scientifically assigned menu [26]. While all the standard 20 Amino acids are alike in the structure but they differ in the side chain, in this case this side chain affects the amino acid reactivity through its physical and chemical properties.
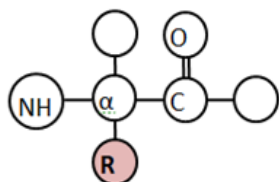

Figure 1. The common structure of the alpha amino acids.

For example the amino acids with polar side chain [27, 28] tend to form the protein surface during the poly peptide chain folding while those with non-polar side chain went to the innermost core of the protein 3D structure. The presence of the polar side chains on the protein surface makes it easily soluble in the polar buffers like water. Some of the 20 basic amino acids are hydrophobic in acidic forms like Aspartic and Glutamic while others have basiceffects like Lysine, Arginine andHistidine. Some hydrophilic amino acids have polarity not from the alkyl side chain but from

the carboxyl and/or the amide group like Serine, Asparagine, Glutamine and Threonine [29,30].

Figure 2.The Structure of the 20 basic amino acids.

3. PRIMARY STRUCTURE OF THE PROTEIN

To form the protein backbone (poly peptide chain) the selected amino acids should be linked via peptide bonds [31-33]. The peptide bonding is a chemical bond from the covalent bonding type. The poly peptide chain is a repeat of amino-alfa carbon- carboxyl (+N-αC-COO-).This bond is formed in general by releasing OH from the carboxyl and H from the amino forming water molecule. As a result of this arrangement it is always the Nitrogen atom and the CO group which are in the location with respect to the alpha carbon along the protein backbone, as a consequence every polypeptide chain have a charged N terminal as start and ends with charged C terminal. There are two types of the peptide bonded amino acids chain, if the amount of the amino acid molecules is between 20 and 30, it is called peptide, otherwise, for longer chains it is called poly peptide chain [34]. Hence the folding process and the forming of the 3D structure from peptides is called complex and that from polypeptide chain called protein and both have a superior role in the biological reactions inside the cell.

4. SECONDARY STRUCTURE OF PROTEIN

After the formation of the polypeptide chain even during the protein elongation, the polypeptide chain starts to form the secondary structure sub units which are called according to its 3D geometry as alpha helices and beta sheets.

4.1 Alpha helix (α helix)

During his X-Ray investigations on the wool fibers in the 30s of the last century, William Thomas Astbury discovered the coil shape in the fiber structure [35-37], or what is called the helical structure of the protein molecules. Alpha helix is a right hand or left hand coiled polypeptide chain or in other words it is a spiral conformation. In this structure every amino group gives an electron to that carboxyl group of the amino acid located in the third or the fourth order before that amino group along the polypeptide chain [38-40]. Some amino acids have a high tendency to form alpha helix like Methionine, Alanine, Leucine,

Glutamine andLysine[41-43]. On the other handProline and Glycine approximately have no tendency to form helices [44-47].In some cases more than one helix could coil together forming what called super helix [48-50].Thesuper helices are more stable than the normal helices. As an example for the presence of super helix is the growth-hormone[51,52] of humans also the Rop protein both contain super helices [53,54] and other many biological molecules.

4.2 Pi helix (π helix)

Pi helix is another form of the protein secondary structure. It is really rare to find a Pi helix in such protein structure as one could speculate that only 15% of the known structures contain Pi helix [55,56]. Founding Pi helix in such structure could be from such inserting just an amino acid into the structure of any alpha helix. This intrusion of such amino acids destabilizes the structure [57].

This structure destabilization makes the formation of Pi helices subjected only to give some functionality advantages, so normally it is located in the active sites [58,59]. In alpha helix the amino acids are arranged in helical structure with approximately amino acid every 100° if the complete turn is 360° which means that every turn contains in average 3.6 amino acid [60-63], but in pi helices there are amino acid every 87° this means that we have 4.1 amino acid every turn (360°). Another difference between pi and alpha helices is that in pi helices every carboxyl group is linked to the amino group of the next fifth amino acid not the fourth one [64- 68]. Typically the Pi helices are very short structure, its sequence contains between 7 and 10 amino acids in its backbone. The foundation of Pi helix in any structure is very difficult because of its shortness [69] it is always found as shown in figure3 in between two alpha helices [64,69-70].
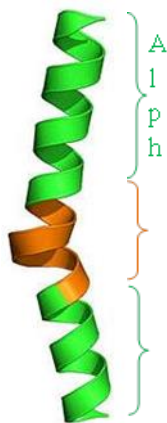

Figure 3. A short secondary structure Pi helix located between two long secondary structure alpha helices

4.3 Beta sheet (β sheet)

β sheet or β plated sheet is a common protein secondary structure it is considered as the second superabundant secondary structure in the protein 3D geometry [38, 71-73]. Beta sheet is constructed by linking laterally two or more polypeptide chains (backbone) by what is called beta strands (β-strands), during the backbone linking by the β-strands a twisting takes place forming the known secondary structure [74-77]. As it is mentioned before the amino acids are directed by the N terminal and C terminal, also the beta sheet is directed as always symbolized in the protein structure (carton method) as a wide arrow aiming to the C terminal as shown in figure 4. Beta sheets could be built up either in parallel method, in this case it is called parallel beta sheet or in anti-parallel method and is called anti-parallel beta sheets [78-82] as shown in figure 5.
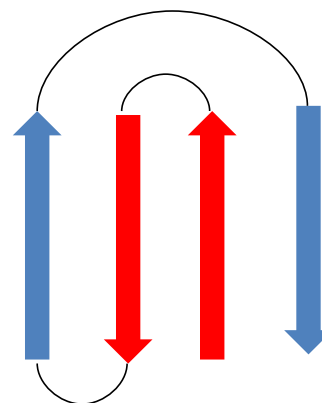
Figure 4.The arrow notation of the beta sheet the direction ims to the C terminal.
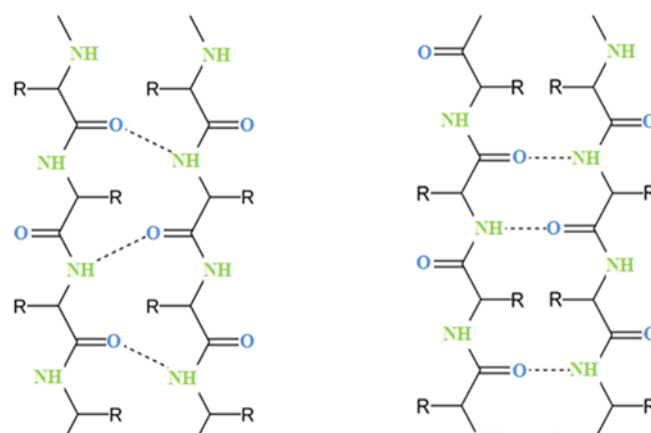
Figure 5.Parallel and anti-parallel beta sheets.

In parallel beta sheets the backbones arranged in a manner that the amino groups direction is the same or are adjacent in both backbones, while in anti-parallel structure the backbones are arranged in a way that the amino groups are adjacent to the carboxyl group in the next backbone [83-87].

The secondary structure of any protein is a mixture between the helices and the sheets [88-90], while the beta strands are hydrogen bonds but the helix structure is more stable than the beta sheets [91-93].

5.TERTIARY AND QUATERNARY STRUCTURE OF THE PROTEIN

From the time that the ribosome start to elongating and synthesizing the protein by linking and elongating the amino acids, the polypeptide chain starts to form 3D structure called the tertiary structure [18, 94-97], by folding the amino acids sequence into a secondary structure then tertiary structure. Any tertiary structure is constructed from one or more clusters every cluster is formed from the folding of part of the secondary structure [98], and called protein domain. The interaction between the amino acids species (Alkyls, amino groups, carboxyl groups or hydrogen atoms) could take place in different ways to form the tertiary structure of such protein. The 3D geometry of such protein could be changed into alternative structures called protein conformation; if the protein environment is a cellular ambient hence the stable conformer of the protein is called the native conformer or the native protein. While some proteins are functional at the level of tertiary structure [99], but the majority needs more complications to become functional. For those proteins with more subunits interact and folded to form the functional protein. If the interacted subunits are two, the quaternary structure is called dimer; if it is constructed from three subunits it called trimer, etc.

Another class of sorting is the subunits similarity; if the quaternary structure is formed from identical subunits it gains the prefix homo, hence called homo-dimer, homo-trimer, homo-tetramer, etc....On the other hand if the quaternary structure sub units are different, then it gains the prefix hetro that one could say hetero dimer and so on.Famous example is the hemoglobin which is one

from the most important mammalian proteins; it is the protein which captures the oxygen and transports it through the blood serum. Hemoglobin is constructed from four subunits two beta sheets and two alpha helices, hence the hemoglobin structure is called hetro-tetramer, while as it is constructed from two beta sheets and two alpha helices if we consider every subunit is constructed from alpha helices and beta sheets, hence it could be named homo dimer of dimers. The 3D structure of any protein is not only important for its functionality but also as any deformation in this structure during unfolding refolding process or the molecular conformations of the protein molecule could cause some diseases. Moreover the miss folding could cause protein aggregation which is also a cause of diseases in some cases. Protein aggregation also in some diseases is a corner stone in the disease mechanism. Alzheimer is an example of the protein aggregation disease, one from the hypothesis of the Alzheimer causes is the beta amyloid peptide aggregation [100-103].

6. MOLECULAR MODELING APPROACH

Protein folding problem was the first step paving the way towards mathematical prediction of (tertiary, 3-dimensional) protein structure given the (primary, linear). Nowadays computational methods are developed specially to define and understand the structure of theprotein. The most challenging problems in this field are becoming problems concerned with different computational approaches not limited to molecular modeling but also including mathematical modeling and numerical analysis. The possible interaction between heavy metal and protein is followed up with molecular modeling [104]. Metals are coordinated through the hydrogen bonding of amide and carboxyl groups. Based on this study, the mechanism describing the interaction between Cr and protein as described [105]. Divalent metals in hydrated form are interacting with two chains of protein through two hydrogen bonding of carboxyl and/or amide groups which is confirming the previous molecular modeling findings for the interaction between metals and protein [106-107]. Molecular modeling was confirming those obtained through docking in order to describe the possible interaction between chitosan in nano scale and αB-Crystallin protein [108]. Recently, a comprehensive review is conducted for modeling studies of monoamine transporters [109]. Molecular modeling could be used effectively for visualization, understanding then predicting the interaction between proteins and surfaces in order to control cellular function [110]. It is stated that, modeling studies of 3D protein structures are considered as an important and essential tool for understanding the BMP-2 release kinetics for orthopedic applications [111]. It is also reported that,the protein engineering is considered as a pivotal tool for designing proteins with improved characteristics [112]. Molecular modeling and different classes of simulation could be used as a very beneficial tool for understanding the relation between the protein structure and different protein function [113-118]. Finally Molecular Modeling is a strong tool in molecular structure identification not only for protein as mentioned before but also for other kinds of molecules [119,121]

7. CONCLUSION

Protein structure recognition and conformation is one from the most important and very sophisticated research topics. some times this conformation is regarded as important part from doing its function in the biological interaction inside, and outsidethe biological cell, even ontop and through the cell membrane.

Studying the protein structure and protein folding even the protein molecular conformation of the native protein and the novo-synthesized protein is the key to understand the majority of biological interaction and diseases mechanisms.

The setting up of new techniques and developing exciting methods to monitor the protein during the folding/unfolding process even the biological interaction is the way to understand fully these interactions and how we can control it.

Molecular modeling with different levels of theories is considered among the most important tools for understanding protein structure, folding and hence is confirming and/or starting the data obtained with experimental techniques dealing with protein issues.

8. REFERENCES

1. Semba, R.D.; Shardell, M.; Sakr, F.A.; Moaddel, R.; Trehan, I.; Maleta, K.M.; Ordiz, M.I.; Kraemer, K.; Khadeer, M.A.; Ferrucci, L.; Manary, M.J. Child Stunting is Associated with Low Circulating Essential Amino Acids. *EBioMedicine* **2016**, *6*, 246-252.

2. Denis, M. *Dietary Reference Intakes: the Essential Guide to Nutrient Requirements*, The National Academies Press, Washington, DC, 2006, https://doi.org/10.17226/11537.

3. Eleanor, C.; Miriam, K.; Galen, J.C.; Paul, D.C.; Benjamin, T.P.; Emma, K.L.; Livnat, A.; Ashley, M.B.; Martin, W.; Florian, H.; Nobuhiko, T.; Colin, J.J. The role of protein dynamics in the evolution of new enzyme function. *NatChemBiol* **2016**, *12*, 944-952, https://doi.org/10.1038/nchembio.2175.

4. Gira, B.; Damian, C.E.; Madeleine, J.; Christian, M.Z.; Lisa, M.T.; Gerard, K.; Jane, D.; Adam, G.; Ian, A.W.; Peter, E.W. Divergent evolution of protein conformational dynamics in dihydrofolate reductase. *Nat. Struct Mol Biol* **2013**, *20*, 1243–1249, https://doi.org/10.1038/nsmb.2676.

5. James, S.F.; Michael, W.C.; Sheena, C.D.; Renske, E.; Dorothee, K.; Tom, A. Hidden alternative structures of proline isomerase essential for catalysis. *Nature* **2009**, *462*,669–673, https://doi.org/10.1038/nature08615.

6. Sophie, M.C.G.; Christopher, M.C.; Jaeok, P.; Donald, G.; Albert, M.B.; Nicolas, D.; Joelle, N.P. Maintenance of Native-like Protein Dynamics May Not Be Required for Engineering Functional Proteins. *ChemBiol* **2014**, *21*, 1330–1340, https://doi.org/10.1016/j.chembiol.2014.07.016.

7. Jackson, C.J.; Foo, J.L.; Tokuriki, N.; Afriat, L.; Carr, P.D.; Kim, H.K.; Schenk, G.; Tawfik, D.S.; Ollis, D.L. Conformational sampling, catalysis, and evolution of the bacterial phosphotriesterase. *PNAS* **2009**, *106*, 21631–21636, https://doi.org/10.1073/pnas.0907548106.

8. Berg, J.M.; Tymoczko, J.L.; Stryer, L. *Biochemistry,* 5th ed, W.H. Freemanand company, NewYork, 2002.

9. Alberts, B.; Johnson, A.; Lewis, J.; Morgan, D.; Raff, M.; Roberts, K.; Walter, P. *Molecular Biology of the Cell,* 6th ed.**,** Garland Science, NewYork**,** 2015.

10. Merri, C.L.; *Proteins, In Problem Sets in Biological and Biomedical Sciences Case Studies in Cell Biology*, Eds., Merri, C.L., Academic Press, California, 2016.

11. Atta, D.; Okasha, A. Single molecule laser spectroscopy. *Spectrochem Acta* **2016**, *135*, 1173-1179, https://doi.org/10.1016/j.saa.2014.07.085 .

12. Singer, B.; Grunberger, D.; *Molecular Biology of Mutagens and Carcinogens***,** Springer Science & Business Media, 2012, https://doi.org/10.1007/978-1-4613-3772-0.

13. Maria, P.; Carmen, C. *Biotechnology: An Introduction*, WIT press, Southampton**,** 2012.

14. Akira, S.; Hideaki, K.; Hisashi, S. Structural studies of amino acids, polypeptides and proteins in the solid state by 1H cramps NMR. *Annu Rep NMR Spectro* **2002***, 45*, 69-150, https://doi.org/10.1016/S0066-4103(02)45010-7.

15. Wu, G. *Amino Acids biochemistry and nutrition***,** CRC Press, Boca Raton, 2010.

16. Osman, O.; Mahmoud, A.; Atta, D.; Okasha, A.; Ibrahim, M. Computational notes on the effect of solvation on the electronic properties of glycine. *Der pharmachemical* **2015**, *7*, 377-380.

17. Atta, D.; Gomaa, F.; Elhaes, H.; Ibrahim, M. Effect of Hydrated Dioxin on the Physical and Geometrical Parameters of Some Amino Acids. *J Comput Theor Nanos* **2017**, *14*, 2405-2408, https://doi.org/10.1166/jctn.2017.6840.

18. Katranidis, A.; Atta, D.; Schlesinger, R.; Nierhaus, K.H.; Choli-Papadopoulou, T. Observing proteins as single molecules encapsulated in surface-tethered polymeric nanocontainers. *Angew. Chem. Int. Ed* **2009**, *48*, 1758-1761, https://doi.org/10.1002/cbic.200800739.

19. Kenneth, J.R.; Nae, S. Nuclear factor-κB1: Regulation and function. *Int J Biochem Cell B* **2008**, *40*, 1452-1466, https://doi.org/10.1016/j.biocel.2007.05.004.

20. Semba, R.D.; Shardell, M.; Sakr, F.A.; Moaddel, R.; Trehan, I.; Maleta, K.M.; Ordiz, M.I.; Kraemer, K.; Khadeer, M.A.; Ferrucci, L.; Manary, M.J. Child Stunting is Associated with Low Circulating Essential Amino Acids. *EBioMedicine* **2016**, *6*, 246-252.

21. Otten, J.J.; Hellwig, J.P.; Meyers, L.D. *Dietary Reference Intakes: the Essential Guide to Nutrient Requirements*, The National Academies Press, Washington DC, 2006, https://doi.org/10.17226/11537.

22. Palani, R.; Selvarasi, J. Molecular interaction studies of some amino acids with aqueous amoxicillin solution at 308.15K. *Biointerface Res. Appl. Chem*. **2017**, *7*, 1969-1975.

23. Wu, G. Amino acids: metabolism, functions, and nutrition. *Amino Acids* **2009**, *37,* 1-17, https://doi.org/10.1007/s00726-009-0269-0.

24. Peter, J. Dispensable and Indispensable Amino Acids for Humans. *J Nutr* **2000**, *130*, 1835–1840, https://doi.org/10.1093/jn/130.7.1835S.

25. Peter, F.; Peter, S. What Are the Essential Elements Needed for the Determination of Amino Acid Requirements in Humans? *J Nutr* **2004**, *134*, 1558–1565, https://doi.org/10.1093/jn/134.6.1558S.

26. Lu, F.; Haga, Y.; Satoh, S. Effects of replacing fish meal with rendered animal protein and plant protein sources on growth response, biological indices, and amino acid availability for rainbow trout Oncorhynchus mykiss. *Fish Sci* **2015**, *81*, 95-105, http://dx.doi.org/10.1007/s12562-014-0818-7.

27. Zhou, A.Q.; O'Hern, C.S. *L. Regan,* Predicting the side-chain dihedral angle distributions of nonpolar, aromatic, and polar amino acids using hard sphere models. *Proteins* **2014**, *82*, 2574-2584, https://doi.org/10.1002/prot.24621.

28. Daniele, F.; Alessio, A.; Giuseppe, F.; Rossella, D.; Ines, M. Analytical pyrolysis of dipeptides containing proline and amino acids with polar side chains. Novel 2,5-diketopiperazine markers in the pyrolysates of proteins. *J Anal Appl Pyrol* **2012**, *95*,145-155, https://doi.org/10.1016/j.jaap.2012.02.001.

29. Kundu, S. Amino acid network within protein. *Physica A* **2005**, *346*, 104–109, https://doi.org/10.1016/j.physa.2004.08.055.

30. Aftabuddin, M.; Kundu, S. Hydrophobic, Hydrophilic, and Charged Amino Acid Networks within Protein. *Biophys J* **2007**, *93,* 225–231, https://doi.org/10.1529/biophysj.106.098004.

31. Bhagavan, N.V.; Chung-Eun, H. *Essentials of Medical Biochemistry,* 2nd ed, AcademicPress, California**,** 2015.

32. Bhagavan, N.V. *Medical Biochemistry,* 4th ed, Academic Press, California**,** 2002.

33. Parker, J. Peptide Bond. In *Encyclopedia of Genetics*, Eds, Sydney, B.; Jefferey, H.M. Academic Press, California, 2001.

34. Stephen, H.S. *Organic and Biological Chemistry*, Cengage Learning, Boston, 2016.

35. Andrei, N.L.; Markus, G. The Structure of α-Helical Coiled Coils. *Adv Prot Chem* **2005**, *70*, 37-38, https://doi.org/10.1016/S0065-3233(05)70003-6.

36. Lydon, J.E. The DNA double helix—the untold story. *Liquid Crystals Today* **2003**, *12,* 1-9, https://doi.org/10.1080/14645180310001603962.

37. Kreplak, L.; Doucet, J.; Dumas, P.; Briki, F. New Aspects of the α-Helix to β-Sheet Transition in Stretched Hard α-Keratin Fibers. *Biophys J* **2004**, *87*, 640–647, https://doi.org/10.1529/biophysj.103.036749.

38. Murray, J.E.; Laurieri, N.; Delgoda, R. *Proteins, In Pharmacognosy*, Eds, Simone, B.; Rupika, D, Academic Press, California, 2017.

39. Behrouz, F.; Eva, J.F.; Krishnan, P.N. Stabilization of alpha-helical structures in short peptides via end capping. *PNAS* **1993**, *90*, 838-842, https://doi.org/10.1073/pnas.90.3.838.

40. Presta, L.G.; Rose, G.D. Helix signals in proteins. *Science* **1988**, *240*, 1632-1641.

41. Marcin, W.; Matthew, B.; Gail, J.B.; Emily, G.B.; Marta, K.; Peter, J.K.; Lorna, D.; Derek, N.W.; Emanuele, P.; Michelle, P. Characterization of long and stable de novo single alpha-helix domains provides novel insight into their stability. *Sci Rep* **2017,** *7*, 44341, https://doi.org/10.1038/srep44341.

42. Hua, L.; Jing, W.; Yugang, B.; Jason, W.L.; Shiyong, L.; Yao, L.; Jianjun C., Ionic polypeptides with unusual helical stability. *Na tCommun* **2011**, *2*, 206**,** https://doi.org/10.1038/ncomms1209.

43. Duncan, A.E.C.; Simon, P.; Andrew, J.D. Effect of the N1 residue on the stability of the α-helix for all 20 amino acids. *Prot.Sci.* **2001,** *10*, 463–470, https://doi.org/10.1110/ps.31001.

44. Jaison, J.; Herve, D.; David, S.C.; The Role of Proline and Glycine in Determining the Backbone Flexibility of a

Channel-Forming Peptide. *Biophys J* **1999**, *76*, 1367-1376, https://doi.org/10.1016/S0006-3495(99)77298-X.

45. Kumeta, M.; Konishi, H.A.; Zhang, W.; Sakagami, S.; Yoshimura, S.H. Prolines in the α-helix confer the structural flexibility and functional integrity of importin-β. *J Cell Sci* **2018**, *131*, https://doi.org/10.1242/jcs.206326.

46. Plat, A.; Kuipers, A.; Crabb, J.; Rink, R.; Moll, G.N. Mutagenesis of nisin's leader peptide proline strongly modulates export of precursor nisin. *A Van Leeuw J Microb* **2017**, *110,* 321-330, https://doi.org/10.1007/s10482-016-0802-6.

47. Pace, C.N.; Scholtz, J.M. A Helix Propensity Scale Based on Experimental Studies of Peptides and Proteins. *Biophys. J.* **1998**, *75,* 422–427**,** https://doi.org/10.1016/S0006-3495(98)77529-0.

48. Saeed, H.K.; Jarman, P.J.; Archer, S.; Sreedharan, S.; Saeed, I.Q.; Mckenzie, L.K.; Weinstein, J.A.; Buurma, N.J.; Smythe, C.G.W.; Thomas, J.A. Homo- and Heteroleptic Phototoxic Dinuclear Metallo-Intercalators Based on RuII(dppn) Intercalating Moieties: Synthesis, Optical, and Biological Studies. *Angew Chem Int Ed* **2017**, *56*, 12628-12633, https://doi.org/10.1002/anie.201707350.

49. Hifsudheen, M.; Mishra, R.K.; Vedhanarayanan, B.; Praveen, V.K.; Ajayaghosh, A. The Helix to Super-Helix Transition in the Self-Assembly of π-Systems: Superseding of Molecular Chirality at Hierarchical Level. *Angew Chem Int Ed* **2017**, *56*, 12634-12638, https://doi.org/10.1002/anie.201707392.

50. Harmand, T.J.; Pattabiraman, V.R.; Bode, J.W. Chemical Synthesis of the Highly Hydrophobic Antiviral Membrane-Associated Protein IFITM3 and Modified Variants. *Angew Chem Int Ed* **2017**, *56,* 12639-12643, https://doi.org/10.1002/anie.201707554.

51. Ralph, A.B.; Edward, A.D. *Handbook of Cell Signaling,* 2nd Ed ,Academic Press, California**,** 2010, https://doi.org/10.1016/B978-0-12-374145-5.X0001-0.

52. Joshi, S.B.; Kamerzell, T.J.; McNown, C.; Middaugh, C.R. The Interaction of Heparin/polyanions with Bovine, Porcine, and Human Growth Hormone. *J Pharm Sci* **2008**, *97,* 1368-1385, https://doi.org/10.1002/jps.21056.

53. Maria, A.; Dina, K.; Mary, P.; Evangelia, G.K.; Georgios, F.; Ioannis, K.; Javier, P.; Michael, K. Structural plasticity of 4-α-helical bundles exemplified by the puzzle-like molecular assembly of the Rop protein. *PNAS* **2014**, *111*, 11049-11054, https://doi.org/10.1073/pnas.1322065111.

54. Hans P.K.; Martin, C.; Gerald, N.; Gerrit, V.; Chris, S.; Helmut, B. Four-helix bundle topology re-engineered: monomeric Rop protein variants with different loop arrangements. *Protein Eng Des Sele* **2001**, *14*, 897–901, https://doi.org/10.1093/protein/14.11.897.

55. Supratim, C. *Bioinformatics for Beginners Genes, Genomes, Molecular Evolution, Databases and Analytical Tools*, The National Academies Press, Washington, DC, 2014.

56. Cooley, R.B.; Arp, D.J.; Karplus, P.A. Evolutionary Origin of a Secondary Structure: π-Helices as Cryptic but Widespread Insertional Variations of α-Helices That Enhance Protein Functionality. *JMolBiol.* **2010**, *404*, 232-246**,** https://doi.org/10.1016/j.jmb.2010.09.034.

57. Keefe, L.J.; Sondek, J.; Shortle, D.; Lattman, E.E. The alpha aneurism: a structural motif revealed in an insertion mutant of staphylococcal nuclease. *PNAS* **1993**, *90*, 3275–3279.

58. Weaver, T.M. The π-helix translates structure into function. *Protein Sci* **2000**, *9*, 201–206, https://doi.org/10.1110/ps.9.1.201.

59. Fodje, M.N.; Al-Karadaghi, S. Occurrence, conformational features and amino acid propensities for the π-helix. *Protein Eng* **2002**, *15*, 353–358.

60. Andrei, N.L.; Jens, B. Coiled Coils – A Model System for the 21st Century. *Trends Biochem Sci* **2017**, *42*, 130-140, https://doi.org/10.1016/j.tibs.2016.10.007.

61. Andrew, J.W. Inhibition of protein–protein interactions using designed molecules. *Chem Soc Rev* **2009**, *38*, 3289-3300**,** https://doi.org/10.1039/b807197g**.**

62. Zhdanov, V.; Kasemo, B. Folding of bundles of α-helices in solution, membranes, and adsorbed overlayers. *Proteins* **2001**, *42*, 81-494, https://doi.org/10.1002/1097-0134(20010301)42:4<481::AID-PROT70>3.0.CO;2-N.

63. Segrest, J.P.; Jones, M.K.; Mishra, V.K.; Anantharamaiah, G.M.; Garber, D.W. apoB-100 has a pentapartite structure composed of three amphipathic alpha-helical domains alternating with two amphipathic beta-strand domains. Detection by the computer program LOCATE. *Arterioscl Throm Vas* **1994**, *14*, 1674-1685.

64. Tarun, N.J.; Pierrick, C.; Nicolas, K.S.; Hubert, S.; Joseph, R.; Catherine, E.; Alexandre, G.D. Dynamics and deformability of α-, 310- and π-helices. *Arch Biol Sci* **2018**, *70,* 21-31, https://doi.org/10.2298/ABS170215022N.

65. Pal, L.; Basu, G.; Chakrabarti, P. Variants of 310-helices in proteins. *Proteins* **2002**, *48*, 571-579, https://doi.org/10.1002/prot.10184.

66. Pal, L.; Basu, G. Novel protein structural motifs containing two-turn and longer 310-helices. *Protein Eng* **1999**, *12,* 811-814, https://doi.org/10.1093/protein/12.10.811.

67. Lisa, J.K.; John, S.; David, S.; Eaton, E.L. The alpha aneurism: a structural motif revealed in an insertion mutant of staphylococcal nuclease. *PNAS* **1993**, *90*, 3275-3279**.**

68. Donohue, J.H. Hydrogen Bonded Helical Configurations of the Polypeptide Chain. *PNAS* **1953,** *39,* 470-478**.**

69. Kumar, P.; Bansal, M. Dissecting π-helices: sequence, structure and function. *FEBS J* **2015**, *282*, 4415-4432, https://doi.org/10.1111/febs.13507.

70. Kyung-Hoon, L.; David, R.B.; Krzysztof, K. Transitions from α to π Helix Observed in Molecular Dynamics Simulations of Synthetic Peptides. *Biochemistry* **2000**, *39*, 13737–13747**,** http://dx.doi.org/10.1021/bi001126b.

71. Jane, S.M.; Julian, M.S.; Lynne, R.R. Sidechain interactions in parallel β sheets: the energetics of cross-strand pairings. *Structure* **1999**, *7*, 1333-1343, https://doi.org/10.1016/S0969-2126(00)80023-4.

72. Richardson, J.S. The Anatomy and Taxonomy of Protein Structure. *Adv Protein Chem* **1981**, *34*, 167–339, https://doi.org/10.1016/S0065-3233(08)60520-3.

73. Levitt, M.; Chothia, C. Structural patterns in globular proteins. *Nature* **1976**, *261*, 552–558, https://doi.org/10.1038/261552a0.

74. Pankaja, N. *Biochemistry,* 4thEd, JBmedical publisherltd, New Delhi, 2016.

75. Nancy, L.C.; Rachel, G.; Orna, C.; Carol, G.; Gisela, S. *Molecular Biology: Principles of Genome Function***,** Oxford University Press, Oxford, 2014.

76. Cozzone**,** A.J. *Proteins: Fundamental Chemical Properties***,** John Wiley and Sons Ltd, Chichester, 2010, https://doi.org/10.1002/9780470015902.a0001330.pub2.

77. Theodore, X.O.; Rayan, P.A.; Thomas, E.B. *Crush Step1E-Book: The Ultimate USMLE Step1 Review*, Elsevier Health Sciences, 2013.

78. Jean-Pierre, S. Amino Acids, Peptides and Proteins. In *Spectroscopy and Modeling of Biomolecular Building Blocks*, Eds S. Jean-Pierre, Elsevier, 2008, https://doi.org/10.1016/B978-044452708-0.50006-X.

79. Yves, M. Geometrical Properties of H-Bonds and H-Bonded Organized Supramolecular Structures. In *The Hydrogen Bond and the Water Molecule*, Eds M.Yves, Elsevier, 2007, https://doi.org/10.1016/B978-044451957-3.50003-2.

80. Nicolae-Viorel, B.; Gerhard H.H. Structure and Dynamics of Parallel β-Sheets, Hydrophobic Core, and Loops in Alzheimer's Aβ Fibrils. *Biophys J* **2007**, *92*, 3032–3039, https://doi.org/10.1529/biophysj.106.100404.

81. Williams, R.J.P., Fraústo da Silva, J.J.R. Outline of Biological Chemical Principles: Components, Pathways and Controls. In *The Chemistry of Evolution*, Elsevier Science Ltd, 2006, https://doi.org/10.1016/B978-044452115-6/50047-6.

82. Jane, S.M.; Julian, M.S.; Lynne, R. Sidechain interactions in parallel β sheets: the energetics of cross-strand pairings. *Structure* **1999**, *7*, 1333–1343, https://doi.org/10.1016/S0969-2126(00)80023-4.

83. Dube, R.C. *Advanced Biotechnology*, *S. Chand & Company PLtd*, Delhi, 2014.

84. Elsie, G.; Elsie, E.G.; Chris, R. *Therapeutics and Human Physiology: How Drugs Work*, Oxford University Press, Oxford, 2013.

85. Daan, J.A.C.; Robert, D.S.; Bernd, M. *Pharmaceutical Biotechnology: Fundamentals and Applications,* 4thEd, Springer, New York, 2013, https://doi.org/10.1007/978-1-4614-6486-0.

86. Judit, P.; Mary, K. *Medical Biotechnology*, Elsevier Science Ltd, 2009.

87. Jane, S.R.; David, C.R. Natural β-sheet proteins use negative design to avoid edge-to-edge aggregation. *PNAS* **2002**, *99,* 2754-2759, https://doi.org/10.1073/pnas.052706099.

88. Murzin, A.G.; Brenner, S.E.; Hubbard, T.; Chothia, C. SCOP: A structural classification of proteins database for the investigation of sequences and structures. *J Mol Biol* **1995**, *247*, 536-540, https://doi.org/10.1016/S0022-2836(05)80134-2.

89. Orengo, C.A.; Michie, A.D.; Jones, S.; Jones, D.T.; Swindells, M.B.; Thornton, J.M. CATH – a hierarchic classification of protein domain structures. *Structure* **1997**, *5*, 1093-108, https://doi.org/10.1016/S0969-2126(97)00260-8.

90. Chengcheng, H.; Patrice, K. Helix-sheet packing in proteins. *Proteins* **2010**, *78*, 1736–1747, https://doi.org/10.1002/prot.22688.

91. Abrusán, G.; Marsh, J.A. Alpha Helices Are More Robust to Mutations than Beta Strands. *PLoS Compu. Biol* **2016**, *12*, https://doi.org/10.1371/journal.pcbi.1005242.

92. Qin, Z.Q.; Buehler, M.J. Cooperative deformation of hydrogen bonds in beta-strands and beta-sheet nanocrystals. *Phys Rev E* **2010**, *82*, https://doi.org/10.1103/PhysRevE.82.061906.

93. Sheh-Yi, S.; Dah-Yen, Y.; Selzle, H.L.; Schlag, E.W. Energetics of hydrogen bonds in peptides. *PNAS* **2003***, 100*, 1 2683-12687, https://doi.org/10.1073/pnas.2133366100.

94. Vanzi, F.; Vladimirov, S.; Knudsen, C.R.; Goldman, Y.E.; Cooperman, B.S. Protein synthesis by single ribosomes. *RNA* **2003**, *9*, 1174–1179, https://dx.doi.org/10.1261%2Frna.5800303.

95. Brar, G.A.; Weissman, J.S. Ribosome profiling reveals the what, when, where and how of protein synthesis. *Nat Rev Mol Cell Bio* **2015**, *16*, 651–664, https://doi.org/10.1038/nrm4069.

96. Angelica, F.; Leyi, W.; Altman, R.B.; Terry, D.S.; Juette, M.F.; Burnett, B.J.; Alejo, J.L.; Dass, R.A.; Parks, M.M.; Vincent, C.T.; Blanchard, S.C. Functional Dynamics within the Human Ribosome Regulate the Rate of Active Protein Synthesis. *Mol Cell* **2015**, *60*, 475-486, https://doi.org/10.1016/j.molcel.2015.09.013.

97. Ingolia, N.T.; Brar, G.A.; Stern-Ginossar, N.; Harris, M.S.; Talhouarne, G.J.S.; Jackson, S.E.; Wills, M.R.; Weissman, J.S. Ribosome Profiling Reveals Pervasive Translation Outside of Annotated Protein-Coding Genes. *Cell Reports* **2014**, *8*, 1365-1379, https://doi.org/10.1016/j.celrep.2014.07.045.

98. Tristan, B.; Michael, B.; Markus, D. Interplay between Secondary and Tertiary Structure Formation in Protein Folding Cooperativity. *J Am Chem Soc* **2010**, *132*, 13129-13131, https://doi.org/10.1016/j.bpj.2010.12.1361.

99. Pelley, J.W. Protein Structure and Function**. ** *Elsevier's Integrated Biochemistry,* Mosby, 2007.

100. Van Broeck, B.; Van Broeckhoven, C.; Kumar-Singh, S. Current Insights into Molecular Mechanisms of Alzheimer Disease and Their Implications for Therapeutic Approaches. *Neurodegener Dis* **2007**, *4*, 349-365, https://doi.org/10.1159/000105156.

101. Huang, Y.; Lennart, M. Alzheimer Mechanisms and Therapeutic Strategies. *Cell* **2012**, *148*, 1204–1222, https://doi.org/10.1016/j.cell.2012.02.040.

102. Yanker, B.A.; Duffy, L.K.; Kirschner, D.A. Neurotrophic and neurotoxic effects of amyloid beta protein: reversal by tachykinin neuropeptides**. ** *Science* **1990**, *250,* 279-282**.**

103. Chen, X.; Yan, S.D. Mitochondrial Aβ A potential cause of metabolic dysfunction in Alzheimer's disease. *IUBMB Life* **2006**, *58*, 686-694, https://doi.org/10.1080/15216540601047767.

104. Ibrahim, M.; Al-Hossain, A.; Al-Fifi, Z. Structural and Spectroscopic Analysis for Metals Interaction with Protein. *J Comput Theor Nanosci* **2010***, 7*, 2244-2248, https://doi.org/10.1166/jctn.2010.1582.

105. Elhaes, H.; Moawad H.; Ibrahim, M. Spectroscopic Analyses of the Chromium Interaction with Protein. *J Comput Theor Nanosci* **2012***, 9*, 1036-1039, http://dx.doi.org/10.1166/jctn.2012.2137.

106. Elhaes, H.; Elkashef, N.M.; Abdel-Gawad, F.K.; Shaban, A.M.; Ibrahim, M. Effect of Divalent Metals on the Molecular Structure of Protein: Modeling and Spectroscopic Approaches. *J Comput Theor Nanosci* **2014**, *11*, 1081-1085, https://doi.org/10.1166/jctn.2014.3465.

107. Ghazaleh, B.; Leila, G.; Kianoush K., Antimicrobial and antioxidant effect of nanoliposomes containing Zataria multiflora boiss essential oil on the rainbow trout fillets during refrigeration. *Biointerface Res. Appl. Chem.* **2018**, *8,* 3594 – 3601.

108. Fatemeh, M.; The effect of biointerface of chemicals and inhibitors in the cerebral cortex of brain on language cognition. *Biointerface Res. Appl. Chem.* **2018**, *8*, 3628 – 3634.

109. Ladefoged, L.K.; Zeppelin, T.; Schiøtt, B. Molecular modeling of neurological membrane proteins − from binding sites to synapses. *Neuro Sci Lett*, In press, https://doi.org/10.1016/j.neulet.2018.05.034.

110. King, M.R. *Principles of Cellular Engineering: Understanding the Biomolecular Interface*, Elsevier Academic Press, Amsterdam, 2006.

111. Likhachev, I.V.; Balabaev, N.K.; Galzitskaya, O.V. Available Instruments for Analyzing Molecular Dynamics Trajectories. *Open Biochem J* **2016**, *10*, 1-11, https://doi.org/10.2174/1874091X01610010001.

112. Rouhani, M.; Khodabakhsh, F.; Norouzian, D.; Cohan, R.A.; Valizadeh, V. Molecular dynamics simulation for rational protein engineering: Present and future prospectus. *J Mol Graph Model* **2018**, *84*, 43-53, https://doi.org/10.1016/j.jmgm.2018.06.009.

113. Ganesan, A.; Moon, T.C.; Barakat, K. Revealing the atomistic details behind the binding of B7–1 to CD28 and CTLA-4: A comprehensive protein-protein modelling study. *Biochim Biophys Acta* **2018**, *1862*, 2764-2778, https://doi.org/10.1016/j.bbagen.2018.08.010.

114. Prates, L.L.; Lei,Y.; Refat, B.; Zhang, W.; Yu, P. Effects of heat processing methods on protein subfractions and protein degradation kinetics in dairy cattle in relation to protein molecular structure of barley grain using advanced molecular spectroscopy. *J Cereal Sci* **2018**, *80*, 212-220, https://doi.org/10.1016/j.jcs.2018.01.008.

115. Sun, B.; Khan, N.A.; Yu, P. Molecular spectroscopic features of protein in newly developed chickpea: Relationship with protein chemical profile and metabolism in the rumen and intestine of dairy cows. *Spectrochim Acta A* **2018**, *196*, 168-177, https://doi.org/10.1016/j.saa.2018.02.008.

116. Calero-Rubio, C.; Ghosh, R.; Saluja, A.; Roberts, C.J. Predicting Protein-Protein Interactions of Concentrated Antibody Solutions Using Dilute Solution Data and Coarse-Grained Molecular Models. *J Pharm Sci* **2018**, *107*, 1269-1281, https://doi.org/10.1016/j.xphs.2017.12.015.

117. Meng, L.; Feng, K.; Ren, Y. Molecular modelling studies of tricyclic triazinone analogues as potential PKC-θ inhibitors through combined QSAR, molecular docking and molecular dynamics simulations techniques. *J Taiwaninst Chem E* **2018**, *91*, 1 55-175, https://doi.org/10.1016/j.jtice.2018.06.017.

118. Atta, D.; Gomaa, F.; Elhaes, H.; Ibrahim, M. Effect of Hydrated Dioxin on the Physical and Geometrical Parameters of Some Amino Acids. *J Comput Theor Nanosci* **2017**, *14*, 2405-2408, https://doi.org/10.1166/jctn.2017.6840.

119. Ibrahim, M.; Elhaes, H.; Atta, D. Computational Notes on the Effect of Sodium Substitution on the Physical Properties of Fullerene. *J Comput Theor Nanosci* **2017**, *14*, 4114-4117, https://doi.org/10.1166/jctn.2017.6794.

120. Okasha, A.; Atta, D.; Badawy, W.M.; Frontasyeva, M.V.; Elhaes, H.;I brahim, M. Modeling the Coordination Between Na, Mg, Ca, Fe, Ni, and Zn with Organic Acids. *J Comput Theor Nanosci* **2017**, *14*, 1357-1361, https://doi.org/10.1166/jctn.2017.6794.

121. Kumbaradoddi, B.U.; Shridevi. D.D.; Chandra, N.S.L.; Javarasetty, C.; Srikantamurthy, N. Novel 1,3,4-oxadiazole tethered pyrazolyl-isoxazoles: synthesis, characterization and pharmacological screening. *Biointerface Res. Appl. Chem*. **2017**, *7*, 1901-1912.

9. ACKNOWLEDGEMENTS