International Journal of
Advance in Molecular Engineering

Volume 2, Issue 1, 2024
January-June
DOI (Journal): 10.37591/IJAME

https://journals.stmjournals.com/ijame/

HYPOTHESIS IJAME

Butrin Tackles Retinoblastoma – A Clinical Hypothesis†

Rakshana Manikandan[1], M. Mala[2], G. Manikandan[3], Prakash Vaithyanathan[4,*]

Abstract

Breach of association of legumain protein activities to the corresponding cellular components results in over-expression of legumain, and constitutes a key biomarker for a variety of life-taxing sicknesses like cancer, Alzheimer's/Parkinson's and acute kidney injury. To suppress the functions of legumain, it is hypothesized that a water soluble and edible biomolecule, namely, butrin (7, 3', 4'-trihydroxy flavanone-7, 3'-diglucoside) may have the therapeutic potential owing to its special ability to bind to the key catalytic sites of legumain, discovered through bioinformatic studies. Insights, into the docking structure of butrin were provided with emphasis on the relative binding abilities of various hydroxyl groups of butrin with the amino acid residues of the legumain protein.

Keywords: Acute kidney injury, Alzheimer's disease, biomarker, butrin, cancer tumor, legumain, molecular level interaction

INTRODUCTION

Butrin is hypothesised to have the therapeutic potential for dreadful diseases like cancer, Alzheimer's and acute kidney damage via suppression of the functions of the protein legumain, the key biomarker of the aforesaid ailments. Details on the strucure, chemical composition and physicochemical properties of butrin ($C_{27}H_{32}O_{15}$ $2H_2O$; 7, 3', 4'-trihydroxy flavanone-7, 3'-diglucoside) can be found in the National Library of Medicine and other standard scientific literature [1, 2]. The author hypothesizes that the sanctity of butrin lies in its ability to treat a variety of cancers (retinoblastoma, oral, lung, liver, breast and many others) as well as prominent diseases like the Alzheimer's and the acute kidney injury. The basis for such a hypothesis lies in the potential of the molecular level interaction of butrin with the amino acid residues of the over expressed biomarker, namely, legumain. Under diseased conditions, there will be a breach to the proper association of legumain (LGMN) activities with the corresponding cellular compartments [3-9]. The chemical structure of butrin as well as the legumain are shown in Figures 1 and 2. [1, 3, 10]. The rich oxygen content and multifunctional grops (hydroxyl, aryl ether, quinone and aromaticity), enabled the butrin molecule to interact with legumain in various ways.

The crystal structure of human legumain [asparaginyl endopeptidase (AEP) or vacuolar processing enzyme (VPE)], activated at pH 4.0 is shown as a green cartoon in Figure. 2. The active site is labelled as the covalent Z-Ala-Ala-AzaAsn-chloro-mehtyl ketone inhibitor (orange sticks). The catalytic residues and the RGD motif are shown as labelled sticks in the image (Figure 2). The legumain's domain has a caspase enzyme like fold as proved by its interaction with substrate moieties (Figure 2). Matured legumain differs from normal caspases in their activation schemes.

The localization of mammalian legumain outside the lysosome under pathophysiological conditions is depcited pictorially in Figure 3. The compartmentalization of legumain in the cytoplasm and in the nucelus and its function over there, though poorly understood, is related to the pathological situations of cancer or Alzheimer's

***Author for Correspondence**
Prakash Vaithyanathan
E-mail: pvaithyanathan@gmail.com

[1]Trustee, Tagore Educational Trust, Chennai, Tamil Nadu, India
[2]Chairperson and Managing Trustee, Tagore Educational Trust, Chennai, Tamil Nadu, India
[3]Secretary, Tagore Educational Trust, Chennai, Tamil Nadu, India
[4]Science Teacher and Innovator, Chennai, Tamil Nadu, India

Received Date: September 10, 2024
Accepted Date: September 14, 2024
Published Date: September 15, 2024

Citation: Rakshana Manikandan, M. Mala, G. Manikandan, Prakash Vaithyanathan. Butrin tackles Retinoblastoma – A Clinical Hypothesis International Journal of Advance in Molecular Engineering. 2024; 2(1): 26–30p.

diseases. The trafficking of legumain (AEP) inside the cell (from lysosome into the cytosol (dark purple arrow) and into the nucleus (light purple arrow) as well as to outside the cell is schematically shown in Figure 3. Based on the preliminary docking studies on the relative interaction of butrin with the residual amino acids of legumain (Figure 4), it is hypothesized that the molecular level interactions of butrin with legumain may tackle the abnormal functions of legumain.

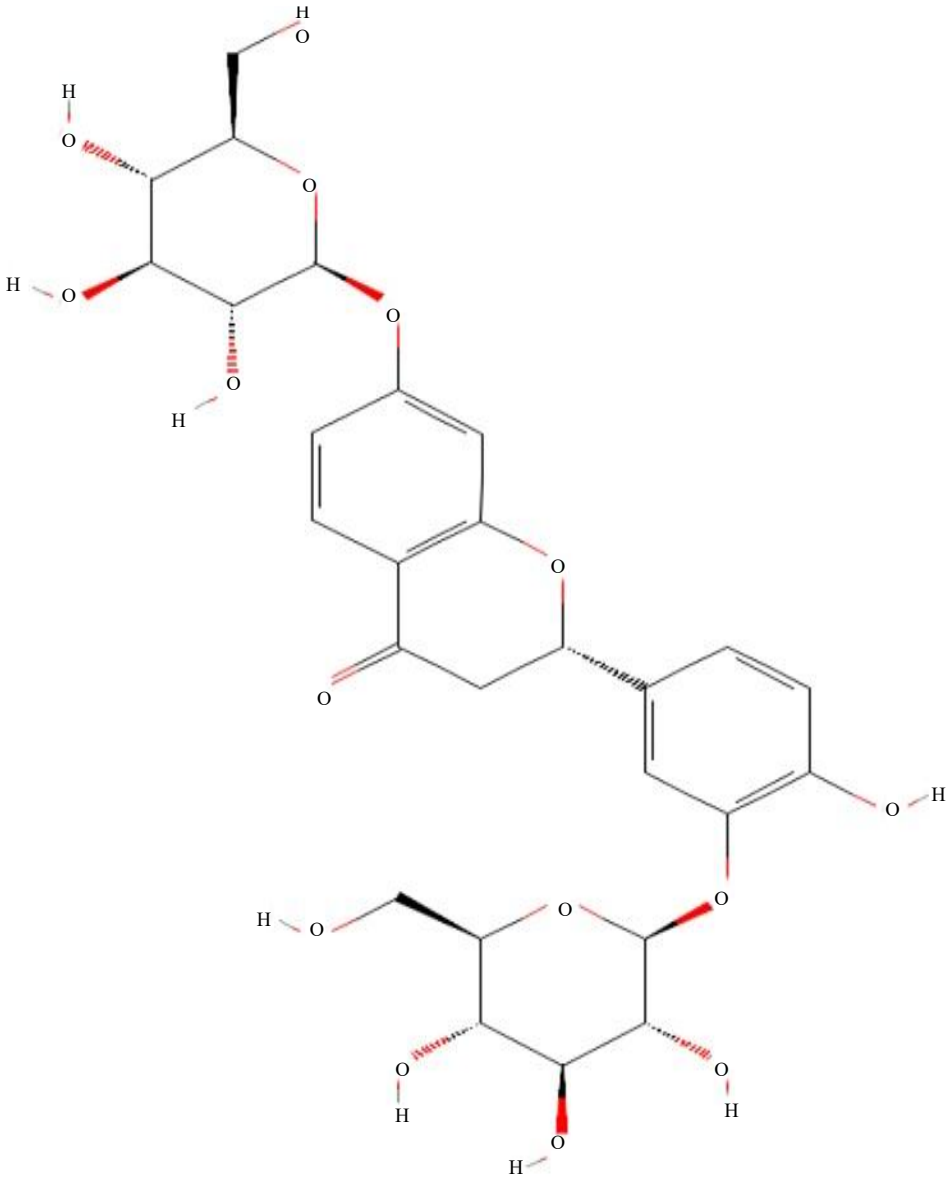

Figure 1. Chemical structure of butrin ($C_{27}H_{32}O_{15}$ $2H_2O$; CAS: 492-13-7; 7, 3', 4'-trihydroxy flavanone-7, 3'-diglucoside) [reproduced with permission from 1].

Over expression of legumain is known to cause acute kidney injury as well [11] and the hypothesis envisioned here, namely, interaction of butrin with legumain may effectively suppress the abnormal functions of legumain.

Butrin's Interaction With Legumain

Legumain is over expressed in retinoblastoma, a paediatric cancer, that affects thousands of children in India every year. Butrin's interaction with legumain is studied through bioinformatic docking studies. The results demonstrated clear interaction of butrin with the residual proteins, Cys 189, Hie 148, Ser

215 and Glu 190 of the legumain protein as shown in Figure. 4. This gives the hope that butrin may play an important role to suppress the over expression of legumain in retinoblastoma, breast, oral, lung and liver cancers. Legumain protein is the key culprit to induce tremendous pain in oral cancer patients and its suppression is very important to promise a painless therapy. Butrin may offer tremendeous hope in that direction.

The author has learnt that butrin has offered promising results in animal trial models of Alzheimer's/Parkinson's disease carried out by a prominent research group in India. The author's discovery about the interaction of butrin with legumain will give mechanistic clues for all the research groups that are pursing animal model studies and clinical trials.

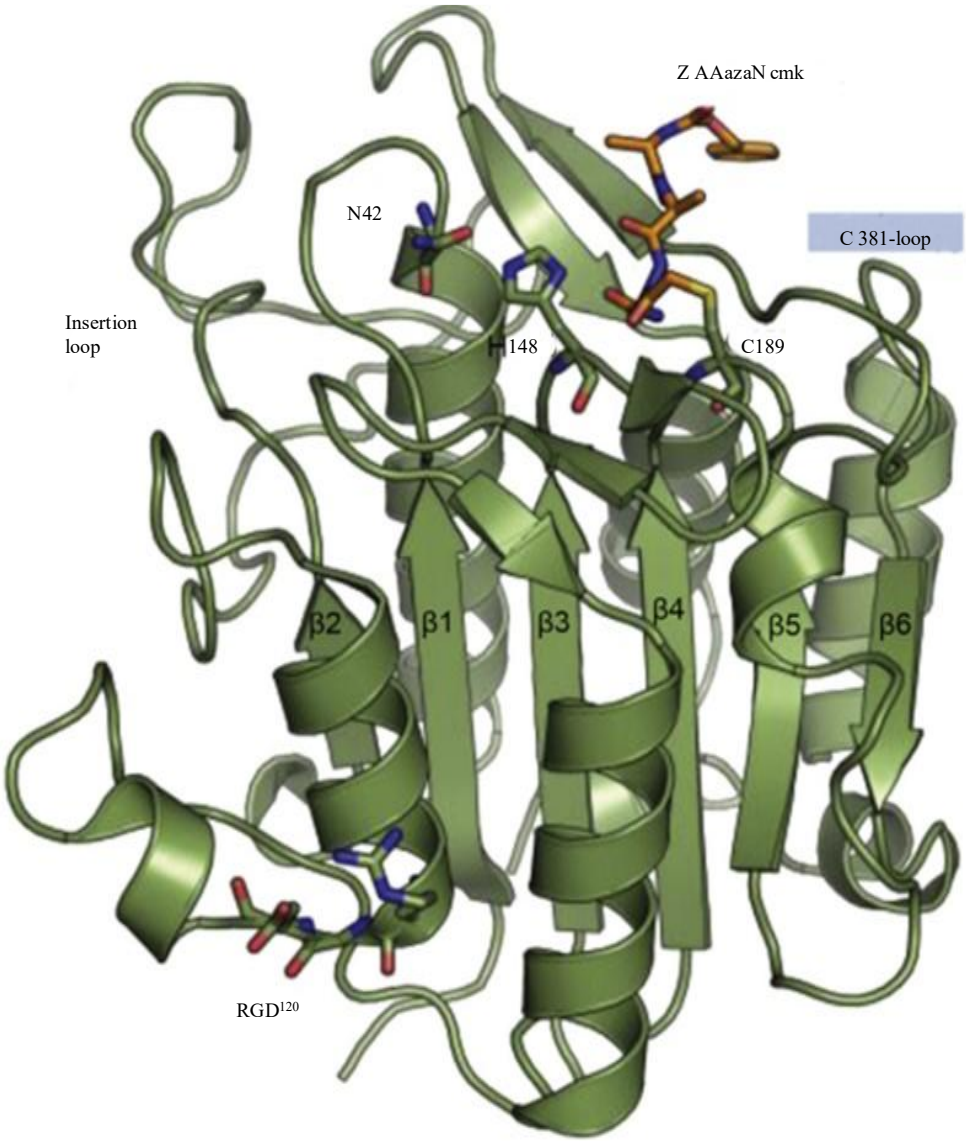

Figure 2. Crystal structure of legumain [asparaginyl endopeptidase (AEP) or vacuolar processing enzyme (VPE)] [Reproduced from reference 3 with permission from Elsevier].

Studies related to animal trials by feeding them on butrin containing diet and monitoring the expression of the biomarkers of cancer and Alzheimer's diseases are underway and they would form the subject of the large research communication later. The author is hopeful of fruitful research collaboration with research groups across the globe.

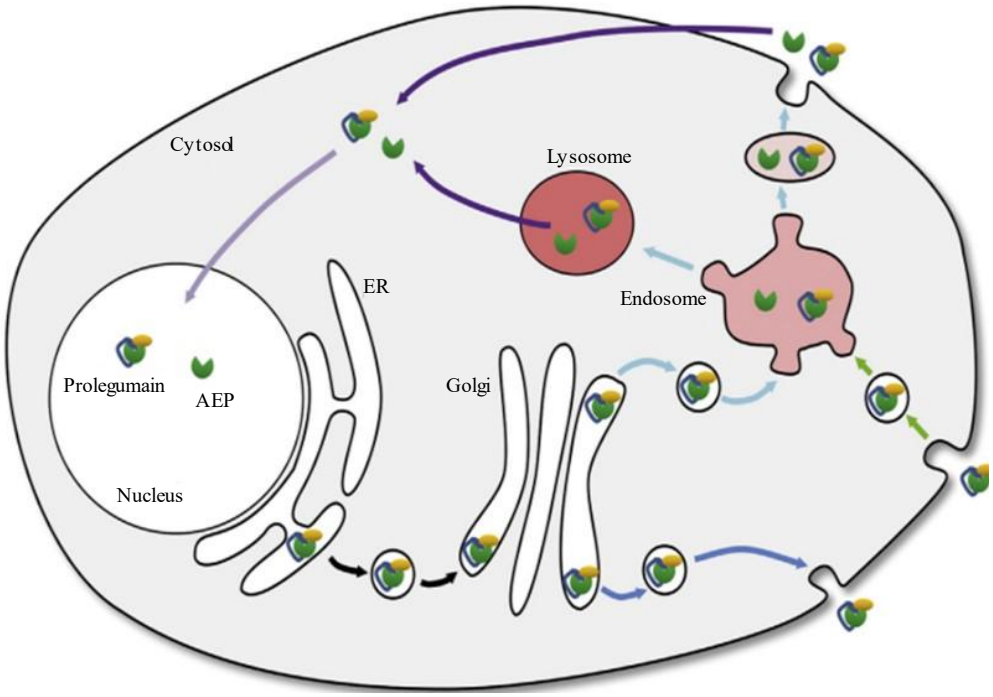

Figure 3. Compartmentalization as well as in and outward mobility and traficking of legumain (marked as AEP in the Figure as shown in near hemispherical shape) leading to conditions like Alzheimer's and Cancer. [asparaginyl endopeptidase (AEP) or vacuolar processing enzyme (VPE)] [Reproduced from reference 3 with permission from Elsevier].

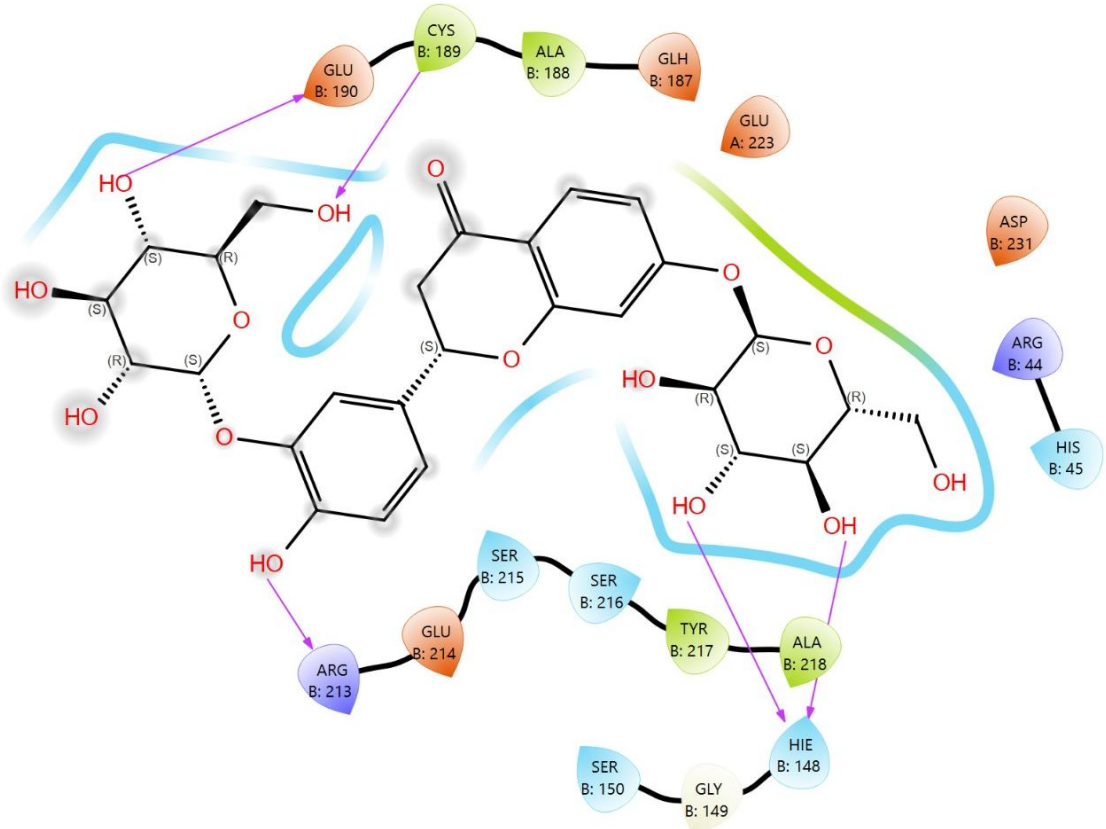

Figure 4. Energetically most favoured structure of butrin in interaction with key amino acids of the legumain protein.

CONCLUSION

Over-expression of legumain is one of the key therapeutic targets in most of the dreadful ailments like cancer (retinoblastoma, brain, lung, liver, breast), Alzheimer's disease and acute kidney injury. A hypothesis, based on butrin's beautiful interaction with legumain through preliminary docking studies gives hope for a positive therapeutic benefit for the patients.

[†]Dedicated to the legendary oncologist Padma Vibhushan Late Dr. V Shanta amma

REFERENCES

1. https://pubchem.ncbi.nlm.nih.gov/compound/Butrin
2. Lal JB. 326. Constitution of the glucoside butrin isolated from *Butea Frondosa* flowers. Part I. Journal of the Chemical Society (Resumed). 1937:1562-4.
3. Dall E, Brandstetter H. Structure and function of legumain in health and disease. Biochimie. 2016 Mar 1;122:126-50.
4. Irfan N, Vaithyanathan P, Anandaram H, Zaidh SM, Varshini SP, Puratchikody A. Active and Allosteric Site Binding MOLECULAR MECHANICS-QUANTUM MECHANICS studies of STEVIOSIDE Derivative in PCSK9 Protein Intended to provide a safe Antilipidemic agent. bioRxiv. 2023 May 5:2023-05.
5. Wang SS, Liu ZK, Liu JJ, Cheng Q, Wang YX, Liu Y, Ni WW, Chen HZ, Song M. Imaging asparaginyl endopeptidase (AEP) in the live brain as a biomarker for Alzheimer's disease. Journal of Nanobiotechnology. 2021 Dec;19:1-8.
6. Tang Q, Xu F, Lin J, Zhang C, Liu X, Dong L, Zhao J, Zhu L, Lin T. Legumain affects the PI3K/AKT tumor progression pathway in retinoblastoma. Experimental Eye Research. 2022 Nov 1;224:109221.
7. Khan SU, Khan IM, Khan MU, Ud Din MA, Khan MZ, Khan NM, Liu Y. Role of LGMN in tumor development and its progression and connection with the tumor microenvironment. Frontiers in Molecular Biosciences. 2023 Feb 7;10:1121964.
8. Elamin T, Brandstetter H, Dall E. Legumain Activity Is Controlled by Extended Active Site Residues and Substrate Conformation. International Journal of Molecular Sciences. 2022 Oct 19;23(20):12548.
9. Tu NH, Jensen DD, Anderson BM, Chen E, Jimenez-Vargas NN, Scheff NN, Inoue K, Tran HD, Dolan JC, Meek TA, Hollenberg MD. Legumain induces oral cancer pain by biased agonism of protease-activated receptor-2. Journal of Neuroscience. 2021 Jan 6;41(1):193-210.
10. Zahra N, Mazhar A, Zahid B, Naeem MA, Sarwar A, Aziz T, Alharbi M, Albekairi TH, Alasmari AF. Evaluation of influence of *Butea monosperma* floral extract on inflammatory biomarkers. Open Chemistry. 2024 Mar 6;22(1):20230199.
11. Chen CA, Wang D, Yu Y, Zhao T, Min N, Wu Y, Kang L, Zhao Y, Du L, Zhang M, Gong J. Legumain promotes tubular ferroptosis by facilitating chaperone-mediated autophagy of GPX4 in AKI. Cell death & disease. 2021 Jan 11;12(1):65.

