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Comparative in Silico Docking Analysis of Phytochemicals from *Murraya koenigii* and Commonly Used Drugs in the Treatment of Cancer

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KEYWORDS

Murraya koenigii, Flavonoids, Phenolic compounds, Carfilzomib, Marizomib, 26S proteasome

A B S T R A C T

Cancer cells exhibit increased proteosomal activity of 26S proteasome. Inhibition of this activity is considered as novel approach to treat cancer. Flavonoids and Phenolic compounds present in *MurrayaKoenigii act* as potent inhibitors of 26S proteasome non-ATPase regulatory subunit 11, a component of the lid subcomplex of the 26S proteasome, which plays a key role in increased proteasome activity. The structure of 26S proteasome non-ATPase regulatory subunit 11is predicted by Homology Modelling with Modeller software and checked with Ramachandran plot–Procheck. Quercetin, Epicatechin,Rutin, Gallic acid and Ferulic acid present in *Murraya koenigii*were subjected to molecular docking analysis for the calculation of binding energies with 26S proteasome non-ATPase regulatory subunit 11.Commonly used drugs that inhibit proteasome activity includes Carfilzomib and Marizomib were also subjected to docking analysis for comparative analysis. Hydrogen bond interaction and docking energy are the parameters taken into account for comparative analysis. Quercetin andEpicatechin shows almost similar binding energy to Marizomib. The binding energies of Rutin, Gallic acid and Ferulic acid is less than that of Carfilzomib. The Quercetin and Gallic acid forms 6 hydrogen bonds each, Epicatechin and Rutin forms 5 hydrogen bonds each and Ferulic acid shows 4 hydrogen bonds with the target whereas Carfilzomib forms only 2 bonds. Hence Flavonoids and Phenolic compounds present in *Murraya koenigii*serve as natural therapeutic agents against proteasomal activity which helps in the treatment of cancer.

Introduction

Cancer is characterized by an uncontrolled growth and spread of abnormal cells.

Cancer cells often have deregulation of apoptotic signalling pathways, leading to the suppression of apoptosis. Such an aberrant

regulation of apoptosis provides a survival advantage to the cancer cells and therefore resistance to chemotherapy. The induction of apoptosis would promote the killing of abnormal cancer cells. Intriguingly, the key factors involved in controlling the apoptosis are regulated by the 26S proteasome complex (Crawford *et al*., 2011;Atoui *et al*., 2005).Unlike normal cells, cancer cells have increased proteasomal activity which is essential for their survival and uninhibited proliferation.

Search for new inhibitors for 26S proteasome from natural sources is one of the most important approaches for cancer prevention and treatment. In recent years, more emphasis is laid on alternative forms of medicine for the treatment of various cancers, among which herbal medicine is now being explored for cancer therapy. Medicinal plants are the richest source of bioactive compounds used in traditional and modern medicine (Park *et al*., 2008). Flavonoids and phenolics are essential groups of plant phytochemicals with superoxide radical scavenging activity, thereby providing anticancer activity (Ghasemzadeh *et al*., 2012; Ahn *et al*., 2013).

Most of the herbal medicines depend on the bioactive compounds which act as a shield to many diseases (Ahn *et al*., 2013; Lee *et al*., 2013; Ajay *et al*., 2010; Pallavi *et al*., 2011; Wei *et al*., 2011; Latha *et al*., 2013; Ramila Devi *et al*., 2011) These compounds are generally rich in many plant foods that are commonly consumed which in addition used in the preparation of traditional medicines and functional foods (Wen *et al*., 2011; Lee *et al*., 2013;Lee *et al*., 2013; Arulselvan *et al*., 2012; Ahn *et al*., 2012) Curry leaf (*Murrayakoenigii*) is among those plant foods which are long used in both medicine and foods for long centuries (Hill *et al*., 1998). In India these leaves are extremely used as seasoning ingredients in most of the curries. *Murraya koenigii* has been traditionally claimed as a remedy for cancer.

The 26S proteasome is a huge 2.4 MDa complex comprising of two sub-complexes – the 19S regulatory subunit and the 20S catalytic subunit (Hershko *et al*., 1998) The 20S sub-unit possesses at least three distinct activities, which are associated with the three different β subunits respectively: chymotrypsin-like activity (β5), trypsin-like activity (β2) and the caspase-like activity (β1) (Groll *et al*., 1997). The 26S proteasome is the major non-lysosomal pathway of protein degradation in eukaryotic cells. This proteolytic machine is involved in the degradation of oxidized, unfolded and misfolded proteins and antigen presentation (Rivett *et al*., 1989; Jung *et al*., 2007; Tambyrajah *et al*., 2007; Chen *et al*., 2004). It regulates several cellular processes such as apoptosis, signal transduction, cell-cycle regulation and cell differentiation (Hilt *et al*., 2000).Two important functions of the proteasome system are to promote tumor cell proliferation and protect tumor cells against apoptosis (Groll *et al*., 1997;Goldberg *et al*., 1995; Hochstrasser *et al*., 1995). So 26S proteosome is considered as the the effective target for numerous cancers and the polyphenols &flavonols acts as effective ligands or inhibitors of 26S proteasome. Recent studies have shown that naturally occurring polyphenols/flavanoids modulate the functionality of the 26S proteasome, a multi-enzymatic, multi-catalytic complex localized both in the cytoplasm and nucleus of eukaryotic cells (Chen *et al*., 2005; Pettinari *et al*., 2006).

The 26S proteasome complex is a non-lysosomal proteolytic machine in eukaryotes (Ciechanover *et al*., 1998; Hershko *et al*.,

1998). It consists of a 20S core particle (CP) and a 19S regulatory particle (RP). The 20S CP confers the proteolytic activities of the proteasome, whereas the 19S RP shows an ATP-dependence and specificity for ubiquitin protein conjugates. The substrate protein is translocated into the catalytic chamber of the 20S CP with the help of the19S RP. The 19S RP recognizes the K48-linked polyubiquitylated-substrate protein, unfolds it, and finally feeds it into the catalytic chamber of the 20S CP for proteolysis in an ATP-dependent manner (Groll *et al*., 2003;Voges *et al*., 1999,Verma *et al*., 1997).The 26S proteasome non-ATPase regulatory subunit 11, a component of the lid subcomplex of the 26S proteasome, a multiprotein complex involved in the ATP-dependent degradation of ubiquitinated proteins, plays a key role in increased proteasome activity in embryonic stem cells (ESCs): its high expression in ESCs promotes enhanced assembly of the 26S proteasome, followed by higher proteasome activity (Vilchez D*et al*., 2012).

In the overview of these reports, Flavonoids and phenolics are subjected to Molecular Docking analysis for the calculation of binding energies with 26S proteasome non-ATPase regulatory subunit 11. I*n silico* docking study is performed in order to prevent cancer in human using Flavonoids and phenolics extracted from the leaves of *Murrayakoenigii* as inhibitors against Cancer. Anticancer drugs like Carfilzomib and Marizomib were also included in the docking study toperform comparative study and to prove that plant phytochemicals could be a potent inhibitor for Cancer.

Molecular docking is one of the most frequently used methods in structure-based drug design, due to its ability to predict the binding-conformation of small molecule ligands to the appropriate target binding site. Characterisation of the binding behaviour plays an important role in rational design of drugs as well as to elucidate fundamental biochemical processes (Ekins *et al*., 2007). It aims to achieve an optimized conformation for both the protein and ligand and relative orientation between protein and ligand such that the free energy of the overall system is minimized.

In silico methods are mainly harnessed to reduce time, cost and risk associatedwith drug discovery (Heger *et al*., 2005).Computational (In silico) methods havebeen developed and widely applied topharmacology hypothesis development andtesting. These in silico methods include database searching, quantitative structure-activity relationships, similarity searching, pharmacophore identification, computational modeling and docking. Such methods have seen frequent use in the discovery and optimization of novel molecules with affinity to a target, the clarification of absorption, distribution, metabolism, excretion and toxicity properties as well as physicochemical characterization.

Materials and Methods

Uniprot

UniProt is a comprehensive, high-quality and freely accessible database of protein sequence and functional information, many entries being derived from genome sequencing projects. It contains a large amount of information about the biological function of proteins derived from the research literature. The UniProt/Swissprot Knowledgebase UniProtKB is the central access point for extensive curated protein information, including function, classification, and cross-reference (Uniprot C., 2009).http://www.uniprot.org/

PFam

The Pfam database contains information about protein domains and families. Pfam-A is the manually curated portion of the database that contains over 10,000 entries. For each entry a protein sequence alignment and a hidden Markov model is stored. Pfam-B contains a large number of small families derived from clusters produced by an algorithm called ADDA (Uniprot, 2009).

Modeller 9.14

Modeller is a computer program for comparative modeling of protein three-dimensional structures. Alignment of a sequence to be modeled is provided with known related structures and modeller automatically calculates a model containing all non-hydrogen atoms. Modeller implements comparative protein structure modeling by satisfaction of spatial restraints. The homology modeling requires sequences of known 3D structure and the target having above 35% of similarity.

RASMOL

RasMol is a molecular graphics program intended for the visualisation of proteins, nucleic acids and small molecules. The program is aimed at display, teaching and generation of publication quality images. The program reads in molecular coordinate files and interactively displays the molecule on the screen in a variety of representations and colour schemes.

CastP

Binding sites and active sites of proteins and DNAs are often associated with structural pockets and cavities. castP server uses the weighted Delaunay triangulation and the alpha complex for shape measurements. It provides identification and measurements of surface accessible pockets as well as interior inaccessible cavities, for proteins and other molecules. It measures analytically the area and volume of each pocket and cavity, both in solvent accessible surface (SA, Richards' surface) and molecular surface (MS, Connolly's surface).

Ligand Preparation

Pubchem

PubChem is a database of chemical molecules and their activities against biological assays. The system is maintained by the National Center for Biotechnology Information (NCBI), a component of the National Library of Medicine, which is part of the United States National Institutes of Health (NIH). PubChem can be accessed for free through a web user interface. Millions of compound structures and descriptive datasets can be freely downloaded via FTP. PubChem contains substance descriptions and small molecules with fewer than 1000 atoms and 1000 bonds. The American Chemical Society tried to get the U.S. Congress to restrict the operation of PubChem, because they claim it competes with their Chemical Abstracts Service (PubChem and the American Chemical Society).

ACDchemsketch

ACD/ChemSketch is an advanced chemical drawing tool and is the accepted interface for the industries best NMR and molecular property predictions, nomenclature, and analytical data handling software. It contains tools for 2D structure cleaning, 3D optimization and viewing.

Open Babel

The molecular format converter tool (Open Babel) is used to convert this file into the PDB format and is used during docking analysis.

Discovery Studio Visualizer

Molecular visualization is a key aspect of the analysis and communication of modeling studies. High Performance Publication Quality Graphics: handle very large macromolecule systems (E.g., Ribosomes); Support a range of stereo graphics options (E.g., split screen, hardware stereo); Hardware graphics acceleration support for a range of AMD(ATI) and nVidia cards; and Depth cueing, blur and shading capabilities. (http://accelrys.com/products/discovery-studio/structure-based-design.html)

AutoDock

Auto Dock is a suite of automated docking tools. The software is used for modelling flexible small molecule such as drug molecule binding to receptor proteins of known three dimensional structures. It uses Genetic Algorithms for the conformational search and is a suitable method for the docking studies. The technique combines simulated annealing for conformation searching with a rapid grid based method of energy evaluation.

Auto Dock tools are used to prepare, run and analyze the docking simulations, in addition to modeling studies. Auto Dock is the most cited docking software because it is very fast, it provides high quality predictions of ligand conformations and good correlations between inhibition constants and experimental ones (http://autodock.s cripps. edu/resources/tools).

Results and Discussion

The sequence of 26S proteasome non-ATPase regulatory subunit 11 is retrieved from Uniprot and its sequence id is O00231 from *Homo sapiens*.

Protein domains are distinct units of three-dimensional protein structures, which often carry a discrete molecular function, such as the binding of a specific type of molecule.

These domains vary in length from between about 25 amino acids up to 500 amino acids. The direct functional and structural determination of all the proteins in an organism is prohibitively costly and time consuming because of the relative scarcity of 3D structural information therefore primary sequence analysis is preferred to identify majority of protein domain families (Sonnhammer *et al*., 1998).The Domain of 26S proteasome non-ATPase regulatory subunit 11 was predicted using Pfam domain analysis. The predicted domain is PCI domain (285–389) and shown in Figure 1.

Comparative Modeling

Homology or comparative protein structure modeling constructs a three-dimensional model of a given protein sequence based on its similarity to one or more known structures (Wheeler *et al*., 2010).

It is carried out in four sequential steps: finding known structures (templates) related to the sequence to be modeled (target), aligning the target sequence with the templates, building the model, and assessing the model (Sahay and Shakya, 2010). Therefore, comparative modeling is only applicable when the target sequence is detectably related to a known protein structure.

3D structure generation by using MODELLER

Identification of Template is an important step in homology modeling and Template structure were selected by a simple search submits the target sequence to programs BLAST-P search along with default parameters was performed against the Brook Heaven Protein Data Bank (PDB). Based on the high identity, lowest e-value and low gaps the high resolution having sequence was selected as a template. In this study, BLAST-PDB was performed for 26S proteasome non-ATPase regulatory subunit 11 sequence and the results between Target sequence and template was shown in Figure 2. The percentage of identity between target–template alignment is 71% and template found is Crystal structure of Rpn6 from *Drosophila melanogoster* with no gaps.

The three dimensional structure of26S proteasome non-ATPase regulatory subunit 11 was predicted using MODELLER 9.14 based on the molecular Probability density function (molpdf) value best model were selected and the modelled summary were shown in Figure 3 and the modelled structure was visualized using RASMOL based on secondary structure colour (Pink: Alpha helix; Yellow beta sheet; White and blue: turns and coils) and ribbon model shown in Figure 4.

Model validation

Ramachandran Plot-Procheck

Quality and reliability of structure was checked by several structure assessment methods including Z-score and Ramachandran plots. Procheck determines the stereochemical quality of a protein structure by analyzing residue-by-residue geometry and overall structure geometry. This tool was used to determine the Ramachandran plot to assure the quality of the model. Ramachandran plot results showed 93.2% of residues in favorable region representing that it is a reliable and good quality model after loop refinement (Figure 5). A model having more than 90% residues in favorable region is considered as good quality model.

Before loop refinement Glu at 21st position and Ala at 102 position are present in the disallowed site. Loop refinement was done using Modeller–Loop.py program. Hence all the amino acids residues came under allowed region.

Superimposition–SPDBV

Target and template proteins have been loaded in SPDBV—superimposed and structurally aligned. The RMSD value found to be 0.90 Å and results was shown in Figure 6.

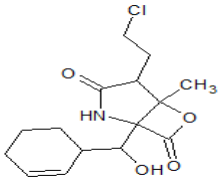
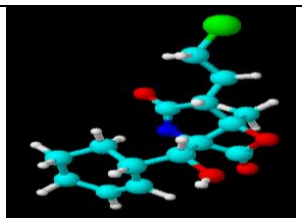
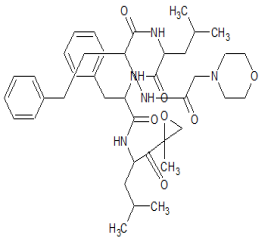
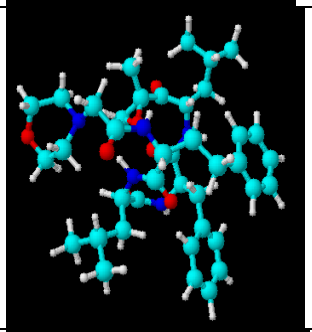
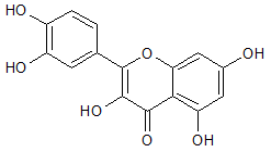
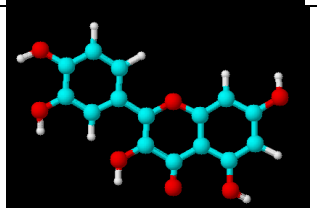
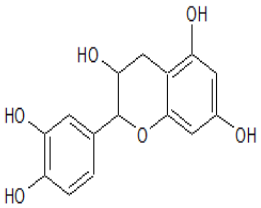
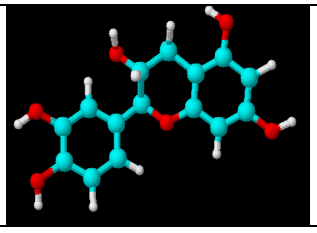
Cast P-Active Site Prediction

The active site of 26S proteasome non-ATPase regulatory subunit 11 was predicted by CASTp. The sites are ARG90, LEU93, ASP94,LEU97,ASP98, GLU100, ALA101, THR103, GLU106, ALA128, LEU129, ALA131, ARG132, VAL134,SER135,LEU136,PHE138, ASP139, THR140, LYS141, TYR143, LEU165, VAL167, GLU168, VAL169, LEU171, LEU172, LYS175, HIS178, ALA179, LYS205, LEU206, THR209, LEU210, MET212, GLN213, ILE216, ILE217, ALA219, ALA220, ASP243, PRO245, LYS246, ILE248, THR249, LYS252, TYR253,GLN283,ALA311, GLU312, ASP315, ASP316, PRO317, ILE318, THR321, HIS322. Active site result was shown in Figure 7.

Table.1 Target (26S proteasome non-ATPase regulatory subunit 11) and Template (3TXM) details

Protein name	Query Coverage	Template	BLAST	Domain
26S proteasome non-ATPase regulatory subunit 11	37–422	3TXM (9–394)	Identity: 71%	PCI domain (285–389)
		Chain: A	Positives: 84%	
Organism:*Homo sapiens*		Organism:*Drosophila melanogaster*	Gaps: 0	
			Query coverage: 91%	

Table.2 Compounds properties and 2D and 3D structure.

COMPOUNDS NAME	2D STRUCTURE	3D STRUCTURE
Marizomib Molecular Formula:$C_{15}H_{20}ClNO_4$ Molecular Weight:313.7766 g/mol		
Carfilzomib Molecular Formula:$C_{40}H_{57}N_5O_7$ Molecular weight:719.90988 g/mol		
Quercetin Molecular Formula:$C_{15}H_{10}O_7$ Molecular Weight:302.2357 g/mol		
Epicatechin Molecular Formula:$C_{15}H_{14}O_6$ Molecular Weight:290.26806 g/mol		

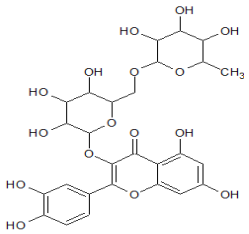
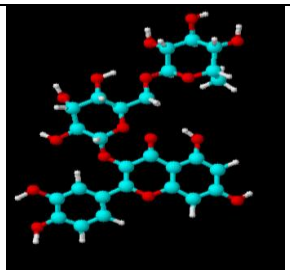
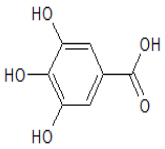
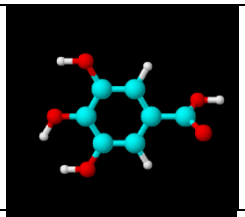
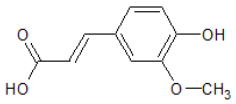
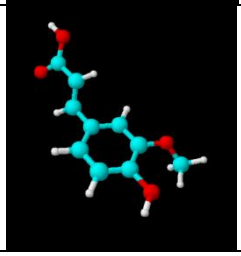
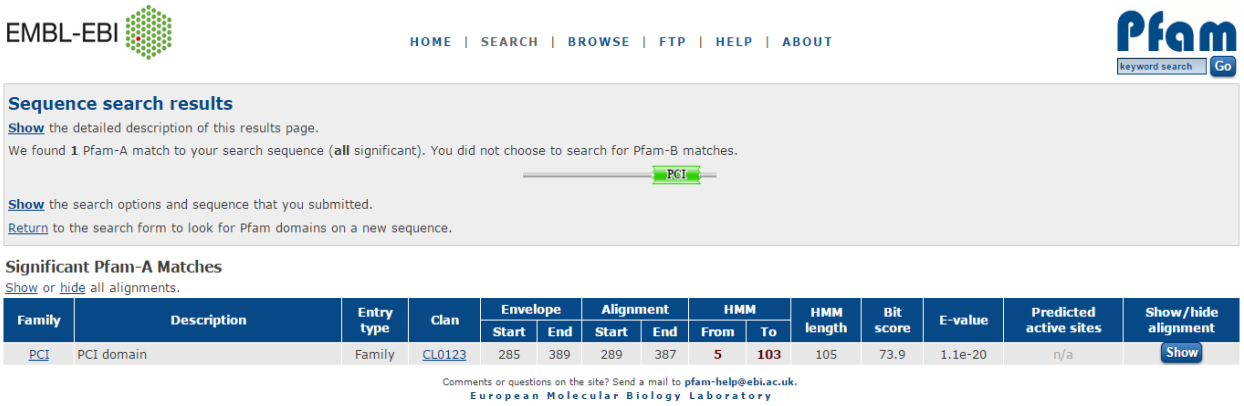
Rutin Molecular Formula:$C_{27}H_{30}O_{16}$ Molecular Weight:610.5175 g/mol		
Gallic acid Molecular Formula:$C_7H_6O_5$ Molecular Weight:170.11954 g/mol		
Ferulic acid Molecular Formula:$C_{10}H_{10}O_4$ Molecular Weight:194.184 g/mol		

Table.3 Over all Docking Results of the Docking Analysis of 26S proteasome non-ATPase regulatory subunit 11 against 3 flavonoids,2 phenolic compounds and 2 commercial drugs.

Compound name	Docking energy (Kcal/mol)	Key Residues	No. of hydrogen bonds formed
Carfilzomib	-3.56	2 TYR143 (OH)	2
Marizomib	-5.75	2 THR103 (OG1), 4 GLU106 (OE1), 2 LEU97 (O), 2 GLU 100	10
Quercetin	-5.67	GLN213 (OE1), 2 TYR253 (OH), TYR143 (OH), ALA179 (N), LYS175 (O)	6
Epicatechin	-5.44	2 ASP139 (O), 2 TYR143 (OH), LYS175 (O)	5
Rutin	-3.72	ASP161 (O), ASP160 (OD2), 3 ARG90 (NH1)	5
Gallic acid	-4.16	2 ASP139 (OD1), LYS246 (NZ), 3 Ser135 (OG)	6
Ferulic acid	-4.53	ARG132 (N), THR209 (OG1), 2 LYS246 (NZ)	4

Fig.1 Pfam Result page



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Sequence search results

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We found **1** Pfam-A match to your search sequence (**all** significant). You did not choose to search for Pfam-B matches.

PCI

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Return to the search form to look for Pfam domains on a new sequence.

Significant Pfam-A Matches

Show or hide all alignments.

Family	Description	Entry type	Clan	Envelope		Alignment		HMM		HMM length	Bit score	E-value	Predicted active sites	Show/hide alignment
				Start	End	Start	End	From	To					
PCI	PCI domain	Family	CL0123	285	389	289	387	5	103	105	73.9	1.1e-20	n/a	Show

Comments or questions on the site? Send a mail to pfam-help@ebi.ac.uk.

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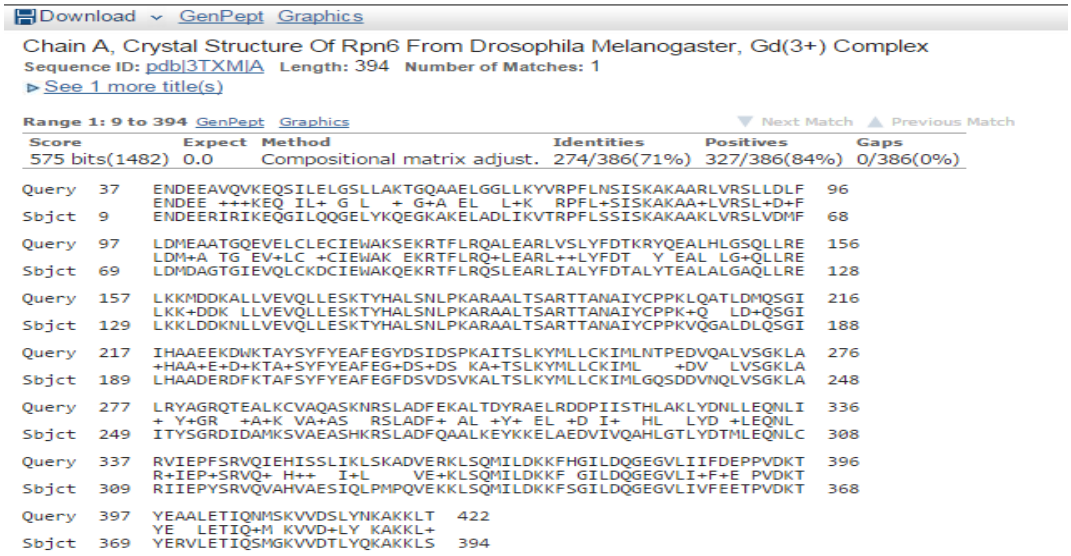
Fig.2 Alignment: Target-Template



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Chain A, Crystal Structure Of Rpn6 From Drosophila Melanogaster, Gd(3+) Complex

Sequence ID: pdb|3TXM|A Length: 394 Number of Matches: 1

See 1 more title(s)

Range 1: 9 to 394 GenPept Graphics Next Match Previous Match

Score	Expect	Method	Identities	Positives	Gaps
575 bits(1482)	0.0	Compositional matrix adjust.	274/386(71%)	327/386(84%)	0/386(0%)

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            ENDEE +++KEQ IL+ G L   + G+A EL   L+K   RPFL+SISKAKAA+LVRSL+D+F
Sbjct  9    ENDEERIRIKEQGILQQGELYKQEGKAKELADLIKVTRPFLSSISKAKAAKLVRSLVDMF  68

Query  97   LDMEAATGQEVELCLECIEWAKSEKRTFLRQALEARLVSLYFDTKRYQEALHLGSQLLRE  156
            LDM+A TG EV+LC +CIEWAK EKRTFLRQ+LEARL++LYFDT   Y EAL LG+QLLRE
Sbjct  69   LDMDAGTGIEVQLCKDCIEWAKQEKRTFLRQSLEARLIALYFDTALYTEALALGAQLLRE  128

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Sbjct  129  LKKLDDKNLLVEVQLLESKTYHALSNLPKARAALTSARTTANAIYCPPKVQGALDLQSGI  188

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Sbjct  369  YERVLETIQSMGKVVDTLYQKAKKLS  394
```

Fig.3 Model Summary

```
>> Summary of successfully produced loop models:
Filename                                  molpdf
--------------------------------------------------
target.BL00010001.pdb                   24.50347
target.BL00020001.pdb                   20.55475
target.BL00030001.pdb                   50.26637
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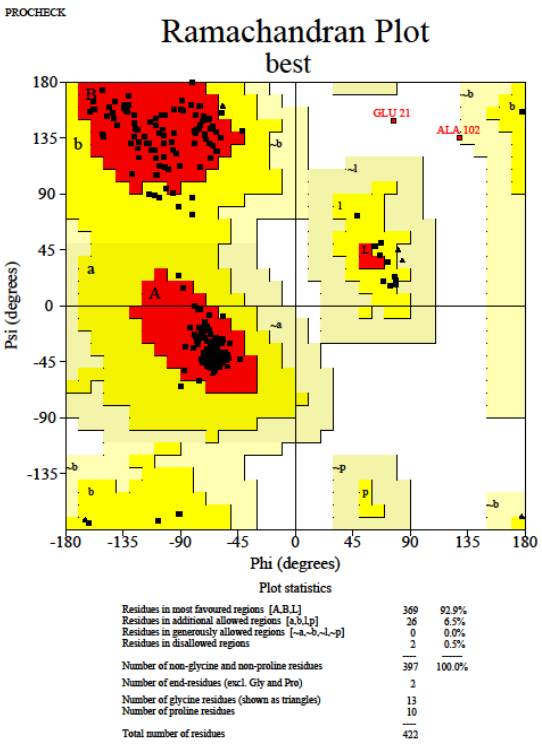
Fig.4 Crystal structure of the 26S proteasome non-ATPase regulatory subunit 11

Fig.5 (a) Before Loop Refinement and (b) After Loop Refinement



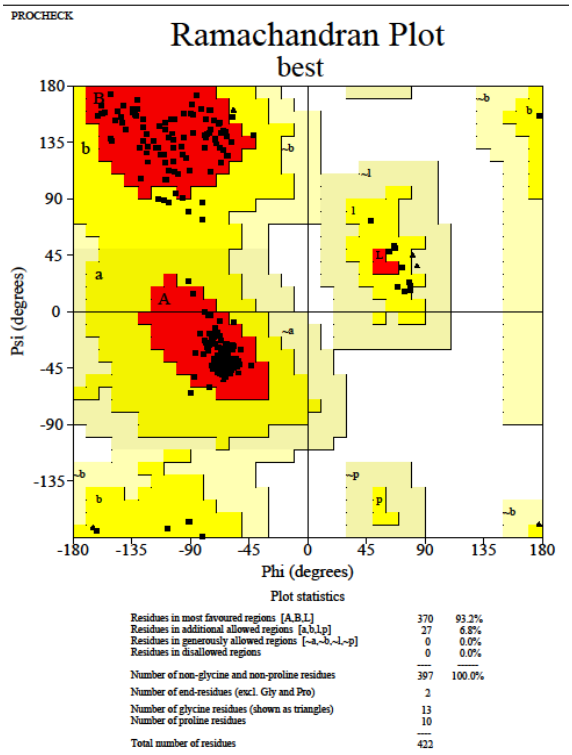


Fig.6 Superimposition between Target and Template

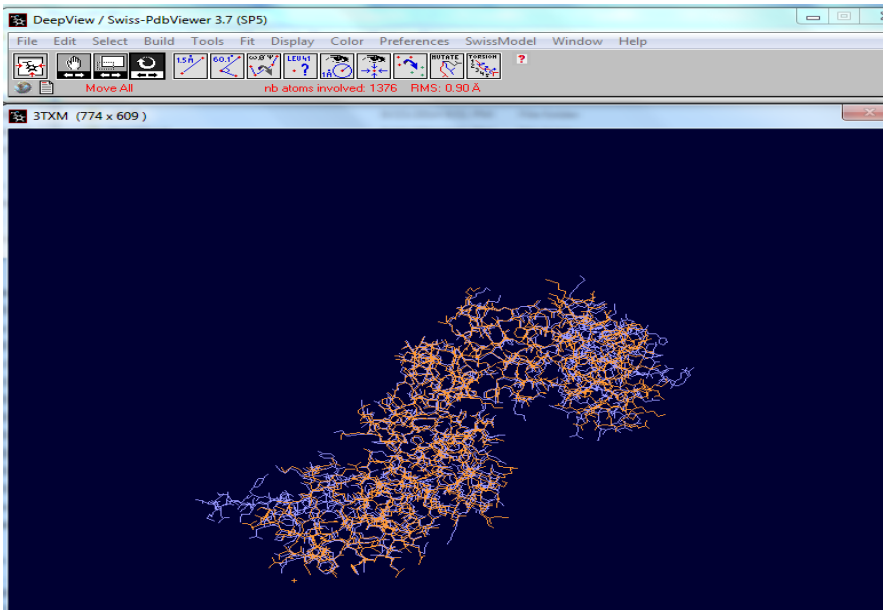


Fig.7 Active site Results of 26S proteasome non-ATPase regulatory subunit 11

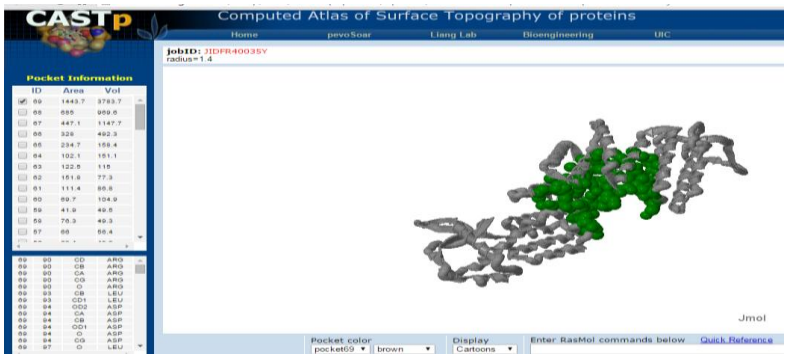
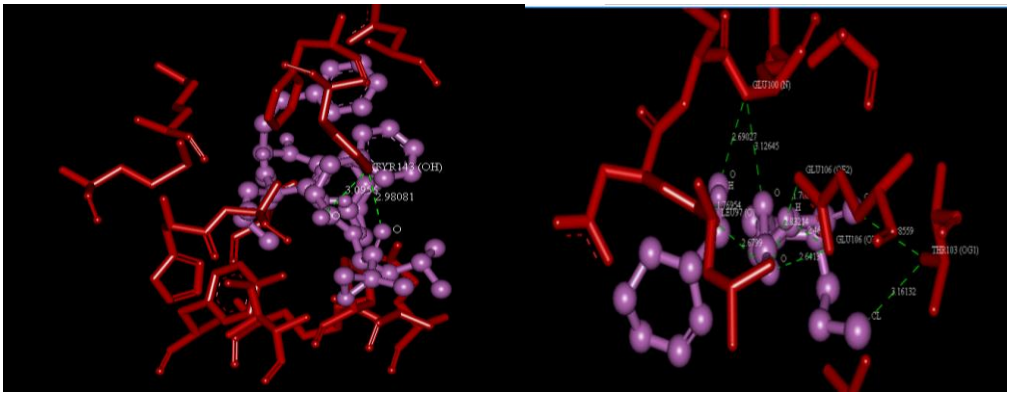
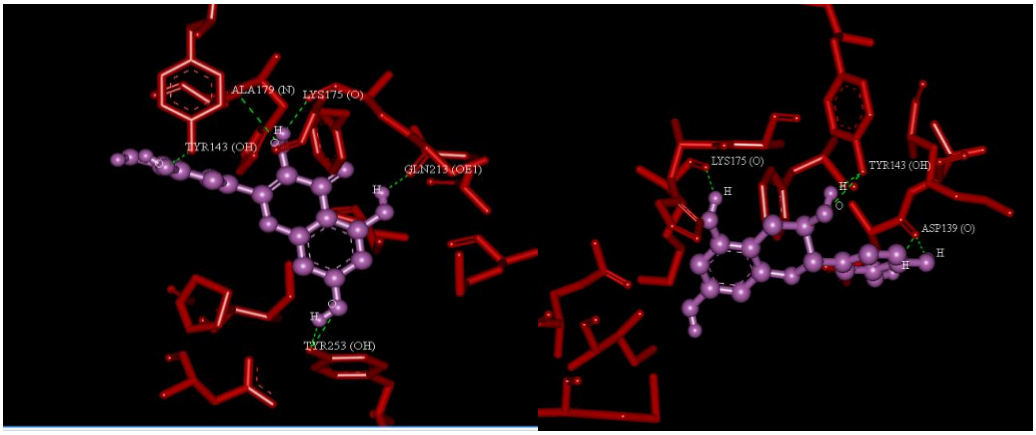


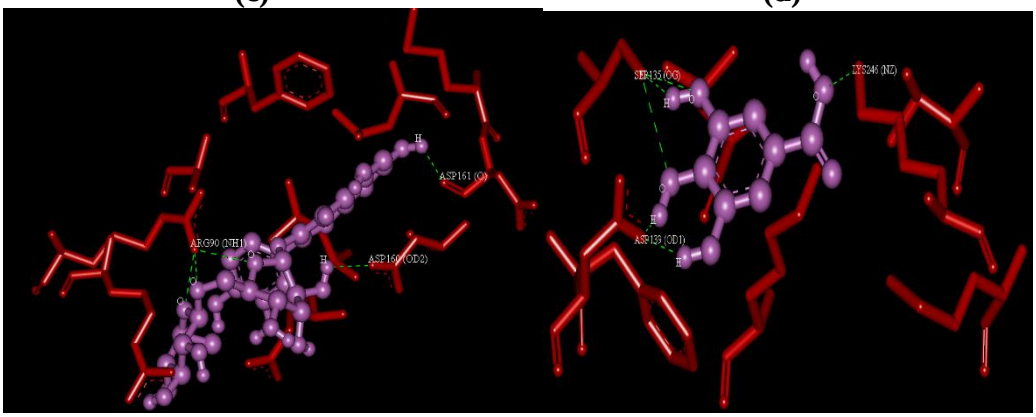
Fig.8 Docking Interactions of 26S proteasome non-ATPase regulatory subunit 11 (Red colour stick model) and against ligands (Purple colour ball and stick model): (a) Carfilzomib; (b) Marizomib; (c) Quercetin; (d) Epicatechin; (e) Rutin; (f) Gallic acid; (g)Ferulic acid visualized using Acceryls Discovery Studio Visualizer



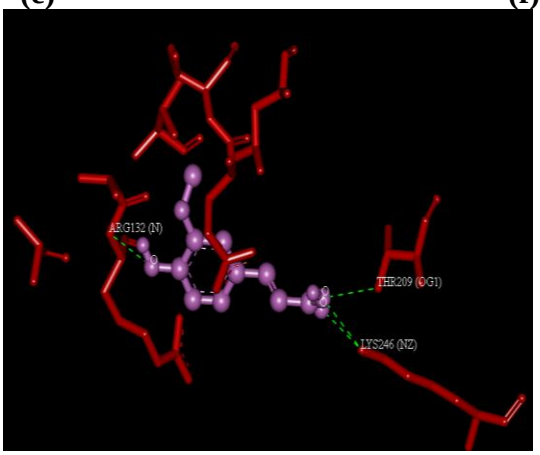
(a) (b)



(c) **(d)**



(e) **(f)**



(g)

Ligand Preparation

For further docking analysis 3 Flavonoids and 2 Phenolic compounds from *Murrayakoenigii*were selected along with 2 commercial drugs used in the treatment of cancer.The two-dimensional structures of the ligands were generated using the ACD/ChemSketch tool. This software contains tools for 2D cleaning, 3D optimization, and viewing. These data are saved as a molecular format file (MDL MOL format). The compound properties, 2D, and 3D structures were shown in Table 2.

Molecular Docking Analysis of Compounds against 26s Proteasome Non-ATPase Regulatory Subunit 11

Molecular docking analysis of 26s Proteasome Non-ATPase Regulatory Subunit 11 against two commercial drugs Carfilzomib and Marizomib and flavonoids (Quercetin; Epicatechin; and Rutin) and phenolic compounds (Gallic acid and Ferulic acid) were carried out using Auto Dock software. The molecular interactions and Hydrogen bonding interaction between 26s Proteasome Non-ATPase Regulatory Subunit 11 and compounds were shown in Figure 8. The over all docking results were shown in Table 3.

The 26S proteasome non-ATPase regulatory subunit 11 is docked against 3 flavonoids (Quercetin, Epicatechin, Rutin), 2 phenolic compounds(Gallic acid, Ferulic acid) and 2 commercial drugs (Carfilzomib, Marizomib). The Binding energy is correlated with the probability of affinity and stable bound between ligand and its receptor. Binding energy values may also predict the bioactivity value for a ligand to the corresponding receptor (Kartasasmita *et al.*, 2009).

The result of this study shows thatthe docking of 26S proteasome non-ATPase regulatory subunit 11 against a) Quercetin and gallic acid shows 6 hydrogen bonds with binding energy of -5.67 and -4.16 respectively b) epicatechin and rutin forms 5 hydrogen bonds with binding energy -5.44 and -3.72 respectively c) ferulic acid shows 4 hydrogen bonds wiyh binding energy -4.53 whereas d) against commercial drugs Carfilzomib and Marizomib shows 2 and 10 hydrogen bonds with binding energy almost similar to that of quercetin, epicatechin and rutin.The overall results are summarized in table 3.

Conclusion

Comparitive docking analysis of commonly used drugs for cancer treatment also suggests that Phenolics and Flavonoids can be an alternative source for treating cancer. From the present *in silico* docking analysis, it could be inferred that Phenolics and Flavonoids from *Murraya koenigii* is capable of interacting with active binding site of the target protein and may serve as a natural therapeutic agent in Cancer treatment.

References

Ahn, Y.J., P. Ganesan, H.S. Kwak. 2013. *Korean J. Food Sci. Ani. Resour.,* 33: 9-15.

Ahn, Y.J., P. Ganesan, H.S. Kwak. 2012. *J. Korean Soc. Appl. Biol. Chem.,* 55: 793-798.

Ajay, K., H.K. Patro, Kewalanand. 2010. *J. Chem. Pharm. Res.,* 2(4): 642-648.

Arulselvan, P., C.C. Wen, C.W. Lan, Y.H. Chen, W.C. Wei, N.S. Yang. 2012. *PLoS One, 7*(9), art. no. e44658

Atoui, A.K., Mansouri, A., Boskou, G., Kefalas, P. 2005. Tea and herbal infusions: their antioxidant activity and phenolic profile. *Food Chem.*, 89(1): 27–36.

Chen, D., Daniel, K.G., Chen, M.S., Kuhn, D.J., Landis-Piwowar, K.R., Dou, Q.P. 2005. Dietary flavonoids as proteasome inhibitors and apoptosis inducers in human leukemia cells. *Biochem. Pharmacol.*, 69(10):1421–1432.

Chen, W.J., Lin, J.K. 2004. Induction of G1 arrest and apoptosis in human jurkat T cells by pentagalloylglucose through inhibiting proteasome activity and elevating p27Kip1, p21Cip1/WAF1, and Bax proteins. *J. BiolChem.*, 279(14): 13496–13505.

Ciechanover, A., Schwartz, A.L. 1998. The ubiquitin-proteasome pathway: the complexity and myriad functions of

proteins death. *Proc. Natl. Acad. Sci. USA*, 95: 2727–2730. [PubMed: 9501156]

Crawford, L.J., Walker, B,. Irvine, A.E. 2011. Proteasome inhibitors in cancer therapy. *J. Cell Commun. Signal*, 5: 101–110.

Ekins, S., J. Mestres and B. Testa. 2007. In silico pharmacology for drug discovery: applications to targets and beyond, *British J. Pharmacol.*, 152(1): 21–37.

Ghasemzadeh, A., Jaafar, H.Z., Karimi, E. 2012. Involvement of salicylic acid on antioxidant and anticancer properties, anthocyanin production and chalcone synthase activity in ginger (Zingiberofficinale Roscoe) varieties. *Int. J. Mol. Sci.*, 13(11): 14828–14844.

Goldberg, A.L. 1995. Functions of the proteasome: the lysis at the end of the tunnel. *Sci.*, 268(5210): 522–523. Review.

Groll, M., Ditzel, L., Lowe, J., Stock, D., Bochtler, M., Bartunik, H.D., Huber, R. 1997. Structure of 20S proteasome from yeast at 2.4 A resolution. *Nature*, 386: 463–471.

Groll, M., Huber, R. 2003. Substrate access and processing by the 20S proteasome core particle. *Int. J. Biochem. Cell Biol.*, 35: 606–616. [PubMed: 12672453]

Heger, A., Wilton, C.A., Sivakumar, A., Holm, L. 2005. "ADDA: a domain database with global coverage of the protein universe". *Nucleic Acids Res.*, 33 Database issue: D188–D191.

Hershko, A., Ciechanover, A. 1998. The ubiquitin system. *Annu. Rev. Biochem.*, 67: 425–479. Review.

Hershko, A., Ciechanover, A. 1998. The ubiquitin system. *Annu. Rev. Biochem.*, 67: 425–479. [PubMed: 9759494]

Hill, A.F., O.P. Sharma. 1998. Economic Botany, Tata McGraw Hill Publishing Co. Ltd, New Delhi, p. 695.

Hilt, W., Wolf, D.H. 2000. Proteasomes: The World of Regulatory Proteolysis. Georgetown, Texas: Landes Bioscience.

Hochstrasser, M. 1995. Ubiquitin, proteasomes, and the regulation of intracellular protein degradation. *Curr. Opin. Cell Biol.*, 7(2): 215–223. Review.

Jung, T., Bader, N., Grune, T. 2007. Oxidized proteins: intracellular distribution and recognition by the proteasome. *Arch. Biochem. Biophys.*, 462(2): 231–237. Review.

Kartasasmita, R.E., Herowati, R., Harmastuti, N., Gusdinar, T. 2009. Quercetion derivatives docking based on study of flavonoids interaction to cyclooxygenase-2. *Indones. J. Chem.*, 9: 297–302.

Kartasasmita, R.E., Herowati, R., Harmastuti, N., Gusdinar, T. 2009. Quercetion derivatives docking based on study of flavonoids interaction to cyclooxygenase-2. *Indones. J. Chem.*, 9: 297–302.

Latha, B., Y. Rumaisa, C.K. Soumya, S. Shafeena, N. Sadhiya. 2013. *J. Chem. Pharm. Res.*, 5(4): 222-228.

Lee, S.B., S. Yoo, P. Ganesan, H.S. Kwak. 2013. *Int. J. Food. Sci. Tech.*, 48: 2159-2165.

Lee, Y.K., M. Al Mijan, P. Ganesan, S. Yoo, H.S. Kwak. 2013. *Int. J. Dairy Technol.*, 66: 417-423.

Lee, Y.K., P. Ganesan, H.S. Kwak. 2013. *Asian Austral. J. Anim. Sci.*, 26: 1197-1204.

McConkey, D.J., Zhu, K. 2008. Mechanisms of proteasome inhibitor action and resistance in cancer. *Drug Resist. Update*, 11: 164–179.

Pallavi, K.J., S. Ramandeep, S. Sarabjeet, S. Karam, F. Mamta, S. Vinod. 2011. *J. Chem. Pharm. Res.*, 3(2): 911- 921.

Park, S.J., Myoung, H., Kim, Y.Y., Paeng, J.Y., Park, J.W., Kim, M.J., Hong, S.M. 2008. Anticancer effects of genistein, green tea catechins, and cordycepin on oral squamouscell carcinoma. *J. Korean Assoc. Oral MaxillofacSurg.*, 34(1): 1–10.

Pettinari, A., Amici, M., Cuccioloni, M., Angeletti, M., Fioretti, E., Eleuteri, A.M. Effect of polyphenolic compounds

on the proteolytic activities of constitutive and immuno-proteasomes. *Antioxid. Redox Signal*, 8(1–2): 121–129.

PubChem and the American Chemical Society. *Reshaping Scholarly Communication*. USA: University of California.

Ramila Devi, M., A. Manoharan. 2011. *J. Chem. Pharm. Res.*, 3(6): 166-172.

Rivett, A.J. 1989. The multicatalytic proteinase. Multiple proteolytic activities. *J. Biol. Chem.*, 264(21): 12215–12219.

Sahay, A., Shakya, M. 2010. In silico Analysis and Homology Modelling of Antioxidant Proteins of Spinach. *J. Proteomics Bioinform*, 3: 148-154.

Sonnhammer, E.L., von Heijne, G., Krogh, A. 1998. A hidden Markov model forpredicting transmembrane helices in protein sequences. *Proc. Int. Conf. Intell. Syst. Mol. Biol.*, 6: 175–182.

Tambyrajah, W.S., Bowler, L.D., Medina-Palazon, C., Sinclair, A.J. 2007. Cell cycledependent caspase-like activity that cleaves p27(KIP1) is the beta(1) subunit of the 20S proteasome. *Arch. Biochem. Biophys.*, 466(2): 186–193.

Uniprot, C. 2009. "The Universal Protein Resource UniProt in 2010". Nucleic Acids Research 38 Database issue: D142–D148.

Verma, R., Annan, R.S., Huddleston, M.J., Carr, S.A., Reynard, G., Deshaies, R.J. 1997. Phosphorylation of Sic1p by G1 Cdk required for its degradation and entry into S phase. *Sci.*, 278: 455–460. [PubMed: 9334303]

Vilchez, D., Boyer, L., Morantte, I., Lutz, M., Merkwirth, C., Joyce, D., Spencer, B., Page, L., Masliah, E., Berggren, W.T., Gage, F.H., Dillin, A. 2012. "Increased proteasome activity in human embryonic stem cells is regulated by PSMD11. *Nature*, 489: 304-308.

Voges, D., Zwickl, P., Baumeister, W. 1999. The 26S proteasome: a molecular machine designed for controlled proteolysis. *Annu. Rev. Biochem.*, 68: 1015–1068. [PubMed: 10872471]

Wei, W.C., S.Y. Lin, Y.J. Chen, C.C. Wen, C.Y. Huang. 2011. A Palanisamy, NSYang; JH Sheu, *J. Biomed. Sci.*, 18(1), art. no. 94.

Wen, C.C., H.M. Chen, S.S. Chen, L.T. Huang, W.T. Chang, W.C. Wei, L.C. Chou, P. Arulselvan, J.B., Wu, S.C. Kuo, N.S.Yang. 2011. *J. Biomed. Sci.*, 18(1), art. no. 44.

Wheeler, K.E,. Zemla, A., Jiao, Y., Aliaga, Goltsman, D.S., Singer, S.W., *et al*. 2010. Functional Insights from Computational Modeling of Orphan Proteins Expressed in a Microbial Community. *J. Proteomics Bioinform.*, 3: 266-274.

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