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**V Ramakrishnan**
Department of Veterinary Pharmacology and Toxicology, Madras Veterinary College, Tamil Nadu Veterinary and Animal Sciences University, Chennai, Tamil Nadu, India

**A Arivuchelvan**
Department of Animal Husbandry Statistics and Computer Applications, Veterinary College and Research Institute, Namakkal, Tamil Nadu, India

**M Parthiban**
Department of Animal Biotechnology, Madras Veterinary College, Tamil Nadu Veterinary and Animal Sciences University, Chennai, Tamil Nadu, India

**M Thangapandiyan**
Department of Veterinary Pathology, Madras Veterinary College, Tamil Nadu Veterinary and Animal Sciences University, Chennai, Tamil Nadu, India

**SP Preetha**
Department of Veterinary Pharmacology and Toxicology, Madras Veterinary College, Tamil Nadu Veterinary and Animal Sciences University, Chennai, Tamil Nadu, India

**Corresponding Author:**
**SP Preetha**
Department of Veterinary Pharmacology and Toxicology, Madras Veterinary College, Tamil Nadu Veterinary and Animal Sciences University, Chennai, Tamil Nadu, India

# Molecular docking study of fucoidan against cyclin-dependent kinase 2 in colorectal carcinoma

**V Ramakrishnan, A Arivuchelvan, M Parthiban, M Thangapandiyan and SP Preetha**

**Abstract**
Over 9.6 million people have died worldwide accounting to one in six deaths due to cancer. Cancer continues to remain as the second main cause of death in the world. Colorectal cancer (CRC) is the most common cancer globally and its incidence has been increasing continuously over the years. It is the third most general cancer in males and the second in females with over 1.4 million new cancer patients being diagnosed every year. The current study was aimed to screen chemo preventive effect of fucoidan for Colon cancer. Cyclin-dependent kinase 2 was taken as a target protein and it was modelled using I-Tasser. The 3D structure of the compound fucoidan was obtained from PubChem database. The target protein was subjected to perform docking studies with fucoidan. Docking studies were done using Discovery Studio 4.0. From the results, the phytocompound fucoidan from marine weeds showed the best Libdcok score (Libdcok score: 96.7373). Hence, the present study was concluded that the phytocompound fucoidan had potential effect against cyclin-dependent kinase 2 in colorectal carcinoma.

**Keywords:** Colorectal carcinoma, Cyclin-dependent kinase, modelling, Fucoidan, docking

## Introduction
Colorectal cancer (CRC) is the most common cancer globally and its incidence has been increasing continuously over the years. It is the third most general cancer in males and the second in females with over 1.4 million new cancer patients being diagnosed every year (Torre *et al.*, 2015) [29]. Cancer is a target that continuously changes. Finding a cure for cancer is complex since the cancer cells mutate and change during the course of the disease. The treatment for cancer in most part contains a mix of treatments depending on the phase of the cancer, including a medical procedure, chemotherapy and radiation treatment (Gutierrez-Rodriguez *et al.*, 2018) [8]. In spite of technical advancement and tremendous research on cancer, there is still no effective drug which offers complete cure from the cancer. Most of the drugs available today are used only for the management of cancer and to prolong the life of the individual.

There is an urgent need for the development of newer anticancer drugs due to the increased incidence of cancer mortality and morbidity and development of resistance towards available anticancer drugs (Collins *et al.*, 2016) [4].

Recently, the use of natural compounds such as fucoidan, curcumin, resveratrol, lycopene, gingerol, and folate has gained much attention as alternatives to conventional therapies. These natural compounds have been shown to possess chemopreventive and/or anticancer activities with minimal side effects (Guilford and Pezzuto, 2008) [7]. Natural compounds have the potential to modulate the signaling pathways involved in cancer proliferation and metastasis (Hazra *et al.*, 2012) [9]. Fucoidans are a family of sulfatedfucose-rich polysaccharides and mainly made up of L-fucose. They are identified in many marine sources like marine cucumbers (Mansour *et al.*, 2019) [16] and brown algae (Zhao *et al.*, 2018) [33]. Fucoidans have many therapeutic properties such as anti-inflammatory, anti-coagulant and anti-proliferative properties on cancer cells (Ale and Meyer, 2013) [2]. Structural make-up, monosaccharide composition, sulfate content, the position of sulfate ester groups and molecular weight determines the therapeutic property of fucoidans (Li *et al.*, 2008) [13]. It has been documented that sulfate groups are essential for the antiviral property of the fucoidans (Ponce *et al.*, 2003; Hemmingson *et al.*, 2006) [20, 10]. Further, Mandal *et al.* (2007) [15] reported that sulfate located at *C*-4 of (1→3)-linked fucopyranosyl units are important for the anti-herpetic activity of fucoidan.

It has been reported that fucoidans extracted from *Eiseniabicyclics* and *L. japonica* have potential effects against sarcoma 180 cells (Usui, 1980 [30]; Song *et al.,* 2000) [30, 27]. It induces apoptosis in HT-29 colon cancer cells (Kim *et al.,* 2010) [12], MCF-7 human breast cancer cells (Yamasaki-Miyamoto *et al.,* 2009) [32] and HS-Sultan human lymphoma cells (Aisa *et al.,* 2005) [1].

Nanoparticle (NP) based delivery system is gaining attention as novel dug carriers and their use is rapidly increasing due to their higher therapeutic potential (Hickey *et al.*,2015 and (Ramakrishnan *et al*.,2009) [11, 24]. Nanoencapsulation systems exhibit high potential as carriers of bioactive substances. Their sub cellular size allows relatively higher intracellular uptake and their permanence in circulation is for longer, therefore extending their biological activity compared to micro-sized systems. Also, nanoencapsulation may be beneficial regarding improved stability and protection capability of labile substances against degradation factors (Preetz *et al.,* 2008) [21]. Layer-by-layer (LbL) deposition technique is one of the most powerful methods to create multilayer nanocapsules, which can be specially engineered with controlled sizes, composition, porosity, stability, surface functionality and colloidal stability and can be used as carriers for bioactive compounds. Also, the step-wise formation of multilayer nanocapsules allows introducing multiple functionalities (Mora-Huertas *et al.,* 2010) [17].

Cyclin-dependent kinase (CDK2) is a serine/threonine protein kinase and regulates the cell cycle transition from G1- to S-phase. It is therefore a key factor in the control of cell proliferation (Morgan, 1997; Sherr *et al*., 1999 and Murray, 2004) [18, 26, 19]. Over expression of CDK2 has been reported in numerous types of human neoplasia, including colorectal, ovarian, breast and prostate cancers (Carnero, 2002; Webster *et al*, 2000) [3, 31]. Therefore, CDK2 inhibitors have the potential to be effective anti-cancer agents. Numerous CDK2 inhibitors have been reported in the literature, including flavopiridol, roscovitine and olomoucine (Senderowicz *et al*, 1999; De Azevedo *et al*., 1997 and Glab *et al*, 1994) [25, 5, 6].

A few bioinformatics tools and databases have been utilized to create productive strategies for encouraging objective recognizable proof, as the initial phase in medication disclosure. Keeping in view the significance and favorable circumstances of mix chemotherapy utilizing marine prescription on the tumor cells, this examination is an endeavor to investigate the impact of herbs utilizing CADD (Computer Aided Drug Design). Bioinformatics software is not only find lead particles and to discover the connection between the structure and the action of little atoms. Thus, the present study is designed to evaluate the fucoidan against Colon cancer using *in silico* methods.

## Materials and Methods

### Ligand selection

Ligand is a small molecule, which interacts with protein's binding sites. There are several possible mutual confirmations in which binding may occur. These are commonly called binding modes (Kittal *et al*.,2009) [13]. After checking Lipinski Rule of five, compound was selected for the study. The 2D and 3D structure of all these compounds were retrieved from PubChem database (Ramakrishnan *et al*., 2021) [23].

### Target selection

The sequence of Cyclin-dependent kinase 2 was taken from UniProt database and their ID is UniProtKBID: P24941.

### Homology modelling and docking studies

As there is no 3D structure available for target protein Cyclin-dependent kinase 2, the sequence was modeled using I-Tasser and it was evaluated using Ramachandran plot. Docking studies were done using Discovery Studio 4.0

## Results and Discussion

### Ligand and Protein Selection

The 3D structure of the ligand fucoidan (SID: 402346915) was retrieved from Pub Chem database. The sequence of target proteins were taken from Uni Prot databases

**Protein Name:** Cyclin-dependent kinase 2
**Gene:** CDK2
**UniProtKBID:** P24941
**PDB ID:** 5IEY

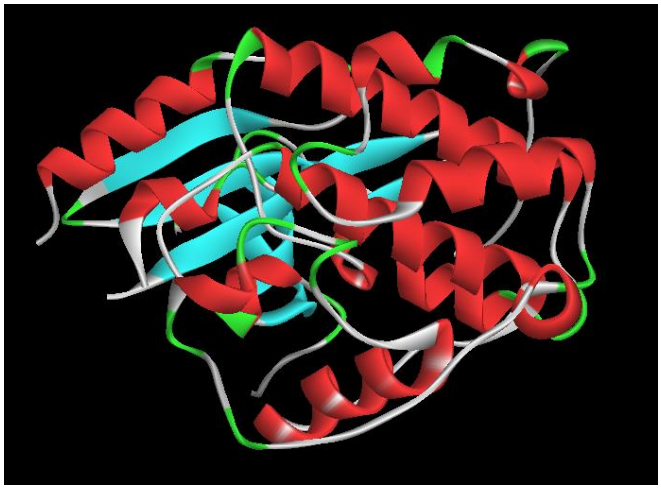

**Fig 1:** Protein Structure

### Ligand and Target selection

Target protein Cyclin-dependent kinase 2 was modeled and evaluated using I-Tasser and Ramachnadran plot. Modeling was done using multi template method. In the Ramachnadran plot, 86.9% residues are present in favored regions and it confirms that the modeled 3D structure is good.

Ligand: Fucoidan

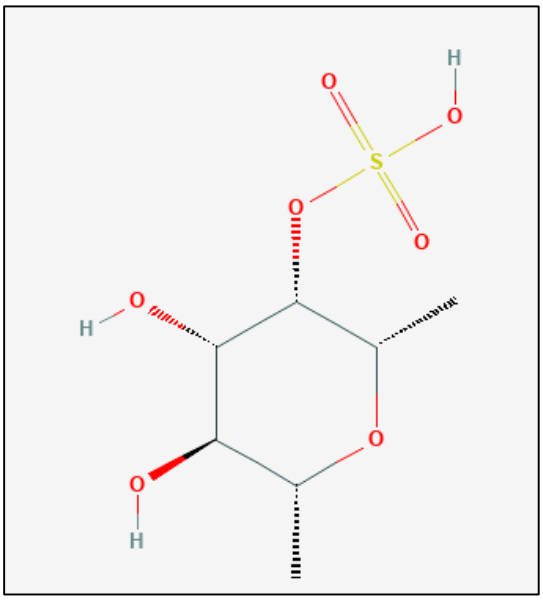


**Fig 2:** Ligand Structure

**Docking studies**

After checking Lipinski rule of five, fucoidan docked with modelled 3D structure of Cyclin-dependent kinase 2 using Discovery studio 4.0 and the results are shown in table 1. From the results, fucoidan showed better interaction with target protein Cyclin-dependent kinase 2. The 2D and 3D structure of docked images are shown in Fig. 3 to 5. When compared to previous report (Sujatha *et al*., 2016 and Ramakrishnan *et al*., 2021) [28, 21], the fucoidan showed very good Libdock score.

**Docking result**

**Table 1:** Interaction fucoidan with Cyclin-dependent kinase 2

| Cyclin-dependent kinase 2 | | | | | | |
|---|---|---|---|---|---|---|
| **S. No** | **PubChem CID** | **Compound Name** | **LibDock Score** | **Number of H-Bond** | **Interacting residues** | **Bond Length (Å)** |
| 1 | 92023653 | Fucoidan | 96.7373 | 7 | THR 14<br>ASP 145<br>ASP 145<br>ASP 145<br>LYS 129<br>ASP 127<br>ALA 149 | 1.98<br>1.79<br>2.85<br>2.69<br>2.58<br>1.89<br>2.49 |

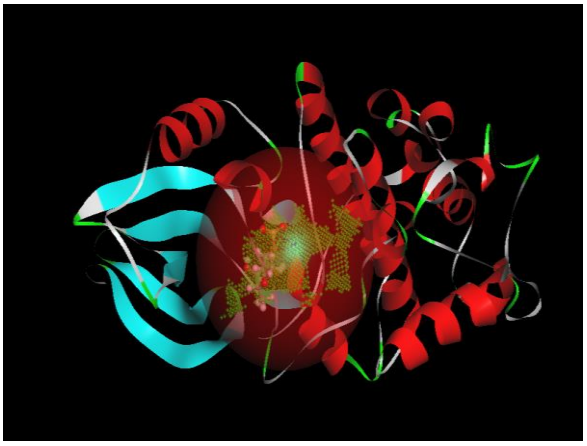

**Fig 3:** The 3D interaction of fucoidan with Cyclin-dependent kinase 2

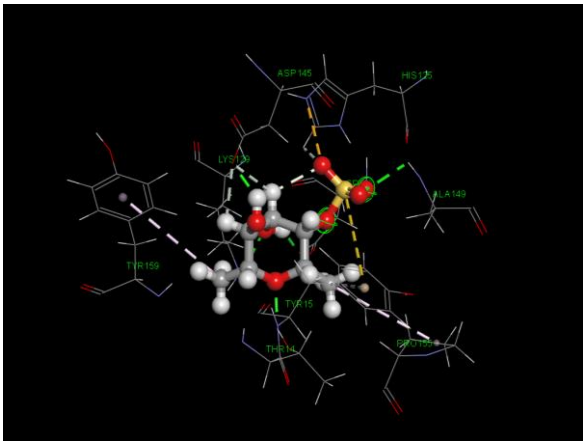

**Fig 4:** The 3D interaction of fucoidan with Cyclin-dependent kinase 2

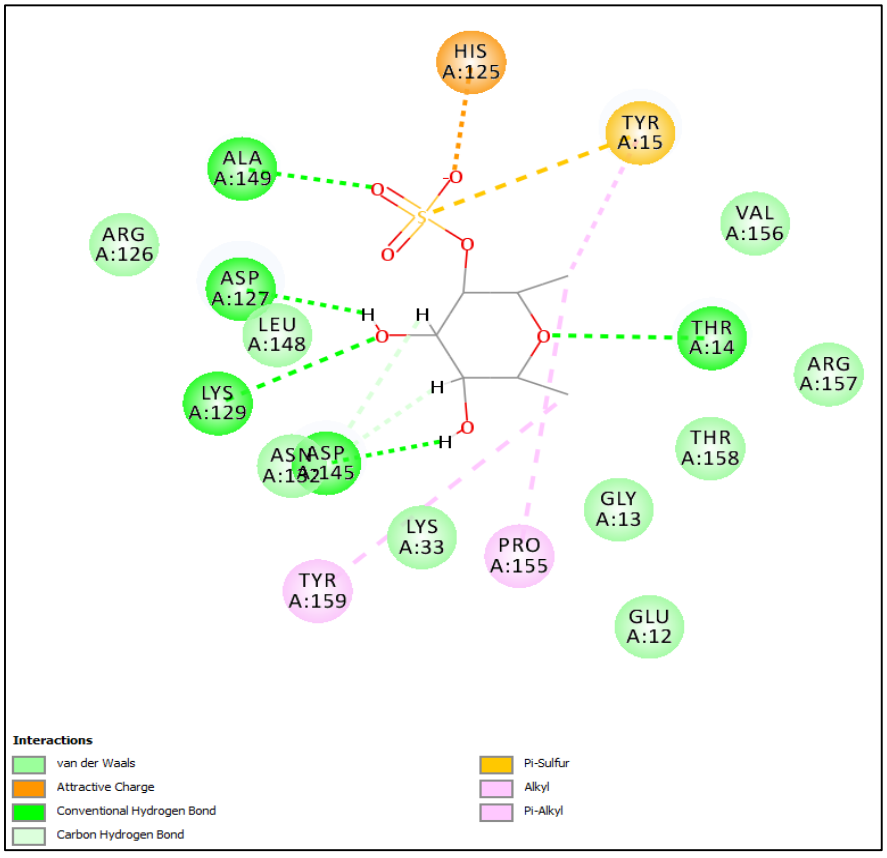


**Fig 5:** The 2D interaction of fucoidan with Cyclin-dependent kinase 2

## Conclusion

Hence, the present study concludes that fucoidan from marine seaweeds showed very good activity with target protein Cyclin-dependent kinase 2 of colorectal carcinoma.

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