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# FLAVONOIDS - NATURAL THERAPEUTIC AGENTS FOR POLYCYSTIC KIDNEY DISEASE

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## ABSTRACT

In the battle for a disease free world, focus is laid more on synthetic compounds as drugs without even bothering about the harmful side effects they produce. This study is a novel approach emphasizing the significance of natural products as a prime solution to unanswered questions like the treatment of the 'Silent Killer'-"Polycystic Kidney Disease" (PKD). Flavonoids are one of the biologically active chemical constituents of plants. These natural products are readily available to man in the form of vegetables and fruits. The emergence of Bioinformatics has provided a platform to explore diseases at the molecular level using Computational techniques. *Insilico* methods are mainly harnessed to reduce the time, cost and risk associated with Drug Discovery. The key protein namely Cystic Fibrosis Transmembrane conductance Regulator which upon mutation plays major roles in cyst formation, fluid accumulation and hypertension in PKD is selected as drug target. The 3D structure is mutated and subjected to Molecular Docking with flavonoids from vegetable sources. Docking scores and *Insilico* Toxicity test result indicates the application of Flavonoids as Potential and Natural Therapeutic agents to combat PKD.

## KEYWORDS

PKD, CFTR, Flavonoids, Molecular Docking, Toxicity Analysis

## INTRODUCTION

**Polycystic kidney disease** (**PKD** or **PCKD**, also known as polycystic kidney syndrome) is a cystic genetic disorder of the kidneys[1]. PKD is characterized by the presence of multiple cysts (hence, "polycystic") in both kidneys. The cysts are numerous and are fluid-filled resulting in massive enlargement of the kidneys. The disease can also damage the liver, pancreas, and in some rare cases, the heart and brain[2]. No treatment is available for the cysts caused by PKD[3]. So, this study is a novel approach emphasizing the significance of natural products as a prime solution to unanswered questions like the treatment of the 'Silent Killer'-"Polycystic Kidney Disease" [4]. Flavonoids are one of the biologically active chemical constituents of plants. These natural products are readily available to man in the form of vegetables and fruits.

The emergence of Bioinformatics has provided a platform to explore diseases at the molecular level using Computational techniques. *Insilico* methods are mainly harnessed to reduce the time, cost and risk associated with Drug Discovery. The key protein namely Cystic Fibrosis Transmembrane conductance Regulator that in humans is encoded by the **CFTR** gene,[5] which upon mutation play major roles in cyst formation, fluid accumulation and hypertension so, this protein is selected as drug targets. The most common mutation, F508 results from a deletion of three nucleotides which results in a loss of the amino acid phenylalanine (F) at the 508th (508) position on the protein. This may result in proteins that may not function, work less effectively, are more quickly degraded, or are present in inadequate numbers [6].

The mutated CFTR is modeled and docked with flavonoids using various Bioinformatics tools. In our present study, we have analyzed that flavonoids can act as an natural therapeutic agent against PKD.

## MATERIALS AND METHODS

### (*i*) *Retrieval of Target Protein sequence*

The protein sequence of Human Cystic fibrosis transmembrane conductance regulator protein (CFTR) was obtained from the protein sequence database of Uniprot (Accession No: P13569) (http://www.uniprot.org/uniprot/P13569) . It was ascertained that the mutated three dimensional structure of CFTR is not available in PDB database; hence an attempt has been made in the present study to determine the mutated structure. CFTR is mutated del f508.

### *(ii) Template identification*

The protein BLAST was used to identify the template for modeling the mutated three dimensional structure of CFTR from *Homo sapiens.* The results yielded by Protein BLAST against the PDB database revealed that CFTR from *Homo sapiens* with p508(PDB ID:2BBO) with a resolution 2.55A$^{o}$ as a suitable template. The template and the target have 96% of residues are identical.

### *(iii) Model generation*

The three dimensional structure of CFTR has been predicted using MODELLER9v5 (http://www.salilab.org/modeller/). The script “align2d.py” has been employed to perform an alignment between the target and template sequence. A rough 3D model was then obtained using the script “model-default.py” based on the generated alignment.

### *(iv) Evaluation*

The backbone conformation of the rough model was inspected using the Phi / Psi Ramachandran plot obtained in the PROCHECK server (http://nihserver.mbi.ucla.edu/SAVES_3/saves.php). The results of Ramachandran plot indicates that the rough model generated had no residues in the disallowed region.

### *(v) Domain analysis*

The functional analysis of CFTR is predicted using Pfam Database (http://pfam.sanger.ac.uk/)

### *(vi) Active site Prediction*

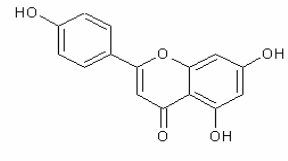
After obtaining the final model, the possible binding sites of CFTR were searched using Q-SiteFinder (http://www.modelling.leeds.ac.uk /qsitefinder/ ). Ten binding sites were obtained.

### *(vii) Docking the inhibitors with the Active Site of Cystic Fibrosis Transmembrane conductance Regulator*

The flavonoids have aroused considerable interest recently because of their potential beneficial effects on human health- they have been reported to have antiviral, anti-allergic, antiplatelet, anti-inflammatory,

antitumor and antioxidant activities[7]. The natural flavonoids from fruits and vegetables such as Apigenin, Catechin, Epicatechin, Isohamnetin, Kaempferol, Luteolin, Myrecetin, Theaflavin, Pelargonidin, Quercetin, Peonidin (as shown in **Figure 2**) Totally eleven inhibitors were docked with CFTR using the Lamarckian Genetic Algorithm(LGA) provided by the AutoDock Program, version 3.0 (http://autodock.scripps.edu/). Polar hydrogens were added to the receptor, kollaman Charges were assigned and salvation parameters were added with the "Addsol" option in AutoDock. For the inhibitors charges of the Gasteiger type were assigned. The internal degree of freedom and torsions were defined using the "Ligand torsions" menu option of AutoDock. The grid maps representing the protein were calculated using the "AutoGrid" option. The protein was centred on the geometric centre prior to docking. Docking simulations were carried out with an initial population of 50 individuals, and a maximum number of 25,000 energy evaluations were used as the docking parameters for obtaining the final docked structures. In the addition to returning the docked structure, AutoDock also calculates an affinity constant for each ligand-recepto configuration. The best ligand-receptor structure from the docked structures was chosen based on lowest energy and minimal solvent accessibility of the ligand.

(a)



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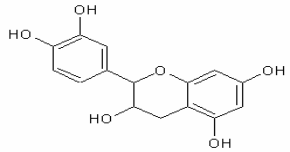

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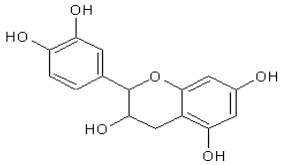

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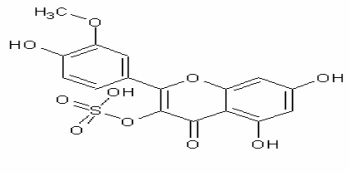
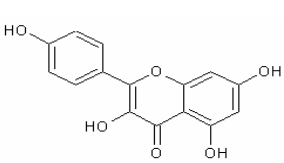


(e)



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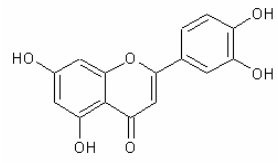
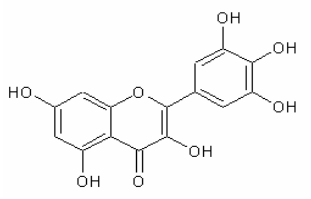


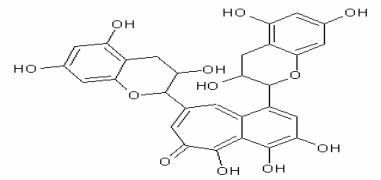
(g)



(h)



(i)



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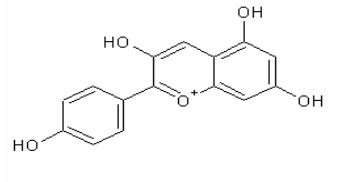

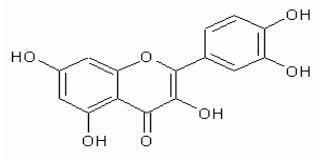

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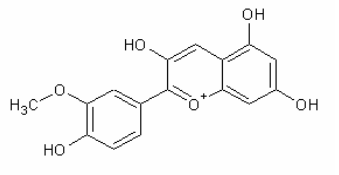


**Figure 1**

***Structure of (a) Apigenin, (b) Catechin, (c) Epicatechin, (d) Isohamnetin, (e) Kaempferol, (f) Luteolin, (g) Myrecetin, (h) Theaflavin, (i) Pelargonidin, (j) Quercetin, (k) Peonidin***

### *(viii) Toxicity prediction*

The toxicity for the eleven inhibitors was identified using ADME/Tox web tool (http://pharma-algorithms.com/webboxes/). The different parameters such as oral bioavailabilty, pka, logD, P-gp substrate and inhibitor specificity, solubility in pure water and in buffer, Abraham salvation parameters, active transport properties, absorption, physiochemical properties, solubility and P-gp specificity can be analyzed for each inhibitor.

## RESULTS

Homology Modeling of CFTR in Homo sapiens. The absence of mutated three dimensional structure of CFTR from *Homo sapiens* in PDB interested has to construct the 3D model. The three dimensional structure provides valuable insight in to molecular functions and also enables the analysis of its interactions with suitable inhibitors. Among the three conformations generated, the one with the least modeler objective function value was considered to be thermodynamically stable and chosen for further refinement and validation. The best modeled structure which is displayed below have MOF value of 1680.90356. Modeled Structure was Mutated (dPHE508). The best Structure was visualized using Rasmol tool (**Figure 2**).

**Figure 2**
***Modeled Structure of CFTR Visualized using RASMOL***

2. Active site identification of Human Cystic fibrosis transmembrane conductance regulator protein Among the ten binding sites obtained from Q-SiteFinder, site 1 is highly conserved. The residues in site1, TRP14, PHE46, SER47, LEU48, LEU49, GLY50, THR51, PRO52, VAL53, LEU54, SER72, THR73, GLY74, ALA75, GLY76, LYS77, THR78, SER79, GLN106, TYR190, HIS233, GLU234, GLY235, THR276, HIS280. Thus, site 1 has been chosen in this study as the most favorable site for docking and the other sites are not further discussed. The residues forming the binding pocket are shown in **Figure 3**.

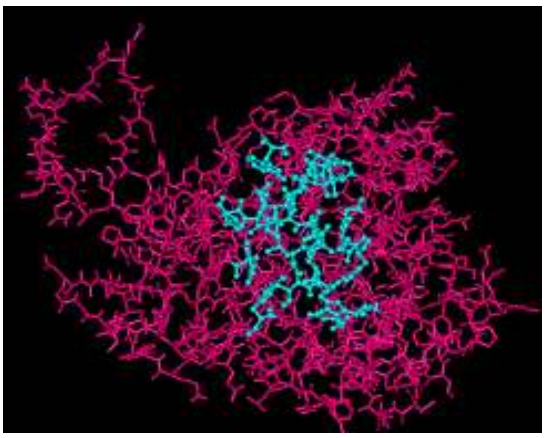


**Figure 3**
***Active site residues taken for docking analysis. Pink color indicates the protein and cyan blue color indicates active site.***

3.

Domain analysis

The functional regions of the Human Cystic fibrosis transmembrane conductance regulator protein is predicted and found to have single domain region such as ABC_tran.

4. Docking of Human Cystic fibrosis transmembrane conductance regulator protein with potential inhibitors. Docking of Human Cystic fibrosis transmembrane conductance regulator protein was performed with eleven inhibitors. The eleven final docked

conformations obtained for the different inhibitors were evaluated based on the number of hydrogen bonds formed. The eleven final docked conformations obtained for the various inhibitors were evaluated based on the Docking Score (Table 1) and number of hydrogen bonds formed between active site and inhibitors are shown in Table 2. Human Cystic fibrosis transmembrane conductance regulator protein in complex with eleven inhibitors was shown in **figure 4.**

**Table 1**

***Docking Score for the eleven inhibitors***

| LIGANDS | DOCKING SCORE(Kcal/Mol) |
|---|---|
| APIGENIN | -8.67 |
| CATECHIN | -6.16 |
| EPICATECHIN | -6.83 |
| ISOHAMNETIN | -7.03 |
| KAEMPFEROL | -8.5 |
| LUTEOLIN | -8.03 |
| MYRECITIN | -7.68 |
| THEAFLAVIN | -2.16 |
| PELARGONIDIN | -8.61 |
| QUERCETIN | -6.97 |
| PEONIDIN | -6.97 |

**Table 2**

***Hydrogen bonds between the eleven inhibitors and active site residues of Human Cystic fibrosis transmembrane conductance regulator protein as deciphered using Web lab Viewer.***

**Inhibitor 1**
***Apigenin***

| Human Cystic fibrosis transmembrane conductance regulator protein | | Inhibitor |
|---|---|---|
| Residue | Atom | |
| Thr 51 | O | O |
| Gly 50 | O | O |
| Gly 74 | O | O |

**Inhibitor 2**
***Catechin***

| Human Cystic fibrosis transmembrane conductance regulator protein | | Inhibitor |
|---|---|---|
| Residue | Atom | |
| Ala 75 | O | H |
| Leu 49 | O | H |
| Gly 74 | O | H |

**Inhibitor 3**
***Epicatechin***

| Human Cystic fibrosis transmembrane conductance regulator protein | | Inhibitor |
|---|---|---|
| Residue | Atom | |
| Thr 51 | O | H |
| Leu 48 | HN | O |
| Gly 74 | O | H |

**Inhibitor 4**
***Isohamnetin***

| Human Cystic fibrosis transmembrane conductance regulator protein | | Inhibitor |
|---|---|---|
| Residue | Atom | |
| Leu 49 | O | H |
| Gly 50 | N | O |
| Gly 74 | O | H |

**Inhibitor 5**
***Kaempferol***

| Human Cystic fibrosis transmembrane conductance regulator protein | | Inhibitor |
|---|---|---|
| Residue | Atom | |
| Thr 78 | OG1 | H |
| Ser 79 | OG | O |
| Val 53 | O | H |
| Leu 49 | O | H |
| Leu 48 | HN | O |

**Inhibitor 6**
***Luteolin***

| Human Cystic fibrosis transmembrane conductance regulator protein | | Inhibitor |
|---|---|---|
| Residue | Atom | |
| Thr 51 | O | O |
| Val 53 | O | H |
| Gly 50 | O | O |
| Gly 74 | O | H |

**Inhibitor 7**
***Myrecetin***

| Human Cystic fibrosis transmembrane conductance regulator protein | | Inhibitor |
|---|---|---|
| Residue | Atom | |
| Thr 51 | O | H |
| Gly 74 | O | H |
| Gly 74 | O | O |

**Inhibitor 8**
***Theaflavin***

| Human Cystic fibrosis transmembrane conductance regulator protein | | Inhibitor |
|---|---|---|
| Residue | Atom | |
| Thr 73 | O | H |
| Gly 50 | O | H |
| Gly 74 | O | H |
| Leu 48 | HN | O |
| Ser 72 | OG | H |
| Ser 72 | HG | O |

**Inhibitor 9**
***Pelargonidin***

| Human Cystic fibrosis transmembrane conductance regulator protein | | Inhibitor |
|---|---|---|
| Residue | Atom | |
| Thr 51 | O | H |
| Gly 50 | O | H |
| Gly 74 | O | O |

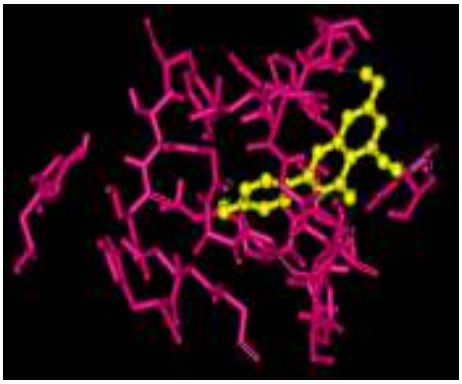
**Inhibitor 10**
***Quercetin***

| Human Cystic fibrosis transmembrane conductance regulator protein | | Inhibitor |
|---|---|---|
| Residue | Atom | |
| Leu 48 | HN | O |
| Pro 52 | O | H |
| Pro 52 | O | H |
| Ser 79 | HG | O |
| Ser 79 | OG | O |

**Inhibitor 11**
***Peonidin***

| Human Cystic fibrosis transmembrane conductance regulator protein | | Inhibitor |
|---|---|---|
| Residue | Atom | |
| Gly 235 | N | O |

**Final docked conformations of CFTR with flavonoids**



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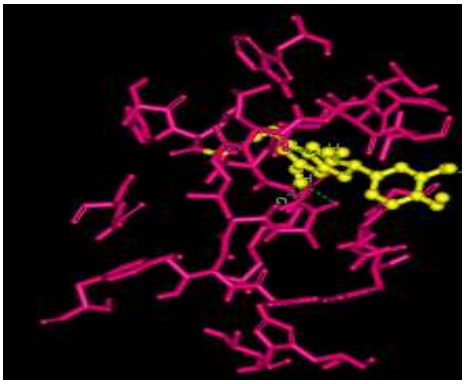

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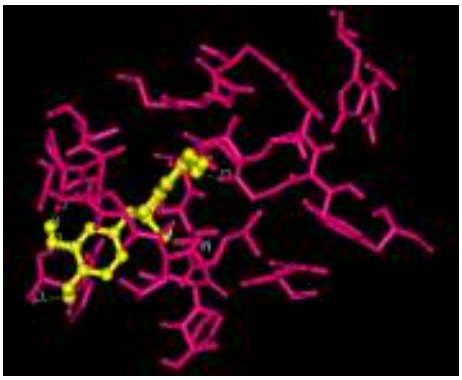

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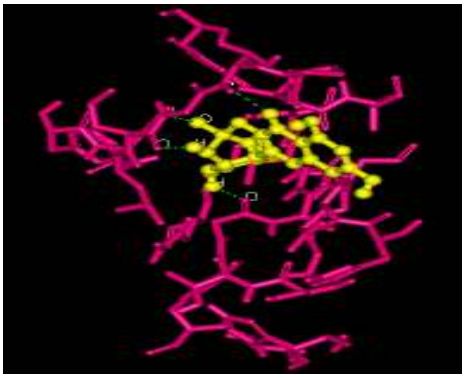

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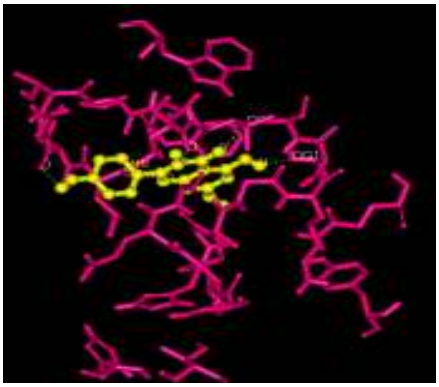

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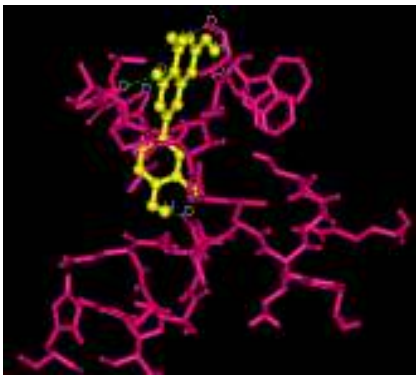

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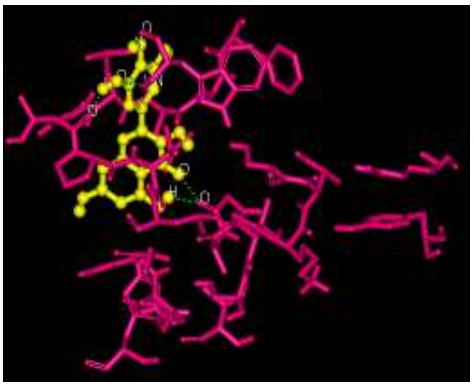

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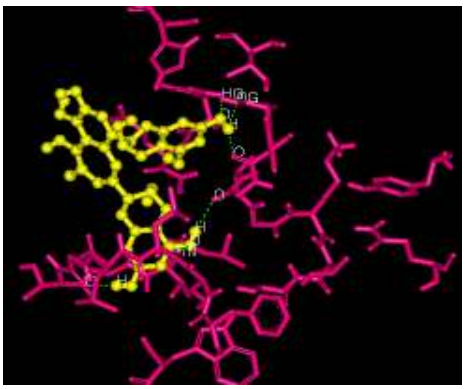

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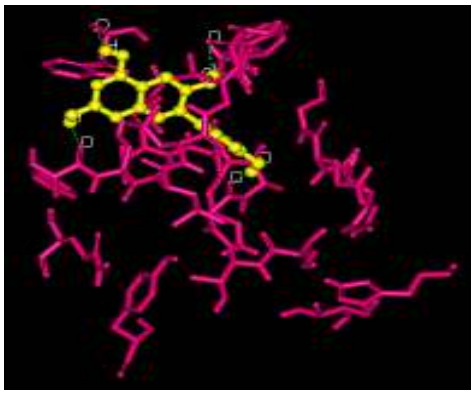

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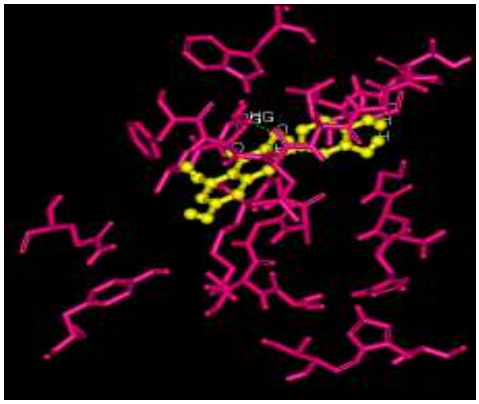

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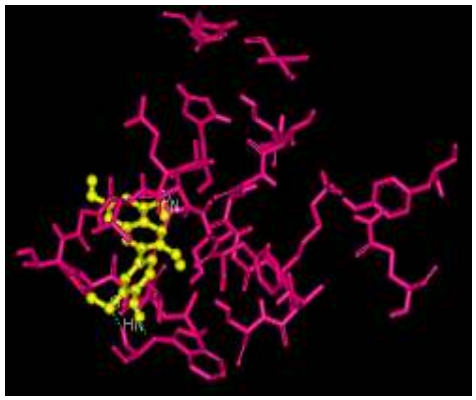

K

**Figure 4**

***(a) Human Cystic fibrosis transmembrane conductance regulator(CFTR) protein in complex with Apigenin; (b) CFTR in complex with Catechin; (c) CFTR in complex with Epicatechin; (d) CFTR in complex with Isohamnetin; (e) CFTR in complex with Kaempferol; (f) CFTR complex with Luteolin; (g) CFTR in complex with Myrecetin; (h) CFTR in complex with Theaflavin; (i) CFTR in complex with Pelargonidin; (j) CFTR in complex with Quercetin; (k) CFTR in complex with Peonidin(Pink color indicates CFTR protein, Yellow color indicates inhibitors and Green color dotted line indicate the hydrogen bond).***

5. Toxicity prediction:

The toxicity properties of all the natural inhibitors were calculated and displayed in Table 3

**Table 3**

***ADME Properties for Flavonoids***

| S.NO | LIGAND | BIO | ABS | Vd | LogD | Pka | PHYSCHEM | LogP | PURE | AMES |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | APIGENIN | 30% TO 70% | Trancellular route =100% Paracellular route = 0% | 0.64 L/kg | LogD at: pH = 1.7 (Stomach): 2.43 pH = 4.6 (Duodenum) : 2.42 pH = 6.5 (Jejunum & Ileum): 2.40 pH = 7.4 (Blood): 2.25 pH = 8.0 (Colon): 1.95 | Strongest pKa(Acid): 7.70+/-0.80 Strongest pKa(Base): No Base pKa Number of ionizable groups: 3 | Molecular Weight: 270.24 No. of Hydrogen Bond Donors: 3 No. of Hydrogen Bond Acceptors: 5 TPSA: 86.99 No. of Rotatable Bonds:1 | 2.43 | LogSw: -3.35 95% confidence interval -4.61 ÷ -2.42 Sw: 0.121 mg/ml | 0.309 |
| 2 | CATECHIN | less than 30% | Trancellular route = 97% Paracellular route = 3% | 1.36 L/kg | pH = 1.7 (Stomach): 0.71 pH = 4.6 (Duodenum) : 0.71 pH = 6.5 (Jejunum & Ileum): 0.71 pH = 7.4 (Blood): 0.70 pH = 8.0 (Colon): 0.67 | Strongest pKa(Acid): 9.00+/-0.50 Strongest pKa(Base): No Base pKa Number of ionizable groups: 4 | Molecular Weight: 290.27 No. of Hydrogen Bond Donors: 5 No. of Hydrogen Bond Acceptors: 6 TPSA: 110.38 No. of Rotatable Bonds: 1 | 0.71 | LogSw: -2.51 95% confidence interval -3.77 ÷ -1.58 Sw: 0.892 mg/ml | 0.028 |
| 3 | EPICATECHIN | less than 30% | Trancellular route = 97% Paracellular route = 3% | 1.36 L/kg | pH = 1.7 (Stomach): 0.71 pH = 4.6 (Duodenum) : 0.71 pH = 6.5 (Jejunum & Ileum): 0.71 pH = 7.4 (Blood): 0.70 pH = 8.0 (Colon): 0.67 | Strongest pKa(Acid): 9.00+/-0.50 Strongest pKa(Base): No Base pKa Number of ionizable groups: 4 | Molecular Weight: 290.27 No. of Hydrogen Bond Donors: 5 No. of Hydrogen Bond Acceptors: 6 TPSA: 110.38 No. of Rotatable Bonds: 1 | 0.71 | LogSw: -2.51 95% confidence interval -3.77 ÷ -1.58 Sw: 0.892 mg/ml | 0.028 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 4 | ISOHAMNETIN | less than 30% | Trancellular route = 94% Paracellular route = 6% | 0.25 L/kg | pH = 1.7 (Stomach): -3.42 pH = 4.6 (Duodenum): -5.63 pH = 6.5 (Jejunum & Ileum): -5.72 pH = 7.4 (Blood): -5.73 pH = 8.0 (Colon): -5.73 | Strongest pKa(Acid): -3.00+/-0.50 Strongest pKa(Base): No Base pKa Number of ionizable groups: 4 | Molecular Weight: 396.33 No. of Hydrogen Bond Donors: 4 No. of Hydrogen Bond Acceptors: 10 TPSA: 168.20 No. of Rotatable Bonds: 4 | 1.27 | LogSw: -2.65 95% confidence interval -4.21 ÷ -0.80 Sw: 0.893 mg/ml | 0.766 |
| 5 | KAEMPFEROL | less than 30% | Trancellular route = 100% Paracellular route = 0% | 0.61 L/kg | pH = 1.7 (Stomach): 2.80 pH = 4.6 (Duodenum): 2.80 pH = 6.5 (Jejunum & Ileum): 2.77 pH = 7.4 (Blood): 2.62 pH = 8.0 (Colon): 2.32 | Strongest pKa(Acid): 7.70+/-0.80 Strongest pKa(Base): No Base pKa Number of ionizable groups: 4 | Molecular Weight: 286.24 No. of Hydrogen Bond Donors: 4 No. of Hydrogen Bond Acceptors: 6 TPSA: 107.22 No. of Rotatable Bonds: 1 | 2.80 | LogSw: -3.86 95% confidence interval -5.59 ÷ -2.07 Sw: 0.0393 mg/ml | 0.684 |
| 6 | LUTEOLIN | less than 30% | Trancellular route = 100% Paracellular route = 0% | 0.63 L/kg | pH = 1.7 (Stomach): 1.96 pH = 4.6 (Duodenum): 1.96 pH = 6.5 (Jejunum & Ileum): 1.94 pH = 7.4 (Blood): 1.79 pH = 8.0 (Colon): 1.49 | Strongest pKa(Acid): 7.70+/-0.80 Strongest pKa(Base): No Base pKa Number of ionizable groups: 4 | Molecular Weight: 286.24 No. of Hydrogen Bond Donors: 4 No. of Hydrogen Bond Acceptors: 6 TPSA: 107.22 No. of Rotatable Bonds: 1 | 1.96 | LogSw: -3.85 95% confidence interval -5.56 ÷ -2.08 Sw: 0.0402 mg/ml | 0.606 |
| 7 | MYRECITIN | less than 30% | Trancellular route = 99% Paracellular route = 1% | 0.59 L/kg | pH = 1.7 (Stomach): 1.75 pH = 4.6 (Duodenum): 1.75 pH = 6.5 (Jejunum & Ileum): 1.72 pH = 7.4 (Blood): 1.57 | Strongest pKa(Acid): 7.70+/-0.80 Strongest pKa(Base): No Base pKa Number of ionizable groups: 6 | Molecular Weight: 318.23 No. of Hydrogen Bond Donors: 6 No. of Hydrogen Bond Acceptors: 8 TPSA: 147.68 No. of Rotatable Bonds: 1 | 1.75 | LogSw: -3.61 95% confidence interval -6.18 ÷ -1.56 Sw: 0.0776 mg/ml | 0.976 |

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|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | pH = 8.0 (Colon): 1.27 | | | | | |
| 8 | THEAFLAVIN | less than 30% | Trancellular route = 100% Paracellular route = 0% | 0.81 L/kg | pH = 1.7 (Stomach): 2.57 pH = 4.6 (Duodenum): 2.57 pH = 6.5 (Jejunum & Ileum): 2.32 pH = 7.4 (Blood): 1.71 pH = 8.0 (Colon): 1.15 | Strongest pKa(Acid): 6.60+/-0.80 Strongest pKa(Base): No Base pKa Number of ionizable groups: 5 | Molecular Weight: 564.49 No. of Hydrogen Bond Donors: 9 No. of Hydrogen Bond Acceptors: 12 TPSA: 217.60 No. of Rotatable Bonds: 2 | 15 | THEAFLAVIN | less than 30% |
| 9 | PELARGONIDIN | less than 30% | Trancellular route = 98% Paracellular route = 2% | 1.15 L/kg | pH = 1.7 (Stomach): 2.28 pH = 4.6 (Duodenum): 2.28 pH = 6.5 (Jejunum & Ileum): 2.28 pH = 7.4 (Blood): 2.28 pH = 8.0 (Colon): 2.28 | Strongest pKa(Acid): 8.00+/-1.90 Strongest pKa(Base): Permanent charge found. Number of ionizable groups: 4 | Molecular Weight: 271.24 No. of Hydrogen Bond Donors: 4 No. of Hydrogen Bond Acceptors: 5 TPSA: 80.92 No. of Rotatable Bonds: 1 | 2.28 | LogSw: -4.76 95% confidence interval - ÷ - Sw: 0.00468 mg/ml | 0.494 |
| 10 | QUERCETIN | less than 30% | Trancellular route = 100% Paracellular route = 0% | 0.60 L/kg | pH = 1.7 (Stomach): 2.34 pH = 4.6 (Duodenum): 2.34 pH = 6.5 (Jejunum & Ileum): 2.31 pH = 7.4 (Blood): 2.16 pH = 8.0 (Colon): 1.86 | Strongest pKa(Acid): 7.70+/-0.80 Strongest pKa(Base): No Base pKa Number of ionizable groups: 5 | Molecular Weight: 302.24 No. of Hydrogen Bond Donors: 5 No. of Hydrogen Bond Acceptors: 7 TPSA: 127.45 No. of Rotatable Bonds: 1 | 2.34 | LogSw: -3.88 95% confidence interval -5.72 ÷ -2.10 Sw: 0.0395 mg/ml | 14 |
| 11 | PEONIDIN | less than 30% | Trancellular route = 98% Paracellular route = 2% | 1.10 L/kg | pH = 1.7 (Stomach): 2.18 pH = 4.6 (Duodenum): 2.18 pH = 6.5 (Jejunum & Ileum): 2.18 | Strongest pKa(Acid): 7.40+/-0.80 Strongest pKa(Base): Permanent charge found. Number of | Molecular Weight: 301.27 No. of Hydrogen Bond Donors: 4 No. of Hydrogen Bond Acceptors: 6 TPSA: 90.15 | 2.18 | LogSw: -5.57 95% confidence interval - ÷ - Sw: | 0.003 |

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|---|---|---|---|---|
| | pH = 7.4 (Blood): 2.18 pH = 8.0 (Colon): 2.18 | ionizable groups: 4 | No. of Rotatable Bonds: 2 | 0.00082 mg/ml |

## DISCUSSION

Polycystic kidney disease is a cystic genetic disorder of the kidneys, which poses a threat to human kind. CFTR is an ABC transporter-class ion channel that transports chloride and thiocyanate[8] ions across epithelial cell membranes. Mutations of the CFTR gene affect functioning of the chloride ion channels in these cell membranes, leading to cystic fibrosis. Mutations consist of replacements, duplications, deletions or shortenings in the CFTR gene. This may result in proteins that may not function, work less effectively, are more quickly degraded, or are present in inadequate numbers [9]. In this work, we have constructed a 3D model of CFTR and the modeled structure was mutated, the structure was visualized in RASMOL (**Figure 2**).The CFTR protein has ABC_tran domain from 451-622 was predicted using Pfam. Ten Active site regions of CFTR was analyzed using Q-SITEFINDER, site 1 was considered to be the best. The docking scores and H-bond formation defines the best interaction between the Flavonoids and the CFTR. Among the eleven inhibitors Kaempferol was found to be the best inhibitor having 5 H-bonds and -8.5 Kcal/mol.

## CONCLUSION

Thus the interactions between Flavonoid inhibitors and CFTR *Insilico* are useful to understand the underlying mechanism of enzyme inhibition. Favorable results of Toxicity analysis show, Flavonoids as best therapeutic drug. Docking scores and *Insilico* Toxicity test results indicate the application of Flavonoids as Potential and Natural Therapeutic agents to treat Polycystic Kidney Disease.

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