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IN SILICO MOLECULAR DOCKING AND ADME POTENTIAL OF KIWI FRUIT ISOLATED COMPOUNDS AGAINST APOPTOTIC PROTEINS

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ABSTRACT

The four isolated fractions from the methanol extract of kiwi fruit pulp when tested for their anticancer potential revealed that two fractions of 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one and 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate had very good anticancer properties. Hence the ligands of two compounds such as 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4H-chromen-4-one and 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate were docked with apoptotic proteins like Caspase-3 and Beta-Actin by ArgusLab software. The docking score was highest in 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one ligand which showed the docking score of -10.94 kcal/mol for Caspase-3, and -9.71 kcal/mol for Beta-Actin. Likewise, 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate compound showed the docking score of -8.76 kcal/mol for Caspase-3 and -9.43 kcal/mol for Beta-Actin. When compared among the ligands, 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one ligand showed the least score for both Caspase-3 and Beta-Actin. Hence, 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one compound seems to possess higher apoptotic activity than 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate compound. The interaction of 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one ligand with Caspase-3 formed 4

hydrogen bonds, whereas with Beta-Actin it formed 6 hydrogen bonds. The interaction of 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate ligand with Caspase-3 formed 2 hydrogen bonds and with Beta-Actin also formed 2 hydrogen bonds. This results show that there is presence of binding site between the proteins and the ligands.The potential drug candidate can further be validated by wet lab studies for its proper function.

Keywords: 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one, 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate, Caspase-3, Beta-Actin, ArgusLab.

INTRODUCTION

Drug discovery is the most prominent process in current days and that begins with target and lead discovery, followed by lead optimization and pre-clinical *in vitro* and *in vivo* studies to recognize the potent compounds which assure the main criteria for drug development **[1]**. To develop a drug through *in vitro* and *in vivo* methods, it takes long time and will have high expenditure **[2]**. For that reason *in silico* drug designing is useful to predict the active molecules and this will give an idea about the drug discovery process **[3-15]**. The drug discovery through pharmaceutical industry will take approximately 12 to 14 years to bring a drug from discovery to market, costing up to 1.2 to 1.4 billion dollars **[16, 5]**. The way of drug discovery by pharmaceutical industry is a time-consuming multi-step process against a battery of *in vivo* biological validations and further investigating the active candidates for their pharmacokinetic properties (ADME), metabolism and potential toxicity **[5]**.

Today, the process of drug discovery has been revolutionized with the advent of genomics, proteomics, bioinformatics and efficient technologies like, combinatorial chemistry, high throughput screening, virtual screening, *de novo* design, *in vitro*, *in silico* ADME screening and structure-based designing **[17]**. In view of this, *in silico* molecular docking and ADME studies were carried out to assess the potential of *A. deliciosa* isolated compounds.

MATERIALS AND METHODS

To predict the mode of action of the 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one ligand 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4H-chromen-4-one) and 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate ligand (3'5'-dihydroxy-2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate) against the apoptotic proteins Caspase-3 and β-actin,

the following databases and tools were used:

Databases

Swiss-Prot and Protein Data Bank.

Tools used for docking

RasMol, ChemSketch, Open Babel, ArgusLab and PyMol Viewer.

Tools used for ADME study: admetSAR

Absorption

Human Intestinal Absorption (HIA)

Human Oral Bioavailability (HOB)

Blood-Brain Barrier (BBB) Penetration

Caco-2 Permeability

Transporter

P-glycoprotein Substrate, Inhibitor, *etc*…

Renal Organic Cation Transporter (OCT2/SLC22A2)

Distribution

Plasma Protein Binding (PPD)

Volume of Distribution (VOD)

Metabolism

» Cytochrome P450 (CYP450) substrate, inhibitor, inducer, activator (endpoints Ki, IC50, AC50).

Substrate: CYP1A2, 2C9, 2C19, 2D6, 3A4 *etc.*

Inhibitor: CYP1A1,1A2, 2A5, 2A6, 2C9, 2C19, 2D6, 3A4 *etc.*

Inducer: CYP1A2, 2C9, 2C19, 2D6, 3A4 etc...

Activator: CYP1A2, 2C9, 2C19, 2D6, 3A4 etc...

» Other metabolism-relationship Enzyme Contains UDP-glucuronosyl transferase (UGT) substrate, inhibitor.

Excretion

Half time (t1/2)

Renal Clearance

Ligand 1: 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4H-chromen-4-one

SMILES: c12c(ccc(c1)O)c(=O)cc(o2)c1ccc(c(c1)OC)O

Ligand2: 3'5'-dihydroxy-2'-(methoxy carbonyl methyl)-phenyl-3,4-dihydroxy benzoate

SMILES: c1(c(c(cc(c1)O)O)CC(=O)OC)OC(=O)c1ccc(c(c1)O)O

RESULTS AND DISCUSSION

To study the interaction of between 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one (7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4H-chromen-4-one) and 3’5’-dihydroxy -2’-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate ligands (3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate) and apoptotic proteins (Caspase-3 and β-Actin) and to explore their binding mode, docking study was performed using ArgusLab.

Retrieval of Protein Sequences from Swiss-Prot

Protein sequences of Caspase-3 and Beta-Actin were downloaded from Swiss-Prot database; their respective IDs being P42574 for Caspase-3 and P60709 for Beta-Actin.

Retrieval of Protein Structures from PDB

The 3D structures of apoptotic proteins *viz*., Caspase-3 and Beta-Actin were derived from PDB database. Their IDs are P42574 for Caspase-3 and P60709 for Beta-Actin.

Visualization of Proteins by RasMol

Using RasMol tool, the 3D structures of Caspase-3 and Beta-Actin apoptotic proteins were visualized.

Creation of Ligands by ChemSketch

Ligands of isolated 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one and 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate compounds were drawn and created in 2D form, and converted to 3D form in 'mol' format using ChemSketch. The created structures are presented in **Figure 1 and Figure 2**.

Conversion of Ligands by Open Babel

As the protein structures are in PDB format and the ligands are in mol format, it is essential to convert the ligands from mol format to PDB format; this conversion being achieved by Open Babel tool. In the present study, the 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one and 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate compound ligands which were in mol format was converted in to PDB format by Open Babel tool.

***In Silico* Docking by ArgusLab**

The 3D structure of Caspase-3 and Beta-Actin were docked with 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one and 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate ligands using ArgusLab software to assess the interaction between the apoptotic proteins and ligands and the docked complex is presented in **Figure 3 and Figure 4**.

Visualization of Docked Complex by PyMol Viewer

The docked protein ligand complexes were analyzed using PyMol Viewer visualization tool **(Figure 3)**.

In silico docking study revealed the interactions between ligand and protein and also calculated the minimum binding energy (kcal/mol) between the protein and ligand. The 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one ligand showed the docking score of -10.94 kcal/mol for Caspase-3, and -9.71 kcal/mol for Beta-Actin. Likewise, 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate compound showed the

docking score of -8.76 kcal/mol for Caspase-3 and -9.43 kcal/mol for Beta-Actin **(Table 1)**. When compared among the ligands, 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one ligand showed the least score for both Caspase-3 and Beta-Actin. Hence, 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one compound seems to possess higher apoptotic activity than 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate compound.

The interaction of 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one ligand with Caspase-3 formed 4 hydrogen bonds, whereas Beta-Actin formed 6 hydrogen bonds. The interaction of 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate ligand with Caspase-3 formed 2 hydrogen bonds and with Beta-Actin also formed 2 hydrogen bonds. This results show that there is presence of binding site between the proteins and the ligands. The docking is also valid by the formation of hydrogen bond between them. 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one ligand formed 4 and 6 hydrogen bonds with Caspase-3 and Beta-Actin, respectively, while 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate ligand formed 2 hydrogen bonds with Caspase-3 and Beta-Actin. The results revealed that bond formation was stronger in 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one ligand than that of 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate ligand, thus again proving that 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one compound has more apoptotic potential than that of 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate ligand. From the above docking results, it is pragmatic that both 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one and 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate ligands docks well with apoptotic proteins with good docking scores and strong hydrogen bond formation, and hence can be considered to be the best compounds. The results of Lipinski rule suggest that the analyzed 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one and 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate compound as best therapeutic drugs.

ADME Studies

Absorption, distribution, metabolism and excretion (ADME) properties of drug candidates or environmental chemicals play a key role in drug discovery and environmental hazard assessment. The ADME structure-activity

relationship server, entitled admetSAR, is a comprehensive knowledge and tool for predicting ADME properties of drug candidates and environmental chemicals.

The 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one and 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate ligands, which are best therapeutic agents based on the Lipinski Rule, are also found to be absorbed, distributed and metabolized well. The ligands were also found to be 'Non-Ames Toxicity' and 'Non-carcinogens'. Both 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one and 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate ligands have a 'Human Intestinal Absorption' value of 0.59 and 0.98, respectively. The 'Distribution Subcellular localization-Mitochondria' value was 0.72 and 0.81 for 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one and 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate compounds, respectively. The 'Metabolism Process' and 'Low CYP Inhibitory Promiscuity' was 0.92 and 0.78, and 'Excretion Human Ether-a-go-go-Related Gene Inhibition' was 0.9701 and 0.9766 as shown in the **Figure 4 and Figure 5**.

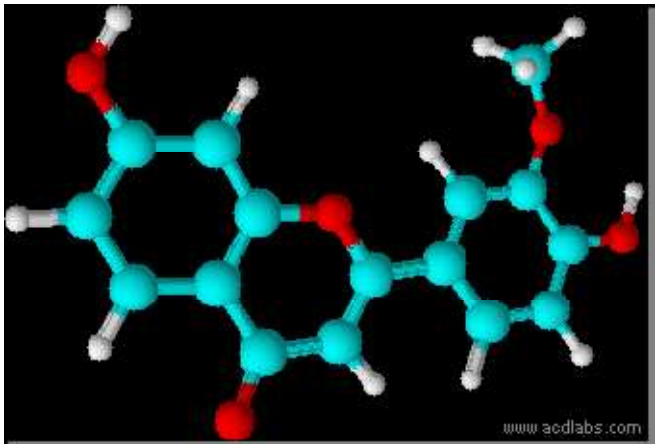

Figure 1: 3D structure of 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one compound

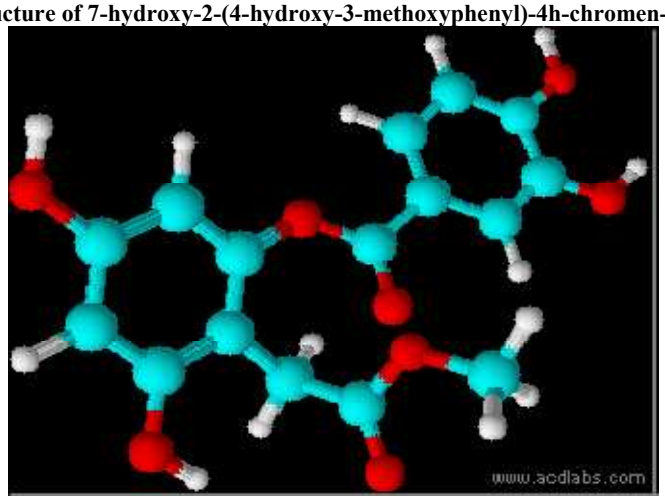

Figure 2: 3D structure of 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate compound

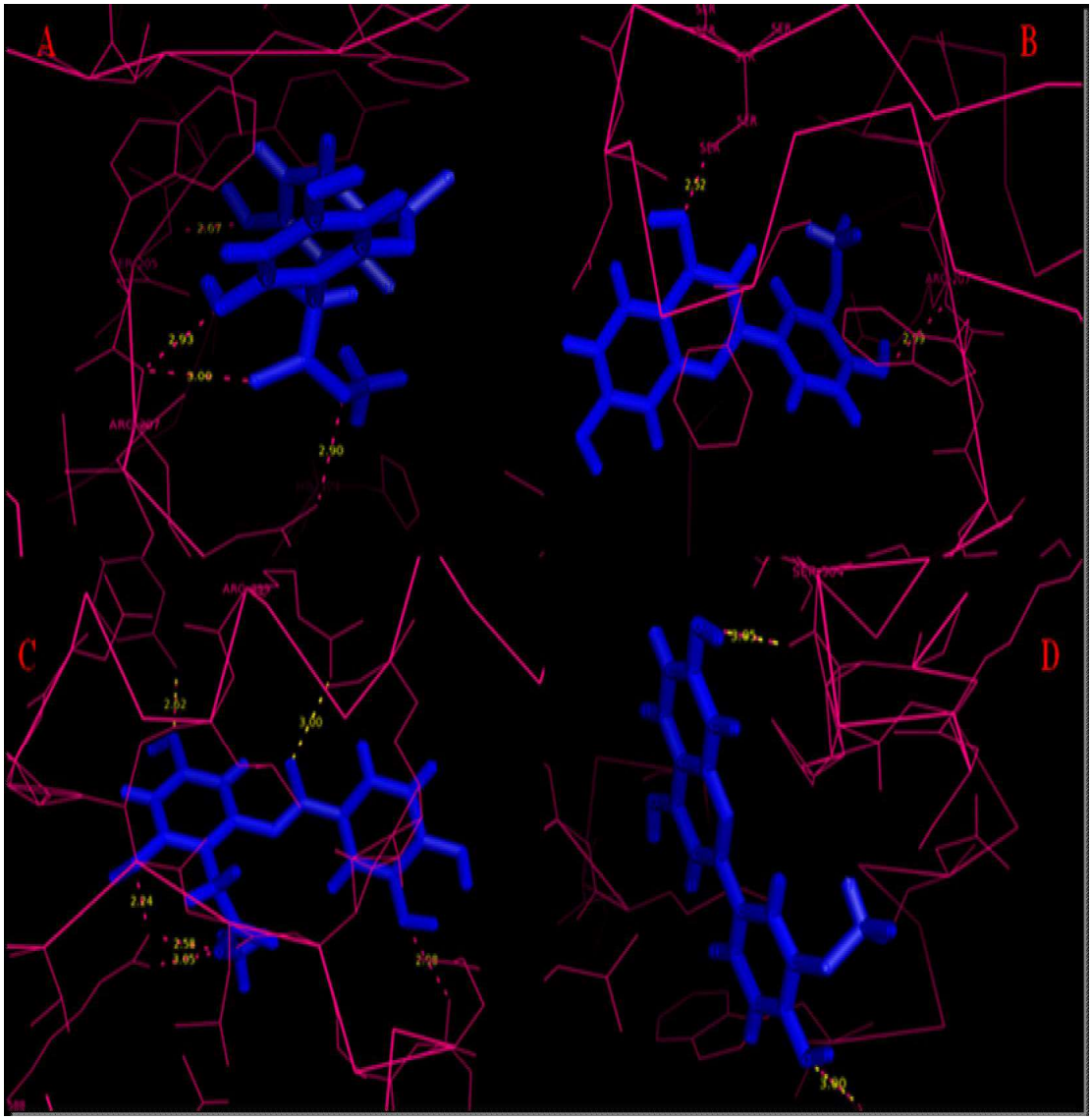

Figure 3: Visualization of docked complex using PyMol Viewer

A – Caspase-3 with 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one compound

B – Beta-Actin with 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one compound

C – Caspase-3 with 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate compound

D – Beta-Actin with 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate compound

Table 1: Docking score between proteins and ligands

S. No.	Protein	Ligand	Docking score (Kcal/Mol)	H-Bond
1	Caspase-3	7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one	-10.94	4
2	Beta-Actin	7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one	-9.71	6
3	Caspase-3	3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate	-8.76	2
4	Beta-Actin	3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate	-9.43	2

Model	Result	Probability
Absorption		
Blood-Brain Barrier	BBB-	0.5447
Human Intestinal Absorption	HIA+	0.9898
Caco-2 Permeability	Caco2+	0.8934
P-glycoprotein Substrate	Substrate	0.6272
P-glycoprotein Inhibitor	Non-inhibitor	0.6246
	Inhibitor	0.8101
Renal Organic Cation Transporter	Non-inhibitor	0.8876
Distribution		
Subcellular localization	Mitochondria	0.8113
Metabolism		
CYP450 2C9 Substrate	Non-substrate	0.7553
CYP450 2D6 Substrate	Non-substrate	0.8918
CYP450 3A4 Substrate	Non-substrate	0.5917
CYP450 1A2 Inhibitor	Inhibitor	0.9264
CYP450 2C9 Inhibitor	Inhibitor	0.8876
CYP450 2D6 Inhibitor	Non-inhibitor	0.8064
CYP450 2C19 Inhibitor	Inhibitor	0.9315
CYP450 3A4 Inhibitor	Non-inhibitor	0.6447
CYP Inhibitory Promiscuity	High CYP Inhibitory Promiscuity	0.7815
Excretion		
Toxicity		
Human Ether-a-go-go-Related Gene Inhibition	Weak inhibitor	0.9766
	Non-inhibitor	0.8625
AMES Toxicity	Non AMES toxic	0.7578
Carcinogens	Non-carcinogens	0.9360
Fish Toxicity	High FHMT	0.9206
Tetrahymena Pyriformis Toxicity	High TPT	0.9964
Honey Bee Toxicity	High HBT	0.6819
Biodegradation	Not ready biodegradable	0.9150
Acute Oral Toxicity	III	0.7641
Carcinogenicity (Three-class)	Non-required	0.5580

Figure 4: ADME analysis of 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one ligand

Model	Result	Probability
Absorption		
Blood-Brain Barrier	BBB-	0.7522
Human Intestinal Absorption	HIA+	0.5939
Caco-2 Permeability	Caco2-	0.7637
P-glycoprotein Substrate	Substrate	0.6187
P-glycoprotein Inhibitor	Non-inhibitor	0.8080
	Non-inhibitor	0.8811
Renal Organic Cation Transporter	Non-inhibitor	0.8884
Distribution		
Subcellular localization	Mitochondria	0.7266
Metabolism		
CYP450 2C9 Substrate	Non-substrate	0.7506
CYP450 2D6 Substrate	Non-substrate	0.9012
CYP450 3A4 Substrate	Non-substrate	0.6164
CYP450 1A2 Inhibitor	Non-inhibitor	0.6853
CYP450 2C9 Inhibitor	Non-inhibitor	0.8704
CYP450 2D6 Inhibitor	Non-inhibitor	0.9006
CYP450 2C19 Inhibitor	Non-inhibitor	0.9079
CYP450 3A4 Inhibitor	Non-inhibitor	0.9094
CYP Inhibitory Promiscuity	Low CYP Inhibitory Promiscuity	0.9211
Excretion		
Toxicity		
Human Ether-a-go-go-Related Gene Inhibition	Weak inhibitor	0.9701
	Non-inhibitor	0.8830
AMES Toxicity	Non AMES toxic	0.6371
Carcinogens	Non-carcinogens	0.9468
Fish Toxicity	High FHMT	0.9894
Tetrahymena Pyriformis Toxicity	High TPT	0.9890
Honey Bee Toxicity	High HBT	0.6099
Biodegradation	Not ready biodegradable	0.5616
Acute Oral Toxicity	III	0.7569
Carcinogenicity (Three-class)	Non-required	0.7332

Figure 5: ADME analysis of 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate ligand

Thus, it might be concluded that both 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one and 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate ligands act as best therapeutic agents to treat diseases by Absorption, Distribution, Metabolism and Excretion (ADME) process. Docking and *in silico* toxicity study results proves the application of 7-

hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one and 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate compounds as potential and natural therapeutic agents to treat diseases.

It is interesting to know that *in silico* molecular docking and ADME studies of isolated 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one and 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate ligands present in *A. deliciosa* against apoptotic proteins has not been carried out and this is the first report that is recorded. *In silico* molecular docking study revealed that 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one ligand recorded minimum docking score for both Caspase-3 and Beta-Actin when compared with that of 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate ligand. Hence, 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one compound seems to possess higher apoptotic activity than 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate compound. Likewise, the interaction between the ligands and apoptotic proteins showed that bond formation was stronger in 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one ligand than that of 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate ligand, thus again proving that 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one compound has more apoptotic potential than that of 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate compound.

According to Lipinski *et al.* (2001), the ligand should have good absorption with a log p value *i.e.,* partition coefficient below 5, molecular weight lower than 500 daltons and 10 H_2 bond acceptors *i.e.*, N_2 and H_2 atoms and based on these parameters the ligands can attain a drug-likeness and hence are also used to predict whether a chemical or isolated compound possess a pharmacological or biological activity as an orally active drug in humans or not **[18]**. In a similar way, our ligands also obeyed the rules of Lipinski to attain the nature of drug-likeness. Similar observations were reported in hespertin and naringenin polyphenolic compounds against HER2 tyrosine kinase inhibitors **[19]**, camptothecin, epigallocatechin, coumarin and gallic acid against Caspase-3 **[20]**. The authors also stated that recognition of binding site between the ligand and the protein receptor may pave the way for drug discovery and also identify the functions of selected protein **[20]**.

The results of the present study *in toto* show that there is presence of binding site between the proteins and ligands. The docking is also valid by the formation of hydrogen bond between them. The result of Lipinski rule suggests that the analyzed compound as best therapeutic drugs. Docking and *in silico* ADME studies proves the application of 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one and 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate compounds as potential and natural therapeutic agents to treat diseases. The *in silico* docking and ADME study in the present study was substantial enough to identify the binding mechanism and interaction between the isolated compounds (7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one and 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate) against the apoptotic proteins (Caspase-3 and Beta-Actin) and the results obtained in our study could be useful for future drug designing and development of novel compounds with higher inhibitory activity against various types of cancer.

4. CONCLUSION

In this study, molecular docking was carried out to explore the binding interaction of 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one and 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate compounds with apoptotic proteins and to correlate its docking score with the activity of 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4h-chromen-4-one and 3'5'-dihydroxy -2'-(methoxycarbonyl methyl)-phenyl-3,4-dihydroxy benzoate compounds. The results are helpful for designing and developing a novel drug that has better inhibitory activity against several types of cancers. From this study, we conclude that kiwi fruit compounds are one of the best phytochemical anticancer agents. This potential drug candidate awaits further validation by wet lab studies for its proper function as an anticancer drug.

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