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In silico Molecular Docking Studies of compounds from *Rumex vesicarius* against GFAT1

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ABSTRACT

Introduction: In spite of the global occurrence of T2DM infection and lack of auspicious treatment for Diabetes patients, there are only a few drugs accepted for the managing of infected patients. There is an urgent need to discover newer anti-Diabetic drugs with novel mechanism of action and with efforts to reduce attrition rate in early drug discovery stages.
Objective: The objective of this study is the evaluation of *Rumex vesicarius*compunds for anti-T2DM activity.
Methods:*In silico* anti-T2DM lead prioritization was performed on a set of known compounds from *R.vesicarius* medicinal plant. The energy minimized structures of these molecules were docked into GFAT1. Docking experiments were done using Autodock software.
Results: Physcion was found to be a lead with better docking score (-7.66 kcal/mol). In the present study, 9 compounds of *Rumex vesicarius* were docked into GFAT1 enzyme and out of eight one compound, physcion indicated high binding source, that residues GLY:374,423 GLN:421 SER:376,420,422,473 LYS:675 VAL:471 LEU:419,673 ALA:674 GLU:562 THR:375,425,428 CYS:373 and might play important roles in binding with these compounds.
Conclusion: The results showed that there is scope for the improvement of activity of Physcion analogs to discover a potent anti-T2DM compound.

Key words: Docking, GFAT1, *Rumex vesicarius,* Diabetes mellitus.

INTRODUCTION

Diabetes mellitus is most common metabolic disease all over the world and number of diabetic patients is still on rise. Reports of 2017 indicate that about 380 million people are diagnosed with diabetes globally, and this may rise to 572 million by the year 2030 . The global prevalence of diabetes and impaired glucose tolerance in adults has been increasing over recent decades [1–3]. Diabetes mellitus is characterized by abnormally high levels of glucose in the blood. Majority of diabetic people are insulin dependent and depend on insulin injections. Instead of injections or pump which is a painful procedure oral consumption of insulin is preferable choice.

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To supplement the insulin needs, metabolites that can be administered orally and mimic insulin action are to be considered.

Rumex vesicarius Linn. (Polygonaceae) is commonly called as Chukka kura in Telugu, Chukra in Hindi, Bladder Dock in English [4]. Rumex vesicarius L. is a wild edible plant used as a sorrel and collected in spring season and eaten fresh or cooked. *Rumex vesicarius* L. has many important medicinal uses such as treatment of hepatic diseases, bad digestion, diurectic, laxative, tonic, analgesic, purgative and antibacterial agents. The plant can be used to reduce biliary disorders and control cholestrol levels [5]. Diabetes mellitus is the sixth leading cause of death globally. Many of the drugs have been used in the management of this disease. These drugs have many side effects and a search for new class of compounds is essential to overcome diabetic problems. Traditionally, a number of plants have been used in various herbal preparations in the management of diabetes and only few of them have been proven scientifically [6-8]. Anti-bacterial and Antioxidant activities of *Rumex vesicarius*was performed. So far there is no in silico anti-diabetic study report so this paper is aimed to report the in silico docking of phytochemicals present in

this plant against target enzyme, glutamine fructose-6-phosphate amidotransferase (GFAT1).

Glutamine-fructose-6-phosphate amidotransferase GFAT1 is the first and rate-limiting enzyme of the hexosamine pathway. GFAT1 controls the flux of glucose into the hexosamine pathway and catalyzes the formation of glucosamine 6-phosphate. The majority of glucose will enter the glycolysis pathway, with a small percentage entering the hexosamine pathway. GFAT1 regulate the hexosamine pathway products. Therefore, this enzyme involved in a therapeutic target against Type 2 DM (Chou 2004) [9].

MATERIALS AND METHODS

Data Set:

Phytoconstituents from the *R. vesicarius* and standard drug compounds (3D PDB) were downloaded from the IMPPAT database (https://cb.imsc.res.in/imppat/home). The molecular properties and structure of the selected compounds (apigenin, beta-carotene, Chrysophanol, emodin ,Isovitexin, Orientin, Physcion, retinol, thiamine and Vitexin) were shown in table-1.

Bioactivity score prediction

Drug score values indicate overall potential of a compound to be a drug candidate. Mol inspiration is a web-based tool used to predict the bioactivity score of the synthesized compounds against regular human receptors such as GPCRs, ion channels, kinases, nuclear receptors, proteases and enzymes.

Evaluation of drug likeliness based on Lipinski's rule of five

Lipinski's rule of five is helpful in describing molecular properties of drug compounds required for estimation of important pharmacokinetic parameters such as absorption, distribution, metabolism, excretion and toxicity (ADMET). The rule is helpful in drug design and development.

The drug-likeness and molecular property prediction were done by molsoft server (http://molsoft.com/mprop/).

Computational Docking Studies:

Preparation of Ligand and Protein:

The three dimensional structure of the target Glutamine fructose-6-phosphate amidotransferase (2ZJ3) was obtained from Protein data bank database (https://www.rcsb.org/) and downloaded in PDB format. The ligands and water molecules were removed from the protein and the chemistry of the protein was corrected for the missing hydrogen followed by the energy minimization of the protein. Drug molecule and phytoconstituents optimization, addition of charges and hydrogen bonds was carried out using Autodock tools.

Docking

The docking of GFAT1 with selected phytochemical molecules were performed by using Autodock 4[10]. The docking calculations were verified using docking server. Gasitier partial charges were added to ligand. Nonpolar hydrogen atoms were merged and rotatable hydrogen bonds were defined. Docking calculations were carried out onreceptor. Essential hydrogen atoms, kollaman charges and savlavation parameters were added affinity (grid) maps25 Å grid points and 0.500Å were generated using the autogrid program. Autodock parameters set and distancedependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms,respectively.

Docking simulations were performed using Lamarckian algorithm (LGA) and Solis and Wet local search methods. Initial position torsion and orientation of the drug molecules were set randomly. All rotatable torsions were released during docking. Each docking experiment was derived from 10 different runs that were set to terminate after 250000 energy calculations[11]. The population size was set to 150. During search the translational step 0.2 Å and quaternion and torsion step 5 were applied.

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Table -1. Evaluation of drug likeliness based on Lipinski's rule of five of ligands.

Sl.No	Compound name	Molecular formula	Molecular weight	No.of H bond acceptors	No.of H bond donars	LogP	molPSA
1	apigenin	$C_{15}H_{10}O_5$	270.24	5	3	2.46	73.57 A2
2	Chrysophanol	$C_{15}H_{10}O_4$	254.24	4	2	3.54	59.28 A2
3	emodin	$C_{15}H_{10}O_5$	270.24	5	3	3.01	76.89 A2
4	Isovitexin	$C_{21}H_{20}O_{10}$	432.38	10	7	0.52	143.44 A2
5	Orientin	$C_{21}H_{20}O_{11}$	448.38	11	8	0.03	159.67 A2
6	Physcion	$C_{16}H_{12}O_5$	284.27	5	2	2.98	66.82 A2
7	retinol	$C_{20}H_{30}O$	286.46	1	1	5.92	17.09 A2
8	thiamine	$C_{12}H_{17}N_4O_S$	265.36	4	3	0.51	57.00 A2
9	Vitexin	$C_{21}H_{20}O_{10}$	432.38	10	7	0.52	144.19 A2

RESULTS AND DISCUSSION

Computational docking is an extremely useful tool to gain an understanding about synthesized compounds and their interactions with biological drug targets, which is very important in drug discovery research. The Molecular Docking software predicted the amino acids in active site region of the studied target proteins.

Lipinski's parameters

Lipinski's rule of five (RO5) is used to evaluate drug likeliness of a chemical compound possessing properties that would make it a likely or potential drug in humans [12-13]. The oral activity of a drug compound is predicted by calculating certain molecular parameters like log P (partition coefficient), polar surface area, number of hydrogen bond donors, number of hydrogen bond acceptors, and molecular weight. The rule states that most metal complexes with good membrane permeability have log P ≤ 5, number of hydrogen bond acceptors ≤10, and number of hydrogen bond donors ≤5. In general, an orally active drug has no more than one violation of the given criteria. In the present study, the synthesized ligand and its complexes were found to be in good agreement with the given criteria and can be said to possess good oral bioavailability.

Evaluation of drug likeliness based on Lipinski's rule of five of ligands were showed in Table-1. Based on the drug likeliness evaluation, all ligands are maintained the Lipinski's rule of five.

Bioactivity score prediction

The pharmacological activity describes the beneficial effects of drugs in living beings. The drug is supposed to bind with a biological target.

Biological targets are the most common proteins such as enzymes, ion channels, and receptors. The biological target is also referred to as drug target. The bioactivity scores of the synthesized complexes were calculated for different parameters such as binding to G protein-coupled receptor (GPCR) ligand and nuclear receptor ligand, ion channel modulation, kinase inhibition, amaidotransferase inhibition, and enzyme activity inhibition. All the parameters were calculated with the help of online software Molinspiration (www.molinspiration.com), which predicted moderate biological activity for the synthesized complexes. The bioactivity score is given in Table2. It is known that for metal complexes, if the bioactivity score is more than 0.0, then the complex is active; if it is between −5.0 and 0.0, then the complex is moderately active, and if the bioactivity score is less than −5.0, then it is inactive.

As seen in Table-2, the bioactivity scores of the ligand as well as all the complexes were above −5.0 and 0.0, which clearly indicate that they possess such properties as are required for the complexes to act as potential drugs with some modifications in chemical structure.

Docking interactions

Physicochemical properties of the compounds of *R.vesicarius* were examined and the results of docking were tabulated. On docking against GFAT1, the compound Physcion showed greater binding affinity towards enzyme and got a best ligand pose energy of -7.66 and the residues involving in the interaction are : GLY:374,423 GLN:421 SER:376,420,422,473 LYS:675 VAL:471 LEU:419,673 ALA:674 GLU:562 THR:375,425,428 CYS:373.

The former compound is thus an effective inhibitor among the other compounds that can stop the function of GFAT1

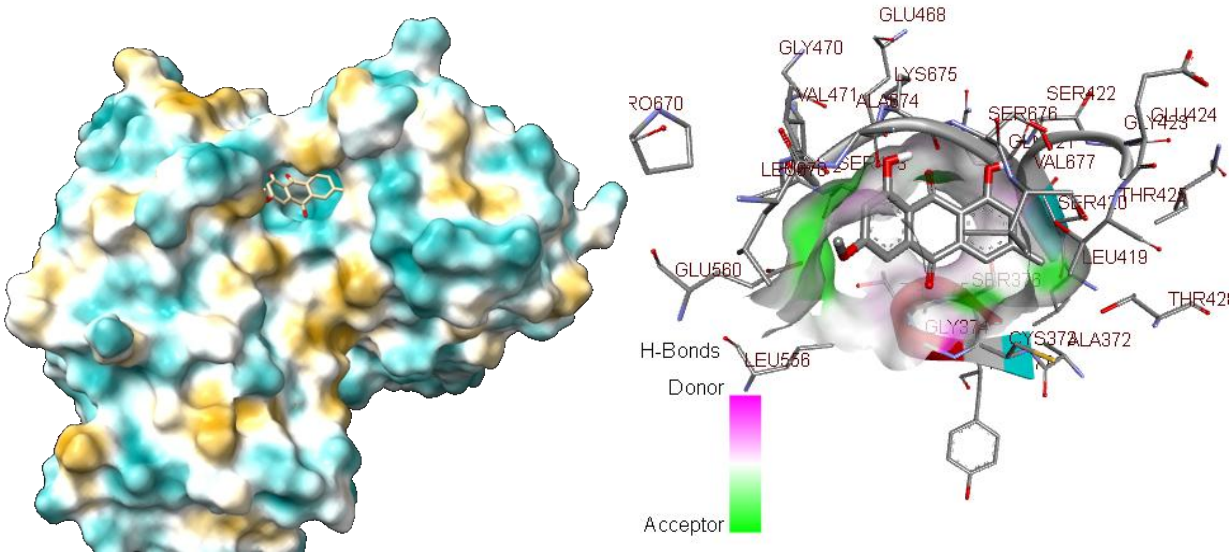
Table -2. Bioactivity score of the ligands

S. No.	Compound	Parameters of Bioactivity score					
		GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	Apigenin	-0.07	-0.09	0.18	0.34	-0.25	0.26
2	Chrysophanol	-0.23	-0.17	0.06	0.02	-0.26	0.16
3	Emodin	-0.14	-0.14	0.07	0.17	-0.21	0.21
4	Isovitexin	0.12	0.02	0.15	0.23	0.04	0.47
5	Orientin	0.12	-0.14	0.20	0.20	0.01	0.45
6	Physcion	-0.17	-0.23	0.04	0.11	-0.23	0.14
7	Retinol	-0.01	0.32	-0.25	1.02	-0.16	0.66
8	Thiamine	0.26	0.01	-0.37	-1.72	-0.64	1.12
9	Vitexin	0.13	-0.14	0.19	0.23	0.03	0.46

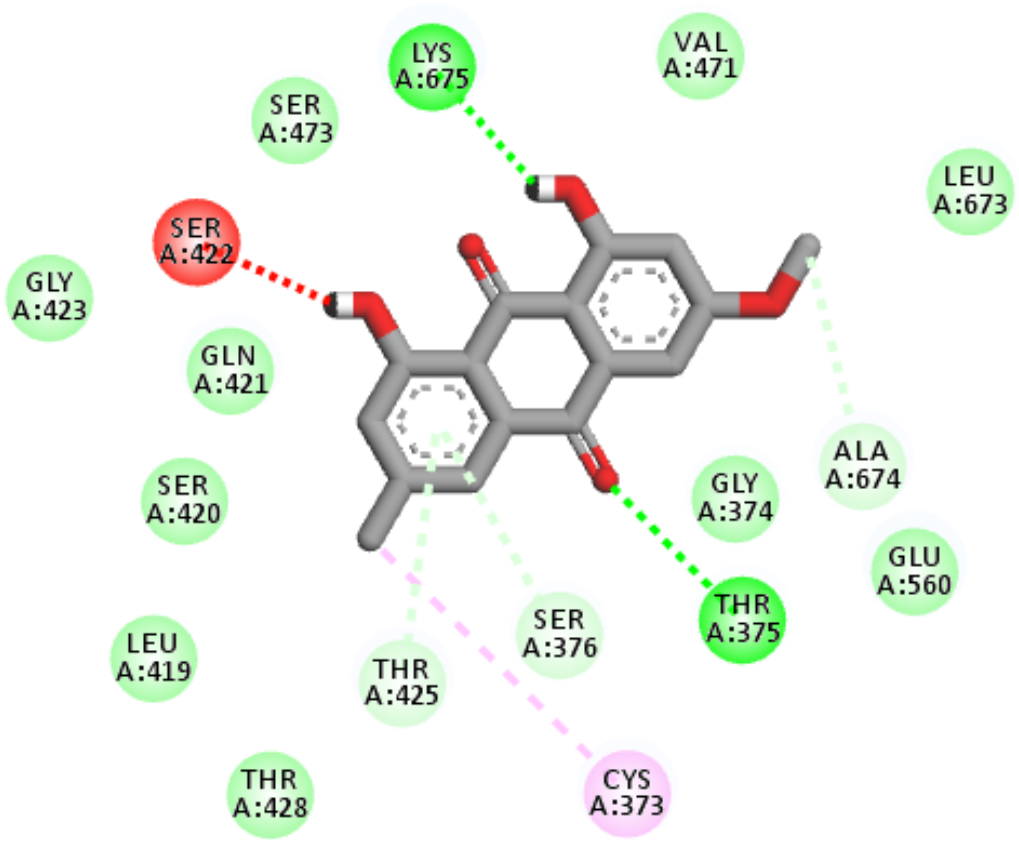
Table-3. Phytochemical compounds docked against T2DM-GFAT1

Sl.No	Compound Name	Binding energy	Residue involving interaction	No. of H bonds	Interaction of residues forming H_2 bonds
1	apigenin	-7.30 kcal/mol	ALA:372,472,674SER:422,420,473,676,376 GLN:421GLY:374 THR:428,425 VAL:677,471,375LYS:675 LEU:419,673 GLU:560CYS:373	3	LEU:419 ALA:674 GLU:560
2	Chrysophanol	-7.59 kcal/mol	THR:428,425CYS:373 LEU:419SER:376,420,422,473,676 ALA:372,674GLY:423,374 GLN:421, GLU:560L, YS:675VAL:471	3	SER:420,422 LYS:675
3	emodin	-7.54	LYS:557,675VAL:471SER:376,422,420,473,676 GLU:560ALA:472,372THR:375,428,425 GLY:374,423TYR:377 CYS:373, GLN:421LEU:419	5	LYS:675 CYS:373 SER:422,420
4	Isovitexin	-7.21 kcal/mol	ALA;382,549TYR:546,548,377 HIS:547GLY:545 VAL:381,397 ARG:384LEU:570,399,552 GLN:385	4	TYR:377,546
5	Orientin	-5.55 kcal/mol	GLU: 388, GLN:385 ALA:382,549, VAL;381, TYR;377,546,548 GLY:545, LEU:570,552, ARG:384	5	VAL:381 GLU:388 TYR:377,548
6	Physcion	-7.66 kcal/mol	GLY:374,423, GLN:421, SER:376,420,422,473 LYS:675, VAL:471, LEU:419,673, ALA:674 GLU:562, THR:375,425,428, CYS:373.	2	LYS:675 THR:375
7	retinol	-6.71 kcal/mol	SER:376,422,474,676, THR:375,425 VAL:471,677, GLN:421, LYS:559,675 GLU:560, LEU:556,673, ALA:674.	0	0
8	thiamine	-6.50 kcal/mol	GLU:388, ARG:384, THR:383,550 VAL;381,381, TYR:546,548 ALA;382,549 HIS:547 GLY:545 ARG:384	4	GLY:545 GLN:385 GLU:388 ARG:384
9	Vitexin	-6.00 kcal/mol	SER:521 LEU:520 PRO:332 LYS:326 GLU:330,333, ASN:319, LYS:517 PHE:320,329	4	GLU:333 PHE:329 ASN:319

Figure-1.Schematic representation of the interactions between the Physcion selected from *Rumex vesicarius L.*with GFAT1 (PDB ID: 2ZJ3).

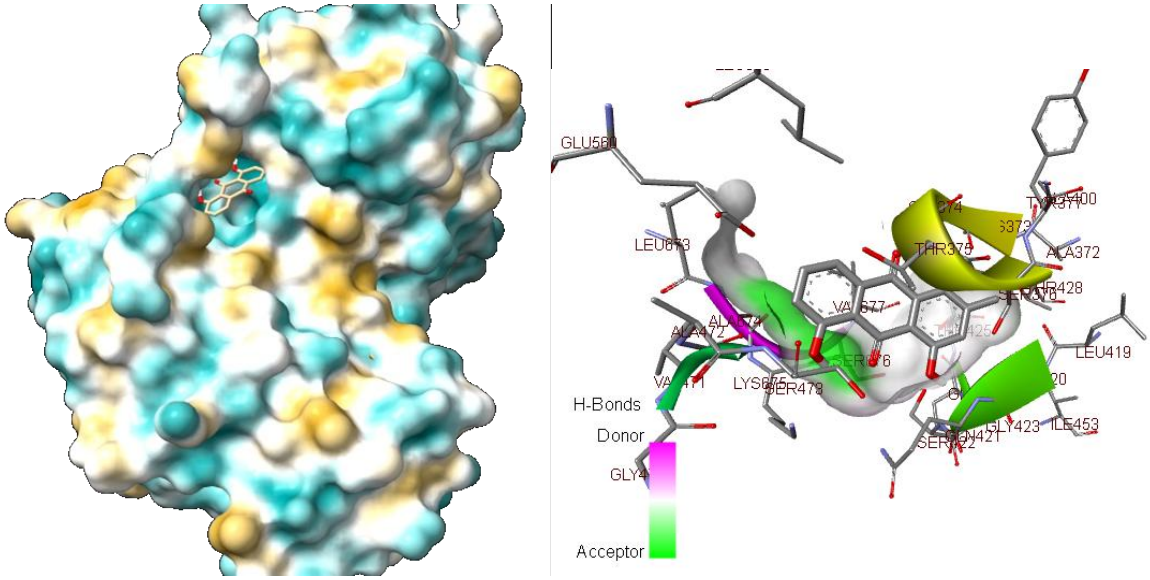


3.a) **3D images of Physcion and GFAT1 complex file**

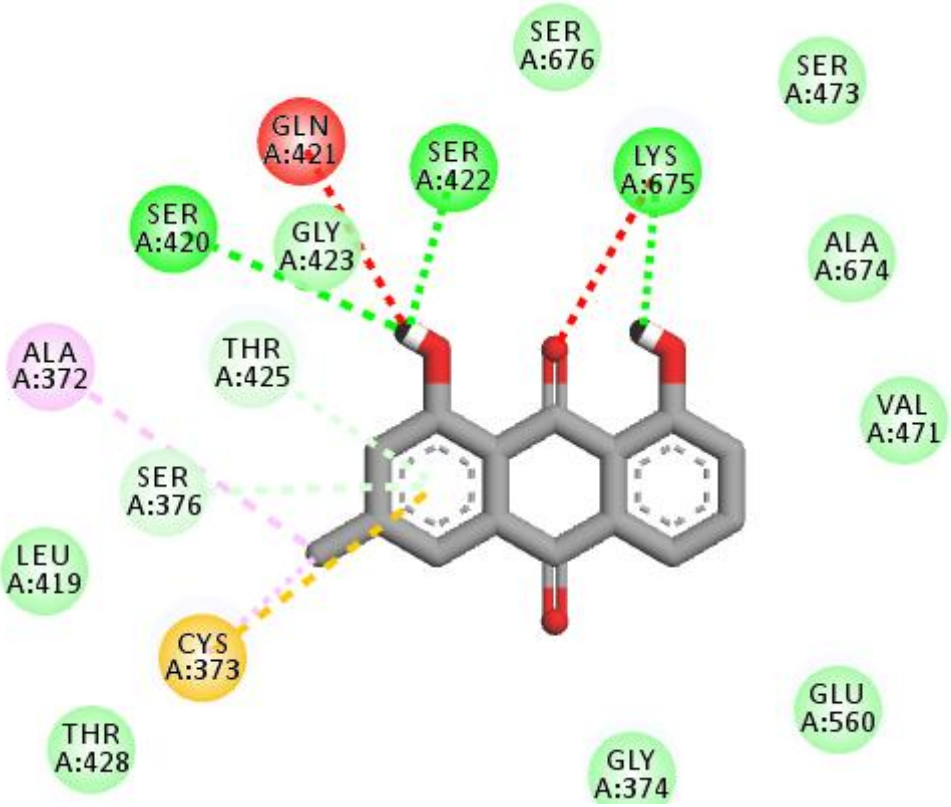


3.b) **2D Image of interaction between Physcion and GFAT1**

Figure-2. Schematic representation of the interactions between the Chrysophanol selected from *Rumex vesicarius L.* with GFAT1 (PDB ID: 2ZJ3).



2. a) **3D images of Chrysophanol and GFAT1 complex file**



2.b) **2D Image of interaction between Chrysophanol and GFAT1**

However, further *in vitro* and *in vivo* studies of individual phytoconstituents is needed to validate their biological potential. Ball and socket model of respective drug molecule and phytoconstituents interacting with active site are shown in Fig-1.

CONCLUSION

Understanding the interactions between proteins and ligands is crucial for the pharmaceutical and functional food industries. The emergence of bioinformatics has offered a platform to explore diseases at molecular level using computational tools. The Protein-Ligand interaction plays a significant role in structure based drug designing. Finally from this analysis it was found that, among the all compounds Physcion (-7.66 kcal/mol)is effectively inhibit T2DM-GFAT1 than standard drug Metformin (-5.69 kcal/mol) and the phytochemicals of this plant can act as T2DM-GFAT1 inhibitors. Therefore, this study emphasizes the importance of small molecules from various plant sources and their use to enhance protein-ligand interaction studies *in silico*. Further investigations can be done on our *in silico* approach to produce more effective and potential T2DM-GFAT1 inhibitors through ligand based drug designing approaches.

Conflicts of Interest

Authors declare that there is no conflict of interests regarding the publication of this paper.

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