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Molecular Docking Studies of Medicinal Compounds against *Aldose reductase* Drug Target for Treatment of Type 2 Diabetes

Pratistha Singh*[1], Preeti Yadav[2], V.K. Singh[3] and A.K. Singh[1]

[1]Department of Dravyaguna, Faculty of Ayurveda, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India
[2]School of Biotechnology, Institute of Science, Banaras Hindu University, Varanasi, India
[3]Centre for Bioinformatics, School of Biotechnology, Institute of Science, Banaras Hindu University, Varanasi, India

*Corresponding author: pratistha123456@gmail.com

ABSTRACT

Type 2 Diabetes is a disease that manifests from combined effect of genetic and environmental stress on multiple tissues over a period of time. An enzyme, Aldose Reductase play an important role in oxidative stress and Diabetic Mellitus was selected as a target protein for *in silico* screening of suitable herbal inhibitors using molecular docking. In the present work best screened ligands Ajoene, 3-O-methyl-D-chiro-inositol (D-pinitol), Butein, Leucopelargonidin, Nimbidinin, Tolbutamide and Coumarin were used for docking calculation and isolated from *Allium sativum, Glycine max, Butea monosperma, Thepsia populena, Ficus benghalensis, Azardirachta indica, Nelumbo nucifera, Aegle marmelos* respectively. Herbacetin and Quercetin from *Thepsia populena*. The residues Gly^{18}, Thr^{19}, Trp^{20}, Lys^{21}, Asp^{43},Val^{47}, Tyr^{48}, Gln^{49}, Asn^{50}, Lys^{77}, His^{110}, Trp^{111}, Thr^{113}, Ser^{159}, Asn^{160}, Asn^{162}, His^{163}, Gln^{183}, Tyr^{209}, Ser^{210}, Pro^{211}, Leu^{212}, Gly^{213}, Ser^{214}, Pro^{215}, Asp^{216}, Ala^{245}, Ile^{260}, Val^{264}, Thr^{265}, Arg^{268}, Glu^{261}, Asn^{262}, Cys^{298}, Ala^{299} and Leu^{300} were found conserved with binding site 1, which is major active site involved in interaction. In comparison with all screened ligands only 7 ligands (Butein, Herbacetin, Quercetin, Leucopelargonidin, Nimbidinin, Tolbutamide and Coumarin) were observed as best suitable ligands, which can be prominent herbal compounds for diabetes treatment.

Keywords: Type 2 diabetes, *In-silico* docking, *Aldose reductase*, anti-diabetic compounds, medicinal plants

Diabetes is presumably one of the oldest diseases known to world as an Egyptian manuscript, written about 3000 years ago, mentions about this disease (Ahmed, 2002). Diabetes is a disease in which blood glucose level of body get elevated, either because of inadequate insulin production, or because of improper response of body's cells to insulin, or both. High blood glucose may often lead to problems such as heart disease, stroke, kidney disease, eye problems, dental problem, nerve damage, foot problems etc. The characteristic symptoms of diabetes are polyuria, polydipsia, poly-phagia, pruritus and unexpected weight loss etc. Diabetes is also associated with increased induction of oxidative stress in cells which often results into higher levels of oxidized proteins, DNA and lipids (Wiernsperger, 2003). Under high level of glucose, oxidative stress induction may arise by several mechanisms. First, by disruption of electron transport chain in mitochondria that leads to excessive generation of superoxide anions (Nishikawa *et al*., 2000). Second, by auto-oxidation of glucose (Wolff and Dean, 1987). Third, by advanced

glycation that leads to Advanced Glycation End Product (AGE) formation which in turn binds with receptor of AGE and accelerates Reactive Oxygen Species (ROS) formation (Schmidt *et al*., 1994). Fourth, through Polyol Pathway (Drel *et al*., 2008). Further, there are three potential mechanisms by which the polyol pathway contributes to oxidative stress i.e. by Aldose Reductase (AR) dependent pathway which depletes NADPH and subsequently reduces Glutathione (Cheng and Gonzalez, 1986) during conversion of sorbitol to fructose by Sorbitol dehydrogenase (Morre *et al.*, 2000) and by conversion of fructose to potent non-enzymatic glycation agents, fructose-3-phosphate and 3-deoxyglucosone (Hamada *et al*., 1996).

At the beginning of 21st century, 171 million people were affected by diabetes and this toll is expected to burgeon to 366 million by 2030. It is further anticipated that prevalent type 2 DM in adults may surge in the next two decades across the globe and such surge in the incidents of disease in patients aged between 45 and 64 years, may be more prominent among developing countries (Wild *et al*., 2004).

Diabetes is broadly categorized as, type 1 diabetes, type 2 diabetes and gestational diabetes. In 1936, type 1 diabetes was lucidly distinguished from type 2 DM. Type 1 Diabetes (insulin-dependent diabetes mellitus) is a chronic autoimmune disease caused both genetic and environmental factors, which over the time results into an immune-mediated destruction of pancreatic β-cells resulting into loss of its functions and further leads to symptomatic diabetes and long-lasting dependence on external insulin doses. Type 1 diabetes often causes visual impairment and terminal blindness (Eisenbarth, 1986; Atkinson *et al.,* 2014). In 1988, type 2 DM was first described as a component of metabolic syndrome (Kudva and Butler, 1997). It is characterized by a progressive decline in beta-cell function, impaired insulin secretion and chronic insulin resistance (Defronzo 1987; Maitra *et al*., 2005). About 90 % of people have type 2 diabetes.

The toll of the people living with type 2 DM is surging rapidly across the globe and low and middle-income countries accounts for with 80% of total Type 2 DM cases. It is estimated that DM was the cause of loss 4.6 million lives globally in 2011(Burke *et al*., 1999). There were 69.1 million cases of diabetes in India in 2015 (International Diabetes Federation). Obesity is a major risk factor for the development of type 2 diabetes (Center for Disease Control and Prevention (1980-1994); Ludvik *et al*., 1995) and may confer type 2 diabetes through the mechanism of linked to insulin resistance (Spencer *et al.,* 2008). Diabetes mellitus also elevates chances of coronary heart disease and ischemic stroke (Sanker *et al.,* 2008). Type 2 DM results from interaction between genetic, environmental and behavioral risk factors (Chen *et al*., 2011, Center for Disease Control and prevention 2004). It is associated with various forms of both short- and long-term complications, which often leads to premature death of the patients. Since, type 2 DM is most common of all types of diabetes and its insidious onset along with late recognition of disease, hence it causes increased morbidity and mortality, especially in developing countries or resource-poor countries like Africa (Azevedo and Alla, 2008). Gestational diabetes develops in some women when they are pregnant. Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy (Metzer and Coustan, 1998). According to analysis by the CHYPERLINK "http://www.cdc.gov/pcd/issues/2014/13_0415.htm"enters for Disease Control and pHYPERLINK "http://www.cdc.gov/pcd/issues/2014/13_0415.htm"revention performed in 2014, the prevalence of gestational diabetes is high.

In mammalian cells, under normal glucose concentration (3.8–6.1mmol/L), a cytoplasmic enzyme known as hexokinase, phosphorylates 97 percent of cellular glucose and commits them for glycolytic pathway (Morrison *et al*., 1970) while rest 3 percent of glucose enters polyol pathway. However, percentage of glucose entering polyol pathway increases to 30 percent under elevated glucose concentration (>7 mmol/L) (Yabe-Nishimura, 1998). Polyol pathway is a minor pathway for glucose metabolism in most of the tissues but under hyperglycemic condition,

it plays a pivotal role in tissues having insulin independent glucose metabolism. In polyol pathway, an enzyme known as AR catalyses the reduction of glucose to sorbitol which is the rate limiting step of pathway. AR (EC 1.1.1.21) is a monomeric, NADP-dependent oxidoreductase enzyme. It is a member of aldo-keto reductase multigene superfamily (Petrash, 2004). In the first step of polyol pathway, AR catalyzes the reduction of glucose to sorbitol in nicotinamide adenosine dinucleotide phosphate-dependent manner that often leads to excessive accumulation of intracellular reactive oxygen species (ROS) causing oxidative stress in various tissues of heart, vasculature, neurons, eyes and kidneys (Fig. 1). Accumulation of sorbitol in the body causes various complications including cataract, neuropathy, nephropathy and cardiovascular disease and increases diabetic complication (Schrijvers *et al.*, 2004). Inhibitors of aldose reductase e.g. sorbinil, have shown to prevent diabetic complications, thus indicating possible role of sorbitol in diabetes (Jennings *et al*., 1990). But the clinical efficacy of AR inhibitors is relatively low. The possible roles of AR in diabetes associated complications, AR has become a suitable target for drugs and low clinical efficacy of current AR inhibitors, encourages many person to find a drug of higher clinical efficacy.

Nowadays, medicinal plants are gaining importance across the globe for their possible roles blood glucose regulation and mitigating the effects of diabetes. There are several medicinal plants that contain some specific compounds *viz*. glycosides, alkaloids, terpenoids, flavonoids, carotenoids *etc*., which have anti-diabetic, anti-hyperlipidemic, anti-hyperglycemic properties (Malviya *et al*., 2010). Such medicinal plants are readily available and are thought to elicit low side effects. Further, plants have always been an ideal source of drugs. The present article important anti-diabetic compounds were collected to screen best suitable inhibitors for AR.

MATERIALS AND METHODS

Structure Retrieval &Verification

AR is a key target to control diabetes complications. For AR structure retrieval PDB database was used.

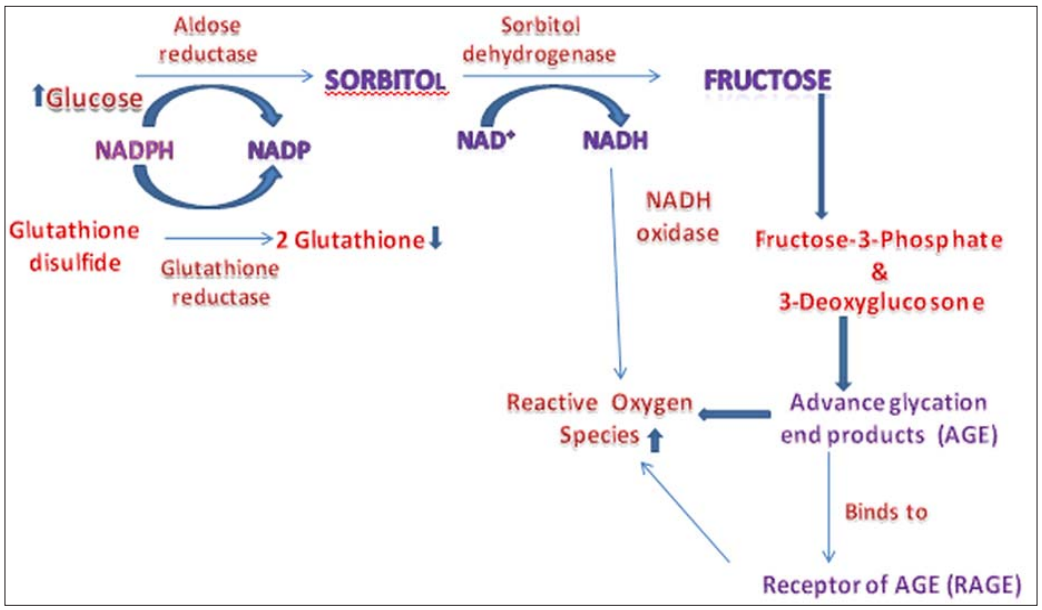


Fig. 1: Role of Aldose Reductase (AR) in hyperglycemia-induced oxidative stress. AR competes with glutathione reductase (GR) for their co-factor NADPH, leading to a decrease in Glutathione. Increased NADH causes NADH oxidase (NOx) to produce ROS. Fructose-3-phosphate (F-3-P) and 3-deoxyglucosone (3-DG), metabolites of fructose, increases AGE formation. AGE and binding of AGE to receptor of AGE (RAGE) increases oxidative stress (Chung *et al*., 2003).

The PDB database is a major database in area of structural biology and computational biology for research and education (Berman, 2008; Laskowski *et al*., 1997). For structural verification of retrieved AR structure, RAMPAGE and PDBSum server were used (Kim *et al*., 2016).

Active site identification

For active site residues identification CDD BLAST was used (Marchler *et al*., 2012)**.** CDD is conserved Domain Database for identification of functional site of protein sequence using alignment with available structure models in database. Further Metapocket server was used for identification of probable active sites. Identification of active sites predicted on the basis of four methods *viz.* LIGSITE(cs) (Hendlich *et al*., 1997), PASS (Brady *et al*., 2005), Q-SiteFinder, (Laurie and Jackson, 2005) and SURFNET (Laskowski,1995). Discovery Studio 3.0 developed by Accelrys, was also used for visualization of three dimensional complex structures and active site residues visualization (http://accelrys.com/).

Ligands retrieval and assessment

The anti-diabetic ligands were collected on the basis of literature mining (Mamun or Rashid *et al.,* 2014; Vikrant and Sharma, 2011; liu *et al*., 2006; Eidi *et al*., 2006; Frode and Medeiros., 2008; Bnouham *et al*., 2006; Ayodhya *et al*., 2010; Singh *et al*.,2011; Chauhan *et al*., 2010). The retrieval of anti-diabetic ligands were done with Pubchem compound database (Kim *et al*., 2016). For drug likeness analysis Lipinski's rule of five (RO5) was done using Lipinski Filters – SCFBio. According to the rules, a compound is more likely to act as a drug if it complies with two or more rules i.e. molecular mass less than 500 Dalton, high lipophilicity (expressed as cLogP less than 5), five or less hydrogen bond donors (HBD), ten or less hydrogen bond acceptors (HBA) and Molar refractivity between 40-130 (Lipinski *et al*., 2001, 2004). FAF-Drug3 (Free ADME-Tox Tool version 3.0) is a server used for *in-silico* screening, which perform computational prediction of ADEM-TOX (Adsorption, Distribution, Metabolism, Excretion, and Toxicity) properties and help in selection before chemical synthesis (Cumming *et al*., 2013).

Docking calculation and visualization

The docking calculation was done using YASARA Autodock VINA tool. Yet Another Scientific Artificial Reality Application (YASARA) is user friendly software for molecular graphics, modeling and simulation (Krieger and Vriend, 2014). The docking analyses of potent ligands were visualized using Discovery Studio 3.0.

RESULTS AND DISCUSSION

Receptor protein selection for screening of natural anti-diabetic compounds

The AR protein structure (PDBID: 1US0) was used for structural verification (Fig. 2; Howard *et al*. 2004). Structural verification revealed that selected AR protein structure have 98.7% residues in favoured region and 1.3% residues in favoured region residues in allowed region and no residues in outlier region (Fig. 2). PDBSum PROCHECK statistics mainly Ramachandran Plot statistics resulted that 90.6% residues in most favoured regions [A, B, L] and 9.4% residues in additional allowed regions [a, b, l, p]. There are no residues were found in generously allowed regions [~a, ~b, ~l, ~p] and Disallowed regions [XX]. For a good quality model 90% residues should be in the most favoured regions [A, B, L]. In this case 90.6% residues was found in most favoured regions [A, B, L], which indicated the good quality of selected model. Further model was used for active site and active site residues identification for docking calculation with selected best natural anti-diabetic compounds.

Active site identification

For active site identification CDD BLAST was used (Fig. 2). MetaPocket server was used for 3 potential active site prediction and residues identification (Table 1). The residues Gly^{18}, Thr^{19}, Trp^{20}, Lys^{21}, Asp^{43}, Val^{47}, Tyr^{48}, Gln^{49}, Asn^{50}, Lys^{77}, His^{110}, Trp^{111}, Thr^{113},

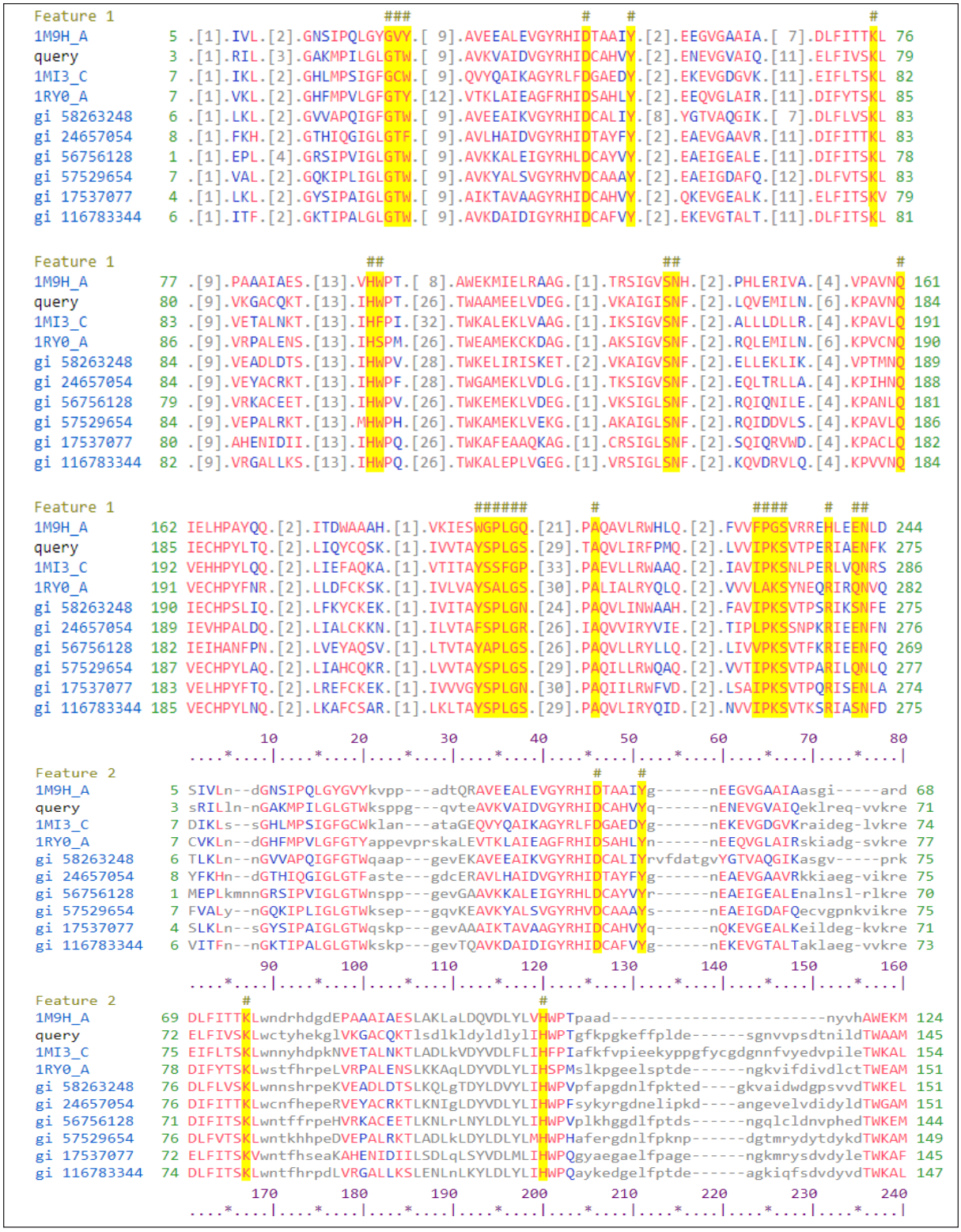


Fig. 2: Active site residues identification using CDD BLAST

Table 1: The potential 3 ligands binding sites in AR protein (PDBID: 1US0)

Ligand binding site no.	Active site residues	Binding site residues
1	Gly^{18}, Thr^{19}, Trp^{20}, lys^{21}, Asp^{43}, Val^{47}, Tyr^{48}, Gln^{49}, Asn^{50}, Glu^{51}, Asn^{52}, Glu^{53}, Lys^{77}, lys^{94}, Asp^{98}, His^{110}, Trp^{111}, Thr^{113}, Ser^{159}, Asn^{160}, Asn^{162}, His^{163}, Gln^{183}, Lys^{194}, Leu^{195}, Tyr^{209}, Ser^{21}0, Pro^{211}, Leu^{212}, Gly^{213}, Ser^{214}, Pro^{215}, Asp^{216}, Ala^{245}, Ile^{260}, Pro^{261}, Lys^{262}, Ser^{263}, Val^{264}, Thr^{265}, Arg^{268}, Glu^{261}, Asn^{262}, Cys^{298}, Ala^{299}, Leu^{300}	Trp^{20}, lys^{21}, Pro^{218}, Trp^{219}, Trp^{79}, Cys^{80}, Trp^{111}, Thr^{113}, Phe^{115}, Phe^{122}, Leu^{300}, Cys^{303}, Tyr^{309}, Ala^{299}, Cys^{298}, His^{110}, Val^{47}, Tyr^{48}, Asn^{160}, Tyr^{209}, Ser^{159}, Gln^{18}, Ser^{210}, Lys^{77}, Asp^{43}, Ile^{260}, Thr^{19}, Gly^{18}, Lys^{262}, Ser^{214}, Pro^{211}, Asp^{216}, Leu^{212}, Pro^{215}, Pro^{261}, Leu^{228}, Arg^{268}, Ser^{263}, Asn^{272}, Ala^{245}, Glu^{271}, Thr^{243}, Thr^{244}, Glu^{229}, Ser^{226}, Val^{264}, Thr^{265}, Val^{297}, Ser^{302}, Leu^{124}, Leu^{301}, Phe^{311}, Pro^{310}, Gln^{49}, Phe^{121}, His^{46}, Leu^{108}, Val^{130}, Gly^{213}, Glu^{267}, Asn^{50}, Ser^{22}
2		Phe^{161}, Asn^{162}, Gln^{192}, Leu^{195}, Arg^{296},Pro^{310}, Phe^{311}, His^{163}, Lys^{194}, His^{312},Leu^{190}, Asn^{294}, Glu^{193}, Asn^{292}, Asn^{160}, Ile^{184}, Glu^{185}, Trp^{111}, Tyr^{209}, Tyr^{309}, Leu^{164}, Glu^{313}, Thr^{191}, Trp^{295}, Arg^{293}
3		His^{163}, Lys^{194}, Leu^{195}, Tyr^{198}, Glu^{193}, Gln^{197}, Ser^{201}, Gln^{254}, Arg^{255}, Met^{285}, Leu^{289}, Ile^{196}, Gln^{200}, Ser^{282}, Leu^{280}, Ser^{281}, Glu^{279}, Leu^{190}, Thr^{191}, Gln^{192}, Asn^{292}, Asn^{294}, Asn^{162}, Phe^{161}, Arg^{296}

Ser^{159}, Asn^{160}, Asn^{162}, His^{163}, Gln^{183}, Tyr^{209}, Ser^{210}, Pro^{211}, Leu^{212}, Gly^{213}, Ser^{214}, Pro^{215}, Asp^{216}, Ala^{245}, Ile^{260}, Val^{264}, Thr^{265}, Arg^{268}, Glu^{261}, Asn^{262}, Cys^{298}, Ala^{299} and Leu^{300} were found conserved with binding site 1, which is major active site to study docking calculation.

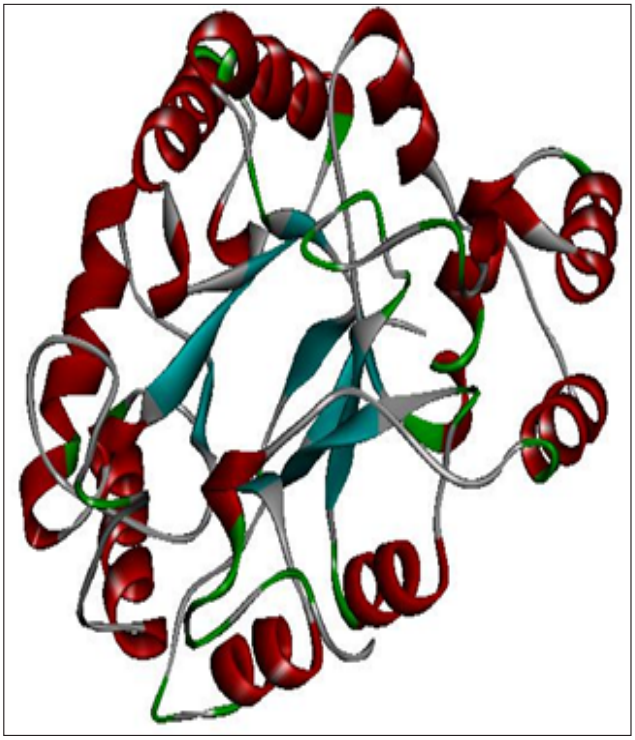


Fig. 3: 3-D structure of Aldose Reductase (AR)

Ligands retrieval and assessment

Collection of 49 anti-diabetic compounds from medicinal plants was collected using literature survey (Table 2; 3). The natural medicinal compounds were collected from anti-diabetic plants. On the basis of Lipinski filter analysis total 25 compounds out of 49 were selected, which were following Lipinski rules of 5 (Table 4). Screening of suitable natural compounds was done on the basis of drug likeness, absorption, distribution, metabolism, excretion and toxicity profile analysis. Further screened 25 compounds were taken for ADEM-TOX (Adsorption, Distribution, Metabolism, Excretion, and Toxicity) analysis using FAF-Drug3 (Table 5).

Docking calculation and visualization

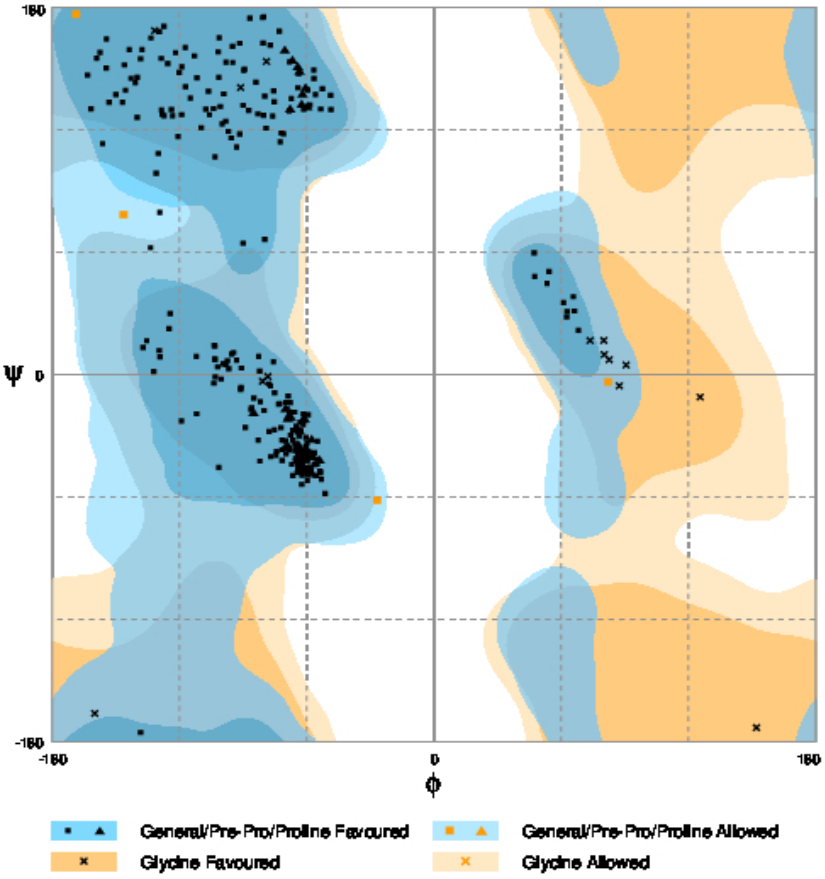
Docking analysis between receptor (AR) and screened ligands (Butein, (Herbacetin, Quercetin) Leucopelargonidin, Nimbidinin, Tolbutamide and Coumarin) were performed using YASARA tool. Interactions were calculated on the basis of Binding Energy(kcal/mol), Dissociation Constant [pM] and Contacting receptor residues (Table 6; 7). The residues Gly^{18}, Thr^{19}, Trp^{20}, Lys^{21}, Asp ^{43}, Val^{47}, Tyr^{48}, Gln^{49}, Asn^{50}, Lys^{77}, His^{110}, Trp^{111}, Thr^{113}, Ser^{159}, Asn^{160}, Asn^{162}, His^{163}, Gln^{183}, Tyr^{209}, Ser^{210}, Pro^{211}, Leu^{212}, Gly^{213},

Table 2: List of selected natural anti-diabetic compounds with plant scientific, common name and isolation source

Sl. No.	Plant name	Common name	Isolation source	Compounds	References
1	*Allium sativum*	Garlic	Root	Ajoene	(Mamun or Rashid *et al.*,2014; Vikrant and Sharma, 2011; liu *et al*., 2006; Eidi *et al*., 2006; Frode and Medeiros, 2008; Bnouham *et al*., 2006; Ayodhya *et al*., 2010; Singh, 2011)
2	*Abelmoschus esculentus*	Gumbo,	Fruit	Gum	(Mamun or Rashid *et al.*,2014; Vikrant and Sharma, 2011; liu *et al*., 2006; Eidi *et al*., 2006; Frode and Medeiros, 2008; Bnouham *et al*., 2006; Ayodhya *et al*., 2010; Singh, 2011; Sabitha *et al*., 2011)
3	*Aegle marmelos*	Golden apple	Leaf, Seed , Fruit	Coumarin, Aegeline,	(Mamun or Rashid *et al.,* 2014; Vikrant and Sharma, 2011; liu *et al*., 2006; Eidi *et al*., 2006; Frode and Medeiros, 2008; Bnouham *et al*., 2006; Ayodhya *et al*., 2010; Singh, 2011; Kesari *et al*., 2006)
4	*Acacia arabica*	India gum Arabic	Seed , bark	Polyphenol	Vikrant and Sharma, 2011; Makheswari *et al*.,2012)
5	*Azadirachta indica*	Neem	Leaf ,Seed	Nimbidinin	(Vikrant and Sharma, 2011; Khosla *et al*., 2000)
6	*Artocarpus heterophyllus*	Jack Fruit	Fruit	Sapogenin	(Vikrant and Sharma, 2011; Chackrewarthy *et al*., 2010)
7	*Aloe barbadensis*	Barbados aloe	Leaf	Lophenol	(Mamun or Rashid *et al.,* 2014; Vikrant and Sharma, 2011; Liu *et al*., 2006; Eidi *et al*., 2006; Frode and Medeiros, 2008; Bnouham *et al*., 2006)
8	*Allium cepa*	Onion	Bulb	Allypropyl disulphide	(Mamun or Rashid *et al*., 2014; Vikrant and Sharma, 2011; liu *et al*., 2006; Eidi *et al*., 2006; Frode and Medeiros, 2008; Bnouham *et al*., 2006; Kumari *et al.,* 1995)
9	*Butea monosperma*	Bastard teak	Fruit	Butein	Mamun or Rashid*et al*., 2014; Makheswari *et al*., 2012; Sharma and Garg, 2009)
10	*Brassica Juncea*	Musturd	Seed ,leaf	Isorhamnetin 3,7-diglucoside	(Mamun or Rashid *et al.,* 2014;Vikrant and Sharma, 2011; Liu *et al*., 2006; Singh, 2011)
11.	*Beta vulgaris*	Ginger	Bulb	Polydextrose	(Mamun or Rashid *et al*., 2014; Frode and Medeiros, 2008; Makheswari *et al*., 2012)
12	*Cucumis Metuliferus*	Jelly Melon	Fruit	Beta-carotene	(Mamun or Rashid *et al*., 2014; Makheswari *et al*., 2012)
13	*Capsicum frutescens*	Chilli	Fruit	Capsaicin	(Mamun or Rashid *et al*., 2014; Bnouham *et al.,* 2006; Tolan *et al*., 2004)
14	*Coccinia indica*	Ivy-gourd	Fruit	Beta-amyrin, Lupeol	(Mamun or Rashid *et al*., 2014; Vikrant and Sharma, 2011; Ayodhya *et al*., 2010; Singh, 2011)
15	*Cinnamomum zeylanicum*	Cinnamon	Leaf, Bark	Cinnamaldehye	(Mamun or Rashid *et al.,* 2014;Vikrant and Sharma, 2011; Liu *et al*., 2006; Makheswari *et al*., 2012)
16	*Curcuma longa*	Turmeric	Root	Curcuminoid	(Mamun or Rashid *et al*., 2014; Vikrant and Sharma, 2011; liu *et al*., 2006; Honda *et al*., 2006)
17	*Coriandrum sativum*	Coriander	Leaf	L-alanine	(Mamun or Rashid *et al.,* 2014; Vikrant and Sharma, 2011)
18	*Carica papaya*	Papaya	Fruit	Saponin	(Mamun or Rashid *et al.,* 2014; Vikrant and Sharma, 2011)

19	*Cassia auriculata*	Tanners Cassia	Flower	Triterpenoid, Flavonoids	(Mamun or Rashid*et al.*, 2014; Ayodhya *et al*., 2010; Hatapakki *et al*., 2005)
20	*Diospyros peregrine*	Gaub persimmon	Fruit	Butelin	(Mamun or Rashid*et al*., 2014)
21	*Ficus benghalensis*	Banyan	Bark	Leucopelargo-nidin	(Mamun or Rashid *et al*., 2014; Ayodhya *et al*., 2010; Cherian and Augusti, 1993)
22	*Feronia elephantum*	Wood apple	Fruit	Bergapten	(Mamun or Rashid *et al*.,2014; Vikrant and Sharma, 2011)
23	*Glycine max*	Soya beans	Seeds	3-Omethyl-D-chiro-inositol	(Mamun or Rashid *et al*., 2014; Kang *et al*.,2006)
24	*Gymnema sylvestre*	Suger destroyer	Leaf	Gymnemic acid	(Mamun or Rashid *et al.*, 2014; Vikrant and Sharma., 2011; Makheswari and Sudarsanam, 2012)
25	*Hordeum vulgare*	Barley	Seed	Beta-glucan	(Mamun or Rashid *et al.*, 2014; Makheswari and Sudarsanam, 2012)
26	*Jatropha curcas*	Barbados Fruit	Whole Plant	Diterpene	(Mamun or Rashid *et al.*,2014; Vikrant and Sharma., 2011; Makheswari and Sudarsanam, 2012)
27	*Momordica balsamina*	Balsam Tree	Fruit	Cucurbitacin, Saponin	(Mamun or Rashid *et al.*, 2014; Vikrant and Sharma.,2011)
28	*Mangifera indica*	Mango tree	Leaf, Steam, Bark ,Fruit	Mangiferin	(Mamun or Rashid *et al.*, 2014; Vikrant and Sharma., 2011; Makheswari and Sudarsanam, 2012; Ojewol, 2005)
29	*Momordica charantia*	Bitter melon	Whole plant	Momordicin,	(Mamun or Rashid *et al* 2014; Vikrant and Sharma., 2011; Makheswari and sudarsanam, 2012; Saxena *et al*., 2004; Sekar *et al*., 2005; Yadav *et al*., 2005; Reyes *et al*., 2006; Harinantenaina *et al*., 2006; Reyes *et al*., 2006)
30	*Morinda citrifolia*	Indian mulberry	Fruit	Steroid, Saponin	(Vikrant and Sharma., 2011)
31	*Musa paradisiaca*	Banana	Fruit	Pectin	(Mamun or Rashid *et al.*, 2014; Vikrant and Sharma, 2011; Makheswari and Sudarsanam, 2012)
32	*Musa sapientum*	Sweet banana	Flower	Steroid	(Mamun or Rashid *et al.*, 2014; Vikrant and Sharma, 2011)
33	*Mentha piperita*	Peppermint	Leaf	Vanadium	(Mamun or Rashid *et al.*, 2014; Vikrant and Sharma, 2011)
34	*Nigella sativa*	Roman coriander	Whole plant	Thymoquinone	(Mamun or Rashid *et al.*, 2014; Vikrant and Sharma, 2011)
35	*Nelumbo nucifera*	Sacred lotus	Flower	Tolbutamide	(Mamun or Rashid *et al*., 2014; Vikrant and Sharma, 2011).
36	*Psidium guajava*	Guava	Leaf, Fruit	Pedunculagin, Strictinin	(Vikrant *et al*., 2011; Ojewole, 2005)
37	*Phyllanthus emblica*	Indian gooseberry	Fruit	Tannic acid	(Mamun or Rashid *et al*., 2014; Vikrant and Sharma., 2011; Makheswari *et al*., 2012)
38	*Rhus coriaria*	Sicilian Sumac	Fruit	Nonanal	(Mamun or Rashid *et al*., 2014; Vikrant *et al*., 2011)
39	*Thespesia populnea*	Portia tree	Fruit	Herbacetin, Qurecetin	(Mamun or Rashid *et al.*, 2014; Vikrant and Sharma., 2011; Makheswari and Sudarsanam., 2012)
40	*Terminalia chebula*	Chebulic myrobalan	Seed, Fruit	Palmitic acid	(Mamun or Rashid *et al*., 2014; Vikrant and Sharma., 2011; Makheswari and Sudarsanam., 2012; Bnouham *et al*., 2006; Nalamolu and Nammi, 2006)

41	*Urtica dioica*	Nettles	Leaf	Lectin	(Mamun or Rashid *et al.*, 2014 ; Vikrant and Sharma, 2011; Makheswari *et al.*, 2012)
42	*Withania somnifera*	Winter cherry	Leaf	Withanolide	(Mamun or Rashid *et al.*, 2014; Vikrant and Sharma, 2011)
43	*Withania coagulans*	Vegetable rennet	Fruit	Esterase	(Mamun or Rashid *et al.*, 2014; Vikrant and Sharma, 2011)
44	*Xanthocercis zambesiaca*	Nayal Tree	Leaf	Castanospermine	(Mamun or Rashid *et al.*, 2014; Vikrant and Sharma, 2011; Makheswari *et al.*, 2012)
45	*Zingiber officinale*	Ginger	Bulb	Gingerol	(Mamun or Rashid *et al.*, 2014; Vikrant and Sharma, 2011; Bnouham *et al.*, 2006; Kato *et al.*, 2006)



Evaluation of residues

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Residue [A  21 :LYS] (  82.16,  -3.60) in Allowed region
Residue [A  85 :LYS] ( -26.74, -61.61) in Allowed region
Residue [A 187 :HIS] (-168.70, 176.74) in Allowed region
Residue [A 190 :LEU] (-146.34,  78.38) in Allowed region
Number of residues in favoured region    (~98.0% expected) :  307 ( 98.7%)
Number of residues in allowed region     (~2.0% expected)  :    4 (  1.3%)
Number of residues in outlier region                       :    0 (  0.0%)
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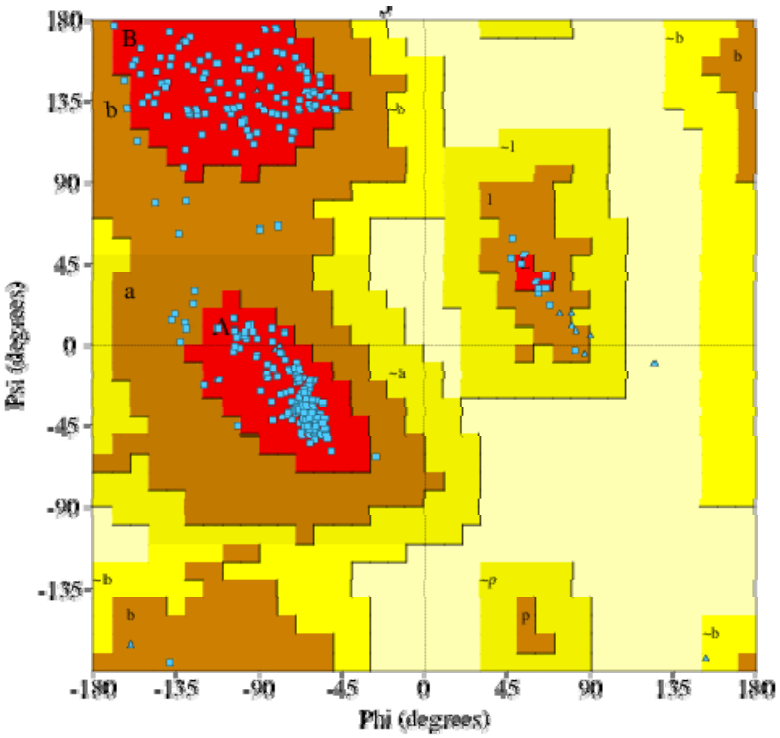
Fig. 4: RAMPAGE statistics



PROCHECK statistics

1. Ramachandran Plot statistics

residues	%-tage	No. of	
Most favoured regions	[A,B,L]	250	90.6%
Additional allowed regions	[a,b,l,p]	26	9.4%
Generously allowed regions	[~a,~b,~l,~p]	0	0.0%
Disallowed regions	[XX]	0	0.0%
Non-glycine and non-proline residues		276	100.0%
End-residues (excl. Gly and Pro)		2	
Glycine residues		16	
Proline residues		20	
Total number of residues		314	

Based on an analysis of **118** structures of resolution of at least **2.0** Angstroms and *R*-factor no greater than **20.0** a good quality model would be expected to have over **90%** in the most favoured regions [A,B,L].

Fig. 5: PROCHECK Ramachandran Plot and statistics obtained from PDBSum server

Table 3: List of selected anti-diabetic compounds and their details

Sl. No.	Plant	Compounds	PubChem CID	Molecular Formula	Molecular Weight	Canonical SMILES
1	*Allium sativum*	Ajoene	5386591	$C_9H_{14}OS_3$	234.39 g/mol	C=CCSSC=CCS(=O)CC=C
2	*Abelmoschus esculentus*	Gum	44134661	$C_{10}H_{14}N_5Na_2O_{12}P_3$	535.146 g/mol	C1C(C(OC1N2C=NC3=C2N=CN=C3N)COP(=O)(O)OP(=O)([O-])OP(=O)(O)[O-])O.[Na+].[Na+]
3	*Aegle marmelos*	Coumarin	323	$C_9H_6O_2$	146.145 g/mol	C1=CC=C2C(=C1)C=CC(=O)O2
4	*Aegle marmelos*	Aegeline	15558419	$C_{18}H_{19}NO_3$	297.354 g/mol	C O C 1 = C C = C (C = C 1) C (C N C (= O) C=CC2=CC=CC=C2)O
5	*Acacia Arabica*	Polyphenol	996	C_6H_6O or C_6H_5OH	94.113 g/mol	C1=CC=C(C=C1)O
6	*Azadirachta indica*	Nimbidinin	101306757	$C_{26}H_{34}O_6$	442.552 g/mol	CC12COC3C1C(C(CC2O)O)(C4CC(=O)C5(C(CC=C5C4(C3O)C)C6=COC=C6)C)C
7	*Artocarpus heterophyllus*	Sapogenin	101281204	$C_{30}H_{46}O_4$	470.694 g/mol	CC1(CC2C3=CCC4C(C3(CCC25CC1OC5=O)C)(CCC6C4(CC(C(C6(C)C)O)O)C)C)C
8	*Aloe barbadensis*	Lophenol	160482	$C_{28}H_{48}O$	400.691 g/mol	C C 1 C (C C C 2 (C 1 C C = C 3 C 2 C C C 4 (C - 3CCC4C(C)CCCC(C)C)C)C)O
9	*Allium cepa*	Allyl propyl disulphide	16591	$C_6H_{12}S_2$	148.282 g/mol	CCCSSCC=C
10.	*Butea monosperma*	Butein	5281222	$C_{15}H_{12}O_5$	272.256 g/mol	C1=CC(=C(C=C1C=CC(=O)C2=C(C=C(C=C2)O)O)O)O
11	*Brassica juncea*	Isorhamnetin 3-7 diglucoside	4425935	$C_{13}H_{18}BrFN_2$	301.203 g/mol	CN1CCCN(CC1)CC2=C(C=CC=C2Br)F
12	*Beta vulgaris*	Polydextron	71306906	$C_{12}H_{22}O_{11}$	342.297 g/mol	C(C1C(C(C(C(O1)OCC2C(C(C(C(O2)O)O)O)O)O)O)O)O
13	*Cucumis metuliferus*	Beta-carotene	5280489	$C_{40}H_{56}$	536.888 g/mol	CC1=C(C(CCC1)(C)C)C=CC(=CC=CC(=CC=CC=C(C)C=CC=C(C)C=CC2=C(CCCC2(C)C)C)C)C
14.	*Capsicum frutescens*	Capsaicin	1548943	$C_{18}H_{27}NO_3$	305.418 g/mol	CC(C)C=CCCCCC(=O)NCC1=CC(=C(C=C1)O)OC
15	*Coccinia indica*	B-amyrin	73145	$C_{30}H_{50}O$	426.729 g/mol	CC1(CCC2(CCC3(C(=CCC4C3(CCC5C4(C-CC(C5(C)C)O)C)C)C2C1)C)C)C
16	*Cinnamomum zeylanicum*	Cinnamaldehyde	637511	C_9H_8O	132.162 g/mol	C1=CC=C(C=C1)C=CC=O
17	*Curcuma longa*	Curcuminoid	101341353	$C_{22}H_{20}N_2O_7$	424.409 g/mol	C C 1 = C (C = C (C = C 1) C = C C (= O) C C (= O) C=CC2=CC(=C(C(=C2)OC)C)[N+](=O)[O-])[N+](=O)[O-]
18	*Coriandrum sativum*	L-alanine	5950	$C_3H_7NO_2$	89.094 g/mol	CC(C(=O)O)N
19	*Coccinia indica*	Lupeol	259846	$C_{30}H_{50}O$	426.729 g/mol	CC(=C)C1CCC2(C1C3CCC4C5(CCC(C(C-5CCC4(C3(CC2)C)C)(C)C)O)C)C

20	*Carica papaya*	Saponin	198016	$C_{58}H_{94}O_{27}$	1223.363 g/mol	CC1(C2CCC3(C(C2(CCC1OC4C(C(C(CO4)OC5C(C(C(CO5)O)O)O)OC6C(C(C(C(O6)CO)O)O)O)OC7C(C(C(C(O7)CO)O)O)OC8C(C(C(C(O8)CO)O)O)O)C)CCC91C3(CC(C2(C9CC(CC2)(C)C=O)CO1)O)C)C)C
21	*Cassia auriculata*	Triterpenoid	451674	$C_{30}H_{48}O_7S$	552.767 g/mol	CC1(CCC2(CCC3(C(=CCC4C3(CCC5C4(C-CC(C5(C)COS(=O)(=O)O)O)C)C)C2C1)C)C(=O)O)C
22	*Diospyros peregrine*	Butelin	72326	$C_{30}H_{50}O_2$	442.728 g/mol	CC(=C)C1CCC2(C1C3CCC4C5(CCC(C(C-5CCC4(C3(CC2)C)C)(C)C)O)C)CO
23	*Ficus benghalensis*	Leucopelargonidin	3286789	$C_{15}H_{14}O_6$	290.271 g/mol	C1=CC(=CC=C1C2C(C(C3=C(C=C(C=C3O2)O)O)O)O)O
24	*Feronia elephantum*	Bergapten	2355	$C_{12}H_8O_4$	216.192 g/mol	COC1=C2C=CC(=O)OC2=CC3=C1C=CO3
25	*Glycine max*	3-Omethyl-D-chiro-inositol	164619	$C_7H_{14}O_6$	194.183 g/mol	COC1C(C(C(C(C1O)O)O)O)O
26	*Gymnema sylvestre*	Gymnemic acid	91826975	$C_{49}H_{76}O_{19}$	969.128 g/mol	CC=C(C)C(=O)OC1C(C2(C(CC1(C)C)C3=CCC4C5(CCC(C(C5CCC4(C3(CC2O)C)C)(C)CO)OC6C(C(C(C(O6)C(=O)O)O)OC7C(C(C(C(O7)CO)O)O)O)O)C)COC(=O)C)O
27	*Hordeum vulgare*	Beta-glucan	439262	$C_{18}H_{32}O_{16}$	504.438 g/mol	C(C1C(C(C(C(O1)OC2C(OC(C(C2O)O)OC3C(OC(C(C3O)O)O)CO)CO)O)O)O)O
28	*Jatropha curcas*	Diterpene	392471	$C_{20}H_{32}O_3$	320.473 g/mol	CC1(C2CCC34CC(CCC3C2(CCC1=O)C)C(C4)(CO)O)C
29	*Momordica balsamina*	Cucurbitacin	5281316	$C_{32}H_{46}O_8$	558.712 g/mol	CC(=O)OC(C)(C)C=CC(=O) C(C)(C1C(CC2(C1(CC(=O)C3 (C2CC = C4C3CC(C(=O)C4(C)C)O)C)C)C)O)O
30	*Mangifera indica*	Magniferin	5281647	$C_{19}H_{18}O_{11}$	422.342 g/mol	C1=C2C(=CC(=C1O)O)OC3 = CC(=C(C(=C3C2=O)O)C4C(C(C(C(O4)CO)O)O)O)O
31	*Momordica charantia*	Momordicin	57518366	$C_{31}H_{50}O_3$	470.738 g/mol	CC1CCC2(CCC3(C4(CCC5C(C(=O)CCC5(C4C=CC3(C2C1C)O)C)(C)C)C)C)COC
32	*Musa paradisiaca*	Pectin	16738707	$C_{12}H_{16}O_{13}^{-2}$	368.247 g/mol	C1(C(C(OC(C1O)OC2C(C(C(OC2C(=O)[O-])O)O)O)O)C(=O)[O-])O)O
33	*Musa sapientum*	Steroid	439726	$C_{18}H_{24}O$	256.389 g/mol	CC12CCCC1C3CCC4=C(C3CC2)C=CC(=C4)O
34	*Mentha peperita*	Vanadium	23990	V	50.941 g/mol	[V]
35	*Nigella sativa*	Thymoquinone	10281	$C_{10}H_{12}O_2$	164.204 g/mol	CC1 = CC(=O)C(=CC1=O)C(C)C

36	*Nelumbo nucifera*	Tolbutamide	5505	$C_{12}H_{18}N_2O_3S$	270.347 g/mol	CCCCNC(=O)NS(=O)(=O)C1=CC=C(C=C1)C
37	*Psidium guajava*	Pedunculagin	442688	$C_{34}H_{24}O_{22}$	784.544 g/mol	C1C2C(C3C(C(O2)O)OC(=O)C4=CC(=C(C(=C4C5=C(C(=C(C=C5C(=O)O3)O)O)O)O)O)O)OC(=O)C6=CC(=C(C(=C6C7=C(C(=C(C=C7C(=O)O1)O)O)O)O)O)O
38	*Psidium guajava*	Strictinin	73330	$C_{27}H_{22}O_{18}$	634.455 g/mol	C1C2C(C(C(C(O2)OC(=O)C3=CC(=C(C(=C3)O)O)O)O)O)OC(=O)C4=CC(=C(C(=C4C5=C(C(=C(C=C5C(=O)O1)O)O)O)O)O)O
39	*Phyllanthus embilica*	Tannic acid	16129778	$C_{76}H_{52}O_{46}$	1701.206 g/mol	C1=C(C=C(C(=C1O)O)O)C(=O)OC2=CC(=CC(=C2O)O)C(=O)OCC3C(C(C(C(O3)OC(=O)C4=CC(=C(C(=C4)OC(=O)C5=CC(=C(C(=C5)O)O)O)O)O)OC(=O)C6=CC(=C(C(=C6)OC(=O)C7=CC(=C(C(=C7)O)O)O)O)O)OC(=O)C8=CC(=C(C(=C8)OC(=O)C9=CC(=C(C(=C9)O)O)O)O)O)OC(=O)C1=CC(=C(C(=C1)OC(=O)C1=CC(=C(C(=C1)O)O)O)O)O
40	*Rhus coriaria*	Nonanal	31289	$C_9H_{18}O$	142.242 g/mol	CCCCCCCCC=O
41	*Thespesia populnea*	Herbacetin	5280544	$C_{15}H_{10}O_7$	302.238 g/mol	C1=CC(=CC=C1C2=C(C(=O)C3=C(O2)C(=C(C=C3O)O)O)O)O
42	*Thespesia populnea*	Quercetin	5280343	$C_{15}H_{10}O_7$	302.238 g/mol	C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O
43	*Terminalia chebula*	Palmitic acid	985	$C_{16}H_{32}O_2$	256.43 g/mol	CCCCCCCCCCCCCCCC(=O)O
44	*Terminalia chebula*	Chebulic acid	5281711	$C_{28}H_{10}O_{16}$	602.372 g/mol	C1=C2C(=C(C(=C1O)O)O)C3=C(C(=C4C5=C3C(=O)OC6=C(C7=C(C8=C(C(=C(C=C8C(=O)O7)O)O)O)C(=C56)C(=O)O4)O)O)OC2=O
45	*Urtica dioica*	Lectin	466371	$C_{31}H_{39}N_3O_4S_2$	581.79 g/mol	CC1=CC=C(C=C1)S(=O)(=O)N2CCCN(CCCN(CC(=C)C2)S(=O)(=O)C3=CC=C(C=C3)C)CC4=CC=CC=C4
46	*Withania somnifera*	Withanolide	161671	$C_{28}H_{38}O_6$	470.606 g/mol	CC1=C(C(=O)OC(C1)C(C)(C2CCC3C2(CCC4C3CC5C6(C4(C(=O)C=CC6O)C)O5)C)O)C
47	*Withania coagulans*	Esterase	153099	$C_{21}H_{26}N_2O_3S$	386.51 g/mol	C1=CC=C(C=C1)COC(=O)NC(CCCCN)C(=O)SCC2=CC=CC=C2
48	*Xanthocercis zambesiaca*	Castanospermine	54445	$C_8H_{15}NO_4$	189.211 g/mol	C1CN2CC(C(C(C2C1O)O)O)O
49	*Zingiber officinale*	Gingerol	3473	$C_{17}H_{26}O_4$	294.391 g/mol	CCCCCC(CC(=O)CCC1=CC(=C(C=C1)O)OC)O

Table 4: Drug Likeness using Lipinski Filter

Sl. No.	Plant name	Compounds	Mass Molecular mass less than 500 Dalton	Hydrogen bond donor (Less than 5 hydrogen bond donors)	hydrogen bond acceptor (Less than 10 hydrogen bond acceptors)	LOGP High lipophilicity (expressed as LogP less than 5)	Molar Refractivity Molar refractivity should be between 40-130	Status
1	*Allium Sativum*	Ajoene	235.000000	1	1	3.344799	69.310791	Accepted
2	*Abelmoschus esculanetus*	Gum	523.000000	11	16	-5.314199	95.658279	Not Accepted
3	*Agele marmelos*	Coumarin	146.000000	0	2	1.618800	41.110996	Accepted
4	*Agele marmelos*	Aegeline	297.000000	2	4	2.558200	86.439468	Accepted
5	*Acacia Arabica*	Polyphenol	94.000000	1	1	1.392200	28.106796	Not Accepted
6	*Azadirachta indica*	Nimibidinin	444.000000	3	6	2.902400	115.582352	Accepted
7	*Artocarpus hallophyllus*	Sapogenin	472.000000	2	4	5.735000	131.722565	Accepted
8	*Aloe barbadensis*	Lophenol	400.000000	1	1	7.634703	123.599739	Not Accepted
9	*Allium cepa*	Allyl propyl disulphide	148.000000	0	0	2.963799	45.403992	Accepted
10	*Butea monosperma*	Butein	272.000000	4	5	2.405100	72.907692	Accepted
11	*Brassica Juncea*	Isorhamnetin 3,7-diglucoside	640.000000	10	17	-2.954500	143.891541	Not Accepted
12	*Beta vulgaris*	Polydextrose	342.000000	8	11	-5.397200	68.619385	Not Accepted
13	*Cucumis metuliferus*	Beta-carotene	536.000000	0	0	12.605807	181.392334	Not Accepted
14	*Capsicum frutescens*	Capsaicin	305.000000	2	4	3.789599	88.951477	Accepted
15	*Coccinia indica*	Beta-amyrin	426.000000	1	1	8.168902	130.719757	Not Accepted
16	*Cinnamomum zeylanicum*	Cinnamaldehyde	132.000000	0	1	1.898700	41.539997	Accepted
17	*Curcuma longa*	Curcuminoid	424.000000	0	7	4.383338	114.917770	Accepted
18	*Coriandrum sativum*	L-alanine	89.000000	3	2	-2.633300	17.357100	Not Accepted
19	*Coccinia indica*	Lupeol	426.000000	1	1	8.024802	130.649750	Accepted
20	*Carica papaya*	Saponin	1222.000000	15	27	-3.496513	284.220825	Not Accepted
21	*Diospyros peregrine*	Triterpenoid	550.000000	1	7	5.436600	140.072235	Not Accepted
22	*Cassia auriculata*	Butelin	442.000000	2	2	6.997202	132.061554	Not Accepted

23	*Ficus bengalensis*	Leucopelargo-nidin	290.000000	5	6	1.331400	72.213989	Accepted
24	*Feronia elephantum*	Bergapten	216.000000	0	4	2.373600	57.434994	Accepted
25	*Glycine max*	3-Omethyl-D-chiro-inositol	194.000000	5	6	-3.180501	40.830990	Accepted
26	*Gymnemssa sylvestre*	Gymnemic acid	971.000000	9	19	0.839671	0.839671	Not Accepted
27	*Hordeum vulgare*	Beta-glucan	472.000000	9	14	-5.862198	98.723137	Not Accepted
28	*Jatroph acurcas*	Diterpene	320.000000	2	3	3.321599	88.769569	Accepted
29	*Momordica balsamina*	Cucurbitacin	558.000000	3	8	3.499300	147.766479	Not Accepted
30	*Mangifera indica*	Magniferin	422.000000	8	11	-0.639399	95.769852	Not Accepted
31	*Momordica charantia*	Momordicin	472.000000	1	3	7.054302	137.335800	Not Accepted
32	*Musa paradisiaca*	Pectin	368.000000	5	13	-7.437499	63.776997	Not Accepted
33	*Musa sapientum*	Steroid	256.000000	1	1	4.405699	76.407784	Accepted
34	*Mentha piperita*	Vanadium	0.000000	0	0	0.000000	0.000000	Not Accepted
35	*Nigella sativa*	Thymoquinone	164.000	0	2	1.666900	46.691990	Accepted
36	*Nelumbo nucifera*	Tolbutamide	270.000000	2	5	2.863820	69.851395	Accepted
37	*Psidium guajava*	Pedunculagin	784.000000	11	22	0.742501	171.597733	Not Accepted
38	*Psidium guajava*	Strictinin	634.000000	9	18	-0.188199	137.671677	Not Accepted
39	*Phyllanthus embilica*	Tannic acid	1700	25	46	3.209100	381.854187	Not Accepted
40	*Rhus coriaria*	Nonanal	142.0000	0	1	2.935899	44.056988	Accepted
41	*Thespesia populnea*	Herbacetin	302.000000	5	7	2.010900	74.050476	Accepted
42	*Thespesia populna*	Quercetin	302.000000	5	7	2.010900	74.050476	Accepted
44	*Terminalia chebula*	Palmitic acid	255.000000	0	2	4.217598	75.318977	Not Accepted
44	*Terminalia chebula*	Chebulic acid	602.000000	8	16	2.225401	134.260376	Not Accepted
45	*Urtica dioica*	Lectin	582.000000	1	6	5.581741	159.180878	Not Accepted
46	*Withania somniferum*	Withanolide	470.0000	2	6	3.495399	124.511551	Accepted
47	*Withania coagulans*	Esterase	387.000000	4	4	3.153599	107.900772	Accepted
48	*Xanthoceris zambesica*	Castanospermine	190.000000	5	4	-3.899200	43.128891	Accepted
49	*Zingiber officinale*	Gingerol	294.000000	2	4	3.233799	82.752579	Accepted

Table 5: FAF Drug Results. Best selected compounds on the basis of adsorption, distribution, metabolism, excretion and toxicity

S.N.	Compound Name	Heavy atom	Hetero atom	Solubility (mg/l)	Oral Bioavliblity (EGAN)	Oral Bioavliblity (VEBER)	Ratio (H/C)	Status
1	Coumarin	11	2	18680.96	Good	Good	.22	Accepted
2	Aegeline	22	4	14204.51	Good	Good	.22	Accepted
3	Sapogenin	34	4	702.8912	Good	Good	.13	Accepted
4	Allyl propyl disulphide	8	2	20620.21	Good	Good	.33	Accepted
5	Butein	20	5	9231.889	Good	Good	.33	Accepted
6	Capsaicin	22	4	9356.726	Good	Good	.22	Accepted
7	Cinnamaldehyde	10	1	18411.1	Good	Good	.11	Accepted
8	Lupeol	31	1	75.6509	Good	Good	.03	Accepted
9	Leucopelagronidin	21	6	30803.51	Good	Good	.40	Accepted
10	Bergaptan	16	4	14084.11	Good	Good	.33	Accepted
11	3-O methyl-D chiro-inositol	13	6	538058.3	Good	Good	.85	Accepted
12	Diterpene	23	3	8114.772	Good	Good	.15	Accepted
13	Steroid	19	1	1605.191	Good	Good	.05	Accepted
14	Thymoquinone	12	2	18597.83	Good	Good	.2	Accepted
15	Tolbutamide	18	6	16010.2	Good	Good	.5	Accepted
16	Nonanal	10	1	14066.93	Good	Good	.11	Accepted
17	Nimibidinin	13	4	37130.75	Good	Good	.44	Accepted
18	Herbacetin	22	7	10239.43	Good	Good	.46	Accepted
19	Quercetin	22	7	15228.15	Good	Good	.47	Accepted
20	Withanolide	34	6	4771.677	Good	Good	.21	Accepted
21	BLT Esterase	27	6	8186.257	Good	Good	.28	Accepted
22	Castenospermia	13	5	281732	Good	Good	.62	Accepted
23	Gingerol	21	4	17226.19	Good	Good	.23	Accepted
24	Ajoene	13	4	37130.75	Good	Good	.44	Accepted
25	Curcuminoid	31	9	3565.719	Good	Good	.40	Accepted

Table 6: YASARA Autodock VINA calculation

Compound Name with (CID No.)	Bind. Energy (kcal/mol)	Dissoc. Constant [pM]	Contacting receptor residues
3-o-methyl-D-chiro-inositol (164619)	000005.9760	00000041642224.0000	Gly^{18}, Thr^{19} , Trp^{20}, Lys ^{21} Asp^{43}, Tyr^{48} Lys^{77}, His^{110}, Trp^{111}, Asn^{160}, Gln^{183}, Tyr^{209}, Ser^{210}, Pro A^{211}, Ser^{214}, Ile^{260}, Pro^{261}, Lys^{262}, Cys^{298}
Ajoene (5386591)	000005.6470	00000072559472.0000	Trp^{20}, Tyr^{48}, Lys^{77}, Trp^{79}, His^{110}, Trp^{111}, Thr^{113}, Phe^{115}, Phe^{122}, Asn^{160}, Gln^{183}, Tyr^{209}, Ser^{210}, Trp^{219}, Cys^{298}, Leu^{300}, Cys^{303}, Tyr ^{309}
Butein (5281222)	000007.7090	00000002234745.5000	Trp^{20}, Lys^{21}, Val^{47}, Tyr^{48}, Gln^{49}, Trp^{79}, His ^{110}, Trp^{111}, Phe^{121}, Phe^{122}, Trp^{219}, Cys^{298}, Ala ^{299}, Leu^{300}
Herbacetin (5280544)	000008.3270	00000000787459.1875	Trp^{20}, Val^{47}, Tyr^{48}, Trp^{79}, His^{110}, Trp^{111}, Thr^{113}, Phe^{115}, Phe^{122}, Pro^{218}, Trp^{219}, Cys^{298}, Ala^{299}, Leu^{300}, Cys^{303}, Tyr^{309}, Pro^{310}

Leucopelargonidin (3286789)	000007.2640	00000004736062.0000	Trp^{20}, Val^{47}, Tyr^{48}, Gln^{49}, Trp^{79}, Trp^{111}, Phe^{121,} Phe^{122}, Trp^{219}, Cys^{298}, Ala^{299}, Leu^{300}
Nimbidinin (101306757)	000007.7100	00000002230976.7500	Trp^{20}, Lys^{21}, Pro^{23}, Pro^{24}, Val^{47}, Tyr^{48}, Gln^{49}, His^{110}, Phe^{121}, Phe^{122}, Pro^{218}, Trp^{219}
Coumarin (323)	000008.5520	00000000538642.8125	Trp^{79}, Cys^{80}, Trp^{111}, Thr^{113}, Phe^{115}, Phe^{122}, Trp^{219}, Cys^{298}, Ala^{299}, Leu^{300}, Cys^{303}, Tyr^{309}, Pro^{310}
Tolbutamide (5505)	000008.7870	00000000362279.3750	Trp^{79}, Cys^{80}, Trp^{111}, Thr^{113}, Phe^{115}, Phe^{122}, Leu^{124}, Trp^{219}, Cys^{298}, Ala^{299}, Leu^{300}, Ser^{302}, Cys^{303,} Tyr^{309}
Quercetin, (5280343)	000008.7500	00000000385624.8125	Trp^{20}, Tyr^{48}, Trp^{79}, Trp^{111}, Thr^{113}, Phe^{115}, Phe^{122}, Pro^{218}, Trp^{219}, Cys^{298}, Ala^{299}, Leu^{300}, Cys^{303}, Tyr^{309}, Pro^{310}, Phe^{311}

Table 7: Interacted residue, active Site and their residues and common interacted residues with compound name

Compound Name	Interacted residue	Active Site and their residues	Common Interacted Residues
3-o-methyl-D-chiro-inositol	Gly^{18}, Thr^{19}, Trp^{20}, Lys^{21}, Asp^{43}, Tyr^{48} Lys^{77}, His^{110}, Trp^{111}, Asn^{160}, Gln^{183}, Tyr^{209}, Ser^{210}, Pro A^{211}, Ser^{214}, Ile^{260}, Pro^{261}, Lys^{262}, Cys^{298}	Trp^{20}, Lys^{221}, Pro^{218}, Trp^{219}, Trp^{79}, Cys^{80}, Trp^{111}, Thr^{113}, Phe^{115}, Phe^{122}, Leu^{300}, Cys^{303}, Tyr^{309}, Ala^{299}, Cys^{298}, His^{110}, Val^{47}, Tyr^{48}, Asn^{160}, Tyr^{209}, Ser^{159}, Gln^{183}, Pro^{211}, Lys^{77}, Asp^{43}, Ile^{260}, Thr^{19}, Gly^{183}, Lys^{262}, Pro^{211}, Pro^{211}, Asp^{216}, Leu^{212}, Pro^{215}, Pro^{261}, Leu^{228}, Arg^{268}, Ser^{263}, Asn^{272}, Ala^{245}, Glu^{271}, Thr^{243}, Thr^{244}, Glu^{22}, Ser^{226}, Val^{264}, Thr^{265}, Val^{297}, Ser^{302}, Leu^{124}, Leu^{301}, Phe^{311}, Pro^{310}, Gln^{49}, Phe^{121}, His^{46}, Leu^{108}, Val^{130}, sGly^{213}, Glu^{67}, Asn^{50}, Ser^{22}	Gly^{18}, Trp^{20}, Thr^{19}, Asp^{43} Tyr^{48} Lys^{77}, Trp^{111}, Tyr^{209} Asn^{160}, Pro^{211}, Ile^{260}, Lys^{262} Cys^{298}, His^{110}, Gln^{183}, Pro^{261}, Lys^{262}, Cys^{298}
Ajoene	Trp^{20}, Tyr^{48}, Lys^{77}, Trp^{79}, His^{110}, Trp^{111}, Thr^{113}, Phe^{115}, Phe^{122}, Asn^{160}, Gln^{183}, Tyr^{209}, Ser^{210}, Trp^{219}, Cys^{298}, Leu^{300}, Cys^{303}, Tyr^{309}		Trp^{20}, Tyr^{48}, LYS^{77}, Trp^{79} His^{110}, Trp^{111}, Thr^{113}, Phe^{115}, Phe^{122}, Asn^{160}, Gln^{183}, Tyr^{209}, Ser^{210}, Trp^{219}, Cys^{298}, Leu^{300}, Cys^{303}, Tyr^{309}
Butein	Trp^{20}, Lys^{21}, Val^{47}, Tyr^{48}, Gln^{49}, Trp^{79}, His^{110}, Trp^{111}, Phe^{121}, Phe^{122}, Trp^{219}, Cys^{298}, Ala^{299}, Leu^{300}		Trp^{20}, Val^{47}, Tyr^{48}, Gln^{49}, Trp^{79}, His^{110}, Trp^{111}, Phe^{121}, Phe^{122}, Trp^{219}, Cys^{298}, Ala^{299}, Leu^{300}
Herbacetin	Trp^{20}, Val^{47}, Tyr^{48}, Trp^{79}, His^{110}, Trp^{111}, Thr^{113}, Phe^{115}, Phe^{122}, Pro^{218}, Trp^{219}, Cys^{298}, Ala^{299}, Leu^{300}, Cys^{303}, Tyr^{309}, Pro^{310}		Trp^{20}, Val^{47}, Tyr^{48}, Trp^{79}, His^{110}, Trp^{111}, Thr^{113}, Phe^{115}, Phe^{122}, Pro^{218}, Trp^{219}, Cys^{298}, Ala^{299}, Leu^{300}, Cys^{303}, Tyr^{309}, Trp^{219}, Pro^{310}
Leucopelargo-nidin	Trp^{20}, Val^{47}, Tyr^{48}, Gln^{49}, Trp^{79}, Trp^{111}, Phe^{121} Phe^{122}, Trp^{219}, Cys^{298}, Ala^{299}, Leu^{300}		Trp^{20,} Val^{47}, Tyr^{48}, Gln^{49}, Trp^{79}, Trp^{111}, Phe^{121}, Phe^{122}, Trp^{219}, Cys^{298}, Ala^{299}, Leu^{300},
Nimbidinin	Trp^{20}, Lys^{21}, Pro^{23}, Pro^{24}, Val^{47}, Tyr^{48}, Gln^{49}, His^{110}, Phe^{121}, Phe^{122}, Pro^{218}, Trp^{219}		Trp^{20}, Val^{47}, Tyr^{48}, Trp^{20}, Gln^{49}, His^{110}, Phe^{121}, Phe^{122}, Pro^{218}, Trp^{219}
Coumarin	Trp^{79}, Cys^{80}, Trp^{111}Thr^{113}, Phe^{115}, Phe^{122}, Trp^{219}, Cys^{298}, Ala^{299}, Leu^{300}, Cys^{303}, Tyr^{309}, Pro^{310}		Trp^{79}, Cys^{80}, Trp^{111,} Thr^{113}, Phe^{115}, Phe^{122}, Trp^{219}, Cys^{298}, Ala^{299}, Leu^{300}, Cys^{303}, Tyr^{309}, Pro^{310}

Tolbutamide	Trp^{79}, Cys^{80}, Trp^{111}, Thr^{113}, Phe^{115}, Phe^{122}, Leu^{124}, Trp^{219}, Cys^{298}, Ala^{299}, Leu^{300}, Ser^{302}, Cys^{303}, Tyr^{309}		Trp^{79}, Cys^{80}, Trp^{111}, Thr^{113}, Phe^{115}, Phe^{122}, Leu^{124}, Trp^{219}, Cys^{298}, Ala^{299}, Leu^{300}, Ser^{302}, Cys^{303} Tyr^{309}
Quercetin	Trp^{20}, Tyr^{48}, Trp^{79}, Trp^{111}, Thr^{113}, Phe^{115}, Phe^{122}, Pro^{218}, Trp^{219}, Cys^{298}, Ala^{299}, Leu^{300}, Cys^{303}, Tyr^{309}, Pro^{310}, Phe^{311}		Trp^{20}, Tyr^{48}, Trp^{79}, Trp^{111}, Thr^{113}, Phe^{115}, $Phe^{122}Pro^{218}$, Trp^{219}, Cys^{298}, Ala^{299}, Leu^{300}, Cys^{303}, Tyr^{309}, Pro^{310}, Phe^{311}

Ser^{214}, Pro^{215}, Asp^{216}, Ala^{245}, Ile^{260}, Val^{264}, Thr^{265}, Arg^{268}, Glu^{261}, Asn^{262}, Cys^{298}, Ala^{299} and Leu^{300} were found conserved with binding site 1, which is major active site involved in interaction with 7 best screened compounds (Fig. 6, 7 and 8).

There are several medicinal plants which contains certain phytochemicals that are reported to have anti-diabetic properties. Such phytochemicals are often used to either treat or mitigate the effects of diabetes. In the present study, 45 medicinal plants and their active anti-diabetic compounds were selected. Using Lipinski filter, the drug-likeness and non-drug-likeness of the selected compounds were estimated. The compounds which showed high drug-likeness were further analyzed by 'FAF Drug analysis' tool and seven anti-diabetic compounds were selected which possessed most effective properties in terms of adsorbtion, distribution, metabolism, excretion and toxicity. Using these seven compounds as ligands and AR receptor as target molecule, docking was performed using YASARA tool. *Butea monosperma*, commonly known as Palash belongs to buteia genus of Fabaceae family.

A Butein compound isolated from *B. monosperma* has been well reported to have anti-diabetic property (Vikrant and Sharma, 2011). Its stem and bark can be used for the treatment of dyspepsia, diarrhea, dysentery, diabetes, ulcers, sore throat and snake bites (Jayaweera, 1981). *Thespesia populnea* belongs to Malvaceae family. It has Herbacetin and Qurecetin compounds that helps in diabetic management (Sofara, 1984; Kumar and Clark, 2002). *T. populnea* also possess useful medicinal properties such as anti-fertility, anti-microbial, anti-inflammatory, antioxidant, purgative and hepatoprotective activity (Arthanari *et al*., 2009). *Ficus benghalensis*, also Know "Indian banyan" belong to Moraceae Family. Leucopelargonidin, a compound isloated from *F. benghalensis*, has anti-diabetic property (Mamun or Rashid *et al.,* 2014; Vikrant and Sharma, 2011). A glycoside isolated from the bark of *Ficus benghalensis*, has been shown to raise significant serum insulin and has hypoglycaemic, hypolipidemic effects in moderately diabetic rats. Dimethoxy ether of leucopelargonidin-3- O-alpha-L rhamnoside at a dose of 100 mg/kg, p.o. showed significant hypoglycaemic and insulin-mimetic activity in healthy and alloxan induced-diabetic rats during a period of 2 hour (Bouham *et al*., 2006). *Azadirachta indica*, commonly known as Neem, is a tree that belongs Meliaceae family. *A. indica* has been shown to possess hypolipidemic, hypoglycemic, immunostimulant and hepatoprotective properties (Govind *et al*., 1990; Ara *et al*., 1989).

The compound Nimbidinin has been isolated from *A. indica* leaves that help in diabetic treatment (Basak and Chakroborty, 1969). *Aegle marmelos*, is known as bael in India, that belong Rutaceae Family. It leave, seeds contain Coumarin and Aegeline that are anti-diabetic compound (Mamun or Rashid *et al.,* 2014; Kesari *et al*., 2006). It leave has been used in Ayurvedic Unani and Siddha system in India that used as anti-diabetic and hypoglycemic activity (Sankeshi *et al*. 2013). *Nelumbo nucifera*, is known as Indian lotus belongs to Nelumbonaceae family.

Tolbutamide is anti-diabetic compound which is isolated from *N. nucifera* (Mamun or Rashid *et al.* 2014). *N. nucifera* leaves containing compound appear to exert comprehensive inhibitory effects against oxidative stress-related diabetic complications, and or preventive agents for diabetic complications and

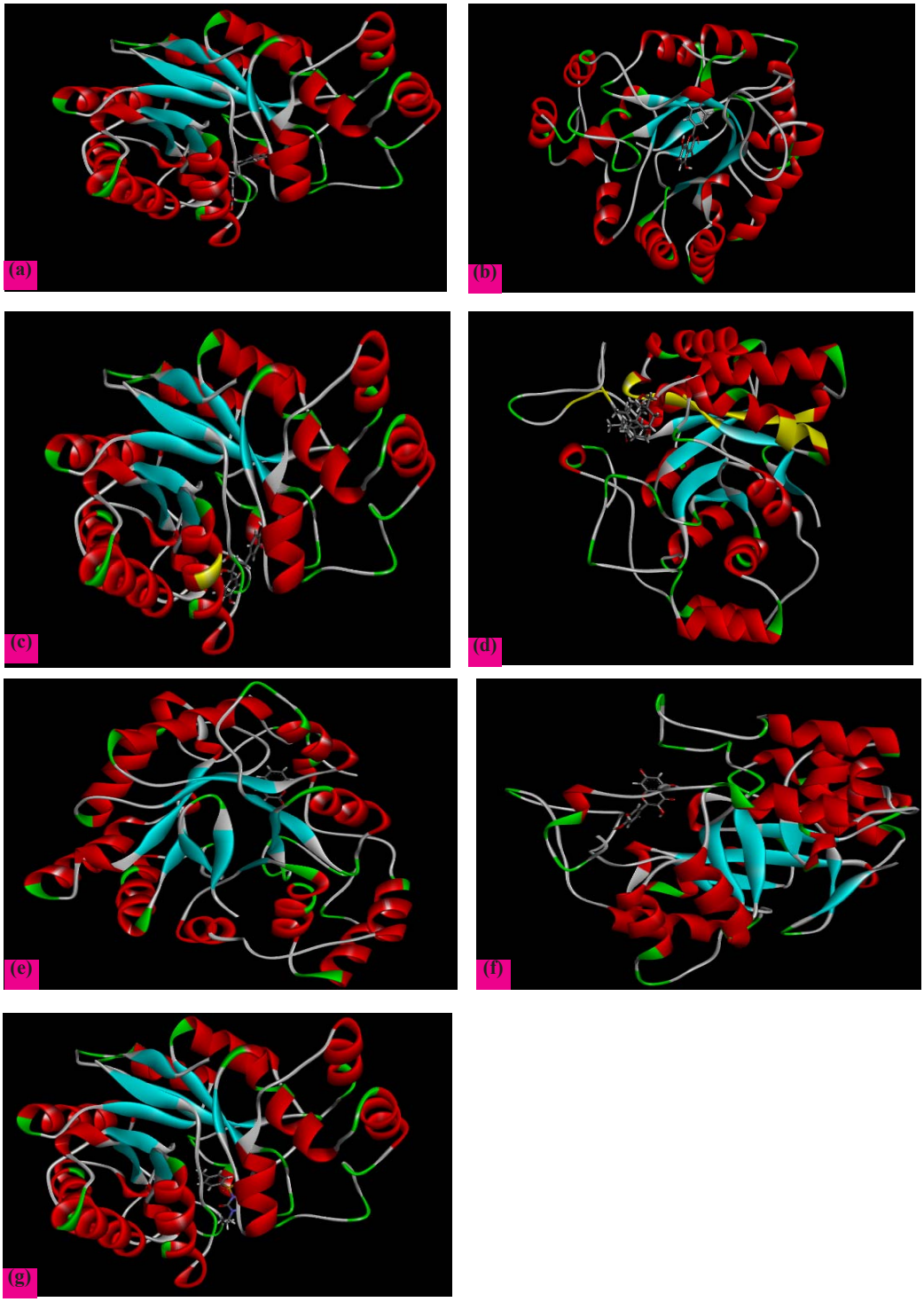
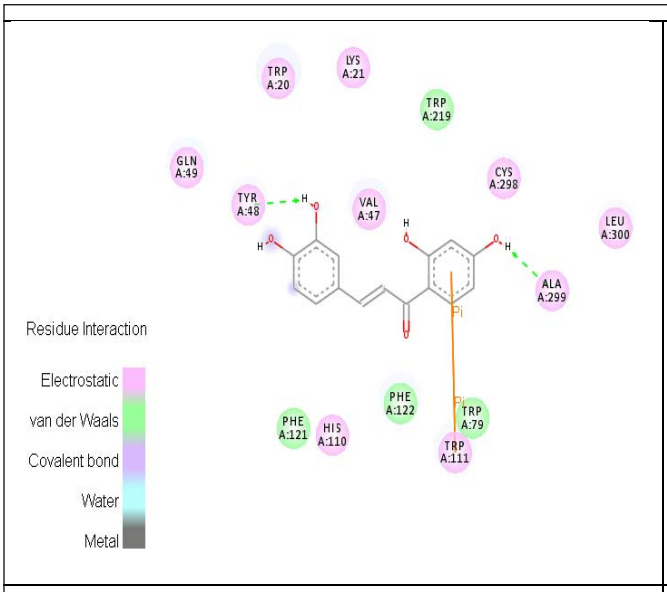
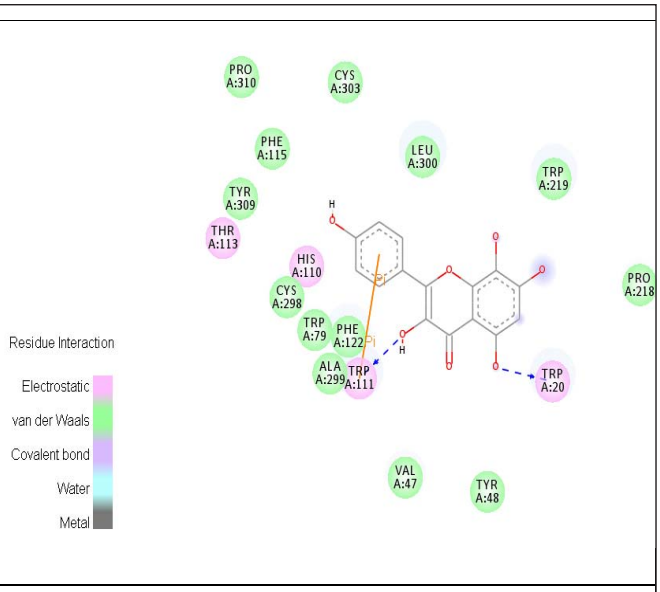


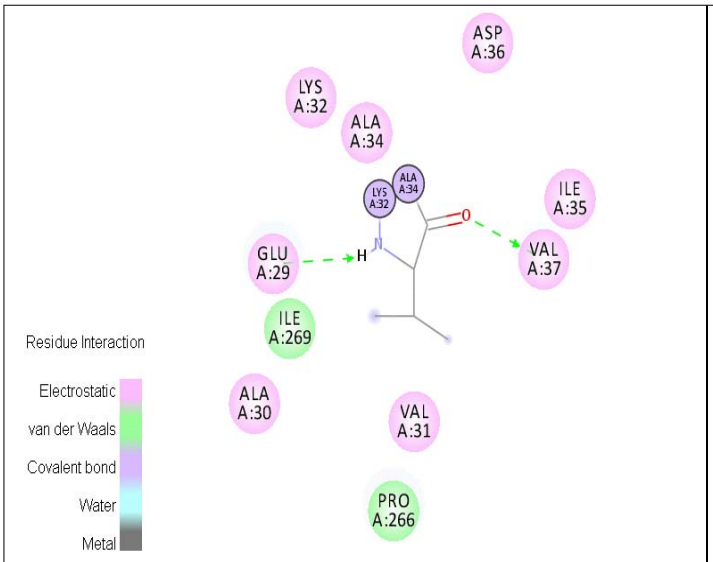
Fig. 6: Interaction between AR receptor and ligands (a) Butein (b) Herbacetin (c) Leucopelargonidin (d) Nimbidinin (e) Coumarin (f) Quercetin (g) Tolbutamide



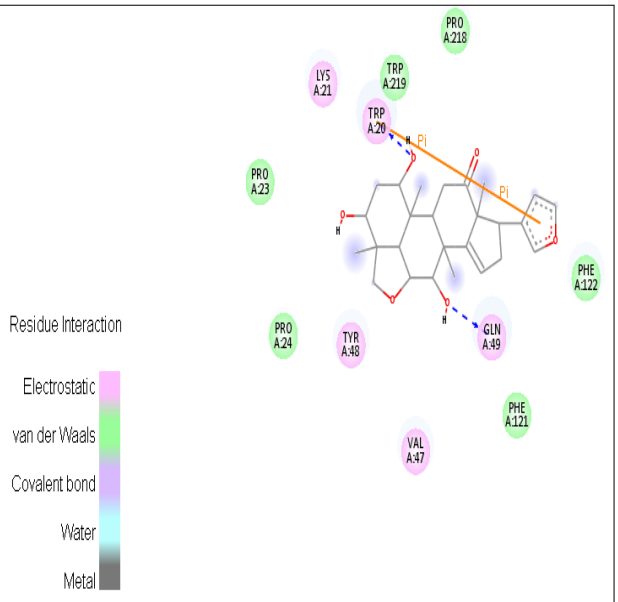
Butein



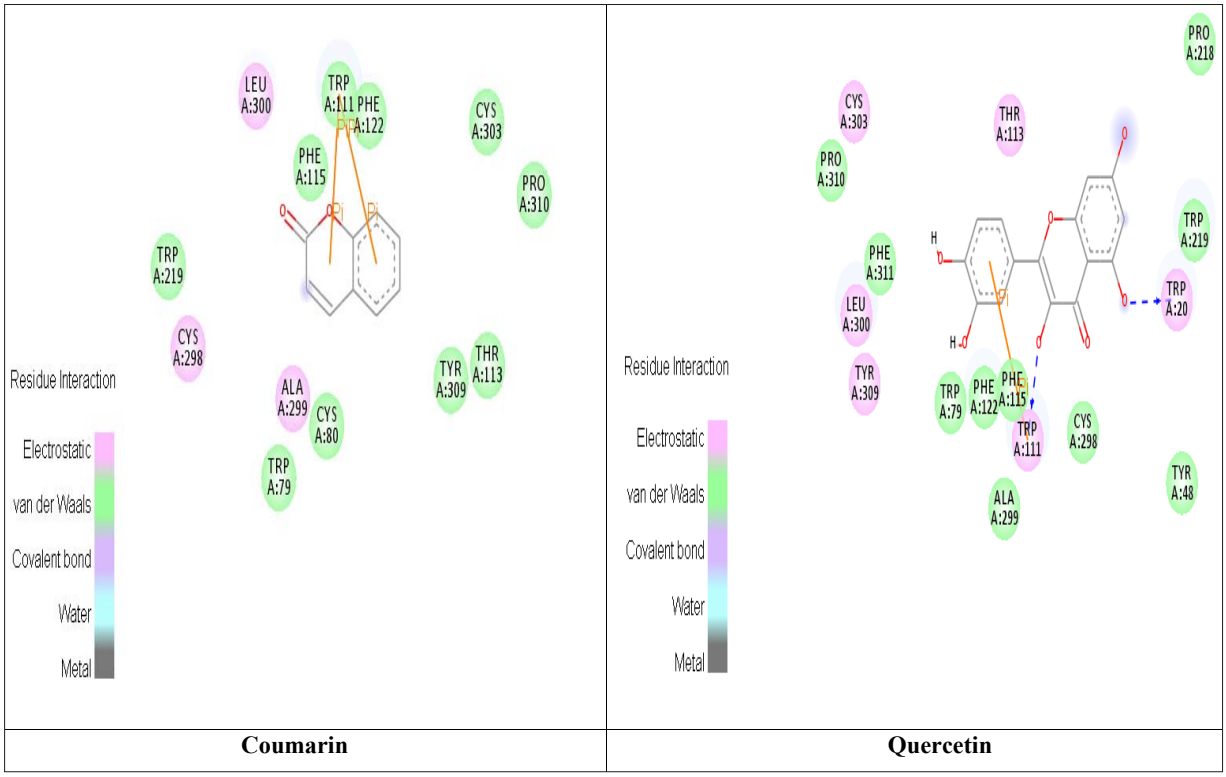
Herbacetin



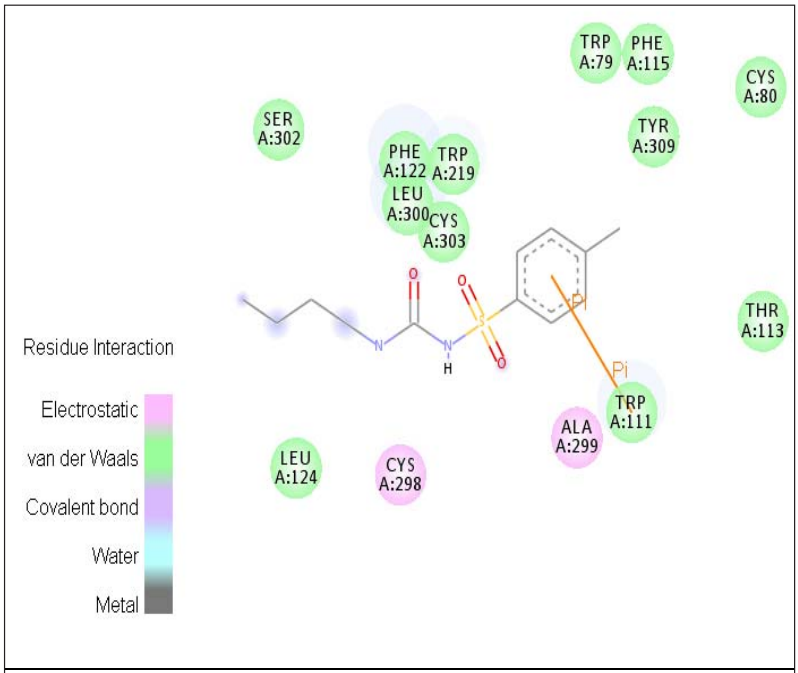
Leucopelargonidin



Nimbidin



Coumarin | **Quercetin**



Tolbutamide

Fig. 7: 2-D interaction between receptor (AR) and ligands (Butein, Herbacetin, Leucopelagronidin, Nimbidinin, Coumarin, Quercetin and Tolbutamide)

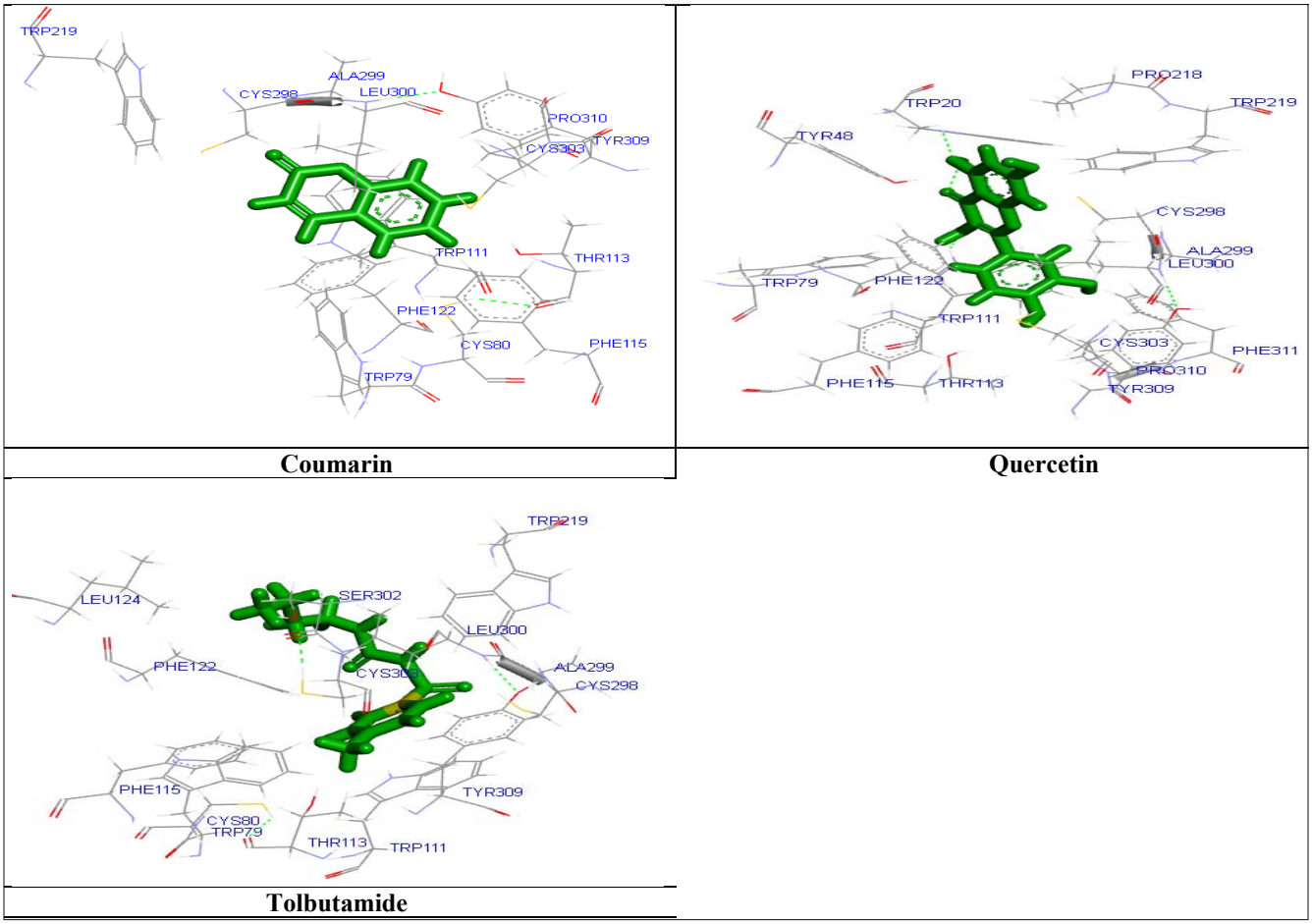


Fig. 8: 3-D Interaction between ligands (Butein, Herbacetin, Leucopelagronidin, Nimbidinin, Coumarin, Qurecetin and Tolbutamide) and Receptor (AR)

aging-related diseases. (Jung *et al*., 2008). Tolbutamide is a first-generation, sulfonylurea, oral-hypoglycemic agent used in the treatment of type-2 diabetes (Brian, 2007).

CONCLUSION

AR was selected as a prominent target protein to study the interaction of selected anti-diabetic compounds isolated from various medicinal plants. Through *in-silico* screening, total nine anti-diabetic compounds (3-O-Methyl-D-chiro-inositol (D-pinitol), Ajoene, Butein, (Herbacetin, Qurecetin), Leucopelargonidin, Nimbidinin, Coumarin, and Tolbutamide) were selected out of 49w reported anti-diabetic compounds isolated from 45 medicinal plants. The docking calculations between selected nine anti-diabetic compounds and target protein were performed successfully using YASARA tool. Based on parameters like good oral bioavailability, Non-toxicity and Drug likeness, Adsorption, Distribution, Metabolism, Excretion, Toxicity showing strong binding affinity with prominent binding site residues and good dissociation constant, only seven out of nine compounds were selected as the best possible ligands. Docking results showed seven anti-diabetic compounds (Butein, (Herbacetin, Querecitin), Tolbutamide, Coumarin, Leucopelagrodin and Nimbidinin) as effective compounds can be used for the treatment of diabetes.

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