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"Study of Computer-based molecular docking of Insulin Plant in Drug design and development"

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ABSTRACT

Many success stories for the use of computer-assisted drug design in the identification of new mechanism- or structure-based medications have been made possible by new molecular modelling methodologies, driven by fast increasing computational platforms. Due to improvements in high throughput experimental techniques and the accessibility of high performance computing resources, the process of drug creation has now become much more scientific and logical, leading to a greater knowledge of biological processes and the underlying chemistry. Since the technique has advanced, medications are now developed rather than accidentally discovered.

KEYWORDS: Drug design, Insulin Plant, Docking analysis, Costus igneus, Diabetes mellitus

INTRODUCTION TO DRUG DESIGN

Predicting whether and how strongly a given chemical will attach to a target is the primary objective of drug design. The most popular method for determining the strength of the intermolecular interaction between a tiny molecule and its biological target is molecular mechanics, often known as molecular dynamics. Computer modelling approaches are commonly, but not always, used in drug design. Computer-aided modelling is another name for this kind of modelling. A type of computational modelling of complexes created by the interaction of two or more molecules is known as molecular docking. According to the binding characteristics of the involved ligands and target molecules, it makes predictions about the three-dimensional structure of adducts. Different potential candidate structures are generated by molecular docking and are sorted and categorised using the A type of computational modelling known as molecular docking is used to represent complexes that result from the interaction of two or more molecules.

INDRODUCTION TO DIABETES MELLITUS

A hallmark of diabetes mellitus is unusually high blood sugar (glucose) levels. The hormone insulin is released by the pancreas when the blood's level of glucose rises, such as after eating. Circulation sugar levels return to normal as a result of insulin's stimulation of the liver's metabolism of glucose and the removal of glucose from the blood by muscle and fat cells. Blood sugar levels in diabetics continue to be high. This could be as a result of insulin not being created sufficiently, not being produced at all, or not being as effective as it should be. Type 1 diabetes (5%), an autoimmune condition, and type 2 diabetes (95%), a metabolic illness, are the two most prevalent types of diabetes. (which is connected to obesity). Other types of diabetes are extremely uncommon

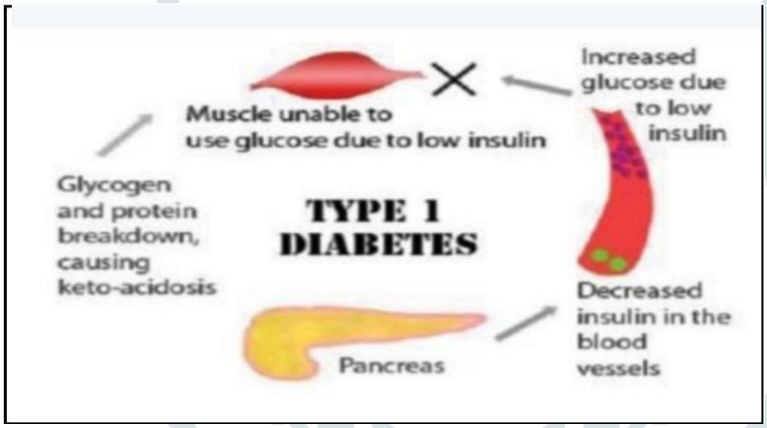
and are brought on by a single gene mutation. Gestational diabetes is a kind of diabetes that develops during pregnancy.

TYPES OF DIABETES

According to a 2007 poll by the American Diabetes Association, 23.6 million Americans have diabetes, making it a common condition (CDC, 2008). Sadly, that number is rising as an additional 1.6 million Americans are diagnosed with diabetes each year (CDC, 2008). Diabetes has two main types. And a third, less typical version.

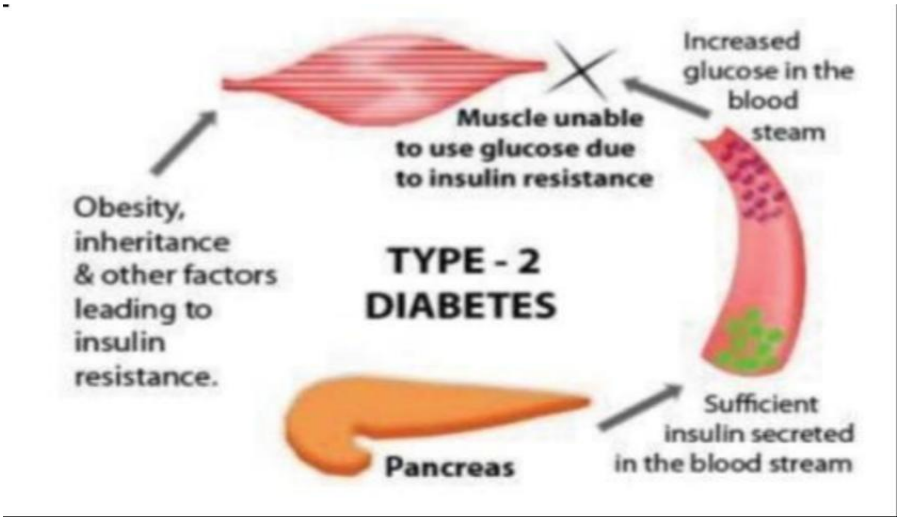
TYPE 1 DIABETES

The body's own immune system assaults and kills the cells in the pancreas that create insulin in the first main form of diabetes, also known as Type 1 diabetes, leaving the affected individual unable to manufacture insulin naturally. These kinds of Insulin Dependent Diabetes Mellitus used to be the incorrect name for diabetes. Because insulin treatment is possible for both of the main kinds of diabetes. Likewise called juvenile diabetes, Often, type 1 diabetes develops in children. As just about 5% of all cases, it is relatively uncommon. Cases of diabetes. If insulin production occurred outside of the body, the condition would be fatal. Intentionally administered into the body to replace what it can no longer do To maintain normal blood sugar levels, people with Type 1 diabetes must learn to routinely check their blood sugar and self-administer insulin doses. Although Type 1 diabetes cannot be cured, dietary changes should still be made in order to keep blood sugar oscillations to a minimum.



TYPE 2 DIABETES

In contrast to Type 1 diabetes, which develops from an abrupt shutdown of actual insulin production, Type 2 diabetes starts with a progressive decline in the body's capacity to respond to insulin (a condition known as "insulin resistance"). When the body is regularly exposed to high levels of insulin in the blood stream, insulin resistance develops. After some time, the cells stop responding to insulin as strongly as they once did. To get the same quantity of glucose into the cells at this point, more insulin is needed. This is comparable to "the child who cried wolf" in several ways. At first, everyone responded promptly and effectively to the boy's cries. But after sprinting to the villagers started running to the boy, but after seeing him totally safe, they stopped. Actual insulin production doesn't decline until the condition has advanced.



OBJECTIVE OF STUDY

1. To Find New Chemical Entities With Wanted Pharmacological Characteristics

2. It Is Very Important For Cellular Biology

3. It Is Essential For Ethical Drug Design.

4. To anticipate potential derivatives that enhance drug activity.

5. To screen, improve, and assess the compound's activity in relation to the target.

6. De Nova Design,

INDRODUCTIONTOPLANTCOSTUS IGNEUS

Diabetes can be magically cured with a medicinal herb called Costus igneus. It is frequently referred to as the "insulin plant" in India because its leaves aid in the production of insulin in the human body.

 COMMON NAMES: Costus, Spiral flag Banda, Bija-Sal, Peisar, Jarul, Insulin Plant,

Fiery Costus.

 SYNONYMS: Costus Cuspidatus, Costus igneus, Globbacuspidata.

 SCIENTIFIC CLASSIFICATION

Binomial name: Chamaecostus cuspidatus

Kingdom: Plantae

Phylum :Tracheophytes

Clade: Angiosperms

Clade: Monocots

Subclass:Commelinids

Order:Zingiberales

Family:Costaceae

Subfamily: Asteroideae

Genus: Chamaecostus

Species: C cuspidatus

CHEMICAL CONSTITUENTS

Protein, iron, and antioxidants such Corosolic acid, ascorbic acid (Vitamine C), -tocopherol, -carotene, terpinoids, steroids, and flavonoids are all abundant in the leaves of C. igneus, according to phytochemical analysis. Another investigation demonstrated that methanolic extract contained the highest concentration of Carbohydrates, triterpenoids, proteins, alkaloids, tannins, saponins, and other phytochemicals Flavonoids.

DESCRIPTION

The family Costaceae includes the genus Costus, which includes perennial tropical herbaceous flowering plants. It is a perennial plant that spreads uprightly and grows to a height of about 60 cm. It has spirally arranged leaves, a sturdy stem, and lovely flowers. Large, fleshy-looking leaves are present. These's' undersides Large smooth, light purple-hued leaves are a dark green colour. The leaves are grouped around the stem in a spiral. Stem that develops into lovely, arching bunches from underground rootstocks. The highest height Is approximately two feet for these plants. The flowers are 1.5 in (3.8 cm) in diameter and orange in hue. Summertime is when flowers bloom. Moreover, they resemble cone-shaped heads at the tips of Branches.

South East Asia is the species' original home, particularly the larger Sunda islands in Indonesia. It is a recent arrival in Kerala and India. Due to its therapeutic compounds, this plant, which was grown in America, is becoming more and more well-liked in India.

MATERIAL AND METHODOLOGY

CULTIVATION AND COLLECTION:

Its roots are cultivating it. It is a relative of gingers and was formerly a member of the Zingiberaceae family. Birds disseminate seeds as they eat fruits, and the species reproduces vegetatively by rhizomes. The edible Costus products, sometimes known as CostusComosus, are available. It's a lower growth that is excellent as a ground cover. The plant develops rapidly, and its reproduction is by severing a stem. It requires sunlight but may also thrive in a little shade. It is grown for food in India. its role in the system of conventional medicine.

MACROSCOPY :

The leaves were simple, alternate, entire, oblong, smooth, parallel venation and spirally arranged

around stem.

MICROSCOPY :

Transverse section of the leaf through midrib and lamina was taken and observed for their

characteristic features.

An upper and lower epidermis that is embedded in a large mesophyll tissue made of parenchyma that is embedded in continuous strands of fibrovascular bundles may be seen in the transverse section of a leaf. The huge parenchyma cells make up the majority of the mesophyll tissue. Upper body cells Comparatively speaking, epidermis cells are smaller than lower epidermal cells. The lower epidermis Stomata are embedded, and epidermal cells frequently have beads on them. Vascular bundles contain Embedded in continuous strands of elongated or spherical chlorenchymal cells, and Large vessels are located in the centre of the vascular bundles, which are encircled by phloem tissue. The The parenchymas next to the fibre bundles are rich with rosette crystals of Oxalate of calcium.

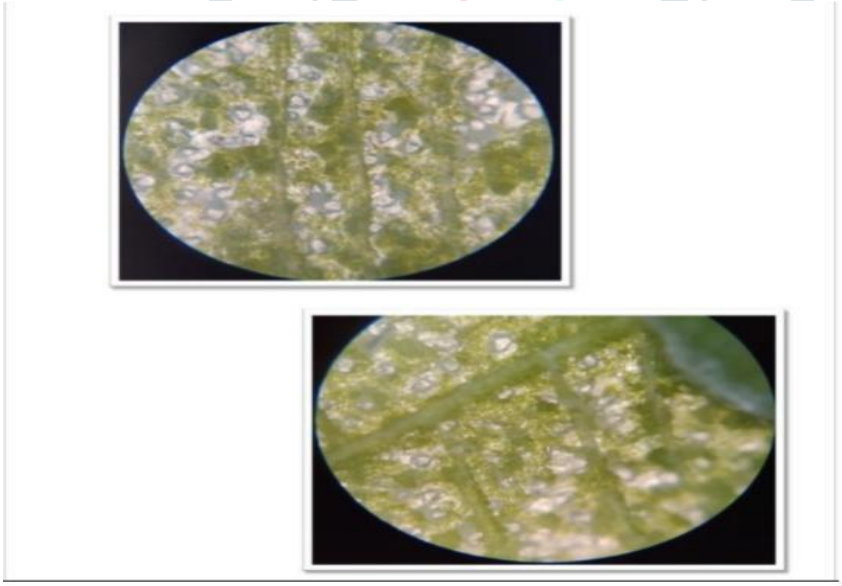
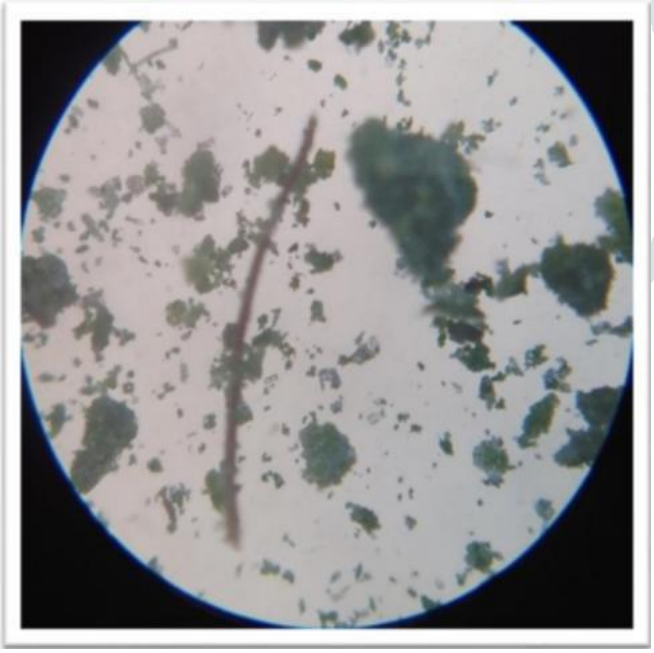


Figure: Transverse section of costus Igneus leaf

POWDER MICROSCOPY & CHARACTERISTICS

A small amount of leaf powder was put on a microscopic slide, stained with safranin, and examined using a trinocular microscope to identify the features.

The powder displays fragments of lower epidermis with anomocytic stomata and beaded walls, fragments of the mesophyll region with cells embedding chloroplasts and plenty of calcium oxalate druses, bundles of thin-walled fibres associated with parenchyma containing, among other things, calcium oxalate druses. Crystal fiber-forming druses; pieces of or complete vessels thickened spirally.



EXTRACTION

The extract of costus igneus leaves are obtained by Maceration method.

MACERATION

In this method, the entire solvent is combined with the solid ingredients in a sealed container, and the mixture is let to stand for at least three to seven days while being frequently stirred to dissolve any soluble materials. The combined liquids are then clarified by straining the mixture, pressing the marc, and decantation.

PROCESS OF MACERATION

METHOD:A

Costus igneus plant leaves in good health were harvested, thoroughly cleaned in tap water, and dried at room temperature for 30 days. The powdered dry leaves were then steeped for three days in 225 ml of methanol at a rate of 25 gm per day. Whatman was used to filter the extract. The top filter paper (Repeat this twice with fresh solvent). Similar procedures were used with various solvents, such as petroleum ether, hexane, benzene, and dichloromethane. At the refrigerator, the extract was kept.

METHOD: B

In a blender, the dried leaves are ground into a fine powder, and the powder is then collected in spick-and-span ploythene bags. 50 ml of ethyl alcohol was added to 10 g of leaf powder, which was continuously agitated for 30 minutes. The solution was then allowed to sit at room temperature for at least 24 hours before being filtered. The Once more filtered using Whatman No. 3 filter paper, the solution was then kept at 4 degrees. Celsius until use in a freezer.

METHOD : C

A straightforward maceration process was used to extract about 2.5 kg of fresh air dried powdered costus igneus crude medicine with 90% ethanol over the course of 7 days in a conical flask, sometimes shaking and stirring.

PHYTOCHEMICAL SCREENING (TEST)

TLC (Thin Layer Chromatography) of extracts :

For TLC analysis, extracts created using two different extraction techniques were used. The stationary phase consisted of 20 × 20 cm pre-coated TLC plates. We experimented with many mobile phases before using chloroform. Etidronic Acid: Methanol: The best ratio was standardised as benzene. to get clear areas, use the mobility phase. The samples (10 mL and 20 mL) were equally put onto TLC plates. distance. Following the chromatograph's scanning, Rf values were computed. Using methanol to extract As leaves provided the highest extraction yield, they were selected for further examination.

Rf value: Rf value=distance travelled by sample/distance travelled by solvent

Rf value of insulin = 3.8/5.6

=0.67

Chemical test: Evaluation of the phytochemical content of Costus igneus leaf. Standard procedures were used to conduct phytochemical analyses on the methanol extract to determine the constituents.

TEST FOR ALKALOIDS :

A) Mayer’s reagent:

B) Dragndroff reagent

C) Wagner's reagent:

D) Hager's reagent:

TEST FOR FLAVONOIDS

A) Lead acetate test:

B) Alkaline reagent test:

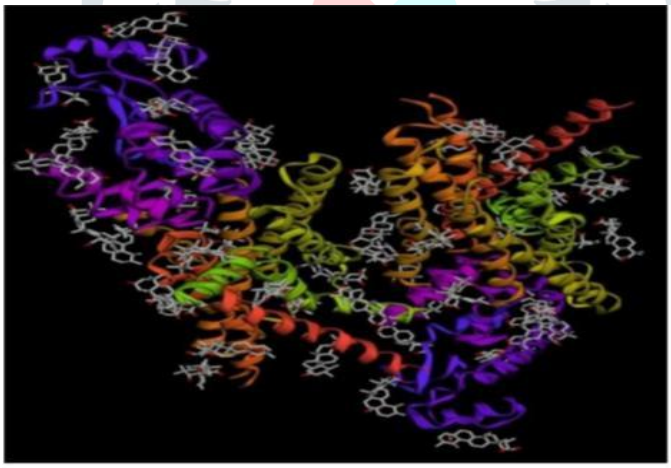
C) Ferric chloride test

RESULT:

Docking Analysis:

Blind Docking calculations of proteins and ligands were carried out via an online molecular modelling programme called Achilles Blind Docking Server. Results for Blind Docking of Vitamine c (mol) on 6wpw (pdb) :

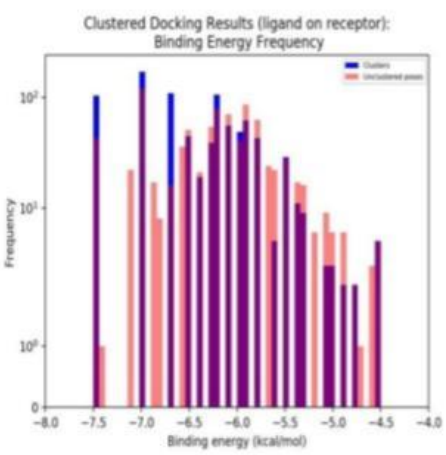
1. Receptor :5vex(pdb)
2. Ligand:corosolic acid (mol)



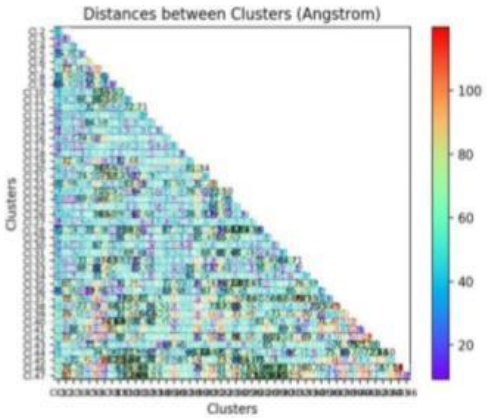
(Visual representation of molecules created with 3Dmol)

Cluster population:

Binding energies distribution:



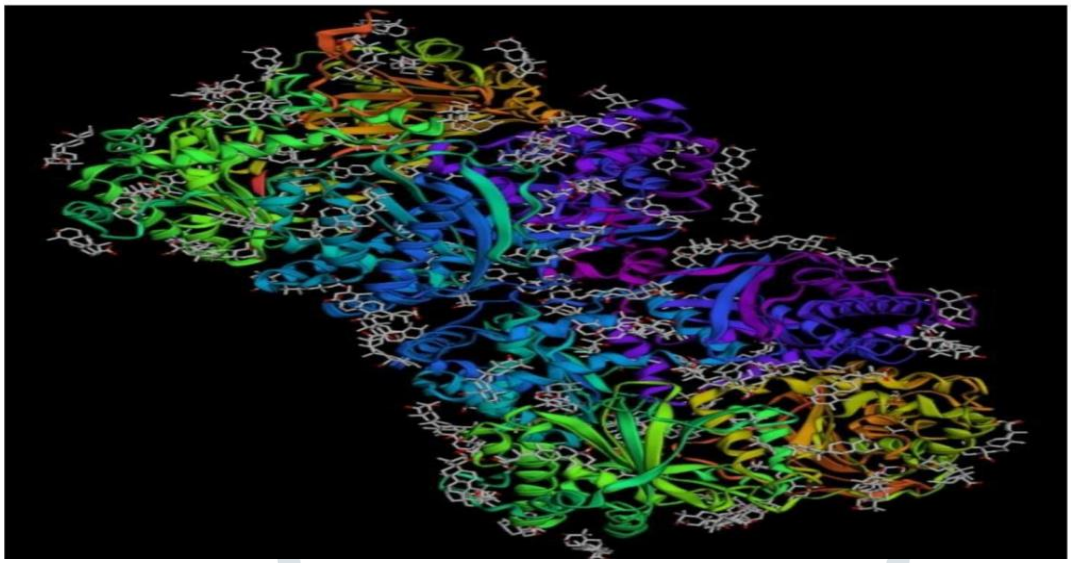
Distance between cluster:



Binding energy (Kcal/mol)	Poses in cluster	Best pose	Binding site coordinates
-7. 50	104	752	(25.11, -21. 67,40.28)
-7.00	46	639	(45.56, -17. 98,76.37)
-7. 00	32	536	(34.16, -19. 33,61.64)
-7. 00	40	339	(25.58, -8. 99,-29.21)
-7. 00	53	109	(13.38, -14. 70,-8.92)
-6. 70	55	624	(36.67, -18. 32,90.69)
-6. 70	55	208	(4.49, -14. 82,5.02)
-6. 50	45	30	(-6.78, -26. 36,27.74)
-6. 40	19	353	(0.49, -14. 71,-24.05)
-6. 30	39	829	(57.34, -11. 01,32.95)
-6. 20	28	856	(47.09, 11.48,-59.48)
-6. 20	24	29	(14.62, -44. 54,26.40)

3. **Receptor: 2g49(pdb)**

   Ligand: Corosolic acid (mol).



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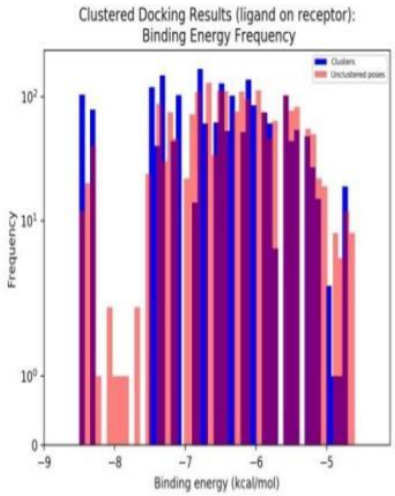
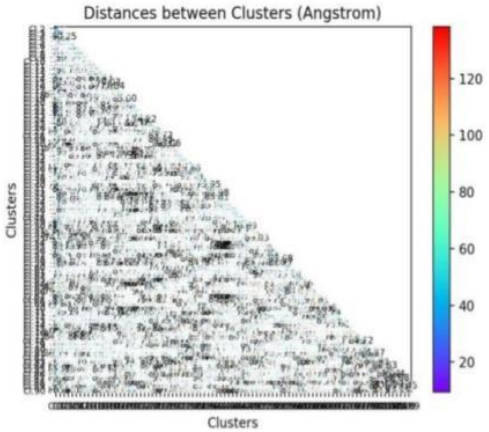
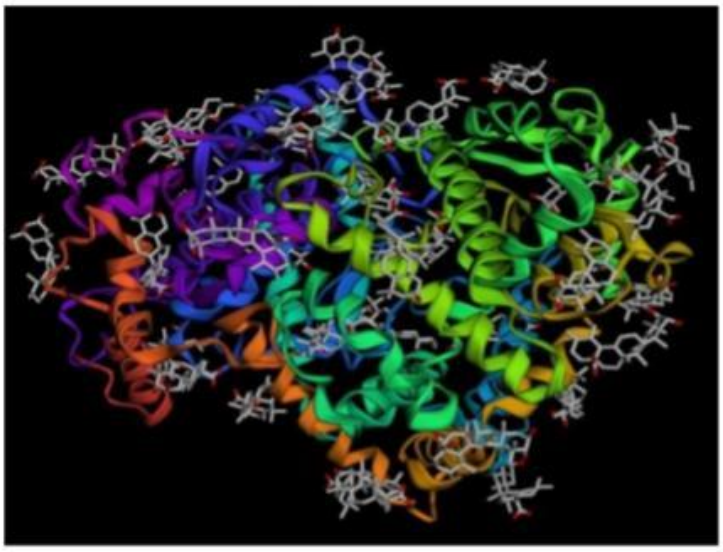
Cluster population:

Binding energies distribution:	**Distance between cluster:**
	

Binding energy (kcal/mol)	Poses in cluster	Best pose	Binding site coordinates
-8. 50	104	870	(168.67, 57.59,-3.58)
-8. 30	79	1731	(202.17, 69.52,-6.25)
-7. 50	56	1361	(217.83,93.58,-16.13)
-7. 50	64	393	(149.32, 44.09,15.55)
-7. 40	40	1651	(200.28, 62.34,8.39)
-7. 30	77	1523	(200.17, 95.18,0.45)
-7. 30	72	616	(162.37, 64.79,21.62)
-7. 20	44	515	(169.47,71.06,-12.52)
-7. 10	68	1249	(219.21, 98.72,-1.32)
-7. 10	35	654	(171.57, 59.53,14.88)
-6. 90	14	1925	(182.99, 69.66,-1.51)
-6. 80	50	1152	(198.71,99.83,-37.36)

3. Receptor:2qpj(pdb)

Ligand:Corosolic acid (mol)



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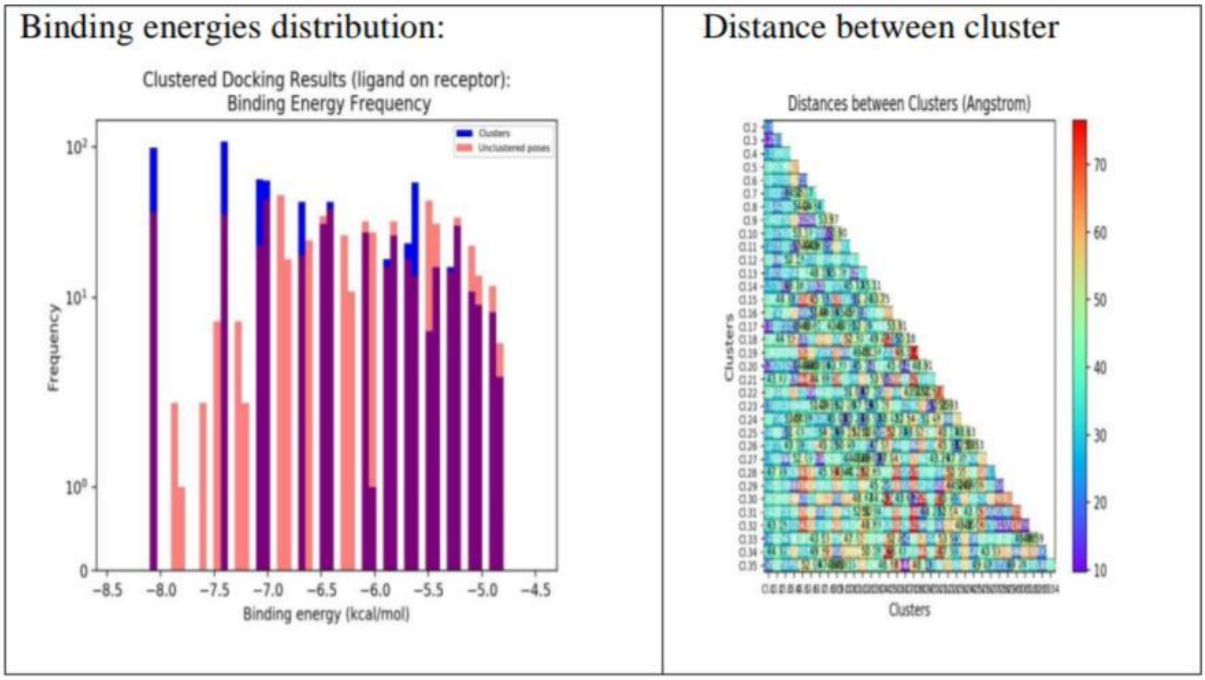
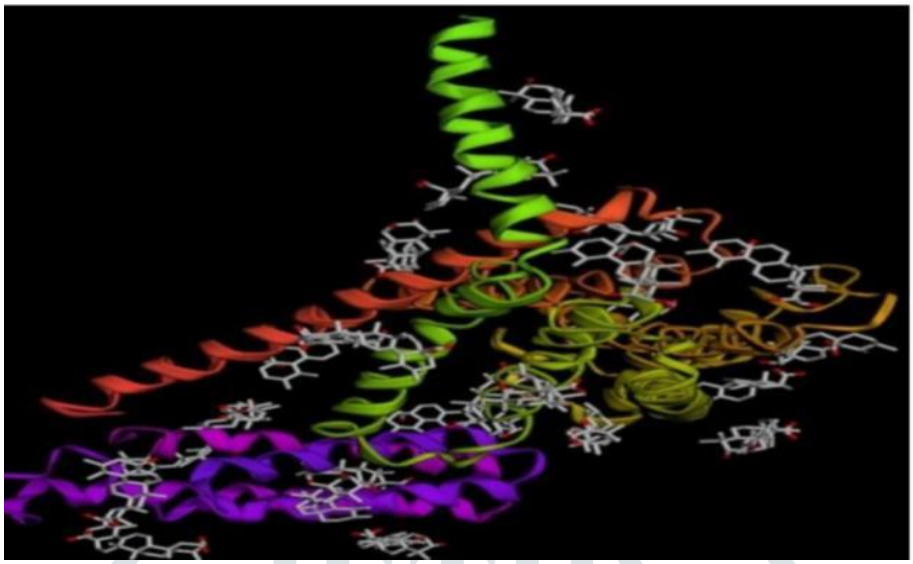


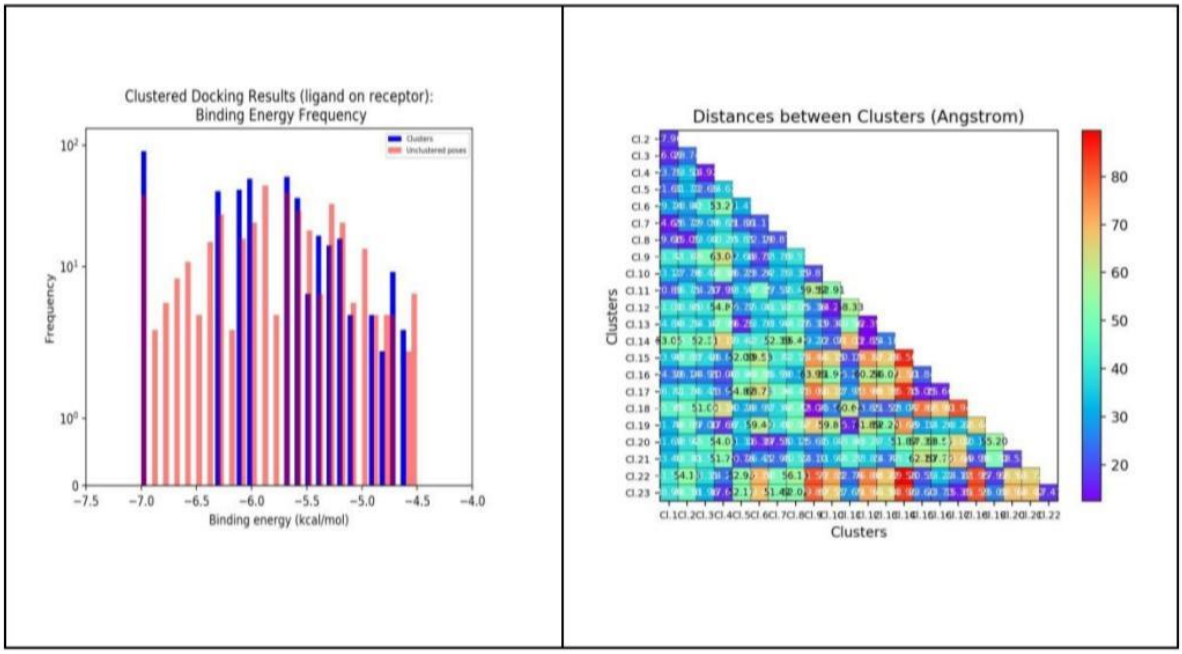
Cluster population

Binding energy (kcal/mol)	**Poses in cluster**	**Best pose**	**Binding site coordinates**
-8. 10	99	589	(24.11,60.46,25.53)
-7. 40	108	351	(33.23,58.44,43.67)
-7. 10	61	475	(32.63,53.37,23.16)
-7. 00	60	573	(1.03, 57.59,34.72)
-6. 70	43	135	(57.38,80.16,33.51)
-6. 50	12	454	(57.91,62.80,33.36)
-6. 50	19	432	(37.41,33.76,24.15)
-6. 40	43	511	(23.44,42.16,52.12)
-6. 10	8	137	(56.09,72.35,21.54)
-6. 10	19	375	(31.44,35.29,46.23)
-6. 00	1	642	(11.32,57.87,48.90)
-5. 90	9	83	(48.82,54.57,55.33)

4. **Receptor:4l6r(pdb)**
   Ligand:Corosolic acid (mol)



Binding energies distribution Distance between cluster:



(Visual representation of molecules created with 3Dmol)

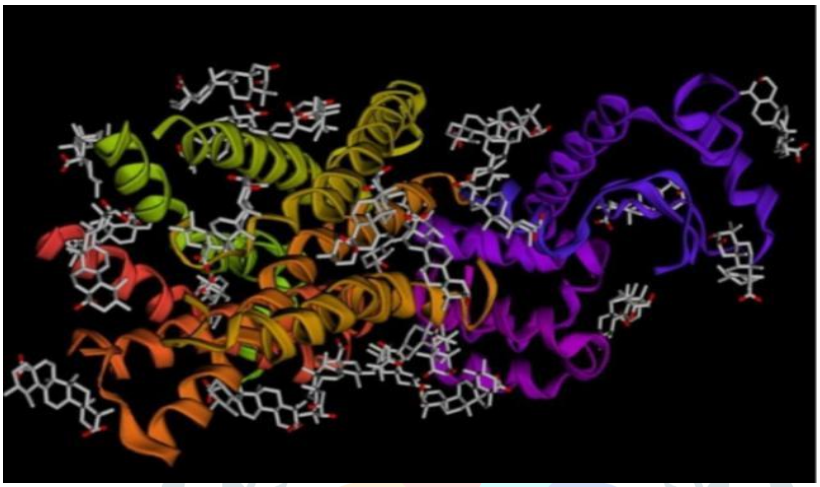
Cluster population:

Binding energy (kcal/mol)	**Poses in cluster**	**Best pose**	**Binding site coordinates**
-7. 00	90	351	(21.84, -5. 07,-27.48)
-6. 30	16	189	(26.67,-22. 37,-27.76)
-6. 30	26	117	(7.85, -9. 60,-20.97)
-6. 10	28	46	(8.57, -2. 26,-7.99)
-6. 10	15	362	(6.51, -2. 85,-42.54)
-6. 00	32	239	(34.56,-12. 01,-53.45)

-6. 00	21	283	(27.57, 1.83,-39.04)
-5. 70	2	245	(38.70,-14. 25,-31.77)
-5. 70	28	223	(23.08,-14. 71,-68.06)
-5. 70	25	159	(15.43,-25. 19,-53.01)
-5. 60	12	32	(18.87, 10.97,-14.53)
-5. 60	17	389	(2.05, -24. 43,-57.74)

5. **Receptor:5ee7(pdb)**

   Ligand:Corosolic acid (mol)



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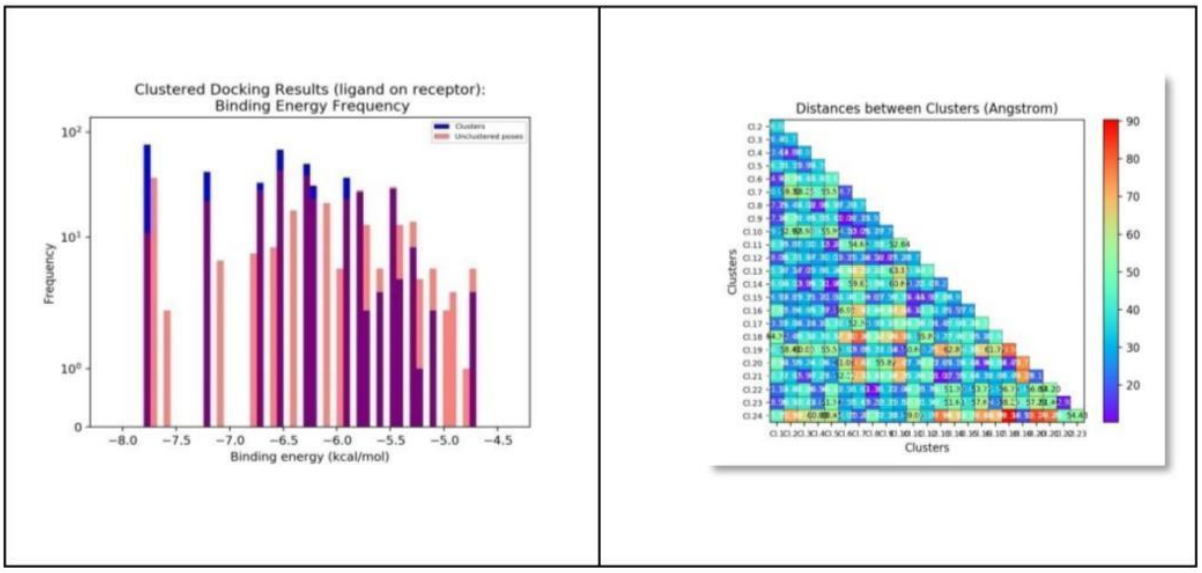

Cluster population:

Binding energy (kcal/mol)	Poses in cluster	Best pose	Binding site coordinates
-7.80	76	35	(-20.32,4.21, -21. 78)
-7. 20	42	51	(-6.44, 19.62,-51.25)
-6. 70	33	382	(-29.32, -1. 76,-45.87)
-6. 50	19	28	(-9.14, 18.45,-36.66)
-6. 50	31	371	(-12.36,-11.25,53.70)
-6. 50	18	172	(-19.25, -6. 19,-11.14)
-6. 30	50	208	(-5.32, -7. 93,1.26)
-6. 20	19	246	(-5.46, 12.15,-25.91)
-6. 20	12	113	(-15.17,-11.80,18.40)
-5. 90	20	243	(0.51, 3.47,-1.28)
-5. 90	17	290	(-0.44, -5. 47,-53.15)
-5. 80	11	114	(-5.72, -5. 98,-24.92)

CONCLUSION

Drug design is the process of coming up with new treatments based on an understanding of a biological target. This overview examines the fundamentals of drug design, various drug design methodologies, lead finding, lead modification, and various drug discovery techniques. Bioisosterism is a crucial factor. alteration strategy that has been proven effective to reduce toxicity or change the It may significantly affect how a lead's pharmakinetics are altered. activity of a lead. The process of finding new drugs through laboratory testing takes a long time and costs a lot of money in contrast to computational techniques.

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