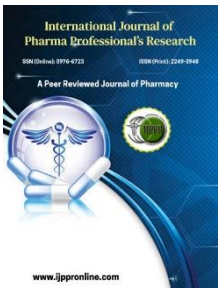
INTERNATIONAL JOURNAL OF PHARMA PROFESSIONAL'S RESEARCH



An overview of Quinazolines: Applicability of molecular docking in Cancer therapy

Manoj Kumar Yadav*[1], Triloki Prasad*[2], Rubal Rathi[3], Vivek Kumar Kushwaha[4], Vinay Kumar[5], Sachin Kumar Yadav[6], Deepak kumar[7], Satyam Rai[8]

[1]MIET, Meerut

[2,3]MIIT college of Pharmacy, Ghat Road Meerut

[5]KN Modi Institute of Pharmaceutical Education and Research, Modinagar

[4,7,8]Swami Sahazanand College of Pharmacy, Harraiya, Azamgarh [6]Parmarth College of Pharmacy, Hapur

Keywords: Quinazoline, Molecular docking, Anti-cancer activity, Computer-Aided Drug Design.

Corresponding Author-
Triloki Prasad,
MIIT College of Pharmacy, Ghat road Meerut, UP

Email: -
Phone no: -

ABSTRACT:
Medicinal chemistry is distracted with the elaboration, discovery, confirmation of physical and chemical approaches, and the synthesis in laboratory. Quinazoline derivatives occupy crucial positions in modern medicinal chemistry and possess established application as medicine. Several researches have been accomplished on derivatives of the quinazoline for different many pharmacological activity are reported recently. The most important process molecular docking modification is the preliminary step in the drug designing of novel drugs. The main aim of this review is to quiz or examine recently molecular docking strategies used in medicinal chemistry and in the drug discovery, Investigating the advancement in the field of computer aided drug design, and important role play through the ligand-based method. The drug discovery and the field of CADD is fast flourishing area that has seen various successes. Several giant pharmaceutical industries, in additionally to academia, adopt computer-aided drug design and discovery for drug lead discovery.

Introduction:
Cancer is leading cause of human death worldwide because of its uncontrolled and rapid proliferation properties **[1]** Cancer is become leading cause of death in overall world, and in 2008 as it accounted for 7.6 million deaths and to continue the estimated 11 million deaths in 2030 **[2]** Cancer is called as malignant tumor

and today cancer is the most danger disease all over the world **[3]**. Chemotherapy, Radiotherapy and the surgery are three options for cancer treatment and the chemotherapy drugs provide an alternate or unique method for the treatment of cancer **[4,5]** A major claiming for antineoplastic drugs is design or develop new drug that will more selectivity and inhibited the cancer cells to avoid the side effect on normal cancer cells. In current treatment of cancer, the targeted cancer therapy may be more usefully or effective, due to less harmfull to normal cancer cells and more effective and safe than cytotoxic chemotherapies **[6, 7]** ICRA propound that the global cancer burden will increase up to 13 million death and 21.7 million cases by the year 2030.[8] Cancer is a lethal uncontrolled disease mainly in developing countries. In 2030 the mortality rates will be increased to be 13.1 million deaths of people. [9] The disease of cancer may be the effect of people all ages and tend to increase with age, such cancer is a killer disease caused by uncontrolled or abnormalities (genetic material) growth of cells. The cells of cancer are characterized by three properties such as a lake of differentiation, uncontrolled proliferation, and the capability to invade various tissues in another location in the body**[10].** There is always a real challenge for oncologists and chemists with cancer chemotherapy and anti-tumor agents. This is due to acute toxicity, non-selectivity, and the cellular drug resistance of various anticancer agents. So, there is a continuing requirement for developing and designing new chemotherapeutic agents for cancer treatment**. [11]**

MAJOR FACTOR THAT INFLUENCE CANCER RISK:

DIET: Diet also the leading cause of death thought to account the diet is one-third of risk of cancer[12].

ALCOHOLIC BEVERAGES: Alcohol Beverages cause inflammation, cancer of liver and also cirrhosis of the liver. Alcohol is a most important cause of esophageal and oral cancer and possibly contributes to colorectal cancer. **[13, 14, 15]** Tobacco used to expose 3209 people all over the world in 1990, if this smoking rage continues to increase, then 10 million deaths per year a few decades from now. **[16]** All over the world the total number of deaths by cancer is caused by smoking in develop and developed countries will be about sixty million deaths per year. **[17]**

CAUSE AND PREVENTION OF CANCER: Cancer develops when normal cells grow out of control. All the cancer cells in our body grow rather than die and continue to grow and divide into many parts and again divide and form new abnormal cells. Some cancer cells also travel to other parts of the body by blood circulation and metastasis, where they start to grow. We can still recognize breast cancer when breast cancer cells spread to the liver by circulation. Basically, cancer cells develop from the normal cell due to damage to DNA. Most of the time whenever DNA was damaged, the body can repair it, but DNA cannot be repaired in cancer cells. Sometimes exposure to smoke causes a person's DNA to deteriorate. There are some cancers that do not make tumor, such as blood cancer. Instead, blood cancer cells involve in blood formi9ng organ and circulate by other tissue where they grow. Many types of cancer cells behavior differently. We can reduce the risk of cancer by changing our lifestyle like we stop smoking and low fat diet. If we come to know about cancer early, we can get cancer treatment done well and we can come out of danger**. [18]** In the treatment of cancer the quinazoline play most important role in design and synthesis of parent moiety. Quinazoline(Fig.)1 has a six membered aromatic ring with benzene and pirimidine ring fused attached to it. Quinazoline is a bicyclic compound, earlier also known as benzo- 1,3-

diazene and it was first prepared by Gabriel in laboratory. **[19]**

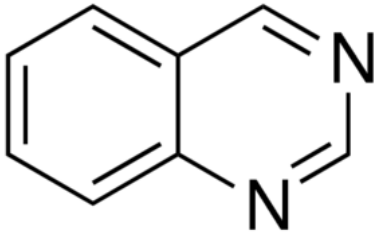


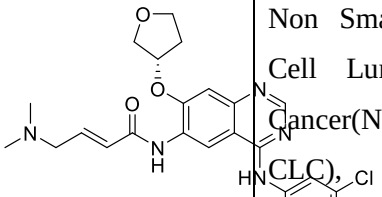
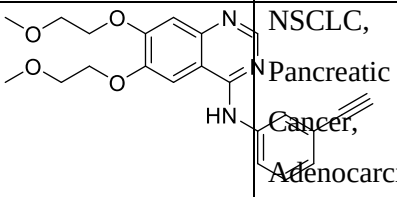
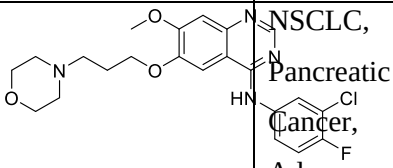
Figure 1. Quinazoline

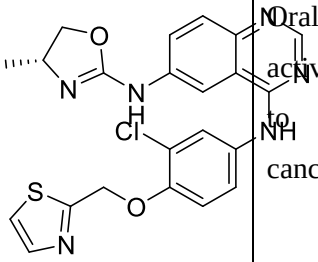
Quinazoline is one of the important heterocycles in chemistry and the quinazoline possesses have various biological properties such as antifungal, anti-inflammatory,, analgesic activity, and the anti-cancer activity etc. **(**Fig. 2**).**

Figure 2: Biological importance of Quinazolines

In these activities of quinazoline we only focus as anti-cancer property. The so many quinazolines derived anti-cancer drugs are available for the treatment. These types are given below in table.1. [**20**]

Table1: Some types of anti-cancer drugs

Anti-cancer Drugs	**Structure**	**Uses**
AFATANIB(N-[4-[(3-chloro-4-fluorophenyl) amino]-7-[[(3S)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4-(dimethylamino)-,(2E)-, (2Z)-2-butenedioate (1 :2),)		Non Small Cell Lung Cancer(NSCLC), Breast Cancer, Head and Neack Cancer
ERLOTINIB (*N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy) quinazolin-4-amine)		NSCLC, Pancreatic Cancer, Adenocarcinoma
GEFITINIB **(**N-(3-chloro-4-fluorophenyl) -7-methoxy-6-(3-morpholin-4-ylpropoxy)quinazolin-4-amine**)**		NSCLC, Pancreatic Cancer, Adenocarcinoma

VARLATINIB ((R)-N4-[3-Chloro-4-(thiazol-2-ylmethoxy)-phenyl]-N6-(4-methyl-4,5-dihydro-oxazol-2-yl)-quinazoline-4,6-diamine)		Orally active Drug to treat cancer	

Integration of computational and experimental strategies has been very important in the identification and development of quinazoline compounds. In modern drug design, the molecular docking tool explores the ligand authentication adopted within the binding site of macromolecular target. This approach also estimates the ligand- receptor binding free energy by evaluating critical phenomena involved in the intermolecular recognition process. Today we have a lot of docking algorithms from which we understand the advantages and limitations of each method in the development of generation of relevant results and the effective strategies**. [21]**

1. Structure-Based Drug Design (SBDD): We usually derive the term structure based drug design by computational or experimental modeling that we use to refer to protected data such as macromolecular targets. The purpose is to conceive ligand with specific steriochemical and electrostatic attribute to achieve high receptor binding affinity. The availability of three dimension structure approves a diligent inspection of the binding sites topology such as sub pockets, cavities, and the presence of clefts. Electrostatic properties like charge distribution, can also be thoughtfully examined. Current structure based drug design tools permit for the design of ligand containing the required features for efficient modulation of the target receptor. [**22,23**]

2. Molecular Docking: Molecular docking is the most commonly used tool in structure-based drug design because its accuracy is very predictable the authentication of small molecule ligands within the applicable target binding sites (Figure 2). **[24]** Afterward the advancement of the first algorithm in 1980, the molecular docking become an important tool in drug discovery. For example, investigation involved molecular events such as corresponding intermolecular interaction and ligand binding modes that stabilized the ligand receptor complex can be conveniently performed. Additionally the molecular docking algorithms execute quantitative prediction of binding energetics, provides ranking of the docked compound depend on the binding affinity of ligand receptor complex**.** [**25,26**] The identification of the most likely binding conformations requires two steps:

(i) Analysis of large authorization space representing many potential binding sites.

(ii) Accurate forecasting of the interaction energy associated with each of the forecast binding authorization**. [27]** Molecular docking programs performs these tasks by cyclical process, in which the ligand confirmation is appraise through specific scoring function. [**26,28**]

Molecular docking follows the following process criteria:

1. Conformational Search
2. Evaluation of Binding Energetics
3. Covalent Bonds in Molecular Docking
4. Molecular Dynamics
5. Structural Water

6. Protein-Protein Interaction Inhibitors and Molecular Docking. **[29, 30, 31, 32, 33, 34]**

TYPES OF DOCKING:

1. Rigid or lock and key model: In lock and key model, During docking the internal geometry of the receptor and ligands is kept constant.

2. Flexible docking: In this docking, the energy for different conformations of the ligand is calculated in the protein and the side chains and the ligands of the protein are kept flexible.

APPLICATION OF DOCKING:

1.Hit identifications: Combined docking with a scoring function is also used, but this docking is used to identify molecules to screen big database of potential drugs in silico to identify molecules that are likely to bind to protein target of interest.

2. Lead optimization: Docking can be used to predict the relative oeientation of a ligand that binds to a protein. This information may be used to design selectively and more potent analogs.

3. Bioremediation: Protein-ligand docking can also be used to predict pollutants can be degraded by enzymes. **[35]**

DOCKING SOFTWARE USED IN STUDY:

1.CCDC (Cambridge crystallography data center) GOLD: (Genetic optimization for ligand docking) is a genetic algorithm for docking flexible ligands into protein binding sites. Gold is supplied as part of the gold suite such as included two software like-Goldmine and Hermes.

2. Schrodinger Glide: Glide docks flexible ligand/ flexible receptor structure by the rapid sampling of the orientation, authorization, and positional degrees of freedom of the ligand.

3. Auto-Dock Vina: Auto-dock vina provides high performance and increased accuracy and easy for multicore capacity. Basically the autodock vina is comparatively open source program for virtual screening and drug discovery. In 2010 Auto-dock vina was designed by doctor Oleg Trott in the molecular graphics research lab**.[36]**

SOME EXAMPLES OF QUINAZOLINE DERIVATIVES PREPARED BY DOCKING SOFTWARE:

Mathew. J Alex et.al 2009: : In this work the scientist Mathew identified medicines used against breast cancer. When the receptor was docked with the drug the energy values obtained were Torimefene (fig.3) and Raloxifene (fig.4).When the modified drug was docked against the same receptor the energy value observed were Toremifene analog 6 (181.0) and the Raloxifene analog 7 (175.0). The scientist Mathew came to the end andconcluded that the modified medicines was better than the commercial drugs available in the market.

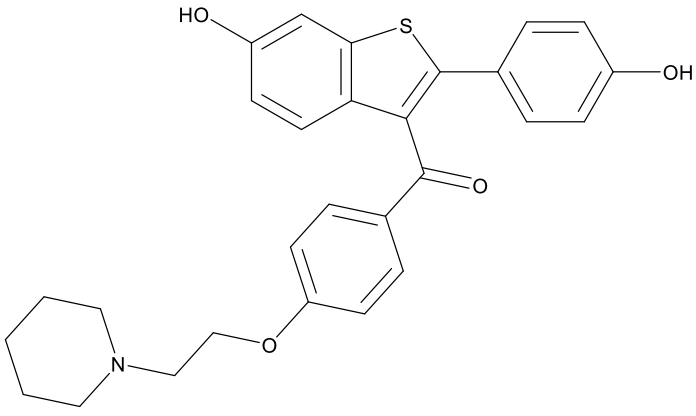


Figure 3: Raloxifene

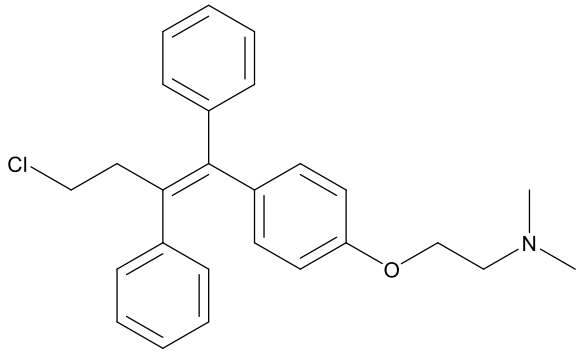


Figure 4: Torimefene

They further concluded that in future research work of the ADME/T such as Absorption, Distribution, Metabolism, Excretion/Toxicity properties of these compound can becalculated using the commercial absorption, Distribution, Metabolism, and the excretion/ toxicity approaches available this reducing the time and cost in drug discovery process. **[37]**

Speck Planche et.al 2011: In their work we elaborate the first multi-target tools for the planning and theb developed the first multi-target approach for the planning and forecasting of anti-prostate cancer agents alongside various cell lines. This planning represents a fragments depends- Quantitative Structure Activity Relationship model that used a heterogeneous database of compound for the answerable anti PC activity based on the many types of PC cell lines. In these 6 molecules were deliberates favorable concerning fragments for anti-PC activity. **[38]**

Adebayo A. et.al 2013: formulated
Some of the anticancer complex of Ru (2) like as the Rapta- depends complex such as –(Ru(n6-p-cymene) L2 (PTA) and those which unusual ligands were designed. In cancer chemotherapy, the complexes that are based on metal and which contain carbonic anticancer are very much above the essence flourishing application of cis-platin derivatives have been perceived as the easiest means to prevent the increasing growth of cancer. The introduction of unusual ligands was found to extensively enhance the activity most of the complex study. Strong interaction were detected for the expected binding sites and the orientation of the complexes within the binding site by the 3 methods of docking. Autodock and Gold software od docking have better relationship with each other and the high level disparities beetwen Glide and the othjer docking tools was bounded to bias towards the steric hindrance in the study. [**39**]

Tiwary et.al 2014: : Petrform in-silico study and the molecular docking to appraise the drug campaigm of some quinazoline -4-(3H)-ones as the inhibitors of human dihydrofolate reductase enzyme. This enzyme play an important role in the synthesis of purine and the pyrimidine, so this enzyme are one of the good target for cancer medicines.It also preserve intracellular biochemically active reduced folate pools. [**40**]

Widiyana Anita Puspa et.al 2016: used quinazoline derivatives to design a lot of new active soul as cytotoxic agents through selective COX-2 inhibition. The study suggested that the possible activity of the quinazoline derivative got accelerate through substitution in position two and three of the quinazolinone. One of the protein targets of cancer as selective cyclooxygenase-2. Selective COX-2 inhibitors was the regulator of cell augmentation or proliferation [**41**]

Budiati T et.al 2016: Synthesized series of derivatives 4 -chlorophenylquinazoline-4-[3H]- ones,

with yield % of 65% to 86%. The molecular docking study of the developed pharmacophore significantly that the novel compounds can work as COX-2 inhibitor and can be used in the future to develop and design new drugs. [**42**]

Al-Shamary et.al 2017: performed molecular docking study to receive a percepcivity into the binding modes of the compound with butyrylcholinesterase enzyme, cyclin dependent kinase-2, and the GABA. Basically has various activities such as anti-cancer and the anti-oxidant, anti-bacterial etc. so, the quinazoline is an important part of the medicinal compounds. In the end, it was concluded that thioxoquinazoline activity should be further searched because thioxoquinazoline was a very good anti-tumor agents. **[43]**

Asadi. Parvin et.al.2017: synthesized and studied antimicrobial and cytotoxic activities of the newly developed sequence of novel hybrids bearing quinazolinone, and the imidazole moiety etc. The Cytotoxic activities of the synthesized compounds were performed on [MCF-7] Breast cancer cell line of human through using the MTT assay.

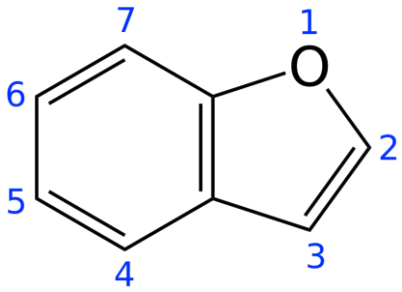


Figure 5: Benzofuran

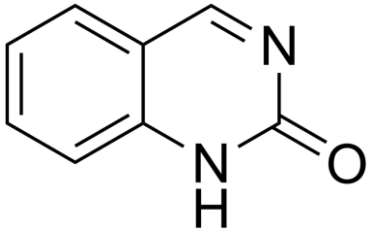


Figure 6: 2-Quinazolinone

While the docking studies of anticancer derivatives derivatives were accomplished an aromatase enzyme. Interestingly, study revealed that compound with two halogen atom on benzofuran and the quinazolinenone were attempt to the most active alongside whole the tested strains of the microorganism. [**44**]

N.Cabrera et.al.2019: We used molecular modeling simulation for the Pin1(peptidyl-prolyl cis-trans isomerase NIMA-interacting 1) inhibition through organic compounds bearing an aromatic rings in their structure was appraise through using the quantitative structure activity relationship tools. Pin1 is straightly involve in cell cycle regulation of cancer because catalyzes the cis-trans isomerization of prolyl amide bonds in proteins. A total of 51 compounds, divided randomly as training (78%) and test set (22%), were used in the calculations and the topological descriptor was employed for the model construction. Models were captured through various regression tools like-MLR, and the RF etc. Observent the docking simulation, a binding affinity between the molecules and the active site for the Pin1 inhibition into the protein was estimated through the calculation of the binding free energy (BE), with values in the range of−5.55 to−8.00 kcal/mol. [**45**]

Mehta et al.2019: In their work to achieve the molecular docking investigation and Perform molecular docking analysis and established that the compound observed good docked score with good potency and resembling to the standard drug and native ligand of the protein. The finding of the docking resembling with the assay of anticancer activity.

Docking information stay in awesome comparability with the conclusion of anticancer activity and these molecules can be used as a lead in the design of new anticancer agents. Further the synthesized quinazoline derivatives i.e compound showed promising antimicrobial activity due to appearance of electron releasing group at meta position of the substituted benzylidene nucleus and comparable to the control drug. In case of anticancer activity indicated that compound displayed moderate anticancer activity towards human colorectal carcinoma (HCC) and mouse leukemic monocytes macrophages cancer cell lines due to the appearance of EWG on the substituted benzylidene nucleus. [**46**]

A. Misra et.al 2020: In their work prepared a new series of pyrimidine and quinazoline analog of 1,5-benzodiazepines via its nitrile-derived amidoximes and nitrilium ions, separately using one pot Domino reaction with DMAD in the appearance of DABCO catalyst and benzanilide in appearance of Tf2O and 2-chloropyridine. The ready molecules were tested for their biological property namely apoptotic, Antiproliferative effects by cell cycle arrest using breast cancer cell lines of human. It was found that designed compound demonstrate inhibitory effects on cell proliferation in a concentration hanging fashion (20-100lg/ml). Autodock 4.2.6 molecular modeling tool used to achieve molecular docking on the human epidermal evolution factor receptor (HER-2). [**47**]

ACTION OF QUINAZOLINE AS ANTI-CANCER AGENT:

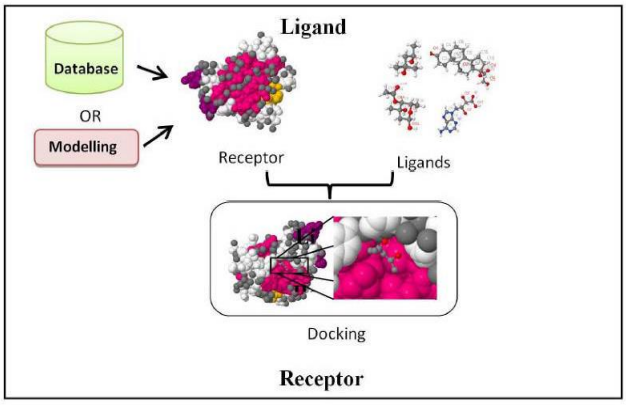
Quinazoline is one the most important scaffold among natural and synthetic bioactive compound. Although the first natural quinazoline-based alkaloid, Paganini, was discovered in 1888, the literature about quinazoline chemistry effectively began only in the 1940s. **[48]** Quinazoline scaffold parallel the purines nucleus and the petridine one. As the repercussion, some compound able to inhibited the purine **[49],** folic acid **[50,51]** and the metabolic pathways have been discovered. During the years, the efforts of the medicinal chemists have allowed the identification of a large number of drugs, including antiparasite and antimicrobial **[52,53],** antiviral, anti-inflammatory **[54,55],** bronchodilators **[56,57],** antihypertensive **[58,59],** anticancer compounds. **[60,61]** Currently we can use many cytotoxic medicines alone and also with any other medicines for the treatment of cancer, and variety of these medicines are currently being run in different phase of clinical trials. Cytotoxic are not able to discriminate between cancer cells and the normal cells as these drugs are associated with many deficiency, so these medicines cause various danger side effect. These anti-neoplastic drugs are associated with many Those anti-cancer drugs in current clinical trials are associated with short half-life, angiogenesis, and the organ toxicity etc. And a noticeable tendency to induce resistance in target cells. **[62**] that is why there are constant efforts to prevent people from cancer and anticancer drug with minimal side effects. Many different tools are being used for the treatment of cancer. Some comprise the targeting of specific molecular alterations that occurs in tumor cells. This tool has yielded various molecules with significant clinical activity and minimum toxicity. **[63, 64]** The tools used in cancer chemotherapy inhibit the protein kinase enzyme in tumour growth and also inhibited the transcription of DNA. Afterall, various drawbacks have been documented like- participation of a number of enzyme such as topoisomerase 1 and topoisomerase 2, and the ribonucletide reductase, and the several stages of cancer, the cells of cancer survival even under anaerobic condition and the problem of MDR (Multi-Drug Resistance) that develop in cells of cancer. **[65,66,67,68]** The heterocyclic compounds was investigated bioactive molecule and are

considered important synthetic target for the development of novel chemotherapeutic agents. **[69,70,71]** Quinazoline is one of the most important heterocyclic compound foer which considerable research has been done in order to examine of biomedical applications. **[72]**

MOLECULAR DOCKING: Molecular docking is a method that anticipants the favored orientation of ligand against protein or receptor to make a stable complex. [73] The main object of molecular docking is to accomplish an optimized confirmation and computationally stimulate the molecular identification process so that the free energy of the overall system is minimized. The process of discovery of a new drug is a very difficult task. Modern drug discovery mainly depends on In-silico–chemical-biological approach. The use of computer-aided techniques in development and drug discovery process is rapidly gaining appreciation, popularity, and the implementation.

COMPUTER-AIDED DRUG DISCOVERY (CADD):

1. Use of computational ability to streamline the development process and drug discovery.
2. Advantages of biological and chemical information about ligand and target to discover and optimize novel drugs.



3. Designing of in-silico filters to get rid of chemical compounds with unwanted properties the poor Absorption, Distribution, Metabolism, Excretion and Toxicity, and the poor activity and select the most promising candidates.
4. Virtual screening is applied to find out novel drug candidates from various chemical scaffolds by exploring databases. [**74,75**]

DIFFERENT TYPES OF INTERACTIONS:

Interaction forces are generally separated into four classes:

(1) Electrostatic forces: charged –dipole, dipole-dipole, and the charge-charge.

(2) Electrodynamics forces: Vander walls interaction.

(3) Steric forces caused by entropy.

(4) Solvent related forces: hydrophobic interaction and Hydrogen bond. **[76,77,89-99]**

MOLECULAR DOCKING: Molecular docking can be unattached into two parts such as follows,

SEARCH ALGORITHM: The algorithmThe algorithm have bring out an optimum number of configuration that grant by experimentation methods adjudging binding modes. Many algorithms applied for docking analysis such as distance geometry, systematic research Monte Carlo, Point complementary, etc. **[78-79, 100-102]**

SCORING FUNCTION: The scoring function furnishes a mode to rank appointment of ligand commensurate to some other, And the core have authorization directly to the binding affinity of the ligands. Directly or receptor for

the protein so, that the good scoring ligand was the better binders. The scoring function must be knowledge based, molecular mechanics, , and empirical- based. Scoring was compiled of 3 many expressions applicative to drug design, and the docking;

(1) Prompted configuration ranking through the docking search.

(2) Ranking distinctive ligand against the protein.

(3) One or more ligand rankings alongside distinctive protein through their selectivity by their selectivity and specificity **[80,81,82,83]**

MAJOR STEP INVOLVED IN MECHANICS OF MOLECULAR DOCKING:

Molecular docking is a process in which interaction occurs between two molecules and the consist of macromolecule protein receptors, and the ligand which can work as inhibitor. So, the various process involve in the docking process such as follows:

PREPARATION OF PROTEIN: Three dimensional structures of protein have to be retrieved from Protein Data Bank (PDB) and after the retrieved the structures have to be preprocessed. This should permitted take off the water molecule of the cavity, filling the missing residue, stabilizing the charges, and the generation thee side chain.

ACTIVE SITE PREDICTION: The active site of protein is expected, after the preparation of protein. The receptor The receptor potency possesses a lot of active sites merely one of the conceren have to be picked out.Basically the water molecule and heteroatoms are takeoff if presents. **[84,85]**

PREPARATION OF LIGANDS: Ligand can be recovered to various various database such as pubchem etc., and can be sketched appeartaining the chemsketch software. Stretch picking out of the ligands the Lipinsky rule of five have been utilized. It promise altitudinous chances of success and default due to drug likeness from molecules enduring through with two or more than of complying rule set promise the or more than of complying rules.For the choice of a ligand allowing to the LIPINSKY'S RULE:

(1) Less than 5 hydrogen bond donors.

(2) Less than 10 hydrogen bond acceptors.

(3) Molar refractivity should be between 40 to 130.

(4) High lipophilicity represent as LogP, not over five.

(5)Molecular mass less than 500 Da.

DOCKING: Ligand is docked against the protein and the interactions are analyzed. The scoring function gives a score based on the best-docked ligand complex that is picked out.

DOCKING SOFTWARE: Various docking programs have been formulated throughout the last twenty years. **Table (1)** summarizes basic features like-endorsed platforms, license conditions, algorithms, and scoring functions of currently available docking tools. While **Table (2)** summarizes the cons and pros of existing protein-ligand docking tools based on their codes.

Characteristic of protein-ligand docking tools: (TABLE-1)

Serial No./Entry	program reference	Licence terms	Company/Designer	Docking approaches	Supported platforms	Scoring function
1	AUTODOCK (5)	Free for academic uses	D. S. Goodsell and A. J. Olson The Scripps Research institute	Genetic algorithm Lamarckian genetic algorithm Simulated Annealing	Unix, Mac OS X, Linux, SGI	Force field method
2	DOCK (6)	Free for academic uses	I. Kuntz University of California, San Francisco	Shape fitting (sphere sets)	, Linux, Sun, IBM AIX, Unix ,Mac OS X, Windows	GB/SA solvation scoring, ChemScore
3	FlexX [7]	Commercial free eval	T. Lengauer and M. Rarey	Incremental	Unix, SGI, Sun	Screen Score, FlexXScore,
		uation	Bio Solve IT	Construction	Windows, Linux	PLP, Drug Score
4	FRED [8]	Free for academics use	Open Eye Scientific Software	Shape fitting (Gaussian)	Unix, Linux, SGI, Mac OS X, IBM AIX, Windows	Screen Score, PLP, Gaussian shape score, user defined
5	Glide [9]	Commercial	Schrödinger Inc.	Monte Carlo Sampling	Unix, Linux, SGI, IBM AIX	Glide Score, Glide Comp
6	GOLD [10]	Commercial free evaluation	Cambridge Crystallographic Data Centre	Genetic Algorithm	Linux, SGI, Sun, IBM, Windows	Gold Score, Chem Score user defined

7	Ligand Fit [11]	Commercial	Accelrys Inc.	Monte Carlo Sampling	Linux, SGI, IBM AIX	LigScore, PLP, PMF

Cons and Pros of docking tools such as folloes: (TABLE-2) [**86,87,88**]

PROGRAM	**Cons**	**Pros**
GOLD	Ranking very polar ligands Ranking ligands in large cavities	Small binding sites Small hydrophobic ligands
FRED	Small polar buried ligands.	Large binding sites Flexible ligands Small hydrophobic ligands High speed
QXP	Sensitivity to input coordinates	Optimizing known binding modes
SURFLEX	Low speed for large ligands	Large and opened cavities Small binding sites Very flexible ligands
DOCK	Flexible ligands Highly polar ligands	Small binding sites Opened cavities Small hydrophobic ligands
FLEXX	Very flexible ligands	Small binding sites Small hydrophobic ligands
SLIDE	Sensitivity to input coordinates	Side chain flexibility

Conclusion: In this review we discussed the importance of Molecular Docking in anti-cancer therapy by using the Quinazoline and its derivatives. The various modification around the fused ring, quinazoline, and subsequently evaluate their usefulness in treating cancer. Quinazoline, being the central body of the pharmacophores holds different types of substituents. Based on various physicochemical properties, they exerted a diversified range of therapeutic efficacy.

Thus we can conclude that this review will provide the understanding of Molecular Docking in quinazoline and its derivatives to cure cancer, also design new Docking derivatives. Molecular Docking provides an array of valuable tools for drug design and analysis. Simple visualization of molecules and easy access to structural databases has become essential components on the desktop of the medicinal chemistry.

References:

1. Tsai C, Nussinov R. The molecular basis of targeting protein kinases in cancer therapeutics. Seminars in Cancer Biology. 2013; 23(4):235-242.

2. Sandor Eckhardt B. Recent Progress in the Development of Anticancer Agents. Current Medicinal Chemistry-Anti-Cancer Agents. 2002; 2(3):419-439.

3. Lee, C. W.; Hong, D. H.; Han, S. B.; Jong, S. H.; Kim, H. C.; Fine, R. L.; Lee, S. H.; Kim, H. M. Biochem. Pharmacol. 2002, 64, 473.

4. Asai N, Aoshima M, Ohkuni Y, Otsuka Y, Kaneko N Indian J Palliat Care. 2012 Jan; 18(1):40-4.

5. S. Singhal, B.S. Chakraborty, Signal Detection of Docetaxel in Canadian Spontaneous Adverse Event Reports, J. Pharm. Res., (2012), Vol. 5, Issue 2, 1070.

6. Macri G, Greco A, Gallo A, Fusconi M, Marinelli C, de Vincentiis M. Use of electrochemotherapy in a case of neck skin metastasis of oral squamous cell carcinoma: Case report and considerations. Head & Neck. 2014(36) E86-E90.

7. M. Mubeen, S.G. Kini, A Review on: The Design and Development of EGFR

Tyrosine Kinase Inhibitors in Cancer Therapy, Int. J.Ther. Appl., 2012(5)29-37.

8. Kawakita Y, Miwa K, Seto M, Banno H, Ohta Y, Tamura T et al. Design and synthesis of pyrrolo[3,2-d]pyrimidine HER2/EGFR dual inhibitors: Improvement of the physicochemical and pharmacokinetic profiles for potent in vivo anti-tumor efficacy. Bioorganic & Medicinal Chemistry. 2012; 20(20):6171-6180.

9. P.N. Dube, M.N. Waghmare, S.N. Mokale, Chem. Biol. Drug Des. (2016) 87 608.

10. H.A. Bhuvaa, S.G.J. Kinib, Mol. Graph. Mod. (2010) 29, 32.

11. Hussain M, Ansari M, Yadav N, Gupta P, Gupta A, Saxena R et al. Design and synthesis of ERα/ERβ selective coumarin and chromene derivatives as potential anti-breast cancer and anti-osteoporotic agents. RSC Adv. 2014; 4(17):8828-8845.

12. Doll R, Peto R. The Causes of Cancer: Quantitative Estimates of Avoidable Risks of Cancer in the United States Today. JNCI: Journal of the National Cancer Institute. 1981; 66(6):1192-1308.

13. International Agency for Research on Cancer, *Alcohol Drinking* IARC Monograph Lyon, France: International Agency for Research on Cancer, 1988.

14. Glynn S, Albanes D. Folate and cancer: A review of the literature. Nutrition and Cancer. 1994; 22(2):101-119.

15. Giovannucci E, Rimm E, Ascherio A, Stampfer M, Colditz G, Willett W. Alcohol, Low-Methionine-Low-Folate Diets, and Risk of Colon Cancer in Men. JNCI Journal of the National Cancer Institute. 1995; 87(4):265-273.

16. Peto R, Boreham J, Lopez A, Thun M, Heath C. Mortality from tobacco in developed countries: indirect estimation from national vital statistics. The Lancet. 1992; 339(8804):1268-1278.

17. Peto R, Lopez AD, Boreham J, Thun M, Heath Jr. C, *Mortality from Smoking in Developed Countries 1950-2000*,Oxford: Oxford University Press, 1994.

18. Sudhakar A. History of Cancer, Ancient and Modern Treatment Methods. Journal of

Cancer Science & Therapy. 2009; 01(02): i-iv.

19. Gabriel S. Ueber das Chinazolin. Berichte der deutschen chemischen Gesellschaft. 1903; 36(1):800-813.

20. Kavitha k et al. *World journal of pharmacy and pharmaceutical sciences*, 2018 vol.7, issue 4.

21. 15. Ferreira L, dos Santos R, Oliva G, Andricopulo A. Molecular Docking and Structure-Based Drug Design Strategies. Molecules. 2015; 20(7):13384-13421.

22. Blaney, J. A very short history of structure-based design: How did we get here and where do we need to go: *J. Comput. Aided Mol. Des.* 2012, 26, 13–14.

23. Mandal, S.; Moudgil, M.N.; Mandal, S.K. Rational drug design, *Eur. J. Pharmacol*, 2009,625, 90–100.

24. Meng X, Zhang H, Mezei M, Cui M. Molecular Docking: A Powerful Approach for Structure-Based Drug Discovery. Current Computer Aided-Drug Design. 2011; 7(2):146-157.

25. Lopez-Vallejo F, Caulfield T, Martinez-Mayorga K, A. Giulianotti M, Nefzi A, A. Houghten R et al. Integrating Virtual Screening and Combinatorial Chemistry for Accelerated Drug Discovery. Combinatorial Chemistry & High Throughput Screening. 2011; 14(6):475-487.

26. Huang S, Zou X. Advances and Challenges in Protein-Ligand Docking. International Journal of Molecular Sciences. 2010; 11(8):3016-3034.

27. Kapetanovic I. Computer-aided drug discovery and development (CADDD): In silico-chemico-biological approach. Chemico-Biological Interactions. 2008; 171(2):165-176.

28. Yuriev, E.; Agostino, M.; Ramsland, P.A. Challenges and advances in computational docking, *J. Mol. Recognit*. 2011, 24, 149–164.

29. Sousa S, Fernandes P, Ramos M. Protein-ligand docking: Current status and future challenges. Proteins: Structure, Function, and Bioinformatics. 2006; 65(1):15-26.

30. Foloppe N, Hubbard R. Towards Predictive Ligand Design With Free-Energy Based Computational Methods? Current Medicinal Chemistry. 2006; 13(29):3583-3608.

31. Kumalo H, Bhakat S, Soliman M. Theory and Applications of Covalent Docking in Drug Discovery: Merits and Pitfalls. Molecules. 2015; 20(2):1984-2000.

32. Lin J. Accommodating Protein Flexibility for Structure-Based Drug Design. Current Topics in Medicinal Chemistry. 2011; 11(2):171-178.

33. Sousa S, Ribeiro A, Coimbra J, Neves R, Martins S, Moorthy N et al. Protein-Ligand Docking in the New Millennium – A Retrospective of 10 Years in the Field. Current Medicinal Chemistry. 2013; 20(18):2296-2314.

34. Gonzalez M, Kann M. Chapter 4: Protein Interactions and Disease. PLoS Computational Biology. 2012; 8(12):e1002819.

35. Abagyan R, Totrov M, Kuznetsov D. ICM? A new method for protein modeling and design: Applications to docking and structure prediction from the distorted native conformation. Journal of Computational Chemistry. 1994; 15(5):488-506.

36. Ferreira L, dos Santos R, Oliva G, Andricopulo A. Molecular Docking and Structure-Based Drug Design Strategies. Molecules. 2015; 20(7):13384-13421.

37. Alex Mathew J, Nixon Raj N, Docking Studies on Anticancer Drugs for Breast Cancer Using Hex; *International MultiConference of Engineers and Computer Scientists*, 2009,Vol I,IMECS,3,18-20.

38. Speck-Planche A, Kleandrova V, Luan F, Cordeiro M. Multi-target drug discovery in anti-cancer therapy: Fragment-based approach toward the design of potent and versatile anti-prostate cancer agents. Bioorganic & Medicinal Chemistry. 2011; 19(21):6239-6244.

39. Adeniyi A, Ajibade P. Comparing the Suitability of Autodock, Gold and Glide for the Docking and Predicting the Possible Targets of Ru(II)-Based Complexes as Anticancer Agents. Molecules. 2013; 18(4):3760-3778.

40. Bipransh Kumar Tiwary,Ravi Kant Pathak, Kiran Pradhan, Ashis Kumar Nanda, Asim Kumar Bothra, Ranadhir Chakraborty; Evaluation Of Drug Candidature Of Some Quinazoline- 4-(3h)-Ones As Inhibitor Of Human Dihydrofolate Reductase Enzyme: Molecular Docking And In Silico Studies; *Int J Pharm Pharm Sci*,2014 Vol 6, Suppl 2,ISSN- 0975-1491, 393-400.

41. Anita Puspa Widiyana, Galih Satrio Putra, Luthfi Ahmad Muchlashi, Mellany Ika Sulistyowaty, Tutuk Budiati; Design and Molecular Docking Studies of Quinazoline Derivatives as Antiproliferation; *Jurnal Farmasi Dan Ilmu Kefarmasian Indonesia*, 2016Vol. 3 No. 2,12.

42. Tutuk Budiati, Suko Hardjono, Melanny Ika Sulistyowaty; Synthesis and Molecular Docking Study of 4-Chlorophenylquinazoline-4-[3h]-One Derivatives as COX-2 Inhibitor, 2016*IJPCR*,8(12),1605-1609.

43. Al-Shamary D, Al-Alshaikh M, Kheder N, Mabkhot Y, Badshah S. Molecular docking and biological evaluation of some thioxoquinazolin-4(3H)-one derivatives as anticancer, antioxidant and anticonvulsant agents. Chemistry Central Journal. 2017; 11(1).

44. Parvin Asadi, Ghadamali Khodarahmi, Ali Jahanian-Najafabadi, Lotfollah Saghaie, Farshid Hassanzadeh; Synthesis, characterization, molecular docking studies and biological evaluation of some novel hybrids based on quinazolinone, benzofuran and imidazolium moieties as potential cytotoxic and antimicrobial agents; *Iran J Basic Med Sci*, 2017,Vol. 20, No. 9, 9.

45. Cabrera N, Mora J, Marquez E. Computational Molecular Modeling of Pin1 Inhibition Activity of Quinazoline, Benzophenone, and Pyrimidine Derivatives. Journal of Chemistry. 2019; vol.19, 1-11.

46. Mehta S, Kumar S, Marwaha R, Narasimhan B, Ramasamy K, Lim S et al. Synthesis, molecular docking and biological potentials of new 2-(4-(2-chloroacetyl) piperazin-1-yl)-N-(2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl)acetamide derivatives. BMC Chemistry. 2019; 13(1).

47. Misra A, Kishore D, Verma V, Dubey S, Chander S, Gupta N et al. Synthesis,

biological evaluation and molecular docking of pyrimidine and quinazoline derivatives of 1,5-benzodiazepine as potential anticancer agents. Journal of King Saud University - Science. 2020; 32(2):1486-1495.

48. Eguchi S, Eguchi S. Quinazoline Alkaloids and Related Chemistry Bioactive Heterocycles I. Springer Berlin; Heidelberg: 2006. p. 113-56

49. Dempcy R, Skibo E. Rational design of quinazoline-based irreversible inhibitors of human erythrocyte purine nucleoside phosphorylase. Biochemistry. 1991; 30(34):8480-8487.

50. Skelton L, Ormerod M, Titley J, Kimbell R, Brunton L, Jackman A. A novel class of lipophilic quinazoline-based folic acid analogues: cytotoxic agents with a folate-independent locus. British Journal of Cancer. 1999; 79(11-12):1692-1701.

51. Martin GJ, Moss J, Avakian S. Folic acid activity of N-(4-(4-quinazoline)-benzoyl) glutamic acid. J Biol Chem 1947;167:737

52. Cavalli A, Lizzi F, Bongarzone S, Belluti F, Piazzi L, Bolognesi M. Complementary medicinal chemistry-driven strategies toward new antitrypanosomal and antileishmanial lead drug candidates. FEMS Immunology & Medical Microbiology. 2010; 58(1):51-60.

53. Rohini R, Shanker K, Reddy P, Ho Y, Ravinder V. Mono and bis-6-arylbenzimidazo[1,2-c]quinazolines: A new class of antimicrobial agents. European Journal of Medicinal Chemistry. 2009; 44(8):3330-3339.

54. Chao Q, Deng L, Shih H, Leoni L, Genini D, Carson D et al. Substituted Isoquinolines and Quinazolines as Potential Anti-inflammatory Agents. Synthesis and Biological Evaluation of Inhibitors of Tumor Necrosis Factor α. Journal of Medicinal Chemistry. 1999; 42(19):3860-3873.

55. El-Bendary ER, el-Ashmawy MB, Barghash AM, et al. Synthesis of some new quinazolines and quinoxalines of potential antiinflammatory activity. Boll Chim Farm 1996;135:617-20

56. Jindal D, Bhatti R, Ahlawat S, Gupta R. Synthesis and bronchodilatory activity of some nitrogen bridgehead compounds. European Journal of Medicinal Chemistry. 2002; 37(5):419-425.

57. Combs DW, Rampulla MS, and Russell RK, et al. Design, synthesis and bronchodilatory activity of a series of quinazoline-3-oxides. Drug Des Deliv 1990;6:241-54

58. Chen Z, Hu G, Li D, Chen J, Li Y, Zhou H et al. Synthesis and vasodilator effects of rutaecarpine analogues which might be involved transient receptor potential vanilloid subfamily, member 1 (TRPV1). Bioorganic & Medicinal Chemistry. 2009; 17(6):2351-2359.

59. Tseng CJ, Chen SY, Tao PL, et al. Antihypertensive effects of AT-112, a newly synthesized quinazoline derivative, in spontaneously hypertensive rats. Proc Natl Sci Counc Repub China B 1995;19:159-65

60. Uckun F, Sudbeck E, Mao C, Ghosh S, Liu X, Vassilev A et al. Structure-Based Design of Novel Anticancer Agents. Current Cancer Drug Targets. 2001; 1(1):59-71.

61. Marzaro G, Guiotto A, Pastorini G, Chilin A. A novel approach to quinazolin-4(3H)-one via quinazoline oxidation: an improved synthesis

of 4-anilinoquinazolines. Tetrahedron. 2010; 66(4):962-968.

62. Lengauer T, Rarey M. Computational methods for bimolecular docking. Current Opinion in Structural Biology. 1996; 6(3):402-406.

63. Salerno S, Da Settimo F, Taliani S, Simorini F, La Motta C, Fornaciari G, Marini A M.Recent advances in the development of dual Topoisomerase I and II inhibitors as anticancer drugs. Curr Med Chem 2010; 17: 4270-4290.

64. Baselga J, Swain S M. Novel anticancer targets: revisiting ERBB2 and discovering ERBB3. Nat Rev Cancer 2009; 9: 463-475.

65. Brown C H J, Lain S, Verma C H S, Fersht A R, Lane D P. Awakening guardian angels: drugging the p53 pathway. Nat. Rev. Cancer 2009, 9, 862-873.

66. Ljungman M. Targeting the DNA Damage Response in Cancer. Chem Rev 2009; 109: 2929-2950.

67. Semenza G L. Hypoxia and cancer. Cancer Metastasis Rev 2007; 26: 223-224.

68. Eckford P D W, Sharom F J. ABC efflux pump-based resistance to chemotherapy drugs. Chem Rev 2009; 109: 2989-3011.

69. Ullah M F. Cancer multidrug resistance (MDR): a major impediment to effective chemotherapy. Asian Pac J Cancer Prev 2008; 9: 1-6.

70. Shagufta, Ahmad I. Recent insight into the biological activities of synthetic xanthone derivatives. Eur J Med Chem 2016; 116: 267-280.

71. Ahmad I, Shagufta. Recent developments in steroidal and nonsteroidal aromatase inhibitors for the chemoprevention of estrogen-dependent breast cancer. Eur J Med Chem 2015; 102: 375-386.

72. Ahmad I, Shagufta. Sulfones: An important class of organic compounds with diversebiological activities. Int J Pharm Sci 2015; 7: 19-27.

73. Demeunynck M, Baussanne I. Survey of recent literature related to the biologically active 4(3*H*)-quinazolinones containing fused heterocycles. Curr Med Chem 2013; 20: 794–814.

74. Pozzan A. Molecular Descriptors and Methods for Ligand Based Virtual High Throughput Screening in Drug Discovery. Current Pharmaceutical Design. 2006; 12(17):2099-2110.

75. Green DV. Virtual screening of virtual libraries. Prog Med Chem. 2003; 41: 61-97.

76. Goodsell D, Olson A. Automated docking of substrates to proteins by simulated annealing. Proteins: Structure, Function, and Genetics. 1990; 8(3):195-202.

77. Kuntz I, Blaney J, Oatley S, Langridge R, Ferrin T. A geometric approach to macromolecule-ligand interactions. Journal of Molecular Biology. 1982; 161(2):269-288.

78. Rarey M, Kramer B, Lengauer T. Journal search results - Cite This For Me. Journal of Computer-Aided Molecular Design. 1997; 11(4):369-384.

79. Schulz-Gasch T, Stahl M. Binding site characteristics in structure-based virtual screening: evaluation of current docking tools. Journal of Molecular Modeling. 2003; 9(1):47-57.

80. Friesner R, Banks J, Murphy R, Halgren T, Klicic J, Mainz D et al. Glide: A New

Approach for Rapid, Accurate Docking and Scoring. 1. Method and Assessment of Docking Accuracy. Journal of Medicinal Chemistry. 2004; 47(7):1739-1749.

81. Jones G, Willett P, Glen R, Leach A, Taylor R. Development and validation of a genetic algorithm for flexible docking 1 1Edited by F. E. Cohen. Journal of Molecular Biology. 1997; 267(3):727-748.

82. Venkatachalam C, Jiang X, Oldfield T, Waldman M. LigandFit: a novel method for the shape-directed rapid docking of ligands to protein active sites. Journal of Molecular Graphics and Modelling. 2003; 21(4):289-307.

83. Abagyan R, Totrov M, Kuznetsov D. ICM?A new method for protein modeling and design: Applications to docking and structure prediction from the distorted native conformation. Journal of Computational Chemistry. 1994; 15(5):488-506.

84. Mcmartin C, Bohacek R. Journal search results - Cite This For Me. Journal of Computer-Aided Molecular Design. 1997; 11(4):333-344.

85. Schnecke V, Kuhn L. Journal search results - Cite This For Me. Perspectives in Drug Discovery and Design. 2000; 20(1):171-190.

86. Jain A. Surflex: Fully Automatic Flexible Molecular Docking Using a Molecular Similarity-Based Search Engine. Journal of Medicinal Chemistry. 2003; 46(4):499-511.

87. Internet addresses of selected docking tools: Auto Dock, DOCK, FlexX, FRED, Glide, GOLD, and ICM.

88. Kellenberger E, Rodrigo J, Muller P, Rognan D. Comparative evaluation of eight docking tools for docking and virtual screening accuracy. Proteins: Structure, Function, and Bioinformatics. 2004; 57(2):225-242.

89. Pal N, Mandal S, Shiva K, Kumar B. Pharmacognostical, Phytochemical and Pharmacological Evaluation of Mallotus philippensis. Journal of Drug Delivery and Therapeutics. 2022 Sep 20;12(5):175-81.

90. Singh A, Mandal S. Ajwain (Trachyspermum ammi Linn): A review on Tremendous Herbal Plant with Various Pharmacological Activity. International Journal of Recent Advances in Multidisciplinary Topics. 2021 Jun 9;2(6):36-8.

91. Mandal S, Jaiswal V, Sagar MK, Kumar S. Formulation and evaluation of carica papaya nanoemulsion for treatment of dengue and thrombocytopenia. Plant Arch. 2021;21:1345-54.

92. Mandal S, Shiva K, Kumar KP, Goel S, Patel RK, Sharma S, Chaudhary R, Bhati A, Pal N, Dixit AK. Ocular drug delivery system (ODDS): Exploration the challenges and approaches to improve ODDS. Journal of Pharmaceutical and Biological Sciences. 2021 Jul 1;9(2):88-94.

93. Ali SA, Pathak D, Mandal S. A REVIEW OF CURRENT KNOWLEDGE ON AIRBORNE TRANSMISSION OF COVID-19 AND THEIR RELATIONSHIP WITH ENVIRONMENT. International Journal of Pharma Professional's Research (IJPPR). 2023;14(1):1-5.

94. Shiva K, Mandal S, Kumar S. Formulation and evaluation of topical antifungal gel of fluconazole using aloe vera gel. Int J Sci Res Develop. 2021;1:187-93.

95. Vishvakarma P, Mandal S, Verma A. A REVIEW ON CURRENT ASPECTS OF NUTRACEUTICALS AND DIETARY SUPPLEMENTS. International Journal of Pharma Professional's Research (IJPPR). 2023;14(1):78-91.

96. Ali S, Farooqui NA, Ahmad S, Salman M, Mandal S. CATHARANTHUS ROSEUS (SADABAHAR): A BRIEF STUDY ON MEDICINAL PLANT HAVING DIFFERENT PHARMACOLOGICAL ACTIVITIES. Plant Archives. 2021;21(2):556-9.

97. MANDAL S, JAISWAL DV, SHIVA K. A review on marketed Carica papaya leaf extract

(CPLE) supplements for the treatment of dengue fever with thrombocytopenia and its drawback. International Journal of Pharmaceutical Research. 2020 Jul;12(3).

98. Mandal S, Vishvakarma P, Verma M, Alam MS, Agrawal A, Mishra A. Solanum Nigrum Linn: An Analysis Of The Medicinal Properties Of The Plant. Journal of Pharmaceutical Negative Results. 2023 Jan 1:1595-600.

99. Vishvakarma P, Mandal S, Pandey J, Bhatt AK, Banerjee VB, Gupta JK. An Analysis Of The Most Recent Trends In Flavoring Herbal Medicines In Today's Market. Journal of Pharmaceutical Negative Results. 2022 Dec 31:9189-98.

100. Mandal S, Pathak D, Rajput K, Khan S, Shiva K. THROMBOPHOB-INDUCED ACUTE URTICARIA: A CASE REPORT AND DISCUSSION OF THE CASE. International Journal of Pharma Professional's Research (IJPPR). 2022;13(4):1-4.

101. Mandal S, Shiva K, Yadav R, Sen J, Kori R. LEIOMYOSARCOMA: A CASE REPORT ON THE PREOPERATIVE DIAGNOSTIC CRITERIA. International Journal of Pharma Professional's Research (IJPPR). 2022;13(4):1-4.

102. Mandal S, Vishvakarma P, Mandal S. Future Aspects And Applications Of Nanoemulgel Formulation For Topical Lipophilic Drug Delivery. European Journal of Molecular & Clinical Medicine.;10(01):2023.