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A Review on Advances in Drug Design with Epigallocatechin Gallate (EGCG): A Natural Platform for New Therapies

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Abstract

Epigallocatechin gallate (EGCG), the predominant catechin in green tea, has attracted significant attention for its wide-ranging pharmacological properties, including antioxidant, anti-inflammatory, anticancer, neuroprotective, and antimicrobial effects. Its unique polyphenolic structure offers multiple interaction sites, enabling the modulation of diverse biological pathways and molecular targets. This review explores EGCG as a promising natural scaffold for modern drug design, highlighting structural features that lend themselves to chemical modification and optimization for enhanced bioavailability, stability, and target specificity. We examine current advances in in silico modeling, structural-activity relationship (SAR) studies, and nanodelivery systems aimed at overcoming EGCG's physicochemical limitations.[1] Special emphasis is placed on translational insights that bridge natural product pharmacology with synthetic medicinal chemistry, paving the way for innovative therapeutic agents derived from EGCG. The synthesis of existing literature underscores EGCG's potential as a versatile molecular template for developing next-generation therapeutics across oncology, neurodegenration, infectious disease, and metabolic disorders.Current literature suggests EGCG is not only a leading candidate for developing next-generation therapeutics across oncology, neurodegeneration, cardiovascular, immune, and infectious diseases, but also a model molecule for innovative drug delivery and multi-drug systems. Future research should aim to address existing challenges in pharmacokinetics and clinical validation, paving the way for EGCG-based therapies to transition from promising natural product to clinical reality.[2]

Keywords: Epigallocatechin gallate, Molecular Scaffold, Anticancer Agents, QSAR, Computer Aided Drug Design, Molecular Docking

1. Introduction

Drug design is an integrated developing discipline which portends an era of "Tailored drug".It is a development process involves use of variety of computational techniques, such as structure activity relationship, quantitative structure activity relationship (QSAR), molecular mechanics, quantam mechanics, molecular dynamics and drug protein docking. Drug development and Discovery Includes preclinical research on cell based and animal models and Clinical trials on humans, and finally move forward to the

step of Obtaining regulatory approval in order to market the drug. Modern drug Discovery involves the identification of screening hits, medicinal Chemistry and optimization of those hits to increase the affinity, Selectivity (to reduce the potential of side effects), efficacy/potency, Metabolic stability (to increase the half-life), and oral Bioavailsability. Once a compound that fulfills all of these requirements Has been identified, it will begin the process of drug development prior To clinical trials.[1] Drug discovery can be described as the process of identifying chemical Entities that have the potential to become therapeutic .Drug design frequently but not necessarily relies on computer modeling techniques and bioinformatics approaches in the big data era. In addition to small molecules,biopharmaceuticals and especially therapeutic antibodies are an increasingly important class of drugs and computational methods for improving the affinity, selectivity, and stability of these protein-based therapeutics have also gained great advances. Drug development and discovery includes preclinical research on cell-based and animal models and clinical trials on humans, and finally move forward to the step of obtaining regulatory approval in order to market the drug.

Cancer remains one of the leading causes of morbidity and mortality worldwide, necessitating the continuous exploration of novel therapeutic agents. While conventional treatments like chemotherapy and radiotherapy have significantly advanced, they are often associated with serious adverse effects and the development of multidrug resistance. These limitations have sparked renewed interest in natural products as a source for new, effective, and less toxic anticancer drugs. With approximately 60% of all existing oncopharmaceuticals originally derived from natural sources, their therapeutic potential is undeniable. Natural compounds offer unique chemical diversity and structural complexity, providing a rich starting point for drug discovery and modification. [3] Green tea (*Camellia sinensis*) consumption is known for its health benefits. The majority of green tea's positive effects on human health can be attributed to the high polyphenol and flavonoid content of the beverage. Catechins, which are the primary flavonoids found in green tea, account for about 30–40% of the solid components of this plant. Epicatechin (EC), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epigallocatechin-3-gallate (EGCG) are the primary catechins found in tea.

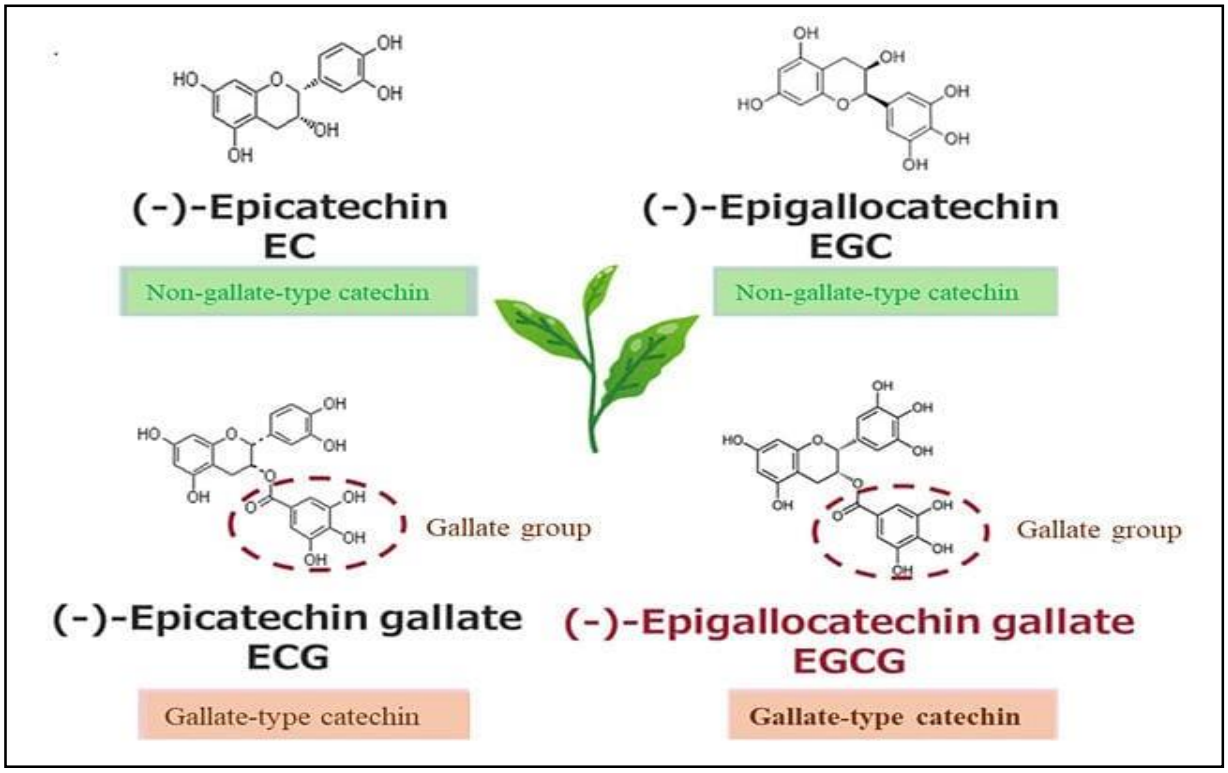

Fig no.1. Structural Classification of Catechins in Green Tea: Gallate-Type and Non-Gallate

EGCG has gained particular scientific interest in the past decade due to its numerous health benefits resulting from its antioxidant, anti-inflammatory, anti-fibrotic, and anti-cancer properties . EGCG is consumed mainly via brew drinking. One cup of green tea contains approximately 177 mg of EGCG . Therapeutic advantages of green tea consumption have been observed in inflammatory diseases and several types of cancer . The anti-tumor activity of EGCG has been linked to the inhibition of the proteins involved in cellular signaling pathways that are frequently disrupted in cancer. These include the protein networks mediated by epidermal-growth-factor receptor (EGFR), tyrosine-protein kinase JAK (JAK), signal transducer and activator of transcription (STAT) (JAK/STAT pathway), phosphoinositide-3-kinase (PI3K), RAC-alpha serine/threonine-protein kinase (AKT), serine/threonine-protein kinase mTOR (mTOR) (PI3K/AKT/mTOR pathway) and mitogen-activated protein kinases (MAPK/ERK pathways). Moreover, EGCG exhibits antioxidant, anti-inflammatory, and anti-angiogenic effects and may promote both caspase-dependentand caspase-independent cell death. [4]

However, the clinical application of native EGCG is significantly limited by its poor oral bioavailability, chemical instability, and rapid metabolism, which prevent it from reaching effective plasma concentrations. This has led researchers to explore innovative strategies, such as structural modifications and advanced delivery systems, to overcome these limitations. The complex yet therapeutically active scaffold of EGCG, with its multiple hydroxyl groups, makes it an attractive natural template for the development of novel, more effective derivatives through modern drug design methodologies.[5]

1.Drug Design and Discovery

Drug design is an integrated developing discipline which portends an era of "Tailored drug".It is a development process involves use of variety of computational techniques, such as structure activity relationship, quantitative structure activity relationship (QSAR), molecular mechanics, quantam mechanics, molecular dynamics and drug protein docking. The QSAR establish a statistical relationship between biological activity or environmental behaviour of the chemicals of interest and their structural properties. QSAR predict chemical behaviour of directly from chemical structure and stimulate adverse effect in cells ,tissues and lab animals minimizing the need to use animals test to comply with regulatory requirements for human health and ecotoxicology. [6]Drug designing is the process of discovering drug candidate on the basis of the pharmacological and molecular targets1 . Generally, a drug target is a skeleton molecule associated with particular signalling pathway related to specific disease or pathological condition or antimicrobial efficacy against pathogen. The shape of the drug candidate specific to a drug target molecule can be designed with the help of computational techniques. Rational drug design is an effective and prime approach in pharmaceutical sciences as well as life sciences. Rational drug design deals with the discovery of drug candidate by methodological target-based designing, employing novel computational techniques, this technique is more economic and expeditious than previous dug development techniques. The aim is to establish a crucial drug destination based on detailed understanding of regulatory networks and metabolic pathways. Rational drug design emphasized to develop a highly specific drug based on a known three-dimensional (3 D) structure of that target.[7]

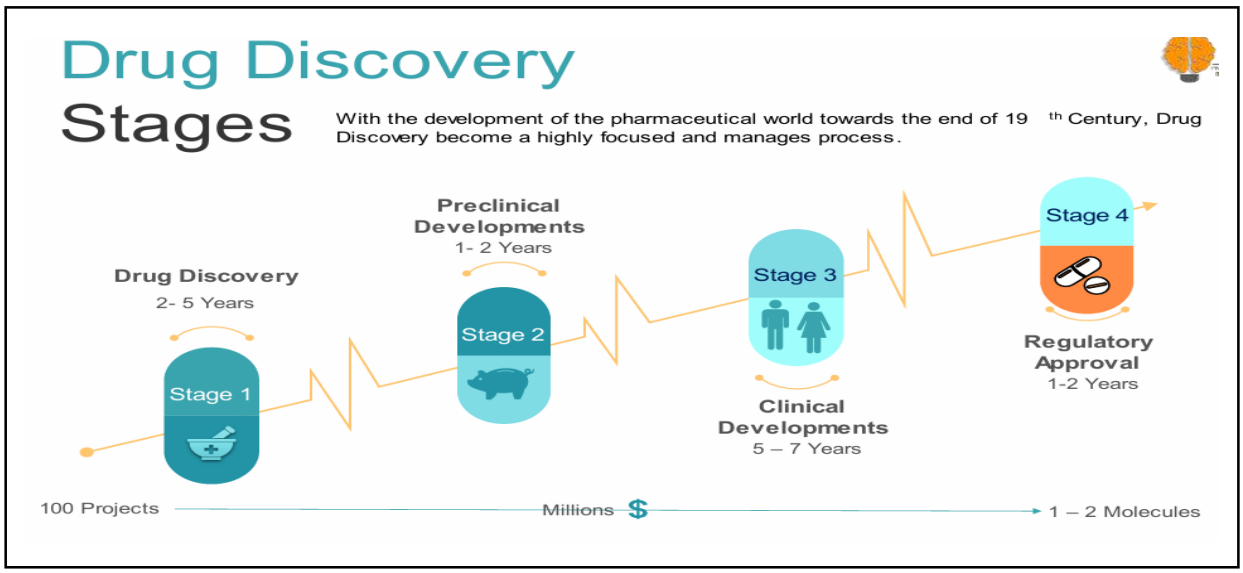

Fig. no.2 : Stages of Drug Development from Discovery to Reulatory Approval

Stages of Drug Discovery

1.Drug Discovery (2-5 years)
Involves identifying and validating drug targets, and finding lead compounds.About 100 projects may start, but only a few promising moleculesmove forward.

2. Preclinical Development (1-2 years)

o Laboratory and animal studies toevaluate safety, efficacy,pharmacokineticstoxicity.

o Only the safest and most effectivemolecules enter human trials.

3. Clinical Development (5-7 years)

o Human testing in three phases:

Phase I: Safety and dosage inhealthy volunteers.

Phase II: Efficacy and side effectsin patients.

Phase III: Large-scale testing forEffectiveness and monitoring ofadverse reactions.

4. Regulatory Approval (1-2 years)

o Data is submitted to authorities (e.g.,FDA, EMA, CDSCO).[9]

1.1 Principle of Drug Design

1.Finding the Right Target (Target Identification & Validation)

Every successful drug starts with a target—usually a protein in the body that's behaving badly and contributing to a disease. The goal is to find something that the drug can interact with in a helpful way. Once scientists find this target, they have to confirm that changing its activity will actually help the patient. This step is like figuring out which switch controls a light in a dark room before flipping it.

2. Discovering a Starting Point (Hit Identification)

Now, we need a molecule that can interact with that target. This is where we look for a "hit." Scientists use large databases and lab techniques to test thousands of small molecules to see if any of them stick to the target. When a few promising candidates are found, we call them "hits."These hits are then double-checked using different tools (like lab tests or computer models) to make sure they actually work and aren't just flukes. It's like auditioning actors for a movie—you might find some good ones, but they need to be tested in different scenes before getting the role.[10]

3. Fine-Tuning the Molecule (Lead Optimization & SAR)

Once a promising molecule—or "lead"—is found, scientists begin improving it. This part of the process is like customizing a suit. Small changes are made to improve how well the molecule fits the target, stays in the body, and avoids causing side effects.

This is also where **Structure-Activity Relationships (SAR)** come in. Scientists look at how each tweak to the molecule changes its behavior. If adding a certain group improves the effect, they explore more of those changes.

4. Making Sure It Looks Like a Drug (Drug-Likeness)

Even if a molecule works well in the lab, it might not work in the human body. To check if a molecule has the right characteristics to become a pill, scientists follow some general guidelines known as **Lipinski's Rule of Five**. This rule says a good oral drug should:

- Not be too heavy (under 500 molecular weight)
- Not be too greasy (logP under 5)
- Not have too many groups that love water (less than 10 acceptors and 5 donors)

This helps predict whether a molecule can be absorbed when swallowed. However, not every drug follows these rules perfectly—some break them and still work well. So, it's a guide, not a law.

5. Designing Without a Map (Pharmacophore & Ligand-Based Design)

Sometimes, we don't have the 3D structure of the target protein. In those cases, scientists use information from other molecules that are known to work. They create a kind of "feature blueprint" of what the molecule needs to have—called a **pharmacophore**—and use that to design or search for new drugs.

6. Understanding the Journey in the Body (ADME and Safety)

Even the best-designed molecule is useless if it doesn't behave properly inside the body. That's why scientists test for **ADME**—which stands for:[11]

- **Absorption**: Can the drug get into the bloodstream?
- **Distribution**: Can it reach the right parts of the body?
- **Metabolism**: Is it broken down safely by the body?
- **Excretion**: Can it leave the body without causing harm?

Principles of Drug Design

Principle	What It Means	Example
Targeting	Pick the right molecule to block or activate.	HIV protease
Validation	Prove the target controls the disease.	Lab/animal testing
Lead Finding	Find a molecule that works on the target.	Penicillin
Optimization	Improve strength, reduce side effects.	Refined beta blockers
Selectivity	Hit the disease target, not healthy cells.	Imatinib (leukemia)
ADME	Ensure the drug is absorbed and works well.	Oral meds with good uptake
Safety	Confirm it's safe at useful doses.	Clinical trials
Delivery	Choose the best way to give the drug.	mRNA via lipid nanoparticles

Table no.1 Strategic Framework for Drug Development

1.2Drug design Development

Drug design and discovery is a critical aspect of pharmaceutical sciences, involving the identification and development of new therapeutic agents to treat various diseases. For pharmacy professionals, understanding this process is essential, as it forms the foundation of modern pharmacotherapy. The journey begins with target identification, where a biological molecule (such as a receptor, enzyme, or gene) linked to a disease is selected. This is followed by target validation, confirming that modulating the target can produce a therapeutic effect.Once the target is validated, the next step is lead compound identification. This involves screening chemical libraries (using techniques like high-throughput screening) or employing computer-aided drug design (CADD) to find compounds that interact effectively with the target. Pharmacy professionals should also be familiar with structure-based drug design (SBDD) and ligand-based drug design (LBDD), which use knowledge of the target's 3D structure or known ligands to design new drugs.[12]

After a lead is identified, it undergoes lead optimization to enhance properties such as potency, selectivity, bioavailability, and safety.The optimized compounds are then tested in preclinical studies, using in vitro and in vivo models to assess pharmacokinetics (ADME) and toxicity. Successful candidates move into clinical trials, which are conducted in four phases: Phase I (safety), Phase II (efficacy), Phase III (comparison with existing therapies), and Phase IV (post-marketing surveillance).The optimized compounds then enter preclinical testing, which involves in vitro (test tube) and in vivo (animal) studies to assess pharmacokinetics, pharmacodynamics, and toxicity. Compounds that pass these stages proceed to clinical trials, which are conducted in four phases: Phase I tests safety in healthy volunteers, Phase II assesses efficacy in patients, Phase III involves large-scale trials for regulatory approval, and Phase IV

monitors long-term safety after the drug is marketed. Throughout this process, pharmacy professionals play a key role—not only in understanding and applying pharmacological principles but also in clinical trial management, regulatory compliance, and ensuring patient safety.[13]

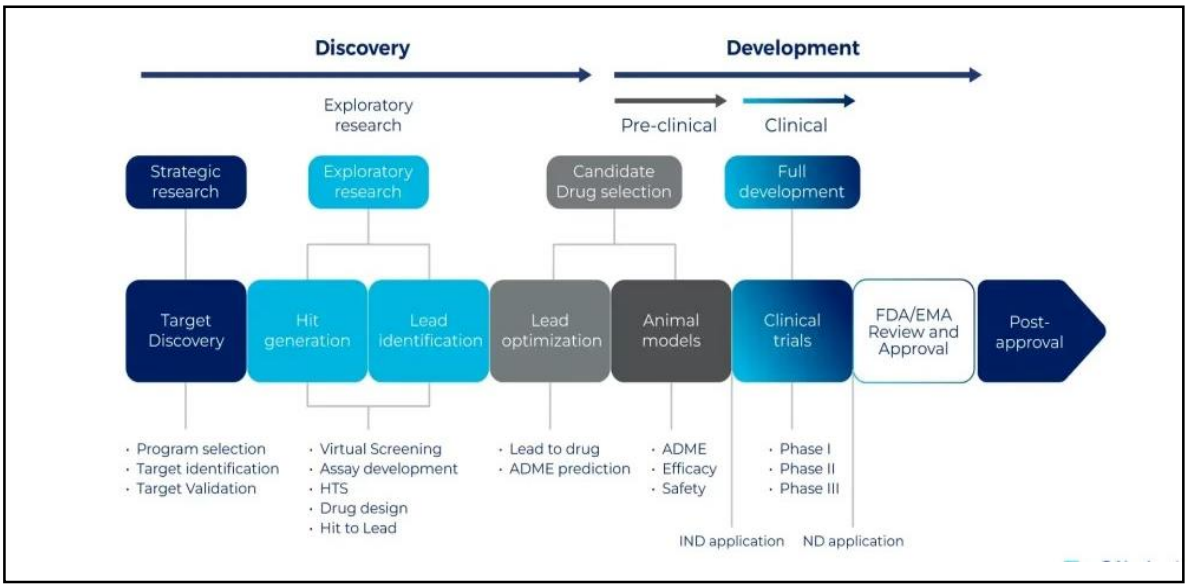

Fig. no.3 The journey of a Drug: From Target Discovery to Post-Approval

2. QSAR (Quantitative Structure Activity Relationship):

Quantitative structure activity relationship (QSAR)studies represent a non experimental part of drug design encompassing the study of both structure activity and structure property relations in broad sense. The most commonly used mathematical techniques in classical quantitative structure activity relationships (QSAR) work is multiple regression analysis. QSAR is an intellectual exercise of assembling , manipulating , and examining data obtained from physical , chemical, and biological experiments, and correlating them to biological activity . Biological activity of a drug depends on the types and magnitude of interactions between the receptor and the drug molecule . Various structural attributes of a drug molecule, such as electronic distribution , steric features etc. ,are the determining factors regulating the interactions . Parameters must be properties that are capable of being represented by a numerical value. These values square measure wont to manufacture a general equation relating drug activity with the parameters. The goals QSAR studies include a better understanding of the modes of actions, prediction of newer analogs with better activity , classification of active /inactive compounds and optimization of the lead compound to reduce toxicity and increase selectivity.[14]

The main properties of a drug that seem to influence its activity measure its lipophilicity, the electronic effects within the molecule and the size and shape of the molecule. Lipophilicity is a measure of a drug's solubility in lipid membranes. This is usually an important factor in determining how easily a drug passes through lipid membranes. It is used as a live of the convenience of distribution of a drug to its target website. The parameters commonly used to represent these properties are partition coefficients and lipophilic substitution constants for lipophilicity, Hammetts constants for electronic effects and tafts Es steric constants for steric effects .So QSAR is mathematical or statistical approaches to define the

relationship between biological activity (experimental data) of a molecular system and its geometrical, physical,electronic, and chemical properties

Activity = function (property 1, property 2 …)

Activity = function (xi)

xi- descriptor

Property (xi)- size, shape, no. of H-bond, electrostatic [15]

In molecular docking the geometrical structure of both the ligand and the target protein must be known. But the Quantitative Structure-Activity Relationships (QSAR) is a method which can be applied regardless of whether the structure is known or not.QSAR explore how a given protein interacts with some tested compounds. As an example,it may be known from previous experiments that the protein under investigation showssigns of activity against one group of compounds, but not against another group.[16]

2.1 QSAR Parameters

1. Electronic descriptors

Electronic properties define how a molecule's charge distribution affects its interaction with a biological target, influencing ionization, polarity, and binding affinity.

- **Hammett Constant (σ)**: A value that measures the electron-donating or electron-withdrawing ability of a substituent group, derived by measuring the dissociation of substituted benzoic acids. A positiveindicates an electron-withdrawing group, while a negative indicates an electron-donating group.
- **Dipole Moment**: A measure of charge separation within a molecule. Molecules with higher dipole moments are more polar, influencing their interactions with polar biological environments and targets.
- **HOMO and LUMO**: Quantum chemical descriptors for the Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO) energy levels. The energy gap between these orbitals relates to a molecule's reactivity.
- **E-state Index**: Electrotropological state indices that quantify the electronic accessibility and density of atoms within a molecule. [17]

2. Hydrophobic descriptors

Hydrophobicity, or lipophilicity, is crucial for a drug's ability to cross lipid-rich cell membranes to reach its target and is also important for its interactions at the receptor site.

- **Partition Coefficient (Log P)**: The ratio of a compound's concentration in a lipid phase (typically 1-octanol) versus an aqueous phase. A higher Log P indicates greater lipophilicity. A positive Log P suggests the compound favors the lipid phase, and a negative value means it favors the aqueous phase.
- **Distribution Coefficient (Log D)**: The Log P value at a specific pH. Unlike Log P, it accounts for the ionization state of the molecule, providing a more accurate measure of hydrophobicity under physiological conditions.

- **Substituent Hydrophobicity Constant (π)**: A value used to quantify the relative hydrophobicity contributed by a specific substituent group compared to a hydrogen atom.

3. Steric descriptors Steric parameters describe a molecule's shape and size, which are critical for determining how well it can physically fit into a receptor's binding site.

- **Taft's Steric Factor (E)**: Measures the steric bulk of a substituent, influencing the closeness of contact between a drug and its receptor.
- **Molar Refractivity (MR)**: Accounts for both the size and polarizability of a molecule or substituent.
- **Verloop Steric Parameter (STERIMOL)**: Describes the dimensions of a substituent based on bond angles, van der Waals radii, and bond lengths, providing a more nuanced measure of shape.
- **Topological Indices**: Numerical values derived from a molecule's graph representation, reflecting its size, shape, and branching. Examples include the Wiener index and Balaban index. [18]

4. Constitutional descriptors
These are simple properties that depend on a molecule's composition but are insensitive to its topology or 3D arrangement.

- **Molecular Weight (MW)**: The sum of the atomic weights of all atoms in a molecule.
- **Atom Count**: The total number of atoms of a specific type (e.g., nitrogen, oxygen)
- **Number of Rings**: The count of cyclic structures within the molecule.

5.Hansch Analysis

QSAR based on Hammett' s relationship utilize electronic properties as the descriptorsof structures. Difficulties were encountered when investigators attempted to applyHammett-type relationships to biological systems, indicating that other structuraldescriptors were necessary. In 1962, Hansch et al entered the scenario with the numerical information on lipophilicity,electronic, and steric effect on the model development. The general form of Hansch equation is as follows:

Log BA = a log p + b o + c Es + constant (linear)

Log BA = a log p + b (log p)2 + c o + d Es + constant (nonlinear)

Partition coefficient; log P

Hammett constant; o

Taft's steric parameter; Es

Hansch model correlates biological activity with physicochemical properties. The coefficients (a, b, c, d, and constant) are determined by multiple regression analysis.

6. Free-Wilson Analysis

It is also known as the additivity model or de novo approach. This method is based on the assumption that the introduction of a particular substituent at a particular molecular position always contributes in the same way to the biological potency of the whole molecule, as expressed by the equation:

Log BA = contribution of unsubstituted parent compound + contribution of corresponding substituents.

$$\text{Log BA} = \mu + \Sigma \text{ ai aj}$$

where ai = number of positions at which substitution occurs

aj = number of substituents at that position

u = overall average.

The equation is solved by MLR using the presence (1) or absence (0) of the different substituents as independent parameters, while the measured activity variable.[19]

2.2 Types of QSAR

Types of QSAR based on dimensionality

0D QSAR: The "Basic ID"
Imagine you are a security guard checking IDs. A 0D QSAR model is like only being allowed to see a person's name and weight. It uses simple, basic molecular properties that don't depend on the molecule's shape or arrangement in space.

It uses easy-to-calculate properties like molecular weight, the number of specific atoms (e.g., nitrogen, oxygen), or the number of bonds.

- **Example:** A model might predict that as a drug's molecular weight increases, its solubility in water decreases.

1D QSAR:
This is like having a list of a person's unique parts or features, such as "one mole," "a functional group," and "a ring." It looks at the molecular fragments or groups that make up the molecule.

It breaks the molecule into smaller pieces and uses these "fragments" as descriptors. A famous example is the **Free-Wilson analysis**, which assumes each part of the molecule adds a specific, constant amount to the overall biological activity.

• **Example:** For a series of related drugs, it can predict how changing a specific group (e.g., adding a chlorine atom) will affect its activity.[20]

2D QSAR: The "Blueprint"
This is like looking at a molecule's 2D blueprint. You can see how all the atoms are connected and bonded, but not their specific 3D shape. It uses properties that describe the molecule's connectivity and branching patterns.

This is the classic Hansch analysis. It uses simple descriptors like **lipophilicity** (how well the drug dissolves in fats, measured by log P) and **electronic effects** (how electrons are distributed, measured by Hammett constant, σ). It then creates a mathematical equation to relate these properties to biological activity.

- **Example:** The Hansch equation might look something like this:Biological Activity=k1·logP+k2·σ+k3·Steric+constantBiological Activity equals k sub 1 center dot log cap P plus k sub 2 center dot sigma plus k sub 3 center dot Steric plus constant

$$\text{Biological Activity} = k1 \cdot \log P + k2 \cdot \sigma + k3 \cdot \text{Steric} + \text{constant}$$

3D QSAR: The "3D-Printed Model"
This is a major step up. It's like having a full, 3D model of the molecule. This type of QSAR considers the molecule's shape and the surrounding energy fields (steric and electrostatic) that influence how it interacts with a receptor.

All the molecules are first aligned, or "superimposed," to find a common orientation. Then, a "probe" (a tiny atom) is used to scan the area around each molecule. The computer calculates the energy of interaction between the probe and the molecule at many points in space.

- **Key methods:**

CoMFA (Comparative Molecular Field Analysis): The original 3D-QSAR method. It maps out the steric (shape) and electrostatic (charge) fields around the aligned molecules.

CoMSIA (Comparative Molecular Similarity Indices Analysis): An improvement on CoMFA that adds more fields, such as hydrogen bonding and hydrophobicity, giving a more complete picture.[21]

4D QSAR and Beyond:
This takes 3D-QSAR to the next level by considering multiple conformations (shapes) of the drug molecule. A 4D QSAR model is like a flipbook, analyzing the drug in all its possible poses.

- **5D QSAR** adds the possibility of different binding poses at the receptor, like seeing how a key fits into a lock in multiple ways.
- **6D QSAR** even includes the changes that happen during a molecular dynamics simulation, essentially a "movie" of the drug-receptor complex in motion.[22]

2.3 Methodology of the QSAR

QSAR Methodology Steps

1. Data Collection and Curation

Prepare a dataset of compounds with known chemical structures and measured biological activities (such as IC50, EC50, Ki).Standardize chemical structures and ensure consistency in biological activity measurements across the dataset for robust analysis.Curate and clean data to remove duplicates, structural errors, and outliers.

2. Calculation of Molecular Descriptors

Compute numerical descriptors that represent structural, physicochemical, and electronic properties of molecules.Use descriptor calculation software such as PaDEL, Dragon, RDKit, ChemAxon, or OpenBabel.Descriptor types include constitutional (atom count), topological (connectivity indices), electronic (charge distributions), geometric (shape), and thermodynamic (energy parameters).

3. Data Preprocessing and Variable/Descriptor

SelectionReduce the pool of descriptors by removing highly correlated or irrelevant variables—using statistical, filter, wrapper, or embedded methods like correlation analysis, ANOVA, LASSO regression, or random forest.Normalize or scale descriptors if needed to ensure comparability.

4. Model Building

Split the dataset into training, validation, and test sets, using methods such as the Kennard-Stone algorithm.Develop mathematical or statistical models correlating selected descriptors with biological activity. Common modeling algorithms include Multiple Linear Regression (MLR), Partial Least Squares (PLS), Support Vector Machines (SVM), and Neural Networks.Fit models using training data and tune model parameters on validation data.

5. Model Validation

Validate the predictive performance using internal methods (e.g., k-fold cross-validation, leave-one-out) and external test sets to ensure robustness and prevent overfitting.Assess model quality using metrics like R^2, Q^2, RMSE (Root Mean Square Error), and receiver operating characteristic (ROC) curves.

6. Applicability Domain and Interpretation

Define the chemical applicability domain—region of descriptor space where the model makes reliable predictions.Interpret model coefficients (for linear models) or feature importance to elucidate which molecular properties drive biological activity.Visualize relationships through scatter plots of predicted vs. observed activity, heatmaps, and pharmacophore models.[23]

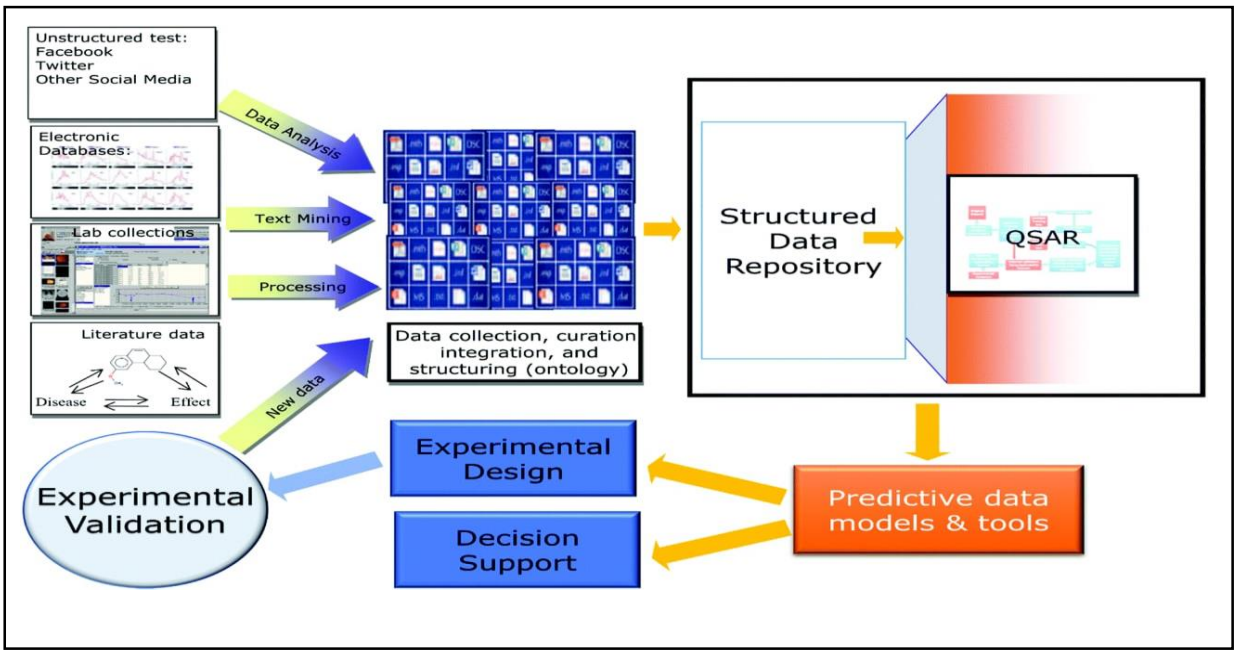

Fig .no.4.Workflow of Computer-Aided Drug Design (CADD)

3. Introdaction to CADD:

Computer-aided drug design (CADD) is a process of designing drugs using computational tools and techniques. It involves the use of computer software to predict biological activity, pharmacological properties, and toxicity of potential drug compounds. One of the applications of CADD is in the design of targeted drug delivery systems. Targeted drug delivery systems are designed to deliver drugs specifically to the affected site, reducing the side effects associated with traditional drug delivery methods. The use of CADD in targeted drug delivery allows for the development of drugs with improved efficacy and reduced toxicity .Different types of drug delivery vehicles, such as polymeric micelles, liposomes, lipoprotein based drug carriers, nano-particle drug carriers, dendrimers, etc. are being used in TDDS .Drug discovery and development represent complex, multifaceted processes requiring extensive resources, time, and interdisciplinary collaboration. Traditional drug development typically spans 10-15 years from initial discovery to market approval, with estimated costs exceeding $2.6 billion per successful drug. This process involves target identification, lead discovery, optimization, preclinical studies, and clinical trials, each phasedemanding significant investment and expertise. The traditional approach to drug development, primarily relying on experimental methods, faces significant challenges including high failure rates and substantial costs.

The attrition rate in conventional drug development is particularly concerning, with approximately 90% of drug candidates failing during clinical trials. These failures often occur due to unforeseen toxicity issues, poor pharmacokinetic properties, or lack of efficacy, highlighting the limitations of traditional experimental approaches.Computer-Aided Drug Design emerged in 1981 as a revolutionary approach, implementing computational methods to streamline the drug discovery process. This paradigm shift introduced systematic, rational approaches to drug design, moving away from serendipitous discoveries. The initial CADD methods focused on structure-activity relationships and molecular

graphics, laying the foundation for more sophisticated computational techniques. CADD integrates various computational techniques with experimental methods to identify, optimize, and evaluate potential drug candidates. This integration encompasses multiple stages of drug discovery, from virtual screening of large compound libraries to lead optimization and prediction of drug-like properties. The synergy between computational and experimental approaches has revolutionized the efficiency of drug discovery pipelines.[24]

Method	Primary Applications	Computational Requirements	Advantages	Limitations
Molecular Docking	Protein-ligand binding prediction	Moderate	Fast screening of large databases	Limited accuracy in flexibility prediction
Molecular Dynamics	Protein motion and binding kinetics	High	Detailed atomic-level interactions	Computationally intensive
QSAR Analysis	Activity prediction	Low to Moderate	Rapid property prediction	Requires quality training data
Quantum Mechanics	Electronic properties calculation	Very High	Highest theoretical accuracy	Limited to small systems
AI/Machine Learning	Multiple prediction tasks	Moderate to High	Can handle large datasets	Requires extensive training data

Table no 2-Major Computational Methods in Drug Design and their application

These methods incorporate quantum mechanics, molecular mechanics, and statistical mechanics to evaluate chemical and physicalproperties of molecules . Quantum mechanical calculations provide detailed electronic structure information, while molecular mechanics enables rapid evaluation of conformational energies. Statistical mechanics bridges microscopic and macroscopic properties, offering insights into system behavior under various conditions . The primary computational techniques include molecular docking, molecular dynamics simulations, and quantitative structure-activity relationship (QSAR) analyses. Molecular docking predicts binding modes and affinities between drugs and targets, while molecular dynamics simulations reveal the dynamic behavior of these complexes. QSAR analyses establish mathematical relationships between molecular properties and biological activity, enabling activity prediction for novel compounds. [25]

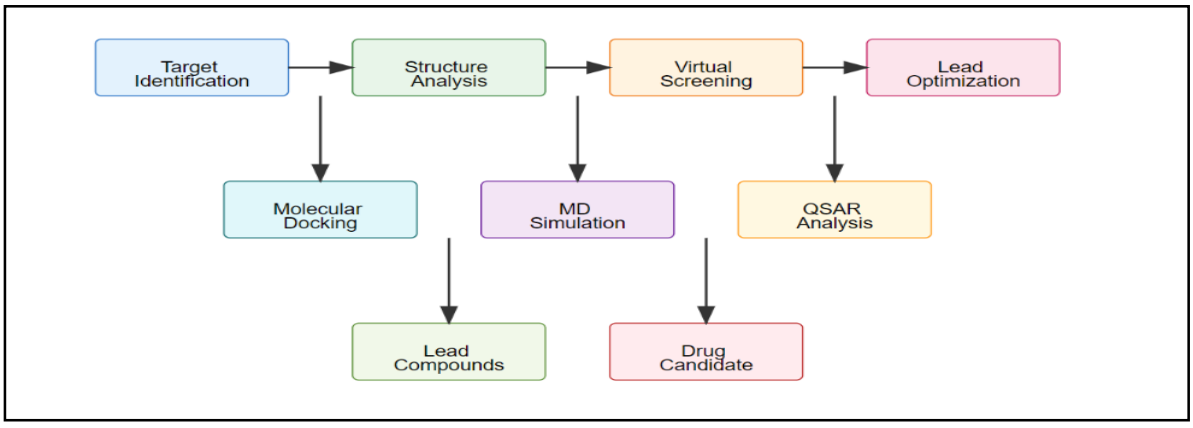

Figure no.5: Pipeline of Computer-Aided Drug Design

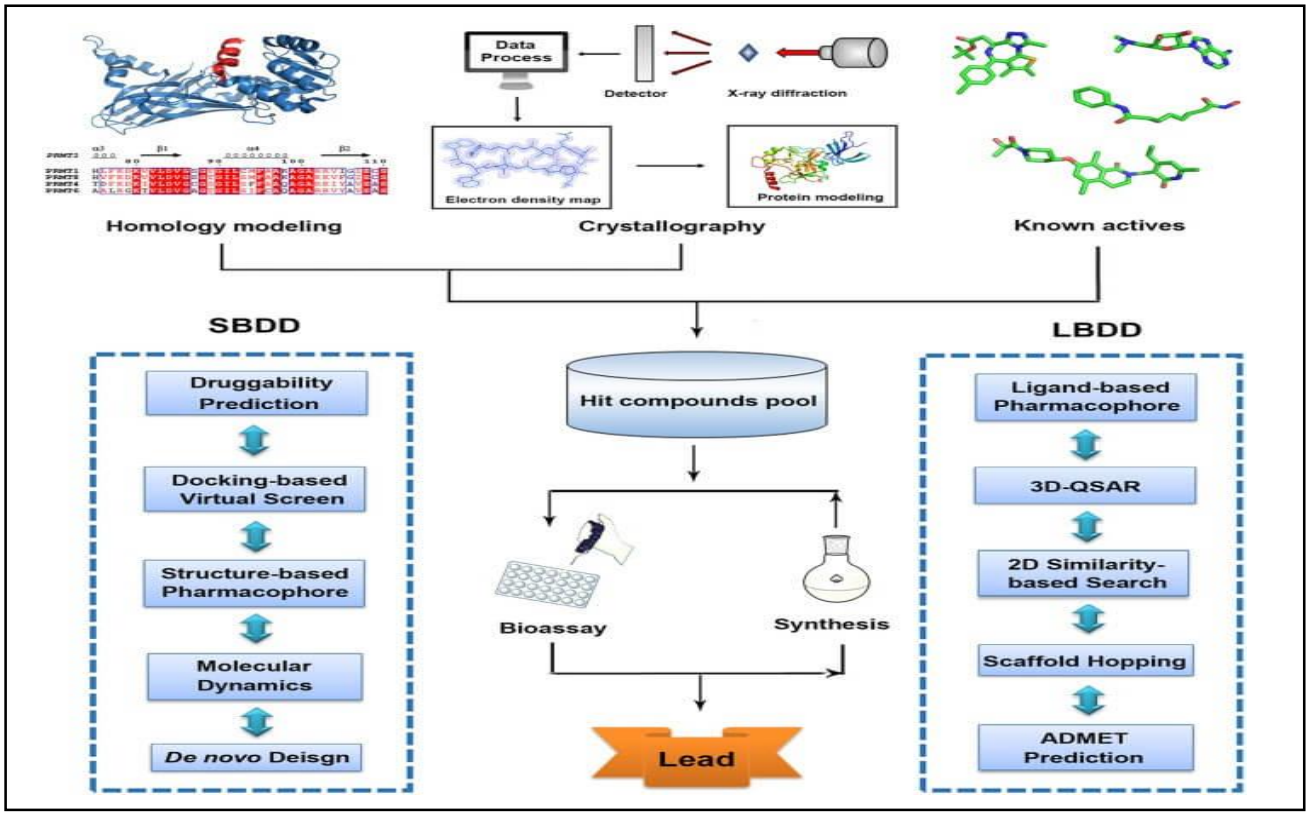

Fig.no.6.Overview of Structure-Based (SBDD) Ligand-Based (LBDD) Drug Design Methods

3.1 Types of CADD

1) Structure-based drug design or direct drug design:

The goal of structure-based drug design (SBDD), also known as direct drug design, is to create new therapeutic molecules that interact with the target protein more effectively. In SBDD, the structure of the target protein is known, and interaction or bio-affinity for all tested compounds iscalculated following the docking procedure. De novo drug design and virtual screening are both steps in the process known as "structure- based drug design" (SBDD). These techniques offer a highly effective alternate strategy for discovering and creating new medication designs. Drug chemical compounds are computationally screened against known target structures during virtual scanning. Rational drug design is very expensive and effective in traditional, advanced, or legacy drug design anddevelopment. Finding intriguing target proteins for small compound library screening is the first stage in the reverse pharmacology approach to rational drug creation.

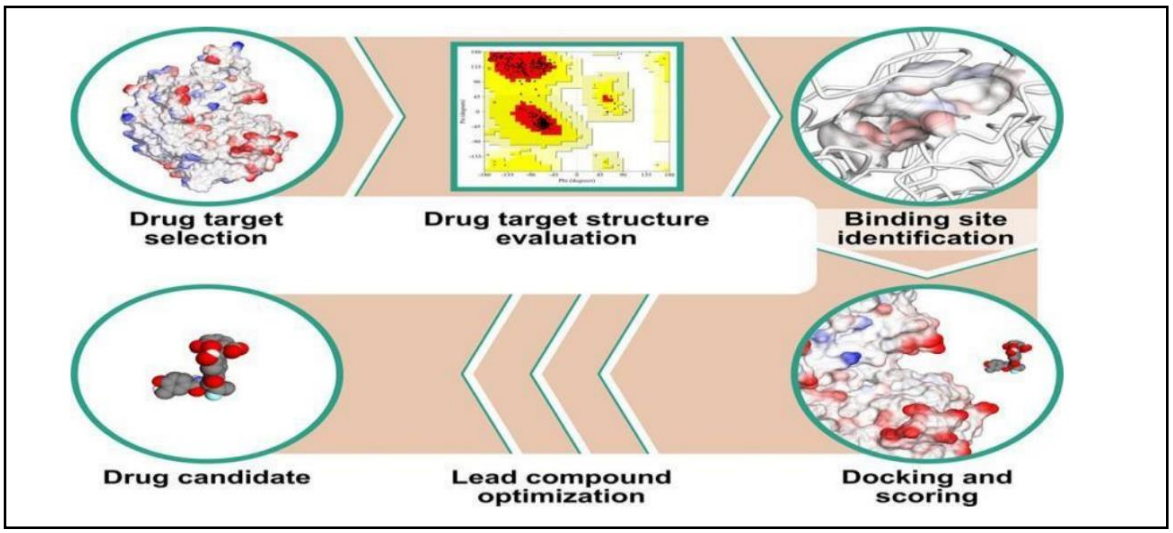

Fig.no.7 Structure-Based Drug Design from Target Selection to Drug Candidate

Because they are roughly related to the 3D structure of a Target protein, technologies including structure-based virtual scanning (SBVS), molecular docking, and molecular dynamics (MD) are utilised in SBDD, a more focused, effective, and quick procedure for lead discovery and optimisation. Analysis of disease and molecular binding energies, ligand protein interaction induction process. With the aid of some methodologies, SBDD has identified numerous medications, including thymidylate synthase inhibitors, raltitrexed, and possible HIV protease inhibitors. These were found using MD simulation and the drug norfloxacin. More than 100,000 proteins' three-dimensional (3D) structures are presented in SBDD.

2) Ligand Based Drug Design:

Target is a ligand in this approach. A relationship between a molecule's structural and electrical features and its biological activity is known as a structure-activity relationship (SAR).Compounds are designed using data from the CADD methodologies and then put through chemical synthesis and biological testing. In LBDD, the target protein's 3D structure is unknown, but it is known which ligands bind to the intended target location. These ligands can be used to create molecules or pharmacophoremodels that have all the structural characteristics required to bind to a target active site. Pharmacophore-based approaches and quantitative-structure activity relationships (QSARs) are two common ligand-based methodologies. In LBDD, it is presummated that substances with structural similarities also share the same biological properties and interactions with the target protein. Indirect drug design, also known as ligand-based drug design, is dependent on understanding the other molecules that bind to the desired biological target. These additional molecules can be utilised to create a pharmacophore model that specifies the minimal structural requirements for a chemical to bind to the target .A strategy called ligand-based drug design, which focuses on understanding of compounds that bind to the desired biological target, is employed in the lack of 3D information about the receptor. The most significant and often used methods in ligand-based drug design are pharmacophore modelling and 3D quantitative structure activity relationships (3D QSAR). They can offer forecasting models appropriate for lead optimisation and lead identification. Othersections of the

study provide more details on these techniques and how to use them to design andproduce 5-LOX inhibitors.[26]

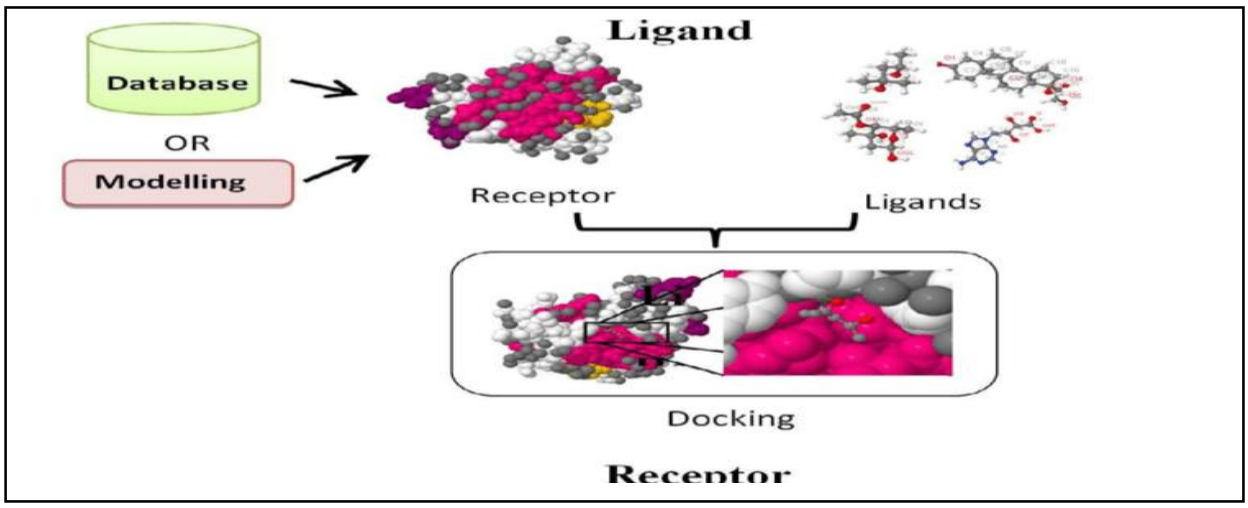

Fig.no.7.Workflow of Computer-Aided Drug Design (CADD) using Molecular Docking

Recently used Example of CADD:

Cancer:

Recently, the creation of anticancer drugs has been significantly impacted by the exponential expansion of computational techniques like computer-aided drug discovery (CADD). Faster, less expensive, and more effective medication creation is made possible by CADD, which also offers useful insights into the field of cancer therapy. Drug development is a difficult, drawn-out, expensive, and time-consuming process. It involves collaboration between various disciplines, such as medicinal chemistry, pharmacology, clinical research, drug metabolism, process chemistry, etc.

Drug : EGCG (Epigallocatechin-3-gallate)

Epigallocatechin-3-gallate (EGCG), the most abundant and well-studied catechin found in green tea, is a potent natural polyphenol recognized for its extensive therapeutic potential in preclinical research. It exerts its biological effects through multiple mechanisms, including its powerful antioxidant properties that protect against cellular damage from reactive oxygen species (ROS), as well as its anti-inflammatory, anticancer, and neuroprotective activities. In cancer studies, EGCG has been shown to interfere with various cancer hallmarks by inhibiting tumor growth, inducing programmed cell death (apoptosis), and suppressing the formation of new blood vessels (angiogenesis) necessary for tumor survival. For neurodegenerative diseases like Alzheimer's and Parkinson's, EGCG offers protection by combating oxidative stress and neuroinflammation and by inhibiting the aggregation of neurotoxic proteins. However, the promising results from laboratory studies have faced significant challenges in translating to effective clinical applications, primarily due to EGCG's poor oral bioavailability and rapid metabolism, which prevents it from reaching sufficiently high and stable concentrations in the bloodstream.[27]

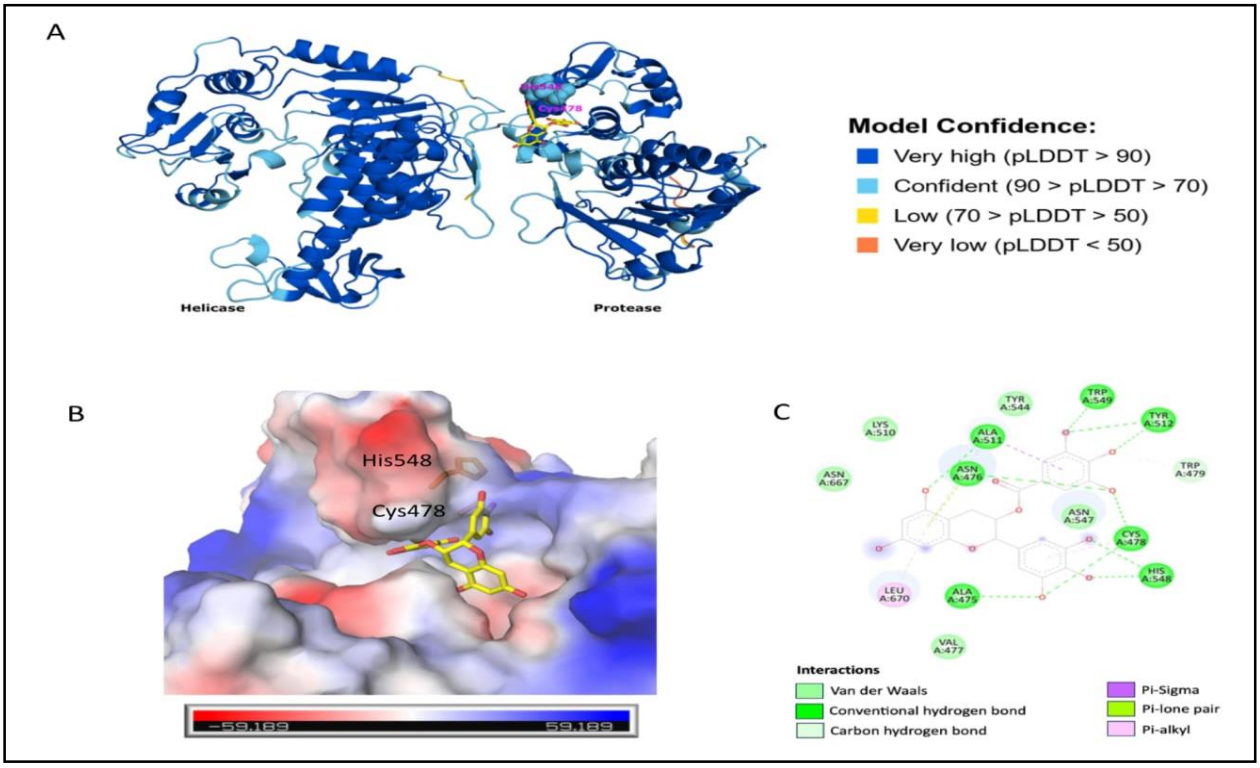

Fig.no.8.Molecular Docking Interaction of EGCG with Target Protein Involved in Cancer Inhibition

A) Main Mechanisms of EGCG in the Inhibition of Cancer

1. Inflammation

Inflammation a vital hallmark of progression and development of cancer, and raised inflammatory mediators are related to bad prognosis in patients with cancer. Some of the cancer related inflammatory factors involved in the development of cancer are tumor necrosis factor, chemokines, inflammasomes, transcription factors, cytokines, infiltrating or circulating immune cells, and ROS.[28] Tumor necrosis factor (TNF-α) is an important pro-inflammatory cytokine and is associated with inflammatory diseases or its altered function has been noticed in various cancers. However, suppression of NF-κb is an imperative footstep in the inhibition of cancer development and progression. Therefore, discovery of new anti-inflammatory compounds might be an auspicious line to inhibit the of inflammation-related cancers. EGCG, the essential compound of green tea has been found to possess anti-inflammatory potentiality and inhibits the pro-inflammatory cytokine activity. A study provided evidence that EGCG plays a starring role in the inhibition of TNF-α and can protect TNF-α-mediated lung inflammation through down-regulation of oxidative stress and intercellular adhesion molecule-1 expression (ICAM-1).

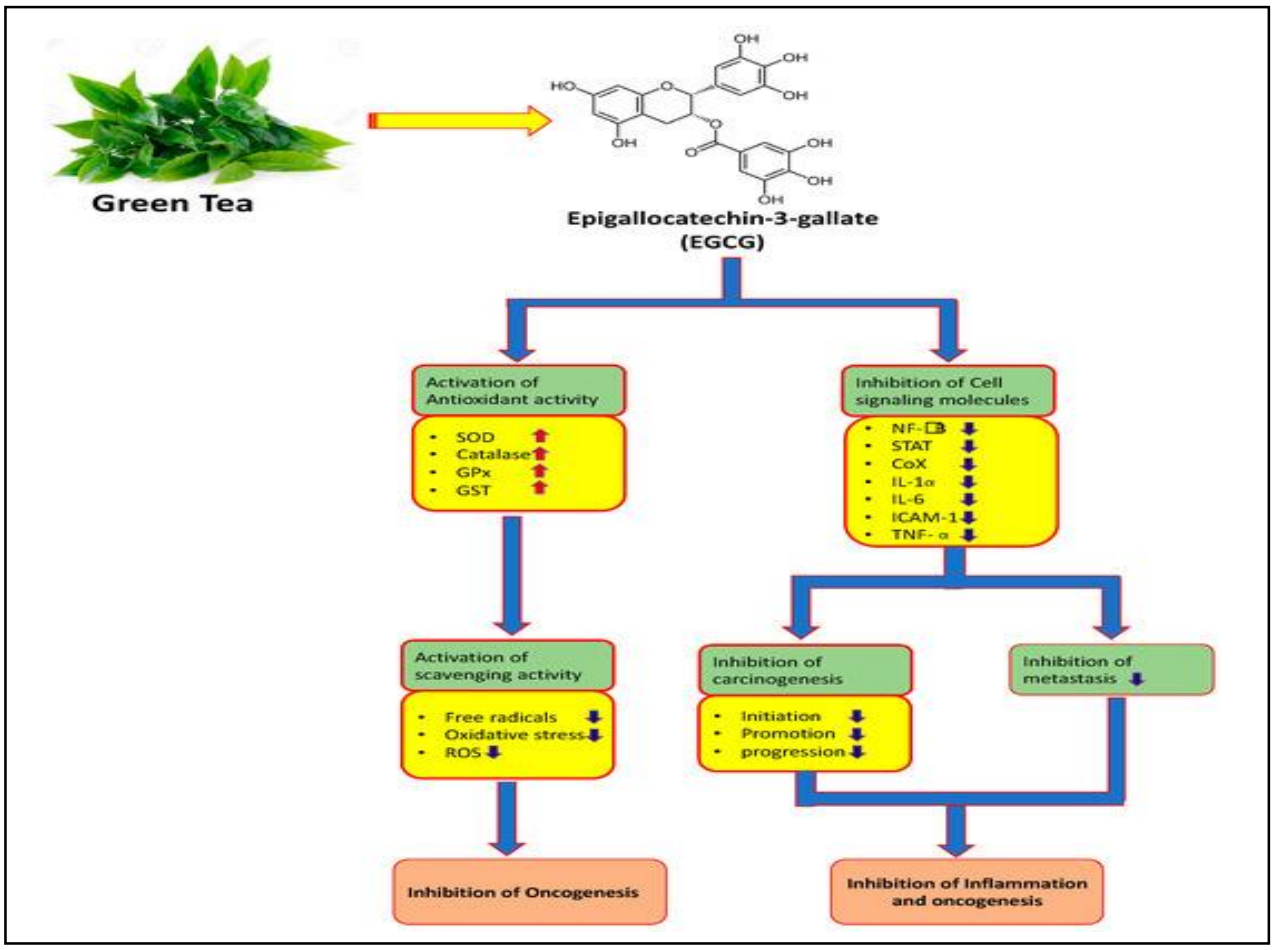

Figure no.9. EGCG shows role in the inhibition of inflammation and inhibition of oncogenesis through the abrogation of the reactive oxygen.

EGCG has been found to inhibit tumor necrosis factor-α (TNF-α)-induced production of monocyte chemoattractant protein-1 (MCP-1) in human umbilical vein endothelial cells. The result confirmed that EGCG meaningfully decreased the TNF-α-induced protein and mRNA expression of MCP-1. Moreover, EGCG suppresses TNF-α-induced MCP-1 expression in human umbilical vein endothelial cells and such effect was arbitrated by 67LR and was via the inhibition of NF-κB activation. Cyclooxygenase (COX)-2 overexpression has been noted in various cancers. However, its regulation is an important step towards cancer management. EGCG inhibits cyclooxygenase-2 without affecting COX-1 expression at both the mRNA and protein levels, in androgen-sensitive LNCaP and androgen-insensitive PC-3 human prostate carcinoma cells. Based on this finding, it is appealing to propose that a combination of EGCG with chemotherapeutic drugs could be a better plan for prevention and treatment of prostate cancer.[29]

2.Apoptosis

Apoptosis is known as controlled cell death and organized physiological process involve in the removal of damaged cells . The alteration in pro-apoptotic, anti-apoptotic proteins and, decreased caspase function has been noticed in many cancers. Natural/active compounds from medicinal plants play important role in cancer inhibition through induction of apoptosis. The induction of cancer cell apoptosis is the chief concern in anticancer compound research. A study based on the role of resveratrol in cancer described its anticancer action in pancreatic cancer cells through suppression of the expression of NAF-1

in pancreatic cancer cells via inducing cellular reactive oxygen species (ROS) accumulation and activating Nrf2 signaling.[30]

3.Tumor Suppressor Genes

Tumor suppressor genes are important gene as they are involved in inhibition of cell division, DNA damage repair and stimulation of apoptosis . Consequently, altered tumor suppression genes function lead in the development and progression of cancer. However, normal functioning of tumor suppressor genes is crucial in the inhibition of tumor development and progression. Reported that EGCG activates p53 in human prostate cancer cells . EGCG plays crucial role in the inhibition of anchorage-independent growth of human lung cancer cells through upregulating p53 expression. Besides, EGCG action can considerably increase p53 stability and encourage nuclear localization of p53. EGCG is capable of decreasing proliferation and inducing the apoptosis of pancreatic cancer cells linked with the expression of PTEN. Moreover, EGCG subdues the expressionof p-Akt and p-mTOR through PTEN to regulate the PI3K/Akt/mTOR pathway [31]

4. Cell Cycle

The uncontrolled cell cycle plays a crucial role in the development and progression of cancer. The simultaneous action of several cellular signaling pathways which control cell cycle and apoptosis, is an important strategy to control cancer cell proliferation and the growth and progress of a tumor.Natural products or active compounds from medicinal plants show anti-tumor activity through the induction of cell cycle arrest. A pioneering study demonstrated that combined EGCG and cisplatin treatment showed a synergistic cytotoxic in biliary tract cancer cell lines. Furthermore, EGCG decreases the mRNA levels of innumerable cell cycle-related genes, but enhances the expression of the cell cycle inhibitor p21 and the apoptosis-related death receptor 5. Moreover, EGCG induces apoptosis in various ways including modulating pro- and anti-apoptotic proteins and cell
cycle regulator proteins .[32]

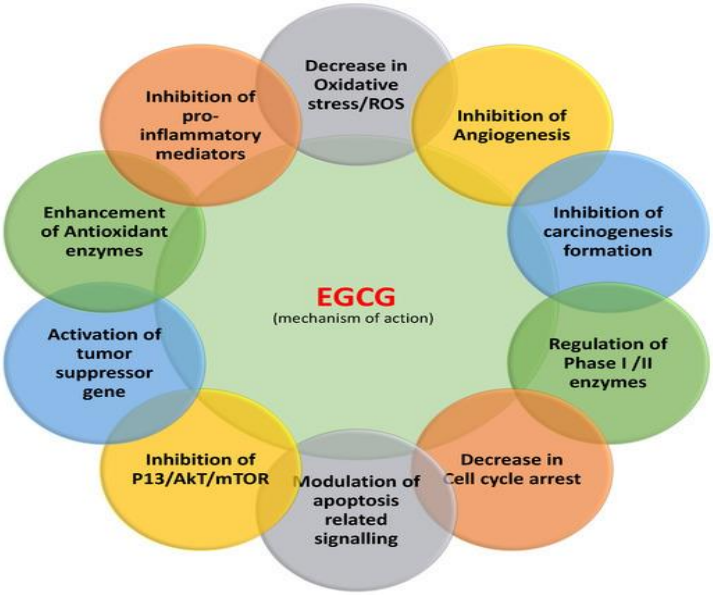

Fig no.10. Mechanism of action of EGCG in cancer management through modulating various cell signaling pathways.

Conclusions

Despite considerable recent progress, cancer continues to represent a major cause of mortality and morbidity worldwide. It is a notorious killer, and risk factors linked with cancer seem to be increasing day by day. Anticancer drugs are e_ective in the treatment of cancer but cause adverse side including fatigue, hair loss, infection, nausea and vomiting, appetite complications and changes in physiological and biochemical processes. Natural products have been shown to play significant role in cancer prevention and inhibition through modulating various biological activities. Epigallocatechin-3-gallate, the most abundant catechin in tea, and its implication in health care and disease prevention has been described. EGCG is reported to possess antioxidant, anti-inflammatory and anticancer activities.Preclinical and clinical evidence clearly shows that EGCG plays a significant rolein the inhibition and prevention of cancer. Cancer development and progression is a multi-step process and normal cells convert to the metastatic stage through carcinogenesis. EGCG shows an anti-cancerous inhibition of initiation, promotion and progression stages. The additive or synergistic e_ect of EGCG with chemopreventive agents has been proven to enhance the anti-cancerous activity and reduce the toxicities. Poor bioavailability, rapid metabolism and fast elimination of EGCG compound caused a limitation of this compound in health management. However, nanotechnology-based strategies are being used as delivery means to enhance the bioavailability of EGCG.[33]

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