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(REVIEW ARTICLE)

Drug discovery, explain how lead compound delivers to the target site and claim if there are recommended antiviral drugs to COVID-19.

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Abstract

Drug design is a long and costly process taking many stages; start with target identification passing through target validation, lead identification, and candidate optimization of pre-clinical and clinical trials. Drug design types depend on screening of a large number of molecules to distinguish and can select the most effective drug with high pharmaceutical effect. Ligand and Structure Based Drug Design are the two types of drug design. The drug takes journey when administered into the body through several ways (oral, inhalation, Intravenous (IV), Intramuscular (IM)) to deliver its target site. Twenty years ago, Computational strategies applied to understand particular target molecules with hits achieving lead target and that helps in lead Identification and Optimization stages of drug design and development. Screening, molecular modification and rational drug design are the three approaches to search for a modern drug. Bioinformatics plays a vital role in the discovery of drug as Bioinformatics includes both the programmed preparing of huge amounts of existing information and the creation of modern sorts of data resource. Both required in case the information is to be changed into data and utilized to assist in drug discovery. This work will discuss what is the meaning of drug design? What are the stages of drug design? What are the drug design types? Computer- Aided Drug Design (CAAD), Approaches in the search for a new drug, What is the journey of drug to deliver its target site? What are the methods of drug delivery? And will discuss the recommended antiviral therapy in the management of COVID-19.

Keywords: Drug design; CAAD; Antiviral drugs; COVID-19; Lopinavir-Ritonavir; Drug delivery.

1. Introduction

The drug is a small organic molecule that has a role in stimulating another biomolecule or blocking its function like protein, which leads to a therapeutic benefit for the patient, so drug design by includes designing molecules that relate to and interact with the biomolecular target, and which complement it in shape and charge [1].

Drug design is a long and costly process that includes different fields of activity. Drug administration depends on dosages that based on the individual size and age. "Dose-response curves" are graphs show a relationship between the desired effect of the drug and the drug administered amount, and another curve showing the sum of medicate that causes maximal side effects. Pharmacologists prove drug efficiency using this data and provide a drug safe dosage for doctors to describe the safe dose to their patients [2].

Often the computer is used in drug design - this type of design is called computer aided design, but it is not necessary to rely entirely on it. Drug delivery is a pharmaceutical process to achieve a therapeutic effect in a person or animal in order to deliver the active material (lead) to the place to be treated (target). There are several ways to deliver the drug such as: mouth, skin, through the mucous (nose, oral / hypersensitive, vaginal, visual and cross rectum) and by inhalation. Like many peptide and protein drugs, antibodies, vaccines and genetic drugs [3].

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2. Drug design stages

Drug discovery and design starts with the selection of a disease then drug target after that define biological assay to test biological activity, design of the drug depends on many variables including how drug deals with the body and also the response of the body to administrated drug, so affected by drug absorbency into the body, its activity, how long it still active, and its toxic effect. Knowledge the complementary structures of target molecules that fit the drug, creating the most suitable and effective drug. Subsequently, molecules that clearly don't fit the target will consequently be known to not work in its show state and ought to be ignored [3].

Developing a new drug is a complex process prolongs from 12 to 15 years and costs more than $1 billion. It takes many years to make evidence before choosing a target. Once a target selected, the pharmaceutical industry and academic centers launched processes to identify suitable molecules with characteristics to make acceptable drugs. When academia finds disease without suitable medical products, the programme of drug discovery starts. First research is generating data to build a hypothesis that indicates protein inhibition or activation or shows disease state. The selection of a target is the result of this activity, that require more validation to progression into the phase of lead discovery in order to verify effort of drug discovery as shown in (figure 1). During lead discovery, the search finds a drug-like small molecule that called development candidate that will lead to preclinical, and if it is successful, will progress to clinical development as shown in (Figure 2) and then go to market [4].

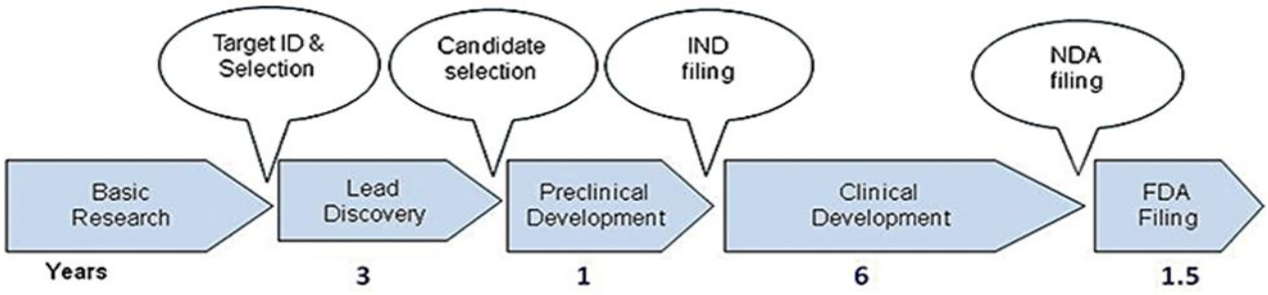

Figure 1 Drug discovery stages from target identification and validation until filling through FDA (Food and Drug Administration); IND (Investigational New Drug); NDA (New Drug Application) [4].

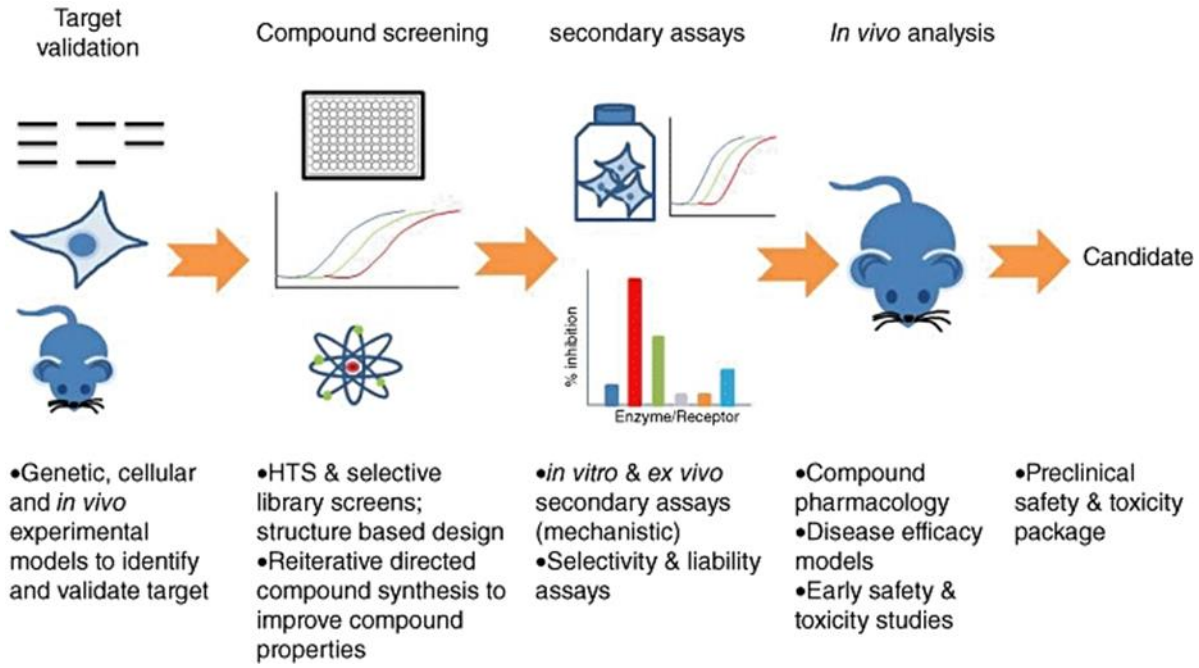

Figure 2 Drug discovery screening assays overview [4].

2.1. Target identification

Is the most important stage in drug development process, a target is a biological molecules such as; proteins, RNA and genes. Target required being: safe, officious and fulfill commercial and clinical needs. This stage examines the level of mRNA/protein expression and determines if they correlate with the disease. Or search for genetic associations as disease changes genetic polymorphism function; for example: (AD) Alzheimer's disease causes mutation in amyloid precursor protein or presenilin genes that lead to the production and deposition in the brain with increased amounts of the Abeta peptide. Or use phenotypic screening to recognize disease that relevant to targets [4].

2.2. Target validation

Once the target selected, start determine SAR (Structure-Activity Relationship) and predict molecular target, target validation performed at three levels: the molecular, the cellular and the whole animal model level [5].

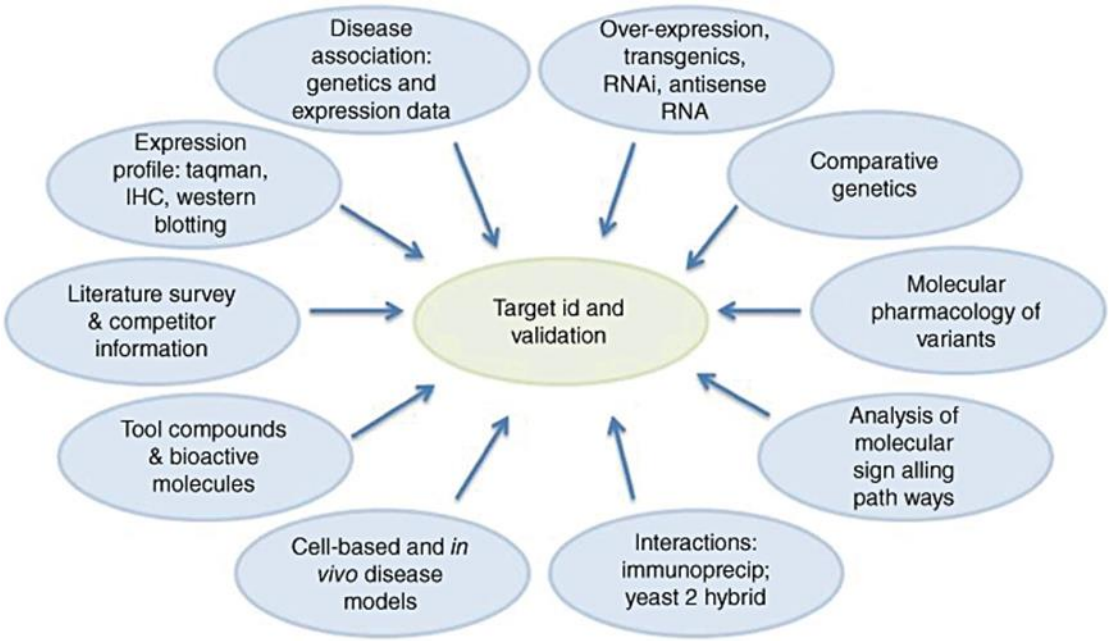

Figure 3 Validation techniques from in vitro tools to use whole animal models [4]**.**

Pharmaceutical companies built organizations to screen compounds to distinguish at first hit molecules from HTS or other screening standards and to optimize those screening 'hits' into clinical candidates. **[**4**]**.

2.3. The hit discovery process

(or lead identification) after target validation, 'hit' is a molecule that has the desired activity identified after screening as shown in (table 1)**.**

Table 1 Screening process [4].

Screen	Description
High throughput	Analyze huge number of compounds in plate with 384 wells.
Focused screen	Screening previously identified Compounds (ex: kinases).
Fragment screen	Soak small compounds to get low mM activity compounds.
Structural aided drug design	Design molecules by using crystal structures.
Virtual screen	Develop more compounds depending on integration of virtual compound with the X-ray structure of target protein.
Physiological screen	Determine the effects of a drug on the tissue.
NMR screen	Screen small compounds.

2.4. Candidate optimization phase

It is important to maintain desirable properties in lead compounds and minimize side effects to be ready to final characterization before preclinical trials [4].

3. Types of Drug Design

Drug discovery and design based type depends on screening of huge number of molecules to distinguish and select an effective drug.

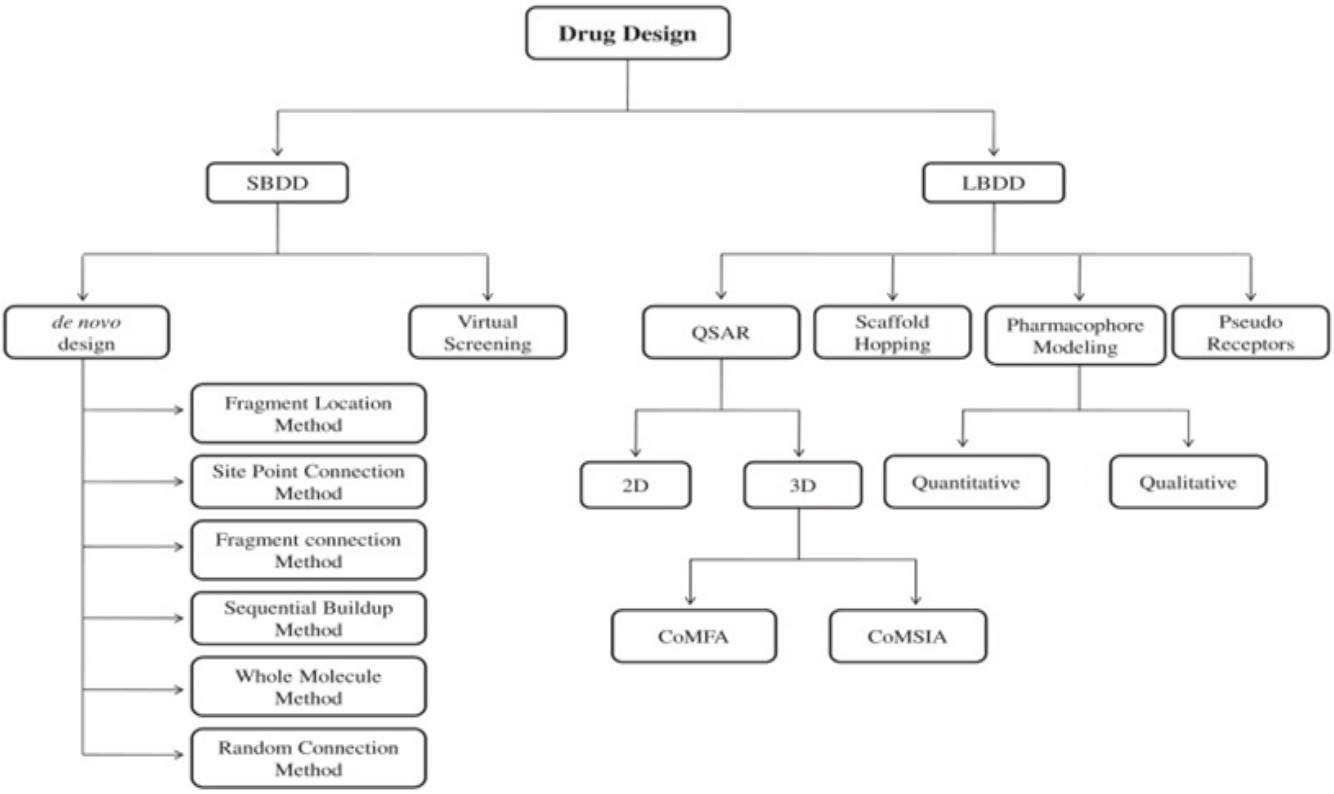

Figure 4 Ligand and Structure Based Drug Design [3].

3.1. ligand Based Drug Design

Is an approach utilized within the nonappearance of the receptor 3D data and it depends on information of molecules that tie to the organic target of intrigued. 3D quantitative structure movement connections (3D QSAR) and pharmacophore modeling are the foremost imperative and broadly utilized tools in ligand based medicate plan. The other type of drug design is (structure base design) [3].

3.2. Structure Based Drug Design

Process of structure-based drug design continues through different cycles some time recently an optimized lead goes into phase I clinical trials. The primary cycle incorporates the cloning, purification and structure assurance of the target protein or nucleic acid by one of three vital strategies: X-ray crystallography, NMR, or homology modeling. Utilizing computer algorithms, compounds or parts of compounds from a database are situated into a chosen locale of the structure. These compounds are scored and positioned based on their steric and electrostatic intuitive with the target location, and the leading compounds are tested with biochemical tests. Within the second cycle, structure assurance of the target in complex with a promising lead from the primary cycle, one with at least micro molar inhibition in vitro, uncovers locales on the compound that can be optimized to extend potency. Extra cycles incorporate synthesis of the optimized lead, structure determination of the unused target- lead complex, and assist optimization of the lead compound [6].

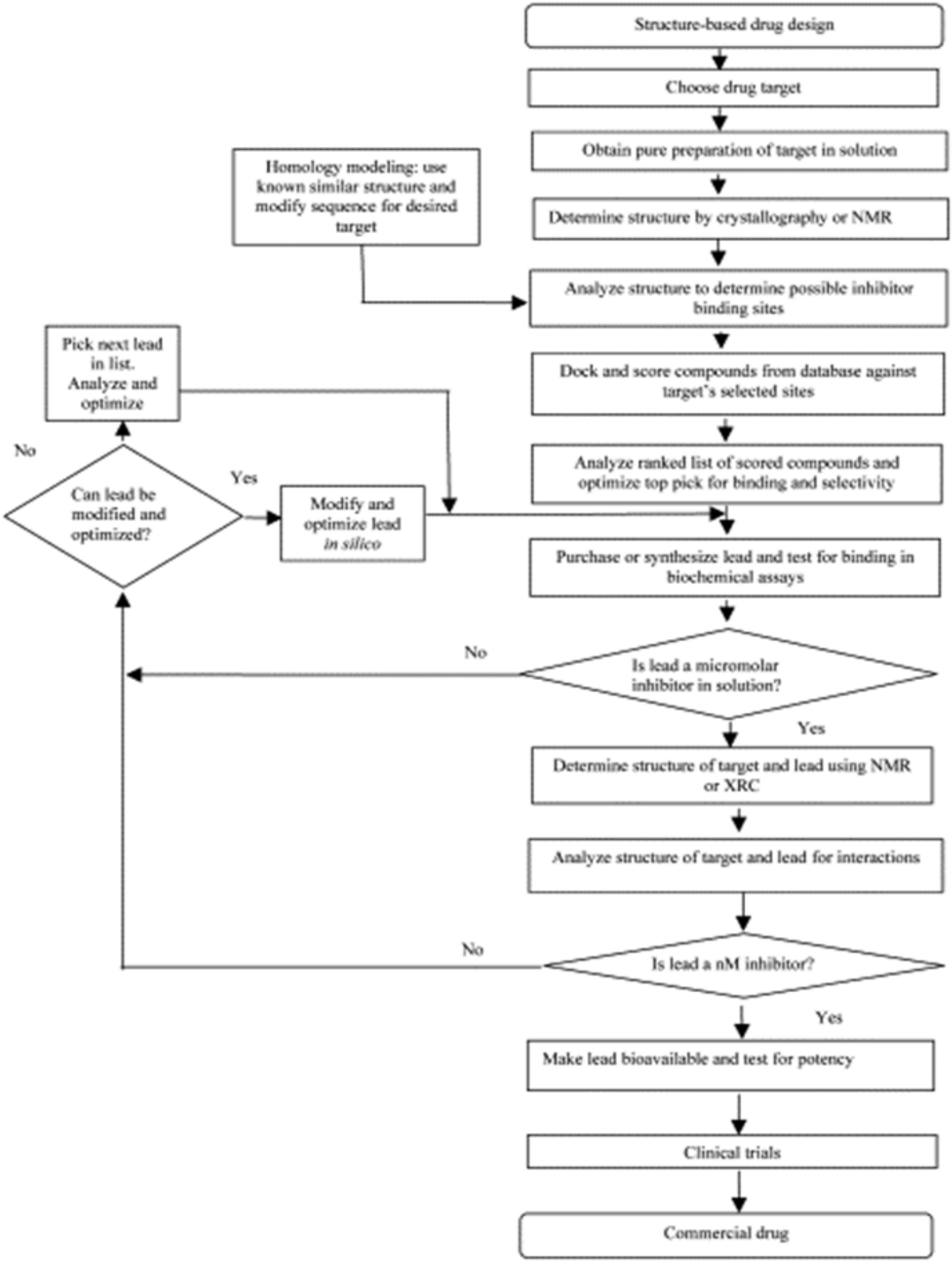

Figure 5 Structure-Based Drug Design process [6].

4. Computer-aided drug design

Traditional ways to drug design are costly and time consuming processes. From twenty years ago efforts exerted to apply computational control to the combined chemical and natural space in arrange to streamline sedate revelation, plan, improvement and optimization.

Computational strategies are anticipated to play a basic part in understanding the particular molecules acknowledgment occasions of the target macromolecule with candidate hits driving to the plan of made strides leads for the target. CAAD approaches have been widely employed in Lead Identification and Optimization stages of drug design and development.

When compare CAAD to conventional drug design strategies bring down the time and taken a toll included in drug advancement prepare. It can be utilized to identify/design modern inhibitors de novo or for optimization of assimilation, conveyance, digestion system, excretion and harmfulness profile of distinguished particles from different sources. Progresses in computational procedures and equipment have encouraged the application of in silico strategies within the disclosure handle [3].

CAAD employments computational approaches to find, create, and analyze drugs and comparative naturally dynamic atoms. The ligand-based computer-aided drug discovery (LB-CADD) approach includes the examination of ligands known to associate with a target of intrigued.

The fundamental objective of these strategies is to anticipate the nature and quality of binding of given molecule a target and use a group of reference structures collected from compounds known to connect with the target of intrigued and analyzes their 2D or 3D structures [8].

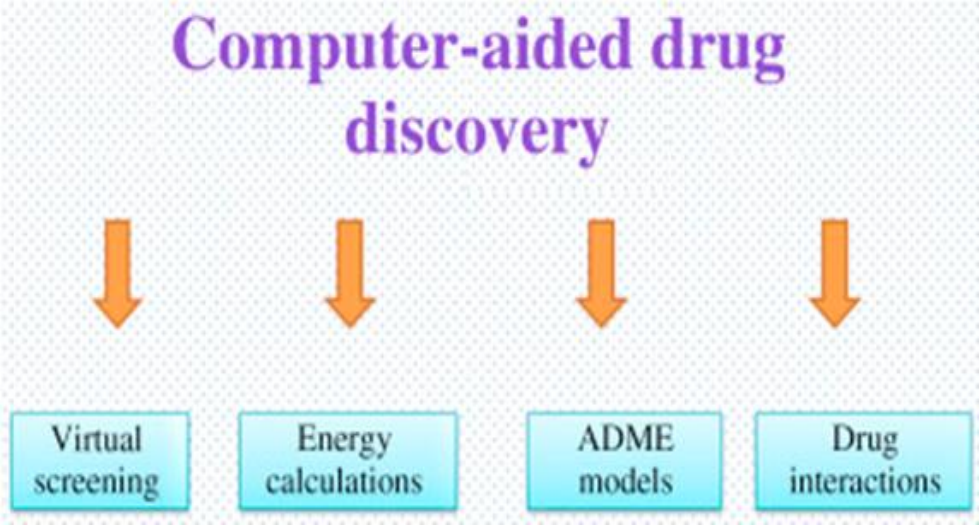

Figure 6 Computer-Aided Drug Design [7].

5. Three approaches in the search for a new drug

5.1. Screening approach

- Random screening: only approach before 1935; for example: (streptomycin- tetracyclines).
- Non-random: (targeted) screening compounds related to active matter (lead).

5.2. The molecular modification approach

This approach of presenting basic changes into known drugs can, for case, increase the action, or adjust the range of movement, diminish side effects or increase the length of activity of the drug. Noteworthy efforts have been made to connect structural and physicochemical parameters with bio pharmacological properties. These efforts have been effective some of the time. Regularly, auxiliary changes known to be associated with the particular impact have been

attempted, for case, to esterify side bunches in arrange to drag out the length of activity. For example; (neuroleptic drugs) [1].

5.3. Rational Drug Design

Rational drug design is the development of medications depend on the structures and functions of target molecules and use a methodological approach to design a new drug instead of testing randomly hundreds of drug molecules hoping for finding one of them can bind to a receptor and give a therapeutic effect. it is done in three stages

- Stage 1. Recognize a receptor or protein that's pertinent to a disease they are aiming to design a drug for.
- Stage 2. Illustrate the receptor or enzyme structure and function.
- Stage 3. Use information from stage 2 to design an effective drug binding with receptor therapeutically perfect [9].

6. Development of antiviral drugs and recommended drug for COVID-19

6.1. Overview of antiviral drugs discovery

Antiviral drugs discovery is a complex process, the first antiviral drugs directed to treat herpes, polio, smallpox and influenza. Now there are almost 50 antiviral drugs approved from FDA [10].

Table 2 Developed antiviral compounds approved for use in humans) [10].

Name	Class	Target virus	Year of discovery
β-Thiosemicarbazone	imine derivative	*Broad Spectrum*	1949
Interferon	cytokine (Immunomodulator)	*Broad Spectrum*	1954, 1957
Idu	NA	*Herpes Simplex*	1959
Hydroxybenzyl-Benzimidazole	UD	*Broad Spectrum*	1961
Marboran	UD	DNA viruses	1963
Tft	NA	*Herpes Simplex*	1964
Amantadine, Rimantadine	UD	Influenza	1964
Ara-A	NA	*Herpes Simplex*	1964
Aciclovir	NA	Herpes	1971
Ribavirin	NA	*Broad Spectrum*	1972
Dhpa-Dihydroxypropyladenine	NA	*Broad Spectrum*	1978
Phosphonoformicacid (Foscarnet)	PA	Herpes, Cytomegalovrus	1979
Bvdu (Brivudin)	NA	Herpes	1979
Ganciclovir	NA	Herpes, Cytomegalovrus	1982
Azidothimidine (Azt, Zidovudine)	NARTI	HIV	1985
Ddc (Hivid, Zalcitabine)	NARTI	HIV	1986
Ddl (Videx, Didanosine)	NARTI	HIV	1987
D4t (Serit, Stavudine)	NARTI	HIV	1987
Cidofovir	NA	HIV	1988
Famciclovir	NA	HIV	1989
Hept/Tibo	NNRTI	HIV	1990

Nevirapine (Viramune)	NNRTI	HIV	1990
3tc (Epivir, Lamivudine)	NARTI	HIV	1991
Saquinavir	PI	HIV	1991
Doconasol	FI	HIV	1991
Zanamivir (Relenza)	NI	HIV	1993
Delavirdine (Recriptor)	NNRTI	HIV	1993
Indinavir (Crixivan)	PI	HIV	1994
Tenofovir	NA	HIV	1995
Efivarenz	NNRTI	HIV	1995
Amprenavir (Agenerase)	PI	HIV	1995
Ritonavir (Norvir)	PI	HIV	1995
Enfuvirtide	FI	HIV	1996
Oseltamivir (Tamiflu)	NI	influenza	1997
Lopinavir	PI	HIV	1998
Entecavir	NA	Hepatitis b	2000
Peramivir	NI	Influenza	2000
Adefovir	NARTI	HBV	2000
Atazanavir	PI	HIV	2000
Darunavir	PI	HIV	2003
Taribavirin	NA	*Broad Spectrum*	2003
Telaprevir	PI	HCV	2004
Maraviroc	RA	HIV	2005
Raltegravir	II	HIV	2005
Boceprevir	PI	HCV	2006
Elvitegravir	II	HIV	2006

6.2. Mchanism of Action of Antiviral Drugs

6.2.1. Anti-viral targeting

Antiviral drug discovery idea is to identify viral proteins. The target protein should be common across many virus strains or among different species. When targets identified, drugs selected and designing the drug at the molecular level with a CAAD .The target proteins can also manufactured in the lab then testing by inserting the synthesized gene into bacteria[11].

6.2.2. Approaches by Virus life cycle stage

We can inhibit any of this stage to prevent virus causing infection.

6.2.3. Immune system stimulation

Or synthesize antibodies, protein molecules bind to a pathogen and mark it for attack by other immune system elements. Once target identified on the pathogen, they can synthesize amounts of identical "*monoclonal*" antibodies to connect up that target [11].

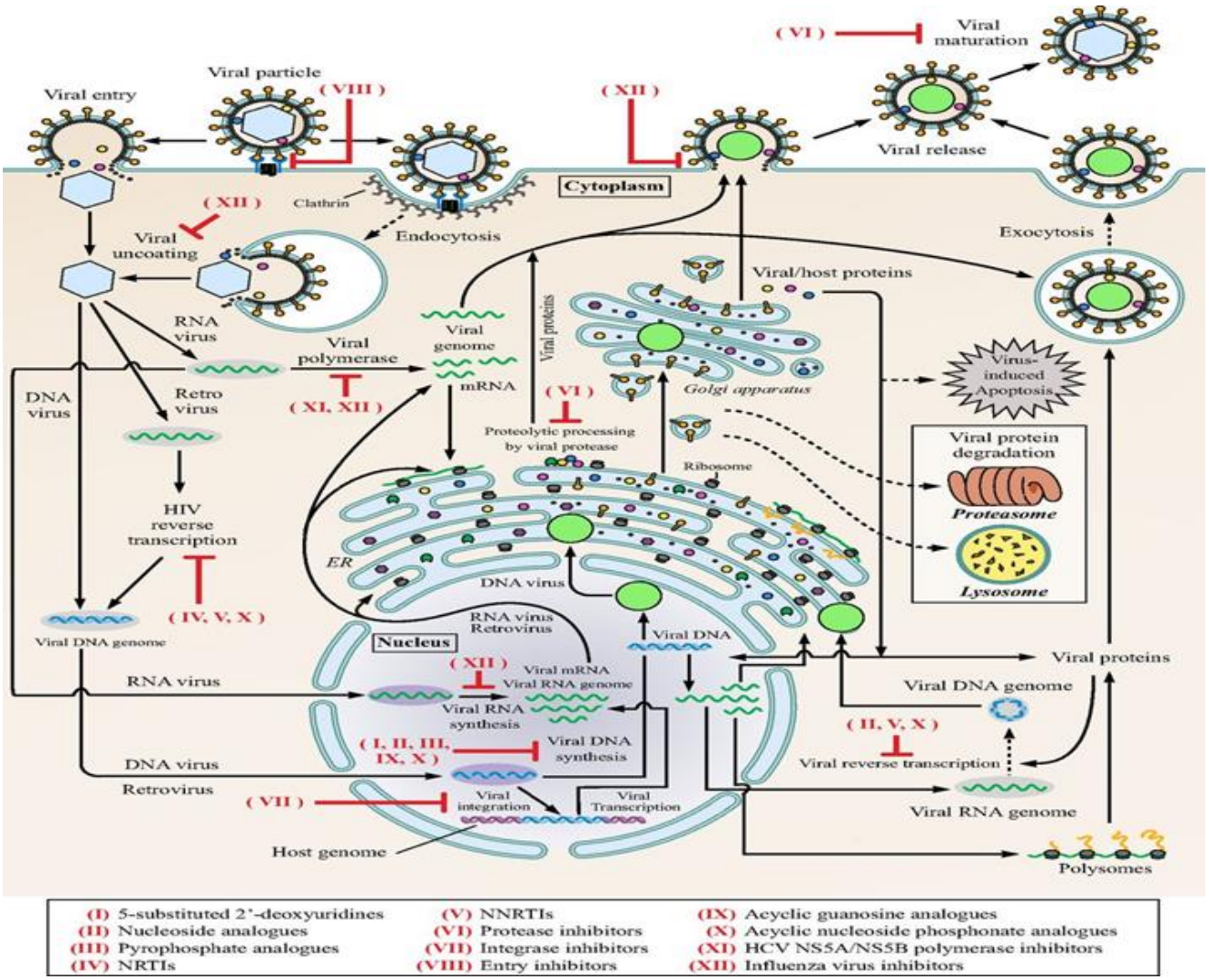

Figure 7 Mechanisms of drug actions during the viral life cycle from attachment target protein to the host cell membrane receptor, uncoding nucleocapsids and entering viral genome to cytoplasm of host, replication of viral genome and protein synthesis, assembly of viral components to form complete viral particles and release of viral particles [11].

6.3. Recommended antiviral therapy in management of COVID-19

There is only one clinical trial to test the efficiency of antiviral therapy in management of other corona viruses and performed on COVID-19 patients by using Lopinavir-Ritonavir regimen, unfortunately has no benefits and showed the inefficacy of antiviral drugs in treating COVID-19 [12].

Table 3 Anti-viral therapy clinical studies in management of COVID-19 [12].

Sample size	Age (year)	Patients status	Antiviral agent	Recovered patients (n)	Dose	Comment
199	58 (50 to 68)	Severe COVID-19 patients	Lopinavir/Ritonavir	99	400 mg/100 mg twice daily	Clinical improvement and mortality rate are similar in lopinavir–ritonavir treated and standard care groups.
99	21 -82	COVID-19 patients	Oseltamivir	75	75 mg twice a day	Recovery rate: 31%; Mortality rate: 11%
9	14 - 56	Symptomatic COVID-19	Lopinavir/Ritonavir	9	800 mg/200 mg daily	No mortality
1099	47.0 (IQR: 35.0–58.0)	severe and Non-severe COVID-19 patients	Oseltamivir	393	NR	did not reduce ICU and in bad need to ventilator or will death
24	5 – 95	Asymptomatic COVID-19 infection	Not specified	21	NR	No mortality, no ICU and no severe complication
41	49 (IQR 41·0–58·0)	Symptomatic COVID-19	Oseltamivir	38	NR	6 patients died 28 patients discharged
137	20 - 83	Severe COVID-19	Not specified	105	NR	during the study 16 patients died.
51	16 - 68	Discharged COVID-19 patients	Lopinavir/Ritonavir Oseltamivir Arbidol	51 7 2	NR	Stay at hospital from 9 to13 days. 1 patient died.
89	23 - 86	All COVID-19 patients admitted to a center	Lopinavir/Ritonavir Other anti-viral	84 5	NR	16 patients discharged and 1 patient died.
416	49 (IQR: 36-61)	Survived and dead COVID-19 patients	Not specified	380	NR	mortality rate (5.6% in non-treated), and 12.9 treated; p=0.288)
138	22 - 92	ICU and Non-ICU admitted COVID-19 patients	Oseltamivir	124	NR	6 patients died and 36 patients admitted to ICU
80	46.10± 15.42	All severity ranges of COVID-19	Ribavirin	80	NR	21 patients discharged and 59 patients stayed in hospital.

62	41 (IQR: 32-52)	Symptomatic COVID-19	Lopinavir/ritonavir Arbidol Lopinavir/ritonavir + Arbidol	25 1 21	Lopinavir 400 mg twice daily ritonavir 100 mg twice daily Arbidol 200 mg three time daily	One patient discharged. Other patients stayed in hospital
149	45.11± 13.35	All COVID-19 patients admitted to a center	Not specified	140	NR	No mortality. 73 patients discharged and 76 stayed in hospital.
18	31 -73	Symptomatic COVID-19	Lopinavir/ritonavir	5	NR	Two patients recovered and 2 other patients deteriorated. Only one patient completed the 12-day planned protocol. Four patients experienced antiviral therapy side effects
221	20 -96	Non-severe and severe confirmed COVID-19 patients	Not specified	196	NR	12 patients died. Chest CT improved after administration of ECMO and IMV
10	29 - 68	Confirmed COVID-19 patients	Lopinavir/ritonavir Arbidol	8 3	NR	1 patient died, 5 patients stayed hospitalized and 4 patients discharged
1	23	Diabetic patient with COVID-19	Oseltamivir/ Gancivlovire	1	NR	Patient discharged from hospital after 15 days
5	10 Months to 6 years	Children with COVID-19	Not specified	2	NR	No effect
1	54	Symptomatic COVID-19 patient	Lopinavir/ritonavir	1	75 mg twice a day/50 mg twice daily	Good recovery. It is not clear that the decreased load of virus is due to the nature of healing process or a result of anti-viral therapy
4	19-63	COVID-19 patients	Lopinavir/ritonavir Arbidol SFJDC	4	400 mg/100 mg twice daily 0.2 g, three time daily 2.08 g, three time daily	2 patients recovered and 2 patients remained in hospital
2	38	Symptomatic COVID-19 patients	oseltamivir and Arbidol	2	NR	Both patients recovered and discharged

7. How does the drug deliver its target?

7.1. Targeting of drugs

Drug faces two challenges to deliver target site and achieve ideal drug action; first one is to synthetize a drug molecule highly specific for the target. The stronger the relationship between drug and target, the less side effects. Second is releasing the drug (active material) from the carrier on the target site. Maybe best fitted as carriers are the generally insoluble polar phospholipids. These substances form in water a requested framework of one or more lipid bilayers known as liposomes that can carry distinctive water dissolvable drugs. Moreover, a lipid dissolvable substance, counting the hydrophobic regions of proteins, can be suited into the lipid space within the bilayers. A few of the physical characteristics of liposomes, for illustration measure, surface range and permeability for encased drugs, can be changed in a particular way. Through the control of the surface characteristics of liposomes, their capacity to recognize the specific target cells can be altogether increased [1].

The focusing on of drugs with liposomes can continue in two stages. Within the first stage, the carrier with the captured drug will recognize and enter the common target range. In the moment arrange, the drug will be freed from the carrier and will continue for target recognition and the modulation of the target work at the molecular level. In this way the drug will perform a specific remedial task which can be recognized as a helpful impact. For illustration, the carrier-drug complex comprising of a liposome and actinomycin D associated with a carrier-recognizing receptor on the cell membrane, actuating endocytosis of the liposome-actinomycin D complex. After a subsequent interiorization into the lysosome, lysosomal esterases free actinomycin D. This drug enters the nucleus, ties to DNA and restrains DNA-directed RNA blend [1].

8. Conclusion

Research centers work on drugs to design effective pharmaceutical drugs and develop the quality of drug in the market seeking to overcome diseases and help patients' recovery in rapid and more effective way, within the future the objective is to supply tailor-made drugs for each person. The thought is that a drug will be planned based on the people DNA grouping which describes the individual's personal organic chemistry. The desire behind usually for a drug that's more successful which causes less side impacts. The want for tailor-made drugs was not indeed a reasonable venture less than a decade back, but with the extraordinary progresses in DNA sequencing this dream may ended up a reality in a few of decades.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no conflict of interest.

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