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Emerging Concepts in Medicinal Chemistry for Development of High Potency Drugs and Diagnostics

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Abstract

This article explains dire need of highly effective drugs as most of the antibiotics are either failed to do action as microbes have developed multiple resistance. This article pertains with new innovative methods of synthesis or development of new drug, its delivery, biological interactions and safety measurements. It also sketches out important views to have potential drug molecules to minimize health concerns, enhancement of biosafety, fastest analytical and bio-analytical diagnostics. It also explains combination of multifunctional nano scale system, synthesis of enzyme inhibitors, chemo selective conjugates, synergistic combinatorial drugs, epigenetic therapy to obstruct metabolic pathways in microbes that could control pathogenicity. It also explains use of carbon-based nano materials, various metal complexes are used for inhibition of tumor growth and progression. This article shortly emphasize new polymeric molecules i.e. dendrimers, composite drugs, drug stabilizers, conjugates and carriers, pharmacophore which have great therapeutic value. Modern therapeutics needs molecular recognition of a ligand by specific receptors on cell surface, modifiers and carriers are in high need. Heterocyclic compounds are good antimicrobial and anticancer agents as they show wide spectrum of biological activities. Antimicrobial peptides (AMPs), critical components of the innate immune system, are widely distributed throughout the animal and plant kingdoms. Animal toxins can be used as drug templates, these natural molecules specifically target ion channels and receptors of both the central and peripheral nervous system, interfering with action potential conduction and/or synaptic transmission. These could be used for treatment of infectious diseases and cancer. Cheminformatics is used to design new drugs with help of computer, simulations and *In Silico* testing of drugs is done that has reduced a range of problems in the field of medicinal chemistry. Development of new effective drugs and disease control is a greater task because of multiple drug resistance. It could be solved by using natural compounds as drug molecules by making some modifications and additions to them. Drug must be of low cost so that under privileged class can easily get a treatment with new novel drug molecules, it will help us to fight against drug resistance.

Keywords: Broad spectrum antibiotics; Drug catabolizing genes; Biological scissor; Biological interactions; Microbial diseases.

Abbreviations: AMPs: Antimicrobial Peptides; QqTOF: Hybrid Quadrupole-Time-of-Flight; NCE: New Chemical Entities; UHPLC: Ultra High Performance Liquid Chromatography; FRP: Fibre-Reinforced Plastics; iNOS: Inducible Nitric Oxide Synthase; NO: Nitric Oxide; VEGF: Vascular Endothelial Growth Factors; AC: Androctonus Crassicauda; LQ: Leiurus Quinquestriatus; AAP: Analgesic-

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Antitumor Peptide

Introduction

In last three decade thousands of drugs have been failed and lost their anti-pathogenic potential. Almost against old drug formula microbes have acquired resistance. They have proved much stronger as their genetic system favors for acquiring micro-adaptations very fast. A far reaching truth about microbes is that they are unconquered because of their survival capacity in extremes of temperatures, deficient nutritional conditions and very high reproduction ability for their very fast multiplication. They show wider host selection, niche variability inside host body, hence they generate so many pathogenicity types or generate spectrum of diseases. There is a strong tug of war between drugs mainly antibiotics and pathogens which possess drug catabolizing genes. There are thousands of broad spectrum antibiotics are in use to control disease pathogens, but unfortunately developing drug resistance to most of these drugs has created situation more alarming and a large scale pharmaceutical business seems to be worthless because drug target specificity or killing power has been foiled by the microbes as they have developed drug cleaving enzyme system. There is an open struggle going on between man and microbes since their genesis on the earth.

Microbes have had three special weapons i.e. genes for high survival and selection in nature, high reproduction rate; and pathogenicity and rising resistance against chemical drugs and environmental factors. They have much stronger genetic system that favors them for gearing micro-adaptations very fast. A far reaching truth about microbes is that they are unconquered because of their survival capacity in extremes of temperatures, deficient nutritional conditions or on minimal medium and finest reproduction ability which they use for their very fast multiplication. They show wider host selection, niche variability inside host body, hence they generate so many pathogenicity types or generate spectrum of diseases. There is a strong tug of war between drugs mainly antibiotics and pathogens which possess drug catabolizing genes [1,2].

Microbes are good example of negative and positive selection, as they are increasing their genetic ability to catalyze broad spectrum drugs and converting non-pathogenic strains into pathogenic one. In spite of the fact that new medicines are coming with an increase in killing power to eliminate microbes, but it seems very hard because nature has provided them enormous power inform of biological scissor i.e. enzyme system I and II to nullify the action of drug. There is no single drug that is not under enzyme catalysis because microbes generate resistance accordingly. Are we ready to fight war against drug-resistant strains, only answer is to search alternates of these drugs? As we stand and find easy way under artificial selection, but nature favors those who follow the path of natural selection that will take much longer time to seek fitness and success against self-generated resistance.

Man is a societal wise animal that is facing many risks due to opting artificial selection or developing non-natural drug spectrums whose accidental spills are responsible for rising resistance and eruption of communicable epidemics. There is circumstantial invasion of human society living in unhealthy environment under non sanitation habitat. Potential drugs for to treat debilitating human disorders. Recent thrust areas in medicinal chemistry such as drug absorption, metabolism, distribution, new and emerging drug targets, natural products, pharmacogenomics and structure and activity relationship are highly promoted and extended for most recent discoveries. It deals with the design, optimization, and development of chemical compounds for use as drugs.

Drug Resistance and Re-Emerging Diseases

Now condition is so verse that microbiologists, chemists, geneticists, molecular biologists and environmentalists are not finding much appropriate way to fight against emerging drug resistant strains [3]. The entire human society is living under fear of transformed multidrug resistant non treatable virus and bacteria generated diseases and their rising invading power across the continents. There is fight between non-compromising and compromising genetic system, it crushing control measures and challenging diagnostics. There is a rising helplessness in clinicians that large piles of antibiotics become worthless as proven potential of drug target has been foiled by the pathogens and increased the lethality in treated cases. Bacterial and virus genes are even pathogenicity in single host and utilizing inorganic elements from drug source for making their own structures and bio-organic molecules which are much harmful to human health. For attainment of workable resistance we have to go for organics and natural foods and bio-organics as controlling agents for microbes and even insects. It is true that we intake very few allelopaths or naturals in daily meals that is not sufficient to achieve sizable protection, immunity to combat the disease.

Normally we depend for utilizables from 30-40 plant species or 20-30 animal species only. As our intake has little diversity of bio-molecules, that is not enough to fight against much diversified enzymatic system found in microbes. It is still unjustifiable that who will win the race, a less ecologically fit or highly fit with micro-adaptations.

It is true that our faults are read by microbes to have more mutations, more selection and survival. We have to follow nature's path and believe in control, not in elimination or eradiation. More apparently mutations have occurred in favor of bacterial survival that allows the microbes even in the presence of drug. Microbes much ably altered the protein receptors by making change in their structure. These make site specific changes in epitopic regions by replacing amino acid through mutation. This is two side attacks one through changing receptor structure and function, and second cleaving the drug structure. It reduces the toxicity of drug and enhanced the drug dose level. In normal environment or micro-niche mutations that confer resistance to drug are rare or remain undetected.

Furthermore, the genetic switches found in bacterial genome accelerate recombination and induce genetic transformation. Thus, microbe become less susceptible to particular drug and show severe changes in behavior of genes and their prompt expression in new systems. On other side directive selection is going on bacteria and viruses and nonpathogenic strains becoming pathogenic or there is a shift from low virulence to high virulence. Few decades' back it was in thought that mutations conferring resistance are actually caused of induced by the drug but it is not true. It is a natural phenomenon that drug resistant mutations arise in bacterial cells irrespective of presence or absence of the drug. This is nature of pathogens that mutations occur simultaneously without exposure to drug, in confined or selective way.

Drugs and Their Usage

These wonder drugs have shown exceptional effectiveness against certain disease producing bacteria and contribute immeasurably to the saving of human lives since long past. But this effectiveness of drugs has been reduced by the emergence of resistant strains of bacteria. Development of new effective drugs and disease control is a greater task and fighting drug resistance [4]. In the past disease was an evil spirit now it is an evil behavior of microbes towards the drug. From time to time medicines have been passed through successive modifications in chemical formula reviewed for accomplishments, error corrections and tested for their modified target specificity against pathogens. It has been lead to advent of new drugs with increased cost and complexity of formula. With globalization of market, microbes have been adopt global attacks and transported through human traffic to new locations. Through modern human transport system and migration of refugee population, raw food materials, vectors, vaccines and shipping, microbes are spreading from endemic to epidemic zones where they are causing more devastation and lethality. Rising diseases and remerging diseases have been much favored by global climate change.

In addition, instant mutations in microbes failed the general methods of their identification, and new diagnostic facilities are costly and lacking in many countries. Hence, both most recent, effective and most appropriate drugs remain unaffordable to large section of people, and old drugs have very low effect or no effect. It has led to emergence of drug resistance and creating problems to new drugs as they are under cover of cross resistance. Besides, drugs microbes mainly viruses have reduced the effectiveness of vaccines, and converting vaccine strains into pathogenic strains. This is one of the major reasons that communicable diseases become out of control. Though modern medicines are more curable, preventive and based on multi-factorial causation, but these will become affordable at global level so that resistant strains could be suppressed before time. This will strengthen fight against diseases without discrimination of poor and rich, developed or undeveloped. However, all ultra-modern modalities, armamentariums, tools, techniques, drugs are to be used honestly to accomplish the objective. There are other treatments i.e. alternative, regenerative, preventive and social medicines besides chemical medicines which have great future to combat the disease mainly its significant count down in near future.

With strong medicinal chemical other supporting requirements i.e. prophylaxis, sanitary awakening, socialization of medicines, values, and conceptual changes be needed to improve the public health. In this fight all forces including, social, economic, political, and environmentalists, and researchers working in medicine, basic sciences, pharmaceuticals and medicinal chemistry, population biologists, microbiologists, and existing quarantine and information systems come together for achieving the target public health protection and eradication of diseases. Treatment of pathogens in endemic confinement is highly needful before its spread to new area. For achieving successful disease control, elimination and eradication are to be streamlined by applying the recent methods of monitoring, surveillance, and intervention in changing pattern of diseases.

Nano-scale drugs

For treatment of cancer new nano-therapeutic compounds have been synthesized by using various base materials such as hyaluronic acid-base, bacterial polyketides and saccharides and polymeric nano-particles conjugated with peptides. Nano-structured materials functionalized with ruthenium complexes are also made for targeted drug delivery for treatment of tumors. These

are also used to deliver natural active bioactive organics for prevention and treatment of cancer. Drug-Conjugate derivatives are prepared to control brain metastases for cancer treatment. Curcumin analogue 1,5-bis(4-hydroxy-3-((4-methylpiperazin-1-yl)methyl)phenyl)penta-1,4-dien-3-one, urosolic acid. BET Inhibitors, alkaloids and perillyl alcohol, lipoic acid, carntine esters are used for controlling metastasis [5]. Artemisinin-derived dimers, semi-synthetic artemisinin and whole sporozoite vaccination is used against malaria [6]. Indazole-based anticancer agents, fungal silver nano-particles, coumarin hybrids, dihydropyrimidinones, nucleoside analogues, nano scale antiretroviral agents such as dolutegravir, heterocyclic N-Oxides are made for the treatment of HIV. Few potential antiviral drugs are developed in form of peptides and small molecular HIV-1 RNase H Inhibitors. Interferon-based therapies and intranasal immunization with dry powder vaccines are also developed to fight against communicable viral diseases [7]. Nuclear factors are also used for getting anti-oxidant response signaling targets for otologic drugs [7]. Efforts are going on to reversing multidrug resistance, tumour-specific target ability and improved anticancer efficacy of nano-scale drug molecules.

Drug Delivery Methods

New innovative methods have been developed for drug and gene delivery [8]. Their main aim is to minimize health concerns and enhancement of biosafety [9]. However, non-invasive drug delivery methods have been developed and various biomolecules such as plasmonic, lumniscent, photocatalytic or self-organizing nanoparticles, bioactive peptides, proteins, nucleic acids (polynucleotides) are used for targeted therapeutics. By using natural templates of bioactive compounds composite drugs have been prepared which show low toxicity, easy binding to carrier molecules and display high pharmaceutical efficacy [8]. These low molecular weight drugs significantly increase their lipophilicity or act as a pro drug found more appropriate for brain tumor therapy. More specifically, nano-scale drugs such as PLGA nanoparticles, PLGA-based nanoparticles [10] and PPEGylated PAMAM dendrimers are prepared to enhance anticancer efficacy and reduction of toxicity in experimental models [11].

Low toxic drug anticancer drug-loaded hydrogels are developed for drug delivery for the local treatment of glioblastoma. For fighting cancer diazyenyl derivative and their complexes, C-4 substituted coumarin derivatives, Arene Ruthenium antitumor complexes, chimeric NSAIDs, synthetic xanthone derivatives, artemisinin-derived dimmers, and receptor tyrosine kinases targeted anticancer therapeutics have been developed [12]. Carbon nanomaterials (fullrenes, graphenes) are used to enhance drug loading capacity, biocompatibility and lack of immunogenicity [13]. For drug discovery, efficacy and safety assessment pharmacodynamic and pharmacokinetic parameters have been integrated for the translation of medicine from the nonclinical to the clinical field. Nanomedicines are also used for delivery of cancer therapeutics.

Fastest Analytical and Bio-Analytical Diagnostics

Synthetic combination of multifunctional nano scale system is successfully done to decide optical detection limit, selectivity and response time for establishing facts about molecular changes occurred in pathogenicity. Similarly, optical detection system is developed for measurement of reactive oxygen species in biological samples [14]. Hybrid quadrupole-time-of-flight (QqTOF) mass spectrometry is used for efficient screening of new chemical entities (NCE). Ultra high performance liquid chromatography (UHPLC) coupled with orthogonal acceleration is proved highly useful for pharmaceutical industry. Technology has been developed to record pharmacodynamic parameters by telemetry, for preserving and improvement physiological data. Such all-important changes provided more appropriate, authentic and precision based results when we use bio-imaging and bio-sensing methods. These methods are used for detection of neuroendocine tumors at an earlier stage. Similarly, PET brain imaging is performed to explore HIV associated neuro-cognitive disorders for combination anti-retroviral therapy. FTIR techniques are used for characterization of therapeutic nanomaterials and nano structures, enantiomeres and chiral anti-histamine drugs [15]. A chemo-selective catalytic oxidative system is developed by making radical transformations in techniques [16] for finding very high precision level in analytical and bio analytical work [17].

Synthesis of Enzyme Inhibitors

Various enzyme inhibitors such as aromatase inhibitors, florescent CMP-sialic acid mimetics for polytransferase, inhibitors of tubulin polymerization [18], histone deacetylase inhibitors, uresae inhibitors (nickel dependent metalloenzyme [19] are prepared to control cancer cell progression [20]. Phosphodiestrase 10 an inhibitor is used as a potent immunogens, to protect gastric mucosa and used in treatment of schizophrenia CNS related disorders. A complex of multimeric protease inhibitors is developed by using 26 S proteasome. It shows high anti-cancer potency [21]. Rho GTPases and statins, HIF-1α-p300/CBP Inhibitors, indoleamine 2,3-

Dioxygenase inhibitors, p53-Mdm2 interaction inhibitors are used in tumor therapy (Table 1).

Drug	Source	Major activity	*Therapeutic rating	*Tolerance
Animal toxins as drug templates	Animal venom	Display profound anticancer effects and are potential therapeutic agents.	High	High
Anti-infective peptides	Insects/ defensins	Antimicrobial and anticancer, protect against a broad array of infection	High	High
Interferons	Human and animal body	Group of signaling proteins secreted by host cells, show high immune response	High	High
Interleukins	Human and animal body	larger group of cellular messenger molecules	High	High
Cytokines	Human and animal body	Interferon, interleukin, and growth factors. Immune-modulating agents	High	High
Active CTLs	Human and animal body	*Active* immunotherapeutic interventions	Moderate	Low
Engineered antibodies/enzymes	Animal source/ Laboratory	Rebuilt into multivalent molecules and fused with, for example radio-nuclides, toxins, *enzymes*, liposomes and viruses.	High	High
Vaccines	Animal source/ Laboratory	provides active acquired immunity to a particular disease	High	High
Metal based drugs	Synthetic Laboratory	Therapeutic molecules of synthetic origin	High	High
Heterocyclic compounds	Synthetic Laboratory	good antimicrobial and anticancer agents, spectrum of biological activities	High	Moderate
Composite drugs	Half natural and half synthetic	made from two or more constituent materials	High	High
Pharmcophores	molecular framework of novel medicines	Supramolecular interactions with a specific biological target	High	High
Dendrimers	New class of polymeric materials	highly branched, mono- disperse macromolecules	High	High
Drug, conjugates and carriers	polymeric *carriers* utilized for *drug conjugation*	Drug delivery and therapeutic targeting	High	Low
Stabilizers	Multiple sources	prevent highs (mania) and lows (depression), prevent shock in sick or injured people	Low minimal use of *stabilizer*	
Epigenetic drugs	DNA methylation inhibitors and histone deacetylase inhibitors	Treat illnesses influenced by epigenetic mechanisms	High	Low
Synergistic combinatorial drugs	*combinatorial* partner *drug*	*Synergistic* effect is greater than the summed effects of the partner *drugs*	High	High
Chemo selective conjugates	conjugation of azide-containing target compounds	achieve high levels of selectivity for peptide or protein modification	High	High
Enzyme inhibitors		.	High	High
Neurotransmitters	endogenous chemicals that enable neurotransmission	chemical messenger of any group released by neurons (nerve cells) which stimulate neighboring neurons or muscle or gland cells	Low	High
Hormones	signaling molecules produced by glands	Target distant organs to regulate physiology and behavior.	Low	High
Vitamins	Fruits, leaves, seeds,	helps prevent damage to cells, helps you		

	stems, milk and sea foods	see at night, make red blood cells, and fight off infections	High	High
Phospholipids	lipid containing a phosphate group in its molecule	Use for treatment of fatty liver disease and maintaining liver function.	High	Low
DNA	Animal cells and laboratory	DNA based personalized medicine	High	High
RNA	Animal cells and laboratory	*RNA*-based *medicine* involves *RNA* interference, target specificity of toxins	High	High
Animal toxins	Venom glands/sting glands	target ion channels and receptors of both the central and peripheral nervous system, interfering with action potential conduction and/or synaptic transmission.	display profound anticancer effects	High
BmKn-2 toxin peptide	scorpion species	therapeutically tested for treatment on oral cancer anti-angiogenenic activity	High	High
Chlorotoxin (CTX) peptide	selectively target malignant gliomas	blocks glioma Cl(-) channel activity and shows anti-angiogenic properties		
Lebein	snake	disintegrin which generates anti-angiogenic effects by inhibiting vascular endothelial growth factors		
Bio-organic compounds	Plants and animal sources	Multiple biological activity	Moderate	High

Table 1: Showing various source molecules of various drugs and their associating delivery molecules and carriers.

Chemo selective conjugates

Photo-cleavable phosphonamidate conjugates have been prepared made by using chemoselective CuAAC and Staudinger-phosphonite reactions starting from 2-nitrobenzyl substituted phosphonites [22]. Conjugation of azide-containing target compounds is also made by irradiation with near UV light. Chemo-selective conjugates are prepared by using unsaturated ketones catalyzed by Rhodium Amido complexes [23], copper catalyzed conjugate [24] amino alcohols (cyclic) to unsaturated esters [25]. Cysteine is used for acid-base conjugation for probing protein function to anti-body drug conjugate (Table 1).

Synergistic combinatorial drugs

Drug combination is proved to be a powerful and promising approach for complex disease therapy such as cancer and cardiovascular disease. Synergistic drugs are provided in various combinations for treating a wide range of cancers [26]. These could be developed by using latest strategy in searching optimal dose combination based on real experiment analysis, computational-guided experimental approach and computational-based approach. Among all models bio-molecular network-based model worked well because of its ability to reflect and illustrate the relationships among drugs, disease-related genes, therapeutic targets, and disease-specific signaling pathways as a system. For screening of combinational dose different testing platforms are needed in order to obtain the best anticancer effects. But it is true only few synergistic drugs have been approved so far by Food and Drug Administration department (Table 1).

Epigenetic drugs

Epigenetic therapy is the use of drugs or other epigenome-influencing techniques to treat medical conditions. Effective ways to develop new drugs based on to environmental conditions; because epigenetic therapy influences metabolic pathways in microbes directly. Many diseases, including cancer, heart disease, diabetes, and mental illnesses are influenced by epigenetic mechanisms. All long-term changes in gene expression are possible which may or may not be heritable. But it is true that all such changes occur due to chemical modifications to DNA and chromatin, or can be caused by changes to several regulatory mechanisms [27]. These may be inherited in some cases, and can change in response to environmental stimuli over the course of an organism's life. Few epigenetic drugs like Pyridinone ring derivatives and its conversion into chelators are used in analytical environmental and clinical science [28], Quinazoline derivatives, Indazole-based anticancer drugs, β-carbolines, Ru-arene Complexes and marine natural products are used for preparation of multi-targeted drugs for cancer treatment. RiPPs (Ribosomally synthesized and

post translationally modified peptides [29]. Both alkaloids and their analogues are proved anticancer agents [30] (Table 1).

Metal based nanomaterials

Carbon-based nanomaterials are made up of mostly carbon and presented in a variety of shapes. Most of them are hollow tubes, cylinders, and ellipsoids [31]. They include nanotubes and fullerenes. These are prepared after reconfiguration of carbon from a flat plane into a rolled tube shape [32]. Though carbon is not soft but its nanomaterial such as soft though has crystalline structure [33] the benefit of carbon nanotubes is that they offer amazing strength and structure to products. They very easily conduct heat and electricity that is used in preparation of improved batteries [34]. Multiwalled carbon nanotubes are prepared which are used as carriers of Ruthenium complexes for treatment of cancer [35]. Moreover, synthesis of nanotubes can occur in a variety of ways by using electric-field-directed growth and patterned growth (Table 1).

Metal Based Nanomaterials

Various metal complexes are used for inhibition of tumor growth and progression by using metal complexes [36]. Transition metal based drug complexes are prepared by packing them inside liposomes [37]. Similarly, cobalt and copper based metal complexes are prepared combined with solid lipid nanoparticles [38-40]. Phenylazomethine dendrimers are prepared with metallo-porphyrin core are used for treatment of cancer [40]. Other metal based materials used in drug therapeutics are quantum dots, nano gold, nano silver and oxides (Titanium dioxide) with metal bases [31]. Metal-based nanomaterials are also synthesized through a variety of means such as micro emulsions and colloids. These are used in biomedical and pharmaceutical industries. These metal-based nanoparticles offer showed good chemical binding and conjugated properties that in multi-bond materials or where they align chemically with antibodies or pharmaceuticals. For making magnetic metal-based nanoparticles manipulation of iron salts via chemical co-precipitation is used [41] Metal based nanomaterials are used in healthcare such as contrast dyes that work with MRI and scanning devices for diagnostic purposes (Table 1).

Dendrimers

Dendrimers are a new class of polymeric materials. They are highly branched, star-shaped macromolecules mono-disperse macromolecules with nanometer-scale dimensions. These possess a central core, an interior dendritic structure (the branches), and an exterior surface with functional surface groups. Branched components that form polymers and whose surface exhibit chain ends suited for chemical manipulation as tools. Dendrimers are combinable to create hollow cavities or used as part of a catalysis [31]. The structure of these materials has a great impact on their physical and chemical properties because they represent a half step between molecular chemistry and polymer chemistry. Dendrimers nanoparticles possess branched appendages. Preparation of dendrimers is either via divergence or convergence. Either the branches grow and then attach to the core or the branches grow from the core. The process is via cascade reaction that is a natural reaction that nanotechnology has stolen from simply biology [42]. In the human body, protein synthesis is the building of more complex structures from parts. That is the same concept for dendrimers. Dendrimers have an amazing capability, and their current application is through biomedicine with applications as anticancer drugs, pain management, and timed released medications such as a transdermal patch or in gene therapy (Table 1).

Composite Drugs

A composite material is made from two or more constituent materials with significantly different physical or chemical properties. After formation of composite or a combined material, it displays stronger and different characteristics from the individual. Metallurgy is main craft work which generates composites but recently, fibre-reinforced plastics (FRP), are a combination of reinforcements and matrix. These unique nanomaterials have been prepared by using nano-particles [31]. The preparation of composites involves thermal reduction of metallic oxides and polyamide 6 [43]. Composite nanomaterials remain orderly, but perhaps at a twisted level. PA6 is just one method of preparing composite nanomaterials. Nanoparticles are population of particles with families, genus, and a ton of potential. These are used to male nano-materials that make unique solutions possible no pun intended. Electro-spinning is used to generate morphs the physical object with the chemical solution to create single dimension composites that are somehow both organic and inorganic [44] within these four families of nanomaterials exists a wide array of properties array of usefulness that nanomaterials bring to manufacturing, military technology, pharmaceuticals, and environmental industries. There is much more to discover in the world of nanoparticles, and the potential of this industry is a doubled edged sword. For example, while metallic nanomaterials make internal diagnostics work, metals are typically harmful. More research can lead to better understanding and a more informed decision about

how to use nanotechnology to benefit the planet, and mankind (Table 1).

Drug stabilizers, conjugates and carriers

Drug Nano crystals are considered as most stable drugs, these possess a simple structure with a solid drug core that is surrounded by a layer of stabilizing agent. These are versatile option for drug delivery because poorly soluble drugs are very hard to deliver at target site. It is true that simple drug structures need selection of an appropriate stabilizer for a much longer release. Mostly, the stabilizer selection is based on the requirement of physical stability. For maintaining the nano sized particle size is only possible after the formation of drug nano crystals. Drug stabilizer can affect the bioavailability in the final formulation via interactions with cells and cell layers. In addition, formation of nano crystals is only one process step, and for the final formulation, more excipients are often added to the composition. The role of the stabilizers in the final formulation can be more than only stabilizing the nano crystal particle size. A good example is the stabilizer's role as cryoprotectant during freeze drying (Table 1).

Pharmcophores

Pharmacophore is a combination of steric and electronic features which is necessary to ensure the optimal supramolecular interactions with a specific biological target. These are necessary for molecular recognition of a ligand by a biological macromolecule [45]. Pharmacophores are also used as the starting point for developing 3D-QSAR models. These assist in finding privileged structures or to prepare molecular framework of novel medicines. A well-defined pharmacophore possesses hydrophobic centroids, aromatic rings, hydrogen bond acceptors or donors, cations, and anions. It includes both hydrophobic volumes and hydrogen bond vectors. All these properties of pharmacophoric nature is either located on the ligand itself or presumed to be located in the receptor. Multiple pharmacophore is also developed by using pyrrole as heterocyclic ring template [46].

Pharmacophore development is also used for molecular docking by virtual screening process [47]. These are able of providing useful ligands for more than one type of receptor or enzyme target by judicious structural modifications [48]. A pharmacophore model explains how structurally diverse ligands can bind to a common receptor site. Ligand-receptor interactions are typically "polar positive", "polar negative" or "hydrophobic" in nature. In modern computational chemistry, pharmacophores are used to define the essential features of one or more molecules with the same biological activity. These are used to identify through de novo design or virtual screening novel ligands that will bind to the same receptor. The best example of pharmacophore is GABA and Glutamate receptor ligands and their therapeutic potential in CNS disorders [49]. Pharmacophores are privileged structures which are based on concept for the rational design which is used to find new lead drug candidates [48] (Table 1).

Heterocyclic Compounds

Heterocyclic compounds are good antimicrobial and anticancer agents as they show wide spectrum of biological activities [50]. These compounds are highly demanded in medicinal chemistry because of their versatile activity. For treatment of malaria many heterocyclic compounds and their lipophilic analogues are used as they showed very high antimalarial potency because of their higher solubility and the oral bioavailability [51]. New heterocyclic α-aminophosphonates were prepared by following molecular docking, molecular modeling, vibrational and biological functions [52]. Au-1·PF_6 showed the greatest activity toward Gram-positive bacteria [53]. Benzoxazole and its derivatives showed antiproliferative activity against human colorectal carcinoma (HCT 116) cancer cell line and also found active against selected microbial species [50]. Similarly, multi-substituted pyrrolizinone and indolizinones derived from lactam have been designed, synthesized and evaluated for their potential antifungal activities against six species of the plant pathogen fungi (Fusarium graminearum, Sclerotinia sclerotiorum, Phomopsis adianticola, Gloeosporium theae-sinensis, Alternaria tenuis Nees, Magnaporthe oryzae) [54]. Plant origin phenolic compounds are potent antimicrobials and could be used as good food preservatives by making edible coatings of food packaged materials [55]. Schiff base-based metallo-drugs show good anticancer and anti-microbial activity and are used in chemotherapies Schiff bases can be structurally modified to achieve the desired molecule, targeting a particular disease [56] (Table 1)(Figure 1).

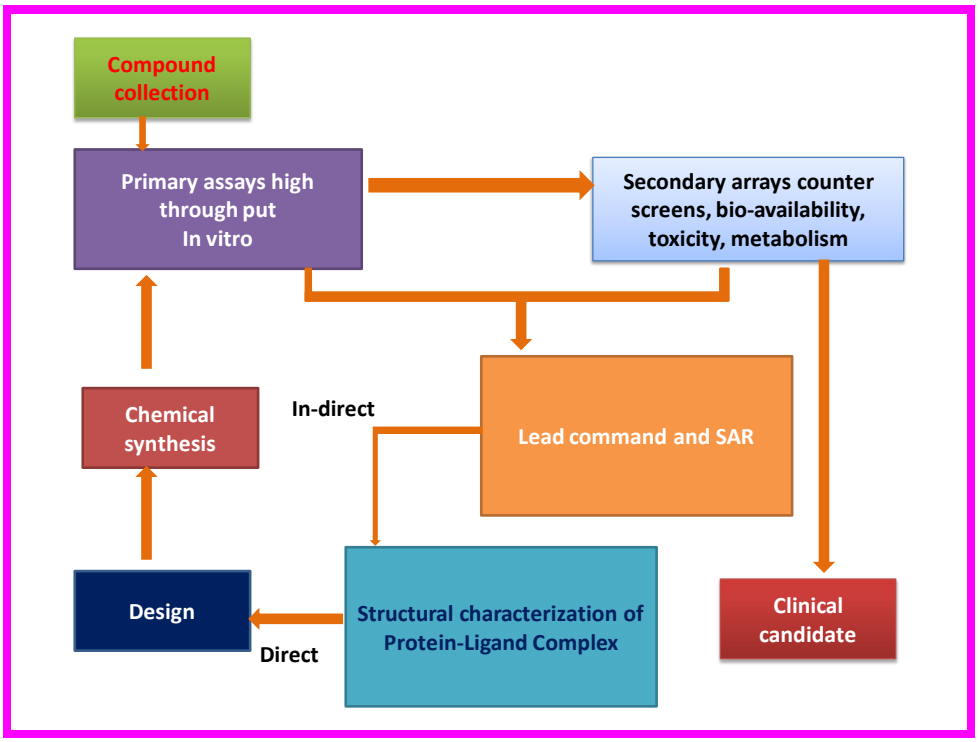

Figure 1: showing various steps of drug discovery cycle for making an active clinical candidate.

Anti-infective peptides

Antimicrobial peptides (AMPs), critical components of the innate immune system, are widely distributed throughout the animal and plant kingdoms. They can protect against a broad array of infection-causing agents, such as bacteria, fungi, parasites, viruses, and tumor cells, and also exhibit immune modulatory activity. AMPs exert antimicrobial activities primarily through mechanisms involving membrane disruption, so they have a lower likelihood of inducing drug resistance. Anti-infective peptides are used to disrupt the endogenous SPSB-iNOS interaction to prolong the intracellular lifetime of iNOS and enhance the production of NO. These are used to treat chronic and persistent infections such as tuberculosis [57]. Inducible nitric oxide synthase (iNOS or NOS2) produces nitric oxide (NO) and related reactive nitrogen species, which are critical effectors of the host innate response and play key roles in the intracellular killing of bacterial and parasitic pathogens.

The SPRY domain-containing SOCS box proteins SPSB1 and SPSB2 are key physiological regulators of this important enzyme. The prophylactic application of antimicrobials that are active against *Staphylococcus aureus* can prevent infections. Similarly, mupirocin are used as prophylaxis for preventing infections with *S. aureus*, particularly in carriers and in the surgical setting or in patients receiving dialysis treatment [58]. The prophylactic application of antimicrobials that are active against Staphylococcus aureus can prevent infections. AMPs have wider applications in food, medicine, and animals [59]. Cationic antimicrobial peptides Teicoplanin are used against Planktonic and Biofilm-Encased *Staphylococcus aureus* [60]. The LL-37-inspired lead peptide SAAP-148 was combined with antibiotics of different classes against *Staphylococcus aureus* and showed synergy with teicoplanin [60] (Table 1).

Animal toxins as drug templates

As it is established fact that toxins/peptides from animal venom typically target ion channels and receptors of both the central and peripheral nervous system, interfering with action potential conduction and/or synaptic transmission. These peptides showed very high degree of sequence homology/conservation of their molecular targets, which makes these toxins active at human receptors. The high selectivity and potency displayed by some of these toxins could be used as pharmacological tools as well as diagnostic probes for detection of morbidity. In present review article important biological effects of toxins, their hydrophobic and ionic interactions, voltage gated channel binding and receptor interactions in cell membranes have been explained. Though animal venom toxins from wasp, bees and scorpion act as

potential therapeutic agents and display profound anticancer effects but partial modification in their structure could increase their anticancer potential. These modifications are possible in hydrophobicity, surface charges, and amino acid substitutions in active site regions, topological folding, hydrophobic pockets and binding affinity. For this purpose modifications like site-specific mutations and gene rearrangements could provide more active recombinant toxin peptides that will show much cytolytic activity and any drug. Few antigenic shifts in toxins cold remove their toxicity against normal animal cells, and might behave as cell-penetrating peptide that will effect cancer cell proliferation, migration, invasion, apoptotic activity and neo-vascularization. It also highlighted miRNA-based therapeutics, with possible directions for improvement in target specificity of toxins when to be used as a complete therapeutic tool against tumor and cancer. Because of their high selectivity, these toxins can be employed as pharmacological tools in disease diagnosis and therapeutic interventions for gliomas (Figure 2). This article also highlighted encapsulation and conjugation of toxins with onconase, drugs, and lipids to develop new highly efficacious therapeutic delivery system.

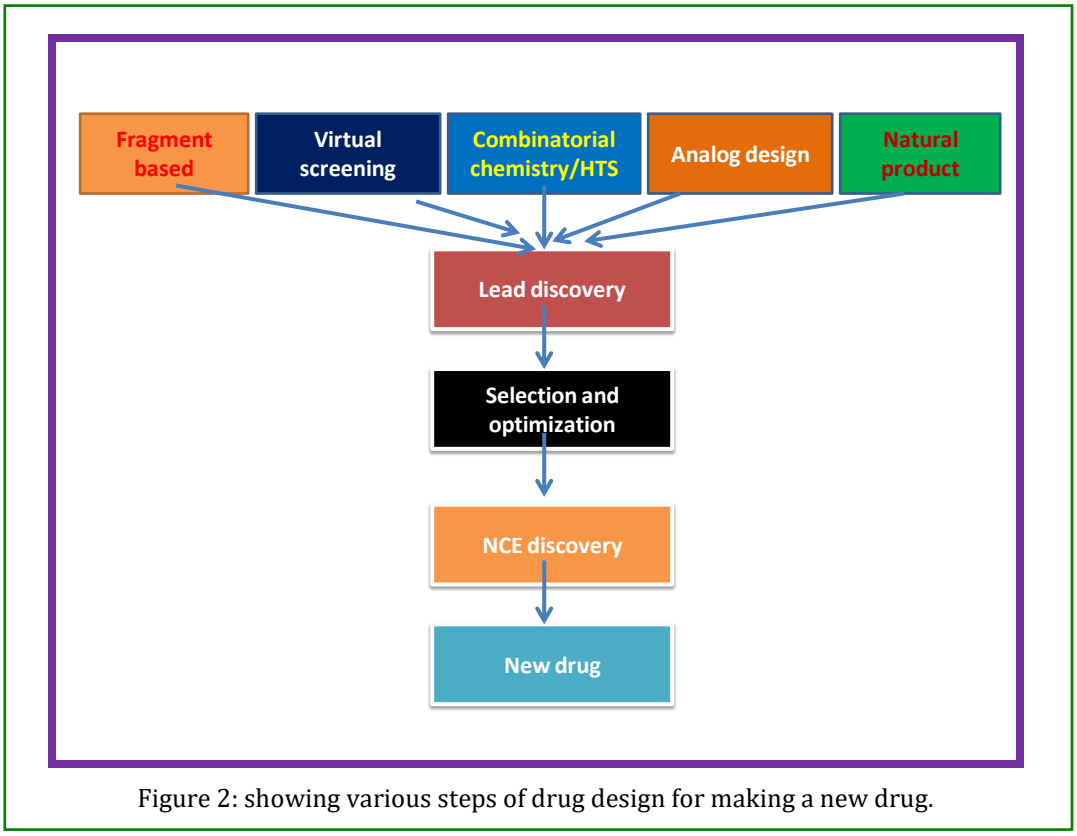

Figure 2: showing various steps of drug design for making a new drug.

Animal venom toxins display profound anticancer effects and are potential therapeutic agents. Toxins purified from snake; bee and scorpion venoms effect cancer cell proliferation, migration, invasion, apoptotic activity and neo-vascularization. Their action mechanism on cancer cells is similar to that of chemotherapeutic agents. Lebein is a snake venom disintegrin which generates anti-angiogenic effects by inhibiting vascular endothelial growth factors (VEGF). Scorpion (*Androctonus bicolor*) venom exhibits cytotoxicity and induces cell cycle arrest and apoptosis in breast and colorectal cancer cell lines. BmKn-2 scorpion venom peptide demonstrates specific membrane binding, growth inhibition and apoptogenic activity against human oral cancer cells [61] (Table 1).

BmKn-2 toxin peptide isolated from scorpion species is a good candidate which has been therapeutically tested for treatment on oral cancer. It exerts selective cytotoxic effects on human oral cancer cells by inducting apoptosis via a p53-dependent intrinsic apoptotic pathway [61]. It induces potent cytotoxic effects towards both HSC4 and KB cells with the associated induction of apoptosis and showed minimal effects on healthy tissue. The venom of *A. bicolor* scorpion does selective induction of apoptosis in MDA-MB-231 and HCT-8 cells and arrest cell cycle in them. Encapsulated scorpion venoms from *Androctonus bicolor* (AB), *Androctonus crassicauda* (AC), and *Leiurus quinquestriatus* (LQ) [62] exhibit better anti-cancer efficacy on the colorectal cancer cell line. Malignant

gliomas are rarely curable malignant tumors arise in the central nervous system. Chlorotoxin (CTX) peptide isolated from scorpion venom, selectively target malignant gliomas. It blocks glioma Cl(-) channel activity and shows anti-angiogenic properties (Table 1). Similarly, an analgesic-antitumor peptide (AGAP), derived from scorpion toxin polypeptides showed antitumor activity. Polybia-MPI shows good antitumor activity [63]. Hemilipin a heterodimeric phospholipase A2 (sPLA2) from *Hemiscorpius lepturus* scorpion venom displays anti-angiogenesis both *in vitro* and *in vivo* [64]. This property remains intact even chemical treatment with p-bromophenacyl bromide that abolishes its enzymatic activity.

Bee venom is a mixture of proteins, polypeptides and low molecular weight aromatic and aliphatic constituents in variable amounts. It also contains some important enzymes i.e. phospholipase A, hyaluronidase, acid phosphatase and D-glucosidase which are highly antigenic. Honey bee wasp venom contains many toxic substances such as melittin, adiapin, apamine, bradykinin, cardiopep, mast cell degranulating peptide, mastoparan, phospholipase A2 and secapin. These toxin components have wider therapeutic applications [65]. Melittin triggers lysis of intracellular membrane found in mitochondria while PLA2 and melittin act synergistically, breaking up membranes of susceptible cells and enhancing their cytotoxic effect [44]. For targeting can cancer cells recombinant molecules are being made which are used as targeted toxins, also known as immunotoxins or cytotoxins. These specifically bind to cell surface receptors which are over expressed in cancer and the toxin component kills the cell. These recombinant proteins consist of a specific antibody or ligand coupled to a protein toxin [66].

Drug discovery: from principle to clinical practice

Drug discovery is a process by which new therapeutic compounds/candidates are discovered by applying the methods of medicinal chemistry, physics, pharmacology, biotechnology and medicine. There are various steps of drug discovery, first step includes target selection & validation, implies studies of disease mechanisms, molecular mechanisms and, pharmacological action confirmation or negative and positive responses of a drug. For initiation of new drug, existing chemical libraries of synthetic small molecules, natural products or extracts are investigated for their therapeutic efficacy and potency. New substances and bio-chemicals have been searched for their therapeutic effect in classical pharmacology. The second step is of drug discovery that specifies the target on cell surface as receptor, ion channels, transporter, and an enzyme or may be a signaling molecule. After finding a right target certain assays are performed to find chemical diversity and target specificity. Finally automation of assay is done to make the process faster. Optimization is done by increasing selectivity, finding efficacy in animal models, tolerability and pharmacokinetics of drug molecules. As for development of drug safety assays, clinical trials are followed in animals human studies in different phases, drug approved and registration. Screening and design, source of drug, elucidation of structure, action, efficacy and potency of drug.

Both chemo-informatics and bioinformatics data available is matched for finding a new desirable drug. Human genome sequences responsible for disease and response elements which could be hypothesized to be disease modifying are screened by applying high through put screening. Since sequencing of the human genome which allowed rapid cloning and synthesis of large quantities of purified proteins, it has become common practice to use high throughput screening of large compounds libraries against isolated biological targets. Hits from these screens are then tested in cells and then in animals for efficacy (Figure 1-3). More specifically, modern drug discovery pertains with 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 bioavailability of drug. In primary screening once a compound fulfill requirements as disease curing; the process of drug development prior to clinical trials can be started. One or more of these steps may, but not necessarily, involve computer aided drug design. Modern drug discovery requires much larger capital investments by corporations as well as national governments (who provide grants and loan guarantees). It is true that drug discovery is lengthy, "expensive, difficult, and inefficient processes despite technological advancements have been done for understanding of biological systems and behavior of therapeutic compound. This is one of the main reasons that a low rate of new therapeutic discovery is prevailing [67].

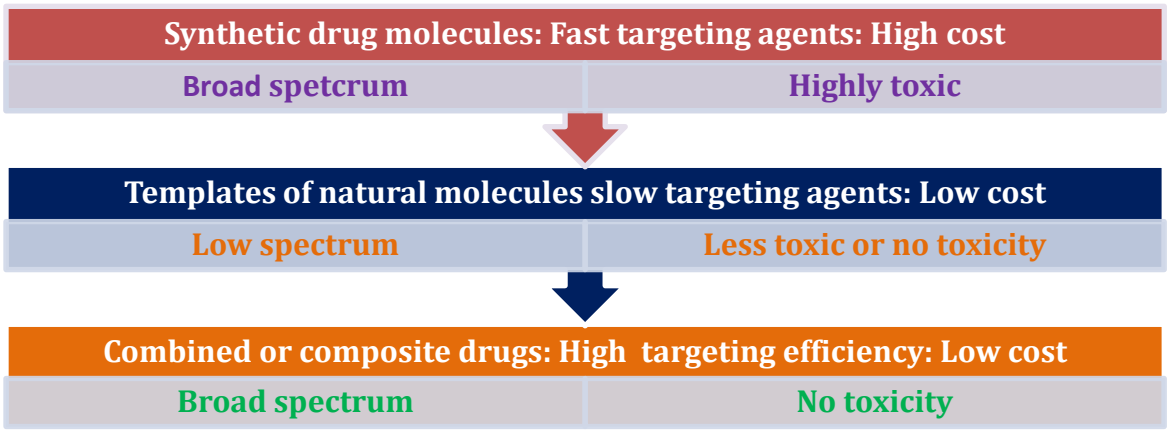

Figure 3: showing sequential progress in drug design for making high efficiency therapeutic candidates.

In 2010, it was estimated that over all expenditures to have each new molecular entity was about US$1.8 billion. This was an investment and expenditure on the research and development [68]. Drug discovery is done by pharmaceutical companies, with research assistance from universities. After discovery of a new potential drug it is placed for seeking an international patent. The drug requires very expensive Phase I, II and III clinical trials, and most of them fail. Small companies have a critical role, often then selling the rights to larger companies that have the resources to run the clinical trials. Today drug discovery is a commercial affair, if remains successful, it is highly useful and important for public health, but it is not easy to establish a sound interaction between investors, industry, academia, patent laws, regulatory exclusivity, marketing and the need to balance secrecy with communication [69].

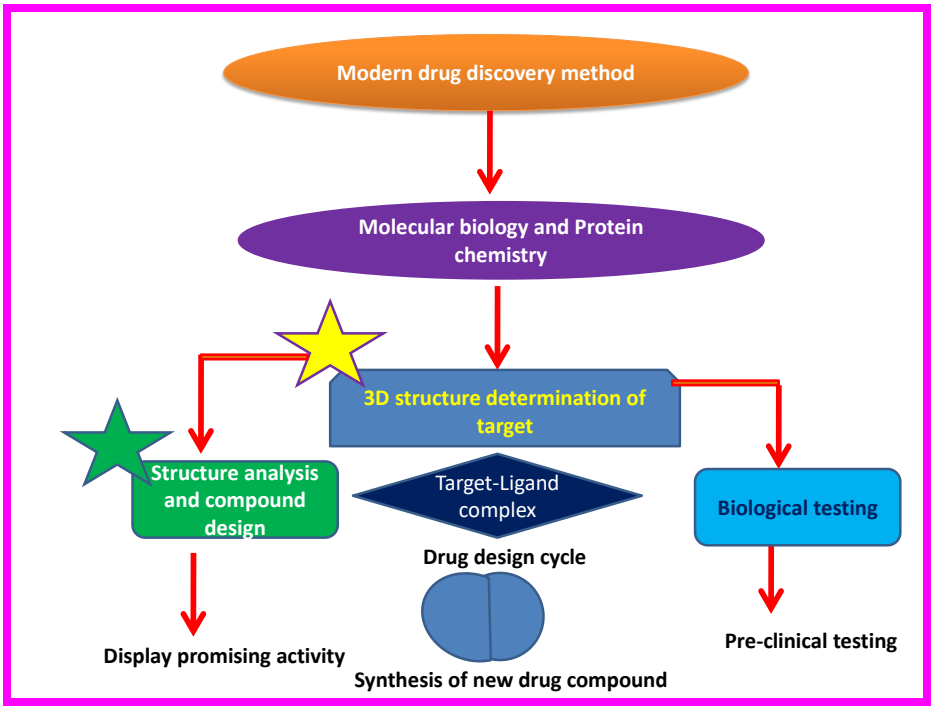

Figure 4: showing various drug discovery methods.

Important data available on pharmacodynamics and pharmacokinetic parameters, physiology, chemistry, structure and function of active chemical compounds is used to prepare highly active, low molecular weight drugs with high efficacy and target specificity. Both mono-scale and multi scale simulation tools are used to find appropriate and possible solutions about structure and activity relationships in drugs [70]. Additionally, virtual chemical libraries containing billions of molecules can be used for simulation studies and therapeutic concepts in clinical sciences [71]. Laser pulse optimization (Optimal control theory), shaping laser pulse act as photonic reagents and shorten the synthetic route toward the desired product [72]. New anticancer drugs having low molecular weight and low toxicity have been formulated by using existing data on organic and inorganic therapeutic molecules. These small size anticancer drugs can be easily delivered using cell penetrating and tumor targeting peptides (Figure 5).

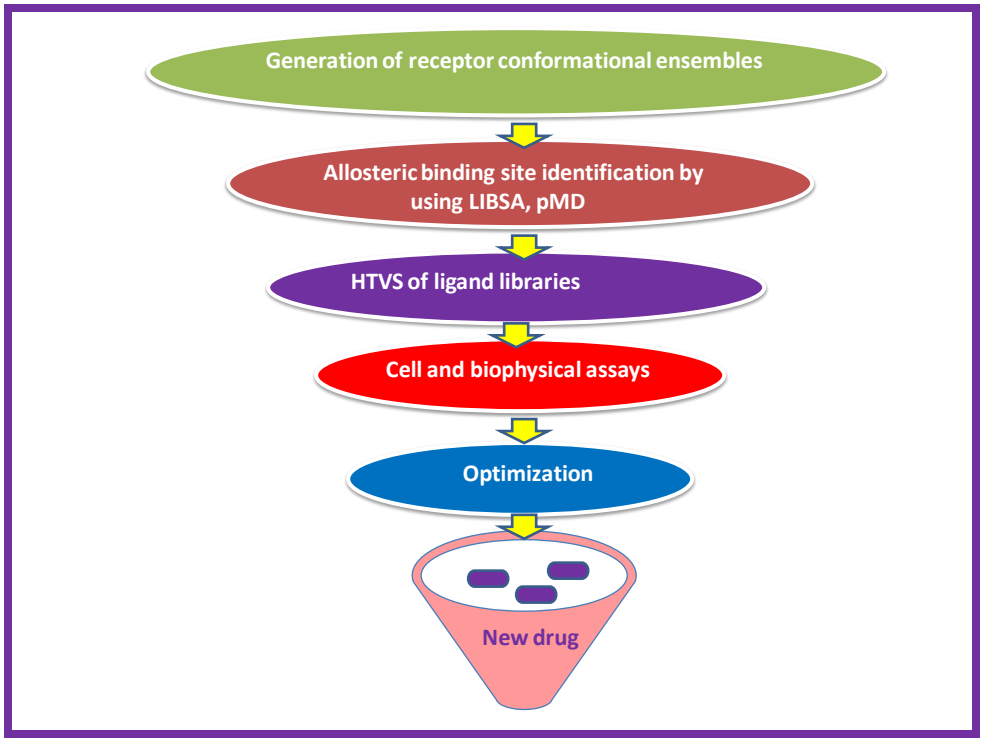

Figure 5: showing receptor ligand approach to have a new drug with optimized efficiency.

Cheminformatics is used to design new drugs with help of computer, simulations and *In Silico* testing of drugs is done that has reduced a range of problems in the field of medicinal chemistry. This huge data is used for discovery of new drugs. These methods can also be used in chemical and allied industries in various other forms. Methods of chemoinformatics (data available on millions of chemical molecules) are used to transform data into information and information into knowledge for making better drug formula, design, identification and optimization of structure activity relationship. Virtual libraries of classes of compounds (drugs, natural products, diversity-oriented synthetic products) were recently generated using the FOG (fragment optimized growth) algorithm [73]. Virtual screening is done by computational methods and comparisons are made with in *Silico libraries* of compounds. Molecular docking is used to identify members likely to possess desired properties such as biological activity against a given target. Synthetic molecules are matched with biological molecules for checking their efficiency, binding and target specificity. Combinatorial chemistry is used in the development of library to increase the efficiency in mining the chemical space. For prediction of activity of synthetic compounds quantitative structure activity relationship and quantitative structure property relationship values are used. Both chemometrics and chemical expert system are used to design drugs with high anti-disease activity. There is a relatively new concept of matched molecular pair analysis or prediction-driven MMPA which is coupled with QSAR model in order to identify activity cliff [74].

Conclusion

Today thousands of medicines are available to combat different microbial diseases, cancer and AIDS whose structure and function are known. Their therapeutic potential depends on functional groups, size, molecular weight, solubility, absorption, distribution and hydrophilicity. But due to rising drug resistance in microbes made most of these therapeutic compounds worthless. It has increased the morbidity and mortality enormously, and created extra burden to clinicians. Repetition of mistakes is real cause of sufferings, there is a big question mark is tagged on safety standards and control of microbial menace not at regional level but at global level. However, to curve on drug resistance new broad spectrum drugs are required based on structure and ligand-based approaches, receptor-ligand binding, nano-size and their interactions with biological targets. Target should be specific for an enzyme and receptor used as target. For synthesis, development of new safer rational drug design multi-disciplinary approaches is to be applied.

Besides, activity and therapeutic potential of drug their metabolism; side effects must be tested in variety of biological models. Antiproliferative and anti-angiogenic molecules to avoid drug resistance/ new derivatives, By using surrogate hosts. Metallo-proteins as relatively underexplored targets in the context of their drug ability is also presented. However, despite the considerably simple structure, the selection of an appropriate stabilizer for a certain drug can be challenging. Development of new effective drugs and disease control is a greater task and fighting drug resistance. For treatment of cancer new nano-therapeutic compounds have been synthesized by using various base materials such as hyaluronic acid-base, bacterial polyketides and saccharides and polymeric nano-particles conjugated with peptides. Howevere, non-invasive drug delivery methods have been developed and various bio-molecules such as plasmonic, lumniscent, photocatalytic or self-organizing nanoparticles, bioactive peptides, proteins, nucleic acids (polynucleotides) are used for targeted therapeutics.

Low toxic drug anticancer drug-loaded hydrogels are developed for drug delivery for the local treatment of glioblastoma. Synthetic combination of multifunctional nano scale system has been successfully done to decide optical detection limit, selectivity and response time for establishing facts about molecular changes occurred in pathogenicity. Various enzyme inhibitors such as aromatase inhibitors, histone deacetylase inhibitors, urease inhibitors (nickel dependent metalloenzyme) inhibitors are used in tumor therapy. Copper catalyzed conjugate Photo-cleavable phosphonamidate conjugates have been prepared made by using chemoselective CuAAC and Staudinger-phosphonite reactions. Conjugation of azide-containing target compounds is also made by irradiation with near UV light. Chemo-selective conjugates are prepared by using unsaturated ketones catalyzed by Rhodium Amido complexes copper catalyzed conjugate ,amino alcohols (cyclic) to unsaturated esters. Cysteine is used for acid-base conjugation for probing protein function to anti-body drug conjugate.

Epigenetic therapy is the use of drugs or other epigenome-influencing techniques to treat medical conditions. A composite material is made from two or more constituent materials with significantly different physical or chemical properties. Heterocyclic compounds are good antimicrobial and anticancer agents as they show wide spectrum of biological activities. Antimicrobial peptides (AMPs), critical components of the innate immune system, are widely distributed throughout the animal and plant kingdoms. They can protect against a broad array of infection-causing agents, such as bacteria, fungi, parasites, viruses, and tumor cells, and also exhibit immunomodulatory activity. Animal toxins can be used as drug templates. Animal venom toxins display profound anticancer effects and are potential therapeutic agents. Conclusively, most appropriate drug should have a minimum dose, biologically active, less toxic, easily catabolizing and low cost with optimal supra-molecular interactions with a specific biological target. Drug combination is proved to be a powerful and promising approach for complex disease therapy such as cancer and cardiovascular disease. Synergistic drugs are provided in various combinations for treating a wide range of cancers.

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