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In-silico approach &Medicinal chemistry study on *Vibrio choleare* species: A review

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ABSTRACT: Cholera is acute intestinal disease caused by *Vibrio cholerae* species. There are different types of cholerae species present in which only few can cause cholera. Currently there are no appropriate effective drug molecules against cholera disease. India is a rich country for its medicinal plants and there various phytochemical constituents which have high antimicrobial compounds even clinically tested. This review shows the efficiency of phytochemical constituents of medicinal plants for treating cholera which could be pre-requirement studies for a medicinal chemistry. This Chemoinformatics approach on medicinal plants can design the new drug novels to inhibit the activity of *Vibrio cholera*. This article can reveal the usage of different bioinformatics tools in the field of drug discovery.

KEYWORDS:Phytoconstituents of medicinal plants, *Vibrio cholerae*, Docking, Drug design.

I. INTRODUCTION

A. CHOLERA

Cholera is an acute intestinal infectious disease caused by *Vibrio cholerae* bacterium. *Vibrio cholerae* secretes cholera toxin which affects transport of water in small intestine and it leads electrolyte imbalance, severe diarrhea and death due to severe dehydration. O1 and O139 strains identified as notable serogroups to cause cholera [1].

B.EPIDEMIOLOGY

In 1992, a novel serotype O139 emerged in India, and spread rapidly into Bangladesh and neighbouring countries of Asia. After the classification of O139 strain from Bengal, later it found as genetic derivative of seventh pandemic O1 strain with its replacement of the O antigen [2]. The Infection of this disease includes watery diarrhea, vomiting, and muscle cramps. The severe condition of cholera is dehydration includes loss of fluid and electrolyte imbalance, the fluid loss may reach1L/h [3, 4]. If dehydration is not treated death may occur within few hours, usually cholera shows its signs and symptoms in the period of 2 to 3 days (range, 6 hours to 5 days). The infection of cholera include asymptomatic illness (75%), mild illness (18%), moderate (5%), and severe illness (2%) [5].

C.INDIAN STRATEGY OF CHOLERA

As per WHO the estimated cholera outbreaks was observed by six institutes located in Kolkata, Nagpur, Chandigarh, Kerala, Vellore and Orissa during 1997 to 2006 in India. The states Assam, Chhattisgarh, Himachal Pradesh, Madhya Pradesh, Tripura and the union territory of Andaman and Nicobar Islands has not reported cholera cases on a regular basis but they were reported outbreaks over the 10-year period. Few states such as West Bengal, Maharashtra, Orissa and union territory Delhi, reported epidemics during multiple years over 1997–2006, in which Orissa has reported four outbreaks from 1999–2003. The number of states affected by cholera outbreaks has varied considerably. Only two states have reported outbreaks in 1997, where as eight outbreaks were reported in 2004. On average, seven outbreaks occurred annually throughout the country [6].
During the studied period of 10-year, highest numbers of reported outbreaks was 60% from West Bengal, Orissa, Maharashtra and Kerala. The range of affected individuals from a low of 4 in Himachal Pradesh to a high of 102778 in Orissa. The overall case fatality rate of India was 0.37%. Figure1 shows distribution of cholera in India during 1997-

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Vol. 2, Issue 6 , June 2015

2006 [6]. In the period of April 2012 to March 2013, 8% of *Vibrio cholerae* O1 serotype infection was found in India [7].

D. ANTIBIOTIC RESISTANCE OF *VIBRIO CHOLERAE*

Currently the WHO administrated two cholera vaccines such as Dukoral and Shanchol, both vaccines are effective to *V. cholerae* O1 and O139 strain. Shanchol recommended as vaccine in India but it is not prequalified by WHO. Dukoral only prequalified vaccine by WHO and available in 60 countries. These vaccines can give in two doses, between seven days and six weeks apart for adults and children aged 6 years and above. Children aged between 2-5 years should give 3 doses, Dukoral is not recommended for children aged less than 2 years. Vaccination should be completed before 7 days before. The vaccines could offer short-term protection up to 85-90% at all age groups (for aged >= 2 years) [8].The present vaccines and antibiotics are not effective against *Vibrio cholarae* infection, this bacteria shows resistance by exporting drugs through efflux pumps, chromosomal mutations or developing genetic resistance via the exchange of conjugative plasmids, conjugative transposanse, integrons or self transmissible chromosomally integrating SXT elements [9].

E. MEDICINAL PLANTS

In developing countries Ayurvedic medicines mainly based on medicinal plants, where modern health services are limited. Safe effective and inexpensive indigenous remedies are gaining popularity among the people in both urban and rural areas especially in India and China. In chemotherapies the information of medicinal groups of plants play an important role in the development of new drug candidates against diseases. Herbal medicines are main source of primary healthcare in all over the world. Still 80 % of world populations dependent on herbal medicines, medicinal plants providing safe, effective and inexpensive medicines to diseases [10].
The use of herbal products and other extract different plant parts for curing different diseases of animals and human beings were described by Indian Vedas. Maximum 30 % of root part of medicinal plant is used in different practices in comparison to other plant parts [11]. India has been identified as one of the top twelve mega bio-diversity center of the world. This is because India has a vast area with wide variation in climate, soil, altitude and latitude. India with its biggest repository of medicinal plants in the world may maintain an important position in the production of raw materials either directly for crude drugs or as the bioactive compounds in the formulation of pharmaceuticals and cosmetics etc. Medicinal plant based drug industries is progressing very fast in India but it is best with a number of problems [12, 13 & 14].

The Ayurvedic concept was described and developed between 2500 and 500 BC in India. The actual meaning of Ayurveda is “science of life,” because ancient Indian system of health care focused views of man and his illness. The practice of Ayurveda therapeutics consisted of 8 sections divided into 180 chapters and listed 314 plants, which are used as medicines in India [15]. In India, around 15000 medicinal plants have been recorded [16]. The traditional communities are using only 7,000 - 7,500 plants for curing different diseases [17-18]. The medicinal plants are listed in various indigenous systems such as Siddha (600), Ayurveda (700), Amchi (600), Unani (700) and Allopathy (30) plant species for different ailments [19]. According to another estimate 17,000 species of medicinal plants have been recorded out of which, nearly 3,000 species are used in medicinal field [20].

F. PHYTOCHEMICAL CONSTITUENTS OF MEDICINAL PLANTS

During metabolic activities all plants produce chemical compounds. These chemical compounds are divided into two catagaries: (1) primary metabolites such as sugars and fats, which are found in all plants; and (2) secondary metabolites—compounds which are found in a smaller range of plants, serving a more specific function [21].

Plants synthesize a variety of phytochemicals, but most are derivatives of a few biochemical motifs: [22]
Alkaloids are chemical compounds containing a nitrogen ring and produced by variety of organisms, including bacteria, fungi, plants, and animals, and are part of the group of natural products (also called secondary metabolites). Many alkaloids can be purified from crude extracts by acid-base extraction. Alkaloids are toxic to other organisms which are causing infection. They also have pharmacological effects and are used as medications to cure illness of human beings. Although alkaloids act on a diversity of metabolic systems in humans and other animals [22].

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International Journal of Advanced Research in Science, Engineering and Technology

Vol. 2, Issue 6 , June 2015

Polyphenols (also known as phenolics) are compounds contain phenol rings. The anthocyanins that give grapes their purple color, the isoflavones, the phytoestrogens from soy and the tannins that give tea its astringency are phenolics [22].

Glycosides are molecules in which a sugar is bound to a non-carbohydrate moiety, usually a small organic molecule. Glycosides play numerous important roles in living organisms. Usually all plants store chemicals in the form of inactive glycosides. These can be activated by enzyme hydrolysis, which causes the sugar part to be broken off, making the chemical available for use. From many medicinal plants glycosides were used as medications. [22].

Terpenes are a large and diverse class of organic compounds, produced by a variety of plants, particularly conifers, which are often strong smelling and thus may have had a protective function. They are the major components of resin, and of turpentine produced from resin. (The name "terpene" is derived from the word "turpentine"). Terpenes are major biosynthetic building blocks within nearly every living creature. Terpenes and terpenoids are the primary constituents of the essential oils of many types of plants and flowers [22].

G. ANTIMICROBIAL ACTIVITY OF MEDICINAL PLANTS

Plant drug Rasayana has always played an important role to treat several diseases of animal's and human beings. According to World health organization (WHO) more than 80% of the world population depends on ayurvedic medicine for their primary health care needs [23]. The use of medicinal plants source used as phytochemical constituents for the treatment of different infections [24]. In drug design field still large amount of medicinal plants potential unexplored to the world. Among only 250'000- 500,000 plant species were estimated by Ayurveda Rasayana and only a small percentage have been investigated phytochemically. And they have submitted to biological or pharmacological screening for development of new drugs. [24, 25 &26]. Medicinal plants are rich sources of antimicrobial agents. Plants are used medicinally in different countries and are the source of potential and powerful drugs [27]. A wide range of medicinal parts are used to get different rasayanas which possess different medicinal properties against different microbes [28].

H. ANTIBACTERIAL ACTIVITY OF MEDICINAL PLANTS

Human infections particularly from bacteria, fungi, viruses, they can cause serious infections in tropical and subtropical countries of the world. In recent years, multiple drug resistance in human pathogenic microorganisms showing the resistance against antibiotics and vaccines.[29, 30]. In general, bacteria have the genetic ability to transmit and acquire resistance to drugs, which are utilized as therapeutic agents [31]. Over the past twenty years, there has been a lot of interest in the investigation of natural materials as sources of new antibacterial agents [32, 33]. Different extracts from traditional medicinal plants have been tested. Many reports have showed the effectiveness of traditional herbs against microorganisms [34]. The increasing interest on traditional ethno medicine may lead to discovery of novel therapeutic agents. Medicinal plants are finding their way into pharmaceuticals, neutralceuticals, cosmetics and food supplements. In this regard, plants have given western pharmacopoeia about 7000 different pharmaceutically important compounds and a number of top-selling drugs of modern time, e.g. quinine, artemisinin, taxol, camptothecin, etc. [35].

II. LITERATURE REVIEW

A. *VIBRIO CHOLERAE*

In 1854, *Vibrio cholerae* causes cholera was discovered by Filippo pacini but this discovery was not widely spread until Robert Koch worked on this disease [36].Cholera is an intestinal infection caused by consuming contaminated food or water in which *Vibrio cholerae* is present. O1 or O139 strains are more notable serogroups to secreate cholera toxin in intestinal part and cause cholera. The signs and symptoms of cholera include watery diarrhoea, occasional vomiting and severe dehydration or water loss. If it is untreated, death can occur within few hours. [1]. The current seventh pandemic caused by the El Tor biotype of *V. cholerae* O1 began in 1961 in Sulawesi, Indonesia and spread rapidly to other countries in Asia, Europe and Africa and finally to Latin America in 1991, after almost a century without cholera[37].

ISSN: 2350-0328

International Journal of Advanced Research in Science, Engineering and Technology

Vol. 2, Issue 6 , June 2015

B.ACTION OF CHOLERA TOXIN

The pathogenesis of *V. cholerae* includes both secretion of cholera toxin (CT) and the colonization of the intestine which acts to stimulate excessive secretion of electrolyte and fluid from the crypt cells of the small intestine [38]. Cholera toxin is a protein which is responsible for cholera infection and it consist of two subunits A and B. The A subunit is larger than the B subunit. It contains 240 amino acids and its molecular weight is 28 KD, located centrally. B subunit consists of five small subunits and each small subunit contains 103 amino acids and 11 KD molecular weight, located peripherally [39, 40]. In cholera toxin, the carboxy-terminal of the A2 transfers through the opening of B subunit doughnut arrangement. The A2 chain includes four carboxy-terminal residues such as Lys-Asp-Glu-Leu (K-D-E-L) [41].

The toxic action of cholera toxin is initiated by binding of its B subunits to the high-affinity monosialoganglioside GM1 receptors and each B subunit monomer has a binding site for GM1. A single amino acid of neighboring B subunit can also play an important role in binding process and it can describe the high binding affinity of cholera toxin B pentamer than cholera toxin B monomer [41]. The Endocytosis of cholera toxin can follow one of three pathways: (i) lipid raft/caveolae mediated endocytic pathway, (ii) clathrin mediated endocytic pathway, or (iii) ADP-ribosylation factor 6 (Arf6)-associated endocytic pathway [42, 43].

The ADP ribosylation activity of cholera toxin is located in cholera toxin A1 domain. Hence, the entry of cholera toxin A1 into the cytosol is essential for intoxication process and this process includes ER-associated degradation pathway. Because of low lysine content, cholera toxin A1 can escape from degradation instead of passing through the degradasome. During transport through the degradasome, cholera toxinA1 can unfold and refold for the reduction by protein disulphide isomerase and reoxidation by E1 Tro. The cholera toxin enter into the cytosol, stimulates the catalysis of the ADP-ribosylation of the trimericGsα component of adenylate cyclase. This catalysis maintains adenylate cyclase in its GTP-bound state, and then it increases the activity of adenylate cyclase and intracellular cAMP concentrations. The high level of cAMP leads to severe problems of cholera [44, 45]

C.ANTIVIRAL ACTIVITY OF MEDICINAL PLANTS AGAINST *VIBRIO CHOLERAE*

Many medicinal plants are present and contain phytochemical compounds and their derivatives against *Vibrio cholerae* infection. 50% of pharmaceutical companies, both national and international, are utilizing the plant based formulations/extractions against cholerae and various infections [46, 47 & 48]. In previous work Neu5Ac2en analogues and Natural Polyphenols were identified as drug novels for the treatment of cholera [49, 50& 51]. Other than these two compounds still many potential chemical compounds are found in different medicinal plants against cholerae but they are unexplored. The aim of this review is can collect the phytochemical constituents from different medicinal plants and identify the better drug candidate for cholerae.

D.DRUG DESIGNING

Drugs are essential for the prevention and treatment of disease. Human life is constantly affected by many diseases. Therefore, ideal drugs are always in great demand. To meet the challenges of ideal drugs, an efficient method of drug development is demanding. But the process of drug design, development and commercialization are tedious, time-consuming and cost-intensive process. To fulfill these challenges, several approaches are required for the process of drug development. These approaches are based in-silico approach in drug design [52].
A drug targets are biomolecule which are participate in signaling or metabolic pathways that are specific to a disease process. Biomolecule play important roles in disease progression by communicating through either protein-protein interactions or protein-nucleic acid interactions leading to the propagation of signaling events and/or alterations of metabolic processes. Recently, drug discovery has significantly increased due to the availability of 3D X-ray or NMR structures of biomolecule, docking tools, and the development of computer aided methodologies. [52].
Drug Design can be categorized as two types: Structure based drug design (SBDD) and Ligand based drug design (LBDD).

A.Structure based drug design

ISSN: 2350-0328

International Journal of Advanced Research in Science, Engineering and Technology

Vol. 2, Issue 6 , June 2015

Structure based drug design is referred as direct drug design depends on knowledge of 3D structures of target molecules generated by X-ray crystallography or NMR spectroscopy method [53]. If an experimental structure of target molecule is not available, it can create homology model of target based on experimental structure of related proteins. The structure based drug design divided into two types:
Finding: In this case searching ligand molecules for given target molecules.
Building: In this case build the ligand molecules within the constraints of binding pockets by the assemble of small fragments [54, 55].

B.Ligand Based Drug Design

Ligand based drug design is referred as indirect drug design depends on knowledge of molecules with known biological activities that binds to the target of interest [56]. In other words a model of target molecules can be built based on the knowledge of what binds to it and this model can be used to design new molecular entities that interact with target [53].

III.MATETIALS AND METHODOLOGY

A. BIOINFORMATICS IN COMPUTER-AIDED

The National Institutes of Health (NIH) created the Biomedical Information Science and Technology Initiative (BISTI) to examine the current state of bioinformatics in the United States. BISTI's working definition of bioinformatics included its use in biomedical research, in particular for drug discovery and development programs. Bioinformatics was seen as an emerging how drugs are found, brought to clinical trials and eventually released to the marketplace [57].

Computer-Aided Drug Design (CADD) uses computational methods and tools to simulate drug-receptor interactions. CADD methods are dependent on bioinformatics tools, application and information technology, in- formation management, software applications, databases and computational resources which provides the infrastructure for bioinformatics. In the scientific field bioinformatics methods are used extensively in molecular biology, genomics, proteomics and other emerging areas (metabolomics and transcriptomics). Figure1 shows the applications of bioinformatics in different fields [58].

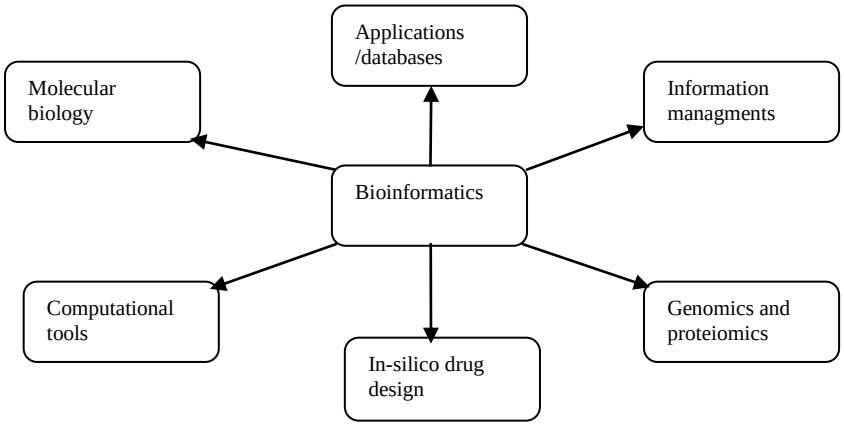

Figure1: Applications of bioinformatics in different fiels [58]

B.CADD STRATEGIES IN THE DRUG DISCOVERY PROCESS

CADD strategies are depending on the physical and chemical properties of targets (enzyme/receptor) and the ligands. In the drug design process currently the two major modeling strategies were used such as "Direct" and "indirect" design. In the indirect approach the design is based on the structural features of active and inactive compounds. In the direct design the three-dimensional structural information of the target (enzyme/receptor) are directly considered [59].

ISSN: 2350-0328

International Journal of Advanced Research in Science, Engineering and Technology

Vol. 2, Issue 6 , June 2015

C.*IN-SILICO* OR COMPUTER-AIDED DRUG DISCOVERY PROCESS

In-silico drug discovery process includes three main stages.
Stage1: This stage involves Identification of target molecules and design or collect small molecules from related database against identified targets. This is followed by the development of a virtual screening protocol initialized by either docking of small molecules or designing the molecules structures within the active site of target molecules by applying De novo design methods.
Stage2: The selected hits are checked for specificity by docking at binding sites of other known drug targets.
Stage3: The selected hits are subjected to detail in silico ADMET profiling studies and those molecules that pass these studies are termed as leads [60]. Figure2 shows applications of CADD in drug design.

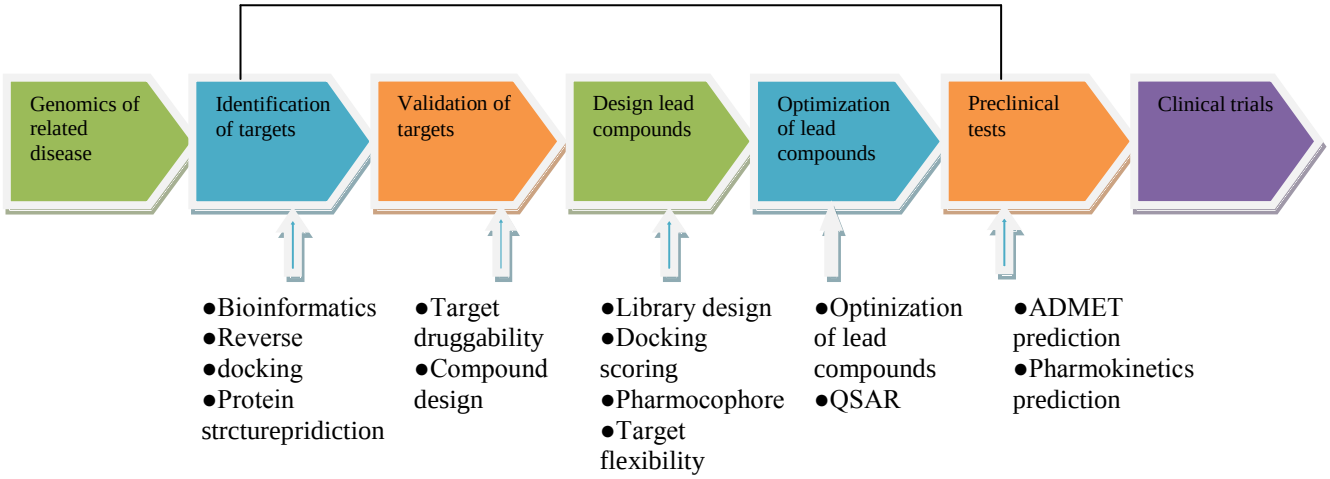

Figure2: Applications of CADD in drug design process [60].

D. DOCKING

Docking is process of formation of complex of macromolecules. Protein-ligand docking is a computational tool used to predict the complex of target (enzyme/proteins) and a small-molecule ligand [61, 62].

E. PROTEIN-LIGAND DOCKING PROGRAMS

Currently there are many docking programs are available and has steadily increasing over the last decades. The most commonly available docking tools are AutoDock, GOLD, DOCK, FlexX, Glide, FTD OCK and QXP are the most cited docking programs, with over 300 citations each in this period. In all tools the top cited docking programs have been available since the 1990s except Glide tool. Hence, they may be regarded as well-established mature docking alternatives, with a large and rather stable number of users. LigandFit, Surflex and FlexE are other more recent highly cited docking alternatives. AutoDock is a versatile protein-ligand docking program developed by Morris & co-workers at the Scripps Research Institute Its free tool with the good accuracy and high versatility [63, 64, & 65].

The most recent version of Autodock tool is AutoDock 4. AutoDock include number of search algorithms such as Monte Carlo Simulated Annealing algorithm, a Genetic Algorithm (GA), and a hybrid local search GA, also known as the Lamarckian Genetic Algorithm (LGA). The program can be used with a visual interface called AutoDock Tools (ADT) which ensures an efficient analysis of the docking results [66, 67].
These are the common docking tools used in previous work but currently for protein-ligand docking Autodock4 is using for the simulation of new drug candidates.

ISSN: 2350-0328

International Journal of Advanced Research in Science, Engineering and Technology

Vol. 2, Issue 6 , June 2015

IV. CONCLUSION

Medicinal plants have effective chemical compounds against *Vibrio choleare*. By using phytochemical constituents of medicinal plants and *in-silico* approach in drug discovery can design and develop better drug candidates for the treatment of cholera disease.

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International Journal of Advanced Research in Science, Engineering and Technology

Vol. 2, Issue 6 , June 2015

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