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Review Article

Medicinal Chemistry for Better Drug Design

A Review on Recent Rational Approaches to Drug Design, Development and Its Discovery

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Abstract: The steps involved in drug design, drug development and drug discovery are highly expensive, extremely challenging and time consuming. Although the drug designing, process has been hastened with the development of newer emerging techniques, and the fabrication of novel computational tool. Researchers are working on structure guided drug designing using a 3-D structure of target, the drug molecule identified by the use of target-based drug design shows great potential in preventing various diseases but also possess many side effects. In the rational drug design, structure-based designing, combinatorial drug designing and computer aided drug design techniques are employed. When gene expression and bioinformatics are incorporated with the combinatorial drug designing, that make the rational drug designing, a more powerful tool for drug discovery. The rational drug designing associated with gene expression and bioinformatical estimation is moderately emerging and expeditiously revamping the drug development with less time consuming, economic, effectiveness and cater novel combinatory therapy in addition to minimization of toxicity. This review discusses in detail about the fabrication of a successful drug candidate using multidisciplinary perspective of combinatorial chemistry with gene expression analysis, structure based and artificial intelligence-based drug designing. In future, more sophisticated computer-based methodologies would be required for developing new drug candidate.

Keywords: Drug Development, Computational Tools, Rational Drug Design, Combinatorial drug designing and Gene Expression Analysis.

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1. INTRODUCTION

Medicinal chemistry deals with structure assessment, synthesizing and separating newly synthesized compounds, which may be applied in medicine. It also establishes s the relations between structure of drug candidate and their pharmacological actions[1]. Drug designing is the process of discovering drug candidate on the basis of the pharmacological and molecular targets[1]. Generally, a drug target is a skeleton molecule associated with particular signalling pathway related to specific disease or pathological condition or antimicrobial efficacy against pathogen. The shape of the drug candidate specific to a drug target molecule can be designed with the help of computational techniques. Rational drug design is an effective and prime approach in pharmaceutical sciences as well as life sciences. Rational drug design deals with the discovery of drug candidate by methodological target-based designing, employing novel computational techniques, this technique is more economic and expeditious than previous dug development techniques. The aim is to establish a crucial drug destination based on detailed understanding of regulatory networks and metabolic pathways. Rational drug design emphasized to develop a highly specific drug based on a known three-dimensional (3 D) structure of that target. The combinatorial techniques added new amplitude to the drug discovery by adding gene expression and bioinformatics with drug design[2]. The excess of data from large scale genome-oriented projects started drug design concept very close to genuineness. The vast mapping of genome series, regulatory networks and metabolic pathways combined with single nucleotide polymorphism (SNP) data, biological samples or health records makes it easier to identify optimal drug targets. Access to superior quality 3 D structures of these targets is a great starting point for rational design of novel drugs. In the past few decades, there has been a hiatus in the momentum of research and discovery of novel medicinal compounds[3]. This peculiar progression in the drug development conceivably is expended due to crucial parameters first is strict empirical and intellectual ideas to drug design and second is high levels of safety and therapeutic potential together with increased costs of research and development and eventually the clinical trials[4]. Drug design or fabricated drugs strive to flourish a drug with a wide therapeutic range and unique action[5]. This mandatorily involves the study of biodynamics of a drug besides the interaction between drug molecules and molecules composing the biological objects[6].

1.1 Rational drug design could explain the following points

(a) Rational drug design can help to establish relation between the receptor and its pharmacological effect with the molecular structures or the physicochemical properties of the drug.
(b) The mechanism of action of the drugs involved in producing pharmacological responses.
(c) The interaction and specificity of drug to the protoplasm for initiating a particular pharmacological response.
(d) The drug metabolism and elimination from the body could be explained.

In short, drug design may be considered as an integrated approach which essentially involves various steps namely chemical synthesis, evaluation for activity spectrum, toxicological studies, biotransformation of the drug and study of various metabolites formed, assay procedures and finally galenical formulation and biopharmaceutics.[7,8] The drug design in an extended sight, entails arbitrary assessment of synthetic as well as natural compounds in bioassay conformity, siring of unused and novel drug molecules based on biologically active prototypes derived from either plant or animal kingdom, synthesis of congeners displaying interesting biological actions, the prime concept of isosterism and bioisosterism and finally precise design of a drug to enable it to interact with a receptor site efficaciously [7,8] Rational drug design comprises various stages. First the 3 D structures of target protein identified by NMR, X-ray crystallography, cryo electron microscopy, computer aided 3 D modelling, and homology method[9]. After identification, validation is done by Ramchandran plot and conformation of ψ and ϕ angles for amino acid. The binding pocket is then identified by calculating the interaction energy between the pockets and lead molecule with the help of Q-site finder that computes the Vander Wall interaction energy with a methyl probe, the protein residue also explain the binding pockets[9] and then the 3D lead is identified by employing latest computational techniques e.g. virtual screening and de-novo design. The lead molecule is optimized by modifying the chemical structure of lead[10]; analogues are created with improved efficacy, pharmacokinetic and pharmacological activities. Lead modification is done with a good knowledge of SAR, and optimized analogues are evaluated by *in-vitro* and *in-vivo* studies.

1.2 PRODRUGS AND ANALOGUES

In drug designing the drug molecule can be modified by the creating two types of molecule one is analogues and other is prodrugs. Prodrug is an inactivated or low activity form that on chemical/enzymatic conversion *in-vivo*, converted into more active drug and produces effects. On the basis of requirement, the prodrug conversion into active is designed to takes place in pre-post or in between the absorption phase or at target site[11]. Prodrugs are categorized into carrier-linked prodrugs and bioprecursor prodrugs. The carrier-linked prodrugs (promoeity) provisionally attached to the active moiety that is detached inside the body by enzymatic or chemical reaction. These prodrugs predominantly include ester and amid, phosphate, carbamates and oximes etc. whereas the bioprecursor do not possess promoeity but are the outcome of molecular conversion inactivated moiety[12]. Inside the body the bio-precursors are converted into active moiety by metabolic conversion[13]. Prodrug improves drug targeting into brain and spontaneously metabolized into the active moiety. L-dopa is a classical example of prodrug, a dopamine precursor used to treat Parkinson's disease, dopamine has low absorption in the brain due to its high hydrophilicity and enzyme susceptibility in the epithelial cells.

1.3 ANALOGUE DESIGN

Analogue design is the technique of modifying a drug molecule to create a new molecule biologically similar to the native molecule. Analogue show improved properties over native molecule. This technique beneficial, simple and vary popular in drug discovery[14]. For last 50 years, several analogue based molecules commercially available e.g. steroids, prostaglandins, anticancer drugs and antibiotics and 66% of small molecule are prepared by this method. The pharmacokinetic and toxic properties are considered before starting the project. Actually, analogue designing works with

the production of new chemical entities, while drug-structure repositioning make old drug in new cloths.

1.3.1 Analogue from natural sources

Various natural sources have been exploited for drug development e.g. alkaloids (acetylcholinesterase inhibitors neostigmine and rivastigmine) cocaine and quinine give rise to develop several analogues. Generally, the synthesized replicates have easier chemical structures than the native molecule. Most of the plant derived molecule exhibit several geometrical conformations, a lot of analogue can be prepared from them.

1.3.2 Analogues of metabolites

The metabolite of natural products also considered for drug designing, they can produce pharmacologically active metabolite with better pharmacokinetics, safe and potent e.g. fexofenadiene[14].

1.3.3 Analogues of existing drugs

Previously synthesized popular molecule is the choice of the researcher for this technique, few modifications are done in order to produce new drug molecule with improved property and safety profile

1.4 LEAD MOLECULE

Lead molecule is a tiny molecule that is specific to a particular target or biomolecule (protein and nucleic acid), play a pivotal role in cellular process with known 3 D structural information[10]. This approach of drug design is authenticated, established well and also applied extensively by pharmaceutical industries[15-16]. In rational drug design, a lead molecule is first identified, that interact with target protein, the lead is the fundamental molecule for discovering new drug entity.[10] In search of new drug entity the following activities are required.

(a) Identification of lead molecule: First the new lead molecule is identified depending on the structural activity with target protein. Lead molecules are screened out by employing latest computational tools.[17]

(b) Optimization of lead molecule: In second step the lead molecule is analysed and modified for improving its pharmacokinetic activities with the help of computational tool, actually the identified lead molecule may have weak efficacy, therefore the editing is done to improve the efficacy and safety feature of drug entity. Development of small molecules with predefined qualities for targets whose cellular functions and their structural information may defined or not defined information of undefined targets (genes and proteins) can be obtained by analysing gene expression data of samples untreated and treated with a drug using advanced computational tools[17, 18]

1.5 APPROACHES USED IN RATIONAL DRUG DESIGN

Various approaches have been utilized in the rational drug design it includes quantum approach, molecular orbital approach, linear free energy, artificial intelligence, structure-based drug design and genome expression profiling etc.,

1. Quantum mechanical approach

Quantum mechanics (QM) are computational method used in high throughput *in-silico* screening[19]. The QM is employed for computing energies and molecular properties; it is also used to optimize structure. QM also used to explain the effectiveness of biologically active molecules. The characteristic features of protons, neutrons and electrons are appropriately enumerated under quantum mechanics. The electronic features of the molecules responsible for chemical alterations are the basis of drug molecule phenomena.[20,21] The QM is employed *in-silico* for docking, scoring, modification of lead and decoding the reaction mechanism [18].

2. Molecular orbital approach

The QM is used for improving the authenticity of lead-target interaction but not viable for large bio-molecule, being a more expensive and time-consuming technique, for this the molecular orbital (MO) or fragmented orbital technique is preferred; it is expeditious and economic technique. In MO the biomolecule is fragmented into small parts, e.g. protein is fragmented into residue (amino acid) likewise the lead or ligand expressed by single or multiple fragments[21]. The MO computes the lead-target and generates interaction corresponding to the chemical structure and also quantifies the energies stabilization of lead- target coupling. Various kind of energies (electrostatic, exchange, repulsion, charge transfer and dispersion) combined together and called pair interaction energy. This represents the polar, non-polar and salt bridge interactions. [21, 22]

3. Linear free energy approaches

This technique inaugurates the active connection between the proper choices of physicochemical factors with a particular biological phenomenon. However, such a correlation may not guarantee and allow a direct interpretation with regard to molecular structure, but may positively offer a possible clue towards the selection of candidate molecules for synthesis.[23] Linear interaction energy used to predict the binding affinity for lead optimization; it provides better understanding between computational speed and accuracy. Molecular mechanics model represents the target lead interaction and consider both solvation and entropic effects. Molecular dynamics (MD) or Monte Carlo (MC) sampling method are employed for generating the thermodynamic average of energies virtual screening of lead [24] and also employable for resting of structural and energy of initial structure. Single-point energy minimization, a simpler technique can also be used; this can be used in relaxing of structural and high energy stage of initial structure. Main function of this technique includes:

1. Linear energy method is good scoring technique that can compute the lead-target binding affection.
2. Linear energy method could compute free binding energy rationally and induced fit effect.
3. it also accurately computes lead-water-target interaction.
4. it can score the estimated dock position for a lead molecule.

Latest computerized methods are available for characterizing lead molecule, generally LE used with MD sampling for virtual screening of lead. The lead-receptor binding is seen, where the lead is transferred from non-aqueous to the binding site of the water-solvated target[24, 25], the binding state of lead and water-solvated target considered for describing the energies fluctuation in lead-target fusion. The energy transfer can be represented by the equation

$$\Delta G_{bind} = \Delta G^{b}_{sol}\, l - \Delta G^{f}_{sol}$$ (Equation 1)

The main difference with respect to a regular transfer process between two solvents is that the standard state in water (1 M and free rotation) is replaced by restricted translation and rotation in a confined receptor-binding site. The resolution of such a thermodynamic cycle leads to the following equation:

$$2\Delta G_{\text{bind}} = \Delta G^{\text{polar}}_{\text{bound}} - \Delta G^{\text{polar}}_{\text{free}} + \Delta\Delta G^{\text{nonpolar}}_{\text{bind}} = \Delta\Delta G^{\text{polar}}_{\text{bind}} + \Delta\Delta G^{\text{nonpolar}}_{\text{bind}}$$ (Equation 2)

Where the entropic confinement contribution, are hidden in the non-polar term. Thus, the free energy of binding can be expressed as a sum of the corresponding polar and non-polar components of the free energy.[25]

4. *Drug design by way of disjunction*

Disjunction is employed where the analogues of prototype is developed sequentially, generically in preparing structurally simple analogue, that could be perceived as segment or pseudo-replicas of the prototype agent. This can be achieved by following methods[31].

a) The aromatic cyclic system converted into saturated system by doing substitution.
b) Curtailing the hydrocarbon part from the parent molecule.

The immense research of the estrogenic function of oestradiol was done by employing the disjunction method of drug designing received fruitful outcomes with great success in synthesizing and evaluating trans-diethylstilbestrol.
The flow chart of estrogen pattern is mentioned below **(Fig 2)**:

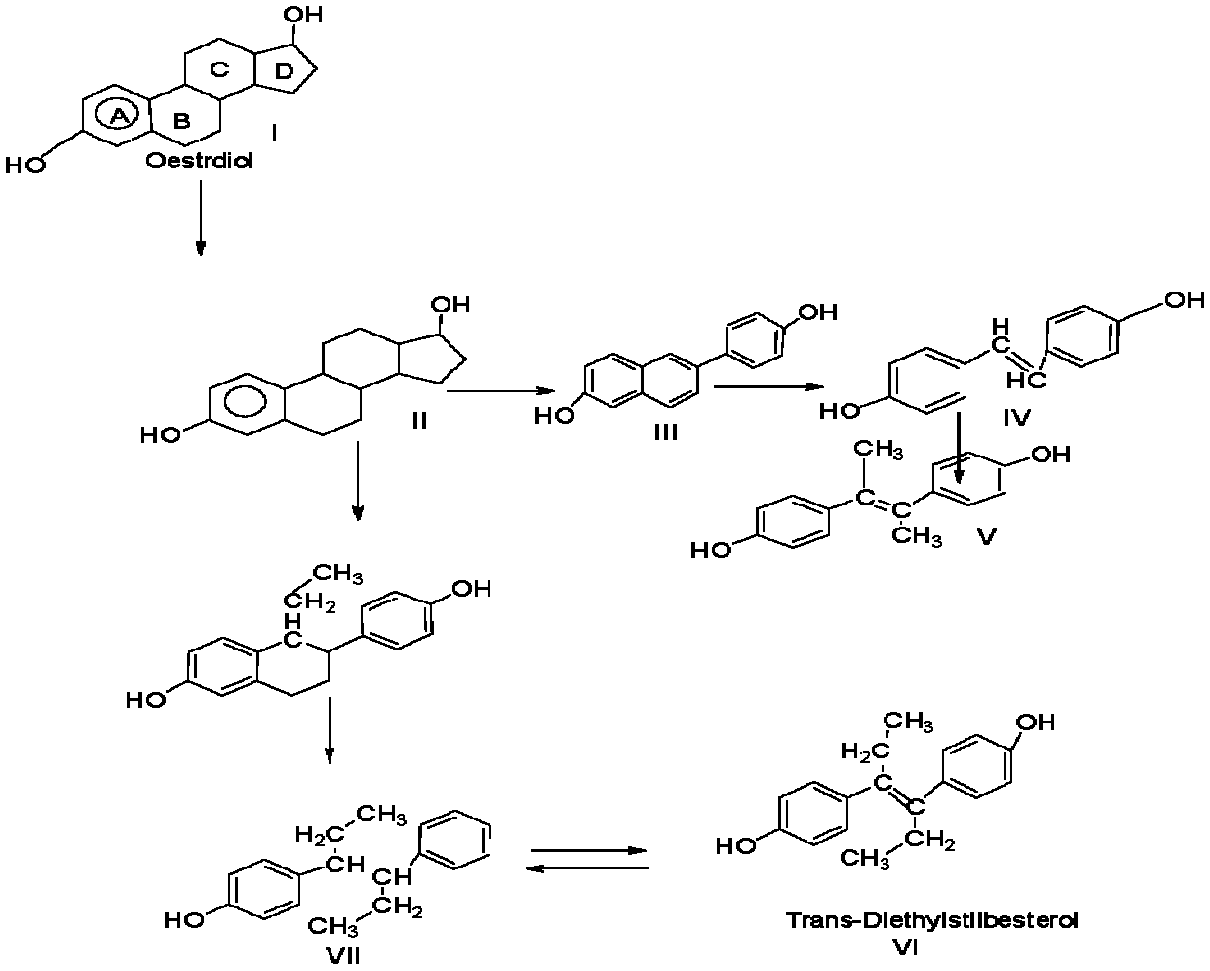


Figure 2: Flow chart of estrogen through disjunction [31]

5. *Drug design through conjunction*

This is known as the organized synthesis of derivatives of a drug of a prototype agent. Generally, toward structurally more complex products, which may be viewed as structures embodying in general or specified way, sometimes certain or all types of features of the prototype.[31]

6. *Combinatorial technique in rational drug design*

The progression of collaborative or combinatorial approaches of drug evolution and advancement, is more advantageous for a number of reasons. Generally combinatorial rational drug design is multidisciplinary technique, the genomic data and bioinformatics added to the rational drug designing[2]. The benefits would range from improvement in diseases, elimination/minimization of toxic effects and side effects, reduction in biotransformation, improvement in distribution (bioavailability), overcoming drug resistance, and improvement of immune response respectively.[32,33]

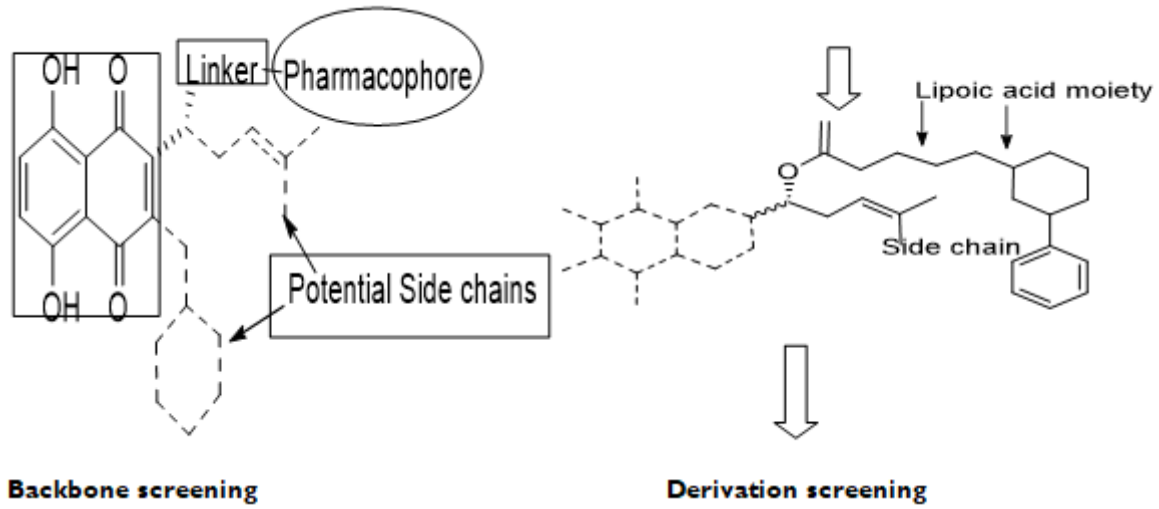
7. Structure based drug design (SBDD): A direct approach

X-ray crystallography and NMR spectroscopy etc. techniques are very beneficial and fruitful for studying the biological targets and also 3 D structure of the compound could be elucidated by the same technique. Atomic resolution is essential for 3 D protein structure. In shortcomings of structural information related to target[43,44,45], the structure of target protein can be elucidated by implementing homology modelling. Programs that involve the utilization of the structure based virtual screening. SBVS compares GLIDE, FlexX and GOLD. SBVS comprises explicit molecular docking of each ligand into the target binding site, developing a predicted binding mode for each compound and measuring the quality of fit of the compound in the target binding site based on the fitness function[46]. This is accompanied by ranking of compounds to select a small subset for investigation of biological activity.[45]

1.6 MOLECULAR HYBRIDIZATION

The molecular hybridization (MH) is rational approach employed in designing of new lead on the basis of identification of molecular structure of pharmacophores of known drugs analogue and the combining of these take on to create new hybridized structure with predetermined properties of original template[26]. A well-known template is used because of the better understanding of the physiochemical, pharmacokinetic and pharmacodynamic properties and a comprehensive chemical library is generated, with a number of homologous molecular hybrids. It gathers information about structure, lead-target interaction and QSAR, the prerequisite for developing new drug candidate with high efficacy[27]. If template hybridization is not existed well than lead could be identified by screening of chemical libraries. MH is based on the biological phenomenon of genetic-crossing, hybridized daughters with identical properties are produced from parent molecule. Several new chemical entities (NCE) created and added to the library, with a promising lead molecule of known pharmacokinetic and pharmacodynamic characteristics due to their structural homology with parent template. The library is validated by *in-vitro* and *in-vivo* experiments and available data base.

Lin HY *et al.,* 2017, used a Shikonin (Skn) a naphthoquinone compound obtained from *Lithospermum erythrorhizon* and alpha-lipoic acid (LA), a naturally-occurring co-factor for targeting PDK1 and tubulin.[28] Shikonin and LA both possess antineoplastic activity by inducing cell apoptosis. Molecular hybridization technique was used to yield a scaffold. the scaffold has three parts: i) Skn scaffold as an anticancer pharmacophore fragment against tubulin; ii) co-factor LA as the medium-chain and iii) various aromatic aldehyde units attached with LA fragment as another anticancer pharmacophore fragment **(Figure:1)** against PDK1. Modification in shikonin structure found extraordinary. Based on computer aided drug design (CADD) screening, the biochemical and pharmaceutical assays revealed LA-shikonin ester analogue synergistically provides antineoplastic activity by simultaneously acting on two targets.



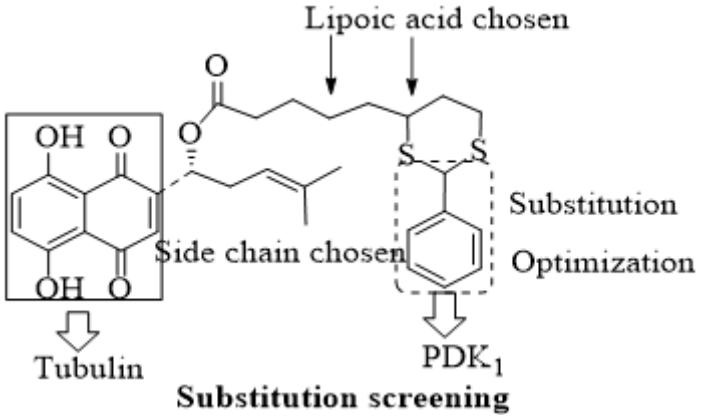


Figure 1: molecular Hybridization technique for tubulin and PDK1 receptor by Shikonin and alpha-lipoic acid.[28]

1.7 ARTIFICIAL INTELLIGENCE FOR RATIONAL DRUG DESIGN

Artificial intelligence is described as an extended term that includes the design and involvement of algorithms for analysis of, learning from and interpreting data. Artificial intelligence is computer based human simulation process[29], includes several esteems of statistical and machine learning, pattern recognition, logics and probability theory. It also deals with biologically motivated approaches like neural networks, evolutionary computing or fuzzy modelling, collectively called "computational intelligence. Drug design faces numerous challenging obstacles in terms of selection of relevant information, data modelling, classification, prediction and optimization that insist the development and applications of tailored AI approaches. A lot of AI methods have been developed in recent past years[28]. Enormous challenges such as the predictive toxicology challenge and the feature selection challenge is also taken into consideration. The impact of computational methods on drug design, testing and discovery will surely grow even further in future. Yet now, various results reveal that computational methods are indispensable in drug design and preclinical evaluations. Attempts to combine predictive, data driven technique with molecular modelling and simulations are likely to bring further progress in this field. By applying ontologies, analysis of symbolic as well as textual data to build complex models of biological organisms is alternating growing trend[29]. An Example is the Eco Cycle model (http:// ecocyc.org/) of the *Escherichia coli* bacterium encompasses the entire genome, transcriptional regulation, transporters and metabolic pathways. Other organisms are being annotated in a similar, integrated manner (e.g. http://biocyc.org/), with the potential to result in new approaches and enhanced tools for drug design. Artificial intelligence procedures are being applied to get correlations between patterns of genetic variations and expression profiles with clinical and other phenotypes and used to determine predictive fingerprints of disease states, progression and results of therapeutic interventions. Aforesaid creates both challenges and chances for artificial methods, encouraging their future developments.[30]

1.8 GENOMIC DATA POOLING

Genomic data pooling is precious technique, which exhibit novel perception in investigating the pathology of biological process and their disorders including cancer and diabetes, this is achieved by identifying the particular genetic sequence responsible for disorders. Polling or collection of genomic expression provide us the factual knowledge of consequence of genomic expression in biological process and help out in understanding the importance of genome as target for therapeutic manipulation[34].

Various platforms are available for identification of genome; among them widely employable platforms are MA (Microarray) and SAGE (Serial analysis of gene expression) respectively [34, 35]. MA and SAGE provided empowerment to the researchers to explicate various facets of bioscience in global perspective. SAGE emerge an exhaustive genomic profiling without any previous genomic details, and that results in recognition of novel transcripts. The MA analysis creates catalogue of genome and their activities and illustrate their working manner with the cellular environment. MA could be used in discovering and recognizing novel targets, biomarker and lead molecule. MA could be used to search uncharacterized genome and recognizes the disease-causing genome. MA is most popular platform due to its reproducing capability, economic and high-speed data accessibility. The high-density microarray (HDMA) chips are composed of immobilized oligonucleotides and cDNA on solid surface. The amalgamation of both platforms can be fruitfully employed to overcome the complexities of gene expression data[36,37]. Outcome of amalgamated form are highly sensitive and précised with high accuracy and can distinguish two closely alike cellular type. Various MA platforms are now available in the market.[36,37] The HDMA are accepted globally and attracted researcher of the world for scrutinizing genomic sequences pattern of tissues. For accelerating the data mining both the platforms are added with the latest computer software and that logically compute the biological details, these computer-based technologies are knows as bioinformatics tools, that permit the systematic arrangements of genome expression data globally and genomes are categorized into various pathways and interaction networks.[38]

1.9 GLOBAL GENE EXPRESSION ANALYSIS-BIOINFORMATICS TOOLS

The explication of genomic expression pooling by comprehensive manual investigation and literature search incorporated with bioinformatics provide simpler high efficiency method. Bioinformatics also provide scientist visual view of genomic expression data by a lot of means likewise by genome clustering, pathways or by protein-protein interactions by functional categories, some specific database also furnish scientists with repositories of genome expression data worldwide and are available for accessible to public. e.g.

such databases include the Gene Expression Omnibus (GEO), SAGE data repository (Absolute Level Lister, SAGE Map, Stanford microarray database and many other similar such databases[39]. A prerequisite element for arranging the genomic expression data is the clustering of genes that permits the reorganization genomic signature with the annoted genome. For annotation, a tool DAVID (Data Annotation Validation and Integrated Discovery) is most applicable for annotation of various genomes for genome Ontology, protein domain and pathways respectively[40]. Other most applicable tool for computation is the Gene Set Enrichment Analysis (GSEA) tool. GSEA evaluate whether a previously explained group of genome exhibits statistical significance and differences between two biological states for example treated v/s. untreated or normal v/s abnormal states[41]. The genome annotation process produces protein; this genome annotation pathway could be visually seen with help of pathway visualizing tool GenMAPP. The network survey can also used for envisaging genome. The ingenuity pathway analysis (IPA), a licensed tool can also be used in this regard. That provides a pictorial and illustrative way. The tools and software are updated regularly for as per requirements of researcher. The bioinformatics tools are very user friendly. Various bioinformatics software is available in the market for industrial and institutional purpose, for genome expression data searching. The selection of suitable software is determined by the end user on the basis of their requirement. For rational drug designing good understanding of genome that are regulating the over or under expression, or with unaltered expression required to discover the target protein for a lead molecule. Identification of responsible genome is done with consciousness by comparing the normal, treated or untreated states. The details of genome expression are useful for the modification of drug candidate or to evolve approaches for combinatory therapy. The assessment procedure is continuously replicated for several times to achieve a required outcome of the combinatory therapy. A well understanding of the database management system (DBMS) likewise MS Access or other DBMS is required because bioinformatics tools employed the MS Access with MS excel. MS excel is marvellous software for genome expression data, but attention is required while exploiting the genome expression data on it, due to its auto correction system an error in genome symbol can arise e.g. the gene name Septin 09 and its symbol is SEPT 9, is converted to Sep-09. Such type of error generally happen for other genomes and data can be misinterpreted.[37,42] Thus, successful data mining sometimes requires careful manual inspection, especially when using this DBMS.

1.10 GENOME EXPRESSION PROFILING IN DRUG DISCOVERY

The genome expression profiling studies of tissue or its fragment is major part of the drug discovery. The information gathered from the studies affects the target recognition, optimization, compound selection, pharmaco-genomics, biomarker evolution, clinical trial and toxic studies. Various pharmaceutical industries made setup for database of genome profiling from human. For achieving benefit from the recourses, a single array platform is selected and all tissue profiling studies are conducted on arrays from a single provider using standardized methodologies. This creates extensive species-specific databases that provide result with accuracy because all array using same quality control standard. Amalgamation of peculiar database could be done with this that allow the array data from single or multiple homologus gene from divergent species, it rapidly compare data. While designing a drug, it is evaluated that the required genome expressed from the same tissue with same intensity in all the species or not. For drug discovery the genomic profiling of whole tissue or fragment is isolated and data are produced.[36]

1.11 RIGIDITY AND FLEXIBILITY VS DRUG DESIGN

There is no any logical uncertainty while designing a lead molecule that the SAR exhibits molecular interactions between the lead molecule and target molecule.[31] For a single, fixed configuration or structure of protein, the structure should be rigid such system, this kind of system are correlated with lock and key theory of binding.[47] The protein existed only in a single well differentiated, rigid form, having affinity to a specific optimized ligand only[48], however the protein can also exists in less rigid form that may have low or no functionality. There two circumstances may be occurred

1. Increased rigidity: that could finally enhance the lead efficacy.
2. Increased flexibility: that may provide good activity.

Both the aforementioned situation is illustrated here with suitable examples for better comprehension of these factors in drug designing for a new targeted drug candidate.

1. Increased rigidity

Abundantly the drug molecules are found innately flexible in nature. They can acquire diverse shape (spatial positioning), from these structurally divergent molecules few are precisely not unacceptable to interact with the target molecule[31]. For designing or discovering a drug molecule analogue should have high rigidity. An accurate and desired spatial arrangement is searched to achieve a most efficacious drug molecule. The gap between two fundamental functional moieties may be fixed arbitrarily in rigid structurally divergent molecule. The strategic modification and positioning of new chemical entity undergo critical evaluation and characterization with the help of latest sophisticated analytical instruments (X-RDs, NMR, optical rotary dispersion, FTIR and Mass spectral analysis).[49]

2. Increased flexibility

The complications appeared with the molecule having low flexibility, high rigidity and compactness that resulted in immovability, relatively much or less, in another way it can be explained as the molecular structure has insignificant or frivolous ability to make the reorganize into a more suitable conformation that may eventually give rise to improved activity. Upgradation of latest computational technology in the past 10 years achieved new venues of discovering the target flexibility and guided by improved algorithms, computer power as well as a growing body of experimental data.[50] Computer aided designing allow to change the orientation of molecular coordinates for resolving flexibility complications and their consequences and also predict the lead-target interaction, thermodynamics of interactions and binding kinetics as well. There are also static methods for describing system in simple manner, ignoring target dynamics, as case of rigid docking (rigid receptor and flexible ligand) approach, a widely employed approach for predicting docking

position in virtual screening, the target is kept as rigid object. This give rise to false result, the specific target conformation could be targeted by certain leads and restructuring of binding site is required, for this soft-docking" approach is employed, in which the Vander Waals radius of target, lead atoms or both are lowered to minimize steric confrontation. However, it also generates false positives, as the target becomes incompetent. Rigid docking may apply for ensembles derive modelling; the target flexibility designing is always done prior to ligand docking. Rigid docking only provides rough estimation about the thermodynamics of binding, enables high throughput performance.[51]

1.12 DOCKING

Docking is the computational assurance of binding affinity between a protein structure and a ligand. This method involves proficient sampling of all possible poses of ligands in the binding pocket of target protein to ease optimal binding geometry as measured by defined scoring functions. Docking of small molecules have been carried out mainly in three ways (1) Rigidity docking, in which the target and ligand are treated as rigid (2) Flexible ligand docking, in which the target is held rigid (3) Flexible docking in which both the target and ligand are considered flexible[52]. Molecular docking protocols can also define a blend of search algorithm and a scoring function. At present algorithm is supposed to provide assistance and freedom to the protein ligand coordination to enable accurate and sufficient sampling including the binding modes. Rationally the search algorithm is supposed to provide support and freedom to the protein ligand coordination to enable accurate and sufficient sampling including the binding modes. The search algorithm is supposed to have good speed and effectiveness while the scoring function must be able to analyse physicochemical properties of molecules and thermodynamics of interaction. The complexity of docking increases in the order of rigid docking, flexible ligand docking and flexible docking[52]. A reliable docking algorithm should exhaustively search all possible binding modes between the ligand and target; however, this is impractical because of the larger size of search space. Therefore constraints, restraints and approximations are applied to reduce the dimensionality of the problem in any attempt to locate the global minima as efficiently as possible. Since large conformational space is available to protein structures, partial flexibility has recently been incorporated into some docking algorithms e.g. GLIDE, GOLD, AUTODOCK, Flex X etc. Genetic algorithms (AUTODOCK, GOLD) and Monte Carlo simulated annealing algorithms (GLIDE) are widely used. The genetic algorithm is an iterative process that sustains a population of individuals that are candidates of the solutions to the problem being elucidated. However, simulated annealing is an iterative procedure that constantly apprises one candidate solution until it reaches a termination condition.[53,54,54]

1.13 VIRTUAL SCREENING

Virtual screening (VS) is a computational approach for the discovery of new drugs that has successfully complemented High Throughput Screening (HTS) for hit detection. The purpose is to apply a computational access for quick cost-effective evaluation of large virtual databases of chemical compounds to find novel leads that can be synthesized and examined experimentally for their biological activity.[45] Disparate HTS, virtual testing and examination does not expect on brute force search and it is instead based on starting information of the receptor under inspection or its active ligands. VS methods can be divided into two different categories: structure based and ligand based.[54]

1.14 Structure based virtual screening

Structure based virtual screening (SBVS) encompasses a variety of sequential computational phases including target and database preparation, docking and post docking analysis and prioritization of compounds for biological testing.[45] SBVS is employed in situations in which the 3D structure of the target protein is known, various physical features such as Van Der Waals (VDW) interactions, electrostatic interactions and bond stretching/bending/torsional forces. Force-field or molecular mechanics-based scoring functions utilize parameters derived from both experimental and ab initio quantum mechanical calculations[38]. These scoring functions estimate the binding free energy of protein ligand complexes by the sum of Van der Waals (VDW) interactions.[45]

1.15 Homology modelling

In homology modelling or comparative modelling, the similar drug analogues are identified. It is employed in predicting the 3D structure of proteins. First the structural segment of amino-acid is identified and then a 3 D model of protein is created in computer.[56,57]

1.16 QSAR

Conventional QSAR (quantitative structure activity relationship) techniques are rooted on connection of pharmacological and biological activity with local features of atoms, whole molecular properties (e.g. charge), substituent effects (e.g. fragment hydrophobicity indices). QSAR manifests a number of illustrations that one can use in deciding new QSAR relationships. A descriptor is a molecular property that can be estimated by QSAR.[57]

1.17 STRATEGY USED IN DRUG DESIGNING

Here the illustrative example is discussed to understand the process of drug design

Strategy 1

Chao et.al, 2007 selected Indole-3-carbinol is a naturally occurring substance for development of anticancer agent by using rational drug design technique, exhibit anti-proliferative against tumour cell; it has 4 analogues DIM (2), LT (3), CT (4), and ICZ (5) (Figure: 3) with other 20 analogue.[58] All 4 analogue are inactive and converted into active by gastric acid with a low efficacy, are screened out as lead molecule for developing an effective drug entity by employing lead-based rational drug design performed computer-aided structural analysis using SYBYL 7.0 software package (Tripos, St. Louis, MO).[58]

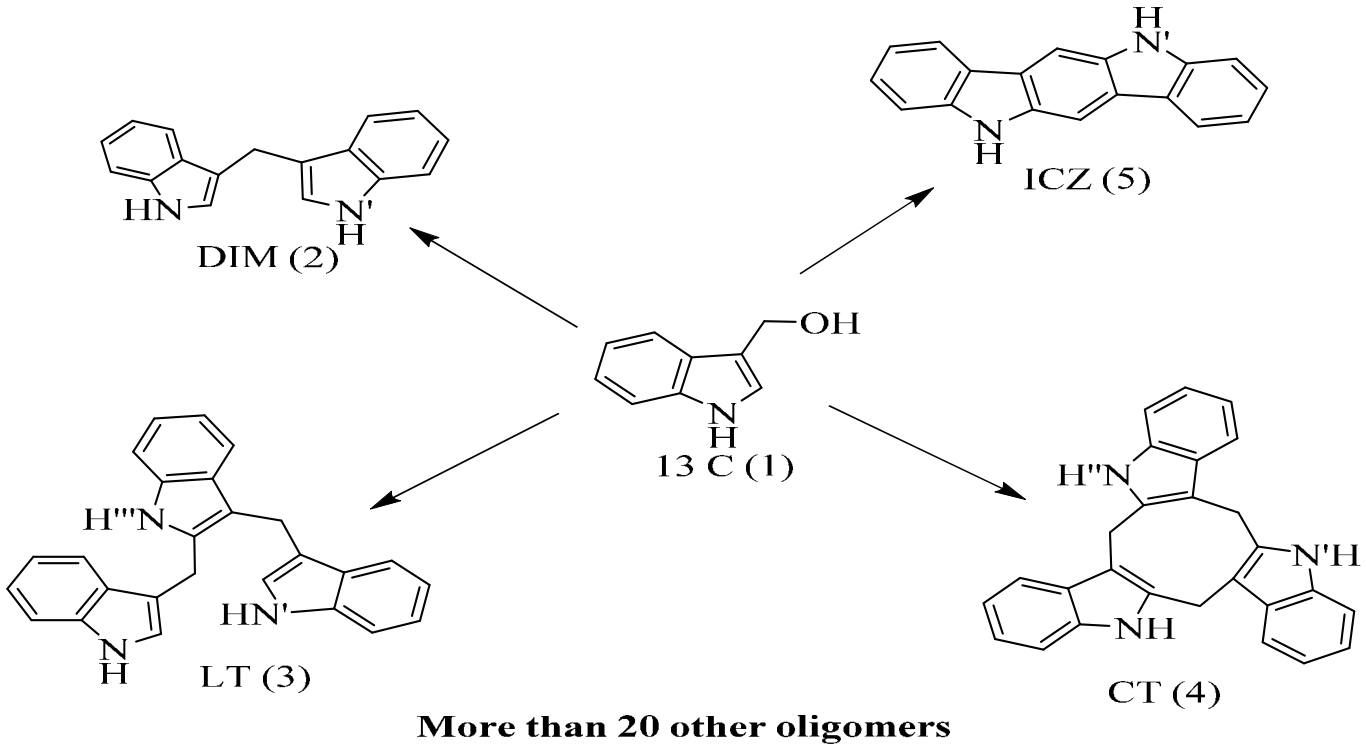


Figure 3: Depicting the structure of lead molecule [58]

On superimposing low energy was observed indicating superb overlapping on the target. Figure: 2. SAR indicates N-N′ distance affects the anticancer activity. The leads are modified to enhance the efficacy and safety. Four analogues 6,7,8 and 9 were prepared using DMI2 skeleton with a changing N-N′ distance, as the distance increased (in 6 and 7) the efficacy was decreased, and on decreasing the distance (in 8) the efficacy increased. Analogue 8 is selected as template for further development. Analogue 10 was prepared by modifying the planarity of 9 and optimum N-N′ distance (Table: 1), good *in-vitro* anticancer activity (MCF breast cancer cell) was found on i.p. administration rather than oral due to low oral bioavailability[58].

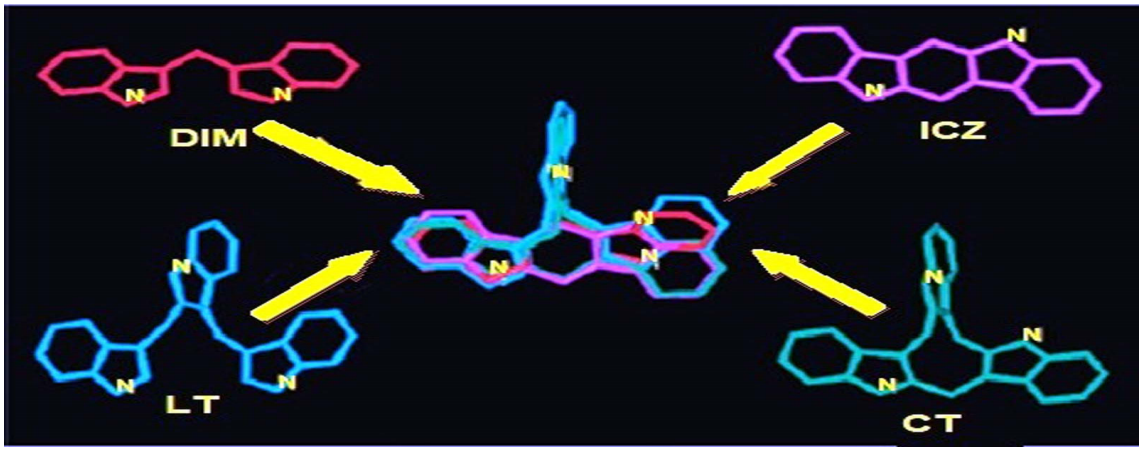
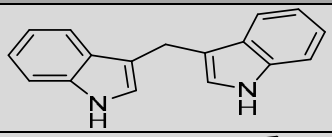
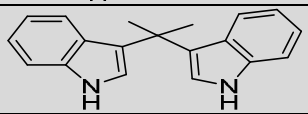
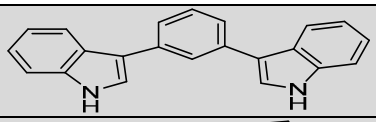
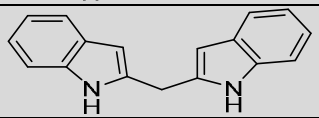
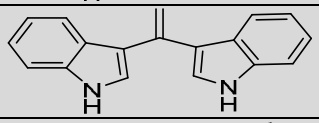
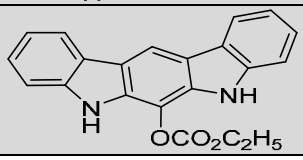


Figure: 2 depicting the superimposing of lead molecule on target [50]

Table: 1 Modification N-N′ distance and planarity of DIM

Compound	Structure	N-N′ distance(A^0)	MCF7 IC50 µm
DIM 2		5.9	0.5
6		7.0	>10

7		9.0	>10
8		4.7	0.94
9		5.8	3.3
10		9.1	0.08

On addition of electron removing group at C-5 and C-5′ positions of DIM, enhances the oral bioavailability but with no anti-proliferative activity (Analogs 24 and 27) except 24 with ester substituent. Computer analysis reveals, the addition of ester at C-5 position enhances both dipole movement and efficacy. Addition of ester at C-5 and C-5′ position of analogue 10 generate 35 with raised dipole movement than its predecessor. The carbonate group of 35 is then replaced with heptafurfuryl group and 36 was generated, on introduction of methoxy and ester group on 10 generated 37 with highest dipole movement and highest efficacy than 10, 35 and 36 (Table: 2).

Table: 2 Introduction of Polar substance into DIM

Analogue	C-5	C-5′	Dipole Moment	Anti-Proliferative activity
DIM 24	CO_2-C_2H_5	--	*	**Improved**
25	COOH	--	**	**NO**
26	$CON(CH_3)2$	--	**	**NO**
27	SO_2-CH_3	--	**	**NO**
10	H	OCO_2-$C2H_5$	**	**26%**
35	CO_2-C_2H_5	OCO_2-C2H5	**	**40-60%**
36	CO_2-C_2H_5	C_3F_7	***	**40-60%**
37	CO_2-C_2H5	OCH_3	****	**40-60%**

**** indicates low, ** indicates medium and *** indicates high dipole moment***

Analogue **37** containing one electron removing and one electron pumping group at C-5 and C-5′ substitution was found with high solubility and high anti-Proliferative and selected as best analogue.

Strategy 2

S. Subramanian et al., selected phytoconstituents gymnemic acid (GA), trigonelline (Tg), and ferulic acid (Fa), (Figure: 3) as ligand for anti-diabetic activity [58], the 3D structure created in Chemsketch and converted into PDB format. The molecular target glycogen synthase kinase-3 (Gsk3-α and Gsk3-β) collected from RCSB PDB.

Figure: 3 Depicting structures of lead[58]

Molecular docking and molecular interactions between the ligand and target were performed on Auto Dock Tools (Trott and Olson, 2010). The outcomes were examined to understand the interaction and bonding energies of the docked structure. The ligand-target complex with lowest energy was selected as best ligand. GA, Tg and Fa were docked to Gsk3-α and Gsk3-β, the interaction and hydrogen bonding distance with amino acids were computed and the results are shown in table: 3, table: 4 and table:5.

Table 3: Docking energy for GA with Gsk-3α and Gsk3-β

Gsk-3α		GA	Distance	Docking energy (Kcal/mol)	Gsk-3β		GA	Distance	Docking energy (Kcal/mol)
Residue	Atom				Residue	Atom			
TYR123	OH	O	2.43	-5.33	ARG148	NH1	O	2.68	-4.69
TYR123	OH	O	2.98		ARG148	NH1	O	3.16	
TYR123	OH	H	1.87		ARG148	NH2	O	2.85	
VAL108	N	O	3.14		ARG144	NH2	O	2.80	
ARG110	NE	O	2.61		ARG144	NH2	O	2.67	
ARG110	NE	O	3.05						

Table 4: Docking energy for Tg with Gsk-3α and Gsk3-β

Gsk-3α		Tg	Distance	Docking energy (Kcal/mol)	Gsk-3β		Tg	Distance	Docking energy (Kcal/mol)
Residue	Atom				Residue	Atom			
ARG62	NH1	O	2.87	-6.85	ARG180	NH1	O	3.19	-5.51
ARG62	NH2	O	2.95		ARG180	NH2	O	3.16	
LYS147	NZ	O	2.83		ARG180	NH2	O	2.82	
VAL180	N	O	3.05		LYS205	NZ	O	2.80	
ARG146	NH2	O	2.92		ARG96	NH1	O	2.99	
ARG146	NH2	O	3.18						
ARG146	NH1	O	2.84						

Table 5: Docking energy for FA with Gsk-3α and Gsk3-β

Gsk-3α		FA	Distance	Docking energy (Kcal/mol)	Gsk-3β		Tg	Distance	Docking energy (Kcal/mol)
Residue	Atom				Residue	Atom			
SER169	OH	H	2.07	-7.0	ARG180	NH1	O	3.19	-5.51
SER169	OH	H	3.02		ARG180	NH2	O	3.16	
ARG146	NH2	O	3.04		ARG180	NH2	O	2.82	
VAL180	N	O	2.95		LYS205	NZ	O	2.80	
LYS171	NZ	O	3.00		ARG96	NH1	O	2.99	
LYS171	NH2	O	2.98						
ARG146	NH2	O	2.98						

Table 6: Inhibition constant and intermolecular energies for GA, Tg and TA

Leads	Inhibition Constant		Intermolecular energies	
GA	124.16	362.83	-10.4	-9.76
Tg	9.5	92.5	-7.15	-5.8
FA	7.4	197.29	-8.49	-6.55

The study reveals all the 3 leads have shown very good inhibition constant and low bond energy, all the lead has good inhibitory effect on glycogen synthase kinase-3. Those lead can be used pharmacophore to develop the new for anti-diabetic drug.

2. CONCLUSION

Scientific information and thorough understanding of the relationship between chemical structure and other factors greatly facilitate the drug designing and drug discovery. Intensive involvement of structure-based drug design methods increased our ability to craft more efficient and more specific ligands. Rational approaches of drug designing leads to evolve pharmaceutical novelties and became a significant tool with the help of computational techniques. Drug design and drug discovery provides encouragement and growth of any pharmaceutical firm and also to the welfare of society, as newly synthesized safer drugs are launched in the market with the view to improve the therapeutic index and better safety. Pharmaceutical industry and drug research organisations are using latest techniques, include genome expression profiling of cancer and diabetes regulating receptor with high throughput screening, for designing and discovering drugs, Random screening can be performed with chemical libraries and have relatively great probability to get a novel molecule. There are several approaches such as metabolomics, genomics, proteomics also compliments well with other techniques, from our study it can be concluded, the latest drug designing techniques could be employed for discovering drug molecule that have more target specificity, accuracy, safety with reduced discovery time and low investment.

3. AUTHORS CONTRIBUTION STATEMENT

All author contributed equally in conceptualizing the theme and collecting data and preparing the manuscripts.

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5. CONFLICT OF INTEREST

Conflict of interest declared none.

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