Abstract

Computer backed medicine design is a recently developed and a veritably effective fashion extensively used in medicine design and development. Now a days CADD is used in nanotechnology, molecular biology, biochemistry and in numerous fields. Cost effectiveness is the main benefit of CADD in exploration and development of medicines. CADD visualization include different ways similar as homology, molecular dynamic, energy minimization molecular docking, QSAR, etc. Grid computing, window grounded general PBPK/ PD modeling software, PKUDDS, APIS, JAVA, Perl & python are some ranges of software used in CADD. Computer backed medicine design is applicable in numerous fields similar as cancer, medicine transportation at the specific point of body, collection and storehouse of organic and natural data.(1) Computer backed medicine design( CADD) is an evolving waterfall of exploration area encompassing numerous angles. Computer- backed medicine design( CADD) is an instigative and different discipline where colorful aspects of applied and introductory exploration merge and stimulate each other. The theoretical base of CADD involves amount mechanics and molecular modeling.
studies like structure grounded medicine design; ligand-grounded medicine design; database searching and binding affinity grounded on the knowledge of a natural target. In this present review we present the areas where CADD tools support medicine discovery process. As fliespeck design is presently a major development of supercritical fluids operations, substantially in the medicinal, nutraceutical, ornamental and specialty chemistry diligence, number of publications are issued and multitudinous patents filed every time. This document presents a check (that can not pretend to be total!) of published knowledge classified according to the different generalities presently used to manufacture patches, microspheres or microcapsules, liposomes or other dispersed accoutrements (like microfibers). This acronym refers to ‘Rapid Expansion of Supercritical results’; this process consists in solvating the product in the fluid and fleetly depressurizing this result through an acceptable snoot, causing an extremely rapid-fire nucleation of the product into a largely dispersed material. Known for long, this process is seductive due to the absence of organic solvent use; unfortunately, its operation is confined to products that present a reasonable solubility in supercritical carbon dioxide (low opposition composites).

**KEYWORDS:** Computer aided drug design, Molecular modeling, Biological target, Drug discovery process

1. **Introduction**

Computer backed medicine design is an in-depth fashion used to discover, design and optimize new, effective, and safe medicines with the computer backing. There are some pioneering advances similar as recent technological developments in biochemistry, biomedical wisdom and nanotechnology which determine the molecular base of CADD. Medicine discovery and development is a very time
consuming as well as coffers consuming process. At the same time it's necessary to fid a chemical emulsion which can fit to a specific depression on a protein target both by chemically and geometrically. The development of a new and implicit medicine starts with numerous times of scientific study for the determination of the conditions biochemistry and the inventions possible in medicinals. These results, determine the target which is specific receptor.(2) In the present script computer backed medicine design (CADD) has extended its range of operations nearly all stages of the medicine discovery that's from target identification to lead discovery, lead identification to chemical trials. CADD technology on adding as a approach in R&D, may lead to reduction up to 50 in the cost of medicine design and development. CADD is useful to explain the molecular base of remedial exertion as well as it also helps to prognosticate possible derivations that would ameliorate exertion. Two general ways are used to classify CADD on the base of structure grounded and ligand grounded. Interaction energy for all composites is tasted by the knowledge of the target protein structure, where as the knowledge of known active and inactive motes through chemical similarity quests or construction of prophetic, quantitative structure exertion relationship model and be exploited by ligand grounded CADD. When the high resolution structural data of target protein are available, at that time structure-grounded fashion and in case of lower structural information frequently for membrane proteins targets, ligand-grounded CADD is preferred.(3) At last, the high thing of CADD is to design medicines that bind to the target tightly, specifically reducing free energy, perfecting DMPK/ADMET parcels and which is target specific.
3 medicine discovery and computer backed medicine design

The complete medicine discovery cycle takes, from supereminent identification through to clinical trials, 14 times with the cost of about 800 million US bones. In the period of 1990s, rapid-fire developments were seen in the field of combinatorial chemistry and high-outturn webbing technologies have used the terrain for the discovery process by taking huge libraries of emulsion to be synthesized and screened in short time. This was the great reason behind the fail of new molecular realities launching, but it also lead to the irritated situation. In this condition it's seen that, the megahit rates are low and numerous successes fail to be optimized into factual leads and preclinical. numerous times at last, about 40-60 failure set up due to immersion, distribution, metabolism, excretion and toxin (ADMR/ tox.) scarcities. In 1970s CADD were established in the use of conflation of mortal hemoglobin ligands as well as in the structural biology to modify the natural exertion of insulin. The advances in combinatorial chemistry, screening technologies and computer structure are responsible to fill up the gap between theoretical modeling and medicinal chemistry. There are plenitude of exemplifications which show the success similar as Zanamivir for the prophylaxis of influenza response, Dorzolamide for the treatment of cystoids molecular edemas and Amprenavir (13) for the treatment of HIV infection.(8)
CADD in drug discovery/design pipeline.

2. Software used in CADD

There are several software used in computer backed medicine design. Among the software programs are operations programmed in Grid computing, window grounded general PBPK/ PD modeling software, PKUDDS for structure grounded medicine design, APIS, JAVA, Perl and Python, CADD as well as software including software libraries.(14)
An overview of the GaussDal database structure for storing molecular properties.

CADD Strategies in the Drug Discovery Process

Strategies for CADD vary depending on the extent of structural and other information available regarding the target (enzyme/receptor) and the ligands. — Direct || and — circular || design are the two major modeling strategies presently used in the medicine design process. In the circular approach the design is grounded on relative analysis of the structural features of known active and inactive compounds. In the direct design the three-dimensional features of the target (enzyme/receptor) are directly considered.

User

A flow Chart for Peking University Drug Design System
Preparation of a Target Structure

Success of virtual webbing depends upon the quantum and quality of structural information known about both the target and the small motes being docked. The first step is to estimate the target for the presence of an applicable list fund.(12-13) This is generally done through the analysis of given target-ligand-co-crystal structures or using in-silico styles to identify new list spots. A target structure experimentally determined through X-ray crystallography or NMR ways and deposited in the PDB is the ideal starting point for docking. Structural genomics has accelerated the rate at which target structures are being determined. In the absence of experimentally determined structures, several successful virtual webbing juggernauts have been reported grounded on relative models of target proteins. Homology Modeling In the absence of experimental structures, computational styles are used to prognosticate the 3D structure of target proteins. Relative modeling is used to prognosticate target structure grounded on a template with a analogous sequence, using that protein structure is better conserved than sequence, i.e., proteins with analogous sequences have analogous structures. Homology modeling is a specific type of comparative modeling in which the template and target proteins partake the same evolutionary origin. Relative modeling involves the following way (1) identification of related proteins to serve as template structures, (2) sequence alignment of the target and template proteins, (3) copying coordinates for confidently aligned regions, (4) constructing missing snippet equals of target structure, and (5) model refinement and evaluation. Fig. 1.4 illustrates the way involved in homology modeling. Several computer programs and web waiters live that automate the homology modeling processes e.g., PSIPRED and MODELER.
occasionally makes it inadequate to use a single static structure to prognosticate apparent list spots. Multiple conformations of target are frequently used to regard for structural dynamics of target. Classic molecular dynamic (MD) simulations can be used for carrying an ensemble of target conformations beginning with a single structure. The MD system uses principles of Newtonian mechanics to calculate a line of conformations of a protein as a function of time. Classic MD styles tend to get trapped in original energy minima.

4. Structure- Grounded Computer backed Drug Design

The determination & analysis of 3D structure of natural motes is the high significance of structure grounded computer backed medicine design the capability of patch to interact with protein and giving the asked natural effect is the core thesis approach behind the structure grounded computer backed medicine design x-shaft crystallography and NMR spectroscopy and similar biophysical ways may led to the explication of a number of 3D structures of mortal and pathogenic proteins are used in expansive manner. medicine discovery process are sped up and led to the development of numerous clinical medicines and the credit goes to the medicine discovery juggernauts. Rapid webbing of a large emulsion library and determination of implicit binders through modeling/simulation and visualization ways are allowed by the computational styles in medicine discovery.

Monte Carlo Search with Metropolis Criterion (MCM) Simulations

MCM samples conformational space briskly than molecular dynamics in that it requires only energy function evaluation and not the outgrowth of the energy functions. Although traditional MD drives a system toward a original energy minimum, the randomness introduced with Monte Carlo allows hopping over the energy walls, precluding the system from getting stuck in original energy minima. MCM simulations have been espoused for flexible docking operations similar as
in MCDOCK. Inheritable Algorithms introduce molecular inflexibility through recombination of parent conformations to child conformations. In this dissembled evolutionary process, the “fittest” or stylish scoring conformations are kept for another round of recombination. In this way, the stylish possible set of results evolves by retaining favorable features from one generation to the coming. In docking, a set of values that describe the ligand disguise in the protein are state variable. State variables may include set of values describing restatement, exposure, conformation, number of hydrogen bonds, etc. The state corresponds to the genotype; the performing structural model of the ligand in the protein corresponds to the phenotype, and binding energy corresponds to the fitness of the existent.

3. Ligand-Based Computer Aided Drug Design

The analysis of ligands which interact with a target of interest is the approach involved in the ligand grounded medicine design. Reference structures are used in this system to which are collected from the composites to interact with the target of interest and analyses their 2D or 3D structures. It's necessary that the physicochemical parcels which are most important for their asked commerce should be retained and the extraneous into which isn't related to the commerce is discarded. This is only the thing behind it. The knowledge of the structure of the target of interest isn't necessary as it's considered as an circular approach behind the medicine discovery. There are two main approaches act behind LBDD are the selection of composites grounded on chemical structure analogous, which activates by using some similarity measure or the natural exertion from chemical structure which is prognosticated by the quantitative structure exertion relationship (QSAR) and construction of it. There are colorful operations of the same system or in silico webbing for new composites enjoying the natural exertion of interest, optimization in megahit to lead and lead-to-medicine, and for the DMPK/ADMET optimization also. The motives that are structurally analogous having analogous parcels, is the main principle behind LBDD which is also known as “analogous property star”. When the structure of the natural target is unknown the LBDD approaches in discrepancy to SBDD approaches can also be applied. The ligand-grounded computer-backed medicine discovery (LBDD)
approach involves the analysis of ligands known to interact with a target of interest. These styles use a set of reference structures collected from composites known to interact with the target of interest and assay their 2D or 3D structures. The overall thing is to represent these composites in such a way that the physicochemical parcels most important for their asked relations are retained, whereas extraneous information not applicable to the relations is discarded. It's considered as an circular approach to the medicine discovery in that it doesn't bear knowledge of the structure of the target of interest. The two abecedarian approaches of LBDD are( 1) selection of composites grounded on chemical similarity to known actives using some similarity measure or( 2) the construction of a quantitative structure exertion relationship( QSAR) model that predicts natural exertion from chemical structure. The styles are applied for in silico webbing for new composites enjoying the natural exertion of interest, hit- to- lead and lead- to medicine optimization, and also for the optimization of DMPK/ ADMET parcels. LBDD is grounded on the analogous property principle which states that motes that are structurally analogous are likely to have analogous properties. LBDD approaches in discrepancy to SBDD approaches can also be applied when the structure of the biological target is unknown. Additionally, active compounds identified by ligand-based virtual high-throughput screening (LB-vHTS) methods are often more potent than those identified in SB-Vhts.

**Molecular Descriptors**

Molecular descriptors can include parcels similar as molecular weight, figure, volume, face areas, ring content, rotatable bonds, interatomic distances, bond distances, snippet types, planar and nonplanar systems, molecular walk counts, electronegativities, polarizabilities, harmony, snippet distribution, topological charge indicators, functional group composition, aromaticity indicators, solvation parcels, and numerous others.( 36) These descriptors are generated through knowledge-grounded, graph-theoretical styles, molecular mechanical, or amount-mechanical tools( 37- 38) and are classified according to the dimensionality ‖ of the chemical representation from which they're reckoned( 39) 1- dimensional( 1D), scalar physicochemical parcels similar as molecular weight; 2D, molecular constitution-deduced descriptors; 2.5 D, molecular configuration-deduced descriptors; 3D, molecular conformation-deduced descriptors.
4. Application of computer in drug design

**Anticancer agent**

The major scientific trials of this century are represented by the sequencing of the mortal genome. A major aspect of the application of the information will be the provision of small motes which will fete named sequences, by switching off particular genes in cancer remedy is the thing behind it. In case of cancer, excrescences admit lower blood force and hence less oxygen as compare to normal towel. In principle, it come possible, to contemplate having a ligand which is present in two forms, that's in oxidized and reduced. In normal towel the redox eventuality is applicable, where as if compared to the tambours form bind to the macromolecular target, it causes cell death, also isolation in action between cells which it's desirable to destroy and normal cells is attainable, with attendant reduction in side-goods.

**Target Enzyme**

Designing impediments which will block acting in the test-tube should be a problem which can be detected if the enzyme structure is known. CADD has its own significance in the target enzyme discovery.

**Drug Transport** Biological membrane transportation of medicine is veritably essential. To pass the membrane, the emulsion must be answerable enough in the lipid, but att the same time, it shouldn't be too important answerable to remain there itself. (partition measure between water and n-octanol is the main parameter used in the pharmaceutical assiduity as companion to membrane transport. piecemeal from these operations structure determination of protein, biochemical metamorphosis, molecular similarity and molecular diversity are the main fields in which CADD has a great significance.

5. Success Story of CADD

In the development of new and potent medicine seeker in the medicine discovery, there's a veritably large list which describes the successful operations of CADD. The topmost conceded operations of CADD is the development of medicines in HIV and flu(influenza) during the 1990s.
there are two further successful issues of CADD, similar as relenza(13) and HIV protease impediments. Around the same time, a number of HIV proteases were linked, which includes saquinavir and nelfinavir. These medicines have a great significance in the HIV treatment metamorphosis. also, tirofivin, zaminevir, oseltamivir, aliskiren, boceprevir, and rupintrivir are also results in CADD. The combination of LBDDD, SBDD and MD reported successful operation of CADD in tuberculosis. Which was result in identification of a novel and veritably potent asset of mycobacterium tuberculosis. It’s set up that CADD has been extremely successful in design and identification of impediments against several important conditions, including, diabetes mellitus, and MDR, cancer and neurodegenerative diseases.

Discussion

Mortality related to the Indian Ocean ruffle in 2004 was concentrated in the first many days of the disaster and no death was reported from one week after the ruffle up to two and a half months of the study period. At least six deaths could have been anticipated among the 3076 survivors and the recall period of 80 days in our study, on the base of an assumed crude mortality of 0.25 per 10 000 person days, a standard for displaced populations in South Asia.1 The massive fresh mortality due to contagious conditions, as advised by the World Health Organization, 2 wasn’t substantiated. Our finding can be incompletely explained by the miracle of the — harvesting effect — that is, dropped mortality after a large number of deaths as a result of an adverse health event among a vulnerable population. This effect has been proved in other disaster settings, similar as the earthquake in Taiwan3 and the heat swells in the Czech Republic.4 The low mortality may also indicate successful aid conditioning. Prompt transnational responses were started with sufficient finances. also, the Sri Lankan government worked sufficiently to coordinate the affluence of aid by using its well structured executive and public health systems. However, still, also the use of the vast available finances may be questioned, if this low position of mortality was primarily due to the nature of the disaster.
6. Literature survey

- Case reports of suspected adverse drug reactions: a review

Methodical literature check of follow-up Yoon Kong Loke, Deirdre Price, Sheena Derry, Jeffrey K Aronson Main outgrowth measures Primary the number of suspected adverse responses subordinated to formal confirmation studies and the findings of these studies. Secondary the number of cases in which the warning from the case report was incorporated into the product information. Results We estimated 63 suspected adverse responses and set up that utmost (52/63, 83) hadn't yet been subordinated to further detailed evaluation. Data from controlled studies that supported the supposed link between the medicine and the adverse event were available in only three cases. Of the 48 agents listed in the medicine reference sources, details of the suspected response were latterly added to the Medicines Compendium in 15 cases, and to the BNF in seven cases. In each case, only one response had been verified. Conclusions Published case reports of suspected adverse responses are of limited value as reservations are infrequently subordinated to confirmational disquisition. likewise, these cautions aren't incorporated into medicine reference sources in a methodical manner. Case reports of suspected adverse medicine responses are common in the medical literature — for illustration, further than a thousand stories were cited in the Side goods of medicines Annual (2000) in one time alone. While information on medicine safety is of irrefutable significance, the extravagancy of case reports and the pronounced variation in their quality produce a grueling riddle. Should croakers and cases alter their treatment plans in response to every fresh report of a suspected adverse response? Opinion is divided. Hoffman argues that case
reports are of extremely limited value and that it would be foolhardy to restate the information into clinical practice without stronger substantiation. On the other hand, exploration carried out by Venning in the 1980s is occasionally cited as an illustration of the — astonishingly good || prophetic delicacy of case reports, 6 in that — further than half of suspected adverse medicine responses were verified by posterior, more detailed exploration. || 7 Venning ‘s findings, still, haven't been replicated( seebmj.com). How also can we be comforted that case reports of adverse medicine responses are authentically precious information coffers? We need to be certain that the reservations raised in similar stories are constantly validated by farther exploration. also, an early warning alert is of limited value if the information comes to the attention of only the confined readership of learned medical journals. Are the safety enterprises from such reports communicated to clinicians and patients via the commonly used drug information sources

A review of methods

We recaptured case reports of suspected adverse medicine responses published in 1997 and established whether each case report had been followed by further definitive studies. We also determined whether the warning Case reports of adverse medicine responses in general drug, neurology, and psychiatry are frequently cited in the Side goods of medicines Annual. 1 We thus chose four high impact journals two general medical journals( British Medical Journal and Lancet) and two specialist journals( Neurology and American Journal of Psychiatry). We also included a haematology journal( American Journal of Hematology) to broaden our content as there are smaller anecdotal reports of adverse responses in haematology.1 Identification and selection of case reports We searched Medline using the following hunt string( — journal title || in SO) and( case - report in TG) and( py = 1997). We estimated the titles and objectifications( when available) of the recaptured papers and barred those that were easily not case reports of adverse medicine responses. We also checked the full textbooks of the remaining papers for applicability grounded on preliminarily published criteria.8 We barred those cases for which former reports of the adverse response were set up in Medline and the adverse response was formerly listed in the product datasheet of the 1996-7 Medicines Compendium9 or the September 1996 issue of the British National Formulary( BNF) 10( seebmj.com for details).
A review Outcome measures

stimulated 34 detailed studies, while the report on hepatitis induced by indinavir stimulated 15 published studies, all within five years.

We may not have identified all relevant validation studies, even though such studies may have been carried out. Studies performed by pharmaceutical companies or regulatory authorities but not published form one category of possible omissions. Alternatively, if a validation study did not cite the original case report, we would not have found it through the citation index search. We took steps to address this by conducting a parallel Medline search, but we are aware that computerised searches for adverse effects do not pick up all relevant articles.

A review of contributors:

TA, NN, and OK designed and coordinated the study. TA, DGMC, and

We used two styles to establish whether confirmation studies had been carried out after publication of the early warning signals. Originally, we carried out a cited reference hunt of the Web of Knowledge Citation indicator (April 2003). We believed that a follow-up study to probe recently reported adverse medicine responses would generally cite the original reports in its reference list. We examined the citing papers to determine which bones were studies conducted for the specific purpose of validating the suspected adverse response (seebmj.com). The alternate system allowed for the possibility that there might be studies in which the suspected adverse response had been estimated without the original case report being cited. We checked Medline 1998-2003 using the adverse medicine response term and medicine name to identify any fresh confirmation studies. We also determined whether the suspected adverse effect had been added to the product information after the publication of the anecdotal report. The medicine reference sources were issues of the Medicines Compendium published from 1996 to 2002 and its electronic interpretation from 20039 and issues of the BNF No 32 (September 1996) to No 45 (September 2003) 00 A review changes in published product information We estimated 48 datasheets and studies to see
whether they had been streamlined with the information from the case report. By October 2003, 15 product datasheets in the Medicines Compendium had been amended to include details of the suspected adverse response. Still, only two of these had been subordinated to follow-up evaluation. By September 2003 (No 45) seven studies in the BNF had been revised, three with follow-up studies. There were five products for which the information on adverse goods had been revised in both the Medicines Compendium and the BNF. Of these, only two had follow-up studies. Both reference sources have added hepatotoxicity to the list of adverse goods for acarbose, indeed though the published substantiation suggests else. A review of discussion Case reports of suspected adverse responses are common in medical journals, but the value of similar stories remains far from certain. Though anecdotal reports should serve to initiate farther exploration, we set up that 83 of reports of suspected new adverse medicine responses from 1997 hadn't been subordinated to any farther confirmation. This finding contrasts sprucely with the findings of Venning, who allowed that only 26 of new adverse responses had been left unverified. Venning looked at 47 case reports of adverse medicine responses in four general medical journals using colorful criteria grounded on point of response, time course, pharmacological plausibility, and goods of repeated administration. He concluded that 28 of the 47 stories were — satisfying || and demanded no farther study. Meyboom and associates challenged the trustability of such an approach. Studies have shown that assessors of adverse events were frequently unfit to reach complete agreement with each other when judging the strength of a unproductive link and determining the malefactor medicine. To avoid these risks, we quested that the suspected response demanded to have been estimated by a more formal study. Venning 's original evaluation left 19 reports of adverse responses unconfirmed, and he progressed to search the posterior literature and reference sources (published papers, nonsupervisory authority databases, and handbooks of adverse medicine responses) for fresh information about any of these stories. From this, he judged that seven of the 19 had latterly been — satisfactorily vindicated || and were — generally accepted. || Venning handed no details about whether his opinions were grounded on farther case reports, expert opinion in handbooks, or formal evaluation of safety. In discrepancy, we defined — confirmation || studies explicitly(
seebmj.com for details). Adverse response reports are transmitted into product information in an erratic way, leaving clinicians and cases inadequately informed. Lower than half of anecdotal reports led to updates, conceivably because of the lack of data attesting the link between the medicine and the adverse event. Manufacturers might justifiably argue that in the absence of a further definitive study, they’re right not to include the adverse medicine response in the datasheet. On the other hand, in some cases (similar as acarbose) both the florilegium and BNF entries were altered, despite the lack of substantiation in posterior studies. Further than doubly as numerous product rosters were altered in the Medicines Compendium as in the BNF. The tract content of the BNF is the responsibility of a common formulary commission, whereas pharmaceutical companies work together with nonsupervisory authorities to draw up product information for the florilegium. How can prescribers and cases negotiate a path between benefit and detriment when the updating of product information doesn't conform to any clear pattern of accumulation of substantiation? A review of limitations of our study We studied only one time and the journals weren’t aimlessly named. Utmost of the case reports, still, came from journals with high impact factors, giving them a advanced profile and therefore the topmost chance of being followed up. Suspected adverse responses that have a major impact on opinions about treatment should be delved, irrespective of the journal or time of publication. Compared with Venning’s analysis, which encompassed 18 times, our follow-up period of five times was short. Still, Venning included only 19 reports of adverse medicine responses in this long term hunt, and he’d formerly classified 28 responses without any farther checking. We consider that five times is sufficient time for farther studies to be carried out and the results published, especially if the adverse responses had been considered important enough to be reported in a high impact medical journal. Indeed the single case report on vigabatrin that we linked SDD carried out and supervised the field study. TA, NN, and KM analysed and interpreted the data. NN wrote the draft and all authors revised the manuscript. NN is the guarantor. Funding: Grant in aid for special purposes (No 16800056), Ministry of Education, Culture, Sports, Science, and Technology, Japan. Competing interests: None declared. Ethical approval: Ethical review committee of the Faculty of Medicine, University of Peradeniya, Sri Lanka.
Results

We linked 696 case reports from the Medline hunt, of which 63 met the addition criteria as reports of suspected new adverse medicinereactions. Studies validating adverse medicine response reports From the citation indicator, we set up that 56 of the 63 case reports had been cited at least formerly. still, only nine of these reports were confirmation studies. The table gives details of these nine reports. Follow-up studies handed controlled data that supported the hypothesised link between three medicines and the adverse signal from the report had been incorporated into posterior performances of published medicine information. Clarithromycin- disopyramide commerce; indinavir and lipomatosis; and vigabatrin and visual field blights. In discrepancy, detailed studies on acarbose constantly failed to confirm its hepatotoxicity. In Medline, we linked two confirmation studies that estimated the supposed link between medicine and adverse event. The 1997 case reports, still, weren't cited by these confirmation studies, and it's possible that the after examinations may have been instigated by other factors.

7. Conclusion

In the use of medicine design and development these are several reasons to use the ultramodern ways of CADD. The backbone of ultramodern CADD process is the structure-grounded ligand-grounded medicines design styles along with molecular dynamics simulation. colorful success stories of CADD and their limitations are bandied in the same design. To ameliorate exploration quality and to grease identification of new chemical realities leading to development of useful medicines, it's necessary to use the clear conception and advanced knowledge of CADD system.
8. Reference


