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REVIEW ARTICLE OPEN ACCESS

Computational Drug Repurposing Resources and Approaches for Discovering Novel Antifungal Drugs against *Candida albicans* N-Myristoyl Transferase

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Abstract

Candida albicans **is a yeast that is an opportunistic fungal pathogen and also identified as ubiquitous polymorphic species that is mainly linked with major fungal infections in humans, particularly in the immunocompromised patients including transplant recipients, chemotherapy patients, HIV-infected patients as well as in low-birth-weight infants. Systemic *Candida* infections have a high mortality rate of around 29 to 76%. For reducing its infection, limited drugs are existing such as caspofungin, fluconazole, terbinafine, and amphotericin B, etc. which contain unlikable side effects and also toxic. This review intends to utilize advanced bioinformatics technologies such as Molecular docking, Scaffold hopping, Virtual screening, Pharmacophore modeling, Molecular dynamics (MD) simulation for the development of potentially new drug candidates with a drug-repurpose approach against *Candida albicans* within a limited time frame and also cost reductive.**

Keywords: Benzofurans, Benzothiazoles, Biofilm, Inhibitors, Myristoylation, Simulation

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INTRODUCTION

Invasive infections caused by fungal pathogens are life threatening opportunistic infections, having a high rate of mortality and morbidity in patients. It infects billions of individuals and is responsible for 1.5-2 million deaths annually[1-4]. Fungal infections have risen dramatically in patients over the last decades which are immunocompromised, because of cancer chemotherapy, solid and hematologic organ transplantation, broad use of antibiotics, surgery, and long-term use of corticosteroids[5]. Invasive fungal infections are particularly exposed to patients receiving cancer treatment, transplant recipients, intensive care unit (ICU) care, and also with acquired immune deficiency syndrome (AIDS). The immunocompromised hosts are having a great risk of these infections with mortality rates from 20% to 40% and it continues to be high, which is relied on what kind of infecting fungal species and the clinical treatment. Several fungal species are present in the world; however, some species, including *Candida*, *Cryptococcus*, as well as *Aspergillus*, lead to life threatening infection in more than 90% of the population. One species of fungus well known as *Candida albicans*, an *ascomycete*, and a polymorphic fungus. It is capable of reversibly transforming to various morphologies, include (1) yeast forms, (2) pseudohyphae forms, and (3) true hyphae forms. It's both commensal as well as opportunistic pathogen among humans and ranks as the fourth most common threat of nosocomial bloodstream infections in modern hospitals with roughly 40% death rates[3, 6-17]. Pathogenicity of invasive infection caused by *Candida albicans* is regulated by several factors namely invasive (a) filamentation, (b) biofilm development, and (c) the ability to escape from the immune system[18]. Studies of metabolic labeling state that *Candida albicans* synthesize protein N-myristoyl (20-kDa). Myristoyl-CoA: N-myristoyl transferase (NMT), was reported as a target for antifungal as well as antiviral treatment[19]. Antifungal drugs may be used to handle such infections; however, the mortality rates remain high around 50% and there was also a high prevalence of Invasive fungal infections. Discussing treatment options, Antifungals Azoles, echinocandins, and polyenes are existing for the curing of fungal infections which are limited and clinically available[18]. Azoles and polyenes target different biological fungal processes relevant to ergosterol metabolism as well as echinocandins targets cell wall β-1,3 glucan production. 5-flurocytosine is usually used as adjunctive therapy. Fazly et al. described filastatin (a small molecule) that prevents filamentation, adhesion, and virulence of *Candida albicans*[20]. Garcia et al. reported (N1-(3,5-dichlorophenyl)-5-chloro-2 hydroxybenzamide) halogenated salicylanilide and its analogs Niclosamide, an antifilament molecules that inhibited *Candida albicans'* biofilm development and had similar antibiofilm and anti-filamentation activities[21]. Siwek et al. investigated the antifungal effect of 4-arylthiosemicarbazides and found the isoquinoline-thiosemicarbazide compound to exhibit greater affinity compared to the native ligand[22]. These antifungal agents have significant clinical failures such as unfavorable pharmacokinetic profiles, restricted antifungal range, significant side effects, minimal clinical effectiveness, drug-drug interactions, as well as increased drug-resistance. Therefore it is an urgent need to use all the advanced Bioinformatics tools and techniques to improve the existing fungal drugs or designing novel drugs against it. Existing drugs and the same structural analogous shows the resistant problem on the antifungal targets. Therefore, searching out the new inhibitor is the most promising approach to tackle the resistant fungal infections[23-35]

This review is the effort to use advanced bioinformatics techniques such as Molecular docking, Scaffold hopping, Virtual screening, Pharmacophore modeling, Molecular simulation for developing novel drug candidates with drug repurposing approach against *Candida albicans* within a short period, cost-reducing and solve the resistant problem in fungal infections.

Candida Albicans: Biofilm Formation

Earlier, microbiologists have studied planktonic cells which are free-floating cells in pure culture. Later they have discovered that there is a link available between sessile cells, microbial pathogenesis, and infections associated with humans and it differs basically from a planktonic cell present in the same species[36]. A broad variety of fungi alternately connecting planktonic

cells (freely suspended cells) and multicellular populations, known as biofilms[37]. Biofilms are characterized as well-structured microorganism populations that are interconnected with the surface as well as enclosed by an extracellular matrix (ECM) produced by themselves[38]. The biofilms-associated microorganism is related with several human diseases such as cystic fibrosis, native valve endocarditis and to colonize an extensive range of medical devices which taking into consideration that these structures are very much associated with antimicrobial-resistant and it is very difficult to manage such kind of infections within the clinical setting[39]. A short time ago it has been understood that fungal species form biofilms and it is associated with the escalating clinical problem[38,40,41]. So many *Candida* Species have been identified but the most famous studied species is *Candida albicans* as a well-developed biofilm activity with the most adaptable opportunistic pathogen[42]. There have been so many *Candida* species reported, but as a well-developed biofilm operation with the most adaptable opportunistic pathogen, the most popular species studied is *Candida albicans*. Biofilm is developed on various medical devices such as dentures, neurosurgical shunts, speech prostheses, breast implants, prosthetic joints, endotracheal tubes, intracardiac prosthetic devices, urinary catheters, dialysis catheters for peritoneal and hemodialysis, peripheral and venous catheters[43]. It exists in various types, such as yeast, hyphae, and multicellular biofilm[44]. *Candida albicans* adherence and colonization to denture acrylic substrates as well as oral mucosa is the first step of pathogenesis[45-48]. *Candida albicans'* initial attachment to the surface is limited by the pH, osmolarity, flow of the nearby medium, such as urine, antimicrobial agents, bacteria, saliva, Mucus, temperature, blood, as well as the host immune factors[49-54]. *Candida albicans* biofilm formation having different phases of development. It contains substrate adhesion, colonization, extracellular material production,

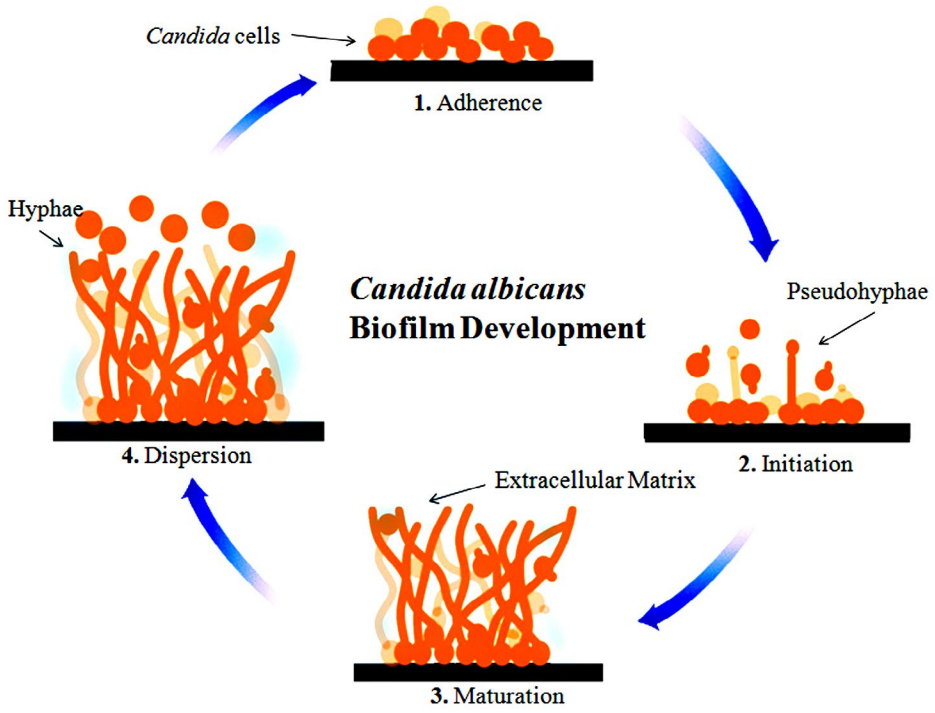


Fig. 1. Better describe the development of different phases such as early, intermediate and Mature. Adhesion and germination occurred in the early phase. Hyphal development as well as Extra cellular material production in the intermediate phase and the last one is maturation phase, in which dispersal occurred. In this Fig. light blue color represent ECM, circle correspond to *Candida albicans* cells, hyphae is also able to be seen.

and maturation[53-62]. Biofilm development has been shown in Fig. 1.

The yeast cell's ability to shape biofilms on the implanted medical devices or on the surface in the host enhances its virulence. *Candida albicans* adhere to the surface with the support of Eap1p (cell wall protein) and Als3p (agglutinin like sequence protein)[63,64]. Als3p and Eap1p are initiations to the formation of microcolonies and further Efg1 regulatory protein is essential for the production of biofilm and its development of pseudo-and true-hyphae to form a complex association of hyphal structures with budding yeast-like cells spread throughout[52,65]. Further, the growth and the maturation of Biofilms, *Candida albicans* biofilm cells encompass a beta-glucan rich extracellular matrix that protects from environmental stresses, antimicrobial agents, and host defenses[66]. The existence of the hypoxic environment is correlated with the maturation of biofilm and this condition induces Tye7p-dependent up-regulation of glycolytic genes required to respond to hypoxia and prevent uncontrolled hyphal formation[67]. In the final step, planktonic yeast cells dispersed from the mature biofilm and established a new colony on a new surface to grow a new biofilm from *Candida*[68]. *Candida albicans* Biofilm formation has been presented in Fig. 2.

The diverse transcription factors such as Efg1p, Ace2p, Zap1p, and Bcr1p are the regulator which controlled the formation of Biofilm[63, 69-71]. The various genes have been presented in Fig. 2, for controlling and maintaining the development of biofilm. The most important thing is to understand the mechanism of those genes so inhibition such kind of infections in the populations. The key sites of the infections are biomaterials[43], wounds[72], Urinary tract[73,74], Gastrointestinal tract[75], lower respiratory tract[76], upper respiratory tract[77, 78], oral cavity[79], etc.

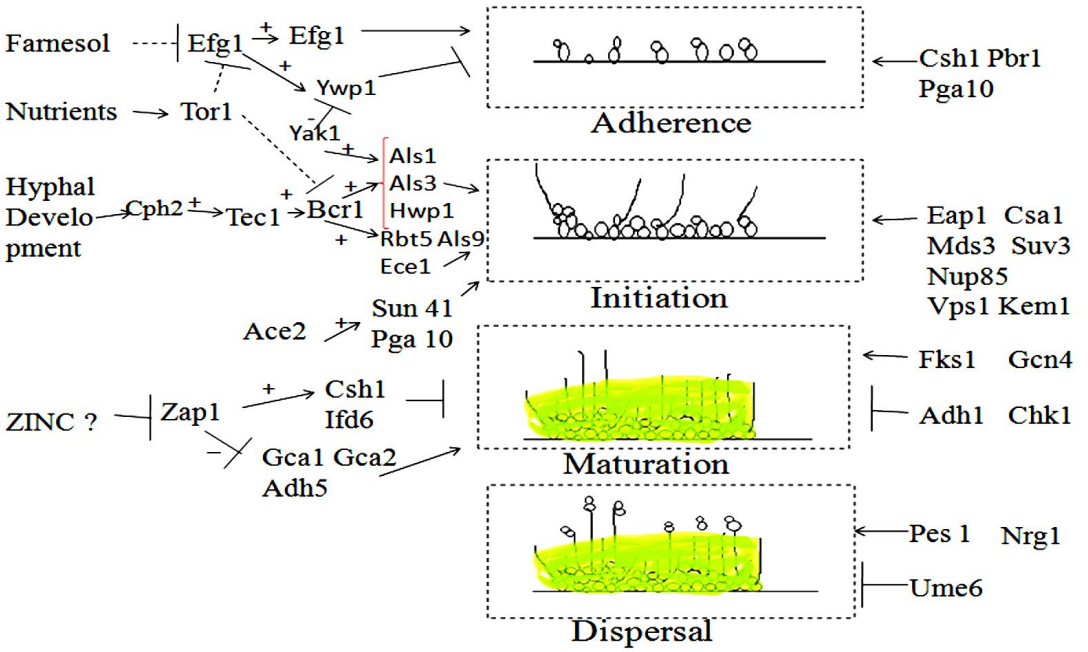


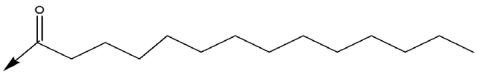
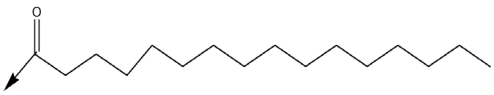
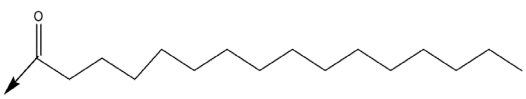
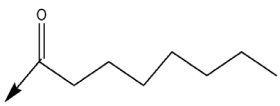
Fig. 2. Different genes are presented here which showed function in Biofilm formation. It has four steps (I) Adherence, (II) initiation, (III) maturation, and (IV) dispersal. In the right-hand side part of the diagram, the genes are connected and involve in pathway but in the left hand side part, the genes may not attach to an established pathway but function in a particular step. Arrows signify positive connection, the Dashed line signify repression by an indirect mechanism. "+" sign indicates that an upstream gene stimulates the expression of the downstream target and "-" sign is opposite of it. "T-shaped" indicated a negative relationship (repression by an indirect process).

***Candida albicans:* NMT [N-Myristoyl-transferase] as a drug target**

Post-translational modification is a very important step for proteins to function in a specific way through further modification. Post-translational modification occurs at the protein's C- or N-terminal or on the amino acid side chain[80]. The modification occurs during the post-translational modification are different according to the different transformation such as C terminal amidation, N-terminal acetylation, phosphorylation of threonine, tyrosine or serine residues mainly in kinases, methylation of arginine and lysine residues mostly in histones, acylation of lysine residues and oxidation mainly in proline residues[81]. A less common type of post-translational modification is lipidation. Lipidation is the covalent attachment of the lipid moiety to the protein. Lipidation increases stability, membrane interaction, protein hydrophobicity, changes in conformation, trafficking, etc. Different types of lipidation are known, differing according to the group being attached and the position of attachment[82]. Lipidation attachment has been presented in (Table 1).

Regarding the attachment of longer chain fatty acid acylation, myristoylation (attachment of linear chain c-14), and palmitoylation (c-16)[86, 87]. Researchers did extensive research and identified *Candida albicans* as an antiviral and antifungal therapy target. N-myristoyl transferase is indeed a monomeric cytosolic enzyme that is vital for the function and growth of fungi[88,89]. NMT is present in eukaryotes such as animals, protozoa, and fungi excluding bacteria. Protein N-myristoyl transferase is associate with the Gcn5-related *N-acetyltransferases* superfamily[90]. *Candida albicans* NMT contains 451 residues of amino acids and 45% of the human enzyme sequence identity. NMT is a compact globular, wedge-formed structure in which a big saddle-shaped beta-sheet present and it occupies the center of the protein structure, also, it is surrounded by several helices means consisting of an N-terminal strand, preceded by two helices, three anti-parallel beta strands, preceded by a signature (central helix) and last beta-strand[91]. The NMT protein structure has been illustrated in Fig. 3. C-terminal half is crucial for the peptide binding site and N-terminal half is important to form mainly Myristoyl-CoA binding site[90]. N-Myristoyl-transferase catalysis reaction is catalyzed by N-myristoyl-transferase, the co-translational addition of myristic acid (14-C saturated fatty acid) to the N-terminal Glycine (GLY) residue of the substrate protein via amide bonding. The N-myristoyl transferase catalysis reaction is performed by the ordered Bi-Bi reaction mechanism, the enzyme forming

Table 1. Representation of the structures of lipidation attachments

Attachment to the	Attachment	Post translation
N-terminus		Myristoylation[83]
Cysteine		Palmitoylation[84]
N-terminus		Palmitoylation[85]
Serine		Octanoylation[85]

a high binary selectivity complex (Myristol-CoA-NMT). This binary complex is essential to the further interaction of N-Myristoyltransferase with peptide and produces a ternary complex recognized as NMT-Myristoyl-CoA-Peptide, following the catalytic transfer of myristate to the peptide substrate. The first free CoA is released, followed by the N-myristylated protein. In general, Myristoylation is irreversible as well as a significant post-translational modification is defined as N-terminal lipidation of eukaryotic and viral proteins[92]. Myristoylation mechanism has been shown in Fig. 4.

Myristoylation involved in anchoring and directing proteins to membranes and their effects such as signal transduction, cellular regulation, numerous pathologic processes caused by viruses, apoptosis, and translocation[93, 94]. The binding of

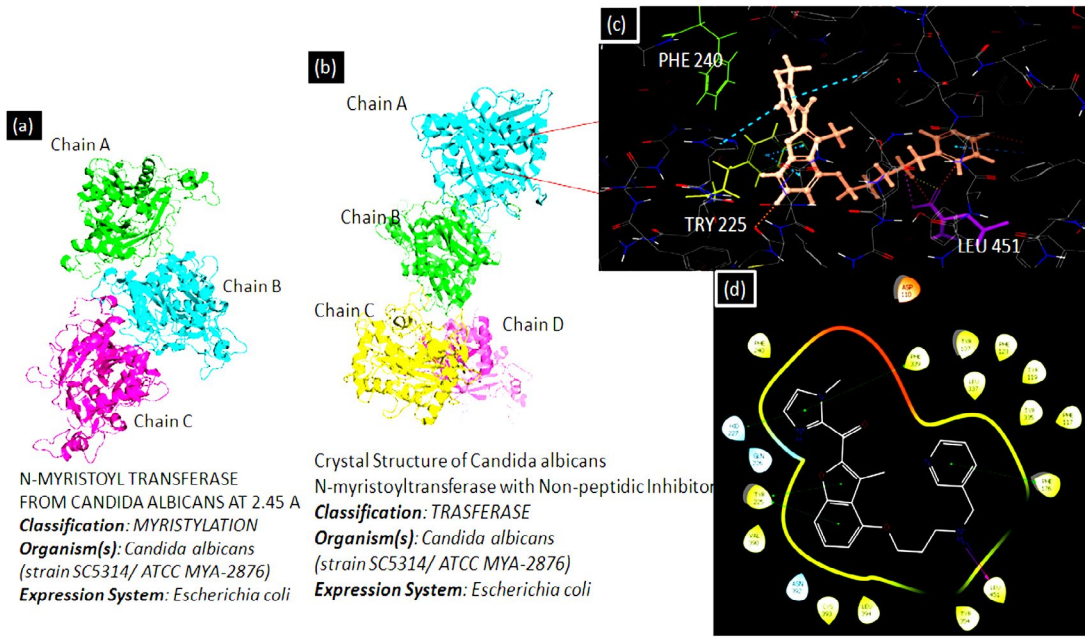


Fig. 3. PDB ID [1NMT] represents NMT from *Candida albicans* species at 2.45Ao and PDB ID [1IYL] represents *Candida albicans* NMT with Non-peptidic Inhibitor. The Ligplot interaction diagram has been generated using the Schrodinger software suit. The ligand is showing its major interaction with a certain amino acid such as PHE 240, TRY 225, and LEU 451.

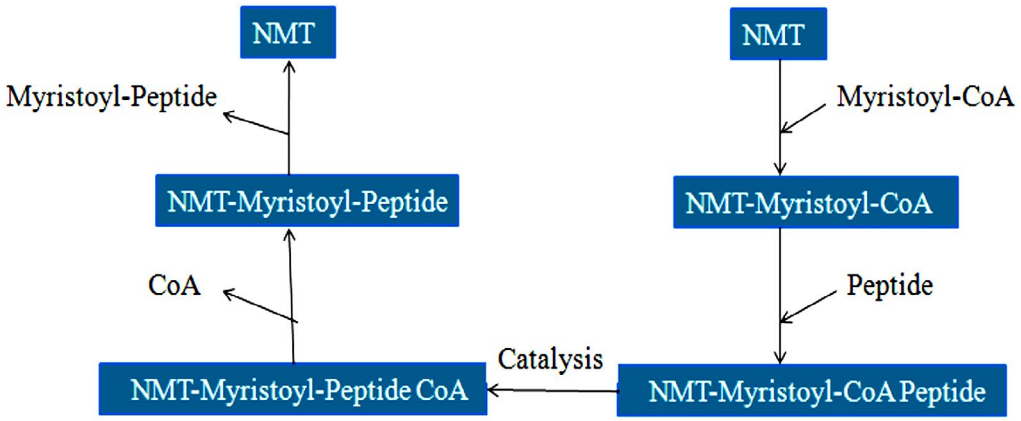


Fig. 4. The catalytic mechanism (Bi-Bi Reaction) of NMT.

myristoyl residues enables hydrophobicity to affect protein partitioning to the cell membrane and promote the interaction of protein-proteins. It is important for the overall biological expression of viral and cellular protein activity[95-97]. In Fungi, the myristoyl is associated with the cellular membrane and myristoyl-protein interactions. This protein takes part in protein and vesicular trafficking and signals transduction cascade. In *Candida albicans* with defective NMT unable to infect mice[98,99]. Genetic studies showed that the enzyme is important for pathogenic *Candida albicans* to grow vegetatively[100]. NMT is a good antifungal agent target because it is responsible for systemic fungal infections and lacking its expression is related to significantly decrease cell growth and increased cell death.

***Candida albicans:* NMT inhibitors**

Several potent and selective inhibitors have been identified against *Candida albicans* NMT which showed low inhibitory activity against hNMT. All NMT polypeptides have similar folding but different inhibitor binding sites because of their particular amino acid differences[90,101-104]. As we studied earlier that NMT is responsible for the survival and growth of diverse fungal species, therefore so many different inhibitors have also been identified for reducing its fungal activity such as Benzofurans inhibitors[101-103], Benzothiazole inhibitors[104], Myristic acid analogs[105,106], Peptidomimetic inhibitors[88,107], p-toluene sulphonamide inhibitors[108], etc. Devadas et al. reported a peptidomimetic inhibitor against *Candida albicans* NMT. This inhibitor was structured dependent on octapeptide substrate GLYASKLS-NH2 that was obtained from the N-terminal fragment of ARF2 (ADP ribosylation factor 2) and its analogous ALYASKLS-NH2[107]. Due to the lower antifungal activity of peptidomimetic inhibitors, Devadas et al. explored new forms of non-peptide inhibitors which represent simply one chiral core and demonstrate fungicidal activity[109]. Parang et al. have tested myristic acid analogs as putative inhibitors of NMT. Quite a lot of (+)-2-halotetradecanoic acids including (+)-2-bromotetradecanoic acid presented strong activity against *Candida albicans* (MIC = 39µM). These compounds illustrated antifungal action

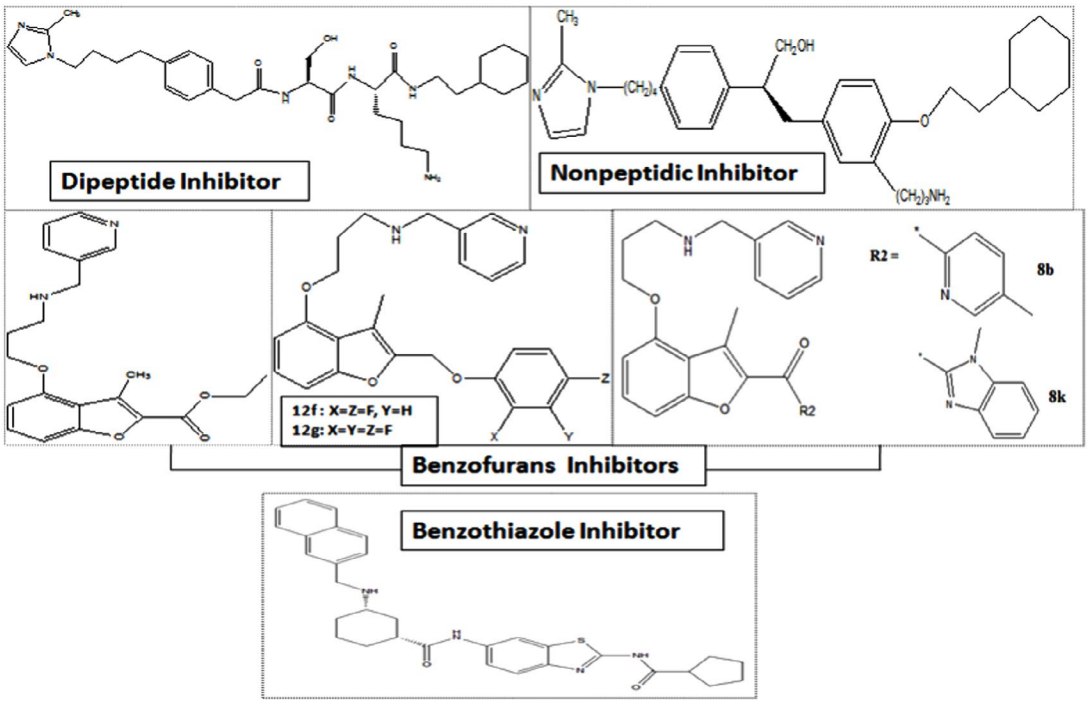


Fig. 5. *Candida albicans* NMT inhibitors.

in vitro but not showed in vivo[106]. A new class of inhibitor was also reported named as p-toluene sulfonamides[110].

In the journey of finding out the novel compounds with high selectivity, Benzofurans and Benzothiazoles are more promising than the previously reported compounds[102-104]. From the viewpoint of the development of antifungal drug candidates, other inhibitors were also developed such as 4-arylthiosemicarbazides derivatives[22], novel benzofuran-semicarbazide hybrids and 1,3-dialkoxybenzene-semicarbazide hybrids, etc.[111]. *Candida albicans* NMT inhibitors are presented in Fig. 5.

MATERIALS AND METHODS

Computational drug discovery approaches really works for finding out the novel agents as new medications. Day by Day pharmaceutical and biotech companies are growing to help the society but the major problems we have to face today is the cost of the drugs are increasing and the expenses which we have to pay for the medicine are increasing. The drug productivity measures are unable to meet the increasing demands. Thus, advanced bioinformatics tools and techniques were discussed to find out the novel antifungal agents using drug repurposing approach.

Virtual Screening and molecular docking

Protein-ligand docking is a technique commonly used to determine a drug candidate's binding orientation to their specific target. In our survey, we are in consideration of *Candida albicans* NMT as a drug target for drug designing purpose. Typically molecular docking technique is performed either to searched out that how a specific ligand molecule bind to a target protein or illustrate binding interaction with the target-specific amino acid residues either H-bonding, Hydrophobic interaction, disulfide bond formation, salt bridge, pi-pi interaction or to find out the potent compound from the available databases that can bind with the target protein[112-119]. The docking can be categorized into two key steps, the initial positioning of the ligand structure at the active site of the target protein using the docking algorithm. followed by uses of the scoring function to assess the potency of the binding interaction. There are a huge number of docking algorithms, tools, techniques are available to highlight the diverse orientation of the interaction between the ligand and the target structure as shown in (Table 2).

In the early days, the docking algorithm did not treat the protein and ligand as flexible objects, only the six translations and also the

Table 2. List of the protein-ligand docking software

S. No.	Docking Programs	Conformational searching methods	Scoring Function	Investigated by
1.	AutoDock	Genetic algorithm	Empirical	(Morris et al., 1998)[120]
2.	Dock	Incremental construction	Force field	(Ewing et al., 2001)[121]
3.	FlexX	Incremental construction	Empirical	(Rarey et al., 1996)[122]
4.	Glide	Incremental construction / Monte Carlo optimization	Empirical	(Friesner et al., 2004)[112]
5.	Gold	Genetic Algorithm	Force field	(Jones et al., 1997)[123]
6.	Surflex	Incremental construction, surface-based molecular similarity	Empirical	(Jain, 2003)[124]
7.	ICM	Monte Carlo simulation	Force field/ Empirical	(Abagyan et al., 1994)[125]
8.	LigandFit	Monte Carlo Simulation	Empirical	(Venkatachalam et al., 2003)[126]
9.	eHiTS	Exhaustive systematic	Knowledge-based/ Empirical	(Zsoldos et al., 2007)[127]

rotational degree of freedom was incorporated. Currently, we are having more consistent docking methods which give the options for flexible docking that the target protein is treated as fixed during the docking process, but the ligand is capable to move around the target.

In this situation, the active site of the protein shall not be considered to undergo any significant changes in conformity with the binding of the ligand. The flexible docking is broadly used with parallel computing resources to relatively, accurately, and quickly search databases for potential ligands to a target protein. The more precise algorithms which consider both ligand and receptor flexibility are very time-consuming, therefore have not been developed extensively. The algorithm which treats flexibility of the ligand is partitioned into three categories, for example, stochastic methods, systematic methods, and simulation methods. The docked poses are ranked and assessed using docking scoring functions which estimate a ligand's binding free energy to a receptor, which is very important to differentiate the right poses from incorrect ones. The scoring function incorporates diverse sorts of terms that express electrostatic interactions, solvation effects, non bonded interactions, and van der Waals interactions[128]. The structure-based virtual screening framework was presented in Fig. 6.

Pharmacophore modeling

The initial idea of a pharmacophore was developed by Paul Ehrlich during the late 1800s. The theory in the past was that in a molecule there were some chemical groups or functions that were responsible for a biological effect and that certain effect molecules even had similar functions. Fig. 7, revealed the pharmacophore, with its applications. Later in 1960, Schueler coined the term pharmacophore in his book "Chemobiodynamics and Drug Design". It elucidated that a molecular structure that expresses the essential characteristics liable for the biological activity of the drug. The Pharmacophore has been illustrated by IUPAC since 1997[129].

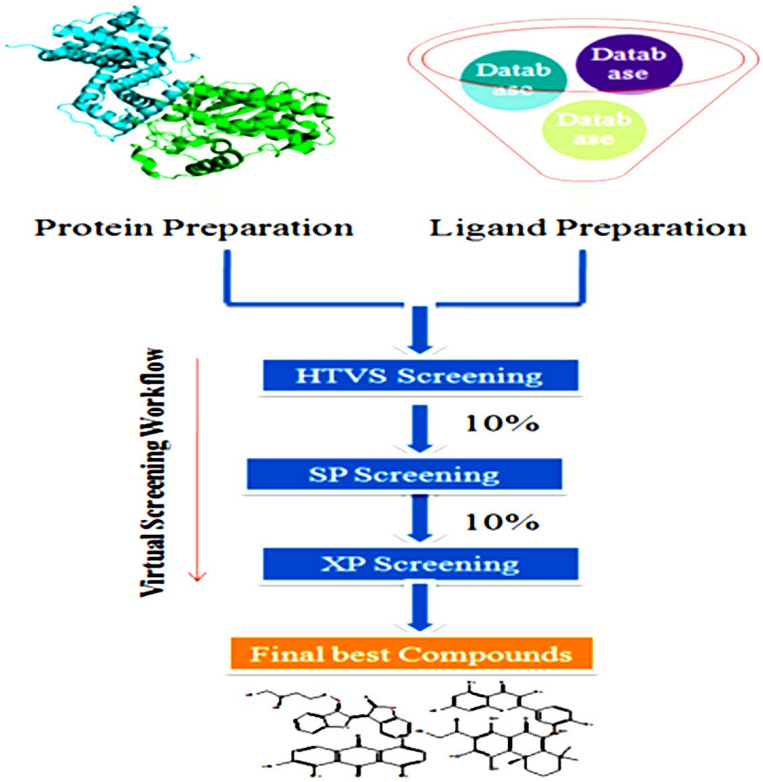


Fig. 6. Structure-based virtual screening Framework.

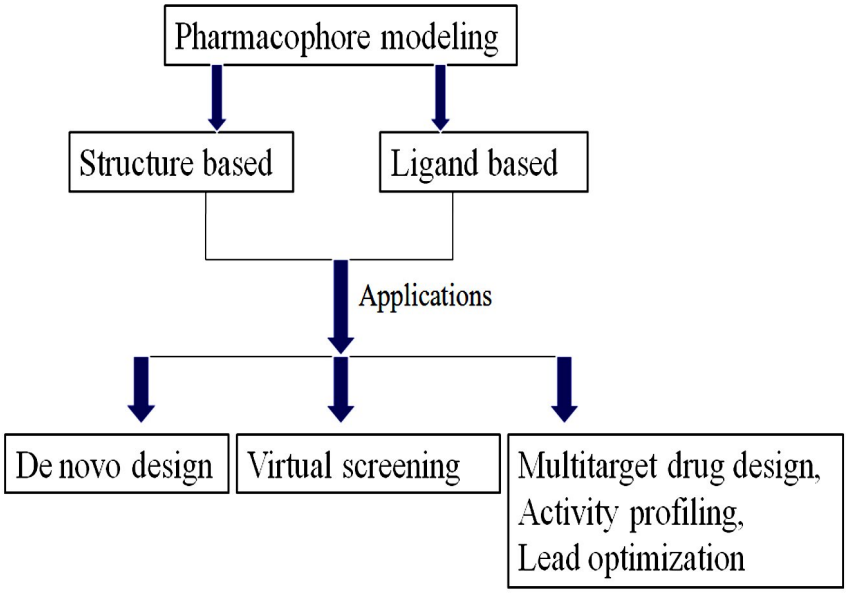


Fig. 7. Pharmacophore modeling and its application.

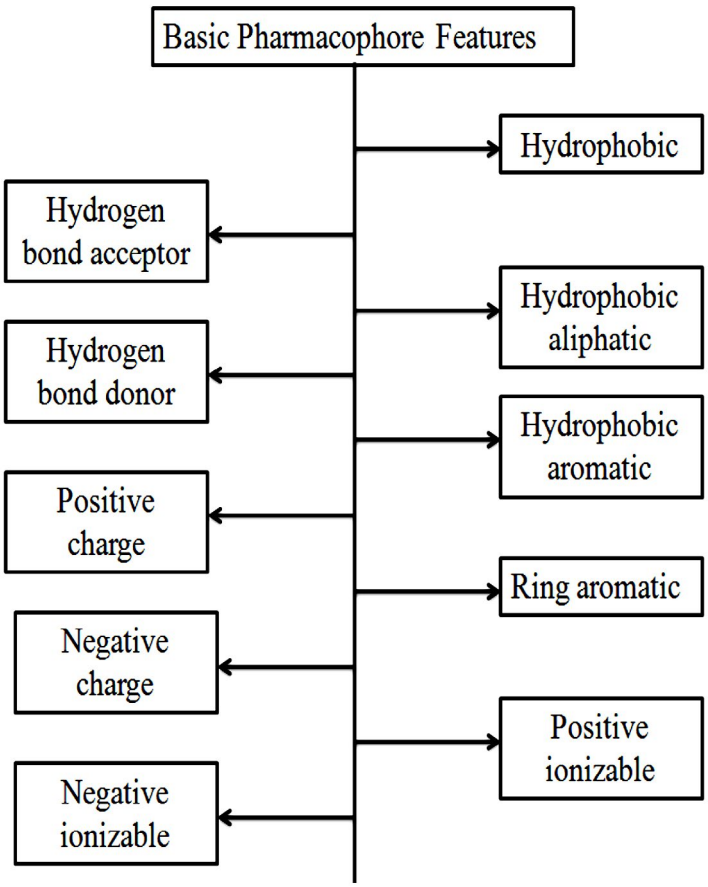


Fig. 8. Basic Pharmacophore features of a molecule.

It projected that a pharmacophore is the collection of features known steric and electronic that are original to ensuring the mainly desirable supramolecular contacts linked with the desired protein target and blocking its biological activity[130]. The pharmacophore reveals an abstract idea. it relies on the features shared by a group of active molecules or it is the pattern of the features of a molecule that is responsible for a biological effect. Forms of molecular features patterns are hydrogen-bond acceptors, hydrogen-bond donors, hydrophobic, anionic, cationic, aromatic plus any such type of possible combinations presented in Fig. 8.

Pharmacophore modeling (Structure-based)

The structure-based approach to pharmacophore modeling describes the relevant presentation of important interactions in a protein-binding pocket. This pharmacophore modeling is appropriate in aspects of a free structure or a complex target-ligand structure. The free structure is classified as apo, and the holo known as the target-ligand complex. The structural pharmacophore modeling was performed using free ligand without protein, using only protein-active site details and when the pharmacophore modeling uses protein-ligand structure complexes utilize the possible interactions involving protein and ligand, shown in Fig. 9. Structure-based pharmacophore modeling is a very effective tool for virtual screening such as multi-target drug design, scaffold hopping, parallel screening, QSAR, and multi-target drug development[131, 132].

Pharmacophore modeling (Ligand-Based)

Pharmacophore modeling based on ligand structure is a powerful computational tool of great importance for helping to discover a new drug compound. It is done by extracting the important and crucial chemical features, among the set of ligands. The ligands have been divided into training and test for alignment and generating a pharmacophore model, presented in Fig. 10. This model can be utilized further for the virtual screening process for finding a similar feature molecule that behaves like a drug[133, 134].

Software available for performing pharmacophore modeling

There are diverse software and tools are available to perform structure and ligand-based pharmacophore modeling, presented in (Table 3–4).

Scaffold Hopping

Schneider et al. (1999) presented Scaffold hopping, in 1999. It is a method for the discovery

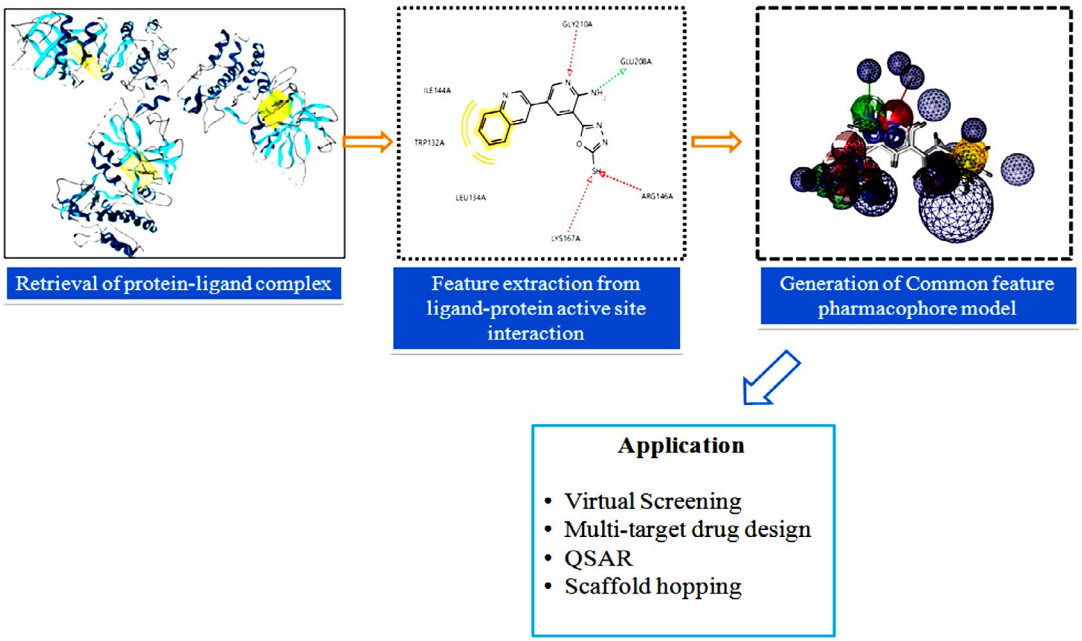


Fig. 9. Structure-based Pharmacophore modeling and its applications.

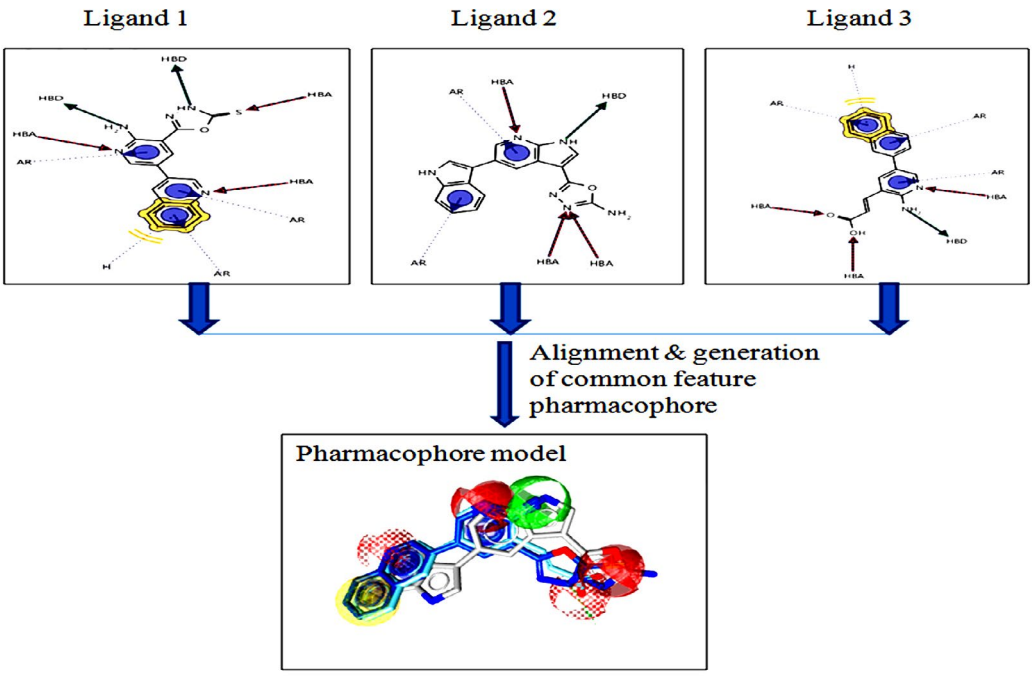


Fig. 10. Representation of ligand-based Pharmacophore modeling.

Table 3. Structure-based pharmacophore modeling software

S. No.	Software	Molecular Alignment	Commercialization	References
1.	LigandScout	Complex-based	Marketed by Inte: Ligand	135
2.	GBPM	Complex-based	Not commercialized	136
3.	Pocket v.2	Complex-based	Not commercialized	137

Table 4. Ligand-based pharmacophore modeling software

S. No.	Software	Molecular Alignment (methods)	Commercialization	Reference
1.	DISCO	Bron-Kerbosh Clique detection algorithm	Tripos Inc., Sybyl interface	138
2.	APOLLO	Feature-based	Not commercialized	139
3.	GALAHAD	Atom-based	Tripos Inc., Sybyl interface	140
4.	HipHOP	Feature-based	Discovery Studio (Biovia)	138
5.	MOE	Property-based	Chemical Computing Group	141
6.	MPHIL	Atom-based	Not commercialized	142
7.	HypoGen	Feature-based	Discovery Studio (Biovia)	143
8.	HypoRefine	Feature-based	Discovery Studio (Biovia)	144
9.	Apex-3D	Feature-based	Catalyst (Biovia)	145
10.	CLEW	Feature-based	Not commercialized	146
11.	GAMMA	Atom-based	Not commercialized	147
12.	GASP	Atom-based	Tripos Inc., Sybyl interface.	138
13.	PHASE	Feature-based	Schrodinger Inc.	148-149
14.	PharmaGist	Feature-based	http://bioinfo3d.cs.tau.ac.il/PharmaGist/	150
15.	LigandScout	Matching pattern-based alignment	Marketed by Inte: Ligand	151

of isofunctional molecular structures by way of considerably different molecular backbones[152]. Traditionally, a large fraction of the medicines produced is extracted from natural hormones, other medications, and natural products by scaffolding modification[153]. Recently published papers and reviewing these relevant examples provide useful guidance for a medicinal chemist for developing a new bioactive molecule. Scaffold hopping, also known as lead hopping[154, 155]. It is one of those approaches for finding out the new lead candidates[156]. Scaffold hopping intends to discover a structurally novel substance structure starting from previously identified active compounds by altering the center core structure of the molecule[157]. Scaffold hopping is commonly used in lead optimization. Since using HTS, so many compounds are unsuccessful compounds with poor PK properties and poor physiochemical properties. To overcome this, side-chain modification is sufficient sometimes, the core structure of the parent molecule or the scaffold may often be changed[152,158-160].

Why Scaffold hopping is so important

- Central scaffolds are also specifically involved in target protein interactions. An enhanced binding affinity can result from a change in the scaffold.
- Replacing a lipophilic scaffold by an extra polar one could enhance the solubility of the compounds (lipophilic compound soluble in fats, oils, lipids etc. for increasing solubility, lipophilic scaffold can be change by an extra polar side chain or fragment).
- Replacing a very flexible scaffold known as peptide backbone by an inflexible central scaffold would also considerably advance the binding affinity and on the total DMPK characteristics.
- Changes in the core of the structure may lead to a patentable novel compound.
- Replacing a metabolically labile scaffold via a reduced amount of toxic, and an additional stable one will improve pharmacokinetic properties.

Insilico approaches for scaffold hopping

There are different approaches are available for scaffold hopping but the main idea behind is (1) matching of shape, (2) searching for pharmacophores, (3) replacement of fragments, (4) looking for similarities, and (5) machine learning, etc.

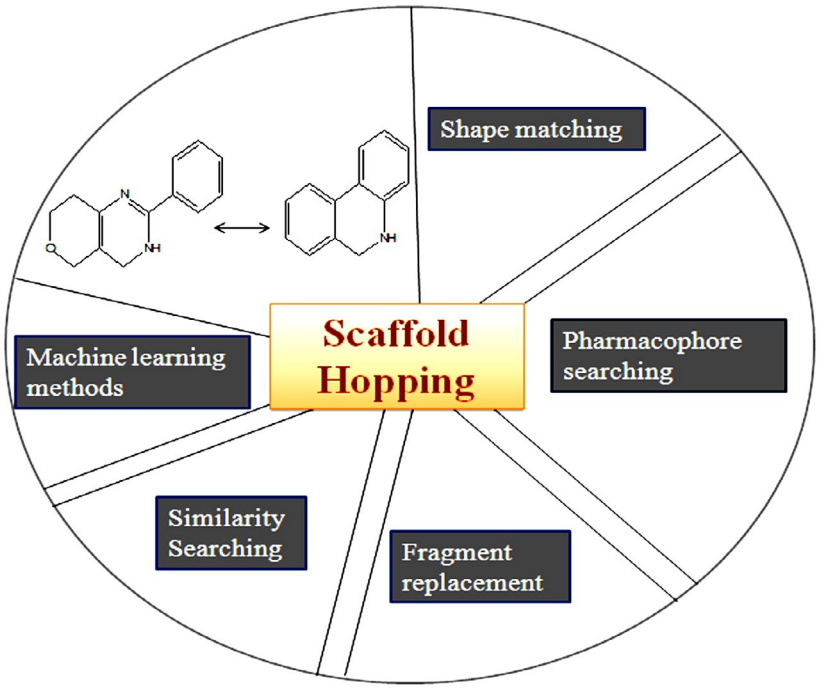


Fig. 11. Scaffold hopping: Computational Approaches.

The Shape matching approach describes if the compounds are structurally related means display similar biological activities and if the compounds are more distantly related, the less probable to show the same biological effects. In shape matching, it is possible to find out the compounds which mimic accurately this structure, but it is not possible to get the same features that are significant for binding to the target structure[161,162]. If the ligands are structurally different however, can adopt similar shape and share common features, It is possible to derive 3D pharmacophores, which is used for shape matching scaffold hopping.

But the drawback is for searching out the 3D pharmacophore using different chemical structure databases is not sufficient to find out the novel scaffold because it searches from the known compound databases[163-166]. Another approach to scaffold hopping is fragment replacement, in which no need for the replacement of the entire compounds but searching for a replacement of fragment of an active compound[167-169]. Similarity searching is also used for scaffold hopping. The chemical structures are assembled in these algorithms using fragment joining as well as the novel scaffolds are resolved by their match to the query[170-172]. Also, machine learning methods are used for scaffolds hopping, methods together with self-organizing maps that allow compound distributions to be visualized[173, 174]. The computational methods of scaffold hopping are shown in Fig. 11. The software tools is listed out in (Table 5).

Molecular Simulations And Advancement

Since the first protein (folded globular protein) MD simulation is discussed in 1977[186]. In December 1999, IBM declared a five-year intend to build up a massively parallel computer for studying biomolecular phenomena, in which they

Table 5. List of Software and tools for scaffold hopping

S.No.	Software & tools	Applications	Ref.
1.	1-Click Scaffold Hop	It is ready to use drug discovery platform for scaffold hopping	175
2.	Spark™	Spark works in Shape space and electrostatic so it can go with the nature of reference molecules	176
3.	Core Hopping	The core-hopping technique is to test several possible scaffolds as protocores) against a template and look for alignments of possible (also known attachment points on the scaffold with the attachment points on the template.	177
4.	LigCSRre	LigCSRre is a modern effective and standardized method for 3D matching screening of tiny compounds, the modular plan of which opens the door to lots of improvements.	178
5.	e-LEA3D	The approach is perfectly appropriate for scaffold-hopping, this section moreover permits a search for potential substitutes to a selected scaffold.	179
6.	ChemMapper	ChemMapper using the user given the chemical structure of the molecules as the query, the highest alike structure in respect of 3D similarity is sent back using related pharmacology annotations.	180
7.	SHOP	It is a grid-based technique for Scaffold bouncing. In a database, scaffolds were predictable utilizing 3 types of 3D-descriptors.	181
8.	LeadGrow+	Creating a molecular library for efficient scaffold hopping.	182
9.	Recore	Recore is a rapid and flexible scaffold hopping method based on conformations of small molecule crystal structures.	183
10.	HTSFPs	(HTSFPs), It is a method that matches patterns of actions in investigational screens.	184
11.	MORPH	MORPH is a software tool for scaffold hopping which can scientifically alter aromatic rings in molecular 3-dimensional models exclusive change of the non-hydrogen atom co-ordinates in the rings.	185

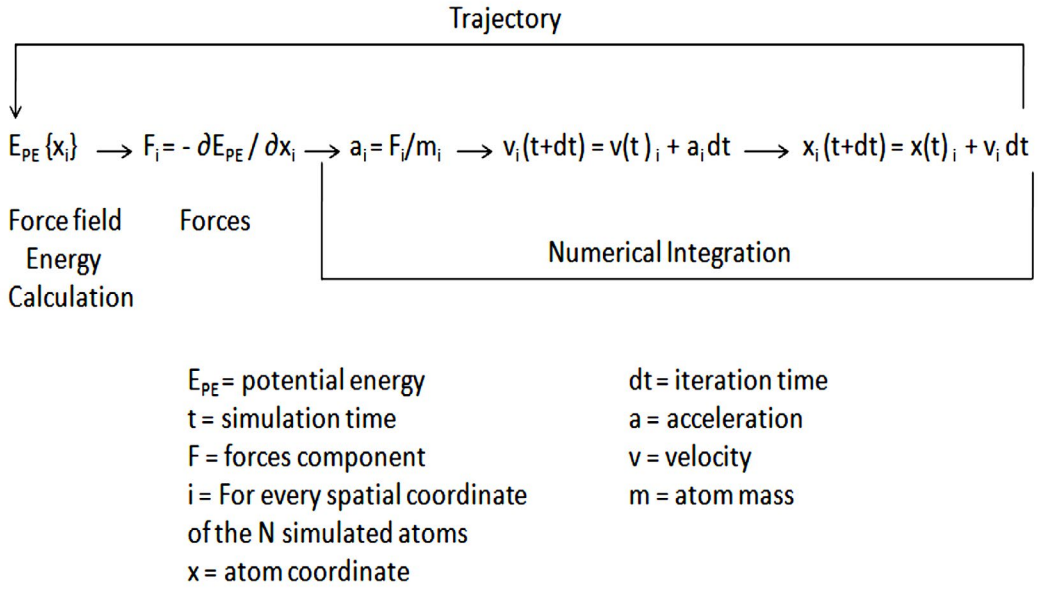


Fig. 12. A Basic algorithm for Molecular Dynamics.

have discussed for increasing longer simulation time as well as developing computing software and hardware for bimolecular MD simulation[187]. Certain software packages were also developed for simultaneously scales well-organized MD simulation very well on machines[188]. A massively parallel machine such as Anton was introduced which was able to reach millisecond time-scale simulation for biomolecular systems[189]. In recent times graphical processing unit which is known as GPU achieved remarkable progress with high-performance computing capability for MD simulations[190,191]. currently, MD simulation is very important for studying protein, DNA, and RNA systems. In the MD simulation so many terms are used in which force field is very significant where a protein force field included bonded (bond angle, dihedral angles, bond length) and also non-bonded interactions (electrostatic, van der Waals). The development of improved sampling methods and escalating computational performance came with more inaccuracies in the protein force field[192]. In these aspects, the classical protein field has been improved with Gromacs[188], AMBER[193], CHARMM[194], and NAMD[195]. A basic algorithm for MD simulation has been represented Fig. 12 and a list of software has been shown in (Table 6). apart from this MD simulation software, there are other software also available such as Desmond[196], TINKER, DL_POLY[197], ESPResSo[198], etc. so that it is understood that MD is already an important tool in serving to understand biology.

RESULTS AND DISCUSSION

The anticipated outcome could be development and searching out the novel, specific inhibitors for *Candida albicans* MyristoylCoA: Protein N-Myristoyltransferase as anti-fungal agents using advanced computational approaches. A humble beginning made towards this end needs patronage for further development. All the more interesting on this aspect is, still as on date, no successful attempt has been made towards development of a best, specific inhibitor for *Candida albicans* MyristoylCoA: Protein N-Myristoyltransferase which again augments support.

Table 6. List of major Software and tools for MD Simulation

About	GROMACS	AMBER	CHARMM	NAMD
Developer (s)	Martin Karplus, Accelrys	Peter Kollman's, research group (at first Developed) at the University of California.	Martin Karplus, Accelrys	The University of Illinois at Urbana–Champaign
Initial release	1991; 29 years ago	2002; 18 years ago	1983; 37 years ago	1995; 25 years prior
Stable release	2018.4/12 November 2018; 16 months prior	Amber18, AmberTools19/ April 26, 2019; 10 months ago	c40b1, c40b2 / 2015; 5 years ago	2.12 / December 22, 2016; 3 years ago
Written in	C++, C	C, C++, Fortran 95	FORTRAN 77-95, CUDA	C++
Operating system	Linux, Windows macOS, some other Unix variety	Windows, OS X, Linux, Unix, CNK	Unix-like: Linux, macOS, AIX, iOS	Cross-platform: Windows, Linux, macOS, Unix
Platform	Many	x86, Nvidia GPUs, Blue Gene	x86, ARM, Nvidia GPU; Cray XT4, XT5	x86, x86-64
Available in	English	English	English	English
License	LGPL variants >= 4.6, GPL variants < 4.6	Amber: Proprietary AmberTools: public domain , GPL, other open-source	Proprietary	Proprietary, freeware for noncommercial use
Website Sources	www.gromacs.org	ambermd.org	www.charmm.org	www.ks.uiuc.edu/Research/namd

CONCLUSION AND FUTURE PERSPECTIVE

N-myristoyl transferase is a monomeric cytosolic protein that is vital for the function and growth of fungi. There are so many inhibitors that have been designed against *Candida albicans* NMT for reducing fungal infections in humans but at present antifungal drugs are not perfect in the expressions of the antifungal spectrum, efficacy, and protection. Drug repurposing is one of the most significant, more affordable, and increasingly proficient techniques in drug discovery. So right now, we have examined in silico drug repurposing approach which joins Molecular docking, Virtual Screening, Pharmacophore demonstrating, Scaffold hopping, and Molecular dynamics (MD) simulation for the advancement of a novel *Candida albicans* NMT inhibitors.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

All authors have made substantial, direct,

and intellectual contribution to the work and approve it for publication.

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DATA AVAILABILITY

All datasets generated or analyzed during this study are included in this manuscript.

ETHICS STATEMENT

Not applicable.

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