Advances in drug discovery on the biofunctionalities of bioactive peptides: The role that molecular docking plays in targeted therapy development

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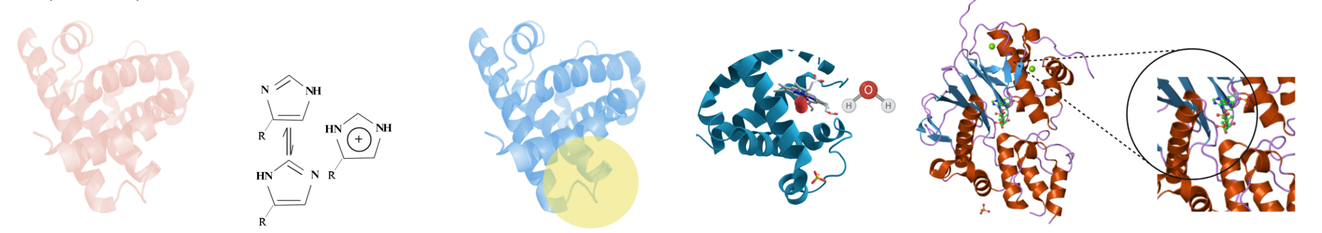
1. INTRODUCTION BIOFUNCTIONALITIES OF BIOACTIVE PEPTIDES (BAPs)

BAPs are sequences of 3 to 40 amino acid residues in length. These proteins, which have similar properties to those of endogenous peptide hormones, are derived from parental polypeptide sequences through controlled and specific proteolytic cleavages. In the first half of the 20th century, BAPs fundamental to medicine were discovered, such as insulin, regarded as one of the largest scientific achievements.



Better scoring methods and their integration with structural biology not only streamline the process, but also progress the comprehension of protein-peptide relationships and aid in the discovery of more targeted and effective drugs. **The review seeks assess the scope of this field and underline the crucial role that proteins play in the drug's discovery and development.**

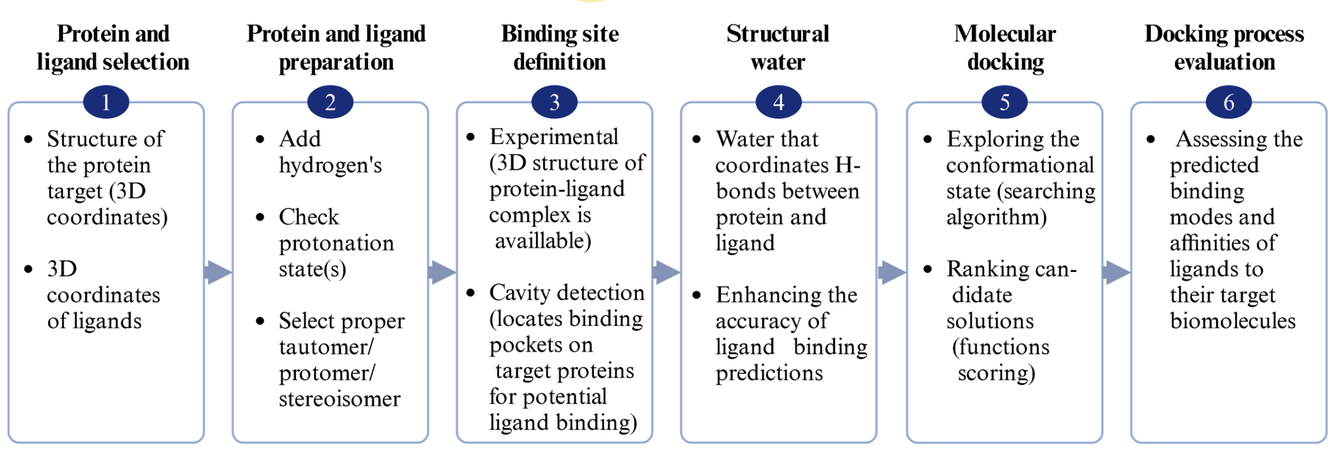


Figure 1. Molecular docking workflow. Created with BioRender.com.

2. METHODOLOGY: Assessing Binding Affinity of BAPs in Molecular Docking

Tailored methodologies address these features to provide accurate binding affinity predictions:

1. Positioning algorithms:

- **Shape Matching:** Quickly identifies potential binding sites by aligning BAP structures with the protein receptor based on a geometric fit.
- **Stochastic Methods:** Explores various BAP conformations using random changes (e.g., Monte Carlo).
- **Systematic Methods:** Thoroughly checks all conformations but is computationally intensive.

2. Flexibility handling:

- **Rigid Body Docking:** Assumes both peptide and protein are rigid; rarely suitable for BAPs.
- **Semi-Flexible Docking:** Adjusts BAPs conformation while keeping the receptor rigid.
- **Flexible Docking:** Allows both peptide and receptor to adapt, capturing dynamic interactions.

Figure 2 visualizes the three techniques in an illustrative way.

3. Simulation methods:

- **Molecular Dynamics (MDs):** Simulates BAPs movement over time to explore various conformations and binding dynamics.
- **Energy Minimization:** Refines the ligand-receptor complex to achieve the lowest energy state, enhancing the accuracy of binding pose predictions.

4. Scoring functions:

- Evaluate the strength and quality of ligand-receptor interactions by calculating binding energy, providing a quantitative measure of affinity.

Challenges: Include ensuring structural accuracy and accounting for protein flexibility to improve prediction reliability.

Figure 2. Main techniques used in docking methodologies. Created with BioRender.com.

3. APPLICATIONS IN DRUG DISCOVERY: Hit Identification - Lead Optimization

1. Hit Identification:

- **MD:** Screens BAP libraries by simulating their interactions with protein receptors to identify promising candidates.

2. Lead Optimization:

- **Binding mode prediction:** Refines BAP structures for better affinity and effectiveness.
- **Pharmacological enhancement:** Optimizes drug properties like affinity, potency, and selectivity

3. Biological Activity Prediction:

- **MD and Quantitative Structure-Activity Relationship (QSAR) models:** Analyze BAP-receptor dynamics and chemical properties to predict biological effectiveness and mechanisms of action.

4. Pharmacophore Models:

- **Structure-Based (BS) and Ligand-Based (BL) models:** Use receptor structures or active ligands to predict new compounds.

5. Absorption, Distribution, Metabolism, Excretion (ADME) and Toxicity Assessment:

- **Early evaluation:** Screens pharmacokinetics and toxicity to ensure BAP safety and therapeutic viability. The typical computer-aided drug discovery (CADD) workflow is shown in **Figure 3.**

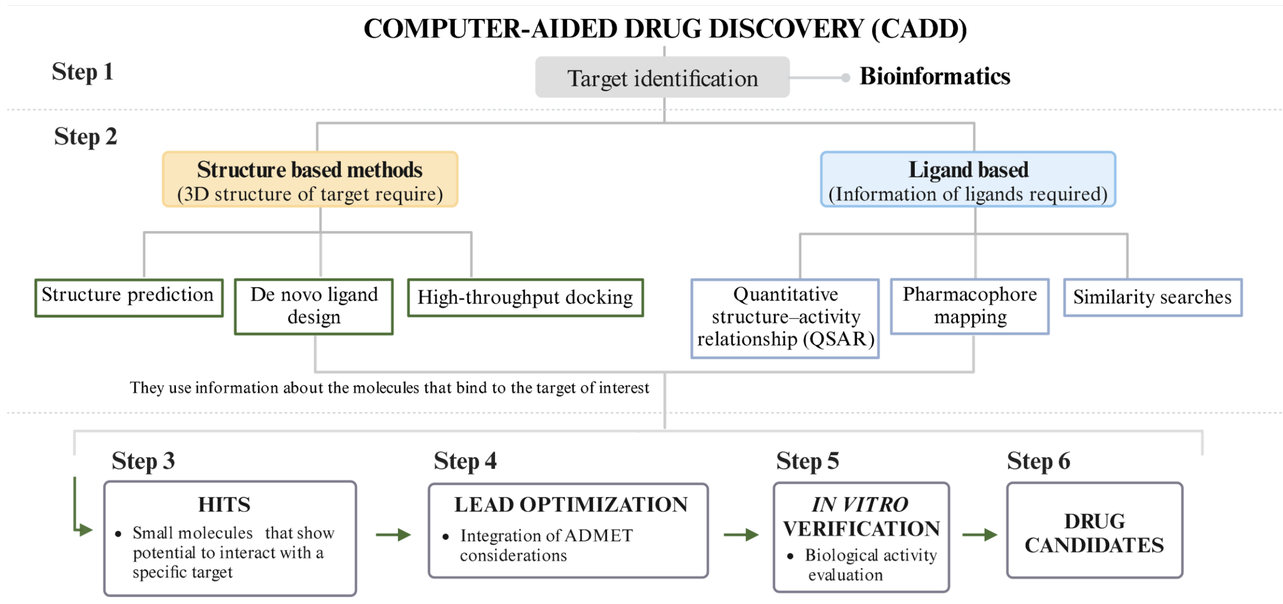


Figure 3. Computational drug design workflow. Created with BioRender.com.

4. MEETING CHALLENGES: Technological Advances

Recent advancements in molecular docking for bioactive peptides have been driven by increased computational power and improved scoring methods, including machine learning. These developments enhance the accuracy and speed of simulations, providing better predictions of binding affinities and modes Integration with structural biology leverages high-resolution data for precise predictions, aiding in understanding protein interactions and refining docking procedures. **High-resolution protocols** and rescoring methods improve conformational sampling and scoring precision, optimizing docking accuracy. **These advancements boost efficiency and accuracy, paving the way for new therapeutic potential of BAP-based drug candidates.**

Conclusion

- MD is essential for **advancing BAP-based drug development** by analyzing peptide-target interactions.
- **Technological advancements** have significantly enhanced MD, driving progress in drug discovery.
- **With computational chemistry**, MD is an essential tool for **new medical treatments.**

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