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Antimicrobial packaging based on molecular docking of natural products

Embalagens antimicrobianas baseadas em docking molecular de produtos naturais

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ABSTRACT

For a long time, studies on food packaging focused on antimicrobial agents, without, however, explaining the mechanisms. Therefore, in this analysis and opinion text, we approach the promising scenario, regarding the use of molecular docking techniques in the development of antimicrobial packaging. Molecular docking was identified as an important guidance tool, showing researchers which molecules had effective antimicrobial activity and their mechanisms. Furthermore, based on molecular docking studies, researchers were able to optimize in vitro and in vivo antimicrobial experiments. The targeted approach was efficient in developing antimicrobial packaging, which increased the shelf life of several foods. We consider molecular docking an indispensable tool for studies on antimicrobial packaging and a promising field of research.

Keywords: Molecular docking; Food packaging; Antimicrobial potential; Shelf life; Molecular docking.

RESUMO

Durante muito tempo, os estudos sobre embalagens de alimentos focaram-se nos agentes antimicrobianos, sem, no entanto, explicar os mecanismos. Portanto, neste texto de análise e opinião, abordamos o cenário promissor, no que diz respeito à utilização de técnicas de docking molecular no desenvolvimento de embalagens antimicrobianas. O docking molecular foi identificado como uma importante ferramenta de orientação, mostrando aos pesquisadores quais moléculas tinham atividade antimicrobiana eficaz e seus mecanismos. Além disso, com base em estudos de acoplamento molecular, os pesquisadores conseguiram otimizar experimentos antimicrobianos in vitro e in vivo. A abordagem direcionada foi eficiente no desenvolvimento de embalagens antimicrobianas, o que aumentou a vida útil de diversos alimentos. Consideramos o docking molecular uma ferramenta indispensável para estudos sobre embalagens antimicrobianas e um campo de pesquisa promissor.

Palavras-chave: Docagem molecular; Embalagem de alimentos; Potencial antimicrobiano; Vida útil; Acoplamento molecular.

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INTRODUCTION

The food safety of fresh produce is a persistent challenge that has profoundly impacted the food industry and strategic plans for a more sustainable world. The problem of food spoilage is an urgent issue, given the challenging scenario for the next 20 years. Current projections show that the global population tends to continue growing, as does the need for food. This scenario seems like a fictional story, but it is not, and along with the demand for food, we have growing outbreaks of diseases spread by contaminated food. The challenge is global and requires joint efforts and economically viable strategies (Silva et al., 2021; Barbosa and Carvalho, 2022).

Food spoilage refers to the process by which food loses its quality and safety for consumption due to several factors, such as microbial action, oxidation, enzymes, humidity and inadequate temperature. Food spoilage is a complex process that can be the result of a succession of enzymatic reactions originating from spoilage microorganisms or from the food matrix itself, such as lytic enzymes present in tissues. This can lead to bad smells, unpleasant tastes, and even deterioration in the texture of the food. Refrigeration and sterilization are common methods to prevent microbial spoilage (Barbosa et al., 2021).

With the growing global demand for sustainable initiatives in all parts of the food production chains, there is a need to improve food preservation processes, without losing focus on quality and efficiency. For this purpose, it is necessary to understand the processes related to microbial deterioration of food and chemical and physical changes in order to find efficient strategies. One of the most efficient strategies is active packaging, especially those with antimicrobial activity. Among the innovations, some have attracted attention, such as the development of protective matrices for antibacterial molecules, controlled delivery systems, metallic and organic nanoparticles, and sulfated polymers with antibacterial potential (Vieira et al., 2018; Barone et al., 2021; Santos et al., 2024).

Although the science of antimicrobial packaging is advancing, we still have many gaps related to antimicrobial mechanisms and how this can influence food preservation. A promising strategy to elucidate the antimicrobial mechanisms of packaging may be the use of molecular docking. Although this technique is consolidated, little has been used in studies on food packaging. Therefore, in this analysis and opinion text, we will discuss

how molecular docking can be an indispensable tool in studies involving the development of antimicrobial packaging.

DOCKING FOR DESIGN OF NATURAL ANTIMICROBIAL AGENTS

Natural Antimicrobial Chemical Library

Natural chemical compounds that have antimicrobial activity can be isolated compounds or concentrated extracts. Many chemical compounds have recognized antimicrobial activity, and include complex classes of phytochemicals, essential oils, and some polymers. Researchers have focused efforts on creating chemical libraries with results from in vitro or in vivo studies on antimicrobial activity. We sometimes have reports of pure, isolated chemical structures that are active against a diverse class of microorganisms (Chen, 2015). Below, we summarize some molecules of interest with broad antimicrobial activity (Table 1).

It is expected that virtual screening of libraries against antimicrobial targets will lead to a new era of research in the area of food, and in studies for the development of antimicrobial packaging. In fact, making a parallel, during the COVID-19 pandemic, several research groups expanded the sampling of potential antivirals using virtual screening of possible active agents. For example, the potential of sulfated polysaccharides and derivatives have been extensively investigated by in silico studies and then confirmed in in vivo studies (Barbosa and Lourenço, 2023).

An antimicrobial chemical library is a collection of chemical compounds designed and organized for research and development of new antimicrobial agents, such as antibiotics and antivirals. These libraries are used by scientists and researchers to search for new substances that can combat bacteria, viruses, fungi and other pathogenic microorganisms. These libraries can contain thousands or even millions of different chemical compounds and are a valuable tool in the search for new antimicrobial treatments. They are used in high-throughput screens, where compounds are tested in cultures of microorganisms to identify those that have promising antimicrobial activity. To access an antimicrobial chemical library, you can contact academic research institutions, pharmaceutical laboratories, or companies specializing in research chemicals. Many of these institutions have their own libraries or can provide access to shared libraries. Of course, you can also find commercial vendors that sell antimicrobial chemical libraries for research.

Table 1 – Set of organic molecules of interest with broad antimicrobial activity.

Raw material	Molecule with antimicrobial potential	Antimicrobial inhibition	Protein target	Comments	Reference
Hexane extract of *Mesua ferrea L.*	Linoleic acid and oleic acid	Inhibited the bacteria at 78 µg/mL.	2B35, 2GP6 E 4FIX	The study also revealed the high antioxidant potential of the compounds	(Kalita et al., 2018)
Cinnamomum zeylanicum, Cinnamomum tamala, Amomum subulatum, Trigonella foenumgraecum, Mentha piperita, Coriandrum sativum, Lactuca sativa e Brassica oleraceae var. itálico.	Rutin, kaempferol, quercetin, terbinafine	Antifungal activity against strains tested at a concentration of 100 µg/disk: 13mm, 11.3mm, 13.6, 9.3mm, 10.0mm, 7.6mm, 9.3mm, 8.3mm and 20mm, respectively for each extract.	Rutin with 14 alpha demethylase (CYP51). Quercetin with CYP51. Terbinafine with CYP51. Rutin with nucleoside diphosphokinase (NDK). Kaempferol with NDK. Terbinafine with NDK.	Overall, the study demonstrates that plant-derived products have a high potential to control fungal infections.	(Khanzada et al., 2021)
Ethanolic extract of *B. serrata*	Highlight for C29 H46 O6, Cholan-24-oic acid, 3,12-bis (acetyloxy), methyl ester.	Inhibited bacteria (K. pneumoniae and S.aureus) at 60 µg/mL.	Active site of beta-lactamase protein	In this work, docking also reveals the connection of beta-lactamase with methyl diacetyl chenodeoxycholate, proving its inhibitory activity.	(Vakayil et al., 2021)

Methanolic extract from *Pistacia lentiscus bark*	Methyl gallate, gallic acid, kaempferol, quercetin, kaempferol 3-O-α-rhamnoside, kaempferol 3-O-β-glucoside and Quercetin-3-O-β-glucoside	Zones of inhibition ranging from 10 to 25 mm wide, with emphasis on Pseudomonas aeruginosa	Protease-3CL binding pocket.	The constituents of the extract have high levels of binding affinity to the 3CL-protease protein, suggesting that this extract could be used against SARS-CoV-2 infection.	(Selim et al., 2022)
Essential oil of *Piper nigrum L*.	Monoterpene hydrocarbons	-	F. oxysporum cutinase (PDB 5AJH), F. oxysporum cutinase (PDB 5AJH), F. solani cutinase (PDB 1AGY, 1XZL and 1XZM), F. oxysporum endoglucanase (PDB 4OVW), F. oxysporum feruloyl esterase (PDB 6FAT) and xylanase from F. oxysporum (PDB 5JRM).	Total phenolic contents were higher in leaves compared to fruits.	(Barata et al., 2021)
Ethanolic extract of *B. monnieri*	Luteolin	S. aureus – 13.22 to 15.33 mm and MIC 75 µg/mL.	DNA Girase	Isolated bioactive compounds can establish structural activity relationships in the development of antimicrobial drugs.	(Emran et al., 2015)
Euphorbia dendroides L ethanolic extract	Genistein	B. subtilis (3.125 µg/mL), S. aureus (1,562 µg/mL.), E. coli (1,3125 µg/mL), A. Níger (25 µg/mL)	VEGFR-2 e DNA	Genistein acts as a direct antioxidant and reduces the harmful effects of free radicals.	(Ali et al., 2022)

Chitosan nanoparticles loaded with *Jatropha pelargoniifolia*	Linarine	B. subtilis (15mm), S. aureus (11mm), E. coli (22mm), P. aeruginosa (19mm), C. albicans (18mm). (11 µg/mL for E. coli and 20 µg/mL P. aeruginosa)	Bacterial DNA gyrase B and human DNA topoisomeraseIIα	Linarin, a flavonoid glycoside, which is essential for the survival of all bacteria and some eukaryotes, has been shown to inhibit DNA gyrase	(Alqahtani et al., 2021)
Cellulose-based nanofibrillated biopolymer matrix	Cellulose/TiO 2 nanocomposite	S. aureus (13mm) and E. coli (14mm)	Dihydrofolate reductase and dihydropteroate synthase	The cellulose/TiO nanocomposite has shown promise in food packaging, public health and biomedical applications.	(Arularasu; Harb; Sundaram, 2020)
Methanolic extract of *A. integrifolia*	Flavonoids, quercetin, myricetin and rutin and phenolic acids, gallic acid, chlorogenic acid and syringic acid.	Shigella spp (17,67mm), E. coli (3,33)	VcDHO	Considerable activity of the aerial part of A. integrifolia against Shigella spp., the potential anti-shigellosis activity was evaluated. VcDHO was selected as a drug target for its role in the proliferation of pathogenic bacteria.	(Tessema et al., 2023)
Methanolic extract of *A Ixora brachiata Roxb*	β-amyrin, β-sitosterol, δ-tocopherol, γ-sitosterol, lupeol and squalene.	Escherichia coli and Staphylococcus aureus, yielding 5mm and 4mm, respectively, at a concentration of 10 mg/mL	PI3K , MMP-9, mTOR e ERβ.	In some cases, plant compounds performed better (in terms of ΔG and K i) than commercially available inhibitors of the respective receptor proteins.	(Veeramuthu et al., 2023)

The ligand and the protein target

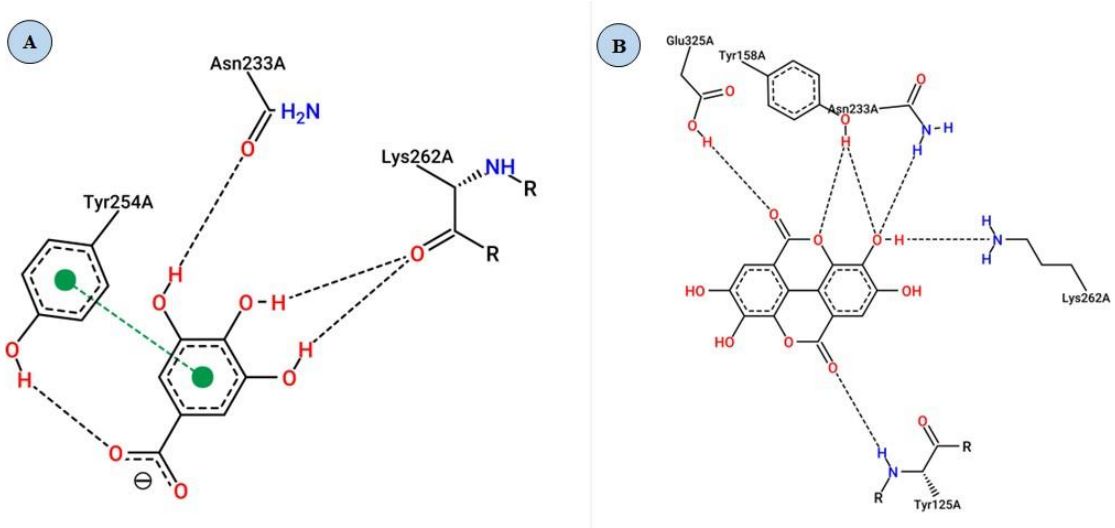
The ligand is a molecule that binds to a target protein of interest. The goal of molecular docking is to predict how a molecule, such as a drug or a ligand, fits into the target protein. This interaction between ligand and protein is critical to understanding how drugs interact with their targets at the molecular level. Online platforms like https://coconut.naturalproducts.net. https://cocon, they make a set of data on natural products available free of charge. The molecular structure of the ligand must be in its 3D form for docking studies to be performed. Database like PubChem (available for free in https://pubchem-ucbi-nlm-nih.ez3.periodicos.capes.gov.br), provides several molecules in 3D.

Protein or enzymatic targets are selected based on functionality, and therefore, their inhibition harms the survival of microorganisms. Proteins from different microorganisms and related to diseases can be found in different databases such as: the RSCB Protein Data Bank (PDB) (https://www.rcsb.org/), AlphaFold Protein Structure Database (https://alphafold.ebi.ac.uk/) and the database SWISS-PROT (https://www.uniprot.org/). Understanding the molecular target is extremely relevant for designing drugs and verifying interactions with ligand molecules.

Molecular docking

Molecular docking aims to simulate the best energetic, conformational potential and binding affinity between ligand molecules and target proteins. The molecular anchoring process begins with the positioning of the ligand to the active site of the protein receptor. The molecular structure of the ligand is fitted, and the spatial organization is optimized, until it finds the perfect fit between the receptor and the protein target. (Figure 1). Molecular targets that have the most suitable natural conformation and that have the most affinity with the receptor can be selected for docking using the scoring function (Li et al., 2022). During the molecular coupling process, the bonds must meet the criteria of mutual correspondence theory, which depends on geometric complementarity, hydrophobic interactions, hydrogen bonds and charge potential allocated between the ligand and receptor (Yuan and Hao, 2023).

Figure 1 – Molecular docking approach. (a) 2D image of Gallic acid interacting with the active site 2q85 through amino acid residues from the bacteria Escherichia coli. (b) 2D image of ellagic acid interacting with the active site 2q85 through amino acid residues of the Escherichia coli bacteria (Docking carried out by the authors).



Source: Authors (2023).

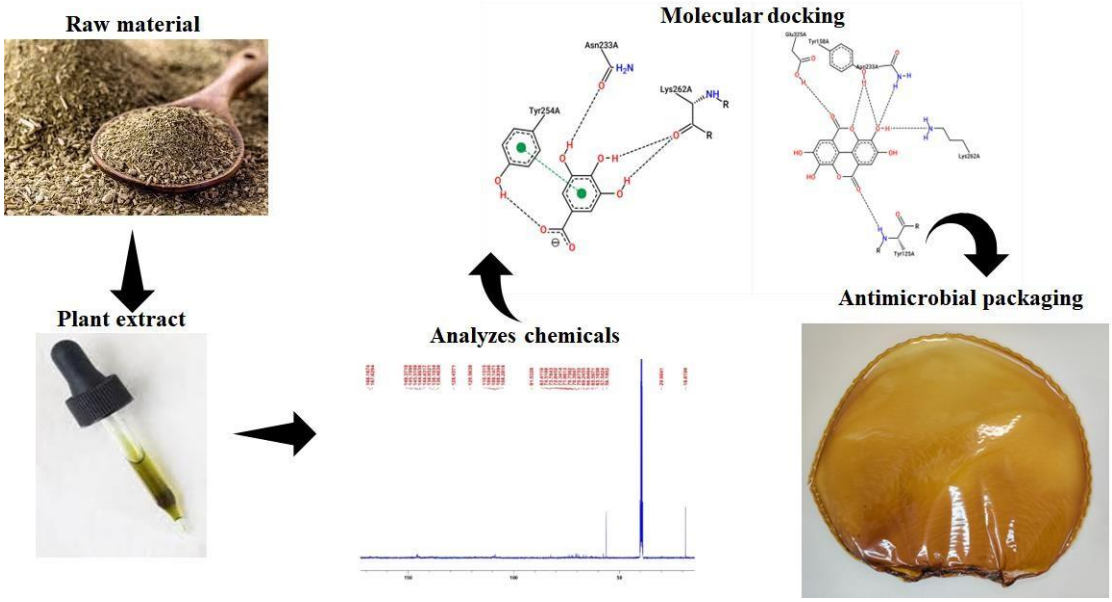
The entire molecular membrane methodology is based on the Lock-Key model, which describes how certain molecules release and interact with active sites of enzymes and proteins, proposed by Fischer (1894). Although the Lock-Key model has undergone significant improvements, the basic premises remain unchanged. The model predicts the connection characteristics, and brings the concept of key – lock, as fixed systems, which today we understand as a rigid model (Wang et al., 2022). However, the molecular conformations of enzymes and substrates vary with the binding process, which could make substrate recognition difficult. Therefore, considering the dynamics of protein and enzymatic sites, the theory of induced fit was proposed in 1958 (Koshland, 1995).

According to the induced fit theory, when a substrate binds to an enzyme, the structure of the enzyme can undergo a conformational change. This is because the enzyme adjusts or "dovetails" more precisely with the substrate upon binding to create an ideal active environment for the chemical reaction to occur. In other words, the binding of the substrate to the enzyme induces a change in the enzyme's shape, making it more effective in catalyzing the reaction. This theory is fundamental to understanding how enzymes work and how they are highly specific for their substrates. It helps explain why enzymes are so efficient at accelerating chemical reactions, and why each enzyme specializes in a particular type of substrate (Galburt and Tomko, 2017).

Antimicrobial packaging based on molecular docking

In recent years, research has addressed the development of food packaging using biodegradable materials and functional ingredients, especially those with antimicrobial potential. For a long time, packaging with antimicrobial potential was developed based on in vitro studies, using a series of experiments to identify which compounds would have activity. These processes are onerous, expensive and require a lot of investment. Therefore, more recently, the approach to antimicrobial packaging has been undergoing a gradual change in the way antimicrobial compounds are identified (Figure 2). More recent studies have used artificial intelligence to identify the best packaging composition and others have used molecular docking tools to identify molecules with antimicrobial potential efficiently and faster (Albuquerque et al., 2020; Pereira et al., 2021; Farouk et al., 2022; Freitas et al., 2022; Brito et al., 2023). The following flowchart summarizes the methodological paths used to produce antimicrobial packaging based on molecular docking. (Figure 3).

Figure 2 – Antimicrobial packaging based on molecular docking of natural products.



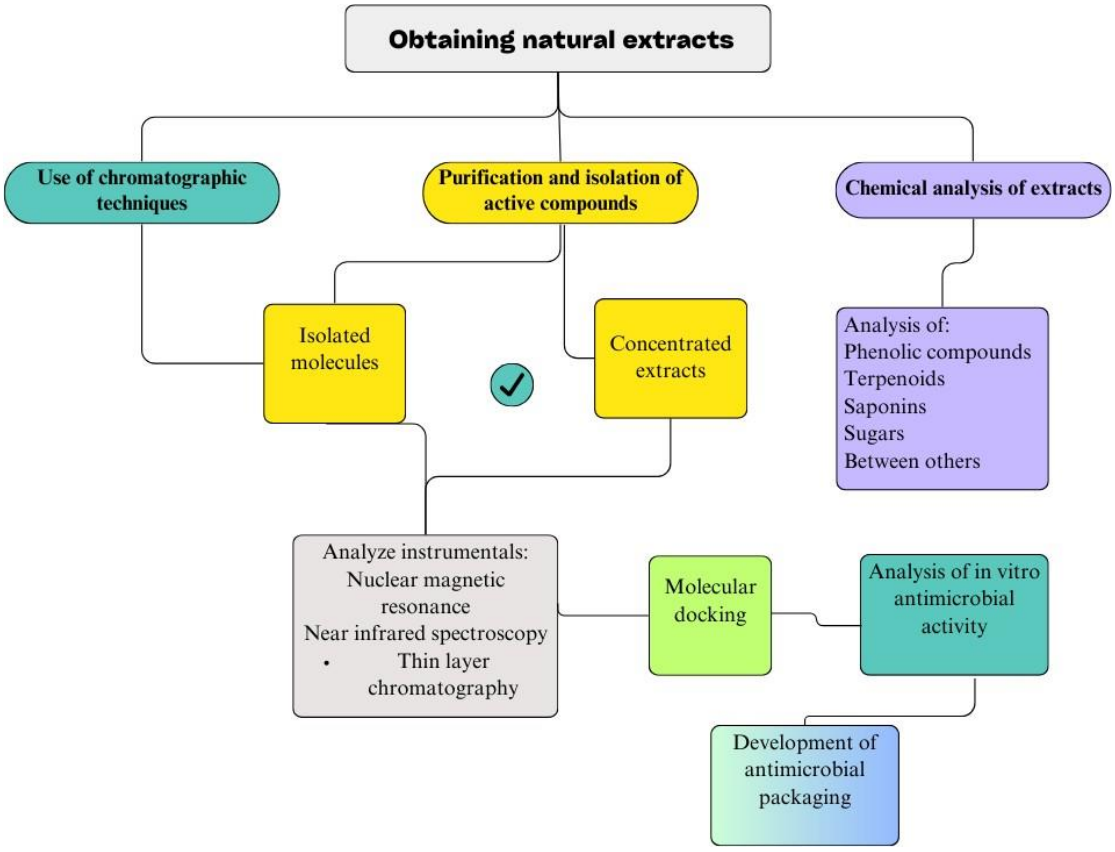
Source: Authors (2023).

Natural oils have long been used as potential antimicrobial agents in food packaging. However, the mechanisms of action have been little explored (Martins et al., 2021). A recent study proposed the use of an edible coating with ginger oil nanoemulsions to prevent the occurrence of aflatoxin. The in silico approach showed that sesquiterpenes from ginger oil have the highest binding free energies against the enzymes responsible

for the production of aflatoxins. Furthermore, α-bisabolene and urcumene bound and activated the cytochrome P450 polyketide synthase and monooxygenase enzymes, being responsible for the antifungal activity (Farouk et al., 2022).

The bacterium P. fluorescens is recognized as one of the main spoilage agents of seafood, leading to serious economic losses and representing a threat to food safety (Ding; Li; Li, 2019). A recent study proposed that hesperidin, a flavanone glycoside found in citrus fruits, has the ability to inhibit the development of bacteria. Using packaging with hesperidin made it possible to increase the shelf life of fish and food safety. The in silico approach showed that hispiridine blocked the binding of signaling molecules to the LuxR-type protein, reducing the expression of the QS pathway and the QS phenotype of P. fluorescens (Ding; Lin; Tan, 2022).

Figure 3 – Graphic abstract of the main methodological routes used in studies with molecular docking for the development of antimicrobial packaging.



Source: Authors (2023).

Packages of polyvinylpyrrolidone and magnetite nanoparticles coated with chitosan (Fe3O4) were efficient as an antibacterial agent against Escherichia coli. The in silico study indicated that the nanoparticles are promising inhibitors of dihydrofolate

reductase (DHFR) and DNA gyrase (Ayesha et al., 2023). In another study, chitosan and polyphenol coatings increased the shelf life of fish under refrigeration. The in silico study showed that catechins bind to rotated DNA through hydrogen bonds and hydrophobic interactions, inhibiting bacterial DNA synthesis (Wang et al., 2023).

CONCLUSIONS

Molecular docking is an indispensable tool for studies with antimicrobial packaging. Molecular docking was used by researchers as a guidance tool, showing which molecules have a greater capacity for interaction with protein targets from microorganisms. It is clear that this tool must be better explored and has the potential to make packaging research more assertive. Furthermore, the Docking study helped to properly select which molecules or extracts would have greater antimicrobial efficiency and increased the confidence of the data. Finally, with computational evidence, researchers were more assertive in making decisions regarding the experimental planning of in vitro and in vivo studies.

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