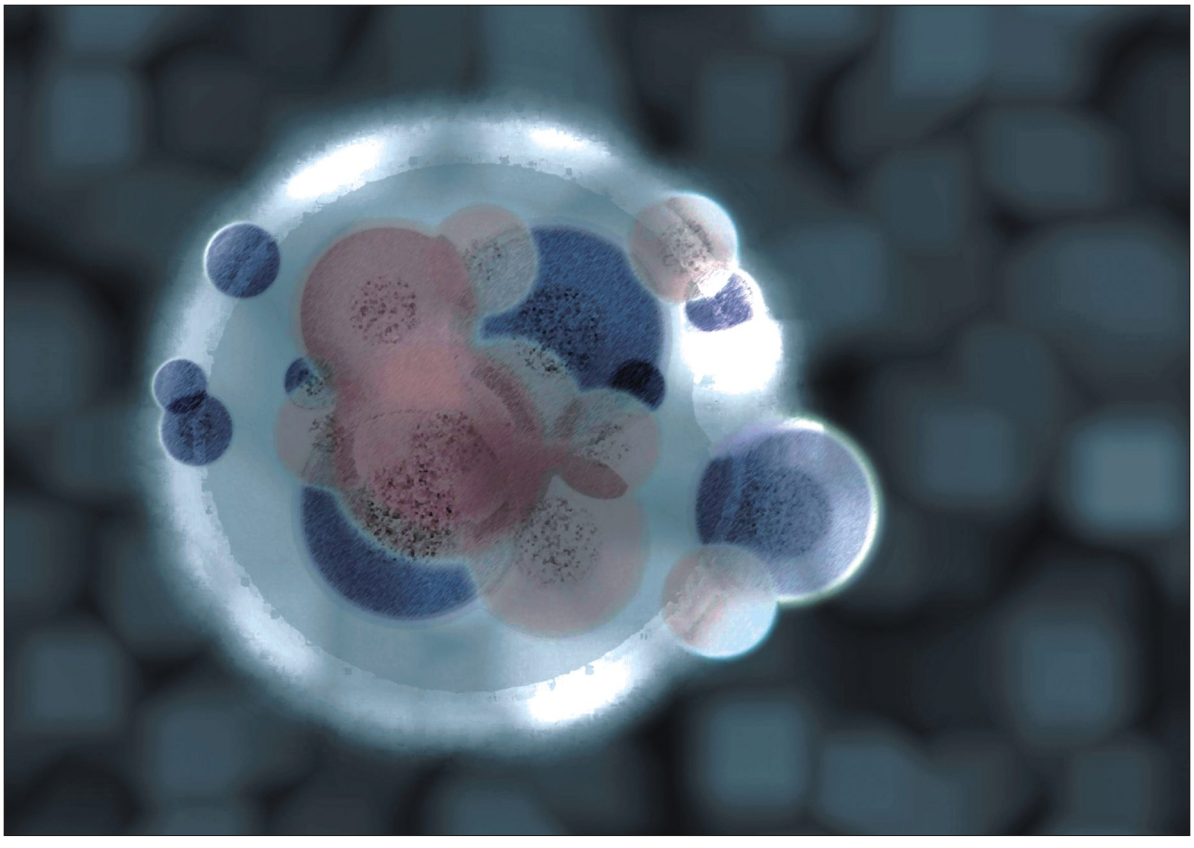

Journal of Biological Sciences

ISSN 1727-3048

science alert

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OPEN ACCESS Journal of Biological Sciences

ISSN 1727-3048
DOI: 10.3923/jbs.2024.1.5

Review Article
Molecular Docking Perspectives on Phytochemicals: Optimizing Dairy Animal Health through Feed Additives

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Abstract
Animal feed plays a crucial role in ensuring optimal milk production and overall health. In recent years, there has been a growing interest in the use of phytochemicals as feed additives to enhance the well-being and performance of dairy animals. It explores the potential health benefits of phytochemicals in dairy feeds, with a specific focus on molecular docking studies to elucidate their mode of action at the molecular level. It discusses the inclusion of phytochemicals in feed additives not only improves animal health through natural antioxidants, antimicrobials and reproductive advantages but also aligns with consumer preferences for sustainable and high-quality livestock products. Furthermore, it explores the potential of phytochemicals to modify ruminal fermentation, reduce methanogenesis and boost livestock performance is a primary focus. This study highlights the challenges in determining optimal concentrations of phytochemicals for enhancing animal performance, as well as the adaptation of ruminal microflora to the feed additives, leading to variable and inconclusive outcomes. Finally, it concludes by illustrating the possibility of using phytochemicals to enhance livestock production and the sustainable agriculture. Further research is required in this area.

Key words: Phytochemicals, feed additives, animal health, livestock production, molecular docking

Citation: Safdar, M., Y. Junejo and M. Ozaslan, 2024. Molecular docking perspectives on phytochemicals: Optimizing dairy animal health through feed additives. J. Biol. Sci., 24: 1-5.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Molecular docking is a complex computational method that involves predicting the interactions between small molecules and macromolecular targets such as proteins, enzymes, RNA or DNA[1]. The method is based on the principles of thermodynamics and molecular mechanics and it is used to predict the binding affinity and orientation of a ligand to a receptor[2]. In recent years, molecular docking has undergone significant advancements and several new techniques have been developed to improve its accuracy and efficiency[1-3]. One such technique is the use of machine learning algorithms to predict the binding affinity of a ligand to a receptor[2]. Another technique is the use of molecular dynamics simulations to study the dynamic behavior of ligand-receptor complexes[4]. Molecular docking has several applications in animal nutrition, including the prediction of the interactions between feed additives and enzymes in the digestive tract of animals[5,6]. Therefore, it can help researchers to design more effective feed formulations and improve animal health and productivity.

Technologies are getting update day by day. Some researchers explore the crucial role of molecular docking as a computational technique in drug design, utilizing ligand-protein interactions to predict thermodynamic affinity. They explained that serving as the "new microscope", molecular docking has proven invaluable over decades, offering cost-effective insights into molecular chemistry. They emphasis the progress from old docking methods to current software technologies, critically analysing emerging trends and addressing challenges, such as molecular flexibility and binding entropy[7].

Phytochemicals are naturally occurring compounds found in plants that have been shown to have beneficial effects on animal health and productivity[8]. In animal, phytochemicals are used as feed additives to improve the growth performance, health and well-being of animals. Particularly, polyphenolic phytochemicals such as carvacrol oil, thymol oil, oregano oil and tannins oil have been shown to have antimicrobial properties and can be used as natural feed additives to control bacterial pathogens in the chicken gut. These phytochemicals help to reduce the prevalence of antibiotic-resistant bacterial strains in poultry and improve the overall health of the birds[9,10].

In addition, phytochemicals, found in plants, may influence epigenetic mechanisms such as DNA methylation and histone modification. Compounds like EGCG in green tea and sulforaphane in cruciferous vegetables have been studied for their potential impact on gene expression[11-13]. These bioactive compounds could play a role in modulating epigenetic changes associated with health, including antioxidant effects and potential cancer prevention[11,14,15]. However, further research is needed to fully understand the precise interactions between phytochemicals and epigenetics in animal feeds.

Furthermore, feed additives encompass non-nutritive substances that enhance animal well-being and performance by influencing immune, endocrine, microbiome, gut health, or receptor functions. The use of feed additives in dairy cattle nutrition is aimed at improving feed efficiency and rumen metabolism, enhancing gut health and reducing methane emissions[16,17]. In the present era, diverse forms of natural products, such as plant extracts, fatty acids, dietary lipids, essential oils, probiotics and condensed tannins, exhibit considerable potential. According to research findings, the utilization of feed additives like polyphenols, ruminant nutrition, alternative protein sources, animal products, milk and meat quality, feed evaluation, methane and ammonia emissions can be employed to enhance animal production[18]. An additional research study proposes that feed additives are incorporated into animal nutrition with the aim of enhancing both the quality of feed and the quality of food derived from animals. This inclusion serves to improve the overall performance and health of the animals[19].

Therefore, the aim of this review was to provide a comprehensive exploration of molecular docking perspectives on phytochemicals, with a specific focus on their application in optimizing dairy animal health through feed additives.

Phytochemicals and their potential impact on dairy animal health: Phytochemicals are naturally occurring compounds found in plants that have the potential to improve animal health and productivity. According to a review study, phytochemicals have been proposed as an alternative to antibiotics for promoting growth and enhancing host health in food-producing animals[20]. Furthermore, the study underscores the imperative to formulate strategies for replacing antibiotics in the context of food-producing animals, particularly in poultry and livestock[20]. Another study suggests that phytochemicals and their inclusion in animal feed have been proposed as a replacement for traditional growth promoters[21,22]. However, there are still doubts regarding their true worth within animal production[21,22]. A study suggests that grass-fed animals have higher levels of health-promoting phytonutrients than grain-fed animals[23]. The elevated phytochemical diversity in productive vegetation holds the potential to enhance the well-being of animals and, in turn, extend these nutritional benefits to positively impact human health as well[23].

Finally, the exploration of phytochemicals and their potential impact on dairy animal health shows a promising way for optimizing nutritional strategies. The diverse range of bioactive compounds present in phytochemicals holds significant promise in promoting animal well-being and overall health. As we direct through this expanding field, it becomes apparent that leveraging phytochemicals as feed additives contribute not only to enhanced health outcomes but also to sustainable and holistic approaches in dairy farming. However, recognizing the complexity of interactions and potential variations across different phytochemical sources is crucial. Therefore, precise formulation and strategic implementation are essential to reveal the benefits that phytochemicals offer for the optimal health and productivity of dairy animals.

Applications of molecular docking to evaluate feed additives: Molecular docking stands as a computational method employed to forecast the interaction between two or more molecules, resulting in the formation of a stable adduct. This technique is utilized in bioinformatics modeling to gain insights into the interactions between drugs and biomolecules, facilitating rational drug design and discovery. Additionally, molecular docking is employed to position molecules (ligands) into the preferred binding sites of specific regions on DNA/protein (receptor) targets during mechanism research[2,3]. Molecular docking has the capability to anticipate an optimized orientation of a ligand on its target, enabling the prediction of various binding modes of the ligand within the groove of the target molecule. This predictive capacity proves valuable in the development of more potent, selective and efficient drug candidates[2,3]. Molecular docking has brought about a revolutionary impact across various domains. Notably, it plays a pivotal role in screening extensive databases *in silico* to identify potent drug candidates capable of targeting specific molecules of interest. Additionally, this technique can be applied to predict the activation or inhibition of enzymes by forecasting interactions between small molecules (ligands) and protein targets (enzymes). In this context, some researchers are exploring the applications of deep learning methods in genomic selection (GS). This approach offers a comprehensive overview of GS performance and sheds light on how these tools can effectively address complex challenges in plant breeding. The authors of these studies also offer general guidance on the judicious use of deep learning methods, covering the fundamentals of deep learning and the essential requirements for their appropriate application[24]. In addition, according to these analysis such as LSTM and CNN algorithms are the most used deep learning algorithms for sentiment analysis of various applications[25]. More forward, some studies provide deep learning techniques and their applications in various fields such as automated driving, clinical devices and more[26]. In this regard, the applications of molecular docking in evaluating feed additives provide a sophisticated ways through which to scrutinize and enhance nutritional strategies. The precision afforded by molecular docking techniques enables a better understanding of the interactions between feed additives and biological targets. This approach not only facilitates the selection and design of more effective feed formulations but also opens new ways for innovation in animal nutrition. Therefore, it is evident that molecular docking serves as a powerful tool in refining the assessment and application of feed additives, contributing to advancements that hold great promise for the improvement of livestock health and overall agricultural sustainability.

Optimizing feed formulations

Integrating molecular docking studies: Molecular docking is a computational method used to predict the binding modes of small compounds or macromolecules when in contact with a receptor, forecasting their molecular interactions[27]. It is an *in-silico* method employed to rank compounds based on a hierarchy determined using specific scoring functions[27]. On the other hand, molecular dynamics simulations serve the purpose of optimizing the structures of final complexes obtained from docking. These simulations go beyond by calculating more detailed interaction energies and offering insights into the ligand binding mechanism[27]. The study offers an overview of the utilization of molecular docking and molecular dynamics simulations. These techniques are employed to optimize the structures of final complexes obtained from docking, calculate more detailed interaction energies and find application in various contexts[28].

Another study discusses recent advances in molecular docking and structure-based modelling and further many applications[29]. Furthermore, the optimizing interactions to protein binding sites by integrating docking and molecular dynamics simulations describes how molecular docking and molecular dynamics simulations can be used to optimize interactions to protein binding sites[30]. Another study explained and gave the overview of how molecular docking can be used to study nutritional components and food safety[28]. Finally, the integration of molecular docking studies in optimizing feed formulations represents a step towards precision nutrition in animal husbandry. By the molecular details of interactions between feed components and biological targets, molecular docking provides valuable insights for formulating feeds that align with the specific

nutritional needs of animals. This approach holds great promise for achieving a balance between enhancing nutrient uptake, promoting health and ensuring cost-effective feed production. Therefore, it is clear that the molecular docking techniques with feed formulation practices is a dynamic way to revolutionize the efficiency and efficacy of animal nutrition strategies in the livestock production.

FUTURE PROSPECTUS AND RECOMMENDATIONS

- Molecular docking and modeling are extensively utilized in drug discovery and design, as well as in the investigation of protein-ligand interactions
- It has been used to study the interactions between feed components and proteins, such as enzymes and transporters, to improve feed efficiency and animal health
- A study used molecular docking to investigate the binding of phytogenic compounds, such as carvacrol and thymol, to the digestive enzymes of poultry. The selected compounds could potentially improve the digestibility of feed and enhance the growth performance of poultry
- In another study, it is used to identify potential inhibitors of the African Swine Fever Virus (ASFV). The ASFV is a highly contagious and deadly virus that affects domestic pigs and wild boars. The study identified several compounds that could potentially inhibit the replication of the virus, which could lead to the development of effective treatments for ASFV
- It evolves molecular docking algorithms using advanced computational techniques
- It incorporates machine learning methods to enhance predictive accuracy
- It will help to collaborate between computational biologists, nutritionists and feed industry experts
- It addresses the complexities such as the impact of gut microbiota on nutrient absorption
- It bridges the gap between theoretical advancements and practical implementation
- Develop interfaces that are accessible to non-experts in the feed industry
- It establishes standardized protocols to ensure consistency and reliability of results
- It takes a holistic approach to molecular docking, considering the dynamic nature of feed matrices
- It improves the tool's ability to predict and optimize nutrient interactions in feed formulations
- It utilizes molecular docking to contribute to sustainable agriculture, improved animal health and increased feed efficiency

CONCLUSION

The molecular docking for optimizing dairy animal health through phytochemical-based feed additives holds immense promise. This approach, by uncovering essential molecular interactions, paves the way for precision nutrition in dairy farming. Future efforts should focus on refining protocols and fostering interdisciplinary collaboration to translate theoretical insights into practical applications. The integration of molecular docking stands as a transformative force, poised to enhance health outcomes and sustainability in dairy animal nutrition.

SIGNIFICANCE STATEMENT

This study on phytochemicals in dairy feeds explores the molecular mechanisms behind improved animal health, aligns with sustainable livestock practices and highlights the need for further research to optimize concentrations of phytochemicals in dairy feeds and address adaptation challenges in ruminal microflora. Overall, it offers promising insights for enhancing livestock production and meeting consumer preferences for high-quality, sustainable products.

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