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ORIGINAL ARTICLE

Computational strategies for the discovery of biological functions of health foods, nutraceuticals and cosmeceuticals: a review

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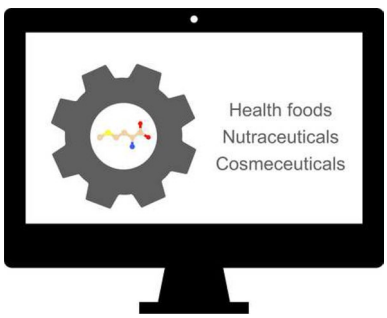
Abstract

Scientific and consumer interest in healthy foods (also known as functional foods), nutraceuticals and cosmeceuticals has increased in the recent years, leading to an increased presence of these products in the market. However, the regulations across different countries that define the type of claims that may be made, and the degree of evidence required to support these claims, are rather inconsistent. Moreover, there is also controversy on the effectiveness and biological mode of action of many of these products, which should undergo an exhaustive approval process to guarantee the consumer rights. Computational approaches constitute invaluable tools to facilitate the discovery of bioactive molecules and provide biological plausibility on the mode of action of these products. Indeed, methodologies like QSAR, docking or molecular dynamics have been used in drug discovery protocols for decades and can now aid in the discovery of bioactive food components. Thanks to these approaches, it is possible to search for new functions in food constituents, which may be part of our daily diet, and help to prevent disorders like diabetes, hypercholesterolemia or obesity. In the present manuscript, computational studies applied to this field are reviewed to illustrate the potential of these approaches to guide the first screening steps and the mechanistic studies of nutraceutical, cosmeceutical and functional foods.

Graphical Abstract



Keywords Health foods · Nutraceuticals · Cosmeceuticals · Machine learning · QSAR · Docking · Molecular dynamics

Introduction

In the last decade, the number of research papers on nutraceuticals, cosmeceuticals and functional foods has grown exponentially, with more than 11,000 manuscripts compiled in the Pubmed repository [1] during this time interval. Despite this increase, there is still a lot of controversy with these terms and their corresponding definitions.

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Stephen DeFelice coined the term "nutraceutical" in the 1980s, as a combination of the words "nutrient" and "pharmaceutical", which he defined as "a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease" [2]. Although this definition has evolved through the years, there is still no clear consensus over it, and a standard definition for this term is yet to be adopted. In general, the categorization and regulation of these products depends on their intended use and may vary across countries and regions. [3]. While the Food and Drug Administration (FDA) defines nutraceutical as "any substance that is a food or a part of a food and is able to induce medical and health benefits, including the prevention and treatment of disease" [4], there is no official definition for this term in the EU to date; nutraceutical claims submitted to the European Food Safety Authority (EFSA) are evaluated based on the Regulation of Nutritional and Health Claims (Regulation (EC) No 1924/2006) for possible authorization. However, this regulation does not cover medicinal applications in the EU [5]. A "functional food", is defined by the FDA as a "nutrient consumed as part of a normal diet, delivering one or more active ingredients (that have physiological effects and may enhance health) within the food matrix" [4]. As is the case for nutraceuticals, this term has no legal definition in the EU; instead, one can refer to healthy foods or food constituents when health claims have been approved according to the EU Regulation [6].

The concept of cosmeceutical arises by merging the words "cosmetic" and "pharmaceutical". Albert Kligman, defined a cosmeceutical as a "cosmetic product that exerts a pharmaceutical therapeutic benefit but not necessarily a biologic therapeutic benefit" [7]. Just as in the case of the nutraceutical concept, there is neither consensus on the definition of cosmeceuticals nor on the regulation of these kind of products.

Even though there is no consensus on the way to regulate and define these terms globally, they are widely used in labels to attract customers to commercialized products. The global nutraceutical market was worth USD 382.52 billion in 2020 and is expected to reach USD 722.49 billion by 2025 [8], with the United States as the leading country in nutraceutical production, followed by Europe, Asia, Latin America, Middle East and Africa [3]. Also, this market is expected to grow following the outbreak of the COVID-19, given potential benefits of these products on the immune system [9]. Moreover, the functional food market reached a worth of USD 177.41 billion and is projected to reach USD 275.77 billion by 2025 [10]. The cosmeceutical market peaked at USD 55.4 billion in 2020 and is projected to reach USD 70.0 billion by 2025 [11]. The main reason for the growth of the nutraceutical market worldwide is the trend to adopt healthier dietary habits by the population nowadays. Consumers skeptical or unsatisfied with the existent therapeutic approaches are seeking complementary products or alternatives that could help to prevent and/or improve the treatment of diseases [12].

In the last ten years, the number of patents of these products has increased with the growth of the market. Figure 1 illustrates the trend in the number of entries indexed at Google Patents [13] during the period 2010–2019 worldwide. As it may be observed, the number of filed patents has grown to approximately 20,000 patents per year in the last decade. A drop in this positive trend was observed in 2019, probably due to the drop in fillings by China-based inventors

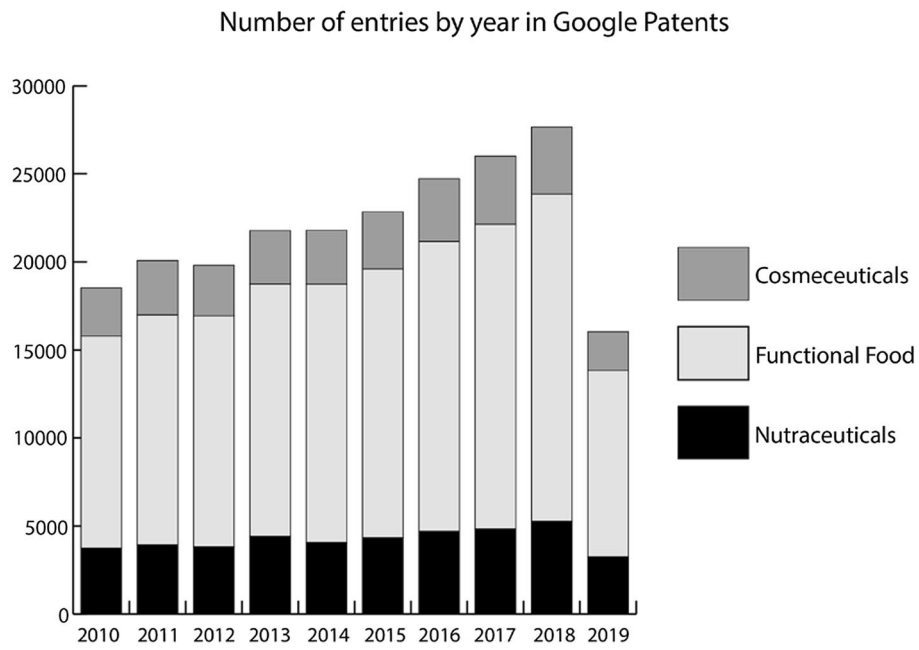

Fig. 1 Number of patents of every term by year on Google Patents

amidst an overall shift in regulations there. Even then, an acceptable number of patents was filled [14].

Several studies have demonstrated the global health benefit of consuming nutraceuticals, cosmeceuticals and functional foods, further stimulating research in this field to improve the quality of life of the society by promoting health and preventing disease. The main targets of nutraceuticals and functional foods are the antioxidant gastro-intestinal, reproductive and renal health-effects as well as the reduction of the risk of cardiovascular diseases, oral diseases, ostheoarthritis, diabetes or obesity [15, 16]. Furthermore, cosmeceuticals are intended not only to prevent the signs of aging, but also attenuate problems such as skin blemishes [17].

Nutraceuticals, cosmeceuticals and functional food have been studied in recent years, although the main challenge for this field continues to lie in the difficulty to substantiate with clinical evidences the efficacy of these compounds as well as to determine their mechanisms of action [3].

Computational techniques have been widely applied in the fields of chemistry and biology, particularly in the context of drug discovery applications in the pharmaceutical industry [18]. Many of the principles and tools employed in drug discovery may also be extrapolated to nutraceutical, cosmeceutical and functional food research, particularly in the identification of complementary leads and targets using molecular modelling, quantitative or qualitative "structure–activity" relationships ((Q)SAR), and pattern recognition methods [19]. Other possible applications of chemoinformatics and bioinformatics tools in the field of nutraceuticals, cosmeceutical and functional foods include the prediction of toxicity, activity and the elucidation of the corresponding mechanisms of action. The goal of this paper is to provide a comprehensive review on the use of computational techniques in the context of nutraceuticals, cosmeceutical and functional foods. Moreover, a prospective analysis of the impact of these techniques in this field will be provided.

Computational Methods

Chemical databases

Chemical databases have progressed over the past years from being simple repositories of chemicals, to playing an important role in chemoinformatic and bioinformatic applications [20]. A list of some of the most relevant chemical databases for computational purposes is provided in Table 1. These chemical databases allow for the querying of compounds following different criteria:

By structure allows for the query of structurally similar molecules or that share the same functional groups. Such a query is useful for paradigms where the bioactivity or target-ligand binding profile of a molecule is known, but structurally similar molecules with better bioactivity or binding profiles are desired. Also, this kind of search could be useful in ligand-based modeling

By target searches by target are an interesting option when the target which is studied is well-known. This type of query allows to obtain datasets of molecules with information related to a specific target.

By properties A search of molecules based on properties of interest may also be performed e.g. molecules whose hydrophobicity values have been reported may be compiled generating a dataset of compounds for this property to be used in posterior modeling studies.

In addition to the previously mentioned searches, there are other computational strategies that may be followed to find new active molecules structurally different from the existing ones for the cases when, for example, a molecule is shown to have activity, but also undesirable effects and as a result one needs to identify alternatives [21].

Chemical databases have become a fundamental tool in the first steps of computer aided molecular discovery (CAMD) research workflows. Due to the large number of molecules that they offer, it is often necessary that different query criteria and data mining strategies are applied to extract data with the necessary characteristics for each experiment in a more efficient way.

Chemoinformatic techniques

Chemoinformatics is a field of information technology that involves the use of computer techniques to collect, store, analyze and manipulate large sets of chemical data. This data is composed of chemical structures and requires special approaches to represent, store (*i.e.*, using molecular descriptors or SMILES annotation) and retrieve them. Moreover, these techniques seek to establish clear relationships between structural patterns and the corresponding properties or activities [41, 42].

The application of chemoinformatic methods such as pharmacophore modelling, scaffold-hopping, read-across, similarity searching, as well as statistical and machine learning (ML) modeling, has contributed to optimizing and accelerating chemical research in various fields including toxicology, CAMD and biochemistry. Noteworthy among the chemoinformatics approaches employed in the context

Table 1 Chemical databases for nutraceutical, cosmeceutical and functional food research

Database	Description	Organization	Website access
PubChem [22]	Open chemistry database with more than 100 million compounds. PubChem contains numerous small molecules but also larger molecules such as nucleotides, lipids, peptides and more	National Institutes of Health (NIH)	https://pubchem.ncbi.nlm.nih.gov
Zinc [23]	A free database of commercially available compounds with more than 230 million compounds	University of California	http://zinc.docking.org
ChEMBL [24]	A manually curated database of bioactive molecules with drug-like properties with 2 million compounds and their abstracted bioactivities	European Bioinformatics Institute	https://www.ebi.ac.uk/chembl/
NCI [25]	A database with more than 275.000 small molecules for research in the field of cancer/AIDS	National Cancer Institute	https://cactus.nci.nih.gov/ncidb2.2/
ChemDB [26]	Chemical database that contains about 5 million of small molecules and its physicochemical properties	Institute for Genomics and Bioinformatics from the University of California	http://cdb.ics.uci.edu
ChemSpider [27]	Free chemical structure database with over 67 million structures from hundreds of data sources	The Royal Society of Chemistry	http://www.chemspider.com
BindingDB [28]	A database with information from about 1 million binding data for more than 6000 protein targets and near 400.000 small molecules	Skaggs School of Pharmacy and Pharmaceutical Sciences at the University of California	https://www.bindingdb.org/bind/index.jsp
PDB-Bind [29]	A collection of more than 21.000 entries of binding affinities for protein–ligand complexes	Shanghai Institute of Organic Chemistry	http://www.pdbbind.org.cn
PDBeChem [30]	A database with more than 30.000 entries that contains small molecules, ligands and monomers searched in the Protein Data Bank	The European Bioinformatics Institute	https://www.ebi.ac.uk/pdbe-srv/pdbechem/
KEGG [31]	A database that integrates genomic, chemical and systemic functional information	Kaneisha Laboratories	https://www.kegg.jp/kegg/
HMDB [32]	The Human Metabolome Database contains detailed information about small molecules found in the human body	The Metabolomics Innovation Centre	https://hmdb.ca
SMPDB [33]	The Small Molecule Pathway Database with about 50.000 entries with pathway information about the human body	The Metabolomics Innovation Centre and DrugBank	https://smpdb.ca
BIAdb [34]	Database of benzylisoquinoline alkaloids with more than 800 entries	Indraprastha Institute of Information Technology	https://webs.iiitd.edu.in/raghava/biadb/index.html
DrugBank [35]	A database that combines chemical and pharmaceutical data with comprehensive drug target information. DrugBank contains more than 13.000 entries of which more than 130 are about nutraceutical molecules	Wishart Research Group	https://www.drugbank.ca
SuperNatural [36]	Freely available database of natural compounds with more than 300.000 entries	Charite University of Medicine	http://bioinf-applied.charite.de/supernatural_new/index.php
NPACT [37]	Curated database of plant derived natural compounds that exhibits anti-cancerous activity. Contains more than 1.500 entries	The Institute of Cytology and Preventive Oncology	https://webs.iiitd.edu.in/raghava/npact/index.html

Table 1 (continued)

Database	Description	Organization	Website access
TTD [38]	Therapeutic Target Database that provides information about the known therapeutic protein and nucleic acid targets and the corresponding drugs directed at each of these targets	Zhejiang University	http://db.idrblab.net/ttd/
PharmGKB [39]	A pharmacogenomics database that encompasses clinical information of drug molecules with more than 600 entries	PharmGKB	https://www.pharmgkb.org
SuperDrug [40]	Database that contains about 2500 3D-structures of active compounds of marketed drugs	Charite University of Medicine	http://cheminfo.charite.de/superdrug2/index.html

of nutraceuticals, cosmeceuticals, and functional foods are Quantitative Structure-Activity Relationship (QSAR) models.

QSAR methodology, proposed over one hundred years ago by Crum Brown, is based on the idea that there exists a relationship between a chemical structure and its activity [43]. QSAR development involves the generation of a mathematical model relating the chemical structure of a dataset of molecules with a specific physicochemical, chemical or biological property. The development of these models requires the previous characterization of the molecules using numerical descriptors and the subsequent application of different statistical and ML tools to generate the algorithms that relate these descriptors with the studied parameter. After the development and validation of a QSAR model, it can be employed as a prediction tool for the property/activity of new molecules with known chemical structures [44, 45]. Figure 2 illustrates a general workflow for constructing QSAR models, which starts with the curation of the dataset of molecules to be employed. Next, a series of molecular descriptors are calculated for this dataset yielding an $n \times m$ data matrix, where n is the number of molecules and m the number of descriptors. The data matrix is split in train and test sets and the model training is performed over the training set using different techniques to yield a predictive model. This model is subsequently validated using the test set (also known as the external validation procedure).

QSAR techniques may naturally be applied to the field of nutraceuticals, cosmeceuticals and functional foods to study the relationship between food components and a diversity of properties. Indeed this methodology has already been employed in several studies, allowing to translate experimental information on particular molecules into general knowledge on the corresponding biological or physicochemical mechanisms [46]. Here, the most relevant studies will be discussed.

The QSAR methodology has been employed to build multiple linear regression models for the antioxidant capacity of a series of flavonoids, hydrolyzates from various natural proteins (such as soybean or casein), tripeptides derived from β-lactoglobulin (β-LG), as well as peptides with sequences of up to 20 amino acids. Chemical structural interpretation of the flavonoid model revealed that the C-terminus is important for the antioxidant activity [47] and the bulky hydrophobic residues of this terminus were related to the antioxidant activity in three different free radical systems [48]. Moreover, the electronic and hydrogen-bonding properties of the amino acids in the sequences, as well as the steric properties at both terminus, were found to play an important role in the antioxidant activities of β-LG derived tripeptides [49].

QSAR models have been employed to evaluate some nutraceutical activities, such as the possible ACE inhibitory

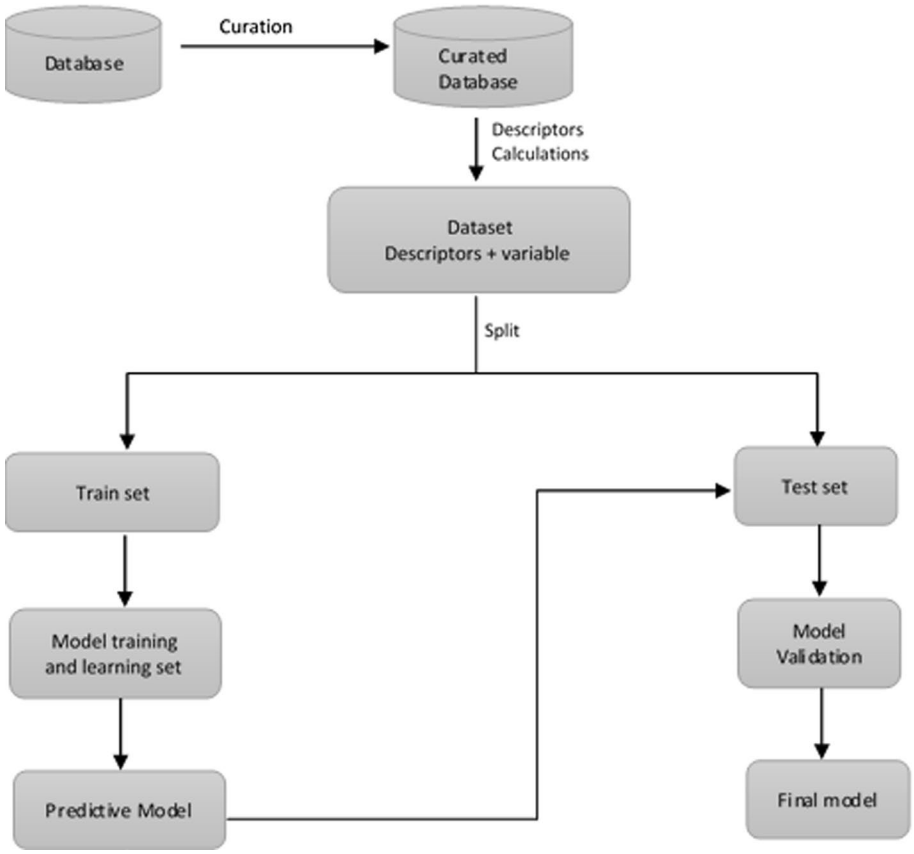

Fig. 2 QSAR general workflow

activity of food product components. To this end, models were developed for peptides obtained from plant derived inhibitors and posteriorly used for screening large libraries of peptides obtained from 15 major food commodities. Results showed that peptides from pork, beef and chicken, contained the highest number of potent inhibitory peptides, followed by proteins from egg, soybean and canola [50]. Specifically egg derived peptides were evaluated with the developed QSAR models to predict their ACE inhibitory activity. The obtained results revealed that eggs contained relatively large-chain peptides with this activity, some of them previously reported in the literature, which confirms the validity of the model [51]. Another QSAR model was developed with a dataset of milk-derived tripeptides with known ACE inhibitory activity. The built model (with an R^2 of 0.845) was used for the screening of different milk-derived tripeptides with possible ACE inhibitory activity. Four tripeptides were selected from the results as a promissory candidates for this activity and further studied with in vivo experiments, which validated two of the tripeptides (*i.e.* IVP and VIP) [52].

ML approaches have also been employed in building QSAR models to study the properties of nutraceuticals, cosmeceuticals and functional foods. The main goal for ML is to optimize the performance of a model given an objective function and training dataset. These prediction models help to guide decisions on chemical compound prioritization in drug discovery efforts, predicting toxicity, etc. [53].

ML techniques generally comprise three main paradigms depending in how models are created and trained.

a. In the case where the model is developed using both input (e.g., molecule descriptors) and output (e.g., IC_{50}) data, we refer to supervised learning. This is one of the most prominent paradigms and uses algorithms such as: support vector machine (SVM) which aims to identify the most optimum hyperplane that separates class instances, decision trees (DT)-employ a rule-based tree structure representation to label instances, or neural networks (NN) which aim to approximate underlying data relationship pattern through a process that mimics the functioning of the human brain, among others.
b. Contrary to this, if only input data is given then unsupervised learning is performed. ML algorithms attempt, in the context of unsupervised learning, to identify structure within the data (clustering) or reduce the dimensionality.
c. Finally, reinforcement learning is the part of ML that deals with decision-making, in which an agent learns good responses by modifying or acquiring new responses incrementally [54]. In this case, algorithms follow a sequential experience-driven learning para-

digm in that for each step (or state) a mapping to certain actions is performed to maximize the cumulative reward, without the need of labeled data [55, 56].

We will now briefly overview of the most relevant case studies on the use of ML in nutraceuticals, cosmeceutical and functional foods QSAR modeling.

In recent years, ML approaches have been employed to build classification models for identifying antioxidants and made available using web servers. Firstly, the SeqSVM, a sequence-based classification model for the antioxidant activity of proteins extracted from the Universal Protein Resource (Uniprot) was built using the SVM algorithm. This model yielded an overall accuracy of 89.46% [57]. A year later, the AOPs-SVM model, a classifier of antioxidant proteins was developed. For this model, a library was obtained from Uniprot and 473 discrete features were extracted to construct the model, using the 473D feature extraction algorithm [58], based on the PSI-BLAST [59] and PSI-PRED [60] profiles. The built model yielded an average accuracy value of 94.2% and thus improved the performance of the previously obtained SeqSVM classifier. The AOPs-SVM model has been made available via an online platform (http://server.malab.cn/AOPs-SVM/index.jsp) [61].

On the other hand, ML algorithms have also been employed to model the antihypertensive activity. Dietary habits are crucial in the regulation of blood pressure and hypertension. In this sense, nutraceuticals combined with the diet could help to enhance the antihypertensive effect [62]. An in silico platform for antihypertensive peptides of different length has been developed by Kumar et al. Different databases such as AHTPDB [63] with peptides derived from different foods such as milk, eggs or fish were used for this work. For small peptides, a regression model based on the SVM algorithm was developed, yielding an R^2 of 0.701 for dipeptides and 0.543 for tripeptides. In another study, classification models were built for tetrapeptides, pentapeptides, hexapeptides, medium peptides (7–12 aa's) and large peptides (> 12 aa's), and accuracy values of 76.67%, 72.04%, 77.39%, 82.61%, and 84.21%, were obtained, respectively. A web based platform was created for these models (http://crdd.osdd.net/raghava/ahtpin/) to help in predicting, screening and designing antihypertensive peptides with possible nutraceutical application [64]. Based on this study, another ML classification model was developed with the same dataset but, without considering the length of the peptides. This model yielded an accuracy of 84.73% and was subsequently implemented in a server, called PAAP (https://codes.bio/paap/) which allows to predict, screen or design peptides with antihypertensive activity [65].

ML approaches have been employed in the cosmetics field as well, particularly in finding anti-ageing compounds. A deep learning model was developed with a set of compounds with known antioxidant activity and subsequently employed to screen a database of natural compounds. A lead compound, called pep_RTE62G, was identified and subsequent in vitro and in vivo evaluations corroborated the in silico predictions, thus demonstrating the predictivity of the built model [66]. Furthermore, systemic toxicity of peptides employed in cosmeceutical products is a major concern. Models based on ML approaches using various properties of peptides in cosmeceutical field were developed for predicting their toxicity. The performance of dipeptide model was of 94.50% in terms of accuracy. Also, a hybrid model was developed combining the dipeptide model with information extracted on toxic motifs of peptides yielding an accuracy of approx. 90%. A webserver called ToxinPred (http://crdd.osdd.net/raghava/toxinpred/) has been developed with these models to facilitate the evaluation of the toxicity of peptides [67].

Molecular modelling (MM)

Molecular modelling comprises all theoretical and computational techniques employed to model or mimic the behavior of molecules in nature. These techniques are applied in diverse domains including drug discovery and development, computational chemistry, and materials science, among others, to study molecular systems of different sizes and complexity [68]. The MM techniques may be employed to elucidate reaction mechanisms and interaction modes involving molecular systems, and/or to predict macroscopic physicochemical, chemical or biological properties. These methods include mainly molecular docking and molecular dynamic simulations and are collectively denominated as structure-based computational methods. Each of these methods has proven to be useful in nutraceutical, cosmeceutical and functional food compounds research [69].

For these structure-based methods, good quality (high resolution) three-dimensional (3D) structures of molecules are deemed as a fundamental starting step for successful molecular modelling [70]. The most important techniques for obtaining these 3D structures are shown in Table 2.

Molecular docking

The goal of this technique is to predict the target-ligand binding affinity and possible binding modes, ultimately contributing to understanding molecular recognition process. Molecular docking includes structure-activity studies, finding potential leads by virtual screening, providing binding hypotheses and lead optimization [75]. Figure 3 shows an example of a docking pose of natural compound curcumin bonded to acetylcholinesterase, generated using Chimera [76].

Table 2 Main techniques for obtaining the 3D structure of macromolecules

Experimental	Technique	Definition
	X-Ray crystallography	One of the most used technique for structure determination of proteins and macromolecules. A purified sample at high concentration is crystallized and exposed to an x-ray beam. Those results can be processed allowing to obtain the 3D structure of the molecule [71]
	Nuclear Magnetic Resonance Spectroscopy	Analytical chemistry technique that reveals the atomic structure of macromolecules in highly concentrated solutions based on the fact that certain atomic nuclei (such as H, ^{13}C, ^{19}F, ^{23}Na, or ^{31}P) are intrinsically magnetic [72]. Provides unique information about dynamics and interactions but the determination of the atomic structure is restricted to small complexes
	Cryo-Electron Microscopy	Based on the imaging of frozen-hydrated molecules by electron microscopy. Allows obtaining molecular resolution but in recent studies atomic resolution has been achieved [73]
Computational	Homology modelling	Computational prediction method that allows to determine the protein 3D structure from its amino acid sequence based on 3D structure templates of proteins with similar sequences[74]

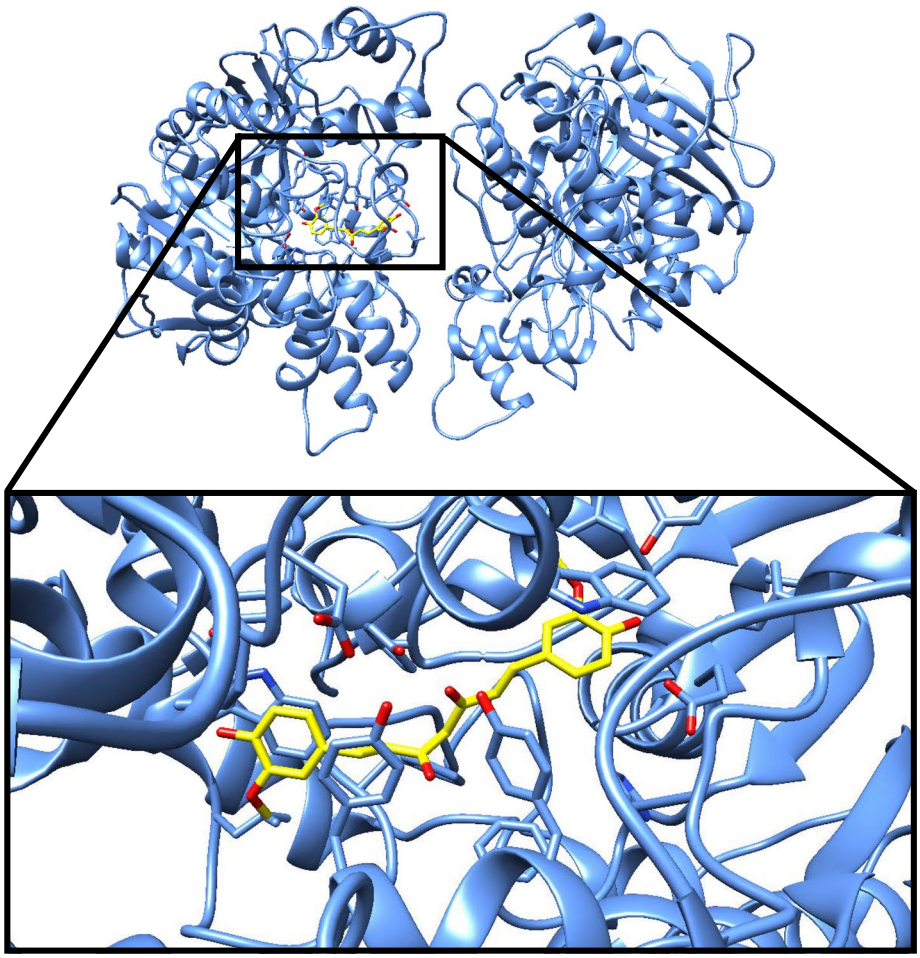

Fig. 3 Example of a docking pose result of the binding of curcumin in yellow with acetylcholinesterase(PDB ID: 6U3P) in blue

Molecular docking studies have been employed in the nutraceutical's field, providing information on the first steps of nutraceutical research prior to the in vitro studies. Various molecular docking tools have been developed to date, employing specific algorithms and for different purposes. Some of the most known tools are provided in Table 3. We provide herein a review of the most relevant applications of molecular docking in the evaluation of the possible health benefits of nutraceuticals.

The multidrug resistance-associated protein 2 (MRP2) is a transporter located in the membrane that acts as an important transporter of food product compounds with poor oral bioavailability. However, its mechanism of action is not well-known, and the corresponding crystal structure is yet to be solved. Fang et al. obtained the homology 3D structure

Table 3 Different molecular docking tools and their algorithms

Molecular Docking tool	Algorithm	Website
AutoDock [77]	Monte Carlo Simulated Annealing, Genetic Algorithm, and Lamarckian Genetic Algorithm	http://autodock.scripps.edu/
Gold [78]	Genetic Algorithm	https://www.ccdc.cam.ac.uk/solutions/csd-discovery/components/gold/
Glide [79]	In-house algorithm using different search criteria and refinement using the Monte Carlo method	https://www.schrodinger.com/products/glide
Haddock [80]	In-house algorithm that encodes information from identified or predicted protein interfaces in ambiguous interaction restraints to drive the docking process	https://wenmr.science.uu.nl/
PyDock [81]	Fast protocol which uses electrostatics and desolvation energy to score docking poses generated with FFT-based algorithms	https://life.bsc.es/pid/pydock/
SwissDock [82]	Based on the docking software EADock DSS	http://www.swissdock.ch/
Rosetta [83]	Monte Carlo based multi-scale docking algorithm	https://www.rosettacommons.org/software
DOCK [84]	Based in a Geometric Matching Algorithm	http://dock.compbio.ucsf.edu/
DockingServer [85]	Includes the PM6 semi-empirical method to AutoDock	https://www.dockingserver.com/web
Medusa Dock [86]	In-house algorithm using a stochastic rotamer library of ligands	https://dokhlab.med.psu.edu/cpi/#/MedusaDock

which was subsequently used in a docking experiment of different flavonoids to understand the selectivity of the transporter. This study allowed to separate the flavonoids two in groups: flavonoids that seem to interact with the transporter and those that seem to not interact with the transporter. Further studies will be necessary but this analysis brings greater insight on the chemical-structural profiles responsible for the differences in the flavonoids bioavailability [87].

Legume-derived peptides are known to have diverse benefits in the organism as they present antioxidant and anti-inflammatory properties [88]. Among these, lentil-derived peptides seem to play a dual role presenting both antioxidant and Angiotensin Converting Enzyme (ACE) inhibitory properties. P. García-Mora et al. carried out a study aimed at identifying lentil-derived peptides with dual antioxidant and ACE inhibitory activity, in order to propose them as ingredients for functional foods. After a gastrointestinal digestion simulation, the selected peptides (ligands) and two structures of somatic ACEs (receptors) were prepared with Maestro [89], and induced fit docking studies performed using the Glide 5.7 [79] and Prime 3.0. [90] modules available in the Schrödinger suite. The obtained results showed the possible dual activity of lentil-derived peptides which could guide subsequent in vitro studies to assess this activity [91].

Also, molecular docking studies of tetrapeptides from Atlantic salmon with possible ACE inhibitory activity were performed, with the aim of elucidating their binding modes and determine the corresponding binding energies. For this study, the CHARMM-based program (CDOCKER) was employed. Ten conformational models were obtained but only the best ones were selected for further analysis to identify the implicated residues and the best tetrapeptide conformation. This study showed that residue Glu376 of ACE might play an important role in the interactions with peptides. The IC_{50} value of two potent ACE inhibitory peptides, PGAR and IGPR, were calculated as 0.598 ± 0.12 and 0.43 ± 0.09 mmol L^{-1}, respectively. Although compared to the clinical hypertension drug lisinopril, both peptides showed lower ACE inhibitory activity, they still have potential for use in hypertension prevention [92].

Ursolic Acid (UA), a plant-derived nutraceutical compound, has been shown to regulate multiple proinflammatory transcription factors and inflammatory enzymes [93]. In a study aimed at identifying specific targets for this compound, the PharmMapper database was explored for potential targets [94] followed by molecular docking studies to select the most favorable ones, based on the corresponding scoring functions. An analysis of the interaction modes of the selected ursolic acid-target complexes allowed to identify the residues critical for the binding process. For this study, the Autodock [77] and MOE software were employed. The UA was observed to bind to Caspase 3 and the obtained results were used for posterior in vitro studies, which further validated this binding and allowed to hypothesize that the anti-inflammatory effect may be mediated by the MAPK signaling pathways [95].

Curcumin seems to have beneficial effects in Alzheimer, by inhibiting the formation of β-amyloid plaques related to this disease. This inhibition seems related to the interaction of curcumin with the acetylcholinesterase (AChE) receptor, which in turn affects the amyloid precursor protein. Molecular docking was employed by Sriraman et al. to evaluate the interaction between curcumin and eight different targets related to Alzheimer disease. The results revealed that that curcumin binds most favorably to AChE compared with the other studied targets [96].

Finally, molecular docking has been applied in the cosmetics sector, for example, to evaluate the possible interaction between tyrosinase and ginsenoside Re, a compound extracted from the roots of the ginseng plants. Tyrosinase plays an essential function in modulating the production of melanin, the primary protective barrier against ultraviolet damage and whose excessive production may result in severe skin ailments such as patches, ephelis and melasma [97]. The computational results of the performed docking study suggested that ginsenoside Re inhibits Tyrosinase and subsequent in vitro studies confirmed the predicted interaction profile. It was thus inferred that ginsenoside Re may be used as potential agent in cosmetics for the inhibition of melanogenesis [98].

Molecular dynamics (MD) simulation

This computational technique is employed to study the physical displacements of atoms and molecules based on Newtonian mechanics laws. To carry out MD simulations, molecular mechanics forcefields, defined as a set of equations that describe the dependence of the energy of a system on the coordinates of its particles and the interatomic potentials, are required [99, 100]. The impact of MD simulations in CAMD has grown dramatically in the last years. Using this technique, it is possible to predict the behavior of atoms in a molecular system over time based on a general model of the physics governing the inter-atomic interactions. These simulations could be very useful in studying important biomolecular processes such as ligand binding, protein folding or conformational changes. Also, such simulations can predict at an atomic level how these biomolecules will act with perturbations such as protonation, mutation or the addition or removal of ligands [101].

Food systems are complex and undergo lots of physical and chemical transformations during processing and storage. These transformations may be analyzed by MD simulations, providing key leads on the energetic and interaction profiles, as well as information on the conformational stability and/or preference [102].

MD simulations have been employed in the nutraceutical and cosmetical field to study the influence of pH and temperature on the corresponding chemical-biological profiles. For example, MD simulations have been employed to study the influence of temperature on the stability of gliadins, major antigenic wheat proteins reported to be responsible of food allergy and coeliac disease [103]. For this study, models of different gliadins were simulated at 25 ºC and 100 ºC until equilibrium was achieved, using the Gromacs platform [104]. This experiment showed that the exposure of linear epitopes and their location changed with temperature and this could affect the allergenicity of these proteins [105].

In another study, Stănciuc et al. applied MD simulations to explore how the conformational changes of β-LG, commonly used in the food industry due to its high nutritional value, contribute to its thermally induced behavior as a result of the chemical and/or physical processing in the food industry. For the MD simulation, the β-LG system was heated over a range of 30-90 ºC with equilibrations for every 10 ºC increment. The HyperChem software was employed for this study [106]. The obtained results indicated that at higher temperatures, β-LG structure was in a more flexible state that favored the hydrophobic exposure, allowing for a better understanding of the structure-function relationship [107]. Also, β-LG plays an important role as a carrier of flavonoids which could improve their bioavailability. The obtained results contributed to understanding the behavior of the studied complexes and how the ligands affect the conformational changes and the stability of β-LG, showing that quercitrin and rutin changed the conformation of β-LG, although the similarity of the atomic fluctuations profiles for β-LG and the β-LG –ligand complexes suggested that the structure of the ligand-binding site remained approximately rigid during the simulation [108].

MD simulations have been employed to study the solubility of nutraceutical and functional foods such as polyphenols, carbohydrates, or lipids. In this case, three polyphenols were employed to create different systems simulated using NAMD [91]. Hydration free energies were computed for each compound and the obtained results showed an exponential relationship between solubility and the hydration free energy [92]. Likewise, Zhang et al.sought to examine how the hydrothermal annealing treatment improves the low heat stability and crystal homogeneity of starch, particularly when mixed with other molecules [93]. Systems formed with cornstarch (CS) and fatty acids were simulated for 1 ns using Gromacs [104]. These results revealed that the total and potential energy were higher (in magnitude) for the lipids-CS complex when compared to CS alone, which led to the inference that more energy is necessary to damage the complex since it has more stability than CS alone [109].

MD simulations have also been employed to evaluate how the variation of the pH affects the physicochemical behavior of components in functional foods. For example, long chain fatty acids used as surfactants in the food industry may present varying aggregation behavior at different pH conditions. In a study by Benett et al. constant pH coarse-grained MD simulations were performed on systems of oleic acid (alone and in a bilayer) to assess the impact of different pH values using coarse-grained MD simulations. The following pH values were considered: 2.0, 5.5 and 9.0, respectively. The obtained results showed that the acidic behavior of oleic acid depend on the local chemical environment, observing an increment of the pK_a and a large degree of anticooperativity in small micelles [110].

Conclusion/ expert opinion

Nutraceuticals, cosmeceuticals and functional foods combined with healthy lifestyles could aid in the preservation of health and the reduction of the risk of developing chronic diseases. Moreover, some of the bioactive molecules could be useful to reinforce or complement existing pharmacological therapies, extending their use beyond food boundaries. Despite the potential health benefits of these products and the steady market growth, important challenges remain in this field. One of the main challenges is to prove the specificity of their action during the premarket approval, through the understanding of the mechanism of action of the active molecules in the organism, just as is the case for drugs in the pharmaceutical sector.

Computational techniques can help with these challenges, especially in the first steps, when there is not so much knowledge on the active component(s), the molecular target or mode of action. The inclusion of machine learning approaches in the development phases constitutes an important breakthrough for this field. Indeed, ML methods have contributed to the development and refinement of predictive models, as well as in accelerating molecular docking and molecular dynamics simulations. The implementation of these techniques in studies related to this field not only do they contribute to generating more knowledge at a molecular level, but also allow for the analysis of bigger sets of molecules, for example, in screening of dataset repositories to select those that could possibly present the studied activity for posterior in vitro and in vivo studies. The field of ML has grown exponentially in the recent years as well as its role in CAMD paradigms. This growth is accompanied with an improvement and sophistication of the methods that contribute to better and more precise predictions.

Computational techniques could also help to elucidate the mechanisms of action of molecules of interest by providing information on the binding modes of molecules with macromolecular targets. By means of structural approaches such as molecular dynamics, it is possible to predict not only the binding of two molecules, but also how they interact with time. Also, it is possible to predict how a system of molecules will evolve following changes in parameters such as temperature or pressure, and how these modifications can affect the studied molecules. This can be useful for quality control during the shelf-life analysis as well as to understand and improve the production processes of these products.

Nonetheless, the use of computational techniques in nutraceutical, cosmeceutical and functional foods is still at an early stage when compared to the pharmaceutical field. Also, these methods have some limitations that need to be addressed in order to increase not only their presence but also their functionality in the field. As a case in point, QSAR modelling is not well established for mixtures, which means that QSAR models mostly analyse independent components in mixtures and thus do not contemplate possible synergic or antagonist effects. Also, techniques as molecular docking and molecular dynamic simulation depend on having quality 3D structural models of the studied molecules (ligands, lipids, proteins) or analogues.

Computational approaches could contribute to making the approval process of these products more robust and consolidate the knowledge on their mode of action, thus helping to support the effectiveness and safety of the products that are launched on the market. Also, the limitations that these technologies seem to have when applied to foods may be viewed as future challenges to be solved and opportunities to improve the usefulness of computational approaches in a broader context.

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Declaration

Conflict of interest The authors declare no conflict of interest.

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