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Computational assessment of the toxicological profiles of various chemicals to which humans are exposed. A review

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Abstract. This study contains a brief description of the common computational methods used in the prediction of the toxicological effects of chemical substances, and a synthetic review of the literature on the results of computational studies on the prediction of the toxicological effects of substances to which humans are frequently exposed: food additives, food contaminants, cosmetic ingredients, drug-related compounds and pesticides. The advantages and limitations of using current computational toxicology in assessing the toxicity of chemicals are also discussed.

***Keywords*:** pharmacokinetics; ADMET profile; food additives; pesticides; drug-related compounds.

1. Introduction

Xenobiotic is a term used for a chemical of natural or synthetic origin to which an organism is exposed and which is extrinsic to the normal metabolism of that organism [1]. The term includes drugs, food additives, personal care products, pesticides, household products and industrial chemicals, all of which can affect both people and the environment, especially with prolonged exposure. It has been assessed that humans are exposed to 1-3 million xenobiotics in their lifetimes as xenobiotics enter the body through food, drug administration, air, drinking water and various consumer products [2]. This exposure can cause human health problems and should be studied in detail.

Due to the large number of chemicals to which humans are exposed, it is impossible for all these xenobiotics to be experimentally tested for their possible effects on human health. Furthermore, in the last years there was a constant pressure on scientists and regulatory agencies to avoid the animal testing of every chemical and the development of *in vitro* and *in silico* approaches has been encouraged and supported [3-5]. For example, the EU Cosmetics Regulation No. 1223/2009 excludes testing on animals for cosmetic products (http://data.europa.eu/eli/reg/2009/1223/oj - accessed 28.03.2024). It underlines that computational tools for predicting toxicity play an important role, new algorithms, new models and new versions of existing applications are constantly being made available and the confidence in the predictions obtained by computational means is constantly increasing.

The majority of available computational tools for pharmacokinetics prediction have been developed for datasets including mostly drugs or drug-like compounds, but they proved the ability to predict human toxicity for other classes of chemicals like degradation products of drugs carriers or / and implanted materials [6-9], steroids [10-13], food constituents and nutritional supplements [14-16], cosmetics and packaging ingredients [17-20], and pesticides [14, 21-23]. This is due to the overlap of the chemical space between cosmetics, drugs, and pesticides [17]. Furthermore, numerous molecular docking studies emphasize the adverse effects of xenobiotics on proteins involved in human physiology [19-27].

The aim of this study is to synthetize from the published data in the last 10 years the available information concerning the use of computational approach for predicting the pharmacological profiles of several classes of xenobiotics: food constituents and food contaminants, cosmetic ingredients, drug-related compounds such as steroids and degradation products of polymers used for medical applications, and pesticides. We do not consider in this study drugs and the bioactive compounds extracted from plants that are used in the pharmaceutical industry. In addition, a general review of the main computational tools that are available for online use to evaluate the toxicokinetics of xenobiotics is provided.

2. Methods

2.1. Pharmacological profile prediction tools

Adverse pharmacokinetic properties and/or unwanted toxicity are the main reasons for the failure of drug candidates in the clinical trial stage. Over the past decade, numerous computational tools have been developed to assess the absorption, distribution, metabolism, excretion and toxicity (ADMET) profiles of drug candidates and have also proven useful for predicting the toxicokinetics of other types of chemicals. Moreover, many such calculation tools have been made available online and have facilitated the studies in an efficient manner.

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A diversity of methods has been integrated in web servers allowing the accurate prediction of ADMET profiles based on rules considering the molecular properties and quantitative-structure activity relationship (QSAR) approaches based on artificial intelligence (AI) modeling: machine-learning (ML) and deep-learning (DL) methods [28, 29].

It is not the aim of this study to describe the computational tools used in predicting the ADMET profiles, but we mention several online servers allowing this type of predictions: SwissADME (http://www.swissadme.ch/) [30], admetSAR3.0 (http://lmmd.ecust.edu.cn/admetsar3/) [31-33], ADMETLab3.0 (https://admetlab3.scbdd.com/) [34-36], ProTox3.0 (https://comptox.charite.de/protox3/) [37, 38], FAF-Drugs4.0 (https://fafdrugs4.rpbs.univ-paris-diderot.fr/) [39-42], PreADMET (https://preadmet.webservice.bmdrc.org/adme/) [43].

2.2. Organ toxicity prediction tools

Chemical compounds may cause local and / or systemic effects and may have adverse effects in one or several human organs. Depending on the concentration and time of exposure, the adverse effects can be reversible or irreversible. Literature data concerning the use of drugs reveal that human adverse drug reactions are usually related to toxicities to liver, heart, and neurological organs [44]. Consequently, the use of computational methods for the evaluation of the organic toxicity potential of different types of chemical substances is of great interest nowadays, especially for the agrochemical, cosmetic, food, household products and pharmaceutical sectors, since computational approaches can be used both in the context of new product development and for regulatory purposes. Computational methods currently used to predict organ toxicity consist of biokinetic models, dose-response and time-response models, rule-based expert systems, read-across and QSAR [45]. These computational methods are especially used for predicting the main toxicological endpoints: carcinogenicity, cardiotoxicity, developmental toxicity, hepatotoxicity, mutagenicity, nephrotoxicity, and skin sensitization.

Beside several computational tools used for predicting ADMET profiles of chemicals that were already mentioned above, there are available others online tools allowing prediction of a single organ toxicity: CarcinoPred-EL (http://112.126.70.33/toxicity/CarcinoPred-EL/index.html) [46], PRED-hERG for predicting cardiotoxicity (http://predherg.labmol.com.br/) [47], ENDOCRINE DISRUPTOME for assessing developmental toxicity (http://endocrinedisruptome.ki.si/) [48], PredSkin3.0 for assessing skin sensitization potential (http://predskin.labmol.com.br/ [49].

2.3. Molecular docking

The effects of xenobiotics on the human body are the result of their interactions with the targeted cellular macromolecules. One of the methods that can be used to evaluate such interactions is molecular docking as this method is focusing on prediction of the binding mode(s) (BMs) of a ligand with a protein [50]. There are multiple computational tools that allow implementation of molecular docking, numerous of them being accessible online and facilitating the access of a wide audience including users that do not have access to computational power and generalizing the use of molecular docking beyond the molecular modeling community. A comprehensive list of docking web services added to databases and computer-aided drug design tools can be found on the Click2Drug server (http://www.click2drug.org/ - accessed 11.04.2024).

Specific literature is abundant in molecular docking studies that present the estimation of interactions of various types of xenobiotics with different molecular targets to assess possibly toxic effects. To highlight just a few examples, molecular docking studies have revealed the binding of several synthetic steroids and their analogs to the human androgen receptor and other nuclear and hormone receptors [10], to cytochromes involved in drug metabolism [11], and to liver polypeptides that transport organic anions [51]. Moreover, numerous molecular docking studies have highlighted the interactions of pesticides with various human proteins affecting their activity [22, 23, 27, 52-56]. Molecular docking studies also revealed the interactions of other xenobiotics with human proteins: (i) chito-oligosaccharides with plasma proteins [24] and lysozyme [26]; (ii) the food additive butylated hydroxytoluene with several molecular targets in the central nervous system [57]; (iii) di-iso-nonyl phthalate and its metabolites with sulfotransferases [20]; (iv) acyclic monoterpenes found in essential oils with human cytochromes [19], etc.

3. Toxicological profiles of various chemicals to which humans are exposed

3.1. Food constituents, food contact chemicals and cosmetics ingredients

The current food industry implies the use of food additives as chemical compounds that are sweeteners or contribute to preserve the flavor or enhance the taste. Food additives being controverted substances, the European Food Safety Authority (EFSA) established guidance documents concerning the evaluation toxicity of food additives (https://www.efsa.europa.eu/en/applications/food-improvement-agents/regulationsandguidance - accessed on 12.04.2024). A computational study considered adipic, alginic, ascorbic and guanylic acids and para-hydroxyethyl benzoate as food additives and reveled the possible toxicity of para-hydroxyethyl benzoate [14]. Furthermore, the same study revealed that among the investigated food additives used as sweeteners (amaranth, biphenyl, glycerol triacetate, saccharin sorbitol), the biphenyl was predicted as being toxic [14]. Another computational study considered the intensive sweeteners acesulfame K, aspartame, advantame, cyclamates, glycyrrhizin, neotame, neohesperidin dihydrochalcone, saccharin, sucralose, steviol and tagatose and predicted the ADMET properties of these compounds [15]. The obtained predictions showed that the advantame, glycyrrhizin and neohesperidin dihydrochalcone have h-ERG blocking potential, while

acesulfame K, cyclamates and saccharin can produce eye and skin damages, saccharin can produce hepatotoxicity, glycyrrhizin and steviol can lead to hypotension, and acesulfame K and sucralose have mutagenic and carcinogenic potential [15].

Molecular docking techniques revealed that butylated hydroxytoluene (BHT), a food additive commonly used as an antioxidant, binds strongly to several molecular targets in the central nervous system (serotonin 5-HT2C receptor, aminobutyric acid type A receptor, noradrenaline transporter, dopamine transporter) and these interactions lead to the observed side effect of BHT, anxiety and reduced heartbeat activity. ADME analysis also indicated that BHT is able to cross the blood-brain barrier [57].

Dantas and his coworkers (2022) predicted the ADMET profiles for *N*-acetyl-L-tyrosine, caffeine and 1,3,7,9-tetramethyluric acid as constituents of gymnastic and nutrition pre-workout supplements [16]. According to this study, each of the analyzed compound revealed a good bioavailability, did not present structural alerts for substances with promiscuous substrate behavior and / or substances with poor pharmacokinetic properties, did not inhibit the cytochromes (CYP) involved in xenobiotics metabolism, had not mutagenic properties and did not produce skin sensitization. Toxicity assessment indicated that N-acetyl-L-tyrosine and caffeine may cause human hepatotoxicity, caffeine demonstrated potential to produce cardiotoxicity and 1,3,7,9-tetramethyluric acid was able to produce drug induced liver injury [16].

Phthalates are the main chemicals in contact with food because they are used as plasticizers in food packaging containers. A computational study considered 25 of the most commonly used phthalates and revealed that they have good bioavailability and skin permeability, are able to interact with important molecular targets in human organisms (membrane receptors and transporters, kinases, phosphatases, cytochromes, factors of transcription) leading to harmful effects: skin and eye irritations, toxicity and irritations of the gastrointestinal and respiratory tracts, endocrine disorders, carcinogenicity. Among the investigated phthalates, di(2-ethylhexyl) phthalate revealed the highest number of toxic effects [18]. A molecular docking study showed that di-isononyl phthalate and its metabolites can cause liver damage, inhibit peroxisome proliferator-activated receptors and the activity of several members of the human sulfotransferase family 1 [20]. Arulanandam and colleagues (2022) used several computational tools to evaluate the toxicity of 14 phthalates and revealed that bisphenol F is mutagenic and that benzyl butyl phthalate, dibutyl phthalate, di-(2-ethylhexyl) phthalate, and dioctyl phthalate are predicted carcinogens [58].

Parabens (a general term for p-hydroxybenzoic acid esters), due to their low cost and to antibacterial and antifungal properties, are chemicals largely used as additives in cosmetics and personal care products, pharmaceuticals, agrochemicals and food industry. A computational study revealed that several parabens (butylparaben, ethylparaben, methylparaben, propylparaben) reveal good skin penetration, no mutagenic and carcinogenic effects, a weak potential of cardiotoxicity and are able to inhibit the human cytochromes involved in the metabolism of xenobiotics. Furthermore, they are able to penetrate the blood brain barrier and to affect the central nervous system [59].

Chalcone is an important scaffold within medicinal and cosmetic chemistry as its structure enables multiple modifications resulting in compounds with desirable bioactivity. One of its derivatives, 4-methoxychalcone is a known cosmetic ingredient considered an antioxidant, bleaching, and skin conditioning substance. *In silico* study of 4-methoxychalcone revealed its potential of skin sensitization and phototoxic potential [60].

Acyclic monoterpenes are constituents of essential oils used in cosmetic practices and it explains human exposure to these chemicals. A computational study focusing on several acyclic monoterpenes (citronellal, beta-myrcene, beta-ocimene, citrolellol, geranial, citronellyl acetate, geraniol, linalool, linalyl acetate) found in the common essential oils revealed that these chemicals are usually safe for humans, the identified side effects concerning the eye and skin irritation, skin-sensitization potential and respiratory toxicity [19].

3.2. Drug-related compounds

In this section we focus on steroids and their derivatives, chito-oligosaccharides and their derivatives, lactic acid oligomers and low molecular weight oligo-hydroxyalkanoates as degradation products of polymers used in biomedical applications (drug delivery systems, medical devices, implants, wound dressings, etc.).

Steroids and their derivatives are synthetic molecules derived from testosterone and are controlled substances in many countries around the world, but some athletes, amateurs and teenagers use steroids because they are interested in improving performance or body appearance. Computational studies regarding the side effects of such substances have revealed their good human intestinal absorption, dermal irritation and skin sensitization potential, the ability to inhibit the main cytochrome P450 enzymes involved in xenobiotic metabolism and the potential to induce endocrine disruption, reproductive toxicity, hepatotoxicity, respiratory toxicity, carcinogenicity, cardiovascular, hematotoxic, genitourinary effects, renal damage, and glomerular toxicity [11, 13, 51, 61, 62].

Chito-oligosaccharides result from the degradation of chitosan, a polymer that, due to its favorable properties, is widely used in biomedical applications [26]. The computational study showed that chito-oligosaccharides are potential inhibitors of the organic anion transporter peptides OATP1B1 and OATP1B3, they reveal a weak potential of producing cardiotoxicity and phospholipidosis, and a low probability of affecting the androgen receptor [8]. As for chito-oligosaccharide derivatives, they can produce acidosis, gastrointestinal toxicity and respiratory failure [6].

To the best of our knowledge, there is only one study dealing with ADMET profiles of low molecular weight oligomers ($\leq$ 32 units) of polyhydroxyalkanoates. The compounds that were considered in the computational study consisted of 3-hydroxybutyrate (3HB), 4-

hydroxybutyrate (4HB), 3-hydroxyvalerate (3HV), 4-hydroxyvalerate (4HV), 3-hydroxybutyrate-co-3-hydroxyvalerate (3HB-HV) and a hypothetical polyhydroxyalkanoate consisting of 4-hydroxybutyrate-co-4-hydroxyvalerate (4HB-HV). The result of the study showed that they can produce eye and skin irritation and corrosion, have antagonistic effect on the androgen receptor and inhibitory potential against the organic anion transporters OATP1B1 and OATP1B3 [9]. As for lactic acid oligomers, they can cause eye damage and hepatotoxicity, affect androgen and glucocorticoid receptors, and have a weak potential to inhibit the organic anion transporter peptides OATP1B1 and OATP1B3 [7].

3.3. Pesticides and their transformation products

Pesticides are chemicals widely used in private gardens, agricultural land and in some industries to kill various fungal, bacterial, plant and/or animal species, which means they are toxic by definition [63]. The toxicity of different types of pesticides has been considered in both experimental and computational approaches and various types of immediate and delayed human toxicity produced by these substances have been highlighted [64].

ADMET profiles of the pesticides aminopyralid, difenoconazole, drazoxolone, cetrimonium bromide, phenothrin, benzalkonium chloride and fosthiazate reveal their possible toxicity against humans. Among their effects we mention the inhibition of serine hydrolases [14]. A molecular docking study showed that chlorsulfuron (a herbicide) and difenoconazole (a fungicide) strongly inhibit human CYP2C8, CYP2C9 and CYP2C19 enzymes, with the fungicide showing higher binding affinity than the herbicide [27].

In a computational study, 608 herbicides were screened for assessing their endocrine disrupting potential and 252 herbicides showed high affinity with at-least three androgen receptors, the majority of the herbicides showed antagonist activity towards androgen receptor [65].

Prediction of ADMET profiles of several triazole fungicides (cyproconazole, metconazole, epoxiconazole, tebuconazole, flutriafol, paclobutrazol, tetraconazole, triadimenol and triticonazole) revealed that these fungicides demonstrate good oral bioavailability, are able to penetrate the blood-brain barrier, and interact with P-glycoprotein and with cytochromes. The toxicological targets considered for these fungicides are: skin sensitization potential, cardiotoxicity by blocking hERG K^+ channels, and endocrine disruption. Of the fungicides studied, triadimenol and epoxiconazole are predicted to have the highest probabilities of producing numerous harmful effects in humans [21].

The output of a computational study emphasized that epoxiconazole, flurprimidol and ancymidol were able to inhibit 11β-hydroxylase and aldosterone synthase, enzymes that catalyze the formation of cortisol and respectively aldosterone in the adrenal cortex and it can lead to osteoporosis, kidney disease, cardio-metabolic diseases, and immune-related disorders [66]. The outputs of another computational study regarding the transformation products of the pesticides boscalid, fenbuconazole, glyphosate and pyraclostrobin resulting from oxidative processes suggested that these compounds have carcinogenic potential and several of them are potential developmental toxicants [67]. Molecular docking studies revealed that the herbicide glyphosate is able to strongly interact with various molecular targets in human organism, all implicated in human diseases and illustrating the human toxicity of this herbicide [68, 69].

The *in silico* approach was used to predict and evaluate the binding interactions of 98 diphenyl ether pesticides and their metabolites with 10 thyroid hormone-related proteins. The results indicated that several pesticides (diclofop, difenopentene, ethoxyfen fluoroglycofen, rafoxanide) were able to interfere with proteins involved in thyroid hormone biosynthesis, blood transport, receptor binding and metabolism. The herbicide fluoroglycofen showed the strongest interaction with the thyroid hormone beta receptor [70].

Molecular docking and ADMET predictions were performed to investigate the binding properties and modes of action of 1, 1'-(2, 2, 2-trichloroethylidene) bis(4-chlorobenzene) (DDT) and its main derivatives l, l-dichloro-2, 2-bis(p,p-chlorophenylethane) (DDD) and l, l-dichloro-2, 2-bis(p,p-chlorophenylethylene) (DDE) against the human estrogen receptor and serine/threonine-protein kinase PIM-2. DDE and DDD have high binding affinity against both proteins. All the compounds show hepatotoxicity, neurotoxicity, and carcinogenic properties [71].

Molecular docking and interaction analysis, added to prediction of ADMET properties and the activity spectra of six derivatives of triazine (atraton, atrazine, prometon, secbumeton, terbuthylazine, trietazine) disclose the high binding affinity of triazine derivatives for the cancer proteins reflecting their carcinogenic potential and other different types of adverse effects: adrenal cortex hypoplasia, embryogenic effects, endocrine disruption, teratogenicity [72].

Several published studies have addressed the issue of the distinct biological activity of pesticide stereoisomers. Difenoconazole is a fungicide that is marketed as a mixture of four stereoisomers: (2R,4R)-, (2R,4S)-, (2S,4R)-, and (2S,4S)-difenoconazole. Predictions of ADMET profiles revealed several toxicological effects for all stereoisomers: hepatotoxicity, neurotoxicity, skin sensitization potential, mutagenicity, high plasma protein binding, cytochrome inhibition, potential to produce endocrine disrupting effects. Distinctive results were obtained for (2S,4S)-difenoconazole which exhibited reasonable probabilities of inducing cardiotoxicity and carcinogenicity, and of adversely affecting numerous nuclear receptors [23]. Triticonazole is another fungicide marketed as a racemate containing (R)- and (S)- isomers. Computational evaluation of the human toxicological effects of triticonazole stereoisomers showed that both stereoisomers were able to bind to human plasma proteins, produce cardiotoxicity and endocrine disorders and inhibit human cytochrome. The enantiomer (S)-TTZ exhibited higher interaction energies with human cytochromes. As distinct effects,

(R)-TTZ was estimated to cause skin sensitization, carcinogenicity and respiratory toxicity [22].

4. Discussion

The wide use of the food additives and food supplements, cosmetics and personal care products, drug-related products and pesticides highlights the need for toxicity testing of these chemicals. The information contained in this synthetic study is valuable especially for those exposed at workplaces where the investigated types of chemicals are produced and/or packed, as well as by everyone as a consumer of these chemicals. For pesticides, the information is also important for those who live near fields with agricultural crops or near parks where pesticides are used.

CAS REGISTRY contains over 127 000 000 unique organic and inorganic chemical compounds (https://www.cas.org/cas-data/cas-registry - accessed 20.04.2024) used for various purposes. Considering the large number of chemicals to which humans are exposed, assessing the human health risks of chemical exposures is a complex task, and some chemicals have never been tested for their effects on human health. However, there is a large amount of data on the biological activity and/or toxicity of chemicals, which allows the use of artificial intelligence to create predictive models of the potential toxicity of each chemical entity. This computational approach offers the advantage of being fast and cheap by comparison to experimental approaches, speeding up chemical screening and reducing animal testing. Furthermore, the use of predictive models for regulatory decision making is recognized by regulatory agencies.

There are also some limitations of the computational approaches used to predict toxicity: (i) they are limited to assessing the toxicity of chemicals that are similar to those used to develop the models; (ii) they usually do not take into account the concentrations of the investigated compounds; (iii) the way of contamination with chemicals is not always taken into consideration, the oral ingestion being usually assumed; (iv) simultaneous exposure of humans to several types of xenobiotics is not taken into account; (v) the results provided do not inform on the mechanistic interpretation of the toxicological effects.

5. Conclusions

The information presented in this synthetic study underlines that computational toxicology, by involving various computational techniques, is a promising tools for chemical toxicity evaluations as it can quickly predict the toxicity of a large number of chemicals during the risk assessment process and prioritizes theoretically hazardous compounds for experimental testing. Even if computational screening of chemical compounds proved to be applicable in safety assessment of chemicals, the limitations of this method emphasizes that the results should not be used in isolation and the combination of computational screening with experimental testing is required for an efficient safety assessment of chemicals.

Conflict of interest

The authors declare no conflict of interest.

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