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Elucidating the mechanism of action of mycotoxins through machine learning-driven QSAR models: Focus on lipid peroxidation

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ABSTRACT

Understanding the mechanisms of mycotoxin toxicity is crucial for establishing effective guidelines and preventive strategies. In this study, machine learning models based on quantitative structure-activity relationship (QSAR) were employed to predict the lipid peroxidation activity of mycotoxins. Two different algorithms using Linear Discriminant Analysis (LDA) and Artificial Neural Networks (ANNs) have been trained using a dataset of 70 mycotoxins. The LDA model had an average correct classification rate of 91%, while the ANN model achieved a perfect 100% classification rate. Following an internal validation process, the models were utilized to predict mycotoxins with known lipid peroxidation activity. The machine learning models achieved an 88% correct classification rate for these mycotoxins. Finally, by utilizing classified algorithms, the study aimed to infer the mechanism of action related to lipid peroxidation for 91 unstudied mycotoxins. These models provide a fast, accurate, and cost-effective means to assess the potential toxicity and mechanism of action of mycotoxins. The findings of this study contribute to a comprehensive understanding of mycotoxin toxicology and assist researchers and toxicologists in evaluating health risks associated with mycotoxin exposure and developing appropriate preventive strategies and potential therapeutic interventions to mitigate the effects of mycotoxins.

1. Introduction

Mycotoxins are secondary metabolites produced by filamentous fungi with potential toxic effects on cells and tissues. Mycotoxins are present in food and feed, representing a threat to human and animal health. As a consequence, different countries have adopted regulations to limit the overall mycotoxin dietary exposure, safeguarding the consumers and animal health (Manyes and Font, 2022). The estimation of mycotoxin occurrence in food crops around the world is nowadays up to 60–80% of the samples. Anyways, the impact of climate change on the higher incidence will increase the level of contamination in the future (Eskola et al., 2020).

Apart from the limited number of mycotoxins that have been regulated to date, there exists a wide range of additional mycotoxins, commonly known as "emerging mycotoxins," that can potentially contaminate both food and feed. However, due to the absence of a definitive consensus regarding their toxicity and underlying mechanisms of action, it remains challenging to establish suitable guidelines (Dellafiora et al., 2018). The toxicological effect of mycotoxins in humans and animals can be exerted by different mechanism of action such as DNA damage (Wang and Groopman, 1999), protein synthesis inhibition (Kiessling, 1986), enzyme inhibition (Balázs et al., 2023), immune system modulation (Surai and Mezes, 2005), hormonal disruption (Yang et al., 2020) and oxidative stress (Omar, 2013).

Achieving a comprehensive understanding of mycotoxin mechanisms of action requires an interdisciplinary approach, and computational methods can play a crucial role in supporting the scientific community in this endeavor (Dellafiora et al., 2018). In the present study, machine learning (ML) quantitative structure–activity relationship (QSAR) models have been developed to predict the lipid peroxidation activity of mycotoxins. Lipid peroxidation is a damaging process caused by free radicals that affects cell membranes, leading to various harmful effects on cells and tissues. It disrupts membrane integrity and function, causing issues with nutrient transport, signaling, and enzyme

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activities (Catalá and Diaz, 2016). This process generates reactive lipid peroxidation products that can further damage cellular components, including proteins, DNA, and other molecules (Repetto et al., 2012). Prolonged or excessive lipid peroxidation is associated with oxidative stress, inflammation, mitochondrial dysfunction, and cell death, and it has been implicated in neurodegenerative diseases, cardiovascular diseases, liver damage, cancer, and aging (Leyane et al., 2022). In this context, predicting whether a mycotoxin will induce lipid peroxidation is highly relevant because, as reported, lipid peroxidation is a key mechanism through which mycotoxins can cause cellular damage and contribute to various adverse health effects.

The present computational study focuses on analyzing the chemical structure of mycotoxins through a molecular topology-based approach (Zanni et al., 2015, 2022), by studying the connectivity between atoms in a molecule by applying graph theory. In Fig. 1, we can see an example of how the chemical structure of a mycotoxin can be represented as a graph. Molecular graphs are constructed where atoms are depicted as vertices, and chemical bonds are represented as edges. Once the molecular graph of the mycotoxin is created, the adjacency matrix is constructed by assigning a value of 1 to atoms (i, j) if there is a link between them (i and j), and 0 otherwise.

Finally, by manipulating different types of matrices it is possible to compute different molecular descriptors encoding different chemo-mathematical information regarding molecules. These descriptors when derived from a topological or adjacency matrix (as example in Fig. 1), are called topological descriptors. These descriptors are independent of the molecule's conformation, eliminating the need for conformational analysis, geometric optimization, or orientation considerations. Molecular topology descriptors have found wide application in correlating and predicting various molecular properties (Galvez-Llompart et al., 2022; Galvez et al., 2021). These descriptors are the key basis for QSAR studies based on Molecular Topology, a methodology focused on establishing a relationship between a chemical structure (encode with molecular descriptors) and biological or physical-chemical properties.

Here, we sought to develop two ML models through the application of linear discriminant analysis (LDA) and artificial neural networks (ANNs). The employ of *in silico* methods to predict the lipid peroxidation activity of mycotoxins represent a fast, accurate and cost-effective method to predict whether a specific mycotoxin can induce lipid peroxidation. In turn, this ML-based tool could help researchers and toxicologists to evaluate the health risks associated with mycotoxin exposure and develop appropriate preventive strategies to identify potential therapeutic interventions to mitigate the effects of mycotoxins.

2. Material and methods

The main goal of the present study is the development of computational models capable to predict whether a mycotoxin will exert harmful effects through lipid peroxidation. A quantitative method for classifying mycotoxins based on their ability to induce lipid peroxidation is provided, thereby improving scientific understanding of their biological activities.

In order to create ML QSAR models utilizing Molecular Topology to predict the lipid peroxidation activity of mycotoxins, a stepwise workflow was implemented, as depicted in Fig. 2.

2.1. Data set compilation

The initial step of the computational approach involved the construction of a comprehensive database of mycotoxins, utilizing information sourced from freely accessible open databases (Habauzit, 2022; Renau and & Sumarah, 2018). Following data collection, an extensive analysis was conducted to differentiate between genuine mycotoxins and secondary metabolites, resulting in a refined database comprising 277 molecules. Additionally, a literature search was performed to ascertain whether lipid peroxidation activity had been reported for these 277 mycotoxins. As a result, a final database of 112 mycotoxins with documented lipid peroxidation activity was identified, while no information regarding the lipid peroxidation activity was found for the remaining 165 mycotoxins.

2.2. Molecular descriptors calculation

Starting from the 2D chemical structure of our database of mycotoxins, it is possible to calculate thousands of molecular descriptors by employing the open-source Python library Mordred (Moriwaki et al., 2018). Mordred allows the calculation of different types of 2D molecular descriptors such as constitutional (capture the molecular composition and connectivity), topological (characterize the structural topology of a molecule), electronic and geometrical (provide information about electronic and geometric properties of a molecule) and

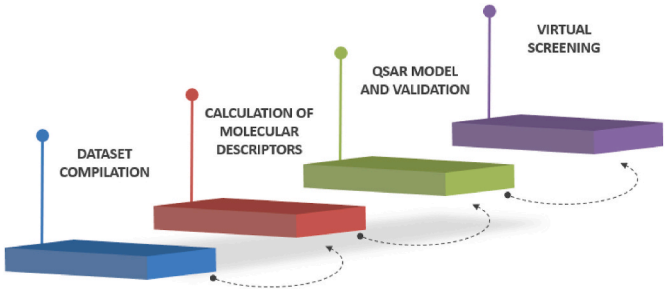

Fig. 2. Research workflow followed to determine the chemo-mathematical pattern of mycotoxins with lipid peroxidation activity through ML QSAR models based in Molecular Topology.

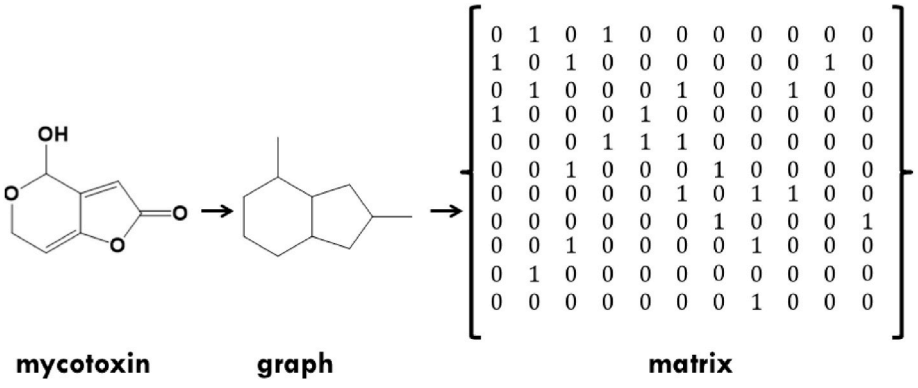

Fig. 1. Example of the conversion process from Patulin mycotoxin to a graph representation, followed by the construction of an adjacency matrix.

hybridization-based descriptors (takes into account the hybridization states of atoms in a molecule).

3. Machine learning techniques

For the creation of the algorithms, two different ML techniques have been employed: LDA and classification ANN. Both statistical techniques will yield a qualitative prediction by categorizing mycotoxins into two distinct groups based on whether they are likely to induce lipid peroxidation or not.

From the overall number of mycotoxins with reported lipid peroxidation activity results in the literature (112 mycotoxins), a group of 42 mycotoxins has been left out of the training set to guarantee the structural chemical diversity of the data set, i.e., so that a specific chemical scaffold is not overrepresented when training the QSAR models.

The ML-QSAR models were developed using 70 mycotoxins (61 inducing LP and 9 mycotoxins that do not induce LP).

3.1. Linear discriminant analysis

LDA aims to establish a linear combination of variables to discriminate between different categories or objects (Hussain and Uraibi, 2023). In the present study, LDA is applied to differentiate between mycotoxins with potential to cause lipid peroxidation from those with none.

The discriminant function is represented as:

$$DF = A_0 + \Sigma A_i X_i$$

where DF is the discriminant score, A_o is the intercept term, A_i is the coefficient and X_i represents the molecular descriptors (predictor variables). The first stage of the LDA is the training phase of the models, in which the optimal combination of descriptors and coefficients to maximize the separation between different classes or groups in the data is searched. In our study, mycotoxins with and without reported lipid peroxidation activity.

The selection of the molecular descriptors was performed by using the forward stepwise method based on p-value criteria, this procedure is centered on iteratively adding descriptors to the model based on their statistical significance as determined by the p-value (0.05). The quality of the discriminant function is assessed using Wilks' statistic (λ), this parameter ranges from 0 to 1, with a smaller value indicating a better prediction model (Hussain and Uraibi, 2023). Finally, the model' discriminating significance is determined by the F value or Fisher-Snedecor parameter (Agresti, 2023). The highest the F value the more substantial separation between the classes, whereas the lowest the F value the less statistically significant will be the discrimination achieved by the model. The total amount of the data available for training the model was employed in the construction of the discriminant function.

3.2. Artificial neural network

An ANN is an information-processing approach that draws inspiration from the functioning of biological nervous systems. ANNs are powerful and flexible neural network architectures that can learn complex linear and non-linear relationships in data.

In the present study, both Multilayer Perceptron (MLP) and Radial Basis Function (RBF) ANN algorithms were employed. The typical architecture of these ANN is characterized by three or more layers, namely: the input layer, hidden layer(s), and output layer, comprised of interconnected neurons. The input layer receives data from input files (molecular descriptors in our study), while the output layer transmits information to the external world (classification of mycotoxins in two different groups: those that exert lipid peroxidation and those that do not). Hidden layers, positioned between the input and output layers, may comprise numerous interconnected neurons (Haykin and Network, 2004; Montazer et al., 2018).

MLP ANN is a type of feedforward neural network that consists of multiple layers of artificial neurons or nodes. Commonly used activation functions include identity, sigmoid, hyperbolic tangent, and negative exponential, whereas RBF (Radial Basis Function) ANN, utilizes radial basis functions (Gaussian functions and sigmoid functions) as activation functions in its hidden layer. In supervised ANN models, a training set with known outputs is utilized to train the network by assigning weights to each neuron (Bishop, 1995).

In this study, we employed Gradient descent and Broyden-Fletcher-Goldfarb-Shanno (BFGS) algorithms to train the ANNs. The input layer of our ANNs is formed by the top relevant descriptors previously selected by forward stepwise method based on p-value criteria. The ANN was trained with 80% of the dataset (train set), while the remaining 20% was randomly set aside for internal test set validation.

3.3. Models' validation

In order to check a reasonable estimate of the model's performance of the LDA model, an internal validation technique following the leave-some-out (LSO) approach has been performed. In LSO internal validation procedure, after selecting a subset or a fixed number of data points to leave out as the validation set, it's processed to train the model on the remaining data points and finally, it is evaluated the trained model's performance on the left-out validation set. This procedure repeats several times with different combinations of left-out data points each time. The performance metrics are then averaged across the iterations to obtain an overall estimation of the model's performance (Wong, 2015; Schaffer, 1993).

3.4. Biological distribution diagram

A Biological Distribution Diagram (BDD) is a graphical representation that provides an easy way to visualize DF intervals, showing the areas of minimal overlap between mycotoxins with and without lipid peroxidation activity (Gálvez et al., 1996). In fact, BDD is a frequency distribution plot of the dependent variable, where the ordinate represents the expectation (probability of activity) and the abscissa represents the interval of DF values. For any range of values for a given function, "activity expectation" can be defined as $Ea = a/(i + 1)$, where "a" is the number of active compounds in the range divided by the total number of active compounds, and "i" is The number of idle connections in the interval divided by the total number of idle connections. The expectation of inactivity is defined symmetrically as $Ei = i/(a + 1)$. In our case, active mycotoxins will be those with lipid peroxidation activity whereas inactive ones, those without this activity. These graphs make it easy to visualize time intervals with the greatest probability of discovering compounds with specific biological activity. For a given equation, one can immediately identify the region of minimal overlap between Ea and Ei, thus deciding whether the equation under study can be used for molecule selection or design (virtual screening).

3.5. ROC curve

The ROC (Receiver Operating Characteristic) curve is a graphical representation of the performance of a binary classification model, such as a classification neural network analysis. It is commonly used to assess the model's ability to discriminate between two classes by plotting the true positive rate (sensitivity) against the false positive rate (1 - specificity) at various classification thresholds. The ROC curve provides a visual representation of the trade-off between the true positive rate and the false positive rate. A better-performing model will have a ROC curve that is closer to the top-left corner of the plot, indicating higher sensitivity and lower false positive rate across various thresholds. The area under the ROC curve (AUC-ROC) is often used as a summary measure of the model's performance, with a value of 1 indicating a perfect classifier

and 0.5 indicating a random classifier (Carter et al., 2016).

4. Results and discussion

As mentioned before, the present study reports the development of ML QSAR models capable of predicting whether a mycotoxin could exert a harmful effect through lipid peroxidation. The models were trained with 70 mycotoxins for which information regarding lipid peroxidation was available from the literature.

For the creation of the two algorithms, we employed two different statistical techniques: LDA and classification ANN. Both techniques will give us a qualitative prediction, that is, they will classify into two different groups the mycotoxins, according to their capacity to perform lipid peroxidation.

5. Linear discriminant analysis

5.1. QSAR model and validation

In order to obtain the discriminant function (DF), LDA was applied to a training set comprised of 70 mycotoxins distributed in two categories: 61 causing lipid peroxidation (LP group) and 9 mycotoxins not causing lipid peroxidation (No LP group) (see Table 1).

The discriminant function and statistical parameter of the LDA model are:

$$\mathbf{DF} = (-0{,}832 \times \text{VSA\_EState7}) - (4804 \times \text{piPC7}) + (4724 \times \text{piPC8}) + (2736 \times \text{n6HRing}) - (304{,}057 \times \text{JGI7}) + 5885 \quad \text{Equation 1}$$

$$N = 70 \text{ Wilks' Lambda} = 0.523 \; F = 11.685 \; p < 0.00001$$

where N = number of data compounds; λ = Wilks'lambda; F= Fisher−Snedecor parameter; p = p-value.

The discriminant function is composed of five different types of molecular descriptors: constitutional descriptors, such as n6HRing (6-membered hetero ring count); topological descriptors such as piPC7 (7-ordered pi-path count (log scale)) and piPC8 (8-ordered pi-path count (log scale)); variable sphere excluded volume (VSA) descriptor such as VSA_EState7 (VSA EState Descriptor 7 ($6.07 \leq x < 6.45$)) and topological charge descriptors such as JGI7 (7-ordered mean topological charge).

Table 1 outlines the results of the prediction obtained for every compound of the train set.

From the LDA model, a mycotoxin will be classified as causing lipid peroxidation if gets a DF value > 0 whereas a mycotoxin will be classified as non-causing lipid peroxidation if DF < 0. The classification matrix for DF (Table 2) is very significant for the training set: 93,44% of correct classification for the LP group in DF, i.e., 57 of 61 compounds, were correctly classified as mycotoxins causing lipid peroxidation, whereas 8 out of 9 were correct classified (88,88%) in the group of mycotoxins not causing lipidic peroxidation (No LP).

To assess the stability of the model, the LSO technique was employed. In this approach, 20% of the compounds were randomly removed from the train set (serving as an internal test set), and then the model was trained using the remaining mycotoxins (80% of the data set). The test set is classified using the new algorithm, and this process was repeated five times to ensure reliability. Table 2 shows the values of λ and the classification matrix for compounds in both training and test sets series. The variability of λ is little for each subset, and the average, after five trials following the procedure described in Materials and Methods ($\lambda = 0.570$), is similar to that obtained with the selected model ($\lambda = 0.523$). Moreover, the LSO average percentage of correct classification is similar to that obtained with the LDA model (93% and 89% for the train set and 94% and 86% for the internal test set, respectively).

5.2. Biological distribution diagram

Fig. 3 shows the biological distribution diagram (BDD) obtained for

Table 1
Classification of mycotoxins (training set) based on their LP activity using the LDA model.

Mycotoxin	CID	DF	Class.	C.L.
Mycotoxins with lipid peroxidation activity[a]				
3-Acetyldeoxynivalenol	5458510	3.717	LP	0.976
3-Nitropropionic Acid	1678	6.214	LP	0.998
Aflatoxin B1	186907	2.691	LP	0.936
Aflatoxin G2	2724362	7.853	LP	1.000
Aflatoxin G2A	105095	8.172	LP	1.000
Alamethicin	16132042	1.430	LP	0.806
Alpha-Amanitin	2100	6.075	LP	0.998
Altenuene	34687	3.754	LP	0.977
Alternariol	5359485	0.607	LP	0.646
Alternariol Methyl Ether	5360741	4.162	LP	0.985
Altersolanol A	89644	3.973	LP	0.981
Altertoxin I	104860	4.544	LP	0.989
Antimycin A2	3084471	−0.144	NO LP	0.537
Antimycin A3	245869	1.831	LP	0.862
Antimycin A4	3084472	1.493	LP	0.816
Aurofusarin	99586	7.890	LP	1.000
Beauvericin	3007984	5.407	LP	0.996
Citrinin	54680783	0.169	LP	0.542
Cladosporin	13990016	3.268	LP	0.963
Culmorin	115285	1.665	LP	0.841
Deoxybostrycin	193579	0.540	LP	0.631
Deoxynivalenol	40024	6.465	LP	0.998
Diacetoxyscirpenol	15571694	1.145	LP	0.758
Dihydromethylsterigmatocystin	5280636	6.048	LP	0.998
DON-10-Gamma-Glutamylcysteine	146026615	6.736	LP	0.999
DON-10-Glutathione	146026618	7.322	LP	0.999
DON-10-Isoleucine	146026614	4.431	LP	0.988
DON-10-Phenylalanine	146026623	6.133	LP	0.998
DON-10-Tyrosine	146026625	6.178	LP	0.998
DON-13-S-Cysteine	146026622	6.559	LP	0.999
DON-15-Penicillin G	146026627	6.251	LP	0.998
DON-15-Sulfate	101899453	2.760	LP	0.940
DON-Sulfonate 3	146026608	8.433	LP	1.000
Enniatin A	57339252	2.857	LP	0.946
Enniatin A1	57339253	3.386	LP	0.967
Enniatin B	164754	4.456	LP	0.988
Enniatin B1	11262300	3.919	LP	0.980
Fumonisin B1	2733487	4.840	LP	0.992
Fumonisin B2	2733489	1.714	LP	0.847
Fumonisin Py2	137628394	2.734	LP	0.939
Fumonisin Py4	137628494	−0.378	NO LP	0.594
Gliotoxin	6223	7.154	LP	0.999
HT-2 Toxin	10093830	4.406	LP	0.988
Macrosporin	159926	1.508	LP	0.818
Moniliformin	40452	5.885	LP	0.997
Neosolaniol	426719	3.784	LP	0.978
Nivalenol	5284433	9.551	LP	1.000
Ochratoxin A	442530	3.506	LP	0.971
O-Methylsterigmatocystin	104940	3.690	LP	0.976
Patulin	4696	7.228	LP	0.999
Paxilline	105008	0.916	LP	0.713
Penicillic Acid	1268111	5.298	LP	0.995
Penitrem A	6610243	2.648	LP	0.934
Satratoxin H	5477707	0.450	LP	0.610
Sterigmatocystin	5280389	3.818	LP	0.978
T-2 Toxin	5284461	4.358	LP	0.987
T2 Toxin Triol	13797589	5.115	LP	0.994
Tentoxin	5281143	−0.069	NO LP	0.518
TR 2 Toxin	100721	8.146	LP	1.000
Trichothecene	21117948	1.305	LP	0.786
Zearalenone	5281576	−4.416	NO LP	0.988
Mycotoxins Without Lipid Peroxidation Activity[b]				
Curvularin	296197	−2.990	NO LP	0.952
Cytochalasin A	5458383	−4.847	NO LP	0.992
Cytochalasin C	53229983	−2.726	NO LP	0.939
Cytochalasin E	5458385	−3.435	NO LP	0.969
Cytochalasin J	3555370	−4.497	NO LP	0.989
Emodin	3220	−2.185	NO LP	0.899
Kojic Acid	3840	−10.023	NO LP	1.000
Myriocin	6438394	−7.041	NO LP	0.999
Pseurotin A	9845622	2.148	LP	0.895

CID: compound identifier (from Pubchem); DF: discriminant function; Class.: classification; LP: lipid peroxidation; C.L.: confidence level.

Scientific papers discussing the mycotoxins' impact on lipid peroxidation activity.

[a] . (Pierzgalski et al., 2021; Pérez-De La Cruz et al., 2006; Shen et al., 1994; Verma and Mathuria, 2008; Zeidler et al., 1996; Zheleva et al., 2007; Chung, 2012; Fernández-Blanco et al., 2014; Zhang and Dong, 1986; Haraguchi et al., 1996; Del Favero et al., 2020; Batjuka et al., 2017; Tani et al., 2003; Huang et al., 2005; Dvorska et al., 2002; Mallebrera et al., 2015; Kumar et al., 2017; Peever et al., 1989; Kamle et al., 2022; Wang et al., 2018; Liu et al., 2023; Sivakumar et al., 2001; Wang et al., 2020; Prosperini et al., 2013; Yin et al., 1998; Chen et al., 2023; Kövesi et al., 2020; Kang and Suh, 2022; Reams, 1995; Xue et al., 2020; Cheat et al., 2015; Omar et al., 1990; Jahanshiri et al., 2015; Ramalingam et al., 2019; Steinle et al., 2011; Stoev et al., 2004; Goda et al., 2016; Nusuetrong et al., 2008; Rizzo et al., 1994; Novacky, 1991; Karppanen et al., 1989; Yang et al., 2018).

[b] . (Dong et al., 2014; Chapla et al., 2018; Xia et al., 2019; Wang et al., 2023; Ottaviano et al., 2020; Chen et al., 2019).

Table 2
Classification matrix obtained from DF and internal validation analysis (LSO).

Set	λ	F	p-value	Percentage of correct classification			
				Train		Internal test (LSO)	
				LP	No LP	LP	No LP
LDA model (DF)	0.523	11.685	0.00001	93	89	–	–
LSO1 (DF)	0.541	8.499	0.00001	94	86	100	100
LSO2 (DF)	0.644	6.079	0.00020	96	86	92	50
LSO3 (DF)	0.525	9.043	0.00001	94	86	92	100
LSO4 (DF)	0.602	7.285	0.00001	93	86	100	50
LSO5 (DF)	0.537	8.635	0.00001	94	86	92	100
LSO Average (DF)	0.570	7.908	0.00005	94	86	95	80

λ: Wilk's lambda; F: Fisher–Snedecor parameter; LDA: linear discriminant analysis; LP: lipid peroxidation; LSO: leave-some-out.

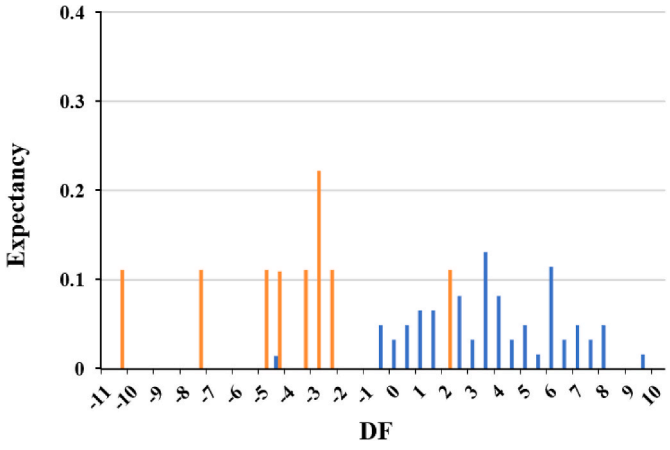

Fig. 3. Biological distribution diagram for mycotoxins with and without lipid peroxidation activity obtained using the discrimination function (DF). (The blue colour represents mycotoxins with lipid peroxidation activity and the orange colour, mycotoxins without lipid peroxidation activity).

DF model. In this figure, we can observe the distribution of mycotoxins from the training set in terms of DF value, with those causing lipid peroxidation shown in blue color and those that do not in orange color. In general terms, we have the highest expectancy of finding mycotoxins with lipid peroxidation activity when mycotoxins adopt DF values greater than 0, whereas the highest expectancy of finding mycotoxins without lipid peroxidation is expected for mycotoxins with DF values lower than 0.

5.3. Chemo-mathematical pattern related to mycotoxins lipid peroxidation activity

DF descriptors give key information regarding the chemo-mathematical pattern related to mycotoxins lipid peroxidation activity. According to equation (1), there are two descriptors directly linked to lipid peroxidation activity, namely piPC8 and n6HRing. The other three descriptors (VSA_Estate7, piPC7 and JGI7) establish an indirect relationship with the property understudy, i.e., lipid peroxidation.

From these descriptors n6HRing, i.e., the 6-membered hetero ring count molecular descriptor has a straightforward interpretation. This index represents the number of 6-membered rings containing at least one heteroatom (an atom other than carbon) in a molecule.

The model emphasizes the significance of 6-membered rings containing at least one heteroatom in mycotoxins structure for the development of lipid peroxidation activity. This is supported by the observation that 59% of mycotoxins exhibiting lipid peroxidation have 6-membered rings with at least one heteroatom, whereas only 11% of mycotoxins lacking lipid peroxidation activity possess such rings. Although the presence of these specific rings with heteroatoms is not the sole determinant of the chemo-mathematical pattern associated with mycotoxins causing lipid peroxidation, it is met by 6 out of 10 mycotoxins complying with this criterion. An example of n6HRing descriptor value for two mycotoxins with and without lipid peroxidation activity (Aurofusarin and Myriocin, respectively) from the training set can be seen in Fig. 4.

In addition, electrostatic distribution (VSA_Estate7), presence of sp2-hybridized carbon atoms at topological distances 7 and 8, respectively (piPC7 and piPC8), and the amount of charge transferred between atoms located at a topological distance of 7 (JGI7) are determinant in defining the chemo-mathematical pattern of mycotoxins with lipid peroxidation activity.

6. Artificial neuronal network

The LDA model employs linear functions to determine the relationship between the chemical structure of mycotoxins and lipid peroxidation activity. On the other hand, the ANN classification model enables the incorporation of non-linear functions to establish correlations between mycotoxins and the specific property being studied.

Table 3 shows the relevant information regarding the classification ANN trained. The architecture of the ANN (Fig. 5) is MLP type, defined by 5 input layers (one for each molecular descriptor, same descriptors used in the LDA model), 3 hidden layers, and two out layers (represents categorical output LP = lipid peroxidation activity and No LP = no lipid peroxidation activity).

The ANN trained is able to correctly classify the totality of mycotoxins from training set and 93 % of mycotoxins from internal test set. Therefore, good results were found employing a logistic activation function for the hidden layer and maintaining the identity function as the output layer activation function. A BFGS (Broyden-Fletcher-Goldfarb-Shanno) algorithm was used to train this network.

In Table 4, it can be seen how the algorithm classifies mycotoxins from both training and internal test set as either having lipid peroxidation activity (LP) or not having lipid peroxidation activity (no LP). The classification is accompanied by a confidence level that is associated with the algorithm's prediction.

Fig. 6 shows the ROC curve for the ANN classification model. This graphical representation illustrates the relationship between the true positive rate (sensitivity) and the false positive rate (1-specificity) at various threshold settings, allowing the evaluation of the ANN model's ability to discriminate between mycotoxins with and without lipid peroxidation activity.

The area under the curve for train (AUC = 1) and internal test set (AUC = 0.91) indicates that the model is both accurate and robust, showing great discrimination between the classes.

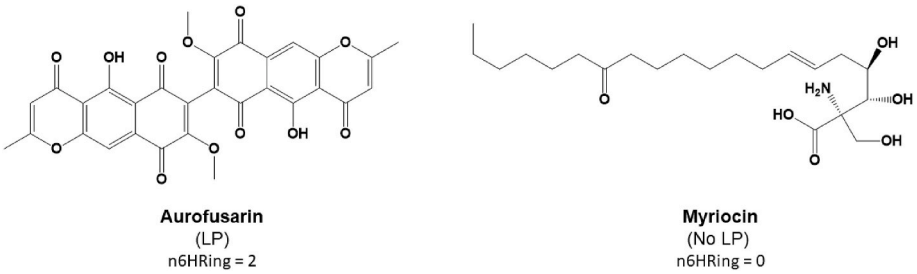

Fig. 4. Example of n6HRing descriptor value for different mycotoxins of the training set (LP: lipid peroxidation).

Table 3
Information about the ANN model created to classify mycotoxins based on their lipid peroxidation activity.

Class. ANN	Training perf. (%)	Test perf. (%)	Training algorithm	Error function	Hidden activation	Output activation
MLP 5-3-2	100	93	BFGS 42	SOS	Logistic	Identity

ANN: Artificial Neural Networks; Perf.: performance; MLP: Multilayer Perceptron; BFGS: Broyden-Fletcher-Goldfarb-Shanno; SOS: sum-of-squares.

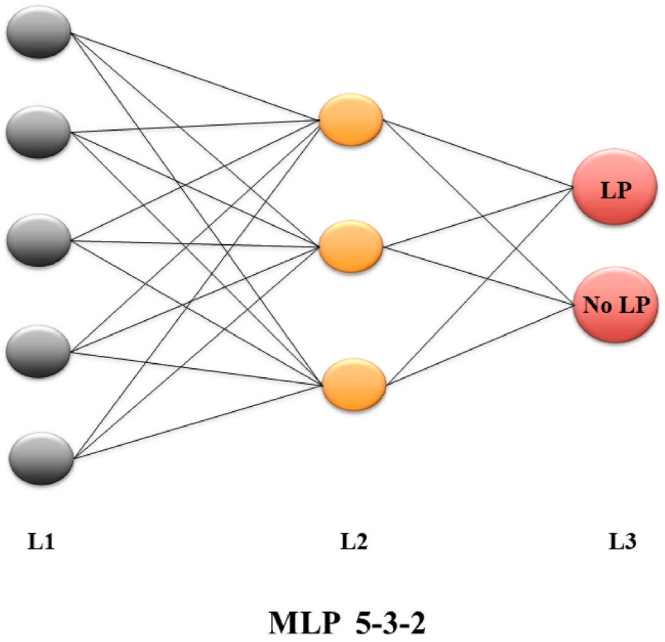

Fig. 5. Layout of the neural network used in this research: input layer with the 5 descriptors selected, hidden layer with 3 neurons determined empirically, output layer corresponding to the dependent variable value (LP: lipid peroxidation activity and MLP: multilayer perceptron).

6.1. Virtual screening of mycotoxins: identification of lipid peroxidation activity

In the preceding sections, we introduced two ML-driven QSAR models based on Molecular Topology. These models demonstrate a strong classification performance, as evidenced by their high percentages of correct classification. Specifically, the LDA and ANN models achieved high average percentages of correct classification for the training set of compounds (91% and 100% respectively). Furthermore, during the internal validation procedures, both models exhibited a remarkable success rate, with the LDA model achieving an 88% correct classification and the ANN model achieving a 93% correct classification.

Having trained and internally validated the two classification algorithms developed in this study, now, it is time to achieve the final goal of the computational approach, to identify whether mycotoxins could exhibit lipid peroxidation activity or not, providing valuable insights into their potential effects on cellular processes and human health.

In this screening process, our algorithms are applied to a diverse selection of mycotoxins.

a) Virtual Screening-1: mycotoxins with lipid peroxidation activity reported in the literature (not included in the model to ensure a broad representation of structural diversity).
b) Virtual Screening-2: mycotoxins for which the lipid peroxidation activity remains unknown.

When applying our algorithms to classify mycotoxin regarding its lipid peroxidation activity, our criterion will be.

a) LP mycotoxin: A mycotoxin will be classified as causing lipid peroxidation if it receives a LP classification from both models and has a classification confidence level of at least 70% for each model.
b) No LP mycotoxin: A mycotoxin will be labeled as non-causing lipid peroxidation if it receives a No LP from both LDA and ANN models and has a classification probability of at least 70% for each model.

This criterion ensures that the classification of a mycotoxin, based on its potential to cause lipid peroxidation activity, is considered valid only if both computational models identify it with a confidence level of at least 70%. This requirement enhances the reliability of the classification process.

For mycotoxins that do not meet this criterion, they will receive the following labels.

a) Possible LP (LP ?) mycotoxin: Assigned when both models classify the mycotoxin as causing lipid peroxidation, but at least one model's confidence level is below 70%.
b) Possible No LP (No LP?) mycotoxin: Given when both models classify the mycotoxin as not causing lipid peroxidation, but at least one model's confidence level is below 70%.
c) Unclassified (−) mycotoxin: Used when there is a discrepancy between the classifications provided by the models, i.e., one model labels the mycotoxin as LP and the other as No LP.

By applying this criterion and using appropriate labels for uncertain or unclassified cases, the classification process becomes more accurate and reliable in assessing the mycotoxin's impact on lipid peroxidation activity.

Table 5 shows LDA and ANN model prediction for the virtual screened-1 mycotoxins set regarding lipid peroxidation activity.

Analyzing the results offered by the virtual screening-1 (Table 5), it could be appreciated that from a total of 42 mycotoxins with known LP activity, 37 were correctly classified by our models (correct classification rate of 88%). Being mycotoxins with structural similarity to those

Table 4
Classification of mycotoxins (training and internal test set) based on their LP activity using the ANN model.

Training set			Internal Test set		
CID	Class.	C.L.	CID	Class.	C.L.
Mycotoxins with LP Activity			Mycotoxins with LP Activity		
2100	LP	0.731	1678	LP	0.519
6223	LP	0.732	4696	LP	0.692
34687	LP	0.732	40452	LP	0.520
40024	LP	0.732	164754	LP	0.734
89644	LP	0.723	426719	LP	0.732
99586	LP	0.732	1268111	LP	0.520
100721	LP	0.732	2733487	LP	0.736
104860	LP	0.729	3084472	LP	0.735
104940	LP	0.732	5280636	LP	0.732
105008	LP	0.731	15571694	LP	0.732
105095	LP	0.732	137628494	LP	0.817
115285	LP	0.766	**Mycotoxins With LP Activity**		
159926	LP	0.707	3220	No LP	0.955
186907	LP	0.732	3840	No LP	0.563
193579	LP	0.630	3555370	No LP	0.814
245869	LP	0.734	9845622	LP	0.728
442530	LP	0.732			
2724362	LP	0.732			
2733489	LP	0.768			
3007984	LP	0.731			
3084471	LP	0.740			
5280389	LP	0.732			
5281143	LP	0.705			
5281576	LP	0.564			
5284433	LP	0.732			
5284461	LP	0.732			
5359485	LP	0.685			
5360741	LP	0.731			
5458510	LP	0.732			
5477707	LP	0.732			
6610243	LP	0.731			
10093830	LP	0.732			
11262300	LP	0.735			
13797589	LP	0.732			
13990016	LP	0.732			
16132042	LP	0.716			
21117948	LP	0.703			
54680783	LP	0.732			
57339252	LP	0.736			
57339253	LP	0.735			
101899453	LP	0.732			
137628394	LP	0.752			
146026608	LP	0.732			
146026614	LP	0.732			
146026615	LP	0.732			
146026618	LP	0.732			
146026622	LP	0.732			
146026623	LP	0.732			
146026625	LP	0.732			
146026627	LP	0.732			
Mycotoxins Without LP Activity					
296197	No LP	0.663			
5458383	No LP	0.712			
5458385	No LP	0.772			
6438394	No LP	0.707			
53229983	No LP	0.603			

CID: compound identifier (from Pubchem); Class.: classification; LP: lipid peroxidation; C.L.: confidence level.

that make up the training set (employed for training the algorithms), this is an expected result. Furthermore, the results suggest that the ANN model exhibits a higher predictive capacity compared to the LDA model, as all mycotoxins in the virtual screening-1 set were correctly classified by the ANN algorithm (42 mycotoxins).

But the real strength of this computational study, is the capacity of categorizing mycotoxins with unknown lipid peroxidation activity

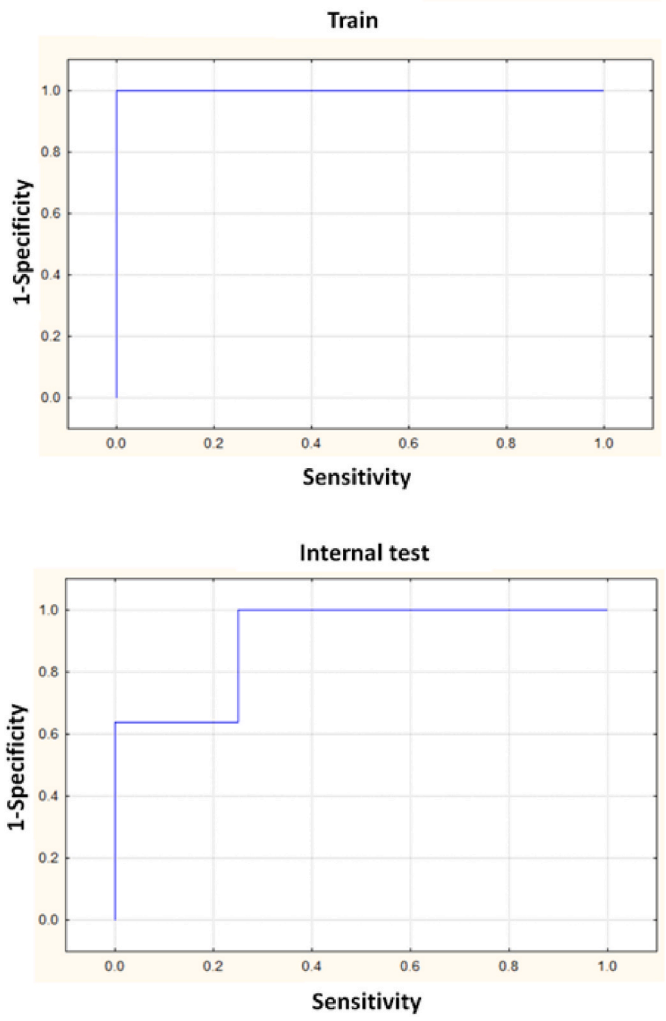

Fig. 6. ROC curve for ANN model: train (AUC = 1.00) and internal test set (AUC = 0.91).

(virtual screening-2 set). From 165 mycotoxins under investigation (with unknown lipid peroxidation activity), our algorithms labeled 91 mycotoxins as having potential lipid peroxidation activity (classified as LP and LP? by the models), while 26 as mycotoxins non-causing lipid peroxidation (classified as No LP and No LP? by the models) (see Table S2 for details). An overall classification has not been obtained for forty-eight mycotoxins.

Si analizamos el ratio mostrado por aquellas micotoxinas del virtual screening-2 clasificadas por ML QSAR models como LP y No LP, advertimos un ratio de 0.8 (74 micotoxinas clasificadas como LP/total 89 clasificadas LP + no LP); mientras que un ratio de 0.2 (15 micotoxinas clasificadas como no LP/89). Se aprecia una tendencia similar en el ratio de micotoxinas que causan LP respecto al total tanto en el training como en el virtual screening-2. Esto refuerza la capacidad predictiva del modelo y logra overcome el mayor constraint encontrado a la hora de entrenar los distintos ML models que ha sido el bajo número de micotoxinas identificadas como no inductoras de LP.

In addition, if we analyze the ratio of mycotoxins that cause LP (103 in total, 61 mycotoxins from training + 42 mycotoxins from virtual screening-1) in relation to the total number of mycotoxins whose information about their LP activity is known in the literature (112), we observe that the proportion of mycotoxins causing LP with respect to the total is 0.9, while the proportion of mycotoxins not causing LP with respect to the total is 0.1 (9/112). If we analyze the ratio shown by those mycotoxins from virtual screening-2 classified by ML QSAR models as LP

Table 5
Classification of mycotoxins from virtual screening-1 based on their LP activity using both LDA and ANN models.

Mycotoxin	CID	LDA			ANN		Overall Class.
		DF	Class.	C.L.	Class.	C.L.	
Reported lipid peroxidation activity in literature[a] (from Li to Khezri)							
15-Acetyldeoxynivalenol	10382483	2.442	LP	0.920	LP	0.732	**LP**
2,3-Epoxyaflatoxin B1	104756	5.331	LP	0.995	LP	0.732	**LP**
3,15-Diacetyldeoxynivalenol	21120844	2.916	LP	0.948	LP	0.732	**LP**
Aflatoxicol	104744	3.021	LP	0.953	LP	0.732	**LP**
Aflatoxin B1 8,9-dihydrodiol	44224029	6.884	LP	0.999	LP	0.732	**LP**
Aflatoxin B1 endo-8,9-epoxide	53297449	5.331	LP	0.995	LP	0.732	**LP**
Aflatoxin B2	2724360	4.737	LP	0.991	LP	0.732	**LP**
Aflatoxin B2A	104825	4.911	LP	0.993	LP	0.732	**LP**
Aflatoxin G1	14421	5.801	LP	0.997	LP	0.732	**LP**
Aflatoxin M1	15558498	3.441	LP	0.969	LP	0.732	**LP**
Aflatoxin M2	23318	5.333	LP	0.995	LP	0.732	**LP**
Aflatoxin Q1	104757	3.955	LP	0.981	LP	0.732	**LP**
Aflatoxin-M1-8,9-Epoxide	53297448	6.297	LP	0.998	LP	0.732	**LP**
Alternariol Monomethyl ether	5360741	4.162	LP	0.985	LP	0.731	**LP**
Citrinin hydrate	190886	2.197	LP	0.900	LP	0.732	**LP**
Dihydrosterigmatocystin	21596453	5.906	LP	0.997	LP	0.732	**LP**
DON-10-leucine	146026624	5.076	LP	0.994	LP	0.732	**LP**
DON-10-S-cysteine	146026609	5.582	LP	0.996	LP	0.732	**LP**
DON-3-sulfate	101899454	4.238	LP	0.986	LP	0.732	**LP**
DON-sulfonate 1	146026630	13.809	LP	1.000	LP	0.732	**LP**
DON-sulfonate 2	146026617	8.433	LP	1.000	LP	0.732	**LP**
Enniatin B4	3010886	4.037	LP	0.983	LP	0.734	**LP**
Fumonisin B3	3034751	1.719	LP	0.848	LP	0.763	**LP**
Gliotoxin cysteine	44363028	7.154	LP	0.999	LP	0.732	**LP**
Gliotoxin G	3007092	1.898	LP	0.869	LP	0.735	**LP**
Gliotoxin Monoacetate	86278268	4.789	LP	0.992	LP	0.732	**LP**
Iso-T-2 Toxin	198704	5.434	LP	0.996	LP	0.732	**LP**
Ochratoxin A methyl ester	177733	3.604	LP	0.973	LP	0.732	**LP**
Ochratoxin B	20966	3.863	LP	0.979	LP	0.732	**LP**
Ochratoxin B ethyl ester	609665	4.460	LP	0.989	LP	0.732	**LP**
Ochratoxin B methyl ester	91733735	3.939	LP	0.981	LP	0.732	**LP**
Ochratoxin C	20997	4.127	LP	0.984	LP	0.732	**LP**
Penitrem B	3084087	1.825	LP	0.861	LP	0.730	**LP**
Penitrem E	3086087	2.468	LP	0.922	LP	0.730	**LP**
Penitrem F	3086086	2.004	LP	0.881	LP	0.730	**LP**
T-2 Tetraol	3034745	7.605	LP	1.000	LP	0.732	**LP**
T-2 toxin tetraol	3034745	7.605	LP	1.000	LP	0.732	**LP**
alpha-Zearalenol	5284645	−4.921	NO LP	0.007	LP	0.516	-
Fumonisin B4	42608359	−1.398	NO LP	0.198	LP	0.836	-
Fumonisin La4	137628520	−0.196	NO LP	0.451	LP	0.813	-
Penitrem C	119470	−0.317	NO LP	0.421	LP	0.721	-
Penitrem D	3035208	−0.496	NO LP	0.378	LP	0.720	-

CID: compound identifier (from Pubchem); DF: discriminant function; Class.: classification; LP: lipid peroxidation; C.L.: confidence level.
[a] Reported lipid peroxidation activity in literature: (Li et al., 2016; Shen et al., 1994; Wang et al., 2020; Verma, 2004; Gündüz et al., 2021; Verma and Mathuria, 2008; Güven et al., 2020; Dhakal et al., 2023; Zhang and Dong, 1986; Flajs and Peraica, 2009; Hassan et al., 2020; Wu et al., 2014; López et al., 2004; Chen et al., 2023; Bojarska et al., 2021; Faixová et al., 2007; Höhler, 1998; Gupta et al., 2018; Berntsen et al., 2013; Weber et al., 2010; Khezri et al., 2018).

and Non-LP, we notice a ratio of 0.8 (74 mycotoxins classified as LP out of a total of 89 classified as LP or non-LP), while a ratio of 0.2 (15 mycotoxins classified as non-LP out of 89). A similar trend in the ratio of mycotoxins inducing LP is observed both for mycotoxins described in the literature and those with unknown LP activity (virtual screening-2). This reinforces the predictive capacity of the model and successfully overcomes the main constraint encountered when training the various ML models, which was the low number of mycotoxins identified as non-LP inducers.

7. Conclusions

Toxicological characterization of mycotoxins, particularly from a mechanistic perspective, requires an interdisciplinary approach to enhance scientific knowledge. In this study, we propose a ML-driven QSAR methodology to investigate the chemo-mathematical patterns associated with mycotoxins that induce lipid peroxidation.

Two algorithms, employing LDA and classification ANN, have been used to develop models for the classification of mycotoxins based on their lipid peroxidation activity. These models have undergone a validation phase to assess their performance. Subsequently, they have been utilized for predicting the lipid peroxidation activity of both known and unknown mycotoxins.

These algorithms elucidate the chemo-mathematical pattern of mycotoxins with lipid peroxidation activity, by linking the presence of 6-membered rings containing at least one heteroatom in mycotoxins structure with lipid peroxidation activity.

This pioneering computational study focused on the use of ML QSAR models based on Molecular Topology, introduces a novel approach to unravel the potential mechanisms of action of mycotoxins. By shedding light on the MOA (mechanism of action) of emerging and understudied mycotoxins, this research offers valuable insights that can inform decision-making processes for toxicologists.

It presents a new tool that empowers researchers to better understand the toxicological implications of mycotoxins and make informed judgments based on comprehensive information.

Statement of authors' contributions to the manuscript

Maria Galvez-Llompart: conceptualization, investigation and

writing. Riccardo Zanni: investigation, data curation and writing. Lara Manyes: conceptualization and critical review of the manuscript. Giuseppe Meca: conceptualization and critical review of the manuscript.

CRediT authorship contribution statement

Maria Galvez-Llompart: Conceptualization, Investigation, and writing. **Riccardo Zanni:** Investigation, Data curation, and writing. **Lara Manyes:** Conceptualization, and critical review of the manuscript. **Giuseppe Meca:** Conceptualization, and critical review of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2023.114120.

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