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Research Paper

Study of some citrus flavanones against zearalenone accumulation by *Fusarium graminearum*

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ABSTRACT

Zearalenone (ZEA) is produced by *Fusarium* fungi in grains, in particular by *Fusarium graminearum*. ZEA is a non-steroidal estrogenic mycotoxin widely distributed. The flavanones naringin (NAR), hesperidin (HES) and neohesperidin (NEO) were extracted from citrus industry wastes, such as immature fruits, and tested against ZEA accumulation by *F. graminearum*in rice. Response Surace Methodology (RSM) was applied in order to optimize flavanones concentrations to achieve total ZEA reduction. Using this methodology, the optimal combinations obtained were HES -NAR: 0.232-0.299, HES-NEO: 0.400-0.001 and NAR-NEO: 0.423-0.001 mmol/kg rice in dry basis. However, NEO seems to have no effect on ZEA inhibition. When it is mixed with other flavanones, they need to be used in higher concentrations than when used alone. These theoretical concentrations obtained by RSM were assayed to verify the results, achieving total inhibition of ZEA accumulation in rice media. The use of the studied flavanones, obtained inexpensively from the residues of citrus industry, would tend to reduce food waste, improve profitability of these industries and diminish ZEA occurrence in rice.

Key words: Zearalenone, flavanones, *Fusarium graminearum*, Response Surface Methodology, rice.

Abbreviation: ACN, Acetonitrile; **EtOH,** ethanol; **HES,** hesperidin; **MEA,** malt extract agar; **MeOH,** methanol; **NAR,** naringin; **NEO,** neohesperidin; **RSM,** response surface methodology; **ZEA,** zearalenone.

INTRODUCTION

Zearalenone (ZEA) is a mycotoxin produced mainly by fungi belonging to the genus *Fusarium* in different foods and feeds, associated primarily with *F. graminearum* but also with other species, such as *F. culmorum*and *F. equiseti* that are able to produce it (Döll and Dänicke, 2011), particularly in cereals such as maize, barley, oats, wheat, rice and sorghum(Darsanaki et al., 2015; Ok et al., 2014). Since it is heat stable, it can be found in food products obtained with contaminated raw materials (Döll and Dänicke, 2011; Neme and Mohammed, 2017).

Based on substrates where ZEA can be found, rice is one of the world's largest cereal production, being the basis of human nutrition (FAO, 2017). "Regarding this cereal, ZEA is often in co-occurrence with other mycotoxins, produced by *F. graminearum* as well, or by other species during postharvest, namely deoxynivalenol, fumonisins, aflatoxins, ochratoxins, citrinin, among others (Neme and Mohammed, 2017; Ok et al., 2014). Moreover it has been detected as rice contaminant in different countries of the world (Darsanaki et al., 2015; Lee et al., 2015; T. Lee et al., 2011; Mojtaba, 2012).

ZEA is a resorcylic acid lactone from which five metabolites are produced when contaminated feed is consumed by animals: zearalanone, α-zearalanol, β-zearalonol, α-zearalenol and β−zearalenol (Ouanes et al., 2005). These mycotoxins cause reproductive disorders of farm animals and hyperoestrogenic syndromes in humans (Marin et al., 2013). There is evidence that ZEA and its metabolites possess estrogenic activity in pigs, cattle and sheep (Gromadzka et al., 2008). The provisional maximum tolerable daily intake has been established for ZEA and its metabolites (including α-zearalenol) at 0.5 μg/kg of body weight per day (JECFA, 2000). One of the most strict regulation limit is set at 100 μg/kg of ZEA for trading cereals in the European Union(EC, 2007).

Flavonoids are a group of natural compounds of variable phenolic structures with antioxidant capacity, produced by plants(Cömert and Gökmen, 2018). Its structure is composed of two aromatic rings, which are connected through a hydropyrone ring (Gattuso et al., 2007). The various classes of flavonoids differ in the level of oxidation and pattern of substitution of the hydropyrone ring, while individual compounds within a class differ in the pattern of substitution of the aromatic rings (Kumar and Pandey, 2013). In particular, flavanones are found in citrus as glycosides. The most common citrus flavanone glycosides are hesperidin which is found in oranges, lemons and other citrus; naringin in grapefruits and sour oranges and neohesperidin in sour oranges (Majo et al., 2005; Tripoli et al., 2007). Their structure can be observed in Figure 1.

Global warming leads to changes in mycobiota of certain crops, favouring *F. graminearum* growth (Paterson and Lima, 2011), thus making its control significant in order to avoid its secondary metabolites occurrence, such as ZEA and deoxynivalenol, in foodstuff.

Also, industries are pressed to find alternatives to replace the use of the synthetic additives commonly applied as food preservants. Consumer trends show that natural additives are preferred since they are perceived as safer and beneficial for health (Dwivedy et al., 2016; Viuda-Martos et al., 2008).

There are some works that demonstrate that flavonoids present activity against fungal growth and mycotoxin production(Chepkirui et al., 2014; Cushnie and Lamb, 2011; Iranshahi et al., 2010). On the other hand, some flavonoids have been easily extracted from the remains of citrus juice processing, particularly flavanones, that could present antifungal and antitoxigenic properties (Salas et al., 2011; Maria et al., 2012). In the case of *F. graminearum* mycotoxin production, it was possible to completely reduce DON accumulation in rice, applying NAR, NEO and HES at various concentrations (Salas et al., 2016a). Besides, regarding ZEA accumulation, no study has been conducted to test isolated flavonoids, but there are some interesting assays that use natural products such as essential oils. As an example, it is possible to reduce *F. graminearum* growth and ZEA production in maize grains with certain combinations of temperature, a_w and plant essential oils (Velluti et al., 2004). Clove, lemongrass and palmarosa oils prevented ZEA accumulation by *F. graminearum* when applied at a_w=0.950, 30°C, in non sterilized maize kernels(Marín et al., 2004). Also, ZEA accumulation was reduced up to 89% using 200 μl of mint essential oil during *in vitro* essays (Hoseiniyeh et al., 2012).

The effect of two or more factors on a response can be assessed using factorial designs (Grum and Slabe, 2004). Response Surface Methodology (RSM) is an efficient methodology for the modelling and analysis of situations in which several variables control a response of interest (Ibrahim and Elkhidir, 2011), resulting in less laborious and time-consuming assays, with much less effort than the classical approaches (Esbensen et al., 2002).

The aim of this study was to analyze the utilization of three flavanones cheaply obtained from the wastes of citrus industries, NAR, HES and NEO, to inhibit ZEA accumulation caused by *F. graminearum* contamination in rice, and applying RSM to determine optimal mixtures concentrations.

MATERIALS AND METHODS

Reagents and chemicals

Acetonitrile (ACN), methanol(MeOH) and ethanol (EtOH) of HPLC grade were purchased from Sintorgan (Buenos Aires,

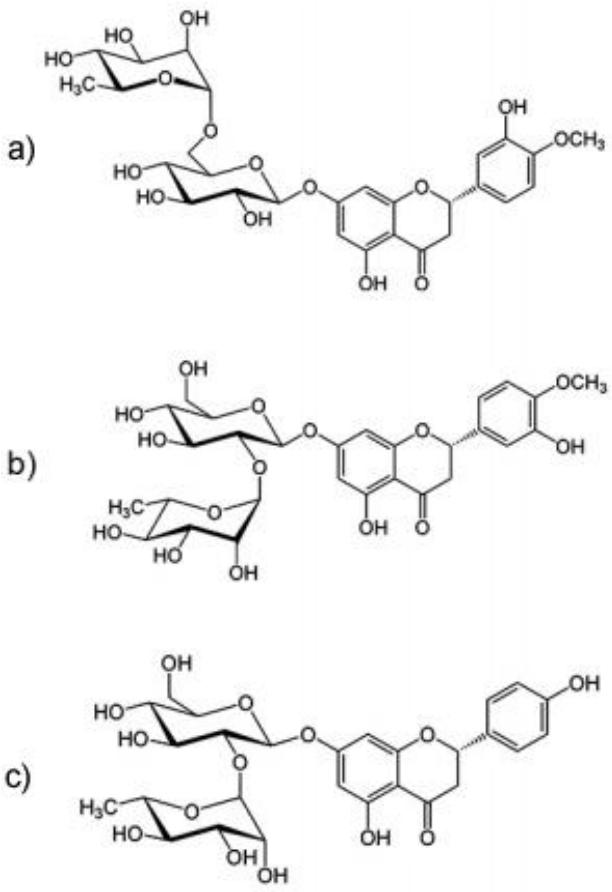

Figure 1: The structure most common citrus flavanone glycosides.

Argentina). The culture medium, malt extract agar (MEA), and the Tween 80 were purchased from Biokar (Allone, France). The water (H_2O) for all the procedures was distilled in a distiller, 6 L capacity, 0716 model (Rolco, CABA, Argentina), and purified through a Nano pure Diamond purification system, model D11911 (Barnstead International, Dubuque, IA, USA).

ZEA standard, article number 001109, was purchased from RomerLabs (Getzersdorf, Austria). ZEA standard stock solution was prepared according AOAC Method 985:18, at a concentration of25 µg/ml in ACN (AOAC, 2005).

Flavanones

The flavanones naringin (NAR), hesperidin (HES) and neohesperidin (NEO) were obtained in the "Instituto de Investigaciones para la IndustriaQuímica" (Universidad Nacional de Salta, Salta, Argentina) according to previously published studies (Geronazzo et al., 2002; Macoritto et al., 2001; Macoritto et al., 2004). Concisely, the flavanones obtained procedure was simple and inexpensive, and consisted of grinding to an average size of 2 mm in diameter, discarding of fruits or the residues of juice process. Thereafter, an extraction in fixed bed column was performed using distilled water at 80°C to obtain NAR, aqueous solution, pH 10.0-10.5 at 70°C for HES, and EtOH:H_2O (25:50 v/v) at 25°C was utilized to extract NEO. In all cases, the extract obtained was cooled, leading to the crystallization of the flavonoids. Then, the precipitates were filtered, washed and finally dried in an oven at 50°C. The final purity of the flavanones was 95, 95 and 99% for NAR,

HES and NEO, respectively. These procedures were considered easy and economical as no special and expensive equipment nor solvents were needed and the steps did not require specialized operator training.

Fungal strain

F. graminearum CIM 30425 used was isolated from blueberries (Munitz et al., 2013) and identified using ITS consensus sequence, in which a fragment of the rDNA ITS1–5.8S–ITS2 region was amplified, using the universal primers ITS5/ITS4 (Munitz et al., 2014) and is kept in the Type Culture Collection of the Natural Science Faculty, University of Buenos Aires, Argentina. This mould was previously cultivated during 7 days in slant agar tubes containing MEA. Then, 10 ml of Tween 80:H_2O (0.02%,v/v) were added and the tubes were shaken for 1 min in a vortex to separate the conidia from the rest of the medium. The concentration of conidia in suspension was 1.6 10^8 conidia/ml determined using a Neubauer counting chamber.

Sample preparation

The samples comprised 25 g of white polished rice obtained in the local market. Flasks were sterilized at 40% humidity at 121°C for 15 min. The studied flavanones, NAR, HES and NEO, were dissolved in EtOH:H_2O (5:95, v/v) at 3 different concentrations alone (0.15; 0.30; 0.60 mM) and in nine different binary mixtures: NAR-HES, NAR-NEO and HES-NEO at the concentrations 0.15-0.15; 0.30-0.30; 0.60-0.60 mM, respectively. 15 ml of the flavanone solutions and 50 µl of the conidia suspension of *F. graminearum* prepared in 2.3 were correspondingly added to the samples, after sterilization, at room temperature and then, thoroughly shaken. The final concentrations of flavanones in the samples were 0.11, 0.21 and 0.42 mmol/kg rice in dry basis, for NAR, NEO and HES, and 0.11-0.11, 0.21-0.21 and 0.42-0.42 mmol/kg rice in dry basis for the mixtures. The Erlenmeyer flasks containing the samples were incubated at 25°C for 30 days.

Extraction and HPLC procedures

This procedure is based in AOAC Method 985.18 (AOAC, 2005) with some modifications. Briefly, extraction was performed blending 25 g of the cultivated samples with 100 mlof ACN:H_2O (84:16, v/v) for 3 min. Thereafter, 5 ml of the supernatant were passed through a clean-up column (TC-M Puritox 160, Trilogy Lab). 1 ml of the filtrate was evaporated to dryness and resuspended in 1 ml mobile phase with agitation. Quantification was performed in HPLC Agilent 1100 Series equipped with a degasser (G1322A), an auto sampler (G1313A), a fluorescence detector (G1321A), quaternary pump (G1311A) and a temperature controller (G1316A). For HPLC separation, a Microsorb-MV 100 C18 reversed phase column, 5 µm, 150 mm × 4.6 mm, was used (Varian, CA, USA). The mobile phase was H_2O:ACN:MeOH (50:27:23, v/v/v) at a temperature of 35°C, flow rate 1 ml/min and injection volume of 100 µl. Fluorescence detector excitation wavelength was 236 nm and emission 460 nm. The retention time of ZEA was approximately 18.45 min.

Methodology validation

To validate the method, linearity, matrix effect, limit of detection (LOD), limit of quantification (LOQ), repeatability, and recovery were taken into account. Calibration curves were obtained using a series of standard solutions ranging from 2.5 to 955 ng/ml. Repeatability was evaluated in a certified sample T2209 (Trilogy Lab). Toxin recoveries were measured from spiked samples and this procedure was done in triplicate.

The LOD and LOQ were evaluated for the spiked matrices. LODs were calculated from the signal to noise ratio (S/N) as LOD= 3 S/N and LOQs were defined as LOQ= 3 LOD. The terms considered for repeatability and recoveries for each toxin complied with the European Commission criteria for ZEA(EC, 2014).

Factorial designs and response surface methodology

The behaviour of the system is explained by the following second-degree polynomial equation:

$$Y = a_0 + \sum_{i=1}^{n} a_i x_i + \sum_{i=1}^{n} a_{ii} x_i^2 + \sum_{i<j=2}^{n} a_{ij} x_i x_j$$

Y is the response function, a_0 is a constant term, a_i, a_{ii} and a_{ij} are the coefficients of the linear, quadratic and interactive terms, respectively. Accordingly, X_i and X_j represent the

Table 1: ZEA accumulation in rice control samples and in those treated with flavanones. Three replicates were evaluated.

Flavanones (mmol/kg db)		ZEA (µg/kg)	
		Mean	SD
Control	0	3250	2761
NEO	0.11	1931	618
NEO	0.21	3757	3318
NEO	0.42	4102	2926
NAR	0.11	142	247
NAR	0.21	<LOD	0
NAR	0.42	<LOD	0
HES	0.11	<LOD	0
HES	0.21	<LOD	0
HES	0.42	157	192
NAR-HES	0.11 - 0.11	<LOD	0
NAR-HES	0.21 - 0.21	599	1037
NAR-HES	0.42 - 0.42	<LOD	0
NAR-NEO	0.11 - 0.11	1123	1945
NAR-NEO	0.21 - 0.21	1495	816
NAR-NEO	0.42 - 0.42	669	628
NEO-HES	0.11 - 0.11	1575	2727
NEO-HES	0.21 - 0.21	2562	4262
NEO-HES	0.42 - 0.42	1668	1581

coded independent variables (Li et al., 2007). The analysis was performed using the Statgraphics Centurion XVI package.

The four levels studied were 0, 0.11, 0.21 and 0.42 mmol/kg rice, for each flavanone. The experimental design consisted of ten factorial points evaluated in triplicate. The mean values and the standard deviation of those triplicates were calculated and used in the model.

RESULTS AND DISCUSSION

As regards methodology validation, the response of standard solutions prepared in ACN and that of standards added to negative samples were assessed and no matrix effect was found. Linearity remained greater than 0.999 in the range from 51 to 3700 µg/kg. LOD and LOQ were 17 and 51 µg/kg, respectively. Recovery was 94 at 228 µg/kg. The repeatability at a concentration of 89 µg/kg was 9.2% and at 798 µg/kg was 4.1%

After the application of the treatments, ZEA level were quantified in all samples. The results of the accumulation based on control without flavanones are shown in Table 1.

As can be appreciated, HES at 0.11 mmol/kg, NAR and HES at 0.21 mmol/kg, NAR at 0.42 mmol/kg and the mixtures NAR-HES 0.11-0.11 and 0.42-0.42 mmol/kg completely inhibited ZEA accumulation. NAR 0.11 and HES 0.42 mmol/kg achieved at least 95% ZEA inhibition, NAR-HES 0.21-0.21 mmol/kg inhibited 82%. On the other hand, NEO at 0.11 mmol/kg only diminished 41% ZEA accumulation and moreover, it stimulated this mycotoxin production by 16 and 26% at 0.21 and 0.42 mmol/kg, respectively. None of the mixtures containing NEO with NAR or HES could totally inhibit ZEA, achieving reductions of its accumulation between 21 and 79%. This response could indicate that NEO would represent a promoter of ZEA accumulation in the conditions of the study (Geisen et al., 2017), contrary to previous results obtained utilizing RSM technique, that showed that applying optimal flavanones mixtures in *A. flavus* cultures in MEA completely prevented aflatoxins accumulation, with less concentrated mixtures as compared with the flavanones separately

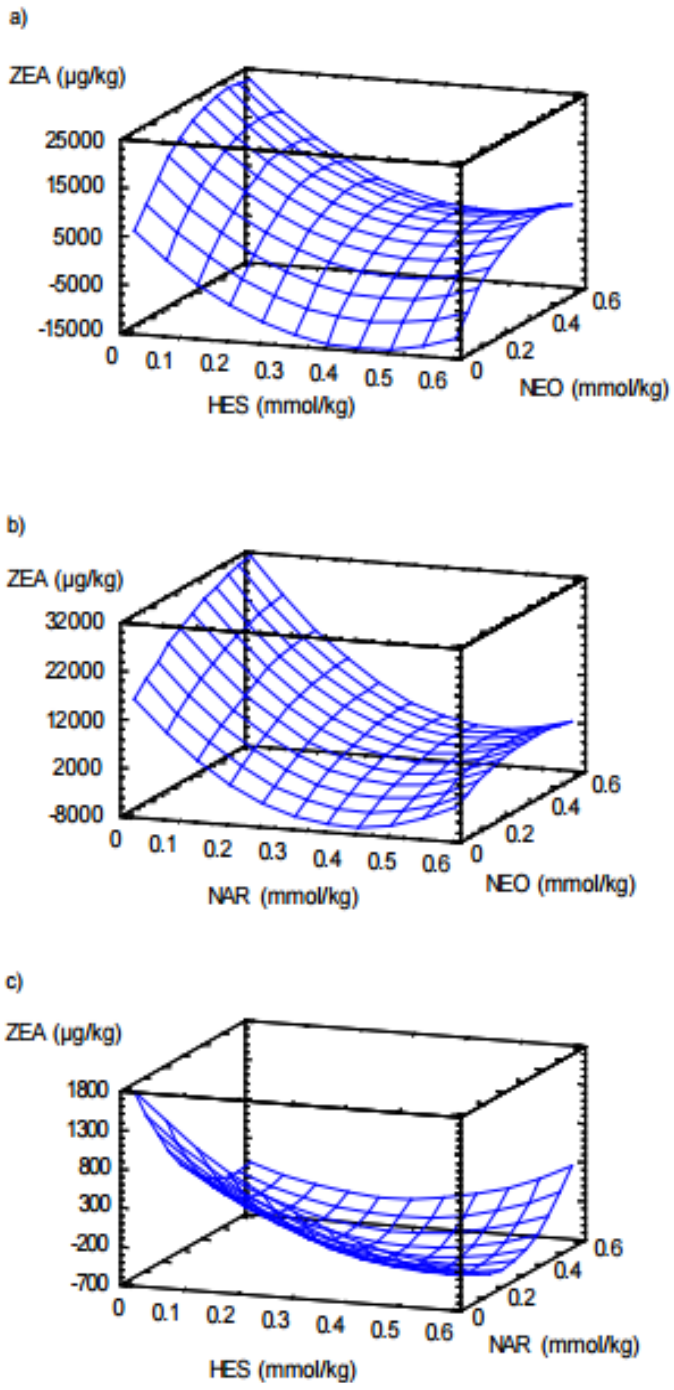

Figure 2: The response surfaces obtained for ZEA.

applied (Salas et al., 2016b).

To determine the most suitable mixture with minimal flavanones concentrations that would lead to total inhibition of ZEA accumulation, RSM methodology was employed as described in the methodology validation section. Figure 2 shows the response surfaces obtained for ZEA. The Response Surfaces allow obtaining the second degree equations to calculate the concentration of each flavanone in order to minimize the accumulation of this mycotoxins. The equations for ZEA concentration, in which *Nar*, *Neo* and *Hes* are the concentration levels of the flavanones in rice after incubation time were as follows:

HES-NAR

$ZEA=987.80 - 10259.61Hes + 6383.96Nar + 10345.80Hes^2 – 898.00HesNar - 7330.18Nar^2$

Mixture concentration to minimize the accumulation of ZEA is HES 0.232-NAR 0.299 mmol/kg rice in dry basis.

HES-NEO

$ZEA = 1963.40 - 9339.61Hes + 7832.96Neo + 10345,80Hes^2 - 872.70HesNeo - 7230.18Neo^2$

Mixture concentration to minimize the accumulation of ZEA is: HES 0.400 –NEO 0.001 mmol/kg rice in dry basis.

NAR- NEO

$ZEA = 2254.72 - 11578.30Nar + 4928.70Neo + 13036.60Nar^2 - 2943.22NarNeo - 2967.11Neo^2$

Mixture concentration to minimize the accumulation of ZEA is: NAR 0.423 –NEO 0.001 mmol/kg rice in dry basis.

The mixtures calculated as the optimal by the RSM model were prepared for verification of the results as specified in methodology validation section. It was found that all the flavanones mixtures suggested by RSM reduced 100% ZEA accumulation. HES and NAR seem to be more effective against ZEA, whereas NEO was practically dismissed in these mixtures.

In previous studies carried out on this group, it was pointed out that flavanones could affect the accumulation of mycotoxins. For example, patulin accumulation was reduced by HES, NAR, and NEO in 95, 96 and 99% (Salas et al., 2012). But so far, there is dearth of information regarding these particular citrus flavanones and their effect on ZEA. In a study, it was shown that certain compounds related to flavonoids, such as phenolic acids, were not capable of reducing ZEA accumulation by *F. graminearum* in potato dextrose agar (Pagnussatt et al., 2014), contrary

to the results presented in this study, where HES and NAR completely inhibited ZEA accumulation.

Conclusions

These results demonstrated the possibility to achieve the inhibition of ZEA production utilizing natural and inexpensive products obtained from citrus residues, such as NAR, NEO and HES.

The three mixtures proposed by RSM completely prevented the accumulation of this toxin. However, total concentration of these mixtures were higher than those of the flavanones HES and NAR which could also achieve complete inhibition of ZEA accumulation when applied alone. NEO was uneffective against ZEA inhibition, and it may be responsible for promoting mycotoxins formation. When it was used in combination with the other flavanones, higher concentrations were needed to obtain the same effect.

The use of naringin and hesperidin, inexpensively obtained from the residues of citric industry, is an interesting option for improving the value chain of these industries, and reducing the impact of organic wastes on the environment. Due to these promising results, other components of the mentioned residues will be studied in their capacity to achieve mycotoxin reduction.

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