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Title

Ochratoxin : Occurrence, Toxicity, Epidemiology, Detection & Prevention.

Defended on 19/ 06/2023 in front of the jury composed of:

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Dedication

It is with deep gratitude and sincere words, that we dedicate this modest work to our dear parents; who sacrificed their life for our success and enlightened us the way by their judicious advices.

We hope that one day, we will be able to give them back a little of what they have done for us, may God grant them happiness and long life.

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List of abbreviations

$(NH_4)_2SO_4$: Ammonium sulphate.

10-OH-OTA: 10 -Hydroxy-Ochratoxin A.

4-OH-OTA: 4R and 4S-hydroxy-Ochratoxin A.

AAC: Aptamer-affinity columns.

ACP: AcylCoA precursor carrier.

AT: Acyltransferase.

AFs: Aflatoxins.

AKT: serine/ threonine-specific.

ASK-1: Apoptotic signal regulated kinase 1.

Bax: Bcl-2 associated x protein.

C/EBP: CAAT/enhancer-binding protein.

CCD: Charge coupled detector.

CDK2: Cyclin dependent kinase 2.

Cdk4: Cyclin dependent kinase 4.

CH_4N_2O: Urea.

CHOP: Homologous protein.

CIN: Chronic Interstitial Nephropathy.

C-Met: C-methyltransferase.

CypD: Cyclophilin D.

DH: Dehydratase.

DNMT1: DNA methyltransferase 1.

DSPE : Dispersive-SPE.

EIS: Electrochemical immunosensors.

EMT: Epithelial-to-mesenchymal transition.

ER: Enoyl reductase.

EPO: Erythropoietin.

ER: Endoplasmic Reticulum.

ERK 1/2: Extracellular signal-regulated kinases1/2.

FD: Fluorescence Detection.

FN: Flou Nanobody.

FPIA: Fluorescence Polarization Immunoassay.

FTIR: Fourier Transform Infrared.

GAP: Good Agricultural Practices.

GRP-75: Glucose-Regulated Protein 75.

List of abbreviations

GRP78: Glucose Regulated Protein 78.

H3K9: Histone 3 lysine 9.

HACCP: Hazard Analysis Critical Control Points.

HAT: Histone acetyltransferase.

HDAC1: Histone deacetylase1.

HIF-1α: Hypoxia inducible factor-1 alpha.

HK-2: Human proximal tubular epithelial cells.

HLB: Hydrophilic-lipophilic balance.

HO-1: Heme oxygenase-1.

HPLC: High-performance liquid chromatography.

HPTLC: High-Performance -Thin-Layer Chromatography.

HSP: Heat shock proteins.

IAC: Immunoaffinity columns.

ICA: Immunoaffinity column assays.

Ig: Immunoglobulins.

IL-2 : Interleukin-2.

IrO2 NPs : Iridium oxide nanoparticles.

JAK2: Janus kinase 2.

KR: Ketoreductase.

KS: β-ketosynthase.

LFAs: Lateral flow immune chromatographic assays.

LOD: Limit of detection.

LOQ: Limits of quantification.

LPE: Liquid phase extraction.

l-SPE : Micro-SPE.

MAPK: Mitogen-activated protein kinase.

MAX: Mixed-mode anion-exchange.

MBS: Magnetique billes.

MDA: Malondialdehyde.

MIPs: Molecularly imprinted polymers.

MS: Mass Spectrometry.

Nb: Nanobody.

NBL: Nanobody/nanoBIT.

NF-kB: Nuclear factor kappa-light-chain-enhancer of activated B.

Ng: Nanogramme.

NH_4Cl: Ammonium chloride.

NH_4NO_3: Ammonium nitrate.

NO: Nitric oxide.

Nrf-2: Erythroid 2-related factor 2.

NRPS: Non Ribosomal Peptide Synthases.

OATPs: Organic anion transporter polypeptides.

OATs: Organic anion transporters.

OTA: Ochratoxin A.

PADs: Paper-based analytical device.

PCR: Polymerase chain reaction.

PI3K: Phosphoinositide 3-kinases.

PKS: Polyketide Synthases.

PCR: Polymerase chain reaction.

PTEN: Phosphatase and tensin homolog.

QSM-D: Quartz crystal microbalance with dissipation.

QuEChERS: Quick Easy Cheap Rough and Safe.

RNA: Repressor protein known as CreA.

ROS: Reactive oxygen species.

RT-qPCR: Quantitative Real-Time polymerase chain reaction.

SA-gal: Senescence-associated-galactosidase.

SBME: Solid bar microextraction.

SERS: Surface-enhanced Raman spectroscopie.

SOCS3: Signaling pathway and increasing the expression of suppressors of cytokine signaling3.

SPME: Solid-phase microextraction.

STAT3: Signal transducer and activator of transcription 3.

TC: Deterpenes Cyase.

TEM: Transmission Electron Microscopy.

TGF-β: Transforming growth factor beta.

TID: Target-induced dissociation.

TLC: Thin-layer chromatography.

TRAP-1: Tumor necrosis factor receptor-associated protein 1.

Terpenes: Trichothecenes.

List of abbreviations

UHPLC: Ultra haute perfermance liqide chromatographie.

UPLC: Ultra-performance liquid chromatography.

VALDS: Vortex Assisted Low Density Solvent-microextraction.

VEGF: Vascular endothelial growth factor.

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Abstract

Ochratoxin A (OTA) is a mycotoxin produced by several species of *Aspergillus* and *Penicillium* fungi that structurally consists of a para-chlorophenolic group containing a dihydroisocoumarin moiety that is amide-linked to L-phenylalanine. OTA is detected worldwide in various food and feed sources. Studies show that this molecule can have several toxicological effects such as nephrotoxic, hepatotoxic, neurotoxic, teratogenic and immunotoxic. OTA detection methods were also reviewed, as they relied on conventional methods such as chrommatography and emerging methods such as nanoparticles. Therefore, various strategies for the detoxification of OTA, including pre-harvest prevention strategies and post-harvest detoxification procedures were reviewed.

Key-words: Ochratoxin A; food; toxicological effects; detection; prevention strategies.

ملخص

الأوكراتوكسين هو سم فطري ينتج عن عدة أنواع من فطريات *Aspergillus* و *Penicillium* التي تتكون هيكليا من مجموعة شبه كلوروفينول تحتوي على جزء ثنائي هيدروايزوكامين المرتبط بالاميد L-فينيل الانين .تم اكتشاف الأوكراتوكسين في جميع انحاء العالم في كل من مصادر الغذاء والاعلاف المختلفة, حيث تواجد هذا الأخير في الأغذية والاعلاف يمكن ان يكون له تأثيرات سمية مثل السمية الكلوية, التسمم الكبدي, التسمم العصبي, السمية المناعية و التأثيرات المسخية. تم تطوير طرق تحديد واكتشاف الاوكراتوكسين حيث اعتمدت هذه الطرق على طرق تقليدية كالكروماتوغرافيا و طرق ناشئة مثل الجسيمات النانوية, لذلك تمت مراجعة استراتيجيات مختلفة لإزالة الاوكراتوكسين بما في ذلك الوقاية قبل الحصاد وإجراءات إزالة السموم ما بعد الحصاد.

الكلمات المفتاحية: أوكراتوكسين أ ؛ طعام؛ تأثيرات سمية؛ كشف؛ استراتيجيات الوقاية.

Introduction

Mycotoxins are natural products, synthesized by fungi, capable to cause a toxic response when they penetrate naturally in animals or in the human organism. They attract attention worldwide due to economic losses important which is linked to their effects on human health, animal productivity and national and international trade **(Capriotti *et al.*, 2012; Ben Miri *et al.*, 2018)**.

Several thousand mycotoxins have been identified but fortunately, only around twenty families pose problems in human and animal food. Six families are frequently encountered in food commedities: aflatoxins, ochratoxins, fumonisines, trichotécenes, zearalenone and patline **(Ben Miri *et al.*, 2023)**.

Due to the importance and diversity of their toxic effects, the presence of mycotoxins in food is potentially dangerous. In addition, their high stability thermal means that they are generally more resistant than mold having them synthesized **(Shukla *et al*., 2012)**.

Exposure to mycotoxins can originally be of acute and chronic toxicities ranging from death to deleterious effects on the nervous system central, cardiovascular apparatus and respiratory system, as well as on digestive devices and urinary. The power that some to alter the immune system and, thus, to reduce resistance to infections, is now largely considered to be their effect most important **(Anfossi *et al.*,2010; Prakash *et al.*, 2012; Kedia *et al.*, 2015)**.

OTA is a naturally occurring foodborne mycotoxin found in a wide variety of agricultural commodities worldwide, ranging from cereal grains to dried fruits to wine and coffee. It is produced by several different fungi belonging mainly to the genre *Aspergillus, Penicillium* and *Fusarium* including *A. ochraceus, A. carbonarius, A. niger* and *P. verrucosum* **(Alshannaq & Yu, 2017)**. Contamination generally occurs because of poor storage of commodities and suboptimal agricultural practices during the drying of foods **(Li *et al.*, 2021)**.

Several studies have shown the teratogenic, immunosuppressive, genotoxic and mutagenic effects of OTA **(Malir *et al.*, 2013).**

OTA remains stable during the periods of transformation and cooking of food. Because this substance can never be completely absent or eliminated foodstuffs, and in order to identify the problems caused, several countries have established standards fixing the maximum tolerated contents of this mycotoxin in a specific food product **(Ramirez *et al.*, 2021)**.

Since 2002, European regulation has fixed the maximum eligible contents in the raw cereals (5µg/kg) and their products derived from cereal (3µg/kg) as well as in the grapes dry (10µg/kg) (EU 472/2002). More recently, these regulations have been extended to coffee (5µg/kg), wine and grape juices (2µg/l). These new maximum contents are defined by the Regulation (EC) No. 123/2005. The maximum rate in infant food has been set to 0.5µg/kg.

Under these conditions, it is essential to create OTA determination methods for a variety of meals. In fact, numerous quantitative analytical techniques for OTA determination have been published **(Ha, 2015; Malir *et al*., 2016; Pérez *et al*., 2017)**.

From the very early discovery of OTA until the present, a variety of analytical techniques have been employed, including thin-layer chromatography (TLC), high-performance liquid chromatography (HPLC) in combination with a variety of detectors (e.g., fluorescence, diode array, UV), liquid chromatography coupled with mass spectrometry (LC-MS), and liquid chromatography-tandem mass spectrometry (LC-MS/MS) for mycotoxin analysis **(Alshannaq & Yu, 2017)**. Contrarily, immunoassay-based techniques, such as the enzyme-linked immunosorbent test (ELISA) etc **(Zhang *et al*., 2018; Al-Jaal *et al*., 2019; Alshannaq & Yu, 2017)**.

Two strategies prevention of their generation and detoxificationare used to control OTA contamination **(Taheur *et al*., 2019)**. All mycotoxins can not be eliminated by conventional cooking methods. Numerous food processing techniques as well as numerous physical, chemical, and biological techniques are used to partially or completely remove OTA from food **(Kumar *et al*., 2017)**.

This study focused on OTA, its occurence in food, distribution, and toxicological effects. Additionnally, critical developments in detection technology and prevention strategies for control and detoxification measures were reviewed.

Bibliographic Synthesis

I.An overview of mycotoxins

I.1.Fungi

Fungi or mycetes are heterotrophic and ubiquitous eukaryotes. In the classification of the living world, fungi are a separate kingdom from plants and animals **(Chabasse *et al*., 2002)**. Fungi are uni or pluricellular organisms including macroscopic species (macromycetes) and other microscopic species (micromycetes) of filamentous or yeast-like appearance these can become visible when their development is important. Fungi are commonly called "molds", real agglomerates of mycelial filaments and fruiting bodies able to colonize very diverse substrates (plants, paper, leather and walls ... etc.) **(Costa *et al*., 2019)**.

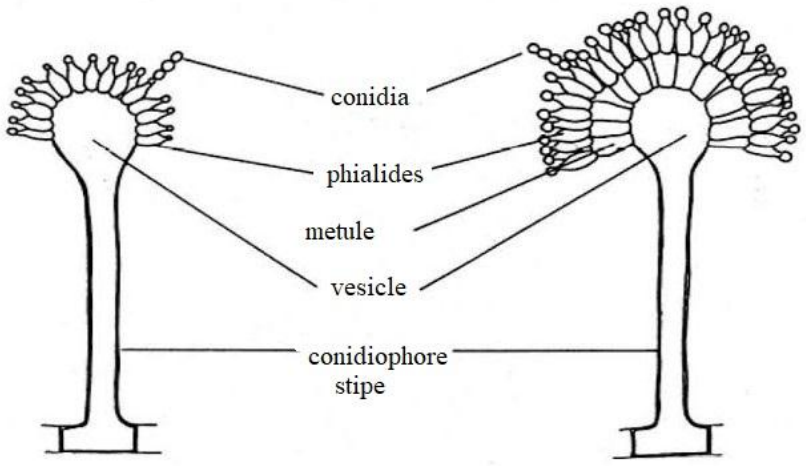
I.1.1.Toxigenic fungi

Toxigenic fungi are a real danger to human and animal health. The majority of known fungal species producing most of the mycotoxins belong to the genera *Aspergillus, Fusarium, Penicillium and Alternaria.* These molds and their associated mycotoxins are likely to contaminate food throughout the production chain, from the field to the consumer's plate **(Ukwuru *et al*., 2017)**.

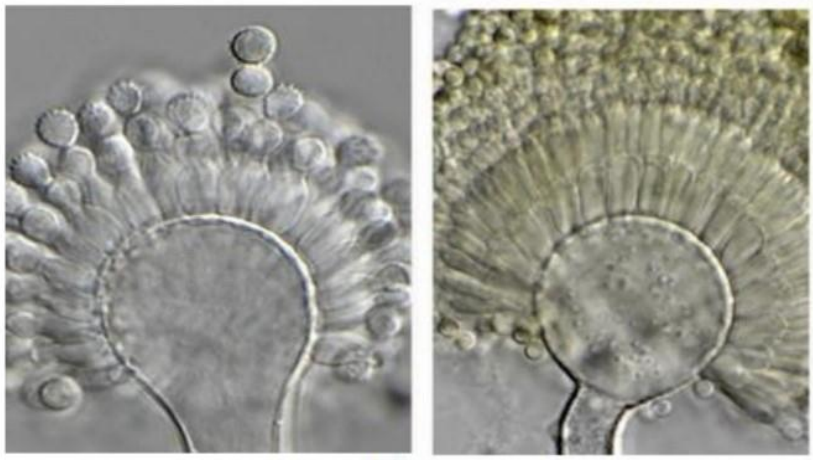
I.1.1.1.Genus *Aspergillus*

The genus *Aspergillus* includes saprophytic, ubiquitous and environmentally essential species found on soils, compost piles, fruits, organic debris, animals and humans **(Sugui *et al*., 2015)**. Several species of the genus *Aspergillus* **(Figure 1)** are known for their ability to produce mycotoxins responsible for human and animal pathologies **(Samson *et al*., 2014)**. Of the mycotoxins produced by this genus, aflatoxins (AFs) and ochratoxins (OTAs) pose the greatest health risks. Some species can be directly pathogenic for humans and animals due to their ability to invade living tissues and cause *Aspergillos is* such as pulmonary mycoses **(Seyedmousavi *et al*., 2015)**.

Some species of *Aspergillus* are used in the food industry and in the industry of biotechnological products in particular for the fermentation of various substrates and the production of enzymes or organic acids **(Houbraken *et al*., 2014)**.



A



B

Figure 1. A : *Aspergillus* structure ; uniseriate and biseriate head, **B**:Microscopic appearance **(Chabasse *et al*., 2002; Frisvad *et al*., 2019)**.

I.1.1.2.Genus *Penicillium*

Penicillium is one of the most important genera of fungi, with more than 400 described species distributed worldwide in four subgenera belonging to the division Deuteromycetes **(Visagie *et al.*, 2014)**. Teleomorphic forms of some of them are known and belong to the class Ascomycetes, the most representative genera of which are *Eupenicillium* and *Talaromyces* **(Figure 2) (Pitt & Hocking, 2009)**.

The genus *Penicillium* has at least 18 mycotoxigenic species namely, *P. crustosum*, *P. chrysogenum*, *P. hirsutum*, *P. expansum*, *P. roqueforti*, *P. viridicatum*, *P. commune*,

P.aurantiogriseum, P. citrinum, P. verrucosum, P. cyclopium, P. canescens, P. madriti, P. palitans, P. thomii, P. baarnense, P. fenneliae and *P. frequentans.*

These species produce OTA, citrinin, patulin, cyclopiazonic acid, penicillic acid, roquefortin, frequentin, palitentin, mycophenolic acid, gliotoxin, citreoviridin and rubratoxin B **(Samson & Frisvad, 2004)**. Moreover, these species and the mycotoxins produced invade the seeds after harvest, causing significant economic losses in different regions of the world **(Ismaiel & Papenbrock, 2015)**.

Penicillium are ubiquitous and polyphagous and can degrade several substrates. They are widely present in the soil and contaminate several substrates including cereals, peanuts and dairy products. Many species of *Penicillium* are used at the industrial level for the manufacture of cheeses and cured meats or for the production of different metabolites of interest **(Visagie *et al*., 2014)**.

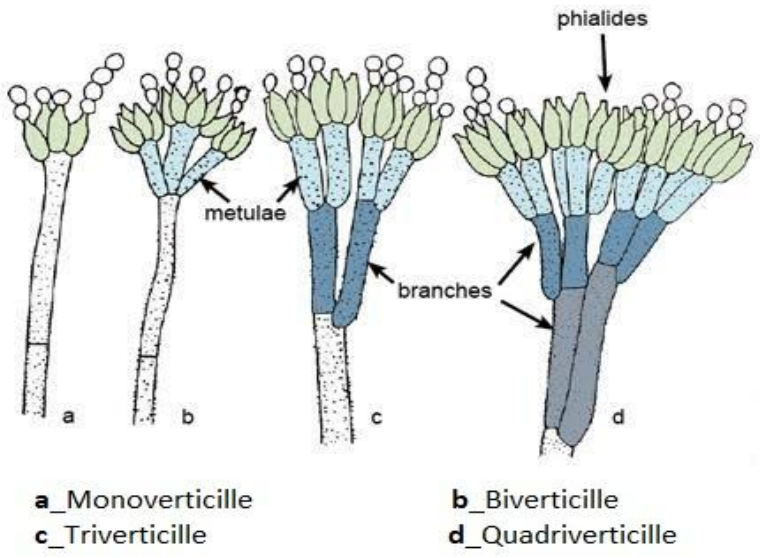


Figure 2. Diagram of the different arrangements in *Penicillium sp.* **(Frisvad *et al*., 2004)**.

I.1.1.3. Genus *Fusarium*

The genus *Fusarium* **(Figure 3 A)** includes a large number of phytopathogenic species **(Rosa *et al*., 2021)**. It develops preferentially on senescent or stressed plants. It is involved in stem, fruit and root **(Crous *et al*., 2021)**. Because of their ability to produce mycotoxins, *Fusarium* are capable of causing serious infections and intoxications in humans and in

animals, especially livestock. These infections are grouped under the term fusariosis **(Ferrigo *et al.*, 2016)**.

I.1.1.4. Genus *Alternaria*

The majority of species of the genus *Alternaria* are phytopathogenic fungi belonging to a plant family or to a specific plant **(Figure 3B)**. They are usually present on seeds, causing emergence failure or seedling failure. Only about ten individuals of the genus *Alternaria* produce toxins such as Tenuazonic acid, Altertoxins I, II, III **(Woudenberg *et al.*, 2015)**.

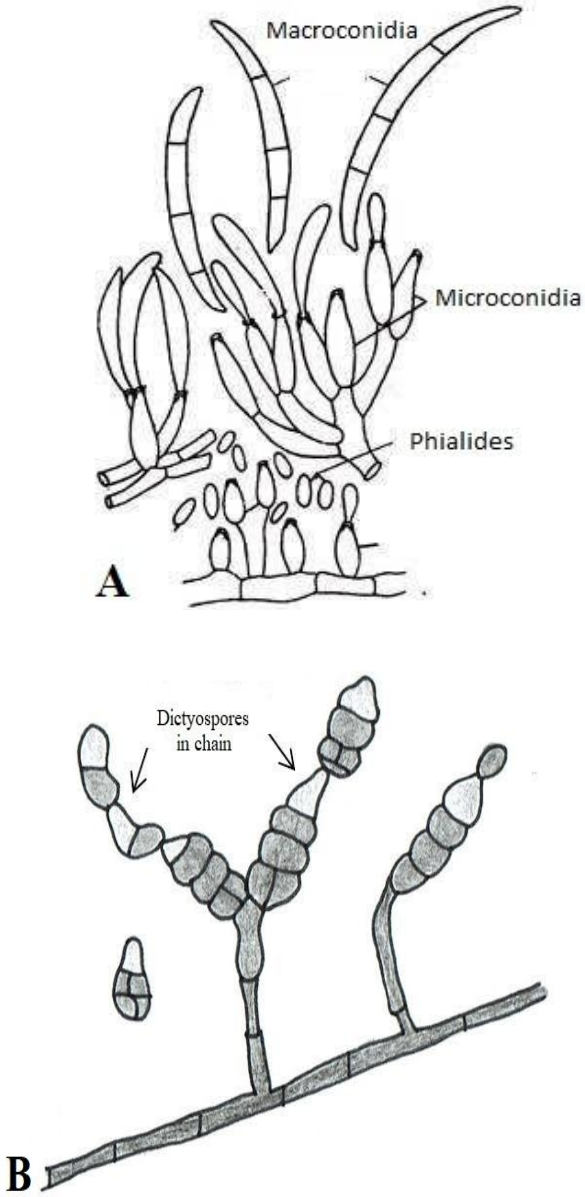


Figure3. A: Morphological characteristics of Fusarium; B: Scheme of conidia of *Alternaria* **(Okungbowa & Shittu, 2012; Pastor & Guarro, 2008)**.

I.2.Mycotoxins

Mycotoxins are fungal toxins (about 400 in number), non-protein of low molecular weight (<1000 daltons). They are synthesized and formed mainly by the mycelial structure of filamentous parasites, which pose serious risks to human and animal health **(Hussein & Brasel, 2001; Bryden, 2012)**. They have low volatility and are found in the mycelium and spores of fungi **(Flores *et al.*, 2015)**. Mycotoxins are distributed worldwide in the environment and are of particular interest to agriculture and food safety. The presence and growth of mycotoxenogenic fungi can alter the quality and quantity of food **(Nguyen *et al.*, 2017)**.

I.2.1.Mycotoxin occurrence in food commodities

Mycotoxins are produced in many products ranging from raw to process such as bread, flour, pasta, or fruit juice **(Ukwuru *et al.*, 2017)**. They have the ability to remain stable during food processing **(Bullerman & Bianchini, 2007)**, which indicates difficulty in getting rid of them. Reports that mycotoxin is naturally quite distributed as a contaminant of many cereals and animal feeds throughout the food chain **(Streit *et al.*, 2012; Marin *et al.*, 2013)**. The main mycotoxins, producing species and associated commodities are represented in **Table 1 (Bünger *et al.*, 2004; Grigoriadou *et al.*, 2005; Hymery *et al.*, 2006)**.

Table 1. Main mycotoxins and fungal producing species and main contaminated foodstuffs.

Mycotoxins	**Main fungal species**	**Main contaminated foodstuffs**
AFs	*A. flavus, A. parasiticus, A.Nomius*	cereals, fruits, dried fruits, milk.
Trichothecenes	*F.graminrarum, F. culmorum*	Cereals and legumes.
Ergot alkaloid	*Claviceps purpurea*	Cereals.
Cyclopiazonic acid	*A.flavus,P. cyclopium, P.citrinum, P. viridicatum, P. expansum*	Cereals.
Citrine	*P. citreoviride, P. verrucosum, Monascus purpureus*	Cereals and fruits.
Deoxynivalenol	*F. culmorum, F. graminearum, F. sporotrichioides*	Cereals.
OTA	*A. ochraceus, P. nordicum, P. verrucosum, A. carbonarius, A. niger, A. Alliaceus, A. terreus*	Wine, grapes, coffee, cocoa, cereals.
Sterimatocystin	*A. versicolor, A. nidulans*	Cereals.
Fumonisins	*F. moniliforme, F. verticillioides, F. Proliferatum*	Cereals (corn).
Patulin	*A. cyclopium, P. expansum, P. granulatum, Paecilomyces variorti*	Cereals and fruits.
Zearalenone	*F. graminearum, F. culmorum, F. semitectum*	Cereals.

Thus, the same merchandise can be subject to multiple contaminations. Moreover, a toxigenic fungus can produce several mycotoxins, and fungi of different natures and species can synthesize identical mycotoxins. In addition, the presence of a mycotoxin-producing fungus is not always synonymous with the presence of these persistent mycotoxins in foodstuffs, even if the fungi responsible for their production may be absent **(Oswald & Massin, 2020)**.

Consequently, humans and animals are not exposed to a single mycotoxin at a time but in almost all cases, to a mixture of mycotoxins **(Dorninger *et al*., 2019; Agriopoulou, *et al*., 2020)**. Indeed, multi-exposure to mycotoxins can lead to antagonistic, additive, or in some cases, synergistic effects **(Grenier & Oswald, 2011; Smith *et al*.,2016; Meneely *et al*., 2018)**.

I.2.2.Mycotoxin Biosynthesis

Mycotoxin biosynthetic pathways are long and complex and the reactions are catalyzed by enzymes of different specificity from that of the primary metabolism **(Figure 4)**. The structural diversity of mycotoxins results from the variety of chemical reactions (cyclization, aromatization, glycosylation, hydroxylation and epoxidation) involved in their biosynthesis **(Modrzewska *et al*., 2022)**.

Mycotoxins have three main biosynthetic origins, and derive from precursors of primary metabolism, such as Acetyl-CoA (AFS, fumonisins, sterigmatocystine, zearalenone, OTA), amino acids (ergot alkaloid, OTA) and terpenes (trichothecenes). Some syntheses are called mixed they use the fusion of biosynthetic pathways **(Boettger & Hertweck, 2013)**. As a result, mycotoxins form 4 classes: polyketoacids, cyclopeptides, terpenes, and the hybrids, all of which are metabolized from glucose. The production of these toxins is catalyzed by certain enzymes, including, polycetide synthase (PKS), nonribosomal peptide synthase (NRPS) and deterpenes cyase (TC). All the enzymes necessary for the successful formation of the mycotoxin must be present at the same time. The genes coding for these enzymes are organized in cluster (enzyme cluster) within the genome of the fungus.

The presence of a gene cluster does not systematically mean that the fungal species is able to synthesize the corresponding mycotoxin. Thus, that within the same fungal family some strains have only a part of the cluster, thus express part of the cluster, and thus express a toxin different from the other strains. A large number of clusters of genes associated with

secondary metabolism are identified **(Khaldi *et al.*, 2010)**. In 2016, the OTA biosynthetic pathway was confirmed in *A. carbonarius* **(Ferrara *et al.*, 2016)**.

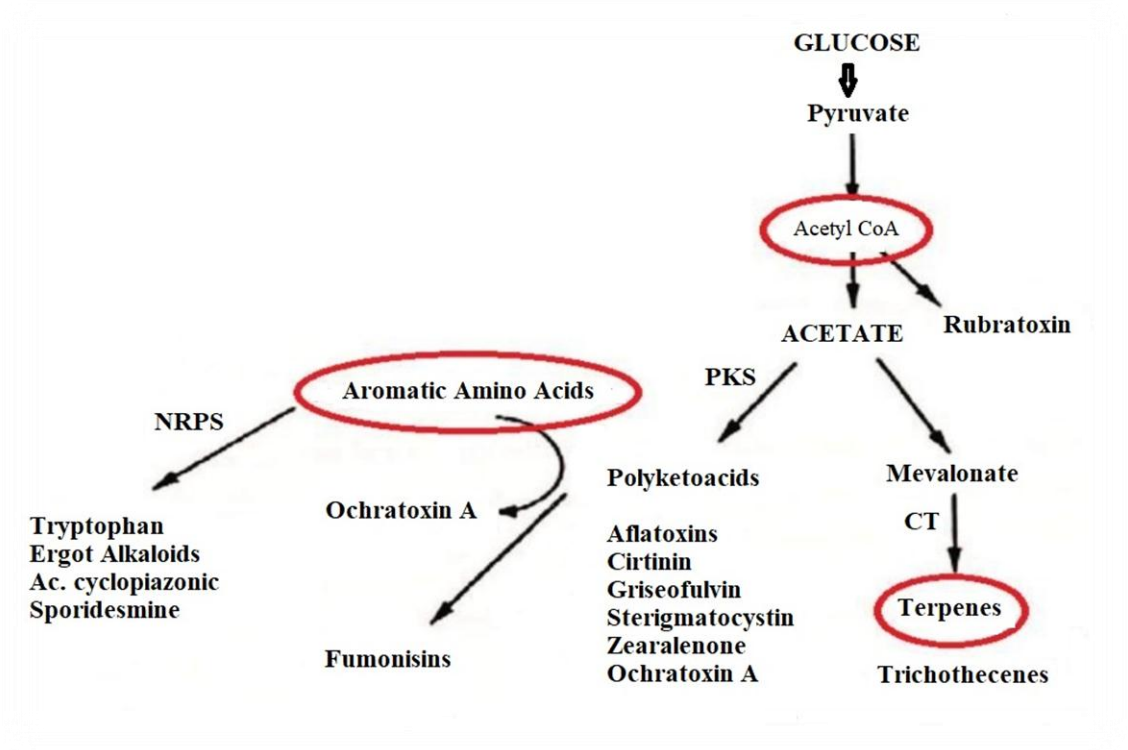


Figure 4. Biosynthetic pathways of mycotoxins **(Tabuc *et al.*, 2009**).

External environmental factors, such as pH, temperature, light, and substrate nature can influence the regulation of gene clusters in the metabolism of mycotoxin **(Brakhage, 2013)**. Mycotoxin production is dependent on the fungi present, agronomic practices, commodity composition, and conditions of harvest, handling, and storage conditions **(Bryden, 2012)**. The amount of toxin produced will depend on physical factors (moisture, temperature and mechanical damage), chemical factors (carbon dioxide carbon (CO_2), oxygen (O_2), substrate composition, pesticide, and fungicides) and (plant variety, stress, insect and fungal spore load Geographical distribution of the main mycotoxins **(Modrzewska *et al.*, 2022**).

The appearance of mycotoxins in an environment results from a complex process. Thus, the mapping of the distribution of toxins throughout the world is not very precise. **Figure 5** shows the map of mycotoxin contamination rates in different regions of the world. In Africa and Asia, aflatoxins are mainly found. In the temperate zones of the areas of the world, such as Europe and North America, the most common mycotoxins are fusariotoxins

(Smith *et al*., 2016). However, climatic conditions and agricultural practices specific to each region can specific to each region may favor the production of some mycotoxins over others **(Rodrigues & Naehrer, 2012)**.

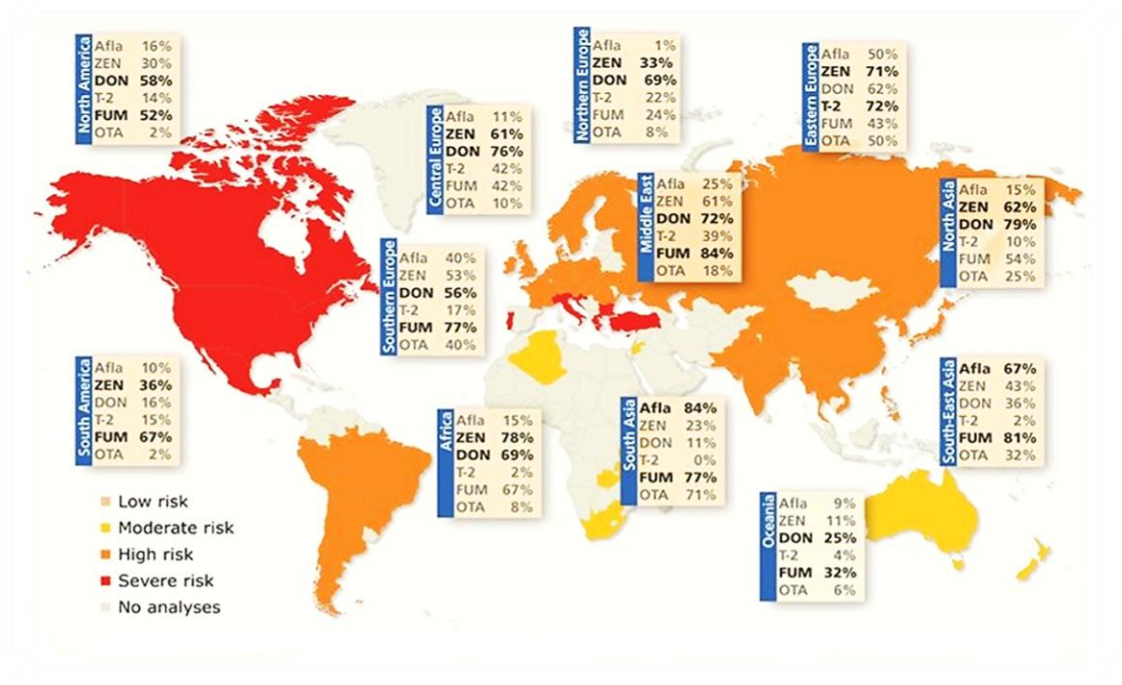


Figure 5. Map of food contamination rates of major mycotoxins indifferent regions of the world **(Naehrer, 2015)**.

I.2.3.Exposure

The clinical manifestations of mycotoxin exposure for humans and animals, can be either acute (hemorrhages, diarrhea, convulsions, tremors, vomiting, lethargy, edema and even death), observed after exposure to a single high dose; or chronic (mutagenic, teratogenic, carcinogenic) occurring after ingestion of moderate doses of toxin for a long period of time **(Wen *al*., 2016)**. Animals fed food contaminated with mycotoxins release products that may be dietary sources of some mycotoxins **(Kępińska-Pacelik & Biel, 2021)**.

Carcinogenic toxins are classified according to the groups established by the International Agency for Research on Cancer **(Žegura *et al*., 2011)** into:

Group 1: the agent is carcinogenic to humans.

Group 2 A: the agent is probably carcinogenic to humans.

Group 2 B: the agent is possibly carcinogenic to humans.

Group 3: the agent is unclassifiable as to its carcinogenicity to humans.

Group 4: the agent is probably not carcinogenic to humans.

I.2.4.Mycotoxin regulation and legislation around the world

In Africa, fifteen countries are known to have specific mycotoxin regulations, most of which relate to aflatoxins **(Ukwuru *et al*., 2017)**. Table 2 shows limits for OTA and other mycotoxins in food and raw materials in a few North African countries. Many countries (about 100) have adopted regulations regarding the levels of fungal toxins in food and feed (Food and Agriculture Organization of the United Nations) **(Van Egmond & Jonker, 2004)**.The regulations and recommendations of the European Commission (EC) related to cereal control are summarized in **Table 3**. The limits for OTA are 5µg/kg in raw cereals and 3µg/kg in cereal products.

Table 2. Maximum levels (µg/kg) of mycotoxins in various human foods in some North African countries **(Egmond & Jonker, 2004; Zinedine *et al*., 2006).**

Mycotoxins	Foodstuffs	Morocco	Tunisia	Algeria	Egypt
AFB1	Wheat flour	3			
	Cereals	10	2	10	5
	Corn, peanuts, pistachios, nuts and almonds, peanuts and oilseeds	1			10
AFB1, B2, G1 and G2	Cereals except corn				10
	Corn				20
	Peanuts and oilseeds				10
AFM1	Milk for adults	0.05			0.5
	Milk for children	0.03			
OTA	Cereals	30			
	Coffee				5
Zearalenone	Cereals	200			1000
Deoxynivalenol	Wheat and wheat flour				700
	Barley and barley flour				1000

Table 3. Maximum levels (µg/kg) of mycotoxins in various human foods **(European Commission, 2006)**.

Mycotoxins	Foodstuffs	Level Maximum
AFB1	All cereals and their derivatives intended for human consumption.	2
	Cereal-based preparations and baby food intended for infants and young children	0.1
	Dietary foods for special medical purposes specifically intended for infants.	0.1
Deoxynivalenol	Unprocessed wheat other than durum wheat.	1250
	Unprocessed wheat.	1750
	Cereals intended for direct human consumption, flour, bran and germ in the form of finished product for direct human consumption (excluding food for infants and young children).	750
	Pasta (dry).	750
	Bread, pastries, cookies, cereal snacks and breakfast cereals (including small bakery products).	500
	Processed cereal-based foods and foods intended for infants and young children.	200
B2, G1 and G2	All cereals and their derivatives intended for human consumption human food.	4
Zearalenone	Unprocessed wheat.	100
	Cereals intended for direct human consumption, flour, bran and germ in the form of finished product for direct human consumption (excluding food for infants and young children).	75
	Bread, pastries, cookies, cereal snacks and breakfast cereals, except for with the exception of corn-based products.	50
	Processed cereal-based foods and foods for infants and for infants and young children.	20

OTA	Unprocessed cereals.	5
	Unprocessed cereal products and processed cereals. In addition, products intended for direct human consumption (excluding wheat gluten not sold directly to the consumer as well as foods for infants and young children and dietary children and dietetic foods for special medical purposes and specifically intended for infants).	3
	Wheat gluten not sold directly to the consumer.	8
	Processed cereal-based foods and foods for infants and young children.	0.5
	Dietary foods for special medical purposes intended specifically for infants.	0.5
Sclerotia of Ergot	Wheat unprocessed.	50000

II. Ochratoxin A

II.1.Nature and structure

OTA was first isolated in 1965 by a group of South African researchers from an isolate of *A. ochraceus* **(Van der Merwe *et al.*, 1965)**. It was subsequently identified under natural conditions in the USA in 1969 in a sample of maize, then in all countries of the world **(Mahideb & Merrouche, 2022)**. The formula of OTA is $C_{20}H_{18}ClNO_6$. Its scientific name is L-Phenylalanine, N-[(5-chloro-3, 4-dihydro8-hydroxy-3-methyl-1-oxo-1H-2-benzopyran-yl-7)-carbonyl],(R) **(Weidenbörner, 2001)**. OTA is a mycotoxin, derived from the dihydrocoumarin family. It is formed by a substituted isocoumarin group (7-carboxy-5-chloro-8-hydroxy-3, 4-dihydro-3R methyl isocoumarin) linked to L-ß-phenylalanine by an amide bond **(Gauthier, 2016)**. This group includes a general structure that can depending on the R groups, in addition to OTA, give different analogs of structures **(Asma & Maizi Nahla, 2021)** (**Figure 6**).

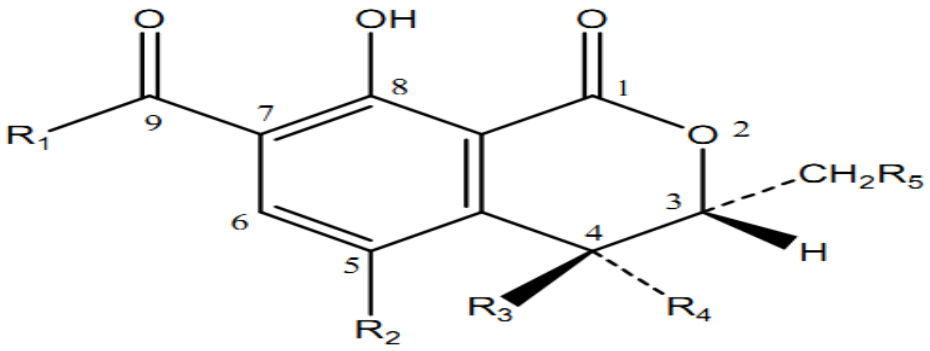


Figure 6. General structure of OTA **(El Khoury & Atoui, 2010)**.

II.2.Physico-Chemicals Properties of Ochratoxin A

OTA is a white solid with a molar mass of 403.8 g/mole. Its melting point is 90°C when crystallized in benzene, and 169°C when crystallized in xylene**.** OTA is a weak acid with a pKa of 7.1. At neutral and acid pH, OTA is soluble in polar organic solvents and very slightly soluble in aqueous solutions. At basic pH, it is soluble in aqueous solutions of sodium bicarbonate, and generally in alkaline aqueous solutions **(Elsaadani, 2019).** OTA exhibits significant fluorescence under ultraviolet (UV) rays: green in acid medium, and blue in

alkaline medium. This fluorescence is at the origin of OTA detection and assay methods **(Azémar, 2000)**. Generally, OTA is stable **(Duarte *et al.*, 2010)** and can be stored in the refrigerator dissolved in ethanol or methanol. Several studies show its stability with respect to temperature and γ radiation when dissolved in methanol OTA Producing Fungi **(Elsaadani, 2019)**.

II.3.Ochratoxin A producing fungi

OTA is produced by a wide variety of species belonging to the genera *Aspergillus* (section *Flavi, Circumdati* and *Nigri*) and the genus *Penicillium* **(Table 4) (Elmholt & Rasmussen, 2005; Özcan *et al.*, 2015)**. The main fungi responsible for the production of OTA in food and foodstuffs are *A. alliaceus, A. carbonarius, A. ochraceus, A. steynii, A. westerdijkiae, P. nordicum* and *P. verrucosum* **(Frisvad *et al.*, 2006)**.

Table 4. Ochratoxin A production mainly by *Aspergillus* and *Penicillium* species.

Organism/Name	SubGroup	Section	References
A.*westerdijkiae*	Ascomycetes	*Circumdati*	**(Han *et al*., 2016).**
A.melleus	Ascomycetes	*Circumdati*	
A. ochraceus	Ascomycetes	*Circumdati*	
A. steynii	Ascomycetes	*Circumdati*	
A.subramanianii	Ascomycetes	*Circumdati*	
A. sesamicola	Ascomycetes	*Circumdati*	
A. affinis	Ascomycetes	*Circumdati*	**(Yan Wang *et al*., 2016).**
A. muricatus	Ascomycetes	*Circumdati*	
A. occultus	Ascomycetes	*Circumdati*	
A. ochraceopetaliformis	Ascomycetes	*Circumdati*	
A. flocculosus	Ascomycetes	*Circumdati*	
A. pseudoelegans	Ascomycetes	*Circumdati*	**(Frisvad *et al*., 2004).**
A. roseoglobulosus	Ascomycetes	*Circumdati*	
A. sclerotiorum	Ascomycetes	*Circumdati*	**(Han *et al*., 2016).**
A. persii	Ascomycetes	*Circumdati*	
A. salwaensis	Ascomycetes	*Circumdati*	

Table 4. Cont.

Organism/Name	SubGroup	Section	References
A. carbonarius	Ascomycetes	*Nigri*	**(Abarca *et al*., 2004;**
A. niger	Ascomycetes	*Nigri*	**Samson *et al*., 2007).**
A. lacticoffeatus	Ascomycetes	*Nigri*	
A. sclerotioniger	Ascomycetes	*Nigri*	
A. alliaceus	Ascomycetes	*Flavi*	**(Bayman *et al*., 2002).**
A . avenaceus	Ascomycetes	*Flavi*	
A. bertholletius	Ascomycetes	*Flavi*	
A. coremiiformis	Ascomycetes	*Flavi*	
A. flavus	Ascomycetes	*Flavi*	
A. leporis	Ascomycetes	*Flavi*	**(Baranyi *et al*., 2015;**
A. nomius	Ascomycetes	*Flavi*	**Camiletti *et al*., 2017;**
A. tamarii	Ascomycetes	*Flavi*	**(Saldan *et al*., 2018;**
A. pseudotamarii	Ascomycetes	*Flavi*	**Frisvad *et al*., 2019)**.
A. vandermerwei	Ascomycetes	*Flavi*	
A. neoalliaceus	Ascomycetes	*Flavi*	
P. nordicum	Ascomycetes	*Verrucosa*	**(Larsen *et al*., 2001);**
P. verrucosum	Ascomycetes	*Verrucosa*	**(Lund & Frisvad, 2003).**

II.4.Biosynthetic Pathway and Regulatory Mechanisms

II.4.1.Biosynthetic Pathway

Although OTA is one of the most threatening mycotoxins to food safety, its biosynthetic pathway is still not fully understood, compared to other mycotoxins **(Huffman *et al.*, 2010)**.

The OTA biosynthetic pathway was confirmed following the identification and sequencing of the gene encoding a haloase/choloperoxidase in *A. carbonarius*. The mutation of this gene resulted in the excessive production of OTB, without any detection of OTA. The metabolites that precede the formation of formation were also detected, placing chlorination as the last step in the biosynthetic pathway **(Ferrara *et al.*, 2016)**. The chemical structures of intermediates in OTA production, such as OTB and OTβ, as well as OTα are shown in **figure 7**.

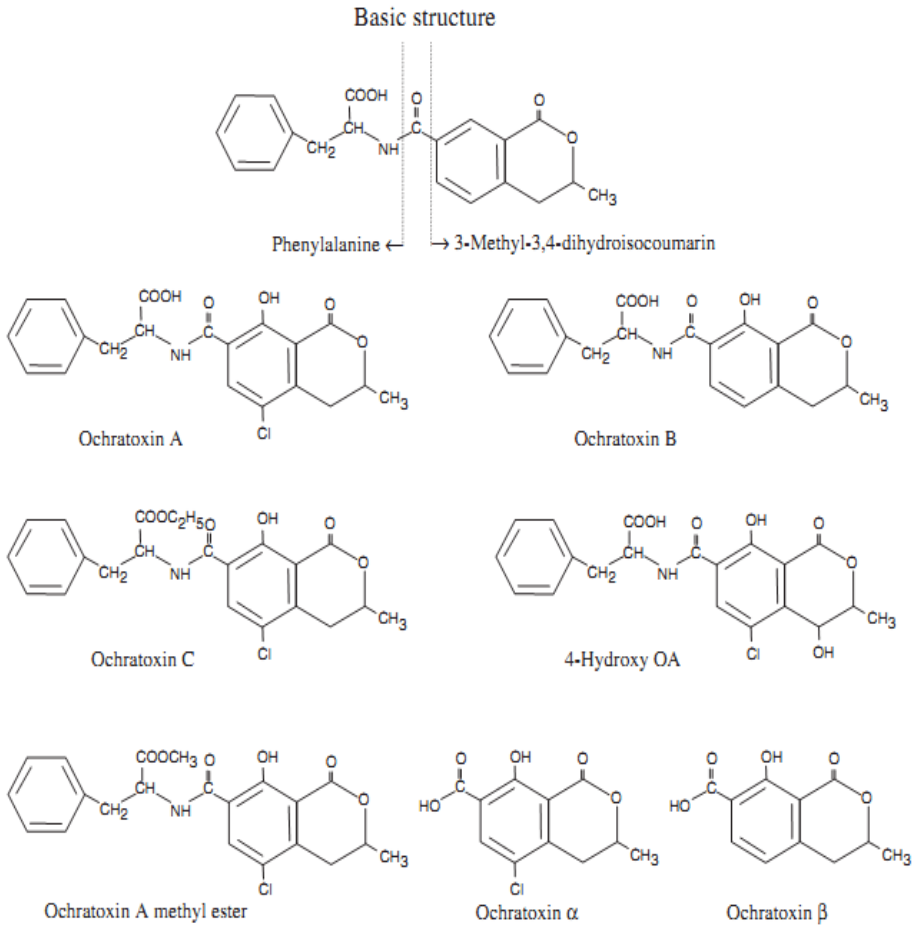


Figure 7. Chemical structure of OTA metabolites **(Almela *et al.*, 2007)**.

II.4.1.1.Genes for OTA biosynthesis in *A. Carbonarius*

Polyketide Synthases (PKS) and Non Ribosomal Peptide Synthases (NRP) have been identified as multi-module enzymes involved in the biosynthesis of polyketides and peptides. Modules, involved in polyketide and peptide biosynthesis, respectively, essential for the production of secondary metabolites in fungi **(Gallo *et al*., 2013)**. The chloroperoxidase responsible for the addition of a chlorine atom present in OTA has been similarly identified in several ochratoxinogenic strains **(Figure 7)**.

a) Polyketide Synthases of OTA

The family of polyketides includes metabolites derived from the repetitive condensation of acetate units (-CH_2-CO-) via enzymes known as "polyketide synthases or "PKS"

- Gene identified in*A. Carbonarius*: AcOTApks (PI no. 173482), consisting of 8,063 bp, was sequenced by **Gallo *et al*. (2014)**.
- PKS in *A. Carbonarius:*
- Domains: KS (β-ketosynthase), AT (acyltransferase), DH (dehydratase), C-Met (C-methyltransferase) responsible for the addition of the methyl group to the OTA molecule.
- The C-terminus contains the ER (enoyl reductase) domains, KR (ketoreductase) and ACP (acylCoA precursor carrier) domains.

b) Non Ribosomal Peptide Synthases (NRPS)

Fungal NRPS are multifunctional enzymes composed of enzyme modules used to extend the amino acid chain. In NRPS, the number and order of modules represent the number and order of amino acids found in the final acids product **(Amoutzias *et al*., 2008; Schwarzer & Marahiel, 2001)**:

- Gene identified in *A. Carbonarius*: acOTAnrps, consisting of 5691 bp (PI no. 132610) **(Gallo *et al*., 2012)**.
- NRPS in *A. Carbonarius:* Consisting of 1875 amino acids and characterized by the presence of three core domains and an adenylation domains.

c) Halogenase/chloroperoxidase

The involvement of a choloroperoxidase in the OTA biosynthetic pathway has been postulated based on the chemical structure of this toxin**.** The first evidence for the involvement of this enzyme was reported in *P. nordicum* following the detection of the *otachlPN* gene encoding a halogenase. In this study carried out on this fungus, 30 activated genes were detected during OTA synthesis, when the fungus is grown under conditions that favour OTA production **(Färber & Geisen, 2004 ; Karolewiez & Geisen, 2005)**. Recently, Ahaloase/chloroperoxidase has been identified in *A. carbonarius* by **Ferrara *et al*. (2016)** which has the role of adding a chlorine atom to OTB (a non-chlorinated analogue of OTA) in order to OTA to give the final structure of OTA, bearing a chlorine atom on its C5 carbon.

II.4.2.Regulation Mechanisms of OTA Biosynthesis

The regulation of OTA biosynthesis is complex and depends on many factors, such as the presence of nutrients, oxygen concentration and the expression of genes involved in biosynthesis. Studies have shown that signaling pathways involving hormones and transcription factors regulate OTA biosynthesis.

II.4.2.1.Light and the velvet complex as regulators of OTA production

The velvet complex "VelB/VeA/LaeA" has been widely described, containing domains conserved throughout the fungal kingdom **(Bayram & Braus, 2012)**. This complex is localized mainly in the nucleus in the absence of light **(Bayram *et al*., 2008)**. In the presence of light, VeA is located in the cytoplasm and VelB promotes the formation of asexual spores. In the dark, the VelB / VeA complex is transported to the nucleus and causes an increase in the activity of LaeA, a master epigenetic regulator of secondary regulator for secondary metabolism in the genus *Aspergillus* (**Figure 8**) **(Bok & Keller, 2004)**.

As for the regulatory genes, VeA and laeA in *A. carbonarius* were identified by **(Sempere *et al*., 2013)**. These genes respectively code for two called VeA (PI no. 202676) and LaeA (PI no. 5941). Indeed, following inactivation of these genes in *A. carbonarius*, vegetative growth is affected not significantly, however, a significant reduction in conidial production was production is noticed **(Sempere *et al*., 2013)**.

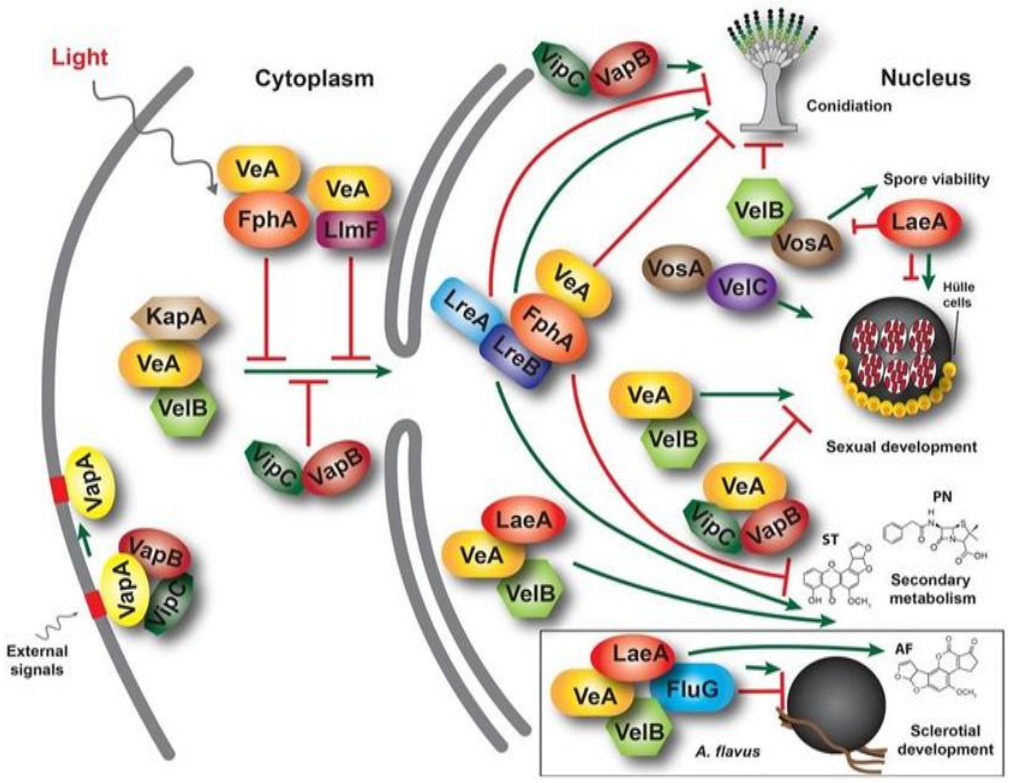


Figure 8. Interaction between the velvet family complexes and the LaeA protein in *nidulans***.** (KapA: transport protein) **(Calvo & Cary, 2015)**.

II.4.2.2.Oxidizing molecules and oxidative stress

The hypothesis of the involvement of oxidative stress in the of OTA synthesis in *A. ochraceus* was confirmed by the disruption of the AyloxA gene, encoding a lipoxygenase in this fungus **(Reverberi *et al*., 2012)**. The inactivation of this gene induces a change in of the phenotypes and conidia formation, a decrease in lipoxygenase activity, and a significant inhibition of OTA production in *A. ochraceus*. Oxidative stress not only affects the production of OTA, but can also induce production of citrinin instead of OTA, thus revealing the phenomenon of "cross-regulation of the OTA/citrinin biosynthetic pathway in *P. Verrucosum* **(Heydt *et al*., 2015)**.

II.4.2.3.Nutrient factors: source of carbon and nitrogen

Fungi prefer easily metabolized carbon sources to other hydrocarbon sources. This is because easily metabolized carbon suppresses the synthesis of enzymes related to the catabolism of other hydrocarbons, thus ensuring preferential use of the carbon source for each species. This mechanism, known as 'carbon repression', has been well studied in *A. nidulans* and *A.niger* and involves the repressor protein known as CreA (RNA). In the presence of

glucose, CreA inhibits the transcription of many target genes by binding to the specific consensus sequence of G/CPyGGGG in the promoter region of these genes **(Medina *et al*., 2008)**. Genes related to secondary metabolism such as ipnA (involved in the biosynthesis of penicillin biosynthesis in *A. nidulans*) belong to the category of genes influenced by CreA, CreA has shown its involvement in the regulation of proline, ethanol and xylene utilization in *A. nidulans* **(Wang *et al*., 2016)**. In his study, **Hashem *et al*. (2015)** evaluated the growth of *A. carbonarius* cultured with several carbon sources and its ability to produce and its ability to produce OTA under these conditions.

Similarly, **Hashem *et al*. (2015)** studied the effect of different nitrogen sources on OTA production, and found that the use of yeast extract and ammonium nitrate (NH_4NO_3) is optimal for the growth of this fungus and OTA production. In contrast, ammonium chloride (NH_4Cl), urea (CH_4N_2O) and ammonium sulphate $(NH_4)_2SO_4$) do not support OTA production and OTA production and fungal growth.

II.4.2.4.Effect of the pH of the medium

Fungi, like many other microorganisms, are able to adapt to environmental changes. In particular, fungi can grow and adapt to extreme pH levels. This phenomenon has been studied in several classes of fungi. These fungi are able to modify the expression of certain genes, allowing them to survive in a wide range of pH. This transcriptomic reorganisation affects the genes involved in the production of molecules intended for communication with the external environment. In other words, these are ligands located on the cell surface or enzymes and metabolites intended for secretion **(Peñalva *et al*., 2008)**. It was in the 1960s that pH-specific regulation was demonstrated in *A. nidulans* following the isolation of the so-called pal mutants (alkaline phosphatase deficient) and "mutant pac" (acid phosphatase deficient) **(Yan Wang *et al*., 2016)**.

Later, **Caddick *et al*. (1986)** demonstrated that the genes palA, palB, palC, palE, palF and pacC are involved in the regulation of metabolite biosynthetic pathways in fungi in the face in response to pH changes. Subsequently, it was shown that translation products of the pal and pacC genes form a signalling cascade in response to extracellular pH variation that ends with the PacC protein **(Peñalva *et al*., 2008)**. This protein contains three zinc motifs that attach to the '5'-GCCARG' consensus sequence of the gene promoter region in *A. nidulans* **(Yan Wang *et al*., 2016)**.

In *A. ochraceus*, however, the variation of the pH of the medium seems to have a non-significant effect on OTA production, compared to that of water activity and temperature **(Kapetanakou *et al.*, 2009)**. This may be due to the absence of the PacC binding site in the promoter region of the PKS gene in *A. carbonarius*. Indeed, in his study on the regulation of OTA production by external stimuli, **Thomas *et al.* (2015)**found that this site was found that this site was present in only 4 isolates among 18 strains of belonging to the *Nigri* section and producing OTA. This observation could be the reason why pH is not considered an important factor in the regulation of OTA production in fungi belonging to section *Nigri*, especially *A. carbonarius*.

II.4.2.5.Osmotic stress

A. carbonarius generally produces high amounts of OTA, compared to those produced by *P. nordicum*. In contrast, *P. verrucosum* generally produces only moderate amounts of OTA compared to *P. nordicum*. In fact, the production of OTA production by the genus *Penicillium* is highly dependent on environmental conditions such as osmotic and oxidative stress. Indeed, *P. verrucosum* is able to produce citrinin instead of OTA following oxidative stress, whereas under osmotic stress citrinin production is shifted to OTA **(Heydt *et al.*, 2012)**. The biosynthesis and excretion of OTA can be seen as a kind of adaptation to NaCl-rich environments. The excessive production of OTA in a NaCl-rich environment by the genus *Penicillium* is considered a means of transporting chlorine out of the cell, to ensure a certain homeostasis, thus favoring the survival of these fungi under such conditions **(Heydt *et al.*, 2012)**.

Unlike the two *Penicillium, A. carbonarius* has never been found in environments rich in NaCl. This indicates that it is not adapted to this type of habitat. Changes in the osmolarity of the medium, at the transcriptional level via signal cascades. Fungi have various signaling cascades, which are activated by different external signals **(Rispail *et al.*, 2009)**. The signal cascade activated by high osmolarity, is known as 'HOG' (High Osmolarity Glycerol) **(Rispail *et al.*, 2009)**. The latter is composed of a receptor sensitive to external osmolarity changes, located at the membrane and which transmits the signal to a set of three consecutive protein kinases (MAP kinases), the last of which is the HOG protein kinase **(Rispail *et al.*, 2009)**. The phosphorylated form of kinase is the active form and can activate downstream transcription factors by phosphorylation. This adaptation mechanism promotes the continuous production of OTA production that ensures the viability of the producing organism in NaCl-rich

environments. The mechanism should theoretically be present in all organisms producing this toxin. However, this is not the case for *A. carbonarius*, which has drastically lost its capacity for OTA biosynthesis as well as its ability to grow when growth when grown in medium supplemented with 40 g/l NaCl **(Stoll *et al*., 2013)**. This may be because phosphorylation and activation of OTA biosynthesis are apparently not coupled in this fungus. Thus, following osmotic stress caused by NaCl, *A. carbonarius* seems to have difficulties in adapting and produce OTA under these conditions **(Stoll *et al*., 2013)**.

II.5.Regulation and legislation

In 1990, JECFA decided to establish a weekly tolerable daily intake of 112 ng OTA/kg body weight, which was determined based on pig nephropathy data.

The high council of public hygiene of France, based on carcinogenicity studies, proposed a carcinogenicity studies, has proposed a tolerable daily exposure of 5ng/kg bw/day, which implies a maximum this contamination in cereals of 5µg/kg **(Asma & Nahla, 2021)**.

The Scientific Committee on Food considered in its opinion on OTA of 17 September 1998, that it would be prudent to reduce exposure to OTA as much as possible OTA, ensuring that exposures are close to the lower range of tolerable exposures (between 1 and 2 µg/kg). Range of tolerable exposures (between 1.2 and 14 ng/kg body weight per day), for example, below 5ng/kg body weight per day **(Hayat *et al*., 2012)**.

For products derived from cereals, contamination is limited to 3µg/kg. EC Regulation No. 683/2004 of 13 April 2004 amending Regulation No. 466/2001 included a directive limiting OTA contamination to 0.5µg/kg of food in cereal-based preparations, processed cereal-based foods, baby foods intended for infants and young children, as well as in dietary foods for special medical purposes intended for infants (**Table 5**) **(EC, 2001)**. It includes a new guideline that also aims to limit OTA contamination in coffee; it sets the maximum level of OTA at 5µg/kg in roasted coffee beans and 10µg/kg in soluble coffee **(EC, 2005)**.

EC Regulation 466/2001 recalls that it is forbidden to mix products that comply with the non-compliant products in order to reduce the level of contamination, and that the use of products not complying with the established levels for the preparation of other foods is prohibited. The sampling method and the methods of analysis for the determination of OTA in foodstuffs are described in Directive 2002/26/EC. OTA in foodstuffs published in the Official Journal No. L075. These directives aim to estimate and limit the presence of OTA in

various foodstuffs, imply that plans are in place to reduce the contamination of foodstuffs by this mycotoxin **(Asma & Maizi Nahla, 2021)**.

Most of the existing mycotoxin regulations in Africa relate to AFs. Algeria has, to our knowledge, not yet set maximum levels for OTA in food **(Riba, 2008)**.

Table 5. Maximum levels of Ochratoxin A in foodstuffs expressed in µg/kg **(Regulation (EC) No 1881, 2006)**.

Foodstuff	**Maximal content (µg/kg)**
Unprocessed cereal grains (including unprocessed rice and buckwheat).	5
Cereal products (including processed cereal products and cereal grains for direct consumption).	3
Cereal-based preparations for young children for special medical purposes specifically for infants.	0.5
Sultanas (currants, sultanas and other sultanas).	10
Roasted coffee beans and ground roasted coffee.	5
Soluble coffee (instant).	10
Wine (red, white and rosé and other wine-based drinks and/or grape must).	2
Grape juice, ingredients in other beverages,drinks, including grape nectar and reconstituted concentrated grape juice.	2

III.Occurrence of OTA in food

OTA has been discovered in numerous agricultural products from the majority of the world's countries such as rice, wheat, corn, rye, barley, oats, millet, and other cereals, as well as their byproducts, are staple foods in people's diets all over the world. They are the primary source of OTA contamination and fungus development because of climate factors and storage procedures. Human exposure sources **(Duarte *et al*., 2010)**. OTA was found on the continents of Asia, North America, Africa, and Europe, as stated in **table 6**. While crops are being harvested, dried, and stored, the humidity, temperature, and water activity of the environment have a crucial role in the formation of OTA. About 15% of the examined feed samples had positive results, according to a ten-year global survey **(Dorninger *et al*., 2019)**. In terms of total dietary intake in Europe, wine is in second place to cereals as a source of OTA **(Authority, 2010)**. Damaged grapes are prone to ochratoxigenic fungal infection, and the high sugar matrix offers the ideal environment for OTA synthesis. Several factors, including geographic and climatic parameters, have been shown to impact OTA levels in wine. Contamination appears to occur in the vineyard. Europe is a significant producer and consumer of wine. Thus, in Regulation 1881/2006 **(Valero *et al*., 2008)**, the EC established the maximum OTA levels in wine at 2 g/l. As seen in **Table 7**, although OTA occurs frequently in wines, it rarely reaches this maximum residue limit (MRL).

About 9% of all OTA intake in Europe comes from coffee, the third-largest source of exposure **(Li *et al*., 2021)**. The MRL for OTA in coffee has been determined by the EC at 5 g/kg. Tropical regions are where coffee trees are grown; although coffee is roasted all over, both the plant environment and the processing conditions significantly influence the world. Worldwide, there is a huge beer market. OTA may be transferred from contaminated cereals to beverages made from cereals (**Table 8**). A crucial component of many meals, especially chocolate, is cocoa. A significant mycotoxin found in cocoa is OTA. Tropical regions are used to produce cocoa. While during the steps of preparation and storage, fungus and OTA can contaminate the beans. The EC has set an MRL for OTA in cocoa at 2 g/kg as a result. Despite the fact that the majority of production occurs in Western Africa, there are not many reports of OTA in cocoa. Even though fruits, dried fruits (figs, raisins) and nuts (almonds, pine nuts, hazelnuts, chestnuts, and walnuts) are one of the more nutrient-dense and widely consumed foods, OTA contamination is a significant problem with them **(Covarelli *et al*., 2012)**. Many spices are frequently used in meals. The OTA contamination is more harmful

due to their production and storage conditions, even though their consumption quantity is not similar to the items previously mentioned. According to EC Regulation 1881/2006, the MRLs for OTA in spices were 15-20 g/kg **(Li *et al*., 2022)**.

Cereals are a component of animal feed, and OTA can build in these species through the food chain (**Table 9**). Animal-derived food consumption, particularly pig, has long been associated with health concerns **(Duarte *et al*., 2012)**.

However, Regulation 1881/2006 of the EC and GB 2761 of China did not set the MRLs for OTA in meat and derivative products. A study of the distribution of OTA in pig tissues found that the following tissues had the highest concentrations: blood plasma, lung, kidney, heart, bile, liver, fat, and muscle **(Altafini *et al.*, 2017)**. Because of dietary OTA consumption by animals, OTA was also found in milk products. According to EC Regulation 1881/2006, the MRLs for OTA in infant formula were 0.025g/kg **(Li *et al*., 2022)**.

Table 6.OTA occurrence and contamination level in cereals.

Matrix	Nation	Year of Production	No. of Samples	Occurrence (%)	Maximum (mg/kg)	Mean (mg/kg)	References
Wheat	100 nations	2008–2017	74,821	115	2000	/	**(Dorninger *et al*., 2019).**
Rice	China	2009–2011	370	4 4,9	3.2	0.85	**(Lai *et al*., 2015) .**
Corn, wheat	Pakistan	2015	40	27.5	360	/	**(Majeed *et al*., 2018).**
Maize	Pakistan	2016–2017	46	71	218.25	/	**(Hassan *et al*., 2020).**
Rice, corn, and corn product	Pakistan	2011–2012	275	32	/	/	**(Majeed *et al*., 2013)**
Rice	Pakistan	/	208	19	24.9	/	**(Iqbal *et al*., 2016).**
Cereal based baby foods	Iran	2017–2018	64	41	1.1	0.42	**(Khoshnamvand *et al*., 2019).**
Rice	Iran	/	308	9.4	11.4	/	**(Taghizadeh *et al*., 2020)**
Barley and wheat	USA	2011–2012	262	12.2	185.2 4	/	**(Kuruc *et al*., 2015).**
Corn, oat, wheat and rice	USA	2012–2013	144	53	7.43	0.61	**(Nguyen & Ryu, 2014).**
Infant cereal	USA	2012–2014	155	30	22.1	/	**(Cappozzo *et al*., 2017).**
Corn, rice, wheat and oat based	USA	2012–2014	489	41	9.3	/	**(Lee & Ryu, 2015).**

Table 6. Cont.

Matrix	Nation	Year of Production	No. of Samples	Occurrence (%)	Maximum (mg/kg)	Mean (mg/kg)	References
Wheat	Canada	2011–2014	232	2.2	/	14.7	**(Limay-Rios *et al*., 2017).**
Wheat and derived samples	Algeria	2012–2013	81	76.65	34.75	/	**(Zebiri *et al*., 2019).**
Cereal based foods	Portugal	2015	20	50	0.263	0.061	**(Assunção *et al*., 2016).**
Flour	Serbia	2012–2016	114	29	23.04	0.46	**(Torović, 2018).**
Rye	Poland	2017–2019	60	3	2.75	/	**(Kosicki *et al*., 2020).**
Wheat	100 nations	2008–2017	74,821	115	2000	/	**(Gruber-Dorninger *et al*., 2019).**
Rice	China	2009–2011	370	4 4,9	3.2	0.85	**(Lai *et al*., 2015).**
Corn, wheat	Pakistan	2015	40	27.5	360	/	**(Majeed *et al*., 2018).**
Maize	Pakistan	2016–2017	46	71	218.25	/	**(ul Hassan *et al*., 2020).**
Rice, corn and corn product	Pakistan	2011–2012	275	32	/	/	**(Majeed *et al*., 2013).**
Rice	Pakistan	/	208	19	24.9	/	**(Iqbal *et al*., 2016).**
Cereal based baby foods	Iran	2017–2018	64	41	1.1	0.42	**(Khoshnamvand *et al*., 2019).**
Rice	Iran	/	308	9.4	11.4	/	**(Taghizadeh *et al*., 2020).**

Table 6.Cont.

Matrix	Nation	Year of Production	No. of Samples	Occurrence (%)	Maximum (mg/kg)	Mean (mg/kg)	References
Barley and wheat	USA	2011–2012	262	12.2	185.2 4	/	**(Kuruc *et al*., 2015).**
Corn, oat, wheat and rice	USA	2012–2013	144	53	7.43	0.61	**(Nguyen & Ryu, 2014).**
Infant cereal	USA	2012–2014	155	30	22.1	/	**(Cappozzo *et al*., 2017).**
Corn, rice, wheat and oat-based breakfast cereal	USA	2012–2014	489	41	9.3	/	**(Lee & Ryu, 2015).**
Wheat	Canada	2011–2014	232	2.2	/	14.7	**(Limay-Rios *et al*., 2017).**
Wheat and derived samples	Algeria	2012–2013	81	76.65	34.75	/	**(Zebiri *et al*., 2019).**
Cereal based foods	Portugal	2015	20	50	0.263	0.061	**(Assunção *et al*., 2016).**
Flour	Serbia	2012–2016	114	29	23.04	0.46	**(Torović, 2018).**
Rye	Poland	2017–2019	60	3	2.75	/	**(Kosicki *et al*., 2020).**

Table 7.OTA occurrence and contamination level in other plant-derived food.

Matrix	Nation	Year of Production	No. of Sample	Occurrence (%)	Maximum (µg/kg)*	Mean (µg/kg)*	Reference
Soluble coffee and coffee substitutes	Portugal	2012	40	87.5	11.8	/	**(Casal *et al*., 2014).**
Roasted coffee	Portugal	/	11	27.3	10.31	1.13	**(Benites *et al*., 2017).**
Roasted coffee	Spain	2008	72	48.6	4.21	2.17	**(Coronel *et al*., 2011).**
Roasted coffee	France	/	30	100	11.9	/	**(Tozlovanu & Pfohl-Leszkowicz, 2010).**
Coffee and coffee products	Italy	2011	50	96	6.4	/	**(Vecchio *et al*., 2012).**
Roasted and instant coffee	Czech	2016–2018	103	80.6	12.8	/	**(Jonatova *et al*., 2020).**
Coffee bean roasted coffee and soluble coffee	Argenti-na	/	51	69	20.3	/	**(Vanesa & Ana, 2013).**
Roasted and instant coffee	Chile	/	63	33	7.25	1.3	**(Galarce-Bustos *et al*., 2014).**
Fermented coffees	Brazil	2017	14	21.4	0.87	0.18	**(Silva *et al.*, 2021).**
Green coffee	9countries	2015–2016	71	28	12.2	1.3	**(Bessaire *et al*., 2019).**
Beer	Italy	/	30	16.6	/	0.35	**(Prelle *et al*., 2013).**
Lager beer	Czech	/	49	90	1.2 µg/l	0.06 µg/l	**(Lhotská *et al*., 2016).**

Table 7.Cont.

Matrix	Nation	Year of Production	No. of Sample	Occurrence (%)	Maximum (µg/kg)*	Mean (µg/kg)*	Reference
Lager and ale beer	Portugal	2018	84	10.6	11.25	3.14	**(Silva *et al*., 2020).**
Beer	China	2008–2009	20	0	0	0	**(Wu *et al*., 2011).**
Beer	Spain	2017–2018	40	20	3.38	1.83	**(Carballo *et al*., 2021).**
Cocoa bean	Nigeria	/	59	90	0.28	/	**(Dongo *et al*., 2008).**
Cocoa bean	Brazil	2006	54	92.5	4	0.45	**(Magalhães *et al*., 2011)**
.Cocoa bean	Brazil	2015–2017	123	22.8	7.2	1.2	**(Pires *et al*., 2019).**
Cocoa and chocolate	Italy	/	300	59.7	1.82	/	**(Brera *et al*., 2011).**
Chocolate products	Turkey	2017	130	24.6	0.75	/	**(Kabak, 2019).**
Cocoa and chocolate	Canada	/	60	100	7.8	0.95	**(A-M Turcotte & Scott, 2011).**
Cocoa products	Canada	2011–2012	85	89.4	4.72	0.66	**(Anne-Marie *et al*., 2013).**
Dried grapes	Iran	2012–2013	66	40.9	8.4	2.98	**(Covarelli *et al*., 2012).**
Fruit and dried fruit	Pakistan	2016–2017	72	18	18.5	3.58	**(Heshmati & Mozaffari Nejad, 2015).**
Palm dates	Egypt	2016	28	11	6070	/	**(Iqbal *et al*., 2018).**
Palm dates	Tunisia & Algeria	2018	19	5.3	0.75	0.75	**(Abdallah *et al*., 2018).**

Table 7. Cont.

Matrix	Nation	Year of Production	No. of Sample	Occurrence (%)	Maximum (µg/kg)*	Mean (µg/kg)*	Reference
Raisin	USA	/	40	93	11.4	0.7	**(Nikolchina & Rodrigues, 2021).**
Dried fruit and nuts	China	/	253	1.6	9.39	6.23	**(Palumbo *et al*., 2011).**
Grapes, juice and raisin	China	2016	556	8.4	10.14	/	**(Yujiao Wang *et al*., 2018).**
Dried jujube	China	2013	20	100	0.18	0.14	**(Dongmei Wei *et al*., 2018).**
Chili	Pakistan	/	170	34.7	64.5	/	**(Zhang *et al*., 2015).**
Chili sauce	Pakistan	2018	252	71	114	/	**(Iqbal *et al*., 2013).**
Dried chili	Malaysia	2009	80	81.25	101.2	7.15	**(Iqbal *et al*., 2021).**
Chili and pepper	Italy	2011–2012	130	23.8	19.06	6.18	**(Jalili & Jinap, 2012).**
Allspice, pepper, chili, cinnamon, ginger, and mixture	Italy	/	94	30	34	7.1	**(Prelle *et al*., 2014).**
Chili flake, chili powder, black pepper powder, cumin and cinnamon	Turkey	2010–2011	105	24.7	98.2	5.7	**(El Darra, Gambacorta, & Solfrizzo, 2019).**
Red Pepper flakes	Turkey	2012–2013	75	94.6	31.7	3.5	**(Ozbey & Kabak, 2012)**

Table 7.Cont.

Matrix	Nation	Year of Production	No. of Sample	Occurrence (%)	Maximum (µg/kg)*	Mean (µg/kg)*	Reference
Pepper, chili, prickly ash, cinnamon, aniseed, fennel, curry powder and cumin	China	2009	480	9.6	30.73	/	**(Tosun & Ozden, 2016)**
Ginger	Nigeria	2014	120	47.5	12.02	1.77	**(Zhao *et al*., 2014).**
Astragalus propinquus	Czech	2015–2016	40	100	1700	451	**(Lippolis *et al*., 2017).**

* The default unit is µg/kg except for some values with units **(Li *et al*., 2022)**.

Table 8.OTA occurrence and contamination level in animal-derived food.

Matrix	Nation	Year of Production	No. of Sample	Occurrence (%)	Maximum (µg/kg)*	Mean (µg/kg)*	Reference
Swine kidney liver and muscle	Poland	2014–2016	430	23.5	/	2	**(Pietruszka *et al*., 2017).**
Swine livre and muscle	France	2014	70	64.3	3.65	0.15	**(Hort *et al*., 2018).**
Wild boars	Italy	2014–2015	48	/	3.23	/	**(Luci *et al*., 2018).**
Dry-cured hams	Italy	/	110	76.4	5.64	/	**(Dall'Asta *et al*., 2010).**
Salami	Italy	2013	50	10	103.69	/	**(Armorini *et al*., 2016).**
Salami	Italy	2015–2016	172	12.8	5.66	0.51	**(Altafini *et al*., 2019).**
Bovine, goat and sheep milk	Italy	/	83	3.6	0.11	/	**(Pattono *et al*., 2011).**
Jenny milk	Italy	2020	33	36.4	82 ng/l	/	**(Lippolis *et al*., 2020).**
Hard cheese	Italy	2011	40	15	54.07	14.94	**(Biancardi *et al*., 2013).**
Breast milk	Italy	2007	57	78.8	75.1 ng/l	10 ng/l	**(Biasucci *et al*., 2011).**
Breast milk	Iran	2019	90	0	0	0	**(Samiee *et al*., 2020).**
Breast milk	Chile	2008–2010	50	79	186 ng/ l	52 ng/l	**(Muñoz *et al*., 2014).**
Breast milk	Morocco	2017	82	55	10.04 µg/ l	2.17	**(Hassani *et al*., 2022).**

* The default unit is µg/kg except for some values with Units.

Table 9.OTA occurrence and contamination levels in wine.

Matrix	Nation	Year of Production	No. of Sample	Occurrence (%)	Maximum (mg/L)	Mean (mg/L)	Reference
Sweet wine	Italy	2007–2011	30	96.6	1.56	0.246	**(Stefano *et al*., 2015).**
Red and white wine	Italy	2012–2013	100	72.7	0.711	0.255	**(Gentile *et al*., 2016).**
Wine	Italy	/	470	0.2	/	/	**(Vella *et al*., 2019).**
Red wine	Spain	1995–2008	100	57	0.179	0.035	**(Quintela *et al*., 2011).**
Red and white wine	Portugal	/	60	20	2.4	/	**(Pena *et al*., 2010).**
Red and white wine	Portugal	1984–2017	92	3.2	/	/	**(Silva *et al*., 2019).**
Wine	Portugal	2010	30	6.7	0.45	0.42	**(Fernandes *et al*., 2013).**
Red, rosé and white wine must	Greece	1999–2006	150	69.4	2	0.26	**(Labrinea *et al*., 2011).**
Red wine	Croatia	2011–2015	110	98.2	0.163	0.040	**(Žurga *et al*., 2019).**
Red, rose and white wine	Serbia	2011–2016	113	52.2	0.134	0.026	**(Torović *et al*., 2020).**
Wine	Spain	2017–2018	40	47	2.28	1.13	**(Carballo *et al*., 2021).**
Tokay wines	Slovak	1959–2017	59	6.8	1.2	/	**(Kholová *et al*., 2020).**

Table 9. Cont.

Matrix	Nation	Year of Production	No. of Sample	Occurrence (%)	Maximum (mg/L)	Mean (mg/L)	Reference
Red and white wine	USA	2010–2015	41	85.4	8.6	1.3	**(Jesus *et al*., 2017).**
Red and white wine	Chile	2007–2009	1188	2.9	0.35	/	**(Vega *et al*., 2012).**
Red, rose and white wine	China	/	223	45.2	0.98	0.15	**(Zhong *et al.*, 2014).**
Red and white wine	China	/	70	62.8	/	0.61	**(Sun *et al*., 2018).**
Wine	China	2007–2016	42	4.8	1.27	1.27	**(Zhang *et al*., 2018).**

IV.Toxicity and epidemiology

IV.1.Toxickinetics of OTA

IV.1.1.Absorption

As important contaminants in food and feed, mycotoxins frequently are exposed to the intestinal mucosa **(Akbari *et al.*, 2017; Kpembi *et al.*, 2019).** OTA is absorbed from the stomach and jejunum. The absorption of the non-ionized form takes place by passive diffusion through the digestive wall, or by active transport via phenylalanine transporters **(Malir *et al.*, 2016)**.

IV.1.2.Distribution

OTA is rarely present in its free form in the bloodstream because it has a strong affinity for plasma proteins, and in particular human albumin: the rate of binding to this protein varies between 90% and 99% **(Brochard & le Bacle, 2009)**. The predominant OTA-binding site on human serum albumin has been shown to be on the IIA subdomain (Sudlow site I) **(Perry *et al.*, 2003; Il'ichev *et al.*, 2002*;* Perry *et al.*, 2004)**. Warfarin, which also has a coumarin backbone, has a primary binding site almost comparable to OTA **(Il'ichev *et al.*, 2002)**. While the phenyl group is surrounded by amino acids K199, H242, Y211, L238 and W214, the isocoumarin moiety of OTA is located in an apolar cavity between amino acids A291, L238, I260, I264, I290, R257 and S287 **(Perry *et al.*, 2004)**.The carboxylic group orients towards the amino acids R218 and/or R222, while the oxygen atoms of the carbonyl and phenolic hydroxyl groups orient towards R257; the results reported for modified albumin clearly confirm the crucial function of the arginines R257 and R218 in the interaction **(Perry *et al.*, 2004)**. The dianionic form of OTA is related to albumin because arginine R257 can deprotonate the phenolic hydroxyl group of OTA, resulting in the formation of a very stable ion pair with albumin.

OTA is then distributed throughout the body via the portal system (portal vein or portal trunk) in the liver. Skeletal muscle, adipose tissue and the brain contain smaller amounts of OTA, although the kidneys and the liver are the main targets **(Ringot *et al.*, 2006)**.

The main molecular entities responsible for the active cellular uptake of OTA in the kidneys are organic anion transporters (OATs), whereas in the liver, organic anion transporter polypeptides (OATPs) play this role **(Jung *et al.*, 2001; Anzai *et al.*, 2010)**.

OATs and OATPs are membrane transport proteins belonging to the family of solute transporters. Although basolateral OATs are primarily responsible for the uptake of OTA from the blood into renal tubule cells, the apical transporter OAT4 may be involved in the urinary reabsorption of OTA, leading to the reabsorption of OTA in renal cells tubules **(Anzai *et al.,* 2010)**. Certain kidney-specific OATPs may also participate in the cellular uptake of OTA **(Takeuchi *et al.,* 2001)**.

IV.1.3.Biotransformation

OTA continues to accumulate in the kidney more than a month after the contamination has stopped, thus leading to a possible return to the bloodstream. The liver and kidneys are the main target organs of OTA **(Gauthier, 2016)**. Metabolization of OTA leads to the formation of about twenty different compounds, the most abundant of which are presented in **figure 8**.

After ingestion, OTA undergoes a first hydrolysis by proteolytic digestive enzymes, carboxypeptidase A and α-chymotrypsin, leading to the formation of non-toxic OTα and phenylalanine **(Heussner & Bingle, 2015)**. At the hepatic level, peroxidases of the cyclo-oxygenase, lipo-oxygenase and glutathione peroxidase types allow the biotransformation of OTA into OTB. Another route of hepatic transformation involves cytochromes of the complex (CYP450) which allow the metabolization of OTA into minor, hydroxylated and less toxic metabolites: 4R and 4S-hydroxy-Ochratoxin A (4-OH-OTA) and 10 -hydroxy-Ochratoxin A (10-OH-OTA) **(Steinmeyer *et al.,* 2002; Tozlovanu *et al*., 2012)**.

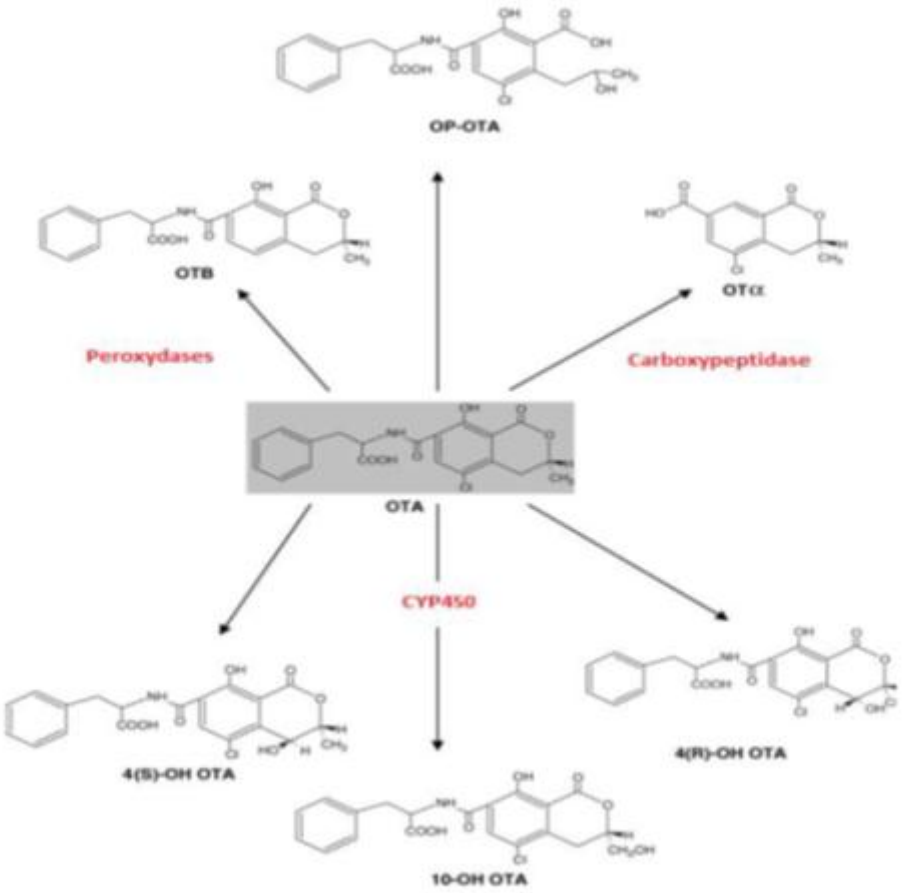


Figure 9. the main metabolites of OTA **(Ringot &chango, 2009)**.

IV.1.4.Excretion

The elimination pathways of OTA are multiple: the urinary, faecal and biliary tracts are the elimination pathways of OTA **(Malir *et al*., 2016)**. 30 to 40% of the OTA absorbed is mainly eliminated in the urine in unchanged form or in the form of OTα. The hydroxylated ochratoxin are eliminated via the bile **(Afssa, 2009)**. Part of this OTA excreted in the urine is reabsorbed and recirculated in the blood. OTA is eliminated very slowly unlike its metabolites, which are much faster **(Gauthier, 2016)**. Serum and urinary concentrations of OTA are used to assess human exposure to this toxin **(Malir *et al*., 2016)**.

IV.2.Toxicological Profile

OTA has been reported nephrotoxic, teratogenic, immunosuppressive. Its toxicity remains highly variable and depends on sex, species and cell type **(O'Brien *et al*., 2001)**. However, OTA toxicity is characterized more by subacute toxicity, linked to the chronic ingestion of low doses of toxin. Some toxic effects, related to subchronic exposure to OTA (**Figure 10**) **(Marquis, 2005)**.

IV.2.1.Nephrotoxicity

OTA exposure has been linked to swine nephropathy and BEN, Chronic Interstitial Nephropathy (CIN) and other kidney diseases, and has been detected in human blood samples from healthy individuals around the world **(Khoi *et al*., 2021)**.

OTA increases malondialdehyde (MDA) and lipid peroxidation while decreasing glutathione, catalase, and superoxide dismutase in the rat kidneys and liver, causing oxidative stress and DNA damage **(Meki & Hussein, 2001)**. After OTA exposure, apoptotic signal-regulated kinase 1 (ASK-1) expression is increased, which controls the generation of reactive oxygen species (ROS) and lowers mitochondrial membrane potential **(Liang *et al*., 2015)**. Nitrosative stress develops in renal and liver cells because of OTA-induced protein nitration and expression. By inhibiting Nitric oxide (NO) synthase, **Lee *et al*. (2018)** discovered that OTA decreased NO production and increased superoxide generation.

OTA has been shown to cause apoptosis and oxidative stress in renal cells **(Cavin *et al*., 2009)**, human proximal tubular epithelial cells (HK-2), and rat renal tubular cells **(Yang *et al*., 2019)**. It also induces NADPH oxidase expression, which controls ROS production in renal mesangial cells, and promotes ER stress and apoptosis through activation of calpain **(Sheu *et al*., 2017)**. The development of lipid rafts, which controls the death of HK-2 cells by controlling the (phosphatase and tensin homolog/phosphoinositide 3-kinases/serine/ threonine-specific) (PTEN/PI3K/AKT) pathway, is disrupted by OTA attenuating cholesterol and sphingomyelin **(Özcan *et al*., 2015)**.

Hypoxia, epithelial-to-mesenchymal transition (EMT), apoptosis, and the xenobiotic metabolism pathway are all impacted by OTA **(Pyo *et al*., 2021)**. Tumor necrosis factor receptor-associated protein 1 (TRAP-1) was found to boost the expression of Bcl-2 while inhibiting the expression of cyclophilin D (CypD), Bcl-2 associated x protein (Bax), glucose-regulated protein 78(GRP78), and CAAT/enhancer-binding protein (C/EBP) homologous protein (CHOP) to prevent apoptosis **(Song *et al*., 2021)**.

OTA can cause apoptosis and DNA damage in PK15 cells and porcine alveolar macrophages by activating the DNA methyltransferase 1 (DNMT1) dependent Janus kinase 2/ signal transducer and activator of transcription 3 (JAK2/STAT3) signaling pathway and increasing the expression of suppressors of cytokine signaling 3 (SOCS3). According to **Ozden *et al*. (2015)**, OTA induced hypermethylation and hypomethylation on the various rat kidney genes implicated in the mTOR signaling pathway may be a factor in renal carcinogenesis **(Ozden *et al*., 2015)**. OTA can also cause global methylation in rat kidneys, hypermethylation of E- and N-cadherin by OTA exposure leads to decreased expression, and the generation of ROS activates DNMT1 and histone deacetylase1 (HDAC1) to cause cytotoxicity and apoptosis **(Li *et al*., 2015; Zhou *et al*., 2017)**. Additionally, OTA inhibits histone acetyltransferase (HAT), which causes a decrease of acetylation on histone 3 lysine 9 (H3K9) and suppresses gene expression. Finally, OTA caused HK-2 cell cycle arrest in the G0/G1 phase **(Zhang *et al*., 2020)**.

OTA has been shown to inhibit protein synthesis in a variety of organs, including the kidney, liver, and spleen, and to bind to a shared site on phenylalanine-tRNA synthase to prevent protein synthesis **(Creppy *et al*., 1984)**. The cell cycle was disrupted by OTA, which raised cell counts throughout the G0/G1 and G1/G2 phases while lowering them during the S phase **(Kamp *et al*., 2005)**. By increasing the expression of cyclin A2, cyclin E2, and cyclin dependent kinase 2 (CDK2), N-acetylcysteine has the potential to reverse the cell cycle arrest caused by OTA **(Yang *et al*., 2014)** P53-mediated OTA-induced cell cycle arrest was identified by inhibition of cyclin D1, Cdk2, and cyclin dependent kinase 4(Cdk4) in HK-2. This study proposed that the status of genes and proteins should be revealed after being regulated by an upper mediator like p53 **(Çelik *et al*., 2020)**.

The stability of the mitochondria depends on the mitochondrial membrane potential, which is created by the hydrogen ion's transmembrane potential. At the beginning of the OTA treatment, **Argawal *et al*. (2020)** discovered a decrease of mitochondrial membrane potential followed by hyperpolarization at 24 hours. **Chebotareva *et al*.(2017)** found that OTA reduced intracellular ATP and reduced complex I and II of the mitochondrial respiratory chain, suggesting that OTA damaged the mitochondria in the proximal tubule of the rat kidney. Heat shock proteins (HSP) have an intracellular protective role that enhances the ability to fend off apoptosis and necrosis. Glucose-regulated protein 75 (GRP-75) may serve as a biomarker for renal tubular necrosis brought on by OTA and other foodborne toxins **(Yang *et al*., 2019)**.

OTA exposure has been linked to increased miRNA expression and increased cell death, as well as increased PI3K/AKT and mitogen-activated protein kinase/extracellular signal-regulated kinases ½(MAPK/ERK1/2) signaling pathways. Autophagy has also been found to protect PK cells from OTA-induced apoptosis, leading to the development of a new therapeutic drug against OTA toxicity **(Qian *et al*., 2018)**.

Human embryonic kidney cells were inflamed by OTA through thenuclear factor kappa-light-chain-enhancer of activated B cell(NF-kB) pathway, and when OTA concentration rose, the inflammatory milieu changed to one that was pro-apoptotic **(Raghubeer *et al*., 2017)**. Pig kidney and spleen OTA induced endoplasmic reticulum stress (ER stress), autophagy, and enhanced phosphorylation of extracellular signal-regulated kinases1/2(ERK 1/2) and p38 **(Gan *et al*., 2017)**. OTA accelerated senescence in human renal proximal tubular cells through an increase in senescence-associated-galactosidase (SA-gal), DNA damage, cell spreading, activation of the p53-p21, p16-pRB signaling pathway, and an unbalanced cell cycle. Heme oxygenase-1 (HO-1) has a cytoprotective function in renal illness, and OTA generated HO-1 to prevent apoptosis, fibrosis, and inflammation in porcine kidney cells **(Jarmi & Agarwal, 2009)**. At 24 hours, exposure to OTA may enhance the expression of the hypoxia inducible factor-1 alpha(HIF-1α) and erythropoietin(EPO) genes, while after 48 hours, the expression of transforming growth factor beta (TGF-β) and the vascular endothelial growth factor (VEGF) may significantly rise.

OTA may disrupt normal metabolic function. OTA-induced hypoxic state may help to shed light on OTA-related carcinogenesis **(Raghubeer *et al*., 2019)**. **Loboda *et al***. (**2017)** discovered that the nuclear factor erythroid 2-related factor 2 (Nrf-2) pathway controls the OTA-induced nephrotoxicity, which is sex-dependent.

Imaoka *et al*. (2020) developed a 3D model of the human kidney's proximal tubule to validate OTA dose-response toxicities. OTA is metabolized by P450(s). However, the use of MPS is constrained by technical issues that make it difficult to evaluate toxicological, including a lack of throughput, a limited cell number, and difficulties with cell sorting.

IV.2.2.Carcinogenicity

OTA is a potent rodent carcinogen **(Zhao *et al*., 2017)**. As early as 1971, Purchase and der Watt Van hypothesized the carcinogenicity of OTA in mice fed an OTA-contaminated diet. The carcinogenic effects of OTA on mice were verified by the study of **(Bondy *et al*., 2015)**. **Schwartz.(2002)** showed that animals exposed to OTA contain OTA in their tests and OTA causes adducts in testicular DNA. In addition, the authors, **Al-Anati & Petzinger.(2006)** and **Hope & Hope.(2012)**, also report that there is a correlation between the consumption of pork and coffee, contaminated by OTA with testicular carcinomas. The data available so far from Tunisia **(Zaied *et al*., 2012)** and Côte d'Ivoire **(Thé *et al*., 2015)**, point to OTA as a likely aggravating factor in the development of urinary tract tumors (bladder mainly).

IV.2.3.Genotoxicity and mutagenicity

OTA is carcinogenic by a direct mechanism of genotoxicity by covalent adduct formation at the covalent adduct formation at the level of carbon 8 of the guanine **(Marquis, 2005)**. Other published works confirm that cytotoxic activity of OTA would lead to DNA damage **(Gautier *et al*., 2001; Zepnik *et al*., 2003)**. Similarly, the genotoxic potential of OTA has been demonstrated by the search for DNA single strand breaks, sister chromatid exchange, micronuclei formation or DNA adducts **(Leszkowicz & Manderville, 2007)**.

IV.2.4.Immunotoxicity

OTA is immunotoxic in the animals studied. Bone marrow disorders were observed in animals administered. OTA affects humoral immunity by inducing regression of IgG, IgA and IgM immunoglobulins (Ig). It is also responsible for inhibiting cellular immunity **(Clark & Snedeker, 2006; Hope & Hope, 2012). Gan *et al*. (2022)** showed in a study that doses of 2.5 mg OTA/kg feed to pigs decreased macrophage phagocytic activity and interleukin-2 (IL-2) production. The pig immune system is sensitive to OTA doses below 1 mg/kg (10% inhibition of the immune response is observed with 0.06 mg/kg OTA) under normal rearing conditions **(Gan *et al*., 2022)**.

IV.2.5.Teratogenicity

OTA is teratogenic in animals; the mechanism of induced teratogenicity has not been clearly defined. OTA seems to cross the placenta and, by accumulating in fetal tissues, alter certain tissues, altering a number of parameters associated with the differentiation of embryonic cells **(Gupta *et al*., 2018); (Feutz & De Geyter, 2019)**. However, the development is influenced both by the direct effect of the molecule on the fetus and by the indirect effect via the mother **(Anatik, 2010; Al-Anati & Petzinger, 2006)**.

OTA can cause various morphological abnormalities in rat, hamster, mouse, pig and chicken embryos **(Leszkowicz *et al*., 2011)**. However, the severity of the malformations depends on the route of administration and the gestational age. Repeated oral administration of 0.75 mg/kg OTA to rats from day 6 to day 15 results in abnormal visceral and skeletal malformations in the pups **(Stoev, 2022)**. In traperitoneal administration of 5 mg/kg of OTA to pregnant rats leads to embryonic malformations and even death. The most common effects are exencephaly, eye, finger and tail anomalies **(Stoev, 2022)**.

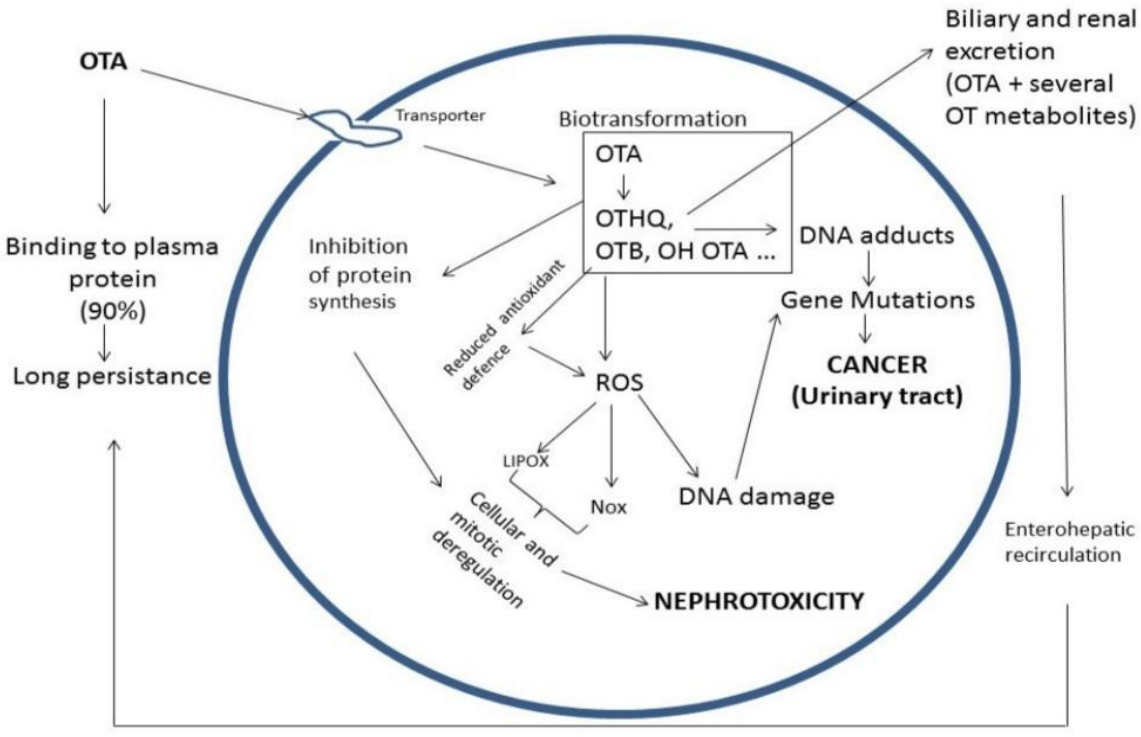


Figure 10.summary of biochemical effects of OTA: othq: hydroxyl quinone ochratoxin; OTB: dechlorinated ochratoxin; lipox: lipoperoxidation; nox: nitrogen oxide; ros: reactive oxygen species **(Malir *et al*,. 2016)**.

V.Detection and prevention methods of OTA

V.1.Detection methods of ochratoxin

Due to the complexity of the food matrix and the fact that OTA is typically present in food at extremely low concentration levels, food samples cannot typically be tested without some previous sample processing. As various matrices require different approaches, sample preparation is frequently a crucial and challenging step in the whole analytical process. Prior to determination, liquid phase extraction (LPE) has traditionally been commonly utilized. Most matrix alkaline extractions result in improved recoveries overall. Nonetheless, OTA deterioration in the open ring may lead to underestimate **(Tozlovanu & Pfohl-Leszkowicz, 2010)**. Nonetheless, due to its ease of use and economy in terms of time and solvent use, many laboratories have attempted to employ solid phase extraction (SPE) during the past ten years **(Huertas-Pérez *et al*., 2017)**. OTA has been captured using a variety of conventional nonspecific sorbents; including C18, Mixed-mode anion-exchange (MAX), and Hydrophilic-lipophilic balance (HLB). Emerging selective sorbents include Aptamer-affinity columns, immuno-affinity columns, and molecularly imprinted polymers (MIPs) (AAC). They are thought to be rather basic and regarded as being quite easy to perform and offer sample extract that is often devoid of interferences. These adsorbents are used in additional miniaturized SPE-related procedures, such as solid-phase microextraction (SPME), micro-SPE (l-SPE), dispersive-SPE (dSPE), and solid bar microextraction, in addition to the traditional SPE cartridges (SBME) **(Li *et al*., 2022)**.

V.1.1.Spectroscopic Methods

The fluorescence that OTA and emit is measured using fluorescence spectrophotometry **(Satyanarayana *et al*., 2019)**.

The presence of OTA in wheat and rice products was determined using this method, the excitation wavelength was set to 333nm and the emission wavelength was set to 354 to 546nm, the limit of detection (LOD) of OTA was between 0.74-9.32 ng/ml. The finished solutions were put into a spectrofluorimetric cell for each experiment in order to track the fluorescence against wavelength **(Saidi & Mirzaei, 2016)**. Fourier transform infrared (FTIR) analyzes were used to determine the presence of OTA in cereals, fruits, nuts, meats, spices and medicinal herbs **(Bilal *et al*., 2020)**.

V.1.2.Thin-Layer Chromatography

For mycotoxin detection, TLC is a straightforward, reliable, and qualitative approach that may be enhanced for quick screening. TLC with a charge-coupled detector (CCD) is used to determine the presence of OTA in 88 Brazilian red wine samples from the 2009 vintage. The technique involved utilizing image software to analyze fluorescent photos that were taken under UV light. The average recovery of OTA using immunoaffinity columns (IAC) was 82.3%. The limits of quantification (LOQ) and LOD were, respectively, 0.8 and 0.2 g l1. Five positive samples were found to contain 5.7% OTA contamination, including three Cabernet Sauvignon and two Merlot **(Teixeira *et al*., 2011)**.

V.1.3.High-Performance -Thin-Layer Chromatography

High-Performance -Thin-Layer Chromatography (HPTLC) technology is an advanced analytical technology from TLC, but it is more accurate, more efficient and more advanced. It operates on the same principles as TLC, where the components are separated by capillary action, the analytes move according to their affinities towards the stationary phase **(Gupta *et al*., 2022)**.

The HPTLC has been standardized using hexane, ethyl acetate, and acetic acid (18:4:1.5) as mobile phase. After extracting ochratoxin from flour by adding dried magnesium sulfate and sodium chloride as salts to the extraction solvent acetonitrile/water (2:1), the characteristic fluorescent spots were observed on a plate with aluminum chloride in 15% methanol under UV light plat. The validated method allows the detection of ochratoxin between 0.22to0.85µg/kg in 20 wheat flour samples **(Kupski & Badiale-Furlong, 2015)**.

After a dispersive liquid-liquid micro-extraction, OTA in wines was examined by HPTLC and HPLC. Using HPTLC, a linearity of 0.03–1.00 g/l was found with a strong connection to the HPLC technique, the enrichment factor was found to be 34.5 and the extraction recovery to be 63.9% under ideal conditions **(Antep & Merdivan, 2012)**. Furthermore, the HPTLC technique enabled the simultaneous examination of several wine samples and an OTA standard on the same plate. With a mean recovery of 90.4%with LOQ and LOD of 0.1 g/l and 0.016 g/l, respectively, improved the HPLTC technique for wine **(Welke *et al*., 2010)**.

V.1.4.High-Performance Liquid Chromatography

Ochratoxin may be found in food samples using HPLC, which measures retention time using sensitive fluorescence, ultraviolet, or diode array detectors and mass spectrometry (MS). A chromatography column like C-18 is used as the stationary phase in the HPLC procedure, along with a mobile phase that flows through the column and a detector that shows the retention periods of the separated molecules. Immunoaffinity column purification is frequently necessary before HPLC analysis for mycotoxin in order to get rid of other impurities **(Satyanarayana *et al*., 2019)**.

According to **Mohebbi *et al*.(2022)** after fine-dispersed solid phase extraction of OTA extract from fruit juice samples using vitamin B3 and cobalt ions as active adsorbents for extraction, OTA was quantified by HPLC-tandem mass spectrometry using Agilent Eclipse Plus column (150 mm × 4.6 mm, and 3.5 µm particles size) held at 40°Cto separate analyses. As the mobile phase, 0.45 mL/min of methanol containing 0.1% formic acid (A) and water containing 25 mM ammonium acetate (B) were used with gradient elution. The LOD and LOQ for OTA were 24.8 and 82.6 ng/l, respectively, according to the findings of the technique validation, OTA recovery rate during extraction were 87 %.

To determine the characteristics of OTA removal by lactic acid bacteria strains in Algerian fermented foods, separation and quantification were performed by HPLC-FLD using a C-18 reverse phase column. Chromatographic separation was performed for 100µl of the injected sample under an isothermal flow rate of 1ml/mint using a mixture containing water-acetonitrile- acetic acid, 69:30:1, v/v/v as a mobile phase. Excitation was set at 333nm, emission at 440nm for OTA detection.0.085 g/ml and 0.25mg/ml were LOD and LOQ, respectively **(Badji *et al*., 2023)**.

OTA contamination of homemade vinegar produced from fruits was determined by HPLC after pretreatment of 31 vinegar samples using acetonitrile: water: acetic acid (51:47:2 v/v/v) at a flow rate of 1 ml/ min as a stage. Mobile, C18 column at 40 ◦C in OTA separation after injecting 100µl of sample. OTA was quantified by HPLC after recovery with methanol: acetic acid (98:2 v/v) and then 1.5 ml water was added and vortexed within 12%. Recovery values were obtained of validation was 94% and 85% in 0.1 µg/l and 2.0 µg /l for OTA **(Heperkan *et al*., 2023)**.

V.1.5.Liquid Chromatography Coupled Mass Spectroscopy

With a high degree of sensitivity and accuracy, the technology of LC/MS/MS using database searching may be employed for precise mycotoxin analysis. By maximizing the electrospray settings, retention periods, and UV spectra, the precise weights of protonated fungal metabolite molecule ions are determined **(Satyanarayana *et al*., 2019)**.

To determine the presence of OTA in animal derived foods, LC-MS/MS was relied upon with pre-treatment of samples, where samples were extracted with PLE and clean up with SPE. Acetonitrile/hexane was used as the extraction solvent in an 11 ml ASE cell under the following conditions: 1500 psi, 100 °C, 5 min static time, and 60% flush volume. During cleanup, an inexpensive and frequently used SPE column was utilized. Using the LC system, the separation procedure was carried out on a C-18 column with a graded elution. Quantitative spectrometry was carried out by electrospray where the curtain gas was set at 6 psig while the ionic gas sources 1 and 2 were set at 60 and 50 psig. LOD was variable between 0.07µg/kg to 0.59µg/kg OTA was detected in pig muscles and liver, eggs and milk as follows (1.25/1.46/1.32/1.46 µg/kg) respectively **(Chen *et al*., 2012)**.

The simultaneous measurement of OTA in feed and food using UPLC-ESI+/MS/MS was developed. After sample preparation, extraction and cleaning, the analysis was carried out by LC-MS/MS using the UPLC system and Waters Xevo® software. TQ-S triple quadruple mass spectrometer for data acquisition and processing. Analyzes were separated chromatographically using an UPLC column with a gradient elution on a mobile phase consisting of 0.05% acetic acid (v/v) and 5 Mm ammonium acetate in water (eluent A) and Me OH (eluent B) at allow rate of 0.4ml/min.Multiple reaction monitoring (MRM) with positive (OTA) was used to conduct MS studies. The simultaneous presence and OTA LOQ 5.60 g/kg were found in more than 50% of the food and feed samples that were examined **(Meerpoel *et al*., 2018)**.

V.1.6.PCR and Quantitative Real-Time PCR Detection

RT-qPCR is a technique for performing quantitative PCR (polymerase chain reaction) on a sample of RNA. Quantitative PCR or qPCR or real-time PCR, is a particular method of polymerase chain reaction that measures the initial amount of DNA. In reality, quantitative PCR measures the number of amplicon (portion of DNA defined by a pair of primers). Detection can be done using SYBR green, a fluorescent organic compound that binds to

nucleic acids, or probes, Taqman or FRET. In later stages of fungal growth, mycotoxins are metabolites formed by the interaction of various metabolic processes; however, the genes involved in the mycotoxins pathway are expressed much earlier. Hence, mycotoxins may be discovered earlier by detecting the mycotoxins gene expression. Traditionally, mycotoxins-producing fungi like *Aspergillus* and *Penicillium* are found in food using PCR-based molecular approaches **(Rahman *et al*., 2020)**.

To detect grain contamination with OTA a PCR Test (apta-qPCR-RT) was developed based on aptamer-assisted target dissociation. After hybridization the aptamers were transferred to beads using complementary sequences. The microtube, which contains the hybridized aptamer, was filled with 25 L of selection buffer with various OTA concentrations, and it was then incubated for 20 minutes. Target-induced dissociation (TID)-released aptamer was gathered in the supernatant and quantified using qPCR. There sulting assay had a dynamic range of 0.039 to 1000 ng/ml and could detect OTA at 0.009 ng/ml **(Modh *et al*., 2017)**. A polymerase reaction approach that could discriminate between chemical patterns of OTA and identify *A. westerdijkiae* was developed for the early detection and monitoring of OTA-producing fungi. Five *A. Westerdijkiae* strains isolated from the surface of cheese had their genome sequence data analyzed by PCR. The PCR primers used in this method were complementary to conserved regions flanking OTA and produced amplicons of various sizes from strains with various chemotypes **(Susca *et al*., 2021)**.

The microtube which contains the hybridized aptamer was filled with 25 L of selection buffer with various OTA concentrations, and it was then incubated for 20 minutes. TID-released aptamer was gathered in the supernatant and quantified using qPCR. There sulting assay had a dynamic range of 0.039 to 1000 ng/ml and could detect OTA at 0.009 ng/ml. Multiplex PCR and high-performance liquid chromatography (HPLC) analyses were utilized in a Korean study to evaluate 32 *A. niger* isolates' capacity to produce mycotoxin. Although OTA-producing strains of *A. niger* isolates displayed positive PCR patterns for ochratoxin biosynthetic genes, it did not explain why positive PCR products were present in the non-mycotoxin-producing bacteria **(Kim *et al*., 2014)**.

According to **Atoui *et al*.(2007)**, the ochratoxin-producing fungus *A. carbonarius* is frequently linked to wine and grape contamination. A 141 bp PCR product was amplified using specific primers to the polyketide synthase (AT domain) sequence of *A. carbonarius*. Similar primers were also utilized in 72 grape samples for qPCR in order to directly quantify

the fungus. The acyl transferase gene expression and OTA concentration were positively correlated. Thus, qPCR-based quick *A. carbonarius* detection in grapes may provide an alternative to the established techniques for OTA detection and culture identification.

V.1.7.Immunochemical Methods

In analytical laboratories around the world, immunochemical techniques are widely used to track the prevalence of mycotoxins in the food chain **(Puertollano *et al*., 2021)**.

All immunochemical procedures are based on the binding of antibodies and their complement aryantigens. An antibody is typically utilized as a reagent to identify antigen in an immunochemical examination since antibodies have a high affinity and specificity for their respective antigens **(Larry *et al*,.2016)**. These techniques are numerous, ELISA and immunoaffinity column assays (ICA) are sensitive, selective, and less time-consuming immunosensors, immunochemical approaches have drawn a lot of interest due to their affordability and speed in the last decade. The focus of the current review is on immunochemical techniques for OTA analysis **(Meulenberg, 2012)**.

V.1.7.6.Enzyme-Linked Immunosorbent Assay

Due to the development of mycotoxin detection tools and methods, ELISA has been developed to detect OTA in a wide range of food commodities. One of the most sensitive monoclonal antibodies described in the scientific literature, with an IC^{50} of 0.13 ng/ml, served as the foundation for the new OTA ELISA created in this study. Analyzing proficiency test and reference samples provided additional evidence of both ELISAs' accuracy. To make this new OTA ELISA an even more useful screening tool for the presence of OTA, it can be further validated for other agricultural commodities that are frequently contaminated with OTA **(Stachowiak *et al*., 2017)**.

The ELISA methods for determining the amounts of OTA in the medicinal herbs *Zataria multiflora* and *Foeniculumvulgare* from Ahvaz, Iran, were shown to have a high correlation by Ekhtelat direct ELISA format that was created to be competitive had an IC^{50} value of 0.07 ng/ml. Using 50% methanol as the extraction medium and the ELISA technique, spiked sample recoveries ranged from 74 to 110 %. Food samples included barley, wheat, oat, corn, rice, raisins, grape juice, and beer samples were diluted with PBS. A good connection was seen between the new ELISA method and the HPLC method **(Ekhtelat, 2018**).

Zhang and colleagues, in their work, the anti-idiotypic nanobody VHH 2-24 was first produced and then, utilizing it as a surrogate standard, a toxin-free enzyme immunoassay for OTA was established. ELISA test kits have been widely used to determine mycotoxins in agricultural goods and foods. The VHH 2-24 surrogate standard-based ELISA had an IC^{50} value of 0.097 g/ml and a linear range of 0.027-0.653 g/ml. Spike-and-recovery studies were used to examine the average recoveries, which ranged from 81.8% to 105.0%. Using HPLC method, the developed ELISA's accuracy for detecting OTA was further confirmed, and an excellent correlation was seen **(Zhang *et al*., 2019)**.

V.1.7.7.Immunosensors

Detecting antibodies that specifically respond with their target antigen with immunosensors. Detection strategies have made use of electrochemical, optical, piezoelectric, and colorimetric techniques to quantify target analytes **(Aydin *et al*., 2021)**.

a) Electrochemical Immunosensors

Electrochemical immunosensors (EIS) are effective tools for sensitive and focused analytes detection. They are inexpensive, easy to use, and only require tiny sample sizes. In most cases, electrochemical immunosensors work by first directly immobilizing antibodies and then adding the appropriate analytes to conduct an electrochemical test **(Aydin *et al*., 2021)**.

Zhang *et al.*(2018), the development of an ultrasensitive EIS for the detection of OTA. The immunoassay had a significant current response and was carried out using square wave voltammetry. The suggested immunosensors produced results with a LOD of 39 fg /ml and a wide linear range of 0.1 pg/ ml to 10 ng /ml.

According to **Mazaafrianto *et al*.(2018)**, sensitive and label-free detection over OTA based developed using a small at the EIS aptamere's base, a set of three electrodes on the couch, or production methods utilizing common microfabrication techniques on a polystyrene substrate (25 mm x 25 mm). The LOD for OTA was 78.3pg/ml, and the standard curved is played broad linearity spanning from 0.1 to 300ng/ml, additionally, the OTA-recuperations with the capture's position in the commercial coffee and beer samples ranged from 86.4 to 107%.

b) Optical Immunosensors

Despite having some similarities in theory to traditional immunoassays, the great majority of which are based on optical signal/detection, optical immunosensors have gained a lot of popularity. They represent the next technical step in comparison Nanotechnology for mycotoxins Detection **(Karachaliou *et al*., 2022).**

V.1.8.Nanotechnology of OTA

Nanotechnology can aid in the identification of tainted food and animal feed. Nanoparticles can be used to monitor food quality, detect mycotoxins and mycotoxin producers, and aid in food security regulations to provide safe and wholesome food. Nanoparticles have the potential to be developed in a variety of colorimetric, fluorometric, enzymatic, and electrochemical diagnostic assays **(Kim & Park, 2005; Vo-Dinh, 2007; Clemons *et al*., 2019; Selvan *et al*., 2010)**.

This is because of their size- and shape-dependent physical and chemical properties. Many imaging and sensing applications make use of semiconductors, noble metals, and metal oxide nanoparticles. To provide a detection approach via signal amplification, nanoparticles as labels can be coupled with molecular recognition components as DNA, RNA, antibodies, or enzymes. In lateral flow immune chromatographic devices, which rely on a straightforward chromatographic flow separation to produce a colorimetric visual signal based on the affinity of antibodies labeled with gold nanoparticles to the antigen in either a direct or indirect format, gold nanoparticles are frequently used. The use of nanoparticles bearing imaging probes to measure mRNA expression in melanoma cells in culture was demonstrated. The probe contained thiol-terminated hairpin oligonucleotides with citrate-capped gold nanoparticles covalently linked to them. Tyrosinase mRNA was positively detected in melanoma cells by hairpin DNA-coated gold nanoparticles **(Harry *et al*., 2010)**.

The human parasite *Cryptosporidium parvum* was detected using gold nanoparticles functionalized with oligonucleotides that are complementary to specific sequences found on heat shock protein 70 **(Javier *et al*., 2009)**.

V.1.8.8.Nanoparticle-Assisted Electrochemical Immunoassay

Liu *et al*.(2013) modified a glassy carbon electrode with a composite film of polythionine and self-assembled gold nanoparticle monolayer to create an electrochemical sensor in the indirect competitive immunoassay format for detection of OTA. The ochratoxin antibody-ovalbumin conjugates fixed on the film and the sample competed for binding with the anti-ochratoxin monoclonal antibodies. By oxidizing the 1-naphthyl phosphate substrate, the secondary antibodies that were alkaline phosphatase-labeled coupled to the monoclonal antibody to provide the electrochemical signal. At a LOD of 0.2ng/ml, the electrochemical reaction was inversely proportional to the OTA concentration from 1 to 1000 ng/ml.

Created a dual-signal electrochemical ratiometric platform for OTA detection that uses a DNA walker to ignore fluctuations in environmental and instrumental parameters and DNA load densities. Toluidine blue and cobalt metal-organic frameworks (Co-MOFs) were utilized as the internal reference probe and the electrochemical signal tag, respectively. This newly created apparatus produced DNA labeled-Co-MOFs far from the electrode when OTA was present. As a result, toluidine blue signal at 0.28 V increased while the Co-MOFs signal at 1.18 V decreased. LOD 0.31 fg/ml; linear range 1–50 ng/ml; this suggested method has demonstrated excellent sensitivity and great repeatability. The sensor was also used to determine the OTA content in samples of red wine, and the findings met expectations and were on par with those of commercial enzyme-linked immunoassay kits **(Guan *et al.*, 2023)**.

In order to create an electrochemical impedance-based sensor, **Rivas *et al*.(2015)** electropolymerized a polythionine sheet on a carbon electrode that had been screen-printed before assembling iridium oxide nanoparticles (IrO2 NPs). Electrostatic interactions held the aminated aptamer, which was OTA-specific, to the IrO2 NPs. In comparison to antibodies, aptamers are single- or double-stranded synthetic oligonucleotides that attach to the target with specificity. They are more favorable due to their chemical and thermal stability and affordable manufacture. The sensor showed great repeatability and detected 14 pM OTA in samples of white wine.

V.1.8.9.Nanoparticle-Assisted Lateral Flow Assay

In recent times, sensitive, easy-to-use, quick, and ready-to-use devices called lateral flow immune chromatographic assays (LFAs) have been utilized to detect the presence of a target analytes in samples without the use of specialist, pricey equipment. The following is a

list of some of the most common questions we get asked about our services. The capturing agents are immobilized in spatially limited zones on the nitrocellulose membrane, and the antibody tagged with gold nanoparticles is pre-adsorbed on the conjugate pad **(González & Merkoçi, 2015)**. According to **Moon *et al*.(2013)**, the detection is based on either the competitive or direct formats. The quick detection of analytes, as a red band on the membrane, is made possible by the high specificity and sensitivity of antibody-antigen reactions as well as the colorimetric visibility of the gold nanoparticles used as labels.

By using a one-step lateral flow immunoassay, **Anfossi *et al*.(2012)** detected OTA semi-quantitatively in wines and grape musts. The LOD and IC_{50} of matrix-matched calibration curves performed in blank wines were 1 g/l and 3.2 g/ l, respectively. The created assay had a 5-minute detection time for OTA that was accurate and sensitive. With 38 wines and 16 musts, the assay agreed with the reference HPLC method. For the quantitative detection of OTA with LOD as low as 1.5 g/kg, a quick immune chromatographic assay was paired with a straightforward sample treatment of cereals. The matrix effects brought on by various cereals (maize, wheat, and durum wheat) were lessened when OTA was isolated from the cereal samples in the presence of polyethylene glycol. The recoveries were between 87% and 119%. The assay that was created was used to evaluate 15 maize, 4 wheat, and 6 durum wheat samples. It demonstrated a strong correlation when compared to be reference method **(Laura *et al*., 2011)**.

V.1.8.10. Aptamer-/Peptide-Coupled Nanoparticles for OTA Detection

The sensitivity of the sensors can be improved using aptamers and peptides **(Piro *et al*., 2016)**. Using a cationic polymer and gold nanoparticles (AuNPs), a label-free aptamer-based assay for the highly sensitive and precise detection of OTA was created. The colorimetric detection of OTA based on the aggregation of AuNPs by the cationic polymer utilized the OTA aptamer as a recognition component. In the presence of other interfering toxins, the colorimetric test could identify OTA down to 0.009 ng/mL with good selectivity using spectroscopic quantitative analysis. This study provides a fresh, quick, and sensitive visual detection method for OTA detection **(Luan *et al*., 2015)**

In a microfluidic paper-based analytical device (PADs), a 36-mer aptamer was used as a molecular recognition element paired with AuNPs for colorimetric detection of OTA. Control, detection, and sample zones made up the three parts of the "PADs," which were connected via channels. AuNPs and AuNPs/Aptamer were characterized using UV-vis

spectroscopy, dynamic light scattering, and transmission electron microscopy (TEM). LOD was determined by the colorimetric test to be 242, 545.45, and 95.69 ng/ml in water, corn, and groundnut, respectively **(Shahdeo *et al*., 2022)**.

In order to identify OTAs, **Soh *et al*.(2015)** produced a noticeable colorimetric response at samples of red wine with cocaine at samples of red wine with cocaine at nanomolar levels (1 nM). Such tests are applicable for diagnostics and food sampling because to the sensitive and precise visual identification of pollutants without the requirement for complex equipment.

For the one-step detection of OTA in maize samples, **Zhang *et al*.(2018)** proposed a competitive lateral flow strip format with a fluorescent aptamer. The test line on the nitrocellulose membrane was fixated using biotin-cDNA, to put it briefly. The Cy5-labeled aptamer joined with the cDNA to create a stable double helix in the absence of OTA. The creation of Cy5- aptamer/OTA complexes in the presence of OTA decreased the capture of free aptamer in the test zone, which in turn reduced the fluorescent signals on the test line. For samples of spiked maize, a linear relationship from 1 to 1000 ng/ml with a LOD of 0.40 ng/ml and recoveries ranging from 96.4% to 104.67% was reported.

Using a lateral flow strip in a competitive format and aptamers against OTA, on-site quick detection of OTA contamination in Astragals membranaceus, used in Chinese medicine, was created. In order to minimize matrix and methanol interferences, the sample extraction was optimized using 2.5 ml of methanol/water (80:20, v/v) for 1 g. This was followed by fourfold dilution with running buffer. Within 15 minutes, a visual LOD of 1ng/ml was attained without any appreciable cross-reactivity with other comparable toxins. Tests of membranaceus samples revealed that just one of the nine samples that agreed with the LC-MS/MS analysis was positive for OTA **(Zhou *et al*., 2016)**.

In two separate forms, Velu and DeRosa investigated the use of OTA aptamer probes modified with 5′-biotin in conjunction with silver or gold nanoparticles in lateral flow colorimetric assays for OTA detection. First, in the "adsorption-desorption" method, aptamers were adsorbed onto the surfaces of the metal nanoparticles. In addition to OTA, this caused aptamer-ochratoxin binding, which released the NPs. This method allowed for a detection limit of 6.3 nM for both metal nanoparticles. In the second method, biotinylated metal nanoparticles with aptamer functions were built into linkage inversion assembled nano-aptasensors (LIANAs) utilizing a DNA linker that had a 5′-5′ linkage inversion (5′5′ linker). In a nutshell, the release of the linker and breakdown of LIANA aggregates into scattered nanoparticles were induced by OTA coupled particularly with its aptamer. The LFA format yielded a LOD of 0.63 nM. The "adsorption-desorption" LFAs and LIANA-based LFA strips were contrasted, and it was shown that the former was more sensitive **(Velu & DeRosa, 2018)**.

Table 10. Detection methods for OTA.

Methods	Year	Biological material	LOD	LOQ	Reference
Clfia	2017	Grape, juice and wine	0.06 (µg/l)	_	**(Jiang *et al*., 2017).**
FPIA	2017	Rye and rye based products	0.6 (µg/Kg)	_	**(Lippolis *et al*., 2017).**
Optical immunosensors	2017	food and beverages	4.4 (Pg/kg)	_	**(Myndrul *et al*., 2018).**
QSM-D	2017	Red wine	0.16 (ng/ml)	_	**(Karczmarczyk *et al*., 2017).**
ELISA	2017	Millet and Maize	0.005, 0.001, and 0.001 (ng/ml)	_	**(Zhang *et al*., 2017).**
ELISA	2018	Rice	0.059 (ng/ml)	_	**(Sun *et al*., 2018).**
QPCR	2018	Coffee	_	_	**(Potipun *et al*., 2018).**
E-AB-sensor	2018	Food	_	_	**(Somerson & Plaxco, 2018).**
QCM-based immunosensors	2018	Food and feed	17.2-200 (ng/ml)	_	**(Pirinçci *et al*., 2018).**
Optical immunosensors	2018	Food commodities	0,01-1	_	**(Viter *et al*., 2018).**
2D-HPLC	2018	Food (beer-wine-corn-cooffe)	21.2 (pg/ml)	64.3 (pg/ml)	**(Armutcu *et al*., 2018).**
ELISA	2019	Cereals	0.097 (µg/ml)	_	**(Zhang *et al*., 2019).**
NB-based FRET	2019	Food	0.06-0.012 (ng/ml) for OTA-OTB	_	**(Tang *et al*., 2019).**
FRET-LFI	2019	Coffee	0.88 (ng/ml)	_	**(Oh *et al*., 2019).**

Table 10. Cont.

Methods	Year	Biological material	LOD	LOQ	Reference
LC- LC-MS/MS	2019	Cereals	0.001 (ng/kg)	-	**(Kresse *et al*., 2019).**
ELISA	2020	Food	0.03 (ng/ml)	_	**(Fadlalla *et al*., 2020).**
ELISA	2020	Cereal	0.003(ng/ml)	_	**(Zhang *et al*., 2020).**
Nb-FRET immunosensor	2020	Cereal	5 (ng/ml)	_	**(Tang *et al*., 2020).**
HPLC-FD	2020	Wines	_	0.1;0.2 (µg/l) for OTA-OTB	**(Kholová *et al*., 2020).**
EIS	2020	Coffee	0.096 (ng/ml)	_	**(Kunene *et al.*, 2020)**
SERS-nanoparticle	2020	Wine and wheat	_	_	**(Rojas, Qu, & He, 2021).**
Biosensor	2020	Rat urine	1.9×10^{-12}(ng/ml)	_	**(Santovito *et al*., 2020).**
HPLC-FLD	2020	Food	0.2 (mg)	0.5 (mg/g)	**(Karami-Osboo, 2020).**
LC- MS/MS	2020	Human plasma	-	0.04-0.05 (ng/ml)	**(López *et al*., 2020).**
Aptamer based sensors	2021	Food	0.88 (Pg/ml)	_	**(Zhang *et al*., 2021).**
Immunoenzym-atic	2021	Biological liquids	0.0197 (ng/ml)	0.0474 (ng/ml)	**(Cuciureanu *et al*., 2021).**
EIS	2021	Food	0.028(µmol/ml)	_	**(Chen *et al*., 2023).**

Table 10. Cont.

Methods	Year	Biological material	LOD	LOQ	Reference
FN-Nanosens	2021	Cereals	5 (pg/ml)	_	**(Su *et al*., 2022).**
LC-MS/MS	2021	Cacao beans	0.03 (µg/kg)	1.0 (µg/kg)	**(Abreu *et al*., 2023).**
NBL-Immunosens	2022	Food	0.01 (ng/ml)	_	**(Xie *et al*., 2022).**
WRLS	2022	Flours	0.03 (ng/ml)	_	**(Karachaliou *et al*., 2022).**
FRET based Immunosensor	2022	Wine	0.02 (ng/ml)	_	**(Serebrennikova *et al*., 2022).**
WRLS	2022	Flours –cereal- wine	60 (pg/ml)	_	**(Karachaliou *et al*., 2022).**
FN-Nanosensor	2022	Cereals	5 (pg/ml)	_	**(Su *et al*., 2022).**
HPLC-MS/MS	2022	Maize	-	0.02-1.67 (µg/kg)	**(Dan Wei *et al*., 2023).**
UHPLC-ESE-MS/MS	2022	Coffee	0.003 (ng/g)	0.001 (ng/g)	**(Prakasham *et al*., 2023).**
			0.03(ng /ml)	1.0 (ng/ml)	**(Palma *et al*., 2023).**
HPLC-FLD	2022	Spices			
LC-MS	2022	Cheese	25.05 (µg/ kg)	-	**(Pietri *et al*., 2022).**
LC-MS/MS	2022	Bovine meat	0.059 to 291.36 (µg/kg)	0.081 to 328.13 (µg/kg)	**(Hajrulai-Musliu *et al*., 2021).**
MBS-ELISA	2023	Cereal	(1.7 ng/ml)	_	**(Zuo *et al*., 2023).**

Table 10. Cont

Methods	Year	Biological material	LOD	LOQ	Reference
qRT-PCR	2023	Kindney	_	_	**(Yang *et al*., 2023).**
MSPE-HPLC-FLD	2023	Beer-vinegre	0.03 (µg/L)	_	**(Yang *et al*., 2023).**
EIS	2023	Food comodities	39 (Fg/ml)	_	**(Chen, *et al*., 2023).**

V.2.Prevention strategies of OTA Contamination

OTA contamination in food and feed can happen in agriculture at the pre-harvest, harvest, and postharvest stages. Similarly, producers can use OTA control measures at the farm level, including during the pre-harvest, harvest, and postharvest phases. Prevention, decontamination, and detoxification are the major methods employed to control OTA contamination at various stages. However, the reduction and detoxification of OTA mycotoxins in the food and feed chain continue to be significant issues that demand OTA control strategies that are efficient, manageable, and sustainable **(Adebiyi *et al*., 2019)**.

V.2.1.Pre-harvest and during harvest prevention strategies of OTA Contamination

Using good agricultural practices (GAP) like soil cultivation, crop rotation, irrigation during droughts, proper application of fungicides and fertilizers, harvesting at the right time, and the use of fungal resistant crop varieties are some of the common ways that pre-harvest controls the growth of fungi in plants **(Abrunhosa *et al*., 2010; Wafula *et al*., 2022; Roudsari *et al*., 2022)**. However, in order to prevent product damage during harvest and to prevent the growth of fungi, agricultural produce must be handled in clean, dry containers that are free of moisture. Agricultural products can become contaminated by fungus and accumulate OTA mycotoxin during storage as a result of these ineffective pre-harvest and harvesting procedures **(Loi *et al*., 2017)**.This might be because *P. verrucosum*, a generator of OTs, and *A. flavu*s are fungi that invade plants before harvest and contaminate products with mycotoxins afterward **(Tola & Kebede, 2016)**.Therefore, once mycotoxin has been produced, the bio-detoxification of OTA mycotoxin in food and feed should be based on postharvest methods **(Mwabulili *et al*., 2022)**.

V.2.2.Post-harvest prevention strategies of OTA contamination

Removal of the fungus-infected items and the use of various treatment techniques on the products are the mainstays of postharvest OTA contamination control. These activities are based on the food and/or feed distribution chain's storage and distribution stages. However, this also includes the use of antagonistic yeast, fungi, and bacteria to prevent the production of OTA in food and feed. The presence of fungi-infected items does not necessarily indicate the existence of OTA, however, as the right parameters (nutrient availability, temperature, oxygen, moisture, and time) must exist for OTA formation **(Amézqueta *et al*., 2009)**. The common treatment techniques for OTA reduction or elimination in food and feed are divided

into three categories: biological, physical, and chemical. The physical methods used to remove the most contaminated product sections include sorting, segregating, shelling, peeling, and cleaning procedures. OTA can be bound or destroyed using chemical Compounds, while microorganisms and/or their metabolites are mostly used in biological approaches to convert, adsorb, or degrade OTA.

The biological method is the most promising of these detoxification techniques because it is accessible, affordable, and has superior organoleptic qualities, nutritional quality, better flavor, and safety **(Loi, *et al*., 2017; Chen *et al*., 2018)**. Furthermore, according to **Farbo *et al*. (2016); Cho *et al*. (2016) ; Čolović *et al*. (2019)**, the biological detoxification method is environmentally friendly.

V.2.3.Good Storage Practice

In summary, to limit fungal growth during food storage, one should: - dry the harvested products quickly after harvesting avoid damage to the grains during harvesting, transport, threshing and drying keep the storage cool and dry avoid the formation of condensation water (keep the temperature in the storage always constant; if possible, shade the storage avoid) the development of a high insect population dry again if the maximum permissible moisture content is exceeded **(Nadjet *et al*., 2016)**.

V.2.4. Detoxification methods of OTA

OTA decontamination has reportedly been explored extensively over the years using three basic strategies: physical, chemical, and biological techniques. All of these methods have had some success in OTA detoxification, but there are still a lot of issues that need to be overcome **(Wang *et al*., 2022)**. The methods are summarized in the tables 11, 12, and 13.

Table 11. Detoxification of OTA by physical methods.

Method	Condition	Samples	Results	References
Heat treatment	180 ◦C for 60	Grains	Resulted in a 2–18% reduction in OTA	**(Lee, 2020).**
	roasting (150 ◦C for 50	Pistachios	Reduced more than 60%of OTA without adverse	**(Jalili *et al.*, 2020).**
	min) and microwave		effect on the taste and appearance of pistachios	
	heating			
Ultraviolet	1 h of UV irradiation		500 µg/kg OTA could be reduced to 100 µg/kg	**(Ameer Sumbal *et*
radiation	8 h of UV irradiation	poultry feed	completely decontaminated	***al*., 2016).**
Gamma	20 kGy,	Maize	reduction rate of 61.1%	**(Khalil *et al*., 2021).**
radiation	30.5 kGy	wheat flour,	24%, 12% and 23% of OTA could be degraded	**(Calado *et al*., 2018).**
		grape juice and		
		wine		
Cold plasma	30 W input power and 850	Coffee	Completely inhibited the Fungal growth and reduced	**(Casas-Junco *et al*.,**
	V output		50% OTA content.	**2019).**
	voltage with helium at			
	1.5 l/min			

Table 12. Detoxification of OTA by chemical methods.

Method	Agents protective and condition	Samples	Results	Reference
Alcalinisation	Potassium carbonate	Graps	Dropped up to 50% of OTA	**(Özcan & Gökmen, 2016).**
Acidification	Organic acids	Grape Pomaces	More effective in reducing OTA	**(Yu *et al*., 2020).**
Izonation	100 mg/l ozone for 180 min	Corn	Caused OTA in corn to significantly decrease by 70.7%	**(Qi *et al*., 2016).**
	12.8 mg/l gaseous ozonefor 120 min	Sultans	Resulted in 60.2% reduction in OTA content and more than 2.2 log reduction in the fungal population without remarkable variation in the content of phenolic compounds	**(Torlak, 2019).**

Table 13.OTA degradation by microorganisms and enzymes.

Microorganism or enzymes	OTA concentration	Removal (%)	Incubation time/condition	Degradation products	References
Peroxidase	0.01 µg/ml	27	72 h in PBS	unknown	**(de Oliveira Garcia *et al*., 2020).**
Laccase	0.5 µg/ml	27	72 h in sodium acetate buffer	unknown	**(Loi *et al*., 2018).**
Carboxypept-idase	1 µg/ml	71.3	48 h in PBS	unknown	**(Xu *et al*., 2021).**
Carboxypept-idase	1 µg/ml	33	Overnight in Tris buffer	OTα	**(Liuzzi *et al*., 2017).**
A.oryzae M30011	2 µg/ml	94	72 h in liquid medium	OTα	**(Xiong *et al*., 2021).**
Lysobacter sp. CW239	0.03µg/ml	86.2	24 h in liquid medium	OTα	**(Wei *et al*., 2020).**
A. niger W-35	1 µg/ml	78	12h in liquid medium	OTα	**(Zhao *et al*., 2020).**
A.niger M00120	0.25 µg/ml	99	2d in liquid Medium	OTα	**(Xiong *et al*., 2017).**
Lactobacillus plantarum CECT 749	0.6 µg/ml	95	24h in liquid medium	OTα	**(Luz *et al*., 2018).**

V.2.5.Hazards analysis and critical control points system of OTA

Hazard Analysis Critical Control Points (HACCP) is a preventive, structured and systematic approach to controlling food safety **(Elbadri, 2021)**. It is in fact a logical plan of all controls to be implemented to prevent food safety hazards. This plan is specific to the risk that we seek to avoid. It establishes regular and systematic controls throughout the food production chain. It also provides for corrective actions to be implemented if a risk is identified during a control or if a control is found to be *defective*. It is above all a question of anticipating the risk **(Nadjet *et al*., 2016)**.

Implementation of advanced agricultural technologies, good agricultural practices, good manufacturing practices, and good storage practices can mitigate mycotoxin contamination **(Kamle *et al*., 2019)**.

V.3.Prevention of toxicity of OTA for human and animal health

It is inevitable that both people and animals will consume food that has been contaminated with OTA; however, the molecular basis of OTA toxicity has been revealed, and this is a significant issue that has led to additional opinions and strategies, such as prophylactic food or feed additives that could counteract OTA toxicity to protect both human and animal health **(Khoi *et al*., 2021)**. Adsorbents have been used in some attempts to prevent the gastrointestinal tract from absorbing OTA **(Leszkowicz *et al*.,2015; Trailović *et al*., 2013)**.

Other feed additives, such as Roxazyme-G, artichoke extract, sesame seed (which contains high levels of Phénylalanine (PHE)), the herbs with *ania somnifera* and *Silybum marianum*, and the herbal extract *Silymarin*, have been found to protect against the toxic and immunosuppressive effects of OTA **(Stoev *et al*., 2021)**. These substances should be further researched for potential protective effects against OTA-carcinogenicity **(Stoev, 2022)**.

Numerous studies showed that antioxidants can offset the negative effects of chronic OTA consumption and supported the potential efficacy of dietary counter measures to OTA toxicity **(Sorrenti *et al*., 2013)**.

Conclusion

OTA produced primarily by the genera *Penicillium* and *Aspergillus* growing on a very large number of food products depending on conditions (temperature, pH and humidity). It has also been explored in relation to the interaction between regulators and the environment factors.

The toxicological profile of OTA has been investigated in numerous studies and also extensively reviewed. In summary, these studies showed that OTA is nephrotoxic, hepatotoxic, neurotoxic, teratogenic and immunotoxic in various animals, with renal toxicity and carcinogenesis being the key adverse effects.

Given that OTA is a food contaminant and the impact of its toxicity on human health, sensitive and reliable methods have been developed for its detection, which represent a top priority. The sample requires application of cleaning and extraction protocols before quantitative detection of OTA. Although there are a large number of analytical techniques and their continuous development, the LC/ MS/MS are the essential analytical tool for OTA because of its effective sensitivity, accuracy and reliability.

OTA is considered one of the most important mycotoxins and the most dangerous ones related to food security. Therefore, it is of concern all over the world due to its toxicity and its impact on human and animal health. The application of prevention methods before, during and after harvesting, the application of detoxification methods allows the emergence of highly toxic foods quality and avoiding major problems in the marketing, distribution and consumption of foods.

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