Review Article

MYCOTOXIN INDUCED ANTIBIOTIC RESISTANCE, AN UNSUSPECTED PUBLIC HEALTH IMPACT: A PERSPECTIVE REVIEW

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ABSTRACT

Resistance-to-antibiotics (ABR) in bacteria is an ever increasing critical global public health concern, as is the prevalence of mycotoxins in human food and animal feed. Mycotoxins are toxins produced by fungi, and so are antibiotics, albeit some soil bacteria also produce antibiotics. While fungal compounds toxic to humans and animals were categorised as mycotoxins, compounds having bactericidal/bacteriostatic activity were pharmacologically used as antibiotics. Nevertheless, the line of demarcation between antibiotics and mycotoxins is not absolute, as many mycotoxins possess antibiotic properties. However, until now mycotoxins were usually not-suspected to induce cross-resistance to antibiotics. The current article demonstrates the plausible mechanistic link for the induction of cross-resistance by mycotoxins to antibiotics. Evidence presented shows that in addition to common origin both mycotoxins and antibiotics have similar chemical structures, genetic backbone, biosynthetic pathway as well as role in the life of producing organism and even induce similar resistance mechanisms in bacteria, scientifically substantiating that mycotoxin induced ABR is a plausible phenomenon. Further the unavoidable presence of mycotoxins in animal feed albeit at low levels, mimics long-term exposure of commensal bacteria in farm animals to antibiotic-growth-promoters at low levels. Additionally, chronic low-level antibiotic exposure in animals is argued to be a serious factor contributing to antibiotic-resistant bacteria in humans. Finally the article provides experimental design to help evaluate the mycotoxin-induced-ABR. The given scientific evidence necessitates future investigations through appropriate studies to confirm the potential of mycotoxins as critical inducers of ABR, from possibility to plausibility.

Key words: Mycotoxins, Antibacterial activity, Cross-resistance, Induced antibiotic-resistant,

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INTRODUCTION

Mycotoxins are chemically and functionally diverse group of fungal toxins. But not all toxic compounds produced by fungi are called mycotoxins. In fact, fungi also produce other toxic metabolites that are toxic to plants (fungal phytotoxins) and even to other microorganisms (antibacterial/antifungals)

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(Bennett and Klich, 2003). Some of the fungal toxins find their use as antibiotics (penicillin), antifungals (griseofulvin), immunosuppressive drugs (cyclosporin A, mycopheloic acid), cholesterol-lowering agents (lovastatin), etc. (Boruta, 2018). In medical terms, mycotoxins are fungal compounds that cause various acute and chronic toxic effects in humans and animals, while antibiotics are mostly used medically for bactericidal/bacteriostatic activity. But, the line of demarcation between mycotoxins and antibiotics is not absolute. In reality there is overlap between the mycotoxic and antibiotic activities that remains the "focus" of this prospective article, in-turn helping us to understand the role of mycotoxins on public health from the perspective of antibiotic resistance (ABR).

Antibiotics, mycotoxins and their relationship: "Antibiotics and mycotoxins are fundamentally the same"

Antibiotics and mycotoxins are fundamentally the same (Shier, 2011). Infact, the literal meaning of "anti-biotic" means "against–life", but in general medical usage, antibiotics refers to agents that kill other bacteria or prevent their growth. Antibiotics are chemically diverse group of antibacterial molecules, commonly categorized into classes based on similar structures and modes of action.In nature the antibiotics are primarily produced by soil bacteria (eg:*Streptomyces species*) and fungi (eg:*Penicillium* species). Similar to production of antibiotics the fungi also produces mycotoxins. Analogous to antibiotics, mycotoxins are also *chemically and functionally diverse group of fungal toxins* (secondary fungal metabolites), but these are commonly found as contaminants in food and animal feed.Unfortunately the occurrence of mycotoxins in foodstuff is not completely avoidable (Bhat *et al*., 2010), raising their public health concern. Medically, mycotoxins are attributed with various complicated and overlapping toxicities that include carcinogenicity, hepatotoxicity, nephrotoxicity, immunosuppression, etc. (Alshannaq and Yu, 2017). The technical term mycotoxins is a human derived label, to those fungal metabolites identified to cause deleterious effects on health of human and animals despite having other pharmacological activities including antibiotic activity (Bennett and Klich, 2003). Those mycotoxins possessing pharmacological activities without major deleterious health effects, however, were classified and used as accordingly, eg: antibiotics, antifungals, cholesterol-lowering agents, etc.(Bennett and Klich, 2003).

Apart from having common origin, the similarity between mycotoxin and fungal origin antibiotic is substantiated based on scientific evidence on various parameters, the most important factor being chemical structure. Many mycotoxins and antibiotics belong to similar structural class. For example, mycotoxin aflatoxin (AFB1) and antibiotic tetracycline both are simple acetogens, whereas mycotoxin FB1 and antibiotic Leptomyci in B are modified lipids (Shier, 2011). The chemical classification of mycotoxins and antibiotics belonging to similar structural class is summarized in Table 1. Moreover, the genetic structure and the clustering of genes involved in production of both mycotoxins and antibiotics indicate a striking similarity among genes that

orchestrate their biosynthetic pathways and their regulation (Shier, 2011).Additionally, the functional role of mycotoxins or antibiotics in the life of their producer (fungi), and the ecology of their sources exhibit a similar evolutionary significance.For example, initially thought to be waste products, mycotoxins (fungal secondary metabolites) are now considered as important players in ecological settings from acting as virulence factors to providing protection against competing or invading microbes (Venkatesh and Keller, 2019). Furthermore, many fungi produce mycotoxins and antibiotics simultaneously (eg: *Penicillium chrysogenum* produced both antibiotic penicillin G and the mycotoxin patulin) (Gaucher and Behie, 1987), indicating that from the perspective of fungi that produce antibiotics and mycotoxins are the same (Shier, 2011).

Antibiotic activity of mycotoxins and its implications

While most interest on mycotoxins is focused on their toxic property, very little interest is given towards their antibiotic activity and plausible role in antibiotic resistance (ABR). The plausible relationship for such consideration is supported by the evidence that many mycotoxins are known to possess antibiotic activity (Table 2). Similarly many antibiotics have toxic effects in humans and animals (aminoglycosides are nephrotoxic and ototoxic) (Prayle *et al*., 2010; Rosenberg *et al*., 2020). The antibiotic properties of mycotoxins is not a recent discovery and has been known at-least for over several decades (Boutibonne, 1979; Boutibonnes, 1976, 1979; Boutibonnes *et al*., 1984). Indeed, antibiotic property of patulin (a well-knownmycotoxin in apple

Table 1.Antibiotics and mycotoxins with similar structural classes (Shier, 2011)

S. No	Structural class	Antibiotic	Mycotoxins
1.	Simple acetogens	Tetracycline	Aflatoxin B1
2.	Macrolide acetogens	Geldamycin Rifamycin B	Zearalenone Rorindin A
3.	Poly-ether acetogens	Ionophore antibiotics - monensin, salinomycin, and lasalocid	dinoflagellate toxins – Okadaic acid, maitotoxin, brevetoxins, and yessotoxins
4.	Cyclic peptides	Bacitracin	Nodularin
5.	Modified aminoacids	Penicillin G Clindamycin	Ochratoxin A Gliotoxin
6.	Modified steroid	Fusidic acid	Wortmannin
7.	Modified lipid	Leptomyci in B	Fumonisin B1

juice) prompted clinical trials in humans in cure for common cold (Birkinshaw *et al*., 1944; Raistrick, 1943), until its toxicity to animals rendered it clinically unacceptable (Hopkins, 1993). Aflatoxin B1 (AFB1), one of the most potent naturally occurring carcinogenic mycotoxin, was shown to possess antibiotic property against both Gram-positive and Gram-negative bacteria, including *Yersinia enterocolitica*, a zoonotic pathogen that causes yersiniosis in both humans and animals. But, AFB1 is classified as mycotoxin owing to its toxic properties on human and animal tissues (hepatotoxicity, carcinogenicity). Similarly, deoxynivalenol (DON), the most commonly detected mycotoxin worldwide, was demonstrated to exhibit antibiotic activity against common human pathogens including *S. agalactaie, S. aureus, E. coli, M. luteus* (Ali-Vehmas *et al*., 1998; Praveena and Padmini, 2011).

Further, as bacteria resistant to a particular antibiotic can express cross-resistance against antibiotics belonging to similar structural class (termed as cross-resistance) (Barker, 1999; Courvalin and Pasteur, 2009), similarly bacteria resistant to one mycotoxin express resistance to mycotoxin of similar class (Boutibonnes, 1976). In effect,bacteria *Bacillus thuringiensis* resistant to AFB1 was shown to be resistant to other mycotoxins having similar chemical structure (aflatoxins B2, G1, G2, and sterigmatocystin) (Boutibonnes, 1976). Plausibly, it could be inferred that similar mechanistic cross-resistance could be exhibited by bacteria against antibiotics belonging to similar structural class as the mycotoxins (as in Table 2).

The evolutionary basis for antibiotic activity of fungal mycotoxins and possible ABR induction

The mechanistic understanding for the antibiotic property of mycotoxin could be explained by the roles played by antibiotics and mycotoxins in the lives of their producing organisms. Microorganisms are ubiquitous and omnipresent. Bacteria, fungi, virus, protozoa, etc. are all part of the nature, as they co-exist. Such co-existence could be mutualistic, symbiotic, but also competitive. Evolutionarily, microbes have gained several mechanisms to gain competitive-advantage over the competing-microorganisms in a given ecological niche. One such mechanism is production of toxins acting against competing-microorganism. Those compounds that act against bacteria are termed antibiotics (Eg:penicillin, cephalosporin, etc.) and against fungi as antifungal agents (Eg: griseofulvin).

Evolutionarily, fungi are eukaryotic organisms that thrive in diverse ecological niche. Most, fungi are found in soil (on dead and decaying material - saprophytic fungi), herbivore dung (coprophilous fungi), insects (entomopathogenic fungi) and even live plants (endophytic, parasitic, and mycorrhizal fungi) (Gunatilaka, 2010). Further, few fungi are also vertebrate pathogens though relatively low. But, fungi under favourable conditions of warmth, humidity and moisture can also grow on cereals and food grains, in turn releasing mycotoxins in foodstuffs. Evolutionarily, from fungal perspective, such diverse environments also pose diverse survival challenges including competition from bacteria. For example, in environment

Table 2. Antibacterial properties of mycotoxins

S. No.	Mycotoxin/s	Bacteria inhibited	Reference
1.	Ennantins (ENs) A, A_1, A_2, B, B_1 and B_4	22 *Saccharomyces cerevisiae* strains and 9 *Bacillus subtilis* strains	(Roig *et al*., 2014)
2.	Aflatoxin, Malformin, Penitrem, Patulin and Deoxynivalenol (DON)	*Escherichia coli, Micrococcus luteus*, *Staphylococcus aureus* and *Proteus mirabilis*	(Praveena and Padmini, 2011)
3.	Aflatoxin, gliotoxin, Penicillin, Patulin, Terrecyclic acid, Deoxynivalenol, Malformin, Fumonisin and Trichorzin	*Micrococcus* sp., *Pseudomonas aeuroginosa, Bacillus subtilis, Staphylococcus aureus, Proteus species, E.coli*	(Bisht *et al*., 2011)
4.	Citrinin	*Gram-positive strains (Staphylococcus aureus, Bacillus pumilus, Bacillus subtilis, Bacillus cereus, Klebsiella pneumoniae, Streptococcus pneumoniae, Lactobacillus arabinosus) Gram negative strains (E.coli, Shigella dysenteriae, Shigella sonnei, Shigellaboydii, Salmonella typhimurium, Proteus mirabilis and Vibrio cholera)*	(Mazumder *et al*., 2002)
5.	Fusaric acid and deoxynivalenol (DON)	*Ruminococcus albus* and *Methanobrevibacter ruminantium*	(May *et al*., 2000)
6.	T-2 toxin, deoxynivalenol (DON), ochratoxin A (OTA), aflatoxin B1 (AFB1) and fumonisin B1 (FB1)	*Escherichia, Streptococcus,Staphylococcus, Yersinia, Salmonella, Erysipelothrix* and *Lactobacillus*	(Ali-Vehmas *et al*., 1998)

(soil and decaying matter), fungi compete with more rapidly proliferating flagellated bacteria (Eg: *Bacillus subtilis*) as well as with relatively less-rapidly proliferating non-flagellated bacteria (*Streptomycete* species) (Shier, 2011). Such diverse evolutionary pressure forces the fungi to produce various toxins that help improve their chances of survival against these bacteria, which were in turn extracted as antibiotics for medical (human) use. Emerging studies emphasise the direct ecological role of mycotoxins in fungi-bacteria battle. For example, in the complex interaction of rice phytopathogens *Fusarium fujikuroi* (fungi) and *Ralstonia solanacearum* (bacterium), *F. fujikuroi* is known to produce bikaverin and beauvericin to prevent invasion by *R. solanacearum* that together show additive antibacterial activity against *Ralstonia* (Spraker *et al*., 2016).

Though antibiotic helps fungi limit bacterial-competition, in the natural "evolutionary struggle for existence and survival of the fittest process" the competing-bacteria also naturally evolve to evade the bactericidal and/or bacteriostatic effect of antibiotics. This gain in function in bacteria is called Antibiotic Resistance (ABR). For example, in response to the antibacterial activity of Fusaric acid (a mycotoxin produced by numerous *Fusarium* species), bacteria *Pseudomonas protegens* has been demonstrated to produce siderophores, pyoverdine, and ennantio-psychelin contributing to the resistance of the bacterium to fusaric acid (Ruiz *et al*., 2015).

Molecular mechanism of resistance to mycotoxins and antibiotics are similar: Possible connection in emergence of antibiotic resistance by exposure to mycotoxins

Understanding the molecular basis for resistance to different mycotoxin is important to evaluate and establish the possible link between mycotoxins and ABR. Bacteria employ several mechanisms of resistance against antibiotics that includes changing drug target, efflux of antibiotic molecules, antibiotic specific neutralising enzymes (Eg: against penicillin), etc. (Sanders, 2001). However, little was known regarding the molecular strategies of resistance to mycotoxins. Recently, using deoxynivalenol (DON) as an example, the molecular mechanisms of bacterial resistance to mycotoxin were studied mainly by transcriptome profiling (Hassan *et al*., 2019). Alarmingly, scientific evidence supports the rationale of the current article that the bacteria exposed to mycotoxin show similar molecular mechanism of resistance against mycotoxin, similar to development of ABR mechanism. The processes involved include activation of transport proteins, mycotoxin-specific (DON-specific) deactivation enzymes, upregulation of auxillary proteins – porins,phosphotransferases, etc. (Hassan *et al*., 2019). Hence, there exists a clear mechanistic supportive evidence for mycotoxin-induced antibiotic cross-resistance (MABR).

Moreover, cross-resistance may also occur between antibiotic belonging to unrelated drug class (Sanders *et al*., 1984), and across different classes of agents, eg: biocides and antibiotics (Kampf, 2018). Such cross-

resistance could be a result of overlapping drug targets or if there is a drug efflux pump with a broad range of activity (SCENIHR, 2009). Further, biocides are also associated with co-resistance to antibiotics through the selection of multiple resistance genes, eg: Methicillin-resistant *Staphylococcus aureus* in commercial swine were associated with biocide benzalkonium (Slifierz *et al*., 2015) or through indirect selection.This raises concerns that if chemically unrelated class of compounds (eg: biocides) could induce cross-resistance to antibiotics then the possibility for mycotoxins being more analogous to antibiotics in structure, drug-target and mechanism could be easily more damaging in ABR induction. Though, such co-resistance and indirect selection process are not established for mycotoxins until now, nevertheless the possible threat of MABR, demands investigation into such processes. A brief summary of factors that correlate the resistance to mycotoxins and antibiotics is enlisted in Table 3.

Factors that relate the public health impact of mycotoxins to induced antibiotic resistance: Feed mycotoxins and gut-microbiome interactions

From the above reasoning, it is clear that persistence of the mycotoxin in feed is certainly an evolutionary selective pressure for an adaptive response of bacteria and could possibly favour induction of ABR. However, there are certain factors that could potentially accentuate the complications of MABR from mycotoxins in food and feed, implying the previously unsuspected public health

Table 3. Factors that link the mycotoxins and antibiotics in terms of ABR

1.	Structural similarity	Many mycotoxins and antibiotics belong to similar structural class.
2.	Role in the life of producing organisms	Mycotoxins and antibiotics have similar function, majorly fighting competing organisms in a given ecological niche.
3.	Antibacterial activity	Both mycotoxins and antibiotics have antibacterial activity.
4.	Bacteria resistant to mycotoxin could transmit ABR genes – horizontal gene transfer	*Pseduomonas* carrying resistant to Fusaric acid, could transmit resistant genes to other bacteria through horizontal gene transfer
5.	Mechanism of resistance against mycotoxins and antibiotics	Bacteria employ similar strategies in overcoming toxicity of antibiotics and mycotoxins
6.	Effect on GIT commensals	Both mycotoxins and antibiotics are known to cause dysbiosis in animals.

impact of mycotoxins. Majorly, it involves the presence of mycotoxins in foodstuff, the level of mycotoxins and their interactions with commensal bacteria in the gastrointestinal (GIT) of animals and humans.The factors that link the mycotoxins and antibiotics in terms of ABR from public health perspectiveis presented in Table 4.

Presence of mycotoxins in environment or foodstuff is variable, but unfortunately the occurrence of mycotoxins in food/feed is not completely avoidable and thus mycotoxin exposure is far more common than we might suspect (Bhat *et al*., 2010). Given their unavoidable occurrence even government regulatory bodies (FDA, EFSA, etc.) allow them in limited levels (maximum permissible limit) for mycotoxins in food and feed (Bennett and Klich, 2003). The international reference values for regulated mycotoxins is summarized elsewhere (Alshannaq and Yu, 2017).In real world scenario, the inevitable occurrence of mycotoxins are associated with long-time exposure to low concentrations of mycotoxins and resultant chronic toxicities (Vanhoutte *et al*., 2016). However, such long-term chronic exposure could mimic the continuous exposure of animal intestinal microbiota to sub-MIC antibiotics used as growth promoter in food animals.Growing scientific evidence supports that low concentrations of antibiotics can cause high antibiotic resistance to develop in bacteria (Wistrand-Yuen *et al*., 2018). Indeed, long-term low dose antibiotics usage as growth promoters is commonly correlated to the prevalence of antibiotic resistance in animals and humans, including zoonotic pathogens, an emerging public health problem (Milanov *et al*., 2016; Vidovic and Vidovic, 2020). Given the similarity of mycotoxins to antibiotics in terms of chemistry, genetic structures, biosynthetic pathways, mechanism, etc., mechanistically it could imply that such chronic low level mycotoxin might pose similar risk for ABR induction as antibiotic growth promoters.

While the mycotoxins are of global food safety concern for both animals and humans (Grenier and Oswald, 2011), the guidance limits for mycotoxins are higher in animals than humans (Knutsen*et al*., 2017; FDA, 2010). For example, advisory levels for deoxynivalenol (DON) is 1 ppm in food for humans, while it is 5 ppm for swine, 10 ppm in ruminants and birds (FDA, 2010). This implies that practically animals are exposed

Table 4. Factors that influence resistance to mycotoxins and MABR

1.	Presence of mycotoxins	Unavoidable in food/feed
2.	Exposure of bacteria to mycotoxins	Bacteria within the animal through feed. Bacteria in environment – soil, silage (animal feed), etc.
3.	Dose of mycotoxins that favour ABR	Long-term low dose enough for ABR induction
4.	Emerging mycotoxins	Unknown effects

to higher levels of mycotoxin than humans. Further, concerning the effect of mycotoxins the gastrointestinal tract (GIT) is considered the first tissue exposed to mycotoxins in food and often to higher levels than other tissues (Broom, 2015).However, GIT of animals and humans harbour billions of bacteria (rumen of cattle, gizzard of poultry, large-intestine of pigs and humans). Thus, in addition to epithelial cells of GIT, the bacteria in the GIT are first exposed to mycotoxins in food, and recently interactions between mycotoxins and gut microbiota is gaining more importance (Guerre, 2020). This indicates that GIT act as hotspot for the interaction between mycotoxins and bacteria relevant for ABR. Such exposure hotspots are more relevant in farm animals such as ruminants, because they harbour bacteria in fore-stomach (anatomically before actual exposure of animals in true-stomach), increasing interaction between gut microbes and mycotoxins, even before interaction with intestinal epithelial cells. Indeed, such GIT-bacteria and mycotoxin interaction have been shown to have both beneficial and deleterious effects to animals. For instance, degradation of mycotoxins to less active metabolites by rumen bacteria renders ruminants less susceptible to mycotoxin (DON to de-epoxy-deoxynivalenol) in comparison to monogastric animals (Gallo *et al*., 2015). On the contrary, mycotoxins have been demonstrated to disrupt gut microbial homeostasis, with potential consequences for gut and host health (Liew and Mohd-Redzwan, 2018). Mycotoxins, FB1 and DON were shown to cause microbial dysbiosis in intestine of pigs (monogastric animals that harbour bacteria in the large intestine anatomically after stomach) (Burel *et al*., 2013; Waché *et al*., 2009).More-severely, the influence of mycotoxins on GIT microbial interaction is shown to increase pathogenic bacterial infection in animals. For example, in calves a combination of aflatoxins and fumonisins enhanced the growth of Shiga-toxin-producing *Escherichia coli, a known disease causing organism* in humans, rising serious public health concern (Baines *et al*., 2013). Such impacts of mycotoxins involving modulation of gut microbial composition substantiates the similarities between mycotoxins-causing GIT dysbiosis (Liew and Mohd-Redzwan, 2018)to antibiotic-induced GIT dysbiosis (He *et al*., 2017; Neuman *et al*., 2018), at the level of animal physiological.

Indeed, the recent strategy in the biological control of mycotoxins employs bacterial deactivation of mycotoxins. *Eubacterium* BBSH 797 isolated from rumen fluid capable of biotransforming the epoxide group of DON, was the first microorganism used as an additive for deactivating mycotoxin in feed (Nešić *et al*., 2021). Such developments might pose a question that when bacteria are deactivating the mycotoxins, how can the resistance to mycotoxins and in-turn ABR arise. However a closer inspection reveals that bacteria employ similar genetic mechanism for deactivation of mycotoxins as used against antibiotics (Hassan *et al*., 2019). Considering the widespread phenomenon of horizontal gene transfer (HGT) among GIT bacteria (Li *et al*., 2020; Shterzer and Mizrahi, 2015), the genetic basis of bacterial response against mycotoxins increases the chances for exchange of resistance genes through HGT. Thus the possibility of transfer of resistance genes against antibiotics having similar structure to

mycotoxins is a more likely threat. Overall, taking into account the similarities between the mycotoxins and antibiotic in chemistry, genetic structure as well as similarities in their mechanism on bacteria from molecular level to physiological level of animals, it could be inferred that a similar mechanism of cross-resistance to antibiotics induced by mycotoxins could be a mechanistic plausibility as well as public health crisis. However, until now the studies involving the influence of mycotoxin on GIT microbes is limited to their relation to pathogenesis of disease, but their influence on MABR needs to be evaluated.

Possible experimental design to evaluate the mycotoxin induced antibiotic resistance (MABR): Using an *in-vitro* model

In the light of such similarities between mycotoxins and antibiotics, it is imperative to understand whether bacteria can produce cross-resistance to antibiotic upon previous exposure to mycotoxins. Several experimental protocols have already been designed to evaluate the potential a compound to induce antibiotic cross-resistance (Hong *et al*., 2016). Protocols are also available to evaluate both short-term (Hong *et al*., 2012) and long-term (Hong *et al*., 2016) selection pressure of exposure for induction of ABR. Briefly, a particular strain of bacteria is grown in appropriate conditions (media – nutrition, temperature) with or without the presence of compound in question (mycotoxin) at half MIC (minimal inhibitory concentration) for several passages. After appropriate number of passages (short-term or long-term), the mycotoxin-resistance-spectrum is measured by modified Kirby-Bauer (KB) susceptibility test to measure the induction of resistance to mycotoxin. The diameter of zone of inhibition represents the bacterial susceptibility to the antimicrobial agent. Later, using the same KB disc diffusion method, the antimicrobial susceptibilities of resistant bacteria to several antimicrobial agents could demonstrate induction of cross-resistance to antibiotics.

Their do exist certain drawbacks in the use of the experimental design proposed above. Majorly, the use of stepwise training involving "passaging of bacteria to increasing concentrations of a mycotoxin", might not reflect conditions *in-situ*. These studies could however, yield many insights on possibility of such bacterial-resistance and the resistance mechanisms. Nevertheless, such *in-vitro* studies provide valid proof-of-concept that could later be evaluated using *in-vivo* animal models. Further, since animals are frequently exposed to multiple mycotoxins with potential additive and synergistic effect (Christiane *et al*., 2019), such combined multiple-mycotoxin effect also needs to be determined. We anticipate the current article and the proposed experimental design to be a starting point for more sophisticated *invitro* models. Additionally, the role of emerging mycotoxins in their impact on complication of MABR remains a topic of interest. Because, while over 300-400 mycotoxins are identified, only few mycotoxins are regulated and much is unknown about the remaning mycotoxins. Finally, we should consider the fact that the development of anti-mycotoxin resistance, the nature of resistance to mycotoxin and possible MABR depend on the bacterial isolates investigated, the type of mycotoxins, combination of mycotoxin exposed, etc.

CONCLUSION

Mycotoxins and antibiotics are considered fundamentally similar largely in terms of chemical architecture, genetic structure, biosynthetic pathways and mechanism of effect on bacteria (table 5). Moreover the resistance mechanism against antibiotics resembles mechanism of ABR in bacteria, indicating possibility of mycotoxin induced ABR. However, there exists various gaps that needs to be filled to replicate the natural scenario that might contribute to the development of resistance to mycotoxins and mycotoxin induced ABR. Majorly, we should consider the fact that development of anti-mycotoxin resistance and the nature of resistance to mycotoxin depend on the bacterial isolates investigated, the type of mycotoxins, combination of mycotoxin exposed, etc. Finally, given the diverse factors as explained the current article that could potentially influence the complications of mycotoxin-bacterial interaction and bacterial response to mycotoxins, the mycotoxin induced ABR (MABR) remains an open yet critical topic to be investigated.

REFERENCES

Ali-Vehmas, T., Rizzo, A., Westermarck, T. and Atroshi, F. (1998). Measurement of Antibacterial Activities of T-2 Toxin, Deoxynivalenol, Ochratoxin A, Matoxin B1 and Fumonisin B1 Using Microtitration Tray-based Turbidimetric Techniques. *Journal of Veterinary Medicine*, **458**: 453–458.

Alshannaq, A. and Yu, J.H. (2017). Occurrence, toxicity, and analysis of major mycotoxins in food. *International Journal of Environmental Research and Public Health*, **14**(6). https://doi.org/10.3390/ijerph14060632

Baines, D., Sumarah, M., Kuldau, G., Juba, J., Mazza, A. and Masson, L. (2013). Aflatoxin, fumonisin and shiga toxin-producing *Escherichia coli* Infections in calves and the effectiveness of Celmanax®/Dairyman's choice™. Applications to Eliminate Morbidity and Mortality Losses, 1872–1895. https://doi.org/10.3390/toxins5101872

Barker, K.F. (1999). Antibiotic resistance : a current perspective. *British Journal of Clinical Pharmacology*, **48**(2): 109–124.

Bennett, J.W. and Klich, M. (2003). Mycotoxins. *Clinical Microbiology Reviews*, *16*(3), 497–516. https://doi.org/10.1128/CMR.16.3.497–516.2003

Bhat, R., Rai, R.V. and Karim, A.A. (2010). Mycotoxins in food and feed: present status and future concerns. *Comprehensive Reviews in Food Science and Food Safety*, **9**(1): 57–81. https://doi.org/10.1111/j.1541-4337.2009.00094.x

Birkinshaw, J.H., Michael, S.E., Bracken, A. and Raistrick, H. (1944). Clinical trial of patulin in the common cold. report of the Patulin Clinical Trials Committee, Medical Research Council. *The Lancet*, **244** (6316): 373–375.https://doi.org/10.1016/S0140-6736(00)45330-4

Bisht, S.S., Praveen, B., Panda, A., Behera, S., Panda, K.K., Mishra, R. and Patro, S.K.

(2011). Comparative study of various mycotoxins against few bacterial test organisms. *International Journal of Pharmacy and Pharmaceutical Sciences*, **3**(SUPPL. 5): 288–291. https://doi.org/10.18579/jpcrkc/2011/10/3/89005

Boruta, T. (2018). Uncovering the repertoire of fungal secondary metabolites: From fleming's laboratory to the international space station. *Bioengineered*, **9**(1): 12–16. https://doi.org/10.1080/21655979.2017.1341022

Boutibonne, P. (1979). Determination of the antibacterial activity of various mycotoxins using *Bacillus thuringiensis* (Berliner). *Mycopathologia*, *67* (1), 45–50.

Boutibonnes, P. (1976). Antibacterial effect of various mycotoxins and fungal metabolites against *Bacillus thuringiensis* (Berliner) strains sensitive or resistant to aflatoxin B1. *Canadian Journal of Microbiology*, *22*(6), 884–886. https://doi.org/10.1139/m76-127

Boutibonnes, P. (1979). Antibacterial activity of zearalenone. *Canadian Journal of Microbiology*, *25*(3): 421–423. https://doi.org/10.1139/m79-064

Boutibonnes, P., Auffray, Y., Malherbe, C., Kogbo, W. and Marais, C. (1984). Proprietes antibacteriennes et genotoxiques de 33 mycotoxines. *Mycopathologia*, **87**(1–2): 43–49. https://doi.org/10.1007/BF00436626

Broom, L. (2015). Mycotoxins and the intestine. *Animal Nutrition*, **1**(4): 262–265. https://doi.org/10.1016/j.aninu.2015.11.001

Burel, C., Tanguy, M., Guerre, P., Boilletot, E., Cariolet, R., Queguiner, M.*et al*. (2013). Effect of Low dose of fumonisins on pig health: Immune Status, Intestinal Microbiota and Sensitivity to *Salmonella*. *Toxins*, *5*(4), 841–864. https://doi.org/10.3390/toxins5040841

Christiane G-D, Timothy Jenkins, G. S. (2019). Global Mycotoxin Occurrence in Feed. *Toxins*, **11**(375).

Courvalin, P. and Pasteur, I. (2009). Antibiotic Resistance ´. In *Encyclopedia of Microbiology* (Third, pp. 193–204).

FDA. (2010). Advisory Levels for Deoxynivalenol (DON) in Finished Wheat Products for Human Consumption and Grains and Grain By-Products used for Animal Feed. U.S. Food and Drug Administration Guidance Document, 20855, 4. Retrieved from http://scholar.google.com /scholar?hl=en&btnG=Search&q = intitle: Guidance +for+Industry+and+FDA+ :+Advisory + Levels+for + Deoxynivalenol + (+DON+)+in+ Finished + Wheat + Products + for + Human + Consumption+and + Grains+ and+ Grain+ By-Products + used+ for+ Animal + Feed#0

Gallo, A., Giuberti, G., Frisvad, J.C., Bertuzzi, T. and Nielsen, K.F. (2015). Review on mycotoxin issues in ruminants: occurrence in forages, effects of mycotoxin ingestion on health status and animal performance and practical strategies to counteract their negative effects, 3057–3111. https://doi.org/10.3390/toxins7083057

Gaucher, G.M. and Behie, L.A. (1987). Cell immobilization in the production of patulin and penicillin by *Penicillium urticae* and *Penicillium chrysogenum*. *Methods in Enzymology*, **136**, 329–342. https://doi.org/10.7868/s0424857017010029

Grenier, B. and Oswald, I. P. (2011). Mycotoxin co-contamination of food and feed: Meta-analysis of publications describing toxicological interactions. *World Mycotoxin Journal*, **4**(3), 285–313. https://doi.org/10.3920/WMJ2011.1281

Guerre, P. (2020). Mycotoxin and Gut Microbiota Interactions. *Toxins*, **12**(12), 1–33. https://doi.org/10.3390/toxins12120769

Gunatilaka, A. A. L. (2010). Fungal secondary metabolites. *Access Science - The Science Authority*, 100063 (1985): 1–5. https://doi.org/doi.org/10.1036/1097-8542.YB100063

Hassan, Y. I., He, J. W., Lepp, D. and Zhou, T. (2019). Understanding the bacterial response to mycotoxins: The transcriptomic analysis of deoxynivalenol-induced changes in devosia mutans 17-2-e-8. *Frontiers in Pharmacology*, **10** (November): 1–11. https://doi.org/10.3389/fphar.2019.01098

He, S., Wang, Q., Li, S., Ran, C., Guo, X., Zhang, Z. and Zhou, Z. (2017). Antibiotic growth promoter olaquindox increases pathogen susceptibility in fish by inducing gut microbiota dysbiosis. *Science China Life Sciences*, **60**(11): 1260–1270. https://doi.org/10.1007/s11427-016-9072-6

Hong, J, Dai, J., Guan, W., Jin, G., Huang, Z., Zhang, L. and Zhang, Y. (2012). Tachyplesin I induce drug resistance in bacteria *in vitro*. *Journal of Animal and Veterinary Advances*, 11: 939–945.

Hong, J., Hu, J. and Ke, F. (2016). Experimental Induction of Bacterial Resistance to the Antimicrobial Peptide Tachyplesin I and Investigation of the Resistance Mechanisms, **60**(10): 6067–6075. https://doi.org/10.1128/AAC.00640-16. Address

Hopkins, J. (1993). The toxicological hazards of patulin. *Food and Chemical Toxicology*, **31**(6), 455–456. https://doi.org/10.1016/S0195-6698(80)80053-9

Kampf, G. (2018). Biocidal agents used for disinfection can enhance antibiotic resistance in gram-negative species. *Antibiotics*, **7**(4). https://doi.org/10.3390/antibiotics7040110

Knutsen, H.K., Alexander, J., Barregård, L., Bignami, M., Brüschweiler, B. *et al*. (2017). Risks to human and animal health related to the presence of deoxynivalenol and its acetylated and modified forms in food and feed. *EFSA Journal*, **15**(9). https://doi.org/10.2903/j.efsa.2017.4718

Li, C., Chen, J. and Li, S.C. (2020). Understanding horizontal gene transfer network in human gut microbiota. *Gut Pathogens*, **12**(1): 1–20. https://doi.org/10.1186/s13099-020-00370-9

Liew, W.P.P. and Mohd-Redzwan, S. (2018). Mycotoxin: Its impact on gut health and

microbiota. *Frontiers in Cellular and Infection Microbiology*, **8**(FEB). https://doi.org/10.3389/fcimb.2018.00060

May, H. D., Wu, Q. and Blake, C. K. (2000). Effects of the *Fusarium* spp. mycotoxins fusaric acid and deoxynivalenol on the growth of *Ruminococcus albus* and *Methanobrevibacter ruminantium*. *Canadian Journal of Microbiology*, **46**(8): 692–699. https://doi.org/10.1139/cjm-46-8-692

Mazumder, P. M., Mazumder, R., Mazumder, A. and Sasmal, D. S. (2002). Antimicrobial activity of the mycotoxin citrinin obtained from the fungus Penicillium Citrinum. *Ancient Science of Life*, *21*(3): 191–197. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22557053%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC3331043

Milanov, D., Ljubojevic, D., Cabarkapa, I. and Aleksic, N. (2016). Impact of antibiotics used as growth promoters on bacterial resistance. *Food and Feed Research*, **43**(2): 83–92. https://doi.org/10.5937/ffr1602083m

Nešić, K., Habschied, K. and Mastanjević, K. (2021). Possibilities for the Biological Control of Mycotoxins in Food and Feed. *Toxins*, **13**(3): 198. https://doi.org/10.3390/toxins13030198

Neuman, H., Forsythe, P., Uzan, A., Avni, O., Koren, O., Medicine, F., *et al*. (2018). Antibiotics in early life : dysbiosis and the damage done, (December 2017), 1–11. https://doi.org/10.1093/femsre/fuy018

Praveena, Y.S.N. and Padmini, P.P.C. (2011). Antibacterial activities of mycotoxins from newly isolated filamentous fungi. *International Journal of Plant, Animal and Environmental Sciences*, **1**(1): 8–13.

Prayle, A., Watson, A., Fortnum, H. and Smyth, A. (2010). Side effects of aminoglycosides on the kidney, ear and balance in cystic fibrosis. *Thorax*, **65**(7): 654–658. https://doi.org/10.1136/thx.2009.131532

Raistrick, H. (1943). Patulin in the common cold. *The Lancet*, **241**(6227): 1–3. https://doi.org/10.1016/s0140-6736(00)70684-2

Roig, M., Meca, G., Marín, R., Ferrer, E. and Mañes, J. (2014). Antibacterial activity of the emerging Fusarium mycotoxins enniatins A, A1, A2, B, B1, and B4 on probiotic microorganisms. *Toxicon*, **85**: 1–4. https://doi.org/10.1016/j.toxicon.2014.04.007

Rosenberg, C.R., Fang, X. and Allison, K.R. (2020). Potentiating aminoglycoside antibiotics to reduce their toxic side effects. *PLoS ONE*, **15**(9 September): 1–17. https://doi.org/10.1371/journal.pone.0237948

Ruiz, J.A., Bernar, E.M. and Jung, K. (2015). Production of siderophores increases resistance to fusaric acid in *Pseudomonas protegens* Pf-5. *PLoS ONE*, **10**(1): 1–16. https://doi.org/10.1371/journal.pone.0117040

Sanders, C.C. (2001). Mechanisms responsible for cross-resistance and dichotomous resistance among the quinolones.

Clinical Infectious Diseases, **32**(Suppl. 1). https://doi.org/10.1086/319369

Sanders, C.C, Sanders, W.E., Goering, R.V, Werner, V., Pharmaceuticals, M. and Haven, W. (1984). Selection of multiple antibiotic resistance by quinolones , 1- lactams , and aminoglycosides with special reference to cross- resistance between unrelated drug classes. *Antimicrobial Agents Chemotherapy*, **26**(6): 797–801.

SCENIHR (2009). Scientific Committee on Emerging and Newly-Identified Health Risks. Assessment of the Antibiotic Resistance Effects of Biocides. *Environment*, (June), 68. Retrieved from http://ec.europa.eu/health/ph_risk/risk_en.htm

Shier, W.T. (2011). On the origin of antibiotics and mycotoxins, 30 (December 2010), 6–30. https://doi.org/10.3109/15569543.2011.550862

Shterzer, N. and Mizrahi, I. (2015). The animal gut as a melting pot for horizontal gene transfer. *Canadian Journal of Microbiology*, 61, 603–605. https://doi.org/10.3390/life4020217

Slifierz, M.J., Friendship, R.M. and Scott, J. (2015). Methicillin-resistant *Staphylococcus aureus* in Commercial swine herds is associated with disinfectant and zinc usage. Applied and *Environmental Microbiology*, **81**(8): 2690–2695. https://doi.org/10.1128/AEM.00036-15

Spraker, J.E., Sanchez, L.M., Lowe, T.M., Dorrestein, P.C. and Keller, N.P. (2016). *Ralstonia solanacearum* lipopeptide induces chlamydospore development in fungi and facilitates bacterial entry into fungal tissues. *ISME Journal*, **10**(9), 2317–2330. https://doi.org/10.1038/ismej.2016.32

Vanhoutte, I., Audenaert, K. and De Gelder, L. (2016). Biodegradation of mycotoxins: Tales from known and unexplored worlds. *Frontiers in Microbiology*, **7**(APR): 1–20. https://doi.org/10.3389/fmicb.2016.00561

Venkatesh, N. and Keller, N.P. (2019). Mycotoxins in conversation with bacteria and fungi. *Frontiers in Microbiology*, **10**, 403. https://doi.org/10.3389/fmicb.2019.00403

Vidovic, N. and Vidovic, S. (2020). Antimicrobial resistance and food animals: Influence of livestock environment on the emergence and dissemination of antimicrobial resistance. *Antibiotics*, **9**(2). https://doi.org/10.3390/antibiotics9020052

Waché, Y.J., Valat, C., Postollec, G., Bougeard, S., Burel, C., Oswald, I.P. and Fravalo, P. (2009). Impact of deoxynivalenol on the intestinal microflora of pigs. *International Journal of Molecular Sciences*, **10**(1): 1–17. https://doi.org/10.3390/ijms10010001

Wistrand-Yuen, E., Knopp, M., Hjort, K., Koskiniemi, S., Berg, O.G. and Andersson, D.I. (2018). Evolution of high-level resistance during low-level antibiotic exposure. *Nature Communications*, **9**(1). https://doi.org/10.1038/s41467-018-04059-1