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Role of biotransformation in the mutagenicity of Versicolorin A, a precursor of Aflatoxin B1

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Introduction

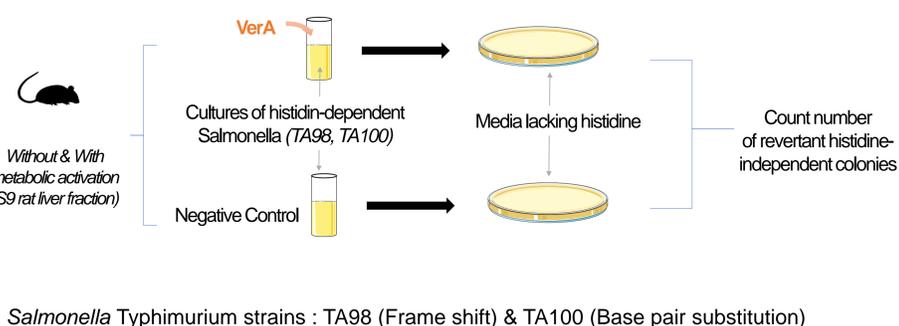
Aflatoxin B1 (AFB1) exhibits the most severe toxicological effects of all known mycotoxins [1]. Versicolorin A (VerA) is a precursor in the biosynthesis of AFB1. Both toxins are produced by the same aflatoxigenic species and can therefore co-contaminate food commodities. It is well established that the *in vivo* bioactivation of AFB1 into a highly reactive molecule is the key step in the mutagenic process [2]. In contrast, much less is known about the toxicity of VerA and no information is available on its metabolization.

Objectives

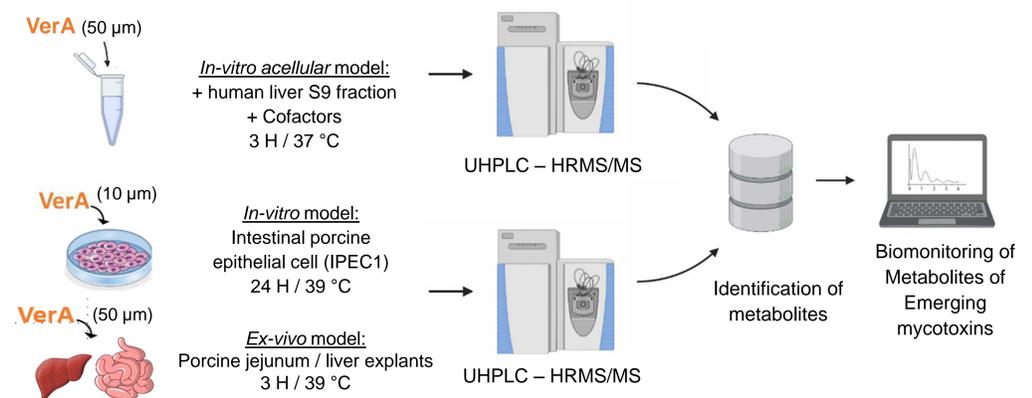
1. Evaluate the mutagenicity of VerA in the absence and presence of metabolic activation.
2. Provide the first qualitative characterization of metabolites derived from the metabolization of VerA.

Materials and Methods

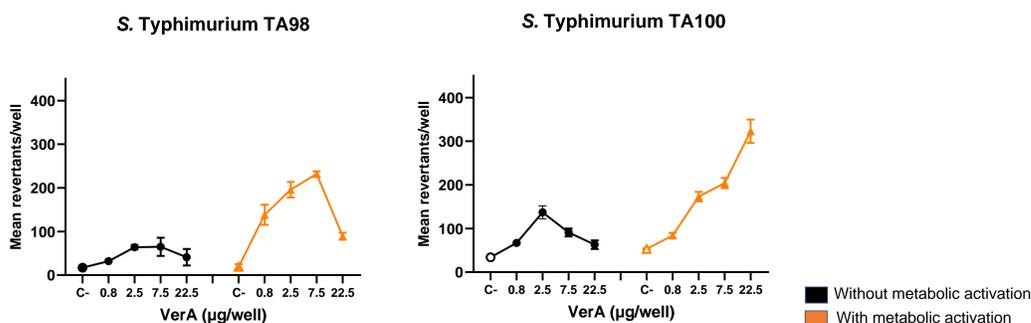
1- In-vitro mutagenicity assay : Miniaturized Ames



2- Characterize the metabolites derived from the metabolism of VerA



• Mutagenicity of VerA (Mini-Ames assay)



- In the absence of metabolic activation, no induction of revertant colonies was significantly observed at all VerA concentrations in both strains.
- In the presence of metabolic activation, VerA induced a more than twofold increase in the number of revertant colonies in a concentration-response trend in both strains, except for TA98 at 66,6 µg/well (toxic concentration).
- **VerA is only mutagenic with metabolic activation.**

• VerA metabolites identified in intestinal cells, intestinal and hepatic tissues

Compound	In vitro (intestinal cells)	Ex vivo (intestinal explants)	Ex vivo (liver explants)
VerA	Yes	Yes	Yes
M + O	Yes	No	Yes
M + H ₂ O	No	No	No
M + GlcAc	No	Yes	Yes
M + O + GlcAc	No	No	Yes
M + SO ₃	Yes	No	No
M + O + SO ₃	No	No	No
M + CH ₂	No	No	Yes

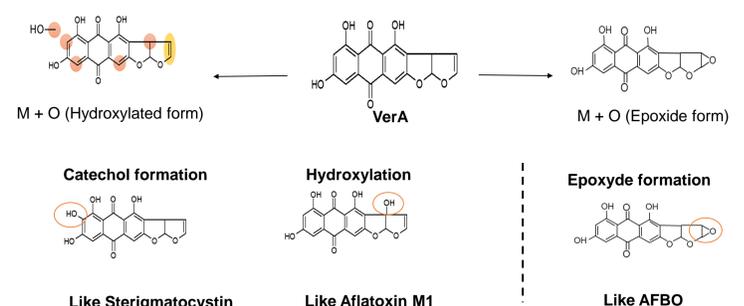
- Two additional metabolites (M + O and M + SO₃) were identified in exposed cells.
- One additional metabolite (M + GlcAc) was identified from intestinal explants samples.
- Four compounds were identified from liver explants samples, all characterized metabolites based on data acquired from human liver S9 incubations, except for one metabolite (M + CH₂).

• Construction a library of VerA metabolites using the *in vitro* S9 fraction

Compound	Measured m/z	Error (ppm)	Molecular formula	Retention time (min)	Observed product ions m/z (relative abundance)
VerA	337.0359	-2.1	C ₁₈ H ₁₀ O ₇	23.2	309.1 (100), 308.1 (55), 293.1 (14), 337.1 (12), 320.0 (5), 265 (5), 252 (4), 280 (3)
M + O	353.0304	-2.8	C ₁₈ H ₁₀ O ₈	18.9	309.1 (100), 335.2 (97), 325.1 (93), 281.1 (23), 310.1 (17), 265.1 (11), 297.1 (10), 307.1 (5), 308.0 (5), 311.1 (3), 324.2 (3), 353.0 (2)
M + H ₂ O	355.0465	1.7	C ₁₈ H ₁₂ O ₈	18.4	337.1 (100), 309.1 (60), 310.1 (24), 327.1 (21), 355.2 (14), 299.1 (13), 325.1 (9), 311.1 (6), 293.2 (5), 284.0 (5), 297.2 (4), 270.1 (3)
M + GlcAc	513.0677	2.7	C ₂₄ H ₁₈ O ₁₃	19.1	337.1 (100), 175.0 (2), 513.1 (2)
M + O + GlcAc	529.0619	-2.1	C ₂₄ H ₁₈ O ₁₄	14.2	353.1 (100), 529.1 (2)
M + SO ₃	416.9910	-2.9	C ₁₈ H ₁₀ O ₁₀ S	22.0	337.1 (100), 417.0 (2)
M + O + SO ₃	432.9859	-2.8	C ₁₈ H ₁₀ O ₁₁ S	14.9	353.1 (100), 433.0 (2)

- Six compounds were detected including phase I and phase II biotransformation metabolites along with intact VerA.

• Detection of phase I metabolite (M + O)



- Phase I metabolite (VerA + O) may be compatible with hydroxylated or epoxyde form of VerA and be involved in its mutagenic effects

Conclusions

- VerA is a mutagenic compound strongly dependent on its metabolic activation, emphasizing the importance of its bioactivation in mutagenicity.
- VerA is able to be biotransformed in intestinal cells and intestinal and liver tissues.
- The metabolization of VerA, as AFB1, suggests a bioactivation of the molecule into mutagenic compounds.

References

1. Schrenk D. et al., 2020, Scientific opinion, Risk assessment of aflatoxins in food. EFSA J. 18, 112
2. Eaton D.L. et al., 2010, Hepato. Mycotox. Compr. Toxicol. 9, 527

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