

PRACTITIONER TECH SHEET | Zearalenone

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Zearalenone is regarded as strictly an ingested mycotoxin, but this is a misunderstanding. The source species of Fusarium molds are commonly found in water-damaged buildings. Environmental exposure is an issue.

As a non-steroidal estrogenic mycotoxin, Zearalenone is an endocrine disruptor which can bioaccumulate and affect both men and women. It has potent estrogen receptor binding affinity, with the same binding affinity to ER β as ER α , correlated to associated risk factors for metabolic, cardiovascular, and neurological diseases, as well as osteoporosis and some estrogenic cancers.

Zearalenone is globally recognized to have causative associations in the development of early thelarche and/or precocious puberty in exposed children.

Zearalenone has significant impacts on the neurology and function of the heart, including second degree AV block.

Additionally, Zearalenone is immunotoxic, including toxic effects on immune glands themselves.

Similar to Ochratoxin, Zearalenone also binds to and reduces blood albumin, deeming it a mild persister mycotoxin. It also poses a risk for developing Clostridia difficile infections.

Zearalenone is metabolized in the liver primarily via glucuronidation, and via enterocytes. This mycotoxin can be activated by Candida and Saccharomyces species.

HEALTH IMPACTS

Xenoestrogenic, xenogenic, cardiotoxic, immunotoxic, hepatotoxic, hematoxic, embryotoxic, genotoxic, plausible carcinogen.

Reproductive. Estrogen receptor binding affinity as potent as coumestrol and genistein. Zearalenone has the same binding affinity to ER β as ER α , carrying associated risk factors for females. Embryotoxic with mitochondrial aberrations. In males, causes damage to germ cells and testicular structure.

Arrhythmic. 2nd-degree AV block, atrial and neurocardiogenic bradycardia. Decreases the total contractile power of the cardiac muscle.

Immunotoxic. Impairs macrophage function and toxic to thymus. Reduces B-cells.

Hepatotoxic. The liver is the major organ of distribution. Induces histopathological changes, with the possible subsequent development of liver cancer. May cause an increase in serum transaminases and bilirubin levels.

Hematoxic. Hematotoxic effects by disturbing blood coagulation and modifying blood parameters.

MOLD SOURCES

Fusarium spp. primarily

COLOR

White “dust” to tan, pink, light purple, and brown, but can change color depending on species and substrate

FAVORITE BUILDING MATERIAL

Basements, crawlspaces, HVAC systems, ducts, humidifiers, CPAP machines, stored foodstuffs

SIGNS

Increased MCV, hematocrit
Reduced total protein, albumin
Increased transaminases, bilirubin
ECG: 2° AV block Mobitz type II > I

SYMPTOMS

Hyperestrogenic syndromes
Acne
PMS, menstrual alterations
Precocious puberty
Osteoporosis
Hypoandrogenism in men
Central weight gain
Infertility, both genders
Fatigue
Dyspnea, with or without chest pain
Bradycardia
Palpitations
POTS
Neurocardiogenic syncope
Dizziness/vertigo
Tinnitus
Edema
Sinusitis
Frequent infections, pneumonia
EBV reactivation
C. difficile
Onychomycosis

Genotoxic. Can form DNA adducts, cause DNA fragmentation, micronucleus formation, chromosomal aberration, cell proliferation, and cell apoptosis. Can mimic the ability of 17- β -estradiol to stimulate estrogen receptor transcriptional activity.

TREATMENT OPTIONS

*Note: the doses listed are intended for when each item is used as a standalone therapy. When multiple items are combined, they often work synergistically, meaning lower doses can typically achieve similar effectiveness due to their complementary effects.

Therapeutic Diet ~

Kefir. Protection against Zearalenone-induced oxidative damage.

Brassicaceae family (broccoli, broccoli sprouts, cauliflower, kale, Brussels sprouts, cabbage, turnips)

Spices: Ginger, Cinnamon, Turmeric, Thyme, Lemongrass, and Rosemary.

Anti-mycotoxigenic and antifungal against Fusarium.

Ginger. Active constituent zerumbone prevents Zearalenone-induced liver injury.

*Avoid the use of Saccharomyces yeasts, as they bioactivate Zearalenone.

Probiotics. Lactobacillus plantarum. 15 CFU qd-bid.

Organoprotective against Zearalenone toxicity.

Binder. Insoluble fiber up to 4 Tbsp daily.

DIM + Indole-3-carbinol. 200mg each, qd-bid.

Enhances xenoestrogen metabolism.

Grape seed extract. 100mg up to three times daily.

Hepatoprotective. Reduces maternal developmental defects.

N-Acetyl Cysteine (NAC). 500mg, qd-bid.

Nephroprotective. Preserves mitochondrial function. Protective to reproductive organs, testes.

Milk thistle. Minimum effective dose 750mg up to 1500mg, best divided.

Alleviates Zearalenone-Induced hepatotoxicity and reproductive toxicity.

Melatonin. 20mg taken before bed. May cause morning grogginess. Use lower doses for sensitive patients.

Significantly ameliorates Zearalenone-induced impairments in kidneys, reproductive cells, and embryonic development.

Hawthorne (Crataegus oxyantha). ½ tsp solid extract up to three times daily.

Cardiotonic. Dilates arteries. Antioxidant via carotenoids which are effective in the protection against Zearalenone-induced toxicity in cardiac tissue.

Resveratrol. Minimum therapeutic dose: 1000mg daily, best divided.

Protective bioflavonoid against Zearalenone-induced oxidative damage, some genoprotective activity.

Glutamine. 1 gram qd-bid.

Attenuates the Zearalenone-induced increase in cytotoxicity, cell apoptosis, and intestinal permeability.

*Not appropriate for PANDAS/PANS.

Selenium as Selenomethionine. 200mcg qd-bid, best with food for enhanced absorption.

Splenoprotective. Lymphoprotective. Protective against reproductive system damage.

Vitamin E as Tocotrienols. 200IU daily.

Genoprotective against Zearalenone-induced effects on kidney and bone marrow.

Lactoferrin. 100mg qd-bid.

Iron-free form of this glycoprotein may help to reduce hematocrit.

REFERENCES

- Jing S, Liu C, Zheng J, Dong Z, Guo N. Toxicity of zearalenone and its nutritional intervention by natural products. *Food Funct.* 2022 Oct 17;13(20):10374-10400. doi: 10.1039/d2fo01545e. PMID: 36165278.
- Lee R, Kim DW, Lee WY, Park HJ. Zearalenone Induces Apoptosis and Autophagy in a Spermatogonia Cell Line. *Toxins (Basel).* 2022 Feb 17;14(2):148. doi: 10.3390/toxins14020148. PMID: 35202175; PMCID: PMC8878478.
- Romoli JCZ, Silva MV, Pante GC, Hoeltgebaum D, Castro JC, Oliveira da Rocha GH, Capoci IRG, Nerilo SB, Mossini SAG, Micotti da Gloria E, Svidzinski TIE, Graton Mikcha JM, Machinski M Junior. Anti-mycotoxigenic and antifungal activity of ginger, turmeric, thyme and rosemary essential oils in deoxynivalenol (DON) and zearalenone (ZEA) producing *Fusarium graminearum*. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess.* 2022 Feb;39(2):362-372. doi: 10.1080/19440049.2021.1996636. Epub 2021 Dec 2. PMID: 34854801.
- Savard C, Gawhary S, Boyer A, Chorfi Y. Assessment of Zearalenone-Induced Cell Survival and of Global Gene Regulation in Mouse TM4 Sertoli Cells. *Toxins (Basel).* 2022 Jan 26;14(2):98. doi: 10.3390/toxins14020098. PMID: 35202126; PMCID: PMC8874968.
- AbuZahra HM, Rajendran P, Ismail MB. Zerumbone Exhibit Protective Effect against Zearalenone Induced Toxicity via Ameliorating Inflammation and Oxidative Stress Induced Apoptosis. *Antioxidants (Basel).* 2021 Oct 12;10(10):1593. doi: 10.3390/antiox10101593. PMID: 34679730; PMCID: PMC8533127.
- Gu A, Yang L, Wang J, Li J, Shan A. Protective effect of glutamine and alanyl-glutamine against zearalenone-induced intestinal epithelial barrier dysfunction in IPEC-J2 cells. *Res Vet Sci.* 2021 Jul;137:48-55. doi: 10.1016/j.rvsc.2021.04.027. Epub 2021 Apr 24. PMID: 33932823.
- Mahato DK, Devi S, Pandhi S, Sharma B, Maurya KK, Mishra S, Dhawan K, Selvakumar R, Kamle M, Mishra AK, Kumar P. Occurrence, Impact on Agriculture, Human Health, and Management Strategies of Zearalenone in Food and Feed: A Review. *Toxins (Basel).* 2021 Jan 26;13(2):92. doi: 10.3390/toxins13020092. PMID: 33530606; PMCID: PMC7912641.
- Ropejko K, Twarużek M. Zearalenone and Its Metabolites-General Overview, Occurrence, and Toxicity. *Toxins (Basel).* 2021 Jan 6;13(1):35. doi: 10.3390/toxins13010035. PMID: 33418872; PMCID: PMC7825134.
- Faisal Z, Vörös V, Fliszár-Nyúl E, Lemli B, Kunsági-Máté S, Poór M. Interactions of zearalanone, α -zearalanol, β -zearalanol, zearalenone-14-sulfate, and zearalenone-14-glucoside with serum albumin. *Mycotoxin Res.* 2020 Nov;36(4):389-397. doi: 10.1007/s12550-020-00404-w. Epub 2020 Aug 1. PMID: 32740802; PMCID: PMC7536148.
- Virk P, Al-Mukhaizeem NAR, Bin Morebah SH, Fouad D, Elobeid M. Protective effect of resveratrol against toxicity induced by the mycotoxin, zearalenone in a rat model. *Food Chem Toxicol.* 2020 Dec;146:111840. doi: 10.1016/j.fct.2020.111840. Epub 2020 Oct 31. PMID: 33137427.
- Castro JC, Pante GC, Centenaro BM, Almeida RTR, Pilau EJ, Dias Filho BP, Mossini SAG, Abreu Filho BA, Matioli G, Machinski Junior M. Antifungal and antimycotoxigenic effects of *Zingiber officinale*, *Cinnamomum zeylanicum* and *Cymbopogon martinii* essential oils against *Fusarium verticillioides*. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess.* 2020 Sep;37(9):1531-1541. doi: 10.1080/19440049.2020.1778183. Epub 2020 Jul 20. PMID: 32684097.
- Rai A, Das M, Tripathi A. Occurrence and toxicity of a fusarium mycotoxin, zearalenone. *Crit Rev Food Sci Nutr.* 2020;60(16):2710-2729. doi: 10.1080/10408398.2019.1655388. Epub 2019 Aug 26. PMID: 31446772.
- Marin DE, Pistol GC, Bulgaru CV, Taranu I. Cytotoxic and inflammatory effects of individual and combined exposure of HepG2 cells to zearalenone and its metabolites. *Naunyn Schmiedebergs Arch Pharmacol.* 2019 Aug;392(8):937-947. doi: 10.1007/s00210-019-01644-z. Epub 2019 Mar 27. PMID: 30919009.
- Yang F, Li L, Chen K, Li C, Wang Y, Wang G. Melatonin alleviates β -zearalenol and HT-2 toxin-induced apoptosis and oxidative stress in bovine ovarian granulosa cells. *Environ Toxicol Pharmacol.* 2019 May;68:52-60. doi: 10.1016/j.etap.2019.03.005. Epub 2019 Mar 7. PMID: 30870695.
- Rogowska A, Pomastowski P, Sagandykova G, Buszewski B. Zearalenone and its metabolites: Effect on human health, metabolism and neutralisation methods. *Toxicol.* 2019 Apr 15;162:46-56. doi: 10.1016/j.toxicol.2019.03.004. Epub 2019 Mar 6. PMID: 30851274.
- Xu Y, Zhang KH, Sun MH, Lan M, Wan X, Zhang Y, Sun SC. Protective Effects of Melatonin Against Zearalenone Toxicity on Porcine Embryos in vitro. *Front Pharmacol.* 2019 Apr 5;10:327. doi: 10.3389/fphar.2019.00327. PMID: 31024301; PMCID: PMC6460015.
- El Goll-Bennour E, Timoumi R, Koroit M, Bacha H, Abid-Essefi S. Protective effects of kefir against zearalenone toxicity mediated by oxidative stress in cultured HCT-116 cells. *Toxicol.* 2019 Jan;157:25-34. doi: 10.1016/j.toxicol.2018.11.296. Epub 2018 Nov 16. PMID: 30448289.
- Althali NJ, Hassan AM, Abdel-Wahhab MA. Effect of grape seed extract on maternal toxicity and in utero development in mice treated with zearalenone. *Environ Sci Pollut Res Int.* 2019 Feb;26(6):5990-5999. doi: 10.1007/s11356-018-4011-x. Epub 2019 Jan 6. PMID: 30613873.
- Xiao Y, Xu S, Zhao S, Liu K, Lu Z, Hou Z. Protective effects of selenium against zearalenone-induced apoptosis in chicken spleen lymphocyte via an endoplasmic reticulum stress signaling pathway. *Cell Stress Chaperones.* 2019 Jan;24(1):77-89. doi: 10.1007/s12192-018-0943-9. Epub 2018 Oct 29. PMID: 30374880; PMCID: PMC6363622.
- Sanad MH, Fouzy ASM, Sobhy HM, Hathout AS, Hussain OA. Tracing the protective activity of *Lactobacillus plantarum* using technetium-99m-labeled zearalenone for organ toxicity. *Int J Radiat Biol.* 2018 Dec;94(12):1151-1158. doi: 10.1080/09553002.2019.1524990. Epub 2018 Oct 1. PMID: 30273080.
- Yang D, Jiang X, Sun J, Li X, Li X, Jiao R, Peng Z, Li Y, Bai W. Toxic effects of zearalenone on gametogenesis and embryonic development: A molecular point of review. *Food Chem Toxicol.* 2018 Sep;119:24-30. doi: 10.1016/j.fct.2018.06.003. Epub 2018 Jun 2. PMID: 29864477.
- di Masi A, Leboffe L, Polticelli F, Tonon F, Zennaro C, Caterino M, Stano P, Fischer S, Hägele M, Müller M, Kleger A, Papatheodorou P, Nocca G, Arcovito A, Gori A, Ruoppolo M, Barth H, Petrosillo N, Ascenzi P, Di Bella S. Human Serum Albumin Is an Essential Component of the Host Defense Mechanism Against *Clostridium difficile* Intoxication. *J Infect Dis.* 2018 Sep 22;218(9):1424-1435. doi: 10.1093/infdis/jiy338. PMID: 29868851.
- Gao X, Xiao ZH, Liu M, Zhang NY, Khalil MM, Gu CQ, Qi DS, Sun LH. Dietary Silymarin Supplementation Alleviates Zearalenone-Induced Hepatotoxicity and Reproductive Toxicity in Rats. *J Nutr.* 2018 Aug 1;148(8):1209-1216. doi: 10.1093/jn/nxy114. PMID: 30137478.
- Zhang W, Zhang S, Zhang M, Yang L, Cheng B, Li J, Shan A. Individual and combined effects of *Fusarium* toxins on apoptosis in PK15 cells and the protective role of N-acetylcysteine. *Food Chem Toxicol.* 2018 Jan;111:27-43. doi: 10.1016/j.fct.2017.10.057. Epub 2017 Nov 7. PMID: 29109043.

REFERENCES

- Zheng WL, Wang BJ, Wang L, Shan YP, Zou H, Song RL, Wang T, Gu JH, Yuan Y, Liu XZ, Zhu GQ, Bai JF, Liu ZP, Bian JC. ROS-Mediated Cell Cycle Arrest and Apoptosis Induced by Zearalenone in Mouse Sertoli Cells via ER Stress and the ATP/AMPK Pathway. *Toxins (Basel)*. 2018 Jan 1;10(1):24. doi: 10.3390/toxins10010024. PMID: 29301253; PMCID: PMC5793111.
- Kowalska K, Habrowska-Górczyńska DE, Piastowska-Ciesielska AW. Zearalenone as an endocrine disruptor in humans. *Environ Toxicol Pharmacol*. 2016 Dec;48:141-149. doi: 10.1016/j.etap.2016.10.015. Epub 2016 Oct 18. PMID: 27771507.
- Long M, Yang S, Wang Y, Li P, Zhang Y, Dong S, Chen X, Guo J, He J, Gao Z, Wang J. The Protective Effect of Selenium on Chronic Zearalenone-Induced Reproductive System Damage in Male Mice. *Molecules*. 2016 Dec 7;21(12):1687. doi: 10.3390/molecules21121687. PMID: 27941626; PMCID: PMC6274099.
- Yang R, Wang YM, Zhang L, Zhao ZM, Zhao J, Peng SQ. Prepubertal exposure to an oestrogenic mycotoxin zearalenone induces central precocious puberty in immature female rats through the mechanism of premature activation of hypothalamic kisspeptin-GPR54 signaling. *Mol Cell Endocrinol*. 2016 Dec 5;437:62-74. doi: 10.1016/j.mce.2016.08.012. Epub 2016 Aug 9. PMID: 27519634.
- Salem IB, Boussabbah M, Neffati F, Najjar MF, Abid-Essefi S, Bacha H. Zearalenone-induced changes in biochemical parameters, oxidative stress and apoptosis in cardiac tissue: Protective role of crocin. *Hum Exp Toxicol*. 2016 Jun;35(6):623-34. doi: 10.1177/0960327115597467. Epub 2015 Jul 30. PMID: 26231423.
- Long M, Yang SH, Han JX, Li P, Zhang Y, Dong S, Chen X, Guo J, Wang J, He JB. The Protective Effect of Grape-Seed Proanthocyanidin Extract on Oxidative Damage Induced by Zearalenone in Kunming Mice Liver. *Int J Mol Sci*. 2016 May 25;17(6):808. doi: 10.3390/ijms17060808. PMID: 27231898; PMCID: PMC4926342.
- Hueza IM, Raspantini PC, Raspantini LE, Latorre AO, Górniak SL. Zearalenone, an estrogenic mycotoxin, is an immunotoxic compound. *Toxins (Basel)*. 2014 Mar 13;6(3):1080-95. doi: 10.3390/toxins6031080. PMID: 24632555; PMCID: PMC3968378.
- O'Donnell K, Sutton DA, Rinaldi MG, Sarver BA, Balajee SA, Schroers HJ, Summerbell RC, Robert VA, Crous PW, Zhang N, Aoki T, Jung K, Park J, Lee YH, Kang S, Park B, Geiser DM. Internet-accessible DNA sequence database for identifying fusaria from human and animal infections. *J Clin Microbiol*. 2010 Oct;48(10):3708-18. doi: 10.1128/JCM.00989-10. Epub 2010 Aug 4. PMID: 20686083; PMCID: PMC2953079.
- Pfeiffer E, Hildebrand A, Mikula H, Metzler M. Glucuronidation of zearalenone, zeranol and four metabolites in vitro: formation of glucuronides by various microsomes and human UDP-glucuronosyltransferase isoforms. *Mol Nutr Food Res*. 2010 Oct;54(10):1468-76. doi: 10.1002/mnfr.200900524. PMID: 20397195.
- Walsh TJ, Groll A, Hiemenz J, Fleming R, Roilides E, Anaissie E. Infections due to emerging and uncommon medically important fungal pathogens. *Clin Microbiol Infect*. 2004 Mar;10 Suppl 1:48-66. doi: 10.1111/j.1470-9465.2004.00839.x. PMID: 14748802.
- Massart F, Saggese G. Oestrogenic mycotoxin exposures and precocious pubertal development. *Int J Androl*. 2010 Apr;33(2):369-76. doi: 10.1111/j.1365-2605.2009.01009.x. Epub 2009 Nov 30. PMID: 20002219.
- Massart F, Meucci V, Saggese G, Soldani G. High growth rate of girls with precocious puberty exposed to estrogenic mycotoxins. *J Pediatr*. 2008 May;152(5):690-5. doi: 10.1016/j.jpeds.2007.10.020. Epub 2008 Feb 20. PMID: 18410776.
- Ouanes Z, Abid S, Ayed I, Anane R, Mobio T, Creppy EE, Bacha H. Induction of micronuclei by Zearalenone in Vero monkey kidney cells and in bone marrow cells of mice: protective effect of Vitamin E. *Mutat Res*. 2003 Jul 8;538(1-2):63-70. doi: 10.1016/s1383-5718(03)00093-7. PMID: 12834755.