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Co-Occurrence and Intoxication Impact of Dietary Ergot Alkaloids on Humans' and Animals' Health

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ABSTRACT

Ergot alkaloids (EAs) are harmful bioactive substances generated by a group of fungi in the genus *Claviceps*. The most prominent member of this group is *Claviceps purpurea*. These endophytic fungi contaminate grasses and parasitize grain crops, including rye, wheat, triticale, barley, millet, oat, and sorghum. This review unveils a comprehensive understanding of EAs-related intoxication, elucidating their multifaceted hazardous impact on human and livestock health. In the Middle Ages, toxic EAs in rye were reported to afflict many people and animals. Since then, the insidious influence of EAs has continued to the present time, causing severe harm to human and livestock health, and exerting a negative impact on our economic profitability. Intake of feedstuffs contaminated with EAs results in ergotism, which is often recognized in two forms: gangrenous and convulsive. Gangrenous ergotism disrupts the blood flow to the lower limbs, while the convulsive type impacts the central nervous system, transforming the homeostasis of animals. Furthermore, while the varieties of EAs diminish the nutritional value of grasses and grains, their pharmacological attributes make them beneficial in treating acute migraines and cluster headaches. Recent incidents of digestion of sclerotia-contaminated grains affecting populations in developing countries underscore ergotism as a significant threat to public health. This review article offers a comprehensive overview of the co-occurrence and intoxication impact of dietary ergot alkaloids encompassing human and livestock health, including the prevalence, toxicity, roles of endophytic fungi, intoxication of dietary exposure, permissible limits, synthesis, and medical applications, as well as their pivotal roles in the context of food and feed security. By examining the multidimensional challenges posed by EAs, this review lays a solid groundwork for understanding and mitigating their detrimental effects on human and livestock health.

Key words: *Claviceps purpurea*, Endophytic fungi, Ergot alkaloids, Ergotism, Human and livestock health, Toxicosis

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INTRODUCTION

The fastidious parasitic fungus *Claviceps purpurea* can infest over 400 species, including commercially important grain crops such as rye, triticale, barley, corn, oats, millet, wheat, and sorghum. Additionally, it grows on pasture grasses in temperate climate zones, producing ergot alkaloids (EAs) as a secondary metabolite (EFSA 2012; Miedaner and Geiger 2015). Turfgrasses such as tall fescue (*Festuca arundinacea*), parasitized by *Claviceps* spp. or *Acremonium coenophialum*, represent another important source of EAs (Krska and Crews 2008). The grains contaminated with the endophytic fungus *C. purpurea* form visible structures, identified as unique purplish or black crescent-shaped bodies, called sclerotia or ergot bodies. These structures are capable of generating about forty different EAs with distinct chemical compositions. These alkaloids can subsequently transform into lysergic acid, posing a risk to humans and animals (Müller et al. 2009; Haque et al. 2020; Schummer et al. 2020; Ülger et al. 2020; Veršilovskis et al. 2020). Fig. 1 illustrates several plants afflicted with ergot. The quantity of alkaloids and the pattern of ergot sclerotium differ greatly based on the type of host species along with the specific fungi (Krska and Crews 2008). The dominant EAs identified in *C. purpurea* ergots include ergocristine, ergotamine, ergocornine, ergocryptine, ergometrine, ergosine, ergocristinine, ergotaminine, ergocryptinine, and ergosinine (Fig. 2), which are reported to have significant effects on people in terms of both benefits and costs (EFSA 2012). Human ingestion of EAs through food can cause hallucinations, dry gangrene, limb loss, dementia, tremors, convulsions, coma, and even death (Young et al. 2015; Schummer et al. 2020). Although the recent development of grain-cleaning techniques has dramatically reduced ergotism in humans, livestock continue to face a serious problem due to the consumption of sclerotia-contaminated feed and parasitized fodder or grasses on pastures (Young et al. 2015; Haque et al. 2020; Schummer et al. 2020). In humans, a wide range of indicators, including stomach discomfort, diarrhea, excessive salivation, excessive sweating, smelly poop, thirst, burning skin pain, pale skin, change in appetite, cold, crawling sensations in the skin, temporary poor vision, difficulty speaking, ringing in the ears, loss of menstrual cycle, and pregnancy loss, are some examples of clinical manifestations of ergotism. It has been determined that sorghum, the fifth-largest grain crop in the world, predominantly grown in Africa, Central America,

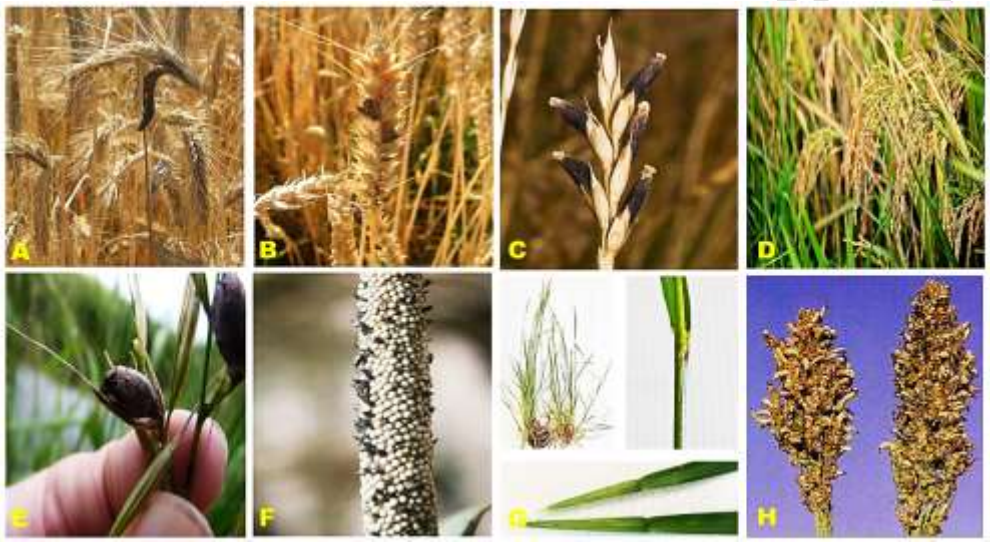

Fig. 1: EAs affected plants A) Ergot (*C. purpurea*) in wheat plant B) Ergot on wheat heads C) Ergot (*C. purpurea*) on wheat D) Ergot on (*Claviceps lutea*) on mature rice E) Ergot (*C. zizaniae*) on grass seed F) Ergot (Claviceps fusiformis) on pearl millet G) Endophyte infection of tall fascue grass H) Ergot (*C. sorghi*) on Sorghum (Crews 2014; Benner et al. 2020; Wikipedia 2025).

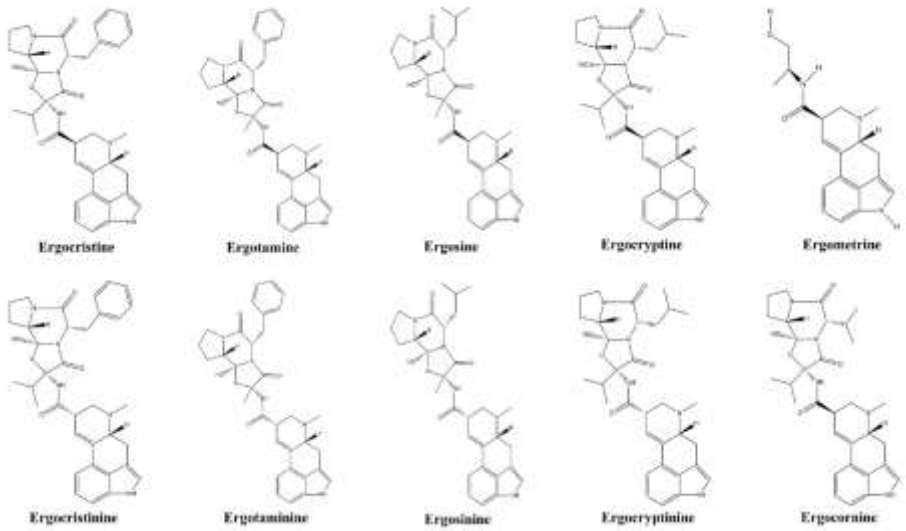

Fig. 2: Configurations of EAs analytes and inner reference (-ine and -inine form).

and South Asia, can cause ergot poisoning (Krska and Crews 2008; Haarmann et al. 2009). Consequently, over the past few decades, ergot infection of sorghum has resulted in production losses of 80% in India and 30-100% in Zimbabwe, respectively, and is increasingly becoming a global threat (Haarmann et al. 2009). *C. africana* has been identified as the dominant causal agent of ergot infection in sorghum worldwide (Haarmann et al. 2009). According to estimates, the accumulation of EAs in feedstuffs costs the agricultural economy enormous sums of money every year, just in the United States, compared to 20% of wheat in Canada, 50% of rye and triticale, 34% of wheat in Europe, and 62.4% of pearl millet feed in India (Malysheva et al. 2013; Robinson and Panaccione 2015; Coufal-Majewski et al. 2016; Kumari et al. 2020).

The 4,000-year-old Eleusinian Mysteries of ancient Greece were linked with ergot-induced hallucinations. However, the use of ergot in obstetrics was reported in Chinese writings as early as 1100 BC. Around 50% of the total population in France experienced a significant epidemic of ergotism in 944-945 AD (Schiff, 2006; Hulvová et al. 2013; Agriopoulou et al. 2020a). About 50 years later, approximately 40,000 deaths from EAs toxicity were reported. Throughout the Middle Ages, ergot poisoning epidemics, sometimes referred to as ergotism, broke out throughout continental Europe, particularly in Germany in 1581, 1587, and 1596 (Schiff 2006). EAs toxicity is reported to be connected with the 1692 Massachusetts Salem witch trials in the USA and the 1700s Finnmark witch trials in Norway. In 1722, an outbreak of ergotism among troops and horses brought the Russian campaign against the Ottoman Empire to a halt. In 1808, ergot was suggested for "quickening childbirth", but in 1824, it was recommended only to treat postpartum hemorrhage (Schiff, 2006; Hulvová et al. 2013; Miedaner and Geiger 2015; Young et al. 2015). However, ergotism was a major cause of death up to the early 19th century, and the mortality rates during certain epidemics not only expanded nearly to 40% but also persisted in some regions of Russia, Ethiopia, and India until the late 20th century (Haarmann et al. 2009; Miedaner and Geiger 2015).

EAs are comprised of three primary indole derivatives, including clavines, ergolines, and ergopeptines/ergopeptides (Fayrer-Hosken et al. 2008; Hulvová et al. 2013; Miedaner and Geiger 2015). Clavines, such as elymoclavine and agroclavine, are tricyclic or tetracyclic compounds that have undergone hydroxylation, prenylation, and acetylation, resulting in a wide variety of properties. They fall under the category of 6,7-secoergolenes, with an open D-ring that is hydroxyl- and/or dehydro-derivatives of 6,8-dimethyl ergolenes (EFSA 2012). Ergolines encompass lysergic acid, lysergol, and ergonovine, while ergopeptines contain ergovaline, ergotamine, ergosine, ergocornine, ergonine, and ergocryptine (Fayrer-Hosken et al. 2008; Young et al. 2015). Each ergot alkaloid molecule has two ketostates (R- and S-epimer) and can be maintained as thin dry films or in 25% ethanol composed of ethylene glycol, 2-propanediol, and tartaric acid below 20°C (Crews, 2015). This review aimed to describe the recent toxicity of EAs and endophytes associated with ergotism, with an emphasis on biotransformation, transmission, co-occurrence, co-exposure, carryover, medical applications, synthetic strategies, prevention, and control.

Role of endophytic fungi in the production of ergot alkaloids (EAs)

Endophytic fungi typically spend most of their life span infecting healthy plant cells without displaying any obvious symptoms of disease. Upon infection, the fungal endophyte secretes compounds such as alkaloids that have antifungal, anticancer, and antiviral properties (Zhang et al. 2012). EAs produced by members of the Clavicipitaceae and Trichocomaceae families have been reported to be simultaneously detrimental and helpful to mankind for millennia. The members of the Clavicipitaceae family synthesize either lysergic acid-derived EAs or dihydro-EAs, whereas certain members of the Trichocomaceae family produce festuclavine-derived EAs (Robinson and Panaccione 2015). Three endophytic fungi from the Clavicipitaceae family, namely *Epichloe*, *Neotyphodium*, and *Balansiagenera*, are symbionts of several grass species and produce EAs (Haarmann et al. 2009). Endophytic fungi have been purposefully encouraged in majestic fescue (*Festuca arundinacea*) and perennial ryegrass (*Lolium perenne*) varieties that serve as significant hosts with drought resistance, intense competition, vegetative growth, tillering, fertilization, and disease tolerance (Duringer et al. 2007; Zhang et al. 2012; Guerre 2015; Florea et al. 2017). However, endophyte-infected (E+) grasses (Table 1) are still harmful for animals because they contain fungus ergot alkaloids, which cause "fescue toxicosis" (summer sickness), and indole-diterpene alkaloids, which cause "ryegrass staggers" (Duringer et al. 2007; Zhang et al. 2012; Guerre 2015). Australia, the United States, and New Zealand are the most often reported countries for fescue intoxication incidents. Several factors, including animal exposure, grass EA levels, physiological condition, and genetic variation, influence toxicity (Guerre 2015). The "drunken horse grass" ailment (*Achnatherum inebrians*) in western China and Mongolia, as well as the "sleepy grass" infection (*A. robustum*) in the southwest of the United States, have been reported to have detrimental effects on animals. The severity is attributed to the amount of intake of endophyte-infected grass containing EAs. While in South Africa and Argentina, toxicities from indole-diterpene alkaloids were recorded in animals ingesting *Melica decumbens* with *Epichloe melicicola* (Dronk-grass) and *Poa huecu* with *E. tembladerae* (Guerre, 2015; Young et al. 2015; Florea et al. 2017). A lot of research was done on *A. inebrians* that were high on drugs in Gansu, Qinghai, Xinjiang, Inner Mongolia, Tibet, and Ningxia Hui, China. It was found that 90% of the native grasslands are affected by *Neotyphodium gansuense*, a fungal endophyte with the highest levels of ergonovine, lysergic acid amide, and other chemicals linked to the narcosis of livestock, particularly horses (Zhao et al. 2012; Zhang et al. 2014). This research also reported that the pure EAs isolated from endophyte-infected (E+) drunken horse grass (*A. inebrians*) significantly harm smooth muscle cells in cattle and also cause toxicity in sheep, compromising kidney and liver function (Zhang et al. 2014). In a recent report, another endophytic fungus, *E. bromicola*, formed a symbiotic association with the cool-season rangeland and forage grass *Elymus dahuricus* from Xinjiang, Beijing, and Shanxi, confirming the presence of ergovaline and other EAs that are harmful to livestock and may also get into agricultural products through seed-

Table 1: Specific endophytic fungi species with their host producing EAs

Grass host species	Endophyte species	Ergot alkaloid	Quantity (ppb)	Country	Reference
Lolium arundinaceum	*Epichloë coenophiala*	TEA	400-1900	USA	Helander et al. 2016
Schedonorus phoenix	*E. coenophiala*	TEA	900–1100	Finland	Helander et al. 2016
Festuca arundinacea	*E. coenophiala*	Ergovaline	998	Poland	Zurek et al. 2017
L. perenne			200		
F. pratensis			125		
Elymus dahuricus	*E. bromicola*	Ergovaline	1.77-2.82 (μmol/kg d.w.)	China	Shi et al. 2017
		Ergotryptamine	0.06-0.09 (μmol/kg d.w.)		
L. arundinaceum	*E. coenophiala*	TAE	1473-1861	USA	Dillard et al. 2019
		Ergovaline	135-402		
Elymus tangutorum	*E. coenophiala*	Ergonovine	470–840	China	Shi et al. 2020
		Ergine	350–1720		
Schedonorus arundinacea	*E. coenophiala*	Ergovaline	259-522	USA	Lea and Smith 2021
L. perenne	*E. coenophiala*	Ergovaline	140-800	New Zealand	Caradus et al. 2022
F. arundinacea	*E.coenophialum*	Ergopeptines	0.5	USA	Mwangi et al. 2024
	Neotyphodium lolii		1.2		
F.arundinacea	*E.coenophialum*	Ergopeptines	1.72–6.81		
F.arundinacea	*E. lolli*	Ergopeptines	1.3		
L. perenne	*E.coenophialum*		2.5		
	E.lolli X E.typhina		4.8		
L. arundinaceum	*E. coenophiala*	TEA	12.6	USA	Llada et al. 2025

Legends: TEA=Total ergot alkaloid; ppb=Parts per billion

transmitted endophytic symbioses (Shi et al. 2018). All known EA-producing fungi share early, conserved enzymatic stages for EA synthesis, after which they diverge, and lineage-specific pathways produce various EA signatures. The members of the Clavicipitaceae family generate lysergic acid- or dihydro-EAs, while the members of the Trichocomaceae family synthesize festuclavine-derived EAs. Chanoclavine-I aldehyde sets up the EA cascade to synthesize festuclavine or agroclavine. Two unique members of the Clavicipitaceae family including *C. africana*, which induces sorghum ergot, and *C. gigantea*, which induces maize ergot, oxidizing carbon 17 to form dihydroergot alkaloids. EA-producing fungi in the family Trichocomaceae generate festuclavine, while those members in the Clavicipitaceae family utilize agroclavineas as a medium. Trichocomaceae fungi, such as *Neosartorya fumigata* and *Penicillium commune*, produce festuclavine and several of its derivatives, collectively known as fumigaclavines (Fig. 3A). Most Clavicipitaceae EA producers have ergopeptines and/or lysergic acid amides in their spectra. In contrast to ergopeptines, some members of the Clavicipitaceae family, including *Epichlo gansuensis* var. *inebrians*, *Periglandula ipomoeae*, and *P. turbinae*, generate lysergic acid simple amides, like ergonovine, lysergic acid hydroxyethylamide (LAH), and ergine, as illustrated in Fig. 3B (Robinson and Panaccione 2015). Endophytic fungi, with their inconspicuous presence within healthy plants, have evolved to secrete compounds like alkaloids that exhibit various properties, including antifungal, anticancer, and antiviral activities. The Clavicipitaceae and Trichocomaceae families, despite their historical significance, exhibit a dual nature, with one aspect being beneficial and the other detrimental, through their synthesis of various types of EAs. This intricate relationship is exemplified by endophytic fungal species like *Epichloe*, *Neotyphodium*, and *Balansia*, which form symbiotic associations with grass and contribute to their host's survival under stressful conditions through developing drought resistance and disease tolerance. However, the coexistence of endophyte-infected grass with harmful ergot alkaloids poses substantial risks to animals, resulting in disorders such as fescue toxicosis and ryegrass staggers (Lee et al. 2021). Notably, the geographical variations in these toxic incidents underscore the complex interplay of factors influencing toxicity. Furthermore, recent research has revealed the presence of harmful endophytic fungi, emphasizing the importance of understanding these interactions for both agriculture and animal welfare. This intricate nexus of endophytic fungi, plant hosts, and alkaloid production offers promising avenues for agricultural management, pharmaceutical research, and ecological balance.

Biotransformation of EAs

Many therapeutically utilized EAs fall within the category of peptide alkaloids. However, a considerable portion of these alkaloids are manufactured through semisynthetic methods that rely on a limited set of fundamental precursor compounds. For instance, lysergic acid and 9,10-dihydrolysergic acid, as well as lysergol and 9,10-dihydrolysergol, which can be sourced from specific *Ipomoea* plant seeds (Olaranont et al. 2022), serve as foundational materials. Additionally, elymoclavine can be produced in substantial quantities through submerged cultivation of certain *Claviceps* strains, such as *C. fusiformis* (Kralova et al. 2021). The resemblances of the tetracyclic ergoline ring (Fig. 3C-i) found in naturally occurring EAs and the biogenic amine neurotransmitters, such as norepinephrine, dopamine, and serotonin (Fig. 3C-ii), allow EAs to cause this "interruption" and produce widespread vasoconstriction and neurotransmitter reflex interference (Fayrer-Hosken et al. 2008; Völkel et al. 2011; EFSA 2012; Klotz 2015). Numerous EAs may interact with these neurotransmitter receptors as either an agonist or antagonist, or possibly partially as both, based on the linkers connected to the carboxyl group of D-lysergic acid (Haarmann et al. 2009). After oral consumption, alkaloids are absorbed in the stomach, and their content and structure affect bioavailability and absorption rate. Some derivatives of EAs can pass across the placenta or the blood-brain barrier. The final excretion is biphasic, involving a first-pass metabolism in the liver due to enterohepatic recirculation, followed by activation of the serotonin-2 receptor, which triggers vascular smooth muscle

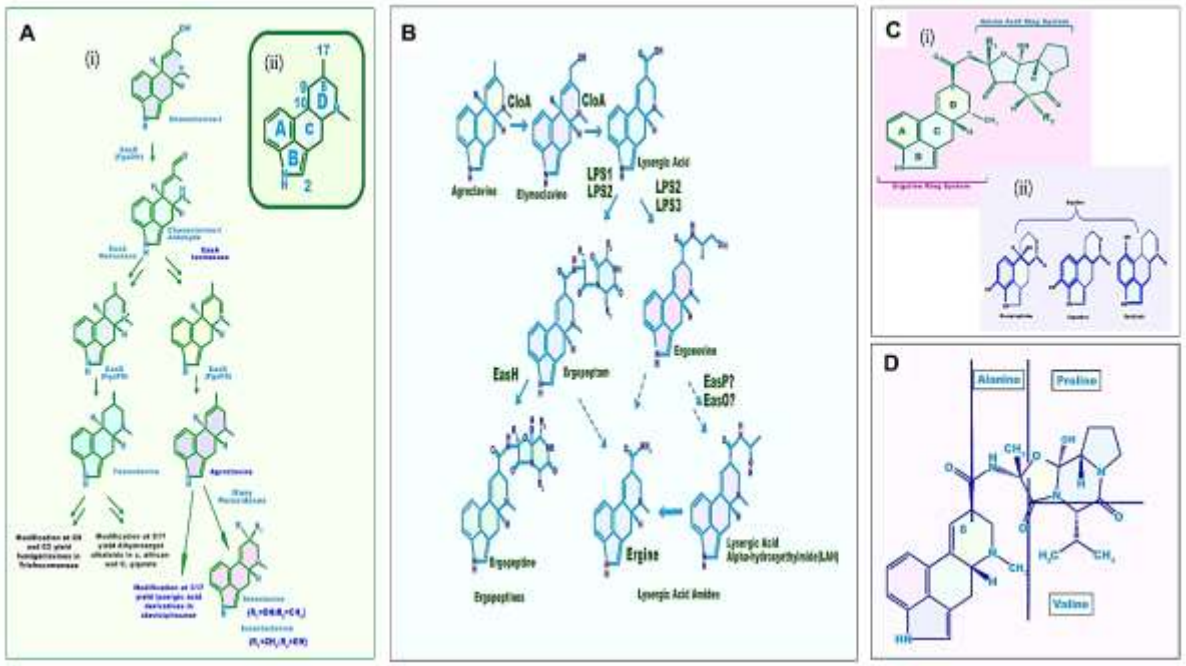

Fig. 3: A) i. EAs synthesized by Clavicipitaceae and Trichocomaceae endophytic fungi. ii. Ergoline ring system with numbering and ring designation. B) EAs biosynthesis and diversification in Clavicipitaceae. C) i. General structure of EAs with variably replaced C-8 and an amino acid ring system that alters at the R1 and R2 side chain to form ergopeptine alkaloids. ii. The resemblances of the tetracyclic ergoline ring and the neurotransmitters norepinephrine, dopamine, and serotonin, and D) Ergovaline's chemical make up: 4-ring ergoline ring and the tri-peptide constituent of alanine, proline, and valine (Duringer et al. 2007; Fayrer-Hosken et al. 2008; Krska and Crews 2008; Haarmann et al. 2009; Hulvová et al. 2013; Guerre 2015; Klotz 2015; Klotz and Nicol 2016; Robinson and Panaccione 2015; Tittlemier et al. 2015; Young et al. 2015; Jakubczyk and Dussart 2020; Schummer et al. 2020).

mitogenesis. Additionally, stimulation of the thermoregulatory centers raises body heat and decreases hunger. Also, the presence of a higher level of angiotensin-converting enzyme has been reported. To increase prolactin production, the EA must stimulate the dopamine D2 receptors and function as a dopamine agonist (Fayrer-Hosken et al. 2008; Völkel et al. 2011). In bovines, vasoconstriction resulting from EA exposure can deplete blood flow to and from the midgut, impairing the midgut's ability to absorb nutrients (Egert et al. 2014).

Ergocristine, one of the most toxic EAs, induces apoptosis in grown human primary cells (Mulac and Humpf 2011). It has been reported that only the 8-(R) form of ergopeptine alkaloids can cross the blood-brain barrier and be absorbed into human primary cells (Mulac et al. 2012). EAs can isomerize at the C-8 site in specific parameters (Fig. 3C-i); however, the epimer ergocristinine (8-(S) form) cannot penetrate the intracellular membrane and hence persists in cells, affecting barrier integrity. An animal's symptoms of EA exposure rely on receptor type and position, alkaloid binding capacity, structural nature, and other natural forces or stimuli (Mulac et al. 2012; Klotz 2015). The tricyclic peptide moiety connected to the 8-carbon of the tetracyclic ergoline ring, or lysergic acid configuration comprised of alanine, proline, and valine, distinguishes the ergopeptide alkaloid known as ergovaline (Fig. 3D). Ergovaline in endophyte-infected ryegrasses may manifest ergotism-like symptoms in animals. Ergovaline made up 40% of the EAs found in endophyte-infected ryegrass, along with ergotamine, ergosine, ergoptine, ergocryptine, and ergocornine, which will likely vary in the total ergot alkaloid (TAE) content based on cultivar, habitat, and time of year (Klotz and Nicol 2016).

Because EAs are structurally similar to biogenic amine neurotransmitters, they affect physiological systems by disrupting neurotransmitter reflexes, inducing vasoconstriction and other complex physiological responses. The intricate interactions between EAs and neurotransmitter receptors, functioning as agonists or antagonists, underscore their complexity. The absorption, distribution, and excretion patterns of EAs are influenced by factors such as alkaloid contents, structural variations, and barrier crossings. The interplay among receptor activations, enzymatic processes, and cellular responses contributes to diverse physiological outcomes. Ergocristine's apoptosis-inducing impact on human cells and the variable abilities of ergopeptine isomers to cross cellular barriers highlight nuances in EA interactions. The prevalence of ergovaline in endophyte-infected ryegrass accentuates alkaloid composition dynamics. Understanding these mechanisms is pivotal for managing potential health risks. The exploration of molecular interactions, along with comprehensive risk assessment, species-specific inquiries, accurate detection techniques, sustainable practices, stakeholder education, regulatory cooperation, and pharmacological considerations, collectively advance comprehension and safety regarding ergot alkaloid exposure.

Transmission and life cycle of ergot fungus

Claviceps purpurea begins its life cycle in spring once wind-blown ascospores fall upon the feather-like stigmas of sensitive natural as well as pasture grasses. Stigmas of flowers in host plants efficiently catch pollen and ascospores. The captured ascospores proliferate and invade the ovary of the flower within a day. Hyphae

germinate in the ovary and migrate downward to the rachilla, imitating pollination. A spacelial stroma forms in the diseased ovary, releasing masses of haploid, one-celled conidia that exude "honeydew," a viscous, syrup-like liquid. Flies and moths love honeydew and help spread infection by passing honeydew to neighboring blooms. The formation of honeydew proceeds until sclerotia form, and it can also be spread by rain, direct contact, and farming instruments. A mature sclerotium, comprised of a compact mass of fungal mycelium containing food reserves, becomes detached and remains dormant until exposed to favourable growth conditions. After four to five weeks, sclerotia replace the seeds (Fig. 4). Ergot sclerotia, embedded inside the ground with seed, overwinter and produce ascospores that are forcibly expelled and lodge on the stigma of florets to generate ascocarps, that mature and will be disseminated at cereal flowering. Infection begins once ascospores land on plant florets. In the autumn, spurs grow on the purple-black sclerotia, where mycelium-mediated penetration of the ovaries by filamentous fungi occurs. Sclerotia, or ergot, is larger than grain kernels and contains a number of poisonous alkaloids. During harvest, the majority of ergots fall to the ground, but some are kept on the plants and mixed with the grain. In contrast to non-infected kernels, a mature head of grain may contain several ergots. The ergots left on the ground over the winter form tiny, black bodies resembling mushrooms. When they explode in the spring, they release a large number of spores, which starts a new wave of infections (Battilani et al. 2009; EFSA 2012; Miedaner and Geiger 2015). Recent studies have revealed the presence of Periglandula, ergot alkaloid synthesis genes, and EAs in the seeds of morning glory species (Beaulieu et al. 2021; Olaranont et al. 2022). Periglandula's symbiosis with Convolvulaceae hosts is macroscopically asymptomatic and is transmitted vertically through seeds. EAs accumulate in morning glory seeds at concentrations up to 1000 times higher than in grasses infected with symbiotic *Epichloë* species. Morning glories are the only dicotyledonous plants known to contain EAs from fungal symbionts. Unlike related Clavicipitaceae in grasses, Periglandula has no known sexual reproduction, spore production, or pathogenic relatives. The vertical transmission of EAs and Periglandula through host seeds suggests that the symbiosis and EA chemistry may vary across host lineages due to evolutionary diversification (Beaulieu et al. 2021). These variations are expected to reflect the ecological costs and benefits associated with this unique symbiotic relationship.

EAs as toxins for humans and livestock

Ergotism, ergot poisoning, ergot toxicosis, and St. Anthony's fire are all terms referring to diseases associated with ergot-contaminated feed or food (Wegulo and Carlson 2011). Fig. 5 illustrates the mode of action and pathogenesis of EAs. Ergot poisoning from contaminated grain can cause convulsive or gangrenous ergotism (Fig. 6A) in people. The convulsive form causes limb distortion, excruciating involuntary finger and wrist flexion, ankle flexion or extension, residual paralysis, nausea, vomiting, headache, diarrhea, lethargic, loss of vision, hallucination, itching, and epileptic seizures.

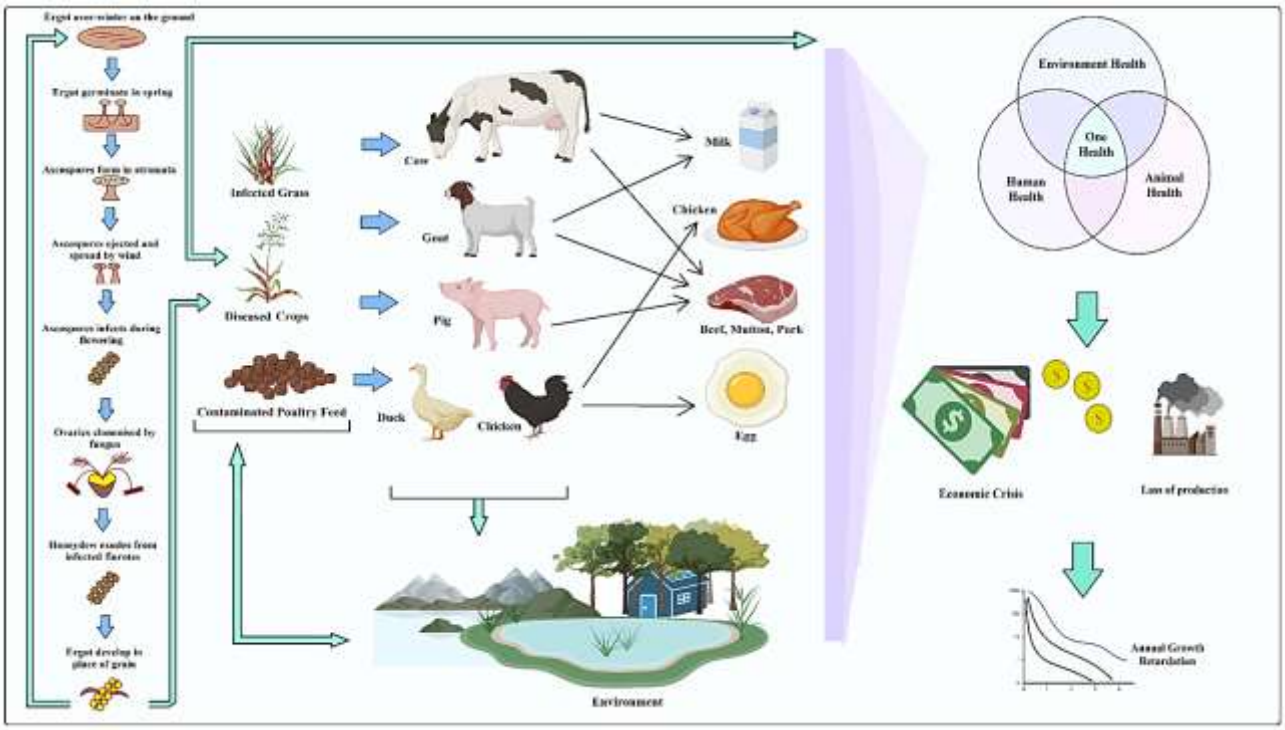

Fig. 4: Life cycle, transmission, and impact of Ergot in one health. *C. purpurea* affects grass, cereal, or other plants and produces sclerotia or ergot kernels. The fungal mycelium devastates various parts, such as the ovary, and produces a sugary substance known as honeydew that surrounds millions of asexual spores, resulting in environmental contamination. Ingestion of ergot-contaminated grass, crops, and feedstuff may have harmful effects on livestock and poultry. Humans are infected with ergot through the consumption of contaminated animal-derived products, resulting in adverse health effects, production losses, and economic crises (Schiff 2006; Haarmann et al. 2009; Wegulo and Carlson 2011; Hulvová et al. 2013; Miedaner and Geiger 2015; Kumari et al. 2020).

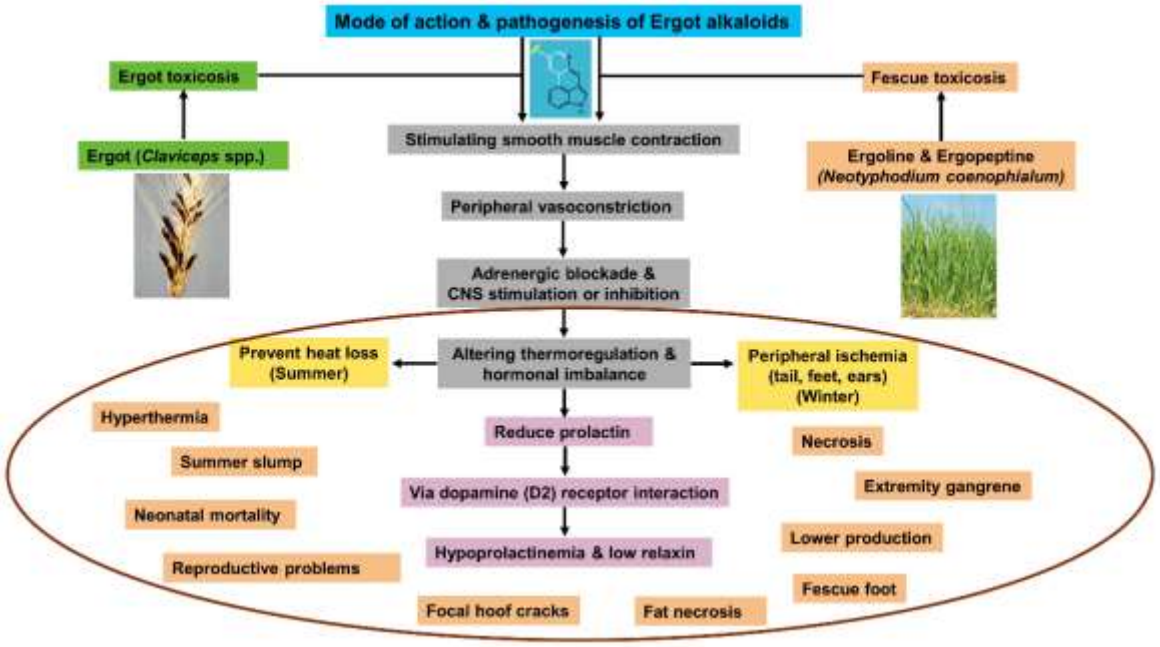

Fig. 5: Mode of action and pathogenesis of egrot alkalois (Botha et al. 2004; Evans et al. 2004; Sebastian 2007; Klotz 2015; EFSA, 2024).

Fig. 6: A) Ergotism in humans. Initial symptoms of ergotism are known as nausea, vomiting, muscle pain and weakness, numbness, twitching, and rapid or slow heartbeat where final stage clinical manifestations are gangrene, vision problems, confusion, spasms, convulsions, unconsciousness, and death. B) Ergotism in animals. Ergotism in animals generally presents as lameness; necrosis of the tip of the tail, ears, and hoof tissue; and decay of the wattle, comb, beak, and feet in birds. Additional adverse effects are possible, such as poor reproduction in animals and agalactia in swine and horse.

Gangrenous ergotism causes peripheral nerve damage, edema, intense pain, and gangrene of the foot, hands, and entire legs. In more severe cases, the affected portions shrank, turned stiff and black, petrified, and fell off without bleeding. Agalactia and sudden abortion were also recorded as a result of ergot poisoning (Haarmann et al. 2009; EFSA 2012; Hulvová et al. 2013). Convulsive ergotism was found in central, eastern, and Scandinavian Europe, whereas the gangrenous form was observed in France, as well as in western European nations (EFSA 2012). A significant outbreak of gangrenous ergot poisoning in humans, caused by consuming contaminated barley, was recorded in Ethiopia in 2002 and subsequently spread throughout Asia (Völkel et al. 2011; EFSA 2012). Ergot poisoning in various animals is shown in Fig. 6B. In animals, ergot toxicoses manifest in four different ways: (i) gangrenous or skin, (ii) hyperthermic, (iii) reproductive, and (iv) convulsive. The gangrenous form is typically noticeable when any of the limbs' digits, ear tips, tail ends, combs, or beaks turn necrotic and develop dry gangrene. Hyperthemic form is linked with prolonged exposure and is aggravated by environmental factors like elevated temperature, humidity, shade availability, animal population, and air flow. Affected animals exhibit respiratory problems, hyperthermia, lower feed intake, weight loss, decreased milk production, and fertility. Reproductive forms can cause fertility failure or abortion, agalactia in sows and mares, and small, unthrifty, or stillborn progeny with no sucking reflex. Convulsive form is caused by the consumption of excessive levels of EAs

over a short duration, leading animals to become excited, act strangely, spasm, and even die (Schiff 2006; Wegulo and Carlson 2011; Klotz 2015; Coufal-Majewski et al. 2016; Ülger et al. 2020). Globally, EA poisoning affects livestock health and production. Due to the complex interactions between plants, fungi, animals, microorganisms, and their habitats, which alter alkaloid levels, accessibility, and dispersion within the animal, it is challenging to assess the impacts of exposure to EAs (Klotz 2015). Table 2 and 3 indicate ergot toxicity in different species and comprehensive feed reference values for animal health.

There have been outbreaks of ergot toxicosis in animals, including water buffaloes in the UK (Millar et al. 2010), dairy cows in South Africa, pigs and dairy cows in Australia and mares in the USA (Fayrer-Hosken et al. 2008; Malysheva et al. 2014). Dairy cows exposed to ergovaline-contaminated pasture may develop a condition known as heat intolerance that results in fescue foot, chronic malignant hyperthermia, feed refusal, fetal loss, slower weight gain, decreased milk outputs, and lower pregnancy rates (Fink-Gremmels 2008; Malysheva et al. 2014; Klotz 2015). In Norway, gangrenous type was being discovered in free-ranging moose and roe deer (Krska and Crews 2008). Clinical signs in mares include preterm delivery, longer labor, dystocia, swelling or retension of placental membranes, agalactia, and higher neonatal death. Comparatively, stallions have lower ejaculate quantities (Fayrer-Hosken et al. 2008). Long-term feeding of rations with elevated levels of ergot sclerotia to chickens can trigger mortality and paralysis, lack of appetite, extreme thirst, nausea, vomiting, diarrhea, and convulsions (EFSA, 2012). Fig. 7 and 8 illustrate the gross and histopathological alterations associated with ergot poisoning in certain animals.

Co-occurrence, co-exposure and carry-over of EAs

Improvements in unprocessed trimmings, along with the composition and concentration of toxin inside the sclerotium and head-to-head and field-to-field levels, have been linked to negative consequences as a result of eating poisoned foods, which are the main causes of the increase in the prevalence of EAs over the past five years (Völkel et al. 2011; Bauer et al. 2016). Despite thorough washing and processing grain to eliminate 82% of ergots, scientists found EAs in German rye flours at levels as high as 7255µg/kg (Krska and Crews 2008). The presence of EAs at the level of poisoning in various foods from different countries is depicted in Table 4. In particular, massive contamination in human food and animal feed, as well as grains or cereals, was recorded in countries (Table 4) like the Netherlands and Czeck Republic (Babic et al. 2020; Agriopoulou 2021), Slovenia (Babic et al. 2020), Poland (Bryła et al. 2018), Italy (Debegnach et al. 2019; Lattanzio et al. 2021), Algeria (Agriopoulou 2021; Carbonell-Rozas et al. 2021), and Canada (Shi et al. 2019; Walkowiak et al. 2022). These results suggest that the

Table 2: EAs toxicity in different species

EAs	Dose (ppb)	Species	Affected	Died	Country	Reference
Dihydroergosine	5000-40000	Sow	208	-	Australia	Blaney et al. 2000
		Dairy cow	350			
Ergotamine	2100-27000	Human	18	3	Ethiopia	Urga et al. 2002
Ergometrine	900-12000					
Ergovaline	1720–8170	Cattle	50	-	South Africa	Botha et al. 2004
Ergotamine	300	Beef calf	60	8	USA	Leuschen et al. 2014
Ergosine	95					
Ergocornine	60					
Ergovaline	40					
TEA	495					
TEA	410	Rabbit	14	-	Germany	Korn et al. 2014
TEA	473-62245	Cattle	8	-	USA	Craig et al. 2015
Ergosine	25	Beef calf	12	-	USA	Miskimins et al. 2015
Ergotamine	30					
Ergocornine	20					
Ergocryptine	35					
Ergocristine	95					
TEA	0.98-7260	Horse	2	-	Germany	Aboling et al. 2016
TEA	3490-8060	Sow	-	13	France	Waret-Szkuta et al. 2019

Legends: TEA=Total ergot alkaloid; ppb=Parts per billion.

Table 3: EAs reference value in complete feed for adverse animal health effects

Species	EAs level (ppb) from *C. purpurea*	EAs level (ppb) from *C. africana*	EAs level (ppb) from *Epichloë spp.*	Reference
Pigs	600	-	-	EFSA 2024
Piglets	600	-	-	
Sows	-	500	-	
Fattening chickens	2100	-	-	
Laying hens	3700	-	-	
Ducks	200	-	-	
Bovine	100	200	100	
Sheep	300	-	200	
Horses	-	-	50-100	

Legends: ppb=Parts per billion.

Table 4: EAs contamination showing concentration and distribution in various food and feed samples around the world reported during 2018-2023

Country	Year	Sample type	Mycotoxin	Number of samples	Incidence (%)	LOQ (µg/Kg)	LOD (µg/Kg)	Mean (µg/Kg)	Minimum (µg/Kg)	Maximum (µg/Kg)	Detection method	Reference
USA	2011	Wheat	TAE[3]	10	70	n.a.	n.a.	n.a.	25	4760	LC-MS/MS	Babic et al. (2020)
Belgium	2012	Cereals and Cereal-based foods	TAE[4]	122	85	0.1-1	n.a.	n.a.	1	1145	LC-MS/MS	Agriopoulou (2021)
Czech Republic	2005-2007	Rye	TAE[5]	15	100	10	5	n.d.	n.d.	1067	HPLC-FLD	Babic et al. (2020)
		Triticale		14	93			n.d.	n.d.	1103		
		Wheat		21	86			n.d.	n.d.	1236		
		Other grains		14	93			n.d.	n.d.	140		
	2012	Barely	Es	15	n.d.	1	n.a.	n.a.	n.a.	n.a.	UHPLC–MS	Agriopoulou (2021)
			Eco			2.5						
			Ekr			2.5						
			Ecr			2.5						
	2013	Rye	TAE[3]	60	67	n.a.	n.a.	n.a.	n.a.	4850	LC-MS/MS	Babic et al. (2020)
Germany	2012-2014	Animal feed	TAE[10]	600	16	1-20	n.a.	961	10	20000	LC-MS/MS	Schwake-Anduschus et al. 2020
Albania	2014-2015	Wheat	TAE[3]	71	33.8	10	3	337.2	17.3	975.4	LC-MS/MS	Babic et al. (2020)
Kenya	2015	Fish feed	Et	78	9	43-730	13-219	301.5	<29.3	1895.6	HPLC-MS/MS	Mwihia et al. (2020)
Slovenia	2014-2017	Wheat	TAE[1]	206	17	10	3	363	14	4217	LC-MS/MS	Babic et al. (2020)
		Barley		136	4			340	27	1177		
		Triticale		101	13			417	14	2587		
		Rye		35	54			502	25	4114		
		Spelt		23	30			715	152	2682		
		Oat		16	50			594	84	2191		
Poland	2016	Rye (Marianowo)	TAE[1]	46	41	1.3-3	0.4-0.9	580.7	9.2	7,091.2	LC-MS/MS	Bryła et al. 2018
	2017	Rye (Marianowo)		42	38			270.1	4.7	1,972.0		
		Rye (Lućmierz)		14	36			427.9	42.9	1,305.2		
		Rye (Uhnin)		20	25			509.5	51.6	2,391.4		
Europe	2018	Wheat	TAE[3]	13	77	3.1-9.8	1.57-2.97	n.a.	n.a.	n.a.	LC-MS/MS	Agriopoulou (2021)
		Maize		15	n.d.							
United States	2013-2019	Corn grain	TAE[11]	711	3.2	0.161-2.677	0.048-0.803	4.0	n.a.	10.2	UHPLC–MS	Weaver et al. (2021)
		Corn silage		1117	20.2			16.5	n.a.	811		
	2019	Wheat	TAE[3]	55	87	2.5	n.a	n.a.	2.5	1142.6	LC-MS/MS	Debegnach et al. (2019)
Italy		Rye		16					2.6	188.6		
	2017-2020	Cereal grains	TAE[2]	67	25	0.6-2.3	0.2-0.7	31.2	2.5	270.7	LC-MS/MS	Lattanzio et al. (2021)
		Cereal products										
Netherland	2007-2010	Rye	TAE[3]	69	50.7	10	2	105	n.a	1231	LC-MS/MS	Babic et al. (2020)
		Triticale		45	33.3			35		297		
		Wheat		18	38.9			79		529		
		Other cereals		4	25.0			240		961		
	2011-2014	Cereals-based food	TAE[8]	113	54	n.a.	0.1-0.5	10	n.a.	115.4	LC-MS/MS	Agriopoulou (2021)
	2020	Wheat	TAE[9]	19	3-100	0.3-1.2	0.1-0.3	24.0	1.2	77.4	LC-MS/MS	Veršilovskis et al. (2020)
		Rye		5				15.0	3.0	43.3		
		Wheat-rye		4				95.3	6.5	334.6		
		Multi-grain		12				25.9	5.4	82.2		
Algeria	2018	Cereals	TAE[3]	60	20	0.49-3.92	0.12-1.18	34.3	3.7	76.0	QuEChERS–UHPLC–MS/MS	Agriopoulou (2021)
	2021	Barely	TAE[1]	30	13.3	0.5-1.52	0.12-1.18	35.4	17.8	53.9	QuEChERS–UHPLC–MS/MS	Carbonell-Rozas et al. 2021
		Wheat		30	26.7	0.49-3.33	0.5-3.92	33.1	3.66	76.0		
Croatia	2021	Wheat		53	1.9	70	50	68.5	<LOD	68.5	ELISA	Pleadin et al. (2022)
		Rye	TAE[1]	11	18	140	125	121.8	76.2	167.4		
Spain	2021	Swine feed	TAE[1]	228	12.7	2.1-21.7	0.6-6.5	44.1	5.9	158.7	QuEChERS–UHPLC–MS/MS	Arroyo-Manzanares et al. 2021
Canada	2014-2016	Cereal crops	TAE[10]	149	5-48	n.a	n.a.	3900	100	78000	HPLC-MS/MS	Grusie et al. 2018
	2016-2017	Barely	TAE[7]	67	73	1.25	n.a.	1150.50	2.21	29424.6	LC-MS/MS	Shi et al. (2019)
	2010-2020	Bread wheat	TAE[1]	60,274	19.5	n.a.	n.a.	n.a.	n.a.	n.a.	LC-MS/MS	Walkowiak et al. (2022)
		Durum wheat		14,323	13.1	n.a.	n.a.	n.a.	n.a.	n.a.		
		Barley		4076	2.4	n.a.	n.a.	n.a.	n.a.	n.a.		
		Rye		256	65.6	n.a.	n.a.	n.a.	n.a.	n.a.		
		Oat		421	0.7	n.a.	n.a.	n.a.	n.a.	n.a.		
	2022	Barely grain	TAE[6]	57	91	1.25	0.5	1079.3	0.7	29424.8	LC-MS/MS	Shi and Yu (2022)
		Wheat grain		80	84			991.8	0.6	21970.4		

Legends: a=µg/L, b= mg/kg, c=ng/g, TAE= Total ergot alkaloid, 1= Sum of Em, Es, Et, Eco, Ekr, Ecr, Emn, Esn, Etn, Econ, Ekrn and Ecrn, 2= Sum of Em, Es, Et, Eco, α-Ekr, Ecr, Emn, Esn, Etn, Econ, α-Ekrn and Ecrn, 3= Sum ofSum of Em, Es, Et, Eco, α-Ekr, Ecr, Emn, Esn, Etn, Econ, α-Ekrn and Ecrn, 4= Sum of Sum of Em, Es, Et, Eco, α-Ekr, Ecr, Emn, Esn, Etn, Econ, α-Ekrn, Ecrn, Mem and Dhe, 5= Sum of Em, Es, Et, Eco, Est, α-Ekrn and Ecrn, 6=Sum of Em, Es, Et, Eco, α-Ekr, β-Ekr, α-Ecr, Emn, Esn, Etn, Econ, α-Ekrn, Ecrn, Agro, Fc, Ely, Ch, Ergn, Lyl, Dhl, Dherg, Dhco, Dhc, Dhe and Dhec, 7=Sum of Em, Et, Eco, Ecr, Es and Ekr, 8=Eco, Econ, α-Ekr, α-Ekrn, β-Ekr, Ecr, Ecrn, Em, Emn, Es, Esn, Et, Etn, Agroclavine, Chanoclavine, Elymoclavine, Ergine, Erginine, Festuclavine and Lysergol, 9=Sum of Em, Es, Et, Eco, α-Ekr, β-Ekr, Ecr, Emn, Esn, Etn, Econ, α-Ekrn, Ecrn, Ch-1, Erg, Fc and Agro, 10=Sum of Em, Es, Et, Eco, Ecr and Eke, 11=Sum of Em, Et, Ekr, Lyl and Mem, Em=Ergometrine, Es=Ergosine, Et=Ergotamine, Eco=Ergocornine, Ekr=Ergokryptine, Ecr=Ergocristine, Emn=Ergometrinine, Esn=Ergosinine, Etn=Ergotaminine, Econ=Ergocorninine, Ekrn=Ergokryptinine, Ecrn=Ergocristinine, Mem=Methylergometrine, Dhe=Dihydroergotamine, Agro=Agroclavine, Fc=Festuclavine, Ely= Elymoclavine, Ch=Chanoclavine, Ergn=Erginine, Lyl=Lysergol, Dhl=Dihydrolysgerol, Dherg=Dihydroergine, Dhco=Dihydroergocornine, Dhc=Dihydroergocryptine, Dhe=Dihydroergotamine, Dhec=Dihydroergocristine.

Fig. 7: Gross pictures of an EA-infected animals. A) Loss of tail and hyperexcitability in bull, B) Loss of tail and recumbency in bull, C) Loss of ear tips in cow D) Episcleral congestion in cow, E) Tissue necrosis near the ear in heifer, F) Cutaneous lesions of the hoof in heifer, G) Sanguineous lesion at the tail region in rabbit, H) Necrotic lesions at the tail region in rabbit, I) Uncoordinated movement in broiler, J) Gangrene at feet in chicken, K) Gangrene of the limb in moose, and L) Dry gangrene of the tail in bull (Botha et al. 2004; Handeland and Vikøren 2005; Korn et al. 2014; Thompson 2016; Dänicke 2017; Friskop et al. 2018; Rahimabadi et al. 2022).

Table 5: Grain standards for ergot sclerotia ergot alkaloids

Authority/country	Type of grain	MPL	TDI	ARfD	Reference
EU	Soft and durum wheat for human consumption	<0.05% by weight of sclerotia	-	-	Miedaner and Geiger (2015);
	All cereals for animal feed	<0.1% of sclerotia	-	-	Malysheva et
	Unground cereals feed	1000 mg/kg rye ergot	-	-	al.(2014);
	Cereal milling products for human consumption	100-500 µg/kg	-	-	Veršilovskis et al.(2020)
	Processed cereal-based food for infants and young children	20 µg/kg	-	-	
Codex Alimentarius	Wheat *(Triticumaestivum)*	0.05% by weight of sclerotia or ergot			Tittlemier et al.(2020)
Australia, New Zealand	Cereal grains	500 mg/kg of ergot sclerotia	-	-	EFSA (2012)
USA	Soft or durum wheat for human consumption	<0.05% by weight of sclerotia or ergot	-	-	Miedaner and Geiger (2015);
	Barley *(Hordeumvulgare)*, oat *(Avena sativa)*, and triticale	0.1% by weight of sclerotia	-	-	Agriopoulou et al. (2020a)
	Rye *(Secalecereale)*	0.3% by weight of scelerotia	-	-	
	Grain	300 mg of ergot bodies/kg grain	-	-	
UK	Feed grain	0.001%by weight of scelerotia	-	-	Scott (2009)
China	Cereals	0.01% of the TEA content in cereals	-	-	Agriopoulou et al. (2020a)
Japan	Wheat (animal feed) *(Triticumaestivum)*	0.04%by weight of sclerotia or ergot	-	-	Scott (2009)
	Wheat (human consumption) *(Triticumaestivum)*	Zero tolerance			

Germany	Cereals for human consumption	400-500 µg/kg	-	-	Krska and Crews (2008)
Switzerland	Cereals for human consumption	100 µg/kg	-	-	Battilani et al. (2009)
Canada	Cereals (Premium quality)	0.01% of the TEA[1]	-	-	Scott (2009);
	Cereals (Poor quality)	0.1%of the TEA[1]	-	-	Völkel et al.
	Wheat *(Triticumaestivum)*	0.01-0.1% sclerotia	-	-	(2011); EFSA
	Rye *(Secalecereale)*	0.05-0.33% sclerotia	-	-	(2012); Crews
	Barley *(Hordeumvulgare)*	0.1% sclerotia	-	-	(2015);
	Oats *(Avena sativa)*	0-0.05% sclerotia	-	-	Tittlemier et al.
	Triticale	0.1% sclerotia	-	-	(2020)
	Durum (Premium grade)	0.02% sclerotia	-	-	
	Western red spring	0.04% sclerotia			
	Poultry feed	100µg/kg TEA[1]	-	-	
	Swine feed	6000µg/kg TEA[1]	-	-	
	Dairy cow, sheep and horses feed	3000µg/kg TEA[1]	-	-	
	Chicks feed	9000µg/kg TEA[1]	-	-	
Uruguay	Animal feeds	450µg/kg TEA[1]	-	-	Crews (2015)
EFSA	Unprocessed cereals with the exception of maize, rye and rice	0.2 g/kg ergot sclerotia	0.6 µg/kg body weight/day	1µg/kg bw	EFSA (2012); EU (2021)
	Unprocessed rye	0.5 g/kg sclerotia 0.2 g/kg sclerotia (as from 1.7.2024)			
	Milling products of barley, wheat, spelt and oats (ash content <900mg/100g)	100µg/kg TEA[1] 50µg/kg TEA[1] (as from 1.7.2024)			
	Milling products of barley, wheat, spelt and oats (ash content ≥ 900mg/100g)	150µg/kg TEA[1]			
	Rye milling products	500µg/kg TEA[1] 250µg/kg TEA[1] (as from 1.7.2024)			
	Wheat gluten	400µg/kg TEA[1]			
	Processed cereal based food for infants and young children	20µg/kg TEA[1]			

Legends: MPL=Maximum permissible limit; ARfD=Acute reference dose; TDI=Tolerable daily intake; TEA= Total ergot alkaloids EU= European Union; EFSA= European food safety authority, [1]Lowerbound sum of the following 12 ergot alkaloids: ergocornine/ergocorninine; ergocristine/ergocristinine; ergocryptine/ergocryptinine (α- and β-form); ergometrine/ergometrinine; ergosine/ergosinine; ergotamine/ergotaminin.

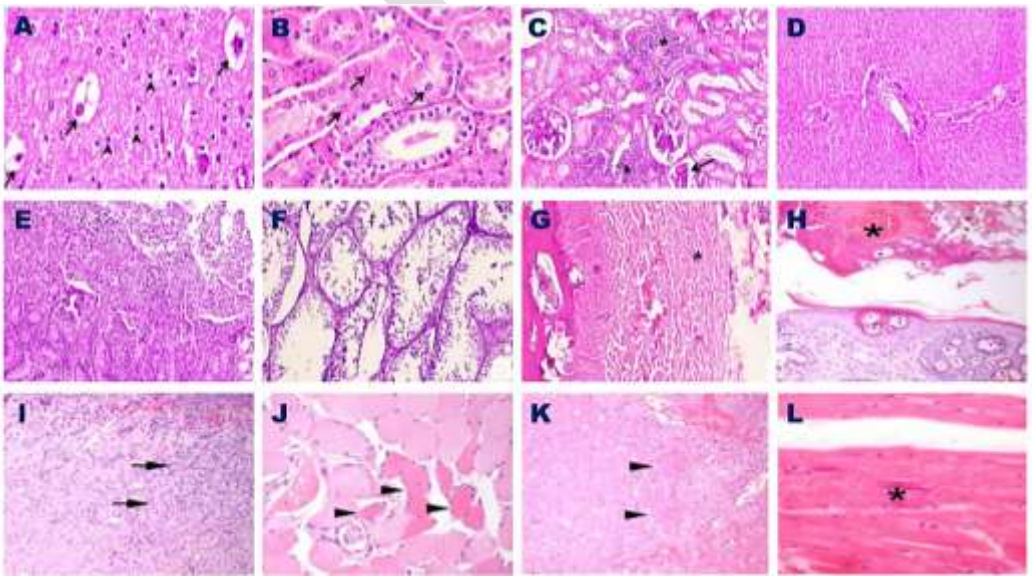

Fig. 8: Histopathological (H and E stain) findings in cattle (A-G) and rabbit (H-L) with ergotism, A) Brain: Perineuronal edema (arrows) and gliosis (arrowheads) (×40), B) Kidneys: Karyomegaly of the tubular epithelium (arrows) (×4), C) Kidneys: Chronic fibrotic interstitial nephritis (asterisks) and glomerular atrophy (arrow) (×10); D) Liver: Portal hepatitis, (×10); E) Duodenum: Mucosal necrosis and mononuclear infiltration, F) Testis. Seminiferous tubules are devoid of primary and secondary spermatocytes, spermatids, and spermatozoids (×10), G) Tail. Zenker's necrosis (asterisk), (×10), H) Tail. Pyodermic with thick serocellular crust (asterisk) composed of degenerated leucocytes, keratin and blood cells (×20), I) Skin. Showing epithelial hyperplasia (arrowhead) and chronic dermatitis with granulation tissue formation (arrows) (×20), J) Muscle. Hypereosinophilia and loss of myofibrils characterize degenerating muscle fibers of the tail (×20), K) Liver. Multiple foci of acute coagulative necrosis (arrowhead), bile duct hyperplasia, chronic cholangitis and pericholangitis (arrow) (×20), and L) Heart. Acute myocardial fiber necrosis with dystrophic mineralization (asterisk) (×20) (Korn et al. 2014; Rahimabadi et al. 2022).

frequency of EA contamination has surged worldwide over the past five years. Currently, the European Union (EU) permits EA content of 0.2µg/kg ergot sclerotia in certain untreated grains as a permissible limit for food and feed, with a 2,4- and 2,6-toluene diisocyanate (TDI) limit of 0.6 µg/kg body weight/day (EU 2021). Table 5 presents the maximum permissible limits of EAs in food and feed established by food safety authorities or their equivalents in various countries. Depending on environmental factors, crops may be affected by numerous species of mycotoxigenic fungi that produce more than one mycotoxin. Co-occurrence becomes even more frequent during the mixing of raw materials for food and feed production. EAs have been found in 84% of rye products, 67% of wheat products, 48% of multigrain meals, 52% of rye feed, 27% of wheat feed, and 44% of triticale feed, with TAE varying between ≤1 (LOQ, limit of quantification) and 12,340µg/kg, and co-occurrence of six EAs was identified in 35% of the confirmed cases (Malysheva et al. 2014). In another study, the TAE content of six EAs in wheat, rye, triticale and barely varied between 0.3 and 2530.1µg/kg (Schummer et al. 2018). In 2016, it was reported that, in addition to deoxynivalenol (DON) and zearalenone (ZEN), the detection limit for EAs in beer was 0.07 to 0.47g/L and was associated with tainted wheat and barley used in the brewing process (Bauer et al. 2016). Several studies have detected little EAs carrying over into mammalian tissue. A 230-day feeding study in bulls given rations up to 421µg TAE/kg DM (2.25 µg·ergot/kg) showed no evidence of EAs in tissue (Völkel et al. 2011). A previous study (EFSA 2012) reported that dairy cows fed alkaloid diets ranging from 4.1 to 16.3g/kg body weight. daily had no EAs discovered in their milk, whereas developing and maturing swine (30-115kg b.w.) whose meals contained up to 4.66mg EAs/kg had no alkaloids in their flesh or back fat. However, Scott (2009) reported that EAs were detected in the milk (8.6mg/L) from both cows and goats up to 8 hours after parenteral ergovaline administration (32mg/kg body weight). The carryover of EAs in animal edible products has been illustrated in Table 6. In 2016, the European Food Safety Authority (EFSA) estimated chronic and acute TAE dietary exposure in people and animals in 15 European countries (Table 7 and 8). The maximum amounts of EAs have been detected in rye and rye-based products. For humans, the maximum upper bound (UB) values for average chronic dietary exposure were found to be 0.47 and 0.46µg/kg bw per day for 'Toddlers' and 'Other Children', respectively. 'Toddlers' had a maximum 95th percentile dose of 0.86µg/kg bw per day. UB values were four times greater than those of the minimum lower bound (LB) values. "Infants" had an average acute dose of 0.02µg/kg bw per

Table 6: Carry-over of EAs in edible animal products

Species	EAs	Dose	Edible products	Observation	Reference
Bull	TAE	0.23% with feed	Liver, kidney, muscle and fat	NOEL	Scott (2009)
	TAE	1.4-8.56µg/kg b.w./day	Bile, urine, tissue samples	NOEL	EFSA (2012)
Cow (*Bos Taurus*)	Ergotamine	0.1% with feed	Milk	NOEL	Scott (2009)
	TAE	1835µg/animal/day	Milk	NOEL	Völkel et al. (2011)
	TAE	50g/animal	Milk	86µg/L	Völkel et al. (2011)
	TAE	125mg/kg dietary DM	Milk	<10% after 2 weeks	Coufal-Majewski et al. (2016)
Goat (*Capra hircus*)	Ergovaline	32mg/kg bwt IV	Milk	Detected up to 8 hours	Scott (2009)
Pig (*Sus domesticus*)	Ergopeptine	4% with feed	Liver, kidney, muscle and fat	NOEL	Scott (2009)
	TAE	0.05-4.66 mg/kg	Serum, bile, liver, meat and back fat	NOEL	EFSA (2012)
	TAE	1–10g/kg body weight with feed	Muscle	NOEL	Coufal-Majewski et al. (2016)
Chicken (*Gallus gallusdomesticus*)	Ergotamine	90-180/kg feed	Muscle	1.5-5µg/kg	Scott (2009)
	Ergotamine	800 mg/kg feed/day	Liver and skeleton muscles	<10µg/kg	Völkel et al. (2011); EFSA (2012)

Legends: EAs=Ergot alkaloids, TAE=Total ergot alkaloids, NOEL = No-observed-effect level.

Table 7: Human dietary exposure to EAs from 2011-2016 (EFSA 2017)

Population		Exposure type	Level (µg/kg bw per day)	Exposure type	Level (µg/kg bw per day)	
					Lower bound (LB)	Upper bound (UB)
Human	Infants	Average acute exposure	0.02-0.21	Average chronic exposure	0.01-0.08	0.03-0.34
		95th percentile of acute exposure	0.26-0.65	95th percentile of chronic exposure	0.05-0.19	0.29-0.76
	Toddlers	Average acute exposure	0.11-0.30	Average chronic exposure	0.03-0.12	0.18-0.47
		95th percentile of acute exposure	0.35-0.79	95th percentile of chronic exposure	0.07-0.30	0.38-0.86
	Other children	Average acute exposure	0.08-0.32	Average chronic exposure	0.02-0.17	0.14-0.46
		95th percentile of acute exposure	0.27-0.98	95th percentile of chronic exposure	0.05-0.39	0.29-0.79
	Adolescents	Average acute exposure	0.04-0.23	Average chronic exposure	0.01-0.15	0.07-0.29
		95th percentile of acute exposure	0.13-0.77	95th percentile of chronic exposure	0.03-0.33	0.14-0.56
	Adults	Average acute exposure	0.03-0.17	Average chronic exposure	0.01-0.05	0.06-0.18
		95th percentile of acute exposure	0.10-0.49	95th percentile of chronic exposure	0.02-0.12	0.12-0.36
	Elderly	Average acute exposure	0.03-0.13	Average chronic exposure	0.01-0.05	0.05-0.14
		95th percentile of acute exposure	0.10-0.37	95th percentile of chronic exposure	0.02-0.10	0.11-0.28
	Very elderly	Average acute exposure	0.03-0.12	Average chronic exposure	0.01-0.06	0.05-0.16
		95th percentile of acute exposure	0.10-0.39	95th percentile ofchronic exposure	0.02-0.09	0.12-0.26

Infants: <12 months old, Toddlers: ≥12 months to < 36 months old, other children: ≥36 months to < 10 years old, Adolescents: ≥10 years to < 18 years old, Adults: ≥ 18 years to < 65 years old, Elderly: ≥65 years to < 75 years old, Very elderly: ≥75 years old.

Table 8: Animal dietary exposure to EAs from 2011-2016 (EFSA 2017)

Population		Exposure type	Level (µg/kg bw per day)
Animal	Dairy cow	Mean concentration scenario	1.41-1.75
		95th percentile	4.53-4.58
	Beef cattle	Mean concentration scenario	0.31-0.46
		95th percentile	1.43-1.45
	Piglets	Mean concentration scenario	6.82-8.07
		95th percentile	16.4-16.6
	Fattening pig	Mean concentration scenario	4.68-5.48
		95th percentile	12.0-12.2
	Lactating sows	Mean concentration scenario	4.92-5.58
		95th percentile	12.3-12.4
	Lactating sheep	Mean concentration scenario	1.14-1.38
		95th percentile	3.74-3.78
	Milking goat	Mean concentration scenario	2.43-4.35
		95th percentile	11.3-11.9
	Fattening goat	Mean concentration scenario	0.82-1.51
		95th percentile	3.80-4.04
	Broiler	Mean concentration scenario	5.78-7.16
		95th percentile	11.8-12.7
	Layer	Mean concentration scenario	4.46-5.65
		95th percentile	8.89-9.74
	Turkey	Mean concentration scenario	3.50-4.50
		95th percentile	10.2-10.4
	Duck	Mean concentration scenario	6.53-7.56
		95th percentile	16.2-16.4
	Rabbit	Mean concentration scenario	1.74-2.98
		95th percentile	7.04-8.19
	Farmed fish	Mean concentration scenario	0.65-0.72
		95th percentile	1.30-1.32
	Dog	Mean concentration scenario	0.53-1.11
		95th percentile	1.50-1.96
	Cat	Mean concentration scenario	0.55-1.16
		95th percentile	1.56-2.04
	Horse	Mean concentration scenario	0.88-1.28
		95th percentile	3.38-3.59

day, while "Other Children" had 0.32µg/kg bw per day. The 95th percentile acute exposure was 0.98µg/kg bw per day for a dietary study in "Other Children." Dietary exposure figures for animals, implying average concentration trends, ranged from 0.31–0.46, 1.41-1.75, 2.43-4.35, 1.14-1.38, 5.78-7.16, 4.46-5.65, 6.53-7.56, 4.46-5.65, 0.65-0.72, 0.53-1.11, 0.55-1.16, 0.88-1.28, 4.68-5.48, and 6.82–8.07µg/kg bw per day in beef cattle, dairy cattle, milking goat, lactating sheep, broiler, layer, duck, turkey, farmed fish, dog, cat, horse, fattening pig, and piglets, respectively, while exposure assessments implying greater concentration trends (95th percentile) ranged from 1.43–1.45 and 16.38–16.61 within the same species (EFSA, 2017). Moreover, co-occurrence of other mycotoxins including fumonisin, FB1 (1,628µg/kg), DON (593µg/kg), ZEN (69µg/kg), ochratoxin, OTA (52µg/kg), and aflatoxin, AFB1 (24µg/kg) were found in poultry feed, as well as breeder eggs' residual contamination of FB1 (320–549 and 151-669µg/kg) and DON (184-658µg/kg and 192–515µg/kg) were reported in albumen and yolk samples, respectively (Wang et al. 2021). Given the persistence of EAs in flour even after thorough cleaning efforts, investigations into the efficacy of current washing and processing methods for grains contaminated with ergot are warranted. Furthermore, efforts should be directed towards refining and expanding the existing regulatory limits for EAs content in food and feed. To achieve these, collaboration with regulatory agencies is essential, and that can lead to more stringent standards that better align with the potential risks of EA exposure. Of course, there is a pressing need to enhance standardized monitoring practices across different grain crops and regions, acknowledging the frequent co-occurrence of multiple mycotoxins within the crops due to varying environmental factors. This necessitates comprehensive surveys that assess the prevalence of EAs and their cumulative effects on various foods and feeds. Lastly, understanding the carry-over dynamics of EAs in animal products is vital for safeguarding both human and livestock health. Long-term studies investigating EA accumulation in different tissues and its potential implications for consumer safety are also critical. By addressing these suggestions, we can advance the comprehension of EA-related risks, refine safety measures, and establish robust regulatory frameworks that better protect public health.

Therapeutical applications of EAs

EAs have a variety of pharmacological effects and have traditionally been utilized in medical treatments. Currently, over 50 formulations carry natural or semisynthetic EAs (EFSA 2012; Schardl 2015; Mukherjee and Menge 2000). Derivatives of EAs are still used to treat migraine, uterine stimulation, and tumor progression. Originally, EAs or their derivatives were employed in obstetrics and intramuscular ergometrine, which played a pivotal role in both inducing childbirth and mitigating uterine bleeding. It was administered at a dosage of 200µg to address post-abortal hemorrhage and prophylaxis against post-abortal haemorrhage. When used in conjunction with oxytocin, the recommended dose was 500µg, to be administered following the delivery of the infant's anterior shoulder or immediately after birth. Furthermore, for prophylaxis against postpartum hemorrhage, a dose ranging from 200 to 500µg was administered through intramuscular injection subsequent to placental expulsion or when bleeding manifested. In cases of emergencies such as severe uterine bleeding or other life-threatening scenarios, a gradual intravenous injection of 250-500µg over a minimum of 1 minute was endorsed (Lv et al. 2005). Bromocriptine and lysergic acid diethylamide (LSD), a semi-synthetic precursor of the EAs for their potent psychoactive effects, are employed as therapies for schizophrenia and cancer (Seo et al. 2018). Furthermore, bromocriptine, functioning as a DRD2 agonist, is employed in clinical settings to address prolactin-related reproductive issues and early Parkinson's disease. Moreover, it exhibits neuroprotective properties and enhances memory capabilities (Liu et al. 2023).

Following the literature review, we infer that bromocriptine holds the potential to mitigate neuroinflammation and memory impairments induced by Aβ1-42 in mice. This effect appears to be mediated via the DRD2/β-arrestin 2/PP2A/JNK signaling axis, thus laying the foundation for bromocriptine's prospective role as a therapeutic agent in mitigating Alzheimer's disease. While bromocriptine is sanctioned for treating diabetes, its precise therapeutic mechanisms remain obscure and require further investigation. The effects of bromocriptine have primarily been linked to brain dopamine D2 receptor (D2R) stimulation and an influence on the pancreas (Aslanoglou et al. 2022). Particularly, bromocriptine is

used to treat Parkinson's disease, beginning with a dosage of 1.25mg twice daily. The dosage is gradually elevated over the course of several weeks as deemed necessary. However, the typical daily dosage does not exceed 100mg. In addition, bromocriptine is used for patients with infertility, pituitary tumors, male hormone issues (male hypogonadism), initiating the menstrual cycle, or ceasing abnormal milk secretion from the nipples. For these cases, adults and individuals who are 16 years of age or older should begin with 1.25 to 2.5mg once a day. It may be raised by 2.5mg every 2 to 7 days, as necessary and tolerated by the patients. Nevertheless, the typical daily dosage does not exceed 15mg. Recently, it has been reported that dihydroergotamine mesylate enhanced the anti-tumor effect of sorafenib in liver cancer cells (He et al. 2023).

When it comes to neuroreceptors, EAs can act as either agonists or antagonists because they are very bioactive (Jakubczyk and Dussart 2020). As pharmaceutical concern over ergoline hallucinogens reemerges, for instance, in the treatment of autism, distinct forms of EAs are now frequently employed as a basic supply for the production of medicinal drugs (Haarmann et al. 2009; Hulvová et al. 2013). Nevertheless, the synergistic antibacterial activity of naturally occurring EAs, like synthetic EAS, is well-known (Jakubczyk and Dussart 2020). Lysergol shows synergistic antimicrobial pharmacological activity when used with broad-spectrum antibiotics. Lysergol should be administered at a 10ng/mL dose to improve antimicrobial potency against a wide range of pathogens, such as *Escherichia coli*, *Bacillus subtilis*, *Mycobacterium smegmatis*, and related germs, by a factor of 2 to 12 (Jakubczyk and Dussart 2020). In animal models, ergotamine, ergocryptine, and ergocornine were capable of suppressing pituitary tumor proliferation. Furthermore, 1-propylagroclavine and dihydroergocristine exhibit strong inhibitory effects against markers linked to the development of leukemia in mRNA microarray studies, which translates into significant cytotoxic effects against a number of human carcinoma cells. It is unclear if dietary exposure to modest amounts of EAs can mitigate the carcinogenic effects of contemporaneous mycotoxins, although the EAs' suppression of pituitary activity may reduce their therapeutic efficacy (De Ruyck et al. 2015).

Synthesis strategy and research progress of ergot alkaloids (EAs)

Biosynthesis of EAs: The biosynthesis of EAs is a complex process that involves several enzymatic reactions leading to the formation of the tetracyclic ergoline ring system. While the complete elucidation of all biochemical pathways has been a subject of research for many years, significant progress has been made in understanding the key steps involved in the formation of EAs. Particularly, scientists engineered the ergot alkaloid biosynthetic pathway in *Aspergillus nidulans* using a Fungal-Yeast-Shuttle-Vector protocol, resulting in strains capable of producing a significant level of a range of EAs and related compounds, including prechanoclavine, chanoclavine, agroclavine, and festuclavine (e.g., 333.8mg/L of PCC). Moreover, the modified fungal system successfully synthesized methyl-oxidized EAs including elymoclavine, lysergic acid, dihydroelysergol, and dihydrolysergic acid, by incorporating the P450 enzyme CloA (Yao et al. 2022). Employing biotechnological advances, strategies like overexpression of Trp-related genes in *Claviceps purpurea* yielded 7-fold higher EAs compared to that of normal gene expression (Kralova et al. 2021). Researchers (Zhang et al. 2021) demonstrated the synthesis of 2,3-seco-clavine-type EAs from human the intestinal fungus *Aspergillus fumigatus* CY018, among which secofumigaclavine B could be considered a potential candidate for the development of MD2 (myeloid differentiation protein 2) inhibitors.

Several enzymes are needed to synthesize EAs in fungi. The first step is to prenylate tryptophan. This creates 4-(γ,γ-dimethylallyl) tryptophan (4-DMAT), which is formed by prenylating tryptophan at the C-4 position of the indole ring. This step is catalysed by an enzyme called DMAT synthase, and the prenyl donor used in this reaction is dimethylallyl diphosphate (DMAPP), a molecule that provides the prenyl group. The resulting 4-DMAT molecule serves as an intermediate for the biosynthesis of various EAs. In addition, the ergot alkaloid pathway is quite complex and involves multiple enzymatic reactions that lead to the synthesis of various alkaloids. The intermediates formed following the prenylation of tryptophan are subsequently modified through additional enzymatic reactions to create the diverse array of EAs found in these endophytic fungi. The biosynthesis of EAs starts with the production of a tryptophan derivative, often tryptamine, through a series of enzymatic reactions, as previously described (Tasker and Wipf, 2021). This normally involves the decarboxylation of tryptophan, and the resulting tryptamine derivative goes through various modifications, including oxidation and condensation reactions, to form the indole ring system. This step is crucial for the subsequent steps leading to the ergoline ring. The indole ring system undergoes a series of enzymatic reactions that lead to the formation of a tetrahydrocarbazole intermediate. This involves the reduction of the indole ring, which is followed by the formation of a second ring system. The tetrahydrocarbazole intermediate is cyclized to form the characteristic ergoline ring structure, which involves various enzymatic reactions, including oxidative processes and intramolecular cyclizations. Following the formation of the ergoline ring, various enzymes catalyze further modifications, such as the introduction of substituents at specific positions of the ring system.

EAs can be divided into the following three groups based on their structures: clavines, lysergic acid amides, and ergopeptines. These groups result from different modifications of the ergoline ring catalysed by specific enzymes. For example, lysergic acid amides involve the incorporation of a carboxylic acid moiety into the structure, while ergopeptines include peptides linked to the alkaloid core (Tasker and Wipf 2021; Jakubczyk and Dussart 2020). In addition, scientists have identified gene clusters in ergot alkaloid-producing fungi through genome mining. These clusters contain genes encoding enzymes involved in various enzymatic steps leading to the production of EAs. Knock-out experiments and biochemical investigations have helped confirm the functions of these enzymes, elucidating the biosynthetic pathways (Yu et al. 2022). It is noteworthy that the biosynthesis of EAs can vary among different fungal species and strains.

Semisynthesis of EAs: EAs with their intricate architectures, serve as ideal candidates for semisynthetic endeavors to enhance the bioactivity, selectivity, and solubility of EAs. semi synthesis involves the modification of naturally occurring compounds using synthetic chemistry while retaining core structural elements. Strategy like sequential radical coupling, which enabled the biomimetic total synthesis of festuclavine and pyroclavine, featured the following pivotal stages: an intramolecular decarboxylative Giese reaction for the central C ring, 4-nitrobenzenesulfonyl (Ns)-guided indole C4–H olefination, and D-ring completion through decarboxylative alkenylation and intramolecular SN2 reaction (Ge et al. 2020). Nonbiomimetic total syntheses of EAs are based on the construction of core structures using alkyne reactions (Ohono and Inuki 2021). The diverse classes of EAs, including clavines, lysergic acid amides, and ergopeptines, offer a versatile canvas for semisynthetic modifications. The introduction of different substituents on the side chains of EAs can alter their pharmacological properties, such as receptor binding affinity and metabolic stability. Semisynthetic strategies involve the introduction of functional groups, such as hydroxyl, amino, or carbonyl groups, into specific positions to impart new activities or enhance interactions. Substitution of specific moieties with bioisosteres can lead to analogs with improved pharmacokinetic profiles, reducing side effects. Leveraging ergopeptines, the addition or alteration of peptide sequences can fine-tune interactions with protein targets, potentially leading to more selective compounds. Combinatorial chemistry techniques were employed to allow the rapid generation of structurally diverse analogs for biological screening. Derivatives like dihydroergotamine and ergotamine have been utilized for their vasoconstrictive properties, effectively reducing the manifestation of migraine symptoms. Dihydroergotamine (DHE), an ergot alkaloid derived from rye fungus, is a versatile compound used in medical practice. Compared to ergotamine, DHE offers advantages such as enhanced alpha-adrenergic antagonist activity, reduced arterial vasoconstriction, and lower emetic potential. It can be administered through various routes, including IV, IM, SC, and IN, making it suitable for both outpatient and inpatient treatment settings. DHE holds potential for managing migraines in both adult and pediatric populations, with established protocols for different clinical contexts (Shafqat et al. 2020). Lysergic acid derivatives have been investigated for their potential in treating depression, mood disorders (Lewis et al. 2023), and anxiety (Adams and Gallahue 2023). Selected ergoline derivatives have demonstrated cytotoxic effects on tumor cells, warranting further exploration of their usage as anticancer agents (Bai et al. 2020). Moreover, semisynthetic EAs have been evaluated for their potential in treating hypertension and other cardiovascular conditions (Reddy et al. 2020). In conclusion, the semisynthesis of EAs holds immense potential for expanding their applications in the therapeutic landscape. Strategic modification of key structural elements allows researchers to fine-tune pharmacological properties and develop compounds with improved efficacy and reduced treatment side effects. While challenges exist, the continued exploration of semisynthetic strategies promises to yield novel ergot alkaloid derivatives that address unmet medical needs and contribute to the advancement of pharmaceutical science, hence human health. Recently, scientists described a potentially scalable asymmetric synthesis of lysergic acid, a fundamental constituent in the ergot alkaloid group (Rathnayake and Garner 2021). While a streamlined pathway to craft the enantiopure tetracyclic framework of EAs has been crafted, featuring a strategic organocatalytic aldol reaction utilizing paraformaldehyde as the C1 building block in the presence of a thiourea ligand, accomplished by a Pd-catalyzed directed coupling (Bhunia et al. 2018).

Prevention and control

Ergot poisoning can be prevented by recognizing and avoiding the risk of feed contamination and taking appropriate steps to limit exposure. Not using contaminated grain, feed, or fodder is the best option. The following two methods can be utilized to check grain or feed for ergot infection: (i) a thorough sclerotia inspection in the feed or fodder is used, and (ii) chemical analysis of feed samples is used. A representative sample from each batch should be analyzed, and if toxic EAs are found, the feed should be appropriately discarded, limiting the risk of feeding the contaminated feed (Wegulo and Carlson 2011). Hydrothermal treatments of ergot-infected cereals with vapor for 2 min at 95°C at 17% moisture and then incubated for 5s at 120°C at 18% moisture reduced (TAE) by 10%. This technique could reduce alkaloids during feed processing, but its effects on alkaloid toxicity require further study before it can be used as feed for livestock. Anaerobic bacteria can detoxify some EAs from the genera *Plantomyce*, *Chloroflexi*, *Bacteroides*, and *Proteobacteria* recovered from rumen, intestinal flora, soil, and water (Perumbakkam et al. 2007; Coufal-Majewski et al. 2016; Haque et al. 2020). To utilize these anaerobic microbes as a direct feed to reduce the ergot's effects on livestock, further research is required to identify and categorize the microbe's competencies in eliminating EAs. The detoxication of EAs has been addressed through various biological agents, including yeast, bacteria, fungi, and enzymes (Haque et al. 2023a) It is operated through mechanisms such as transformation, adsorption, degradation, or absorption (Nesic et al. 2021; Agriopoulou et al. 2020b; Li et al. 2021). These mechanisms play a crucial role in detoxifying agricultural products of both plant and animal origin, as well as animal feed, which may be tainted with mycotoxins (Nesic et al. 2021). Additionally, *Rhodococcus erythropolis* bacteria have been utilized for the degradation of EAs, although the precise mechanism behind this reaction remains somewhat unclear (Lyagin and Efremenko 2019). Genetically resistant grain crops can be selected for ergot resistance; however, genetic engineering and the screening of mold-resistant varieties may be better ways to manage ergot in cereals and cereal products (Coufal-Majewski et al. 2016). Mycotoxin binders are compounds that detoxify animal feed by binding various mycotoxin such as aflatoxin, ochratoxin, zearalenone, patulin, and deoxynivalenol, inhibiting their uptake in the digestive process and allowing the toxin-binder complexes to be excreted through feces or urine (Haque et al. 2020). Alkaloid binders may also reduce ergot alkaloid absorption. However, in one trial, alkaloid binder, polyvinylpyrrolidone, and ammonia carbonate could not mitigate DON's negative effects on swine production (Coufal-Majewski et al. 2016). Recent studies showed that

fumonisin B1-specific nanobodies and phenolic acid compounds, such as protocatechuic acid, were effectively expressed both *in vivo* and *in vitro* and then antagonized the mycotoxin, which could be used as additives for both poultry and humans (Chen et al. 2022; Wang et al. 2022). However, additional investigations are needed to lower the toxicity of ergot-contaminated cereals using alkaloid binders, nanobodies and phenolic acid compounds without reducing nutrient uptake.

Conclusion and perspective

EAs and their derivatives, produced from endophytic fungi including *Claviceps* spp. and *Epichlo*/*Neotyphodium* spp., in ergot poisoning, have a significant threat to the health of both humans and livestock. Preventing ergot alkaloid contamination in human and animal feed is crucial to protecting health, animal welfare, and agricultural productivity while also ensuring compliance with regulations and bolstering consumer confidence in food products. Strict quality control measures and monitoring systems are essential for achieving these goals. It is essential to establish the critical limit of cereal grains used as feed for both livestock and human consumption because the regulatory agency has not yet established any limits for EAs (also known as sclerotia). In the near future, there will continue to be a great need for in depth-studies on the innovative and bioactive alkaloids produced by endophytes that have antibacterial, insecticidal, cytotoxic, and anticancer activities with significant medical, agricultural, and ecological value. Research involving screening genetic resistance to ergot should be conducted among grain crops for a better understanding of the host-endophyte interaction. Mold-resistant host gene recognition may lead to a path controlling ergot in grains. Mold-resistant host gene identification and expression may also be a method of ergot management in grains (Zhang et al. 2012; Coufal-Majewski et al. 2016). Future research should prioritize several key directions to address the multifaceted challenges posed by the co-occurrence, co-exposure, and carry-over of EAs, including an in-depth exploration of the factors contributing to the negative consequences associated with contaminated foods, including variations in toxin concentrations within sclerotia and differences in head-to-head and field-to-field levels. Future research could also focus on cutting-edge techniques like nanobiotechnology, antibody-mediated technology, genetically modified animals, and the involvement of insects in ergot epidemiology in order to find a plant that can potentially stop the propagation of mycotoxins (Coufal-Majewski et al. 2016). Additionally, avoiding grazing livestock on pasture and rangeland grasses that have Epichlo infections, developing nontoxic endophytic consortia (Haque et al. 2023b; Sharker et al. 2023) for forage grasses, identifying toxic fungi down to the species level in perennial rye grass, and conducting in-depth exploration on the taxonomical assessment of *Epichlo* species should all be accomplished on a priority basis to protect the health of human and livestock.

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