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(REVIEW ARTICLE)

Ergot alkaloids as pharmaceuticals: Status and prospects of commercial cultivation of ergot crop for natural alkaloids

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Abstract

Ergot is a plant disease symptom induced by a fungal pathogen of the genus *Claviceps* in grains of cereal crops, wherein the ergot alkaloids are produced in the cereal grains which are transformed into ergot sclerotia. The natural occurrence of ergot grains in cereal crops is dependent on the environmental factors conducive to ergot development. Under natural fungal infection, the ergot percent varies from 1.2 to 3.3 in the infected crops which hamper the yield or recovery of natural ergot alkaloids. Ergot alkaloids are specific pharmaceutical alkaloids used to treat certain ailments like migraines, induction of childbirth, and the control of postpartum bleeding in humans.

Ergot sclerotia contain about 0.15% to 0.5% alkaloids, with medicinally useful compounds. Annual world production of ergot alkaloids has been estimated at 5,000-8,000 kg of all ergopeptines (peptide ergot alkaloids) and 10,000-15,000 kg of lysergic acid, the latter being mainly used in the manufacture of semisynthetic derivatives. The greater part of this production occurs as a result of fermentation (around 60%) while field cultivation of triticale (a hybrid of wheat and rye) accounts for the balance. This is because the artificial cultivation of ergot sclerotia on a host crop plant is lacking as a business module. Due to the low recovery of ergot grains and ergot alkaloids under natural crop production conditions, commercial cultivation for ergot grains is discussed in this paper.

Keywords: Ergot; *Claviceps*; Alkaloids; Pharmaceutical; Human ailments

1. Introduction

Alkaloids are naturally occurring toxic amines produced mostly by plants for their defense mechanism to protect themselves against herbivores. Alkaloids are an assembly of naturally occurring chemical composites, which typically comprise basic nitrogen atoms (Mothes et. al,1985). They may also contain some neutral or weakly acidic compounds (Manske and Holmes, 1952; McNaught and Wilkinson, 1997). The main toxic effects of alkaloids result in disturbances of the central nervous system, digestive processes, reproduction, and the immune system. Alkaloids have been detected in about 15% of plants, besides bacteria, fungi, and even in lower animals. Within the plant kingdom, they occur in primitive groups such as *Lycopodium* or *Equisetum*, in gymnosperms and angiosperms. In higher plants (angiosperms), some families contain more alkaloid-containing taxa like *Papaveraceae, Berberidaceae, Fabaceae, Boraginaceae, Apocynaceae, Asteraceae, Liliaceae, Gnetaceae, Ranunculaceae, Rubiaceae, Solanaceae,* and *Rutaceae* than the other taxa. Also, several food plants and food items may contain alkaloids. A single plant species usually comprises of few kinds of alkaloids but numerous families of plants such as *Solanaceae* (nightshades), *Papaveraceae* (poppies family), *Ranunculaceae* (buttercups), and *Amaryllidaceae* (amaryllis) are predominantly rich in several kinds of alkaloids. Within grain legumes, mainly lupins are known to contain alkaloids in considerable amounts which vary from 80 mg to 700 mg g-1 of total alkaloid depending on the alkaloid.

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Alkaloids are colourless, crystalline, non-volatile, solids; a few such as coniine and nicotine are liquids, and a few are even coloured i. e. berberine is yellow. The free bases (i.e. alkaloids themselves) are insoluble in water but soluble in most of the organic solvents.

The spectrum of alkaloids' activity is very wide showing antiviral, antibacterial, anti-inflammatory, and anticancer properties (Faisal et.al, 2023). Many alkaloids possess potent pharmacologic effects (Kurek, 2019)). These alkaloids include cocaine, nicotine, strychnine, caffeine, morphine, pilocarpine, atropine, methamphetamine, mescaline, ephedrine, tryptamine, codeine, and vincristine. Some alkaloids, such as vincristine, are used to treat cancer. These plant alkaloids typically have physiological effects on humans when they are consumed. These physiological effects range from light stimulants such as caffeine to poisons such as coniine (the poison in hemlock). Vincristine and vinblastine alkaloids are used in the treatment of various types of cancer as chemotherapeutic agents. Tubocurarine alkaloid is mainly used in surgery as a muscle relaxant. Besides plant alkaloids (Qurrat Al-Ain et.al, 2016), another class of alkaloids is Ergot alkaloids (Klotz, 2022) produced by ergot fungi which are used to treat specific ailments in humans. The ergot alkaloids are produced by specialized fungus genera like *Claviceps* when this fungal species infects the grains in cereal crops. The fungus itself or the crop grain itself does not contain these ergot alkaloids. These are formed during the infection process of the grain inflorescences by the fungi for which certain favorable climatic conditions are required. In the absence of these favorable climatic conditions, the infection is hampered, and thereby the ergot alkaloid production. For the production of such ergot alkaloids, a special cultivation technology is required. In the present paper, this technological aspect of the cultivation of ergot sclerotia under controlled conditions is discussed.

2. Issues related to Alkaloids and their productions

2.1. Alkaloids as Special Pharmaceuticals

There are numerous classes of alkaloids, grouped by chemical structure, and are classified as pyrrolizidine, piperidine, pyridine, indole, quinolizidine, indolizidine, diterpenoid, tropane, and steroidal alkaloids. Alkaloid classifications are usually based on structure or origin (Dey et. al,2020). "True alkaloids" are derived from amino acids and have nitrogen in a heterocyclic ring, e. g. atropine. "Proto-alkaloids" are derived from amino acids and do not have nitrogen in a heterocyclic ring, e.g. ephedrine. The range of alkaloids can be a drug or poison with variable biological activity (table 1).

Table 1 Sources of Alkaloids (Plant, Fungi and Lower Animal) and their biological activity

Alkaloids	**Source**	**Biological activity**
Ephedrine and related compounds	*Ephedra, Catha edulis*	Central stimulant
Morphine	*Papaver somniferum, Opium*	Hallucinogen, analgesic
N-Methyltryptamine	Fungi and Plants	Central stimulant
N, N-Dimethyltryptamine, 5-methoxy-N, N-dimethyltryptamine	*Mimosaceae: Anadenanthera (syn. Piptadenia), Mimosa hostilis.* *Myristicaceae: Virola.* *Malpighiaceae: Banisteriopsis,* *Poaceae: Phalaris*	Central stimulant, hallucinogen
Serotonin	Fungi *(Amanita),* Stinging hairs of *Urtica,* *Laportea,* *Jatropha urens,* *Mucuna pruriens,* Seeds & Fruits	Local inflammation
Bufotenine	Fungi (*Amanita*); and Animal poisons (of Cnidaria, spider, scorpions, wasps, and toads)	Central stimulant, hallucinogen

Psilocybin, psilocin	Fungi *(Psilocybe, Stropharia, Conocybe, Panaeolus, Gymnopilus, Psat hyrella etc)*	Central stimulant, hallucinogen
Mescaline	*Lophophora williamsil,* and other cacti	Hallucinogen
Harmaline & other B-carboline alkaloid	*Pegamum harmala, Banisteriopsis caapi*	Hallucinogen
Cocaine	*Erythroxylon coca*	Stimulant, analgesic
Arecoline	Nuts of Areca palm	Stimulant
Caffeine, Theophylline, Theobromine	Coffee, *Thea, Paullinia, Ilex paraguariensis*	*S*timulant
Solanine & other Steroid alkaloid	*Solanum (*Potato and Tomato*)*	Membrane disruption, Acetylcholine esterase inhibition, mutagenicity
Pyrrolizidine alkaloids	*Symphytum (*Comfrey*),* Honey (if bees have visited PA plants)	DNA and protein alkylation, Mutagenicity, Cancer.
Cycasin	*Cycas,* other *cycads*	Mutagenicity
Lupanine & other Quinolizidine alkaloid	*Lupinus,* other *Genistoids*	Interaction with AChR[a], Na^+, K^+ channels
Pelletierine	*Punica granatum*	Interaction with AChR[a]
Saxitoxin	Algae Ends up in food chain (mollusks and fish)	Neurotoxin (Na^+ channel)
Ergot alkaloids	*Claviceps purpurea on Rey, wheat, barley, pearl-millet and sorghum.*	Neuroreceptor interaction, Vasoconstriction, Uterus contraction.

Synthetic derivatives of alkaloids morphine and lysergic acid (from *Claviceps purpurea*) produce heroin and LSD, respectively.

Alkaloid patterns usually vary between the site of synthesis and the sites of accumulation, since a number of secondary substitutions may take place in the latter tissues. Alternatively, transport may be selective, distributing differing cocktails. In addition, the alkaloid profiles of seeds and seedlings often differ from those of the mature plant. Both patterns and concentrations usually change during the development of plants and the annual cycle. In general, alkaloid levels are markedly reduced in senescing tissues, so that shed leaves are often nearly alkaloid-free (Waller & Nowacki, 1978). In some plants, alkaloid concentrations may even fluctuate in a diurnal cycle (Table .2.). Alkaloid formation and storage may be influenced by environmental stress, such as wounding or infection (Waller & Nowacki, 1978)

Table 2 Diurnal cycle of Alkaloid formation

Alkaloids	**Time of maximum alkaloid production**	**Source plant**
Quinolizidines	Noon- early evening	Lupinus, Cytisus, Baptisia, Laburnum
Tropanes	Evening, midnight	Atropa
Nicotine	midnight	Nicotiana
Morphine	noon	Papaver

2.2. Extraction and Test for Presence of Alkaloids

In general, the alkaloids may be extracted by any of the following three well-defined and widely accepted processes, viz. (a) Soxhlet Extraction Process (b) Stas-Otto Process, and (c) Kippenberger's Process. The common methods for the separation and purification of alkaloids are silica gel column chromatography, thin-layer chromatography, Sephadex LH-20, and recrystallization which have the disadvantages of a long cycle, complex steps, high solvent consumption, etc.

The following tests are adopted for testing the presence of alkaloids in the sample

2.2.1. Dragendorff's reagent test:

Add 1 mL of Dragendorff"s reagent to 2 mL of extract. The formation of an orange-red precipitate indicates the presence of alkaloids.

2.2.2. Mayer's test.

Add a few drops of Mayer's reagent to 1 mL of extract. The formation of a yellowish or white precipitate indicates the presence of alkaloids.

(Mayer's reagent is freshly prepared by dissolving a mixture of mercuric chloride (1.36 g) and potassium iodide (5.00 g) in water (100.0 ml).

2.3. Symptoms of Alkaloid poisoning

The general symptoms of alkaloid poisoning (Kamarul Zaman Munirah-Adibah and Mohamad Azzeme Azzreena, 2019) include nausea, fatigue, numbness or tingling sensation in the fingers, and a strong dislike for the leafy green that is currently being consumed. Confusion or memory loss, constipation, difficulty in urination, drowsiness, dryness of mouth, nose, throat, or skin, and unusual excitement, nervousness, restlessness, or irritability (may be more likely to occur in the elderly, who are usually more sensitive than younger adults to the effects of alkaloids, particularly belladonna alkaloids) are the common symptoms of alkaloid poisoning. Because there are different types of alkaloids, the possibility of experiencing a different range of symptoms is possible.

2.4. Ergot Alkaloids

The fungi known as Ergot fungi (genus: *Claviceps*) produce alkaloids which are referred to as Ergot alkaloids. In ancient times, the effects of ergot alkaloids were seen and referred to as ergotism, which is poisoning by ergot alkaloids. Incidents of toxicity induced by *Claviceps purpurea* ingestion have been known in Europe since the sixteenth century. The most severe effects resulting from ergot-contaminated rye are described in the medieval literature as St. Anthony's Fire or Holy Fire, in which intense pain resulting from vasoconstriction and subsequent gangrene with loss of extremities or entire limbs was reported. Other symptoms of ergot alkaloid intoxication include a burning sensation in the skin, hallucinations, tremors, insomnia, excessive salivation, vomiting, spontaneous abortion, agalactia, and even death (Belser-Ehrlich et al., 2012).

Although these incidents of ergot poisoning have become rare due to the use of different farming techniques in cereal grain production, the development of crop varieties resistant to ergot infection, change in the primary type of grain consumed, and cereal cleaning efforts at mills; multiple outbreaks involving ergot food contamination were reported in the twentieth century. Human ergot poisoning occurred in Russia in 1926–27 (Kent and Evers, 1994), in France in 1951 (Fuller, 1968), in India in 1956–57 and 1975 (Bhat et al., 1976; Krishnamachari and Bhat, 1976), and in Ethiopia in 1977–78 and 2001 (Demeke et al., 1979; Urga et al., 2002).

Ergot alkaloids are produced by the fungal species of the genus *Claviceps* typically found in the tropical areas affecting crops grains in cereals like rey, wheat, pearl millet (by *Claviceps purpurea)*, sorghum (by *Claviceps Africana*), and grasses like buffel grass (by *Claviceps fusiformis*), and dallis grass (by *Claviceps paspali*). *C. purpurea* attracts much attention as it commonly affects crossing species such as rye, wheat, barley, and triticale grains and produces alkaloids in these that can cause ergotism in humans and animals. Crop infection involves fungal parasitization of florets in the inflorescence at the time of flowering, and replacement of seeds with masses of fungal tissues or sclerotia which contain up to 1.2% weight of toxic alkaloids (Burrows and Tyr, 2001). The sclerotia are inadvertently harvested with cereal crops, which results in ergot alkaloid contamination of food products and ergotism if ingested.

Ergotism is now primarily a concern in animal feeds, particularly those intended for cattle, horses, sheep, pigs, and chickens (Bennett and Klich, 2003). Ergots are also found in the pastures on which animals feed. Intoxication with ergot

alkaloids results in the syndromes of ergotism, which are characterized by burning sensations in the limbs, hallucinations, irrational behavior, convulsions, vasoconstriction, and even death. Adverse reactions of ergot alkaloids are generally gastrointestinal and are limited to nausea and vomiting (1–10%), muscle weakness, fatigue, tightness in the chest, and diarrhea. A majority of ergot alkaloids are substrates of CYP3A4 metabolism and interact with other medicines metabolized by liver enzymes (including protease inhibitors, some macrolide antibiotics, quinolones, azole antifungals, etc.). Concomitant use with these strong CYP inhibitors is contraindicated due to possible acute ergot toxicity. If poisoning occurs, it leads to vasoconstriction, and gangrenous effects are seen.

Most naturally occurring ergot alkaloids have been isolated from either fungal sclerotia of *Claviceps purpurea* contaminating small grains or grasses or from the tall fescue host infected with *Neotyphodium coenophialum* (Burrows and Tyrl, 2001; Cheeke, 1998). Ergot sclerotia, which are also called "ergot" or "ergot bodies consist of interwoven filamentous fungal hyphae or mycelia, along with the hardened exudate or "honeydew" and contain ergot alkaloids classified primarily as either ergoline alkaloids (e.g., lysergic acid, lysergol, lysergic acid amide, and ergonovine) or as ergopeptine alkaloids (e.g., ergotamine, ergocristine, ergosine, ergocryptine, ergocornine and ergovaline) (Evans et al., 2004). Various ergoline alkaloids and ergovaline are the major ergot alkaloids produced by the intercellular endophytic mycelia of *Neotyphodium coenophialum* (Evans et al., 2004). Ergopeptine alkaloids are potent D2-dopamine receptor agonists that decrease prolactin secretion by the anterior pituitary (Evans et al., 2004), and the most sensitive indicator of ergopeptine alkaloid exposure in animals is hypoprolactinemia. Late-gestational mares exposed to ergopeptine alkaloids from either ergot or fescue endophyte almost always exhibit agalactia, plus varying degrees of prolonged gestation, dystocia, retained fetal membranes, and foal dysmaturity (Evans et al., 2004). These alkaloids can modulate several receptors of neurotransmitters, such as dopamine, serotonin, and norepinephrine. As a consequence, the pharmacological action of ergot alkaloids is rather broad, ranging from vasoconstriction and uterus contraction to hallucinations. Therefore, multiple manifestations of ergotism exist i. e. convulsive ergotism, gangrenous ergotism, enteroergotism, and hyperthermic ergotism. Ergot alkaloids are known to affect the nervous system and to be vasoconstrictors. These effects are largely due to their agonist, partial agonist, and/or antagonistic effects at biogenic amine receptor sites. Ergot alkaloids increase uterine motility, have complex effects on cardiovascular function, and suppress prolactin secretion. The ergot alkaloids are highly toxic and can result in nausea, vomiting, decreased circulation, rapid and weak pulse, and coma.

Nevertheless, ergot alkaloids affect a broad range of physiological features including neurotransmission and circulation, and are medically exploited in interventions such as the treatment of migraines, induction of childbirth, and the control of postpartum bleeding. Specific alkaloids are included in medicines for migraine headaches, hypertension, sexual disorders, or Parkinson's disease. Due to their similarity to noradrenaline, dopamine, and serotonin, they are peripheral α_1-adrenergic inhibitors (except for ergometrine), and may be used as bleeding inhibitors, especially in gynecology (Smakosz et.al, 2021) as drugs shrinking the uterus after childbirth, in postpartum hemorrhage, or after placental expulsion. Their administration induces a long tonic contraction of the uterus. Ergotamine tartrate is also included in complex drugs for tranquilizing and analgesic applications. Ergotamine and ergotoxine are used for the production of 9,10-dihydrogenated derivatives, which are stronger muscle relaxants than the starting alkaloids. Dihydroergotamine inhibits α-adrenergic and serotonin receptors. It is used for the treatment of migraine-type headaches (often with caffeine) and for orthostatic hypotension. Since ergot alkaloids are dopamine receptor agonists, some of them (bromocriptine, cabergoline) are used as anti-Parkinson agents also. However, due to the risk of fibrotic incidents, they are not regarded as frontline medicines. Dihydrogenated derivatives of ergotoxine and ergocristine relax the peripheral vessels leading to hypotension. In addition, ergotoxine is included in geriatric treatments of stroke patients and those with cognitive impairment. Dihydroergocristine is an ingredient of hypotensive drugs and is used for the treatment of impaired peripheral circulation, often together with flavonoids. However, the hydrogenated forms do not exhibit smooth muscle-stimulating properties. A semisynthetic derivative of lysergic acid, LSD (lysergic acid diethylamide), was synthesized by Dr. Albert Hofmann from ergot in 1938 and accidentally was shown to have hallucinogenic effects. Later, it was considered as a psychiatric drug applicable to mind control. As a psychedelic drug, the compound induced altered thinking, visual effects, synesthesia, and spiritual experiences. It also induced psychiatric reactions, such as paranoia or delusions, and was prohibited in the early 1960s.

Over 80 different ergot alkaloids have been isolated, mainly from various *Claviceps* species. Ergot sclerotia contain about 0.15%-0.5% alkaloids, with the medicinally useful compounds separated into 2 classes i. e the water-soluble amino alcohol derivatives (about 20% of the total alkaloid mixture) and the water-insoluble peptide derivatives (up to 80% of the total alkaloids). The nomenclature of this group of alkaloids is quite complex, with the naturally occurring compounds commonly being assigned a trivial name by their discoverer(s). Systematic names tend to be used only for semisynthetic derivatives or to ascribe an exact chemical description of the molecule. Many of the trivial names of these alkaloids are derived from the botanical names of the host plant or producer, for example, ergosecaline (from *Secale spp*), while others are a product of special circumstances of their discovery, such as ergokryptine, an alkaloid that

remained elusive (*cryptic*; *kryptos* [Gr]) and obscured for many years. Ergobasine was so named because of its basic properties, while lysergic acid received its name because it was a product of the lysis of various ergot alkaloids. Some alkaloids bear nomenclature that reflects specific pharmacological properties, such as ergometrine for its actions on the uterus (endometrium uteri). Still other alkaloids have been named to reflect some personal attachment, such as ergocristine for Cristine Stoll, daughter of the scientist Arthur Stoll who isolated ergotamine and later was President of Sandoz AG in Basel, Switzerland. There have been 3 forms of systematic nomenclature reflecting different chemistry that are employed for the alkaloids of this group. The first utilizes a system found in chemical abstracts that employs ergoline as the name for the tetracyclic system present in most ergot alkaloids and ergotaman for the heptacyclic system occurring in most of the peptide alkaloids. The second type employs the name ergopeptine, and is used only for the full heptacyclic peptide alkaloid system. The final type utilizes the IUPAC system, and as such is the most rigorous and rational, albeit complicated. In this variation, the ergoline system is designated as 7-methyl-4,6,6a,7,8,9,10,10a-octahydro-indolo[4,3-f,g]quinoline. Ergot alkaloids contain several centers of chirality of varying configuration, but the R- chirality at C-5 is constant and non-variable, reflecting the derivation of these alkaloids from L-tryptophan (the amino acid precursor of the indole ring) as well as the C-4, C-5, and N-6 atoms. The medicinally useful ergot alkaloids are all C-8 amide/peptide derivatives of (+)-lysergic acid, a compound bearing the R-chirality at C-8.

2.5. Classification of ergot alkaloids (Derivatives & constituents)

Ergot alkaloids are nitrogen-containing natural products belonging to indole alkaloids. The best known producer are fungi of the phylum *Ascomycota*, e.g., *Claviceps*, *Epichloë*, *Penicillium* and *Aspergillus* species among which *Claviceps* is the most important fungal genera producing ergot sclerotia in the infected grains of the cereals. According to their structures, ergot alkaloids can be divided into three groups: lysergic acid amides, peptides (ergopeptines) and clavines. All of them share the first biosynthetic steps, which lead to the formation of the tetracyclic ergoline ring system (except the simplest, tricyclic compound: chanoclavine). Different modifications on the ergoline ring by specific enzymes result in an abundance of bioactive natural products, which are used as pharmaceutical drugs or precursors thereof. From the 1950s through to recent years, most of the biosynthetic pathways have been elucidated (Gerhard et.al,2014).

2.5.1. lysergic acid amides or Amine alkaloids (like Ergonovine, 6-methyl ergoline, lysergic acid, lysergic acid diethylamide (LSD), Ergometrine, and methysergide).

Amidation of the C-8 carboxy-group of lysergic acid results in the formation of 2 types of compounds i.e the simple nonpeptidic amides that bear relatively short carbon chains and the peptidic amides that commonly exist as tripeptides. Common 5R,8R-nonpeptidic amides found in ergot include ergonovine (ergometrine, ergobasine), lysergic acid 2-hydroxyethylamide, lysergic acid amide (ergine), and paspalic acid. Lysergic acid-derived amides are highly active pharmacologically, and ergonovine and its semisynthetic derivatives methylergonovine and methysergide are used medicinally. As a consequence of the adjacency of the C-8 chiral carbon of lysergic acid to a carbonyl, the configuration at this center may be changed as a result of heat- or base-catalyzed enolization (particularly in polar solvents) proceeding through a symmetric intermediate to afford the pharmacologically-inactive epimeric (+)-isolysergic acid and its derivatives. In the bioactive lysergic acid derivatives, the amide group is present in the 8-equatorial position, while in the inactive iso-forms, the group is axial. The lysergic acid derivatives commonly end in the suffix "-ine", while their epimeric counterparts (the isolysergic acid derivatives) are assigned the suffix "inine."

Therapeutical Significance of Lysergic Acid Amide Alkaloids Ergonovine (Ergometrine, Ergobasine)

Ergonovine was discovered in 4 different laboratories almost simultaneously, with 4 different names (ergometrine, ergotocine, ergosterine, and ergobasine) being assigned to the alkaloid. The names ergometrine and ergobasine have persisted in Europe, while ergonovine was adopted in the United States. The structure of ergonovine was elucidated in 1935 when it was shown that hydrolysis of the alkaloid afforded (+)-lysergic acid and (+)-2-aminopropanol. Ergonovine was introduced into world commerce in 1936 and first synthesized in 1938 via amidation of (+)-lysergic acid with (+)-2-aminopropanol. This represented the first synthesis of an ergot alkaloid. Ergonovine is a light-sensitive, water - soluble compound that is commercially marketed as its water- soluble maleate salt. The compound is presently obtained from 3 different sources i.e isolation from field ergot as a minor byproduct, isolation from fermentation broth, and synthesis from (+)-lysergic acid and L-(+)-2-aminopropanol using variable coupling reagents.

Ergonovine is a selective and moderately potent tryptaminergic receptor antagonist in various smooth muscles, being only a partially agonistic or antagonistic at tryptaminergic receptors in the central nervous system. In blood vessels the alkaloid is only weakly antagonistic of dopaminergic receptors and partially agonistic of α-adrenergic receptors. The most pronounced effect of ergonovine is one of direct stimulation of the uterine smooth musculature, resulting in increased muscular tone and an enhancement of the rate and force of rhythmical contractions. This stimulant effect seems to be most closely associated with agonist or partial agonist effects at 5-HT2 receptors. Food and Drug

Administration (FDA) approved indications are for the treatment and prophylaxis of abortion complicated by delayed and/or excessive hemorrhage, and in the treatment and prophylaxis of postpartum hemorrhage due to uterine atony or subinvolution. The drug is administered after the expulsion of the placenta because prior administration may result in placental entrapment. Ergonovine maleate is typically administered intramuscularly or intravenously, with the intravenous route being reserved for emergency use. The drug is contraindicated for use in the induction of labor because it may jeopardize placental blood flow and fetal oxygen supply, and in cases of threatened spontaneous abortion, or in pregnancy (FDA Pregnancy Category X). Adverse reactions are generally gastrointestinal and are limited to nausea and vomiting (1%-10%). Ergonovine derivatives are substrates of CYP3A4 metabolism, and as such are contraindicated for concomitant use with compounds established as strong CYP3A4 inhibitors (including protease inhibitors, some macrolide antibiotics, quinolones, azole antifungals) because of the production of acute ergot toxicity. Finally, the drug has an off-label indication for use as a diagnostic test for Prinzmetal's angina (variant angina, vasospastic angina) in which it has been used successfully for non-invasive diagnosis of coronary vasospasm as a cause of chest pain. The drug is marketed as *Ergotrate* (Eli Lilly and Co., Indianapolis) and is supplied as an intravenous solution (0.2 mg/mL) and oral tablets (0.2 mg).

2.5.2. Peptide alkaloids (like ergotamine, alpha – ergocryptine, and bromocriptine)

The pharmacological effects of the ergot alkaloids as a group tend to be complex and variable, with the net result of their actions being a sum of the effects of partial agonism or antagonism at adrenergic, dopaminergic, and serotonergic receptors. Variables relating to these effects are influenced by the agent, dosage, species, tissue, physiological, and endocrinological state, and experimental conditions.

At much lower concentrations, the alkaloids found in ergot sclerotia and industrially produced synthetic alkaloids are used for therapeutic purposes in human medicine, such as for stimulation of uterine contraction (oxytocic effect) and for relief of migraine headaches. Recently it has been suggested that manipulation of fungal genomes may generate strains that produce therapeutic alkaloids with applications for medicine and agriculture (Panaccione et al., 2012).

Therapeutical Significance of Peptide Alkaloids Ergotamine

The isolation and naming of ergotamine by Stoll occurred in 1925 but the complete elucidation of structure was not achieved until 1951, with synthesis following some 10 years later. Current sources of ergotamine include the isolation from field ergot and fermentation broth, as well as synthesis via coupling of (+)-lysergic acid with the appropriate synthetic peptide moiety. Ergotamine was introduced into world commerce in 1921, and is currently marketed as its water- soluble tartrate salt.

Ergotamine is a partial agonist at various tryptaminergic receptors (including the serotonin receptor [5-HT2]) and at various α-adrenergic receptors in blood vessels and various smooth muscles. It is likely that the major activity of ergotamine and related alkaloids is one of agonism at the 5-HT1B/1D receptors, just as with the “triptan” antimigraine compounds. FDA-labelled indications for ergotamine tartrate are in the abortion or prevention of vascular headaches, such as migraine, migraine variant, cluster headache, and histaminic cephalalgia. The alkaloid is considered useful in the therapy of moderate to severe migraine attacks in which it acts to constrict intracranial blood vessels and inhibit the development of neurogenic inflammation in the trigeminovascular system. Both venous and arterial constriction occur at therapeutic dosage. Ergotamine is most effective when administered early in the migraine attack, preferably at the first indication of an impending event. Dosage requirements to achieve an effective therapeutic sub-nauseating endpoint should be established and adhered to for future attacks. Prolonged administration or excessive dosage may result in severe peripheral vasoconstriction, ergotism, gangrene, or various fibrotic complications (cardiac valvular, retroperitoneal, pleuropulmonary). Ergotamine derivatives are contraindicated in patients with peripheral vascular disease, hepatic or renal disease, coronary artery disease, hypertension, sepsis, or pregnancy (FDA Pregnancy Category X). Ergotamine derivatives are substrates of CYP3A4 metabolism and as such are contraindicated for concomitant use with medications established as strong CYP3A4 inhibitors (protease inhibitors, some macrolide antibiotics, azole antifungals) because of the production of acute ergot toxicity.

2.5.3. Clavine Ergot Alkaloids

The clavines are substituted 6,8-dimethylergolines but include a few members, such as the chanoclavines, that possess a 6,7-seco D-ring. Although at least 35 alkaloids of this type have been isolated and characterized, none of the group is used medicinally.

2.6. Commercial cultivation of Ergot Crop for pharmaceutical Alkaloid production

The fungal genus *Claviceps* mainly involved in the production of ergor alkaloid is a group of phytopathogenic ascomycetes that is composed of approximately 36 different species of filamentous fungi. These species are known to parasitize over 600 monocotyledonous plants of the families *Poaceae, Juncaceae* and *Cyperaceae*, including forage grasses, corn, wheat, barley, oats, millet, sorghum, rice, and rye. Ergot was first recognized as a fungus in 1711 but its lifecycle was not described in the form of a general outline until 1853 by Tulasne. The term ergot or *Secale cornutum* derives from the French word *argot* (a spur) and represents the dark brown, horn-shaped pegs that project from ripening ears of rye in place of rye grains. These tuberous projections are collected before and during harvesting or are separated from the threshed rye. In a histologic sense, these bodies consist of compactly interwoven hyphae of the filamentous fungus *Claviceps purpurea* but biologically these compact grains are designated as sclerotia, the form in which the fungus passes the winter.

The parasitic life cycle of the ergot fungi begins in the spring, with wind-borne ascopores landing on inflorescences of the susceptible host plants, where these ascospores germinate to produce germ-tube and hyphae. The hyphae invade and colonize the ovary, producing masses of anamorphic spores that are exuded into a syrupy fluid (honeydew). Insect vectors, rain-splash, or head-to-head contact transfer this honeydew to other blooming florets, allowing the spread of the ergot fungi in a field. When the sclerotia begin to form, production of honeydew and conidia cease, and the sclerotia mature in about 5 weeks. The number and size of sclerotia produced on each spike of cereal by *C. purpurea* varies according to grain, with rye and pearl-millet usually bearing a considerable number, while wheat has relatively few. The sclerotia are considered as the early stage of sexual differentiation of *Claviceps*. In autumn, the ripe pigmented sclerotium leaves the spike and falls to the ground, ultimately producing asci and non-septate ascospores, thereby completing the cycle. These ergot sclerotia contains specific alkaloids known as ergot alkaloids which has pharmaceutical values.

The industrial production of the ergot alkaloids began in 1918 when Arthur Stoll patented the isolation of ergotamine tartrate, which was subsequently marketed by Sandoz in 1921. Sandoz dominated the world industrial market in ergot alkaloid production up until the 1950s, when other competitors begin to appear. Today Novartis (the successor to Sandoz) still retains leadership in the world production of ergot alkaloids. Some other major producers of these alkaloids market their products as bulk pharmaceutical chemicals, including: Boehringer Ingelheim (Germany), Galena (Czech Republic), Gedeon Richter (Hungary), Lek (Slovenia), and Poli (Italy). Others active in the marketplace include Eli Lilly and Farmitalia.

Annual world production of ergot alkaloids has been estimated at 5,000-8,000 kg of all ergopeptines (peptide ergot alkaloids) and 10,000-15,000 kg of lysergic acid, the latter being mainly used in the manufacture of semisynthetic derivatives. The greater part of this production occurs as a result of fermentations (around 60%) while field cultivation of triticale (a hybrid of wheat and rye) accounts for the balance. This is because the artificial cultivation of ergot sclerotia on host crop plant is lacking as a business module.

The bottleneck in the artificial cultivation of ergot sclerotia lies in the fact that an initiation and occurrence of ergot is greatly influenced by the host-pathogen-environmental interaction where the environmental factor plays a most important role (Workneh and Rush, 2006). Even if the susceptible ergot crop host and invasive pathogen is available, in the absence of suitable environment for disease initiation and occurrence, the ergot will not develop. The most necessary environmental factors for ergot infection are foggy drizzling rains for more than 2-3 days at the time of inflorescence of the crop. The availability of sufficient amount of Claviceps inoculum for infection and spread is the second most important item for sclerotial percentage. Under natural field conditions both these factors are seldomly coincide to produce all the inflorescences and its grains in to ergot grains. Therefore, artificial or commercial cultivation of ergot crop in controlled conditions, particularly in polyhouses is proposed, where the necessary climatic conditions (temp 26-28^{0}C, with foggy and drizzling weather) for ergot infection can be created in a polyhouse cultivated crop during inflorescence for a required period and the inflorescence is spray inoculated with the conidial culture of the *claviceps* fungi during this period which will lead to ovary infection and conversion of all the grains into ergot grain to harvest the ergot alkaloid. When all the inflorescences and its grains are converted in to ergot sclerotia, this will boost the natural ergot alkaloids production. In these polyhouses ergot susceptible crops can be cultivated as multi-model crops susceptible to ergot infection, or more than one generation of susceptible crop can be taken to maximise the ergot sclerotia production

3. Conclusion

Ergot alkaloids are specific pharmaceutical alkaloids used to treat certain ailments like migraines, induction of childbirth, and the control of postpartum bleeding in humans.

The ergot alkaloids are the natural product of fungal infection of the genus *Claviceps* in cereal crops and the natural occurrence of ergot grains in the infected cereal crops is dependent on the environmental factors conducive to ergot sclerotia development. Under natural infection of *Claviceps* fungi in cereal crops, the ergot sclerotia per cent varies from 1.2 to 3.3 which hampers the yield or recovery of natural ergot alkaloids.

Ergot sclerotia contain about 0.15% to 0.5% alkaloids, with medicinally useful compounds. Annual world production of ergot alkaloids has been estimated at 5,000-8,000 kg of all ergopeptines (peptide ergot alkaloids) and 10,000-15,000 kg of lysergic acid, the latter being mainly used in the manufacture of semisynthetic derivatives. The greater part of this production occurs as a result of fermentation (around 60%) while field cultivation of triticale (a hybrid of wheat and rye) accounts for the balance. This is because the artificial cultivation of ergot sclerotia on a host crop plant is lacking as a business module. Due to the low recovery of ergot grains and ergot alkaloids under natural crop production conditions, commercial cultivation module for ergot grains is proposed

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