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Ergot Alkaloids: A Review on Therapeutic Applications

Niti Sharma[1*], Vinay K. Sharma[1], Hemanth Kumar Manikyam[1] and Acharya Bal Krishna[1,2]

[1]Patanjali Natural Coloroma Pvt. Ltd, Haridwar, Uttarakhand - 249404, India.
[2]University of Patanjali, Haridwar, Uttarakhand - 249402, India.

Authors' contributions

This work was carried out in collaboration between all authors. Authors NS and VKS designed the study, wrote the first draft of the manuscript. Authors ABK and HKM supervised the study. All authors read and approved the final manuscript.

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Review Article

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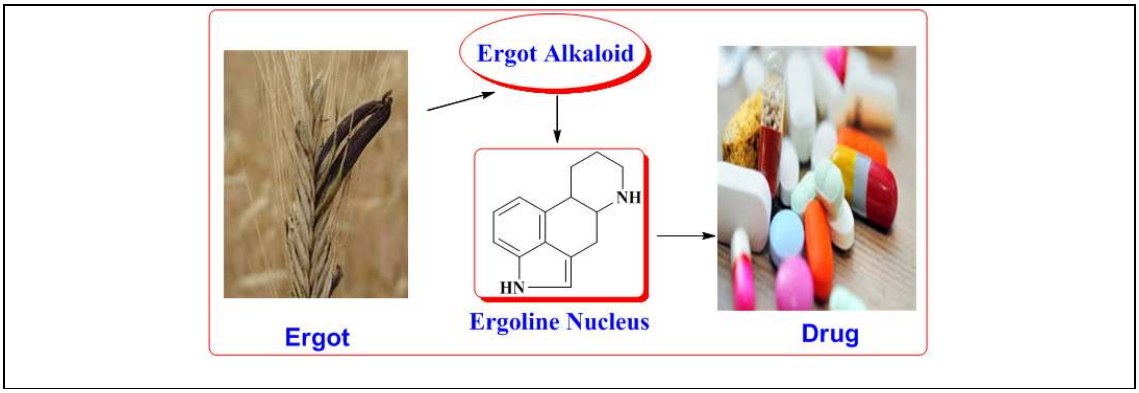
ABSTRACT

Ergot of Rye is a plant disease caused by the fungus *Claviceps purpurea* which infects the grains of cereals and grasses but it is being used for ages for its medicinal properties. All the naturally obtained ergot alkaloids contain tetracyclic ergoline ring system, which makes them structurally similar with other neurotransmitters such as noradrenaline, dopamine or serotonin. Due to this structure homology these alkaloids can be used for the treatment of neuro related conditions like migraine, Parkinson's disease etc. For hundreds of years, it has been used in *obsctrics and gynecology* as an uterotonics. Ergot drugs have important role in treating prolactinomas and type II Diabetes. Their role in cancer treatment has also been established. These drugs constitute an important group of compounds called "Smart drugs" used to improve cognitive function and memory and other age related brain disorders. Structural resemblance with various neurotransmitters allows them to interact with a number of receptors which makes them work on different target thus designing new ergot based drugs with receptor subtype selectivity will be more effective.

**Corresponding author: E-mail: nitivinay@yahoo.co.in;*



Keywords: Ergot alkaloids; smart drugs; ureotonic; type II diabetes; migraine; Parkinson's disease; cancer.

1. INTRODUCTION

Ergot of Rye is a plant disease caused by the fungus *Claviceps purpurea* which infects the grains of cereals and grasses. "Ergot" is the French word for "spur" named after the similarity between sclerotia of fungus and spurs on rooster legs. In Ayurveda it is known as "Annaamaya", or "Sraavikaa" and in Unnani it is called "Agrat". Briefly, the life cycle of *Claviceps purpurea* starts during spring season when the windborne ascospores infects the grain and initiates pathogenesis. The fungal sclerotia develop to produce mushroom-shaped stroma, which release spores. When a mature sclerotium drops to the ground, the fungus remains quiescent until next spring and the process continues [1]. The ergot symptoms are manifested during kernel formation, when ergot bodies are formed in place of kernels. Interestingly, the fungus does not infect any other plant part except the ovary, which is replaced by purplish-black sclerotium, commonly referred to as an ergot. The ergot sclerotium contains high concentrations of the alkaloid ergotamine and several other peptide alkaloids of the ergotamine group (including ergosine and ergocristine). It is possible that ergot infected grasses since farming began but it was first documented only around 600 BC. Chronic ergot poisoning (ergotism) was prevalent in Europe during the middle ages due to the consumption of bread made from contaminated rye. The disease was often referred to as *"Ignis sacer"*, meaning "Holy Fire", or "St. Anthony's Fire" [2-5]. The infection resulted in symptoms such as hallucinations, severe gastrointestinal upset with painful feelings of intense heat in the limbs due to severe restriction of blood flow with concomitant loss of limbs.

Regardless of serious safety concerns, ergot has been used in various systems of medicine (Ayurvedic, Unnani and Western) for hundreds of years. Ergot contains no lysergic acid diethylamide (LSD) but rather ergotamine, which is used to synthesize lysergic acid, the precursor for LSD. Ergot alkaloids are dopamine agonists which activate dopamine receptors (in the basal ganglia and other parts of the brain involved in motor function) and a prolactin inhibitor. Ergot is a strong vasoconstrictor and thus helps to reduce bleeding by narrowing of the blood vessels. In both Ayurvedic and Unnani system of medicine as in western herbal, ergot is employed to stimulate uterine contraction in the final stages of labor. It is also employed though rarely for arresting uterine hemorrhage. Ergot was perhaps first used in medicine as an oxytocic drug, to promote uterine contraction during child birth. They have been used for treating migraine headaches [6] since 1883 and also in treating Parkinson's disease, restless leg syndrome and other purposes. Ergot-derived drugs commonly used to treat Parkinson's disease include bromocriptine (Parlodel), pergolide (Permax), and lisuride (Revanil) [7]. Presently lysergic acid-derived drugs are used to treat Alzheimer's disease, dementia and hyperprolactinemia [8-10]. One of the most recent studies indicates role of ergots (bromocriptine) in treating Type II Diabetes [11]. In 2009, bromocriptine mesylate was approved by the FDA for treatment of type II diabetes.

Although ergotamine and ergometrine are the two naturally obtained ergot alkaloids of medical importance a number of new compounds have been synthesized by chemical modification of existing structures [12]. This article thus aims to

cover the role of different ergot alkaloids in the field of medicine.

2. BIOSYNTHESIS

The steps involved in biosynthesis of ergot ring formation are portrayed in Fig. 1 as described earlier [13-17]. Limited information is available on most of the enzymes involved in biosynthesis of ergot as they are instable in cell free extract, except for Dimethylallyltryptophan (DMAT) synthase. It catalyzes the condensation of L-tryptophan with dimethylallylpyrophosphate to yield dimethylallyltryptophan. All of the enzymatic steps after dimethylallyltryptophan formation ultimately lead to ring formation in ergoline. The DMAT-forming reaction is the committed step in biosynthetic pathway in ergot fungi and provides the carbon skeleton of the ergoline ring system [18]. The following steps are catalyzed by a methyltransferase, followed by decarboxylation and closure of ring C in Chanovlavine I by Chanoclavine-I cyclase. In the next step Agroclavine-17-monooxygenase converts Agroclavine to Elymoclavine [19] which in turn is converted to Paspalic acid by Elymoclavine-17-monooxygenase [20,21]. Both these enzymes are NADPH and dependent and molecular oxygen thus can be considered as Cytochrome P450-monooxygenase [22]. However, the presence of Elymoclavine-17-monooxygenase was not detected in a *Claviceps* strain that produces Agroclavine and Elymoclavine but in a strain that produces D-lysergic acid amides and peptides [20,21]. This shows that the clavine-producing *Claviceps* strain is deficient in the enzyme that converts Elymoclavine to Paspalic acid which isomerizes to form D-lysergic acid in the next step.

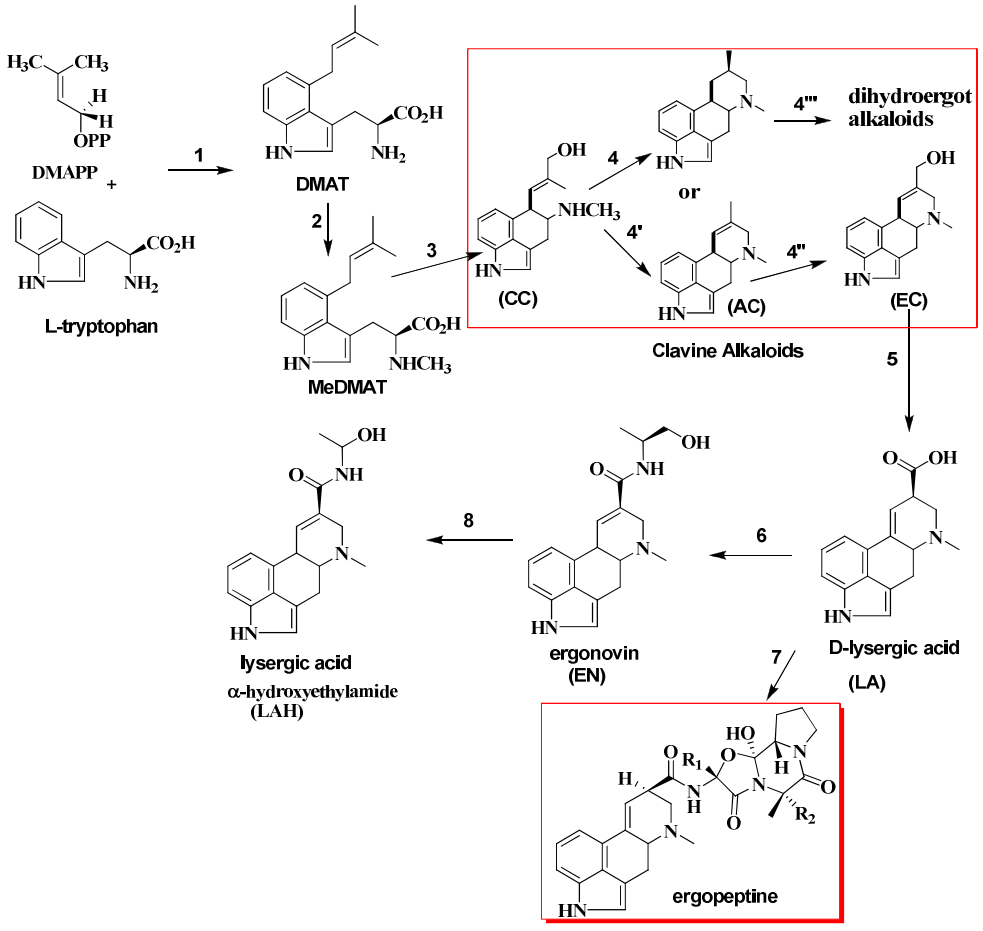


Fig. 1. Biosynthetic pathway of ergot alkaloids

3. CHEMISTRY OF ERGOT ALKALOIDS

The nucleus common to all ergot alkaloids (lysergic acid) was isolated and characterized in 1934 by Jacobs and Craig of the Rockefeller Institute of New York [23]. All the naturally obtained ergot alkaloids contain tetracyclic ergoline ring system, which makes them structurally similar with other neurotransmitters such as noradrenaline, dopamine or serotonin (Fig. 2). This structure homology of ergot alkaloids with these neurotransmitters implies that these alkaloids can be used for the treatment of neuro related conditions like migraine, Parkinson's disease etc.

Structurally the most common features of these alkaloids are methylation at 6th position of nitrogen and substitution at 8th position of carbon in the tetracyclic ring system. Interestingly, due to asymmetric carbon atom at 8th position, the 10-ergolens produce two epimers; ergolenes and isoergolenes [24-27]. Based on the substitution at 8th position these alkaloids can be categorized into four groups as (i) **Clavine alkaloids**: the hydroxy and dehydro derivatives of 6,8-dimethylergolenes and the corresponding ergolines. They also include the chanoclavines with an open D-ring between N-6 and C-7. (ii) **Lysergic acid derivatives**: These derivatives of lysergic acid are amides in which the amidic moiety is formed by a small peptide or an alkylamide. Nonpeptide amides of lysergic acids isolated from ergot fungi are ergometrine, lysergic acid 2-hydroxyethylamide, lysergic acid amide, and paspalic acid [24-26] (iii) **Ergopeptine alkaloids**: the unique feature of these alkaloids is the cyclic part which is formed by the reaction of an *a*-hydroxy-amino acid adjacent to lysergic acid with a carboxyl group of proline. In addition these ergot alkaloids are composed of lysergic acid and a tripeptide moiety. This tripeptide moiety of ergopeptines contains various amino acids such as L-alanine, L-phenylalanine, L-valine, L-leucine, and L-isoleucine, as well as 2-aminobutyric acid. The compounds usually formed by these amino acids are ergotamine, ergotoxine, ergoxine, and ergoannines [24,26] (iv) **Ergopeptam alkaloids**: have structure similar to ergopeptines however the major difference between them is the proline moiety i.e. D-proline (ergopeptam) than L-proline (ergopeptines) and the tripeptide chain is a noncyclol lactam. The examples are ergotamams, ergoxams, ergotoxams, and ergoannams [24,26,27] (Fig. 3)

4. PHARMACOLOGY

4.1 Mode of Action of Ergot Alkaloids

The ergot alkaloids can modulate several receptors of neurotransmitters, such as, dopamine, serotonin and noradrenalin due to the structural similarity of their ergoline ring with biogenic amine receptors [28] (Fig. 2). Till now at least 14 different subtypes of 5-HT receptors [29], 5 subtypes of dopamine receptors [30-32] and at least 10 subtypes of adreno receptors [33-35] could be identified on the basis of information based on different biochemical studies. As they target different receptors their pharmacological action is quite broad. The pharmacologic relevance of ergots is determined by the relative affinity and efficacy of the individual agents for these receptor systems. Many ergot alkaloids

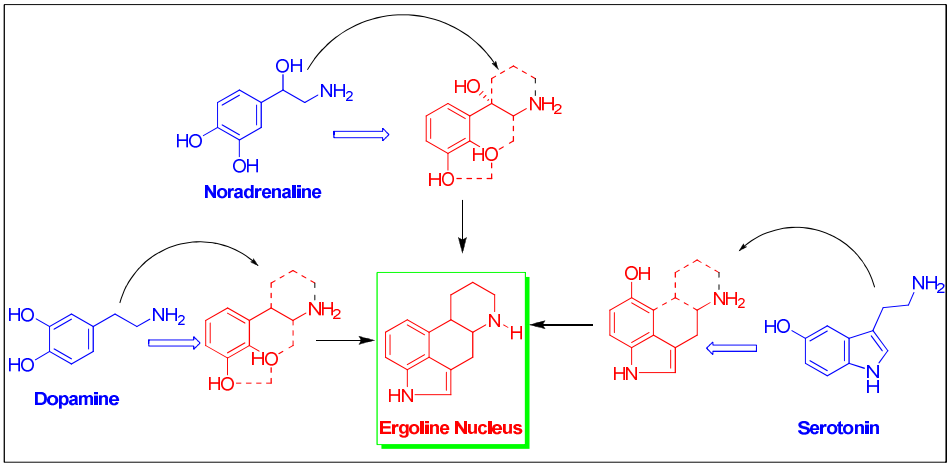


Fig. 2. Structural similarity of ergoline ring with biogenic amine receptors [22]

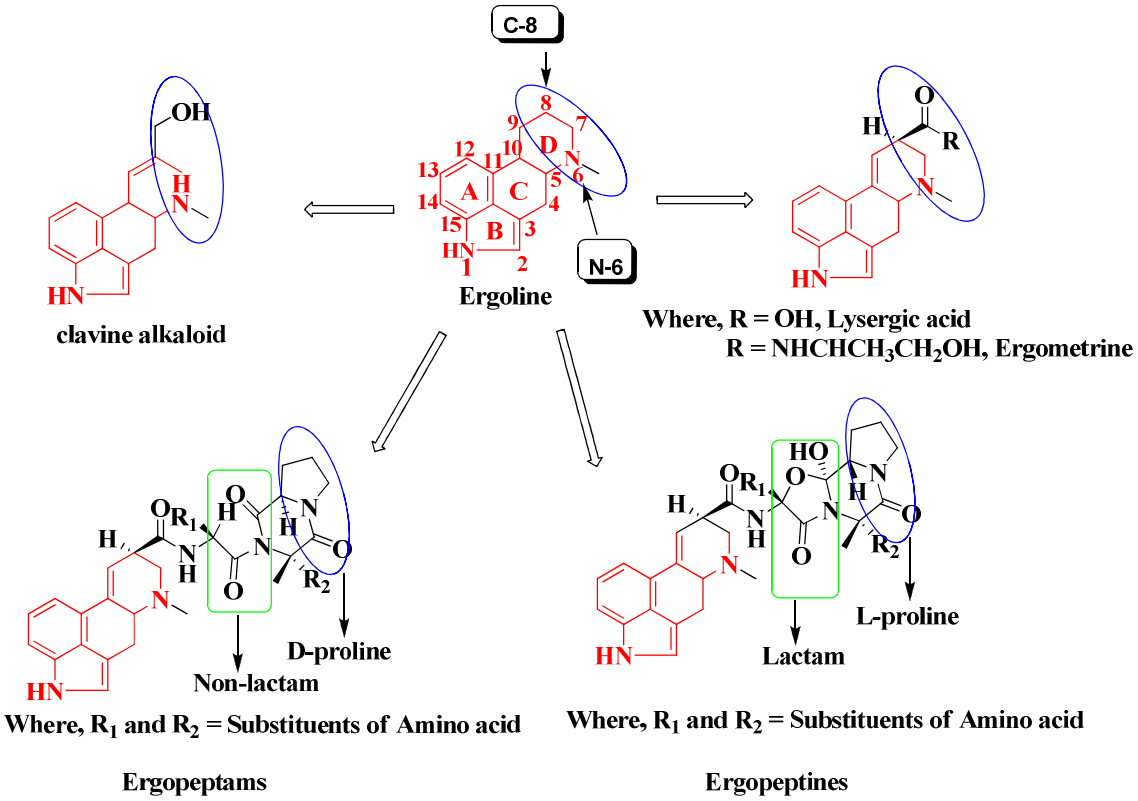


Fig. 3. Chemistry of ergot alkaloids

exhibit partial agonist activities and thus can display either stimulatory or inhibitory effect (Table 1). These receptors and their related neurotransmitters control cardiovascular function, endocrine activity, gastrointestinal tract motility, smooth muscle contraction, temperature regulation, and appetite. Owing to these properties a number of ergot based drugs have been approved by FDA (Table 2).

The important pharmaceutical actions of ergot alkaloid are vasoconstriction and hypoprolactinaemia. Vasoconstriction is linked with inhibition of D1-dopamine receptor and partial activation of the α1-adrenergic and serotonin receptors. Binding of ergot alkaloids to D2-dopamine receptors stimulates the release of dopamine which inhibits prolactin secretion from anterior pituitary [36-40]. Additionally, the binding affinities of ergopeptide and ergoline alkaloids as D2 receptors agonists resemble dopamine itself [41,42].

4.2 Effect on Organ Systems

Central Nervous System: some naturally occurring alkaloids are powerful hallucinogens such as lysergic acid diethylamide. Hofmann [43] (U.S. Patent, 1948) discovered the psychedelic properties of LSD in 1943. It was introduced commercially in 1947 by Sandoz Laboratories as a drug with various psychiatric uses. LSD mimics the effects of serotonin and acts on the human nervous system by rapidly crossing the blood-brain barrier and binding to most serotonin (5-HT) and all dopamine receptors subtypes, with the serotonin agonism (especially the activation of the 5-HT_{2A} receptor) [44-46]. Compounds like bromocriptine acts as D2 dopamine receptors agonist [47] and both agonist and antagonist at D1 receptor, at the level of the hypothalamus and corpus striatum. It directly stimulates ovarian dopamine receptors leading to menses in amenorrhiec women and directly activates lactotrope dopamine receptors, leading to inhibition of prolactin release [48].

Cardiovascular system: The effect of ergot alkaloids on vascular smooth muscles varies with individual agent and type of blood vessel. The natural amino acid alkaloid like ergotamine constricts most human blood vessels including both veins and arteries whereas

dihydroergotamine is more effective in capacitance rather than on resistance vesicles. Ergotamine also acts as α1-receptor antagonist and causes reversal of pressor effects of adrenaline [49]. Ergotamine, ergonovine and methysergide, all are non specific partial agonist of 5-HT2 vascular receptors [50]. These drugs stimulate serotonin, decrease inflammation, and reverse blood vessel dilation around the brain, thereby relieving the migraine or cluster headache symptoms [51].

Uterine smooth muscle: The stimulatory effect of ergot alkaloids on uterus which varies with hormonal status (pregnancy). In small doses, ergot preparations can bring about rhythmic contractions and relaxation of the uterus while at higher doses; it results in a strong and prolonged contraction [52]. As compared to other ergot alkaloids, Ergonovine is more selective and the agent of choice in obstetrics [53]. It directly stimulates uterine smooth muscle contraction resulting in increased muscular tone and enhanced contraction.

4.3 Ergot Derived Smart Drugs

Smart Drugs are nootropics drugs i.e. chemical substance that improves cognitive function and memory or facilitate learning. Three famous ergot derived smart drugs are Bromocriptine, Hydergine and Nicergoline. Few others are Ergoloid mesylates, co-dergocrine and dihydroergotoxine, all with a common ancestry.

4.4 Bromocriptine

Bromocriptine is an agonist of dopamine D2 [47,54] and various serotonin receptors. By reversing the glutamate GLT1 transporter it also inhibits the release of glutamate thus protecting the brain against ischaemia [55]. As bromocriptine has role in dopamine enrichment, it is also referred to as an aphrodisiac and thus a potential drug for the treatment of 'weak orgasm syndrome' as it helps to reinstate normal sexual function in cases where the possible cause is prolactin over secretion [56,57].

4.5 Hydergine

Hydergine (Ergoloid Mesylates) was synthesized for the first time in 1940's by Albert Hofman, the father of LSD. Since then it is being used for memory loss associated with ageing and also as an effective anti-oxidant [58]. Hydergine thought to work by mimicking the effect of nerve growth factor (NGF) therefore, enhancing memory and cognition. NGF has role in stimulating protein synthesis, resulting in the growth of dendrites. These dendrites are communication links between nerve and brain cells and are crucial to memory and learning. Thus an increase in dendrites will ultimately enhance cognitive functions, mental alertness, clarity and mood [59].

Hydergine is regarded as the first effective drug in treatment of Alzheimer's disease [60,61] approved by FDA. It is also used in dementias and for treating psychiatric disorders [62,63]. Even though it is only approved for treating senility and cerebro-vascular insufficiency, it is being used in various European countries to maintain brain oxygen levels after emergencies and accidents that involve shock, hemorrhage, strokes, heart attacks, drowning, electrocution and drug over-dose [64]. An optimum oxygen supply in brain, keeps a check on free radicals production. Hydergine also reduces the accumulation of the age-related toxin, lipofuscin [65-67]. Therefore, it can be regarded as an all-purpose brain booster and also an incredible anti-aging medicine.

4.6 Nicergoline

Nicergoline (trade name Sermion) is another ergot derivative used to treat senility and other disorders with vascular origins. It is used worldwide for the treatment of cognitive, affective, and behavioral disorders in elderly [68,69]. Apart from having neurotrophic and antioxidant properties it is reported to have a vast therapeutic potential as an α1-adrenoceptor antagonist [70] boost cholinergic and catecholaminergic neurotransmitter action; restrain platelet aggregation [71,72] and accelerates metabolism [73]. As it works on wide variety of targets it is used for the treatment of vascular disorders such as cerebral thrombosis and atherosclerosis, arterial blockages in the limbs, increases serum substance P levels, in patients with an ischaemic stroke, which cause reduction in the risk of aspiration pneumonia and with improvement in dysphagia [74,75], Raynaud's disease, vascular migraines, and retinopathy, peripheral arterial occlusive disease [76-78]. The safety profile of nicergoline is better than any other ergot derivatives like ergotamine and ergotoxine as no incidence of fibrosis or ergotism are reported till date, with Nicergoline [79].

Table 1. Receptor mediated actions of ergot alkaloids [49]

Ergot alkaloids	α adrenoreceptor	D2 receptor	5 HT_2 receptor	Uterine smooth muscle
Ergotamine	Agonist/antagonist	agonist(+)	partial agonist	+++
Dihydroergotamine	Agonist/antagonist	agonist(+)	partial agonist	++
Ergonovine	partial agonist	0	partial agonist	+++
Bromocryptin	_	+++	_	0
Methylsergide	+/0	+/0	partial agonist	+/0
LSD	+/0	+/0	partial agonist	+/0

Table 2. FDA approved ergot drugs [160]

Drug	FDA application	Active ingredient	Company address	Current market status
Bromocriptine Mesylate (Tablet; oral)	ANDA (074631)	Bromocriptine Mesylate	LEK PHARMS	Prescription
Bromocriptine Mesylate (Capsule; Oral)	ANDA (075100)	Bromocriptine Mesylate	LEK PHARM	Discontinued
Bromocriptine Mesylate (Tablet; oral)	ANDA (076962)	Bromocriptine Mesylate	MYLAN	Prescription
Bromocriptine Mesylate (Capsule; Oral)	ANDA (077226)	Bromocriptine Mesylate	MYLAN	Prescription
Bromocriptine Mesylate (Tablet; oral)	ANDA (077646)	Bromocriptine Mesylate	PADDOCK LLC	Prescription
Bromocriptine Mesylate (Capsule; Oral)	ANDA (078899)	Bromocriptine Mesylate	ZYDUS PHARMS USA INC	Prescription
Cycloset (Tablet; oral)	NDA (020866)	Bromocriptine Mesylate	VEROSCIENCE	Prescription
Parlodel (Tablet; oral)	NDA (017962)	Bromocriptine Mesylate	US PHARMS HOLDINGS	Prescription
Parlode (Capsule; Oral)	NDA (017962)	Bromocriptine Mesylate	US PHARMS HOLDINGS	Prescription
Digoxin	ANDA (077002)	Digoxin	HIKMA INTL PHARMS	Prescription
Digoxin	ANDA (078556)	Digoxin	IMPAX LABS	Prescription
Digoxin	ANDA (083217)	Digoxin	ABRAXIS PHARM	Discontinued
Digoxin	ANDA (083391)	Digoxin	HIKMA MAPLE	Prescription
Digoxin	ANDA (084386)	Digoxin	WYETH AYERST	Discontinued
Digoxin Pediatric	ANDA (040092)	Digoxin	HOSPIRA	Discontinued
Lanoxicaps	NDA (018118)	Digoxin	GLAXOSMITHKLINE LLC	Discontinued
Lanoxin	NDA (009330)	Digoxin	COVIS INJECTABLES	Prescription
Lanoxin	NDA (020405)	Digoxin	COVIS PHARMA	Prescription
Lanoxin pediatric	NDA (009330)	Digoxin	COVIS INJECTABLES	Prescription

4.7 Other Therapeutic Applications of Ergot Derived Drugs

4.7.1 Role in migraine treatment

Dihydroergotamine is being used to treat migraine headaches for a long time. They were the first 'migraine-specific' drugs [80] as they relieve only severe headaches and symptoms associated with migraines. Because these medicines have serious side effects like ergotism and gangrene [81] they are generally prescribed for patients whose headaches are not relieved by any other pain reliever. The two drugs used for treating migraine, ergotamine (ET) and dihydro-ergotamine (DHE), differ in pharmacokinetic and pharmacodynamic profile. The caffeine present in many ergotamine-containing combinations (e.g. Cafergot) helps ergotamine work better and faster by causing more of it to be quickly absorbed into the body. More recently, orally inhaled DHE (Semprana, Allergan Inc.; formarly known as Levedex by MAP Pharmaceuticals) is currently under process of FDA approval for treatment of migraine and the company expect it to get FDA approval by second quarter of 2015 [82].

The oral assimilation of ergotamine is around 60%, which is improved by the simultaneous administration of caffeine. Ergotamine has a very low bioavailability [83,84] through oral route. As compared to intravenous bioavailability (100%), the oral bioavailability of ergotamine is <1%, owing to high first-pass metabolism. Ergotamine is metabolized in the liver by indeterminate pathways and approximately 90% of the metabolites are excreted in the bile [85]. Ergotamines are well known vasoconstrictors [50,86]. Various *in vivo* experiments show that this vasoconstrictor effect is exerted within the coronary [87], cerebral [86], pulmonary [88] and temporal [89] arteries, selectivity extending to the arteriovenous anastomotic parts. The large arteries (conducting vessels) are affected more compared to the arterioles (resistance vessels). Thus the arterial blood pressure is reasonably increased by these drugs [90,91]. The mechanism of action of ergot alkaloids is quite complex and involves interaction with a range of receptors. Both ergotamine and DHE have affinity for 5-HT (5-hydroxytryptamine), dopamine and noradrenaline receptors [50,86,92-94]. In addition, there is evidence that both ergotamine and DHE can activate novel, as yet uncharacterized receptors [93].

4.7.2 Role as uterotonics

Uterotonics work by directly affecting uterine smooth muscle contraction and used to induce or augment labor by increasing the quality, rate, and force of periodic contractions.

The role of ergot in pregnancy has been known for over 2000 years, and it was used by physicians to stimulate abortion 400 years ago. The first authentic information of use of ergot in obstetrics appeared in Chinese writings in 1100 BC. Adam Lonicer in his *Kreuterbuch* described the use of ergot preparation by midwives to produce strong uterine contractions [95]. The ergot also became popular in France, Germany, and the United States as an oxytocic in childbirth. It was in 1808 when ergot was first used as an official medicine by American physician John for uterine to quicken childbirth [96]. Ergometrine was first isolated by the chemists Dudley and Moir [97-99] and its prophylactic use for treating haemorrhaging lead to a decline in the maternal mortality rate during the early 20th century [100].

Presently, Methylergonovine maleate (Methergine) and Ergonovine (Ergometrine) are the two main ergot based drugs used in Obstetrics as a uterine stimulant to control Postpartum Hemorrhage [101-106].

Ergot alkaloids have a stimulatory effect on the motor activity of the uterus. In small doses, ergot can induce rhythmic contractions and relaxation of the uterus while at higher doses; ergot a powerful and prolonged contraction is observed [107,108]. Ergonovine is more selective thus a preferred drug in obstetric applicants compared to other alkaloids and is on the World Health Organization's List of Essential Medicines [109]. It is generally combined with oxytocin (Syntocinon) as syntometrine which makes it superior to syntocinon alone in lessening occurrence of postpartum haemorrhage in caesarean section and associated maternal morbidity and mortality [110]. The most prominent effect of ergonovine is uterine smooth muscle contraction, increasing both muscular tone and the rate of rhythmic contractions. This stimulatory effect seems to be most closely associated with agonist or partial agonist effects at 5-HT2 receptors [49,111]. Both drugs stimulate alpha-adrenergic and serotonin receptors and inhibition of endothelial-derived relaxation factor release [112,113]. They are less potent vasoconstrictor than ergotamine and

have minor actions on the central nervous system.

4.8 Effect on Prolactin Secretion

Prolactin is also known as "mothering hormone" as one of its primary functions is to promote lactation and weight gain in pregnancy. Bromocriptine, an ergot derivative, suppresses hormone prolactin, leading to their use as fertility drugs by women but it also helps to reduce serum prolactin levels in men although the precise role of prolactin in men is unclear.

Bromocriptine mesylate (also known by its brand name Parlodel) is a non-hormonal, non-estrogenic agent that inhibits the secretion of prolactin in humans, with little or no effect on other pituitary hormones [114]. It works by increasing the levels of dopamine in brain. The drug acts on the pituitary gland, reducing the production of prolactin.

The *in vivo* and *in vitro* effects of ergot derivatives on prolactin and growth hormone biosynthesis in the rat have been studied [115] and it was observed that ergot alkaloids suppress prolactin synthesis and release by the pituitary gland as well as pituitary tumors. The results supported the prior finding [116-120] that ergocornine and ergocryptine inhibit release and synthesis of prolactin. As the ergot derivatives reduce serum prolactin and leutinizing hormone levels [120] it can be proposed that the drugs have a general repressive effect on pituitary function rather than a specific effect on selected pituitary cell receptors. Additionally, the drugs apparently decrease ACTH secretion by the pituitary tumors in view of the fact that the ergots cause degeneration of the adrenal glands [115].

These days another ergot derivative, Cabergoline [121] (brand names Caberlin, Dostinex and Cabaser), is being frequently used as a first-line agent in the treating prolactinomas due to higher affinity for D2- receptor sites and lesser side effects compared to bromocriptine [122].

4.8.1 Role in type II diabetes

The effects of ergot alkaloid on glycaemic variables have been known [123] since 1980 but it was only in 2009, when bromocriptine mesylate was approved by the FDA for treatment of Type II diabetes under the trade name Cycloset (VeroScience). Bromocriptine is a semi-synthetic derivative of a natural ergot alkaloid, Ergocriptin (a derivative of lysergic acid), which is synthesized by bromination of ergocriptin using *N*-bromosuccinimide [124]. It is an ergot alkaloid dopamine-D2-receptor agonist [125]. It is currently unknown how this drug improves glycemic control but somehow it may help resetting the circadian dopamine signal [126-128]. The possible explanation is that it produces its effects by varying the activity of hypothalamic neurons, through a vagal route, to reduce hepatic gluconeogenesis, without increasing insulin concentrations [123,129-132]. In an experiment conducted on a large group of patients with Type II diabetes, Bromocriptine-quick release (as single or in combination with two blood-glucose-lowering drugs) reduced the risk of cardiovascular disease compared with control [133-136]. Even though the mechanism of action is not clear, Bromocriptine-QR's action indicates a vital target in the hypothalamus which may help to reset abnormally elevated hypothalamic drive for metabolic parameter like increased plasma glucose, triglyceride, and free fatty acid levels in fasting and postprandial states in insulin-resistant patients [137,138]. The encouraging cardiovascular risk profile of Bromocriptine-QR proposes its usefulness in the treating patients with Type II diabetes with a history of cardiovascular disease [139].

4.8.2 Role in Parkinson's disease

Ergot alkaloids work as dopamine agonists to trigger dopamine receptors in the basal ganglia and other parts of the brain implicated in motor function. However, the precise mechanism through which this process occurs is not yet clear. Ergot-derived medications commonly used to treat Parkinson's disease include Bromocriptine (Parlodel), Cabergoline (Caberlin), Pergolide (Permax), and Lisuride (Revanil). Bromocriptine has been in normal use as adjunct therapy with levodopa to treat patients with Parkinson's disease [140]. Also in new patients, bromocriptine monotherapy has delayed the need for levodopa treatment [141].

Cabergoline is a potent dopamine receptor agonist on D_2 receptors with a long (~65 hours) plasma half-life [142]. It is also effective as an addition therapy to levodopa in patients with advanced Parkinson's disease [143]. Reports have also established the efficacy of cabergoline in delaying motor complication [144,145]. Pergolide is more beneficial than bromocriptine as it act on both D1 and D2-like receptors, in

comparison with bromocriptine, which stimulates D2-like receptors and is a weak antagonist at D1 sites [146]. A high dose of pergolide has shown to improve motor function without simultaneous levodopa treatment, in some patients with complicated Parkinson's disease [147]. Lisuride, resembles bromocriptine in target and mode of action and has beneficial effect when used in combination with levodopa in patients with advanced Parkinson's disease [148]. It permits reduction of levodopa dose when used as monotherapy and/or in combination with levodopa [149,150]. In a study conducted on a large number of Parkinson's disease patients revealed that two ergot-derived drugs, Pergolide and Cabergoline may increase the risk of cardiac valve regurgitation (CVR) but not in hyperprolactinaemia patients [151-153]. Whereas, results of another study indicate that ergot dopamine agonist use in Parkinson's disease patients are unrelated with an increased risk of newly diagnosed heart failure [154].

Even though agonism of 5-HT (2B) receptors in the heart is apprehended to play an important role, the accurate pathway leading to valvulopathy is still unidentified, as these unfavorable result is not observed in all patients and also it is unclear whether the fibrotic changes are reversible or not. Thus it can be speculated that dopamine agonists devoid of 5-HT(2B) agonistic activity, such as Lisuride (ergolinic dopamine agonists) and non-ergot dopamine, might not induce fibrotic changes in heart valves, but it need more experimental validation [155].

4.8.3 Role in cancer

A vast literature is available on receptor effects of ergot alkaloids but their cytotoxic effect has not been studied much. A low dose of bromocriptine is usually recommended along with the classical antitumor therapies in treatment of metastatic breast cancer and prostate carcinoma patients showing cancer-related hyperprolactinemia [156]. However, for the first time a new role of ergot alkaloid was unveiled by Mulac and Humf [157]. They studied the six main ergot alkaloids (ergotamine, ergocornine, ergocryptine, ergocristine, ergosine and ergometrine, and their isomeric forms) in order to evaluate their toxic effect on human primary cells. The toxic properties changes with the structure of ergot alkaloids; the ergometrine (lysergic acid amide) did not show any effect, while peptide ergot alkaloids showed activity, ergocristine being most effective in human kidney cells. An exciting connection between the alkaloid concentration (in the cell lysate of the receptor-inactive isomers) and cytotoxicity was observed in ergot alkaloids. They displayed strong apoptotic effects in two cancer cell lines (HepG2 and HT-29). Also, by exploiting the natural fluorescence properties of ergot alkaloids, strong accumulative effects were first visualized by fluorescence microscopy [158]. Unfortunately, the mechanism or cytotoxicity is not yet clear and need in depth research in this field. Very recently, six ergot alkaloids (agroclavine, ergosterol, ergocornin E, ergotamine, dihydroergocristine, and 1-propylagroclavine tartrate) were investigated for their cytotoxicity towards tumor cell lines and 1-Propylagroclavine tartrate (1-PAT) found to be most potent. As the cytotoxicity profile of ergot alkaloids does not follow classical mechanisms of drug resistance, it can be used to deal with drug-resistant tumors [159]. The cytotoxicity of ergot alkaloids is not involved in classical mechanisms of drug resistance opening the possibility to bypass resistance and to treat otherwise drug-resistant and refractory tumors.

5. CONCLUDING REMARKS

Ergot alkaloids have had medicinal importance for a long time varying from helping in child birth to headaches to psychological problems. Structural resemblance with various neurotransmitters allows them to interact with a number of receptors which makes them work on different target. However, it becomes very difficult to explain pharmacological profile without identifying receptor homogeneity. As a result of the progress in alkaloid chemistry it is possible to designing new ergot based drugs with receptor subtype selectivity, by different modifications on the ergoline ring, which will resolve the problem of side effects associated with these drugs.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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