REVIEW

BIOACTIVE ALKALOIDS PRODUCED BY FUNGI I. UPDATES ON ALKALOIDS FROM THE SPECIES OF THE GENERA *BOLETUS, FUSARIUM AND PSILOCYBE*

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ABSTRACT

Fungi, in particular, are able in common with the higher plants and bacteria, to produce metabolites, including alkaloids. Alkaloids, along with other metabolites are the most important fungal metabolites from pharmaceutical and industrial point of view. Based on this observation, the authors of this review article have tried to provide an information on the alkaloids produced by the species of genera: ***Boletus, Fusarium and Psilocybef*** from 1981-2009. Thus the review would be helpful and provides valuable information for the researchers of the same field.

Key words: Fungi, alkaloids, Boletus, Fusarium, Psilocybe

DEDICATION

This review article is dedicated to the memory of Late, Khalid Hafiz Khan, Associate Professor, Department of Pharmaceutics, University of Karachi in recognition of his work and contribution in the field of "Fungal Metabolites" especially, "Fungal Alkaloids". This is an honour for the corresponding author to be a research student during early 80's and working under his guidance on fungal alkaloids and antibacterial compounds.

INTRODUCTION

Extensive research work on the ability of various fungi to produce alkaloids had been done and reported by the corresponding authors of present review and some others during 1978 to 1986 working in the Fermentation Research Laboratory – Department of Pharmaceutics, University of Karachi (Akhtar, 1978, Panjani, 1981, Samir, 1983 and Mahmood *et al*., 1983, 1984 and 1986) . However, it was observed that despite the valuable information and material published, less attention was focused or perhaps no further extensive research work was taken into consideration to explore the possibility of isolation and characterization of alkaloids from fungi having biological activities. Though the production of the pharmacologically important ergot alkaloids under saprophytic cultural conditions had been attempted in many laboratories for many years and subsequently, investigators all over the world started working with different approach to establish their findings and as a results, a number of alkaloid were discovered and reported with biological activities. However, despite this fact, the field of fungal alkaloids is demanding the researcher to pay attention and to explore new molecules to combat the new challenges emerging in the field of Health care system.

Alkaloids have been reported as a group of basic organic substances of plant and microbial origin, containing at least one nitrogen atom in a ring structure in the molecule. The first microbial alkaloids to be recognized and studied were those of *Claviceps purpurea*, the agent causing ergot of rye. These alkaloids can be isolated from the sclerotia formed after infection of the ovaries of the plant by *Claviceps ascospores* or *conidia*. Besides the sclerotia of *Claviceps*, other fungi and several higher plants are known to contain, *ergot alkaloids.* Until 1960, however, no attempt had been successful in obtaining more than trace amounts of alkaloids. In 1960, a group of academic and industrial scientists at the Istiuto-Superiore di Sanita in Rome described in a preliminary report (Arcamone *et al*., 1960), followed by a detailed one (Arcamone *et al*., 1961), the production of ergot alkaloids in submerged culture, with a strain of *Claviceps paspali* of reasonable yields (about 1000 mcg/ml) of Lysergic acid hydroxyethylamide, a new simple Lysergic acid derivatives. In the same year some other scientists (Abe *et al*., 1961) isolated Lysergol, Lysergine and Lysergene

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from the saprophytic culture of ergot fungi. After the publication of these papers other groups of investigators described other *Claviceps paspali* fermentation producing the same substances (Pacifici *et al*., 1962, Groger and Tyler, 1963). Further studies (Kobel *et al*., 1964), then described a strain of *Claviceps paspali* able to produce Lysergic acid in a Submerged culture and production of Ergotamine by cultivation of *Claviceps purpurea* (Tonolo, 1966 and Amici *et al*., 1966, 1967). After few years scientists described three new strains of *Claviceps purpurea* able to produce, under submerged conditions, high yields of ergocryptine, ergotamine, ergocornine, ergosine, and ergocristine respectively (Amici *et al*., 1969).

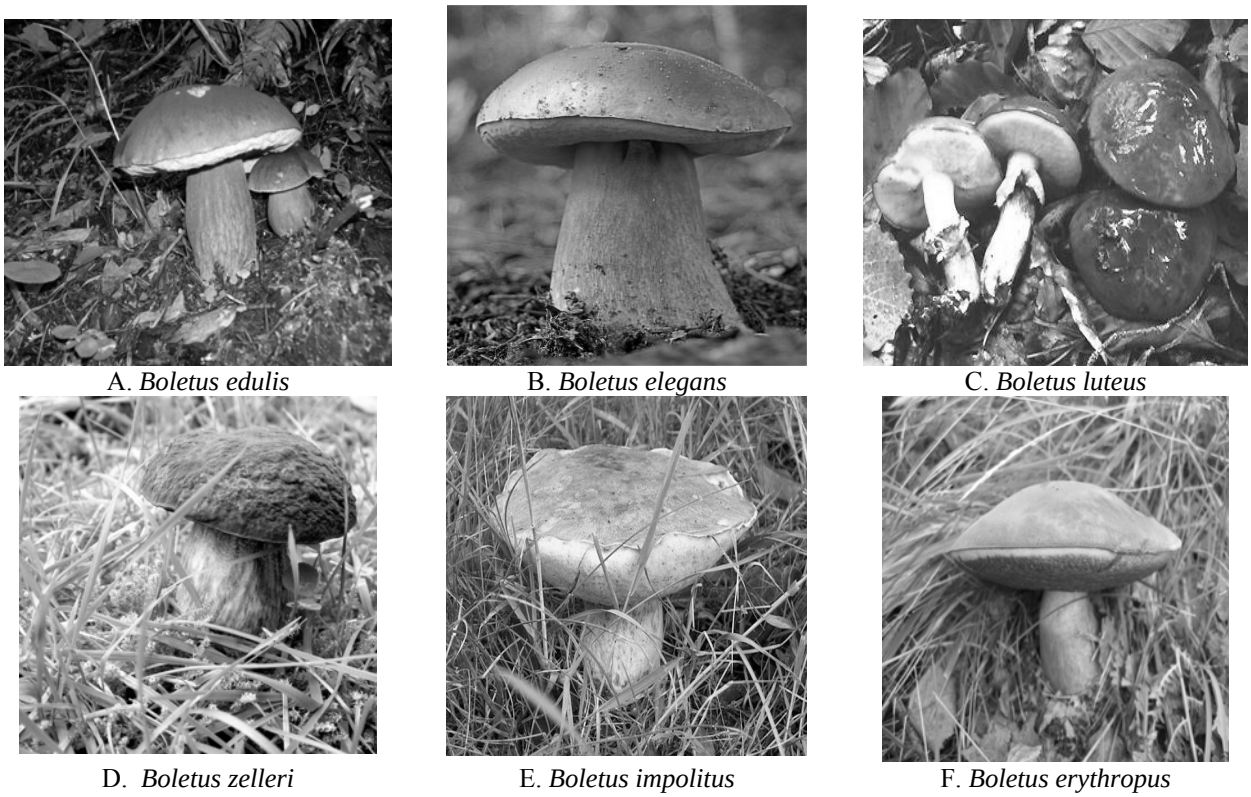
Effect of various factors on the production of ergot alkaloids have been studied by different workers. The optimum pH for the production of alkaloids in saprophytic culture has been reported to lie between pH 5 to 6 (Abe, 1964). Automatically controlled pH value of 5.0 has also been used by for the production of Agroclavine at large scale (Bank *et al*., 1974). Ergot alkaloids are a diverse family of indole-derived mycotoxins that collectively have activities against a variety of organisms including bacteria, nematodes, insects, and mammals. Different fungi accumulate different, often characteristic, profiles of ergot alkaloids rather than a single pathway end product. These ergot alkaloid profiles result from inefficiency in the pathway leading to accumulation of certain intermediates or diversion of intermediates into shunts along the pathway. The inefficiency generating these ergot alkaloid profiles may have been selected for as a means of accumulating a diversity of ergot alkaloids, potentially contributing in different ways to benefit the producing fungus (Panaccione, 2005). It has been reported (Schardl, 2006) that ergot alkaloids have been a major benefit, and a major detriment, to humans since early in recorded history. Their medicinal properties have been used, and continue to be used, to aid in childbirth, with new uses being found in the treatment of neurological and cardiovascular disorders. The surprisingly broad range of pharmaceutical uses for ergot alkaloids stems from their affinities for multiple receptors for three distinct neurotransmitters (serotonin, dopamine, and adrenaline), from the great structural diversity of natural ergot alkaloids, and from the application of chemical techniques that further expand that structural diversity. The dangers posed by ergot alkaloids to humans and their livestock stem from the ubiquity of ergot fungi (*Claviceps* species) as parasites of cereals, and of related grass endophytes (*Epichloë, Neotyphodium*, and *Balansia* species) that may inhabit pasture grasses and produce toxic levels of ergot alkaloids. Further concerns stem from saprophytic ergot alkaloids producers in the genera *Aspergillus* and *Penicillium*, especially *A. fumigatus*, an opportunistic pathogen of humans. Numerous fungal species produce ergot alkaloids with a wide variety of structures and properties. These alkaloids are associated with plants in the families Poaceae, Cyperaceae, and Convolvulaceae, apparently because these plants can have symbiotic fungi that produce ergot alkaloids. Pharmacological activities of ergot alkaloids relate to their specific structures. Known as potent vasoconstrictors, the ergopeptines include a lysergic acid substituent with an amide linkage to a complex cyclol-lactam ring structure generated from three amino acids. Simpler lysergyl amides and clavines are more apt to have oxytonic or psychotropic activities. One of the lysergyl amides is LSD, the most potent hallucinogen known.

Effect of various macro and micro elements used along with carbon & nitrogen sources for the production of ergot alkaloids were also reported (Amici *et al*., 1966 & 1967) , the concentration of phosphate in the medium plays most important role. The exhaustion of phosphate in the medium, which is a growth limiting factor, was considered essential in the production of secondary metabolites (Amici *et al*., 1969). Addition of some chemicals like glycols has been reported to increase the alkaloid yield (Mizrahi and Miller, 1968, Mizrahi *et al.,* 1969). The addition of Tween 80 in 0.075% concentration also increases the yield of alkaloids 2 to 3 times (Kelleher *et al.*, 1969).

Alkaloids Reported from the species of the genera Boletus, Fusarium and Psilocybe

Boletus is a genus of mushroom, comprising over 100 species. Earlier reports and studies indicated presence of alkaloids in *B. edulis, B. elegans* and *B. luteus* L (figs. 1A, B and C). These species are widely distributed in Asia, Europe and America, and grows in sandy soil, in pine or mixed woods or groves. *Boletus edulis* is the most popular member and is a basidiomycete, commonly known as porcini or cep, in the *Boletaceae* family of mushrooms and classified as edible mushrooms. Usually grows symbiotically with conifers upon trees (e.g., pine and fir trees). The fruit body forms a large and imposing brown cap which can grow to reach 25 cm (10 in) in diameter and 1 kg (2.2 lb) in weight. Like other boletes, it has pores underneath the cap instead of gills, in this case whitish when young ageing to a greenish-yellow. The stout stipe, or stem, is up to 25 cm (10 in) tall, and 7 cm (2.8 in) thick. The most common and pharmacologically active alkaloids produced by these species and reported till early 80's include – Putrescine, Hypoxanthine, γ-Butyrobetaine, β-Phenylethylamine and Hercynine (Mahmood *et al*., 1984 and 1986).

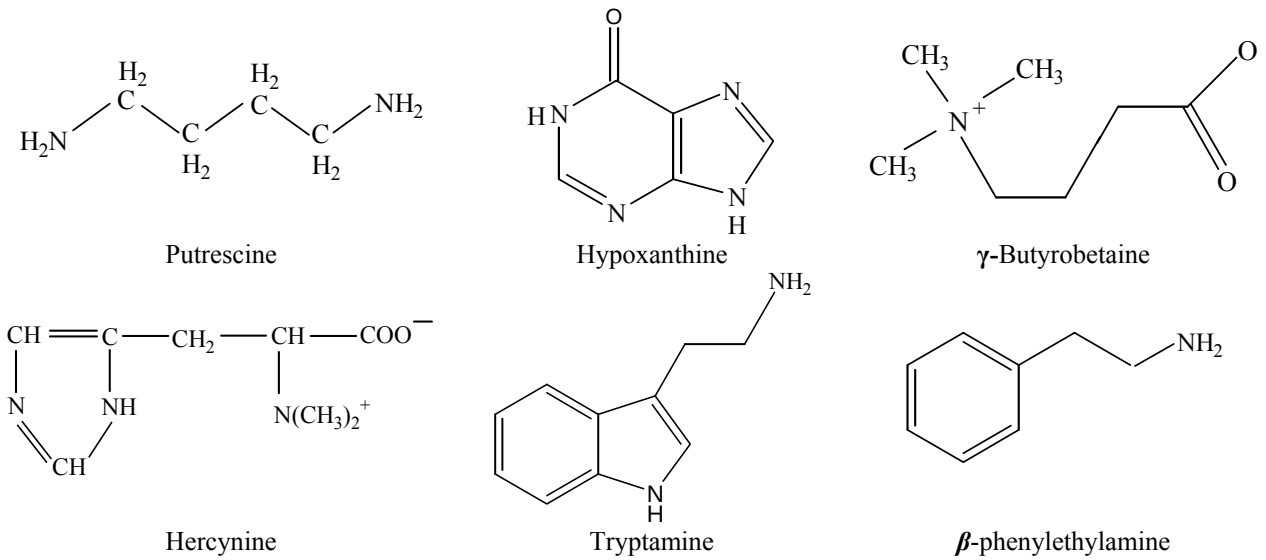
However, some of the alkaloids, though identified earlier but reported in late 80's from three other specie of Boletus, *B. zelleri* , *B. impolitus* and *B. erythrpus (*Figs. 1D, E and F*)*



A. *Boletus edulis* B. *Boletus elegans* C. *Boletus luteus*

D. *Boletus zelleri* E. *Boletus impolitus* F. *Boletus erythropus*

Fig. 1: Species of the genus *Boletus*

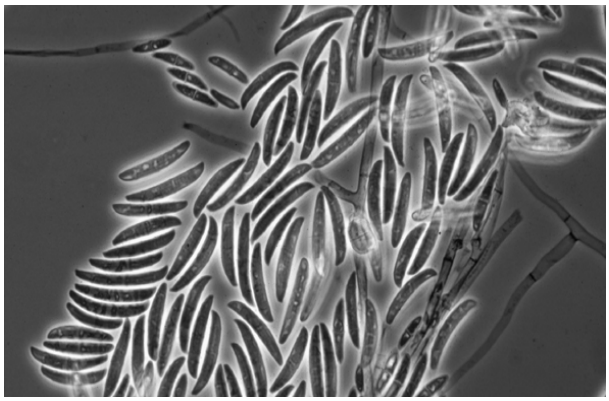


Putrescine Hypoxanthine **γ-**Butyrobetaine

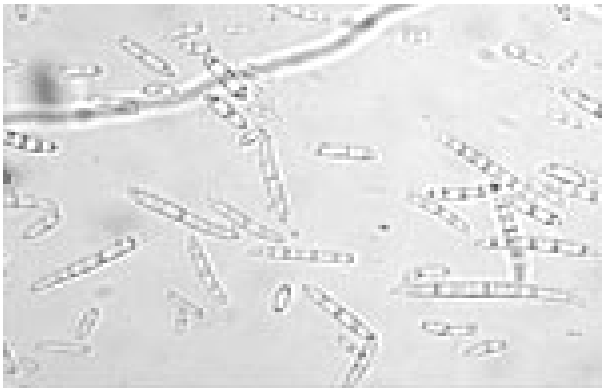
Hercynine Tryptamine ***β*-**phenylethylamine

Fusarium has been reported as a large genus of filamentous fungi. Most species have reported harmles. However, some reported to produce mycotoxins and can affect animals as well as humans. These are widely distributed in soil and in association with plants. chain. The main toxins produced by these *Fusarium* species are fumonisins and trichothecenes.

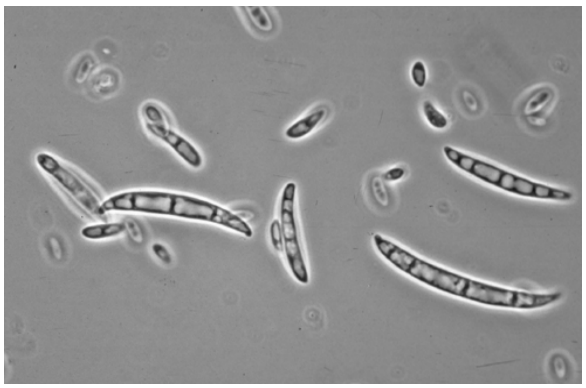
In the earlier report (Rosenberg *et al*. 1976), presence of alkaloids in 30 species of fungi including *Fusarium monilforme* was reported. .In further screening it has been observed that alkaloids Bostrycoidin, Lycomarasmine & Fusaric acid are produced by *Fusarium bostrycoides*, *Fusaruim lycopersici* and *Fusarium Ixysporium*, respectively (Li Jiazao, 1981). Some more studies (Khan & Akhtar, 1978, Khan *et al*. 1981 and Mahmood *et al*.,



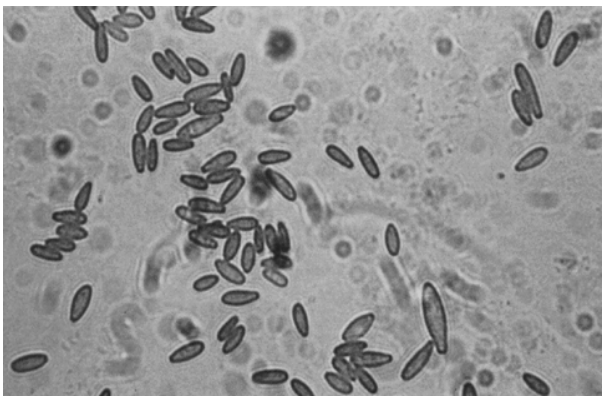
A. *Fusarium solani*



B. *Fusarium bostrycoides*

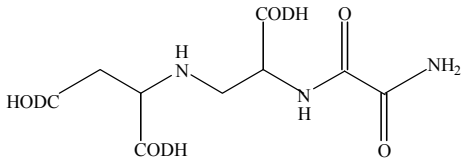


C. *Fusarium oxysprum*

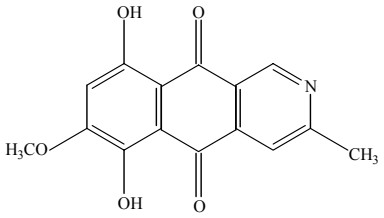


D. *Fusarium moliforme*

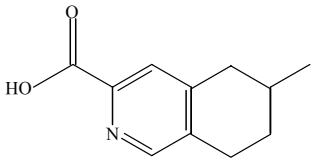
Fig. 2: Species of the genus Fusarium



Lycomarasmine



Bostrycoidin



Fusaric acid

1984) indicated presence of alkaloids in *Fusarium solani* and *F. culmonum.*

The most common and pharmacologically active alkaloids produced by these species and reported till early 80's include:– bostrycoidin, fusarinic acid and lycomarasmine (Hardegger *et al.,* 1963).

A recent study (Tsuchinari *et al*., 2007 and Li *et al*., 2008) reports two new pyrrole alkaloids, N-[4-(2-formyl-5-hydroxymethyl-pyrrol-1-yl)-butyl]-acetamide and N-[5-(2-formyl-5-hydroxymethyl-pyrrol-1-yl)-pentyl]-acetamide, and a new indole derivative (3aR,8aR)-3a-acetoxyl-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-b] indol were isolated, together with (-)-3a-hydroxyfuroindoline, (3aR,8aS)-1-acetyl-1,3,3a,8,8a-hexahydropyrrolo-[2,3-b]indol-3a-ol, and N-acetyltryptamine A, from an endophytic ascomycetous fungus, *Fusarium incarnatum.*

The genus**, *Psilocybe*** is distributed worldwide and comprise of small mushrooms also known as magic mushrooms. Earlier reports and studies indicated presence of alkaloid in *P. aztecorum, P. caerulescens, P. mexicana, P. sempervirens and P. zapotacorum.*

Earlier studies report two alkaloids from various species of Psilocybe include. These include Psilocybin and Psilocin (Hofmann *et al*., 1958 and 1959, Hofmann, 1959). Dr. Albert Hofmann, is best known for fathering his "problem child," LSD. He died at the age of 102 near Basil, Switzerland in 2008. In recognition of his contribution and findings in the field of chemistry,

A. Psilocybe aztecorum

B. Psilocybe caerulescens

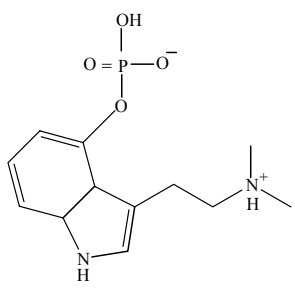
C. Psilocybe maxicana Heim

D. Psilocybe zapotecorum

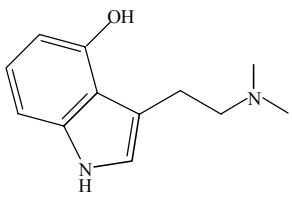
E. Psilocybe species

F. Psilocybe semilanceata

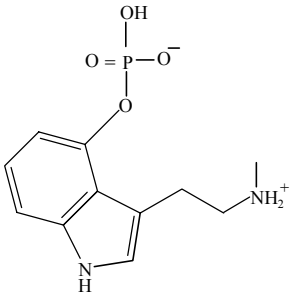
Fig. 3: Species of the genus Psilocybe



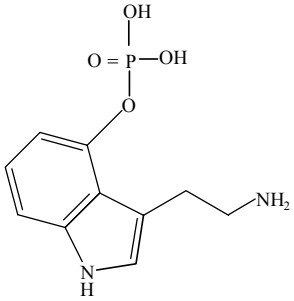
Psilocybin



Psilocin



Baeocystin



Norbaeocystin

authors of the present review would like to reproduce the molecular structure of Psilocybin and LSD as drawn by him in March 1958.

Present literature search indicated presence of two more alkaloids in *Psilocybe semilanceata*. These include Baeocystin and Norbaeocystin (Pedersen *et al*., 2005).

Earlier research studies on alkaloids produced by species of genus ***Boletus, Fusarium and Psilocybe*** have reported by a number of investigators (Hofmann *et al*., 1958, Miller 1961, Turowaska *et al*., 1967 and 1968, Lee *et al*., 1975, Mahmood *et al*., 1983 and Samir *et al*., 1983) and consequently few important molecules with respect to biological activity were reported. The most important and pharmacologically active alkaloids reported in various *Boletus species*, include: **putrescine** (1,4-butanediamine - $C_4H_{12}N_2$), h**ypxanthine** (1,7-dihydro-6H-purin-6-one – $C_5H_4N_4O$), **γ-butyrobetaine** (4-trimethylazaniumyl-butanoate – $C_7H_{15}NO_2$), **β-phenylethylamine** (2-phenyl-ethylamine – $C_8H_{11}N$), h**ercynine** (α-carboxy-N,N,N-trimethyl-1H-imidazole-4-ethanamium hydroxide inner salt – $C_9H_{15}N_3O_2$) and t**ryptamine** (2-(1H-indol-3-yl) ethanamine – $C_{12}H_{10}N_2$). While alkaloids produced by the Fusarium species include, b**ostrycoidin** (5,8-dihydroxy-6-methoxy-3-methyl-2-aza-9,10-anthraquinone - $C_{15}H_{11}NO_5$), **lycomarasmine** (*N*-[2-[(2-amino-2-Oxoethyl)amino]-2-carboxyethyl]-L-aspartic acid - $C_9H_{15}N_3O_7$) and f**usaric acid** (5-butylpyridine-2-carboxylic acid - $C_{10}H_{13}NO_2$). The best known alkaloids

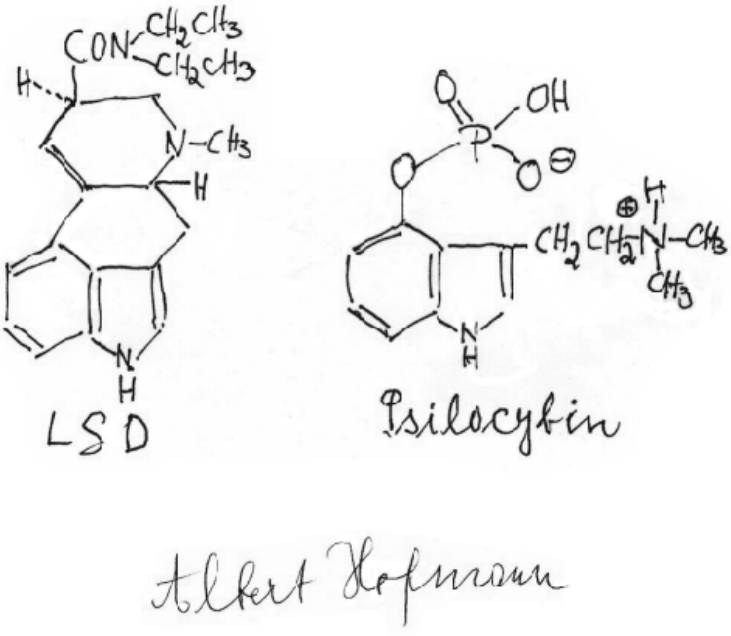


Fig. 4: Molecular structures of LSD and psilocybin, written by Dr. Albert Hofmann in 1958. Courtesy of Dr. Albert Hofmann and The Stain Blue Museum Collection.

produced by Psilocybe species include, p**silocybin** (3-(2-dimethylaminoethyl)-1H-indol-4-yl] dihydrogen phosphate - $C_{12}H_{17}N_2O_4P$), **Psilocin** (4-Hydroxy-*N*,*N*-dimethyl-tryptamine - $C_{12}H_{16}N_2O$), b**aeocystin** (3-[2-(methylammonio)ethyl]-1*H*-indol-4-yl hydrogen phosphate - $C_{11}H_{15}N_2O_4P$) and n**orbaeocystin** (3-(2-ammonioethyl)-1*H*-indol-4-yl hydrogen phosphate - $C_{10}H_{13}N_2O_4P$).

Putrescine is amous for the foul odor of putrefying flesh, bad breath, bacterial vaginosis and reported to be present semen as well (Lewis, 1998 and Kamhi, 2007). Aalong with it's properties to arrest cell growth, differentiation, and cell division, it is reported as toxic in very large doses (2000 mg/kg body weight). However, it's physiological role, i.e., blocking of polyamine synthesis may have broad implications in clinical medicine. (Olle, 1986, Til *et al*., 1997). Whereas, it's industrial application includes the reaction with adipic acid to produce polyamide Nylon-4,6, which is marketed by DSM under the trade name Stanyl (Stanyl Resin) Stanyl is the most successful high temperature thermoplastic in the world with compounding being carried out in the USA, Europe, China, and Japan.. To meet the industrial demand, Putrescine is produced on industrial scale by hydrogenation of succinonitrile which is produced by the addition of hydrogen cyanide to acrylonitrile (DMS, 2007).

Hypoxanthine has been reported as a natural purine derivative necessary for certain cells, bacteria, and parasites. It provides a substrate and nitrogen source to these cells. The best example is *Plasmodium falciparum* requires hypoxanthine for the synthesis of nucleic acid and energy metabolism.

Earlier reports indicated presence of **γ-butyrobetaine** in the tissues of some cold-blooded animals, e.g., python and freshwater eels (Hosein, 1959). γ-butyrobetaine (actinine), is also reported play important role in the synthesis of carnitine, but at the same time as a toxic substance too, which is responsible to accelerates respiration, salivation and lacrimation, as well as pupil dilation, vasoconstriction and heart stop in diastole. (Linneweh, 1929). However, in later research studies, authors reported that γ-butyrobetaine has extremely low toxic (LD_{50} >7000 mg/kg, s.c.) and that the administration of γ-Butyrobetaine, which serve as substrate, increases the level of carnitine biosynthesis in the living organism (Rotzsch, *et al*., 1959).

Phenethylamine (**PEA**), a monoamine alkaloid is reported posses CNS stimulant effects and acts as a neuromodulator or neurotransmitter by releasing norepinephrine and dopamine. As a dietary supplement, it is usually taken for purported mood and weight loss. When taken orally orally it becomes inactive due to extensive first-pass metabolism. The enzyme monoamine oxidase (MAO) converts it into phenylacetic acid and thus prevents the high level of PEA from reaching the brain (Yang and Neff, 1973 and Suzuki *et al*., 1981).

Tryptamine is also a monoamine alkaloid, based around the indole ring structure. It is reportede to be present in very small amounts in the brains of mammals (3.5 pmol/g) and acts as a neuromodulator or neurotransmitter Tryptamine is regarded as backbone for **tryptamines**, a group of compounds which include many bpharmacologically active compounds, including serotonin (neurotransmitters), melatonin (hormone) and psilocybin (psychedelic drugs). The concentration of tryptamine in rat brains is reported in the range of about 3.5 pmol/g. Many synthetic tryptamines are now been synthesized, including the migraine drug sumatriptan which is prescribed in migraine hedache (Jones, 1982).

Bostrycoidin is an antibiotic produced Fusarium bostrycoides. It is reported to be active against Mycobacterium tuberculosis (Arsenault, 1965). **Lycomarasmine** is also an antibiotic produced by Fusarium lycopersici. Whereas **Fusaric acid** is reported as Dopamine beta-hydroxylase inhibitor. Thus, blocking conversion on dopamine to norepinephrine. Apart from this it is also reported to inhibit cell proliferation and DNA synthesis (Suda *et al*., 1969 and Nagatsu *et al*., 1970).

Psilocybin has been reported in about 116 different specis of Psilocybe in which mushroom caps tend to contain more of the psychoactive compounds than the stems (Wurst, *et al*., 1984, Kysilka Wurst 1989 and Keller *et al*., 1999). Most species of Psilocybin producing psilocybin also contain small amounts of **baeocystin** and **norbaeocystin**, analogs of psilocybin (Gartz, 1987, Stijve 1985 and Kuyper 1985, and Repke 1977). Psilocybin is regarded as prodrug which is finally converted into psilocin, the pharmacologically active form of the drug in the body by a dephosphorylation reaction and thus acts as a partial agonist at the serotonin receptor (5-HT_{2A}) in the brain where it mimics the effects of serotonin (5-HT). Based on this mechanisms of action, Psilocin is classified as a 5-HT_{1A} and 5-$HT_{2A/2C}$ agonist and accordingly it's psychotomimietc effect can be blocked by5-HT2A antagonists ketanserin and risperidone in a dose dependent pattern. So far Psilocybin has not been recognized as drug but has been extensively investigated in the treatment of various psychological disorders (Horita and Weber, 1961, Bray and Goddard, 2008, Passie, 2002).

CONCLUSION

The number of alkaloids found in fungi and other microorganisms are not large but it is believed that it would increase rapidly if a more extensive research is carried out. The recent literature survey has indicated that the alkaloids producing ability of fungi has not been studied to the extent as studied the alkaloids produced by plants. Therefore, it is suggested to study the alkaloids produced by fungi. Present review revealed that fungal flora are able to produce diversified and pharmacologically active alkaloids and thus can provide a potential source of new bioactive alkaloids. The objective of this review is to highlight the developments on fungal alkaloids, especially alkaloids produced by the species of the genera ***Boletus, Fusarium*** *and* ***Psilocybe*** with their pharmacological activity.

REFERENCES

Abe M and Yamatodani S (1964). Preparation of alkaloids by saprophytic culture of ergot fungi. *Prog Ind. Microbiol.,* **5**: 203-229.

Abe M, Yamatodani S, Yamano T and Kusumoto M (1961). Isolation of lysergol, lysergene and lysergine from the saprophytic cultures of Ergot fungi. *Agricultural Biological Chemistry.* **25**: 594-599.

Akhtar S (1978). Screening of alkaloid producing soil fungi. M. Pharm Thesis, Department of Pharmaceutics, Faculty of Pharmacy, University of Karachi, Karachi, Pakistan.

Amici AM, Minghetti A, Scotti T, Spalla C and Tognoli L (1966). Production of ergotamine by a strain of Claviceps purpurea (Fr.) Tul. *Experientia,* **22**: 415-416.

Amici AM, Minghetti A, Scotti T, Spalla C and Tognoli L (1969). Production of Peptide Ergot Alkaloids in Submerged Culture by Three Isolates of *Claviceps purpurea*. *Applied Microbiol*., **18**(3): 464-468.

Amici AM, Minghetti A, Scotti T, Spalla C and Tognoli L (1967). Ergotamine production in submerged culture and physiology of *Claviceps purpurea*. *Appl. Microbiol*., **15**: 597-602.

Andersen R, Büchi G, Kobbe B and Demain AL (1977). Secalonic acids D and F are toxic metabolites of *Aspergillus aculeatus*. *J. Org. Chem.*, **21**; **42**(2): 352-353.

Arcamone F, Bonino C, Chain EB, Ferretti A, Pennella P, Tonolo A and Vero L (1960). Production of lysergic acid derivatives by a strain of *Claviceps paspali* Stevens and Hall in submerged culture. *Nature*, **187**: 238-239.

Arcamone F, Bonino C, Chain EB, Ferretti A, Pennella P, Tonolo A and Vero L (1961). Production of a new lysergic acid derivative in submerged culture by a strain of *Claviceps paspali* Stevens and Hall. *Proceedings of the Royal Society*, **155**: 26-54.

Arsenault GP (1965). Structure of Bostrycoidin, *Tetrahedron Lett.*, 4033-4037.

Bank SG, Mantle PT, G and Szczyrbak CA (1974). Large-scale production of clavine alkaloids by *Claviceps fusiforrnis. Journal of General Microbiology,* **82**: 345-361.

Bowden K and Drysdale AC (1965). A novel constituent of *Amanita muscaria*. *Tetrahedron Lett.,* **12**: 727-728.

Bowden K, Drysdale AC and Mogey GA (1965). Constituents of *Amanita muscaria*. *Nature*, **26**; **206**(991): 1359-1360.

Bray JK and Goddard III WA (2008). The structure of human serotonin 2c G-protein coupled receptor bound to agonists and antagonists. *Journal of Molecular Graphics and Modelling*, **27**: 66-81.

Büchi G, Luk KC, Kobbe B and Townsend JM (1977). Four new mycotoxins of *Aspergillus clavatus* related to tryptoquivaline. *J. Org. Chem.,* **21**; **42**(2): 244-246.

Caesar F, Jansson K and Mutschler E (1969). Nigragillin, a new alkaloid from the *Aspergillus niger* group. 1. Isolation and structure clarification of nigragillin and a dioxopiperazine. *Pharm. Acta. Helv*, **44**(11): 676-690.

DSM Engineering Plastics (2007). Ergot Alkaloids by *Claviceps paspali. J. Bacteriol*., **97**(3): 1155-1159.-

Gartz J (1987). Occurrence of psilocybin and baeocystin in fruit bodies of *Pluteus salicinus*. *Planta Medica*, 53(3): 290-291.

Groger D and Tyler VE Jr. (1963). Alkaloid production by *Claviceps paspali* in submerged culture. *Lloydia,* 26: 174-191.

Hardegger E, Liechti P, Jackman LM, Boller A and Plattner PA (1963). Welkstoffe und Antibiotika. 24. Mitteilung. Die Konstitution des Lycomarasmins. *Helv. Chim. Acta* **46**: 60-74.

Hofmann A, Heim R, Brack A and Kobbel H (1958). Psilocybin, a psychotropic principle from Mexican hallucinogenic fungus *Psilocybe mexicanna* Heim. *Experientia*, **14**: 107.

Hofmann A (1959). Psilocybin und Psilocin, zwei psychotrope Wirkstoffe aus mexikanischen Rauschpilzen. *Helvetica Chemica Acta*, **42**: 1557-1572.

Hofmann A and Troxler F (1959). Identifizierung von Psilocybin. *Experientia,* **15**: 101-102.

Horita A and Weber LJ (1961). Dephosphorylation of psilocybin to psilocin by alkaline phosphatase. *Proceedings of the Society for Experimental Biology*, **106**(1): 32-33.

Hosein EA (1959). Pharmacological Actions of γ-Butyrobetaine. *Nature*, **183**(4657): 328-329.

Jones RS (1982). Tryptamine: A neuromodulator or neurotransmitter in mammalian brain. *Progress in Neurobiology,* **19**(1–2): 117-139.

Kamhi E (2007). Alternative Medicine Magazine's Definitive Guide to Weight Loss. Celestial Arts. p.14.

Kelleher WJ, Kim BK and Schwarting AE (1969). Production of lysergic acid derivatives in submerged culture. V. Effect of surfactants on alkaloid accumulation. *Lloydia.* **32**(3): 327-333.

Keller T, Schneider A, Regenscheit P, Dirnhofer R, Rücker T, Jaspers J and Kisser W (1999). Analysis of psilocybin and psilocin in *Psilocybe subcubensis* Guzmán by ion mobility spectrometry and gas chromatography-mass spectrometry. *Forensic Science International*, **99**(2): 93-105.

Kobel H, Schreier E and Rutschmann J (1964). 6-Methyl-A8.9-ergolen-8-carbonsaure, ein neues Ergolinderivat aus Kulturen eines Stammes von Claviceps paspali Stevens et Hall. *Helv. Chim. Acta* **47**: 1052-1064.

Kysilka R and Wurst M (1989). High-performance liquid chromatographic determination of some psychotropic indole derivatives. *Journal of Chromatography*, **464**(2): 434-437.

Levenberg B (1964). Isolation and Structure of Agaritine, a γ-Glutamyl-substituted Arylhydrazine Derivative from *Agaricaceae. J. Biol. Chem*, **239**: 2267-2273.

Lewis RA (1998). *Lewis' Dictionary of Toxicology*. CRC Press, p.212.

Li LY, Diang Y, Groth I, Menzel KD, Peschel G, Voigt K, Deng ZW, Sattler I and Lin WH (2008). Pyrrole and indole alkaloids from an endophytic Fusarium incarnatum (HKI00504) isolated from the mangrove plant. *J. Asian Nat. Prod. Res*., **10**(7-8): 775-780.

Linneweh W (1929). gamma.-Butyrobetaine, croton-betaine and carnitine in the animal metabolism. *Z. physiol. Chem*., **181**: 42-53.

Mahmood ZA, Khan KH and Shaikh D (1983). Screening of antibacterial compounds produced by some fungi. *J. Pharmacy*, **1**(2): 103-107.

Mahmood ZA, Khan KH and Shaikh D (1986). Antibacterial and chemical studies on alkaloids produced by Botryodiplodia species. *J. Pharmacy*, **4**(2): 105-111.

Mahmood ZA, Khan KH, Shaikh D and Usmanghani K(1984). Screening of alkaloid producing fungi - II. *J. Pharmacy,* **3**(1): 1-4.

Miller MW (1961). The Pfizer Handbook of Microbial Metabolites, Chas Pfizer & Co., Medical, published by McGraw-Hill Book Company, Inc., New York, pp.1-772.

Mizrahi A, Izrahi A and Miller G (1969). Role of Glycols and. Tweens in the Production of Ergot Alkaloids by *Claviceps paspali. J. Bacteriol*., **97**(3): 1155-1159.

Mizrahi A and Miller O (1968). Effect of glycols on the production of ergot alkaloids by *Claviceps paspall*. *Biotech. Bioeng*., **10**: 102-103.

Olle H. (1986). NIPS. *Int Union Physiol. Sci/Am Physlol. Sot.,* **1**: 12-15.

Pacifici LR, Kelleher WJ and Schwarting AE (1962). Production of lysergic acid derivatives in submerged culture. I. Fermentation studies. *Lloydia*, **25**: 37-45.

Panaccione DG (2005). Origins and significance of ergot alkaloid diversity in fungi. *FEMS Microbiol Lett,* **1**: **251**(1): 9-17.

Panjani R (1981). Screening of alkaloid producing fungi. M.Pharm. Thesis. Department of Pharmaceutics, Faculty of Pharmacy, University of Karachi, Karachi, Pakistan.

Passie T, Seifert J, Schneider U and Emrich HM (2002). The pharmacology of psilocybin. *Addiction Biology*, **7**(4): 357-364.

Pedersen SB, Rasmussen KE and Sannes E (2005). Strategies for the capillary electrophoretic separation of indole alkaloids in *Psilocybe semilanceata*. *Electrophoresis*, **19**(1): 27-30.

Repke DB, Leslie DT and Guzmán G (1977). Baeocystin in *Psilocybe*, *Conocybe* and *Panaeolus*. *Lloydia*, **40**(6): 566-578.

Reshetilova TA and Kozlovskiĭ AG (1990). Biosynthesis of alkaloids by mycelial fungi. *Prikl Biokhim Mikrobiol,* **26**(3): 291-306.

Rosenberg H, Maheshwari V and Stohs SJ (1976). Alkaloid screening of fungi. *Planta Med*, **30**(2): 146-150.

Rotzsch W, Lorenz I and Strack E (1959). On the toxicity of carnitine and some related substances. *Acta Biol. Med. Ger*., **3**: 28-36.

Samir OH, Usmanghani K and Khan KH (1983). Screening of alkaloid producing fungi–I. *J. Pharmacy.* **1**(2): 93-96.

Schardl CL, Panaccione DG and Tudzynski P (2006). Ergot alkaloids--biology and molecular biology. *Alkaloids Chem Biol,* **63**: 45-86.

Suda H, Takeuchi T, Nagatsu T, Matsuzaki M, Matsumoto I and Umezawa H (1969). Inhibition of dopamine beta-hydroxylase by 5-alkylpicolinic acid and their hypotensive effects. *Chem. Pharm. Bull.*, **17**: 2377-2380.

Suzuki O, Katsumata Y and Oya M (1981). Oxidation of beta-phenylethylamine by both types of monoamine oxidase: examination of enzymes in brain and liver mitochondria of eight species. *The Journal of Neurochemistry,* **36**(3): 1298-1301.

Til HP, Falke HE, Prinsen MK and Willems MI (1997). Acute and subacute toxicity of tyramine, spermidine, spermine, putrescine and cadaverine in rats. *Food and Chemical Toxicology,* **35**(3-4): 337-348.

Tonolo A (1966). Production of peptide alkaloids in submerged culture by a strain of *Claviceps purpurea. Nature*, Lond., **209**: 1134.

Tsuchinari M, Shimanuki K, Hiramatsu F, Murayama T, Koseki and T and Shiono Y (2007). Fusapyridons A and B, Novel Pyridone Alkaloids from an Endophytic Fungus, Fusarium sp. YG-45 *Z. Naturforsch,* **62**b, 1203-1207.

Wurst MM, Semerdzieva M and Vokoun J (1984). Analysis of psychotropic compounds in fungi of the genus *Psilocybe* by reversed-phase high performance liquid chromatography. *Journal of Chromatography,* **286**: 229-235.

Yang HY and Neff NH (1973). Beta-phenylethylamine: A specific substrate for type B monoamine oxidase of brain. *J. Pharmacol. Exp. Ther*., **187**(2): 365-371.