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Mycotoxins: the silent killers inside herbal drugs. A critical review of the literature

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ABSTRACT: Herbal drugs can be defined as the use of medicinal plant preparations as therapeutic practices that have been in existence, often for hundreds of years, before the development and spread of modern medicine and are still in use today. Despite the introduction of antibiotics since the 1940's, even 80% of the population today relies on indigenous medicinal plants as well as on the drugs. Since, herbal drugs are of plant origin, these are often deteriorated by various fungi before harvesting, and during handling and storage and these fungi during growth produces mycotoxins, which are harmful for consumer's health. This fungal and mycotoxin deterioration of herbal drugs not only posing health effects on consumers but also decreases their efficacy and medicinal potential which became one of the major reasons to lagging behind the Indian herbal drug industry. The present review is an important effort to describe the importance, present scenario, fungal and mycotoxin deterioration of herbal drugs.

Key words: Herbal drugs, fungal contamination, mycotoxins, health effects.

INTRODUCTION

Herbal medicines - also known as herbalism or botanical medicine, is the use of herbs for their therapeutic or medicinal value. The art of herbal medicine is extremely ancient, probably as old as humanity itself. One of the remotest works in traditional herbal medicine is "Virikshayurveda", compiled even before the beginning of Christian era and the use of a number of plants as medicines has also been mentioned in the literature available in "Rig Veda" in 2000 B C. (Bentley and Trimen, 1980). The Ayurveda and Siddha, the ancient systems of Indian medicine are also based on plant based formulation in the form of decoction, oil, powder, extract and ash. The philosophy of Ayurveda is based on the theory of Panchmahabhutas (five- element theory) of which all the objects and living bodies are made up of five elements i.e. fire, water, air, earth and sky. The combination of these five elements is represented in the form of Tridosha: Vata (earth & air), Pitta (fire) and Kaph (water & earth).

As the herbal drugs are of plant origin in nature, their comparison with allopathic drugs has been increased. With the passage of time the reliability of herbal drugs increased and this moved the civilization towards nature again. The re-occurrence of green medicines is because of their comparatively safer, cheaper and more eco-friendly nature. These drugs Only cure where modern drugs are either unavailable or unsatisfactory. These drugs only cure where modern drugs are either unavailable or unsatisfactory. It is the only source of health care for 80 per cent population in the developing world. Besides health benefits medicinal and aromatic plants provide crucial livelihood options for millions of rural people, particularly women, tribal and the poorest of the poor (Chauhan, 2006).

This increased use of herbal drugs lead an explosion in the global herbal market with the entry of herbal drug industry. Although the herbalism is now an integral part of medicinal systems globally but, India and China are the two biggest hot spots of herbal trade which collectively

fulfil the half of the demand of herbal medicines. Although, consumption of these herbal drugs increased but still, in developing countries the unscientific traditional methods of collection, storage, processing and transportation of raw material as well as their processed products are in practices (Dubey *et al.*, 2008). Additionally, herbal medicines are of plant origin, their herbal raw material and products are highly sensitive to fungal contamination (Hitokoto, 1978; Chourasia, 1990; Roy and Chourasia, 1990; Chourasia, 1995; Eufuntoye, 2004; Halt, 1998; Bugno *et al.,* 2006). The fungal contamination not only affects the chemical composition or phytochemical properties of the raw materials and, thereby, decreases the medicinal potency of the herbal drugs, but produces certain secondary metabolites known as mycotoxins, which are responsible for several chronic health risks (Purchase, 1974; Richard *et al*., 1978; Muntanola, 1987; Durakovic, 1989; Roy, 2003, Dimic *et al*., 2008; Sareen *et al.*, 2010, Stević *et al.* 2012; Masoumeh and Deokule, 2013; Dubey *et al.*, 2014; Abba *et al.*, 2015). A comprehensive review on fungal contaminations of herbal drugs and related mycotoxins was tried to present article.

Herbal drugs: current status and future scenario

The World Health Organization (WHO) has defined herbal drugs as, "use of medicinal plant preparations as therapeutic practices," that have been in existence, often for hundreds of years, before the development and spread of modern medicine and are still in use today (WHO, 1991). These herbal drugs have been a major source of curing human diseases since time immemorial. Today, one fourth of the world population depends on traditional medicines. Despite the introduction of antibiotics since the 1940's, even 80% of the population today relies on indigenous medicinal plants as well as on the drugs (Pal and Shukla, 2003). Now, the utilization of herbal drugs is on the flow and the market is growing step by step at national and international level (Kamboj, 2000**)**. Today global herbal medicine can broadly be classified into a few basic systems namely, Ayurvedic, Chinese, African and Western herbalism (Bandaranayake 2006).

Presently, the popularity of herbal drugs is not only limited to developing countries, but it is spreading all over the globe. World Health Organization (WHO) has made an attempt to identify all medicinal plants in use globally and listed more than 20,000 species (Farnsworth *et al.*, 1991). It has been estimated that 70% of all medical doctors in France and Germany regularly prescribe herbal medicine for the treatments of many diseases (Murray and Pizzorno, 2000). The number of patients seeking herbal approaches for therapy is also growing exponentially day by day (Alschuler *et al.*, 1997). An estimated report of Export–Import Bank reveal that global trade of plant-derived and plant originated products is around US $60 billion with growth of 7% per annum (Raskin *et al*., 2002; Mathur, 2003). As per the available records, the herbal medicine marketed in 1991 in the countries of the European Union was about of $ 6 billion (may be over $20 billion now), with Germany account for $3 billion, France $ 1.6 billion and Italy $ 0.6 billion. In 1996, the US herbal medicine market was about $ 4 billion, which have doubled by now (Kamboj, 2000).

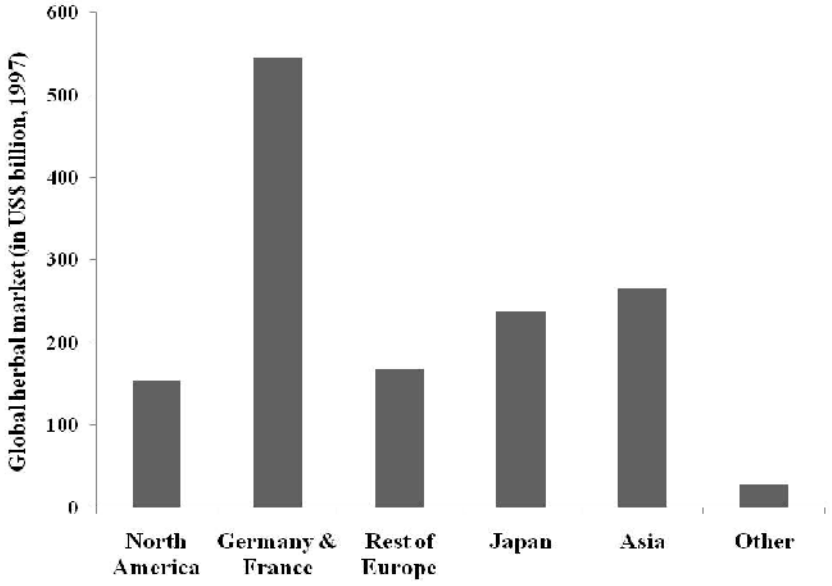

Fig. 1. Percentage revenue (US$) of herbal drugs market in different regions of world *Source:* (*Nutrition Business Journal Jan/Feb., 1997*)

It has already been reported that about 39% of all 520 new approved drugs in 1983-1994 were natural products or derived from natural products (Cragg *et al.*, 1997) whereas, 60-80% of antibacterial and anticancer drugs were derived from natural products only (Harvey, 1999). The global herbal market is valued at US$ 14 billion (1997) as shown in the figure 1. India and China are the two largest producers of herbal drug's raw materials. India has its inherent strength in Ayurveda and other ethnic systems of medicines i.e. Ayurveda, Yoga, Unani, Sidha and Homeopathy (AYUSH, 2005). Ayurveda "The science of life" is one of the important systems, among all the systems of medicines and is an independent *upaveda* of *Atharva Veda*, but it has close links with other Vedas also. In Ayurveda different parts of plants i.e. root, stem, bark, leaves, flowers, seeds, fruits and ash are generally used in the form of powder or decoction and prescribed for the treatment of various ailments. The current value of the Indian system of medicine is estimated to be around Rs.4000 crores. Over 8000 plant species are reported to be used to prepare some 25,000 formulations to treat various ailments (Shivanna, 2004). Regarding Indian herbal drugs scenario that is estimated and reported by Chauhan (2006) indicates that annual Indian herbal drugs trade is 1000-1200 crore, while annual exports is 446 crores.

There are 14,000 codified and 25,000 folklore formulations and 8000 license Pharmacies of Indian system of medicine. According to the report of Task Force on medicinal plants, in March (2006), it is estimated that in near future potential export of herbal drugs will be 10,000 crores, which was 3,000 crores only in the year 2005. Instead of modernization of herbal drugs, there are many tribes in India who are still using the wild plants traditionally for different purposes. The utilisation pattern of wild plants by tribals of India has been summarized in Table 2.

Table 1: Annual growth of herbal drugs trade by region.

Country	Country Growth		Forecast 1993-
	1985-1991	1991-92	
North America	10%	12%	15%
EEC	10%	5%	8%
Rest of Europe	12%	8%	12%
Japan	18%	15%	15%
SE Asia	15%	12%	12%
India and Pakistan	12%	15%	15%

(Purbrick, 1997; Shrikumar and Ravi, 2007; Sharma *et al*., 2008)

Table 2: Utilisation pattern of wild plants by tribals of India.

Utilization pattern	No. of plants
Total wild plants used by tribals	10,000
Medicinal purpose	8,000
Edible Use	4,000
Other Material & Cultural Requirements	750
Fibre & Cordage	600
Fodder	500
Pesticides, Piscicides etc.	325
Gum, Resin & Dye	300
Incense & Perfumes	100

(Chauhan, 2006)

Mycological deterioration of stored herbal drugs

During storage incidence of fungal contamination in most of the herbal drugs and their ingredients of plant origin, is a very common and widespread phenomenon. Generally, most of the herbal drugs are prepared from plants or plant parts like seeds, fruits, leaves, stem, bark and roots. These plant parts very often contaminated by fungal species during storage and processing. There are various sources of microbial contamination for examples harvesting, processing and storage in unhygienic environment, direct exposure to environmental pollutants/ contaminants and climatic conditions. Usually, fruits and seeds may also get contaminated in field before and during harvesting. Usually local manufacturers are used to prepare some of the herbal formulations at home or shops in open environment under unhygienic conditions and stored after packaging in transparent polythene bags rather than in air-tight containers. Most of the raw materials of herbal formulations

are sold in open containers / tins/ gunny bags in the market or even on road side, and they are directly exposed to the biotic environmental factors, air pollutants and other contaminants. All these practices may be a cause of microbial contamination (Ozay *et al.,* 2008; Essono *et al*., 2007).

It has been reported that herbal drugs are often deteriorated by microorganisms before harvesting, and during handling and storage. Additionally, unscientific methods of collection and storage, processing, transportation and congenial climatic conditions also favoured the microbial deterioration of stored herbal drugs. Among the microbial contaminants, fungal contaminants play a very crucial role in deteriorating the stored herbal drugs and in reducing their medicinal potential (Richard *et al.*, 1978; Roy, 2003; Rai and Mehrotra, 2005; Essono *et al.*, 2007). Species of *Aspergillus, Penicillium, Alternaria, Fusarium, Cladosporium, Curvularia, Chaetomium, Rhizopus, Mucor, Absidia, Paecleomyce, Trichoderma,* and *Aureobasidium* (Hitokoto *et al.*, 1978; Roy and Chourasia, 1990a,b; Halt, 1998; Eufuntoye, 1999; Eufuntoye, 2004; Mandeel, 2005; Bugno *et al*., 2006; Donia, 2008; Sareen *et al*., 2010, Gautam *et al.*, 2011; Masoumeh *et al.*, 2013; Dubey *et al.*, 2014; Sharma *et al.*, 2014; Abba *et al*., 2015) have been reported as the most common fungal genera associated with medicinal plants. Further, prolonged storage of herbal drugs is found more favourable for the proliferation of mycotoxigenic fungi in high frequency (Bugno *et al.*, 2006; Singh *et al.*, 2008) (Figs 2 & 3).

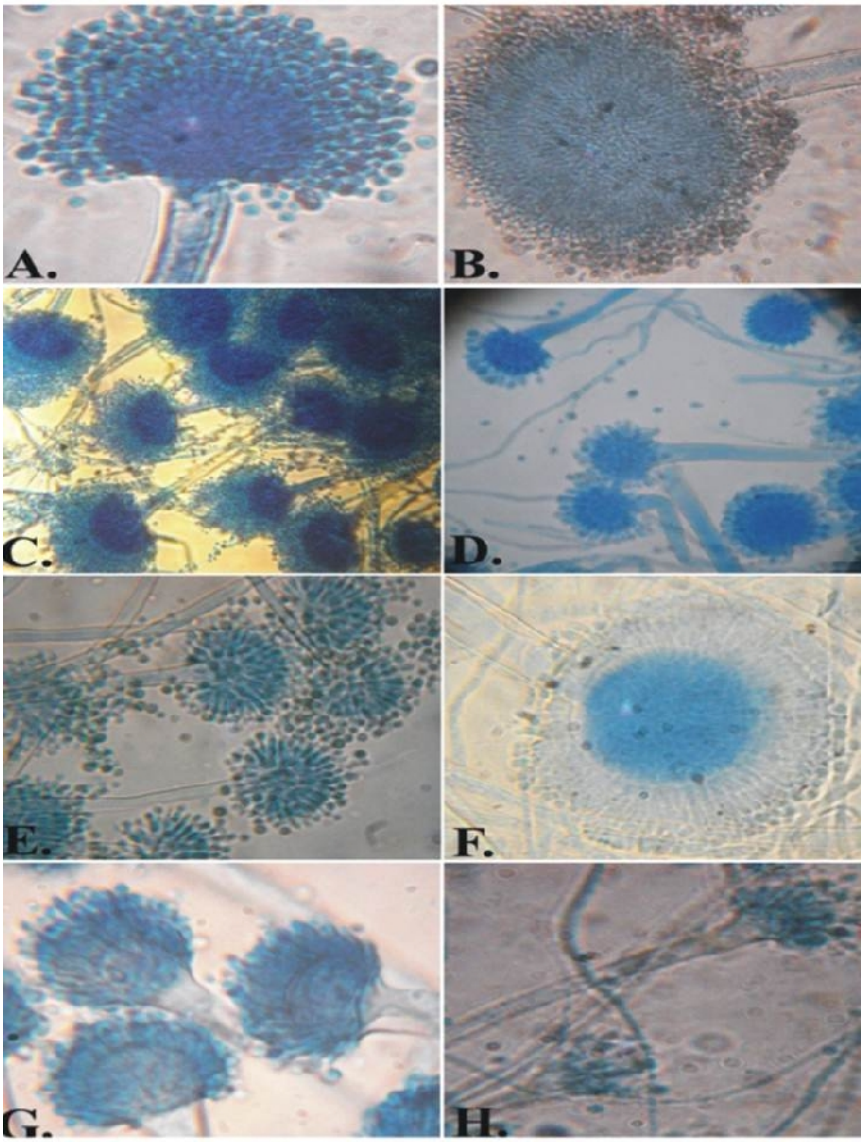

Fig. 2. Different *Aspergillus* species isolated form stored herbal drugs. **(***Photographed by A.K. Gautam*).

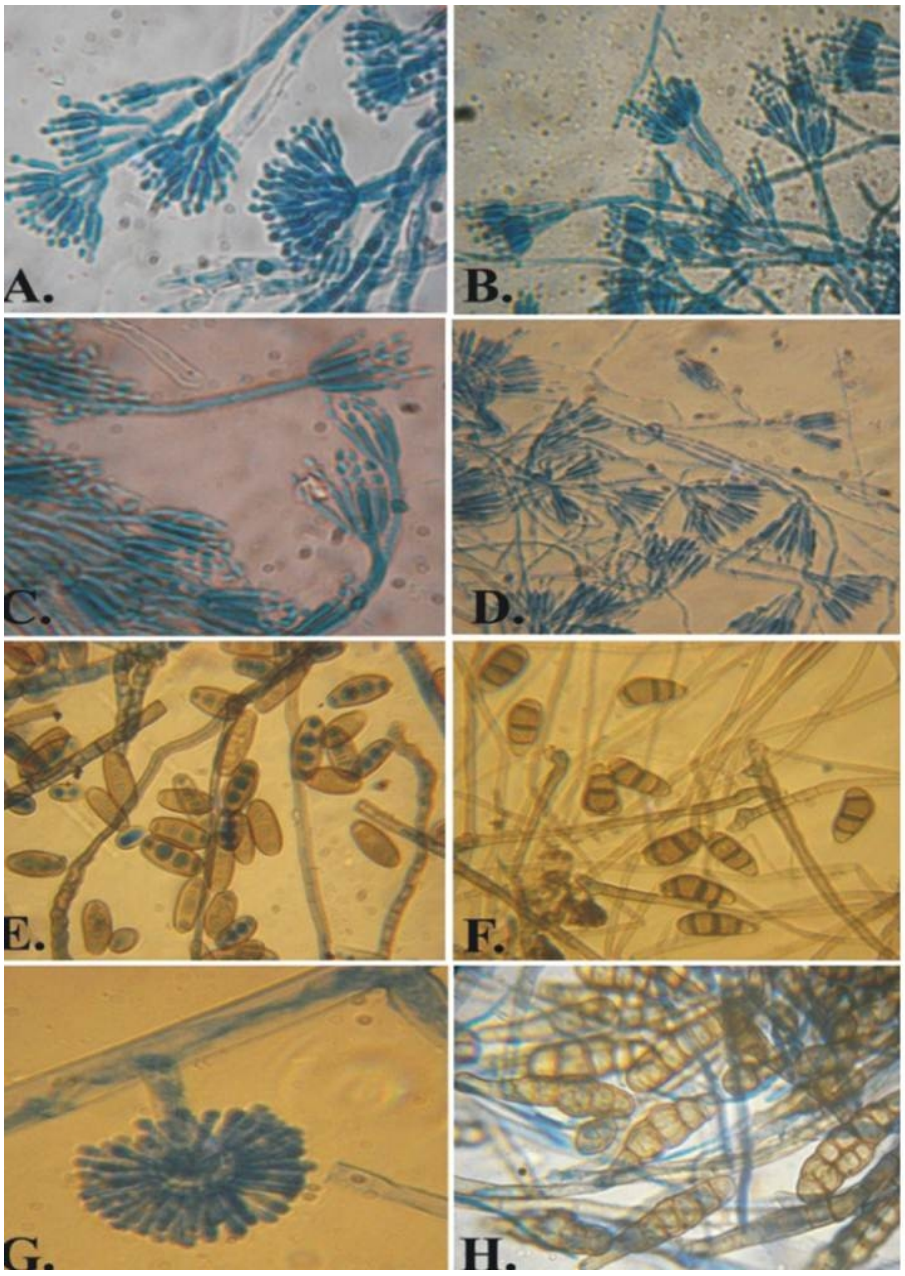

Fig. 3. Different fungal species isolated form stored herbal drugs. **(***Photographed by A.K. Gautam*).

Several studies have been carried out on the association of fungal genera and their mycotoxins with medicinal plants and stored herbal drugs. Most of the medicinal plants and their parts like leaf of *Adhatoda vasica* Nees. , *Pelargonium graveolens* L., *Ocimum basilicum* L., *Marjorana hortensis* L., *Mentha piperita* L. *Mentha viridis, Corchorus oritorius, Anethum grveolens* L., *Petroselinum sativum* Hoffm., *Cuminum cyminum* L., *Thea sinensis* L.; flowers of *Evolvulus alsinoides* Linn. *Matricaria chamomila* L., *Crocus sativus* Linn; Inflorescence of *Sphaeranrhus indicus* Linn.; root of *Asparagus racemosus* Willd., *Glycyrrhiza glabra* Boiss., *Plumbago zeylanica* L.*;* fruit of *Emblica officinalis* Gaertn., *Myristica fragrance* Houtt.*, Tribulus terrestris* Linn.*, Terminalia bellerica* Roxb.*, Terminalia chebula* Retz.; seed of *Mucuna Prurlta* Hook.; whereas root, seed, leaves of *Argyreia speciosa* Sweet. and root & resinous gum of Bombax *malabaricum* D.C. have been reported to be contaminated with various fungi during their storage (Roy *et al.*, 1988; Choursia, 1990; Kumar and Roy, 1994; Choursia, 1995; Singh *et al.*, 2008; Sareen *et al.*, 2010, Gautam and Bhadauria 2011; Gautam and Bhadauria 2012; Stević *et al.* 2012; Masoumeh and Deokule, 2013; Dubey *et al.*, 2014; Sharma *et al.*, 2014; Kedia *et al.,* 2014; Abba *et al.*, 2015).

Factors responsible for fungal contamination of herbal drugs

It has been reported that environmental conditions play a very significant role in contaminating various products by microorganisms, toxigenic fungi as well in mycotoxin elaboration. Higher incidence of fungal contamination in tropical and subtropical areas has been reported by Essono *et al*. (2007) and Ozay *et al.* (1995). According to them harvesting and post harvesting practices, high temperature, moisture contents and relative humidity are the main factors which are conductive to fungal infestation and mycotoxin elaboration (Bandaranayake, 2006).

Harvest

Harvesting of raw materials of herbal drug; is till now carried out by various traditional methods in developing countries. Generally, unripe (earlier to maturity) herbal fruits are harvested manually, or harvesting to a canvas (shaking the branches to collect the herbal fruits in canvas laid under the branches) and harvesting from the ground (''windfall'') methods are adopted by the herbal drugs collectors. These harvesting techniques are often proved destructive because they cause damage on fruit surface or shell (Ozay *et al.,* 2008). The damaged or cracked surfaces, cuts or wounds of stem, root, rhizome, flowers, fruit and seed, during harvesting, can be a good source of fungal invasion and the toxigenic strains of fungi may produce mycotoxins during growth. This implies that safe harvesting is essential for prevention of both mould growth and mycotoxin contamination.

Drying

Immediate, proper drying after harvesting is the most important means to avoid fungal growth and mycotoxin production. Different sun-drying techniques', mainly drying on the ground in the fields /soil, concrete floor, is used by farmers. Sun drying by spreading on a paved floor with intermitted stirring is the most commonly used method especially in developing countries. Usually sun drying requires 6-10 days continuous sunlight for 6 to 8 hrs, to reduce the moisture content of raw materials from 0.38-0.24%, at which herbal raw materials can be stored safely. But in rainy weather it is not possible to dry the crop in a reasonable time. Re-wetting due to insufficient protection from rain or due to vapour condensation at night is a further problem. The result is increased mould growth due to high moisture contents and mycotoxin contamination. This can be avoided by fast mechanical drying at 40°C; it may decrease the risk of mycotoxin contamination (Lacey, 1989; Essono *et al.*, 2007; Saohin *et al.,* 2007; Ozay *et al*., 2008).

Storage

Traditionally, moisture control has been the method of choice for prevention of mould growth in stored herbal drugs. Also the constancy of temperature and relative humidity is of great significance (Ozdemir and Ozilgen, 2001). The rapidity of the moisture transfer depends on the moisture content of the stored material and on the magnitude of temperature differential. Respiration by insects, mites and fungi produces water that also causes spoilage of stored material. Moisture transfer and deterioration can be avoided by maintaining a uniform temperature throughout the bulk (Beuchat, 1978**).** As fungal contamination is correlated directly with temperature, storage at low temperature has been suggested by Bullerman, (1984); Weidenborner, (2001). The optimum temperature conditions reported for growth of *A. flavus* and *A. parasiticus* is 35°C, whereas it is 33°C for aflatoxin production (Beuchat, 1978; Sanchis and Magan, 2004; Abbas, 2005).

Processing

Generally, the equipments and material used for the processing and packaging can be a good source of microbial or fungal contamination. Even the clothes, dirty hands, area of processing including walls, ceiling and floor of the room may carry microbial contaminants and can be good source of fungal and bacterial contamination (Arrus *et al*., 2005).

Since herbal drugs are of plant origin; therefore, along with unscientific methods of per and post processing, the characteristics of herbal raw materials, like moisture content also played an key role in their fungal infestations, and mycotoxins production, which are harmful for consumer's health (Hitokoto *et al.,* 1978; Halt, 1998; Elshafie *et al*., 1999; Roy, 2003; Tassaneeyakul *et al*., 2004; Bugno *et al.*, 2006; Essono *et al.*, 2007; Donia, 2008).

Moreover the diverse abiotic factors operating in the processing and storage conditions as well as chemicals constituents of the herbal drugs might have resulted in variation in mycopopulation in different substrates (Chourasia *et al.*, 2008). It is reported that high moisture contents favours incidence of higher fungal counts in stored herbal drugs (Roy *et al.*, 1988; Halt, 1998, Dutta *et al.*, 1998; Ray and Majumdar, 1976; Chattopadhyay and Bhattacharyya, 2007, Hitokoto *et al.*, 1978; Aryes *et al.*, 1980; Aziz *et al.*, 1998; Arab *et al.*, 1999; Elshafie *et al.*, 1999; Mandeel, 2005; Sareen *et al.*, 2010; Abba *et al.*, 2015).

Mycotoxins in stored herbal drugs

The adoption of unscientific methods of collection and storage, processing, transportation and congenial climatic conditions, exposed the herbal raw materials as well as their final products to many microbial contaminants i.e. bacterial as well as fungal. Since herbal drugs are of plant origin they are prone to fungal infestations, and these fungi during growth produces mycotoxins, which are harmful for consumer's health (Hitokoto *et al.,* 1978; Halt, 1998; Elshafie *et al*., 1999; Roy, 2003; Tassaneeyakul *et al*., 2004; Bugno *et al.*, 2006; Essono *et al.*, 2007; Donia, 2008; Sharma *et al.*, 2014).

Mycotoxins are toxic secondary metabolites produced by various fungal genera on a variety of substrates like grains, cereals, spices, fruits, vegetables, herbal drugs, nuts and legumes, which can cause trouble for humans and animals (Oswald *et al.*, 2005; Golob, 2007). The study of mycotoxins started in 1960, when more than 100,000 turkeys died in England in a short period of time due to 'Turkey X disease'. Post-mortem examination revealed necrotic liver damage and cell proliferation in the bile ducts. Epidemiological investigation eventually traced the contamination of peanut meal which had been used as poultry feed for all these animals, with common fungus, *Aspergillus flavus* and related secondary metabolites (ICMR, 1993). Later on other mycotoxin producing fungal genera were identified which includes *Aspergillus, Pencillium, Fusarium, Helminthosporium* and *Alternaria* (Oswald *et al.*, 2005).

Types of mycotoxins

Toxigenic strains of fungi, growing on various raw materials as well as on the herbal drugs during harvesting, processing and storage produces different metabolites. These metabolites may be harmful/ toxic to living beings or beneficial to man as in the case of antibiotics, like penicillin. More than 300 mycotoxins have been described till now (Akande *et al*., 2006). The major mycotoxins along with their synthesizing fungal genera are given below:

Aflatoxins (AF). The aflatoxins are a group of secondary metabolites produced by strains of *Aspergillus flavus*, *A. parasiticus* and *A. nomius.* Occurrence of Aflatoxins have been reported as a natural contaminant in several food and feed substrates, such as ground nut, peanuts, cotton seed, food grains, cereals, pulses, rice, wheat, maize, barley, vegetables, fruits, dried fruits, canned food and herbal drugs etc. Highest concentration of aflatoxins produced as result of post-harvest spoilage of commodities stored under warm moist conditions while significant concentrations may also be produced in the field before harvest (Hill *et al*., 1985). Aflatoxins are a group of closely related bis-dihydrofurano (Fig. 4 & 7) secondary fungal metabolites that have been epidemiologically implicated as environmental carcinogens in humans.

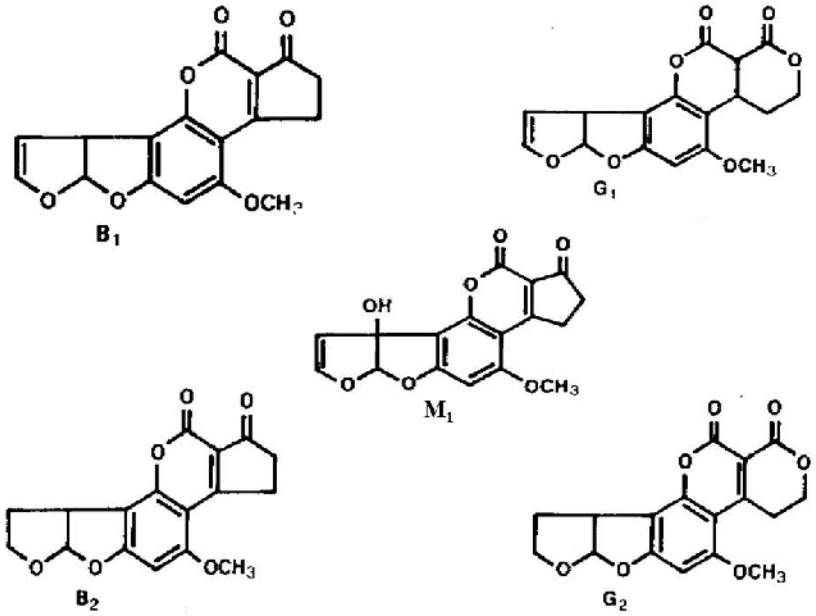

Fig. 4. Chemical structures of Aflatoxins.

There are six aflatoxins of analytical interest. The aflatoxin B group fluoresces blue and the aflatoxin G group green under UV light (365nm). This fluorescence is due to a kojic acid derivative formed by the organism that produces aflatoxin and therefore provides only a "presumptive" indication of the presence of aflatoxin (Moss, 1999). Aflatoxin M is formed by biotransformation. This metabolite is found in milk from cows given contaminated feed. Aflatoxins are very stable and are not destroyed at ordinary cooking temperatures (Golob, 2007) i.e proved resistant to heat (Galvano *et al.*, 2005; Jay *et al*., 2005). Reports are available for the occurrence of aflatoxins from medicinal plants viz. *Argyreia speciosa, Bombax malabaricum, Myristica fragrance, Sphaeranrhus indicus, Tribulus terrestris, Mucuna cuchisinesis, Emblica officinalis, Terminalia bellerica, Terminalia chebula, Piper nigrum* (Kumar and Roy, 1994; Halt, 1998; Singh *et al.*, 2008, Sareen *et al.,* 2010; Gautam and Bhadauria 2011; Gautam and Bhadauria 2012; Stević *et al.*, 2012; Sharma *et al.*, 2014; Abba *et al*., 2015, Lee *et al.*, 2015).

Generally, aflatoxins affect the target organs. Susceptibility varies with breed, species, age, dose, length of exposure and nutritional status. Aflatoxins are extensively linked to human primary liver cancer and are immunosuppressive, hepatotoxic carcinogenic and mutagenic. These mycotoxins may also cause decreased production of milk, eggs and weight gains (Bosch and Peers, 1991). The Food and Drug administration (FDA) has recommended 20 ppb for humans, immature animals (including poultry), and for all dairy animals.

Citrinin. Citrinin was first isolated from *Penicillium citrinum* prior to World War II (Hetherington and Raistrick, 1931). Later on citrinin was reported to be synthesized from many species of *Penicillium* and *Aspergillus* (e.g., *Aspergillus terreus* and *Aspergillus niveus*), including certain strains of *Penicillium camemberti* (Manabe, 2001). Species of *Monascur rubber* and *M. purpureus* used for the production of red pigments were also found to produce citrinin (Blanc *et al.*, 1995**)**. The occurrence of citrinin has been reported from some stored raw and powdered herbal drugs (El-Kady *et al.*, 1995; Trucksess and Scott, 2008) (Fig. 5).

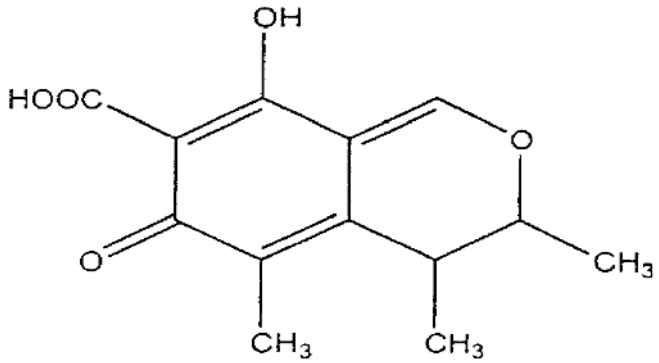

Fig. 5. Chemical structure of Citrinin.

Citrinin is believed to cause procrine nephropathy. This mycotoxin acts as a nephrotoxin in all animal species tested, but its acute toxicity varies in different species (Carlton and Tuite, 1977). The 50% lethal dose for ducks is 57 mg/kg; for chickens it is 95 mg/kg; and for rabbits it is 134 mg/kg (Hanika and Carlton, 1994). Citrinin may act synergistically with ochratoxin A to depress RNA synthesis in murine kidneys (Sansing *et al.*, 1976).

Sterigmatocystin. Sterigmatocystin is a toxic metabolite secreted by *Aspergillus versicolor, A. sydowi, A. nidulans* and a species of *Bipolaris* (Fujii *et al.*, 1976)**.** It has been reported in mouldy grain, green coffee beans and cheese although information on its occurrence in foods is limited. It has also been reported from stored Triphala churn (Singh, 2003), raw and powdered ingredients. Sterigmatocystin is closely related to one of the mycotoxin i.e. aflatoxin, as a precursor in aflatoxin biosynthesis and in 1993, International agency for Research on Cancer (IARC) has classified it as a Group-2B carcinogen. A number of closely related compounds such as o-methyl sterigmatocystin are known and some may also occur naturally of in herbal drugs (Fig. 6).

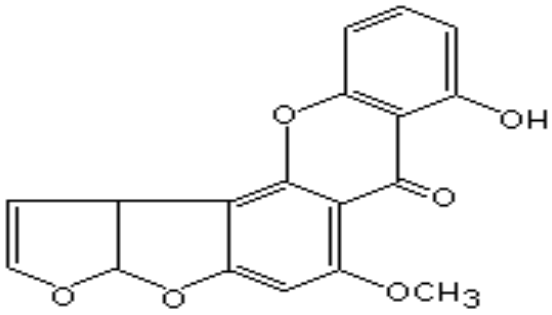

Fig. 6. Chemical structure of Sterigmatocystin.

Sterigmatocystin (ST) is a proximal carcinogen producing squamous cell carcinomas and having the toxic effects much the same as those of aflatoxin B1(Bennet *et al.*, 1982) and resistant to heat (Galvano *et al.*, 2005; Jay *et al*., 2005). It is thus considered as a potent carcinogen, mutagen and teratogen. Toxic effects of sterigmatocystin-fed laboratory animals have included kidney, liver damage, diarrhoea, skin and hepatic tumours induced in rats by dermal application. Cattle exhibiting bloody diarrhoea, loss of milk production and in some cases death were found to have ingested feed containing *Aspergillus versicolor*

and high levels of sterigmatocystin of about 8 mg/kg (Vesonder and Horn, 1985).

Besides these mycotoxins some other mycotoxins identified for herbal drugs and their toxicity are given in the following table 3:

Table 3: Sources and potential toxicities of some important mycotoxins.

Toxins	Producing fungi	Toxicities substrates
Fuminisins	*Fusarium veritcilliodes* & *F. proliferatum*	Hepatoxic
Ochratoxin	*Aspergillus ochraceus*	Nephrotoxic
Citreoviridin	*Penicillium viridicatum*	Cardiac beri-beri
Cyclochlorotine	*Penicillium islandicum*	Hepatoxic
Cytochalasin E	*Aspergillus clavatus*	Cytotoxicity
Maltoryzine	*Aspergillus oryzae*	-------
Patulin	*Penicillium expansum*	Brain and lung haemorrhage
PR Toxin	*Penicillium requeforti*	-------
Rubratoxin	*Penicillium rubrum*	Liver haemorrhage and fatty infiltration
Rugulosin	*Penicillium islandicum*	Nephrosis & liver damage
Tremorgens	*Penicillium* & *Aspergillus*	-------
Trichothecenes		Cytotoxicity
Vomitoxin(Deoxynivalenol)	*Fusarium graminaerum*	Vomiting

(FAO, 1979)

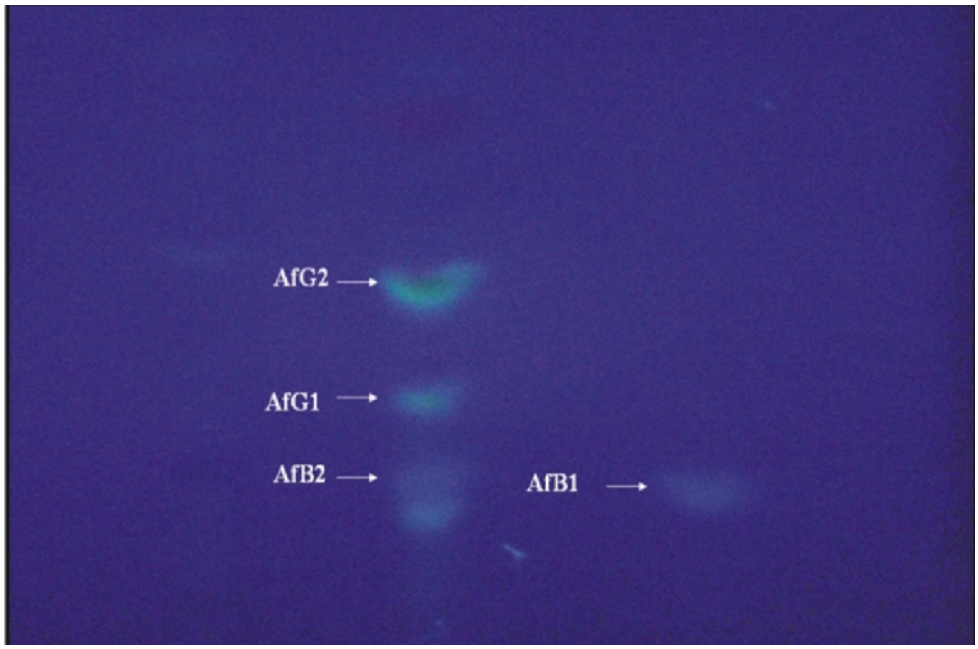

Fig. 7. Thin Layer Chromatographic (TLC) detection of Aflatoxins isolated from stored herbal drugs. (*Photographed by A.K. Gautam*).

Factors affecting mycotoxin production

The factors associated with the mycotoxin production include the type of plant material, geographical location from where it is harvested, method of harvest, post-harvest treatments and climatic conditions of pre and post-processing and storage. Mycotoxin accumulation in herbal drugs can occur in the field, during harvest, postharvest and during storage. If decayed or mouldy raw material is not removed before processing or packaging, it may contribute significant amounts of these mycotoxins (Drusch and Ragab, 2003; Sanchis and Magan, 2004). In addition to above factors, raw materials of herbal drugs are more susceptible to fungal spoilage due to their high water activity, sugar content and presence of

organic acids (Tournas and Katsoudas, 2004). The conditions that promote fungal growth in stored herbal drugs do not necessarily coincide with those responsible for mycotoxin production. Mycotoxin contamination may occur either plant material/ raw material used in herbal drug preparation, harvested in the earlier stages of maturation or if stored under conditions of high relative humidity. Insect, bird damage exposes inner tissues of the herbal raw material to toxigenic fungi which may result into mycotoxin contamination (Ahmed *et al.*, 1997).

Storage of herbal drugs under high moisture/humidity (>14%) at warm temperatures (>20^{0}C) or/and inadequately dried conditions favours the incidences of fungal contamination and mycotoxin production. However, some species of *Fusarium* and *Penicillium* can produce mycotoxins (e.g. trichothecenes and penicillinic acid) at low temperature (5°C) (Bullerman, 1984; Weidenborner, 2001). Harvesting and post harvesting processing have been reported as main factors responsible for fungal infestation (Karaca and Nas, 2006). Along with temperature and moisture, relative humidity of storage conditions also found conductive for mould growth and mycotoxin contamination. It has been reported that the harvesting under higher relative humidity and sudden rain can be helpful in accumulating the aflatoxins (Karaca and Nas, 2006). According to Ozay *et al*., (1995) immediate drying of substrates after harvesting was found suitable in reducing level of aflatoxins. Besides of all above discussed factors, strain specificity along with its ability to synthesize mycotoxins may be an important factor for mycotoxins contamination in stored herbal drugs. McCallum *et al.*, (2002) found extensive differences among *Penicillium expansum* isolates, in terms of patulin production and fungal growth in apple ciders. Genetic variations may have been the ultimate cause of these differences, but environmental factors such as temperature and pH, as well as the storage duration, could contribute greatly to fungal growth and patulin production.

Economic aspects of mycotoxin contamination of herbal drugs

Medicinal plants have been known for millennia as a rich source of therapeutic agents for the treatment of various ailments (Sharma *et al.*, 2008). The US $ 60 billion ever-growing global market of medicinal plants has been growing at a fast pace of 7% annually, capitalizing on the growing awareness of herbal and aromatic plants worldwide. Despite its inherent strength in ayurveda and other ethnic systems of medicine, India has only US $ 100 million (Dubey *et al.*, 2008). The reasons behind, are the unscientific methods of collection, storage, transportation and congenial climatic conditions which make the raw materials of herbal drugs prone to microbial infestations/contaminations. This microbial degradation of herbal drugs decreases their efficacy and medicinal potential which became one of the major reasons to lagging behind the Indian herbal drug industry. There are reports on mycotoxin contamination of different raw and powdered herbal drugs from India (Roy *et al.*, 1988; Chourasia, 1990; Kumar and Roy, 1994; Giridhar and Ready, 1997; Roy, 2003; Singh *et al.*, 2008; Sareen *et al.*, 2010; Gautam and Bhadauria 2011; Gautam and Bhadauria 2012; Sharma *et al.*, 2014; Abba *et al.*, 2015). Along with the decrease of efficacy and medicinal potential of herbal drugs, fungal contamination also resulted into decline in Indian herbal trade globally (Sharma *et al.*, 2008; Dubey *et al.*, 2008). Due to detection of aflatoxin B1 in the black pepper procured from India, some foreign pharmaceutical firms have decided to re-evaluate the suitability of Indian black pepper samples for formulation of phytomedicines (Seenappa and Kempton, 1980). In Egypt, different medicinal plant samples imported from India were reported to be contaminated by different toxigenic strains of fungi (Aziz *et al.,* 1998). Roy and Chaurasia, (1990) reported the contamination of some raw materials by aflatoxins up to a level of 20 ppb.

Appreciable amount of mycotoxins from various stored parts of important medicinal plants, e.g. rhizomes of *Asparagus racemosus* (0.16 µg/g), *Atropa belladonna* (0.27 µg/g), *Withania somnifera* (0.68 µg/g), *Plumbago zeylanica* (1.13 µg/g), fruits of *Terminalia chebula* (1.19 µg/g) and (1.16 µg/g) in seeds of *Mucuna pruriens* (Chaurasia, 1990) have been reported. Singh *et al.* (2008) have reported mould and aflatoxin contamination in stored raw materials of six medicinal plants, viz. *Adhatoda vasica*, *A. racemosus*, *Evolvulus alsinoides*, *Glycyrrhiza glabra*, *P. zeylanica* and *T. chebula*. Fungal contamination has been reported to affect the chemical composition of the raw materials and thereby decrease the medicinal potency of herbal drugs **(**Roy, 2003**).** The icrobial contamination of herbal drugs is a major impediment preventing India from becoming an herbal giant.

Table 4: Mycotoxin contaminations in herbal drugs.

Mycotoxins	Herbal drugs contaminated	Reference
Aflatoxins	*Asparagus racemosus,* *Emblica officinalis, Hibiscus sabdariffa*, *Crocus sativus*, *Mentha piperita*, *Myristica fragrans*, *Nigella sativa, Allium sativum*, *Syzygium aromaticum*, *Piper nigrum*, *Cuminum cyminum*, *Zingiber officinale*, *Elleteria cardamomum*, *Cinnamomum zeylanicum*, *Citrus* spp, *Rhus coriaria*, *Laurus nobilis*, *Thymus vulgaris, Chrysanthemum* sp., *Adhthoda vasica* , *Asparagus racemosus, T. chebula*, *Allium cepa, Curcuma zedoaria, and Zingiber cassumunar, Anethum graveolens, Cissus quadranularis, Cuminum cyminum, Lepidium sativum, C longa, Artemisia indica, Cladogvnos orientalis, Dracaena loureiri, Dryobalanops aromatica, Myristica fragan*	Roy and Chourasia 1990, Kumar and Roy, 1993; Gautam and Bhadauria, 2009, 2011, 2012; Gautam *et al.*, 2011, Toma and Abdulla, 2013, Tournas and Katsoudas 2008, Tansakula *et al*., 2013. Tassaneeyakul *et al*. 2004, Gautam and Bhadauria, 2009,
Citrinin	*Emblica officinalis, Terminalia belerica, T. chebula*	Roy and Chourasia 1990 Gautam and Bhadauria, 2009, 2011, 2012; Koul and Sunbali 2010; Gautam *et al.*, 2011
Zearalenone	*Emblica officinalis, Terminalia belerica, T. chebula*	Roy and Chourasia 1990, Dubey *et al.*, 2004; Gautam and Bhadauria, 2009, 2011, 2012; Gautam *et al.*, 2011; Zhang *et al.*, 2011.
Ochratoxin A,	*Emblica officinalis, Terminalia belerica, T. chebula*	Roy and Kumar 1993; Roy and Chourasia 1990 Gautam and Bhadauria, 2009, 2011, 2012; Gautam *et al.*, 2011

CONCLUSION

Since herbal drugs are now swapping the synthetic drugs industry with the marvellous increase in number of users relying on them for curing various ailments. But it is not actual picture; the other side of the scenario is as herbal drugs are of plant origin and get microbial infestation during harvesting, packing, storage and post storage practices. These unwanted contamination not only make the herbal drugs unfit for consumers but alters their phytochemical properties and therapeutic potential as well. Besides treatment of one disease, these contaminated herbal drugs become the invitation for several other serious ailments such as liver, kidney or nervous system damage, immunosuppression and carcinogenesis among users. Therefore, it is essential to scrutinize these herbal raw materials before processing for the presence of contaminants and only the raw materials of high grade (showing absence of mould/ mycotoxin and other contaminants) should be allowed to use for the preparation of herbal drugs. Moreover, after processing these herbal drugs should also be tested for presence of mycotoxins, prior packing and launching for public use.

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