Article

Recent Advances in Bracken Fern Toxin Research

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Abstract

Bracken fern, commonly found in hilly regions contains toxic substances. It is reported to cause alimentary carcinoma and haematuria in both animals and human beings. Present paper deals with the recent advances in bracken fern toxins research in animals.

Keyword: Bracken fern, *Pteridium aquilinum* Kuhn, Toxin, Carcinogens, Animal, Human, Haematuria, Recent advances.

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Introduction

Bracken fern, *Pteridium aquilinum* Kuhn is found on exposed grassy lands in hills throughout India. It is an ornamental, tufted, fast-growing fern, grown for borders and rockeries and also planted in pots for indoor decoration. In some countries it has become a troublesome weed. In times of scarcity, the rhizomes are boiled or roasted and eaten or are ground into powder and used for making bread after removing its bitterness. It is also used as a feed for stock, especially pigs. The fronds if eaten by the animals in large quantity, it causes severe poisoning (*Wealth of India, 1969*).

In spite of its toxic properties and effects Bracken fern is reported to possess many pharmacological activities. Indenone (structurally similar to pterosins), isolated from the plant is useful in the treatment of Alzheimer’s disease (Potter, 1999) and illudins structurally similar to ptaquiloside have been found cytotoxic to haematopoietic tumours at extremely low concentration (Kelner et al, 1987). Quercetin widely present in bracken fern was proved to be a potent anti-oxidant, anti-inflammatory, anti-allergic and anti-viral (Musonda & Chipman, 1999). In these effects, quercetin enhances the phase-II and inhibit the phase-I enzymes in detoxification and metabolic activation of carcinogen. Other useful properties are: scavenging the free radicals, tumour anti-proliferative effect, tyrosine kinase inhibition and inactivation of mutant P53. It can also modulate cytochrome P450 enzymes in metabolism of certain carcinogens.

Bracken fern poisoning is known to cause various anomalies in domestic as well as laboratory animals. Epidemiological evidence suggests that some cancers in man might result from...
direct or indirect consumption of bracken carcinogens. International Agency for Research on Cancer categorized bracken fern in 2B group. This category is used for agents, mixtures and exposure circumstances for which there is limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals. Bracken fern contains wide range of toxins, viz. thiaminase-1, astragalin, isoquercetin, pterosides, pterosins, fumeric, succinic and shikimic acid, braxin A₁ and A₂, ptaquiloside, d-econdysone and others (Dawra and Sharma, 2001). These toxins have different biological activities, which include mutagenic, clastogenic, carcinogenic, antithiaminic, histamine release from mast cells, etc.

Toxic effect of bracken fern was first recorded by Tophan in 1787. Since then, various toxic effects were reported in both animals and human beings belonging to hilly regions throughout the world. These include thiamine deficiency, acute haemorrhagic disease, bright blindness, enzootic haematuria, upper alimentary carcinoma and profound thrombocytopenia in animals and oesophageal carcinoma, gastric cancer in human beings (Smith et al., 1999). Bracken fern causes wide variety of cancers at terminal portion ileum and urinary bladder due to interaction between ptaquiloside, a norsesquiterpene glycoside and DNA of the tissue at alkaline pH. But the information regarding toxicokinetic, toxicodynamic and some pharmacological activities in body systems are scanty. Hence, present paper mainly deals with recent advances in bracken fern toxins research in animals.

Symptoms of Bracken Fern Toxicity

Under natural conditions, exposure of bracken fern to animals occurs during hunger, scarcity of fodder in drought, winter season or by fodder contamination or by bedding materials. After ingestion, it produces various well-recognised syndromes. But, the exact mechanism by which toxic metabolites of bracken fern absorb into the body system is not known. However, the toxic effect of fern toxins is well documented in brain, eye, ileum, urinary bladder and bone marrow of animals. Cyanogenic potential of bracken fern have been recorded in U.K. and Australia (Low and Thomson, 1989) and death due to cyanogenesis have not been reported, possibly due to the unpalatability of cyanogenic phenotypes. In monogastric animals—like horses, pigs and rodents, the toxicity has been ascribed to the presence of thiaminase enzyme in the fern, which destroys vitamin-B₁ resulting into deficiency of vitamin and symptoms that respond to vitamin-B₁ therapy if started at an early stage. Thiaminase is not completely destroyed in situ by steaming (Evan, et al., 1954). In addition to thiaminase, a thermostable anti-thiamine factor is also present in bracken fern.
Thiaminase activity is highest in rhizomes and crosiers but declines with maturation of plant. It mainly results in hypoglycaemia and leads to various nervous signs-like ataxia, opisthotonus, convolution and irreversible lesions of polioencephalomalacia. Another syndrome called acute haemorrhagic disease occurs most frequently in weaned calves. This is due to degenerative changes in more rapidly growing cells in body, especially in bone marrow. Epithelial cell degeneration also gives rise to severe necrosis of pharynx and larynx. The megakaryocytes, which produce the platelets, are depleted during the bone marrow aplasia and profound thrombocytopenia occurs. This causes severe haemorrhagic crisis. Other stem cells of the haemopoietic systems are also affected, especially those leading to formation of granulocytes and lymphocytes and thereby lead to severe leukopenia (Evans et al, 1958). In sheep, toxic effects of bracken fern are due to progressive degeneration of the retina, which results in blindness (Watson et al, 1972). This retinal atrophy leads to an increased reflectance of the Tapetum lucidum seen especially in semidark conditions, which has given the name bright blindness. Stenosis of retinal vessels is also reported.

In rats, ileocaecal region appears to be the most susceptible to tumours, especially, the terminal three centimeter of the ileum (Hirono et al, 1977). The possibility that a nonspecific dietary irritation was an aetiological agent was eliminated by showing that feeding of a solid residue of bracken (after removal of carcinogen) is not carcinogenic (Evans, 1986). It was suggested that preferential localization of tumours in this part of intestine is due to stagnation of intestinal contents in this region. More over, it is possible that gut microflora may convert ptaquiloside into its aglycon either directly or following conjugation may yield the proximate carcinogen or mutagen (Fenwick, 1988).

Carcinogenic effect

The possible mechanism in toxicodynamic system by which tumour develops due to bracken fern consumption was first proposed by Ojika et al (1987). They stated that ptaquiloside carcinogenicity is expressed via initial DNA damage. It was found that alkaline conditions are essential for its conversion into an active intermediate called dienone, an ultimate carcinogen. This is able to form an adduct with DNA bases (Smith et al, 1994).

In vitro studies revealed the mechanism of DNA adduct formation. The dienone formed due to reaction between ptaquiloside and NaOH (0.01 m) was incubated at 37°C for 1 hr with calf thymus DNA. Adducted DNA was isolated and DNA adducts formed were studied using 32p post-labeling assay (Prakash et al, 1996). In many instances, reaction with DNA is believed to be the first-step in the initiation of chemically induced carcinogenesis. Modified bases in specific codons of proto-oncogene lead to point mutations, which in turn lead to protein products with deleterious effects (Kito et al, 1996).


In short, bracken fern induces carcinogenesis through mutation in codon 12-13 and codon 59-63 which reduces the GTPase activity of ras protein by altering its conformation which in turn triggers the uncontrolled cell growth associated with neoplasia (Benjamin & Voght, 1991).

Enzootic bovine haematuria

In cattle, condition called enzootic bovine haematuria (EBH) was widely reported throughout the world (Datta, 1953; Fujimoto et al, 1951; Smith & Beakson, 1970; Mckenzie, 1978; Somvanshi et al, 1997a). This condition is characterized by intermittent presence of blood in urine, debility, anaemia and leads to death, after prolonged ingestion of bracken fern. The disease is expressed as pre-clinical, clinical and terminal stage. The pre-clinical stage is exhibited by the absence of systemic disturbance or some times rise in temperature may be seen. Onset of clinical stage is gradual. There is frequent micturation with bloody urine, arched back and switching of tail. Blood clots are seen in voided urine, which lead to haemorrhagic anaemia. In later stage,
passage of bloody urine becomes a constant feature and the colour may be as dark as coffee. This will continue till the death of animal. This is characterized by manifestation of multiple mixed tumours of epithelial or connective tissue origin and many are of vascular origin and these, in particular give rise to intracystic haemorrhages (Somvanshi, 2002). Carcinoma of oral cavity, naso-pharynx, oesophagus and forestomach of ruminants were reported in UK and this was due to interaction between BPV-2 and bracken fern as a cofactor.

Toxicity in Human

Animals exposed to bracken fern, excrete the carcinogen in milk (Evans et al, 1972) and urine (Pamukcu et al, 1966). This was explained by administering the milk obtained from fern fed cows into rats, developed tumours in intestine and urinary bladder. In another experiment, urine of bracken fern fed cattle was extracted with ethylacetate and carcinogenicity was described by pellet implantation techniques in mouse. High incidence of transitional cell carcinoma was reported in urinary bladder of these mice. However, the nature of carcinogen excreted in milk or urine was not known.

Effect of bracken fern in human health is of great concern. In Japan, Australia, New Zealand and North America bracken rhizome and crosiers are consumed regularly. The treatment of bracken with water before consumption in these countries, have been tested and found to reduce but not completely eliminate the carcinogenicity (Hirono et al, 1972). Some epidemiological survey in Japan and Brazil indicated the association between gastric and oesophageal cancer after prolonged consumption of cow milk grazed in fern infested area.

Conclusion

Bracken fern causes well-defined syndromes in animals. This is due to toxic and carcinogenic effects of toxins found in this fern. Toxicokinetic effects of ferns draw a special attention to the researchers, as scanty work has been carried out. Further, residual effects of toxic metabolites of this fern in various tissues of the body may pave a new way for effective strategies in controlling the anomalies induced by these fern toxins. Moreover, prime importance is to be given to its ailments, since it involves human health in hilly region.

References

**Ethnoveterinary study conducted by Chinthu and his colleagues in South Kerala on the traditional veterinary treatment methods of local healers revealed following treatments given by local people for the health care of their animals:**

1. **Foot-and-mouth disease in cows** is treated by smearing **Azadirachta indica A. Juss.** oil boiled with **Brassica juncea Hook. f. & Thoms.** (Mustard) seeds on the affected parts. The animals are also fed with gruel prepared from rice porridge and **Cuminum cyminum** Linn. (Cumin) seeds. Rinderpest is treated with a number of drinks that are simultaneously given: Juice of **Oxalis corniculata** Linn. mixed with salted buttermilk; **Murraya koenigii** (Linn.) Spreng. leaves roasted in a mud-pot and mixed with a little water; and rice porridge cooked with the extract of **Aegle marmelos** Correa ex Roxb. To control dysentery, leaves of **Tragia involucrata** Linn., cooked in fermented bran and mixed with **Curcuma longa** Linn. (Turmeric) are fed. Along with this, animals receive the water from boiling **Murraya koenigii** leaves. Stomach pain in cows is treated by feeding the cows with tender shoots of **Piper betle** Linn. (Pan), **Capsicum frutescens** Linn. (Green chillies), and **Terminalia chebula** Retz. (Haritaki) in human urine. To control cough in cows, a decoction of dry **Zingiber officinale** Linn. (Ginger) is fed to the cows. External parasites are controlled by applying a mixture prepared from **Datura stramonium** Linn. (Dhatura) and **Tinospora cordifolia** (Willd.) Miers ex Hook. f. & Thoms. (Amrith). To counteract tapioca leaf poisoning, cows are fed with leaves of **Elephantopus scaber** Linn. (Anachuvadi) in buttermilk. The cows are then made to run, their body is massaged with hot water bags, and they are made to drink hot water with sugar. To treat flatulence in cows, they are fed a mixture of milk, **Allium cepa** Linn. (Onion), and leaves of **Annona squamosa** Linn. (Custard apple). While ethnoveterinary medicine is eco-friendly and cheap, it is tedious to prepare and not standardised. Hence, there is a need to standardise ethnoveterinary practices (http://www.vetwork.org.uk/pune20.htm#12).