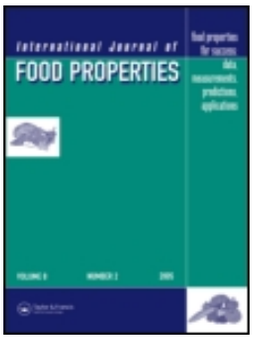

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LATHYRUS AND LATHYRISM: A REVIEW

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ABSTRACT

Over consumption of seeds of *Lathyrus sativus causes* lathyrism, a paralytic disease of legs/hind limbs, in human and animals. Some of these aminoacids and their amine derivatives are neurotoxic to both human and animals. Lathyrism, a paralytic disease is caused by the extensive use of seeds of *Lathyrus sativus.* A nonprotein aminoacid, β-N-Oxalylamino–L-alanine (BOAA) present in these seeds is found to be responsible for this effect. Though it has been banned in many countries from cultivation, there is every possibility of its use as a part of diet during adverse climatic conditions like flood, drought etc. when other crops get ruined but it survives. In this article the authors have reviewed and documented the lethal manifestation of seeds of Lathyrus sp. to create an awareness against the use of this as human diet and animal fodder and the present status of research for developing toxin free species of this agronomically important plant by use of genetic engineering.

BACKGROUND

Plants form an important part of diets of human and animals. Same twenty amino acids are used by both plants and animals for their protein synthesis. Plants synthesize atleast 240 other nonprotein aminoacids, which give rise to corresponding amines by decarboxylation. Several of these aminoacids and amines are neurotoxic to human and animals (Evans and Bell, 1980). The consumption of one such nonprotein amino acid occuring in seeds of grass peas, *Lathyrus sativus* (Khesari in India, Guaya in Ethiopia and Pois carre in France) or its related species, viz. *Clymenum* (Spanish vetch), *Ciera* (flat podded pea) etc. (Strong, 1956; Selye, 1957; Subramanyan et al., 1957; Gardner, 1959; Ressler, 1962; Adiga et al., 1962; Kinsbury, 1964; Stockman, 1917; Sugg et al., 1944) causes Lathyrism, a paralytic disease. The seeds of Lathyrus species had been in use as nutritious, tasty & inexpensive component of human diet among the poor in

certain areas of Africa and Asia. Under adverse climatic conditions e.g. during flood and drought, when other crops are ruined, grass peas because of their hardy drought tolerant nature survives and becomes the survival food for human and cattles. Under such conditions when *Lathyrus sativus* seeds comprised up to two thirds of the diet, men and animals developed the paralytic neurotoxic disease, Lathyrism (Barrow, 1978; Gebre et al., 1978; Gopalon, 1950; Griffin et al., 1978; Rao et al. 1969; Selye, 1957; Sleeman, 1844; Stockman, 1929).

The seeds of grass pea or chickling pea/vetch and flat podded pea have been a foodstuff for atleast 8000 years (Marinval, 1986; Kislev, 1986). The paralytic disease, lathyrism, caused by over consumption of the above legume seeds have been known since ancient days. It has been mentioned about this disease in the ancient Indian & European literature (Spencer and Schaumburg, 1983; Rutter and Percy, 1984; Dwivedi, 1989). The disease was known to ancient Hindus, Hippocrates (Ca. 460–377 BC), Pliny the Elder (23-79 AD), Dioscorides (first century AD) and Galen (ca. 130–210 AD). Because of the paralyzing effects on legs of Lathyrus flour, Duke George of Wurtemburg banned its consumption in his principality in 1671. Today its production and sale are banned in many countries including India. Throughout the 18^{th}, 19^{th} & 20^{th} centuries, outbreaks of lathyrism have been reported in Europe, Northern Africa, Middle East, Afganisthan, Russia and India (Barrow et al., 1978; Griffin et al., 1978; Selye, 1957; Stockman, 1929). Major epidemics have been reported in parts of France (1700–1701,1820s), Algiers (1883), Russia (1892), India (1829,1833,1856), and Spain (1940s) (Sleeman, 1844; Bourlier, 1882; Desparanches, 1829; Grandjean, 1895; Proust, 1883; Semidalov, 1893). Today lathyrism is restricted to North-Central India, Bangladesh and Ethiopia (National institution of Nutrition, India, Report 1980; WHO, 1978) but it can resurface in other countries in adverse conditions *viz.* War, flood, drought etc., while human and animals may be compelled to ingest Lathyrus species for their survival.

The authors in this review have attempted to highlight the toxic effects that occur due to consumption of Lathyrus seeds and to create awareness among people against its use as human diet and animal fodder.

LATHYRISM (PATHOPHYSIOLOGY)

Lathyrism, a form of spastic paraparesis, is a motor system disease caused by consumption of nonprotein aminoacid neurotoxins present in foods made from seeds of *L. Sativus* and related species. The disease is manifested with painful muscle spasms lasting seconds or minutes and are especially disturbing at night and progress ultimately to cause irreversible crippling effects (paralysis) of the lower limbs in human and the hind limbs in domestic animals (Selye, 1957).

Human Lathyrism

In human, individuals of both sexes and all age groups can be affected but the disease is most prominent among young male adults (Spencer and Schaumburg, 1983). The symptoms of the disease as reported (Gebre-ab et al.1978; Gopalon, 1950; Stockman, 1929; Paissos and Demopouls, 1962) usually begin suddenly few weeks or months after consumption of seeds of *Lathyrus sp.* There may be very frequent urination (30–

40 times during the night), prodormal sensory symptoms of pain, prickling numbness and cramps, but commonly the victim suddenly feels weak and heavy in the legs and loins, with tremulous muscles when weight is put on them. There is dragging of the legs, increased reflexes and impaired ability to walk. In mild cases, only ankle and knee joint movements are restricted by muscle spasm, causing the victim to walk rigidly on the balls of his feet, tilting the pelvis. The more severely affected, with abductor spasticity, walk with a characteristic scissoring gait, and require support from a single/pair of crutch/es. The most severely affected ones develop tonic paraplegia in flexion and are compelled to crawl or use a wheel chair. Generally, arms are not involved, and speech, swallowing & eye movements are normal. Cerebrospinal fluid, nerve conduction and electromyogram are usually normal, although signs of anterior-horn cell involvement have been reported in a few cases of lathyrism (Cohn and Streifler, 1981).

Lathyrism in Animals

Lathyrism also occurs in domestic animals when given *Lathyrus* as fodder. The hind limbs of the animals are paralysed. There are reports about the occurrence of this disease in animals in many countries including USA and Britain (Kinsbury, 1964; Stockman, 1917; Sugg et al., 1944). Lathyrism has been reported in many species including the duck, goose, hen, peacock, pig, ox, sheep, elephant and horse. Horse has been reported to be most susceptible to *Lathyrus* neurotoxic agent/s. This animal develops symptoms of the disease after around just 10 days when fed exclusively with *L. sativus* and after 2/3 months while diet contains partially *L. sativus.* Symptoms of the disease include paralysis of the hind legs accompanied by dyspnea and roaring. The disease may be more serious than in man with involvement of long peripheral nerves as well as spinal cord and brainstem.

ETIOLOGIC AGENT FOR LATHYRISM

Many compounds found in several species of *Lathyrus* had been suggested and later discounted as the cause of human laththyrism. Later on β-N-oxalylamino-L-alanine (BOAA), the acute neurotoxic agent was identified on several species of lathyrus plants. On isolation of BOAA from *L. sativus* seeds (Rao et al., 1964; Murty et al., 1964), the neurotoxic property of the agent were studied on various experimental animals. In large doses it was reported to cause neuropathological changes similar to glutamate neurotoxicity e.g. brain and spinal chord damage but it failed to precipitate the clinical or neuropathological characteristics of human lathyrism (Spencer and Schaumburg, 1983). BOAA had been identified 33 years back. But its association with human lathyrism had not been proved till 1986. The absence of direct evidence as the causative agent of human lathyrism and its distribution taxonomically among those Lathyrus species implicated in human lathyrism led to the belief that BOAA is the etiologic agent of lathyrism. Spencer et al. (1986) evidenced the role of BOAA on development of lathyrism by reproducing the features of primate lathyrism and BOAA has been confirmed as the causative agent of human lathyrism. Neurotoxic aminoacid BOAA is reported to be present in the seeds of 21 *Lathyrus sp.*, 17 *Acacia sp.* and 13 *Crotalaria sp.* (Quereshi et al., 1977). Intake of BOAA at the rate of 15-150 mg/kg

Body weight per day (equivalent to ca. 400 g. per day of *L.sativus* seeds) for a few weeks to few months are necessary for appearance of clinical symptoms of lathyrism (Cohn and Streifler, 1981; Ressler, 1947; Paissos & Demopoulos, 1962).

CHEMISTRY

The neurotoxin of *Lathyrus sp.* responsible for human lathyrism has been identified 33 years back as an aminoacid (Rao et al., 1964; Murty et al., 1964).Three nomenclatures have been used to describe the β - isomer of the acutely neurotoxic aminoacid: a) β-N-oxalyl amino-L -alanine (BOAA), b) β-N-oxalyl amino-α, β-diaminopropionic acid (ODAP), and c) L-3-oxalyl amino-2 aminopropionic acid having the following structure:

HOOC - CH (NH2) - CH2 - NH CO COOH

The biosynthetic precursor of the neurotoxic amino acid BOAA is a β-(isoxazolin–5–one –yl)–L–alanine (BIA) .It is a prominent metabolite only during the seedling stage of grass pea, *L. sativus* and its related legume species .The cotyledons are presumably the site for biosynthesis.

MECHANISM

It is generally agreed that excitotoxic aminoacids operate through specific synaptic membrane receptors. While all excitotoxins mimic the ability of glutamate to induce seizures and acute neuronal degeneration in rodents receiving single dose, the members of the excitotoxic family show differential action at sub classes of glutamate receptors (A1–A3) (Foster and Fagg, 1984). The convulsant actions of BOAA are principally mediated directly through A2/A3 glutamate receptor systems present on selected neurons (Ross and Spencer, 1987).

CONCLUSION

The seeds of Lathyrus *sativus,* the grass pea (Khesare dahl) have been used for human consumption and as animal fodder since early history of mankind (Marinval, 1986; Kislev, 1986). The neurotoxic irreversible crippling effect (lathyrism) of this seed has also been known since early historical days. Inspite of this, thousands of people have been affected by this disease and their legs have been paralyzed for life after consumption of this seed. Even today the grass peas form the survival food for very poor in some regions of Africa & Asia during adverse climatic conditions like flood & drought even though cultivation & sale of these legume seeds are banned in many countries including India.

Grass peas form a rich source of nonprotein amino acids (Lambein et al., 1976). *Lathyrus sativus* and its related species are agronomically very important group of plants. They are also important from ecological viewpoint and even for the food supply of a sizeable section of the world population. Because these plants are very

hardy & drought tolerant and can yield nutritious and tasty seeds under adverse climatic conditions while other plants fail to survive (Lambein et al., 1990), it is cultivated on several million hectre in Asia and Africa. Extensive research has been carried out in many laboratories in India and abroad since 1950s to find the etiologic agent responsible for lathyrism. The toxin responsible for human lathyrism was identified 33 years back as a small amino acid and that it is responsible for human lathyrism has been confirmed 12 years back. Presently intensive research for developing zero–toxin variety of *Lathyrus sp.* is going on in many laboratories (Briggs et al., 1983; Kaul et al., 1986; Misra et al., 1979). A number of low– toxin varieties have been isolated but stable zero toxin variety is yet to be found. With sufficient biochemical information available, perhaps genetic engineering can bring the answer to this problem.

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