Litchi is safe and harmless in normal individuals

The paper on 'Determination of tolerable dose of litchi fruit' by Tripathi *et al.*[1] confirms the safety of litchi in mice, and by extrapolation, in normal people. Indeed litchi has never been alleged to be unsafe in normal people.

The authors imply that their results disprove the aetiological association of litchi in outbreaks of acute brain disease in children in Muzaffarpur, contradicting earlier studies that we and others have published[1–4]. That insinuation is unwarranted, as they did not address the question directly or indirectly in mice[1].

The disease in question is 'acute hypoglycaemic encephalopathy', not mere hypoglycaemia or acute encephalitis[2]. Encephalitis (brain inflammation) is caused mostly by neurotropic viruses. Litchi cannot cause encephalitis. The old name of 'encephalitis syndrome' for this disease, as repeated in their paper, is misleading and should be avoided[1,3,4].

The hypoglycaemic encephalopathy in Muzaffarpur has a cause-constellation of three factors – under-nutrition, prolonged fasting and prior litchi consumption[2–7]. The litchi association was proved by us and independently reconfirmed with further evidence by a large panel of investigators[2–7]. The neuronal toxins are endogenous short-chain fatty acids and branched-chain amino acids accumulating in blood as a result of blockage of fatty acid beta-oxidation and gluconeogenesis[2,4,6,7]. Methylene cyclopropyl alanine and glycine (MCPA, MCPG) in litchi are not directly toxic to brain cells[2,6,8].

Fear of toxicity should not affect litchi production in Muzaffarpur[6,8]. Perhaps the term 'hypoglycin' used for MCPA may have misled the authors to ask if litchi may have phytotoxins rendering it unsafe.

Brain needs euglycaemia (normal blood glucose level, >70 mg/dl) all the time. When food-derived glucose level gets low early in the morning, especially following prolonged fasting, liver glycogen is converted to glucose through glycogenolysis. If liver glycogen store is precarious, as in undernourished children, body resorts to fatty acid beta-oxidation and gluconeogenesis. MCPA and MCPG block fatty acid beta-oxidation cycle at several steps and also secondarily inhibits gluconeogenesis, causing accumulation of toxic metabolic intermediates[2–4]. This is why the disease has early morning onset, without exception[3].

Tripathi and co-authors report that litchi fruit, even in unnaturally high dose, did not cause hypoglycaemia in Swiss albino mice[1]. Earlier, Asthana *et al.*[7] had shown that powdered litchi seeds delivering MCPG dose of 7.5 µg/kg body weight did not induce hypoglycaemia in normal Wistar albino rats. Tripathi *et al.*[1] did not find hypoglycaemia in mice fasted for 6 h before giving litchi. Six hours without food is insufficient to stimulate fatty acid oxidation and gluconeogenesis. Asthana *et al.*[7] showed that young rats starved for 24 h and given MCPG developed severe hypoglycaemia (40 mg/dl). Without MCPG, starved rats had decreased glucose levels (79 mg/dl) compared to control animals (117 mg/dl)[7].

The brain function derangement (encephalopathy) is due to neurotoxic metabolites of blocked fatty acid oxidation and gluconeogenesis[4,7]. MCPA and MCPG are not direct 'phytotoxins' in the usual sense, but we may consider them as 'pro-toxins' that stimulate endogenous production of neurotoxic metabolites under conditions of under-nutrition and prolonged fasting. Therefore, it is better to avoid attributing toxicity to litchi fruits[8].

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