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Litchi Toxicosis – A Review

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Abstract- Litchi are subtropical evergreen fruits became famous in various part of the world for its aroma, flavor, taste as well as its high nutritive value. It contains various nutritional property but two main amino acid called MCPG and MCPA (known as neurotoxin) which are responsible for litchi toxicosis in malnourished children, reported first in 2011 in Bihar. Numerous studies have reported that litchi aril are rich in MCPA (12.4 to152.0 µg/g) and MCPG (44.9 to220 µg/g) and plays a major role in toxic outburst in form of hypoglycaemia and acute hypoglycaemic encephalopathy syndrome by interfering major alternative pathways of glucose production (B-oxidation, gluconeogenesis and ketogenesis) resulting hypoglycaemia along with accumulation aminoacidemia which leads to encephalopathy. As a result of that hypoglycaemic encephalopathy happened. An immediate treatment stared with dextrose infusion with 3% saline solution use to prevent edema of brain cells, 5% improves hypoglycaemia, 10% improves moderate to severe hypoglycaemia and 50% cures severe hypoglycaemia or glucose scarcity in blood .Therefore the main of this systematic review is to present an overview on causative agent, diagnostic measures and management of litchi toxicosis. Preventive measures comprise maintenance of poor health status and assurance of hepatic storage among malnourished children to avoid seasonal toxicosis.

Keywords:- Toxicosis, MCPA, MCPG; hypoglycaemia; acute hypoglycaemic encephalopathy.

I. INTRODUCTION

Litchi (Litchi chinesissonn) a subtropical fruit of Sapindaceae family originated from China. [1] In India litchi cultivation was started from 18th century through Burma. Now India is the second largest producer of litchi after china. It became popular and stated as the "queen of fruits" for excellent colour, flavour, aroma, high nutritional value and eye-catching appearance. [2-4] Though India and China produces 91% of litchi, because of climate specificity like soil, temperature and rainfall, it uses to cultivate in very few countries worldwide (China, India, Thailand, and Vietnam). [5,6]

In India main litchi producing states are Bihar, Uttar Pradesh, Uttarakhand, West Bengal, and Haryana/ Punjab. Main interest behind cultivation of this crop is associated with its high nutritional value. [7] Litchi pulp is a good source of nutrients such as polysaccharides, polyphenols (flavonoids, epicatechins, and anthocyanins), vitamins (mainly vitamin C and B-complex), and minerals like magnesium, copper, iron, manganese and folate. But amount used to vary with the litchi variant. [8, 9] However from past few years it became a mysterious fruit for scientists because of its toxic outburst in India.

The outbreak of litchi toxicity reported almost every year after 1995 in Muzaffarpur district of Bihar. This seasonal outbreak of mysterious illness characterized by seizures and changed mental status among children. [3] Paireau et al, in 2012 reported that toxic epidemic of litchi is a seasonal outbreak. [9]

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In 2013-2014, the National centre for disease control (NCDC) in India, and US centre for disease control joint investigation in Muzaffarpur confirm that naturally occurring amino acids (HGA-hypoglycin A and MCPG-methylenecyclopropyl glycine) associated with litchi toxicity. [12]

Singh et al, in 2016 find same association and assure absence of infectious agents such as virus and bacteria as a causal factor. So, association between hypoglycaemia and brain disorder is mainly associated with hypoglycin A and MCPG. [10-12]

II. HYPOGLYCIN A OR MCPA AND MCPG

Hypoglycine A or β- methylenecyclopropyl alanine (MCPA) is non-protein amino acids first isolated from unripen ackee fruit, Blighiasapida. In 1954, Hassal et al first isolates hypoglycin A and hypoglycin B as crystalline metabolites. [13] (Figure1). It is a water soluble natural toxin responsible for Jamaican Vomiting Sickness. [15, 16]

Bowen-Forbes et al, in 2011 reported that in unripen ackee fruit MCPA concentration is 300-10,000 fold higher than ripen one. [17] Whereas, in litchi hypoglycin a concentration is 12.4- 152.0 µg/g. [18].

Methylene Cyclo Propyl Glycine (MCPG) was first isolated in 1962 by Gray and Fowden from the kernel of litchi fruits. It is the lower homologue of hypoglycine A. [19]

MCPG concentration (0.57 µg/g) is much higher in semi ripen and ripen litchi fruit. [20] But in case of litchi fruit toxicity (Muzaffarpur, Bihar) unripen fruit has more MCPA and MCPG content than ripen one. [18](Table 1)

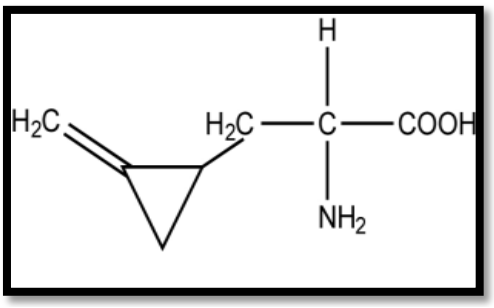
1. Existing Reviews:

Toxicological analysis by Phan et al, in 2018 reported 68% cases in 2008, and <20% cases in 2009-2011 were enterovirus positive, but it cannot explain the epidemiological model of seasonal outbreak.

Next, an alternative study was carried out, with 2 groups (with HGA and low HGA), through CSF (cerebrospinal fluid) analysis, it was confirmed that HGA and MCPG were the main causative agent for hypoglycaemia and brain disorder. But in case of encephalitis, enterovirus was considered as a causal factor. [21]

Shrivastava et al, in 2014 on the basis of case control study reported that acute encephalopathy was associated with both HGA and MCPG, and not related to enterovirus. As litchi aril contain 12.4 to 152.0 µg/g HGA and 44.9 to 220 µg/g MCPA, litchi consumption in empty stomach or after skipping of an evening meal aggravates the symptoms of hypoglycaemia along with abnormal plasma acylcarnitine profiles. [18]

However, numerous in vivo studies were carried out to understand the mechanism of hypoglycaemic effect of MCPA and MCPG. [5, 22, 23, 24, 25]



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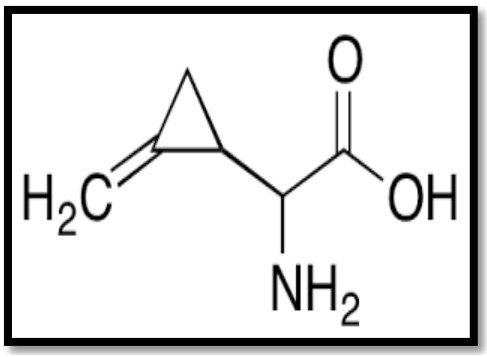

B

Fig 1. A and B respectively shows MCPA and MCPG structure.

Table 1. MCPG and hypoglycineA content of ripen and unripen litchi with 6 homogenates. [18]

Catagory	MCPG (µg/g dry weight)	Hypoglycin A (µg/g dry weight)
1 Ripe Unripe	 66.4 220.0	 74.1 152.0
2 Ripe Unripe	 68.0 112.0	 50.5 136.0
3 Ripe Unripe	 44.9 82.1	 12.4 18.5

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2. Pathogenesis of Hypoglycaemia:

It is well-known that Hypoglycin A or (HGA) or (MCPA) and MCPG are the main causal factors for litchi fruit toxicity. They generally worked by blocking β-oxidation of fatty acids and inhibit gluconeo-genesis, mutually identified as a responsible factor for glucose scarcity in blood. MCPA generally degrades to toxic methylenecyclopropyl acetyl-CoA by deamination or decarboxylation, and inhibits β -oxidation, by blocking short and medium chain acyl-CoA dehydrogenase. [27]

Thus acyl-CoA dehydrogenase declines the amount of hepatic acyl-CoA and upsurges hepatic butaryl-CoA concentration, with slight escalations in short and medium chain fatty acids. Its substrate specificity (C4 and C6- CoA), for short chain acyl-CoA also involves in inhibition of β -oxidation. [28, 26]

Next, it hampers hepatic gluconeogenesis by inhibiting pyruvate dehydrogenase, glutaryl CoA and glyceraldehyde-3-phosphate dehydrogenase enzymes. [29]

On the other hand inhibition of pyruvate oxidation reduces acetylcholine concentration and produces neurological sign and symptoms. [30] It also impairs the capacity of the cell to produce sufficient ATP, and reduces 13% hepatic concentration of ATP and increases 65% hepatic AMP concentration. [26]

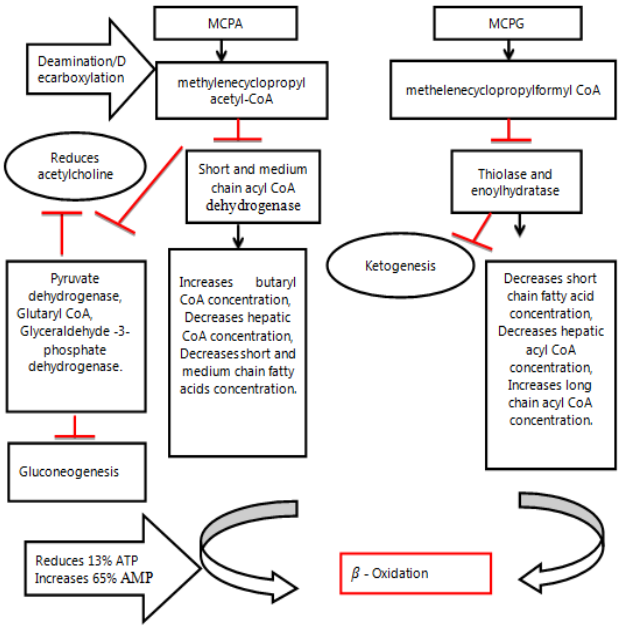

Fig 2. Pathogenesis of MGPA and MCPG induced hypoglycaemia (⊣ Inhibition)

Whereas MCPG degrades to Methelene Cyclo Propyl Formyl CoA, and reduces hepatic short chain fatty acid (C4 - C8- CoA) concentration along with hepatic acetyl- CoA. Reduction in short chain acyl-CoA and increase in long chain acyl- CoA blocks oxidation of short and medium chain acyl-CoA. [26]

However, MCPG-CoA inhibits thiolase and enoyl CoA hydratase reaction instead of medium chain acyl CoA dehydrogenase and suppresses ketogenesis. [24, 31, 32] But it did not cause quantifiable changes in ATP storage. The main difference between MCPG and MCPA is that- MCPG affect moderately endogenous glucose uptake through β -oxidation, while MCPA causes rapid endogenous glucose uptake, and results hypoglycaemia. [33]

3. Acute Hypoglycaemic Encephalopathy:

Acute encephalitis syndrome (AES) is a neurological disorder, with sign and symptoms of mental confusion, disorientation, delirium or coma. Generally viruses are the main causative agent for AES. But from last few decades it has been reported that several bacteria, fungus, parasites, chemical and toxins held responsible for AES. [34, 35]But acute encephalitis and encephalopathy are different disease condition. As encephalitis includes brain inflammation and encephalopathy can cause both inflammatory/ non-inflammatory condition. [35] In this portion of review we will discuss about AHES, as it significantly differs from normal encephalopathy, and encephalitis.

Table 2. Hypoglycaemic effect of MCPA and MCPG in animal model (1978 to 2019).

Animal models	Major outcomes	Reff
Hypoglycin A (HGA) induced rat model	Administration of 100mg/kg body weight of hypoglcin A inhibits gluconeogenesis. It also inhibits glucose recycling through Cori cycle. But this study can't explain the mechanism of steady state glucose normalization after HGA poisoning.	[22]
Mechanism of methylenecyclopropylglycine	Oral administration of MCPG in rats at a dose of 25 mg/kg body weight (BW) didn't cause any significant effect. Whereas,	[23]

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(MCPG) action in starved rats.	administration of 43 mg/kgBW and 50 mg/kgBW decreases 50% and 20% blood glucose level within 2-4h, compared with control rates. On the other hand, within same time range it increases lactate and non-esterified fatty acids concentration (NEFA), along with reduction in the activity of branched chain acyl CoA dehydrogenase and enoyl- CoA hydratase.	
Methylenecyclopropylglycine poisoning in starved rats	MCPG inhibits β-oxidation, and gluconeogenesis more rapidly by decreasing the supply of NADPH. It also supress ketogenesis and, results high plasma concentration of branched-chain amino acid by inactivating acetyl CoA and thiolase enzyme.	[24]
Methylcyclopropylformyl – CoA's (MCPF-CoA) effect on rat, bovine liver and pig kidney.	MCPF-CoA generally deactivates enoyl CoA hydratase (ECH) rather than any other enzymes involved in β-oxidtion. It acts as a competitive inhibitor for rat liver ECH, but in case of bovine liver and rat kidney's ECH, shows irreversible inhibitory effect, which inhibits β-oxidation via covalent trapping of methylenecyclopropane ring.	[25]
Mechanism of MCPA and MCPG induced hypoglycaemia on rats.	Both MCPA and MCPG inhibits β-oxidation. But mechanism differs as MCPA inhibits short chain acyl-CoA enzyme and depletes hepatic ATP storage, whereas MCPG inhibits several short chain enoyl CoA hydratases and causes disruption of β-oxidation.	[26]
Identification of tolerable dose of litchi using mice model	Acknowledged optimal dose of litchi pulp by using 2.48 mg/kg body weight (BW)/day HGA and ~9.0 mg/kg BW/day MCPG in starved and un-starved mice. Therefore it has reported that 3.9 kg fresh litchi pulp/ day for human adult weighing 60 kg, and 0.59 to 1.17 kg fresh pulp/day for children of age between 1 to 5 years is safe for consumption.	[5]

Table 3. Difference between encephalopathy and toxic induced encephalopathy. [40]

Encephalopathy	Hypoglycaemic encephalopathy
Causative factor is virus, bacteria or chemicals or toxin	Causative agent is toxin (MCPG or MCPA)
Onset of fever before inception of brain dysfunction	Fever use to start after inception of brain dysfunction
Fever use to persists for a day or two followed by the symptoms caused by brain damage	Asymptomatic: symptoms used to start next day after ingestion of toxin
Diagnostic symptoms include- mental confusion, disorientation, delirium or coma	Symptoms include- vomiting, convulsion, semi-consciousness and hypoglycaemia
White blood cell (WBC) used to present in cerebrospinal fluid(CSF) i.e more WBC per unit volume of CSF	No significant changes in WBC

(Table 2) Hypoglycaemic encephalopathy is a metabolic encephalopathy occurs as a consequence of serious complications of toxicosis, insulin or oral glycaemic therapy, malnutrition, alcohol abuse, and insulinoma. [36, 37]

Initial symptoms include vomiting, convulsion, semi-consciousness, cytotoxic oedema and even coma. [30, 37, 38] Main prognostic factors for AHES includes-1.prolonged hypoglycaemia (glucose level <50 mg/dl) causes severe damage of cerebral cortex,

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hippocampus of brain. [39] 2. Low lactic acid level. But for toxic induced AHES the mortality and morbidity rate is high among malnourished children, who eat the litchi fruit after skipping of an evening meal. While well-nourished ones are free from this symptoms even if they go to bed in an empty stomach. Main reason behind this includes sufficient glucose reserve as glycogen and the process of gluconeogenesis [40].

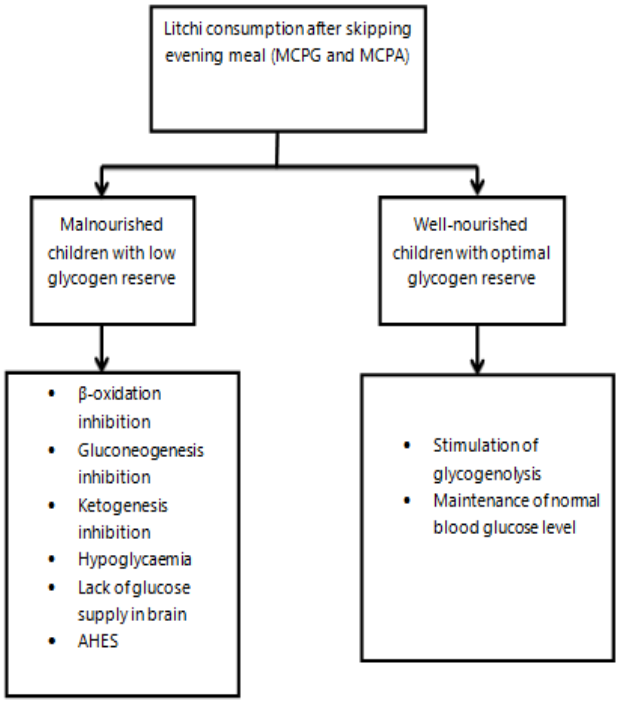

Fig 3. MCPG and MCPA effect on generation of AES among well-nourished and malnourished children.

III. IDENTIFICATION TESTS

Table 4. Identification tests for acute hypoglycaemic encephalopathy (AHE).

Tests name	Identification criteria	References
Rapid blood glucose monitoring (finger prick test)	Plasma blood glucose concentration for hypoglycaemia (HG) - Mild HG <70 mg/dl Moderate HG < 55 mg/dl Severe HG < 40mg/dl	[41, 42]
Diffusion MRI (magnetic resonance imagining)	Earliest changes are visible on DWI (diffusion-weighted imaging) sequencing, and apparent on diffusion coefficient map, It shows bilateral lesion and diffuse abnormal intensity of the posterior limb of the internal capsule, cerebral cortex, hippocampus and basal ganglia, head of caudate, lentiform nucleus, pons and corpus callosum. Short term severe hypoglycaemia does not provide visible changes in DWI scanning, and lesion localization at the first imagining is not predictive enough, although it can causes good outcome in early imaging.	[37,39,43,44-48]

It is some-what difficult to diagnose hypoglycaemic encephalopathy at early stages. But proper diagnosis can reduce mortality and morbidity among individuals affected with AHES. [37] Several studies have reported that rapid blood glucose monitoring along with diffuse MRI imaging can be used as an effective diagnostic tool. [37, 39, 41, 42, 43, 44-48]

IV. PREVENTION

The studies have also described and investigated about the bearable doses of litchi fruit by reviewing MCPG concentration. Basically around 3.9kg of pulp/day and 0.59-1.17 kg pulp/day can be given to adult human and children respectively. [50]

V. MANAGEMENT

Main goals of supportive treatment include restoration of body fluids, electrolytes, and glucose. [42]Treatment comprises rapid glucose therapy,[18] intravenous glucose injection and drip, [37] dextrose therapy (3%, 5%, 10% and 50%) dextrose infusion with 3% saline solution prevents oedema of brain cells, whereas 5% dextrose infusion improves hypoglycaemia, but cannot removes toxic amino acids accumulation in brain, [40] 10% solution in conscious state (moderate to severe hypoglycaemia), 50% solution in unconscious state (severe

hypoglycaemia) will helpful to normalize blood glucose level. [49]

VI. CONCLUSION

MCPA and MCPG both are the responsible factor for acute hypoglycaemic encephalopathy. Generally MCPA works by blocking enzymes (short and medium chain acyl-CoA dehydrogenase, pyruvate dehydrogenase, glutaryl CoA and glyceraldehyde-3-phosphate dehydrogenase) responsible for β–oxidation and gluconeogenesis, with reduction in hepatic ATP concentration. Whereas, MCPG blocks the enzymes (thiolase and enoyl CoA hydratase) involves in β –oxidation, and ketogenosis, without affecting hepatic ATP concentration.

Thus it produces hypoglycaemia and acute hypoglycaemic encephalopathy symptoms. But, in this prospective role of hormones have not been studied yet. Disease vulnerability is high among malnourished children, especially after skipping of an evening meal.

However, rapid blood glucose monitoring and diffuse MRI scanning can be used as an effective diagnostic tool along with glucose, and dextrose therapy implementation. Although, assurance of evening meal for children along with proper diagnostic and corrective measures can prevent toxic amino acid (MCPA and MCPG) induced seasonal epidemic outbreak.

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