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Coconut Water Prevents Renal and Hepatic Changes in Offspring of Monosodium Glutamate-Treated Wistar Rat Dams

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Summary: Monosodium glutamate (MSG) is a widely-consumed taste enhancer which has been implicated in the aetiology of renal and hepatic dysfunction in adults and their offspring. There is increasing evidence on the therapeutic properties of Coconut Water (CW) in kidney and liver disorders. This study investigated the effects of CW on renal and hepatic functions in offspring of MSG-fed dams. Twelve female Wistar rats (120 – 140 g) were grouped into four as follows; Control (10 ml/Kg distilled water), MSG (0.08 mg/Kg), CW (10 ml/Kg) and MSG+CW. Treatments were given orally daily commencing two weeks prior to mating, throughout mating and gestation until parturition. All dams received standard rodent diet and drinking water *ad libitum* throughout the study. After weaning on Post-Natal Day (PND) 28, serum was obtained from offspring for assay of liver and renal function. Histological analysis of the livers and kidneys were performed on both dams and offspring. There was no significant difference in liver enzymes, urea, creatinine and albumin levels amongst the offspring on PND 28. However, liver and kidney sections from MSG dams and their offspring showed early degenerative changes which were not evident in renal and hepatic tissues from CW and MSG+CW dams and offspring. These observations suggest that coconut water protects against monosodium glutamate-induced renal and hepatic dysfunction in dams and offspring.

Keywords*:* Monosodium glutamate, *Cocos nucifera* water, Foetal programming, Kidney, Liver.

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INTRODUCTION

Monosodium glutamate (MSG), the sodium salt of glutamic acid, is a commonly used food additive. Though the arguments for and against the safety of MSG have remained inconclusive, but still ongoing (Walker and Lupien, 2000; Ataseven *et al*., 2016), MSG is generally considered safe for human consumption even during pregnancy and lactation (Walker and Lupien, 2000; Freeman, 2006; Beyreuther *et al*., 2007). This is quite confusing as there have been reports of sensitivity reactions to MSG (ie. the MSG symptom complex) and its consumption has also been associated with growth retardation, neuronal degeneration and endocrine dysfunctions in neonates (Olney, 1969; Bakke *et al*., 1978; Yang *et al*., 1997; Walker and Lupien, 2000).

Changing cultural and societal habits is always a tall order, hence discouraging the consumption of MSG during pregnancy, especially in the absence of conclusive facts, may not be achievable. To forestall any possible side effects to offspring, a more practical solution is to recommend an acceptable antidote to mothers. Coconut water was explored in this study. Coconut water is the liquid endosperm of the *Cocos nucifera* fruit. *Cocos nucifera* is a monospecie palm, commonly found in the tropics and its fruit's endosperm and its fruit's endosperm is a highly nutritious, non-toxic drink (Agyemang-Yeboah, 2011; Prades *et al.*, 2012a). The protective and therapeutic effects of coconut water have been reported in virtually every body system and in several disease states; including those affecting the renal and hepatic systems (DebMandal and Mandal, 2011; Yong *et al.*, 2009). In addition, Coconut water has been reported to prevent the foetal programming effects of harmful maternal diets on renal and hepatic functions of offspring (Lans, 2007; Kunle-Alabi *et al.*, 2015; 2016). Hence, the aim of this study was to investigate the effects of coconut water on the livers and kidneys of offspring from dams fed a nutritional daily dose of monosodium glutamate and their offspring.

MATERIALS AND METHODS

Experimental Animals

All procedures involving animals in this study conformed to the guiding principles for research involving animals as recommended by the guidelines for laboratory animal care of the National Institute of Health (NIH publication no. 85-23, revised 1996). Twelve female Wistar rats weighing 120 - 140 g obtained from the Central Animal House, College of Medicine, University of Ibadan and four proven-

breeder male Wistar rats weighing 140 - 150 g obtained from the Laboratory for Reproductive Physiology and Developmental Programming, Department of Physiology, College of Medicine, University of Ibadan were used for the study.

Monosodium Glutamate

Monosodium glutamate (MSG) of approximately 99% purity (Caraway Foods International Nigeria Limited) was used for this study. The MSG was dissolved in distilled water and administered at a dose of 0.08 mg/Kg body weight daily (Zia *et al.*, 2014).

Coconut Water

Coconut fruits were obtained from a local farm in Ibadan, Oyo state, Nigeria and authenticated at the Department of Botany, University of Ibadan, Ibadan, Nigeria. Fresh coconut water was obtained daily by drilling a hole through the germinal pore of each fruit. Coconut water was administered orally at a dose of 10 ml/Kg body weight daily which has previously been reported to protect offspring from the effects of adverse maternal diet (Kunle-Alabi *et al*., 2015).

Experimental protocol

The female rats were divided into four groups of three rats each and their respective treatments are listed as follows;

1. **Control** (10 mL/Kg distilled water)
2. **MSG** (0.08 mg/Kg monosodium glutamate)
3. **CW (**10 mL/Kg coconut water)
4. **MSG+CW** (0.08 mg/Kg monosodium glutamate and 10 mL/Kg coconut water).

Treatments were given daily via oral gavage starting two weeks before mating commenced, during mating and throughout the gestation period. All treatments were stopped at parturition.

Mating

The female animals were paired with the proven breeder males at the ratio 1:3 (male to female). Mating was confirmed by the observation of spermatozoa in vaginal smears after which the dams were separated into individual breeding cages.

Sample collection

Dams were allowed to litter naturally at which time (i.e. parturition) all treatments ceased. They were allowed to nurse their own respective offspring until Post-Natal Day (PND) 28 (Oštádalová and Babický, 2012; Lutsyk *et al.*, 2013). On PND 28, one male and one female offspring were randomly selected from each dam and were anesthetised along with the dam using sodium thiopentone (Tanimura *et al.*, 1967; Nasrolahi *et al.*, 2013). Blood was then collected from the offspring through cardiac puncture into plain bottles and centrifuged to obtain serum for analysis. The kidneys and livers of the dams and offspring were and fixed post-mortem and fixed in 10% formalin for histological analysis.

Kidney and Liver Function Tests

Serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), urea, creatinine and albumin were determined using spectrophotometry kits according to the manufacturer's instructions (Randox Labs., UK).

Histological analysis

Tissues collected from the dams and offspring were dehydrated in ascending grades of alcohol, cleared in xylene and embedded in paraffin wax. Serial sections of five microns thickness were obtained using a rotatory microtome. The deparaffinised sections were stained routinely with Haematoxylin and Eosin (H&E) and viewed under a light microscope.

Statistical analysis

Data were presented as mean ± standard error of mean (mean ± SEM). They were analysed using ANOVA and Fisher's post-hoc test as appropriate on SPSS (version 20) software. Only p values less than 0.05 ($p<0.05$) were considered statistically significant.

RESULTS

Liver and kidney assays

Maternal intake of monosodium glutamate and/or coconut water before and during pregnancy did not cause any significant alteration in serum alkaline phosphatase, alanine aminotransferase, urea, albumin and creatinine levels (Table 1).

Liver histology of dams and offspring

Histological sections from the livers of dams in Control and CW groups showed normal architecture of the hepatocytes, sinusoids and interstitial tissue (Plate 1). The hepatocytes from liver sections of MSG dams showed signs of degeneration (Plate 1). Liver sections from the MSG offspring showed vacuolation within

Table 1: Effects of maternal monosodium glutamate and coconut water consumption on liver and kidney function assessments of offspring.

Group	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	Urea (mg/dL)	Creatinine (mg/dL)	Albumin (g/dL)
Control	44.2±1.5	31.5±1.3	110.8±3.5	14.7±0.4	0.7±0.1	3.1±0.3
MSG	45.2±1.9	32.5±0.4	116.7±3.6	15.5±0.4	0.7±0.1	3.2±0.1
CW	43.5±2.2	30.2±1.2	106.0±1.9	14.5±0.5	0.7±0.1	3.4±0.2
MSG+CW	46.7±1.4	33.2±0.6	112.3±4.1	15.8±0.5	0.7±0.1	3.4±0.3

MSG – monosodium glutamate, CW = Coconut water, AST – aspartate aminotransferase, ALT – alanine aminotransferase, ALP – alkaline phosphatase. Data represent mean ± SEM. n=6.

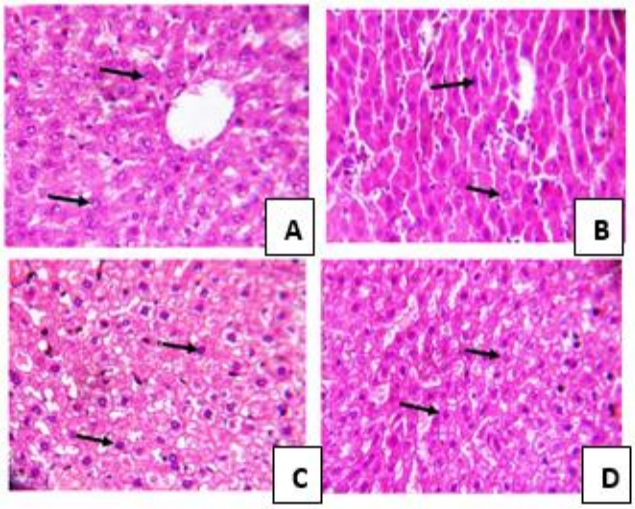

Plate 1: Photomicrographs of longitudinal section of livers from (A) control, (B) Monosodium, (C) Coconut Water and (D) Monosodium+ Coconut Water treated mothers. H&E. Magnification x 400. Hepatocytes (black arrows) appear normal.

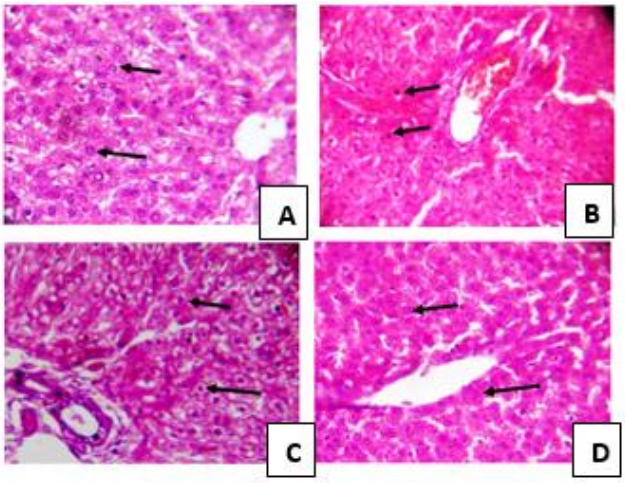

Plate 2: Photomicrographs of longitudinal section of livers from offspring of (A) control, (B) Monosodium, (C) Coconut Water and (D) Monosodium+ Coconut Water treated mothers. H&E. Magnification x 400. Hepatocytes (black arrows) show vacuolation in MSG group and appear normal in other groups.

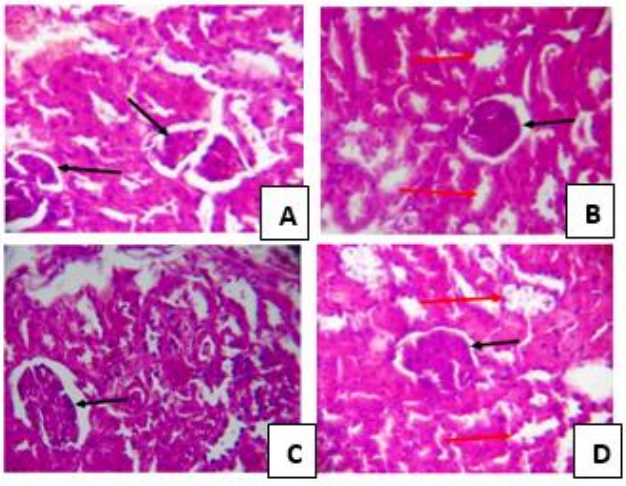

Plate 3: Photomicrographs of transverse section of Kidney from (A) control, (B) Monosodium, (C) Coconut Water and (D) Monosodium+ Coconut Water treated mothers. H&E. Magnification x 400. Glomeruli (black arrows) appear normal. Medullary interstitium shows vascular congestion (red arrows) in MSG and MSG+CW groups.

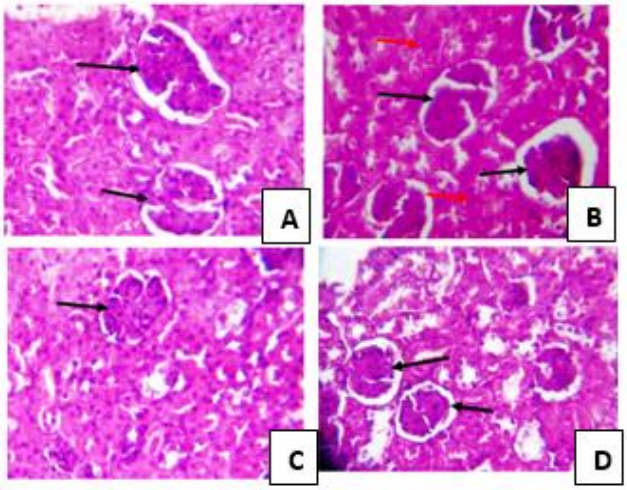

Plate 4: Photomicrographs of transverse section of Kidney from offspring of (A) control, (B) Monosodium, (C) Coconut Water and (D) Monosodium+ Coconut Water treated mothers. Glomeruli (black arrows) appear normal. Medullary interstitium shows disruption in parenchymal architecture (red arrows) in MSG group.

the cytoplasm of the hepatocytes (Plate 2). Kidneys from dams in all groups appeared normal (Plate 3). However, renal tissues from offspring of MSG dams (Plate 4) showed vascular congestion and parenchymal degeneration within the medulla. While the kidneys from offspring of dams in other groups appeared normal (Plate 4).

DISCUSSION

This study investigated the effects of maternal consumption of the popular food additive, monosodium glutamate (MSG), on renal and hepatic functions of dams and offspring, and the actions of coconut water on these effects. Monosodium glutamate is generally believed to be safe for consumption even during the perinatal period (Rezaei *et al*., 2013; Rogers, 2016). However, other reports have demonstrated the disruption of renal and hepatic functions by monosodium glutamate (Ortiz *et al*., 2006; Tawfik and Al-Badr, 2012), which suggest a need for plausible protective interventions. The concept of foetal programming of disease in postnatal life postulates that maternal dietary exposures permanently alter the manner in which various phenotypes are expressed (Langley-Evans and McMullen, 2010; Kamimae-Lanning *et al*., 2015). Hence, the need to explore the effects of maternal monosodium glutamate on renal and hepatic functions of offspring and dosed dam.

The results from the serum assays of markers of renal and hepatic functions [aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), urea, creatinine and albumin], suggest that maternal monosodium glutamate consumption does not cause any adverse effects on renal and hepatic functions of offspring. This corroborates reports that monosodium glutamate

is non-toxic and safe for consumption during pregnancy as it is not alleged to cross the placental barrier (Walker and Lupien, 2000; Beyreuther *et al*., 2007; Rezaei *et al*., 2013; Rogers, 2016). However, the histological presentations of the kidneys and livers in both the dams treated with monosodium glutamate and their offspring suggest otherwise.

The degenerative changes observed in hepatic and renal tissues of dams and offspring, in the absence of concomitant biochemical derangements, serve as early pointers of degenerative changes. Early detection of systemic disorders, especially those involving the liver and kidneys, is essential to improving prognosis and health outcomes. As an early response, hepatocytes may swell due to fluid influx secondary to insults which could lead to membrane disruption and subsequent release of liver enzymes into the circulation (Hayashi and Fontana, 2014). This is described as hydropic degeneration and is usually characterised by destruction of the cytoplasm due to leakage of hydrolytic enzymes from the lysosomes (Gerlyng *et al*., 1993). Vacuolation, which is swelling of the cytoplasm of the hepatocytes, might indicate acute and subacute liver injury (Gerlyng *et al*., 1993; Vásquez *et al.*, 2014). The kidneys play an indispensable role in homeostasis and their function begins almost as soon as they develop (Rosenblum, 2008; Sirin and Susztak, 2012). Thus, the earliest form of detection of systemic disorders is best observed at the cellular level (Korman *et al.*, 1974; Chen *et al*., 2011; Angulo *et al*., 2015). However, the impracticability of this may be one of the reasons for the high occurrence of renal and hepatic disorders worldwide. Global statistics show that the prevalence of renal diseases is 8-16% (excluding high-risk populations who have a prevalence >50%) (Jha *et al*., 2013), while that of hepatic diseases is 25% (Younossi *et al*., 2016). It is also important to note that the clinical reference ranges for serum levels of liver enzymes are relatively wide and dependent on the level of damage of hepatocytes. Thus, an appreciable degree of liver damage must have occurred for a significant change in the enzyme level can be detected. This suggests that apparently normal biochemical indices, as were observed in this study, are not a reliable depiction of correspondingly normal renal and hepatic functions. Consequently, the kidneys and livers of monosodium glutamate-fed dams and their offspring showed visible lesions which may not be detected using routine clinical tests until later in life, at which time irreversible damage may have occurred.

These results also underscore the fact that monosodium glutamate consumption is detrimental to renal and hepatic functions not only in adults, as has previously been reported (El-Meghawry El-Kenawy *et al.*, 2013; Sharma, 2015), but despite conflicting reports, also in their offspring. This consequently suggests that monosodium glutamate may traverse the placental barrier and subsequently alter renal and hepatic functions in offspring. Interestingly, Pitkin *et al.* (1979) had earlier suggested that monosodium glutamate crosses the placental barrier, and more recently, Park and Choi (2016) corroborated this finding. It has been suggested that monosodium glutamate is "metabolically compartmentalised" in the body (Brosnan *et al*., 2014). This explains, to some extent, its limited impact within the tissues without significant effects on circulating biochemical markers. The mechanisms whereby monosodium glutamate causes damage within kidney and liver tissues is still unclear, however, the induction of oxidative stress has been proposed (Tawfik and Al-Badr, 2012). Sharma (2015) reviewed this proposal and concluded that monosodium glutamate indeed up-regulates oxidative stress possibly via enzymatic activation of cellular processes (specifically; α-ketoglutarate dehydrogenase, glutamate receptors and cystine-glutamate antiporter).

The histological analysis also exhibited the reno-protective and hepato-protective effects of coconut water in monosodium glutamate-treated dams and their offspring. The protective properties of coconut water against disorders of the renal and hepatic system have been widely reported (Loki and Rajamohan, 2003; Bhagya *et al.*, 2010; Nwangwa *et al.*, 2012; Pinto *et al*., 2015). The ability of coconut water to prevent against maternal diet-induced foetal programming of renal function has also been reported (Kunle-Alabi *et al*., 2016). Coconut water has numerous properties which may enable it perform this function. These include; antioxidant, anti-inflammatory and growth modulatory actions (Ajeigbe *et al*., 2011; Prades, 2012b; Pinto *et al*., 2015). The mechanisms of foetal programming are highly dynamic and have therefore not been fully elucidated (Chmurzynska, 2010). However, studies have shown that dietary interventions can play a significant role in their prevention (Junien, 2006; Gueant *et al.*, 2013; Kunle-Alabi *et al.*, 2016; 2017).

In conclusion, maternal monosodium glutamate consumption adversely alters renal and hepatic architecture in mothers and offspring. This disruption of the kidney and liver begins early in the life of offspring, and may not be detected until irreversible functional damage has occurred to these organs. Coconut water prevents the kidney and liver damage induced by maternal monosodium glutamate consumption in both mothers and offspring.

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