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IMPACT OF AQUEOUS EXTRACT OF ALLIGATOR PEPPER ON GESTATIONAL WEIGHT GAIN IN ALLOXAN-INDUCED DIABETIC SPRAGUE DAWLEY RATS

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Abstract
Alligator pepper (Aframomum meleguata) is a West African spice used as a vital condiment in ethnomedical preparations for the treatment of snakebites, stomachache-related disorders, hypertension, aphrodisiacs, and measles. It exerts an antidiabetic effect by obstructing the digestion and breaking down carbohydrates and complex sugars. Intra-peritoneal injection of aqueous extract of alligator pepper has also been found to reduce gestational weight gain in obese pregnant Sprague Dawley rats with obesity. This study was conducted to investigate the impact of an aqueous extract of alligator pepper on gestational weight gain in type 1 diabetic pregnant rats. Eighteen female Sprague Dawley rats were randomly allocated into three groups (A, B and C (n=6 each). Type 1 diabetes mellitus was induced in rats in groups B and C. Seventeen female rats that met the inclusion criteria were mated with 17 male rats in separate cages. The pregnant female rats were placed in separate maternity cages and fed with standard rat's chow and water ad libitum. On day 4 of gestation, the rats in groups A and B were given an intra-peritoneal injection of 13.3ml/Kg body weight of distilled water, while the rats in group C were given an intra-peritoneal injection of 13.3mg/Kg body weight of aqueous extract of alligator pepper. There was a non-significant increase in the gestational weight gain from non-treated diabetic rats in group B ($p > 0.05$) and a significant decrease in the gestational weight of treated diabetic pregnant rats in group C ($p < 0.05$). Alligator pepper significantly reduces gestational weight in pregnant Sprague Dawley rats with type 1 diabetic mellitus.

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INTRODUCTION

Alligator pepper (*Aframomum meleguata*) is a West African spice made from the seeds and seed pods of *Aframomum danielle, Aframomum melegueta* (grains of paradise) is known by different names across West Africa but generally called alligator pepper. Alligator pepper is a spice of the ginger family (Zingiberaceaae). It is a medicinal herb that has been used in traditional medicine practices since prehistoric times. Both the seeds and leaves can be used for garnishing salads and preparing assorted dishes such as pepper soup and stews. Its hot peppery and pungent flavor augments dishes and makes them spicy. Alligator pepper is an extraordinary plant with bioactive compounds that provide numerous nutritive and medical benefits. The seeds of Aframomum melegueta are used as ingredients of ethnomedical preparations for the treatment of snakebites, stomachache and diarrhea, hypertension, aphrodisiacs, measles, and leprosy (Kamtchouing *et al*., 2002).This seed has become of great importance in the treatment of wounds and as anti-inflammation (Ilic *et al*., 2014). A 2010 study found that the seed extract of alligator pepper inhibited the growth of all the bacteria species tested, suggesting that the plant extract acts against a wide range of disease-causing bacteria (Doherty *et al*., 2010). In another study, the seed of alligator pepper exerted an anti-diabetic effect by obstructing the digestion and breaking down of carbohydrates and complex sugars (Mohammed *et al*., 2017).

Conversely, adequate gestational weight gain (GWG) is an important measure of maternal health during pregnancy. The Institute of Medicine (IOM) prescribes a range of weight gain for normal, overweight, and obese pregnant women and recommends cutoff values for excessive gestational weight gain (Restall *et al*., 2014). Excessive GWG is associated with a variety of adverse maternal and neonatal outcomes, including hypertensive disorders complicated pregnancy, birth by cesarean section, macrosomia, and large for gestational age (LGA) at birth (Goldstein *et al*., 2017). Excessive gestational weight gain (GWG) is highly prevalent in women with GDM (Carreno *et al*., 2012). The increasing incidence of diabetes mellitus (DM) in the African population, including Nigeria, increases the development of gestational diabetes mellitus (GDM) in pregnant women. The recorded prevalence of gestational diabetes mellitus varies worldwide, ranging from 1–30% due to different diagnostic criteria and regional population characteristics (McIntyre *et al*., 2019), and is also a risk assessment for previously mentioned adverse pregnancy outcomes (Gillman *et al*., 2003, M. Bashir *et al*., 2019). Excessive weight gain during pregnancy is considered a critical period because it affects a woman's long-term weight control and increases the risk of obesity for the mother and the child, thus raising the risk of related diseases (Zheng *et al*., 2019, Rong *et al*., 2014). A large proportion of women with gestational diabetes mellitus in a study sample had excessive gestational weight gain even after receiving nutritional therapy and exercise for gestational diabetes mellitus (Bao-Hua *et al*., 2019). Reports have shown that approximately 50 percent of women with gestational diabetes will develop type 2 diabetes within 5–10 years (Kim *et al*., 2002). These women are also at risk of developing gestational diabetes in subsequent pregnancies. Although some authorities question the clinical value of treating gestational diabetes (Hollander *et al* 2007) a study carried out by Australian Carbohydrate Intolerance provides strong evidence that treatment of this disorder has beneficial effects on maternal and neonatal outcomes. When medical nutritional therapy results in inadequate glucose control, a safe, practical, and inexpensive intervention is necessary to reduce adverse outcomes.

Since intra-peritoneal injection of an aqueous extract of alligator pepper has been found to reduce gestational weight gain in obese pregnant Sprague Dawley rats (Inegbenebor *et al*., 2009), this study was carried out to ascertain the possibility of its use in the treatment of gestational weight gain in type 1 diabetic pregnant Sprague Dawley rats.

MATERIALS AND METHODS

Experimental Animals/Acclimation: 18 female and male Sprague Dawlay rats of proven fertility with weights between 130 and 160g were acclimatized for 2 weeks in a well-ventilated laboratory. The rats were placed in cages and fed with standard rat chow and water *ad libitum* during this period. There beddings, were made of saw

dust and were changed daily. The weight of the animals was measured weekly throughout the duration of the study.

Grouping: Female rats were allocated into three groups (A, B, and C) with six rats per group.

Diabetes Mellitus Induction in Groups B and C:

Twelve female rats in groups B and C were fasted overnight, and diabetes mellitus was induced by the intra-peritoneal administration of 150mg/Kg body Weight of freshly prepared alloxan in normal saline solution as described by Sekar *et al*. (1990). Thereafter, the animals were allowed to drink 5% dextrose in water in order to overcome the drug induced hypoglycemia (Gandhi and Sasikumar, 2012). A period of 1 week was allowed for the development of diabetes mellitus. Thereafter, rats with blood glucose level greater than 200mg/dI (11.1mmol/l) were considered diabetic. However, one of the female rats in group C had a glucose level of 194mg/dl (10.8mmoll) and was excluded, making only 5 female rats available for the study.

Mating Arrangement: Seventeen rats, (6 each in groups A and B and 5 in group C) were mated with male rats of proven fertility as monogamous pairs in separate cages for 3 days. After copulation was confirmed, the female rats were placed in separate maternity cages and fed with water and standard rat's chow *ad libitum* until delivery.

Measurement of gestational weight: All rats were allowed to remain in their maternity cages for 18 to 21days and were weighed within this period. The mean gestational weight was calculated for each of the groups A, B, and C. The weight of the rats at day one of gestations was recorded as the initial weight, whereas the weight on day twenty-one was taken as the final weight.

Data Analysis: The mean and standard errors of the mean of the litter weights for the different groups were calculated. The differences between the mean litter weights of the control and experimental groups were subjected to tests of significance using Daniel Soper's free website for calculating p-values (Soper, 2016). $P<0.05$ was considered significant.

RESULTS

Table 1: Effect of alligator pepper on gestational weight gain in diabetic rats

Groups	Status	Number of SD rats	Initial Mean Weight (g)	Final Mean Weight (g)	Mean Gestational Weight Gain ± SEM (g)
A (n=6)	Non-Diabetic pregnant	6	192.00	255.00	63.00 ± 4.66
B (n-6)	Diabetic-pregnant	6	196.83	263.00	66.17 ± 4.73
C (n=5)	Pregnant with Treated Diabetic	5	202.40	243.80	41.40 ± 4.47

Table 2: comparison between weight gains

Groups	Diabetics Status	Number of SD rats	Mean Gestational Weight Gain ± SEM (g)	Comparison
A (n=6)	Non-Diabetic pregnant	6	63.00 ± 4.66	
B (n-6)	Diabetic-pregnant	6	66.17 ± 4.73	B vs. A
C (n=5)	Pregnant with Treated Diabetic	5	41.40 ± 4.47[a]	C vs. A
C (n=5)	Pregnant with Treated Diabetic	5	41.40 ± 4.47[b]	C vs. B

a indicates a significant difference between groups C and A, whereas b indicates a difference between

Discussion

Gestational weight gain (GWG) is a complication of Gestational diabetes mellitus (GDM). Visceral fat is characterized by high visceral fat and is strongly associated with insulin resistance in obese subjects (Berg and Scherer (2005) with disproportionate weight gain and elevated BMI (ACOG, 2018). Elevated maternal serum glucose levels, which crosses the placenta and produce fetal hyperglycemia, stimulate the fetal pancreas and consequently induce anabolic insulin properties, increase the growth rate of fetal tissues (Spaight *et al* 2016). This explains the relationship between GWG and conception products, especially the placental and fetus, which is usually large as a result of abnormal glucose metabolism and adiposity (saha *et al* 2014 and ozbasli *et al* 2020). This further explained the increase in gestational weight gain observed in diabetic animals.

Gestational weight gain complicated by diabetes results in short- and long-term complications by impacting both the mother and child (Chanda *et al* 2020). Gastaldelli (2011) found that an aqueous extract of alligator pepper fosters weight loss by promoting body metabolism in metabolic disorders. In another study by Inegbenebor *et al* 2016, it was also found that intraperitoneal injection of an aqueous extract of alligator pepper was found to significantly reduce the first trimester insulin level in Sprague Dawley rats, which explains the reduction of gestational weight gain in normal pregnancy (Inegbenebor *et al* 2009). Furthermore, Inegbenebor *et al*. (2016) suggested that the active constituent of alligator pepper with this activity is Beta caryophyllene, which is a common constituent of the essential oils of numerous spice and food plants and a major component in cannabis (Gertsch *et al*,. 2008), which can reduce weight by lipo-oxidation (Zheng *et al* 2013).

In pregnant rats with type 1 diabetes mellitus, as in this study, where there is already a deficiency of insulin, the reduction in gestational weight gain observed was most likely a contribution of reduction in litter weight. Suggesting that aqueous extract of alligator pepper is able to reach the fetus through the fetal-maternal circulation where it produce a relative insulin deficiency in the fetus of a pregnant rat treated with alligator pepper in a previous study (Inegbenebor *et al*., 2016). Thus, lipo-oxidation, which brings about reduction in litter weight of an alloxan induce diabetes pregnant rats after the administration of aqueous extract of alligator pepper , was due to reduction in litter weight (Ehiagwina and Inegbenebor 2016). Sugita *et al*. (2013) reported that orally ingested alligator pepper increases whole-body energy expenditure through the activation of Brown Adipose Tissue in human subjects (Sugita *et al*., 2013). This might also be another mechanism of action of the alligator pepper extract for reducing gestational weight. The amount of weight gained during gestation includes the increase in adipose tissue (Kominiarek and Peaceman 2017, Gilmore *et al.*, 2015).

Conclusion

Intra-peritoneally administered aqueous extract of alligator pepper significantly reduces the gestational weight of Alloxan induced diabetic rats, and is therefore capable of preventing fetal macrosomia in pregnant Sprague Dawley rats with type 1 diabetes.

Authors' Contribution: Edwin Edna Ekeleoseya carried out the research and in combination of the other authors conducted the data analysis and article writing.

Conflict Of Interest: None.

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