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## **Activities of G-6-PDH and LDH in the Kidney, Liver and Pancreas of Adult Wistar Rats Following the Administration of Ethanolic Leaf Extract of Madagascar Periwinkle (*Catharanthus roseus*)**

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### **ABSTRACT**

This study was elucidated in order to evaluate the effects of ethanolic leaf extract of Madagascar periwinkle (*Catharanthus roseus*) (documented for its hypoglycemic effects on experimental animals) on the activities of glucose-6-phosphate dehydrogenase and lactate dehydrogenase on the kidney, liver and pancreas of adult Wistar rats. Thirty-two rats (of the first filial generation) of both sexes (Albino, Wistar) were used. Animals weighed 214-232 g and were about 7-13 weeks old. The animals were divided into four groups designated as A, B, C and D of eight animals in each. Groups A, B and C were administered with 400 mg kg<sup>-1</sup>, 300 mg kg<sup>-1</sup> and 200 mg kg<sup>-1</sup> b.wt. of the plant extract respectively while the control group was administered with equal volume of phosphate buffered saline orally for 21 days. At termination of study, it was observed that there was significant increase in glucose-6-phosphate dehydrogenase and significant decrease in lactate dehydrogenase enzyme activities in the administered groups. The results obtained from this study suggested that the leaf extract of Madagascar periwinkle (*Catharanthus roseus*) consumed for its hypoglycemic effects, alters carbohydrate metabolism in the kidney, liver and pancreas and has no deleterious effect on the organs of study in Wistar rats. Further studies should be done in order to know if such effects seen in Wistar rats may by extension be seen in man.

**Key words:** Kidney, liver, pancreas, lactate dehydrogenase, glucose-6-phosphate dehydrogenase, phosphate buffer saline, *Catharanthus roseus*

### **INTRODUCTION**

A number of plants with acclaimed anti-diabetic properties are being studied in different laboratories throughout the world, especially in developing countries (Saidu *et al.*, 2007) and many of these herbal remedies suggested for diabetes and diabetic complications (Joseph and Jini, 2011). The hypoglycemic properties of plants used in management of diabetes are reported to be due to their content of flavonoids, glycosides, alkaloids terpenoids, plant polysaccharides and other bioactive compounds (Iweala and Oludare, 2011). According to Jaya *et al.* (2010), it was observed that the use of medicinal plant for the treatment of many ailments particularly diabetes dates back to the *Ebers papyrus* and in recent years, the use of traditional and complementary medicine has been of great relevance because it is cheap and readily available with little or no toxic effects. Also, the use of these medicinal plants is traceable to the growing demand by consumers as herbal

remedies are effective (Patrick-Iwuanyanwu and Wegwu, 2008). According to Hasani-Ranjbar *et al.* (2010) many pharmacists are not adequately prepared educationally to meet the patient's request for information about herbal medications and products.

*Catharanthus roseus* (*Vinca rosea*) is known as the common or Madagascar periwinkle. It is a perennial herb of the Apocynaceae family originally native to Madagascar (Hall, 1978). It measures about two feet in height and has dark green glossy leaves and pale pink or white flowers. The organic extracts of *C. roseus* is used in the folklore treatment of diabetes, malaria, leukemia, wasp stings, sore throat, eye irritation, infections (Gaston and Spicer, 2004). It is also used as an astringent, diuretic and expectorant. The plant contains about seventy alkaloids some of which include catharanthine, lochnenine, vindoline vindolinine, vincristine, vinblastine, tetrahydroalstonine, reserpine, serpentine, etc. (Chabner and Longo, 2005).

The production of NADPH which is the principal intracellular reductant depends on glucose-6-phosphate dehydrogenase. The inhibition of glucose-6-phosphate dehydrogenase activity decreases NADPH, a coenzyme essential for the protection against oxidative stress (Zhang *et al.*, 2000). It is involved in the repair of oxidative damage and also plays a crucial role in maintaining the normal 3-dimensional integrity of proteins in the cell membrane (Zhang *et al.*, 2000). The integrity of the cells as well as the antioxidant system and other processes requiring reduction rely on the adequate supply of NADPH. A compromise in the functional integrity of glucose-6-phosphate dehydrogenase will ultimately compromise the supply of energy to the cells (Zhang *et al.*, 2000).

A compromise in the potentials of G6PDH always results into a deviation from the normal functional capacity of NADPH. This may as well subject the various cells regulating vital organs of the body to oxidative stress. These may also account for some of the earlier reports that had been suggested on the medicinal properties of *Catharanthus roseus* (Mostofa *et al.*, 2007; Chattopadhyay, 1999; Iweala and Okeke, 2005; Hsia *et al.*, 2004). The plant is famous for its folklore use in diabetes mellitus (Mostofa *et al.*, 2007; Chattopadhyay, 1999; Iweala and Okeke, 2005; Hsia *et al.*, 2004). The present study was undertaken to elucidate the effects of *C. roseus* on the activities of G6PDH and LDH in the kidney, liver and pancreas of rats.

## MATERIALS AND METHODS

**Collection of plant and preparation of plant extracts:** Fresh leaves of *C. roseus* were collected from the premises of the University of Ilorin Teaching Hospital, Ilorin, Nigeria. The leaves of *Catharanthus roseus* plant were air-dried and the dried plant material was weighed using Gallenkamp (FA2104A, England) electronic weighing balance and grinded with Blender/Miller III, (model MS-223, China).

Five hundred and fifty two grams of the dried powdered sample was however soaked in five liters of 70% ethanol for 24 h at room temperature with constant shaking on a shaker (Stuart Scientific Orbital Shaker, UK) and then filtered through silk cloth (Mostofa *et al.*, 2007). The filtrate was concentrated using a rotary evaporator (Rotavapor® R-210) at 42-47°C to obtain 56.50 g alcohol-free residual extract of *Catharanthus roseus*.

**Animal care and experimental design:** Thirty-two Wistar rats of the first filial generation were randomly assigned into three extract treatment (n = 24) and one control (n = 8) groups. This study was conducted between February and March, 2009. The body weights of the animals were obtained and recorded daily using a digital weighing scale.

Animals in the extract treatment groups A were administered with 400 mg kg<sup>-1</sup> b.wt. of the ethanolic leaf extract of *C. roseus* for 21 days.

Animals in the extract treatment groups B were administered with 300 mg kg<sup>-1</sup> b.wt. of the ethanolic leaf extract of *C. roseus* for 21 days.

Animals in the extract treatment groups C were administered with 200 mg kg<sup>-1</sup> b.wt. of the ethanolic leaf extract of *C. roseus* for 21 days.

Animals in the control group (group D) were administered with equal amount of PBS for 21 days.

All the animals were housed in clean cages of dimensions 33.0×20.5×19.0 cm contained in well ventilated standard housing conditions (temperature: 28-31°C; humidity: 50-55%). Their cages were cleaned everyday. All experimental procedures followed the recommendations provided in the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences and Published by the National Institute of Health (1985). The rats were fed with standard rat chow at a recommended dose of 100 g kg<sup>-1</sup> as advised by the International Centre of Diarrheal Disease Research, Bangladesh (ICDDR, B) daily. Drinking water was supplied *ad libitum*.

Twenty-four hours after the last administration, all the animals were sacrificed using cervical dislocation (Adekomi, 2010), laparotomy was performed and the kidney, liver and pancreas were excised, trimmed free of fat and were homogenized in 0.25 M cold sucrose solution, the homogenized tissue samples were centrifuged at 5000 rpm for 10 min (David *et al.*, 2009). Glucose-6-phosphate dehydrogenase (G6PDH) and Lactate Dehydrogenase (LDH) kits were procured from Sigma (Lagos, Nigeria). The supernatants were carefully and immediately stored in a deep freezer at -20°C. These were assayed within 48 h. The activities of G6PDH and LDH were estimated by the methods of Kind and King (1954) and King and Jegatheesan (1959). The enzymes activities were read spectrophotometrically.

**Statistical analysis:** Data were statistically evaluated using the student's t-test with SPSS/14.0 software (SPSS Inc, Chicago, USA) and Excel 2007 (Microsoft Corporation, USA) and were expressed as Mean±Standard Error of Mean (SEM). A value of p<0.05 was considered to indicate a significant difference between groups.

## RESULTS

**Body weight:** The effects of different doses of ethanolic leaf extracts of *Catharanthus roseus* on the body weight of the animals in the treatment groups when compared with that in the control group was as presented in Fig. 1. After 21 days of treatment, the body weights of the treated animals were observed to increase significantly (p<0.05) in comparison with the control.

Among the treated groups, higher body weight was recorded in the group (A) that were administered with 400 mg kg<sup>-1</sup> b.wt. of the extract followed by the group (B) administered with 300 mg kg<sup>-1</sup> b.wt. and then group (C) administered with 200 mg kg<sup>-1</sup> b.wt. of the extract. Thus, the administration of the ethanolic leaf extract of *Catharanthus roseus* increased the body weight of the treated animals in a dose dependent pattern.

**Glucose-6-phosphate dehydrogenase activity:** The activity of G6PDH was increased significantly (in a dose dependent pattern) in the kidney, liver and pancreas of the treated animals in groups A, B and C compared with the control: group D. The statistical activity of G6PDH in the kidneys of the animals in groups A, B and C were; 19.53±0.15, 18.97±0.88 and 18.63±0.18, respectively. When these values were compared with the control, 17.27±0.18, it was observed that the activity of G6PDH was statistically significant in all the groups administered with the plant extract for 21 days. The highest activity was observed in the group of animals administered with

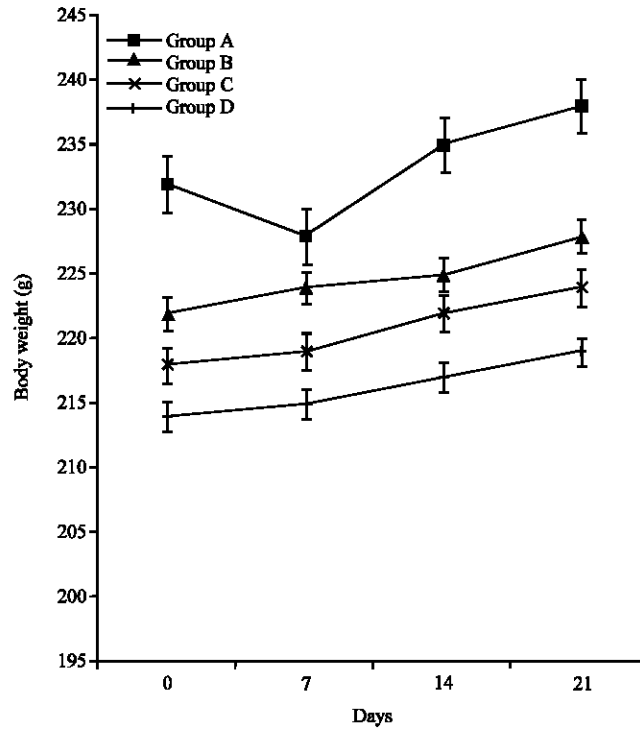


Fig. 1: Changes in body weights of animals at 0, 7, 14 and 21 days of administration. Bar represents Mean±SEM of 8 animals. \*p<0.05 vs. control

Table 1: The activity of G6PDH in the kidney, liver and pancreas of both the treated and control animals

Groups	No. of animals	Activity/reading of G6PDH (Mean±SEM)		
		Kidney	Liver	Pancreas
A	8	19.53±0.15*	69.50±0.76*	42.30±0.12*
B	8	18.97±0.88*	66.50±0.76*	39.73±0.18*
C	8	18.63±0.18*	64.50±0.31*	39.33±0.12*
D	8	17.27±0.18	58.83±0.93	34.73±0.22

\*Represents level of significance at p<0.05

400 mg kg<sup>-1</sup> b.wt. of the plant extract. The statistical values of the activity of G6PDH in the liver in the treatment groups A, B and C were 69.50±0.76, 66.50±0.76 and 64.50±0.31, respectively while that of the control group D was 58.83±0.93. The activity of G6PDH was statistically significant in the entire treated group when compared with the control group. Within the treated groups, animals in group A have the highest activity of G6PDH. In the pancreas, the activity of G6PDH was observed to be statistically significant in all the treatment groups when compared with the control group. The values of the activity of G6PDH in the treated groups A, B and C were; 42.30±0.12, 39.73±0.18 and 39.33±0.12, respectively while that of the control was 34.73±0.22. The significant of the high activity of G6PDH in the kidney, liver and pancreas of the animals treated with plant extract shows that the plant extract has modulating effects on the enzyme of carbohydrate metabolism (Table 1).

Table 2: The activity of LDH in the kidney, liver and pancreas of both the treated and control animals

Groups	No. of animals	Activity/reading of LDH (Mean±SEM)		
		Kidney	Liver	Pancreas
A	8	13.83±0.93*	18.33±0.88*	11.67±1.45*
B	8	11.83±0.44*	14.53±0.26*	8.17±0.44*
C	8	8.47±0.32*	11.37±0.32*	5.70±0.15*
D	8	16.50±1.26	25.67±1.45	16.33±1.76

\*Represents level of significance at p<0.05

**Lactate dehydrogenase activity:** The enzymatic activity of LDH decreased significantly in the kidney, liver and pancreas of the experimental animals administered with ethanolic leaf extract of *C. roseus* compared with the control animals. The statistical activity of LDH in the kidneys of the animals in groups A, B and C were; 13.83±0.93, 11.83±0.44 and 8.47±0.32, respectively. When these values were compared with the control, 16.50±1.26, it was observed that the activity of LDH was statistically significant in all the groups administered with the plant extract for 21 days. The lowest activity of LDH in the kidney of the treated animals was observed in the group of animals administered with 200 mg kg<sup>-1</sup> b.wt. of the plant extract. The statistical values of the activity of LDH in the liver in the treatment groups A, B and C were 18.33±0.88, 14.53±0.26 and 11.37±0.32, respectively while that of the control group D was 25.67±1.45. The activity of LDH in the liver was statistically significant in the entire treated group when compared with the control group. In the pancreas, the activity of LDH was observed to be statistically significant in all the treatment groups when compared with the control group. The values of the activity of LDH in the treated groups A, B and C were; 11.67±1.45, 8.17±0.44 and 5.70±0.15, respectively while that of the control was 16.33±1.76 (Table 2).

## DISCUSSION

At present, there are a large number of medicinal plants which have already been promoted for use in primary health care and classified according to their pharmacological actions and properties (Dhanasekaran and Ganapathy, 2011). The search of available literature(s) revealed no published report on the activities of *C. roseus* on enzymes of carbohydrate metabolism (i.e., G6PDH and LDH). In this study, oral administration of the ethanolic extract of *Catharanthus roseus* to rats produced significant alterations in the enzymatic activities and levels in the kidney, liver and pancreas of the rats after 21 days of administration.

It was observed during the course of this study that the plant extract has a modulating effect on the body weight of rats administered with the extract. There was a decrease in the body weight of the animals in group A administered with 400 mg kg<sup>-1</sup> b.wt. of the extract on the seventh day of administration compared with other animals in the other treatment and the control groups (Fig. 1). Thereafter, the weight of the animals in all the treatment groups began to increase and this was observed throughout the remaining days of study. A similar study by Mostofa *et al.* (2007) showed a statistically significant increase in the body weight of rats treated with leaf extract of *C. roseus*.

Data obtained in the present study showed that the administration of ethanolic leaf extract of *C. roseus* increased the activity of G6PDH significantly in the kidney, liver and pancreas of rats. The pentose phosphate pathway is a cytosolic process that serves to generate NADPH and the synthesis of pentose sugars. There are two distinct phases in the pathway. The first is the oxidative

phase, in which NADPH is generated and the second is the non-oxidative synthesis of 5-carbon sugars. This pathway is an alternative to glycolysis. According to Beutler *et al.* (1996) the primary functions of the pathway is to generate reducing equivalents in the form of NADPH for reductive biosynthesis reactions within cells and provide the cells with ribose-5-phosphate for the synthesis of nucleotides and nucleic acids.

In addition to the synthesis of the precursor of DNA (R-5-P), G6PDH also generates NADPH. The latter is critical for maintaining Glutathione (GSH) in its reduced form. Glutathione is essential for the detoxification of reactive free radicals and lipid hydroperoxides. This may be one mechanism by which *C. roseus* mediates long-term normalization of glycemia in rodent models of diabetes mellitus.

The pathway is one of the three main ways by which the body creates molecules with reducing potentials accounting for about 60% of NADPH production in Man (Zhang *et al.*, 2000). Glucose-6-phosphate dehydrogenase is a rate controlling enzyme (Xu *et al.*, 2005). It is allosterically stimulated by NADP<sup>+</sup>. The ratio of NADPH: NADP<sup>+</sup> is normally about 100:1 in the liver cytosol. This makes the cytosol a highly reducing environment. Formation of NADP<sup>+</sup> by NADPH-utilizing pathway stimulates the production of more NADPH. Glucose-6-phosphate dehydrogenase is a cytoplasmic enzyme that affects the production of reduced form of cytosolic coenzyme (NADPH) by controlling the step from glucose-6-phosphate to 6-phosphogluconate in the pentose phosphate pathway (Zhang *et al.*, 2000; Kletzien *et al.*, 1994). Until recently, the role of this housekeeping enzyme in cell responses to oxidative stress was limited to human erythrocytes that lack any other NADPH producing route (Xu *et al.*, 2005). According to Salvemini *et al.* (1999), it was suggested that G6PDH also plays a protective role against ROS in eukaryotic cells and that G6PDH expression is upregulated by oxidants. The significance of the increased activities of G6PDH in the kidney, liver and pancreas of the treated animals support the claims of Zheng and Wang (2001).

The level of the activities of lactate dehydrogenase was observed to decrease significantly in the groups administered with *C. roseus* compared with the animals in the control group. At high concentration of lactate, the enzyme exhibit feed-back inhibition and the rate of conversion of pyruvate to lactate is decreased. This is an important step in energy production in cells (Butt *et al.*, 2002). Many different types of cells in the body contain LDH and some of the organs relatively rich in this enzyme are the heart, kidney, liver and muscle. Normal LDH levels vary with age. It is higher in childhood due to bone growth (Butt *et al.*, 2002) In medicine, LDH is often used as a marker of tissue breakdown as LDH is abundant in red blood cells and can function as a marker of hemolysis. The activity of LDH in the kidney, liver and pancreas administered with the plant extract was significantly reduced and this is in support of the claim of Butt *et al.* (2002). Tissue breakdown elevates levels of LDH and therefore a measure of it indicates hemolysis (Butt *et al.*, 2002). A low rate of destroyed cells indicates a decreased level of LDH activity and since there was significant reduction in the activity of LDH in the kidney, liver and pancreas of the treated animals, it is inferred that the extract does not cause tissue breakdown.

The significance of the significant increase and decrease in the activities of G6PDH and LDH, respectively has observed in this study may suggested the antidiabetogenic properties of *C. roseus* as reported by Singh *et al.* (2001). This characteristic activity of the plant extract could be as a result of the phytochemical constituents of the plant. The outcome of this study is in support of the claims of Chattopadhyay (1999), Chattopadhyay *et al.* (1991), Chattopadhyay *et al.* (1992) and Elgorashi *et al.* (2003).

## CONCLUSION

Observations and data obtained from this study showed that the ethanolic leaf extract of *C. roseus* alters carbohydrate metabolism. Also the plant extract altered the activities of Glucose-6-phosphate dehydrogenase (G-6PDH) and Lactate Dehydrogenase (LDH) in the kidney, liver and pancreas which may account for some of the earlier reports on the effects of the extract particularly on the integrity of the kidney, liver and pancreas.

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