Effects of Guru (*Cola nitida*) on Drug Metabolizing Enzymes in Rats

A.M. Ahmed, O. S. A. Mohamed and Mohamed .A.M. Homeida

Faculty of Veterinary Medicine, Sudan University of Science and Technology

Abstract: The objective of this study was to investigate the effect of guru on drug metabolizing enzymes in rats. Guru at a dose of 100mg/kg administered orally to rats caused induction of hepatic microsmal mixed function oxidase , but at the dose of 200 and 400 mg/kg inhibited the drug metabolizing enzymes compared to controls that were given rat diet . It is concluded that guru may produce pharmacological effects at the dose of 100mg/kg and toxicological effects at higher doses.

Keywords: Aminopyrine-N-demethylase , Aniline-4-hydroxylase, UDP-glucuronyltransferase Glutathione-S-tranferase, Cytochrome p-450

Introduction

Guru, Cola nut (*Cola nitida*), a central nervous system stimulant has been shown to mediate some pharmacological effects that are similar to the action of caffeine (Carrillo and Bennitez, 2000). Cola nuts have been used in folk medicine as an aphrodisiac and an appetite suppressant, enabling African soldiers who chew them to travel long distances without food (Trindall, 1997). Other uses include increasing the capacity for physical exertion and for enduring fatigue without food, stimulating a weak heart, despondency, brooding, anxiety and sea sickness (The Psychoactive Encyclopedia. (T.P.E) 2008).

Guru is found everywhere in Sudan. An increasing number of people are now consuming the plant for the variety of reasons. However, no detailed behavioral, toxicological or metabolic studies have been carried out.

The objective of this study was to investigate the effect of guru on drug metabolism in rats.

Materials and Methods

Animals were randomly divided into 4 groups of 10 animals per group. Group 1 animals were fed rat diet and kept as controls. Group 2, 3 and 4 animals were given in addition guru at doses of 100, 200 and 400 mg/kg body weight for 4 weeks.

At the end of the experiment rats were killed and liver were immediately removed, weighed and homogenized in ice-cold isotonic KCI. The crude homogenates were then centrifuged at 10,000g for 15min. A microsomal and cytosolic fractions were prepared as described by Mazel (1976). Protein concentrations in these fractions were determined by the method of Lowry *et al* (1951). The activities of aminopyrine-N-demethylase and aniline-4-hydroxylase were determined using the method of Mazel (1976) by estimating the concentrations of formaldehyde and p-aminophenol, respect-ively. The method of Dutton and Storey (1962) was used to determine UDP-glucuronyltransferase activity by estimating o-aminophenyl-glucuronide concentration using o-aminophenol as a substrate. The activity of glutathione-S-tranferase was determined in the cytosotic fraction by estimation of 2, 4-dinitrophenylglutathione concentration according to the method described by Habig *et al*. (1974). The concentration of cytochrome p-450 was determined in the microsomal fraction according to the method of Omura and Sato (1964). The enzyme activities were linear with time, protein and substrate concentration (EL-Sheikh *et al* 1991, 1992).

2.12 Statistical Analysis:-

Result are expressed as mean ±SD and presence of significant differences among means of groups was determined using one

way analysis of variance (ANOVA) with turkey-kramer post-test for significance. Values were considered significant when P <0.05.

Results

Effects of guru on microsomal protein concentration and on the activity of drug

metabolizing enzymes are presented in Table 1. Guru at a dose of 100mg/kg significantly (P<0.05) increased protein concentration in whole homogenate, cytosolic and microsomal fractions in animals of group 2, but significantly P<0.05 decreased protein in animals of group 3 and 4. The activity of cytochrome P-450, amin-opyrine-N-demethylase, aniline-4-hydroxy-lase, were significantly (P<0.05) increased in group 2, but decreased in group 3 and 4. No effect was seen on the activity of UDP-glucuronyl transferase and glutath-ione-S-transferase.

Table 1:- Effect of guru (Mean ± SD) concentration of protein and values of activity of drug metabolizing enzymes in microsomal protein homogenate of liver of rats

Protein (mg g^{-})	Group1 (control)	Group 2 guru treated (100mg/kg)	Group 3 guru treated (200mg/kg)	Group 4 guru treated (400mg/kg)
Whole homogenate	190.31±20.45	215±21.1*	108±2.5*	96±2.46*
Cytosolic fraction	112.31±10.30	125±9.5*	86±3.0*	80±2.91*
Microsomal fraction	30.91±2.11	4.01±3.1*	22±1.61*	20±1.31*
Enzyme activity of microsomal protein (nmol g^{-})				
Cytochrome P-450	0.222±0.012	0.402±0.022*	0.131±0.012*	0.121±0.03*
Aminopyrine-N-demethylase	11.70±1.31	16.3±1.6*	8.31±0.061*	7.11±0.063*
Aniline-4-hydroxylase	0.281±0.02	0.402±0.03*	0.081±0.011*	0.061±0.012*
UDP-glucuronyl transferase	1.103±0.051	1.113±0.050	1.133±0.050	1.061±0.41
Glutathione-S-transferase	172±12	170±13	168±13	173±12

*Significant (P<0.05) different from control group.

Discussion

Feeding of guru at a dose of 100mg/kg body weight to rats increased protein concentration of liver homogenate and activity of phase-I metabolizing enzymes such as cytochrome p 450, aminopyrine-N-demethylase and aniline-4-hydroxylase. Similar effects have been produced by caffeine in rats (Mitoma *et al* 1969, Govindwar *et al* 1988), suggesting that guru at low doses may induce activation of microsomal mixed oxidaze system. However, guru at doses of 200 and 400mg/kg has inhibitory effect on metabolizing enzymes suggesting that guru at these doses may produce toxic effect on the enzymes. Guru failed to produce any effect on phase-2 drug metabolizing enzymes represented by UDP-glucuronly transferase and glutathione. These enzymes were found to be resistant to hepatoxin induced liver injury (Gergus *et al* 1982; El-

Sheikh *et al* 1991). This is probably due to deep location of these enzymes within endoplasmic reticulum close to inner surface of the membrane (Gergus *et al* 1982). Consumption of guru which is capable of modulating activity of drug metabolizing enzymes may result in unpredictable pharmcodynamic and toxicologic effects of drugs and xenobiotics co-administered with guru and therefore human and animals should not be allowed to take the plant and drugs concomittantly.

References

Carrillo, J.A. and Bennitez, J. (2000). Clinically significant pharmacokinetic interactions between dietary caffeine and medications. Clin pharmacokinet., **39** :127-153.

Dutton G.J. and Storey, I.D.E (1962). Glucuronide forming enzymes. In: Method in Enzymology, Colowick SP and Kaplan NO (Eds). Academic Press, New York. Pp: 159-164.

El-Sheikh H.A., Ali, B.H. Homeida, A.M. Lufti A.A.A and Hapke, H.J. (1992). The effects of fascioliasis on the activities of some drug metaboilizing enzymes in desert sheep liver. British Vet. J., **148**: 249-257.

El-Sheikh H.A., B.H. Ali, A.M. Homeida, T. Hassan, O.F. Idris and H.J. Hapke, (1991). The activities of drug metabolizing enzymes in goats treated orally with latex of *Calatropis procera* and the influence of dieldrin pretreatment. J. Comperative Pathol., **104**: 257-268.

Govindwar S.P, Kachole M.S and Pawar. S.S (1988). Effect of caffeine on the hepatic microsomal mixed function oxidase system during Phenobarbital and benzo [a] pyrene treatment in rats. Toxicology letters **42**: 109-115.

Gregus, Z., Wathins, J.B. Thompson T.N. and Klaassen, C.D. (1982). Resistance of some phase II biotransformation pathways to hepatoxins . J. Pharmacology and Experimental Therapeutics, **222**: 471-479.

Habig W.H., Pabst M.J and Jakoby, W.B (1974). Glutathione-S-transferase, the first enzymatic step in mercapturic acid formation. J. Biol. Chem., **249**: 7130-7139.

Lowry, O.H., Rosenburg N.J. and Farr, A.L. (1951). protein measurement with the folin regent.J.Biol. Chem, **193**: 265-275.

Mazel, P., (1976). Experiments illustrating drug metabolism *in vitro*. In: Fundamental of Drug Metabolism and Drug Disposition, La Cu BN, Mandel HG and way El (Eds). Williams and Wilkings, Baltimore, pp: 546-582.

Mitoma C., Lombrozo., La Valley S.E. and Dehn F. (1969). Nature of the effect of caffeine on the drug-metabolizing enzy-

mes. Archives of biochemistry and biophysics, **134**: 434-441.

Omura T. and Sato, R. (1964). The carbon monoxide binding pigment of liver microsomes 1. Evidence for its hemo-protein nature. J. Biol. Chem., **239**:2370-2378.

The Psychoactive Encyclopedia (2008). The History usage, Botanical and Chemical Aspects of Psychoactive Susbtance, Fungi and Plants.

Trindall, R. (1997). Ethno botanical leaflets: the culture of cola: social and economic aspects of a West African domesticate carboondale: southern Illinois University Herbarium.

تأثير القورو (كولا نيتيدا) على نشاط إنزيمات الآيض الدوائية في الجرزان

عبدالباقي مصطفى احمد[1] ، عثمان سعد محمد[2] و محمد عبدالقادر موسى حميدة[3]

جامعة السودان للعلوم والتكنولوجيا – كلية الطب البيطري

المستخلص

لقد أجرى هذا البحث لدراسة تأثير القورو على نشاط انزيمات أيض الأدوية فى الفئران لمدة 28 يوما. لقد اوضحت النتائج وبدلالة احصائية الى فعالية الجرعة 1 00 ملجرام للكيلو جرام الى تحفيز نشاط انزيمات الاكسدة الدوائية بينما تم تثبيط نشاط هذة الانزيمات عند الجرعات 200, 400 ملجرام للكيلو جرام مقارنة بالشاهد تشير هذه النتائج الى ان القورو فى جرعات 100 ملجرام للكيلوجرام ربما كانت جرعات دوائية بينما الجرعات 200, 400 ملجرام للكيلوجرام هى جرعات سمية.