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ARTICLE

Graded and Quantal Dose Response of Total Tannins Isolated from the Stem Bark of Dialium guineense

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Abstract

Background and Objective: The safety of plant-derived bioactive compounds has become a global concern. Getting an appropriate dose of a substance that elicits the desired effect is of utmost importance to Pharmacologists. The present study investigated the graded and quantal dose response of total tannins isolated from the stem bark of *Dialium guineense*.

Methods: Adult male Wistar rats (n = 15) weighing 170 – 190 g (mean weight = 180 ± 10 g) were randomly assigned to three groups (5 rats/group). The rats received varied doses of total tannins isolated from the stem bark of the medicinal plant (50 - 150 mg/kg body weight, bwt) orally for 9 days. Concentration of fasting blood glucose (FBG) was used as the therapeutic index.

Results: Total tannins isolated from the stem bark of *D. guineense* significantly reduced the FBG levels of normal Wistar rats ($p < 0.05$). The graded and quantal dose response curves showed that 150 mg/kg bwt was effective in reducing the blood glucose of rats (produced the best hypoglycemic effect).

Conclusion: These results indicate that total tannins isolated from *D. guineense* stem bark possesses hypoglycemic effect at a relatively good dose.

Keywords: Dialium guineense, Dose response, Effective dose, Therapeutic index, Total tannins.

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1 | INTRODUCTION

Graded dose response relationship is a fundamental aspect of Pharmacology. It is employed to study the effects of increasing drug dose and its response in a system. For instance, individual fibres of the skeletal muscle are capable of eliciting progressively increasing response with in-

creasing dose of a particular drug. The corresponding increase in response can be measured. With increase in response of dose, at first there is considerable increase in response and then, there are smaller increments as the dose approaches the maximum limit. After maximum response has been reached, no further increase in response can be obtained with further increase in dose. Generally, the dose response curve assumes a shape or sigmoid pattern, and as a rule, the relationship between the dose and response is linear and well pronounced in the main body of the curve. This part of the curve (between 25 and 75 % of the curve) is important in analytical and practical Pharmacology. Boundaries of the linearity can be extended by means of certain mathematical transformation of other dose or response [1].

Tannins are astringent, bitter plant polyphenols that either bind and precipitate or shrink proteins. The astringency from tannins is that which causes the dry and puckery feeling in the mouth following the consumption of red wine, strong tea, or an unripen fruit [2]. The term applies to large polyphenolic compounds containing sufficient hydroxyl and other suitable groups (such as carboxyl) which form strong complexes with proteins and other macromolecules [2]. Tannins are found as shapeless yellow or light brown masses like powder, flakes or sponge. They are classified into three broad groups: hydrolysable tannins, condensed tannins, and pseudotannins. Hydrolysable tannins are hydrolyzed by weak acids or bases to produce carbohydrate and phenolic acids. Examples of gallotannins are the gallic acid esters of glucose in tannic acid ($C_76H_{52}O_{46}$), found in the leaves and bark of many plant species [2]. Condensed tannins, also known as proanthocyanidins, are polymers of 2 to 50 (or more) flavonoid units that are joined by carbon-carbon bonds, which are not susceptible to being cleaved by hydrolysis [3]. Pseudotannins do not obey Goldbeaters skin test and are low molecular weight compounds. Chlorogenic acid in coffee and *nux vomica*, *ipecacuanha* acid in *ipecacuanha* and catechins in cocoa are examples [3]. The present study investigated the graded and quantal dose response of total tannins isolated from the stem bark of *Dialium guineense.*

Supplementary information The online version of this article (https://doi.org/10.15520/arjmcs.v9i09.379) contains supplementary material, which is available to authorized users.

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2 | MATERIALS AND METHODS

Experimental Rats

Adult male Wistar rats (n = 15) weighing170 – 190 g (mean weight = 180 ± 10 g) were obtained from the Department of Anatomy, University of Benin, Benin City, Nigeria. The rats were housed in metal cages under standard laboratory conditions: temperature of 25 ^{o}C, 55 – 65 % humidity and 12-h light/12-h dark cycle. They were allowed free access to rat feed (pelletized growers mash) and clean drinking water. Prior to commencement of the study, the rats were acclimatized to the laboratory environment for one week. The study protocol was approved by the Ethics Committee on Animal Use of the Faculty of Life Sciences, University of Benin, Benin City, Nigeria.

Collection of Plant Material

The stem barks of *D. guineense* were obtained from Auchi Area of Edo State, Nigeria and authenticated at the herbarium of the Department of Plant Biology and Biotechnology, University of Benin, Benin City, Nigeria.

Plant Preparation and Extraction

The stem bark was brushed and shade- dried at 30 °C for a period of two weeks and crushed into small pieces using clean mortar and pestle. Total saponins was isolated from the stem bark using standard method [4].

Dose Response Study

The rats were randomly assigned to three groups (5 rats/group). They received varied doses of isolated total tannins (50 - 150 mg/kg bwt) orally for 9 days. Concentration of FBG was used as the therapeutic index.

Statistical Analysis

Data are expressed as mean ± SEM (n = 5). Statistical analysis was performed using SPSS (20.0).

Groups were compared with Duncan multiple range test. Values of $p < 0.05$ were considered statistical significant.

3 | RESULTS

Concentrations of Fasting Blood Glucose

Total tannins isolated from the stem bark of *D. guineense* significantly reduced the FBG levels of normal Wistar rats ($p < 0.05$). The graded and quantal dose response curves showed that 150 mg/kg bwt was effective in reducing the blood glucose of rats (Tables 1 – 3).

Table 1: Concentrations of Fasting Blood Glucose of Rats Treated with Isolated Total Tannins of *D. guineense* Stem Bark

Dose (mg/kg bwt)	Blood Glucose Concentration (mg/dL)				
	Basal	Day 3	Day 5	Day 7	Day 9
50	109.50 ± 4.50	91.00 ± 3.50	87.50 ± 5.50	59.00 ± 4.00	61.50 ± 1.50
100	101.50 ± 2.50	72.00 ± 1.50	74.50 ± 4.50	65.50 ± 3.50	68.00 ± 2.00
150	103.50 ± 2.50	81.00 ± 2.00	55.50 ± 0.50	45.00 ± 0.50	63.50 ± 2.50

Data are concentrations of FBG and are expressed as mean ± SEM (n = 5).

Table 2: Glycemic Change of Rats Treated with Total Tannins

Dose (mg/kg bwt)	Blood Glucose Reduction (mg/dL)			
	Day 3	Day 5	Day 7	Day 9
50	18.50 ± 2.38	22.00 ± 3.00	50.50 ± 5.50	48.00 ± 4.00
100	29.50 ± 4.50	27.00 ± 3.00	36.00 ± 3.00	33.50 ± 5.50
150	22.50 ± 1.50	48.00 ± 5.50	58.50 ± 5.50	40.00 ± 4.00

Data are concentrations of FBG and are expressed as mean ± SEM (n = 5).

Table 3: Percentage Glycemic Change of Rats Treated with Total Tannins

Dose (mg/kg bwt)	Blood Glucose Reduction (%)			
	Day 3	Day 5	Day 7	Day 9
50	16.89 ± 3.41	20.09 ± 2.07	46.12 ± 3.92	43.84 ± 4.81
100	29.06 ± 2.75	26.60 ± 3.95	35.47 ± 3.27	33.00 ± 5.00
150	21.74 ± 2.63	46.38 ± 5.91	56.52 ± 5.11	38.65 ± 4.75

Data are glycemic changes and are expressed as mean ± SEM (n = 5).

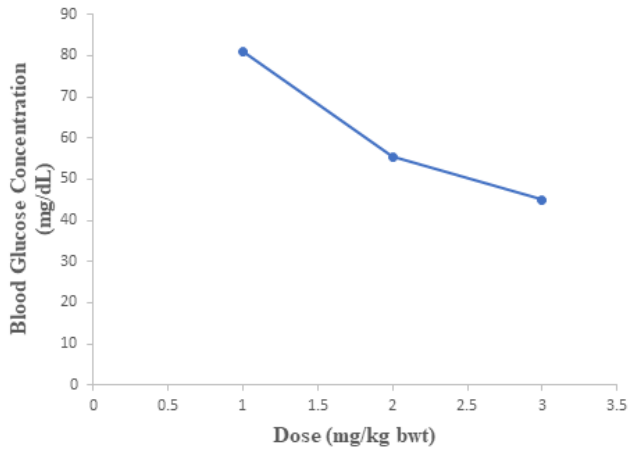

FIGURE 1: Graded Doses Response Curve for Isolated Total Tannins

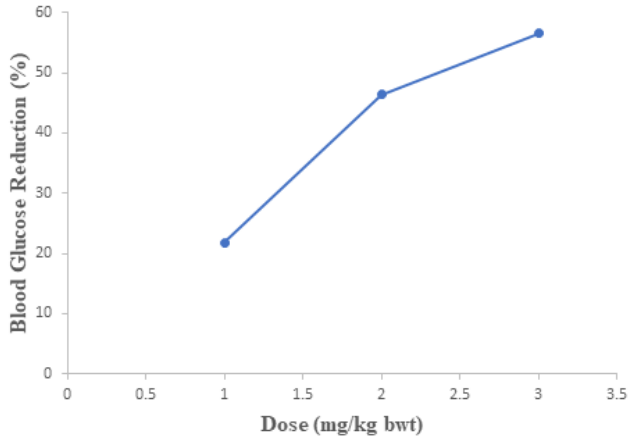

FIGURE 2: Quantal Dose Response Curve for Isolated Total Tannins

DISCUSSION

The safety of plant-derived bioactive compounds has become a global concern [5 – 7]. Getting an appropriate dose of a substance that elicits the desired effect is of utmost importance to Pharmacologists. It is critical when performing dose response analyses to have a clear concept of what type of "dose" to use. There are three basic types of "dose" that arise from scientific investigations: (1) the administered or external dose; (2) the internal (absorbed) dose; and (3) the target or tissue dose. These doses are interrelated, and each of them can be used to express dose response relationships [1]. External dose refers to the amount of an agent or chemical ad-

ministered to an experimental animal or human in a controlled experimental setting by some specific route at some specific frequency. The external dose is often referred to as exposure or intake. External dose, or external exposure, is frequently the dose metric that is used in observational epidemiological studies. Internal dose is the amount that is systemically available and can be regarded as the fraction of the external dose that is absorbed and enters the general circulation [8]. It is a consequence of absorption, distribution, metabolism and excretion of the chemical and can be derived from suitable toxicokinetic mass balance studies. The analytical method used in the toxicokinetic studies determines whether the "dose" refers to the parent compound alone or the parent compound plus first-pass metabolites. Biomarkers of internal dose, such as plasma concentrations or urinary excretion, are sometimes available in epidemiological studies. The tissue dose is the amount that is distributed to and present in a specific tissue of interest. Two parameters are important determinants of dose: the dose frequency and duration of dosing. Dosing can be acute, sub-chronic or chronic. The description of dose reflects the magnitude, frequency and duration over which it applies [9, 10]. Response, in this context, generally relates to an observation or effect seen following exposure *in vivo* or *in vitro*. Possible end-points cover a broad range of observations, from early responses such as biochemical alterations to more complicated responses such as cancer and developmental defects. Responses can be either adaptive or adverse. Adverse effects are defined as a change in the morphology, physiology, growth, development, reproduction or life span of an organism or subsystem (subpopulation of cells) that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences [11, 12]. Most responses of interest in the context of dose–response assessment fall into one of four basic categories: quantal responses, counts, continuous measures and ordinal categorical measures. Quantal responses relate to an effect that is either observed or not observed in each individual subject (laboratory animal or human). For each dose, the number of subjects responding out of the number of subjects available is reported (for example, the proportion of animals with a tumour in a cancer bioassay) [8, 9]. The results of this study showed that total saponins isolated from the stem bark of *D. guineense* significantly reduced the FBG levels of normal Wistar rats. The graded and quantal dose response curves showed that 150 mg/kg bwt was effective in reducing the blood glucose of rats.

4 | CONCLUSION

The results of this study have demonstrated that total tannins isolated from the stem bark of *D. guineense* possesses hypoglycemic effect at a relatively good dose.

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