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Effect of Aqueous Ginger Extract on Hepatic Phase II Xenobiotic Metabolizing Enzyme Induction in Rats

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Abstract

Background: Ginger (*Zingiber officinale*) has been shown to induce hepatic phase II xenobiotic metabolizing enzymes in rats. However, no study has directly evaluated this effect of ginger when it is administered based on the rat's body weight. This study was undertaken to determine the Glutathione S Transferases (GST) induction capacity of aqueous extract of ginger and the impact this has on the metabolism of phenobarbitone when the ginger is administered based on the body weights of the animals.

Materials and methods: Eight female wistar strain albino rats (4 to 8 weeks old) weighing 150 to 200 g were grouped into the control group that received normal saline orally and the treated group that received the ginger extract at a dose of 250 mg/kg orally. Both groups received phenobarbitone at a dose of 40 mg/kg intraperitoneally at the end of three weeks to examine the time of onset and duration of the hypnotic effect of phenobarbitone on the rats, after which, the animals were sacrificed, liver collected, and GST assayed. The results were analyzed using SPSS software version 14.0 for windows and a T-test was used to determine statistical significance.

Results: The result shows no significant change in GST activities between treated and control groups (Mean ± SD; 10.7 ± 1.8 *vs.* Mean ± SD;9.6 ± 1, P>0.05), time of onset of action of phenobarbitone in treated and control groups (Mean ± SD; 1801.7± 0.9 *vs.* Mean ± SD; 2303.5 ± 1.9, p>0.05), and duration of action of phenobarbitone in treated versus control groups (Mean ± SD; 5310 ± 239.7 *vs.* Mean ± SD; 6270 ± 868.7, P>0.05).

Conclusion: Ginger does not induce GST if administered based on the body weights of animals.

Keywords: Hepatic; Xenobiotics; Detoxification; Phase II enzymes; Induction; Metabolism; Phenobarbitone

Introduction

The liver is the primary organ in regulating various physiological processes in the body, such as secretion, storage, and metabolism. A properly functioning liver can render toxic substances harmless and synthesize and secrete useful substances required for health, thus serving as a filtration and detoxification center. The accumulation of unwanted toxic substances in the body may act as carcinogens and mutagens. Therefore, an insult to the liver caused by noxious substances can have dangerous consequences [1-3]. Interestingly, higher animals have evolved ways to eliminate toxic materials, so they do not cause harm namely drug metabolizing enzymes to clear xenobiotics out of our system [4]. In addition, the major mechanism for protection against carcinogens, mutagens, and other forms of toxicity is the induction of enzymes involved in their metabolism particularly phase II enzymes such as Glutathione S Transferases (GST), UDP-glucuronosyltransferases, and quinone reductases. Xenobiotic metabolizing enzymes have been grouped into phase I reactions in which enzymes carry out oxidation, reduction, or hydrolytic reactions, and phase II reactions, in which enzymes form a conjugate of the substrate (the phase I product) [4]. Phase II enzymes facilitate the elimination of drugs and the inactivation of electrophilic and potentially toxic metabolites produced by oxidation. Xenobiotic metabolizing enzymes are found in most tissues in the body, with the highest levels located in the tissues of the gastrointestinal tract (liver, small and large intestines) [5]. Furthermore, research has also shown that medicinal plants such as cruciferous vegetables, citrus fruits, condiments, and spices like garlic and ginger act as chemo preventative and protective agents by stimulating the activity of detoxifying hepatic enzymes [6].

Ginger (*Zingiber officinale*) belongs to the Zingiberaceae family. Fresh ginger contains moisture, protein, fat, minerals, fiber, carbohydrates, and minerals like iron, calcium, and phosphorous [7]. It also contains vitamins such as thiamine, riboflavin, niacin, and vitamin C. The composition varies with the type, variety, agronomic conditions, curing methods, drying, and

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storage conditions. In the fresh ginger rhizome, the gingerols are the primary active components, and gingerol (5-hydroxy-1-(4-hydroxy-3-methoxy phenyl) decan-3-one is the most abundant component in the gingerol series. In dried ginger powder, shogaol a dehydrated product of gingerol is the predominant pungent constituent [8-10]. It is a common spice in Asian and African foods. Different cultures and countries have been using ginger as a condiment and for medicinal purposes. For example, the ancient Greeks and Romans used ginger as a spice, condiment, stimulant, and carminative [11]. Ginger is used to treat a series of medical problems ranging from, nausea, emesis, cancer, diabetes mellitus, asthma, heart conditions, respiratory disorders, obesity, and neurodegenerative diseases [12]. In India ginger is used as a carminative, diaphoretic, antispasmodic, expectorant, peripheral circulatory stimulant, astringent, appetite stimulant, anti-inflammatory agent, diuretic, and digestive aid [13]. Ginger is recommended to relieve and prevent nausea due to motion sickness and can be more effective than dimenhydrinate in this regard. Ginger is also used for the treatment of worsening emesis, especially during the first trimester of pregnancy, and can be used as an adjuvant therapy to treat cancer induced emesis. Ginger powder (500-600 mg) is used to treat migraine [14]. Ginger has been listed in the “Generally Recognized as Safe” (GRAS) document of the US FDA [15]. Some studies have shown that ginger induces hepatic drug metabolizing enzymes, especially phase II enzymes, thereby increasing their activity. In addition, studies have also shown that ginger may lead to enhanced metabolism of other drugs when co-administered together. Consequently, enhanced metabolism of drugs because of enhanced induction of hepatic phase II enzymes by ginger will result in the rapid elimination of such drugs, thereby shortening their duration of action. Additionally, enzyme induction is one of the mechanisms by which drug resistance (tolerance) occurs and may lead to therapeutic failures or toxicity. For example, when barbiturates are administered with the naturally occurring anticoagulant coumarin, they decrease the anticoagulant effect of coumarin by facilitating its metabolism [16]. Therefore a drug or therapeutic agent that is metabolized by enzymes induced by enzyme inducers like ginger may result in therapeutic failure. All these factors underscore the importance of understanding dietary intake and its impact on the metabolism of drugs induced by these compounds. Both direct and indirect methods can determine the impact of enzyme induction on drug metabolism. In the indirect method, typically, we measure the time it takes for the drug's effect to be terminated which provides an index of the extent of enzyme induction. For example, phenobarbitone is a sedative hypnotic metabolized by liver enzymes and the duration of time it takes for the animal to wake up after the sedative effect wears off is an indirect measure of the extent of enzyme induction [17]. The higher the expression of enzymes by enzyme inducers the lesser the duration of action. Unfortunately, no study has directly evaluated ginger’s hepatic phase 11 xenobiotic metabolizing enzyme (GST) induction when it is administered based on the rat's body weight. This study aimed to determine the GST induction capacity of aqueous extract of ginger and the impact this has on the metabolism of phenobarbitone when ginger is administered based on the body weights of the animals (dosage dependent). However, the study shows that ginger does not significantly induce hepatic GST if administered based on the body weights of animals [18].

Materials and Methods

Reagents

Reagents and drugs including phenobarbitone, reduced glutathione, CDNB (1-chloro-2,4 dinitrobenzene), and potassium phosphate buffer were purchased from a commercial reagent/chemical dealer in Anambra State, Nigeria.

Preparation of ginger extract for oral administration

Ginger rhizomes were purchased from the local market (Nkwo OGIDI) in OGIDI Anambra state, Nigeria, and identified by Dr. Okafor Samuel, a botanist from Anambra state, Nigeria. The rhizome of *Z. officinale* was shade dried at room temperature after peeling it and ground using an electric grinder and stored at room temperature until needed.

The dried powdered rhizomes (1000 g) of *Z. officinale* were macerated in 4 liters of distilled water for 96 hrs [19]. At room temperature and then were filtered through a 5 µm filter to obtain the aqueous extract. The solvent was removed by evaporation under reduced pressure at 40°C yielding a semisolid residue. This was dried in an electric oven to obtain a powdered solid residue. For animal administration. 2.5 g of the powder was dissolved in 10 ml of distilled water, to make up to 250 mg/kg of the extract used in this study.

Animals

Adult female wistar albino rats (4 to 8 weeks old), weighing 150 to 200 g were used for this study. They were obtained from the university of Benin Edo state, Nigeria. Animals were divided into 2 groups of 4 each. Random sampling was used to assign animals to the control and experimental groups. Group 1 served as normal healthy control rats, and group 2 served as the experimental group. The rats were monitored daily, and their drinking water was changed every morning. The animals had free access to water and were maintained on standard pelleted rodent chow ad libitum (composed of 55% corn starch, 20% casein, 15% corn oil, 5% salt mixture, and 5% vitaminized starch (Egyptian company of oils and soap Kafr-Elzayat). All animals were housed in the Delta state university Abraka, Nigeria animal house in temperature and humidity controlled rooms under a 12 h/12 h light/dark cycle. All the National Health Research Ethics Committee of Nigeria (NHREC) guidelines were strictly adhered to, and the treatment of the rats was approved by the research, ethics, and grant committee, faculty of basic medical sciences, Delta state university Abraka Nigeria. All efforts were made to minimize animal suffering, reduce the number of animals used, and utilize alternatives to *in vivo* techniques, if available.

The onset of the hypnotic effect of phenobarbitone (time of disappearance of righting reflex/time of onset of sleep) and the duration of action of the drug (time of reappearance of righting reflex/sleep duration) in each group of animals were observed by monitoring the appearance and disappearance of the righting

reflex and recorded. After this, the animals were sacrificed. The liver was harvested for enzyme assay.

Isolation of Microsomes and Cytosol

The tissue (liver) was harvested and rinsed with cold 0.154 M KCL, and the weight of the tissue was recorded. The tissue was then minced, and a 20% (W/V) homogenate was prepared in cold using a polytron homogenizer (Kinematica) for a minute. Homogenate was centrifuged at 15000 x g for 20 min. to sediment the cell debris, intact cells, nuclei, erythrocytes, and heavy mitochondria. The supernatant was decanted and centrifuged at 1,00,000 x g for one hour. The supernatant thus obtained (cytosolic fraction) was carefully decanted into small vials and was used to estimate Glutathione S Transferase (GST) activity.

Glutathione S Transferase (GST) enzyme assay

GST activity was determined spectrophotometrically by using CDNB (1-chloro-2,4, dinitrobenzene) as substrate according to Habig, et al., with some modifications. The reaction mixture has a volume of 3 ml containing potassium phosphate buffer (0.3 M, pH 6.5), reduced glutathione (30 mM), and CDNB (30 mM). The assay was initiated with the addition of cytosolic enzyme (100 µl) in the reaction mixture. All initial rates were corrected for the background nonenzymatic reaction [20]. One unit of activity is defined as the formation of 1 µmol product min^{-1} at 37°C (extinction coefficient at 340 nm=9.6 mm^{-1} cm^{-1} for CDNB. The reaction was continuously monitored for 5 min. at 37°C in Gilford Spectrophotometer at 340 nm.

Statistical analysis

Data analyses were performed using SPSS software version 14.0 for windows. All data were expressed as mean ± SD. A T-test was used to determine statistical significance.

Results

Rats were treated with an aqueous extract of ginger or saline for 3 weeks. To determine if treatment with ginger extract had an effect on body weight, we first measured the weight of rats. The mean initial and final body weight of rats treated with aqueous extract of ginger is represented in Table 1. A summary of the data analyses of the body weight of rats is presented in Table 1. The final body weight of animals that received an aqueous extract of ginger (Mean ± SD; 177.5 ± 17.0) was not significantly different from the mean initial weight of the rats (Mean ± SD; 165.6 ± 6.0).

Table 1: No change in body weight of rats treated with aqueous extract of ginger.

Period of treatment (weeks)	Initial weight (g)	Final weight(g)
Week 3	165.6 ± 6.0	177.5 ± 17.0

Values are expressed as mean ± SD. Group 2 animals (treated animals) received oral ginger extract at a daily dose of 250 mg/kg using an oral syringe, while group 1 animals (control) received normal saline orally. At the end of the experimental period (3 weeks), each group of animals received phenobarbitone at a dose of 40 mg/kg intraperitoneally.

We next wanted to determine the effect of treatment with aqueous ginger extract on liver weight.

The mean liver weight of rats treated with aqueous extract of ginger is represented in Table 2. Like the body weight, the mean liver weight of animals that received an aqueous extract of ginger (Mean ± SD;6.4 ± 1.3) was not significantly different from the mean liver weight of the control animals (Mean ± SD;6.9 ± 1.5).

Table 2: No change in mean liver weight between treated and control rats.

Animal groups	Liver weight (g)
Control (normal saline) group 1	6.9 ± 1.5
Treated (ginger) group 2	6.4 ± 1.3

Values are expressed as mean ± SD. Group 2 animals received oral ginger extract at a daily dose of 250 mg/kg using an oral syringe, while group 1 animals (control) received normal saline orally. At the end of the experimental period (3 weeks), each group of animals received phenobarbitone at a dose of 40 mg/kg intraperitoneally.

There is evidence in the literature that ginger stimulates the hepatic phase II metabolizing enzymes, GST in particular and therefore, we wanted to determine if the aqueous extract of ginger had any effect on this enzyme [21]. The mean liver GST activity in rats treated with aqueous extract of ginger versus the control animals is represented in Table 3. A summary of the data analyses of the liver GST activity of the treated animals compared to the control animals is presented in Table 3. The mean liver GST activity of animals that received an aqueous extract of ginger (Mean ± SD; 10.7 ± 1.8) was not significantly different from the mean liver GST activity of the control animals (Mean ± SD; 9.6 ± 1.1).

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Table 3: No change in the mean liver glutathione-s-transferases activity in treated versus control rats.

Animal groups	Glutathione-s-transferase (units/g)
Control (normal saline) group 1	9.6 ± 1.1
Treated (ginger) group 2	10.7 ± 1.8

Values are expressed as mean ± SD. Group 2 animals received oral ginger extract at a daily dose of 250 mg/kg using an oral syringe, while group 1 animals (control) received normal saline orally. At the end of the experimental period (3 weeks), each group of animals received phenobarbitone at a dose of 40 mg/kg intraperitoneally.

An indirect way to measure hepatic drug metabolizing enzyme induction is *via*. The measurement of barbiturates hypnosis disappearance (duration of action) and the latency of falling asleep (onset of action). Therefore, we wanted to determine if the aqueous extract of ginger had any effect on the onset of action and duration of action of the barbiturate (phenobarbitone).

The average time(s) of onset of the hypnotic effect (sleep) of phenobarbitone in rats treated with an aqueous extract of ginger versus the control animals is represented in Table 4. A summary of the data analyses of the average time (s) of onset of the hypnotic effect of phenobarbitone in the treated animals compared to the control animals is presented in Table 4. The average time (s) of onset of the hypnotic effect of phenobarbitone in animals that received an aqueous extract of ginger (Mean ± SD; 1801.7 ± 0.9) was not significantly different from the average time (s) of onset of the hypnotic effect of phenobarbitone in the control animals (Mean ± SD; 2303.5 ± 1.9).

Table 4: The time of onset of sleepiness in the control and treated rats is similar.

Animal groups	The time of onset of action of phenobarbitone/(sleepiness) (s)
Control (normal saline) group 1	2403.5 ±1.9
Treated (ginger) group 2	1801.7 ± 0.9

Values are expressed as mean ± SD. Group 2 animals received oral ginger extract at a daily dose of 250 mg/kg using an oral syringe, while group 1 animals (control) received normal saline orally. At the end of the experimental period (3 weeks), each group of animals received phenobarbitone at a dose of 40 mg/kg intraperitoneally.

Lastly, we also determined if the aqueous extract of ginger impacted the duration of action of phenobarbitone. The mean duration of the hypnotic effect of phenobarbitone in rats treated with aqueous extract of ginger versus the control animals is represented in Table 5. A summary of the data analyses of the mean duration of the hypnotic effect of phenobarbitone in the treated animals compared to the control animals is presented in Table 5. The mean duration of the hypnotic effect of phenobarbitone in animals that received an aqueous extract of ginger (Mean ± SD; 5310 ± 239.7) was not significantly different from the mean duration of the hypnotic effect of phenobarbitone in the control animals (Mean ± SD; 6270 ± 868.7).

Table 5: The duration of sleepiness in the control and treated rats is similar.

Animal groups	The duration of action of phenobarbitone/sleepiness (s)
Control (normal saline) group 1	6270.0 ± 868.7
Treated (ginger) group 2	5310.0 ± 2396.7

Values are expressed as mean ± SD. Group 2 animals received oral ginger extract at a daily dose of 250 mg/kg using an oral syringe, while group 1 animals (control) received normal saline orally. At the end of the experimental period (3 weeks), each group of animals received phenobarbitone at a dose of 40 mg/kg intraperitoneally.

Discussion

In the present study, we show that the aqueous extract of ginger administered as dosage factoring body weight had no significant effect on liver GST activity; in addition, the aqueous extract of ginger had no effect on the body weight of the treated animals. Furthermore, we observed no change in liver weights of treated animals compared to controls. The results show a faster

time of onset of action of phenobarbitone but no substantial change in the duration of action of phenobarbitone compared to controls. Our results indicate that aqueous ginger extract did not significantly induce the hepatic phase II xenobiotic metabolizing enzyme (GST).

Several factors influence enzyme induction. For example, dietary factors induce specific enzymes that influence xenobiotic metabolism that help detoxify unwanted chemicals and xenobiotics. Among them is the Glutathione S Transferases (GSTs), a phase II enzyme involved in cellular protection [22]. GSTs catalyze the conjugation of electrophilic compounds with reduced glutathione. Generally, enzyme induction is observed at high doses of drug administration or following exposure to toxins with a long half-life [23]. Other factors that impact enzyme induction are gender, species, dose, frequency of exposure, diet, and age of the animals [24].

Several studies in animal and cell culture models have shown that exposure to either ginger powder or an organic extract of ginger induces phase II enzymes. Of particular interest is the significant increase in activity of GST in rats fed different concentrations of ginger in their diet. However, this is in sharp contrast to our studies that show no change in the activity of GST after exposure to the aqueous extract of ginger through oral gavage. The discrepancy in our observations compared to previous studies may be manifold (1) Dose of ginger, (2) Vehicle of administration and (3) Duration of the study. In our study, we utilized an aqueous extract of ginger and administered it by oral gavage based on the animal's body weight (250 mg/Kg) for three weeks. The dose used in our studies is substantially lower than the studies conducted by Polasa, et al. and the study conducted by Nirmala, et al. Both these studies administered different concentrations of ginger corresponding to 0.25, 0.5, and 2.5 g of fresh ginger/15 g of rat diet, and the rat consumed about 15 g of the diet daily. They saw a significant increase in the activity of GST at all doses in the liver [25]. The increase in activity may be likely due to the high concentration of ginger compared to our study. Unlike our study, the dose used in these studies did not consider the animals weight. This dosage is substantially higher than the dose we used in our studies and potentially, this may be one reason they saw a pronounced activity of phase II enzymes. Therefore, the dose (concentration) effect (response) relationship is likely partly responsible for the discrepancy in the two studies. Although the dried ginger powder is pungent, it appears rats eat the diet because it is made very palatable (made up of wheat flour 15%, roasted Bengal gram flour 58%, groundnut flour 10%, skimmed milk powder 5%, casein 4%, refined oil 4%, salt mixture 4% and vitamin mixture 0.2%). Yet another possibility for the conflicting results may be due to the duration of the study [26]. Both Nirmala, et al. and Polasa, et al. administered the drug for a whole month, however, we administered it only for three weeks. It is possible that three weeks may not be sufficient time for the induction of more enzymes.

The results of our study bear some similarities and differences from several other studies that used both mice and rats to determine the effect of ginger on the induction of GST as a mechanism of cellular protection. Like our results, they did not find any significant change in the activity of GST when ginger only groups are compared to control groups [27]. However, these studies are different from our studies with respect to the route of administration as well as the administration of carcinogens. While we used oral gavage, these studies used the parenteral route for the administration of ginger. These studies also administered various toxicants in addition to ginger extract, contrary to our study that administered only ginger extract. It appears that irrespective of the route of administration, enzyme induction may be modulated by the dose of the dietary agent. It also seems that ginger significantly induces GST in the presence of toxicants when the ginger is administered based on the body weight of animals.

Several indirect methods, including determining plasma levels of the drug, urinary excretion of drug metabolite, and examining the proliferation of the smooth surface of the endoplasmic reticulum under an electron microscope may be used as an index for enzyme induction. Similarly, the duration of action of phenobarbitone may also be used as an index to determine enzyme induction. Our studies demonstrate that there is no significant reduction in the onset or duration of action of phenobarbitone upon exposure to an aqueous extract of ginger. These studies indicate that the aqueous extract of ginger does not induce GST. Interestingly phenobarbitone induces its own metabolism on repeated administration of high doses of the drug. However, maximum enzyme activity is achieved only three days after repeated and daily administration of the drug. Hence prolonged administration of phenobarbitone can shorten its own duration of action.

Conclusion

Our results indicate that the aqueous extract of ginger appears not to have any significant effect on the activity of the hepatic xenobiotic metabolizing enzyme specifically GST when administered based on the animals body weight. The result of this study implies that ginger, when taken at a normal dose may not cause drug-drug or drug-food interaction.

Limitations

There are several limitations to this study. Our study did not last long enough compared to previously published studies to observe any substantial changes in the activity of GST. Additionally, it will be important to replicate this study under similar conditions as previous studies, with a longer duration and larger sample size to see its effect on the onset and duration of action of phenobarbitone. Another limitation of this study is that we looked at the activity of only one phase II enzyme. In the future, it will be important to study the effect of ginger on other enzymes and other organs as well. Future studies should consider all these factors in their study design.

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