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Effects of Essential Oil of *Zingiber officinalis* Roscoe on Some Biochemical Parameters, Body Weight and Food Intake on Wistar Rats

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ABSTRACT

The effects of ginger (*Zingiber officinalis* Roscoe) essential oil were determined on some biochemical and physiological parameters on Wistar rats. The hepatic lipids appeared to decrease respectively from group 1 (0.03 g/kg body weight (BW)) to group 5 (1.00 g/kg BW). Also, the liver and serum cholesterol decrease significantly ($P<0.05$) from group 2 (0.15 g/kg BW) to group 4 (0.6 g/kg BW) and highly significant ($P<0.01$) for group 5. However, we noted harmful effects when doses >1.00 g/kg was used on animals. The main side effects were an abnormal development of hepatic cells, an increase of lipids and cholesterol as well as a decrease of protein level. 0.03 g/kg, the commonly published dose and 0.15 g/kg, which is the smallest dose without an observable side effect ($P<0.05$) on cholesterol, can be considered as the advisable doses. Generally, the essential oil of ginger had beneficial effects at doses ≤0.30 g/kg and harmful effects at doses ≥0.60 g/kg.

Keywords: behavior, cholesterol, ginger, lipids, proteins, weight loss
Abbreviations: BSA, bovine serum albumin; **BW**, body weight; **CVD**, cardiovascular diseases; **LMIC**, low and middle income countries

INTRODUCTION

A balanced food diet is one of the essential factors for good health. When our food contains more calories than the body does not spend, the excess of these calories accumulates in the organism in the form of fats and results in serious illnesses known as Cardiovascular Diseases (CVD) (Glinsmann *et al*. 1986; Ferriéres 2002). Cardiovascular disease is the number one cause of death globally and is projected to remain the leading cause of death. An estimated 17.5 million people died from CVD in 2005, representing 30% of all global deaths. Of these deaths, 7.6 million were due to heart attacks and 5.7 million were due to strokes. Around 80% of these deaths occurred in low and middle income countries (LMIC). If appropriate action is not taken, by 2015, an estimated 20 million people will die from CVD every year, mainly from heart attacks and strokes (WHO 2007).

Timely and sustained lifestyle interventions and, when needed, drug treatment will reduce the risk of CVD events, such as heart attacks and strokes, in people with a high total risk of CVD, and hence will reduce premature morbidity, mortality and disability (WHO 2003). Generally, pharmacological and non-pharmacological treatments are used in the treatment of CVD. Yet, people are more and more aware that synthetic drugs yield drawbacks over the short and long term. The side effects of drugs and their action although curative are considered by others as a direct intoxication (Serrano 1990; Ndam 2005). That is why the best treatment is one that can be adapted to particular needs (CRD 2006). In this context, the tendency observed by the field of therapy to return to natural treatment takes the place of conventional drugs and can be justified by the search for less aggressive drugs (Serrano 1990; Ndam 2005). Within this framework, the therapeutic potentialities of several vegetable and animal oils are proven (Sugaya *et al*. 1975 cited by Hikino 1985; Haug and Hostmark 1987; Murray 1999).

Zingiber officinalis Roscoe, which is the subject of this work, is a plant abundantly consumed by humans (Verbois 2001). In addition to the pleasant taste that it brings to food, it has significant ethnopharmacological properties (Hikino 1985; Rahman and Zaman 1989; Verbois 2001). Its essential oil (EO) is supposed to have hypocholesterolemic and hypoglycemic effects. For this reason, it appeared necessary to us to evaluate the effect of this oil in the treatment of certain coronary diseases. Therefore we studied the effect of this oil on the liver lipid and total cholesterol level, the serum total cholesterol level, the food intake and the growth variation of Wistar rats. In addition, we were interested in the side effects of this oil on the general behavior of the animals and the integrity of the body by carrying out macroscopic observations and the evaluation of protein levels on some organs such as the liver, kidney and heart.

MATERIALS AND METHODS

Extraction of essential oil of *Z. officinalis*

Fresh roots of *Zingiber officinalis* were bought on the local market of Dschang (Menoua Division, West Cameroon). 1.5 kg of these fresh roots was then cleaned and crushed in a grinding machine to form a paste which was hydrodistilled for 2 hours using a Clevenger-type apparatus, yielding a yellowish oil (4.5 ml). EO obtained was then dried on a sodium sulphate column.

Experimental animals

The experimental animals used during this study were 7-weeks-old albino Wistar rats. These animals were raised at room temperature (23°C) in the animal house of the department of Biochemistry of the University of Dschang, with a natural light-dark cycle and fed on standard Laboratory rat diet with tap water given *ad libitum*. The study was approved by institutional animal ethical committee.

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Table 1 Distribution of the animals and administrated doses.

	Groups							
	Control	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Doses (g/kg body weight)	0.00	0.03	0.15	0.30	0.60	1.00	1.40	1.80

Table 2 Behavior of the animals during the period of treatment.

Parameters	Doses (g/kg)							
	0.00	**0.03**	**0.15**	**0.30**	**0.60**	**1.00**	**1.40**	**1.80**
Locomotion	N	N	N	N	N	D	D--	D---
Sensitivity to the noise	N	N	N	N	N	N	D--	D--
Sensitivity to the touch	N	N	N	N	N	D	D---	D---
Aggressiveness	N	N	N	N	N	D	D-	D-
Exploration	N	N	N	N	N	N	D-	D--
Rate of respiration	N	N	N	N	N	N-	N--	N--
Aspect of the stools	G	G	G	G	G	G	M	M
Food intake	N	N	N	N	N	N-	D	D---
Water intake	N	N	N	N	N	N-	D	D---

N: Normal, **N-**: Relatively normal, **N--**: not normal, **D**: Relatively low, **M**: Slackness, **M-**: Very slackness, **D-**: low, **D--**: Very low, **D---**: Drop too much, **G**: Granular

Administration of product

The solution of EO at the necessary dose was prepared (mixed) with 8% DMSO (dimethyl sulfoxide) sufficient quantity (SQ) for 0.5 ml of administration solution. Then, it was administered orally once a day over 4 weeks using a probe.

Determination of the therapeutic dose, and choice of dose

The therapeutic dose that was applied derived from the literature which stipulated that a man weighing an average 70 kg body weight can consume two drops of EO of ginger once a day, that is to say 36 µl or 29.3 µg (Jellin *et al*. 2000). The therapeutic dose was thus evaluated at 0.42 µg/kg of body weight.

Eight groups of 8 animals per group were used. Animals of each group received a specific dose of EO (**Table 1**).

Animals of the control group received 0.5 ml 8% DMSO whereas the animals of the test group received the EO at several doses prepared in 8% DMSO sufficient quantity (SQ) for 0.5 ml of administration solution.

Preparation of serum from whole blood

The rats were anesthetized using 1.9% ether and blood was collected by cardiac puncture. Blood was then placed into centrifuge tubes of 4 ml volume each, left at 37° for 60 min to clot and centrifuged at 805 × *g* for 10 min to remove the clots/red blood cells and other insoluble material (Horio *et al*. 1987). Thereafter, aliquots were made and stored at –4° for biochemical analyses.

Preparation of homogenates from liver, kidney and heart

These organs were dissected, washed with 0.9% saline and wrung. After anatomic, macroscopic and comparative observations, they were crushed individually in a mortar then homogenized in a 0.9% NaCl solution. Each homogenate obtained was then placed into the respective centrifuge tubes, left for 30 min and centrifuged at 600 × *g* for 15 min. All these experiments were performed at 4°C. The supernatants were evaluated and collected into eppendorfs tubes, and then stored at –4°C for protein analysis.

Extraction of liver lipids

The hepatic lipid was extracted using chloroform/methanol at a 2:1 (v/v) ratio (Folch *et al*. 1957). Thereafter, the extract solvent was removed using an rotatory evaporator and the lipids evaluated and stored at 5°C. These lipids were dissolved in isopropanol (which was previously stored at room temperature) prior to the assessment of cholesterol.

Estimation of biochemical parameters

Liver total cholesterol and serum total cholesterol were determined using commercial diagnostic kits from Biomerieux Laboratories. Brieftly, a certain quantity of liver lipid previously extracted was mixed to isopropanol at a volum ratio 2:5 (lipid/isopropanol). This mixture was shaked and then used immediately to assessment of liver total cholesterol. For the determination of liver, kidney and heart proteins, the Gornall *et al*. (1949) method was used. For this determination, bovine serum albumine (BSA) was used as standard.

Statistical analysis

The results are presented as mean ± SEM. Differences between means were assessed by one-way analysis of variance (ANOVA) followed by Holm-Sidak's test using Sigma-stat 3.1 software. Values of $P<0.05$ were statistically significant, unless stated otherwise.

RESULTS

Behavioral observation of the animals

The results relating to the behavioral observation of the animals are represented in **Table 2**.

We observed that from the dose of 1.00 g/kg BW, much of the evaluated parameters changed with an increase in the dose administered.

Anatomical examination

The macroscopic observation of the liver of animals is shown in **Fig. 1** and indicates the granular appearance and the presence of white vesicles from 1 to 1.80 g/kg BW. At this dose, the liver appeared diffuse and showed abnormal development, making it be confused with the surrounding bodies (organs).

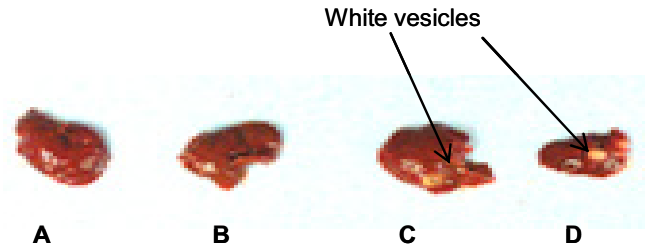

Fig. 1 Livers of some animals of the control and test groups. The following letters show the main variations between the studied groups. (**A**) Liver of control group, (**B**) Liver of group 4, (**C**) Liver of group 6, (**D**) liver of group 7.

Table 3 Food intake (g) during the experimental period.

Groups	Doses (g/kg)	Weeks				M±
		1	2	3	4	
Control	0.00	83.79	86.17	93.64	95.40	89.75 ± 1.01a
1	0.03	83.70	85.70	91.03	95.61	89.72 ± 1.04a
2	0.15	83.40	86.29	92.59	95.38	89.41 ± 0.99a
3	0.30	83.50	86.17	92.67	95.00	89.33 ± 0.97a
4	0.60	79.67	82.99	91.03	90.89	86.14 ± 1.03b**
5	1.00	7648	77.88	78.91	79.75	78.25 ± 0.25c***
6	1.40	74.22	70.83	70.04	67.06	70.53 ± 0.53d***
7	1.80	71.73	67.09	60.87	58.51	64.50 ± 1.09e***
M ± DS		79.56 ± 4.84a	80.39 ± 7.66ac	83.84 ± 12.51bc	84.70 ± 14.70b	

In the last column, values with the same letter are not significantly different.
**: very significant difference compared to the control ($p<0.01$).
***: highly significant difference compared to the control ($p<0.00001$).
In the last line, the affected values of the same letter are not significantly different at $p>0.05$.

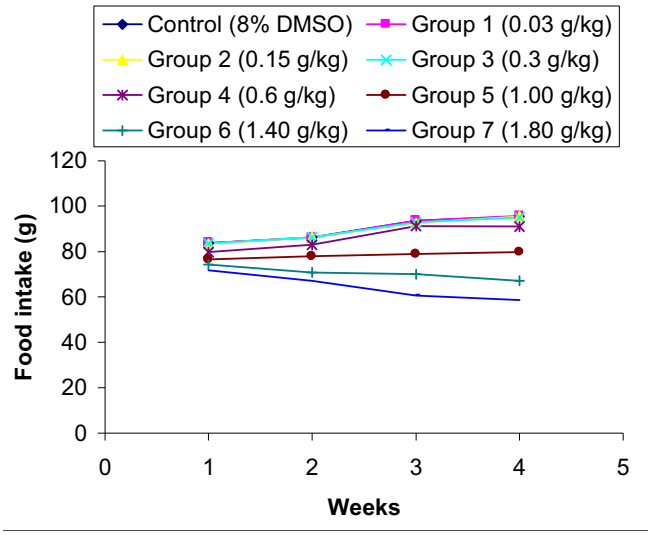

Fig. 2 Food intake (g) during the experimental period.

Food intake

The results related to food consumption in the various groups of animals during the 4 weeks of treatment are presented in **Table 3**.

These results show that from groups 1 to 3, food consumption was comparable to the control group. On the other hand, food consumption decreased significantly from group 4 to group 7.

We also observed that food consumption was comparable in the first two and last two weeks of treatment. However, it increased significantly during the 3rd and 4th week compared to the 1st week (**Table 3**).

Percentage change in body weight

The related results are shown in **Fig. 2**.

From these results, we observed that for a given dose, the weight loss was proportional to the duration of the treatment.

Liver, kidney and heart proteins

The contents of liver, kidney and heart proteins according to the EO dose managed during the four weeks of treatment are shown in **Table 4**.

These results show a significant reduction of hepatic protein level in group 7 compared to the control, and a significantly high level of proteins within groups 4 and 5 compared to group 7. In the other cases, hepatic protein rate is comparable.

We also observed that for the kidney proteins, their level is significantly high in groups 4 and 5 compared to group 7.

The content of cardiac proteins is comparable in all groups.

Liver lipids, liver and serum total cholesterol

The contents of hepatic lipids, hepatic and serum total cholesterol of the various groups are shown in **Table 5**.

These results show a comparable rate of hepatic lipids in the control group to group 6 and a significantly high level

Table 4 Protein rates (mg/g) of liver, kidney and heart after four weeks of treatment.

Groups	Control	1	2	3	4	5	6	7
Doses (g/kg)	**0.00**	**0.03**	**0.15**	**0.30**	**0.60**	**1.00**	**1.40**	**1.80**
Liver proteins (mg/mL)	24.98 ± 12.11a	18.40 ± 0.85ac	21.06 ± 2.12ac	19.43 ± 2.17ac	29.98 ± 6.17ab	26.03 ± 3.78ab	20.32 ± 3.57ad	9.93 ± 1.55d
Kidney proteins (mg/mL)	86.15 ± 12.43a	68.86 ± 0.26a	76.76 ± 2.17a	71.00 ± 12.83a	106.53 ± 21.95ac	98.73 ± 9.10ac	72.08 ± 3.47a	55.61 ± 4.62ab
Heart proteins (mg/mL)	73.63 ± 17.50a	61.53 ± 4.03a	77.46 ± 4.33a	59.70 ± 7.21a	90.15 ± 22.59a	89.40 ± 15.67a	60.18 ± 5.19a	56.33 ± 13.50a

In the lines, the affected values of the same letter are not significantly different ($p>0.05$)

Table 5 Hepatic lipids (mg/g), hepatic total cholesterol (mg/g) and serum total cholesterol (mg/dL).

Groups	control	1	2	3	4	5	6	7
Doses (g/kg)	**0**	**0.03**	**0.15**	**0.30**	**0.60**	**1.00**	**1.40**	**1.80**
Liver lipids	58.33± 0.007a	55.670 ± 0.005a	54.670 ± 0.000a	54.670 ± 0.005a	53.330 ± 0.004a	51.670 ± 0.004a	56.67 ± 0.024a	70.670± 0.009b
Liver total cholesterol	0.286 ± 0.070a	0.201 ± 0.000a	0.180 ± 0.000b	0.170 ± 0.000b	0.170 ± 0.020b	0.160 ± 0.020b**	0.160 ± 0.2b**	0.280 ± 0.02a
Serum total cholesterol	265.77 ± 8.59a	219.04 ± 2.71a	167.26 ± 3.50b	153.56 ± 2.60b	149.40 ± 37.34b	132.73 ± 22.83b**	163.21 ± 51.20b	526.75 ± 103.38c***

In the lines, the affected values of the same letter are not significantly different
** very significant difference ($p<0.01$)
*** highly significant difference ($p<0.00001$)

of hepatic lipids in group 7.

The content of hepatic total cholesterol in groups 2 to 4 is significantly lower than in the control group. On the other hand, groups 2 and 4 show a very significant decrease of hepatic cholesterol compared to groups 5 and 6. Groups 1 and 7 have the same content of liver cholesterol compared to the control group.

As serum total cholesterol is of concern, we observed a significant fall in groups 2, 3, 4 and 6 and a very significant fall in group 5 compared to control. However, in group 7, we noted a high level (P<0.00001) of serum total cholesterol compared to the other groups.

DISCUSSION

Ginger administered at 0.03 to 0.60 g/kg, which does not cause any observable physiological disorder in Wistar rats can be regarded as doses tolerated by rodents. On the other hand, the 1.00 to 1.80 g/kg are not tolerated by the animals and cause several physiological disorders. For example, stools of these treated rats passed from a granular to a pasty state which could be due to the retention of water in the intestine, and which would lead to an increase in the hydration and the volume of stools. One can thus think that in larger amounts, the EO of ginger has purgative effects. The decrease of parameters described in **Table 2** could be linked either to an attack of the effector and receivers, or to an attack of the nerve centers, or again to an inhibition of sensitive or driving conduction nerves. These effects being generally observed in the event of intoxication (La Grande Encyclopédie 1976; Encyclopaedia Universalis 1980; OMS 1992, 2000).

At 1.80 g/kg, the liver appeared diffuse and showed abnormal development making it be confused with the surrounding bodies (organs). These various observations led us to deduce that at higher levels, the EO of ginger could stimulate the abnormal development of hepatic cells with an attack of the surrounding bodies. The same observations were made by Sato *et al*. (1978; cited by Hikino 1985).

Concerning the food intake and the percentage change in body weight, they both decrease with an increase in the amount of EO consumed. These results led us to believe that the EO of ginger at higher doses can lead to a loss of appetite or to a reduction in digestion and postprandial absorption. This lack of appetite and this reduction in the metabolism associated with a lowering of lipid content can partially explain the loss in weight.

The high hepatic protein level at 0.60 and 1.00g/kg could be explained by the fact that at these very high doses, the liver could have reacted by the massive synthesis of enzymes to metabolize and eliminate the surplus of product. In the particular cases of the kidney and heart, this high protein rate could not be related to an increase in the synthesis of lipase enzymes because the metabolism of the lipids on their level is very slow and negligible (Ganong 1997). The rise in the protein rate at these levels could be explained by an increase in secretion of regulatory hormones enabling them to resist the toxic effect of the product in order to preserve their functional integrity.

Reduction in the hepatic and serum total cholesterol level to doses of ≤1.00 g/kg could be explained on one hand by an increase in the synthesis of the enzymes of the catabolism of cholesterol and in addition, by the hyperactivity of specific receivers of the LDL-cholesterol located on the cells. These receivers are charged to fix bad cholesterol circulating in order to metabolize it (Weil 1995; Forman et *al*. 1997). The product would thus act by increasing the affinity of these receivers to the bad cholesterol. Therefore, ginger EO presents a hypocholesterolemic activity at ≤ 1.00 g/kg. These results confirm those of Hikino (1985). An increase in the cholesterol level in response to doses ≥1.40 g/kg could be due to the toxic effect of the product which would have acted by inhibiting the specific receivers of LDL-cholesterol (which reduces the speed to which bad cholesterol is extracted from circulation), or by inhibiting the synthesis of enzymes of this metabolic pathway (Weil 1995; Stanbury *et al*. 1996). It can also be explained by a reduction of HDL-lipoproteins (good cholesterol) and by an increase of LDL-lipoproteins (bad cholesterol). These results are different from those obtained by Afshari *et al.* (2007) who, after the administration at 5% of their consumed food daily of ginger powder in rats, obtained a significant (P<0.001) decrease of total plasma lipid.

Reduction in the hepatic lipid level at doses ≤1.00 g/kg could be explained by a stimulation of the synthesis of enzymes belonging to lipid catabolism or to the reduction of the intestinal absorption of diet fats. Ginger EO thus presents an hypolipidemic effect at small amounts. The hypolipidemic effect of ginger powder and ginger extracts has been shown by other investigators (Sharma *et al*. 1996; Fuhrman *et al.* 2000). In fact, these studies shown that consumption of 250 µg/kg BW of ginger extract/day resulted in reductions (P<0.01) in plasma triglycerides and cholesterol (by 27 and 29%, respectively), in VLDL and LDL (by 53% and 33%, respectively). It is likely that the hypocholesterolemic effects of ginger stems results from the inhibition of cellular cholesterol synthesis. Attenuation of cholesterol synthesis results in augmentation of LDL receptor activity that leads to elimination of LDL from plasma (Ness *et al.* 1996). Our results confirm that, like the ginger extracts or ginger powder, EO of ginger also decreases the lipid level in rats at doses ≤0.3 g/kg BW without any side effects. However, at doses >1.00 g/kg, this effect is associated with toxicity of this EO. It could have acted by blocking certain stages of metabolism of the lipids, either at the level of mobilization, or at the level of degradation.

CONCLUSION

The study revealed the following results:

The hepatic lipid level decrease for EO at doses ≤1.00 g/kg.

The hepatic and serum total cholesterol levels decreased significantly between 0.15 and 0.60 g/kg. At 1.00 g/kg, this reduction is very significant (P<0.01).

Despite these beneficial effects, we observed that a dose >0.60 g/kg results in side effects whose principal ones include an decrease of locomotion and rate of respiration, the softening of stools, a very significant reduction (P<0.01) of food intake and percentage change in body weight, an abnormal development of the hepatic cells, an increase in the total cholesterol and lipid level at doses >1.00 g/kg as well as a fall in the content of liver, kidney and heart proteins.

Taking into consideration that side effects evolved at doses >0.60 g/kg and while waiting for thorough studies to be carried out, we think that the advisable doses are those of 0.03 g/kg which is that prescribed in the literature, and 0.15 g/kg which is the smallest dose having had a significant effect on the hepatic and serum total cholesterol level.

Generally, the EO of ginger presented beneficial effects for rats at doses ≤0.30 g/kg and harmful effects at doses ≥0.60 g/kg.

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