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Serum lipid stabilising effect of sarabat (*Diplazium asperum* Blume) aqueous extract in diet-induced hyperlipidemic wistar albino rats

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Abstract

Hyperlipidemia remains an important modifiable risk factor in cardiovascular diseases. The aim of the present study was to investigate the potential role of the aqueous decoction of *Sarabat (Diplazium asperum* Blume) in lowering plasma lipid profile in albino rats fed a high-fat diet (HFD). Thirty Wistar albino rats were randomly divided into five groups of six rats and, for 42 days, were administered plain water and standard pellets (negative controls), lard and cholesterol (hypercholesterolemic animals), low and high dose *Sarabat* decoction (1 and 2 g/100ml water respectively) and Simvastatin as a positive control. The effects of *D. asperum* Bl. (*Sarabat*) decoction on rat lipid profiles was assessed by measuring the plasma Total cholesterol (TC), triglyceride (TG), Low-density Lipoprotein (LDL), High-Density Lipoprotein (HDL) and Very Low-Density Lipoprotein (VLDL). Administration of lard and cholesterol showed gradual elevation of total cholesterol and similarly for the other lipid parameters with an increasing lipid profile after a two-week metabolic adjustment period. Concurrent administration of *Sarabat* (*D. asperum* Bl.) decoction showed a promising decrease in total cholesterol serum concentration ($p<0.006$), and an increase in High-Density Lipoprotein (HDL) was notable. These findings suggest the cholesterol and lipid buffering or modulating effects of saponin-rich *Sarabat* as potentially useful in the management of hyperlipidemia as part of diet therapy.

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Introduction

Hypercholesterolemia and hypertriglyceridemia are major risk factors, either alone or together, that accelerate the development of coronary artery disease and the progression of atherosclerosis (Lusis, 2008). Atherosclerosis is thought to involve lipid deposition, oxidative modification and cellular uptake followed by the release of inflammatory and growth factors resulting in smooth muscle cell proliferation and collagen matrix production (Singh *et al.*, 2002). Although treatment of hyperlipidemia can cause slow physical regression of plaques, the well-documented reduction in acute coronary events that follows vigorous lipid-lowering treatment is attributable chiefly to mitigation of the inflammatory activity of macrophages (Malloy and Kane, 2012). Pharmacologic treatment of hyperlipidemia includes lipid-lowering drugs like fibrates, statins and bile acid-binding resins, niacin, ezetimibe, proprotein convertase inhibitors are used to treat hyperlipidemia (Baron, 2018) and are known to possess some side effects (Chattopadhyaha *et al.*, 1996). The imperative to use treatments with lesser side effects is necessary, which includes diet therapy. Because oxidation of LDL cholesterol is a potential initiating event in atherogenesis, diets rich in antioxidants found primarily in fruit and vegetables may be helpful. Studies have suggested that when all of these elements are combined into a single dietary prescription, the impact of diet on LDL cholesterol may approach that of statin medications, lowering LDL cholesterol by close to 30 percent (Chattopadhyaya *et al.*, 1996). World ethnobotanical information reports a number of herbal medicines from plants and vegetables that can be used to control hyperlipidemia and related complications in patients (Dahanukar *et al.* 2000; Scartezzini and Speroni, 2000). In our efforts to find sources from natural products with cholesterol-lowering effects, we focus our present investigation on a fern medicinal vegetable commonly called *Sarabat (Diplazium asperum* Bl.) Some natural anti-hyperlipidemic agents from plants and even seeds have been shown to reduce LDL and elevate HDL, as exemplified by seed extracts from *Ricinodendron heudelotii* (Odinga *et al.*, 2020). It has been shown that some fern vegetables possess antidiabetic effects due to their anti-alpha glucosidase activity as well as powerful antioxidant activity (Chai *et al.*, 2012, 2013, 2015). Atherosclerosis prevention potential of the fern *Pteris ensiformisis* supposedly attributed to its glycosylated phenolic acid constituent (7-O-caffeoylhydroxymaltol-3-b-dglucopyranoside) has been demonstrated by Wei *et al.* (2007). The present study examines the anti-hyperlipidemic activity of *Sarabat* (*Diplazium asperum* Bl.), which is a species of wild fern vegetables. The young croziers are gathered in the wild and consumed as vegetables in parts of Northern and Northeastern Luzon, Philippines. Another wild fern "Pako" vegetable (*Diplazium esculentum* Retz.) of the same genera has been demonstrated to possess antioxidant properties due to their contents like phenolics, flavonoids, saponins, terpenoids like triterpenes, diterpenes, phytosterols and glycosides phytocontituents (Tongco *et al.*, 2014). Saponins, phytosterols, phenolics and the rest of the phytoconstituents in particular, have been shown to possess anticholesterol or antihiperlipidemic activity (cLeontowicz, 2002, Rupasinghe *et al.*, 2003, Akdogan *et al.*, 2012).

The presence of the abovementioned constituents in *Diplazium asperum* Bl. particularly saponins and flavonoids prompted us to evaluate its anti-hyperlipidemic properties. Specifically, the study evaluates the anti-hyperlipidemic or anti-hypercholesterolemic activity of the aqueous decoction extract of *Sarabat (Diplazium asperum* Bl.) in hyperlipidemia induced Wistar albino rats through lipid profile parameters; evaluate the high dose (HD) 2gm/100ml and low dose (LD) 1gm/100ml boiled decoction with anti-hyperlipidemic activity and; determine the acute toxicity manifestations in rats fed with the extracts following OECD guidelines.

Materials and Methods

The experimental protocol for this study followed the methods as adopted by Sudha and Mengi (2009) with some modifications, as well as the study by Kaup *et al.* (2011).

Plant Material Collection

Fiddleheads of the vegetable fern locally called *Sarabat (Diplazium asperum* Blume.) were purchased from the public markets of Solano and Bayombong in Nueva Vizcaya province, Philippines. The samples of whole plants were brought to the Biology department of De La Salle University for identification and subsequent authentication by John Rey Callado of the National Museum. Sample specimens were deposited in the DLSU Herbarium under DLSUH voucher sp. no.5602.

Preparation of Extract

The 5kg fern croziers were washed, then air-dried in the shade for one week, then pulverized to fine particles using a mechanical grinder, yielding 320gms powdered fern. About 10gms of the powdered fiddleheads were prepared and added to 90 ml distilled water and continuously stirred. Prepared filtered extracts were then brought to the Chemistry Dept. of DLSU and lyophilized to yield a solid to semisolid consistency of crude extract and stored in sealed plastic opaque containers for future use. Another set of 5 kg *sarabat* was procured, air-dried, and ground following the same procedure; 10gms of dried powdered fern was boiled in 500 ml water with continuous stirring for 30 min until the volume was reduced to 200 ml which made up the 100% *Sarabat* decoction.

The same was filtered and stored for acute toxicity study. The decoction utilized in the study made use of 2g/100 ml aqueous as high dose and 1g/100m as low dose preparations (Fig. 1).

Animals

Healthy albino rats of both sexes weighing about 160-250g were obtained from in-house bred and raised experimental albino Wistar rats at the Philippine Institute of Traditional and Alternative Healthcare in Region 2. The animals were housed under controlled conditions of light (12h) and temperature 25° ± 1°C in the animal house and allowed to acclimatize for 1 week. All had free access to water and a standard laboratory animal diet.

Ethics Clearance

The experimental protocol for this study was reviewed and approved by the Philippine Institute of Traditional and Alternative Health Care Institutional Animal Care Unit Committee (PITAHC-IACUC) and a permit to conduct research using animal models was obtained from the Bureau of Animal Industry under AR-2016-145 of the Department of Agriculture Philippines.

Acute toxicity study

The acute toxicity was performed according to the Organization for Economic Cooperation and Development (OECD) 423 guidelines Ecobichon (1997). Animals were fasted overnight except for water prior to dosing. The rats were divided into groups of four, each containing six animals (n=6). The lyophilized aqueous extract at the dose of 10, 20, 50, 100, 200, 400, 2000 and 5000 mg/kg body weight was administered by oral gavage to rats after overnight fasting. Another set of rats of the same grouping was prepared for acute toxicity testing of the concentrated boiled *Sarabat* decoction. The rats were subsequently observed closely for the first 3 hours for any untoward symptoms such as tremors, convulsions, exophthalmia, salivation, diarrhea and lethargy, followed by observation for 24 hrs. No abnormal behavioral patterns were noted onwards.

Induction of hyperlipidemia in rats

The hyperlipidemic condition was induced in rats by feeding a high-fat diet (HFD) comprising of 1% cholesterol powder, 20% olive oil along with 30% lard oil (pork fat), 1 ml honey admixed with 20gm of standard pellet food for an induction period of 15 days. The fatty food was ensured to be consumed daily by the rats.

Experimental design

The rats were divided into five treatments of six rats each. In treatment 1 (T_1), normal control animals were maintained on a standard laboratory animal diet. This group serves as normal control. However, the remaining animals in treatments 2 to 5 were fed a high-fat diet for a period of 15 days. The induction

period was followed by 20 days of drug/decoction intervention period where the animals continued with the high-fat di*et al*ong with drug and decoction experimental treatments. In treatment 2 (T_2), the rats received a high-fat diet for 14 days and onwards. This serves as a negative control group. In treatment 3 (T_3), the rats received a high-fat diet plus simvastatin 1.8mg/kg dissolved in water per Orem from 16 days onwards. This serves as a positive control group. Treatment 4 (T_4), the rats received a high-fat diet plus boiled *Sarabat* low dose decoction 50% (LD) 1gm/100ml water added on the 16 days onwards. In treatment 5 (T_5), the rats received a high-fat diet plus boiled *Sarabat* high dose (HD) decoction 100%, 2gm/100ml water on the 16th day onwards.

Determination of serum lipid profile

Blood was withdrawn using a tail vein through tuberculin syringe extraction on day 0 (before the induction of hyperlipidemia), on day 15 after lipidemic induction and on day 42 (end of the drug intervention period) of the study. The animals were fasted overnight prior to blood withdrawal. The blood was collected using red marked tubes and centrifuged at 3000 rpm for 10 min to separate serum for estimation of lipid profile. The serum total cholesterol, triglyceride and HDL-C levels were analyzed using a blood chemistry analyzer machine.

Statistical analysis

Statistical analysis was performed by one-way analysis of variance (ANOVA) followed by Tuckey's t-test using SPSS v. 22 to determine significant differences among treatment groups. Values are expressed as means ± SEM and a p-value of <0.05 was considered to be significant.

Results

Acute oral toxicity

The acute toxicity study has shown no behavioral changes. For the boiled decoction, the extract was well tolerated as no death was found up to the maximum dose of 5gm/kg however, in the non-boiled lyophilized concentrated crude extract, one death was noted at the maximum dose of 5gm/kg within 24 h administration.

Table 1. Effects of *Sarabat* extracts on the Total cholesterol (TC) and Triglyceride (TG) level (in $mmolL^{-1}$) of Wistar albino rats at varying periods of data gathering. Superscript with different letters indicates significant mean difference at 0.05 level.

Treatments	Total cholesterol		Triglyceride	
	mean±sd	Sig.	mean±sd	Sig
1st Data Gathering		*0.020*		*0.421*
T_1-Pellet Control	1.72^{a}±0.09		1.72±0.09	
T_2- HFD (high fat diet) control	1.68^{ab}±0.09		1.69±0.09	
T_3-Simvastatin	1.69^{ab}±0.09		1.69±0.09	
T_4- Low Dose(LD)Sarabat	1.59^{ab}±0.09		1.59±0.09	
T_5- High Dose(HD)Sarabat	1.64^{a}±0.09		1.64±0.09	
2nd Data Gathering		*0.608*		*0.649*
T_1-Pellet Control	1.55±0.19		0.69±0.17	
T_2- HFD control	1.63±0.22		0.87±0.56	
T_3-Simvastatin	1.62±0.27		0.82±0.21	
T_4- Low Dose(LD)Sarabat	1.38±0.73		0.72±0.44	
T_5- High Dose(HD)Sarabat	1.74±0.21		1.00±0.35	
3rd Data Gathering		*0.006*		*0.421*
T_1-Pellet Control	2.11^{a}±0.31		1.19±1.13	
T_2- HFD control	2.04^{ab}±0.25		1.55±0.33	
T_3-Simvastatin	2.03^{ab}±0.35		0.97±0.32	
T_4- Low Dose(LD)Sarabat	1.87^{bc}±0.15		0.76±0.24	
T_5- High Dose(HD)Sarabat	1.57^{c}±0.13		1.08±0.74	

Effect of D. asperum Bl. on Serum Lipid Parameters

Results of the lipidemic effects of aqueous decoctions of Sarabat (*Diplazium asperum* Bl.) on Wistar albino rats are shown in this study. Table 1 shows the Total cholesterol (TC) and Triglycerides (TG) data. The first data gathering shows significant mean differences between and among treatments, particularly T_1 and T_5. The total cholesterol-lowering effect is statistically significant at 0.006, more notably with high dose *sarabat* T_5 with respect to other treatments. Cholesterol elevations are noted beginning the third week and 4th week, as shown by elevated mean data during the 3rd data gathering. The serum triglycerides did not show significant differences between and among the various treatment groups, although there was an onset of gradual elevation during the 3rd data gathering period. Table 2 shows the lipidemic effects of Sarabat aqueous decoction on HDL, LDL and VLDL serum lipids of albino rats. HDL data indicates that the rats, after induction of hyperlipidemia, show a decreasing trend of HDL from higher mean values obtained initially in the first data gathering (*p*-value: 0.664) to decreased mean values during the second data gathering (*p*-value: 0.086) which although not statistically significant show a decreasing trend. Concurrent administration of the simvastatin (Group C) and low and high dose sarabat (Groups D and E, respectively) elevated back the HDL serum levels as shown in the 3rd data gathering mean values and reversed back the *p*-value to 0.664. On the one hand LDL data was obtained using the Friedewald formula[18] LDL-c(mg/dl) =TC(mg/dl)-HDL-c(mg/dl)-TG(mg/dl)/5. It will be noted that during the second data gathering of hyperlipidemia induction, there seem a significant statistical difference between the treatment groups, particularly Group E (high dose sarabat), against groups A and B, the negative and positive control groups, respectively, in terms of serum mean LDL level (p-value: 0.016). As with the other tables, the data seem to indicate that it is only towards the end of the 4th week that elevations of LDL begin to increase as the first two weeks of hyperlipidemia induction are periods of metabolic adjustments as shown by mean values obtained in the second data gathering. The concentration of VLDL-cholesterol is estimated according to Fridewalds[18] equation: VLDL-c=Triglyceride/5. Results show that it is consistent with the LDL, TG and HDL columns. The various periods of data gathering show a similar trend with the exception of total cholesterol (TC). For HDL, there is the restoration of the initial mean values (*p*-value: 0.409) obtained at the first data-gathering going back to the same p values obtained during the third data gathering (*p*-value 0.409) where concurrent administration of *sarabat* with the hyperlipidemia induction was undertaken.

Discussion

Cardiovascular diseases remain a major health problem around the world and the presence of high amounts of cholesterol in the diet has been demonstrated to increase total cholesterol and may increase the risk of cardiovascular complications (Kaup *et al.*, 2011). The dietary lifestyles of high fatty foods and saturated fat consumption like pork-based diets greatly contribute to the high incidence of fatal cardiovascular events. World ethnobotanical information reports a number of herbal medicines from plants and vegetables that can be used to control hyperlipidemia and related complications in patients (Dahanukar *et al.* 2000, Scartezzini and Speroni 2000). In the present study, we tested the lipid-lowering effect of a wild fern vegetable locally called *Sarabat* (*Diplazium asperum* Blume) in Wistar albino rats fed with high fat and cholesterol diet for over 4 weeks. It will be noted that there is a gradual elevation in the serum lipids of the high-fat diet-fed rats after over 2 weeks of feeding, consistent with earlier reports that established a correlation between dietary lipids and serum lipid profile (Kaup, 2011). Of particular note is the increase in cholesterol during lipidemic induction yet significantly buffered by concurrent administration of the high dose (HD) *sarabat* (*p*-value: 0.006), as shown in Table 1. This seems to suggest a modulatory influence on cholesterol metabolism and turnover. The possible cholesterol-lowering effect of Sarabat which is consistent with its rich saponin content along with other lipid-lowering phytoconstituents like plant sterols, is known to reduce the absorption of

cholesterol, increasing its fecal excretion (Ghule *et al*., 2006). Other lipid-lowering constituents are polyphenols, flavonoids and tannins. On the one hand, for triglyceride (TG), the second data gathering was undertaken during the end of the second week of lipidemic induction and seems to show that the tests albino rats are undergoing metabolic adjustments including induction of lipoprotein lipases in response to the high-fat diet hence the relative non-lipid elevation. The gradual onset of triglyceride elevations was noted only during the 3rd data gathering period which is the 4th week. Although not statistically significant, it seems to show that elevations are not abrupt and possibly modified and affected by the concurrent administration of the *Sarabat* decoctions which are rich in saponins with detergent-like activity along with plant sterols. Saponins are reported to increase lipoprotein lipase activity (LPL) which is considered helpful in the faster removal of free fatty acids from circulation that causes, in turn, a decrease in total cholesterol (Sidhu *et al*. 1990, Gumaraes *et al*. 2000, Ghule *et al*. 2006).

Table 2. Showing effects of Sarabat extracts on Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL) and Very Low Density Lipoprotein (VLDL) in $mmolL^{-1}$. Superscripts with different letters indicates significant mean difference at 0.05 level.

Treatments	HDL		LDL		VLDL	
	mean±sd	Sig.	mean±sd	Sig	mean±sd	Sig.
1st Data Gathering		*0.664*		*0.421*		*0.409*
T_1-Pellet Control	2.25±0.76		-0.68±0.92		0.54±0.51	
T_2- HFD control	1.78±0.20		-0.45±021.		0.70±0.15	
T_3-Simvastatin	1.98±0.72		-0.39±0.53		0.44±0.14	
T_4- Low Dose(LD)Sarabat	2.02±0.18		-0.49±0.20		0.34±0.11	
T_5- High Dose(HD)Sarabat	2.08±0.13		-1.00±0.38		0.49±0.34	
2nd Data Gathering		*0.086*		*0.649*		*0.644*
T_1-Pellet Control	1.49±0.42		-0.24^{b}±0.35		0.31±0.08	
T_2- HFD control	1.45±0.16		-0.21^{b}±0.25		0.39±0.25	
T_3-Simvastatin	0.87±0.33		0.28^{a}±0.30		0.37±0.20	
T_4- Low Dose(LD)Sarabat	1.30±0.69		-0.24^{ab}±0.23		0.33±0.20	
T_5- High Dose(HD)Sarabat	1.45±0.22		-0.17^{c}±0.26		0.46±0.16	
3rd Data Gathering		*0.664*		*0.421*		*0.409*
T_1-Pellet Control	2.25±0.76		-0.68±0.92		0.54±0.51	
T_2- HFD control	1.78±0.12		-0.45±0.21		0.70±0.15	
T_3-Simvastatin	1.97±0.72		-0.39±0.53		0.44±0.14	
T_4- Low Dose(LD)Sarabat	2.01±0.18		-0.49±0.20		0.34±0.11	
T_5- High Dose(HD)Sarabat	2.08±0.13		-1.00±0.38		0.49±0.34	

Table 2 shows the HDL, LDL and VLDL parameter results with the noticeable increase in the mean values from the second to the third data gathering, in particular between sarabat enriched diet with the controls, indicating an increasing trend of serum HDL, also known as good cholesterol. Although not statistically significant, the reversal back to its initial p-values and possibly increasing trend with continuous administration of the *Sarabat* decoctions seem to indicate a promising HDL elevation with cardioprotective potential. Increased HDL to LDL ratio is beneficial to maintain the continuous translocation of cholesterol from peripheral tissues to the liver for catabolism. The *Sarabat* administered seemed to have influenced the elevation of HDL and restored it to its former prehyperlipidemic levels. Also

noted in Table 2 are the low-density lipoprotein (LDL) and VLDL serum mean estimated values. Although no significant differences are seen, data seem to indicate that towards the end of the third data gathering period, elevations of LDL begin to increase as the second data-gathering period of lipidemic induction are periods of metabolic adjustments with a seeming strong intrinsic lipoprotein lipase activity. A longer period of treatment and observation is therefore warranted to observe any significant effect, as shown by the non-statistically significant differences between the hyperlipidemic control (T_2) and treatments 3,4 and 5 (simvastatin and Sarabat groups, respectively).

While these various lipid types are in a constant state of flux, especially during metabolic readjustments during lipidemic induction, the introduction of *sarabat* crude extracts seems to exert a modulating effect on the steady elevations of cholesterol, perhaps attributable to the predominance of saponins in this plant. Previous studies have shown that saponin lowers serum cholesterol levels in animals, including humans (Sidhu *et al.*, 1990, Gumaraes *et al.*, 2000, Ghule *et al.,* 2006, Matsui *et al.*, 2009, Kuppusamy *et al.*, 2015). Sterols also present in this plant may reduce the absorption of cholesterol and thus increase the fecal excretion of steroids, which results in the decrease of body lipids (Gumaraes *et al.*, 2000, Ghule *et al.*, 2006). It would seem that it is towards the third data gathering period that the onset of some anti-hyperlipidemic activity begins to take effect and thus, a longer period of observation is further necessary for better clarity of observations and results. It is this aspect of protocol timeline adjustment that perhaps needs to be revisited, at least with respect to this particular study. Also, future research can include fecal cholesterol determinations at varying observation periods to complement blood lipid profile results and demonstrate lipid-lowering effects, as well as including weight determinations as metabolic indicators, including fat build-up. Overall, the aqueous extracts high dose (HD) affected a decrease in total blood cholesterol in the hyperlipidemic rats when compared with the controls. HDL was likewise noted to be elevated with the administration of high and low-dose *Sarabat* treatments and thus seems to show beneficial cardio-protective potentials. Boiled *Sarabat* of up to 5gm/kg did not cause any mortality in the acute toxicity test done. A longer period of administration and assessment is, however, warranted for better results.

Conclusions

In this study,we tested the lipid lowering and stabilizing effects of a wild fern vegetable locally called *Sarabat* (*Diplazium asperum* Blume) fiddleheads in Wistar albino rats fed with high fat and cholesterol diet for 4 weeks. There was a gradual elevation in the serum lipids of the high fat diet fed rats after 4 weeks of feeding and in particular increase in cholesterol during lipidemic induction.This was buffered by concurrent administration of the High dose sarabat (p-value 0.006).

The aqueous extracts high dose (HD) effected a decrease in blood cholesterol in the hyperlipidemic rats when compared with the control. High Density Cholesterol (HDL) was likewise noted to be elevated with the administration of high and low dose *Sarabat* treatments which seem to show beneficial effects of this fern vegetable as cardioprotective agents.These maybe attributed to the presence of saponins and flavonoids in this fern .While these wild fern croziers may have potential health benefits, further toxicity and drug- sarabat interaction studies are warranted. A longer period of administration and assessment is likewise suggested for better results.

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