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An *In Vivo* Analysis of the Herbal Compound Essiac®

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Abstract. *Background: Essiac® is a herbal compound that has been in common use with cancer patients in North America for over 80 years. Despite its relatively widespread use, there are no peer-reviewed published reports of in vivo studies regarding the use of this compound. Materials and Methods: Essiac® was administered orally to test animals prior to all experiments. Standard assays to test protection from ethanol-induced gastric ulceration and carbon tetrachloride-induced hepatic injury were performed on Wistar rats. Assays of post-glucose-load serum glucose and cellular and humoral immune modulation were conducted on ICR and BALB/C mice, respectively. Results: Essiac® demonstrated a modest gastric protective effect via reduction of ethanol-induced gastric ulceration. However, Essiac® did not demonstrate significant hepatoprotective, hypoglycemic or immunomodulatory properties. Conclusion: Essiac®, administered in established in vivo experimental models, did not significantly demonstrate its purported physiological modifying effects.*

Complementary and alternative medicine (CAM) use by oncology patients is widespread, with estimates of 60-85% reporting at least one use of CAM therapy (1-3). Essiac® Tea, a proprietary blend of four herbs, is a popular choice among breast cancer patients. Surveys estimate usage rates of between 15%-35% in this population in some sections of North America (2, 4). Though commonly associated with breast cancer patients, Essiac® is not restricted to this population, with its use having been reported in patients suffering from a variety of cancers (5).

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Essiac® is a blend of the four herbs *Arctium Lappa, Rheum palmatum, Rumex acetosella* and *Ulmus rubra* (6). This herbal compound has reportedly been used in the treatment of cancer for over 80 years. Essiac® and Essiac®-like products such as Essiac® Liquid Extract (a pre-packaged liquid form of the herbal compound) are purported to display a variety of therapeutic effects including immunomodulatory, antineoplastic, hepatoprotective, gastroprotective and anti-inflammatory properties (6). Despite a strong recommendation from the Task Force on Alternative Therapies of the Canadian Breast Cancer Research Initiative regarding the need for publication of research into the use of Essiac® (7), no research has been published in the peer-reviewed literature regarding its in an *in vivo* model. There are some brief descriptions available from a series of *in vivo* experiments conducted at the National Cancer Institute and Memorial Sloan Kettering Cancer Center, U.S.A., but these results have not been submitted for peer-reviewed publication (8).

A recent *in vivo* study was published involving a similar herbal compound, Flor-Essence®, which contains the four herbal constituents of Essiac®. This study indicated the potential promotion of mammary tumors after Flor-Essence® exposure in a Sprague-Dawley rat model (9). It should be noted that Flor-Essence® also contains four additional herbal components not present in Essiac® (*Nasturtium officinale, Cnicus benedictus, Trifolium pratense* and *Laminaria digitata*), making it difficult to extrapolate the results to the context of Essiac® administration. However, these results emphasize the importance of further research into the effects of Essiac® administration in pre-clinical models.

There is a considerable amount of pre-clinical research available on the properties of each of the four herbs present in Essiac® (6). Using standard assays developed in rodent models, some of the purported medicinal properties of Essiac®, administered orally in an *in vivo* setting, were investigated to provide preliminary data of these effects.

Materials and Methods

Animals. One strain of rats and two different strains of mice were used in the studies, *i.e.*, male Wistar rats and male ICR-derived mice provided by the animal breeding center of MDS Pharma Services - Taiwan Ltd., ROC, as well as BALB/c-derived male mice, provided by the National Laboratory Animals Breeding and Research Center (NLABRC, ROC). The Wistar rats and ICR mice were housed in APEC cages while the BALB/c mice were housed in individually ventilated cages racks (IVC Racks, 36 Mini Isolator systems) under specific pathogen-free (SPF) conditions. Six rats were allocated 45x23x21 cm living space and the ten mice 29x18x13 cm. All the animals were maintained in a hygienic environment under controlled temperature (22˚-24˚C) and humidity (60%-80%) with 12-hour light/dark cycles for at least 1 week in MDS Pharma Services - Taiwan laboratory prior to use. The rodents had free access to standard laboratory chow (LabDiet Rodent Diet, PMI Nutrition International, St. Louis, MO, USA) and tap water. All aspects of this work, including housing, experimentation and disposal of the animals, were performed in accordance with the Guide for the Care and Use of Laboratory Animals, National Academy Press, Washington, DC, 1996.

Reagents. Essiac® Liquid Extract, supplied as sold in unopened bottles direct from the company (Essiac Canada International, Ottawa, ON, Canada), 5-Fluorouracil (Sigma), acetone (Wako Pure Chemical Industries, Ltd., Osaka, Japan), ALT (alanine aminotransferase) assay kit (Wako), AST (aspartate aminotransferase) assay kit (Wako), carbenoxolone-disodium (Sigma), carbon tetrachloride, CCl_4 (Wako), D (+) glucose (Merck KGaA, Darmstadt, Germany), ethanol (Merck), Glucose-HA assay kit (Wako), glibenclamide (Sigma), Hemolynac.3 Hemolys (Nihon Kohden, Tokyo, Japan), isotonac.3 diluent (Nihon Kohden), lipopolysaccharide (Sigma), olive oil (Wako), oxazolone (Sigma), phosphated-buffered saline, PBS, pH 7.4 (Sigma), rabbit red blood cells (Home-Made), Silymarin (Aldrich, St. Louis, MO, USA), sodium chloride (Wako) and Tween 80 (Wako).

Equipment. Twelve channel pipetman (Costar, Acton, MA, USA), 96-well polystyrene plate (Costar), animal case (ShinTech, Taipei, Taiwan, ROC), automatic analyzer 7050 model (Hitachi, Tokyo, Japan), centrifuge 5417R (Eppendorf, Eppendorf, Germany), disposable syringe (1 ml, Top Corporation, Tokyo, Japan), Dyer Model micrometer gauge (Peacock, Tokyo, Japan), EDTA K tube (Sarstedt, Nürmbrecht, Germany), electronic scale (model 1140, Tanita Corporation, Tokyo, Japan), electronic scale (R160P, Sartorius AG, Goettingen, Germany), glass syringe (2 ml, Mitsuba, Tokyo, Japan), heparinized capillary tubes (Scientific Glass, Inc., Rockwood, TN, USA), hematology analyzer MEK-6108K (Nihon Kohden), orbital shaking incubator (Firstek Scientific, Hsin Chuang, Taiwan, ROC), pH meter (SunTex, Hsi-Chih City, Taipei County, Taiwan, ROC), pipetman (Gilson, Villiers-le-Bel, France), pipette tips (Costar), rat oral needle (Klappenecker, Energiestrasse, Germany), refrigerated incubator (Hotpack, Warminster, PA, USA), round head needle for oral administration (Klappenecker), stainless steel scissors (Klappenecker) and stainless steel forceps (Klappenecker).

Assay for protection by Essiac® from ethanol-induced gastric ulceration. The assay was performed according to the method described by Robert and colleagues (10). The test substance was administered orally (*p.o.*) to a group of three Wistar-derived male, overnight-fasted rats, weighing 200±20 g, 15 minutes before challenge with absolute ethanol (1 ml/rat) *via* oral gavage. One hour later, the animals were sacrificed and gastric ulceration was scored for the degree of hemorrhage and severity of ulcerative lesions, based on the following scoring system: 0 = no hyperemia or lesions (dark red blood clot), 1 = hyperemia, 2 = one or two slight lesions, 3 = more than two slight lesions, 4 = more than two lesions or severe lesions. A reduction of the concurrent control score values by 50% or more was considered significant.

Assay for serum glucose measurement post glucose-load after Essiac® ingestion. The assay was performed according to the method described by Ho and Aranda (11). Four groups of five ICR-derived male mice, weighing 22±2 g, were used. The test substance at doses of 0.4 ml/kg and 4 ml/kg, the vehicle (0.9% NaCl, 10 ml/kg), or the positive control Glibenclamide at 1 mg/kg was administered *p.o.* to overnight-fasted mice 30 minutes before glucose loading (1 g/kg, subcutaneously (*s.c.*)). Blood samples from the orbital sinus were obtained 90 minutes after administration of the vehicle and/or test substances. The serum glucose levels were measured by an enzymatic method (Matarotase-Glucose Oxidase) in samples generated from blood collected *via* the orbital sinus of each animal. A reduction of serum glucose by 20% or more relative to the vehicle-treated control animals indicated significant activity.

Assay for protection from hepatic injury from carbon tetrachloride exposure after Essiac® ingestion. The assay was performed according to the method described by Abe and colleagues (12). The test substance and vehicle were administered *p.o.* to groups of five Wistar-derived male rats, weighing 200±20 g, at 30 minutes before, and 4 and 8 hours after challenge with carbon tetrachloride (CCl_4, 0.5 ml/kg in olive oil/1:1, *p.o.*). The animals were sacrificed 24 hours after the administration of CCl_4 and the ALT and AST levels were measured by an optimized UV method with a HITACHI automatic analyzer (model 7050). A reduction in ALT or AST activity by 30% or more relative to the vehicle-treated control animals indicated significant hepatic protection. In addition, the liver and body weights were recorded and calculated (g liver/100 g body weight) as a reference parameter for hepatotoxicity.

Assay to assess the effect on cellular immune stimulation after Essiac® ingestion. The assay was performed according to the method described by Griswold, DiLorenzo and Calabresi (13). Four groups of five BALB/c male mice, weighing 23±2 g, were used. The pre-shaven abdomens of the test animals were sensitized by application of 50 ml of 2.5% oxazolone solution dissolved in acetone. The test substance and vehicle (0.9% NaCl) were administered *p.o.* 1 hour before 2.5% oxazolone sensitization was performed. The positive control lipopolysaccharide (0.3 mg/kg) was administered intra-peritoneally (*i.p.*) at the same time as the test compound. Eight days later, the animals were challenged with a second application of oxazolone (2% in 25 ml acetone) to the right ear. Twenty-four hours later, the ear thickness of each mouse was measured with a Dyer Model micrometer gauge. A 30% or more increase in ear swelling relative to the vehicle control was considered physiologically significant and indicated possible immunostimulatory activity.

Table I. *Assay for protection by Essiac® from ethanol-induced gastric ulceration.*

Treatment	Route	Dose	No.	Ulceration score		% Inhibition
				No. of ulcers	Total	
Vehicle (0.9%NaCl)	*p.o.*	10 ml/kg	1	4		
			2	4		
			3	4		
					12	0
Essiac® Liquid Extract	*p.o.*	4 ml/kg	1	2		
			2	3		
			3	3		
					8	33
	p.o.	0.4 ml/kg	1	4		
			2	4		
			3	4		
					12	0
Carbenoxolone	*p.o.*	300 mg/kg	1	1		
			2	1		
			3	1		
					3	(75)

The vehicle or test substance was administered orally (*p.o.*) 15 minutes before oral gavage with absolute ethanol (1 ml/rat). Ulceration was measured and scored 1 hour later for degree of hemorrhage and severity of ulcerative lesions as follows: 0 = no hyperemia or lesions (dark red blood clot), 1 = hyperemia, 2 = one or two slight lesions, 3 = more than two slight lesions, 4 = more than two lesions or severe lesions. The reduction of the concurrent control score values by 50% or more, indicated in parenthesis, was considered significant.

Assay for the effect on humoral immune stimulation. The assay was performed according to the method described by Roitt (14). Three groups of five BALB/c male mice, weighing 22±2 g, were used. The test animals were sensitized with an intravenous (*i.v.*) injection of rabbit red blood cells (RRBC, 10^8 cells in 0.2 ml PBS / mouse). The test substance at 0.4 ml/kg and 4 ml/kg and the vehicle (0.9% NaCl) were administered *p.o.* to the test animals 72, 48 and 2 hours before sensitization with RRBC. On the ninth day following sensitization, blood samples were withdrawn from the orbital sinus and the sera heat-inactivated at 56˚C for 30 minutes. Fifty ml of the complement-inactivated serum was then serially diluted two-fold with 50 ml PBS. Fifty µl of this diluted mixture was added to each well of a 96-well microtiter plate. Thirty µl of 2.5% Guinea pig serum (providing complement proteins) in PBS, 150 µl of PBS and 20 µl of RRBC (10^7 cells) in PBS were added into the serially-diluted sample serum in each well to yield a final volume of 250 µl/per well. The serum titer was expressed as the reciprocal of dilution exhibiting hemolysis. A serum titer of 256 or more was considered significant and indicated possible immunostimulatory activity.

Results

Essiac® was administered *p.o.* to the test subjects prior to all experiments. The dosage of Essiac® administered in all assays was calculated on a per weight basis, based upon the recommendations of the supplier. A dose ten-fold higher than the recommended dose was included with the recommended dose in order to assess for a dose-response relationship. Within these parameters, Essiac® at a concentration of 4 ml/kg, but not 0.4 ml/kg, resulted in a 33% inhibition in the ulceration score compared to the control group in the ethanol-induced gastric ulceration assay (Table I). The positive control, the synthetic liquorice derivative carbenoxolone, produced a 75% inhibition in the gastric ulceration model.

In the Wistar rat model of CCl_4-induced hepatocyte injury, administration of Essiac® at both the higher and lower concentrations did not offer any statistically significant protective effect against hepatocyte damage, as measured by elevation in the serum transaminase levels (Table II). However, the higher concentration (4 mg/ml) of Essiac® did decrease the elevation in AST and ALT observed upon CCl_4 challenge by approximately 5% over the vehicle control alone, though this result was not statistically significant.

Essiac®, at both concentrations tested, did not significantly alter the glycemic response to a glucose load after an overnight fast in the ICR mouse model (Table III). Upon challenge with 1 g/kg of glucose, Essiac® administered at both 0.4 ml/kg and 4 ml/kg resulted in non-significant increases in the measured serum glucose of 7% and 3%, respectively. In comparison, the antihyperglycemic sulfonylurea, glibenclamide, decreased the observed glycemic response by 30% in the same model.

Table II. *Assay for protection from hepatic injury from carbon tetrachloride exposure after Essiac® ingestion.*

Treatment	Route	Dose	No.	ALT		AST	
				U/L	% Decrease	U/L	% Decrease
Blank normal control (Non-CCl_4-induced)	*p.o.*	10 ml/kg	1	46		171	
			2	55		158	
			3	47		133	
			4	40		121	
			5	39		116	
				45.4±2.9	– –	139.8±10.7	– –
Vehicle (0.9% NaCl) (With CCl_4-induced)	*p.o.*	10 ml/kg	1	1132		2188	
			2	912		1776	
			3	924		1740	
			4	1772		2920	
			5	1712		3152	
				1290.4±188.7	0	2355.2 ±291.2	0
Essiac® Liquid Extract	*p.o.*	4 ml/kg	1	1036		2356	
			2	1632		2812	
			3	1440		2528	
			4	1068		1972	
			5	936		1576	
				1222.4±133.4	5	2248.8 ±216.3	5
	p.o.	0.4 ml/kg	1	988		1928	
			2	1668		2940	
			3	1720		3156	
			4	1012		2232	
			5	988		1860	
				1275.2±171.2	1	2423.2 ±264.9	–3
Silymarin	*p.o.*	300 mg/kg	1	408		976	
			2	836		1664	
			3	840		2012	
			4	736		1188	
			5	688		1128	
				701.6±79.0	(46)	1393.6±192.7	(41)

The test substances and vehicle were each administered orally (*p.o.*) at 30 minutes before, and 4 and 8 hours after challenge with a single dose of CCl_4 (0.5 ml/kg in olive oil/1:1, *p.o.*). Silymarin was used as a positive control agent and was administered to the test animals, following the same time schedule. The rats were sacrificed 24 hours after CCl_4 administration and the ALT and AST values were determined. A reduction of the ALT or AST by 30% or more relative to the vehicle group was considered to be physiologically significant. Negative sign (–) indicates increase relative to the vehicle control group.

Essiac®, at both the lower and higher doses, did not significantly modulate the cellular immune response as measured by ear thickness in the oxazolone challenge test (Table IV). Neither did Essiac®, at both concentrations, significantly affect the humoral immune response, as measured by serum titer to the RRBC challenge (Table V). However, in both immunomodulatory assays there was a trend towards a reduction in the immune response after administration of Essiac®.

Discussion

Cancer patients commonly use Essiac®, however, very little information is available regarding its potential role as an anticancer agent or cancer supportive agent. This report presents the first peer-reviewed data regarding the effects of the polyherbal compound Essiac® in an *in vivo* model and, thus, provides a reference point from which to direct future investigations.

Table III. *Assay for serum glucose measurement post glucose-load after Essiac® ingestion.*

Treatment	Route	Dose	No.	Serum glucose (mg/dl)	% Decrease
Vehicle (0.9% NaCl)	*p.o.*	10 ml/kg	1	173	
			2	171	
			3	181	
			4	170	
			5	160	
				171.0±3.4	0
Essiac® Liquid Extract	*p.o.*	4 ml/kg	1	176	
			2	166	
			3	192	
			4	170	
			5	180	
				176.8±4.5	–3
	p.o.	0.4 ml/kg	1	172	
			2	185	
			3	183	
			4	195	
			5	181	
				183.2±3.7	–7
Glibenclamide	*p.o.*	1 mg/kg	1	130	
			2	112	
			3	127	
			4	121	
			5	108	
				119.6±4.2	(30)

The test substance and vehicle, as well as glibenclamide, were administered orally (*p.o.*) to fasted mice 30 minutes before glucose loading (1 g/kg, *s.c.*), and blood samples were obtained 90 minutes later. A reduction of the serum glucose by 20% or more relative to the vehicle-treated control animals indicated significant physiological activity.

The classic and principal limitation of this experimental study consisted of the use of a rodent model for *in vivo* analysis of Essiac® administration and physiological activity. It is well-established that drug and compound metabolism are highly species-specific and, thus, the amount and type of active metabolite(s) available in an animal model will be, at least partly, dependent on the species used (15). As such, extrapolation of these results to the clinical arena is only tentative. Another major limitation of the present study is the fact that Essiac® is often taken over an extended period of time. The one-time administration incorporated in our experimental design may not adequately reflect the effects of repeated administration of Essiac®, a dosage schedule that oncology patients would presumably follow. Our data does, however, provide initial and immediate results on the effect of Essiac® administration and future research could attempt to address this unexplored parameter of its use.

To determine whether a dose-response relationship existed, as well as to mitigate against the possibility that the recommended dose is too low, we included a dose ten times the recommended dosage. Within these preliminary parameters, there appeared to be some indication of a dose-response trend in much of the data. Further, these trends were somewhat reflective of the known physiological activities of the constituent herbs found in Essiac®. This strengthens the validity of our experimental approach. It is possible that a dose regimen between the recommended dose and the ten-fold dose may be more effective, however, this seems unlikely given the relatively small pharmacological difference in the doses used.

Essiac® seemed to afford limited cytoprotection to the gastric mucosa when administered *p.o.*, an observation consistent with a similar effect observed with the Essiac®-like compound Flor-Essence® (6). It should be noted that adaptive cytoprotection is non-specifically induced by mild irritants in this gastroprotective model (16). It was unclear, from the present results, whether the mechanism of response elicited by Essiac® is specifically cytoprotective or the result of an adaptive cytoprotective response. Thus, though *p.o.* administration of Essiac® appeared to be cytoprotective, further investigation would help to define the mechanism of cytoprotection more clearly and identify which, if any, of the specific herbal components are responsible for this effect.

Table IV. *Assay to assess the effect on cellular immune modulation after Essiac® ingestion.*

Treatment	Route	Dose	No.	Ear Thickness (x 0.01 mm, X±SEM)			% Increase
				R. Ear	L. Ear	Net	
Vehicle (0.9% NaCl)	*p.o.*	10 ml/kg	1	32	22	10	
			2	25	21	4	
			3	27	23	4	
			4	28	22	6	
			5	26	21	5	
				27.6±1.2	21.8±0.4	5.8±1.1	- -
Essiac® Liquid Extract	*p.o.*	4 ml/kg	1	25	21	4	
			2	33	23	10	
			3	25	21	4	
			4	29	22	7	
			5	24	21	3	
				27.2±1.7	21.6±0.4	5.6±1.3	-3
	p.o.	0.4 ml/kg	1	30	21	9	
			2	28	22	6	
			3	24	21	3	
			4	27	21	6	
			5	25	21	4	
				26.8±1.1	21.2±0.2	5.6±1.0	-3
Lipopolysaccharide (*E. coli* LPS)	*i.p.*	0.3 mg/kg	1	36	22	14	
			2	28	21	7	
			3	32	22	10	
			4	30	21	9	
			5	32	21	11	
				31.6±1.3	21.4±0.2	10.2±1.2	(76)

The test substance and vehicle (0.9% NaCl) were administered *p.o.* to test animals 1 hour before sensitization was performed with oxazolone 2.5% in 50 μl acetone. The positive control lipopolysaccharide (0.3 mg/kg, *i.p.* was given, following the same time schedule. Eight days later, the animals were challenged with a second application of oxazolone and the ear thickness was measured 24 hours later. A 30% or greater enhancement relative to the vehicle-treated control was considered to be physiologically significant.

Table V. *Assay for the effect on humoral immune stimulation.*

Treatment	Route	Dose	No.	Serum titer (reciprocal serum dilution)	
				Individual serum	Pool serum
Vehicle (0.9% NaCl)	*p.o.*	10 ml/kg	5	256 128 128 128 128	128
Essiac® Liquid Extract	*p.o.*	4 ml/kg	5	128 128 64 128 128	128
	p.o.	0.4 ml/kg	5	128 128 64 64 128	128

The test substance and vehicle (0.9% NaCl) were administered orally (*p.o.*) to test animals at 72, 48 and 2 hours before sensitization with rabbit red blood cells (RRBC). The blood samples were collected 9 days after sensitization and the sera were 2-fold serially diluted and titrated with fresh RRBC (antigen) and complement (Guinea pig serum) in a 96-well microtiter plate; the hemolysis titer was measured by visual read-out. The serum titer was expressed as the reciprocal of dilution exhibiting hemolysis

In the Wistar rat model, the administration of Essiac® demonstrated a non-significant trend towards hepato-protection, a finding consistent with previous studies performed in a rat model using samples of a component herb, *Arctium lappa*. The hepatoprotective effect of *Arctium lappa* against CCl_4 hepatotoxicity may be mediated by the substantial free radical scavenging properties of this herb (17).

Previous experimental data in the diabetic mouse model indicate that the consumption of *Arctium lappa* aggravated the serum glucose levels (18). This is in contrast to the observations

shown here, with Essiac® having no mitigating effect on the glycemic response. However, our model differed from the previous study as it involved animals with a presumably physiologically normal response to glucose challenge. Given the potential for the long-term use of Essiac®, it would be prudent for any clinical study design to incorporate measurement of the effects on glycemic control to help clarify these findings.

Essiac® and Essiac®-like products are thought to possess significant ability to modulate the immune response. However, oral administration of Essiac® in our experimental models did not significantly alter the *in vivo* cellular or humoral immune response. As in the previous results, the trend at both concentrations in both assays, though not significant, was consistently towards a reduction in inflammation *versus* the vehicle control.

In summary, to address the paucity of peer-reviewed *in vivo* research regarding the herbal compound Essiac®, we conducted initial investigations into several of its purported medicinal properties. The results indicated that Essiac®, administered *p.o.* at the test concentrations chosen, did not induce any significant effects in the rat model of hepatic protection, nor did it induce any significant effect in the murine models of hypoglycemia. This also applied to cellular and humoral immunomodulation. Essiac® did, however, show a moderate gastroprotective effect from ethanol-induced ulceration, although it is, as yet, unclear if this was a specific or an adaptive cytoprotective response.

Though we acknowledge several limitations to this preliminary study, these findings are significant in that they provide a base of scientific knowledge about the *in vivo* effects of Essiac® consumption from which future investigations can be directed. Specifically, the nature of the gastroprotective response, as well as the cumulative effects of prolonged Essiac® consumption on modulation of the immune system, are newly identified questions that may be of interest to cancer patients and clinicians. In light of the recent study showing a potential detrimental effect of Flor-Essence® in a mammary tumor model (9), as well as an *in vitro* study indicating potential *in vitro* stimulation of human breast cancer cells with both Essiac® and Flor-Essence® (19), a study looking at the *in vivo* effects of Essiac® on tumor cells would be of obvious significance. This study represents the first published report on the effects of Essiac® consumption in an *in vivo* model and has begun to address the paucity of data on this extensively used herbal compound.

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