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Short Paper

Study on effectiveness and user satisfaction of anti-inflammatory ointment of *Curcuma albiflora* Thw. in Bentota divisional secretariat, Southern Sri Lanka

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Abstract. Under the same Sinhalese vernacular name, three plants (*Curcuma albiflora* Thw., *Curcuma zedoaria* Rosc., and *Zingiber zerumbet* Smith) are being reported. Amongst them, *C. albiflora* is an endangered and less explored plant. The current study was conducted to study the anti-inflammatory activity of the ointment produced using *C. albiflora*. Clinical trial was conducted using 175 participants in community based centers (n=2) in Grama Niladari divisions of Bentota Divisional Secretariat, Southern Province, Sri Lanka. Participants treated with the ointment (98 patients) or the placebos (77 patients) were asked to complete the structured questionnaire. Treatment was applied for two weeks and the results were monitored by two Ayurvedic doctors who were involved in the study. Comparisons by chi square test showed that TM users differed from non-users in terms of previous side effects and current inflammatory conditions (P<0.05). By binary logistic regression analysis, treatment group satisfaction was found to be about 31 times the chance of the placebo group. The models indicated that the patients above 60 years of age, female, previous traditional medicine users, duration of current anti-inflammatory condition (≥ 1 year) were more likely to effectively respond to the treatment. Ointment of *C. albiflora* Thw. showed moderate anti-inflammatory activity.

Keywords. Binary logistic regression, *Curcuma albiflora,* Survey.

1 Introduction

Arthritis is a major common health problem in the world, while Osteoarthritis (3.8%) and Rheumatoid arthritis (0.24%) of people are reported globally (Richette and Bardin 2010). According to survey results of the Department of

Census and Statistics on Sri Lankan people, nearly 11.4% were reported to have arthritis. Moreover, the prevalence rate of arthritis reported is 1.25% and 2.8% among the males and females respectively (DCS 2014). To date, chemoprevention is a major strategy in controlling inflammatory diseases (Gustin *et al.* 2002). Non-steroidal anti-inflammatory drugs (NSAIDs) were originally used to alleviate pain and for the treatment of arthritis. NSAIDs lead to a number of side effects in the patients such as pain, gastro-intestinal tract issues, and leading to problems such as high blood pressure (O'Leary 2014). Therefore, day by day herbal medicine becomes popular throughout the world. But, some of the constraints exist in herbal medicine are adulteration of authentic plant materials with other similar looking plant materials (e.g. *Curcuma* species), legal barriers on cultivation (e.g. Kansa-*Canabis sativa*) and restrictions to harvest from forests (e.g. Venivel-*Coscinium fenestratum*, Kotala himbutu- *Salasia reticulate*, Bimkohomba-*Munronia pinnata*, Sudu handun- *Santalum album* and Rath handun-*Pterocarpus santalinus*) (Kankanamalage *et al.* 2014).

'Harankaha' is a medicinal plant used in Traditional Medicine in Sri Lanka. But, under the same common trivial name *Harankaha,* three species are reported; *Curcuma albiflora* Thw., *Curucma zedoaria* Rosc., and *Zingiber zerumbet* Smith (Dassanayaka 1983). Among these three species, *C. albiflora* is an endangered and poorly explored endemic plant (MOE 2012).

However, *C. zedoaria* is one of the most extensively studied species of *Curcuma* due to their high commercial value. Proteins of *C. zedoaria* have shown a significant anti-inflammatory activity (i.e. 77% inhibition after 5h) in the carrageenan induced rat paw oedema model system (Angel *et al.* 2013). According to Ullah *et al.* (2014), ethanol extract of *C. zedoaria* (500 mg/kg) has shown maximum activity (94.67% inhibition) after 3h on carrageenan induced paw oedema test. Moreover, its ethanol extract (500 mg/ml) has significantly inhibited protein denaturation by 77.15%. Makabe *et al.* (2006) reported that furanodiene and furanodienone isolated from *C. zedoaria* using ethyl acetate (in hexane) showed 75% and 53% inhibitory effect on TPA (12-O-tetradecanoylphorbol13-acetate) induced edema of mouse ear test respectively. Further, Kaushik and Jalalpure (2011a) has studied histamine induced rat paw edema test on various extracts of *C. zedoaria* (root) and have shown a significant inhibition. Petroleum ether and chloroform extracts have shown 46.3% and 51.85% inhibition at 200 mg/kg dose after 6h respectively. Further, Kaushik and Jalalpure (2011a) found that petroleum ether and chloroform extracts of *C. zedoaria* have shown 55.81% and 51.16% inhibition at the dose of 200 mg/kg respectively (on carrageenan induced paw oedema model). But standard group (Indomethacin) has shown 53.49% inhibition after 6h. The petroleum ether extract of *C. zedoaria* reduced edema 56.70% in the carrageenan induced paw oedema test on oral administration 200 mg/kg when compared to control group (Kaushik and Jalalpure (2011b). However, *C. albiflora* has not studied to that extent, yet investigation of anti-

inflammatory action of *C. albiflora* is important for Traditional Medicine in Sri Lanka. *C. albiflora* hydro-ethanolic extract significantly impaired the paw oedema, at 1h (by 61%) by 200 mg/kg on carrageenan induced paw oedema model (Herath *et al*. 2017). Moreover, the drug group (400 mg/kg) significantly ($P<0.05$) reduced the paw oedema from the day 5 to 7, when compared with the control (water) on Formaldehyde induced paw oedema model.

Although *in vivo* and *in vitro* assays are used to predict human response to drugs (or other chemicals), it is an argumentative issue (Shanks *et al*. 2009). Hence, the current study was conducted to study the anti-inflammatory activity of ointment which was produced from *C. albiflora* using the modified method of Liu *et al*. (2012) and Anand and Bansal (2016). The ointment was tested through a clinical trial using 175 people, who were selected from community based centers (n=2) in Grama Niladari divisions of Bentota Divisional Secretariat, Southern Province, Sri Lanka.

2 Materials and Methods

2.1 Ethical clearance

Ethical clearance was obtained from the Department of Ayurveda in Sri Lanka to conduct the clinical trial.

2.2 Collection of plants and preparation of the extract

Plants were collected from 2016 to early 2017 in Sabaragamuwa province (Erathna: N 6º 50' 07", E 80º 24' 41", Kitulgala: N 6° 59' 41", E 80° 24' 20" and Bopathella: N 6º 48' 07", E 80º 22' 12"). Voucher specimens (No. 02, 03, 04) of the plants were authenticated from National Herbarium, Peradeniya, Sri Lanka.

2.3 Preparation of *C. albiflora* (CA) ointment

Decoction, sesame oil (2.5 L) as solvent, soft paraffin (5 L), bee-wax were used to prepare CA ointment (n = 100).

2.4 Participants and Settings

A descriptive survey design was used to collect data through a questionnaire about CA ointment. Data were collected from the people gathered at the community based centers (n= 2) in Dedduwa and Mahawila Grama Niladhari

dividions in Benthota, Galle district, Southern province on 22/12/2017 and 14/01/2018.

2.5 Questionnaire

In the present study, a modified version of the questionnaire developed by Swisher was used (Swisher *et al*. 2002). A draft questionnaire was prepared, and it was reviewed by Ayurvedic doctors (n=2). Then a pilot test was performed in two community groups as mentioned in 2.4. The questionnaire used to collect data was attached and it consisted of three parts; the first part on the demographic information of participants (age, gender, educational level, marital status and religions), the second part on participants' clinical condition, use of traditional medicine (TM) (activity of daily life, methods of obtaining information about TM), and the third part on the satisfaction or dissatisfaction on *Curcuma albiflora* (CA) ointment after applying it for two weeks. They were advised to use ointment without using any anti-inflammatory drug during these two weeks. TM users were defined as patients who had used TM at least once before the use of CA ointment.

2.6 Statistical analysis of the survey data

Differences in demographic and clinical characteristics between TM users and non-users were assessed using χ^2 test. Factors associated with TM use were identified via binary logistic regression analysis. The analysis provided an odds ratio and a 95% CI for each variable while simultaneously controlling for the effects of other variables. Data were analyzed with Minitab 17 software.

Logistic regression is applicable when the response is binary and uses a transformation or link function to convert the binomial data into continuous variable using formula Logit(p) = $\ln(\frac{p}{1-p})$. The regression output provides the predicted logit value for each observation, which transform to a binary percentage (Peng 2002). The event probability (E) is the estimated event probability value for that observation.

$$E = \frac{1}{1+e^{-logit(p)}}$$ where logit(p) = constant$+\alpha_1 x_1 + \alpha_2 x_2 \ldots + \alpha_n x_n$

3 Results and Discussion

The survey conducted in the community based centers (Dedduwa and Mahawila) in Benthota division, Galle district, Southern province noted mean

ages as 62 and 58 for two populations (SD 13). Required total sample size was obtained as 166. Total of 175 participants attended the survey from the community based centers (n=2) in Dedduwa and Mahawila Grama Niladhari, in Benthota division (Plate 1).

Plate 1. Survey on two community based centres (A: Dedduwa Grama Niladhari, Benthota division, Galle district, Southern province B: Mahawila-West Grama Niladhari, Benthota division, Galle district, Southern province, Sri Lanka).

Table 1: Demographic and clinical characteristics of the participants.

Variable	Category	TM Users %	TM Non users %	Total %	Chi square value	P value
Age	>60	32.6	40	72.6	0.72	0.39
	<= 60	14.3	13.1	27.4	Ref: 3.84	
Education	Illiterate	4	4.6	8.6	2.75	0.43
	Primary	21.1	25.7	46.9	Ref: 7.82	
	OL	17.1	14.3	31.4		
	> OL	4.6	8.6	13.1		
Marital status	Married	27.4	33.7	61.1	0.44	0.80
	Never	4	4	8	Ref: 5.99	
	Widowed	15.4	15.4	30.9		
Sex	Male	10.9	15.4	26.3	0.77	0.37
	Female	36	37.7	73.7	Ref: 3.84	
Previous Side effects	Free	41.7	53.1	94.8	10.76	< 0.001*
	Simple	5.1	0	5.1	Ref: 3.84	
Food type	Vegetarian	14.3	17.1	31.4	0.06	0.80
	Mix	32.6	36	68.6	Ref: 3.84	
Current inflammatory condition	Never	0	4	4	6.42	0.01*
	Slight	46.3	49.1	95.4	Ref: 5.99	
Duration of current inflammatory condition	<1 year	21.7	29.1	50.9	1.75	0.41
	1-5 years	19.4	20	39.4	Ref: 5.99	
	>5 years	5.7	4	9.7		

Out of these 175 people, 98 (56%) were eligible for receiving CA ointment. After screening past diagnosis, current health status of patients were assessed by Ayurvedic doctors (n=2). Participants (who have chronic diseases such as diabetes, kidney diseases etc.) and healthy participants were recommended to obtain placebo. Patients with arthritis and joint disorders have received the CA ointment. Of the 175 surveyed people consisting of 46 (26.3%) males and 129 (73.7%) females completed the survey with a response rate of 100%. Their mean age was 64.6 ± 11.8 years; most participants were married (n = 107; 61.1%) and were widowed (n=54; 30.9%). Demographic and clinical characteristics of participants were summarized in Table 1. Nine patients (5.1%) reported side-effects of the TM drugs such as traditional mixtures called '*arishta*' and '*kalka*'. These side-effects included gastric upset, stomachache and increase of phlegm, but nobody experienced serious side-effects.

46.9% (n = 82) of the total responders were TM users (patients who had used TM at least once before the use of CA ointment). Comparisons by chi square test showed that TM users differed from non-users in terms of previous side effects and current inflammatory condition (P<0.05). TM users did not differ from non-users in terms of age, education, marital status, sex, food type, and duration of current inflammatory condition (P>0.05). Effect of the CA ointment and placebo were reported in Table 2.

Table 2: Effect of treatment from surveyed result of *Curcuma albiflora* (CA) ointment and placebo.

Exposure	Outcome		Odd ratio
	Improved	No improvement	
Treatment group (CA ointment)	74	24	31
Placebo group	07	70	

Odd ratio equals to 31 indicated the satisfaction of the treatment group who used CA ointment for two weeks is about 31 times that of the placebo group. According to response of the CA ointment users, results were summarized in Table 3.

CA ointment was received by 56% (n = 98) of the surveyed group. Comparisons by Chi square test showed that CA satisfied responders did not differ from dissatisfied in terms of age, education, food-type, sex, and the duration of current inflammatory condition (P>0.05). Some of the factors were studied in detail and reported in Table 4.

Table 3: Bivariate analysis results by survey on satisfaction/dissatisfaction of *Curcuma albiflora* ointment.

Variable	Category	Satisfied %	Dissatisfied %	Total %	Chi-square	P-value
Age	< 60y	25.5	5.0	30.6	1.97	0.16
	>= 60y	64.3	5.0	69.4		
Education	< OL	41.8	7.1	49.0	1.96	0.16
	>= OL	37.8	13.3	51.0		
Sex	Male	16.3	8.2	24.5	1.34	0.24
	Female	59.2	16.3	75.5		
Food type	Vegetarian	23.4	6.1	29.6	2.73	0.09
	Mix	0.64	6.1	70.4		
Duration of current inflammatory condition	<1 year or >5	0.32	6.1	37.8	0.18	0.67
	1-5 years	0.54	8.2	62.2		

Table 4: Factors associated with *Curcuma albiflora* ointment users in the binary logistic regression.

Variable	Category	Response	Test		OR
			Treatment	Placebo	
Age	>60 years	Improved	50	6	24.5
		No improvement	18	53	
	<60 years	Improved	24	1	68
		No improvement	6	17	
Sex	Male	Improved	16	3	12.6
		No improvement	8	19	
	Female	Improved	58	4	46.2
		No improvement	16	51	
Previous TM use	TM users	Improved	35	1	102.1
		No improvement	12	35	
	TM non users	Improved	39	6	19.0
		No improvement	12	35	
Duration of current inflammatory condition	<1 year	Improved	19	5	12.4
		No improvement	8	26	
	1-5 or >5 years	Improved	54	2	69.9
		No improvement	17	44	

The binary logistic models indicated that above 60 years of age, female, previous traditional medicine users, duration of current anti-inflammatory condition ($\geq$ 1 y) were more likely to effectively response for CA ointment. According to binary logistic analysis number of satisfied CA ointment users were reported as 74, and dissatisfied as 24. Predictor variable values were summarized in Table 5.

Table 5. Predictor variable values of *Curcuma albiflora* ointment users by Binary logistic regression analysis (TM= Traditional medicine).

Predictor variable	β	S.E. β	Wald Z	p	Exp (β) OR	95% CI for Exp (β)	
						Lower	Upper
Age	-0.02	0.02	-0.81	0.420	0.98	0.93	1.03
Sex	0.44	0.58	0.76	0.445	1.56	0.50	4.92
Marital status	0.09	0.32	0.30	0.762	1.10	0.58	2.10
Edu1tional level	-0.57	0.31	-1.84	0.06	0.56	0.31	1.04
Food	-0.59	0.60	-0.98	0.32	0.55	0.17	1.81
Previous TM user	-0.39	0.53	-0.74	0.46	0.67	0.23	1.93
Diagnosis/months	0.00	0.00	0.75	0.45	1.00	0.99	1.02
Side effects	0.20	1.25	0.16	0.87	1.23	0.11	14.31
Arthritic condition	0.22	1.37	0.17	0.86	1.26	0.08	18.64

Many researches have revealed effectiveness of curcumin incorporated skin formulations. Gonçalves *et al*. (2014) has assessed topical formulations of curcuminoid extracted from *Curcuma longa* by quantifying skin retention (using pig ear membrane) and skin permeation (modified Franz diffusion cell system). They have prepared various gel formulations by water and hydroxyethylcellulose (at 70°C); the most stable formulation was β-cyclodextrin containing hydro-ethanolic and dry extract of turmeric. Although skin penetration lowered by curcumin, skin retention promoted. Therefore, curcumin is used in anti-aging formulations. Gonçalves *et al.* (2014) has reported that, a tonic prepared from the rhizome of *C. longa* has shown significant reduction in ulcers, cough, and the common cold as well as ointment form increased wound healing. Furthermore, Hamzah (2011) has found that turmeric gel reduced a 30% inhibition in oedema using the carrageenan-induced rat paw edema model. Huang *et al*. (1997) found that curcumin inhibited induced skin tumor formation by topical application. Lin and Lin (2008) showed that curcumin prevents skin tumors, spots or wrinkles effectively.

Kuptniratsaikul *et al*. (2009) performed a single-blind randomized controlled trial to evaluate the efficacy of *C. domestica* extracts (2,000 mg/day) compared with ibuprofen (800 mg/day) of in 107 knee OA patients

for 6 weeks. Further, to determine the efficacy and safety of *C. domestica* extracts (1,500 mg/day) in pain reduction and functional improvement compared with ibuprofen (1,200 mg/day); about 96% were satisfied with the treatment while fewer gastrointestinal issues reported in the *C. domestica* extracts group. Patient's assessment of satisfaction on *C. domestica* extract (n=171) at week 4, satisfied and unsatisfied patients were about 97% and 1% respectively (P > 0.05).
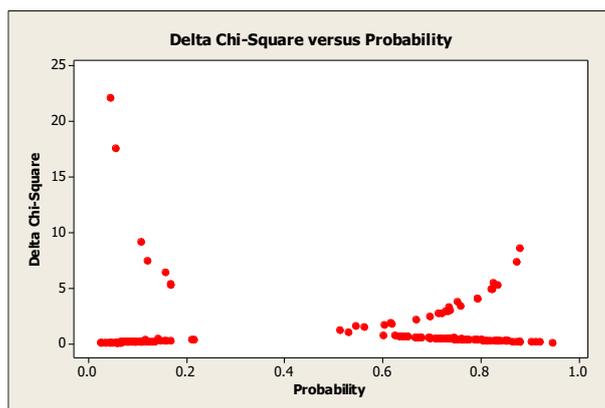
Fig. 1. Diagnostic plot of delta chi-square versus probability

Log-Likelihood and G value were reported as -50.436 and 8.232 respectively. Goodness-of-Fit Tests under the method Pearson was shown higher Chi-Square value (109.854) indicates enough number of data for the analysis. This is supported with the Figure 1.

Hydro-ethanolic extract of *C. albiflora* significantly impaired the paw oedema, at 1h (by 61%) by 200 mg/kg on carrageenan induced paw oedema model as well as from the day 5 to 7 on formaldehyde induced paw oedema model (Herath *et al.*, 2017). From the current study it was revealed that the treatment group satisfaction was about 31 times the chance of the placebo group. Therefore, CA ointment showed moderate anti-inflammatory activity.

4 Conclusion

From the present findings it can be concluded that *Curcuma albiflora* ointment possessed a moderate anti-inflammatory activity.

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