Rev. Latino-Am. Enfermagem
2011 Jan-Feb;19(1):3-10
www.eerp.usp.br/rlae

Original Article

Clinical Application of Chamomilla Recutita in Phlebitis: Dose Response Curve Study[1]

Paula Elaine Diniz dos Reis[2]
Emília Campos de Carvalho[3]
Paula Carolina Pires Bueno[4]
Jairo Kenupp Bastos[5]

This experimental and dose-response curve study aimed to carry out the quality control of the *Chamomilla recutita* sample, as well as to estimate the ideal dose, for anti-inflammatory effect, of the extract of its capitula, in patients with phlebitis due to peripheral intravenous infusion of *antineoplastic chemotherapy* and to evaluate the toxicity of this extract in human beings. The therapeutic efficacy, concerning the anti-inflammatory potential, of different doses of *Chamomilla recutita* extract were analyzed and compared in 25 patients. The time of regression of phlebitis was shorter for groups with 2.5% concentration (mean=29.2h, standard deviation = 8.98) and 5% concentration (mean = 38.8h, standard deviation = 17.47). Local toxicity was almost not observed. This research contributes to the innovation of the nursing clinical practice, since it suggests an alternative for the treatment of phlebitis through the clinical use of phytotherapeutic drugs. (ClinicalTrials.gov Identifier: NCT 00989599).

Descriptors: Matricaria; Phlebitis; Dose-Response Relationship, Drug.

[1] Paper extracted from Doctoral Dissertation "Uso tópico terapêutico da Chamomilla recutita em flebites decorrentes de terapia intravenosa periférica", presented to Programa de Pós-graduação em Enfermagem Fundamental, Escola de Enfermagem de Ribeirão Preto, Universidade de São Paulo, WHO Collaborating Centre for Nursing Research Development, SP, Brazil.

[2] RN, Ph.D. in Nursing, Adjunct Professor, Universidade de Brasília, DF, Brazil. E-mail: pdinizreis@yahoo.com.

[3] RN, Ph.D. in Nursing, Full Professor, Escola de Enfermagem de Ribeirão Preto, Universidade de São Paulo, WHO Collaborating Centre for Nursing Research Development, SP, Brazil. E-mail: ecdcava@eerp.usp.br.

[4] Pharmacy-Biochemistry, M.Sc. in Pharmaceutical Sciences E-mail: paulabueno@yahoo.com.br.

[5] Pharmacist, Ph.D. in Organic Chemistry of Natural Products, Full Professor, Faculdade de Ciências Farmacêuticas de Ribeirão Preto, Universidade de São Paulo, SP, Brazil. E-mail: jkbastos@fcfrp.usp.br.

Corresponding Author:
Emilia Campos de Carvalho
Universidade de São Paulo. Escola de Enfermagem de Ribeirão Preto.
Departamento de Enfermagem Geral e Especializada
Av. dos Bandeirantes, 3900
Campus Universitário
CEP: 14040-902 Ribeirão Preto, SP, Brasil
E-mail: ecdcava@eerp.usp.br

Aplicação clínica da *Chamomilla recutita* em flebites: estudo de curva dose-resposta

Neste estudo, buscou-se realizar o controle de qualidade da amostra de Chamomilla recutita, bem como estimar a dose ideal, para efeito anti-inflamatório, do infuso dos seus capítulos florais, em pacientes com flebite, decorrente de infusão intravenosa periférica de quimioterapia antineoplásica, e avaliar a toxicidade desse infuso em seres humanos. Trata-se de estudo experimental, do tipo curva dose-resposta, no qual foi analisada e comparada a eficácia terapêutica, quanto ao potencial anti-inflamatório, de diferentes doses do infuso da Chamomilla recutita, em 25 pacientes. O tempo de regressão da flebite foi menor para os grupos com concentração 2,5% (média=29,2h, desvio padrão=8,98) e 5% (média=38,8h, desvio padrão=17,47) e praticamente não se observou toxicidade local. Esta pesquisa contribui para a inovação da prática clínica em enfermagem, uma vez que sugere alternativa para o tratamento de flebites, por meio da utilização clínica de fitoterápicos (ClinicalTrials.gov Identifier: NCT 00989599).

Descritores: Matricaria; Flebite; Relação Dose-Resposta a Droga.

Aplicación clínica de la *Chamomilla recutita* en flebitis: estudio de la curva dosis-respuesta

En este estudio, se buscó realizar el control de calidad de la muestra de Chamomilla recutita, así como estimar la dosis ideal, para efecto antiinflamatorio, de la infusión de sus inflorescencias, en pacientes con flebitis proveniente de introducción intravenosa periférica de quimioterapia antineoplásica y evaluar la toxicidad de esta infusión en los seres humanos. Se trata de estudio experimental, del tipo curva dosis-respuesta, en el cual fue analizada y comparada la eficacia terapéutica, en cuanto al potencial antiinflamatorio, de diferentes dosis de la infusión de la Chamomilla recutita en 25 pacientes. El tiempo de regresión de la flebitis fue menor para los grupos con concentración 2,5% (promedio = 29,2h, desviación estándar = 8,98) y 5% (promedio = 38,8h, desviación estándar = 17,47) y prácticamente no se observó toxicidad local. Esta investigación contribuye para la innovación de la práctica clínica en enfermería, una vez que sugiere una alternativa para el tratamiento de la flebitis por medio de la utilización clínica de fitoterapéuticos. (ClinicalTrials.gov Identifier: NCT 00989599)

Descriptores: Matricaria; Flebitis; Relación Dosis-Respuesta A Droga.

Introduction

Phlebitis can be considered a temporary or permanent limiting factor for treatment continuity in cancer patients, as, after its occurrence, the peripheral venous catheter should be immediately removed[1]. Depending on the extent of the inflammatory process established at the venipuncture site, the vascular endothelium suffers irreversible injuries, such as phlebosclerosis, so that the venous segment cannot be used for new intravenous infusion punctures, nor even for simple blood collection[2]. Thus, phlebitis prevention, control of its evolution after its occurrence and reversal of its characteristic inflammatory signs are needed, mainly in patients whose venous network is already very sensitive as a result of antineoplastic chemotherapy.

Conventionally, as a nursing intervention for phlebitis treatment, topical lukewarm compresses are indicated to reduce the local inflammatory process. Depending on the phlebitis intensity, however, applying

compresses alone is not enough to improve the inflammatory process, leading to the need to for medical prescription of systemic anti-inflammatory agents, which constitutes an additional factor for the immune system commitment of cancer patients. Therefore, it is fundamental for Brazilian nursing to start to research, within its professional competency area, on alternative and more effective phlebitis treatment forms, using phytotherapy for example. The Federal Nursing Council establishes and recognizes this practice, through COFEN Resolution 197/1997[3], as a specialty and/or qualification for nursing professionals.

According to the "Guia para a realização de estudos de toxicidade pré-clínica de fitoterápicos"[4] [Guide for preclinical phytotherapeutic drug toxicity studies], any and all phytotherapeutic or vegetal drugs under analysis should obligatorily be submitted to toxicological tests. Toxicity studies need to be conducted with standardized samples of the phytotherapeutic or vegetal drug based on which it is produced. According to the same standard, toxicity should be assessed after the user's exposure to a single or fractionated dose, which should be administered to the patient within 24 hours.

The *Lista de Registro Simplificado* [Simplified Registry] by the Brazilian Health Surveillance Agency[5] already contains *Chamomilla recutita* (L.) Rauschert (Asteraceae), so that proving efficacy and safety is not needed. Infusion is not considered a pharmaceutical form yet in Brazil, however – as opposed to what happens in other countries like Germany, which considers *C. recutita* infusion a pharmaceutical form. This research aimed to estimate the ideal dose, for anti-inflammatory purposes, of *C. Recutita* floral capitula infusion, in patients with phlebitis due to peripheral intravenous infusion of antineoplastic chemotherapy, as well as to assess the toxicity of this infusion in human beings. Besides, the vegetal species used was especially grown, standardized and characterized with a view to certification for medicinal use and later validation of its therapeutic efficacy and safety, as a secondary study goal.

Method

Cultivation, standardization and characterization of *C. recutita*

"*Cultivar* Mandirituba" *C. recutita* seeds were used for planting, donated by Empresa de Assistência Técnica e Extensão Rural do Paraná (EMATER-PR) [Paraná State Rural Technical Assistance and Service Company]. Organic planting was followed, in an aviary bed, located in a nursery in the Medicinal Plant Garden of the Federal University of Mato Grosso do Sul (HPM-UFMS). Sowing occurred in May 2005. During the cultivation cycle, weed control, performed with the help of a hoe, and irrigations through sprinklers were done whenever necessary. No pesticides were used directly on the plants to control plagues or diseases. Manual harvesting occurred in September 2005 by technicians from HPM-UFMS. The drying of the collected floral capitula was done in a forced-air circulation glasshouse with temperature ranging between 36º ± 2ºC, to constant mass, resulting in 56.57 million ha^{-1}, equivalent to 8kg of floral capitula of *C. recutita*. After drying, the floral capitula of *C. recutita* were stored in lidded glass pots and kept refrigerated.

The physical-chemical evaluation of *C. recutita* inflorescences was done in accordance with the methods described in *Farmacopéia Brasileira*[6] and USP 28[7]. A sample of about 500.0 g was grinded and submitted to physical-chemical characterization, including identification, purity and integrity tests and marker dosage. This dosage consisted in the quantification of total flavonoids in the floral capitula and α-bisabolol in essential oil.

After being submitted to the describe cultivation, harvesting, drying and storage processes, the dry floral capitula of C. recutita were destined for laboratory analysis, when the excellent quality of the raw material was verified, as evidenced in the physical-chemical characterization of the sample (Table 1).

Table 1 – Physical-chemical characterization of C. Recutita inflorescences

Test	Result	References
Aspect	Dehydrated, slightly erased inflorescences. Presence of little powder.	USP 28[7]
Organoleptic characteristics	Aromatic, pleasant, sweet scent. Bitter taste.	USP 28[7]
Humidity content	13.0% m/m	Farm. Bras.[6]
Total Ashes	7.4% m/m	Farm. Bras.[6]
Ashes insoluble in HCl	1.1% m/m	Farm. Bras.[6]

(continue...)

Table 1 – (continuation)

Test	Result	References
Strange material	4.8% m/m	Farm. Bras.[6]
Total flavonoid content	2.5% m/m	Dowd(8); Jay[9]
Essential oil content	0.4% v/m, bluish-colored oil	Farm. Bras.[6]
70% ethanol-extractable material	16.9% m/m	Farm. Bras.[6]

Total flavonoid content in the floral capitula of chamomile was determined by 425 nm spectrophotometry, according to an adapted method described in literature[8-9]. Total flavonoid concentration (expressed in quercetin) was calculated per 100.0 g of the sample. The same procedure was applied to determine total flavonoid contents in the four infusion dosages (Table 1), with a view to better characterization and comparison with future study data.

α-bisabolol content was determined by gas chromatography with flame ionization detector (GC-FID). Therefore, the essential *C. recutita* oil was previously extracted, using hydrodistillation with a Clevenger apparatus. Triple analysis was performed, using an analytic α-bisabolol curve ranging from 200.0 to 1000.0 μg/mL, using piperonal as internal standard.

Finally, the main constituent elements present in the essential oil were identified, using gas chromatography with mass detector (GC-MD).

α-bisabolol content in the essential oil could be quantified through the equation of the straight line obtained from the analytic curve with internal standardization (R = 0.9993), corresponding to 10.9% m/m. According to GC-MD analysis of the essential oil, five major peaks of the plant's main active principles could be clearly identified, which should be highlighted: α-bisabolol oxide B (19.6%); α-bisabolone oxide (5.2%); α-bisabolol (9.0%); camazulene (1,3%); α-bisabolol oxide A (40.7%), besides spathulenol, β-elemene, limonene oxide, β-farnesene and *d*-nerolidol.

Clinical Phase

A dose response curve trial was carried out, in which the therapeutic efficacy of different *C. recutita* infusion doses was analyzed and compared in cancer patients with phlebitis deriving from peripheral intravenous infusion of antineoplastic chemotherapy, looking at the anti-inflammatory potential. Dose response curve studies demonstrate the relation between the dose (concentration) of an administered drug and the produced tissue response or effect, permitting knowledge on the adequate dose based on the wanted and unwanted effects obtained during the clinical application[10].

The research was carried out at a public hospital in the Federal District, which is a tertiary referral institution for cancer care and offers 18 hematology and clinical oncology beds. The sample comprised 25 patients who formally agreed to participate by signing the Informed Consent Term (ICT). All patients had been diagnosed with degree-2 phlebitis according to the staging proposed by the Infusion Nursing Society[11] and were between 20 and 30 years old. Thirteen participants were women and 12 men, whose white blood cell count showed adequate normality levels for neutrophil (2000 – 7500/μl) and monocyte (100 - 800/μl)[12] counts, medically diagnosed with Acute Myeloid Leukemia (AML), submitted to the first, second or third cycle of the chemotherapy protocol IDA + ARA-C (idarubicin and cytarabine), through peripheral intravenous infusion.

The exclusion criteria were the patients' affirmative response when asked about previous adverse reactions to chamomile or any plant in the Asteraceae or Compositae family, medical prescription of systemic or topical anti-inflammatory drug on the phlebitis site and refusal to continue participating in the study.

The primary researcher established the criterion to allocate the subjects to the groups as follows: the first selected patient was automatically allocated to trial group A, the second to group B, the third to group C, the fourth to group D and the fifth to the control group. This process was repeated until 25 patients had been allocated.

Data were collected between September and December 2005. Patients who complied with the selection criteria were allocated in five groups, one of which was the control group. A 20 cm^2 cotton compress was used for the intervention, moistened with the C. recutita infusion when applied in the trial groups (Table 1) or with lukewarm water in the control group. In all groups, temperature was set at 38 °C.

The graphs showing the dose-response curve are semi-logarithmic[10], with the dose axis showing the drug concentration in exponential progress. Hence, in this study, the researchers took care to establish the following dose concentrations, specified in Table 1.

Table 2– Distribution of patient groups according to infusion dose

Group	Portion (g) of dehydrated floral capitula of *C. recutita* in 400 mL of water	Dose (%)	Total flavonoid content (mg/mL)
A	5	1.25%	0.02
B	10	2.5%	0.04
C	20	5.0%	0.08
D	40	10.0%	0.19

After removing the peripheral venous device, the moistened compress was applied on the phlebitis evidenced in the subject's upper limb, three times per day (morning, afternoon and night), according to the dose established in the group the patient had been allocated to, i.e. trial group A, B, C, D or control. As soon as the compress had been applied, the limb was wrapped in transparent PVC film to preserve local heat. Compress application time was set at 20 minutes for all groups and compresses were changed every 5 minutes. Only the main researcher applied the intervention in all patient groups. After the phlebitis diagnosis, the application time of the first compress was registered. The treatment site was assessed daily at three distinct times: at 8, 13 and 19 hours, with a view to uniform readings. The intervention was continued until the complete disappearance of the erythema, considered the main outcome.

The erythema was chosen as the parameter to assess the inflammatory regression as this is a classical sign of any inflammation and an objective data, present in degree-2 phlebitis (local pain, erythema and/or edema), according to the staging proposed by the Infusion Nursing Society[11]. Thus, the erythema regression time constituted a safe parameter to monitor the inflammation, offering the advantage that nursing professionals know and identify clinical phlebitis staging criteria very well, entailing additional security for assessment precision. To measure to erythema, transparent paper ruled in one-centimeter squares was used, based on which the erythema area was calculated very precisely, so that any alteration in the dependent variable could be identified.

Like the subject allocation procedure to the respective groups, the same researcher performed the intervention and evaluation.

Toxicity was investigated through visual assessment of the application site, looking for any signal that would indicate any reaction to the infusion, and also for symptoms. For toxicological evaluation, a compress was applied with the dose that presented the best dose-response effect in four other subjects with the same characteristics as the subjects but who did not present phlebitis, in compliance with (ANVISA) [National Health Surveillance Agency] Resolution RE Number 90, issued on March 16th 2004 – about toxicity evaluation of phytotherapeutic interventions – which suggests additional toxicity evaluation in healthy individuals[3].

One-way variance analysis (ANOVA) was used for statistical analysis of the results, followed by multiple comparison test – Bonferroni test[13-14], using Graph Pad Prism* software, demo version, 5.0 for Windows. Significance was set at 5% in all tests. Approval for this research project was obtained from the Institutional Review Board of the Federal District Health Secretary, opinion number 062/2004.

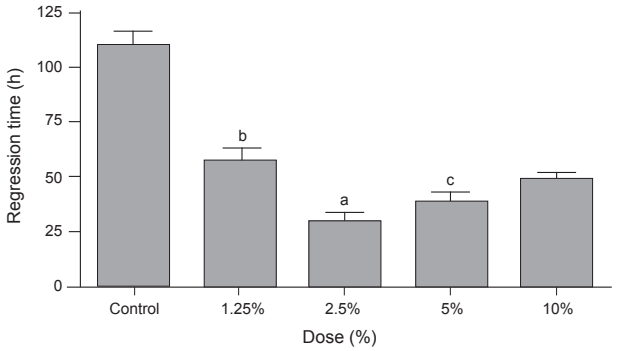
Results

Intergroup comparison showed a statistically significant difference in the groups that received 2.5% and 5% infusions (i.e. corresponding to total flavonoid contents of 0.04 and 0.08 mg/mL, respectively) regarding the phlebitis regression time in comparison with the other groups (concentrations of 1.25% and 10%) and the control group (Figure 1)

Erythema regression time in the study sample ranged between 19 and 120 hours for different dose concentrations used. The group in which the 2.5% concentration compress was used showed the shortest regression times: 19 and 24 hours (Table 3). The dose-response curve (Figure 2) evidences that the average phlebitis regression time was shorter for the 2.5% concentration group (mean = 29.2h, standard deviation

* Available from: http://www.graphpad.com/demos.

= 8.98), followed by the 5% concentration group (mean = 38.8h, standard deviation = 17.47), and longer for the 1.25% (mean = 57.8h, standard deviation = 11.10) and 10% concentration groups (mean = 49.4h, standard deviation = 4.67). Mean regression time in the control group was 110.4h and standard deviation 13.15.



Legend: a = p<0.001 related to control; p<0.01 related to 1.25%; p<0.05 related to 10%; p>0.05 related to 5%, b = p<0.001 related to control; p>0.05 related to 10%, c = p<0.001 related to control; p>0.05 related to 10%. Statistical analysis using ANOVA followed by Bonferroni multiple comparison test.

Figure 1 – Effect of different *C. recutita* infusion concentration on the reduction of phlebitis in patients submitted to peripheral intravenous chemotherapy

Table 3 – Regression time, in hours, of phlebitis according to infusion dose group of *C. recutita* floral capitula

Dose (%)	Regression Time (hours)				
0	96	96	120	120	120
1.25	48	48	54	67	72
2.5	19	24	30	30	43
5	30	30	43	43	48
10	43	48	48	48	54

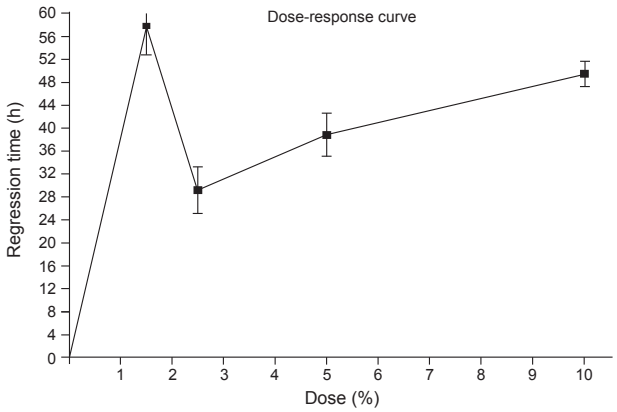


Figure 2 – Dose-response curve according to mean regression times, in hours and infusion concentrations of 1.25%, 2.5%, 5% and 10%, respectively, of *C. Recutita* floral capitula, obtained through ANOVA with Bonferroni post-test

As for toxicity, moderate to severe itching was reported on the left forearm of one of the patients allocated in trial group C, whose compress had been applied on the anterior front forearm. As the itching expanded, the transparent PVC film used on the entire forearm could have caused this. The subject was forwarded to the medical team, medicated with an anti-histaminic drug and showed complete regression of the itching within two hours. Local treatment was continued with warm water compresses at 38° C until the complete regression of the erythema.

With regard to toxicity evaluation in subjects without phlebitis (n=4), no manifestations of hypersensitivity reactions occurred, nor reports of burning, itching or any other symptoms related with possible hypersensitivity to the drug.

Discussion

It is fundamental to determine the total flavonoid contents when assessing a plant's quality, especially in studies that use flavonoids for therapeutic purposes[15]. Tests involving about 100 samples of 12 chamomile varieties cultivate in identical conditions showed flavonoid contents ranging between 1.0 and 2.6%, while twenty other samples of different origins showed total flavonoid content levels varying between 0.3 and 3.0%[15]. The sample used in this study showed 2.5% m/m of total flavonoids, in line with previously found results. As for α-bisabolol content in essential oil, the level identified in the sample (10.9% m/m) surpassed literature recommendations according to the used temperature, which is 7%[15]. Qualitative analysis of the plant's active principles confirmed available literature data about the chemical composition of *C. recutita*, describing terpenes (α-bisabolol, bisabolol oxide A and B, camazulene and sesquiterpenes), flavonoids (apigenin-7-glucoside, luteolin, quercetin), coumarins (umbelliferone) and steroids[16]. It should be reminded that these elements, terpenes, steroids and sesquiterpenes exert anti-inflammatory effects, generally inhibiting the classical route of the complement system, interfering, in turn, in arachidonic acid metabolism[17].

With regard to the clinical phase, research subjects in all groups were comparable, as the main confounding factors, including age, sex, white blood cell count and baseline disease were similar. Among the 25 participants, those in group A (dose 1.25%) showed the longest inflammation process regression time (range: 48 – 72h), while those in groups B and C showed the shortest regression time (range: 19 – 48h). Group D showed a

longer regression time than groups B and C because, despite a higher dose – 40 g of floral capitula of *C. recutita* – the compress could not be totally moistened with the quantity of solvent used. This quantity did not need to be adjusted though, as lower doses had already demonstrated an excellent effect in terms of regression time of the inflammatory process.

Other clinical trials have confirmed the anti-inflammatory effect of *C. recutita* in radiation dermatitis, through the use of ointments with chamomile extract (Kamilosan®)[18], in mucositis, through oral solution (Kamilosan® Solução Oral)[19], in contact dermatitis and eczema, through ethanolic extract[20-21], showing even superior efficacy results when compared with steroidal and non-steroidal anti-inflammatory drugs[21]. Researchers[22] have assessed the efficacy of medical plant infusions (chamomile, salvia and calendula) for topical application in the treatment of Hand-Foot Syndrome resulting from intravenous capecitabine infusion, an antineoplastic chemotherapy drug used in breast cancer patients. The sample comprised 11 patients who immersed their hands and feet into the infusion daily. Significant regression of the inflammatory process was found in all cases.

As for the dose, literature recommends concentrations between 3 and 10% for external use in compresses[23-24]. It was observed, however, that with 2.5% concentrations, results were as satisfactory as with 5% concentrations, to the extent that the shorted regression time of the inflammation process was obtained in two patients, i.e. 19 and 24 hours. Both concentrations showed statistically significant results when compared mutually ($p<0.05$) and with the control group ($p<0.001$). When compared with the other concentrations (1.25% and 10%), the 2.5% dose showed a statistically significant difference ($p<0.05$), while the 5% dose showed no statistically significant difference with the other doses.

Therefore, the researchers decided to choose the 2.5% concentration (10 g/400 mL) for floral capitula infusions of as the standard dose for this study, although literature recommends using concentrations between 3 and 10% for compresses. This small difference of -0.5% between the result obtained in the dose-response curve and the concentration recommended in literature (at least 3%) can be attributed to the excellent quality of the test sample, of Brazilian origins. Besides, it should be highlighted that literature itself shows different variations in terms of quantity definitions and even measurement units. The US Pharmacopeia, for example, indicates the use of two dessert spoons for external use, equivalent to approximately 6g of dry floral capitula of *C. recutita* in 250 mL of water[25], i.e. 2.4%, which is basically the same standard dose found in this research phase. The same source highlights that concentrations between 3 and 10% are indicated for ointments and gels.

It is also important to highlight that using less grams of floral capitula with better results in terms of time for phlebitis regression generates a better cost-benefit relation and, hence, greater advantage for consumers, due to the obvious economy of the main resource.

Itching was reported in one of the patients allocated in trial group C, with a 5% infusion concentration. The reported hypersensitivity reaction – itching – occurred across the subject's left forearm, who classified it as moderate to intense when the researcher asked about the intensity, although the compress had only been applied on the anterior front middle third of the left forearm. With regard to this episode, although allergic reactions to *C. recutita* are quite rare, these can happen, to the extent that one of the exclusion criteria was exactly the patient's affirmative response as to any adverse reaction to chamomile or any plant from the *Asteraceae* or *Compositae* family.

It should be clarified that the sites where the compresses were applied, in the trial as well as in the toxicity control group, were assessed for an additional two days after the application, with a view to investigating late signs and symptoms of toxicity. This was not verified in any of the other subjects who accepted to participate in the research. As for the itching in one of the sample subjects, the symptom regressed within 72 hours, without the need for any medication intervention.

Conclusion

The standardization of vegetal raw material, ranging from the selection of the species, seeding, cultivation, harvesting, drying, storage and quality assessment is fundamental, mainly when used for therapeutic purposes, like in the case of this research.

Based on the results, it can be inferred that, at α = 5%, the *C. recutita* infusion presents minimal or almost zero toxicity for topical application. This study also demonstrated that the 2.5% concentration for floral capitula infusion of *C. recutita*, when applied for anti-inflammatory purposes in case of phlebitis deriving from peripheral intravenous chemotherapy infusion, is as effective as the concentration suggested by literature, i.e. between 3 and 10%.

This research contributes to the innovation of clinical nursing practice, as it suggests a treatment alternative for phlebitis deriving from peripheral intravenous infusion during antineoplastic chemotherapy. Moreover, theoretical support is provided regarding the methods to adopt for the clinical use of phytotherapeutic drugs.

References

1. Machado AF, Pedreira MLG, Chaud MN. Adverse events related to the use of peripheral intravenous catheters in children according to dressing regimens. Rev. Latino-Am. Enfermagem. Maio-junho 2008; 16(3):362-7.

2. Reis PED, Capucho CR, Vasques CI, Carvalho EC. Efeitos adversos identificados em local de infusão intravenosa periférica por drogas quimioterápicas. Cienc Enferm. 2008; 14(2):55-64.

3. Conselho Federal de Enfermagem. Resolução COFEN 197/1997 [acesso em: 23 setembro 2009]. Disponível em: http://www.portalcofen.gov.br/2007/materias.asp?ArticleID=7041

4. Ministério da Saúde (BR). Agência Nacional de Vigilância Sanitária. Resolução RE n. 90, de 18 de março de 2004. Determina publicação do "Guia para a realização de estudos de toxicidade pré-clínica de fitoterápicos". Diário Oficial da República Federativa do Brasil, Brasília (DF): Imprensa Oficial; março 2004. Seção 1.

5. Ministério da Saúde (BR). Agência Nacional de Vigilância Sanitária. Resolução de Diretoria Colegiada (RDC) n. 89, de 16 de março de 2004. Determina a publicação da Lista de Registro Simplificado de Fitoterápicos junto ao Sistema de Vigilância Sanitária. Diário Oficial da República Federativa do Brasil. Brasília (DF): Imprensa Oficial; março 2004. Seção 1.

6. Farmacopéia Brasileira. 4a. ed. São Paulo: Atheneu; 1996. Parte 2, Fascículo 1.

7. . United States Pharmacopeia (USP) 28. 28ª. ed. Rockville:United State Convention; 2005.

8. Dowd LE. Spectrophotometric Determination of Quercetin. Anal Chem 1959; 31(7):1184-7.

9. Jay M, Gonnet J, Wollenweber E, Voirin B. Sur L'analyse. Qualitative des Aglycones Flavoniques dans Une Optique Chimiotaxinomique. Phytochemistry 1975; 14:1605-12.

10. Page C, Curtis M, Sutter M, Walker M, Hoffman B. Farmacodinâmica e a quantificação da droga. In: Page C, Curtis M, Sutter M, Walker M, Hoffman B. Farmacologia integrada. 2ª ed. Barueri (SP): Manole; 2004. p. 57-68.

11. Infusion Nursing Society. Infusion Nursing Standards of Practice. J Infusion Nurs. 2006; 29(1):S58-60.

12. Coutinho V, Coutinho MA. Análise do exame hematológico. In: Zago MA, Falcão RP, Pasquini P. Hematologia: fundamentos e prática. São Paulo (SP): Atheneu; 2001. p. 1081.

13. Armitage P, Berry G. Statistical methods in medical research. 3ª ed. Boston: Blackwell Scientific Publications; 1994.

14. Hamilton LC. Statistics with STATA. Califórnia: Thomson – Brooks/Cole; 2004.

15. Franke R, Schilcher H. Chamomile: industrial profiles. New York (NY): Taylor and Francis Group; 2005.

16. Szelenyi IO, Thiemer K. Pharmacological experiments with compounds of chamomile: Experimental studies of the ulcerprotective effect of chamomile. Planta Med. 1979, 35: 218-27.

17. Schulz V, Hänsel R, Tyler VE. Fitoterapia racional: um guia para as ciências da saúde. 4ª ed. São Paulo(SP): Manole; 2002.

18. Maiche AG, Grohn P, Maki-Hokkonen H. Effect of chamomile cream and almond ointment on acute radiation skin reaction. Acta Oncol. 1991;30(3):395-6.

19. Carl W, Emrich LS. Management of oral mucositis during local radiation and systemic chemotherapy: a study of 98 patients. J Prosthet Dent. 1991;66(3):361-9.

20. Santoro M. Efeito terapêutico do extrato etanólico das flores de camomila em base cremosa no tratamento da dermatite das fraldas – estudo multicêntrico. Rev Paul Pediatr. 1998;16(2):69-76.

21. Aertgeerts P, Albring M, Klaschka F, Nasemann T, Patzelt-Wenczler R, Rauhut K, et al. Vergleichende prüfung von Kamillosan® Creme gegenüber steroidalen (0,25% Hydrocortison, 0,75% Fluocortinbutylester) und nichtsteroidalen (5% Bufexamac) externa in der erhaltungstherapie von ekzemerkrankungen. Z Hautkr 1985;60(3):270-7.

22. Kern E, Schmidinger M, Locker GJ, Kopp B. Management of capecitabine-induced hand-foot syndrome by local phytotherapy. Wien Med Wochenschr. 2007;157(13-14):337-42.

23. Blumenthal, M. The complete german commission E monographs – therapeutic guide to herbal medicines. Boston: American Botanical Council; 1998.

24. WHO. WHO monographs on selected medicinal plants. Genebra: World Health Organization; 1999.

25. PDR for herbal medicines. 2ª ed. Montvale: Medical Economics Company; 2000.

Received: Oct. 7th 2009
Accepted: May. 24th 2010