Cutaneous and Ocular Toxicology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/icot20

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To cite this article: Razieh Mohajerani, Farhad Shahi, Zahra Jafariazar & Minoo Afshar (2021): Efficacy of topical *Lawsonia inermis L*. (Henna) hydrogel in fluorouracil-induced hand-foot syndrome: a pilot randomized double-blind placebo-controlled clinical trial, Cutaneous and Ocular Toxicology, DOI: 10.1080/15569527.2021.1940194

To link to this article: https://doi.org/10.1080/15569527.2021.1940194

Published online: 21 Jun 2021.

CUTANEOUS AND OCULAR TOXICOLOGY
https://doi.org/10.1080/15569527.2021.1940194

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ORIGINAL ARTICLE

Efficacy of topical *Lawsonia inermis L.* (Henna) hydrogel in fluorouracil-induced hand-foot syndrome: a pilot randomized double-blind placebo-controlled clinical trial

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ABSTRACT

Purpose: Hand–foot syndrome (HFS) is a frequent dose-limiting adverse reaction of fluoropyrimidine drugs like capecitabine and 5-flourouracil (5-FU) in breast and gastrointestinal cancers. It has been shown that conventional application of *Lawsonia inermis L.* (Henna) is effective in ameliorating of the skin lesions. To increase the patient compliance, in this study we formulated a standardized topical hydrogel (H.gel) containing the hydroalcoholic extract (10%) of Henna and evaluated its clinical efficacy for the management of fluorouracil associated HFS.

Material and methods: The topical dosage form was standardized based on its Lawsone content. Eighteen patients suffering from HFS were randomized to receive H.gel and the placebo four times a day for 2 weeks. At the baseline and at the end of the trial, HFS grades were determined.

Results and conclusions: Allergic reactions following administration of H.gel were observed in one patient, while no serious adverse events occurred in the others. No statistically significant differences between two arms were observed at the baseline (p-value = 0.133), after treatment (p-value = 0.590) and grade differences (p-value = 0.193). The applied hydrogel showed less efficacy compared to the traditional method of using Henna, meaning that Lawsone may not be a good indicator for standardizing the topical dosage form.

ARTICLE HISTORY
Received 22 September 2020
Revised 19 May 2021
Accepted 1 June 2021

KEYWORDS
Lawsonia inermis; Henna; Lawsone; Hand-foot syndrome; traditional Persian medicine; capecitabine; 5-flourouracil

Introduction

Traditional medicine is an important foundation on which modern medicine has been built. Although, it has been overshadowed by modern therapeutic agents in the past few decades, plants remain the indispensable resource from which even synthetic alternatives are derived[1–2]. By combining the knowledge obtained from traditional medicinal practices with modern science, the possibilities for drug discovery and use of plants in the treatment of a wide array of conditions seems endless[1,3–7].

Lawsonia inermis L.(Henna), commonly referred to Henna, belongs to the Lythraceae family and is the sole species in the genus. Its leaves are well known as hair dye and exhibit antibacterial, anticancer, antifungal, anti-inflammatory, antioxidant and anticonvulsant activities[8–9]. It has been reported that it can accelerate the wound healing process[10] and two different clinical studies have shown that using Henna in its traditional form is effective in ameliorating Hand-foot Syndrome (HFS)[11–12], a frequent side effect of many chemotherapeutic agents including fluorouracil agents like capecitabine and 5-FU, taxanes like paclitaxel together with targeted multi-kinase inhibitors (MKIs) such as sorafenib and sunitinib[13–14]. HFS is bothersome for patients even in low grades and impacts quality of life of patients and can lead the cessation of the therapy or dose reduction, which compromise efficacy. Major symptoms of HFS are erythema, dysesthesia, pain, skin cracks, and desquamation of the palms and soles of the feet[15]. As conventional application of Henna might not be desirable by most of the patients, it is rational to introduce it to them as a suitable standardized pharmaceutical dosage form.

Various compounds, such as coumarins, flavonoids, naphthoquinones, naphthalene derivatives, triterpenoids, aliphatic constituents and phenolic glycosides, have been isolated from the leaves of *Lawsonia inermis* L[8]. However, 2-Hydroxy-1,4-naphthoquinone, generally called Lawsone, is the major constituent of Henna, which is known for its staining ability and many biological activities, including antimicrobial, macrophage stimulating, anti-inflammatory, antipyretic, analgesic and reactive oxygen species inhibitory activities[9,16]. Therefore, quantification of Lawsone could be a suitable approach to standardize the pharmaceutical dosage forms containing Henna extracts.

The aim of this study was investigation of the clinical efficacy of a standardized topical dosage form containing hydroalcoholic extract of *Lawsonia inermis* L. to reduce HFS in cancer patients who have been administrated fluoropyrimidine drugs.

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Material and methods

Reagents

Hydroalcoholic extract (ethanol, 70% v/v) of *Lawsonia inermis* L. (leaf) was supplied by Barij Essence Pharmaceutical Co (Kashan, Iran). This extract was then 6 times concentrated using an industrial rotary evaporator at 60 °C–65 °C. To prevent microbial contamination, the concentrated extract was mixed with propylene glycol (1:1, v/v). Carbomer 940 was provided by Corel Pharma Chem (Ahmedabad, India). All other inactive ingredients were of pharmaceutical grade. Gradient grade acetonitrile and methanol were provided by Ameretat Shimi Pharmaceutical Co. (Tehran, Iran). HPLC grade water was obtained through a Milli-Q system (Millipore, Milford, MA, USA) and was used to prepare all solutions. All other chemicals were of analytical grade and obtained from commercial sources.

Standardization of the hydroalcoholic extracts

Lawsone content of the concentrated hydroalcoholic extract was analysed using the chromatographic procedure reported by Gevrenova[17]. Briefly, the HPLC separation was carried out on a Younglin (Hogye, south Korea), which was equipped with YL9104 Vacuum degasser, YL9110 Quaternary pump, YL9131 Column compartment, and YL9120 UV/VIS detector set at 340 nm. The peak areas were integrated automatically by computer using an Autochro-3000 software program. A 100 μL volume of sample was introduced into a Rheodyne model 7725i injector, equipped with a 20 μL loop.

The elution was carried out on a C18 column (250 mm × 4.6 mm, 5 μm particle size) from Teknokroma (Barcelona, Spain). All analyses were performed at the column temperature of 30 ± 1 °C under isocratic elution using a solvent containing 55% methanol in a 20 mM potassium dihydrogen phosphate buffer (adjusted to pH 3.20 with orthophosphoric acid). The flow rate was 1.0 ml min^{-1}.

Placebo and H. gel formulation

The H.gel (Henna gel) and placebo gel were prepared under Good Manufacturing Practice (GMP) principles in our laboratory. Hydrogels consisted carbomer 940, glycerine, propylene glycol and triethanolamine with or without the standardized concentrated hydroalcoholic extract (10.0%). Compared to H.gel, the placebo was similar in colour; and contained caramel (2.5%). No references were found to demonstrate the effectiveness of caramel on HFS.

Trial design

The Local Ethics Committee of Azad University, Faculty of Pharmacy (No: 11994) approved this pilot, randomized, double-blind, placebo-controlled clinical trial to identify the superiority of the H.gel over placebo to relieve HFS associated with the administration of fluorouracil agents. This study complies with the Helsinki Declaration in its most recent version, and with the principles of Good Clinical Practice (GCP) guidelines. The trial was registered in Iranian Registry of Clinical Trials (IRCT registration number: IRCT2014051017643N1). All participants provided written informed consent before participating in this study.

Patient selection

Patient recruitment of this study happened at the oncology clinics of Fajr and Masih Daneshvari Hospitals (Tehran) from May 2015 to August 2016. To be eligible for this trial, patients must have been scheduled to receive capecitabine or 5-FU as part of their standard anti-cancer therapy while having grade 1–3 HFS. Patients' vital signs, routine complete blood count (CBC) and biochemistry profiles were assessed just before and during the study. Exclusion criteria included sensitivity to the herbal extracts or other related products, simultaneous administration of other anticancer agents and acute or chronic inflammatory conditions or infections of the hands or feet that would complicate safety. Patients were allowed to withdraw from the study at any stage of the investigation without any obligation.

Sample size

To the best of our knowledge, this is the first clinical trial evaluating the efficacy of a standard topical formulation of *Lawsonia inermis*. L. for the management of HFS induced by fluorouracil agents. Therefore, we defined our study as a pilot one and based on the estimated number of patients, who were referred to the aforementioned hospitals, and due to the nature of the study, which was a placebo-control clinical trial in which each patient was compared with her/himself, the sample size was considered to be 10 patients in each group.

Randomization

Twenty patients enrolled in this study and were randomly allocated to two groups. They were considered as 40 pairs of hands and feet randomly assigned to one of the two comparison groups following simple randomization procedure, coin tossing, with a 1:1 allocation ratio[18]. The "heads" were supposed as "feet: H.gel" and the "tails" were assumed as "hand: H.gel". In each case, the reverse extremity was allocated to the placebo group.

Blinding

All treatment allocations were blinded to the patients and clinical investigators and data collector, with only the data analyst having access to the drug assignments for individual patients[19].

Placebo and Herbal hydrogels were packed in separate but similar aluminium tubes (70 g) consecutively labelled based on to the allocation sequence. Each patient was given an order number and received the hydrogels in the corresponding tubes.

Interventions

All topical medications were discontinued from 2 weeks prior to the participation. No topical dosage form was allowed during the treatment course. Participants were instructed to apply one-half to 1 teaspoon of the placebo gel on one extremity and thereafter the same amount of the H.gel on the opposite extremity four times per day on initiation of the chemotherapy period continuing for 2 weeks.

Patients had permission to use standard emollients approximately 2 h after the treatment as part of standard care for HFS. They were also advised to use mild soaps to clean their hands and feet. Before and after the treatment the severity of lesions were checked, photographed and the Hand-Foot Reaction Quality of Life (HF-QoL) questionnaire was completed[20]. Using these data, syndrome was categorized according to NCI-CTCAE, v4.03. During each visit, concomitant medications were recorded.

Patients were asked to report any kind of adverse drug reactions during investigation and were excluded based on the severity of the reporting.

Study outcomes

The primary outcome was to assess the number of subjects who achieved at least one grade improvement in HFS according to (NCI-CTCATE) v 4.03 at any time during protocol treatment.

Statistical analysis

For statistical analysis of the study, sample size of 18 pairs of hands and feet were analysed. In order to evaluate the normal distribution of variables, Shapiro-Wilk test was utilized. Paired t-test and Mann-Whitney U statistic Test were used to compare quantitative variables with normal distribution and Non-normally distributed quantitative variables, respectively. These tests were applied to evaluate a significant difference between the placebo and the H.gel treatment groups at the baseline (before treatment), secondary grade (after treatment) and grade differences between before and after intervention. The significance level was defined as p values ≤ 0.05 and SigmaPlot v12.0 was used for analyses of the data.

Results

Eighteen patients were included in the study. Nine patients, 5 women and 4 men with the age ranged between 44 and 73 years, followed the study protocol and applied H.gel and placebo hydrogels regularly, four times daily. H.gel contained 0.62 mg Lawsone in each 100 g. Nine patients did not complete the study protocol for various reasons; one patient was allergic to the topical herbal formulation and therefore was excluded from the study. The other one was deceased. Other reasons were discontinuation of chemotherapy and wrong usage of the hydrogels. Patient flow in this study is illustrated in a CONSORT diagram (Figure 1).

The efficacy results were evaluated after 2 weeks of intervention. As it was earlier mentioned, allergic reactions to H.gel was observed in one patient. However, H.gel was well tolerated and there were no serious adverse effects in the other patients. There was no unusual report on patients' vital signs, CBC, and biochemistry profiles. Paired t-test failed to find any significant difference between the placebo and the H.gel treatment groups at the baseline (p values $= 0.133$), which emphasizes randomness of the study. Four (45%) out of 9 patients who completed the study showed at least one grade improvements in the treatment arm, while the placebo arm was either the same or worsened. In two patients both arms got better, while in the rest of the patients either no improvements were achieved ($n = 2$), or the symptoms got even worse in H.gel arm ($n = 1$). Statistical analysis showed no significant differences when secondary grade (p values $= 0.590$) and grade differences (p values $= 0.193$) were analysed. Patients' demographic data and determined HFS grades before and after interventions are summarized in Table 1.

Discussion and conclusion

The exact pathogenesis of HFS is poorly understood. The severity and onset of skin symptoms show a high interindividual variability. Other important factors in this respect are the type of chemotherapeutic agent and its dosage. Dose modification, postponement, or even discontinuation of chemotherapy can be necessary since most intervention applied so far showed no satisfactory therapeutic effects[13]. Cyclooxygenase (COX) inhibitors like celecoxib have shown the most promising effects in a few studies. However, many trials have currently been stopped because of data suggesting an increased risk of cardiovascular risks[21].

Capecitabine, an oral fluoropyrimidine, designed to mimic a continuous intravenous infusion of 5-FU, is the most widely used drug for treating breast and colorectal cancers. Capecitabine is absorbed as an intact molecule through the intestinal mucosa and metabolized (mainly in tumour cells) into active 5-FU by thymidine phosphorylase. HFS is one of the most common adverse events occurring in patients who take continuous infusion of 5-FU and capecitabine, with an incidence of $\sim$ 60% in initial clinical trials[22].

There are several theories about the pathomechanism of fluorouracil-induced HFS. As the drug or its metabolites can induce oxidative processes and formation of free radicals in the skin, their accumulation as well as excretion through the sweat glands may cause cytotoxic effects on skin sites with increased density of sweat glands, such as the palmar and plantar areas[23]. Another theory addressing capecitabine-associated HFS is that keratinocytes in the skin might have upgraded levels of the enzyme thymidine phosphorylase. This leads to metabolites accumulation, resulting in a COX inflammatory-type reaction and increased likelihood of developing HFS[13]. Moreover, since 5-FU is known to cause vasospasm and has potent anti-angiogenic properties, this vascular targeting may also be involved in the mechanisms of HFS related to infusional 5- FU and capecitabine, which

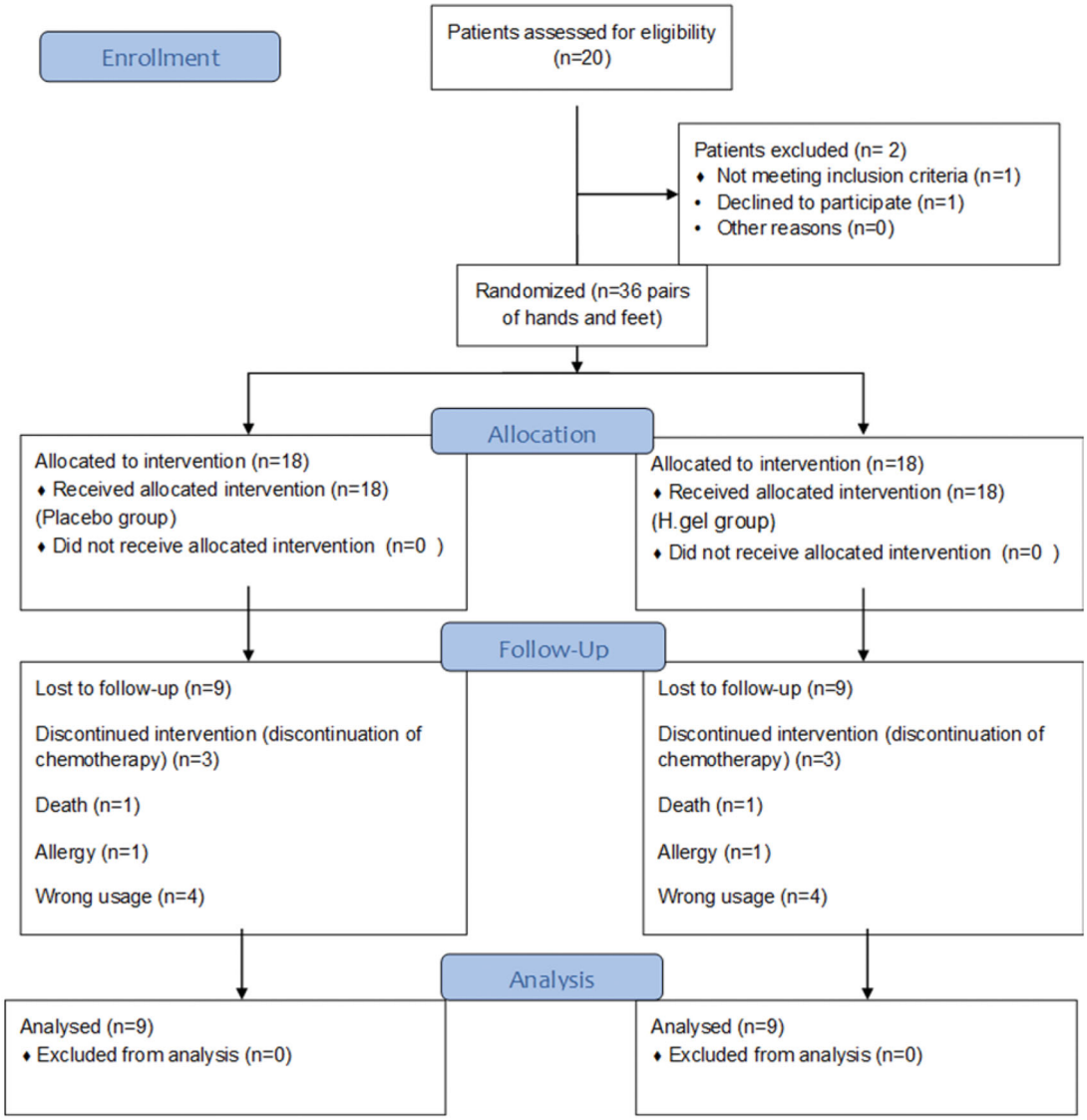

Figure 1. Flow diagram of the trial.

Table 1. Patients' demographic data and determined HFS grades.

				HFS grade (placebo)		HFS grade (drug)		Grade differences	
Patient No.	Age	Gender	Drug	Before	After	Before	After	Placebo	Drug
1	49	Male	CAP*	1	1	2	0	0	−2
2	50	Female	5-FU	1	2	3	0	1	−3
3	67	Male	5-FU	2	3	3	1	1	−2
4	54	Male	CAP	2	1	2	2	−1	0
5	47	Female	CAP	1	0	1	1	−1	0
6	45	Male	CAP	1	0	2	0	−1	−2
7	73	Female	CAP	1	1	2	1	0	−1
8	56	Female	CAP	2	1	2	1	−1	−1
9	44	Female	CAP	1	1	0	2	0	2

*Capecitabine.
When HFS grades before intervention (placebo and drug) were compared (p values = 0.133).
When HFS grades after intervention (placebo and drug) were compared (p values = 0.590).
When grade differences were compared (p values = 0.193).

could impair wound healing in dermal capillary endothelium[21].

One proposed remedy for this side effect is blocking the thymidine phosphorylase activity in skin[24]. Another strategy to protect skin from the destructive effects of free radical formation after systemic chemotherapy would be application of highly concentrated antioxidants and anti-inflammatory agents[23]. This was confirmed by our previous research administrating a standardized polyherbal hydrogel containing *Calendula officinalis* L., *Matricaria recutita* L. and *Salvia officinalis* L. with high antioxidant and anti-inflammatory activity to cancer patients, who developed symptoms of HFS while

receiving fluorouracil agents. In the mentioned work, of 21 patients who completed the study, 57% and 14% showed one and two HFS grade improvements, respectively[25].

Lawsonia inermis L. is another medicinal plant with proven anti-inflammatory and antioxidant effects. However, this natural product comprises a mixture of numerous compounds most of which are poorly characterized both chemically and functionally. The responsible pigment for the red colour after Henna application on skin, is Lawsone, constituting 1–2% of the leaves[9,26].

Lozza et al. demonstrated that a cream containing small amounts of Lawsone had clinical potential for treatment of skin disorders characterized by hyperproliferation and inflammation[26]. Moreover, Adeli-Sardou et al. showed that Lawsone incorporation in the core of polycaprolactone/gelatin electrospun nanofibers could be used as a wound dressing patch in medicine[27]. In another study, topically administration of an ointment containing hydroalcoholic extract of Henna accelerated excisional wound healing process by reducing tissue inflammation and amplifying glucose uptake in Wistar rats[10]. Yucel et al. recommended conventional application of Henna dye to 10 cancer patients with HFS. Surprisingly, complete response was seen in four patients with grade 3 and all patients ($n = 4$) with grade 2 of HFS, while two patients with grade 3 improved to grade 1 (100% efficacy)[12]. In another case report traditional usage of Henna relieved the symptoms in a patient with pancreatic cancer receiving capecitabine[11]. Also, Ansari et al. showed that Alpha® Ointment (Containing Natural Henna with Lawsone as active ingredient) was more effective than hydrocortisone cream (1%) on the healing of radiation-induced dermatitis[28,29].

Considering the above studies, a topical dosage form containing hydroalcoholic extract of Henna which has been standardized by Lawsone could be beneficial for the management of HFS. Although statistical analysis of this preliminary results showed lower efficacy than those of conventional application of Henna[11–12], out of nine subjects finished this study, three patients showed complete response, while two other patients achieved at least one grade improvement after application of H.gel (Table 1). It is worth mentioning that in this work hydroalcoholic extract obtained from different suppliers were analysed and the one with the highest amount of Lawsone was selected. This means that compounds other than Lawsone are effective in ameliorating of the skin lesions and standardising the finished product just based on its Lawsone content is not a suitable approach. These results are in good agreement with the docking and virtual screening study, performed to find the lead compounds in Henna library against thymidine phosphorylase. According to this study diosmetin-3′-O-β-D-glucopyranoside and monoglycosylated naphthalene were respectively the most potent phytochemicals and chemical groups. Flavonoid-like compounds with appropriate interaction energy were also considered as the most probable inhibitors[30]. Parallelly, another double-blind randomized placebo controlled clinical trial reported the efficacy of a topical formulation of henna standardized based on its total phenolic content in contact dermatitis in patients using prosthesis[31].

On the other hand, Lozza et al. showed that the worldwide used natural product Henna and its pigment Lawsone, are sensed by aryl hydrocarbon receptor (AhR), a receptor which activates the expression of genes encoding detoxification enzymes. Consequently, Henna and Lawsone impact skin homeostasis. This fact that different AhR ligands may act as "double-edged sword" and pose harm or benefit depending on the structure and pathophysiological context[26,32], might be an explanation for observing allergic reactions in one subject and worsened condition in the other one (Table 1).

In conclusion, the applied topical hydrogel containing hydroalcoholic extract of Henna (10%), which was standardized base on its Lawsone content had lower efficacy compared to its traditional application for the management of fluorouracil-induced HFS. Moreover, allergic reactions were observed in one patient.

Study limitations

The major limitation to our study was the short (2 weeks) follow-up, which was chosen because of the type of oral chemotherapy regimen. However, it would be interesting to extend the follow-up period in future studies.

Acknowledgements

The authors sincerely thank Dr. Alamdar Ashnagar (Pasteur Institute of Iran) and Poursina Pharmaceutical Co. for donating the Lawsone standard and inactive ingredients, respectively. We also thank the patients for their participation. The presented data were abstracted from a Pharm.D. thesis of Razieh Nohajerani. No specific fund was provided by any other sources.

Author contributions

Minoo Afshar contributed in conception, design and data collection, statistical analysis, supervision and drafting of the manuscript. Razieh Mohajerani contributed in data collection, statistical analysis and drafting of the manuscript. Farhad Shahi helped in patient recruitment, clinical evaluation, and data collection and Zahra Jafariazar contributed in data collection. All authors approved the final version for submission.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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