

## Pure Omental Lipid (P.O.L.) for the Treatment of Fragile Skin: A Pharmacological and Clinical Review

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**Conflict-of-interest statement:** The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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Received: May 14, 2018

Revised: May 28, 2018

Accepted: May 31, 2018

Published online: October 1, 2018

### ABSTRACT

The omentum is a large peritoneal fold. It begins at the stomach and extends down-wards to cover the abdominal organs. It serves a primarily protective role, especially in defending against infective agents and to promote tissue reparation after injuries. The omentum is characterized by extensive vascularization, sign of a metabolically active environment. Furthermore, omentum is the tissue with the highest production of vascular endothelial growth factor (VEGF) in the body. The lipids contained in this tissue carry out very important activities for the organism, and the presence of neutral glycerides, phospholipids, glycolipids, and gangliosides suggests the potential usefulness of heterologous omental lipid fractions in dermatology. Omentum stimulates vascular proliferation, therefore is possible to

speculate its topical use in therapies designed to regenerate skin tissue in clinical conditions characterized by fragile skin. Dermatological products containing purified omental lipids are commercially available. Pure porcine omental lipids (P.O.L.) could be use in topical products in different textures (cream, fluid, emulsions, and cleanser) and at different concentrations (10-25%) for the treatment of fragile skin or other skin conditions at risk of ulcer formation (the so-called dermatoporosis of the elderly, severe skin xerosis in diabetic subjects, skin at risk of pressure ulcers). This review summarizes the pharmacological rationale of purified porcine omental lipids in topical formulations for the use in fragile skin conditions and the clinical efficacy data available in the scientific literature. Several clinical controlled trials conducted in 320 subjects have shown that topical porcine purified omental lipids are able to prevent the formation of pressure ulcers in hospitalized high-risk subjects, to improve wound healing process, to normalize skin hydration in diabetic subjects with moderate-severe skin xerosis and to improve clinical evolution of diabetic foot. Therefore, purified omental lipid could be an effective tool for the management of fragile skin and the skin at high risk of ulcer formation.

**Key words:** Purified Omental Lipids; Fragile skin; Skin ulcer; Xerosis; Diabetic foot

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Puviani M, Milani M. Pure Omental Lipid (P.O.L.) for the Treatment of Fragile Skin: A Pharmacological and Clinical Review. *Journal of Dermatological Research* 2018; **3(1)**: 139-143 Available from: URL: <http://www.ghrnet.org/index.php/jdr/article/view/2335>

### INTRODUCTION: ANATOMY AND PHYSIOLOGY OF OMENTUM

The omentum is a large peritoneal fold<sup>[1]</sup>. It begins at the stomach and extends down-wards to cover the abdominal organs. It serves a primarily protective role, especially in defending against infective agents<sup>[2]</sup>. It is often compared to a closed sack which adheres on one side to the abdominal wall and on the other to the walls of various organs, thus forming the parietal and visceral layers respectively.

The omentum from an anatomical view is divided in two parts: the large and the small omentum<sup>[3]</sup>. The large omentum covers the loops of the small intestine, extending to the pubis. The small omentum, divided into two portions (hepatoduodenal ligament and hepatogastric ligament), covers the hepatic lobe and extends from the first tract of the duodenum to the small curve of the stomach. The omentum is characterized by extensive vascularization<sup>[4]</sup>, sign of a metabolically active environment. In addition to its protective function and contribution to visceral mobility and equilibrium, the large omentum also contains a considerable quantity of adipose tissue<sup>[5]</sup>. The lipids contained in this tissue carry out very important activities for the organism, and the presence of neutral glycerides, phospholipids, glycolipids, and gangliosides suggest the potential usefulness of heterologous omental lipid fractions in dermatology<sup>[6]</sup>. The large omentum is very rich in lipids and neutral glycerides, phospholipids, glycolipids, gangliosides and ceramides<sup>[7]</sup>. Omentum can stimulate *in vivo* tissue neoangiogenic processes which are very much involved in reparative functions<sup>[8]</sup>. Early observations regarding the omentum's ability to stimulate vascular proliferation lead investigators to hypothesize its use in strategic therapies with the aim to regenerate tissues or prevent ischemic conditions<sup>[9]</sup>. Given the importance of regulating angiogenic processes in a wide variety of physiological and pathological conditions, much interest was placed in understanding the mechanisms responsible for the omentum's positive contribution to wound healing and revascularization of ischemic tissue<sup>[10,11]</sup>. Amongst the various polypeptide growth factors with angiogenic activity present in the omentum there is the VEGF (Vascular Endothelial Growth Factor)<sup>[12]</sup>. Thirty years ago, Goldsmith *et al.*<sup>[13]</sup> suggested the existence of a vascular-stimulating factor which appeared to be extracted along with the omentum's lipids component given that the lipid component reproduced the angiogenic properties of the entire omentum. It was only recently, however, that the numerous polypeptide growth factors with angiogenic activity were discovered, and that they could be identified and detected in the omental tissue<sup>[14]</sup>. Experiments carried out in various rat tissues to measure the Vascular Endothelial Growth Factor (VEGF) have demonstrated that the omentum is in fact the tissue with the highest concentration of VEGF<sup>[15]</sup>. Omental VEGF is produced by adipocytes in a constitutive (i.e. continuous) manner<sup>[16]</sup>. In addition, pure omental lipid extracts can completely reproduce the angiogenic activity of the entire organ<sup>[17]</sup>. The omentum's lipid component can be extracted using an organic solvent, or a mixture of organic solvents (e.g. hexane or methanol). The lipid extract obtained from porcine omentum can be separated to facilitate identification of its main components<sup>[18]</sup>. Omental lipids are made up of 97% non-polar neutral triglycerides containing fatty acid types (palmitic acid; stearic acid; oleic acid and linoleic acid)<sup>[19]</sup>. Small quantities of free fatty acids, cholesterol, and di- and monoglycerides are also present. The remaining 3%, separated by using other solvents, contains phospholipids (phosphatidylcholine, sphingomyelin, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol), neutral glycolipids (mainly di-, tri-, and tetraacylceramides), glycolipids and gangliosides.

## THE PURE OMENTAL LIPIDS (P.O.L) IN DERMATOLOGY: PHARMACOLOGICAL RATIONALE

The potential beneficial effects of applying topically the lipids produced in the omentum's adipocytes to areas suffering from pathological processes are supported by following properties<sup>[20]</sup>: (1) reparative effect on epithelial cell membrane; (2) increase in microcirculation

with consequent increase in blood flow to the affected area; (3) improvement of skin barrier function<sup>[21]</sup>. The evidences of these molecular mechanisms come from studies undertaken in a variety of different areas, starting with the findings regarding the stimulation of new vessel production in various tissues<sup>[22]</sup>. At the beginning of the 20<sup>th</sup> century, long before the discoveries made in the fields of biochemistry and molecular biology, some studies were published regarding the possibility of revascularizing ischemic tissues using omentum<sup>[23]</sup>. In the early 1900s omentum was already being used to revascularize ischemic tissues<sup>[24]</sup>. De Renzi for example, experimented on spleen tissue, while other authors studied the possibility of establishing collateral vascular circuits in the presence of heart ischemia; these collateral circuits were in part created through surgical interventions called "cardio-omentopexi"<sup>[25]</sup>. Porcine omental lipids extract possesses considerable angiogenic activity as measured by the Folkman and Cotran method<sup>[26]</sup>. The angiogenic activity of the lipid fraction contained in omentum was also observed in a study conducted on animals whereby an omental extract was injected into muscles adjacent to a surgical wound<sup>[27]</sup>. An increase in vascular perfusion, evaluated with <sup>99</sup>Tc radiolabeled red blood cells, was also observed. Finally, experiments were done to evaluate the ability of porcine omental lipid extracts to stimulate *in vitro* proliferation of human endothelial cells obtained from umbilical cords<sup>[28]</sup>. The results were positive even if lower than those obtained adding bovine endothelial growth factor (EGF). Table 1 summarizes the pharmacological actions of pure omental lipids extracts. Heterologous purified omental lipids of porcine origin have proved to be of great interest for topical use in dermatology as ingredients in varying percentages in creams, emulsions, and cleansers. Numerous reports in scientific literature cite the topical use of pure porcine omental lipids in the management of various skin conditions<sup>[29]</sup>. The omentum has shown itself to be a tissue with great metabolic potential which is able to synthesize a large quantity of growth molecules and factors, amongst which the recently-identified VEGF. The numerous experiments conducted on animals and the surgical interventions developed for humans have demonstrated the possibility of revascularizing ischemic tissues by using omentum transplants or apposition<sup>[30]</sup>. The therapeutic fields with the brightest prospects are plastic and reconstructive surgery and neurosurgery. It has also been amply demonstrated that the omentum's angiogenic properties are contained in the purified lipid fraction which can be easily extracted. Porcine omentum is an ideal source for such substances as it can provide large quantities of angiogenic and safe purified extract<sup>[31]</sup>. Porcine omentum is rich in ceramides and phospholipids. Local treatment with heterologous pure omental lipids has in fact provided significant improvement in skin microcirculation<sup>[32]</sup>, even in the presence of severe local conditions (vascular ulcers, decubitus ulcers, diabetic foot). Purified Omental lipid extract in concentration ranging from 10% to 25% has been used in several topical products (cream, fluid detergent and emulsion and lips stick) indicated in the treatment of skin fragile and prevention of skin lesions such as bed (pressure) sores. The potential mechanisms of porcine pure omental lipids in the prevention of pressure ulcers could be linked also to the presence of high amount of stearic acid and ceramides. Topical

**Table 1** Pharmacological effects of topically applied Pure Omental Lipids.

Pharmacological Effects of omentum's lipids extract	Angiogenic activity on rabbit cornea
	Increased proliferation and migration of endothelial cells and keratinocytes
	Increase in skin flap survival in experimental animal
	Increase turnover of basal keratinocytes
	Acceleration of wound healing

stearic acid could be beneficial in the prevention of pressure ulcer because it can: (1) improve the epidermis's resistance; (2) facilitate the repair of epidermal damage produced by a prolonged pressure; and (3) restore/improve the microcirculation and counteract the negative effects of oxygen radicals produced during reactive hyperemia which are caused by periods of prolonged pressure<sup>[33]</sup>. Porcine pure omental lipids contain high amount of ceramide compounds<sup>[31]</sup>. Shear forces and skin dryness play important roles in persistent erythema and pressure ulcer development<sup>[34]</sup>. The ceramides contained in pure omental lipids could significantly improve the skin hydration of treated areas and reducing, at the same time, the shear forces.

## PURE OMENTAL LIPIDS IN PREVENTION OF PRESSURE ULCERS

Bertoli *et al.*<sup>[35]</sup> evaluated the effectiveness of such products in preventing pressure ulcers during a study conducted on 210 bedridden patients. Twenty-two of the patients presented decubitus ulcers, 45 local dystrophies, and 143 apparently unaffected skin in which the medication was applied for prevention. The skin areas exposed to compression were cleansed 2-3 times daily with a cleansing solution containing porcine pure omental lipids (10%). After cleansing, a cream based on porcine pure omental lipids (25%) was applied. In subjects with pressure ulcers at baseline, the cream was applied to surrounding tissues. The products were applied for 2-6 weeks depending on clinical evolution (average treatment period: 3.5 weeks). During the study, signs and symptoms such as erythema, edema, de-epithelization, maceration and pain were rated according to the following scale: sign/symptom absent = 0, mild = 1, moderate = 2, intense = 3, very intense = 4. After treatment, 144 patients presented no skin lesions or pressure ulcers, two patients (10%) with ulcers at baseline went into complete remission of the lesions and 63 patients showed marked improvement in ulcers and local dystrophy. The overall improvement obtained was statistically significant ( $p < 0.01$ ) and during treatment and afterwards there were no signs of local intolerance. Erythema score was reduced by 63% (from 2.0 to 0.75) after treatment with pure omental lipids. Similar significant improvements were documented for edema, pain, and skin maceration. In another study Lisi *et al.*<sup>[36]</sup> evaluated the efficacy and tolerability of pure omental lipids 25% cream and 10% detergent, both applied twice daily, in patients who were at risk of development of decubitus ulcers ( $N = 20$ ), and in patients with chronic venous insufficiency of the lower limbs ( $N = 20$ ). The products were applied for 6 consecutive weeks. The clinical efficacy was evaluated good or very good in 85% of the treated subjects. No progression or new pressure ulcers were observed. As discussed before, the clinical efficacy of porcine pure omental lipids in preventing pressure ulcers demonstrated in these two trials, could be in part due to the presence of a high concentration of stearic acid in the composition of pure omental lipids. Topical products containing stearic acid have shown to be able to prevent pressure ulcer development in high risk subjects<sup>[37]</sup>.

## PURE OMENTAL LIPIDS IN WOUND HEALING

The effect of heterologous purified omental lipids on wound healing was studied on healthy volunteers who agreed to be subjected to a skin punch-biopsy<sup>[38]</sup>. Measurements were made by evaluating the healing time using a planimetric technique with ultrasonographic images. Fifteen subjects were enrolled in the study, each of which underwent four biopsies with 4mm diameter punches, two on the right para-sacral area and two on the left para-sacral area. One of the

wounds made by the biopsies on each side was treated with a cream containing heterologous purified omental lipids (25%) while the other on each side was used as control. The cream was applied once daily for 28 days even after the wounds had healed. Wounds' diameter and depth measurements were made by mean of a micrometer and an ultrasound technique, respectively, on the first day (baseline) and then at 2, 3, 7, 10, 14, 21 and 28 days. Efficacy was evaluated by recording the number of days necessary to achieve wound complete healing and by evaluating the characteristics of the healing (no scar, pale pink scar, bright pink scar, red scar). Tolerability was also measured by monitoring adverse reactions. All parameters were examined based on validated statistical techniques. The results showed that, especially from the seventh day onwards, the wounds treated with the cream containing heterologous purified omental lipids healed significantly more quickly in comparison with the control wounds. The average time necessary for the healing of the treated wounds was 21.2 days as opposed to 25.1 days for the control wounds ( $p = 0.001$ ), representing a -16% reduction in healing time. Moreover, it was observed that healing time of the control wounds was directly related to the age of the patients: the older the patient, the slower the healing. Such a correlation was not found with the wounds treated with the pure omental lipids. Based on the results, the cream containing heterologous pure omental lipids was thus shown to accelerate wound healing. In addition, it is interesting to note that the evolution of the healing was in many ways like experimental observations made on the Epidermal Growth Factor's wound healing activity.

## PURE OMENTAL LIPIDS IN DIABETIC SKIN

In a study conducted by Federici and Milani<sup>[39]</sup> the authors evaluated the efficacy of topical 25% concentrated pure omental lipids product (P.O.L. cream; Difa Cooper, Italy) in Type 2 diabetic patients with (YES-C) or without (NO-C) vascular or neurological complications in comparison with non-treated healthy volunteers. Presence of vascular or neurological ulcers was an exclusion criterion. They assessed the efficacy of POL-C on skin hydration and skin integrity in a prospective, evaluator-blinded controlled study in 30 type II diabetic patients (YES-C:  $n = 15$ ) (NO-C:  $n = 15$ ), aged 40-75 years, treated with POL-C twice daily for 3 months. Ten subjects, matched for age and sex, without diabetes, formed the control group. Primary outcomes were the Dryness Area Severity Index (DASI) Score evaluating xerosis, erythema, scaling and skin fissuration (minimum-maximum score values: 4-20) and Patient-Assessed Skin Score (PASS) evaluating dryness, itching and irritation (minimum-maximum score values: 3-15). DASI score was evaluated at baseline, after 1 and 3 months by an investigator unaware of treatment allocation (patients or controls) and unaware of the type of diabetes (with or without complications). PASS scores were collected at the same study times in YES-C and NO-C only groups. Results: One subject (YES-C group) dropped out prematurely from the trial. At baseline mean (SD) DASI score was 7.4 (2.5) in YES-C group, 4.9 (0.7) in NO-C group and 5.0 (0.7) in control subjects. DASI score in YES-C was significantly higher in comparison with NO-C and control groups. POL induced significantly DASI score reductions in both diabetic patients' groups at month 1 and month 3 ( $p < 0.001$ ) in comparison with baseline values. At month 3, DASI score was 4.5 (1.5) in YES-C and 4.1 (0.3) in NO-C. PASS score was significant reduced in comparison with baseline in YES-C group (from 5.2 to 3.5;  $p = 0.02$ ) and in NO-C group (from 3.7 to 3.0;  $p = 0.05$ ). The product was well tolerated. In diabetic subjects, skin xerosis is significantly worse in the presence of vascular or neuropathy

**Table 2** Clinical Studies with Pure Omental Lipids.

First Author	Clinical Setting	Subjects evaluated	Main Results
Bertoli	High risk pressure ulcers	210	P.O.L was effective in the prevention of new pressure ulcers. Clinical Improvement was observed in 85% of treated subjects.
Lisi	Venous insufficiency	40	P.O.L induced a significant Clinical improvement in 85% of treated subjects.
NA	Wound Healing	15	Significant increment of healing process speed (-16%)
Rinaldi	Diabetic foot	25	Significant improvement of foot ulcers evolution. Significant improvement of microcirculation (+20%) in comparison with standard cream.
Milani	Xerosis in diabetic subjects	30	Significant improvement of DASI and PASS score vs. controls.

in comparison with diabetic subjects without complication and in comparison, with matched healthy control subjects. The use of pure omental lipids cream improves and normalizes skin xerosis both assessed by the investigator or by the subject with a clinical effect correlated with the baseline level of skin dryness severity. Application of pure omental lipids cream increases skin hydration and relieves the condition of skin dryness in Type 2 diabetic patients with or without complications. The effectiveness of a cream containing 25% heterologous purified omental lipids in promoting the healing of difficult-to-manage diabetic foot lesions was also studied<sup>[40]</sup>. Twenty-five patients were enrolled, all of whom were suffering from polyneuropathic ulcers and widespread skin dystrophy caused by diabetes, in a controlled left-vs-right side study design. The skin areas surrounding the necrotic tissues were treated with 25% pure omental lipids cream on the other side, used as a control, with hyaluronic acid. Both products were applied twice daily for 30 consecutive days. At the end of the study period, evaluation of TEWL (Trans epidermal water loss), sebometry, corneometry, and pH values demonstrated significant improvement on the POL cream treated sites with clinical and instrumental improvement greater than the control site where hyaluronic acid was applied. Pure omental lipids cream treatment, in addition, improved also skin microcirculation (+20%) assessed by laser-Doppler velocimetry. This improvement was not observed in the skin area treated with hyaluronic acid. In this trial, P.O.L cream was also effective in subjects at risk of pressure ulcer. The product was well tolerated.

## CONCLUSION

Purified omental lipids are rich in substances promoting skin reparative processes. This characteristic makes topical products based on these compounds suitable for the treatment of fragile skin and the skin at risk of damage. Several clinical controlled trials conducted in 320 subjects (Table 2) have shown that topical purified omental lipids are able to prevent the formation of pressure ulcers in hospitalized bedridden high-risk subjects, to improve wound healing process, to normalize skin hydration in diabetic subjects with moderate-severe skin xerosis and to improve microcirculation and the clinical evolution of diabetic foot. Therefore, purified omental lipid could be an effective tool for the management of fragile skin and the skin at risk of ulcer formation.

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