

ULCERA PIAGA FISTOLA RAGADE CICATRIZZAZIONE PER SECONDA INTENZIONE MALATTIA EMORROIDARIA

OZONIA 10® crema dermatologica al 10% di olio vegetale ozonizzato, titolata e standardizzata in OZONIDI.

POSOLOGIA E MODALITA' DI APPLICAZIONE

A seconda del tipo di azione da privilegiare, somministrare la crema due o più volte al giorno (antisettica) o una volta al giorno/ogni due giorni (stimolante la riparazione tissutale).

La crema è compatibile con le medicazioni secondarie per la gestione dell'ambiente lesionale.

OZONOTERAPIA CUTANEA RIPARAZIONE E OMEOSTASI TESSUTALE



A 903885616

**OZONIDI E LIPOPEROSSIDI DERIVATI DALL'OZONIZZAZIONE
DI OLIO VEGETALE POLINSATURO**

SCHEDA TECNICA

DENOMINAZIONE DI VENDITA e FORMA

OZONIA 10[®] crema dermatologica al 10% di olio vegetale polinsaturo ozonizzato.

FORMATO E PREZZO AL PUBBLICO CONSIGLIATO

Tubo da 25 ml ad € 12,00.

INGREDIENTI FUNZIONALI ATTIVI

Ozonidi secondari e terziari, Lipoperossidi.

AZIONI CARATTERISTICHE DEGLI OZONIDI

RIPARATIVA TESSUTALE:

- stimolazione nella risposta antiossidante cellulare.
- Stimolazione nella produzione energetica cellulare (aumento nella sintesi di ATP e di conseguenza dello stoccaggio di Fosfocreatina).
- Regolazione dell'infiammazione, produzione di fibroblasti, neo angiogenesi, sintesi e rimodellamento della matrice cellulare.
- Riequilibrio del film idrolipidico cutaneo, sebonormalizzazione.

ANTIBIOTICA:

- (distruzione della parete cellulare): verso Staphilococcus Aureus, Pseudomonas Aeruginosa (funzionalità simile alla neomicina), Staphylococcus Epidermidis, Salmonella Typhimurium, Streptococcus Pyogenes, Escherichia Coli, Proteus Mirabilis, Gardenella Vaginalis, Candida Albicans, Tinea Pedis (funzionalità simile al ketoconazolo), Tricomonas Vaginalis, Giardia.

VIRUSTATICA:

- (inattivazione dei recettori cellulari presenti sulla capsula virale): verso Herpes Simplex (labialis, genitalis), Herpes Zoster, Citomegalovirus,

Parvovirus, Papilloma Virus.

ANESTETICA e ANTIFLOGISTICA:

- ossidazione reversibile delle neurofibrille nocicettive; inibizione della cascata prostaglandinica, azione antitrombotica ed attivante il microcircolo.

EFFETTI COLLATERALI

Il prodotto non ha effetti collaterali a parte una possibile sensazione di calore o di lieve bruciore al primo contatto con l'area trattata: in questo caso è consigliabile applicare la crema fredda, dopo averla conservata in frigorifero. Non sono noti fenomeni di ipersensibilità od allergia. In ogni caso un eccessivo bruciore o prurito rende opportuna l'interruzione del trattamento ed un consulto col Medico.

CONTROINDICAZIONI

Allergia al preparato e ai suoi componenti.

GARANZIE, REQUISITI DI QUALITA', CARATTERISTICHE DEL PRODOTTO

OZONIA 10 si è dimostrata essere un prodotto non irritante (valutazione del potere irritante mediante patch test occlusivo - RIF. 1/96). L'ozono è un gas dall'odore pungente, che nel prodotto è stato tamponato grazie ad un sofisticato metodo produttivo: esso è pertanto espressione della genuinità e dell'efficacia del principio attivo.

CONSERVAZIONE

Conservare il prodotto a temperature non superiori a 22°C.

INDICAZIONI D'USO

Nell'ulcera cutanea:

adiuvante dei processi di cicatrizzazione nelle ulcere degli arti inferiori, diabetiche, da pressione, vasculitiche, traumatiche, post-attiniche; escoriazioni, abrasioni, atrofie, ipercheratosi ulcerate.

In dermatologia:

adiuvante negli stati distrofici cutanei (secchezza, fissurazione, desquamazione), acne, foruncolosi, follicoliti, micosi, ustioni, radiodermi, "dermatite da pannolino", lichen simplex cronico, dermatite seborroica, psoriasi, eczema.

In uro-ginecologia:

adiuvante nel trattamento delle vulvovaginiti, balanopostiti, condilomatosi.

In colonproctologia:

- adjuvante nel trattamento sintomatico della patologia del canale anale: malattia emorroidaria, ragade anale, anite, anodermite, criptite anale, ano umido, proctiti.

- Adjuvante nel trattamento post-operatorio della chirurgia anorettale: patologia endocanalare operata (emorroidectomia, fistulectomia, mucosectomie), escissioni locali di lesioni anorettali, anastomosi coloanali.

- Adjuvante nel trattamento antisettico ed antiflogistico delle cavità residue dopo chirurgia della parete addominale: ferite chirurgiche deiscienti con esposizione del sottocute, infezioni della parete dopo chirurgia addominale, cavità residue dopo chiusura di stomia.

- Cicatrizzazione per seconda intenzione.

EFFICACIA BIOCIDA DI OZONIA 10®

Tabella del valore di riduzione microbica (%) su diversi microrganismi.

Tempo h	Batteri			Lieviti		Protozoi	
	E. coli	Proteus m.	S. aureus	C. albic.	Asp. niger	Trichom. vag.	Trichophyton m.
2	91,25	92,94	91,07	86,00	87,50	0,00	0,00
4	90,63	94,12	96,43	95,00	96,42	36,00	0,00
24	99,83	99,83	99,93	99,64	99,55	90,00	28,00
48	99,94	99,94	100,00	99,99	99,99	98,00	94,80
7 giorni	100,00	100,00	100,00	100,00	100,00	100,00	99,00
inoculo iniziale	1,6x10 ⁶	1,7x10 ⁶	2,8x10 ⁶	1,0x10 ⁵	1,2x10 ⁵	1,0x10 ⁵	1,0x10 ⁵

Report Regressione Lineare / D-Value Method

Università degli Studi di Ferrara – Dipartimento di Medicina Sperimentale e Diagnostica

Sezione di Microbiologia – Ferrara

Ferrara, 10/03/2010

OZONIA 10® & LESIONE CUTANEA CRONICA

Manualetto Pratico per l'Operatore Professionale

OZONIA 10® contiene il 10% di olio vegetale ozonizzato, quantità bilanciata a mediare l'azione antinfettiva locale e l'azione stimolante la riparazione tessutale della crema.

Nelle indicazioni seguenti Ozonia 10 è da intendersi come **fattore potenziante** l'efficacia dei protocolli terapeutici accettati.

Indicazioni:

Ulcere Cutanee con ipossia e/o infezione alla base della cronicizzazione della lesione, come nelle ulcere arteriose, ulcere venose, ulcere vasculitiche, ulcere diabetiche (neuroischemiche-neuropatiche), ulcere da pressione (decubiti-UdP).

Procedura Operativa:

- 1) detersione con Soluzione Fisiologica, Ringer Lattato (o altro detergente secondo i propri protocolli operativi di struttura);
- 2) asciugatura della lesione con modalità sterile;
- 3) applicazione di un sottile strato di circa 1-2 mm di Ozonia 10 anche con l'ausilio di una spatola sterile (in modo uniforme);
- 4) ricoprire la medicazione (primaria) così eseguita con una medicazione secondaria tradizionale (garza grassa) o avanzata diversa a seconda del tipo di lesione/fase in trattamento.

Si spongono a seguire le condizioni e relativa procedura operativa:

- Scala di colore **NERO** (lesione con necrosi secca-coriacea):
usare preferibilmente Ozonia 10 in combinazione con med. secondaria:
- MED. AVANZATE: film di poliuretano, idrocolloide, poliacrilati, idrogeli in placca;
- MED. TRADIZIONALE: garze umide o paraffinate/vasellate.
- Scala di colore **GIALLO** (lesione con necrosi umida-slough-fibrinoide):
usare preferibilmente Ozonia 10 in combinazione con med. secondaria:
- MED. AVANZATE: schiuma di P.U., idrofibre (alginati, carbosimetilcellulosa CMC), anche contenenti Argento Antimicrobico;
- MED. TRADIZIONALI: garze grasse/umide o saline (ipertoniche i T.N.T.);
- Scala colore **VERDE** (lesione INFETTA): usare Ozonia 10 preferibilmente in associazione a med. secondaria:
- MED. AVANZATE: idrofibre (alginati, CMC), anche contenenti Argento Antimicrobico;
- MED. TRADIZIONALI: garza grassa/umida, ipertonica salina.
- Scala colore **ROSSO** (lesione parzialmente GRANULEGGIANTE ma "FERMA"):
in questa fase usare preferibilmente Ozonia 10 in combinazione a med. secondaria sia AVANZATA che TRADIZIONALE, scelta in base all'essudazione, alla perdita di sostanza (cavità e tragitti fistolosi), intervallo di cambio stabilito.

MEDICAL APPLICATION OF LIPOPEROXIDE AND OZONIDE DERIVED FROM OZONIZED OILS

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INTRODUCTION

In the world, there are millions of people affected by dirty traumatic lesions, infected wounds, chronic torpid ulcers, bed sores, burns, herpetic lesions, fungal infections and insect stings, who suffer for a long time because the conventional topical treatments based on antibiotics and anti-inflammatory drugs are not sufficiently effective.

Antibiotic-resistant strains of pathogenic bacteria are increasingly prevalent in hospitals and the community. New antibiotics are needed to combat these bacterial pathogens, but progress in developing them has been slow. Historically, most antibiotics have come from a small set of molecular scaffolds whose functional lifetimes have been extended by generations of synthetic tailoring. The emergence of multidrug resistance among the latest generation of pathogens suggests that the discovery of new scaffolds should be a priority (Fischbach and Walsh, 2009). Unfortunately, most physicians and nurses are not aware of the potency and efficacy of ozonated oil.

I would like to predict that the application of ozonated oil, a simple and inexpensive remedy, will become far more useful than expensive pharmaceutical creams and will herald a medical evolution for the topical treatment of topic ulcers and wounds. Under these terms, it is not exaggerated to proclaim ozone as “the wonder drug of the XXI century” (Bocci, 2005).

Interestingly, in spite of its instability, the O₃ molecule can be stabilized as an ozonide between the double bonds of a monounsaturated fatty acid such as oleic acid (Bocci, 2002). Ozonation of edible oil is performed by bubbling the gas mixture (O₂/O₃) for either five min or up to two days, respectively. One gram of oil can bind up to 160 mg of ozone. As a consequence, ozonated olive oil remains stable for 2 years at 4 °C. This preparation is proving to be ideal for the topical use of O₃ in the treatment of chronically infected cutaneous and mucosal areas of the body (Valacchi et al., 2005). O₃ is widely recognized as one of the best bactericidal, antiviral and antifungal agents and therefore it is profitably and practically employed as ozonated olive oil with well defined peroxide contents.

The ozonated oil is now used topically for the treatment of war wounds, anaerobic infections, herpetic infections (HHV I and II), trophic ulcers and burns, cellulitis, abscesses, anal fissures, decubitus ulcers (bed sores), fistulae, fungal diseases, furunculosis, gingivitis and vulvovaginitis (Bocci, 2005). Even radiodermatitis lesions in patients with cancer have been found to be beneficially influenced by exposure to a simple application of ozonated oil (Matsumoto et al., 2001).

2. LIPOPEROXIDE AND OZONIDE FORMATION

To obtain ozonized oil, edible oil is bubbling with the gas mixture (O₂/O₃). During the reaction of O₃ with the fatty acid present in vegetable oils, lipoperoxides and ozonides are formed. In chemistry, especially biochemistry, a fatty acid is a carboxylic acid often with a long unbranched aliphatic tail (chain), which is either saturated or unsaturated. For example, oleic acid is a mono-unsaturated omega-9 fatty acid found in various animal and vegetable sources. It has the formula CH₃(CH₂)₇CH=CH(CH₂)₇COOH. The term Oleic means related to, or derived from, oil or olive (Fig. 1).

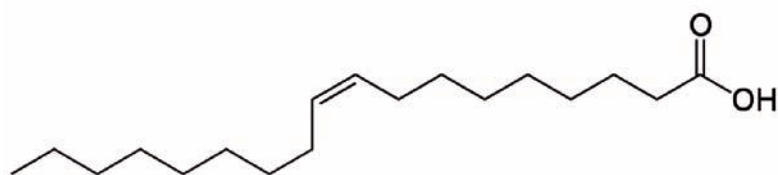


Fig. 1. Representation of chemical structure of oleic acid.

The reaction of O₃ essentially with the unsaturated double bond of the fatty acid form different derivatives as organic ozonides and lipoperoxides. Organic ozonides are formed by addition reactions of ozone and unsaturated compounds. They are intermediates in ozonolysis and have a trioxolane ring structure with a five-membered C-O-O-C-O ring (Criegee, 1975; Diaz et al., 1997) (Fig. 2). They usually appear in the form of foul-smelling oily liquids, and rapidly decompose in the presence of water to carbonyl compounds: aldehydes, ketones, peroxides.

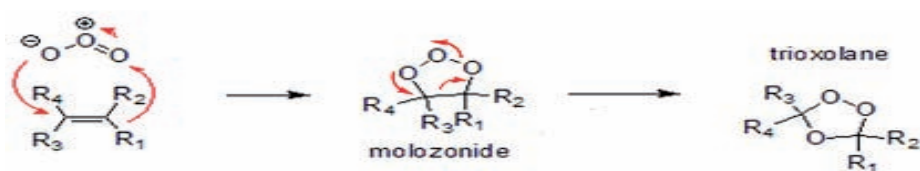


Fig. 2. Representation of the mechanism of Criegee reaction.

In the generally accepted mechanism proposed by Rudolf Criegee in 1953, the alkene and ozone form an intermediate molozonide in a 1,3-dipolar cycloaddition. Next, the molozonide reverts to its corresponding carbonyl oxide (also called the Criegee intermediate) and aldehyde or ketone in a retro-1,3-dipolar cycloaddition. The oxide and aldehyde or ketone react again in a 1,3-dipolar cycloaddition or produce a stable ozonide intermediate (a trioxolane) (Fig. 3). Evidence for this mechanism is found in isotopic labeling. When ¹⁷O-labelled benzaldehyde reacts with carbonyl oxides, the label ends up exclusively in the ether linkage of the ozonide. There is still dispute over whether the molozonide collapses via a concerted or radical process; this may also exhibit a substrate dependence.

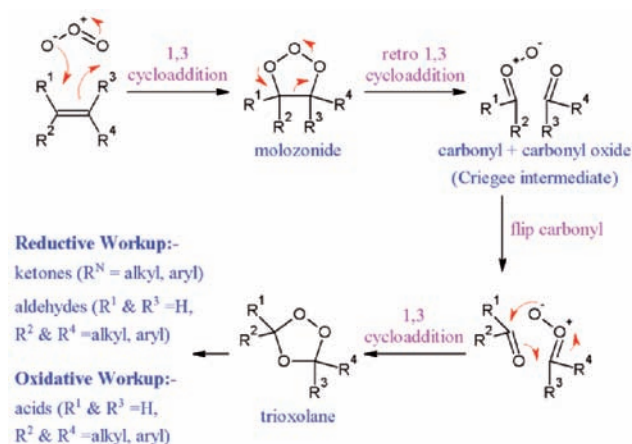


Fig. 3. Representation of the steps of Criegee reaction to form trioxolane

Lipid peroxidation refers to the oxidative degradation of lipids. This process proceeds it most often affects polyunsaturated fatty acids, because they contain multiple double bonds in between which lie methylene -CH₂- groups that possess especially reactive hydrogen (Fig. 4).

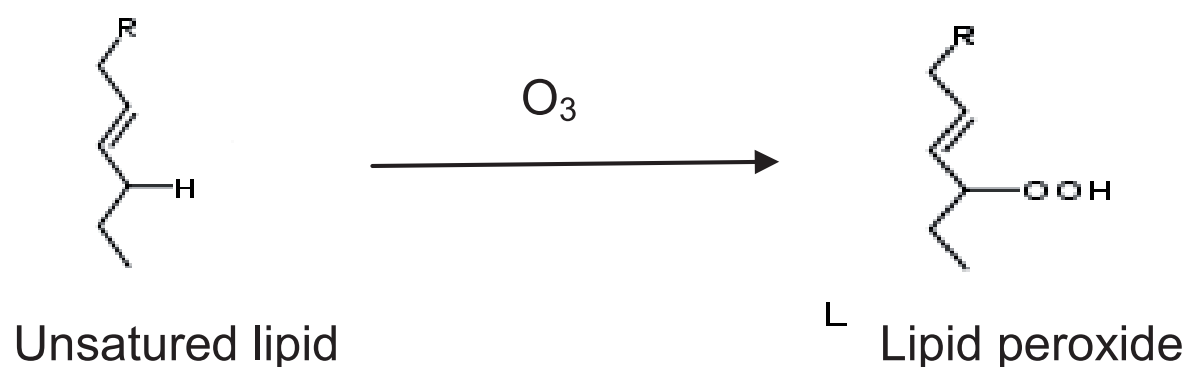


Fig. 4. Formation of lipid peroxide during reaction of unsaturated lipid with ozone.

The reaction of ozone with vegetable oils occurs almost exclusively with the carbon-carbon double bonds present in un-saturated fatty acids producing, in addition to lipid peroxides and ozonides, several oxygenated compounds: aldehydes, diperoxides and polyperoxides; and these compounds could be also responsible for the wide antimicrobial activity of ozonized oils (Ledea, 2003).

3. HOW OZONATED OIL ACTS?

How ozonated oil acts? remains an open question. Probably, when the stable triozone comes into contact with the warm exudates of the wound, it slowly decomposes to reactive ozone, which readily dissolves in water, generating hydrogen peroxide and lipoperoxides that can explain the prolonged disinfectant and stimulatory activity. If it is correct, this reasoning implies that we should have titrated preparations with high, medium or low triozone concentrations to be used during the inflammatory septic phase I, regenerating phase II or remodelling phase III, respectively. These phases have been related to the rapidly changing cell types and to the release of cytokines and growth factors that modulate the complex healing process (Bocci, 2005). On the other hand, it has recently been observed that olive oil, which during ozonation traps O₃ in the form of a stable ozonide, when applied to all sorts of acute and chronic cutaneous infections, slowly release O₃ which, in comparison with conventional creams, displays effective disinfectant and stimulatory activities that lead to rapid healing (Valacchi et al., 2005).

It has been demonstrated that antimicrobial effect is not only attributable to the ozonides present in the ozonated oil, but to the all complex mixture of compound derived from the ozonation process (Menendez et al., 2008). After the contact ozonized oil - microorganism it was observed severe alteration of the cytoplasm (Sechi et al., 2001). In addition, application of ozonized oil leads to a significant reduction in amylase, lipase, keratinase and urease enzyme activities in the microorganism in line with a reduction in nucleic acid content (Neveen, 2006).

Even when the exact action mechanism of the ozonized oil was not describe there are many pre-clinical and clinical evidence of its antimicrobial and as wound healing beneficial efficacy. As antimicrobial se most sensible bacteria was *Staphylococcus aureus* and the main resistant *Pseudomona aeruginosa* (Menendez et al., 2008).

In general a lethal effect of ozonized oil is evident when it was applied to multi-resistant strain of *Staphylococcus epidermis*, *Stafilococcus aureus*, also when was applied to fungi from the genus *Trichophyton*, *Epidermophyton* and *Microsporum*, yeast as *Candida albicans* and protozoan as *Giardia lamblia* (Menéndez et al., 2002; Neveen, 2006; Hernandez et al., 2009).

The wound healing action mechanism of ozonized oil may be connected in part to its antimicrobial effect, but also with its ability to promote the liberation of gawn factors (Schulz, 1981), activate local antioxidant mechanism (Zamora et al., 2007, 2008) and promote tissue reparation (Silveira et al., 2007).

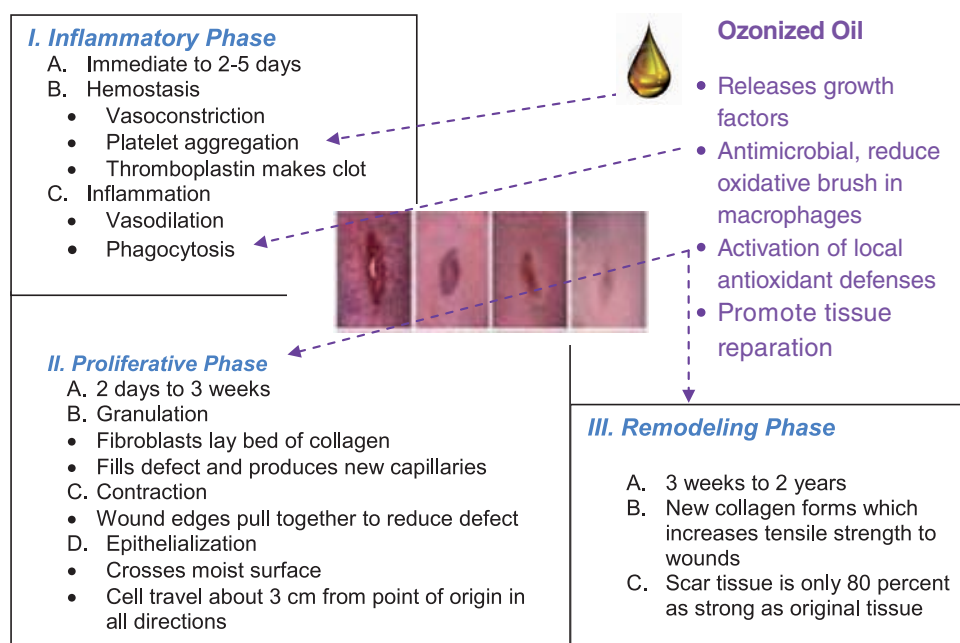


Fig. 5. Probably action mechanism of ozonized oil during wound healing. The entire wound healing process is a complex series of events that begins at the moment of injury and can continue for months to years. Ozonized oil component may act in different step of the wound healing proceed by different action mechanism.

The theoretical sequence of wound healing has been schematically represented to happen in three successive stages. The scheme presented in Figure 5 shows three phases: Phase I indicates the inflammation stage, normally lasting 2-3 days. The bacterial infection successive to a trauma, diabetes, local ischaemia and possibly antibiotic resistance, can become chronic unless and can be intervene with ozonized oils. Phase II corresponds to the intermediate stage and normally lasts two weeks. The synthesis of extracellular matrix (fibronectin, collagen III/I, hyaluronic acid and chondroitin sulphate) is accompanied by an active proliferation of fibroblasts and keratinocytes. The use of ozonated oil, not only prevents a superinfection, but stimulates the initial tissue reconstruction. Phase III, includes the final healing and scar tissue remodeling and may take a long time in elderly and/or diabetic patients. In some cases, excessive release of Transforming Growth Factor (TGF beta 1) may stimulate excessive fibrogenesis with cheloid formation (Bocci, 2005).

In summary, the probably action mechanism of ozonized oil should be due to: 1) Direct oxidation: slowly release of O₃, trioxolane and lipoperoxides can destroy by oxidation the infective germs (Sechi et al., 200; Valacchi et al., 2005). 2) Cytotoxicity: Trioxolane, lipoperoxides and aldehydes are cytotoxic to microorganism, they can inactivates enzymatic pathways by mechanism involved disruption of nuclear mediators (Neveen, 2006). 3) Grow factors Release: O₃ and other oxidized oil components can release grow factor from platelets (Bocci, 2005) that act as tissue remodeling factors. 4) Oxidative pre-conditioning, local oxidation of tissue by oxidized oil components can stimulate the expression of endogenous antioxidant mechanism (Zamora et al., 2007, 2008) and promote tissue reparation (Silveira et al., 2007).

4. USES OF OZONIZED OILS IN DERMATOLOGY

As soon as the medical community will appreciate their efficacy, ozonated oil will become indispensable tools in chronic wound healing units (Bocci, 2005).

The germicidal properties of the ozonized vegetable oil It has been already established. The ozonized vegetable oils have been used in the treatment of microbial infections of the skin (infected wounds, fistulas, acne, infected burns and ulcers), in the treatment of nasal, ear and vaginal infections (U.S. Pat. No. 984,722, U.S. Pat 5,270,344, U.S. Pat 5,364,879, U.S. Pat 2,356,062; U.S. Pat 3,504,038) and in post-operative disorders. They have been also used in the treatment of gastroduodenal ulcers (Pat. WO 01/37829 A1), against intestinal infections (U.S. Pat 5,364,879) or erysipelas (Pat RU 2040235 A) they have been recently used in the treatment of the Giardia lamblia (Pat. WO 01/37829 A1) Tynea Pedis, recidivating genital Herpes simplex, Helicobacter pylori, infection and in external hemorrhoids and bedsores (Menendez et al., 2005).

The ozonized vegetable oils and fats have been also used in cosmetics. Since the 1950s, in France, the ozonized solutions have been used as cosmetics, directly on the skin or in baths, as stimulants, purifiers, as decongestant, tranquilizers and regenerating substances of the epidermal tissue. The properties for stimulating the tissue regeneration, the oxygenation of the cells and tissues and the moderated whitening properties are added to the acknowledged germicidal activity of the products from the ozonation of unsaturated compounds, such as terpenes, fatty acids, triglycerides and vegetable oils in the cosmetic applications. The highly oxygenated compounds, such as the ozonized vegetable oils, favor the flexibility and the softening of the skin and is used also to prepare creams for repairing the epithelial tissue (Pat. WO 01/37829 A1).

Ozonized oil preparation is proving to be ideal for the topical use in the treatment of chronically infected cutaneous and mucosal areas of the body. Ozonized oil has been applied, in human pathologies involve germens, some example of clinical trial are the following:

4.1 Bacterial infections

Application of the Ozonized Sunflower Oil in Periodontitis: In this study, we used ozonized sunflower oil in order to evaluate their effect on the treatment of moderate simple periodontitis and for preventing its recidivation. A random, controlled and single-blind phase III clinical trial was performed in 84 patients, older than 35 years, from both sexes. Ozonized sunflower oil was topically applied to 42 patients on the operated area and on the 7.sup.th, 14.sup.th and 21.sup.st days after operation on the adjacent periodontal tissues. The control group was formed by 42 patients that received the conventional treatment with chlorhexidine (aqueous solution 0.2%). An analytic index of hygiene, clinical and radiographical tests and microbiological controls was applied to the patients, at the beginning, on the 21.sup.st, 90.sup.th and 180.sup.th days and with intervals of 1 month until 9 months after operation.

The effectiveness of the treatment after 180 days was considered as: good (satisfactory clinical and microbiological assessments) in 98% of the patients of the group treated with ozonized sunflower oil and in 78% of the control group; fairly good (some of the assessments were not satisfactory) for 2 and 17%, respectively, and in the category of bad (both assessments were not satisfactory) only 5% appears in the control group. Recidivation was more frequent in the control group (15%) than in the group treated with ozonized sunflower oil (5%). In general, the best clinical results (best evolution and healing during the study) and microbiological results were obtained in the group treated with ozonized sunflower oil, and also a lower percent of recidivation was found in that group. No side effects were observed (CU patent 22749; Menendez et al., 2008).

Application of the Ozonized Sunflower Oil in the Treatment of Alveolitis: The ozonized sunflower oil was used as the only drug in the treatment of alveolitis. The results were compared to those corresponding to a control group, where Alvogil® (iodine) was used as local treatment, besides applying an oral antibiotic.

The sample was formed by 100 adult patients, randomly distributed into two groups, with 50 patients each. Healings were performed every 72 hours and visits to the doctor were carried out as required. The healing criterion considered was the formation of a healing tissue and the decrease or elimination of the pain. The healing was reached in 43% of the patients treated with ozonized sunflower oil and in 41% the patients treated with Alvogil®, without any significant differences between both groups. However, patients treated with ozonized sunflower oil healed most rapidly and they only required two or three visits to the doctor, regarding the patients healed with Alvogil® that required four to six visits to the doctor (CU patent 22749; Menendez et al., 2008).

Treatment of the Acute Ulcer-Necrotizing Gingivitis with Ozonized Sunflower Oil: A random phase III clinical assay was performed in a group of 48 patients suffering from acute ulcer-necrotizing gingivitis. From those patients, 24 formed the group with ozonized sunflower oil, by topical applications on the lesions, three times a day, for 7 days.

The control group (24 patients) was treated with local applications of aqueous solution of sodium perborate, as risings, with similar periodicity to that of the group treated with ozonized sunflower oil. The tests were performed 3 or 7 days after the beginning of the treatments. In the group treated with ozonized sunflower oil, 75% of the patients were healed compared to the control group that reached 29.2%, with a significant difference ($p < 0.01$). Regarding the signs and symptoms assessed: gingival bleeding, signs of local acute swelling and gingival pain, they disappeared more rapidly in the group treated with ozonized sunflower oil (CU patent 22749; Menendez et al., 2008).

Application of the Ozonized Sunflower Oil in the Treatment of Infected Radicular Ducts: The sample was constituted by 200 adult patients presenting radiolucid rarefaction areas, with or without fistulas in monoradicular teeth. The patients for the study were allocated at random. The sample was distributed into two groups of 100 patients each. The test group received healings with ozonized sunflower oil, by sterile cotton balls impregnated with the oil and put it in the cavity, at the entrance of the ducts.

The change of the cure was performed every 48 hours. In the control group, the healing was made at the same place and similarly, using a liquid bactericide (Cresophen®). In this group, a similar application was performed seven days later. Radiological and clinical tests were carried out to the patients at the start and at the end of the treatment. In the group treated with ozonized sunflower oil, the results were better, with 91% of improvement compared to the control group (55%) with significant differences ($p < 0,01$). 88 and 5% of the patients healed with ozonized sunflower oil and Cresophen®, respectively, showing significant differences between both groups. Patients treated with ozonized sunflower oil needed two or three visits to the doctor's office, while most of the healed patients of the control group required four to six visits to the doctor's office (CU patent 22749, Menendez et al., 2008).

Comparative Study of the Effect of the Ozonized Sunflower Oil in Gingivostomatitis in Relation with Conventional Treatments: One hundred sixty children suffering from aphthous gingivostomatitis, between 0 and 15 years old were treated. The clinical symptoms of the children were fever, marked anorexia, salivation, gingival pain, asthenia and uneasiness of several days of evolution. The experimental group (60 children) were daily treated with touches of ozonized sunflower oil and the control groups with three different products (by following a similar procedure that the used for the experimental group): iodouridine (60 children), hibitane (20 children), boroglycerine (20 children). Between the third and the seventh days of treatment, the complete healing of the lesions was reached in 75% of the patients treated with ozonized sunflower oil and in 6% of the patients from the control group, with statistically significant differences ($p < 0.001$), regarding the other control treatments applied in a similar period of time (CU patent 22749; Menendez et al., 2008).

Application of Ozonized Sunflower Oil in Acute Tonsillitis: Fifteen patients suffering from acute tonsillitis were studied and daily treated with ozonized sunflower oil in the oropharyngeal area for a week. Microbiological controls (pharyngeal exudate) and physical tests of the oropharyngeal area were performed to those patients at the beginning and at the end of the treatment.

Among the microorganisms in the first exudate we found *Streptococcus pyogenes*, *Haemophilus influenzae*, *Bordetella pertussis*, and others. At the end of the treatment, all patients were cured, taking into account the microbiological and clinical tests performed (CU patent 22749; Menendez et al., 2008).

4.2. Viral infections

Application of the Ozonized Sunflower Oil in the Treatment of the Acute Herpetic Gingivostomatitis: This study covered the treatment of 113 patients with antecedents of acute herpetic gingivostomatitis, and they were daily treated with ozonized sunflower oil. In 76.9% of those patients, the symptoms disappeared after a three-day treatment; in 20.4%, they disappeared on the seventh day of treatment and in 2.7%, the symptoms disappeared on the tenth day. The microorganism most frequently isolated in the lesions was the *Staphylococcus aureus* (CU patent 22749; Menendez et al., 2008).

Ozonized Sunflower Oil in the Treatment of the Infection Caused by the Human Papilloma Virus: Sixteen women with the human papilloma virus (HPV) in the vagina or in the cervix were studied and treated with embrocations of ozonized sunflower oil on the affected areas, using the speculum for the curing. The treatment was daily performed for 15 days. The results, by colposcopy and cytology, showed an effectiveness of 94%. **Application of Ozonized Sunflower Oil in the Treatment of Lower Limb Ulcers Caused by Chronic Venous Insufficiency** (CU patent 22749; Balkanyi, 2006; Menendez et al., 2008).

4.3. Fungal infections

Application of Ozonized theobroma Oil in the Treatment of Tynea Pedis: Fifty patients with a diagnosis of tynea pedis, randomly distributed into two groups of study, 25 patients in each group, were studied. The experimental group was treated with an ointment containing 20% ozonized theobroma oil, for 6 weeks, twice a day and the control group was treated with Whitfield ointment with no sulfur with a similar plan of treatment. The healing criterion was the presence of negative microbiological exudate.

A healing of 85 and 20% in the experimental and control groups, respectively, with significant differences between both groups was obtained (CU patent 22749; Menendez et al., 2008).

Sun Flower Oil and Olive ozonized oil are fungicide, active against fungi, produceds of superficial mycosis in human, such as *Candida albicans*, *Trichophyton mentagrophytes*, *Microsporum canis*, *Thichophyton rubrum* (CU patent 22749; Balkanyi, 2006; Menendez et al., 2008).

4.4. Mix infections

Application of Ozonized Sunflower Oil in the Treatment of Lower Limb Ulcers Caused by Chronic Venous Insufficiency: A study was performed with 20

patients with lower limb ulcers caused by chronic venous insufficiency with less than five years of evolution. Both groups were treated with venous rest, hyposodic diet and analgesic drugs. Besides, a mechanical disinfection with benzalconium chloride 1/5000 was performed twice a day. After disinfection, ozonized sunflower oil was applied to the experimental group and antibiotic ointments, according to the isolated germ, were applied to the control group. An amelioration of the inflammatory signs after 72 hours and the appearance of granulation tissue after the fifth day were observed in the experimental group, whereas in the control group, both the evolution and the disappearance of signs and symptoms lasted more (CU patent 22749; Menendez et al., 2008).

Application of the Ozonized Sunflower Oil in the Treatment of Bedsores

Twenty patients suffering from bedsores in the sacral region were studied and randomly distributed into two groups of 10 patients each. The experimental group was treated with ozonized sunflower oil, twice a day, and the control group was treated with ointments, according to the germ present, with a similar plan of treatment. All the patients succeeded in the healing of their wounds. In the group treated with ozonized sunflower oil, the time of healing was shorter and it was not necessary to perform any antibiogram, because of its wide germicidal power (CU patent 22749; Menendez et al., 2008).

Application of the ozonized oil in the treatment of fistulae and chronic surgical wounds: In an study involved 28 patients suffering from fistulae and chronic surgical wounds a fully effective in 27 cases without side effect was found (Matsumoto et al., 2001).

Ozonated oil has also proved to be very effective in burns (Bocci, 2005). In addition Ozonized oils are used for the long-term treatment of injuries, burns and local infections such as skin and nail mycosis, as well as in the follow-up treatment of ulcer cruris and decubitus ulcers (Beck et al., 1995).

5. TOXICOLOGY

The diverse tests performed with ozonized sunflower oil showed the safety of this kind of products: toxicological tests, histological tests, mutagenic tests, genotoxic tests and teratogenic tests (Menendez et al., 2008). In clinical assays using ozonized oil in the treatment of infective lesion, side-effect was not reported (Matsumoto et al., 2001; Valacchi et al., 2005).

6. USES

Wide range of antimicrobial effect. Useful to treat topical fungi, bacterial and virus infections. Useful in the treatment of bedsores and in prophylaxis of diabetic food.

7. CONTRAINDICATIONS

Allergy to formula components.

8. WARNINGS

Keep away from eyes.

9. INTERACTIONS, INCOMPATIBILITIES

Interactions: None well documented.

Incompatibilities: Do not mix ozonized oil with any other drugs or cosmetic.

10. ADVERSE REACTIONS

Dermatologic: Skin rashes (rarely).

11. INTOXICATION / FIRST AID

Wash affected area and suppress treatment immediately.

12. Laboratory test interferences

None well documented.

13. Route / Doses

Topical apply lightly to affected area twice daily or as prescribed by the physician. Use smallest amount possible. Continue treatment to maintain remission.

14. Quality

A quality ozonized oil to be used with medical purpose should be prepared follow the good manufacture practice. That mean a strictly quality control during it production in a high quality reactor by fixing the quality of the raw materials and important reaction variables as: time of reaction, ozone concentration, ozone sources, burbling size, reaction temperature and others.

A quality control of the active component (ozonized oil) should involve chemical -physical analysis, microbiological analysis and biological analysis. Biological analysis should be demonstrated the pharmacological effect attributed to the oil and the absence of toxicity. Microbiology should demonstrate the microbiological quality of the preparation. Chemical / physical analysis will be done to guaranty the homogeneous chemical content of active component and the stability.

Chemical analysis will involve the measurement of the content of lipoperoxides and aldehydes, iodine and saponification indices. Physical analysis will take into consideration the acid values, density and viscosity of the active component. Test will be do according to the pharmacopeia methods and should be also used to demonstrate the stability of the preparation.

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