

REVIEW ARTICLE

Risks of ozonated oil and ozonated water on human skin: A systematic review

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Abstract

Ozonated water and oil are emerging as potential dermatologic therapeutics, particularly for the treatment of various wounds. However, the safety of these liquids has not been extensively studied. The aim of this systematic review was to evaluate the risks of ozonated liquids to human skin tissue based on the available literature. We completed a structured search of five scientific databases and identified 378 articles for consideration. Based on pre-established inclusion/exclusion criteria, nine studies were included in this review. Two studies specifically evaluated the cytotoxicity of ozonated liquids on human cells, five studies evaluated ozonated liquids in randomised controlled trials (RCTs), one was a post-market surveillance study, and one was a crossover study in humans. None of the included studies found any significant human dermatologic risks associated with ozonated water or liquid. Because of the small sample size, however, additional short- and long-term RCTs specifically designed to evaluate the dermatological risks of ozonated liquids are recommended.

KEYWORDS

dermatologic agent, drug-related side effects and adverse reactions, ozone, topical administration, wound healing

Key Messages

- ozonated liquids are being used with increased frequency for dermatologic therapeutics with little data on the safety of these products
- the goal of our study was to perform a systematic review of the available literature regarding dermatologic safety of liquid forms of ozone
- all papers fitting our inclusion criteria showed no adverse effects of liquid forms of ozone

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1 | INTRODUCTION

Ozone (O₃) is an inorganic and highly reactive gas composed of three oxygen atoms. It is both a natural and manufactured product with potent oxidative properties. O₃ gas has been studied extensively over the years as a component of the atmosphere as well as in various industrial and commercial applications. Gaseous forms of O₃ have been used in the preparation of organic compounds and for disinfection, deodorization, and decontamination in medical and industrial settings.

Liquid formulations of O₃ include various ozonated oils and ozonated water. Ozonated oils are produced using an ozone generator and bubbling ozone gas into a natural oil for a specified duration in a reaction chamber followed by a controlled cooling process to stabilise the O₃ within the product.¹ Ozonated water is a less stable product produced at the site of usage by one of two methods: coronal discharge, where an electrical discharge is applied to pure oxygen gas or air to create O₃ gas, which is then incorporated with water, and by way of direct water electrolysis using low voltage applied to water flowing across a polymer membrane in a compact electrolytic cell.² The ozonated water rapidly decomposes upon contact with naturally occurring organic materials, returning to free oxygen and water while releasing the free radicals responsible for disinfection.^{1,3}

Ozonated liquids have been used in industrial and residential applications that exploit ozone's oxidising capabilities.⁴ The broad applications for these liquid formulations have included everything from food preparation to decontamination of water pipes. O₃ liquids have gained attention in the literature for many clinical applications, including wound care. In the international literature, there are many such references to the utilisation of ozonated liquids in clinical practice,⁵ implying that these agents are widely used and accepted treatment modalities. A recent systematic review by Wen and colleagues⁶ demonstrated that ozone therapy markedly accelerated the improvement of chronic wounds and reduced the amputation rate. Other studies that include liquid forms of O₃ are often of small sample size and lack validation with large randomised controlled trials (RCTs); however, they have shown promising results in the management of venous stasis ulcers,⁷ burns,⁸ atopic dermatitis,^{9,10} tinea pedis,¹¹⁻¹³ hand sanitation,¹⁴ diabetic foot ulcers,¹⁵ and other dermatologic conditions.

While the mechanisms of topical O₃ therapy remain unclear in some clinical applications, antimicrobial action is thought to be because of its effect of blocking the enzymatic function of bacteria by oxidising glycoproteins and glycolipids. This oxidation of the phospholipids

and lipoproteins of the bacterial cell envelope disrupts the cytosolic membrane integrity.^{12,13}

Although the clinical applications of ozonated liquids may suggest that they are safe for topical use, this is contrary to gaseous O₃, which has known toxicities in high concentrations or over extended periods of time. It is well known that gaseous O₃ is harmful to the human respiratory system.¹⁶⁻¹⁹ On the other hand, there does not seem to be a consensus paper addressing the safety of topically applied ozonated liquids in humans. Therefore, this comprehensive systematic review sought to assess the possible risks of exposure of human skin tissue to ozonated liquids.

2 | MATERIALS AND METHODS

2.1 | Search strategy

To retrieve the list of studies on dermatologic risks of ozonated oil and water, a search was conducted in five⁵ databases for all years up to September 2020: Web of Science Core Collection, Embase, Cochrane Library, Ovid MEDLINE(R) <1946 to September 2020>, and Google Scholar. The search consisted of a combination of keywords and MeSH terms used in the title and the abstract as free-text words (Appendix A). The terms used were associated with ozone in its topical form of oil, gel, ointment, emulsion, water, aqueous, or liquid, in combination with terms related to skin, skin absorption, dermatology, epidermis, epithelium, squamous, or cutaneous. We included proximity or adjacency operators (NEAR or ADJ) to connect search terms in the search string, which were also disaggregated using the truncation symbol ("*"), in most databases to capture different word endings. Limits were added to the searches to exclude non-English papers and review articles. To discover additional relevant grey literature, we conducted equivalent searches in Google Scholar. The results from all databases used were aggregated and de-duplicated for screening. All searches in this study were developed and executed by a medical librarian (M.R.).

2.2 | Inclusion and exclusion criteria

Studies were included if they evaluated human cells, tissues, or patients who had ozonated water or oil applied topically for any duration. Required outcomes included any evaluation of risk of damage to skin tissue. Examples of risk defined a priori included cellular morphology change or destruction, tissue destruction, pathologic

organ change, or antioxidant loss. Inflammatory biomarkers alone were not sufficient, given that there is no consensus from the literature confirming a universally accepted biomarker as an indicator of cellular injury.²⁰

Case studies and series, theoretical papers, review articles, and abstract-only studies were excluded. There were no exclusion criteria based on publication date or study location; however, studies were required to be in English for evaluation.

2.3 | Selection process

The four authors involved in screening articles (D.R., S.L., B.L., and K.B.) participated in two rounds of training with a sample of 20 articles in each training round to attain a high level of inter-rater reliability prior to beginning the article screening process. To assess agreement amongst the four raters, interclass correlations (ICCs) were calculated using SPSS statistical package (IBM SPSS Statistics v. 27, RRID: SCR_019096, 2020). The interclass correlation coefficient using a two-way mixed-effects model with absolute agreement based on average measures indicated excellent inter-rater reliability, ICC = 0.90 (95% CI: 0.80–0.96).

Using the aforementioned criteria in the Covidence review manager software (Covidence, RRID:SCR_016484), the authors first screened study titles and abstracts, and then evaluated full-text studies for inclusion. Two authors reviewed each study at all stages, with a third resolving any disputes.

2.4 | Data extraction and risk of bias assessment

The authors collectively extracted basic information and results from the studies. Additionally, we evaluated the risk of bias relative to our desired outcomes using the Cochrane collaboration's risk of bias tool,²¹ assigning low, high, or unclear risk for the following categories: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Two authors independently assessed the risk of bias for each article, using group consensus to resolve any disputes.

3 | RESULTS

3.1 | Literature search

The literature search returned a total of 378 studies for screening (Figure 1). Following title and abstract

screening, 337 studies were deemed irrelevant as they did not meet pre-determined study criteria. Of the 41 articles that were subject to full-text review, an additional 32 studies were excluded because of incorrect study design, ozone type, or lacking sufficient information on risk-related outcome variables. As a result, nine studies published between 2002 and 2020 were included in this systematic review.

3.2 | Study characteristics

The characteristics and outcomes related to this systematic review of the studies included are listed in Table 1. Overall, the reviewed studies include five RCTs,^{4,7,11,12,22} one crossover study,¹⁴ one clinical trial,¹³ and two in vitro studies.^{23,24} A total of 2628 patients/volunteers participated in the studies included. Four of the nine studies were designed to examine cytotoxicity or adverse side effects of ozonated liquids (oils and water) on skin a priori. The remaining five studies reported adverse side effects of ozonated liquids on skin as a secondary outcome to wound healing or treatment.

3.3 | Cell culture assays

Two studies^{23,24} examined the cytotoxicity of ozonated liquids on skin cells. In the study by Kashiwazaki et al.,²⁴ ozonated water (4 ppm; up to 15-minute exposure time) was found to have no cytotoxic effects on a normal thickness stratum corneum of cultured epidermis as compared with other hand disinfectants (ie, 1% CHG-E, 0.2% benzalkonium chloride, 83% ethanol, and 0.5% povidone-iodine) that destroyed or damaged the stratum corneum. Ozonated water also produced no morphological changes to keratinocytes below the stratum corneum compared

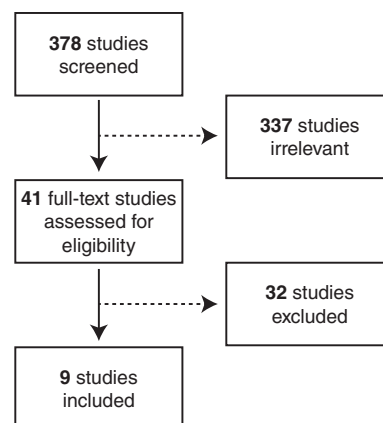


FIGURE 1 PRISMA diagram for study selection

TABLE 1 Main characteristics of included studies

Author	Study aims	Design	Participants	O ₃ Type	Comparator	Risk outcome variable	Results
Aghaei et al. (2019) Iran	Evaluate O ₃ oil + glucantime on leishmaniasis	RCT	30 patients	O ₃ oil (0.5 ml/mm ² , 2×/day for 8week) + glucantime (20 mg Sb5+/kg, 20 days)	glucantime (20 mg Sb5 + /kg, 20 days)	self-report of pain, erythema, and oedema	Transient burning sensation with O ₃ oil in some patients
Breidablik et al. (2019) Norway	O ₃ water vs. ABHR in hand disinfection	Crossover	30 nursing students	O ₃ water 0.8 or 4 ppm (30 seconds)	ABHR (30 seconds)	self-report of burning/dryness	O ₃ water = 0% burning, dryness ABHR = 20% burning, dryness
de Oliveira et al. (2017) Brazil	Cytotoxicity of O ₃ neem oil or O ₃ neem oil + H ₂ O	in vitro	Human skin cell line HaCaT	O ₃ neem oil or O ₃ neem oil + H ₂ O	neem oil 5-Fluorouracil methotrexate	GI ₅₀ values ^a	No cytotoxicity of HaCaT cells with O ₃ neem oil, neem oil + H ₂ O, or control neem oil
Esposito et al. (2020) Italy	Evaluate O ₃ oil-based gel on wound healing	single-blind RCT	114 patients	O ₃ oil-based gel (2×/day; 2-3 week)	hyaluronic acid (2×/day; 2-3week)	Physician assessed ASR	No adverse reaction to O ₃ oil-based gel or hyaluronic acid
Kashiwazaki et al. (2020) Japan	Evaluate O ₃ water for cytotoxicity	in vitro	cultured human keratinocyte	O ₃ water 4 ppm (1, 3, or 15 min)	hand disinfectants or DDW	Damage to SC surface Damage below SC Cell survival	O ₃ H ₂ O or DDW = no SC damage O ₃ H ₂ O = no damage below SC O ₃ H ₂ O ≥ 92.4% cell survival
Lu et al. (2018) China	Efficacy of O ₃ water and oil on tinea pedis	RCT	60 patients	O ₃ water (30 min) + O ₃ oil (1×/day; 4 week)	naftifine hydrochloride + ketoconazole	Investigator observation of ASR	O ₃ H ₂ O + O ₃ oil = desquamation (n = 1 patient); no other ASRs
Menéndez et al. (2002) Cuba	Efficacy of O ₃ sunflower oil on tinea pedis	RCT	200 patients	O ₃ sunflower oil (2×/day; 6 week)	ketoconazole (2×/day; 6 week)	Not specified	No side effects observed with O ₃ sunflower oil or ketoconazole
Menéndez et al. (2008) Cuba	Efficacy and ADR of O ₃ sunflower oil on tinea pedis	Open clinical trial	2165 patients	O ₃ sunflower oil (2×/day; 6 week)	n/a	Biweekly clinical evaluation ADR (mild-very severe)	0.3% (n = 6) patients reported ADR (mild burning sensation, pruritus, and erythema)
Solvästru et al. (2015) Romania	O ₃ sunflower oil + α-bisphenol for venous leg ulcers	RCT	29 patients	O ₃ sunflower oil + α-bisphenol (1×/day; 30d)	TAU	Not specified	No report of pain or irritation in O ₃ and TAU groups

^aGI₅₀, the concentration for 50% maximum inhibition of cellular growth. Higher values indicate less inhibition and greater cell proliferation.

Abbreviations: ADR, adverse drug reactions; ASR, adverse skin reactions; DDW, deionised distilled water; GI₅₀, concentration causing 50% cell growth inhibition; O₃, ozone; SC, stratum corneum; TAU, treatment as usual.

with the other hand disinfectants that produced condensed nuclei and vacuolar cells. However, in a “sensitive skin” model, in which cells were cultured for a shorter period producing an immature stratum corneum and other layers, ozonated water did produce vacuolar cells albeit fewer than those produced by other hand disinfectants (ozonated water = 5 versus 83% ethanol = 10, 0.2% benzalkonium chloride = 29, povidone-iodine = 15, CHG = 19 and CHG-E = 16). Compared with control (deionised distilled water), which demonstrated a 100% cell survival rate after 15 minutes of application, ozonated water performed well with $\geq 92.4\%$ cell survival after 15 minutes. Cell survival rates for the other hand disinfectants decreased below 20% at 15 minutes of application. The study by de Oliveira et al.²³ compared ozonated neem oil and ozonated neem oil plus water to pure neem oil on human keratinocyte cells (HaCaT). Neem oil and neem oil plus water was reacted at concentrations of $63 \text{ mg L}^{-1} \text{ O}_3/\text{O}_2$ for 2, 4, 6, 8, 10, and 12 hours. The ozonated neem oil and ozonated neem oil plus water demonstrated low values of cytotoxicity (GI_{50} range = 325.37 to 164.52) on HaCaT cell lines compared with the positive control, 5-Fluorouracil ($\text{GI}_{50} = 6.82$) but lower than pure neem oil ($\text{GI}_{50} > 600$) and methotrexate ($\text{GI}_{50} > 500$).^a

3.4 | Randomised controlled trials (RCTs)

Five RCTs were included in this review.^{4,7,11,12,22} The primary aim of these RCTs was wound healing or treatment of skin disease and the assessment of adverse skin effects was secondary. A total of 433 patients participated in the RCTs. All five studies evaluated a form of ozonated oil

although one study included the use of ozonated water washes and baths along with ozonated oil¹¹ and one study combined ozonated oil with glucantime.²² Two studies used physician observation to assess adverse skin effects,^{4,11} one used patient self-report²² and two studies did not specify the process by which adverse skin effects were assessed.^{7,12} Three studies reported no adverse skin effects (eg, pain, burning, irritation) of ozonated oils.^{4,7,12} Aghaei et al.²² reported a brief burning sensation following application of ozonated oil in “some” patients. Lu et al.¹¹ reported desquamation of skin in one of 60 patients in their trial and no other adverse skin effects from ozonated oil.

3.5 | Clinical trials

Two articles reported on clinical trial or crossover studies.^{13,14} Breidablik et al.¹⁴ conducted a crossover trial on 30 nursing student volunteers with ozonated water (0.8 ppm or 4 ppm) and alcohol-based hand rub (ABHR) to assess hand decontamination. No students reported burning or dryness with ozonated water but 20% reported burning or dryness with ABHR use. Menéndez et al.¹³ evaluated ozonated sunflower oil on 2165 patients in an open clinical trial to treat tinea pedis. Patients were evaluated for adverse skin effects at regular study intervals and 0.3% ($n = 6$) experienced mild levels of burning sensations, pruritus, and/or erythema from ozonated oil use.

3.6 | Assessment of the risk of bias

Figure 2 summarises the results of the risk of bias assessment using the Cochrane collaboration's risk of bias

	Random Sequence Generation	Allocation Concealment	Participant and Personnel Blinding	Outcome Assessment Blinding	Incomplete Outcome Data	Selective Reporting	Other Bias
Aghaei et al., 2019	-	-	-	-	L	H	L
Breidablik et al., 2019	-	-	H	H	L	H	H
de Oliveira et al., 2017	N/A	N/A	L	-	-	-	-
Esposito et al., 2020	L	L	L	L	L	H	L
Kashiwazaki et al., 2020	N/A	N/A	L	L	-	L	-
Lu et al., 2018	-	-	H	-	L	H	L
Menéndez et al., 2002	-	-	-	-	L	H	-
Menéndez et al., 2008	N/A	N/A	H	H	-	H	-
Solovastru et al., 2015	-	-	H	H	-	H	H

FIGURE 2 Risk of bias, assessed as low (L), high (H) or unclear (-)

tool.²¹ Seven of the nine studies reviewed had at least one bias category rated as having a high bias risk. Only one study had low risk of bias ratings in every category except selective reporting bias, which was rated as high.⁴ Two studies had a mixture of high risk and unclear risk ratings.^{7,13} Two studies had a mixture of low risk and unclear risk ratings.^{23,24} The remaining four studies had a mixture of high, low, and unclear risk of bias in the domains assessed.^{11,12,14,22}

4 | DISCUSSION

This is the first systematic review conducted to evaluate the potential risks of liquid forms of O₃ on human skin tissue. There is increasing interest in the utilisation of O₃ because of the growing evidence that O₃ has antimicrobial,²⁵ immunologic,²⁶ and therapeutic activities.²⁷ Therefore, it is necessary to have a better understanding of the dermatologic safety of these agents. The preliminary evidence suggests that ozonated liquids are well tolerated and pose no significant dermatological risks.

Each of the nine studies included in this systematic review, regardless of study design, assessed the adverse effects of liquid forms of O₃ on human skin tissue. None of the studies found significant evidence of risk with the use of ozonated liquids. Only two studies of those reviewed were designed to specifically evaluate the microscopic cytotoxicity of ozonated neem oil or ozonated water on a human epidermal cell model.^{23,24} Neither study found any evidence of cytotoxic effects of liquid forms of O₃ at concentrations up to 4 ppm on human skin cells. Five studies aimed to evaluate the efficacy of liquid forms of O₃ in clinical therapeutic applications and provided information on post hoc examination or patient self-report of side effects.^{4,7,11,12,22} Three of the five studies found no indications of adverse effects from ozonated liquids. Of the 433 participants in these studies, only one patient reported desquamation and an unclear number of patients reported a transient burning sensation upon application. One clinical efficacy paper had safety and evaluation of adverse drug reactions (ADR) as its primary endpoint.¹³ This study evaluated a branded ozonated sunflower oil in a Phase IV open clinical trial for the treatment of tinea pedis. Of the 2165 patients who completed the trial, only six patients reported any ADR, and these were rated as mild by the study participants. The final study¹⁴ examined the efficacy of ozonated water compared with alcohol-based hand rubs (ABHR) in hand disinfection in a crossover design. None of the 30 participants reported adverse effects with the ozonated water, while 20% of participants reported burning sensations and dryness with the ABHR.

Although our systematic review found no evidence of significant short-term dermatologic risks of ozonized liquids, there are noteworthy limitations to the studies included in this review that limit firm conclusions about the long-term safety of the liquid forms of O₃ on human skin. Sample sizes in most of the clinical studies on human populations were small (N range = 29–1264; median = 60).^{4,7,11–14,22} The formulation, concentration, and exposure duration of liquid O₃ on skin varied across the studies. The study design used (e.g., in vitro, RCT, open clinical trial) and the outcome variables measured varied widely across the nine studies included in this review. While over half the studies were RCTs, procedures of randomization and blinding were not applied or were unclearly applied to the methods of assessing adverse risk variables.^{7,12,22} Moreover, only a few studies, regardless of design, specified *a priori* hypotheses about adverse effects and clearly delineated adverse risk assessment methods.^{13,14,23,24} Many of the papers lacked objective and clear rating systems for adverse risk variables and deferred to subjective assessments of side effects by clinicians who may not have been blinded to group membership.^{7,11–13,22} Finally, there was an absence of longitudinal data with either continuous or intermittent use of O₃ in each of the studies. The longest treatment interval in any of the trials was only 6 weeks.^{12,13}

This systematic review has some additional limitations. Unfortunately, there is very little high-quality literature available on assessing risks and side effects of the liquid forms of O₃ in human tissue. The poor reporting of study methodology made it difficult to assess the quality of the studies and the risk of bias across studies was found to be highly variable. Moreover, meta-analysis could not be conducted because of the range of methods used, lack of clear outcome variables in some cases, and the reporting of only qualitative outcome data of adverse risk in others.

While this review highlights the need for additional thorough research on topical ozone that is well-controlled, longitudinal, and specifically designed to evaluate risk, there is already growing interest in medical applications of liquid O₃. Notably, ozonated water was anecdotally used on a large scale for hand hygiene in a Giardiasis outbreak in Norway in 2004¹⁴ and has several described uses in the field of dentistry.²⁸ The lack of reported adverse effects from these and other international uses, in combination with the outcomes reported in this systematic review, point to ozonated water's seemingly high safety profile when used topically.

5 | CONCLUSION

The results of this systematic review suggest a low likelihood of significant short-term risk to topically applied O₃

liquids. However, the small numbers of studies, high incidence of selective reporting bias, and short follow-up times indicate the need for higher-quality RCTs to confirm the safety and tolerability of ozonated liquids on human skin.

CONFLICTS OF INTEREST

BRL, DJR, SAL, and KNB were compensated through an unrestricted grant from 3Oe Scientific, Inc. BRL also serves on the medical advisory board of and holds equity in 3Oe Scientific, Inc. RML is compensated by and holds equity in 3Oe Scientific, Inc.

DATA AVAILABILITY STATEMENT

Data sharing not applicable - no new data generated

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APPENDIX A: SEARCH STRATEGY

Web of Science Core Collection

Search: September 20, 2020

ID	Search history	Results
#1	TS=(ozon* NEAR/5 topical) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	57
#2	TS=(ozon* NEAR/5 cream*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	6
#3	TS=(ozon* NEAR/5 gel*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	121
#4	TS=(ozon* NEAR/5 oil*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	485
#5	TS=(ozon* NEAR/5 ointment*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	4
#6	TS=(ozon* NEAR/5 emulsion*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	17
#7	TS=(ozon* NEAR/5 water) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	5,786
#8	TS=(ozon* NEAR/5 aqueous) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	1,464
#9	TS=(ozon* NEAR/5 liquid*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	509
#10	#9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	7,838
#11	TS=(skin) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	590,642
#12	TS=dermat* Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	164,173
#13	TS= cutaneous Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	152,168
# 14	TS=squamous Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	158,962
#15	TS=epithel* Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	541,749
#16	TS=epiderm* Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	207,483

ID	Search history	Results
#17	#16 OR #15 OR #14 OR #13 OR #12 OR #11 <i>Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC</i> <i>Timespan=All years</i>	1,536,098
#18	#17 AND #10 <i>Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC</i> <i>Timespan=All years</i>	152
#19	LA=English <i>Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC</i> <i>Timespan=All years</i>	57,086,694
#20	#19 AND #18 <i>Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC</i> <i>Timespan=All years</i>	145
#21	DT=Review <i>Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC</i> <i>Timespan=All years</i>	1,844,020
#22	#20 NOT #21 <i>Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC</i> <i>Timespan=All years</i>	132

EMBASE

Search: September 20, 2020

ID	Search history	Results	ID	Search history	Results
#1	ozon* NEAR/5 topical	71	#22	#10 AND #21	186
#2	ozon* NEAR/5 cream*	8	#23	english:la	31,846,543
#3	ozon* NEAR/5 gel*	44	#24	#22 AND #23	164
#4	ozon* NEAR/5 oil*	249	#25	review/it	2,634,943
#5	ozon* NEAR/5 ointment*	6	#26	#24 NOT #25	152
#6	ozon* NEAR/5 emulsion*	10			
#7	ozon* NEAR/5 water	1,877			
#8	ozon* NEAR/5 aqueous	510			
#9	ozon* NEAR/5 liquid*	145			
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	2,702			
#11	'skin'/exp	392,363			
#12	'epithelium'/exp	364,143			
#13	'epithelium cell'/exp	545,341			
#14	'skin absorption'/exp	7,972			
#15	Skin	1,172,031			
#16	epithel*	698,306			
#17	epiderm*	368,087			
#18	squamous	249,632			
#19	cutaneous	241,406			
#20	dermat*	805,698			
#21	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20	3,067,578			

(Continues)

Cochrane Library

Search: September 20, 2020

ID	Search history	Results
#1	(ozon* NEAR topical)	32
#2	(ozon* NEAR cream*)	4
#3	(ozon* NEAR gel*)	13
#4	(ozon* NEAR oil*)	33
#5	(ozon* NEAR ointment*)	1
#6	(ozon* NEAR emulsion*)	0
#7	(ozon* NEAR water)	55
#8	(ozon* NEAR aqueous)	6
#9	(ozon* NEAR liquid*)	2
#10	#1 OR #2 OR #3 OR #4 OR #6 OR #7 OR #8 OR #9	115
#11	MeSH descriptor: [Skin] explode all trees	4,366
#12	MeSH descriptor: [Epithelium] explode all trees	4,093
#13	MeSH descriptor: [Epithelial Cells] explode all trees	1,996
#14	MeSH descriptor: [Skin Absorption] explode all trees	285
#15	skin:ti,ab,kw	55,803
#16	epithel*:ti,ab,kw	10,207
#17	epiderm*:ti,ab,kw	7,484
#18	squamous:ti,ab,kw	9,923
#19	cutaneous:ti,ab,kw	11,915
#20	dermat*:ti,ab,kw	19,957
#21	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20	99,330
#22	#10 AND #21	24

Ovid MEDLINE(R) < 1946 to September Week 2 2020 >

Search: September 20, 2020

ID	Search history	Results
#1	(ozon* adj5 topical).tw.	33
#2	(ozon* adj5 cream*).tw.	1
#3	(ozon* adj5 gel*).tw.	28
#4	(ozon* adj5 oil*).tw.	133
#5	(ozon* adj5 ointment*).tw.	4
#6	(ozon* adj5 emulsion*).tw.	5
#7	(ozon* adj5 water*).tw.	1,093
#8	(ozon* adj5 aqueous).tw.	315
#9	(ozon* adj5 liquid*).tw.	92

ID	Search history	Results
#10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	1,572
#11	exp skin/	224,315
#12	exp epithelium/	249,477
#13	exp Epithelial Cells/	555,767
#14	exp Skin Absorption/	11,709
#15	"epithel*".tw.	429,540
#16	squamous.tw.	116,200
#17	epidermis.tw.	35,045
#18	dermat*.tw.	143,470
#19	cutaneous.tw.	135,488
#20	skin.tw.	469,690
#21	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	1,774,400
#22	English.lg.	22,429,920
#23	Review.pt.	2,473,191
#24	10 and 21	82
#25	22 and 24	73
#26	25 not 23	67

Google Scholar

Search: September 14, 2020

Exclude patents

Exclude citations

(skin OR "Skin Absorption" OR "Epithelial Cells" OR Epithelium OR Epidermis OR squamous) ("systematic review" OR "Randomised Controlled Trial" OR "Clinical Trial" OR meta-analysis) intitle:"Ozone oil" OR "Ozonated oil" OR "ozonised oil" OR "ozonized oil"

Total results: 104

(skin OR "Skin Absorption" OR "Epithelial Cells" OR Epithelium OR Epidermis OR squamous) ("systematic review" OR "Randomised Controlled Trial" OR "Clinical Trial" OR meta-analysis) intitle:"Liquid ozone" OR "Aqueous ozone" OR "Ozone water" OR "ozonized water" OR "Ozonated water"

Total results: 87

(skin OR "Skin Absorption" OR "Epithelial Cells" OR Epithelium OR Epidermis OR squamous) ("systematic review" OR "Randomised Controlled Trial" OR "Clinical Trial" OR meta-analysis) intitle:"topical ozone" OR "Ozone emulsion" OR "Ozone ointment" OR "Ozone cream" OR "Ozone gel"

Total results: 12