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Effect of micro and nanoemulsions on wound healing: a review

Amira Ayman Hendawy[a] & Amal A. M. Elgharbawy[a,b,*]

[a]International Institute for Halal Research and Training (INHART), International Islamic University Malaysia (IIUM), Jalan Gombak, 53100 Kuala Lumpur, Malaysia.
[b]Bio-environmental Engineering Research Centre (BERC), Department of Chemical Engineering and Sustainability, Kuala Lumpur, Malaysia.
*Corresponding author: E-mail address: amalgh@iium.edu.my

Received:26/7/2024
Accepted:11/1/2025
Published:31/1/2025

Keywords:
Nanoemulsions;
Microemulsion;
Wound healing;
Emulsion;
Encapsulation

Abstract

Emulsions, categorised by their particle size into microemulsions (<100 nm) and nanoemulsions (<200 to <100 nm), hold a position of burgeoning significance in the field of wound healing. Beyond their established role in diverse medical domains, emulsions have emerged as promising agents for drug delivery with wound-healing properties. This review explores a comprehensive analysis of the available literature to shed light on the impact of micro and nanoemulsions on wound healing. Covering research articles published from 2011 to 2022, this study meticulously follows the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines while employing bibliometric analysis tools, PRISMA, and VOSviewer. Through an extensive exploration of databases such as PubMed, Scopus, and ScienceDirect, this study identifies and includes 26 articles that align with the rigorous criteria for investigating emulsions in wound healing. Our bibliometric analysis underscores 'wound healing' as the most prominent keyword in this corpus. In conclusion, this study contributes substantially to the research by combining insights into the effects of nano and microemulsions on wound healing, offering a foundation for future investigations and applications within emerging nanotechnology.

1. Introduction

Emulsions may be found in various industries, including food and beverage, pharmaceuticals, agriculture, cosmetics, and petroleum. To create an emulsion is the process of dispersing one phase into another (Akbari & Nour, 2018). Wound healing has always been a point of interest in many fields; using plant oil emulsions has demonstrated an effect on healing the wound of a zebrafish (Zain *et al.*, 2021). The kinetic stability of the emulsions is determined by the droplet size of the emulsions as well as the presence or absence of interfacial coatings that occupy the water droplets (Raya *et al.*, 2020). A systematic review will frequently compile all the data to respond to a pre-posed question. This entails locating all primary research pertinent to the review question, assessing this research, and combining all the results (Pollock & Berge, 2018). Thisanalysed. This paper thoroughly analysed papers published between 2011 and 2022, and a bibliometric analysis was conducted. From 2011 to 2022, there were 26 publications related to nano or microemulsions and wound healing, with India publishing the most literature on the topic. Institutes in Spain collaborated most on nano or microemulsions and wound healing. Furthermore, 'Wound healing' is the most often used keyword in articles within that period. As a result, this study aims to examine the available papers on nano or microemulsions and wound healing from 2011 to 2022, adopting Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) criteria and bibliometric analysis.

2. Materials and methods

2.1 Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA)

This review was performed based on the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (Page *et al.*, 2021) using the following search databases: ScienceDirect, Scopus, and PubMed. The search terms used were ‘Nanoemulsions OR microemulsions’, ‘emulsions AND wound healing’, ‘microemulsions AND wound healing’, and ‘Nanoemulsions AND wound healing’. The searching techniques were (Terms in title, abstract, or author-specified keywords) for ScienceDirect. Besides, there were limitations in publication in terms of language, article type, and publication date. The results were restricted to literature written in English language only and research articles for ScienceDirect. The literature review covered a ten-year timeframe, from 2011 to 2022, to ensure that recent and relevant findings on emulsions, along with their regulatory aspects and effects on wound healing, were effectively highlighted. These findings are summarised in the PRISMA flow diagram shown in Figure 1.

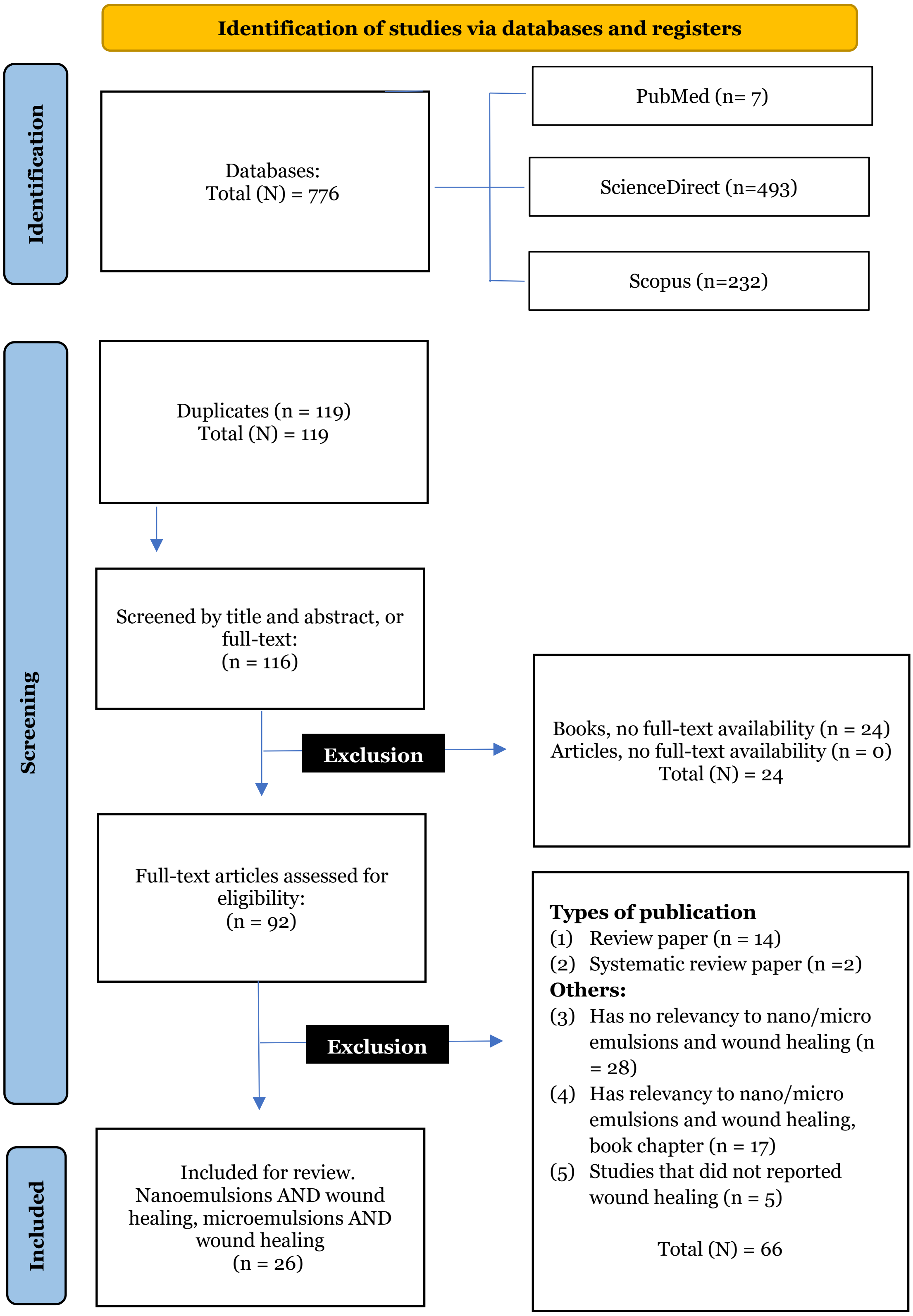

Figure 1: This illustration illustrates the PRISMA flowchart depicting identifying studies through databases and registers. The selected search engines, inclusion, and exclusion criteria led to 66 publications.

2.1.1 Eligibility and study choice

The significance of the effect of micro or nanoemulsions and rules in wound healing was thoroughly reviewed and investigated. The inclusion criteria for papers included in the review in this study included material related to the role of emulsions in wound healing, articles with full-text access or open access, publication type, English-language writing, and studies involving human subjects. The articles that were available in full text were thoroughly examined. This analysis excluded papers containing liposomes and unclassified drug subjects. Furthermore, no books, systematic reviews, review papers, case reports, or conference abstracts were included in this study. Articles that had no bearing on the functions of emulsions or their effects on wound healing were also excluded. This criterion was examined after carefully reviewing the titles and abstracts of the publications.

2.2 Bibliometric analysis

This study downloaded 776 publications on the nano or microemulsion effect in wound healing from the PubMed, Scopus, and ScienceDirect databases. This is the number of papers subjected to bibliometric analysis after being filtered by deleting duplicates, which amounted to roughly 119 documents. All articles from each database were downloaded and saved in a RIS (Research Information Systems) file format. RIS is one of the file formats that the VOSviewer, a software designed to investigate bibliometric links, can utilise and read. Some information obtained from these three databases, PubMed, Scopus, and ScienceDirect, was separated. Still, they were all connected to the nano or microemulsions and wound healing. The data retrieved from the PubMed database included the PubMed unique identification (PMID) number, publication type, publication title, author names, title of source, year published, digital object identifier (DOI) number, author keywords, and publication references. The authors' affiliation was not included in the downloaded file; it was added manually. Following that, data from the ScienceDirect database were retrieved, including publication type, title of publication, author names, title of source, year published, digital object identification (DOI) number, author keywords, and references for the paper. The authors' affiliation was not included; it was manually added for each title. Furthermore, the data gathered from the Scopus database had the title of the article, author names, identification of the source, year published, affiliation of the authors, author keywords, and references for the publication. Those files collected from the three databases were later added to an Excel sheet following Scopus format for further analysis.

3. Results and discussion

3.1 Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) main findings

In all of the included studies, the effect of micro or nanoemulsions on wound healing was acknowledged in Table 1.

Table 1: Table of main findings for all included studies

References	Study design	Population of study	Type of micro or nanoemulsions
(Okur *et al.*, 2020)	- Histopathological - Examination - *In-vitro* - 3 Months controlled	-Twenty-one Male Wistar albino rats	Fusidic acid (FA) loaded microemulsion-based gel.
(Kazemi *et al.*, 2020)	- Randomised - Histopathological - Examination - Real-time PCR - Excisional wound on the dorsal neck - of each rat - Topical application - 14 Days treatment - Controlled	- Eighty-five male Wistar rats	Nanoemulsions lavender essential oil and licorice extract
(Yousry *et al.*, 2022)	- Cytotoxicity test - *In-vivo* - Controlled - 16 Experimental runs - Histopathological - examination - Topical treatment - CLSM micrograph analysis	- Thirty-one male Wistar rats	- Collagen-loaded sunflower nanoemulsions. - Vitamin C-loaded sunflower nanoemulsions.
(Rizg *et al.*, 2022)	- Burn wound - Controlled - Topical application - 14 Days treatment - *Ex-vivo*	-Sixty-nine experimental rats	- Geranium (Gr) oil-based nanoemulsions loaded with Pravastatin PV

	- Rats were slaughtered, and abdominal skin was separated. Donor and receptor cells - An antibacterial test was performed.		
(Alhakamy *et al.,* 2022)	- Diabetic rat - Topical application - Controlled - Histopathological analysis. - Quantitative Real-Time PCR (qRT-PCR). - Histological analysis - 21 Day treatment. - Nes effect on oxidative stress analysis. - Immunohistochemical analysis of PDGF-B protein - Immunohistochemical analysis of TGF-β1	-FiftyMale Wistar rats	- Fluoxetine eco-friendly nanoemulsions (FLX-EFNE)
(Teo *et al.,* 2017)	- Topical application - Relative cell viability analysis. - Controlled - *In-vitro* cell monolayer wound scratch assay analysis. - 48 Hours treatment exposure. - The zeta potential analysis. - HPLC analysis of phenytoin-loaded alkyd nanoemulsions.	- Human adult keratinocytes (HaCaT cells)	- Phenytoin -Loaded Alkyd Nanoemulsions
(P. Alam *et al.,* 2017)	- Histopathological evaluation. - Collagen estimation - Oral administration - Controlled. - ANOVA statistical significance analysis. - 10 Day treatment.	- Twelve female Albino Wistar rats	- Clove oil nanoemulsions
(Gillespie Harmon *et al.,* 2017)	- 135 Day treatment. - 32 Wounds administered. - Controlled. - Topical treatment. - Excision of EGT. - Culture and microbial evaluation - Wound biopsy and histologic examination	- Eight healthy adult horses.	- Silver sulfadiazine cream, triple antimicrobial ointment, or hyperosmolar nanoemulsions on wound healing
(P. Alam *et al.,* 2018)	- Nanoemulsions optimisation. - Oral administration - Histopathological analysis. - Collagen determination by spectrophotometric absorbance.	-Twenty-four female Albino Wistar rats	- Eucalyptus Essential Oil Nanoemulsions
(Ahmad *et al.,*	- Controlled.	- Twenty male	- Eugenol-Nanoemulsion

2018)	- *In-vitro* drug release study. - *In-vivo* skin irritation studies. - Histological evaluation for skin. - Wound healing evaluation. - Anti-inflammatory activity. - *In-vitro* skin permeation study.	Albino Wistar rat	
(Shanmugapriya *et al.,* 2018)	- *In-vitro* cytotoxicity. - Antimicrobial activity. - *In-vitro* wound-healing assay. - Controlled.	- Four cell lines (CT26, HeLa, Panc1, and T24)	- Astaxanthin-alpha tocopherol nanoemulsions
(Akrawi *et al.,* 2020)	- Topical wound healing treatment. - *In-vitro* characterisation. - 14 Day treatment. - *Ex-vivo* Mucoadhesive Strength. - *In-vitro* Cytotoxicity Study. - Histopathological Study. - Controlled.	- Twelve adult female albino Wistar rats.	- Naringenin-Loaded Chitosan-Coated Nanoemulsions
(Farahani *et al.,* 2020)	- *In-vitro* and *In-vivo* analysis. - 22 Day treatment. - Cytotoxicity of the nanofibrous test. - Histopathological study.	- Twenty-one Male Wistar rats.	- Nanoemulsions of *Zataria multiflora*
(Back *et al.,* 2020)	- Controlled. - Skin retention or permeation assay. - Cell death by necrosis assay. - HaCaT migration assay. - Lipid peroxidation evaluation. - Histological evaluation. - 12 Day experiment.	- IAF and NEIAF. The HaCaT cell line (immortalised human keratinocytes) - Twenty-four male heterogenic Wistar rats.	- Soybean isoflavone aglycones rich fraction (IAF) incorporated into lipid nanoemulsions dispersed in acrylic-acid hydrogels
(Koshak *et al.,* 2021)	- Controlled. - *Ex-vivo* skin permeation Studies. - 14 Day treatment. - Histological examination. - RT-qPCR.	- Fifty male Wistar rats	- *Opuntia ficus-indica* Fixed Oil
(Guliani *et al.,* 2021)	- Controlled. - Bacterial growth inhibition studies. - Antibacterial activity studies with the prepared Nes. - Mechanism of bacterial killing by pure oil nanoemulsions.	- *Pseudomonas aeruginosa* bacteria.	- Citral and carvone-reduced oil
(Dolgachev *et al.,* 2021)	- Controlled. - 21 Day experiment. - Histological test.	- Eight pigs.	- Benzalkonium chloride nanoemulsions.

	- Topical burn wound. - Quantitation of soluble Mediators by enzyme. - Detection of neutrophils. - Hair follicle assessment.		
(M. S. Alam *et al.*, 2021)	- Controlled. - Antioxidant activity of Sage oil nanoemulsions. - DNA, protein, and collagen contents. - 12 Day treatment.	- Eighteen Wistar rats male	- Sage oil nanoemulsions
(Chakraborty *et al.*, 2021)	- Controlled. - Evaluation of nanoemulsions. - *Ex-vivo* permeation. - *In-vivo* evaluation. - 14 Day treatment. - Histopathology evaluation.	- Adult albino Wistar rats of either sex.	- Insulin-loaded nanoemulsions with Aloe vera gel
(Abdellatif *et al.*, 2021)	- Controlled. - *Ex-vivo* permeation. - Skin deposition. - *In-vitro* wound healing assay. - Histopathological studies.	- Human skin fibroblast cells.	- Propolis and tea tree oil nanoemulsions loaded with clindamycin hydrochloride
(Maatouk *et al.*, 2021)	- Controlled. - Encapsulation and release studies. - *In-vitro* experiment. - Cellular uptake of NPs investigation.	- HaCaT cell line (immortalised human keratinocytes)	- Sulfated alginate or polycaprolactone double-emulsion nanoparticles
(Vater *et al.*, 2022)	- The EZ4U cell proliferation assay. - The BrdU assay. - *In-vitro* wound healing assays. - *In-vitro* scratch assay. - 48-hour treatment.	- Human fibroblasts. - Human keratinocytes.	- Lecithin-based nanoemulsions
(Almukainzi *et al.*, 2022)	- Controlled. - Fourier-transform infrared spectroscopy (FTIR) analysis. - *In-vitro* Characterisation. - Transmission electron microscopy. - *In-vitro* release pattern. - Skin histological analysis. - *In-vivo* wound healing study.	- Ninety-six male Sprague-Dawley rat	- Gentiopicroside (GPS) nanosphere.
(Singh *et al.*, 2022)	- Controlled. - Permeation study. - Skin irritation test. - The hydroxyproline assay. - *Ex-vivo* permeation and retention analysis. - Histopathology.	- Female Wistar rats	- Raloxifene Nanoemulsions Gel
(Ghosh *et al.*, 2013)	- Controlled. - Antimicrobial activity.	- Twelve male Wistar rats	- Cinnamon oil (*Cinnamomum zeylanicum*) microemulsion.

	- Epithelialisation period. - Antibacterial activity. - Skin irritation assessment. - Wound healing study.		
(de Assis *et al.*, 2020)	- Controlled. - *In-vivo* pharmacological activity. - Morphological analysis. - Microbiological analysis. - 16 Day experiment. - Clinical aspects of skin wounds.	- Twenty-four male and female Swiss mice	- *Melaleuca alternifolia* essential oil (MEO) Microemulsions.
(Ryu *et al.*, 2020)	- Controlled. - *In-vitro* cell Experiment. - *In-vitro* membrane permeation experiment. - *In-vitro* skin permeation experiment. - Permeation experiments. - Effect of CoQ10 on skin regeneration.	- The HaCaT and NIH3T3 cells w	- Q10-Loaded Microemulsion

Table 1 compiles research on the effects of micro- and nanoemulsions on wound healing. Experiments were done in controlled environments for consistency. Commonly used species included Wistar rats, human adult keratinocytes, adult horses, and pigs, all under ethical guidelines. Safety measures were strictly followed before animal testing, essential before human trials. Standard procedures were used, such as acclimating samples, toxicity testing, inducing wounds, applying treatments, and observing systematically. The treatments helped heal wounds across different species, showing the beneficial effects of emulsions on various skin types. Histological analysis and permeation experiments monitored healing progress, which varied from 2 days to four months, depending on the sample and wound size. Control samples without additives were used for accurate comparison. Table 1 proves the positive effects and the future potential of micro- and nanoemulsions on wound healing.

The studies in Table 1 examine using micro and nanoemulsions for wound healing. Researchers often use methods like laboratory testing, histopathological evaluations, and animal models, particularly Wistar rats, which are common in wound healing research. These controlled settings allow detailed observations and comparisons between treated and untreated samples. Many studies explore different active ingredients, including essential oils, plant extracts, and drugs, chosen for their potential to speed up wound closure, reduce inflammation, and promote tissue repair. Researchers often assess formulations for stability, antimicrobial properties, and how well they penetrate the skin, which are critical factors for their effectiveness. Findings show improvements in wound healing with these emulsions, regardless of the specific active compounds. This indicates that the formulation method is important in making the active ingredients more effective. Histological analyses commonly demonstrate faster wound closure, increased collagen production, and reduced inflammation in treated samples. The application of emulsions remains the most common method, designed to adhere to wounds and gradually release active compounds for sustained therapeutic effects. Some studies also investigate oral administration to examine broader effects. Using both *ex-vivo* and *in-vivo* models strengthens the findings. Studies include detailed measurements like PCR immunohistochemistry, and tissue analysis to ensure accuracy. These methods provide a clearer view of how different treatments affect wounds over short and long periods. treated samples than in untreated ones. The studies cover many emulsions, from those based on plant extracts to drug-loaded formulations. This variety highlights the flexibility of micro and nanoemulsions for different types of wounds, such as burns, diabetic ulcers, and surgical incisions. Topical application remains the most common method, designed to adhere to wounds and release active compounds gradually. Some studies also investigate oral administration to examine broader effects. Using both *ex-vivo* and *in-vivo* models strengthens the findings. Studies include detailed measurements like PCR, immunohistochemistry, and tissue analysis to ensure accuracy. These methods provide a clearer view of how different treatments affect wounds over short and long periods.

Safety remains a key focus, with tests for cytotoxicity and skin irritation included to ensure the emulsions are safe. Researchers also examine factors like droplet size, zeta potential, and drug release profiles to balance effectiveness and safety. Adjustments in the formulation are ongoing, aiming to enhance therapeutic benefits while minimising risks. Animal studies and laboratory tests show potential for micro and nanoemulsions in wound care. Positive results suggest they may be suitable for human trials. Nanoemulsions, in particular, are often chosen over traditional treatments because they might offer better penetration, stability, and the ability to carry both water- and fat-soluble substances.

However, a gap remains in human clinical trials. The differences in skin structure between animals and humans mean these promising results need careful interpretation before broader use. Additionally, recent research combines natural compounds like essential oils with synthetic ingredients. This approach combines traditional medicine with modern methods. The increasing focus on essential oils in nanoemulsions for their antimicrobial and anti-inflammatory properties suggests a growing interest in natural remedies for wound care. One challenge is the variation in how nanoemulsions are prepared, which can affect reproducibility and scalability. Standardising preparation techniques are necessary to ensure consistent results. Simplifying complex processes could make these formulations more practical for larger-scale production and clinical application.

3.2 Data extraction and synthesis of findings

In the review process, 776 publications were initially identified through searches employing specific keywords (‘Microemulsions AND Wound healing’, ‘Nanoemulsions AND Wound healing’, and ‘Emulsions AND Wound healing’) across PubMed, Scopus, and ScienceDirect databases. After removing the duplicates using EndNote version X20.2.1 software, 119 duplicate articles were removed—subsequent screening involved examining titles, abstracts, and full texts, excluding 24 articles. The remaining 92 publications were subjected to the eligibility criteria. Twelve articles were eliminated due to their type (comprising review papers and systematic reviews), and 28 were found irrelevant to nano or microemulsions and wound healing. Another exclusion criterion was studies that did not report on wound healing, excluding 5 studies. Seventeen publications were excluded as they pertained to book chapters and did not meet the study's criteria. Consequently, 66 publications were excluded at this stage. Ultimately, 26 articles remained eligible for analysis, focusing on the impact of micro or nanoemulsions on wound healing. These selected papers were then summarised in a table, including authors' names, publication year, study design, study population, and the effects of nanoemulsions and microemulsions on wound healing.

3.3 Bibliometrıc analysis results

3.3.1 Countries analysis

Figure 2, generated using VOSviewer, illustrates the analysis from 2011 to 2022. The data reveals India as the most prolific country in publishing research on micro or nanoemulsions and wound healing, contributing to 12.09% of total publications. Following closely, Saudi Arabia and China, are responsible for 10.03% and 10.03% of the publications, respectively. Noteworthy contributions also come from the United States and Egypt, constituting 7.37% and 7.96% of the publications, respectively. As highlighted in Table 2, numerous countries worldwide have significantly contributed to the research on the impact of micro or nanoemulsions on wound healing, indicating the widespread interest in this area. Figure 2 visually represents these findings, with larger bubbles denoting countries with higher publication rates. These insights are instrumental in understanding the intricate relationships between keywords and research organisations. Table 2 provides a detailed overview of the top 20 countries that have extensively published literature on the effects of nano or microemulsions in wound healing.

Table 2: The top 20 countries contributed to the most literature

Country	Frequency	% (N=349)
India	65	9.46
China	35	4.58
Saudi Arabia	31	8.60
Brazil	31	1.15
United States	28	6.02
Iran	26	2.29
Egypt	21	4.87
Malaysia	17	5.73
Portugal	16	2.87
Australia	10	3.15
Turkey	11	1.15
Spain	13	3.44
Italy	8	2.01
United Kingdom	8	1.43
Pakistan	8	3.72
Greece	5	1.43
New Zealand	3	1.15
Belgium	3	1.72
South Africa	4	3.15
USA	6	1.72
Total	349	100.00

Figure 2: Illustrates the top 20 countries that published the most literature on the effect of nano or nanoemulsions on wound healing generated through VOSviewer analysis from 2011 to 2022, visually representing the global contributions to micro and nanoemulsions in wound healing research. India is the most active publisher, covering 12.09% of total publications, followed closely by Saudi Arabia and China at 10.03% and 10.03%, respectively. The United States and Egypt contributed significantly, with 7.37% and 7.96%, respectively. Larger bubbles indicate higher publication rates, reflecting the extensive global interest in this field

3.3.2 Keywords analysis

Figure 3 shows the relationships among keywords related to wound healing and emulsions. The size of the words indicates how often they occur, while the colour shows when the articles were published. Words like 'wound healing' and 'nanoemulsion' are in light green, indicating their publication dates between 2019 and 2020. 'Wound healing' is the most significant word, meaning it appears the most frequently. The size of the circles and text represent keywords associated with primary terms, such as 'drug delivery system,' 'cell proliferation,' and 'nonhuman.' Key terms like 'wound healing,' 'nanoemulsions,' and 'human' stand out, with 'wound healing' being the most cited keyword, covering 378.70% of all articles. 'Nonhuman' and 'nanoemulsions' follow, constituting 324.52%

Table 3: Top 20 author keywords with the most frequency

Author keywords	Frequency	% (N= 1,713)
Wound healing	185	378.70
Nonhuman	142	324.52
Nanoemulsions	151	309.92
Human	125	296.61
Article	115	253.82
Drug delivery system	99	230.36
Controlled study	94	210.92
Cell Proliferation	36	99.65
Humans	75	185.76
Animals	76	185.46
Animal	70	138.82
Unclassified drug	69	167.72
Nanoparticle	56	145.30
Drug formulation	64	157.21
Chemistry	59	148.98
Animal experiment	68	152.60
Particle size	65	147.58
Animal model	61	141.86
emulsion	47	114.01
microemulsion	57	133.74
Total	1,713	1000.00

and 309.92%, respectively. Table 3 supports these findings, showing that 'drug delivery system' and 'particle size' are among the top 20 keywords. These observations suggest that research focuses on wound healing and nanoemulsions, mainly involving nonhuman experiments in the reviewed studies.

4. Conclusion

The review of PRISMA studies highlights the progress in using nano and microemulsions for wound healing. These formulations have shown significant potential in medical treatments. A bibliometric analysis reveals that India is a leading contributor to nano/microemulsions and wound healing research. Standard terms like 'wound healing' and 'nanoemulsions' appear frequently, reflecting their importance in the studies, which often involve experiments on nonhuman subjects. Institutions such as the Research Institute on Biomaterials are at the forefront of collaborative projects and international partnerships, enhancing the scope and impact of the research. This shared knowledge, analysed through a bibliometric approach, demonstrates how local expertise and global perspectives can foster innovative solutions for wound care. The exploration provides data and insight into the future, where nano and microemulsions could be transformative in advancing wound treatments. Given the potential benefits in pharmaceutical and medical fields, researchers have a strong sense of anticipation. The reviewed papers show the importance of further investigating the unique advantages of these emulsions. The field appears ready for a new phase in medical practice, with micro and nanoemulsions at the forefront of future developments in wound healing.

5. Acknowledgements

The authors would like to acknowledge the support provided by the Sponsored Grant [SPD23-002-0002], and Grant [RMGS24-014-0045] from the Research Management Centre, International Islamic University Malaysia (IIUM), for this publication. Special thanks are also extended to the International Institute for Halal Research and Training (INHART), International Islamic University Malaysia, for providing the necessary facilities and resources to complete this review.

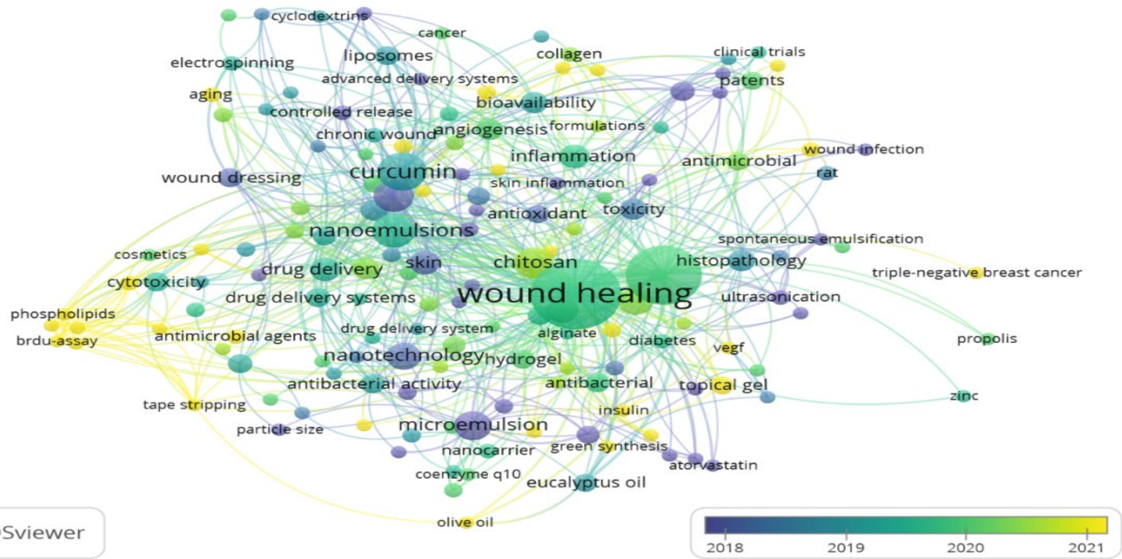

Figure 3: Visually displays the prevalence of 'wound healing' as the dominant keyword (12.09% frequency) alongside related terms like 'nonhuman' and 'nanoemulsions.' Colours and sizes indicate the thematic significance and usage frequency, focusing on wound healing and nanoemulsions in leading publications.

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