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BIBLIOMETRIC ANALYSIS OF LIQUID CRYSTALLINE NANOPARTICLES IN TRANSDERMAL DRUG DELIVERY AND THERAPEUTICS ADVANCES

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ABSTRACT: This systematic review provides a comprehensive overview of recent advancements in liquid crystalline nanoparticles (LCNs) utilized for transdermal drug delivery systems. Recent literature indicates a surge in research emphasizing lipid carriers derived from glyceryl monooleate and monoolein. The inherent nanostructure of LCNs offers superior solubilization capacity for bioactive molecules and controlled release mechanisms. This study underscores the potential of the cubic phase in LCNs as an innovative avenue for sustainable Transdermal Drug Delivery Systems (TDDS). Recent studies highlight the growing interest in cubosomes and hexosomes. Critical analysis necessitates further exploration into the therapeutic efficacy of Alpha lipoic acid cubosomes for anti-wrinkle applications, and the viability of hexagonal phase nano dispersions for in vivo peptide and siRNA delivery. A bibliometric assessment points out China as the leading contributor to LCN-centric publications. To summarize, LCNs are poised as potent TDDS, warranting future exploration in live skin imaging and immunological evaluations in animal model studiesproperties thus increasing residence time of drug with better patient compliance.

INTRODUCTION: Liquid crystalline nanoparticles (LCNs) have emerged as an innovative tool in the realm of drug delivery, especially for transdermal applications. With the growing emphasis on personalized medicine and targeted therapy, there's a dire need to develop efficient and sustainable drug delivery mechanisms [1-3].

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For usage in drug delivery, liquid crystalline (LC) phases of the different lipid self-assemblies have attracted significant study attention [3, 4]. Between liquid and solid crystalline arrays, LC phases exist [5]. LCNs is synthesized when LC phases are converted to nanosized particles without compromising the integrity of the structure of the bulk phases [6].

These nanocarriers serve as unique carriers because they provide protection and facilitate a biocompatible extended release of substances that have been dissolved in the LCN matrix, combining the advantages of liposomes and nanoparticles [7, 8]. The self-assembly of amphiphilic molecules [9–12], mostly lipids, that result in a variety of mesophases,

including hexagon, cube, and micellar phases, is a significant component in the creation of LC phases [13, 14]. The most frequent lyotropic phases among the numerous phases are hexagonal and cubic phases, which are also being extensively researched as drug delivery vehicles [15–17]. LCNs can be synthesized in several ways [18–22], such as by homogenizing, sonicating, or shearing bulk LC phases to reduce their size. According to the kind of energy sources utilized to break the bulk phases, the approaches may be broadly categorized as top-down or bottom-up. Top-down strategies use high-pressure homogenization and sonication, whereas bottom-up strategies use hydrotropes to cut down on energy inputs [17].

Around the world, transdermal preparations have attracted a lot of study attention [23–28]. The conventional external preparation is reportedly found to be effective since it contains a substantial dose [29–32]. However, because it cannot deliver the drug to the skin with continuous release, its therapeutic use is constrained. Recently, researchers have explored the functions and workings of liposomes, phospholipid complexes, and certain monomers [33–35].

Of which, cubic crystal is getting a lot of interest as a novel kind of transdermal delivery technology [36–38]. To increase drug penetration and absorption in the epidermis or skin layer while reducing the quantity of drug entering the bloodstream, [39–43] researchers have developed the ideas of skin-targeted and epidermis-targeted systems, respectively. The carrier technology has developed into a unique transdermal medication delivery system and is being studied for drug skin-targeting [44, 45].

In the case of LCNs for transdermal drug delivery, a thorough systematic review and bibliometric studies was found to be lacking in the literature. Therefore, the present investigation was conducted to provide the first comprehensive overview of LCNs with a focus on their transdermal application. This paper aims to provide a comprehensive overview of the current trajectory of LCN research, underscore its potential in revolutionizing TDDS, and spotlight areas like live skin imaging and immunological evaluations in animal model studies that require further exploration.

The main purpose of this review is three-fold:

Highlight Recent Advancements: To elucidate the recent advancements in LCNs, placing a particular emphasis on their utilization in TDDS. With the field rapidly evolving, it's paramount to understand the current trajectory and the novel applications that are now possible with LCNs.

Evaluate Therapeutic Applications: To provide a comprehensive analysis of emerging therapeutic applications, especially focusing on the therapeutic efficacy of Alpha lipoic acid cubosomes as anti-wrinkle agents and the potential of hexagonal phase nano dispersions in the delivery of peptides and siRNA *in-vivo*.

Understand Global Research Trends: Given the global nature of scientific research, this review will also shed light on the geographical distribution of LCN research, with specific attention to China's predominant role in this domain.

By amalgamating the latest findings, this review aims not only to serve as a reference for those already in the field but also to act as a foundation for future research endeavours, especially in areas like live skin imaging and animal model-based immunological studies.

Literature Review: The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standards were advanced for this explanatory review [46] and Biblioshiny for Bibliometrix by R was used to do the bibliometric analysis.

Criteria for Considering Studies for Inclusion and Exclusion: Literature correlating transdermal application of LCNs published up to September 1, 2022, was searched by using Scopus. In all scientific domains, Scopus contains more than 23,000 indexed journals, moreover, it also incorporates MEDLINE and EMBASE databases [47].

The entire framework was mostly created using key phrases "liquid crystalline nanoparticles", “cubosomes”, “transdermal” and “skin” that were chosen because they were pertinent to our findings. Additionally, important phrases were combined using the Boolean operators "AND" and "OR."

The articles pertaining to the exploration of synthesis and characterization of LCNs associated with the transdermal application were included in this systemic analysis. In total, the search strategy resulted in 159 available publications. Of which review (33), conference proceedings (3), and book and book chapter (2) were excluded from studies. Thorough screening resulted in 121 articles that were suitable and consistent with the aims of this review. Out of which, the top 18 out of 20 globally cited articles were further discussed in detail. **Fig. 1** illustrates the search techniques employed in this investigation as well as the results gleaned from various databases.

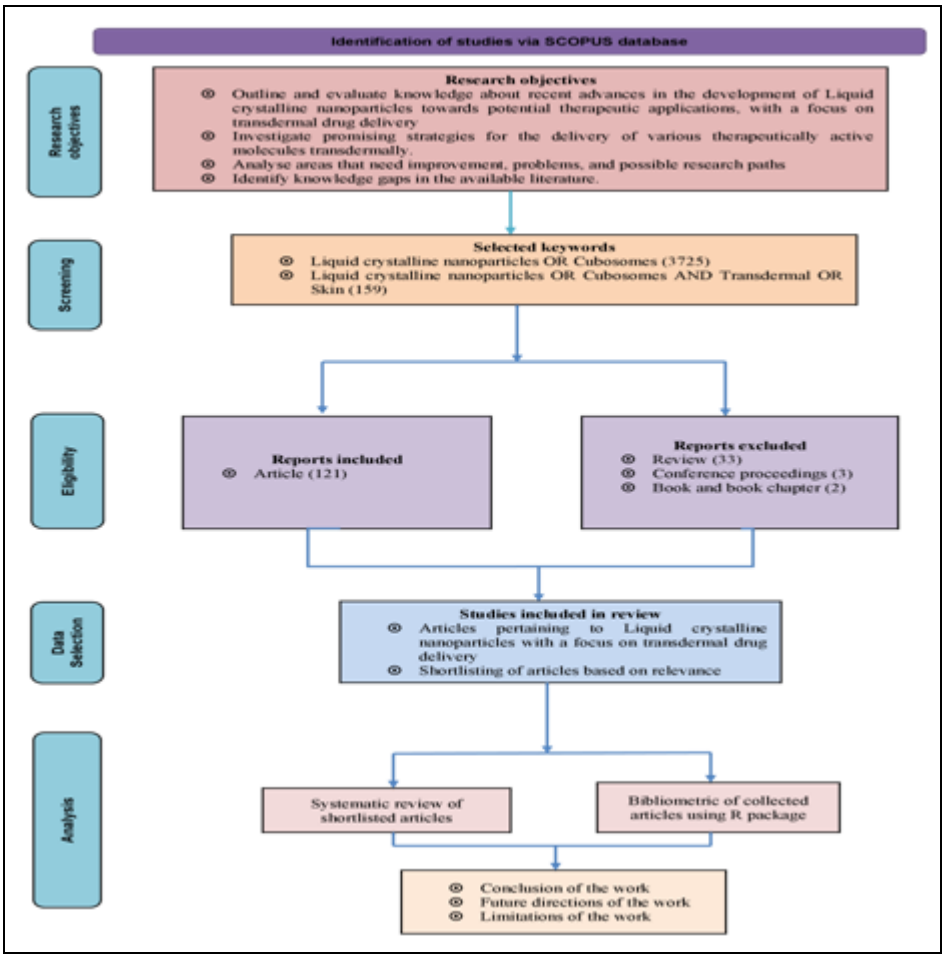

FIG. 1: ILLUSTRATION OF SELECTION CRITERIA OF THE STUDIES

Data Collection and Analysis: A citation network diagram, subject evolution map, and international collaboration network map were employed in the current work's data analysis to evaluate research hot zones, research quality, and the characteristics of the LCNs breakthrough. Five phases served as a roadmap for the scientific mapping process technique [48] that was applied in this investigation.

RESULTS:

Analysis of main Information: The **Table 1** provides a detailed overview of the characteristics of the dataset analysed. It includes information on the timespan, sources, documents, citations, references, document types, keywords, and authors. The period of the data analysed ranges from 2004 to 2022, indicating that the publications included in the dataset were published over 18 years. The sources of the data include 74 different journals, books, and other publications. A total of 121 documents were analysed, with an average of 5.16 years between the date of publication and the analysis. The average number of citations per document was found to be 24.82, indicating that the publications in this dataset were influential and well-received within their respective fields. The average number of citations per year per document was calculated to be 3.535, indicating a sustained level of interest in the publications over time. A total of 5426 references were cited in the 121 documents analysed, indicating that the authors of

these publications conducted thorough research to support their findings. All 121 documents were articles, and they contained a total of 1530 Keywords Plus (ID) and 435 author-defined keywords (DE).

TABLE 1: MAIN INFORMATION ABOUT PUBLICATIONS ON LCNs

Description	Results
Main information about data	
Timespan	2004:2022
Sources (Journals, Books, etc)	74
Documents	121
Average years from publication	5.16
Average citations per document	24.82
Average citations per year per doc	3.535
References	5426
Document types	
Article	121
Document contents	
Keywords Plus (ID)	1530
Author's Keywords (DE)	435
Authors	
Authors	508
Author Appearances	660
Authors of single-authored documents	1
Authors of multi-authored documents	507
Authors collaboration	
Single-authored documents	1
Documents per Author	0.238
Authors per Document	4.2
Co-Authors per Documents	5.45
Collaboration Index	4.22

The dataset analyzed had 508 authors, with a total of 660 author appearances across the documents. Of the 121 documents, only one was single authored, while the majority had multiple authors. The average number of authors per document was 4.2, while the average number of co-authors per document was 5.45. The collaboration index was found to be 4.22, indicating a high level of collaboration among authors in the publications analyzed. The annual trend of academic publications concerning LCNs for transdermal application during an 18-year period, from 2004 to 1 September 2022, is shown in **Fig. 2**. Research began to rise in 2012 and fluctuated between increases and decreases through 2022. The highest year of publishing, shown on the graph as 2021, has 19 publications. Over the span of the investigations, the number of publications were observed to consistently grew. A difference of 111 articles between 2012 and 2022 reveals a significant positive trend. However, the first 7 years show no change in the count movement of publications. While, since 2012, there has been an upsurge in publications. The graph's trajectory makes it evident that there is a sharp increase in 2020, which may be attributed to the worldwide pandemic crisis.

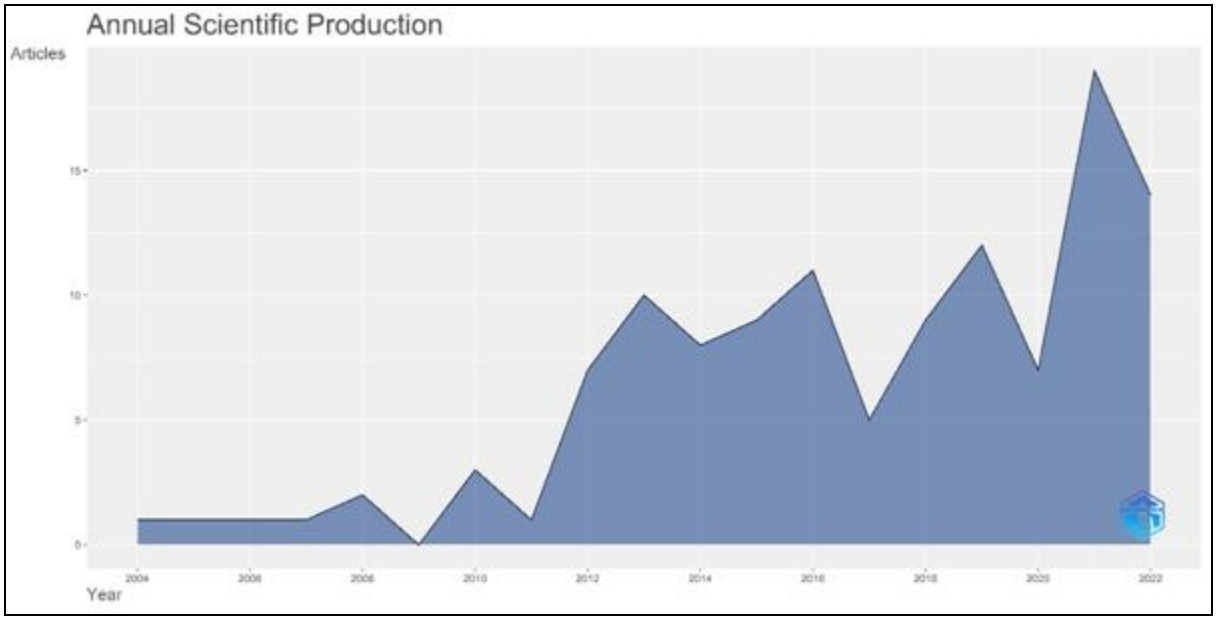

FIG. 2: ANNUAL SCIENTIFIC PRODUCTION CONCERNING LCNs FOR TRANSDERMAL APPLICATION

Fig. 3 shows the top 20 sources on LCNs for transdermal application according to the Scopus database's core collection. The five most productive journals enlisted are International Journal of Pharmaceutics, European Journal of Pharmaceutics and Biopharmaceutics, Drug Delivery and

Translational Research, Journal of Drug Delivery Science and Technology, and Drug Development and Industry Pharmacy. The International Journal of Pharmaceutics is the most pertinent source of all and, out of 358 journals, is the second most cited journal in the "Pharmacy & Pharmacology" category. The journal publishes research papers, reviews, comments, letters to the editor, special issues, and special sections on pharmaceutical nanotechnology and customized medications. This involves analysing the characteristics of pharmaceuticals, excipients including polymers and surfactants, and novel materials. This journal is ranked 40 out of 279 in Pharmacology & Pharmacy by its Impact Factor, which is 6.510 [49].

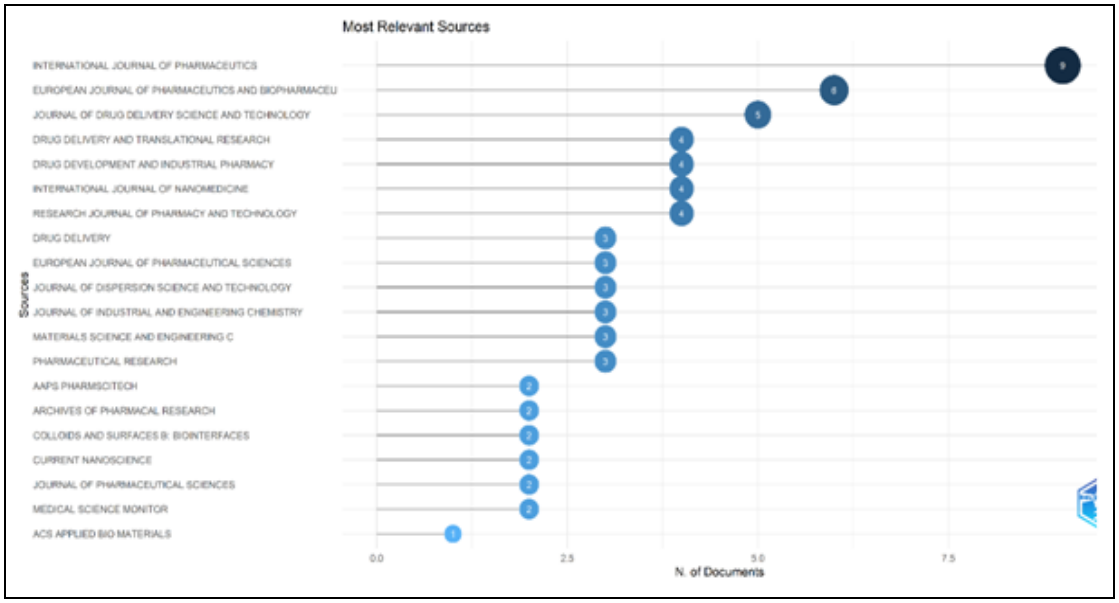

FIG. 3: TOP 20 RELEVANT SOURCES THAT PUBLISH ON LCNs FOR TRANSDERMAL APPLICATION

Analysis of Author Keywords and Authors: By examining the distribution of each keyword, the researchers could ascertain the importance of each author's keyword. The top 20 author-related term frequencies across all publications are shown in **Fig. 4**. According to the statistics, the terms most used by the authors were "particle size," which accounted for 6% of them, "article," which accounted for 5%, "skin," which accounted for 4%, "nonhuman," which accounted for 3%, and "nanoparticle," which accounted for 3%.

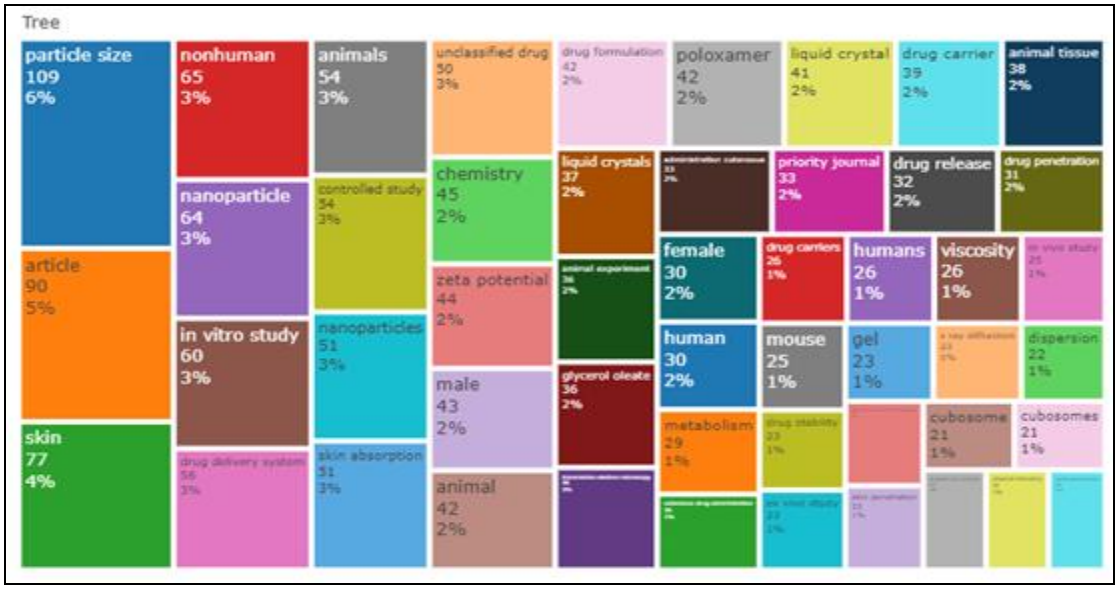

FIG. 4: MOST CITED AUTHOR KEYWORDS CORRELATING WORK ON LCNs FOR TRANSDERMAL APPLICATION

The researchers who have contributed the most to the field of LCNs and their use in TDD are listed in this section. According to **Table 2**, the following authors are acknowledged as the most relevant authors. With a total of 8 publications, Yoo BK leads the list. This is followed by Bentley MVLB and Kim J-C with seven papers each, preceded by Baskaran R, Fantini MCA, and Madheswaran T with six publications, Cortesi R, Drechsler M, Esposito E, and Mariani P with five publications, and so on. When it comes to work connecting LCNs, 33 papers endorsed by Universidade De Sao Paulo, 23 publications fully supported by Yeungnam University, 19 publications facilitated by scholars from the Kangwon National University, 18 publications backed by the University of Ferrara, and 15 publications governed by Alexandria University are recognized among the widely mentioned affiliations **Fig. 5.**

TABLE 2: LIST OF MOST RELEVANT AUTHORS

Authors	Articles	Articles Fractionalized
Yoo BK	8	2.04
Bentley MVLB	7	1.02
Kim J-C	7	2.42
Baskaran R	6	1.21
Fantini MCA	6	0.83
Madheswaran T	6	1.21
Cortesi R	5	0.58
Drechsler M	5	0.58
Esposito E	5	0.58
Mariani P	5	0.58
Hook S	4	0.74
Murgia S	4	0.59
Puglia C	4	0.45
Rattanapak T	4	0.74
Singhvi G	4	0.97
Thapa RK	4	0.96
Yong CS	4	0.71
Depieri LV	3	0.41
Fornasier M	3	0.39
Gorantla S	3	0.87

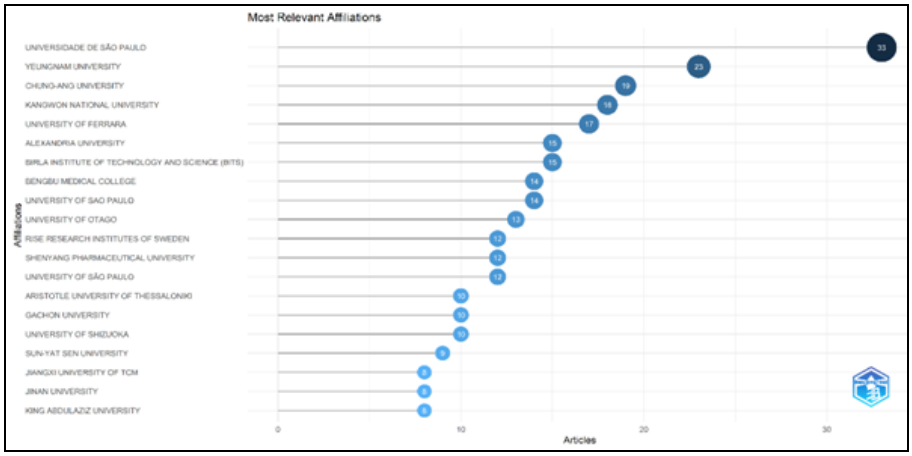

FIG. 5: MOST RELEVANT AFFILIATIONS CORRELATING WORK ON LCNs FOR TRANSDERMAL APPLICATION

Examining the results of the co-citation analysis, which was done using all of the reviews included, it was discovered that 49 individuals had citations in pertinent works.

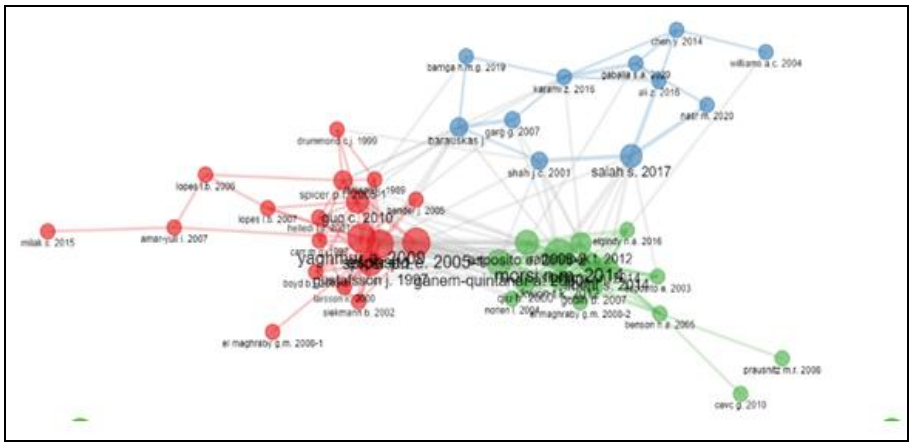

FIG. 6: CO-CITATION MAP SHOWING THE CONTRIBUTION OF AUTHORS TO THE BODY OF KNOWLEDGE IN LCN

As can be observed, the map **Fig. 6** forms a number of clusters. A cluster is formed by authors who have a lot of citations together. Upon initial inspection of the full map, it appears that Yaghmur A. 2009 is positioned in a comparatively central location in the red cluster, Ganem-quintanar A. 2000 in the green cluster, and Salah S. 2017 in the blue cluster. This demonstrates that Yaghmur A. 2009, Ganem-quintanar A. 2000, and Salah S. 2017 were referenced in several research and made contributions to the body of knowledge in LCN disciplines.

Contribution of Regions/Countries: The diffused blue colour illustrates a notable advancement in the field in several nations. **Fig. 7A** demonstrates that many regions have not yet started scientific research linking the transdermal application of LCNs. On the flip side, China tops the list of nations with the greatest number of articles on the subject with 127 publications. It is preceded by India (95), South Korea (85), Brazil (69), Italy (59), Egypt (51), Sweden (22), Japan (21), and Saudi Arabia (16). It is instantly clear how the topic has evolved in nations on many continents, underscoring a rising demand for the transdermal application of LCNs.

The collaborative network is shown in Figure 7(b); most publications are independent works from India. The countries such as Korea, Japan, Australia, Germany, Greece, Mexico, Portugal, Singapore, Sweden, and Thailand mostly concentrate on individual research, while other countries collaborate globally. The scope of the authors' collaboration is clearly shown by the pink lines that link the countries on the national collaboration map **Fig. 7C**. It is interesting to notice the cooperative efforts of the countries that have produced the most papers on LCNs and their transdermal application. The most significant international connections include association of Brazil with Argentina, Nepal, Portugal, and the United States; China with the USA; Egypt with Lebanon and Saudi Arabia; Germany with France and Netherlands; India with Australia, Brazil, Korea, and Nepal; Italy with France, Germany, Israel, Poland, Sweden, and Switzerland.

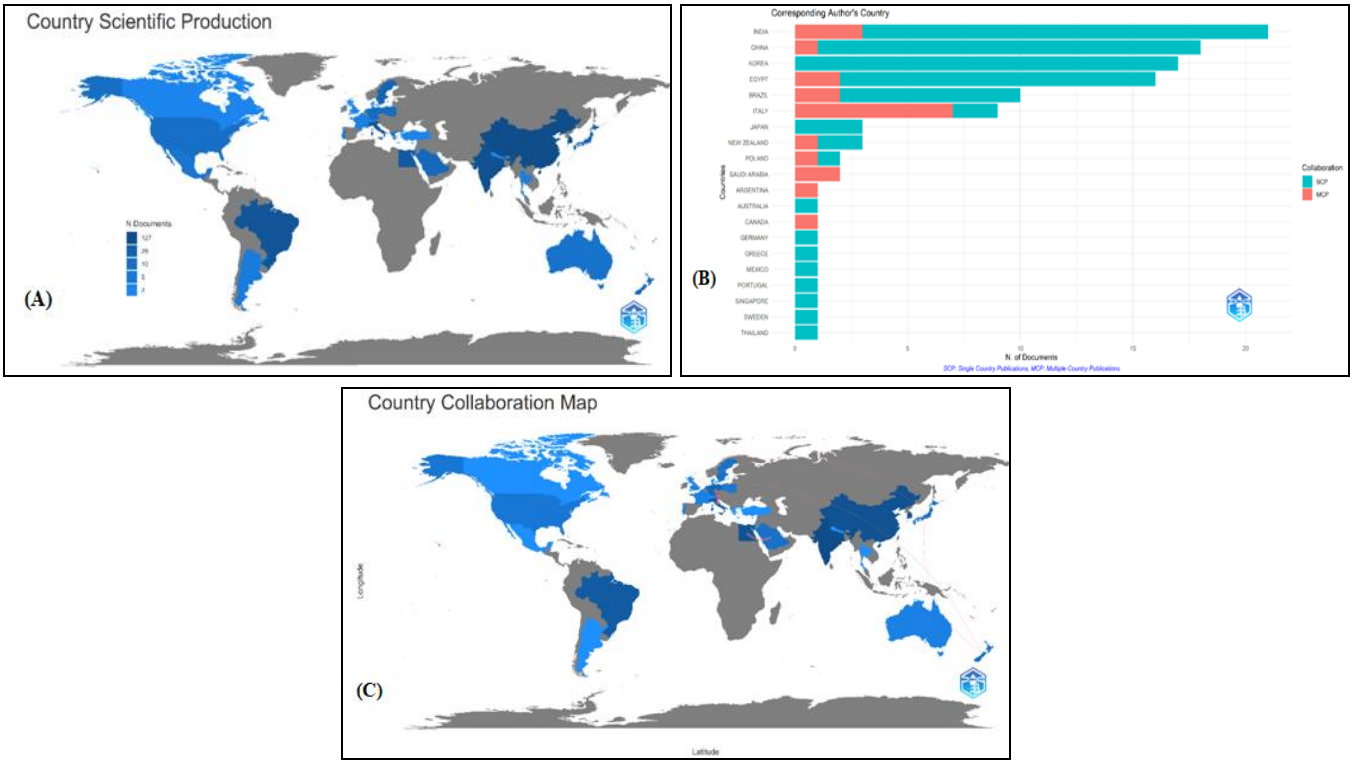

FIG. 7: (A) MAP ILLUSTRATING COUNTRY SCIENTIFIC PUBLICATIONS, (B) GRAPHICAL DEPICTION OF A COLLABORATIVE NETWORK, AND (C) COUNTRY COLLABORATION MAP

Analysis of Research Areas among Most Globally Cited Paper: The most highly cited paper of all, as shown in **Fig. 8**, "Lipid nanoparticles as vehicles for topical psoralen delivery: Solid lipid nanoparticles (SLN) versus nanostructured lipid carriers (NLC)", published in

European Journal of Pharmaceutics and Biopharmaceutics, was written by Fang and team in 2008 [50]. Overall, it has made 386 citations. Following this is the work entitled "Cubosome Dispersions as Delivery Systems for Percutaneous Administration of Indomethacin" by Esposito *et al.*, 2005 [51] published in Pharmaceutical Research (220), "Reverse Hexagonal Phase Nano dispersion of Monoolein and Oleic Acid for Topical Delivery of Peptides: *in-vitro* and *in-vivo* Skin Penetration of Cyclosporin A" by Lopes *et al*., 2006 [52] issued in Pharmaceutical Research (157), "Comparative study of liposomes, transfersomes, ethosomes and cubosomes for transcutaneous immunization: characterization and *in-vitro* skin penetration" by Rattanapak, 2012 and team [53] printed in Journal of Pharmacy and Pharmacology (96), and "Cubosomes for topical delivery of the antimicrobial peptide LL-37" authored by Boge, 2019 and coworkers [54] in European Journal of Pharmaceutics and Biopharmaceutics (87).

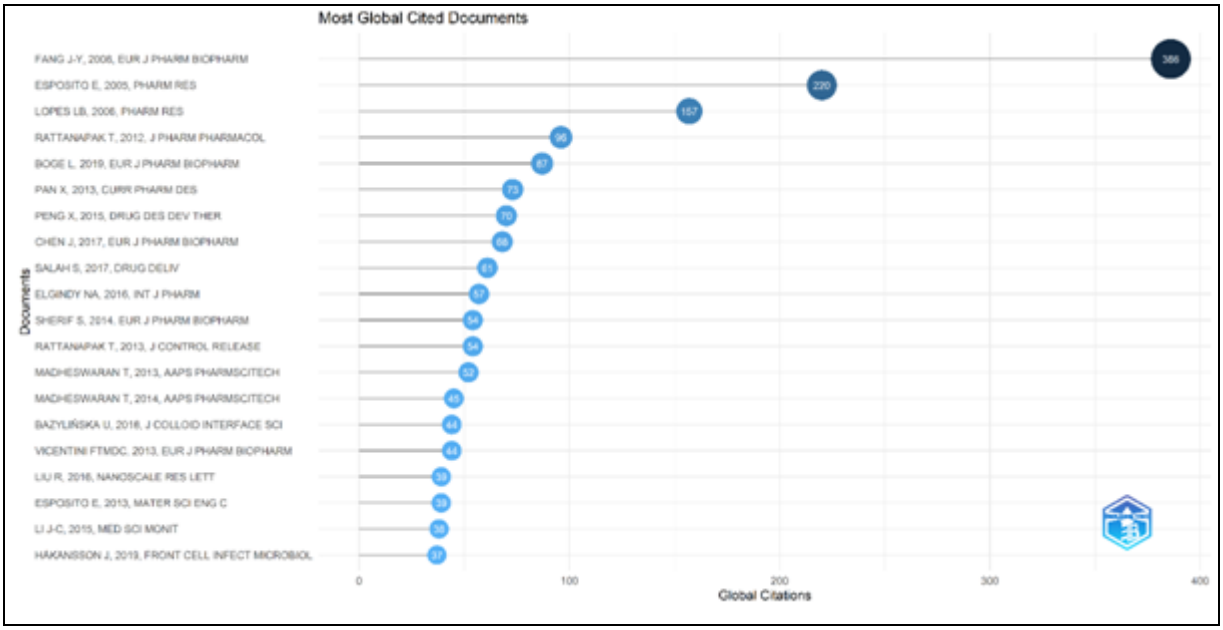

FIG. 8: MOST GLOBAL CITED PUBLICATIONS IN THE CONTEXT OF TRANSDERMAL APPLICATION OF LCNs

The study correlated transdermal application of LCNs in the top 20 papers referenced internationally is discussed in this section, as shown in **Table 3**. Out of which, 2 papers were excluded appertaining to the application as an Ophthalmic Delivery System and critical review on cubosomes.

Solid lipid nanoparticles (SLN) employing Precirol ATO 5 and Nanostructured lipid carriers (NLC) prepared using Precirol and squalene were synthesized by Fang and team [50] for comparative studies. The typical particle sizes in SLN and NLC were found to be around 300 and 200 nm, respectively. Both systems' viscosities displayed Newtonian behaviour, except for the NLC that used Tween 80 and soybean phospholipids as emulsifiers. The DSC thermograms show that after adding squalene to the solid lipid cores (of NLC), reduced particle sizes and flaws in the crystalline lattice of the lipid cores are shown by the shift in the melting peak of Precirol from 58 to 55°C. Enhanced penetration and regulated release of psoralen administration were also obtained utilizing the NLC. The outcomes showed that, in comparison to the free drug in an aqueous control, psoralen entrapment in nanoparticulate systems can diminish the permeability difference between normal and hyperproliferative skin.

Monooleine (MO) dispersions for delivery of indomethacin were prepared and characterized by Esposito *et al.* [51]. Vesicles and cubosomes were found to coexist, according to microscopy investigations. A bicontinuous cubic phase with spatial symmetry Im3m was detected by X-ray diffraction. The dispersion included no free drug, as shown by sedimentation field flow fractionation. Contrasted with the similar formulation using the drug-free both in the carbomer gel-based control

formulation and aqueous phase, indomethacin integrated into viscosized MO dispersions showed a lower flux. By synthesizing and characterizing reverse hexagonal phase MO and oleic acid nanodispersions, Lopes *et al.* [52] evaluated the system's potential to increase cyclosporin A (CysA) skin penetration without irritating the skin. In this work, Cryo-TEM, small angle X-ray diffraction, and polarised light microscopy confirmed hexagonal phase nano dispersion. The size of the particle was recorded to be 181.77 ± 1.08 nm. At 0.6%, Cys A showed no effect on the structure of LCNs. Both *in-vitro* and *in-vivo*, the nano dispersion aided CysA's skin penetration. When CysA was included in the nanodispersion rather than the control formulation, *in-vitro*, the highest concentrations of CysA achieved in the SC and the epidermis without SC (E) + dermis (D) were around two times greater. When the nano dispersion method was used, concentrations in the SC and [E+D] were 1.5 and 2.8 times greater *in-vivo*, respectively.

Rattanapak *et al.* evaluated the ability of lipid colloidal vaccines, such as liposomes, transfersomes, ethosomes, and cubosomes, to boost a peptide vaccination's penetration through the skin of stillborn pigs [53]. There were similarly sized (range: 134–200 nm) negatively charged particles in the various compositions. Quil A, a saponin adjuvant, destabilized the monolayers and decreased peptide loading when added to formulations. Comparatively to the other systems, cubosomes, and ethosomes demonstrated improved skin retention. Greater peptide penetration and accumulation were seen using confocal laser scanning microscopy on skin that had received cubosome and ethosome treatments.

The topical administration of the antimicrobial peptide (AMP) LL-37 was carried out by Boge *et al.* [54] using cubosomes. Data indicated that in the case of sonicated cubosomes, high loading of LL-37 caused the production of vesicles (pre-loading). The fact that LL-37 did not release from the cubosomes, it is likely that the peptide has well adhered to the particles. Studies on proteolysis demonstrated that the peptide LL-37 had a great affinity for the cubosomes because it was completely shielded from enzymatic assaults while attached to them. The cubosomes' lack of risk for skin irritation makes topical delivery possible. The *ex vivo* wound infection model demonstrated that cubosomes loaded with LL-37 killed the majority of the bacteria. Phytantriol and glycerol MO-based cubosomes were developed and studied by Peng *et al.* [55] as a targeted and long-lasting transdermal delivery strategy for capsaicin. Small-angle X-ray scattering verified their Im3m crystallographic space group. Research on *in-vitro* release shows that the cubosomes provide a method for the prolonged release of capsaicin. Franz diffusion cells were used in *in-vitro* diffusion studies to measure skin retention of capsaicin from cubosomes in the SC, which was shown to be much greater than that of capsaicin cream. Up to 10 days of stability were reported for the cubosome formulations under intense light and high temperatures, as indicated by the stress testing. Capsaicin cubosomes and cream caused the least number of negative effects after being applied many times to mouse skin.

SLN and NLC were investigated by Chen *et al.* [56] as possible drug delivery vehicles for both cutaneous and TDD. In SLN, lipid droplets with a significant degree of crystallization and a highly ordered crystalline structure are present. The lipid phase of NLC is a modified SLN that at normal temperature contains both solid and liquid lipids. In this study, LCNs of Resveratrol, Vitamin E, and Epigallocatechin Gallate were designed. Resveratrol and Vitamin E lipid nanoparticles both provided a strong defence against UV-induced degradation of active ingredients. However, in this study, LCNs did not provide protection for Epigallocatechin Gallate from UV destruction.

After 24 hours, an active release analysis showed a continuous release of resveratrol of over 70%. According to research on the penetration of LCNs into the skin, resveratrol penetrates the SC more effectively. The delivery of resveratrol and Vitamin E to the skin to give long-lasting antioxidant effects are suggested to be possible with LCNs as viable carriers. Salah *et al.* [57] designed transdermal cubosomes to provide stable etodolac concentration in the targeted areas. The zeta potential values of the etodolac-loaded cubosomes ranged from -18.40 to -36.10 mV, while the particle sizes ranged from 135.95 to 288.35 nm. All of the cubosomes had drug loading capacities ranging from 1.28 to 6.09%

and an encapsulation efficiency value of about 100%. A regulated drug release profile with a drug release rate of up to 15.08%/h was determined by the *in-vitro* drug release studies. Higher quantities of poloxamer were added to etodolac-loaded cubosomes, resulting in nanoparticles with smaller particle sizes and faster drug release. The particles showed both hexagonal and cubic forms. In the bicontinuous cubosomes, the material was observed to be contained in its amorphous form. Researched cubosomes also showed quick drug absorption through the epidermis of agitated mice, followed by slow drug absorption for up to 24 hours. With evidence of a longer half-life and higher MRT that reached 18.86 and 29.55 h, respectively, the selected etodolac-loaded cubosomes increased the bioavailability of etodolac as compared to the oral capsules (266.11%), according to the pharmacokinetic study in human volunteers.

Elgindy *et al.* [58] studied innovative self-assembled LCNs to treat hormonal imbalances after non-invasive transdermal progesterone administration. Quality by design methodology based on a 2^3 complete factorial design was used to evaluate the fabrication and optimization of progesterone loaded LCNs for TDD. The independent operational variables had a substantial impact on the five dependent responses according to the factorial design. The cubosomes' hydrodynamic dimensions (101-386 nm) were found in the nanometer range and showed strong negative zeta potentials of ≥ −30 mV and ≥ 94% entrapment efficiency. The LCNs used a non-fickian route of drug diffusion to sustain progesterone release for approximately 24 hours.

The TDD of progesterone loaded LCNs was significantly improved up to 6 times in *ex vivo* research as compared to its aqueous solution. While maintaining the cubic structure for at least three months, the improved LCNs showed a high level of physical stability. With the help of the quality by design methodology, a mathematical model that was predictable and facilitated the creation of new LCNs for progesterone TDD while minimizing its oral route adverse effects were successfully developed. 5% topical Alpha lipoic acid (ALA) is prepared by Sherif *et al.* [59] for the treatment of photodamaged skin. This research sought to assess the utility of poloxamer (P407) gel as a delivery mechanism for ALA's cubosome dispersions. The results also demonstrated that cubosome size decreased, zeta potential increased, encapsulation effectiveness increased up to 86.48%, and drug release rate slowed as the amount of Glycerol monooleate (GMO) in the dispersion increased. The cold technique was used to create P407 gels. According to the results, as P407 concentration is increased, the temperature at which gelation occurs drops, and viscosity rises. The Higuchi square root model was found to be followed by drug release in both cases. The release rate from gel loaded with ALA cubosomes was much less than that from gel filled with unencapsulated ALA. The effectiveness of a topical 30% P407 gel loaded showed that most volunteers' skin tone and texture had improved overall, along with a reduction in facial wrinkles and a nearly total disappearance of fine lines around the upper lip and periorbital area.

No incidences of itchiness, peeling, or other obviously negative side effects were observed. In another study, to deliver vaccinations via the skin, Rattanapak *et al.* [60] combined microneedles (MNs) with cubosomes. The use of MNs enhanced the penetration of an aqueous peptide mixture through the skin, whereas cubosome-formulated peptides and cubosomes were shown to be preserved in the skin. In order to effectively transport antigens to immunocompetent cells in the skin, it is suggested that a hybrid strategy utilizing MNs and cubosomes be used. LCNs were suggested by Madheswaran *et al.* [61] as a potential carrier for topical finasteride (FNS) administration in the treatment of and rogenetic alopecia.

By using the ultrasonication approach, FNS-loaded LCNs were prepared. Less than 20% of the drug was released in the first 24 hours from the cubical shaped particles ‘controlled release profile, which had a size range of 153.8 to 170.2 nm. The inclusion of various chemicals drastically changed the release profile. The skin penetration of the formulation with reduced MO was found to be greater, with a flux rate of $0.061 \pm 0.005\ \mu g\ cm^{-2}\ h^{-1}$ in 24 hours. Glycerol, propylene glycol, and polyethylene glycol 400 greatly enhanced the permeability, but oleic acid had the opposite effect. A similar pattern was seen in research on skin retention. The capacity of two surfactants, Cremophor RH 40 and Cremophor EL,

to create LCNs and analyse their impact on the TDD of FNS were examined by Madheswaran *et al.* [62]. The average particle sizes of the formulations were correspondingly between 165.1-208.6 nm and 153.7-243.0 nm. Higher surfactant concentration formulations demonstrated quicker release and noticeably greater skin penetration. Particularly, compared to lower concentrations (0.029 ± 0.007 μgcm^{-2}h^{-1}), LCNs produced with RH 2.5% showed a greater permeation flux (0.100 ± 0.005 μgcm^{-2}h^{-1}). More lipid acyl chain disorder, which may have contributed to the increase in SC fluidity, was shown by the relocation of the usual spectral bands of the lipid matrix of pig skin to higher wave numbers. Cremophor surfactants demonstrated a good propensity to stabilize the LCN and considerably increase the penetration of FNS through the skin when used together.

Cubosomes were synthesized by Bazyliska *et al.* [63] using MO as a building component, propylene glycol as a hydrotrope, and phospholipids as stabilizers. Photodynamic activity assays demonstrated the formulation of cubosomes laden with Chlorin e6 dye's relatively low cytotoxicity in the "dark" condition as well as its strong cytotoxic impact following photoirradiation. It was discovered that the negative effects caused by the free photosensitizer were orders of magnitude less severe than those caused by the photosensitizer contained within the cubosomes. Vicentini *et al.* [64] explored LCNs that deliver siRNA into the skin. The findings indicated that the examined nanodispersions would be a potential new non-viral carrier and might be highly beneficial in the treatment of skin conditions. They were able to lower the levels of the model protein glyceraldehyde-3-phosphate dehydrogenase without irritating the skin and increase the skin penetration of siRNA. MO aqueous dispersions were developed and characterized by Esposito *et al.* [65] as a curcumin drug delivery vehicle. MO produced heterogeneous dispersions made up of unilamellar vesicles, cubosomes, and sponge-like phases in various mixes with sodium cholate, sodium caseinate, bentonite, and poloxamer. It was discovered that the presence of MO-based nanosystems affects the fluxes of curcumin absorbed into MO aqueous dispersions. Particularly, MO aqueous dispersions made with xanthan gum showed superior control over curcumin diffusion. Li *et al.* [41] improved the procedure for manufacture and characterized the features for TDD of MO-based cubosomes containing paeonol. The irritation in the skin-stimulating test may be reduced by the paeonol LCNs, according to research that contrasted the commercial ointment with stimulating investigation. The preclinical *in-vitro*, *ex-vivo*, and *in-vivo* bactericidal activity as well as the propensity to irritate skin of human kininogen-derived antimicrobial peptide DPK-060 was examined by Håkansson *et al.* [66] in different TDD. The results showed that *Staphylococcus aureus* bacterial counts were considerably reduced in vitro by DPK-060 formulations in acetate buffer or poloxamer gel (minimum microbicidal concentration <5 μg/ml).

Furthermore, results utilising two separate animal models of surgical site infections an *ex-vivo* wound infection model using pig skin and an in vivo mouse model showed that DPK-060 in poloxamer gel significantly reduced microbial survival. At 4 hours after treatment, bacterial counts were reduced by ≥ 99 or ≥ 94%, respectively. Under the investigated test conditions, encapsulating DPK-060 in various lipid nanocapsule or cubosome types did not enhance the peptide's ability to kill bacteria. In all the studied formulations, injection of DPK-060 did not result in a decrease in cell viability. The current research suggests that DPK-060 might be a potent and reliable therapeutic choice for the TDD of microbial infections; however, the peptide's adsorption to nanocarriers did not yield any further benefits.

TABLE 3: BRIEF DESCRIPTION OF MOST CITED PAPERS

Authors	Liquid crystalline phase	Lipid carriers	Drug entity	Therapeutic application	Ref.
Fang J-Y, 2008	-	Precirol and squalene	Psoralen	Reduce the permeability difference between healthy skin and skin that is hyperproliferative or	[50]

				psoriasis-like.	
Esposito E, 2005	Bicontinuous cubic	Monoolein	Indomethacin	Frequently prescribed non-steroidal anti-inflammatory medication for the treatment of rheumatic illnesses and dermatitis.	[51]
Lopes LB, 2006	Hexagonal	Monoolein and oleic acid	Cyclosporin A	Therapy of cutaneous disorders.	[52]
Rattanapak T, 2012	-	Monophosphoryl lipid	Quil A	Transcutaneous immunization involves injecting vaccine adjuvants and antigens under the skin.	[53]
Boge L, 2019	Bicontinuous cubic	Glycerol monooleate	Antimicrobial peptide LL-37	Therapy for bacterial skin infections caused by *Staphylococcus aureus*.	[54]
Peng X, 2015	Bicontinuous cubic	Phytantriol- and glycerol monooleate	Capsaicin	Used to treat contact allergies, apocrine chromhidrosis, pruritus, and psoriasis.	[55]
Chen J, 2017	-	Sesame oil	Resveratrol, Vitamin E, and Epigallocatechin Gallate	Deliver the skin with long-lasting antioxidant properties.	[56]
Salah S, 2017	Cubic and hexagonal	Monoolein	Etodolac	Therapy for rheumatoid arthritis.	[57]
Elgindy NA, 2016	Cubic	Glycerol monooleate	Progesterone	Control of hormonal imbalances.	[58]
Sherif S, 2014	Cubic	Glyceryl monoolein	5% alpha lipoic acid	Treatment for photo damaged skin.	[59]
Rattanapak T, 2013	Cubic	Monophosphoryl Lipid A from *Salmonella Minnesota* RE 595	Microneedle arrays	Therapy for transcutaneous immunization.	[60]
Madheswaran T, 2013	Cubic	Monoolein	Finasteride	Therapy for androgenetic alopecia.	[61]
Madheswaran T, 2014	-	Glycerol monooleate	Finasteride	Therapy for androgenetic alopecia.	[62]
Bazylinska U, 2018	Bicontinuous cubic	Monoolein	Chlorin e6 or meso-Tetraphenylporphine-Mn(III) chloride	Treatment for photosensitizers in melanoma skin cancer cells	[63]
Vicentini FTMDC, 2013	hexagonal	Oleylamine and monoolein	Small interfering RNAs	Class of medications that disrupt disease-promoting or disease-causing genes.	[64]
Esposito E, 2013	Cubic	Monoolein	Curcumin	Anti-inflammatory, analgesic, antimalarial, antioxidant, and antiseptic activities.	[65]
Li J-C, 2015	Cubic	Glyceryl monoolein	Paeonol	Anti-tumor, anti-inflammatory, anti-allergy, and anti-atherosclerotic properties.	[41]
Håkansson J, 2019	Cubic	Glycerol monooleate	Peptide DPK-060	Broad-spectrum antibacterial action.	[66]

Thematic Evolution and Trend Topics: Thematic evolution analysis is a technique for discovering the relationships between historical trends and development routes [67]. The text describes a theme analysis of transdermal drug delivery (TDD) of liquid crystalline nanoparticles (LCNs) from 2004 to 2022, which was conducted using a minimum cluster frequency of 5 and a minimum weight index

of 0.1, with the inclusion index weightage by word occurrence. The results of the analysis are shown in **Fig. 9**, which provides a visual representation of the different themes and their significance for future study. The upper right quadrant of the figure is where the "driving" ideas are located, indicating their high density and centrality.

These themes, such as Cubosomes and MO, are significant and should be further developed in future research. The upper left quadrant includes specific and underrepresented topics like "green synthesis," "hydrogel," "liquid crystalline nanoparticles," and "tacrolimus." While these topics have high density, their low centrality indicates that they are not as significant as the themes in the upper right quadrant.

The lower left quadrant includes themes like "nanoparticles," which have been extensively covered in the literature, but their centrality and density suggest that they may be on the decline. The lower right quadrant includes indispensable concepts with great centrality but modest density. These themes, such as "solid lipid nanoparticles," "topical delivery," "nanostructured lipid carriers.

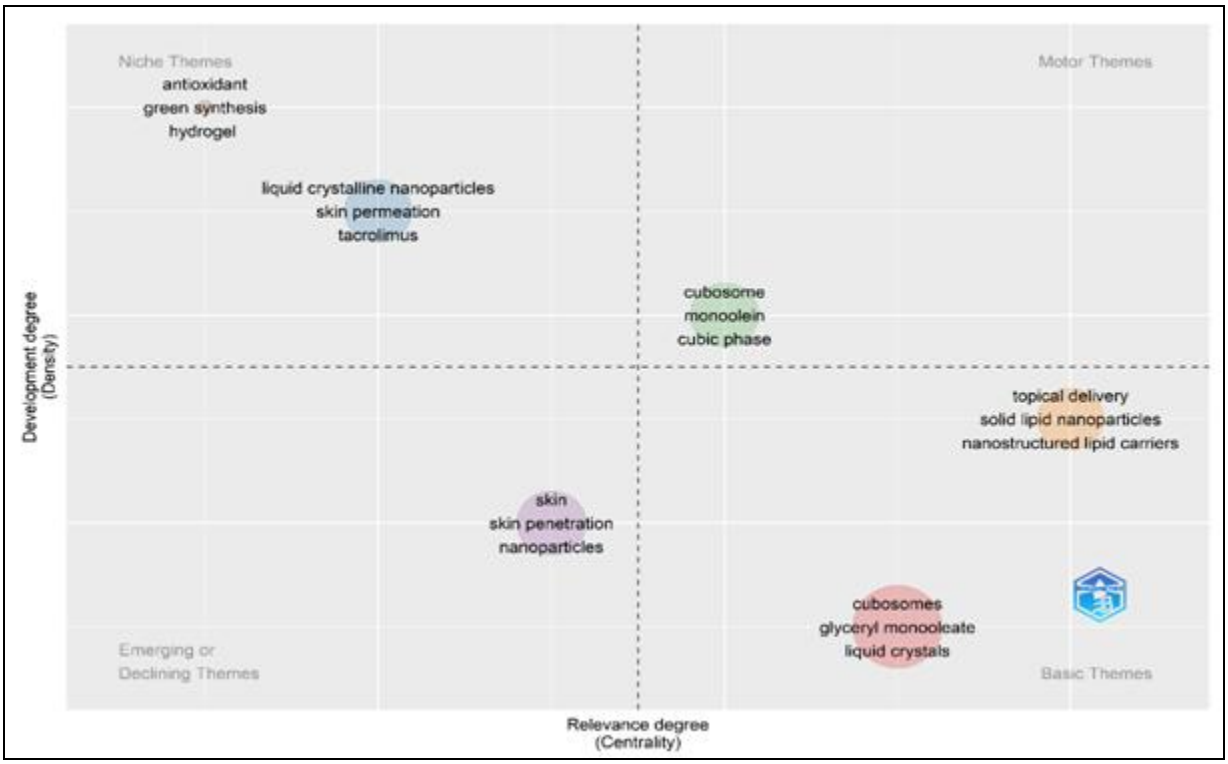

FIG. 9: THEMATIC EVOLUTION OF THE TRANSDERMAL APPLICATION OF LCNs

The trend topics may be able to identify the developing issues by providing a clearer grasp of how the subjects have changed through time. **Fig. 10** provides a snapshot of the topic's development through time, highlighting the research on cubosomes as an example of the fundamental strategy employed by scientists.

The analysis also shows a conceptual approach using LCNs that precedes research on cubosomes. The primary topics covered in the literature on TDD using LCNs are MO and skin permeation investigations. MO is a widely used material in the preparation of LCNs, and its properties have been extensively studied in the context of TDD.

Skin permeation investigations are also a major topic of interest, as they involve the study of the mechanisms by which drugs penetrate the skin and reach the bloodstream. Other topics that have been covered extensively by researchers worldwide include skin penetration, transdermal medication delivery, and solid lipid nanoparticles. Skin penetration involves the study of the mechanisms by which drugs penetrate the skin, while transdermal medication delivery involves the use of LCNs to deliver drugs through the skin and into the bloodstream. Solid lipid nanoparticles are another type of nanoparticle that has been studied extensively for their potential use in TDD.

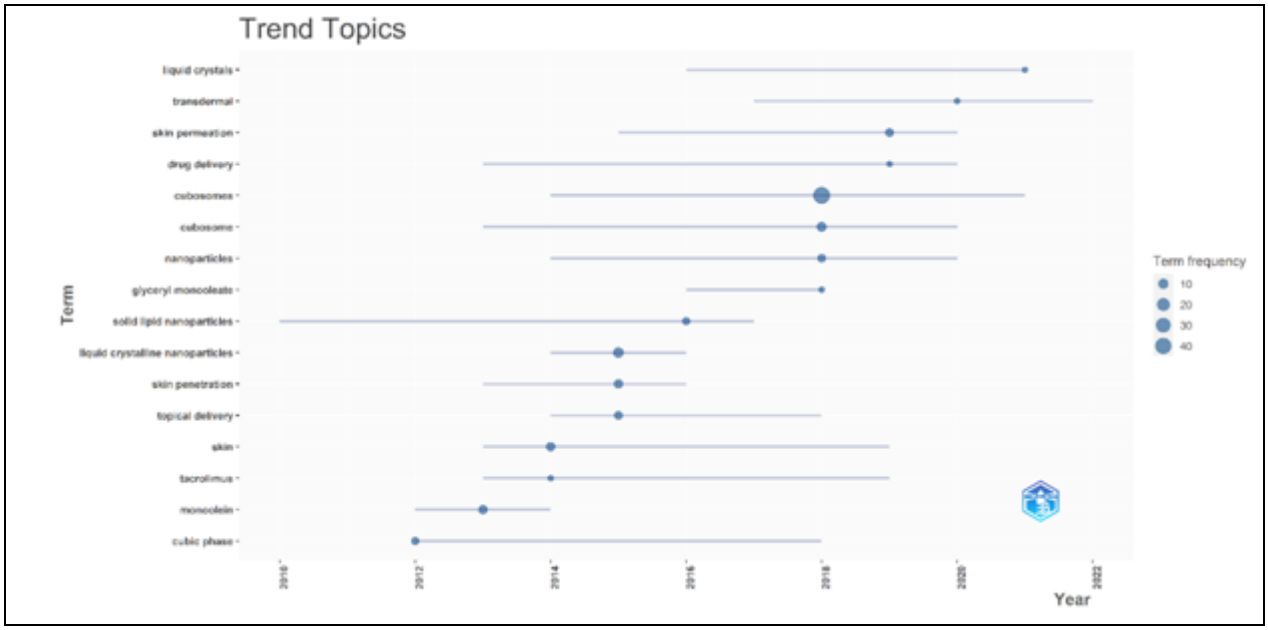

FIG. 10: TREND TOPICS CONCERNING WORK ON THE TRANSDERMAL APPLICATION OF LCNs

DISCUSSION: LCNs have recently attracted more attention as a topical carrier system [68, 69]. Two non-intersecting water channels and a tightly twisted lipid bilayer make up the LCN. High bioactive molecule solubilization ability and regulated release from the LCN are provided by this special nanostructure [70, 71]. In the present work, the keyword analysis has allowed us to identify a new trend that sees the cubic phase of LCNs as a chance to advance a new, more sustainable TDD approach. The delivery of hydrophilic, amphiphilic, and hydrophobic drugs is possible in cubic phases when they are combined with a bi-continuous lipid bilayer, two congruent networks of water channels, and a curved bi-continuous lipid bilayer [72]. The inner cubic phase structure is preserved in nanostructured cubosomes that are created using lyotropic methods or by breaking up large cubic phase gels [73–75]. These cubosomes also have a significantly higher specific surface area and reduced viscosity. Due to their special qualities, cubosomes constitute effective drug delivery systems for parenteral, mucosal, transdermal, and oral routes [1, 76–77].

Over the span of the investigations, the number of publications as well as patents elaborating work on transdermal application of LCNs was found to consistently grow, as shown in **Table 3**. Since 2012, there has been an upsurge in publications. The graph's trajectory makes it evident that there is a sharp increase in 2020, which may be attributed to the worldwide pandemic crisis. The majority of the publications examined were published in esteemed, elevated journals. Of which, the International Journal of Pharmaceutics is found to be the most pertinent source when it comes to publications related to the transdermal application of LCNs. With a total of 8 publications, Yoo BK leads the list of authors acknowledged as most relevant authors. Upon initial inspection of the full map, it appears that Yaghmur A. 2009, Ganem-quintanar A. 2000, and Salah S. 2017 were referenced in several research and made contributions to the body of knowledge in LCN disciplines. According to the author's primary affiliation and the most examined field of research, this analysis identifies China as the nation with the most papers. After China, India and South Korea have the most research studies and the highest representation of publications in terms of the author's major association. All three nations have played a crucial role in the direction of research associating LCNs and are at the forefront of research globally.

Cubosome and hexosome has received a great deal of attention recently **Table 4**. These systems have high environmental stress tolerance, contain both hydrophobic and hydrophilic chemicals, exhibit thermodynamic stability, and have the prospect for controlled release [72]. For a kinetically stable dispersion, observations amply that the LCN may be stabilized by Cremophor surfactants for topical

FNS administration [62]. Given that several researchers have observed similarities between the structures of the cubic phase and the SC [78], it makes sense to assume that SC lipids and cubosomal MO may have formed together. A nanoparticulate system able to modify its percutaneous absorption may be suggested by a cubosome depot that, under controlled circumstances, may release the anti-inflammatory drug indomethacin. Numerous AMPs, including the gramicidin A, melittin, and alamethicin [79], DPK-060 [80, 81], AP114 [80–82], LL-37 [83, 84] have been effectively integrated with cubosomes [54].

TABLE 4: COMPARITIVE STUDY OF CUBOSOMES AND HEXOSOMES

	Cubosomes	Hexosomes
Definition	Self-assembled nanoparticles consisting of a lipid bilayer with a bicontinuous cubic phase structure	Self-assembled nanoparticles consisting of a lipid bilayer with a hexagonal phase structure
Characteristics	Stable and biocompatible	High drug loading capacity
Potential Applications	Transdermal drug delivery, cancer therapy, vaccine delivery	Drug delivery, gene therapy, antimicrobial therapy
Advantages	Enhanced drug stability, sustained release, improved bioavailability	Efficient drug delivery, biodegradable, easy to prepare
Recent Developments	Encapsulation of hydrophilic drugs, combination therapy, use in cosmetic industry	Use in ocular drug delivery, modified drug release kinetics, application in immunotherapy
Research Focus	Optimization of drug loading and release kinetics, clinical translation	Fundamental mechanisms of hexagonal phase formation, optimization of hexosome stability and drug release kinetics
Limitations	High cost, limited scale-up	Limited drug compatibility, potential toxicity
Future Directions	Development of scalable production methods, more clinical studies	Development of safer and more effective formulations, investigation of new applications

Due to the delayed dispersion of the absorbed drug in the skin, cubosomes offered more and longer-lasting skin retention of the medicine than did cream, even though the percutaneous absorption of capsaicin from the GMO-based products is lower than that from the traditional cream. Under diffusion control, the capsaicin cubosomes offered prolonged release. The topical administration of capsaicin for the relief of post-incision pain using cubosomal particles offers an intriguing method due to its skin-targeted, sustained, and thermodynamically stable properties [55].

Recent research has focused on the development of transdermal cubosomes, which offer a non-invasive way to administer drugs through the skin and have a 266.11% relative bioavailability advantage over oral doses [57]. In comparison to its aqueous solution, the cubic phase of progesterone-loaded self-assembled LCNs presents a new perspective on how progesterone can effectively treat hormonal imbalances through skin penetration [58]. Early clinical data therefore indicates the safety and efficacy of 30% w/w P407 gels containing ALA cubosomes when taken for at least 3 months in the vast majority of participants to produce aesthetic rectification of the face region [59]. A blend of quantitative and qualitative research methods has a substantial influence on the study of transcutaneous drug and vaccine delivery [60]. The positive findings of this study suggest that the LCNs may be suggested as a workable substitute for the oral administration of FNS [62]. In addition, recent research has broadened the use of embedded Ce6 and TPP-Mn photosensitizers as participants for efficient bioimaging and maximum tumor damage through photoactivation, potentially leading to the development of a new generation of biocompatible drug delivery nanocarriers with a cubic structure for use in photodynamic therapy of melanoma skin cancer [63].

Self-assembled cubosomes permit prolonged medication release for up to 24 hours and less intense irritation compared to commercial ointment. As a result, the cubic phase of GMO and water represents a viable delivery method for paeonol. The paeonol also inhibits pigmentation as a pharmacological effect. These characteristics suggest that it is a novel drug-loaded system with superior pharmacological and aesthetic qualities, suggesting the need for further study [41]. The research also demonstrates the potential of DPK-060 as a safe and effective treatment option for the topical treatment of microbial infections. However, under the conditions of the tests, the peptide's

adsorption to nanocarriers offered no additional benefits. A longer follow-up time and repeated administration over many days would more closely mimic the clinically relevant scenario and might provide different results in terms of effectiveness and safety [66].

Furthermore, study shows that the nanodispersion of MO and oleic acid in a hexagonal phase enhanced CysA skin penetration both *in-vitro* and *in-vivo* without irritating the skin. Thereby suggesting the use of hexagonal phase nanodispersion to transfer peptides to the skin is a secure and promising method [52]. Due to its intriguing features, the improved hexagonal phase nanoparticles dispersed in an aqueous medium might be used as a skin delivery device for siRNA [64].

This study also covered comparative research done to assess the best formulation for TDD. With NLC, psoralens' enhanced penetration and regulated release were achieved. According to the findings, the NLC synthesized may be used as carriers for psoriasis treatments with better drug permeability [50]. The skin retention data suggest that the cubosome and ethosome formulations demonstrated the greatest penetration. Additionally, the co-entrapment of adjuvants like Quil A can improve peptide penetration through the skin [53]. In order to administer both hydrophobic and hydrophilic actives in a single formulation, the technique was shown to be compatible with a variety of actives and active combinations, including resveratrol, Epigallocatechin Gallate, and Vitamin E. Studies on the penetration of lipid nanoparticles via the skin revealed that resveratrol was more effectively absorbed through the SC. According to research, LCNs are potential carriers that can carry resveratrol and Vitamin E to the skin in order to give the skin long-lasting antioxidant effects [56]. Some of the patented marketed formulations are enlisted in **Table 5.**

TABLE 5: LIST OF PATENTED MARKETED FORMULATIONS CONCERNING TRANSDERMAL APPLICATION OF LCNs

Patent No.	Year	Summary	Assignee	Inventor	Ref.
WO2002066014A2	2002	Delivery of insulin to maintain blood glucose level	-	Seo-Young Jeong, Ick-Chan Kwon, Hesson Chung	[85]
US6936187B2	2002	The techniques for making and using functionalized cubic liquid crystalline phases are covered by this invention.	Cincinnati Childrens Hospital, Medical Center Childrens Hospital Research Foundation	Matthew Lawrence Lynch, Patrick Thomas Spicer	[86]
EP1578325A2	2003	Delivery of insulin to maintain blood glucose level	Transdermal Biotechnology Inc	Nicholas V. Perricone, Chim Potini	[87]
CN103040741B	2012	This work explains the process for making the lysotropic liquid crystal precursor solution.	Neworld Pharmaceutical Co ltd	Wu Chuanbin, Huang Xintian, Qin Lingzhen, Pan Xin	[88]
CN103505420A	2012	The innovation reveals a technique for creating liquid crystal nano-preparations.	Jiangxi Institute of Chinese Medicine, Jiangxi University of Traditional Chinese Medicine	Chen Lihua, Zhu Weifeng, Wang Sen, Guan Yongmei, Wu Dezhi, Cai Jia, Zhou Dongsheng	[89]
CN108078957A	2017	Capsaicin cubic liquid crystal nanoparticle production methodology and uses are the subject of the current invention.	Guangdong Medical University	Peng Xinsheng, Zhou Yanxing, Zhou Zhikun, Zhou Yanfang, Li Baohong, Wang Qin, Yu Qiong, Liu Wenen, Fan Zhiqiang	[90]
CN108403664A	2018	An opposite polarity drug-containing type of gel having nanoparticles with a liquid crystal structure.	Wuhan Best Pharmaceutical Co Ltd	Luo Liang, Huang Liping, Meng Fanling	[91]
CN108420787A	2018	The formulation and preparation technique for a type of cytokine class medicine for wound healing using lysotropic liquid crystal gel are disclosed in the present invention.	Ezhou Institute of Industrial Technology, Huazhong University of Science and Technology	Luo Liang, Huang Liping, Meng Fanling	[92]

CN109125251A	2018	The current invention describes a certain type of thermosensitive gel with liquid crystal structure fabrication and its preparation process.	Wuhan Best Pharmaceutical Co Ltd	Luo Liang, Huang Liping, Meng Fanling	[93]
CN108309927A	2018	The current invention describes a type of liquid crystal gel formulation of doxorubicin hydrochloride that is light-operated and has a sustained release mechanism.	Wuhan Best Pharmaceutical Co Ltd	Luo Liang, Wang Xiuxia, Meng Fanling	[94]
CN109091451A	2018	The invention, which is related to the field of prodrug formulation arts, describes a technique for making hydrophilic medication's oil phase liquid crystalline material gel precursors.	Wuhan Best Pharmaceutical Co Ltd	Luo Liang, Huang Liping, Meng Fanling	[95]
CN108272747A	2018	The invention, which falls under the category of pharmaceutical preparations, describes the precursor for a lysotropic liquid crystal gel preparation for finasteride.	Wuhan Best Pharmaceutical Co Ltd	Luo Liang, Wang Xiuxia, Meng Fanling	[96]
CN108420787B	2018	A lyotropic liquid crystal gel nano formulation of a cell factor wound healing medication as well as a method of preparation are disclosed in the invention.	Ezhou Institute of Industrial Technology, Huazhong University of Science and Technology	Luo Liang, Huang Liping, Meng Fanling	[97]
CN109316440A	2018	The use and kind of thermo-sensitive liquid crystal nano-hydrogels, as well as their preparation process, are disclosed in the invention.	Huazhong University of Science and Technology	Luo Liang, Huang Liping, Zhang Yi, Zhang Yiyi, Meng Fanling	[98]
CN109820824A	2019	The technique of preparing a kind of capsaicine liquid crystal nano-spray for accelerating skin wound healing is disclosed in the current invention.	Affiliated Hospital of University of Qingdao	Zhang Bingqi	[99]

Future Directions: The use of transdermal cubosomes for drug delivery has shown promising results in recent studies. To further explore the potential of cubosomes in medicine, future research should focus on optimizing cubosome formulations for improved drug release and permeation, as well as investigating their use for targeted drug delivery.

Additionally, exploration of cubosomes for vaccine delivery and transdermal delivery of peptide and protein drugs should be pursued. Collaboration with industry partners is also needed to bring cubosome-based drug delivery systems to market. Overall, continued research on the safety and efficacy of transdermal cubosomes and the development of more efficient and effective drug delivery systems using cubosomes will be critical for the future of transdermal drug delivery. Furthermore, research should be conducted to explore the potential of combining cubosomes with other drug delivery technologies. For example, nanotechnology-based systems, such as liposomes, could be used in combination with cubosomes to create more effective drug delivery systems. In addition, the use of cubosomes in combination with other routes of drug administration, such as oral delivery or inhalation, could lead to even greater therapeutic benefits.

Another important area of future research in the field of transdermal cubosomes is the investigation of the long-term safety and efficacy of cubosome-based drug delivery systems. While early clinical data has shown promising results for the use of cubosomes in aesthetic rectification and photodynamic therapy, further research is needed to fully understand the potential risks and benefits of long-term use. This includes exploring the potential for adverse reactions, such as skin irritation or inflammation, and conducting long-term studies to evaluate the effectiveness of cubosome-based drug delivery systems in treating

chronic conditions. By addressing these research questions, the field of transdermal cubosomes can continue to advance and improve patient outcomes in the years to come.

Limitations: This study has limitations, including that not all articles on the subject are included in the Scopus database, and that papers written in languages other than English were not examined. Additionally, due to the increase in publications on the subject, the most relevant data needed to assess the quality of articles could not be found for this study.

CONCLUSION: In conclusion, this study provides a comprehensive review of the literature on LCNs for transdermal drug delivery and identifies key research themes, gaps in the literature, and areas where further research is needed. LCNs offer promise as carriers for delivering therapeutic agents to the skin, but more research is needed to develop more environmentally friendly and sustainable techniques for producing LCNs, establish the therapeutic effectiveness of ALA cubosomes as an anti-wrinkle agent, and explore the potential of hexagonal phase nanodispersion for peptide delivery and siRNA delivery in vivo. Continued scientific advancement and imaging research on living skin and immunological research in animal models will be important for fully evaluating the potential of LCNs in transdermal drug delivery.

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