Review

Research on Silver-Based Wound Dressing: An Ontological Analysis

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Research on Silver-Based Wound Dressing: An Ontological Analysis

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Abstract

Background/Objectives: Silver's ability to kill pathogenic bacteria is being widely researched in environment, consumer, and health related applications. One topic of voluminous research is antimicrobial properties of silver and silver in wound dressings. This research literature has been reviewed in articles using qualitative analysis, meta-analysis, systematic review, bibliometric analysis, and other grounded methods. We present a new strategy of analysis of the population of articles on the subject based on an ontology of this topic. **Methods**: A search of the Scopus database for all peer-reviewed articles on silver in wound dressings yielded a population of 4,711 relevant ones. The ontology is a logical deconstruction of the problem of: "Use of s**ilver** species on **nanosupports** deposited on a **matrix** with **antimicrobial effectiveness** assayed by **methods** to promote **wound healing** of chronic **wounds** as determined by **recovery**". Each bolded term denotes a dimension of the ontology, and each dimension denotes a taxonomy of constituent elements. A Convolutional Neural Network (CNN) was trained using a manually mapped subset of articles. The CNN was then used to map the population of articles. **Results**: Out of the 4711 articles, 3079 dealt with silver and wound dressings, the others involved silver, but were not related to wound dressings, and were not considered. Overall analysis shows that three classes of silver encompass the entire field: silver nanoparticles (AgNP) (78% of papers), inorganic silver ion containing species (7%) and silver associated with organic molecules (15%). AgNP papers have grown exponentially beginning in early 2000s; there is no clear trend regarding inorganic silver containing species papers; whereas there has been modest linear growth with the silver-organics species papers since the early 2000s. Research on the AgNP has primarily focused on in-vitro testing (54%), with very limited animal testing (17%) and human testing (3%). On the other hand, with silver-organics, animal (30%) and human testing (38%) are prominent. Inorganic silver ion species also have been human tested extensively (43%). Thus, in clinical applications of silver wound dressings AgNP lags considerably as compared to the other silver species, though academic research in AgNP is robust. **Conclusions**: From detailed temporal visualizations of the ontological mapping, the antecedents and consequences of silver in wound dressings are presented. This first ontological analysis is a novel way of visualizing an entire research field and the temporal characteristics of the various dimensions of the ontology provides information on the current state of research as well as where the field is headed.

Keywords: ontology; neural network; artificial intelligence (AI); silver in health and medicine; chronic wounds; regulations; research history; research roadmap; research pathways; systematic review; systemic review

1. Introduction

Medicinal properties of silver have been known for centuries [1], earliest reports of use of silver date back to 5000 years ago, as evidenced by archaeological discoveries of a silver canister dating

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back to 1400 B.C. Silver-based wound dressings were used during the first world war (1914-1918), though the exact mechanism of action was unknown [2]. In the early part of the 20th century, silver was used for the treatment of various diseases, such as syphilis [3]. Until the advent of antibiotics, silver enjoyed use as a general-purpose antimicrobial. Now with the advent of antibiotic resistance, silver is enjoying a renaissance. The mechanism of silver as an antimicrobial stem from the coordinating ability of silver to bind to oxygen, sulfur, nitrogen and phosphorus containing ligands [4–7]. Since all living biological entities contain these elements, silver ions can bind to lipids, DNA, RNA, proteins and enzymes and interfere with their activity, thereby manifesting an antagonistic role towards the living species. Silver is known to kill both Gram-negative (e.g. Acinetobacter, Escherichia, Pseudomonas, Salmonella and Vibrio) and Gram-positive bacteria (e.g. Bacillus, Clostridium, Enterococcus, Listeria, Staphylococcus and Streptococcus) [7–9]. Oxidative stress and metabolic disruption with silver have been noted in its antimicrobial mechanism [10–12]. Silver attack on the cell is multi-pronged, and therefore resistance towards silver is difficult for the bacteria to develop, though there have been few reports of resistance to silver [13–16]. Disruption of cell membrane activity, including phosphate and sodium ion uptake inhibition, disruption of proton gradient, and uncoupling of ATP-dependent processes, as well as DNA aggregation has been noted [7,17–20]. The flip side of such activity is that silver will also bind to functioning biological entities necessary for the function of the organism and thereby cause cytotoxicity [21,22]. Argyria risk, which involves a cosmetic effect of bluish skin increases with high levels of silver [23]. So, the amount of silver used in a specific antimicrobial application is important, killing the bacteria but not injuring the host organism. Pathogenic bacteria can colonize and survive in very diverse environments, including living beings and different surfaces [24]. In living beings, bacteria can cause infection. By surviving on surfaces, bacteria can be transmitted via touch and contaminate food. Bacteria can survive and make deposits in pipes, and maintain colonies in water bodies [25]. Therefore, silver continues to be investigated as an antimicrobial in medicine, consumer and environmental applications [26]. Examples include use in swimming pools [27], silver impregnated water filters [28], silver containing textiles [29], silver use in dental materials [30]. In medical applications, silver coated catheters [31] and silver bandages are used [26].

This review article focuses on a very specific application of silver antimicrobials in wound dressings for chronic wounds [32]. Wounds exposed to the environment can be readily infected by bacteria, causing issues with wound healing. The presence of silver in wound dressings can kill the bacteria, minimize the infection and assist in the wound healing. There are many commercial silver wound dressings in use today. One of the first silver species that was used for minimizing infections in burn wounds was silver sulfadiazine [33]. Numerous other silver species have since been introduced in wound dressings and are an area of intense research activity. Different forms of silver and supports that promote wound healing are an active area of basic and applied research. This research activity has led to numerous research articles and patents, and thus it is not surprising that there are many review articles in this area. Such review articles (recent ones referenced here) in the area of silver and wound healing have included qualitative analysis [34], meta-analysis of randomized control trials [35], systematic review of specific features of silver [36], review of clinical studies [37] and bibliometric analysis [38]. So, the question then arises is why another review article?

The approach we have taken in this study is distinct from previous review articles in this area and provides some novel features. Our approach is based on an ontological analysis of the entire field, as captured by an exhaustive search involving silver and wound healing. By focusing on the title, abstract and key words of the manuscript, we ensure that the search net is cast wide. We take the entire search and categorize the results into an ontological map. The design of the ontology is critical since that provides the basis for the classification of the entire published research into possible classes, also specified by dimensions and taxonomies of the ontology. Since the number of papers is large, we train a neural network to do the classification. Such a classification is then mapped onto the ontology, and the map describes the overall state of the field. Because the ontology describes the entire field, there are numerous ways to interpret the findings. One could choose to examine the

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nature of basic research, or particular methodologies or types of samples. We have decided in this review to use the ontological map to examine the practical/clinical aspects of silver used in wound dressings, and where the field may be headed. The rationale for and the method of ontological analysis are based on the research using it in information systems, healthcare, and project management [39–43], and other fields.

2. Ontology of Silver-Based Nanosupport Wound Dressing

To capture the entire field of silver in wound dressings, we developed an ontology of "Use of **silver** species on **nanosupports** deposited on a **matrix** with **antimicrobial effectiveness** assayed by **methods** to promote **wound healing** of chronic wounds as determined by **recovery**". The ontology is presented in Figure 1 and described below.

[Use of] Silver	[species on] Nanosupport	[deposited on] Matrix	[with] Antimicrobial Effectiveness	[assayed by] Method	[to promote] Wound Healing	[in chronic] Wound	[wounds as determined by] Recovery
Elemental	Nanoparticles	Support	Potency	Tests	Hemostasis	Vascular	Dressing
Nano Crystalline	Nanozeolite	Natural Polymers	Humidity	In Vitro	Inflammation	Diabetic	Pain
Metal Ion	Nanolipids/Lipid Nanoparticles	Hydrogel	Cyto-toxicity	Animal	Proliferation	Pressure Ulcer	Healing Time
Inorganic Compound	Nano Metal Organic Framework (MOF)	Collagen/Cellulose	Diffusion	Human	Remodeling	Burn	Scar Tissue
Silver Oxide	Nanopolymers	Alginates	Temporal	Extension			Cost
Silver Chloride	Nanochitosan	Foams	Spatial	Comparison			
Silver Phosphate		Gels		Extrapolation			
Silver Sulfate		Starch		Generalization			
Silver-Zinc, Silver-Copper, Silver-Metal Ion		Hydrofiber		Analogy			
Organic Complexes		Silk Fibroin					
Silver Sulfadiazine		Hyaluronic Acid					
Silver Alginate		Chitosan					
Silver Carboxymethylcellulose		Synthetic Polymers					

Figure 1. Ontology of silver-based nanosupport wound dressing.

Silver, in different forms, is an antimicrobial agent that can be used to treat chronic wounds. The antimicrobial effectiveness of a species of silver can be regulated by encasing it in a nanosupport and depositing it on a suitable matrix for delivery to the wound site. The silver species, nanosupport, and matrix combination must be designed to regulate the antimicrobial potency, the humidity of the wound environment, and the diffusion of the potency over time and at different wound depths. This logic is articulated in the first four dimensions (columns) of the ontology of silver-based nanosupport wound dressing and described next.

2.1. Silver

The first dimension, Silver, denotes the species of silver that can be used in wound dressing because of their antimicrobial properties. The three broad species are elemental silver, inorganic silver compound, and organic silver complexes. The elemental silver species includes nano crystalline and metal ion forms; the inorganic silver compound species includes silver oxide, silver chloride, silver phosphate, silver sulfate, and silver-zinc, silver-copper, and silver-metal-ion combinations; and the organic silver complexes species includes silver sulfadiazine, silver alginate, and silver carboxymethyl cellulose. These silver species and their constituents denote a comprehensive, current taxonomy of silver forms that can be used in wound dressing because of their antimicrobial properties. Table 1 denotes the taxonomy of silver species.

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Table 1. Taxonomy of silver species.

Elemental-Nanocrystalline	Well-defined long-range order of making up the material in its metallic form
Elemental-Metal Ion	Metallic ions, Ag^{+} (same as Ag(I))
Inorganic-Silver Oxide	Ag_2O and other forms having Ag and O in their composition
Inorganic-Silver Chloride	AgCl, any forms having silver and chlorine
Inorganic-Silver Phosphate	Ag_3PO_4, any forms having Ag, P, and O
Inorganic-Silver Sulfate	Ag_2SO_4, any forms having Ag, S, and O
Inorganic-Silver, Zinc, Copper, Metal Ion	Can be any metallic ion, such as copper ion or zinc ion (Cu^{2+} or Zn^{2+}) in combination with silver
Organic- Silver Sulfadiazine	Well-defined chemical substance comprising silver ions and sulfadiazine
Organic- Silver Alginate	Complex of silver and alginate
Organic- Silver CMC	Silver incorporated in carboxymethyl cellulose

Another advantage of the taxonomy approach is that silver species can be extended by adding new species and their corresponding constituents.

2.2. Nanosupport

The second dimension, Nanosupport, denotes the taxonomy of nanosupports currently used for delivering the silver species to the wound. It includes nanoparticles, nanozeolites, nanolipids/lipid nanoparticles, nano-metal organic frameworks (MOF), nanopolymers, and nanochitosan.

The six types of nanosupports in combination with the ten forms of silver denote sixty potential combinations of the two to deliver the antimicrobial agent to the wound. Examples include: (a) elemental nano crystalline silver species in nanoparticles, (b) organic complex of silver sulfadiazine silver species in nanochitosan, and (c) inorganic compound of silver chloride silver species in nanopolymers. Table 2 denotes the taxonomy of nanosupport.

Table 2. Taxonomy of nanosupport.

Nanoparticles	Submicron particles
Nanozeolite	Submicron zeolites, silver is introduced via ion-exchange
Nanolipids/Lipid Nanoparticles	Includes liposomes, any particle made up of lipids and submicron in size
Nano Metal Organic Framework (MOF)	Metal organic framework such as ZIF, imidazolate and submicron in size, often written as zeolitic-like MOF
Nanopolymers	Polymers with any dimensions in submicrons, such as electrospun fibers, silver is incorporated during the electrospinning process
Nanochitosan	Chitosan particles of submicron size

The taxonomy of nanosupport can be extended in the future with the addition of new ones.

2.3. Matrix

The third dimension, Matrix, denotes the substrates that can be used to deliver a silver species and nanosupport combination. There are thirteen types of substrate matrices. The list includes support, natural polymers, hydrogel, collagen/cellulose, alginates, foams, gels, starch, hydrofiber, silk fibroin, hyaluronic acid, chitosan, and synthetic polymers. This taxonomy too can be extended in the future with the addition of new substrates. Table 3 denotes the taxonomy of matrix.

In combination, the first three dimensions denote 780 potential combinations of silver species, nanosupport, and matrix for wound dressing. Examples include: (a) elemental nano crystalline silver species in nanoparticles deposited on support, (b) organic complex of silver sulfadiazine silver species in nanochitosan deposited on silk fibroin, and (c) inorganic compound of silver chloride silver species in nanopolymers deposited on gels.

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Table 3. Taxonomy of matrix.

Support	Any reported material that has the potential to be used as a matrix for wound dressing, whose potential has still not been demonstrated in animals or human studies, also includes scaffolds
Natural Polymers	Any polymer that has building blocks found naturally, such as amino acids, sugars etc.
Hydrogel	3-D network of hydrophilic polymers that retain water
Collagen/Cellulose	Also, a natural polymer
Alginates	Anionic polysaccharide polymers from seaweed
Foams	A porous, low-density polymeric material
Gels	A semi-solid in which liquid phase is immobilized
Starch	Also, a natural polymer
Hydrofiber	Highly absorbent material that can gel
Silk Fibroin	Any form of silk, also a natural polymer
Hyaluronic Acid	A natural glycosaminoglycan polymer
Chitosan	A cationic chitin derived polysaccharide
Synthetic Polymer	Polymer synthesized with chemical components not naturally occurring, e.g., polyurethane

The taxonomy of support can be extended in the future with the addition of new ones.

2.4. Antimicrobial Effectiveness

The fourth, Antimicrobial Effectiveness, dimension denotes the five attributes required in a wound dressing – potency, humidity, cytotoxicity, temporal diffusion (release of actives as a function of time), and spatial diffusion (depth of penetration of released actives into the surrounding medium). The 780 combinations discussed above must be assessed for their antimicrobial effectiveness on these five attributes to be used in wound dressing. Thus, a total of 780 x 5 = 3,900 pathways must be assessed to determine the effectiveness of silver-based nanosupport wound dressing. Examples include: (a) elemental nano crystalline silver species in nanoparticles deposited on support's potency, (b) organic complex of silver sulfadiazine silver species in nanochitosan deposited on silk fibroin's humidity regulation, and (c) inorganic compound of silver chloride silver species in nanopolymers deposited on gels and their cytotoxicity. It would be daunting to empirically list all the 3,900 combinations. One must (a) select the most likely combinations based on prior knowledge about the silver species, nanosupports, and matrices, (b) reject the unlikely combinations, and (c) delete the infeasible ones. Table 4 denotes the taxonomy of antimicrobial effectiveness.

Table 4. Taxonomy of antimicrobial effectiveness.

Potency	Antipathogenic activity towards any pathogens, including bacteria, viruses, fungi
Humidity	Mention of water adsorption, release and retention
Cytotoxicity	Toxicity towards living cells, also cytocompatibility and biological toxicity
Temporal	Release of actives from a material as a function of time, often mentioned as some concentration released into the surrounding environment
Spatial	Depth of penetration of actives into a biological milieu, how far are the actives penetrating

The taxonomy of antimicrobial effectiveness can be extended in the future with new attributes.

2.5. Method

The arguments for the 80 wound healing and recovery properties of the 780 combinations of silver species, nanosupport, and matrix may be based on: (a) empirical evidence from in-vitro, animal, and human tests, (b) extension of the results from similar cases based on comparison,

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extrapolation, and generalization, and (c) analogy to other cases. These methods are denoted by the Method dimension of the ontology. Table 5 denotes the taxonomy of method.

Table 5. Taxonomy of method.

In Vitro	Study of cellular species, like different bacteria
Animal	In vivo studies on animals, birds, wound models are developed and studied on rats, pigs, and rabbits
Human	Explicit study of human subjects (in vitro and prediction that this will apply to humans not considered, coded differently)
Extension - Comparison	Any comparison of two or more materials related to any biological aspect of wounds
Extension - Extrapolation	Extrapolation of results to another system/material
Extension - Generalization	Generalizing observations to more subjects/materials than the focus of the study
Extension - Analogy	Making judgments based on results of a system to another system

The taxonomy of methods can be extended in the future to include other methods.

2.6. Wound Healing

To promote effective healing, the dressing must promote hemostasis, be anti-inflammatory, limit wound proliferation, and stimulate tissue remodeling. These requirements constitute the sixth dimension, Wound Healing, of the ontology. Table 6 denotes the taxonomy of wound healing.

Table 6. Taxonomy of wound healing.

Hemostasis	Mention/discussion of clotting
Inflammation	Mention/discussion of studying inflammation, including inflammatory markers such as TNF
Proliferation	Mention/discussion of studying cell proliferation
Remodeling	Mention/discussion of studying tissue remodeling, including angiogenesis

The taxonomy of wound healing can be extended in the future to include other requirements.

2.7. Wound

The seventh dimension, Wound, denotes the four common types of chronic wounds. They are vascular, diabetic, pressure ulcer, and burn wounds. These wounds require special care compared to other common wounds. Thus, the taxonomy of Wound denotes the following chronic wounds that take more than three months to heal:

- Vascular wounds: wounds perpetuated by impaired blood supply
- Diabetic wounds: wounds in a diabetic person, such as diabetic foot ulcers
- Pressure ulcer wounds: wounds arising from pressure or friction
- Burn wounds: injury caused by thermal, chemical, electrical or radiation

The taxonomy of wounds can be extended in the future to other chronic wounds.

2.8. Recovery

Further, the healing of a wound must result in Recovery, as determined by the ease of dressing, pain management, healing time, scar tissue formation, and the cost, denoted by the last (eighth) dimension of the ontology. Thus, the object of silver-based nanosupport wound dressing is denoted by the 80 combinations of Wound Healing x Wound x Recovery. It includes promotion of: (a) hemostasis of chronic vascular wounds as determined by dressing, (b) antiinflammation of chronic

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diabetic wounds as determined by healing time, and (c) remodeling of chronic burn wounds as determined by scar tissue. Table 7 denotes the taxonomy of recovery.

Table 7. Taxonomy of recovery.

Dressing Application	Tested on animal/human
Pain	Mention of pain in any form
Healing Time	Mention of healing in any form
Scar Tissue	Mention of scar in any form
Cost	Mention of cost in any form

The taxonomy of recovery can be extended in the future to include other requirements.

3. Methodology

All available peer-reviewed articles on silver-based nanosupport wound dressing were collected from one of the largest databases of scholarly articles, Scopus. The corpus of articles was subsequently mapped to the ontology of silver-based nanosupport wound dressing. The search process as well as the process of mapping articles to the ontology are described in detail in the following subsections.

3.1. The Preliminary Search

A systematic search was conducted on Scopus in July 2025. The search strategy was guided by the ontology; individual parts of the search terms were derived from relevant taxonomies of the ontology. The preliminary search primarily focused on the following search terms in title, abstract, and keywords of articles: 1) silver, 2) nano*, 3) substrate OR dressing OR scaffold OR material, 4) wound OR infect*, and 5) healing OR care. The search process is denoted in the PRISMA diagram in Figure 2.

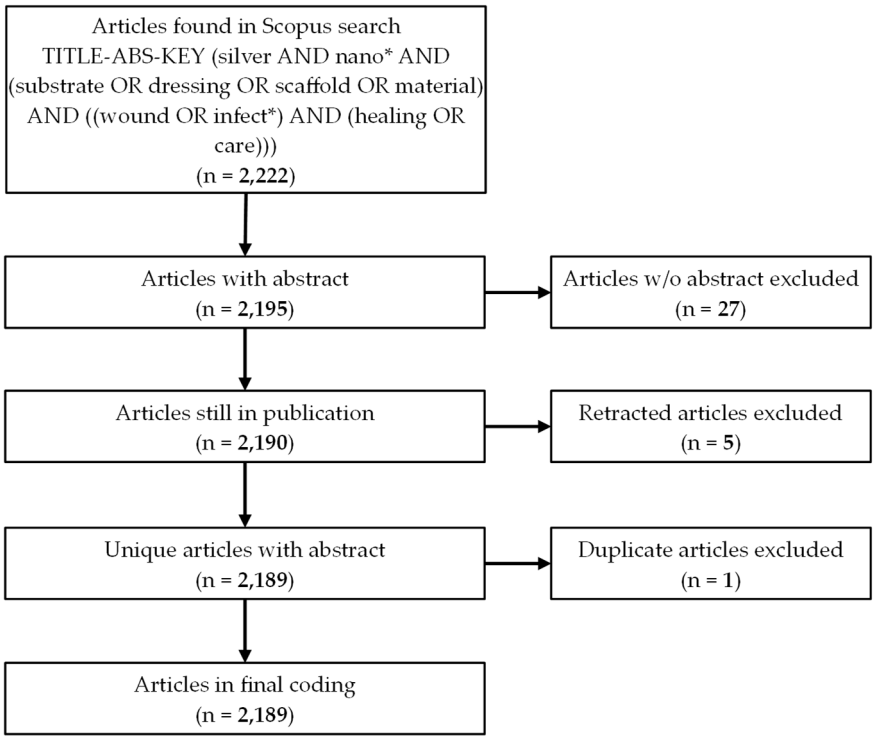

Figure 2. PRISMA diagram of preliminary search.

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The preliminary search returned 2,189 articles after removing duplicate and retracted articles as well as articles without abstract. The corpus of articles was subsequently mapped to ontological elements.

3.2. Mapping of Articles to Ontology

A random sample of 120 articles from the corpus was selected and manually mapped to the ontology by the coauthors. The sample was divided into 3 trenches of 40 articles, and each trench was coded by two coders using the taxonomical definitions described above. Each coder coded 80 articles from two trenches and reconciled to produce a consensus coding set. The coding was recorded in a spreadsheet with lowest level ontological elements arranged in columns together with title, abstract, and keywords of individual articles. The coding is binary indicating the presence/absence of ontological elements in an article, 1 for presence and 0 or blank for absence. This coding set, designated as P0, was used as the initial training for mapping of the remaining articles in the corpus.

Mapping the corpus to the ontology based on large volume of texts in title, abstract, and optionally keywords is a resource intensive process. Moreover, the larger the size of the corpus, the more time-consuming and resource-intensive the mapping process is. Hence, a machine learning technique commonly used in text classification known as Convolutional Neural Network (CNN) was employed to map the large corpus of articles to the ontology. CNN is based on a multilayer Neural Network (NN) architecture associated with deep learning. During the early stages of development, deep learning was mainly applied to handwriting recognition [44,45]. Later on, it has found success in natural language processing such as sentence recognition [46,47]. In natural language text classification, deep learning techniques are often proven to be more effective and efficient than conventional machine learning techniques [48,49]. For instance, an evaluation of various CNN architectures against other text classification techniques such as logistic regression on top of paragraph vectors and Naïve/Multinomial Bayes Support Vector Machine (SVM) revealed that CNN models in general perform comparable to or better than more established techniques in many test cases [47]. Hence, CNN was considered a viable and proven method to perform the larger share of coding in this. The coding process is depicted in Figure 3.

The mapping process followed a semi-supervised learning approach beginning with the dataset P0 containing manual coding of 120 articles. The P0 coding was divided into 10 folds of 12 articles each and validated following k-fold validation, a commonly-used cross validation technique in machine learning [50]. Ten CNN models were trained and tested using ConText software package [51,52]. ConText provides a ready-made environment with a complete set of tools to prepare the vocabulary, train and test CNN models, and perform predictions of coding. The algorithm and hyperparameters used in all CNN models in the mapping process are derived from ConText's packaged code for multi-label text classification. The important hyperparameters for CNN models including patch size and stride, numbers of layers and size, loss function, and pooling algorithm were fine-tuned over multiple iterations. The bag-of-words model was found to perform better than one-hot and bag-of-n-gram models for the vectorization of region or word embedding. A single max pooling layer using the square loss function over 2,000 epochs returned the optimal performance. The performance was evaluated using measures for evaluating regular classification models such as Accuracy, Precision, and Sensitivity, as well as those for multi-class classification models such as F1 Score, Matthews Correlation Coefficient (MCC), Informedness, and Markedness [53,54]. The F1 Score and MCC were found to capture the best performance that balances accuracy, precision, specificity, sensitivity, and used for benchmarking and comparing models in this study.

The CNN model of the best performing fold (see Figure 3) was used to generate coding of another set of 120 articles from the corpus. The coding set, designated as P1, was reviewed, revised, and reconciled by the coauthors. The combined coding of 240 articles from P0 and P1 datasets went through another k-fold validation with 10 folds. The best performing model was applied to coding the entire corpus of 2,189 articles constituting the P2 coding.

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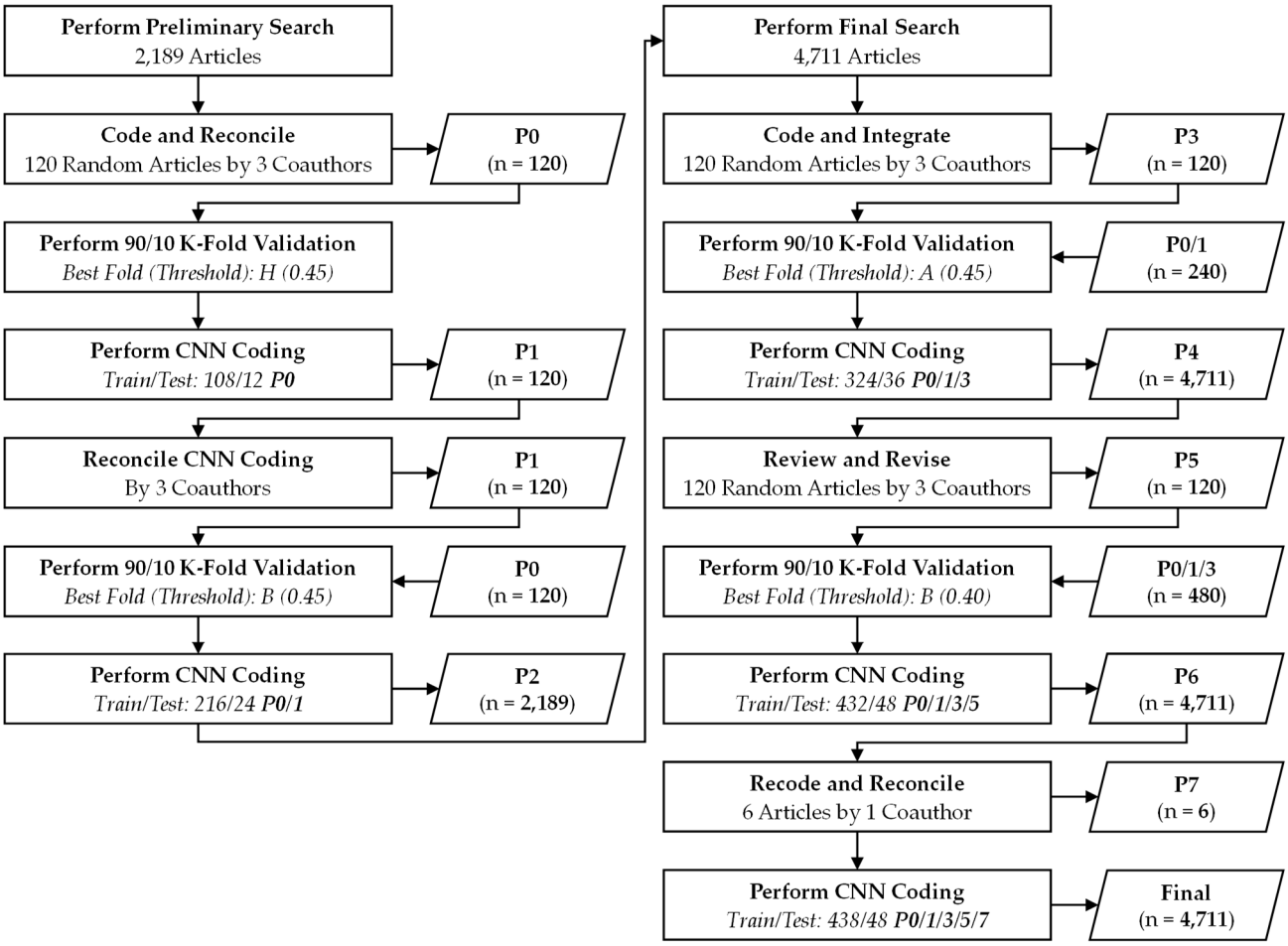

Figure 3. Process of mapping articles to ontology.

3.3. The Final Search

The final search for articles was performed in November 2025 after reviewing P2 coding. During the review, some articles on silver-based nanosupport wound dressing were missing in the coding, hence, there was a need to expand the corpus. Several trial searches with variations of the initial search terms revealed that removing "nano*" would expand the corpus to relevant articles while retaining those articles that were already captured in the initial search. The final search process is depicted in Figure 4.

The final search returned 4,711 articles. A random sample of 120 articles which did not appear in the initial search was selected and coded independently by the coauthors. Three sets of coding were integrated using the majority rule to generate the consensus coding designated as P3. The combined coding of P0, P1, and P3 was used to generate coding for all articles in the final corpus, the P4 coding. A quick review of the coding revealed that many relevant articles with "silver" in title and abstract were not coded. To improve the accuracy of coding, a sample of 120 articles was randomly selected from that subset of articles and coded by the coauthors. The consensus coding after reconciliation was designated as P5 and subsequently used together with coding of P0, P1, and P3 to perform another round of k-fold validation and CNN-based coding of the entire corpus, P6. The final review of the coding by the coauthor with extensive knowledge of subject matter revealed that the coding was underrepresented in Silver Phosphate and Silver Sulfate elements. Six articles with these silver species specified in title and abstract were selected and coded as P7 coding. The final coding of all 4,711 articles in the corpus was generated by the CNN model trained and tested with the combined coding of 486 articles in P0, P1, P3, P5, and P7.

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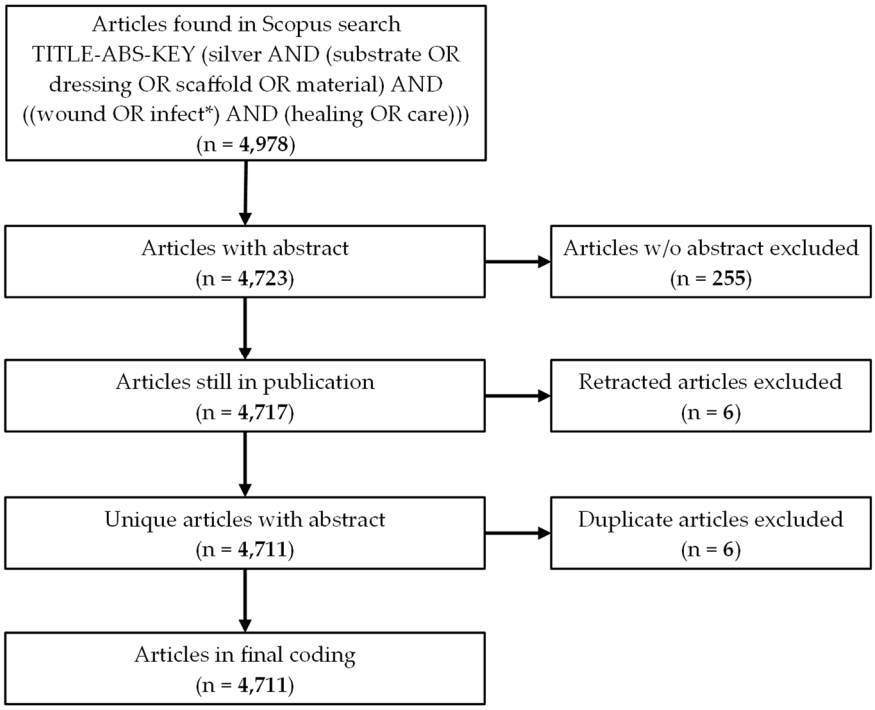

Figure 4. PRISMA diagram for final search.

4. Results

Figure 5 shows the monads map of the entire set of publications. The map shows the frequency of occurrence of: (a) elements of a dimension in the corpus, and (b) each element. The numbers are shown in parenthesis adjacent to the dimension and element labels. The bar below the element visually shows the relative frequency of occurrence of that element compared to the maximum frequency of occurrence in the monads map.

There are many ways of interpreting the monads map, depending on the set of information that one is attempting to extract from the entire collection of publications. Since our goal in this review is to understand the role of silver in wound dressings, we will use as our central theme the classification under silver. There are three broad classes of silver species that are being studied: metallic silver, inorganic species and silver complexed to organic moieties. Monads maps for the three classes are readily obtained from the parent map and are presented in Figures 6–8. An alternate summary pictorial description of the comparison of three species is shown in Figure 9. We analyze each class separately.

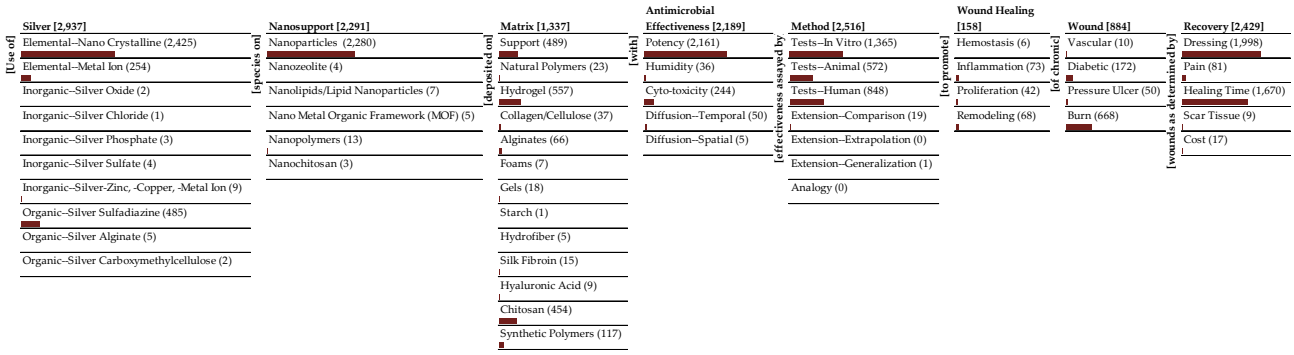

Figure 5. Monads map of the entire corpus.

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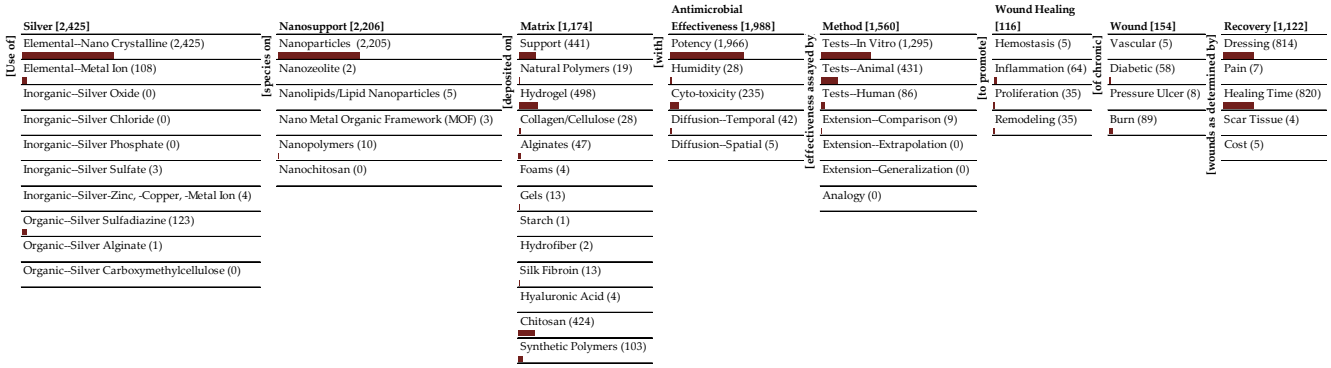

Figure 6. Monads map of metallic silver.

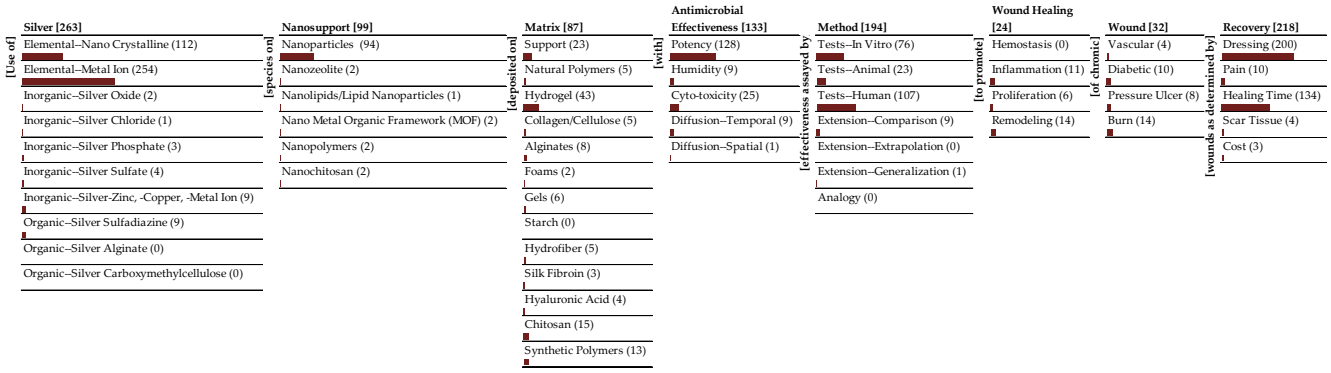

Figure 7. Monads map of inorganic silver species.

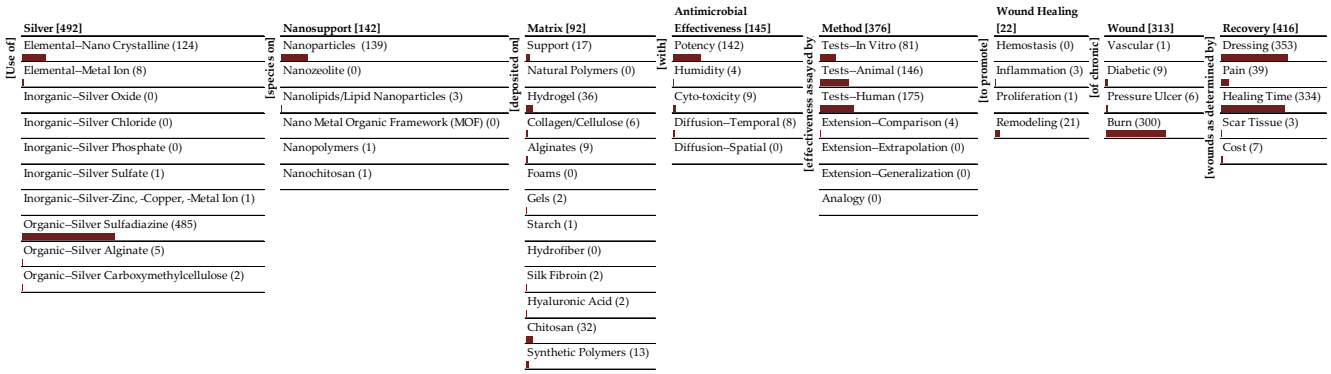

Figure 8. Monads map of organic silver species.

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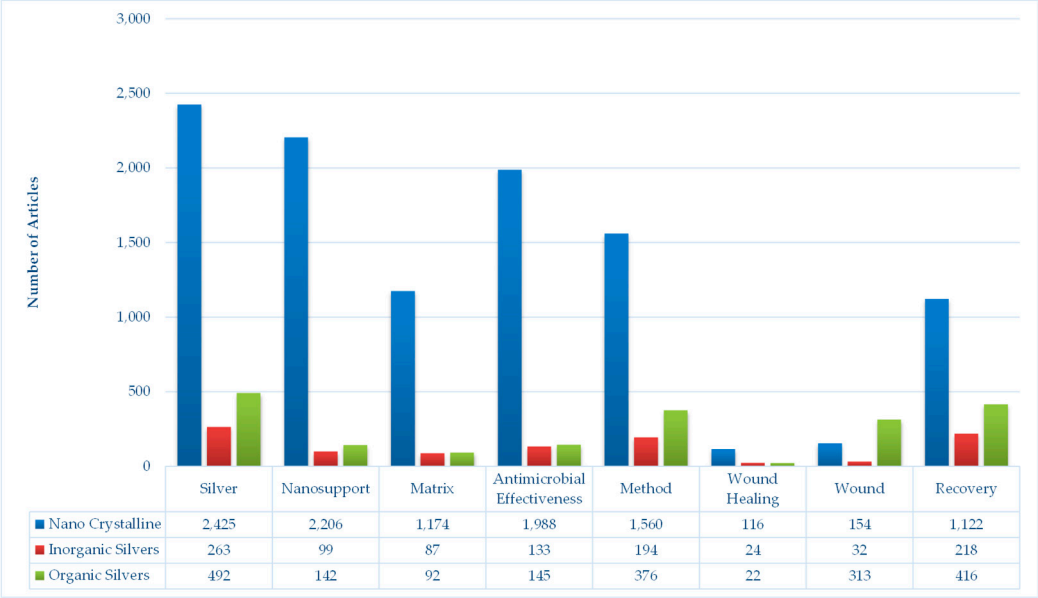

Figure 9. An alternate, simpler visualization of the entire monads map in Figure 5.

4.1. Metallic Silver

Amongst the silver species, this area is the most extensively researched with 2,425 articles (Figure 6). The temporal distribution of these publications is shown in Figure 10. There is an exponential growth of publications in this area over the last 3 decades. This is primarily driven by research on AgNP (metallic Ag particles with sizes less than 100 nm), with 91% articles featuring this form of silver. Analysis of Figures 6 and 9 suggests the following:

- AgNP are the main class of silver that is being investigated for wound dressings.

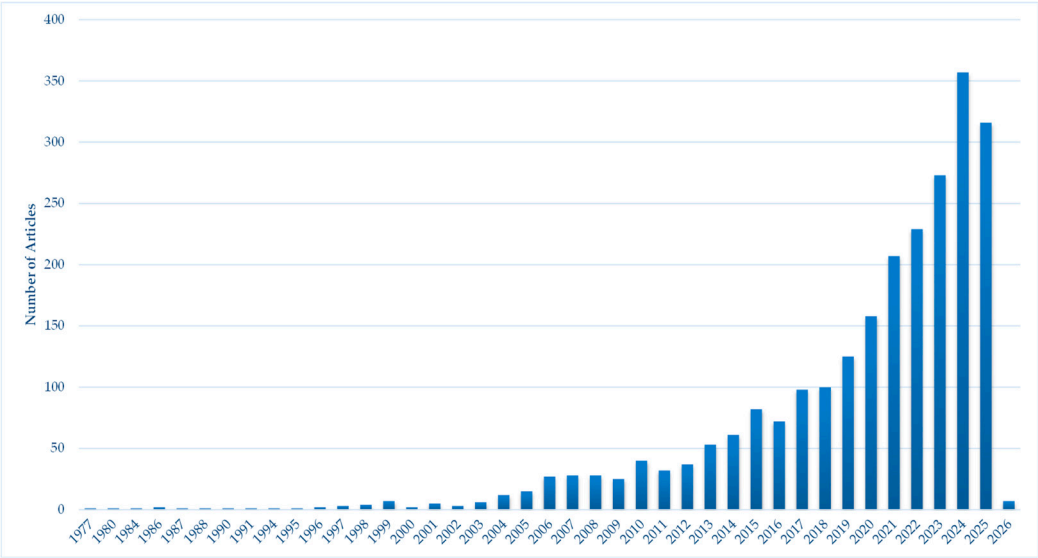

Figure 10. Publications with nanocrystalline silver.

The interest in NP is manifested because of their unique properties including quantum effects, surface effects, reactivity including dissolution chemistry [55]. AgNP are usually synthesized by reduction of silver ion, and there are numerous chemical routes including use of inorganic reducing agents (such as $NaBH_4$) [56], organic reducing agents (such as ascorbate) [57], biological reducing agents (such as natural products) [58]. There is also an incredible diversity in the sizes and shapes of AgNP [59]. These colloidal particles often need to be stabilized by surface active agents that minimize aggregation of the AgNP [60–64]. Release of silver ions from AgNP depends on the size (smaller sizes

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with higher surface area are more prone to dissolution), shape and surface coating [65]. Because of the multifaceted nature of AgNP both via different synthesis methods and physico-chemical characteristics, there is considerable basic research in this area [66].

- Most of the research with AgNP focuses on evaluating the antimicrobial potency by invitro tests with planktonic bacteria and determining cytotoxicity.

This is possibly done to establish the bona fide antimicrobial properties to reduce bioburden. The cytocompatibility of AgNP is also a topic of much research, since cytotoxicity to mammalian cells can delay wound healing [67].

- Significant research on silver dissolution from AgNP, fewer studies focus on how the AgNP is dissolving and the time dependence of the process.
- Not much work on incorporating AgNP onto other nanosupports, rather use of them directly supported on various matrices. There are examples of use of nanozeolites [68] and nano MOFs [69].

The dressing matrix is critical, because contamination by wound exudates can compromise silver release [36]. The main supports used are hydrogel and chitosan. Hydrogels are chosen because they can maintain the humidity in the wound environment, which is important for wound healing. Chitosan provides added antimicrobial power and complements the AgNP. Exploration of support also stems from modifying AgNP dissolution kinetics. Natural polymers are biocompatible and are an attractive feature.

- For mechanistic studies of wound healing, studies on inflammation have been the focus with fewer studies on proliferation and remodeling.
- Considering the large number of publications on AgNP, studies on animals and humans are sparse.

Basic research is still the focus with AgNP, and clinical translational research is yet to materialize [70], as evident from the monads map (Figures 6 and 9).

- A large fraction of the papers on AgNP report dressing design and healing time. Considering that there are only few papers on animal/human studies, our assessment is that this is because the basic research papers claim these as potential advantages.

4.2. Inorganic Silver Species

Examining different inorganic compounds of silver ion does not seem to be an active area of research, as evidenced from the number of publications and their evolution over time, shown in Figure 11. This group also includes encapsulated silver ions, held in supports such as metal organic frameworks, zeolites and zirconium phosphates [71].

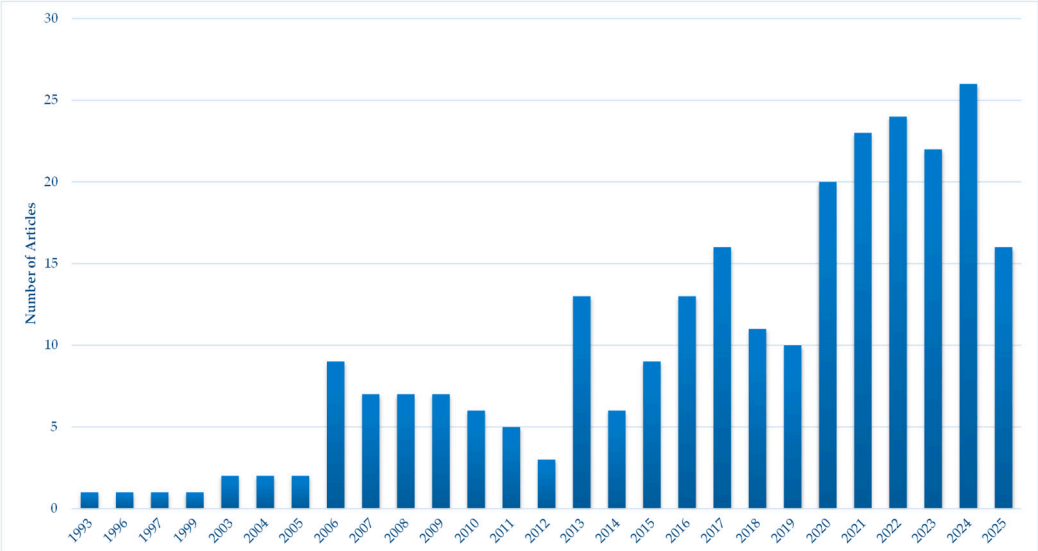

Figure 11. Publications with inorganic silver species.

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The monads map shown in Figures 7 and 9 indicates only 263 articles in this area. The most striking feature of the monads map is the relatively large number of human and animal studies. There are more human studies than in-vitro studies. This is an indication that basic research is not the predominant focus of the research of inorganic silver species, whereas there is considerable clinical research. Why is this the case? A review of FDA-cleared wound dressings provides a possible answer. On the FDA database, there are 123 entries for silver-based wound dressings[1]. Analysis of these FDA-cleared products include 8 AgNP (majority being the Acticoat family of dressings), 90 silver ion/metal, 18 silver organics, 7 miscellaneous compounds. Most of these dressings are based on inorganic silver species (73%), many of which are commercially available. We hypothesize that the commercial availability of FDA-cleared products has facilitated clinical studies. Finally for this class of silver, healing time has been a major focus in wound recovery.

4.3. Organic Silver Species

This class of silver nets 492 articles and is dominated by silver sulfadiazine. There is a significant amount of work in humans and animals, (65% of papers) primarily with burn wounds. Focus has been on healing time. Figure 12 shows the number of publications in this area over time. The growth is linear. It is interesting to consider the reasons why there have been extensive clinical studies with silver organics, in particular silver sulfadiazine (SSD). Prior to 1960's clinical treatment of burns involved silver nitrate solutions that minimized bacterial growth but caused stains [72]. Fox's formulation of SSD as a stable, water insoluble salt that combined the antimicrobial action of silver with the sulfonamide effects of sulfadiazine was reported in 1968 [73], followed by a patent also in 1968, and FDA approved SSD for burn wound infections in 1973. Fox's innovation soon became the gold standard for topical antimicrobial for burns. After introduction of SSD therapy, mortality in burn populations dropped from 38-45% to 14-25% [74]. With burns, the body's resistance to infectious bacteria is reduced. Healing time has been the focus of the wound-recovery, with pain being the secondary focus. The focus on pain is not surprising, early applications of SSD required frequent change, causing patients a lot of discomfort. SSD dressings with controlled release are now available [36]. Wound healing as measured by epithelization has been a focus.

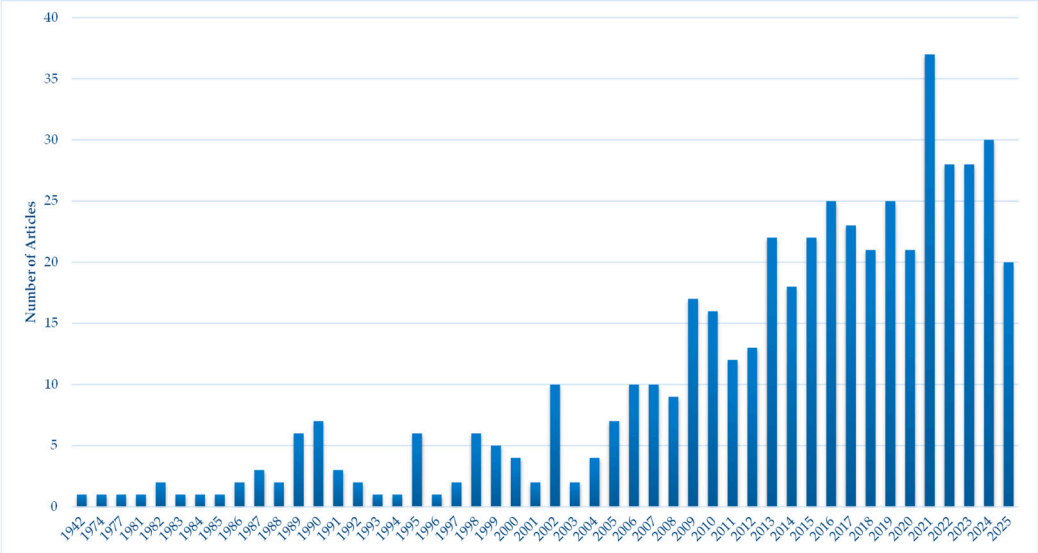

Figure 12. Publications with organic silver species.

[1] Search performed at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/TextResults.cfm with keywords "silver wound dressing" in March 2026.

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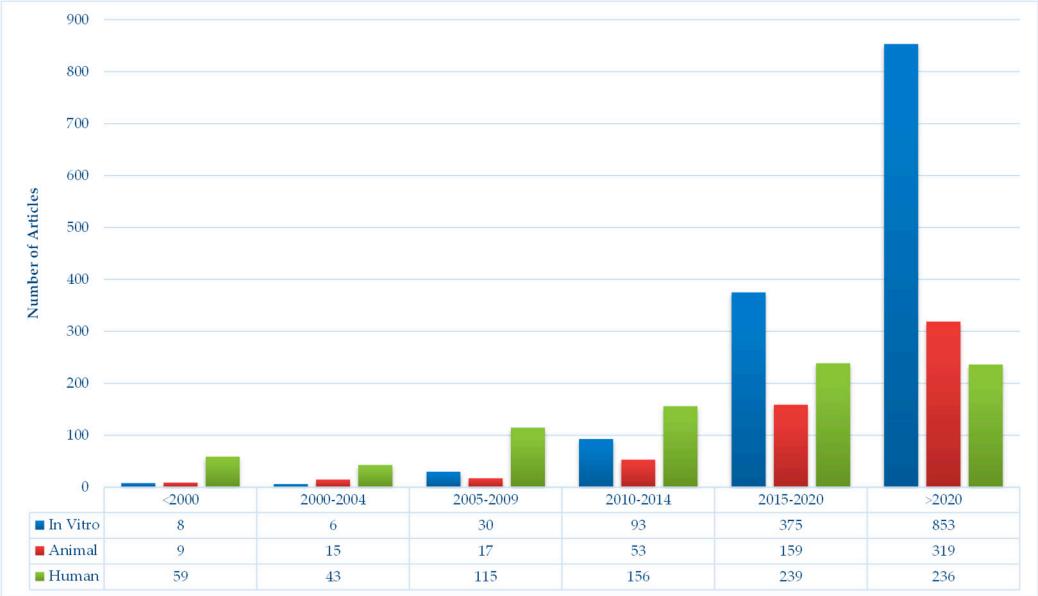
Though scars in wound healing is an important clinical indicator, not much research focuses on this topic for all the silver species. Also lacking is an emphasis on cost, though that will be an important feature of the clinical use of silver wound dressings.

5. Discussion

As we survey the entire monads maps, there are certain issues that stand out and merit discussion. The overriding goal stated in the research papers, even the most basic one, is to develop novel silver wound dressings. There is a certain progression typically for the evolution of medical products: basic research focused on improving potency, animal studies and clinical research. Figure 13 shows how in-vitro, animal and human studies have evolved over the past three decades as determined from the ontology. The increase of animal and clinical studies over the past decade is a good indicator that in the future there will be new silver products for the wound dressing market.



	<2000	2000-2004	2005-2009	2010-2014	2015-2020	>2020
In Vitro	8	6	30	93	375	853
Animal	9	15	17	53	159	319
Human	59	43	115	156	239	236

Figure 13. Distribution over time of papers on silver examining in-vitro, animal and human tests.

5.1. Road to Commercial Products

The ontology shows that there are trends towards more commercial products. We now address some of the issues that need to be dealt with for the successful drive towards practical applications. We frame this discussion based on a series of questions suggested by the ontology:

1. Why are there more human studies with the inorganic and organic silver species than AgNP?

We suggest that this is so because there are few FDA-cleared products featuring AgNP as compared to the other two classes. Figure 14 presents the temporal distribution of AgNP in animal and human studies. This is an encouraging trend, especially the large increase in animal studies, which suggests that the potential for novel effects in clinical studies with AgNP may be forthcoming.

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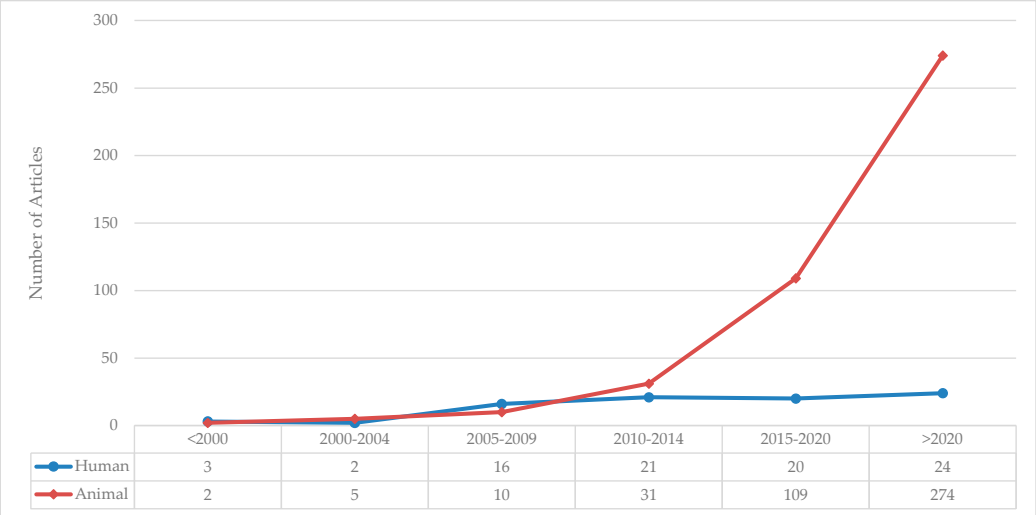

Figure 14. Distribution of papers over time of AgNP in animal and human tests.

2. What will it take for the proof of concepts studies on AgNP (95% of papers) to translate to clinical success?

Translating abundant lab research on silver nanoparticles (AgNPs) into safe, reliable, cost-effective wound dressings is an uphill battle. There is increased regulatory scrutiny around NP, and their environmental impact. Multiple technical, clinical, regulatory and commercial barriers will probably keep most AgNP concepts from reaching the market.

In order to address these barriers, the following needs to be addressed:

- Controlled silver release and stability — the primary activity of AgNP is thought to proceed via oxidative dissolution to Ag^+, and thus any surface modification will influence this activity. The biological milieu also contains numerous ionic species, such as chloride and sulfide, as well as proteins can bind to the surface and influence antimicrobial activity. The size of the AgNP will also influence dissolution, smaller particles dissolving more rapidly. Shape of the NP also influences antimicrobial activity, with nanoprisms > nanorods > nanospheres [75–78]. Effective antimicrobial action requires controlled ion release; this is difficult in a complex biological environment. Many AgNP constructs either release too much (toxic) or too little (ineffective). Nanoparticles also aggregate or change during storage/sterilization. Surface modification and surface charge that determines aggregation will influence dissolution kinetics [79]. Much of the basic research on AgNP correctly deals with these issues.
- Safety and toxicity uncertainties — There is some concern that AgNP may function in additional ways than Ag^+. Toxicity of Ag^+ is manifested as oxidative stress, and alteration of cellular activity due to Ag^+ complexation with important functioning species. AgNP can manifest its toxicity as Ag^+ and additional routes being direct interaction with the bacterial membrane leading to biomechanical changes, formation of pits as well as penetration of the toxic NP into the cell. How this translates to interaction of AgNP with mammalian cells is an active area of research [80,81]. Concerns about long-term systemic or local toxicity of AgNP complicates the regulatory approval process. There is also the issue of microbial resistance of AgNP [82,83]. Argyria, even though cosmetic is a cause for concern [84].
- Reproducibility and standardization — The synthesis methods for AgNP are extremely diverse. Scaling of the synthesis process to make reproducible, tightly controlled nanoparticle batches is nontrivial.
- Manufacturing and cost — Robust GMP manufacturing, including purification of NP, sterilization, packaging, and shelf-life for nanoparticle dressings add complexity and cost versus ionic silver or organic silver dressings. Moreover, there are concerns of AgNP toxicity via inhalation [85], and so the manufacturing process needs to address this concern.

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- Regulatory hurdles — Regulators require well-characterized materials, toxicology, and clinical evidence. Nanomaterials raise extra data expectations (biopersistence, biodistribution) [22] and no harmonized global standards exist.
- Clinical evidence & market adoption — There need to be higher-quality randomized trials showing clear superiority over current silver dressings. Without clear clinical advantage, investors will hesitate.
- Environmental and disposal concerns — Concern over potential ecological impacts of nanoparticle release during manufacture and during use also raise further regulatory and procurement resistance. AgNP will bind to aquatic organisms, altering the marine ecosystem.
- IP and commercialization — The patent landscape needs to be transparent. Licensing issues, and lack of industry partners to scale particular academic formulations will slow translation.
- Effective alternatives exist — Ionic silver, silver sulfadiazine, and advanced dressings already perform acceptably for many indications, reducing the commercial incentive.
- There is always market resistance to experimenting with new products, unless the benefits are clear.

3. What areas of basic research are necessary to provide a breakthrough in clinical applications for any silver-based dressing?

Chronic wounds take longer times to heal (>3 months), the reason being is that the normal phases of wound healing, hemostasis, inflammation, granulation, epithelization, contraction, and remodeling are not functioning optimally. Such wounds have biofilms, and prolonged inflammation and tissue damage [86–90]. The wound environment is ideal for bacterial infection and biofilm development, more so for immunocompromised patients. The surface extracellular polymeric substance (EPS) matrix in a biofilm is difficult to penetrate. For silver alone to disrupt biofilms require high concentrations and can be toxic. So, strategies for disrupting biofilms need to be incorporated into dressings. Several dressings are using adjuncts such as surfactants to disrupt biofilms [91–93]. Another area of basic research is to investigate polymicrobial biofilms. For human chronic wounds, *S. aureus* and *P. aeruginosa* were found with the latter present much deeper inside the wound [87]. This brings up another area that is sparsely investigated, what is the spatial diffusion characteristics of the silver actives in the wound, can they penetrate deeper into the complex three-dimensional wound topologies [93]? The reason that silver actives may not be able to penetrate deeper into the wounds where bacterial colonization has taken place is because of precipitation and deactivation in biological milieu (wound exudate) [36]. The concentration of actives used is relevant for the deeper penetration, but higher concentrations can lead to toxicity.

4. What types of animal/human studies are needed?

Appropriate animal models that mimic chronic wounds are necessary, and there are several available, including ischemic wounds, ischemic reperfusion wounds, pressure ulcers, and diabetic wounds [94–97]. Most valuable human trials are randomized controlled trials, minimizing bias. Focus should be on wound healing (wound area reduction, wound remodeling) versus just reducing bioburden. The opinion on the efficacy of silver dressings is mixed. VULCAN study focusing on randomized clinical studies found no advantage for silver dressings for venous ulcers [98]. International Working Group of Diabetic Foot Ulcers also did not recommend silver dressings for routine ulcer management [99]. Another international group recommended that silver dressings can reduce bioburden and result in shorter hospital stays [100].

5. What is the competition?

There are currently other antimicrobial treatments that are alternatives to silver, including antibiotics, other metals (zinc, copper), natural antimicrobials (honey especially for burns, chitosan), iodine compounds. New treatments on the horizon include antimicrobial biologics, including antimicrobial peptides and proteins, use of near infrared radiation (photodynamic therapy) [101–103].

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5.2. Advantages of the Ontological Method

The present ontological review differs from the traditional qualitative reviews, meta-analyses, systematic reviews, reviews of clinical studies, and bibliometric analysis in four fundamental ways. We discuss them below.

First, the ontological review is a top-down review based on a logically constructed theoretical framework of the problem. The other reviews are bottom-up reviews, grounded in published articles on the subject. The latter are subject to significant errors of omission. Logical elements, segments, and pathways to address the problem not in the literature are unlikely to be discovered. On the other hand, the ontological review highlights these in the elements and dimensions that have received little or no attention in the research. For example, Figure 5 shows that several areas need more research: silver in other nanosupports such as zeolites and MOF for controlled delivery of silver, diffusion of both the amount of silver in the surrounding medium and the depth of the penetration, comparisons to other antimicrobial agents, research on scar tissue and costs of the material, the latter very important for clinical adoption.

Second, the ontological review is inclusive, based on the population of relevant articles on the subject. The other reviews (except bibliometric reviews) are selective, usually based on a sample of articles selected based on specific criteria such as the method, topic, quality, and sample. Consequently, there is no sample bias in the results of the ontological review, and it describes the state-of-the-research regarding the entire problem, and not of a section of the problem. So, the ontology discussed here focused on the entire 4711 articles.

Third, the ontological review is based on a theory of the problem presented as an ontology. The other reviews are methods-based and not theory-based. As a theory, the ontology has the power to be used to: (a) describe the elements, dimensions, and pathways to address the problem, (b) explain its dynamics of the pathways, (c) predict the outcomes of the pathways, and (d) regulate the pathways. The other reviews are atheoretical and their results provide neither a systemic view of the problem nor systematic pathways to address it. This is evident in Figure 5, monads map of the entire corpus of articles.

Fourth, the ontological analysis can be used to develop a systemic roadmap for systematic future research to address the problem. The other reviews often yield local roadmaps and incremental directions for future research. The results highlight the dimensions, elements, and pathways (or segments) that have been heavily emphasized, lightly emphasized, and not emphasized at all. The heavy emphasis may be because of the subject's importance, ease of doing research, long history, or a combination of the three. The light emphasis may be because of the subject's unimportance, difficulty of doing research, short history, or a combination of the three. The absent emphasis may be because of the blindness to the subject's importance, impossibility of doing research, or a combination of the two. Based on the ontological mapping and the above analysis one can formulate a roadmap for research that: (a) reinforces the pathways that are likely to be effective, (b) redirect the pathways that are likely to be ineffective, and (c) experiment with novel, innovative pathways (for example, combinations of silver species and nanosupports) that have not been explored. These pathways can be periodically updated, like a 'Google Map', based on feedback and learning from the published research. A decadal ontology map of the entire field can identify the direction of specific research over time, as we have done in Figure 13 for the in-vitro, animal and human studies.

Overall, the ontology and the method of ontological analysis can complement the traditional reviews in the field and add distinctive value to their advancement.

6. Conclusions

This review is the first attempt at making an ontological map of the research on antimicrobial silver for wound dressings. This issue is logically constructed as: Use of s**ilver** species on **nanosupports** deposited on a **matrix** with **antimicrobial effectiveness** assayed by **methods** to promote **wound healing** of chronic **wounds** as determined by **recovery.** Each bolded term is a

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dimension of the ontology and denotes a taxonomy of constituent elements. Considering this globally, the ontology articulates 780 x 7 x 80 = 436,800 potential pathways to design silver-based wound dressings. An example of a potential pathway is: elemental nano crystalline silver species in nano MOF deposited on support with potency effectiveness tested in vitro to promote healing of chronic vascular wounds as determined by dressing. The ontology expresses the combinatorial complexity of the problem fully. An exhaustive search in the Scopus database led to the discovery of 4711 articles. We mapped the pathways (and segments of the same) that have been researched in 3077 of these peer-reviewed articles on the subject. A Convolutional Neural Network (CNN) was trained and then used to map the entire population of articles. With focus on silver, we could separate the field into 3 classes: nanoparticles of silver (AgNP), inorganic silver compounds and organic silver compounds. Majority of research (78% of articles) over the past decades has focused on AgNP, and the number of papers is enjoying an exponential increase. Interestingly, even though there is enormous focus on AgNP, most human studies are done with inorganic and organic silver compounds. We hypothesize that this is so because inorganic and organic compounds of silver have cleared regulatory clearance early on, and are in clinical use making them accessible for human studies. However, we find that the number of papers of AgNP in animal and human studies are increasing over the past decade, indicating that there is potential clinical products in the future. Based on the ontology, we could also identify areas where more basic and applied research is needed. One such area is the extent of penetration of the silver actives into the complex 3D topology of the wound. We suggest that a decadal ontology map of the field will provide a clear picture of the evolution of the field, a sort of Google map based on the survey of the peer-reviewed research.

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