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Digital intervention to reduce counterfeit and falsified medicines: A systematic review and future research agenda

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ABSTRACT

Counterfeit and falsified medicines have become a threat to public health around the world. The objective of this review study is to analyze all the relevant studies on preventing or reducing falsified and counterfeit medicines through digital intervention following a Systematic Literature Review (SLR) approach. A total of 51 articles were reviewed from an initial set of 1253 articles following an inclusion-exclusion criterion. As an outcome, this review study found that falsified and counterfeit medicines have become a crucial issue for research and investigation over time. Various advanced technologies (like Blockchain, IoT, RFID, image processing, pattern recognition, etc.) are being used to fight against this issue efficiently. The review also reveals future research opportunities to facilitate the existing initiatives for preventing medicine counterfeit that includes: exploring the implications of emerging technologies; discovering the contaminated point over the medicine supply chain; investigating the less emphasized concern of counterfeit and falsified medicines; exploring all possible use-cases or features of any digital solution to reduce falsified and counterfeit medicines; and the development of counterfeit/ falsified incidents reporting system. Thus, the implication of this study is to discover the research gaps and provide future research directions focusing on the prevention of usage of falsified and counterfeit medicines through the effective use of Information and Communication Technology (ICT).

Contents

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1. Introduction

Medicine counterfeit has a great impact to raise concern as a global problem and has become widespread in recent years. Counterfeit and falsified drugs are substandard or unregistered as containing one or more wrong active ingredient(s), correct active ingredients with one or more wrong excipient(s), correct active ingredients and excipients but in an incorrect quantity, or medicine with fake packaging (Kopp, 2019; Fighting counterfeit medicines, 2021; OECD, 2020; CDC, 2021; WHO, 2021). Similarly, a product can be considered as counterfeit or falsified if its source or identity is intentionally mislabelled (Kopp, 2019; Fighting counterfeit medicines, 2021). Counterfeit and falsified medical products are manufactured and packaged falsely to represent their origin, authenticity, or effectiveness information. Consumption of the toxic or replaced element in counterfeit and falsified drugs can cause several health risks like unexpected reactions, side effects, or worsening health conditions even death (Ham, 2003; Rahman et al., 2018).

Factors like lack of formal supply chain, lack of connection among the actors (e.g., manufacturer, supplier, etc.) of the supply chain, weak monitoring, law enforcement, etc. facilitate the medicine counterfeit industry. Though falsified and counterfeit medicines affect all the countries, the problem is more visible in the countries where the procedure of manufacturing, distribution, supply, and sale management are less monitored, and living standard is at a low level since falsified drugs are cheaper, and administration is weak (Amusa and Oluwade, 2020; Isah, 2012). In the global market, it is estimated that around 10% of drugs are counterfeit or falsified whereas the percentage can be more in the case of the developing and underdeveloped countries (Mukhopadhyay, 2007). However, this is an estimation having some limitations like limited reporting sources, adapting inconsistent sampling methods, specific inclusion and exclusion criteria, and the like (Mackey, 2018; McManus and Naughton, 2020). According to the Organisation for Economic Co-operation and Development (OECD) report, the cost of the global trade of counterfeit medicines in 2016 was around 4.4 billion USD (OECD, 2019). Moreover, due to the COVID-19 pandemic, the consumer demand for medicine and medical products is increasing significantly, and similarly, the global trade of counterfeit and falsified medicines is increasing (Interpol, 2020; Tesfaye et al., 2020).

Digital interventions are integrating information and communication technologies like the internet, mobile phone, software system, mobile applications, etc. to accomplish any specific jobs, improve work performance, provide better services, deliver healthcare services, promote self-patient management, and the like (Iivari et al., 2020; Islam and Islam, 2020; Zaman et al., 2020; Islam et al., 2020; Islam et al., 2019). Moreover, a digital system would not be acceptable/adoptable unless the system is technically feasible, effective, efficient, and obtain user satisfaction (Designing digital interventions, 2021; Islam and Inan, 2021). Digital interventions are considered as a more cost-effective solution that requires less human and space for implementation of a system (Goyal et al., 2018). Thus, this is very important to ensure a proper balance between human needs, perceptions, actions, and the functionalities of digital intervention.

Again, to combat against counterfeit and falsified medicines, various areas need to be addressed like securing medical products and their packaging, ensuring traceability and integrity of the medicine supply chain, tracking the movement of a drug over the supply chain, enhanced regulatory procedure, strong law enforcement, raising public awareness, etc. (Berman, 2008; Isah, 2012). Falsified medicines are labeled and packaged almost as the same as the original product. In some cases, medicines produced by renowned (branded) manufacturing companies are falsified by other unregistered and unknown manufacturers (Kopp, 2019). Sometimes original products which are expired, are packaged and labeled and enter the market as a new (non-expired) product (Mukhopadhyay, 2007). So, it is very difficult to detect, investigate, quantify and monitor counterfeit and falsified drugs (Isah, 2012). A few solutions exist to identify counterfeit and falsified medicines, that includes Radio Frequency Identification (RFID) tag to all products (Brusey et al., 2003), blockchain technology to track and trace the medicine supply chain (Sylim et al., 2018), handheld refractometer to measure the gravity of certain dissolved drugs (Sukhlecha, 2007), test-kits to know the amount of the ingredients (Hall, 2012) and, a mobile laboratory for medicine surveillance (Jin, 2009). But these couldn't reduce counterfeiting and falsifying significantly because of the increased extent of medicine counterfeit

due to the revolution of the internet (WHO, 2021). As such, customers/patients have very little chance to check the medicine before purchase online, which makes it comparatively easy to deliver falsified and counterfeit medicines in developing countries. Thus, digital intervention or proposing digital solutions could help to detect falsified medicine by reducing the problems of human-based manual systems and making the surveillance procedure easier. Similarly, digital intervention can also play a vital role to reduce the illegal entry of counterfeit, new, unapproved drugs into the supply chain. Apart from these, a few other research, as well as international organizations like World Health Organization (WHO) cite world 1999 counterfeit, Centers for Disease Control and Prevention (CDC) (Connor, 2020), Interpol (Interpol, 2020), United Nations Office on Drugs and Crime (UNODC) (Economic et al., 2020) have also attempted to address the global counterfeit and falsified medicines by introducing several guidelines and concepts (Mackey and Liang, 2013).

Production, packaging, and sales of falsified and counterfeit medicines depend on the global region also (Antignac et al., 2017). In developing and underdeveloped countries, medicines from illegal and unregulated sources are falsified in most of the cases (Ozawa et al., 2018). Again, many people are not much conscious about falsified medicines and how to make a complaint against any falsified medicine (Tazwar, 2018). Moreover, to the best of our knowledge, no review studies have been conducted on counterfeit as well as falsified medicines to provide a state-of-the-art view of current research and development aiming to reduce counterfeit and falsified medicines through the use of ICTs. Therefore, in this study, the existing studies and the development of systems, concepts, and techniques aiming to prevent medicine counterfeiting and falsifying were reviewed following a Systematic Literature Review (SLR) approach (Kitchenham and Charters, 2007; Kitchenham, 2004).

The systematic literature review is organized as follows: Section 2 contains the related works of this study. The research methodology of this review is discussed in Section 3 which includes three phases of conducting the review – planning, conducting, and reporting the review; Section 4 contains the synthesis and analysis of the data very precisely; an overview of the findings from the analyzed data along with possible research directions is described in Section 5; finally, Section 6 contains a discussion as well as the implications and limitations of this review.

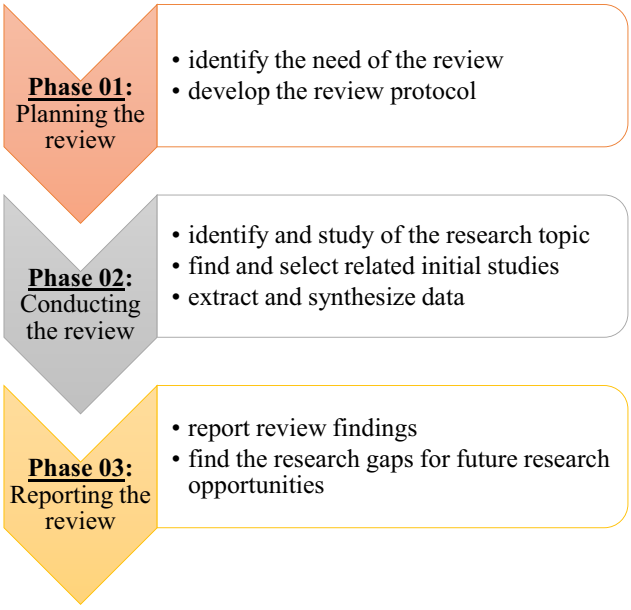

Fig. 1. Outline of a systematic literature review.

2. Related work

Only a few review studies have been conducted focusing on ICT usages, digital intervention, falsified and counterfeit medicine. This section briefly discusses these related review studies.

Mackey and Nayyar (2017) reviewed the existing studies aiming to provide digital (ICT) solutions to prevent medicine counterfeit. They found that five categories of the technology were used, include, mobile, Radio Frequency Identification (RFID), advanced computational approaches, online validation, and blockchain technology. Similarly, Isah (2012) reviewed the existing ICT-based solutions to prevent medicine counterfeit. Existing techniques and strategy highlighted in Isah (2012) includes cloud technology, rapid alert systems, and product recalls, drug product information system, internet pharmacy regulations and website seals, cyber letters, and coded stickers.

Siyal et al. (2019) summarized the existing and latest contributions of using blockchain technology in medicine and healthcare. As applications of blockchain, the review highlighted Electronic Health Records (EHR), medical fraud detection, and the pharmaceutical industry among many. The review also pointed out the future challenges of adopting blockchain like ensuring the security and privacy of stored data, and space management; while the opportunities include transparency, security, cost efficiency, time optimization, etc. Radanović and Likić (2018) explored the opportunities of blockchain implementation in medicine sector. They suggest that since blockchain provides a secured, scalable and accessible platform for the user, it would be beneficial to overcome the existing obstacles and challenges in medicine as well as healthcare.

Amusa and Oluwade (2020) depicted the historical background to facilitate the development of an efficient and effective information system for preventing medicine counterfeit. In this study, the authors highlighted the background of ICT-based telecommunication tools like mobile phone technology, cellular communication technology, SMS, to assist the agencies responsible for counterfeit drug control and health information. They also discussed various approaches of regulation and administration of manufacturing to distribution of counterfeit drugs. Again, some recent review studies (Islam and Islam, 2020; Zaman et al., 2020) highlighted the usages, contributions, and future scopes of digital intervention to combat the pandemic spread of COVID-19 for a specific country context and globally.

In sum, a limited number of studies have been conducted focusing on the usage of counterfeit and falsified medicine while very few studies have explored the existing digital technologies or ICT-based solutions that are proposed to prevent medicine counterfeit. Moreover, no research has explicitly followed the SLR approach to review existing digital interventions to reduce

Table 1
Keyword used for search.

Category	Keywords
Medicine	"Medicine", "Drug"
Medicine Counterfeit	"Medicine Counterfeit", "Drug Counterfeit"
Falsified Medicine	"Fake Medicines", "Falsified Medicine", "Falsified Drugs"
Prevent	"Prevent", "Fight", "Combat", "Solution", "Reduce", "Authentication", "Track", "Trace"
Technology	"Technology", "Digital", "ICT", "IT", "Software", "DBMS", "Blockchain", "RFID", "Barcode", "2D Data Matrix"

Table 2
Inclusion and exclusion criteria used to select relevant articles.

Inclusion/ Exclusion	Criteria
Inclusion Criteria	Articles proposing ICT based solution for preventing or reducing counterfeit and falsified medicines. Articles written in English. Articles being available with full text. Articles published in a conference proceedings, journals, thesis, magazines, and techreport. Articles published since 2000 to 2021. Same articles found from different databases.
Exclusion Criteria	Articles proposing an assumption. Articles not related to the research objective. Articles not referring to ICT based solution Articles lacking of proper justification of the proposal. Articles measuring the chemical composition of medicine.

counterfeit and falsified medicines. Thus, this review study analyzed and synthesized the existing solutions following an SLR approach to reveal the research gaps and to provide future research directions on preventing the usage of falsified and counterfeit medicines.

3. Research methodology

A literature review is an overview of the relevant publications on a specific topic in time duration. Formal methods for Systematic Literature Review (SLR) are more convenient to accumulate all published information about any topic unbiased than chronological literature reviews (Kitchenham and Charters, 2007). An SLR methodologically outlines, evaluates, and finds the gaps of the published information according to some research questions and research topics in an unbiased manner (Kitchenham, 2004). SLR helps to summarize the existing work, its benefits, and limitations, and to depict the study gaps for future research opportunities.

Primarily, each publication is studied individually, and then a structured literature review is performed. The phases of SLR conducted for the study are depicted in Fig. 1. In *planning the review* phase, the need of the review and development of the review protocol is performed. In *conducting the review* phase, selection and assessment of initial studies, data extraction, and synthesis are carried out, while in *reporting the review* phase, the refined review report is presented.

3.1. Planning the review

The planning of this review study includes the research question, source and keywords for searching the review materials, and the inclusion and exclusion criteria.

3.1.1. Research question

This review aims to understand the current status of medicine counterfeit; to explore the existing studies focusing to detect and prevent medicine counterfeit through digital interventions; to provide a comparative view among the studies aiming to reduce or

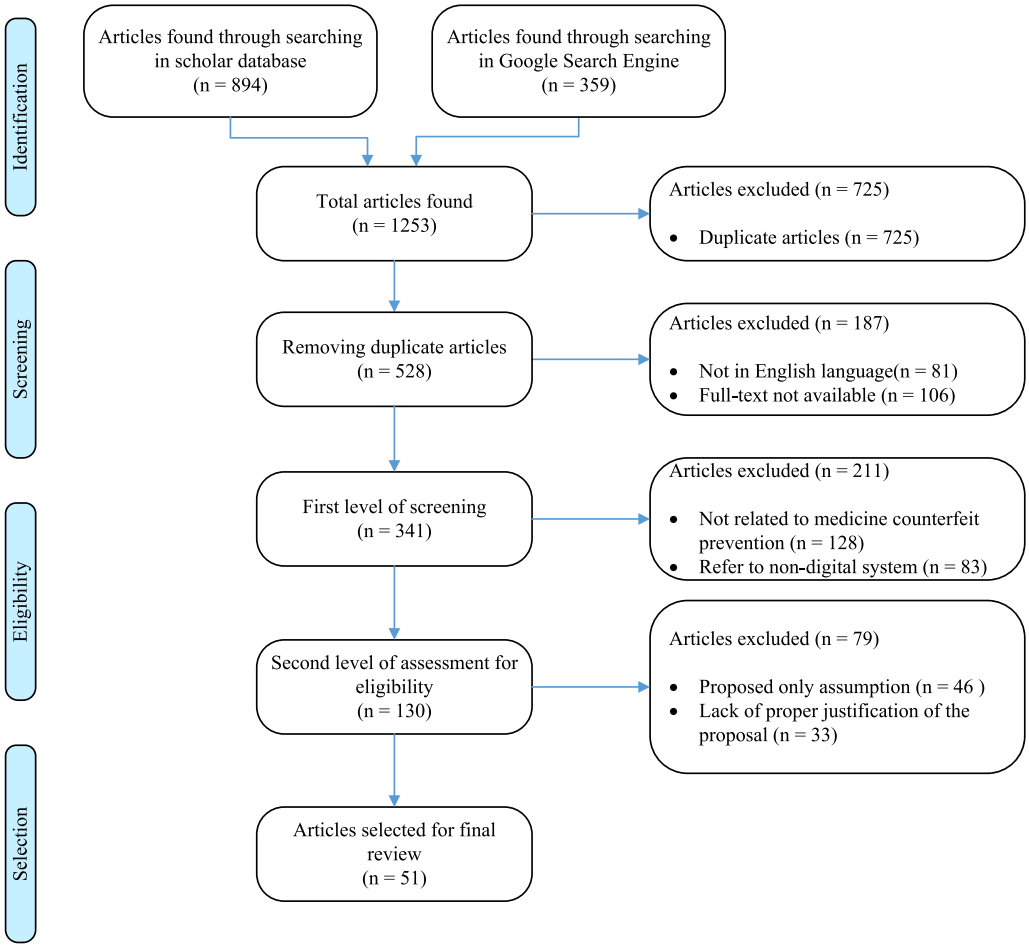

Fig. 2. PRISMA flow diagram for selection of the articles.

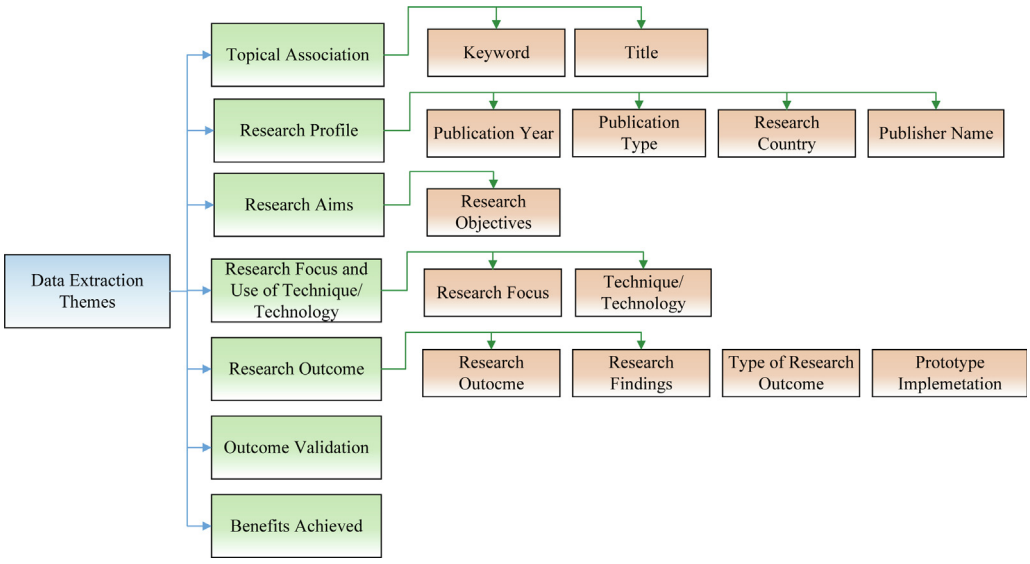

Fig. 3. Themes with features for data extraction.

prevent medicine counterfeit through the use of ICTs; to find out the current research gaps; to provide the possible scopes for pursuing potential future research. To obtain these review aims, the following questions were formulated:

RQ1: What kind of digital solutions does exist to combat counterfeit and falsified medicines?
RQ2: How much do the existing studies contribute to preventing counterfeit and falsified medicines?
RQ3: What are the challenges and limitations of the existing research on falsified and counterfeit medicine?
RQ4: What are the scopes of potential future research to reduce the usage of counterfeit and falsified medicines?

3.1.2. Selection of the article sources and searching keywords

Several scholarly digital databases were searched for selecting the related works; that includes, Google Scholar, ACM digital library, ScienceDirect, SpringerLink, IEEE Xplore, PubMed, Medline, and Wiley Online Library. Global keywords and their synonyms were selected as searching keywords (presented in Table 1) that would answer the research questions. The combination of the selected keywords was also identified as a searching keyword (See Table 1). For this, Boolean operators AND and OR were used with the keywords like the following pattern: (“Medicine Counterfeit”) AND (“Prevent”) (“Falsified Medicine”) AND (“Reduce”).

3.1.3. Inclusion-exclusion criteria

The inclusion and exclusion criteria defined to select the related articles are presented in Table 2.

3.2. Conducting the review

To conduct the review, the study materials were searched, filtered, and selected. Then, the necessary data were retrieved, analyzed, and synthesized for exploring the review results. These activities were conducted from January to December 2021.

3.2.1. Selection of the final articles

Using the keywords, an intensive search was performed in the listed databases and Google search engine. The character ‘*’ (asterisk) was used along with the keywords to select the matching results with one or more characters. The summary of the search and selection of final articles are illustrated in Fig. 2 through Prisma diagram (Stovold et al., 2014). Performing the preliminary search, a total of 1253 research works were found. After removing duplicate or repeated articles, primarily 528 articles were selected. Considering full-text availability and language, 3410 articles were chosen. Analyzing the title, the first level screening resulted in 130 articles and excludes 211 articles that are not related to reducing counterfeit and falsified medicines and discussed non-digital solutions. Then, excluding the articles that proposed solutions based on only assumption and lack of proper justification of the proposal by reading the abstract and introduction, and in some cases, discussion, a final list of 51 articles were selected for this review study.

3.2.2. Data extraction strategy

For data extraction, seven themes were considered to explore the appropriate answers to the research questions. Some of the themes were formulated into features to extract data in a

Fig. 4. Wordcloud for the keywords of the selected articles.

Fig. 5. Wordcloud for the title of the articles.

structured way (Fig. 3). To collect the specific kind of data, a set of questions were outlined on each theme.

1 Topical association: This theme points how the selected articles are correlated;
   (a) Are the articles' keywords reappearing?
   (b) Are the titles closely associated?
2 Research profile: This theme depicts the year of the publication and the publication type;
   (a) When the article was published?
   (b) What was the publication type? Was the article published in a conference, workshop, journal, tech report, or as a thesis dissertation?
   (c) In which country was the research conducted?
   (d) What was the name of the publisher?
3 Research aims: This theme identifies the research aims and objective;
   (a) What was the aim of this research?
4 Research focus and use of technique/ technology: This theme presents the research focus and the usage of technology/ technique to prevent the usage of counterfeit and falsified medicines;
   (a)What was the primary focus of the research in the case of reducing the usage of counterfeit and falsified medicines?
   (b)Which technologies were used to propose the solution?
5 Research outcome: This theme extracted the data portraying the research outcomes;
   (a) Was there a clear statement of research outcome?
   (b) What were the main research findings?
   (c) What was the type of the research outcome?
   (d) Was any prototype implemented?
6 Outcome validation: This theme characterizes the data related to validate the study outcomes;
   (a) Were the results of the study validated?
   (b) How the study outcome was evaluated?
7 Benefits achieved: This theme retrieved the benefits achieved as a result of this research.
   (a) What benefits/ research goals were achieved by conducting this research?

3.2.3. Data synthesis and analysis

Related data against the theme-based questions were retrieved. A sample set of data extracted against each question is included in A. The extracted data were analyzed and synthesized to provide effective answers to the stated research questions.

4. Data synthesis and analysis

This section discusses the outcomes of the synthesis and analysis of the extracted data.

4.1. Topical association

To represent the topical association, the *Word Cloud* approach (Heimerl et al., 2014) was used to depict how the articles are closely associated according to the theme. Word clouds are generally used to summarize text documents. In a word cloud, the bigger and bold word represent its frequency and importance. Here, the word clouds visualize the word frequencies in the keywords (see Fig. 4) and titles (see Fig. 5) of the selected articles.

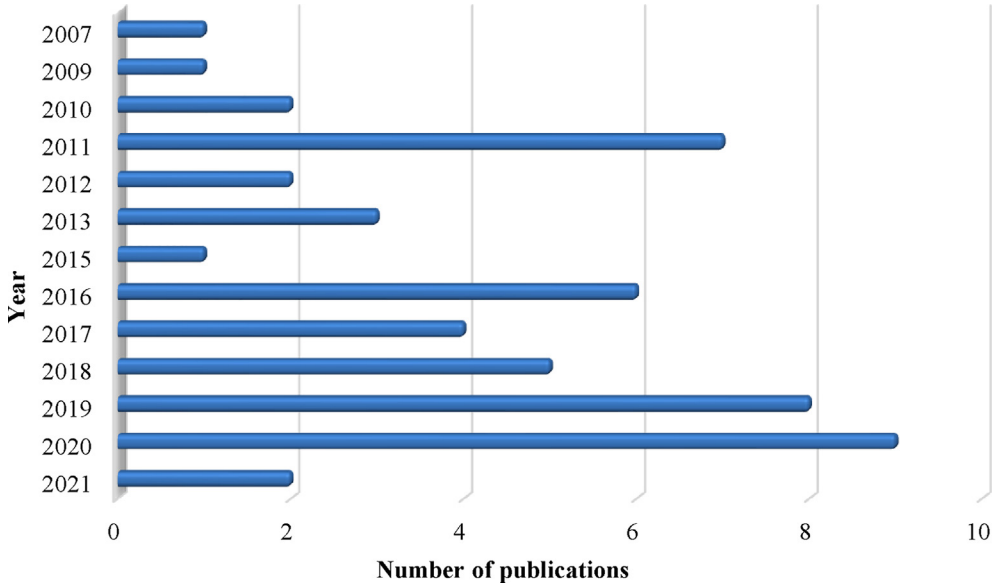

Fig. 6. The number of publications during 2007 to 2020.

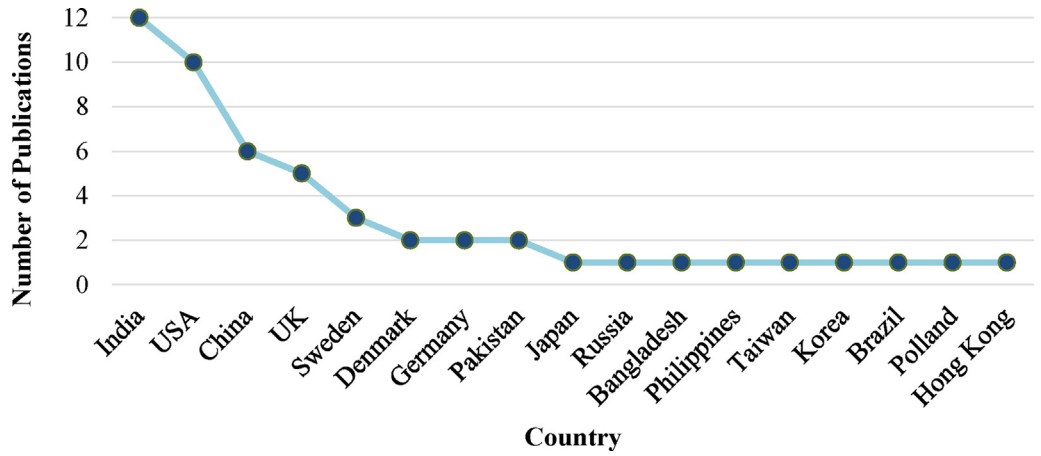

Fig. 7. Number of articles from the country where the first author affiliates.

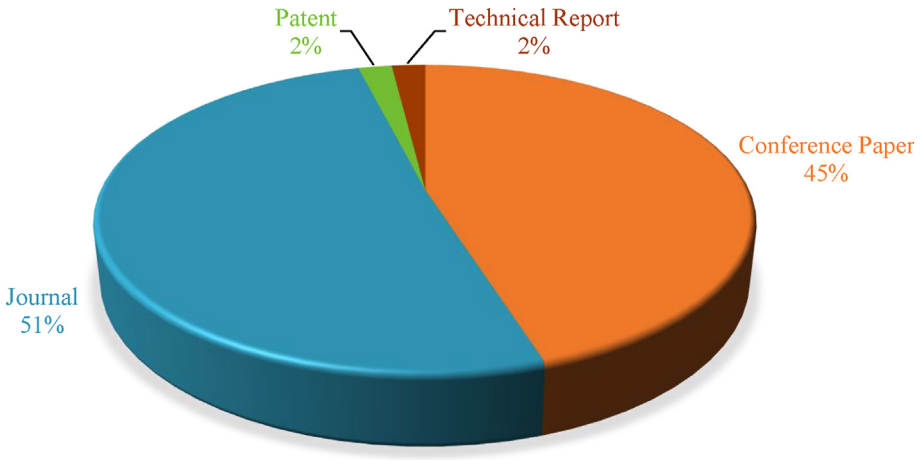

Fig. 8. Number of articles according to publication type.

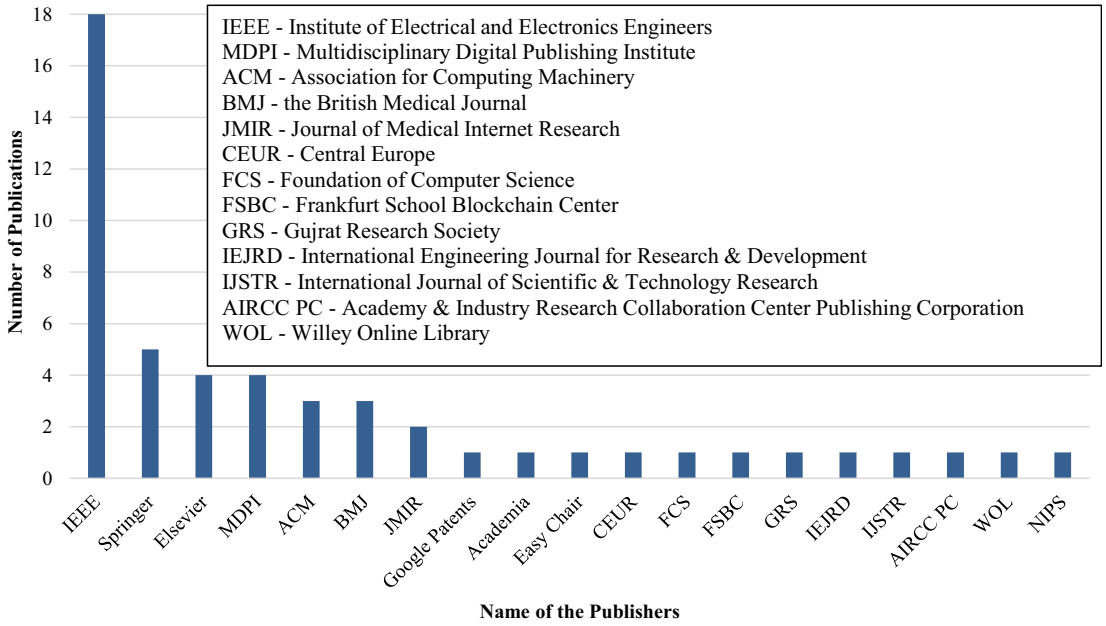

Fig. 9. Name of the publishers with number of articles.

Table 3
Summary of the research aims and their categorization.

Ser	Name of the category	Research Aims	Freq	Total
1	Prevent medicine counterfeit	Authenticate a medicine/ identify counterfeit drug	28	29
		Determine the concentration of a drug	1	
2	Performance and security	Add traceability for real time surveillance	18	39
		Ensure secured logistic supply chain	11	
		Enhance transparency	4	
		Increase trust	2	
		Protect privacy	2	
		Balance between security and performance	2	
		Store and encode large amount of medicine data easily	4	
		Develop a central pharmaceutical turnover control system	2	
3	Smart health care	Enable a viable and resilient smart electronic healthcare ecosystem	3	11
		Reduce the cost of medication	1	
		Ensure proper medication to the patients	1	
4	Public health and awareness	Protect public fitness	2	5
		Raise awareness	2	
		Eliminate the development of unusual information resources and tools	1	
5	Technology acceptance	Explore the applicability of the existing technologies	4	4

The most frequent words used as well as the important keywords (Fig. 4) include blockchain, supply, chain, drug, medicine, counterfeit, security, pharmaceutical, and traceability. These are among the largest and boldest words in the word cloud. Other words in the small font are found fewer times and may be considered as less important keywords for the articles regarding the digital solutions to prevent counterfeit and falsified medicines. On the other hand, the most used words as title (Fig. 5) are blockchain, counterfeit, chain, technology, supply, pharmaceutical, drugs, medicine, using, detection, industry, traceability, falsified, authentication, based, and system. Words found smaller in size in the cloud has been used in some specific articles as the title but they are not the commonly used ones. For example, RFID, mobile, chromatography are used in those research that has been conducted based on these technologies only. So, these words are not too frequent as a title. For both title and keywords, highly focused words are blockchain, chain, counterfeit, drug, medicine, supply, and pharmaceutical.

4.2. Research profile

In response to the question of finding the publication year, Fig. 6 shows the number of publications from 2007 to 2021. The review finding showed that studies focusing on proposing digital solutions to prevent counterfeit and falsified medicines have been published since 2007, while studies focusing on the chemical composition of medicine for preventing medicine counterfeiting and falsifying have been conducted since a long ago. The number of publications in a year increased gradually. In 2020, the number of publications has been increased (n = 9) compared to the previous years 2018 (n = 5) and 2019 (n = 8), pointing that the research in this area has risen significantly. The country of publication is presented in Fig. 7. The name of the country represents the location of the institute to which the first author of the article is affiliated. The highest number of research (n = 12) was conducted in India. Next, ten of the total reviewed articles were published in the USA. After that, six articles were published by authors from China. Five articles were published from the UK and three articles were from Sweden. In the case of Pakistan, Denmark, and Germany, two articles were published per country. Rest nine countries have one publication each.

Moreover, the publication type and publisher name are showed in Fig. 8 and Fig. 9 respectively. Almost half of the reviewed articles (51%) were published in academic journals whereas 45% (n = 23) were published in conference proceedings. Only 2% (n = 1) were patent and rest 2% (n = 1) was published as technical report. Again, IEEE has the highest number (n = 18) of articles. Springer (n = 5), Elsevier (n = 4), MDPI (n = 4), ACM (n = 3), BMJ (n = 3), and JMIR (n = 2) are the next, while rest of the publishers published one article each (see Fig. 9).

4.3. Research aims

The aims of the existing research along with the number of studies are presented in Table 3.

The aims are classified into five categories: prevent counterfeit and falsified medicines, performance and security, smart health care, public health and awareness, and technology acceptance. Again, most of the selected articles focused on multiple research aim like Shrikant et al. (2019) researched to authenticate a medicine as well as to add traceability and transparency over the supply chain. So, the research aims were assembled and categorized into five categories. First, determining the concentration of the elements in a drug and identifying a medicine as counterfeit were considered to prevent medicine counterfeit. Most of the studies (n = 28) were conducted to authenticate or identify counterfeit drugs using any proposed solution. For example, Anand et al. (2020) proposed a blockchain-based management system for the medicine supply chain to detect counterfeit drugs. Another study (Yu et al., 2016) was conducted to measure the concentration of medicine. Second, providing enhanced performance and security were the aims of 39 studies. A total of 18 studies were found that focused on incorporating traceability to the pharmaceutical supply chain with real-time surveillance, while 11 articles aimed to ensure a secured logistic medicine supply chain. Bansal et al. (2013) identified the implications of RFID and 2D barcodes to prevent medicine counterfeit from the pharmaceutical industry perspective. Since the performance and security are negatively correlated, Schapranow et al. (2011) defined a formal approach maintaining a proper balance between security and performance of the medicine supply chain. Third, eleven studies were carried out to provide smart healthcare in the pharmaceutical ecosystem. Two and three studies were conducted to develop a central turnover control system and enable smart electronic healthcare respectively, while four articles worked for storing a large amount of medicine data efficiently. For instance, Bryatov and Borodinov (2019) designed the concept of a blockchain-based medicine turnover control system. Another quantitative study was performed by

Table 4
Mapping between research aims and publication year.

Ser	Aims/ Year		2007	2009	2010	2011	2012	2013	2015	2016	2017	2018	2019	2020	2021	Freq	Total
	Name of the category	Research Aims															
1	Prevent medicine counterfeit	Authenticate a medicine/ identify counterfeit drug	(Koster, 2013)	(Paik et al., 2009)	–	(Wigand et al., 2011; Rehman et al., 2011; Jung et al., 2012; Nilsson et al., 2011; Rehman et al., 2011; Nilsson et al., 2011)	(Han et al., 2012; Abbasi et al., 2012)	(Bansal et al., 2013)	(Corona et al., 2015)	(Yu et al., 2016; Yu et al., 2016; Alzahrani and Bulusu, 2016; Banerjee et al., 2016)	(Kalyanam and Mackey, 2017; Wazid et al., 2017)	(Alzahrani and Bulusu, 2018; Huang et al., 2018)	(Pham et al., 2019; Shrikant et al., 2019; Trenfield et al., 2019; Naughton, 2019)	(Adsul and Kosbatwar, 2020; Anand et al., 2020)	(Shaik, 2021)	28	
		Determine the concentration of a drug	–	–	–	–	–	–	–	(Yu et al., 2016)	–	–	–	–	–	1	29
		Add traceability for real time surveillance	(Koster, 2013)	(Paik et al., 2009)	(Huang et al., 2010)	–	–	(Bansal et al., 2013)	–	–	(Archa and Alangot, 2018; Kalyanam and Mackey, 2017)	(Haq and Esuka, 2018; Tseng et al., 2018; Huang et al., 2018)	(Shrikant et al., 2019; Saxena et al., 2020; Trenfield et al., 2019)	(Kamble et al., 2020; Zhu et al., 2020; Sahoo et al., 2020; Kumari and Saini, 2020; Chen et al., 2020)	(Wang et al., 2021)	18	
		Ensure secured logistic supply chain	(Koster, 2013)	–	–	(Nilsson et al., 2011; Schapranow et al., 2011)	–	–	–	–	(Schöner et al., 2017)	(Sylim et al., 2018; Haq and Esuka, 2018; Alzahrani and Bulusu, 2018)	(Kumar and Tripathi, 2019; Nørfeldt et al., 2019)	(Kamble et al., 2020; Sahoo et al., 2020)	–	11	
	Performance and security	Enhance transparency	–	–	–	–	–	–	–	–	–	(Tseng et al., 2018)	–	(Kamble et al., 2020; Sahoo et al., 2020; Chen et al., 2020)	–	4	
2		Increase trust	–	–	–	(Rehman et al., 2011)	–	–	–	–	–	(Haq and Esuka, 2018)	–	–	–	2	
		Protect privacy	–	–	–	–	–	–	–	–	–	(Haq and Esuka, 2018; Huang et al., 2018)	–	–	–	2	
		Balance between security and performance	–	–	–	(Schapranow et al., 2011)	–	–	–	–	–	–	–	(Pandey and Litoriya, 2020)	–	2	39
		Store and encode large amount of medicine data	–	–	–	–	(Han et al., 2012)	(Shuaib, 2013)	–	–	–	–	–	(Zhu et al., 2020; Kumari and Saini, 2020)	–	4	11

(*continued on next page*)

Table 4 (*continued*)

Ser	Aims/ Year		2007	2009	2010	2011	2012	2013	2015	2016	2017	2018	2019	2020	2021	Freq	Total
	Name of the category	Research Aims															
		easily															
3		Develop a central pharmaceutical turnover control system	–	–	–	–	–	(Shuaib, 2013)	–	–	–	–	(Bryatov and Borodinov, 2019)	–	–	2	
	Smart health care	Enable a viable and resilient smart electronic healthcare ecosystem	–	–	–	–	–	–	–	–	–	–	(Naughton, 2019)	(Singh et al., 2020; Pandey and Litoriya, 2020)	–	3	
		Reduce the cost of medication	–	–	–	–	–	–	–	–	–	–	(Nørfeldt et al., 2019)	–	–	1	
		Ensure proper medication to the patients	–	–	–	–	–	(Kaul and Awasthi, 2013)	–	–	–	–	–	–	–	1	
		Protect public fitness	–	–	–	–	–	–	–	(Naughton et al., 2016)	–	–	–	(Adsul and Kosbatwar, 2020)	–	2	
4	Public health and awareness	Raise awareness	–	–	–	–	–	–	–	(Naughton et al., 2016)	–	–	–	(Adsul and Kosbatwar, 2020)	–	2	
		Eliminate the development of unusual information resources and tools	–	–	–	–	–	–	–	–	–	–	–	(Adsul and Kosbatwar, 2020)	–	1	5
5	Technology acceptance	Explore the applicability of the existing technologies	–	–	(Ting et al., 2010)	(Schapranow et al., 2011)	–	–	–	–	–	–	(Bryatov and Borodinov, 2019; Pham et al., 2019)	–	–	4	4

Naughton et al. (2016) to facilitate the smart electronic healthcare ecosystem. Forth, considering public health and awareness among the people, five articles were found. For example, Adsul and Kosbatwar (2020) aimed to authenticate counterfeit and falsified medicines as well as to protect public fitness and raise awareness among them. Fifth, a total of four studies were carried out to investigate the possibility of applying the existing technologies (i.e: blockchain, IoT, RFID, NFC, etc.) in facilitating information transmission in the pharmaceutical supply chain. Ting et al. (2010) outlined the applicability of RFID and IoT to enhance the data transmission over the pharmaceutical supply chain.

Mapping between the study aims with the publication year (Table 4) showed that a very limited number of studies were conducted till 2015. Among them, most of the studies were conducted aiming to reduce the usage of counterfeit and falsified medicines. Again since 2016, the number of research has been increased significantly focusing on counterfeit and falsified drugs. The mapping also showed that the most focused category of research aim was to improve the performance and security of the medicine supply chain as well as to eliminate counterfeit and falsified medicines. Similarly, the most focused aim was to authenticate a medicine, to add traceability to the supply chain, and to ensure a secured logistic supply chain. These findings thus indicate that in recent days, the supply chain is focused more to prevent counterfeit and falsified medicines.

Table 5
Research focus of the articles.

Ser	Research focus	Freq
1	Supply chain	30
2	Authentication	26
3	Medicine ingredients	3
4	Medicine appearance	2
5	Medicine ownership	1

4.4. Research focus and use of technique/technology

Existing studies primarily focus on five areas (see Table 5) to reduce the usage of counterfeit and falsified medicines while the major portion of the articles (n = 30) focused on the medicine supply chain. The movement and transaction data related to medicine over the supply chain are considered for research. For example, Adsul and Kosbatwar (2020) worked for a secure and easily traceable supply chain of medicine (from the manufacturer to the patient). Authentication of a drug as original or fake is highlighted in 26 studies; for example, an architecture was proposed by Shuaib (2013) detecting any entry of counterfeit drug in the system. Similarly, in a quantitative study, using 2D data matrix (Naughton et al., 2016) determined the medicine authentication and detection rate of some special kind of medicines.

Three articles were found that focused on the medicine ingredients. For example, Yu et al. (2016) conducted smartphone-based

Table 6
Technologies and techniques used to conduct research.

Ser	Name of Technology/ Technique	Ref	Freq
1	Blockchain	(Kumar and Tripathi, 2019; Sylim et al., 2018; Bryatov and Borodinov, 2019; Haq and Esuka, 2018; Tseng et al., 2018; Schöner et al., 2017; Singh et al., 2020; Adsul and Kosbatwar, 2020; Pham et al., 2019; Shrikant et al., 2019; Anand et al., 2020; Pandey and Litoriya, 2020; Alzahrani and Bulusu, 2018; Kamble et al., 2020; Saxena et al., 2020; Zhu et al., 2020; Huang et al., 2018; Archa and Alangot, 2018; Sahoo et al., 2020; Kumari and Saini, 2020; Wang et al., 2021; Nørfeldt et al., 2019)	22
2	RFID	(Koster, 2013; Wigand et al., 2011; Ting et al., 2010; Nilsson et al., 2011; Nørfeldt et al., 2019; Schapranow et al., 2011; Huang et al., 2010; Nilsson et al., 2011; Kaul and Awasthi, 2013; Bansal et al., 2013)	10
3	Image processing	(Jung et al., 2012; Kumar and Tripathi, 2019; Han et al., 2012; Shuaib, 2013; Koster, 2013; Rehman et al., 2011; Trenfield et al., 2019; Shaik, 2021; Chen et al., 2020; Naughton et al., 2016; Bansal et al., 2013)	11
4	Mobile phone technology	(Paik et al., 2009; Yu et al., 2016; Yu et al., 2016; Trenfield et al., 2019; Rehman et al., 2011)	5
5	IoT	(Archa and Alangot, 2018; Ting et al., 2010; Wazid et al., 2017; Nørfeldt et al., 2019; Chen et al., 2020)	5
6	Pattern Recognition	(Corona et al., 2015; Abbasi et al., 2012; Kalyanam and Mackey, 2017; Banerjee et al., 2016)	4
7	NFC	(Alzahrani and Bulusu, 2018; Alzahrani and Bulusu, 2016; Wazid et al., 2017)	3
8	TLC analyzer	(Yu et al., 2016; Yu et al., 2016)	2
9	Cryptography	(Alzahrani and Bulusu, 2016; Shaik, 2021)	2
10	2D Data Matrix	(Naughton et al., 2016; Naughton, 2019)	2
11	Statistical Analysis	(Jung et al., 2012)	1
12	3D Printing	(Trenfield et al., 2019)	1

Table 7
Number of articles with more than one technologies used to conduct research.

Ser	Name of Technologies	Blockchain	RFID	Image processing	Mobile phone technology	Pattern Recognition	NFC
1	RFID	1	–	–	–	–	–
2	Image processing	1	2	–	1	2	–
3	IoT	2	1	1	–	1	–
4	NFC	1	–	–	–	–	–
5	TLC analyzer	–	–	–	2	–	–
6	Cryptography	–	–	1	–	–	1
7	2D Data Matrix	–	–	1	–	–	–
8	Statistical Analysis	–	–	1	–	–	–
9	3D Printing	–	–	1	1	–	–

Table 8
Mapping between technology used and publication year.

Ser	Name of Technologies	2007	2009	2010	2011	2012	2013	2015	2016	2017	2018	2019	2020	2021	Freq
1	Blockchain	–	–	–	–	–	–	–	–	2	5	6	8	1	22
2	RFID	1	–	2	4	–	2	–	–	–	–	1	–	–	9
3	Image processing	1	–	–	1	2	2	–	1	–	–	2	1	1	9
4	Mobile phone technology	–	1	–	1	–	–	–	2	–	–	1	–	–	5
5	IoT	–	–	1	–	–	–	–	–	2	–	1	1	–	5
6	Pattern Recognition	–	–	–	–	1	–	1	1	1	–	–	–	–	4
7	NFC	–	–	–	–	–	–	–	1	–	1	–	–	–	2
8	TLC analyzer	–	–	–	–	–	–	–	2	–	–	–	–	–	2
9	Cryptography	–	–	–	–	–	–	–	1	–	–	–	–	–	1
10	2D Data Matrix	–	–	–	–	–	–	–	1	–	–	1	–	–	1
11	Statistical Analysis	–	–	–	–	1	–	–	–	–	–	–	–	–	1
12	3D Printing	1	–	–	–	–	–	–	–	–	–	–	–	–	1

research to measure the (medicine) components concentration. Apart from these, one article was found related to medicine ownership and two articles considered the external appearance of a medicine. Abbasi et al. (2012) focused on medicine labeling to identify fraudulent medical websites, while Pham et al. (2019) developed a medicine ownership management method using blockchain.

Again, each studied article had a clear indication about the technology or technique used. A summary of the technologies or techniques stated in the existing studies is depicted in Table 6. Most of the studies (n = 22) were conducted based on the blockchain, a distributed ledger containing transaction data in blocks over peer-to-peer networks and provides transparency (Islam et al., 2020). For example, Haq and Esuka (2018) integrated blockchain in the medicine supply chain to track the medicine over the supply chain. Again, ten articles were found which worked using RFID (automatic radio-frequency identification using electromagnetic fields (Sarma et al., 2002)), like Wigand et al. (2011) integrated RFID and related technologies like EPCglobal's Electronic Product Code Information Services (EPCIS) for information management in the medicine supply chain. Similarly, a total of 10 studies used coding (i.e.: QR code, barcode, etc.) and image processing technique while coding techniques represent data in a visual form so that a machine can read it using image processing algorithms. For example, Shuaib (2013) proposed a QR code-based medicine authentication system. Five articles utilized mobile technology like Paik et al. (2009) developed a medical products tracking system using mobile phone built-in technologies (i.e.: GPS, Camera. SMS). Moreover, five articles adopted IoT to propose a solution to reduce the usage of counterfeit and falsified medicines that generally consists of interconnected devices with the transmission of data collected from sensors. For example, Wazid et al. (2017) proposed an anti-medicine counterfeiting scheme in the IoT environment. Then, the usage of the pattern recognition approach for a large amount of data to make a decision was observed in four articles. For instance, Kalyanam and Mackey (2017) detected illegal marketing and promotion of medicine by searching specific patterns among the contents collected from Twitter. Solution based on Near Field Communication (NFC) tags were proposed in three articles. Cryptography, Thin-Layer Chromatography (TLC) analyzer, and 2D Data Matrix were found in two studies each; while statistical analysis and 3D printing techniques were used in a single study each.

Table 7 shows the number of articles using more than one technology to propose a solution. Blockchain was used along with RFID, image processing, and NFC in one article each; two articles implemented blockchain and IoT to prevent medicine counterfeiting and falsifying; RFID technology along with image processing and IoT were found in one article each; two articles implemented pattern recognition with codings using image processing like barcode, QR codes; pattern recognition was adopted with IoT in one article; and image processing was used along with mobile phone technology, IoT, cryptography, statistical analysis, and 3D printing in one article each; Mobile phone technology was used with a TLC analyzer in two articles; and NFC technology and cryptography, mobile phone technology, and 3D printing were used combined in one article each; Image processing and statistical analysis both were adopted in one article. For example, Singh et al. (2020) implemented blockchain in an IoT-based supply chain management system for smart healthcare; while Kumar and Tripathi (2019) proposed a blockchain-based system that also uses image processing to ensure drug safety.

Moreover, the usage of ICT has been changed according to the time (see Table 8). Earlier (2007 to 2016), RFID, NFC, image processing, TLC analyzer, pattern recognition, etc. were quite popular technology to conduct research. But later from 2017 to 2020, it can be found that research based on blockchain technology has been significantly increased to prevent counterfeit and falsified drugs. These findings indicate that blockchain technology could be used to ensure a secured and traceable logistic medicine supply chain (Islam et al., 2020) for reducing the usage of counterfeit and falsified medicines.

4.5. Research outcome

Most of the studied articles (n = 34) clearly stated the research outcomes. The outcomes of the studies were synthesized and classified into six categories: architectural framework, conceptual idea, software, quantitative analysis, algorithm, and edible element (see Fig. 10). Most of the articles (n = 21) proposed an architectural framework to prevent a medicine from counterfeiting and falsifying and primarily includes the system architecture and the workflow with system requirements. For example, Sylim et al. (2018) proposed a blockchain-based surveillance system with a detailed overview of the supply chain and medicine authentication, while Koster (2013) presented the systems and methods using encryption algorithms to detect counterfeit and falsified medicines. Again, 14 articles presented a conceptual idea to fight against counterfeit and falsified medicines. For example, Kumari and Saini (2020) discussed the existing medicine supply-chain scenario with its limitations and how drug traceability can add an extra level of security and then proposed a theoretical solution to add traceability in the medicine supply chain using blockchain. Another 10 studies found that developed a software system, like Huang et al. (2018) developed a scenario-oriented and blockchain-based system named "Drugledger" to improve the existing medicine supply chain with enhanced traceability and regulatory features. Four studies conducted quantitative analysis to reduce counterfeit and falsified medicines, for example, in a study (Naughton et al., 2016) performed into a hospital dispensary the overall medicine

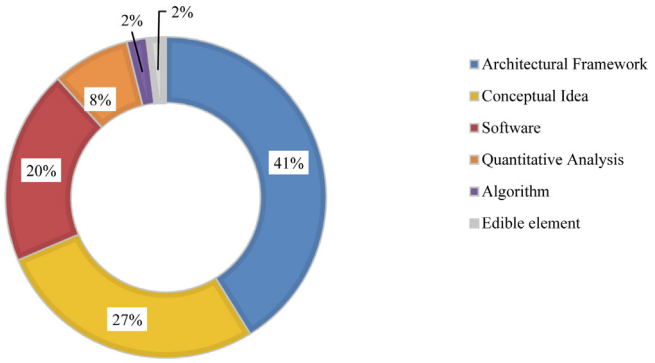

Fig. 10. Number of articles according to the type of research outcome.

authentication and detection rate was measured by using 2D data matrix, cloud based database.

An algorithm was proposed using recursive trust labeling (RTL) to detect fake medical websites over different countries by Abbasi et al. (2012). Similarly, Han et al. (2012) proposed a Quick Response (QR) code-based edible microtaggant encoded system with identification data to be composed in medicine.

From the implementation point of view, prototypical systems were developed in 24 (47%) studies. The rest of them (53%) didn't implement their proposed concept or framework. For example, Saxena et al. (2020) developed a prototypical tool named "PharmaCrypt" to track and trace the medicine supply chain uploading data to the blockchain, while Kamble et al. (2020) simulated their proposed blockchain-based architectural framework by mathematical modeling for three interfaces: user, manufacturer, and retailer. Among the articles that implemented the prototypical solution, thirteen studies included experimental implementation or simulation of their proposed solution, like Yu et al. (2016) simulated the smartphone TLC analyzer to analyze the compound in a medicine. Another study performed by Chen et al. (2020) also implemented their proposed Smart IoT Based Fault-Tolerant Mechanism and demonstrated the feasibility of their design.

A mapping between the research aim and outcomes has been depicted in Table 9. The mapping results showed that most of the studies (n = 39) aimed to enhance the performance and security of the medicine supply chain and management system. Among them, 19 studies presented architectural framework, 10 articles proposed conceptual ideas, 8 software were developed and the remaining one was a quantitative study. To reduce medicine counterfeiting and falsifying a total of 29 studies were conducted that includes architectural frameworks (n = 11), conceptual ideas (n = 9), software applications (n = 4), quantitative analysis (n = 3), algorithms (n = 1), and edible element (n = 1). The results thus indicate that to reduce counterfeit and falsified medicines mostly architectural frameworks and conceptual ideas were proposed. Again, a limited number of studies focused to develop smart healthcare (n = 11), raising public health and awareness (n = 5), and exploring technology acceptance (n = 4).

Considering the relationship between the technology used and the research outcomes as presented in Fig. 11, it can be shown that in the case of blockchain-based studies, mostly architectural

Table 9
Mapping between research aims and outcomes.

Ser	Name of the category	Architectural framework	Conceptual idea	Software	Quantitative analysis	Algorithm	Edible element	Total
1	Prevent medicine counterfeit	11	9	4	3	1	1	29
2	Performance and security	19	10	9	1	–	–	39
3	Smart health care	4	2	3	1	–	1	11
4	Public health and awareness	3	–	–	2	–	–	5
5	Technology acceptance	2	2	–	–	–	–	4

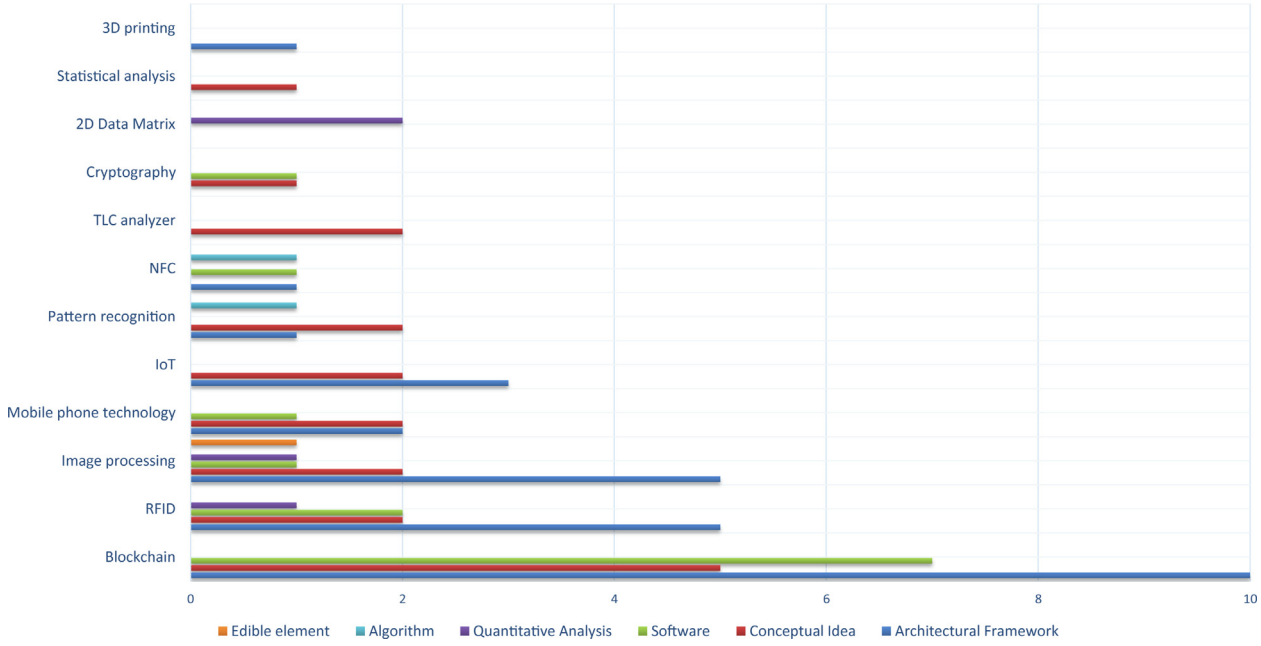

Fig. 11. Relation between the research outcome with technology used.

frameworks (n = 10) were proposed research outcomes. Other outcomes were conceptual idea (n = 5) and software systems (n = 7). RFID technology was used to propose architectural frameworks in five studies, conceptual ideas and software systems in two articles each, and quantitative analysis was performed in one article. Image processing was implemented in five articles that proposed architectural frameworks, two studies presented conceptual ideas, and one article found to develop a software system. Again, one study each was conducted to introduce an edible element, and perform a quantitative analysis using image processing. IoT and pattern recognition-based studies proposed three and one architectural frameworks respectively, and two conceptual ideas while another study adopted IoT to propose an algorithm. Using mobile phone technology one software was developed, and two conceptual ideas and two architectural frameworks were proposed; while studies based on NFC tags presented one architectural framework, developed a software system, and proposed an algorithm. In two quantitative analyses, 2D data matrix were used. TLC analyzer, public-key cryptography, and statistical analysis were used to propose two, one, and one architectural framework as outcomes, respectively.

4.6. Outcome validation

A total of 29 among the reviewed articles (57%) validated their research outcomes (see Fig. 12). Among them, 12 articles conducted computational evaluations, i.e. Singh et al. (2020) evaluated the performance of their proposed system by measuring the propagation time of the blocks over the network using high-speed servers. They also provided a solution to the security requirements of the system like authorization, public key and data ring signature was used, data hashing to ensure data integrity, lightweight encryption to preserve data confidentiality, etc.

Most of the articles (n = 10) presented a comparison with existing systems/ solutions. For example, Saxena et al. (2020) presented a comparison with existing solutions in terms of performance measures. Several studies (n = 6) included a simulation of their proposed solution to validate their outcome. For example, Han et al. (2012) prepared a capsule with microtaggants encoded with drug authentication information. Then, the drug elements were screened through a microscope to find the microtaggant with the QR code. The system decoded the information correctly and the medicine was authenticated successfully. Six articles experimentally implemented their idea as the validation of the research outcomes. For instance, Banerjee et al. (2016) trained the proposed system with k-Nearest Neighbour (kNN), Caffenet, and GoogLeNet algorithms. Then, evaluated the system for each algorithm separately and found the accuracy maximum for Caffenet (94%). Three studies presented theoretical validation by performing mathematical calculations like Zhu et al. (2020) validated his proposed blockchain-based anti-counterfeit system by performing computational evaluation in terms of performance and security. The system was simulated in a blockchain environment and the result was shown in graphical representation.

This review study also found that most of the architectural framework (n = 8) were validated using computational evaluation, while a good number of conceptual ideas (n = 5) have been validated by experimental implementation followed by accuracy

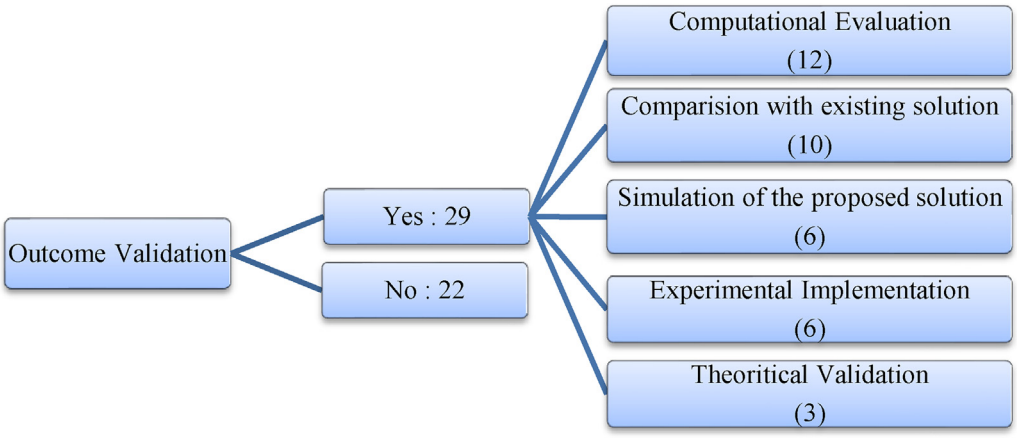

Fig. 12. Number of articles pursued outcome validation.

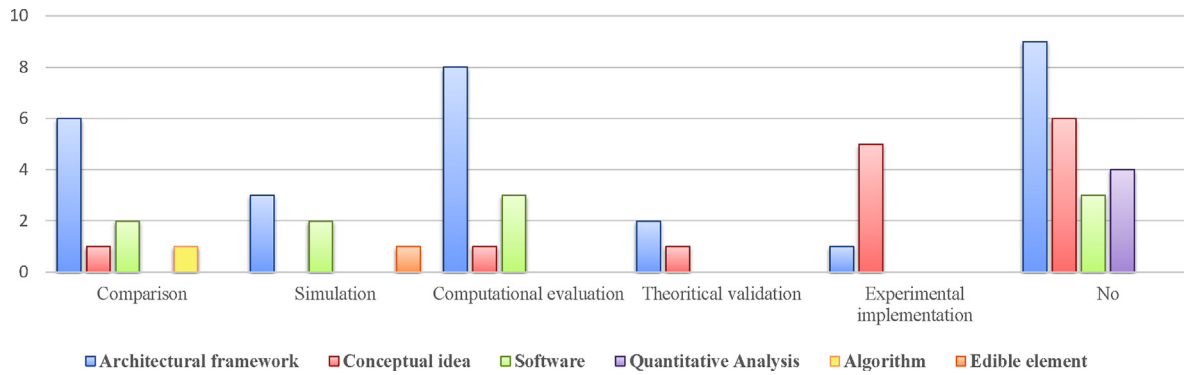

Fig. 13. Relation between the type of research outcome with outcome validation.

measurements (Fig. 13 and Table 10). The edible microtaggant proposed by Han et al. (2012) was simulated for evaluation. Moreover, nine architectural frameworks, six conceptual ideas, three software systems, and four quantitative studies were not validated using any evaluation method.

4.7. Benefits achieved

The summary of the achieved benefits is presented in Table 11. The most acquired benefit was enhanced trust and transparency of the medicine supply chain (n = 20) and the increased performance in terms of efficiency, throughput, or latency of the supply chain (n = 17) followed by monitoring supply chain (n = 10) and authenticated manufacturers (n = 8). For example, Bryatov and Borodinov (2019) proposed a pharmaceutical supply chain system to enhance its trust and transparency with simplified monitoring. As a result, any event of dispute could be easily tracked over the supply chain. Again, the system proposed by Paik et al. (2009) offered the operations of the supply chain to execute at low cost, while Kamble et al. (2020) ensured enhanced performance of the supply chain.

5. Review findings and future research directions

This section briefly depicts the main findings and implications for further research.

5.1. Main findings

5.1.1. Topical association

The word cloud generated using the keywords and titles depicts the depth of the relationship among the fields of the selected articles. The words like blockchain, counterfeit, pharmaceutical, chain, drug, and traceability are the highlighted words for both titles and keywords. This illustrates that the articles selected for the review are closely related and most of them were conducted using 'blockchain' technology.

5.1.2. Research profile

The research profile mainly focused on the publication year, publication type, publisher name, and the country where the first author is affiliated in. The publication year indicates that research focusing on preventing medicine counterfeit is increasing day by day. Most of the research is getting published as conference papers and journals, while various publishers are also involved to publish studies focusing on medicine counterfeit. Again, though medicine counterfeit has become a global problem, authors from India and the USA have researched this topic most.

5.1.3. Research aims

The reviewed articles primarily aimed to propose a digital solution for preventing medicine counterfeit. While some studies intended to enhance the performance and security of medicine supply chain systems to prevent medicine counterfeit. Again, a good number of studies have aimed to emphasize providing smart

Table 10
Mapping between research outcome and the method of outcome validation.

Ser	Method	Architectural framework	Conceptual idea	Software	Quantitative analysis	Algorithm	Edible element
1	Comparison	(Pham et al., 2019; Singh et al., 2020; Wazid et al., 2017; Wang et al., 2021; Rehman et al., 2011; Nilsson et al., 2011)	(Rehman et al., 2011)	(Pandey and Litoriya, 2020; Saxena et al., 2020)	–	(Abbasi et al., 2012)	–
2	Simulation	(Zhu et al., 2020; Adsul and Kosbatwar, 2020; Wang et al., 2021)	–	(Alzahrani and Bulusu, 2016; Shaik, 2021)	–	–	(Han et al., 2012)
3	Computational evaluation	(Pham et al., 2019; Kamble et al., 2020; Zhu et al., 2020; Corona et al., 2015; Wazid et al., 2017; Rehman et al., 2011; Shaik, 2021; Kaul and Awasthi, 2013)	(Alzahrani and Bulusu, 2016)	(Singh et al., 2020; Huang et al., 2018; Paik et al., 2009)	–	–	–
4	Theoretical validation	(Schapranow et al., 2011; Nilsson et al., 2011)	(Nilsson et al., 2011)	–	–	–	–
5	Experimental implementation	(Chen et al., 2020)	(Yu et al., 2016; Jung et al., 2012; Yu et al., 2016; Kalyanam and Mackey, 2017; Banerjee et al., 2016)	–	–	–	–
6	No	9	6	3	4	–	–

Table 11
Benefits Achieved.

Ser	Benefits	Freq
1	Enhanced trust, security and transparency in drug supply chain	20
2	Increased performance (increased efficiency, throughput or reduced latency) of supply chain	17
3	Monitoring the supply chain easily	10
4	Authenticated manufacturer	8
5	Tracking any event of disputes	6
6	Low cost operations of counterfeit unit	4
7	Maintaining patient data privacy	4
8	Facilitate medication to the patients	3
9	Tracing back a medicine with expired date to the real source	2
10	Locate/ trace any product over the supply chain	1
11	Reduced loss related to counterfeit drugs	1

health care to address the medicine counterfeit problem to some extent.

5.1.4. Research focus and use of technique/ technology

The study reveals that the medicine supply chain and identification of fake drugs were focused mostly to propose a solution for medicine counterfeit. As technology, blockchain, image processing, and RFID were most used for proposing a conceptual framework and developing any digital solution for reducing medicine counterfeit.

5.1.5. Research outcome

Most of the review articles proposed architectural frameworks and a few of them also simulated their proposed framework as study outcomes. Apart from these, a limited number of studies presented the development of a system to prevent the business of falsified and counterfeit medicines.

5.1.6. Outcome validation

Most of the selected articles performed an outcome validation. Again, the validation studies largely preferred to perform computational evaluation and to show a comparison between the existing solutions and their proposed ones and conduct a simulation of their framework.

5.1.7. Benefits achieved

The most highlighted benefits achieved through the digital intervention are: enhancing the performance, improving trust and transparency, monitoring the supply chain easily, authenticated manufacturer, and tracking any unusual event that occurred in the pharmaceutical supply chain for reducing medicine counterfeit.

5.2. Implications for Research: Research gaps and recommendations

The outcomes of this systematic literature review present the existing research gaps or limitations in the broad area of healthcare to determine the possible future research directions for preventing the medicine counterfeit. A specific set of research directions revealed from this review study are discussed below:

5.2.1. Explore the implications of emerging technologies

The review showed that several emerging technologies like Blockchain, IoT, RFID, and the like were used to propose different types of digital solutions to prevent counterfeit and falsified medicine (Alzahrani and Bulusu, 2018; Kumari and Saini, 2020; Wazid et al., 2017; Ting et al., 2010); while a few studies adopted multiple technologies to propose a distinct solution for reducing counterfeit and falsified medicines (Archa and Alangot, 2018; Banerjee et al., 2016). Usage of multiple technologies may facilitate the whole system to perform more effectively and efficiently. However, in this vein, further research could be conducted focusing on (i) exploring the necessities and benefits of using multiple technologies (instead of a single technological solution) for developing a digital solution to prevent the usage of counterfeit and falsified medicines; (ii) adopt the artificial intelligence (AI) and machine learning (ML) to bring a revolutionary in the elimination of counterfeit and falsified medicines; and (iii) investigate which emerging technology offers the best performance in terms of effectiveness, efficiency, time, latency, and cost-effectiveness in offering a solution to the medicine counterfeit.

5.2.2. Discover the contaminated point instantly over the medicine supply chain

Some studies (Bryatov and Borodinov, 2019; Haq and Esuka, 2018) were conducted that facilitates to track any event of a dispute over the medicine supply chain . . .but no empirical assessment or evidence has been presented regarding its accuracy and efficiency. Again, although it is very important to detect the point of entry (i.e., retailer, wholesaler) of a counterfeit or falsified drug in the medicine supply chain instantly for the prevention of counterfeit and falsified medicines, the existing studies did not explicitly focus to discover the original scenario or detect the responsible one for contamination over the supply chain. If it could be possible to detect any contaminated point over the medicine supply chain immediately, the medicine will not be able/allow traversing further over the supply chain. Therefore, further research can be conducted to detect the infected point as well as the involved person over the medicine supply chain instantly.

5.2.3. Investigate the less emphasized concern of counterfeit and falsified medicines

A significant amount of research (n = 25) focused to the whole pharmaceutical supply chain to propose a solution (Anand et al., 2020; Shuaib, 2013; Schöner et al., 2017); while a limited number of other studies focused to authentication (Corona et al., 2015; Sylim et al., 2018), medicine appearance (Jung et al., 2012), medicine ingredients (Han et al., 2012; Yu et al., 2016), medicine ownership (Pham et al., 2019). Moreover, some important issues were not focused on in the earlier studies like the process starting from purchasing the raw material to the production of a drug, data security of manufacturer organizations, etc. Future research could be carried out focusing on the less emphasized or ignored issues to enhance or develop new solutions for preventing counterfeit and falsified medicines.

5.2.4. Explore all possible use-cases/features of any digital solution

Several existing studies have proposed a framework or a software solution to reduce the usage of counterfeit and falsified medicines primarily by authenticating a counterfeit/ falsified drug (Adsul and Kosbatwar, 2020, adding traceability in the supply chain for real-time surveillance (Saxena et al., 2020), enhancing transparency over the supply chain (Kamble et al., 2020), and ensuring a balance between security and performance of the supply chain (Schapranow et al., 2011). But none of the studies has been conducted focusing on developing a system considering all these features (or uses-cases) together.

Again, the existing research/solution can detect a medicine as counterfeit or falsified if the code on the label is not stored as a valid one (Anand et al., 2020). On the contrary, a medicine can be falsified or counterfeit but may use a valid code that is already used (in another item of a similar type of medicine); and the existing solution can trace this medicine properly. Similarly, according to the existing blockchain-based solution (Anand et al., 2020), detecting a medicine as an invalid/fake one is not possible at this moment for the following scenario – a medicine that should be located at a shop in city "A". But the same code can be given as input to check the validity from city "B". Here, the medicine at "B" must be the counterfeit/ falsified one; and not detectable through the existing solution. Moreover, the existing research/solutions have focused on the packaging of the drug which is meant for some of the primary packagings like the blister packs or sachets (Huang et al., 2018; Koster, 2013). But in the case of vials, bottles, ampoules, or even for secondary packagings like boxes or cartons, it is very possible to replace the medicines inside of them with fake ones. And using the existing solutions, it is impossible to detect falsified/ counterfeit drugs since the original packaging remains to compel the system to give the wrong output.

Therefore, potential future research scopes are open to reveal all possible use-cases or features; and to develop a digital system considering all the revealed use-cases or features to improve the performance and security of the medicine supply chain and to

reduce the usage of counterfeit and falsified medicines more effectively.

5.2.5. Develop concrete software system

Most of the existing studies have emphasized proposing a conceptual (34%) or architectural framework (42%) rather than implementing concrete digital solutions for preventing counterfeit and falsified drugs. Again, prototypical solutions were discussed in around 42% of articles, while a limited number of studies (18%) presented the concrete software solutions to adopt in real life aiming to reduce the usage of counterfeit and falsified medicines. For example, Nilsson et al. (2011) proposed a conceptual framework for a secured medicine supply chain using time-controlled numeric tokens but no prototypical implementation was conducted. Though a computational measure of performance was performed as theoretical validation, it was not sufficient to validate the proposed conceptual framework. The review thus indicated that most of the proposed conceptual and architectural frameworks are not implemented yet to justify their feasibility, effectiveness, and efficiency. On the other hand, only 23 of the selected articles (Fig. 12) have validated their research outcomes mostly by providing theoretical validation, comparison with existing solutions, or experimental simulations. These findings revealed that implementation/development of the proposed theoretical solutions (architectural frameworks, conceptual design, etc.) is a great concern to evaluate their performances and feasibility in real context for preventing counterfeit and falsified drugs. These in turn indicated that materializing or implementing the existing theoretical proposals and evaluating the implemented solutions in the real context would be potential scopes for future research as well.

5.2.6. Develop falsified and counterfeit incidents reporting system

Existing research has been conducted having research aims like to fight against counterfeit and falsified medicines (Paik et al., 2009; Rehman et al., 2011; Yu et al., 2016), to ensure smart healthcare (Bryatov and Borodinov, 2019; Singh et al., 2020; Pandey and Litoriya, 2020), to provide increased performance and security of the supply chain (Sahoo et al., 2020; Tseng et al., 2018; Haq and Esuka, 2018) and so on, but there is no study explicitly focusing to report any incident occurred to the local authority. Detection of a falsified or counterfeit medicine by any customer can at most refrain him/her to consume that medicine. And so, no one (even the manufacturer and local authority) has any idea about this issue unless the customer/shopkeeper informs them while informing the manufacturer can make aware and help them to be more careful. Again, informing the local authority immediately about such an incident with proper proof and data may help to identify the responsible one, which in turn will prevent people not from doing anything further and prevent the medicine from counterfeiting and falsifying. Thus, potential future research may focus on designing and developing a reporting system (mobile or web portal) to facilitate reporting any incident related to counterfeit and falsified medicines and taking appropriate legal actions to reduce the usage of counterfeit and falsified medicines.

6. Conclusion

This research systematically reviews the studies related to digital approaches to prevent medicine counterfeit. These articles have been selected from several online scholar databases and data extracted from them have been synthesized and analyzed meticulously to retrieve relevant information to obtain the review objectives.

This review provides an overview of the technologies and techniques are used in existing digital solutions and concepts for the prevention of counterfeit and falsified medicines. It also provides a detailed view of the various areas that have been focused to reduce the usage of counterfeit and falsified medicines. Moreover, this review shows that the technologies, as well as the research outcomes, have been changed over the years.

Moreover, this review study revealed the existing research gaps to find out the potential future research opportunities on reducing falsified and counterfeit medicines. One of the future research recommendations includes the implication of emerging technologies like blockchain, IoT, pattern recognition, etc. to fight against counterfeit and falsified medicines. Integrating more than one technology to propose a digital solution may improve the effectiveness and efficiency to detect any incident regarding falsified/ counterfeit medicine. Moreover, technologies and (research) focused areas that are still less emphasized can be considered for future research directions to bring out more fruitful solutions. Developing a reporting system for any incident related to falsified medicine can facilitate the prevention of counterfeit and falsified drugs. Similarly, exploring more possible use cases and features of a digital solution can increase the latency and efficiency of a digital solution. Thus, this review study will greatly contribute to pursuing potential future research and developing innovative solutions to prevent counterfeit and falsified medicines.

One limitation of this literature review is, some relevant articles might be excluded due to specific exclusion-inclusion criteria. For example, some articles could not be included due to the unavailability of full text or being in a different language than English. Also, the keywords identified for searching relevant articles may exclude some related articles. Another limitation is the review was conducted by only two authors whereas one has assembled the articles and extracted data and the other one verified it consciously to validate and acquire necessary information. So, there might be some inconsistency in tabulating and classifying the data.

The findings of this systematic literature review indicate that digital solutions using different technologies and techniques are being adopted to reduce the usage of counterfeit and falsified drugs as well as to ensure more transparency, traceability, and efficiency in the pharmaceutical supply chain. The review also provides an in-depth outline for pursuing potential future research to prevent or reduce counterfeit and falsified medicines.

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Author's contributions

II and MNI formulated research questions, conducted search and finalizing the selection of articles for review; II performed data extraction; II and MNI performed data synthesis and analysis; II prepared the initial draft; II and MNI revised and finalized article; MNI supervised the whole process. All authors reviewed and approved the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Sample data of data extraction against research questions:

Ser	Title	Keyword	Aim	Main finding	Outcome Validation	How	Benefits	Article Type	Outcome	Country	Year	Publisher	Prototype	Technology
1	A Blockchain Based Solution for Medication Anti-Counterfeiting and Traceability (Zhu et al., 2020)	Medication anti-counterfeiting, traceability, blockchain, PBFT consensus, supply chain	to propose a blockchain based method for medication information storage, inquiry, and anti-counterfeiting along a medication supply chain	the proposed method can assure the transparency and openness of medication supply chains	Yes	simulation in terms of enhanced security and performance analysis (transaction delay comparison, throughput comparison, operational efficiency verification, storage space occupancy, and energy cost evaluation)	eliminates the needs for centralized institutions and third-party organizations, and provides a full record of the medication circulation process.	Journal	Architectural Framework	China	2020	IEEE Access	No	Blockchain
2	PharmaCrypt: Blockchain for Critical Pharmaceutical Industry to Counterfeit Drugs (Saxena et al., 2020)	Blockchain, Counterfeit drugs, Pharmaceutical industry, Security, Amazon web service	to create a blockchain driven tool that can be used to record and timestamp the transfer of goods at each point in the pharmaceutical supply chain	a tool to track and trace drugs as they move through the supply chain, uploading the data collected to a distributed Blockchain ledger validating the authenticity of the drug.	Yes	evaluation of effectiveness through comparison with existing solution	record and timestamp the transfer of goods at each point in the pharmaceutical supply chain	Journal	Software	UK	2019	IEEE Computer Society	Yes	Blockchain
3	Information Management and Tracking of Drugs in Supply Chains within the Pharmaceutical Industry (Wigand et al., 2011)	Drug Safety, Pharmaceutical Industry, Tracking, Radio Frequency Identification, RFID, Supply Chain Management	to verify the authenticity of pharmaceutical products, as well as use of RFID as a means to reduce or control the distribution of counterfeit pharmaceutical products	EPCglobal's Electronic Product Code Information Services (EPCIS) and IBM's RFID Information Center system that, in turn, provide a suitable infrastructure for the tracking and tracing of uniquely identifiable, i.e. mass-serialized, products throughout the supply chain.	No	-	provide a suitable infrastructure for the tracking and tracing of uniquely identifiable visibility, transparency and control detect counterfeit drug	Conference Paper	Architectural Framework	USA	2011	IEEE	No	RFID
4	PharmaGuard: automatic identification of illegal search-indexed online pharmacies (Corona et al., 2015)	Detection of Illegal Pharmacies, Search Engines, Pattern Classification, Human-Machine Interaction	to develop a novel system for the automatic discovery of illegal online pharmacies assisting law-enforcement toward their early identification, blacklisting and shutdown.	detect illegal online pharmacy	Yes	theoretical validation in terms of accuracy, learning time, and throughput with respect to state-of-the-art tools	effectively detect online illegal pharmacy	Conference Paper	Architectural Framework	Denmark	2015	IEEE	No	Pattern Recognition

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