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A SYSTEMATIC LITERATURE REVIEW: THE POWER OF THE BLOCKCHAIN TECHNOLOGY TO IMPROVE PHARMACEUTICAL SUPPLY CHAIN

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ABSTRACT

Despite the blockchain's considerable potential to solve traditional supply chain problems, research on its deployment in pharmaceutical supply chains (PSC) is sparse. Therefore, the objective of this paper is to provide a conceptual framework for blockchain implementation within the pharmaceutical supply chain. To document the twelve-year research's, 78 transdisciplinary publications published between 2010 and 2022 were examined using a comprehensive literature review and text mining method. Descriptive and thematic research highlights emerging Blockchain trends in pharmaceutical supply chain. Future research will primarily focus on the use of Blockchain for drug counterfeiting and recall issues, as well as other sector-specific challenges like patient health data sharing, compliance, and clinical trials. The arguments and obstacles for technology acceptance, implementation steps and applications highlighted through the thematic analysis will help build the orientation for the research. Compared to other industries, research on blockchain for PSC has lagged, but it has picked up speed since the Covid-19 pandemic. Researchers and professionals will be guided by the identified influencing factors and implementation roadmap for adopting Blockchain in the pharmaceutical business. The suggested framework is original and offers manufacturers, ministry of health, and private sectors helpful guidelines to Leverage the power of blockchain technology.

Keywords: *Blockchain Technology, Pharmaceutical Business, Supply Chain Management, Adoption, Implementation, Systematic Literature Review, Framework, Counterfeiting Drug*

1- INTRODUCTION

In the recent years, pharmaceutical industry provides innovative drugs to many actors, including patients, pharmacies, hospitals, humanitarian organizations and board of health. The ongoing Covid-19 pandemic and current Ukraine/Russia crisis have elevated pharmaceutical supply chains to the top of various governments' priorities due to the drug scarcity. The World Health Organization (WHO) estimates that close to 10% of distributed medicines are subpar, while close to 50% of drugs purchased online are fake [1]. Pharmaceutical companies are increasingly producing drugs with harmful, risky components, endangering the public's health [2] [3] [4], increasing the threats to the general public's health [5]. Food and Drug US Agency is accountable for keeping an eye on the effectiveness, quality, and safety of medicines [6]. The medicine Supply Chain Security Agreement, which was originally signed in 2013, asked players in the drug and medical supply chains to work together and create an electronic and

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interoperable system to track prescription pharmaceuticals through their physical movement by 2023 [7]. Drug breach incidences continue to increase, putting millions of people around the world at danger and costing the healthcare business billions in fraud, despite rigorous restrictions by governments & global institutions. Pharmaceutical supply chain effectiveness is limited due to a lack of collaboration between participants and stakeholders [8]. The increased illness progression, treatment resistance, medication side effect, and death are fundamentally caused by the lack of transparency and visibility of the drug supply within PSC [9] [10]. The worldwide sourcing and e-commerce make it simpler to get and deliver drugs in other nations. However, they present a higher danger to people health because it is impossible to track their origin. Furthermore, the mafia organizations are particularly interested by the leftover & expired stock for the counterfeiting activities. They recondition it and redistribute it through the informal trade [8]. Counterfeiting continues to be a significant concern for the global pharmaceutical supply chain despite the use of strict regulations and cutting-edge technology (like as serialization, 2D barcoding) to protect the integrity of pharmaceutical goods. The global Interpol operation has seized 11 million USD of illicit medicines during COVID-19 and Ukraine/Russia war [11].

Blockchains, most recognized as the technology behind cryptocurrencies, is a shared digital ledger adopted by the peer to peer connection to provide immutable recording and self-executive transactions [12] [13] [14]. Due to its unique intrinsic properties like decentralization, immutability, and auditability, blockchain technology has a high potential for implementation in the pharmaceutical industry with increasing focus and successful implementation attempts in other industries like bank, energy, and automotive industry [15] [16]. Decentralization might be utilized to undermine the healthcare system's hierarchical structure by creating new tools to assist people in managing their data [17] [18]. By maintaining patients' sovereignty and ownership over their personal data, blockchain technology might provide the most accurate information for precision medicine [19], [20] Additionally, the Blockchain's high data transparency can increase trust in medicine distribution, conditions, documentation, and end-to-end visibility, notably for the management of the cold chain. Blockchain's significant potential for pharmaceutical supply chains has been highlighted by several studies [21]–[25]. Nevertheless, A thorough SLR analysis on Blockchain's interface within the pharmaceutical supply chain is still lacking [26]. Most critically, there is no structure for potential Blockchain application in PSC in the literature now in existence[27]. In order to provide a conceptual framework, this study intends to perform a comprehensive evaluation of the deployment of Blockchain in PSC. To examine the improvements in Blockchain application in the PSC, the authors [26] [28] used a systematic literature study paired with a text mining technique. The creation of an implementation framework and the agenda for future research are both influenced by the theme analysis. This study gives scholars and professionals a comprehensive grasp of the relationship between Blockchain and pharma supply chain. The paper is organized as follows: The research approach used to perform a systematic literature review is presented in Section 2. The illustrative analyses & thematic assessment are presented in Sections 3 and 4. Section 5 presents a methodological foundation for using Blockchain in the PSC and identifies potential directions for future study. Section 6 provides a summary, a contribution to theory and practice, and a list of limitations.

2- RESEARCH APPROACH

A thorough, clear, and transparent summary of the research is provided by a systematic literature review (SLR) [29] . In addition, compared to narrative literature reviews, the SLR is more objective [30], [30]. Text mining has been successfully employed for literature review analysis to make the SLR process objective and resilient in its approach [28], [31] . Additionally, by automating a few laborious, iterative tasks like search string identification and data synthesis, the text mining technique assists the SLR process. Figure 1 shows a structured procedure for conducting a systematic literature review assisted by text mining that was adapted by the authors Tranfield [29] and Kalawsky [31]. Identification of data sources, Data extraction & synthesis, and Data analysis & Dissemination may be considered the three steps of the process. Below is a quick summary of the actions involved in each step of SLR.

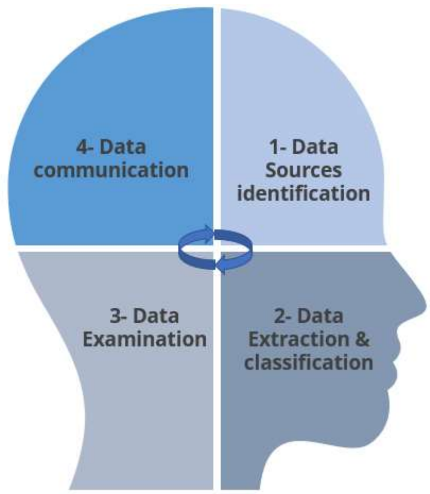

Figure 1: Systematic literature review steps

A. Data sources Identification

A crucial phase of the SLR is information identification, which aims to precisely specify the scope and assess the investigation [32]. We have selected the keywords for seeking pertinent data across several data sources. The testing search outputs for the keywords 'Blockchain technology' and 'Pharmaceutical supply chain' received respectively 92 and 23 hits from EBSCO and Web of Science[26]. Other keywords were found after carefully going through these few papers. The technical terminology or equivalents like "shared ledger," "distributed ledger," and "Smart contracts" were discovered to be often utilized in the Blockchain review papers [5], [14]. Similar to this, there is significant cooperation and association between the pharmaceutical and healthcare sectors [33]. The terms "drug product," "pharmaceutical item," and "medicine" are frequently used interchangeably in the pharmaceutical industry [34]. In order to find peer-reviewed, excellent papers for the SLR, two widely utilized web databases, Scopus and Web of Science, were employed. Both databases have demonstrated to deliver findings that are sufficiently thorough and are frequently used to evaluate data sources [35]. The purpose of choosing two distinct databases was to completely document the cross-disciplinary activity. Table 1 lists the precise selection of search terms utilized for this investigation.

Keywords	Synonyms
Blockchain technology	"Cryptographic ledger" / "Digital ledger" / "Distributed ledger" / "Public transaction ledger"
Pharmaceutical	"Medication" / "Drug"' / "Medicine" / "Healthcare"
Supply chain	"Value chain" / "Process chain" / "Cold chain" / "Logistics" / "Demand plan" / " Supply plan"

Table 1: Search strings used for SLR.

To cover a twelve-year horizon, predefined inclusion criteria included studies published between 2010 and 2022 (From January to October). Although the first Blockchain-related paper was released in 2014 [26], a longer time period was chosen to cover the PSC's overall progress. Books, book chapters, and other grey literature were omitted in favor of only peer-reviewed academic publications. The 'grey literature' is excluded from SLR research in order to concentrate on the high-quality papers [36].
To ensure the study is comprehensive and objective, papers published in journals with a wider readership were taken into consideration. This is due to the interdisciplinary nature of the study, which captures the relationship between Blockchain and the pharmaceutical industry.

B. Data extraction & classification

This stage contributes to select publications that are extremely pertinent. We have eliminated duplicates material from the two databases. Then, each paper was thoroughly analyzed by considering the subject, headline, keywords, abstract and introduction to choose 162 publications that were determined to be pertinent to the SLR. After an iterative procedure, 78 papers were picked for final evaluation after a full-text analysis of the chosen paper. Figure 2 illustrates the workflow used to screen the dataset using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) technique, a methodical way to visualize the research selection process [37]. In this study, the data synthesis activity makes use of text mining. To verify the search terms discovered in the earlier stage and add to the support for the data analysis, text mining was done on a small sample of publications [31]. The platform for text mining was QDA Miner, a qualitative data analysis program created by Provalis Research. By term frequency and inverse document frequency, Table 2 & 3 displays the most crucial terms or phrases found in the chosen database (TF-IDF).

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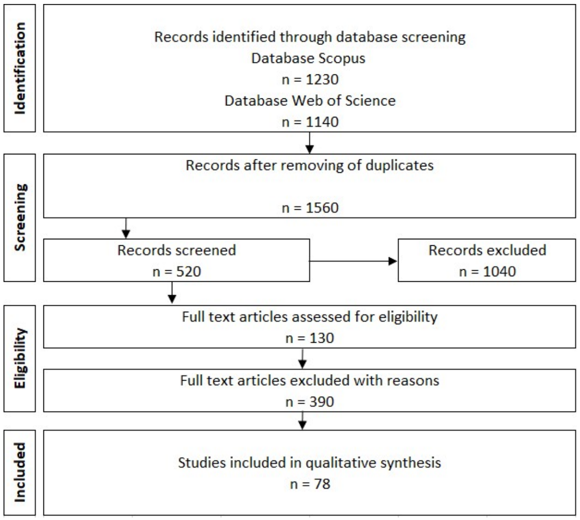

Figure 2: Data screening for systemic literature review and meta-analyses (PRISMA) statement adopted from [38]

Keywords	Frequency	% of cases	TF • IDF
Blockchain	5035	94,52%	123
Healthcare	898	45,57%	292
Drug	805	56,59%	193
Smart	734	85,23%	37,4
Traceability	696	85,54%	57,6
Transaction	604	86,61%	45,8
Medical	543	77,88%	74,8
Health	478	79,97%	49,8
Logistics	424	76,38%	64
Trust	423	87,71%	36,6
Contracts	398	79,85%	39,8
Security	393	91,37%	18,9
Patient	363	64,32%	66,4
Operations	336	73,55%	52,4
Framework	302	85,26%	24
Adoption	299	74,67%	58
Performance	292	74,75%	24,8
Pharmaceutical	283	87,27%	22,4
Organisation	234	37,89%	102
IoT	245	79,78%	31,8

Table 2: Keywords selected by text mining.[28]

Phrases	Frequency	% of cases	TF • IDF
Blockchain Technology	898	85,34%	47,5
Supply Chains	523	73,45%	36
Smart Contracts	341	74,46%	71,2
Blockchain-Based	234	69,67%	67,3
Blockchain network	192	59,89%	65,1
Drug Supply Chains	192	36,85%	45,3
Blockchain Application	165	64,45%	79,9
Traceability Systems	154	26,49%	56,2
Drug SCM	112	21,95%	63,4
Healthcare	99	34,45%	45,1
SC Performance	94	28,52%	13,3
Supply Network	84	27,52%	85,3
Counterfeit Drug	84	45,31%	64,2
Healthcare Records	64	45,31%	56,3
Supply Chain Partners	72	44,41%	67,6
Blockchain Platform	76	46,64%	32,3
Logistic &Transport	75	25,59%	56
Medical Data	76	29,52%	43,3
Pharmaceutical SC	69	53,53%	23
Blockchain integration	68	15,39%	85,83

Table 3: Phrases selected by text mining.[28]

The number of times a certain word or phrase appears in the chosen dataset is revealed by the significance metric TF-IDF [39]. Through text mining and analysis, it is clear that the terms "Blockchain technology", "supply chains," and "smart contracts" are the most often used[40]. Additionally, the majority of the searched terms for data identification substantially correspond with the majority of the detected words and phrases (see Table 2 & 3). The trustworthiness of the method used for data identification and analysis is assured by this retrospective assessment of the preidentified search strings. Furthermore, using the clustering and correlation technique, data sources were (text) mined to discover patterns and create appropriate themes. As indicated in Figure 3, the resulting themes were then employed to create a typology for theoretical study.

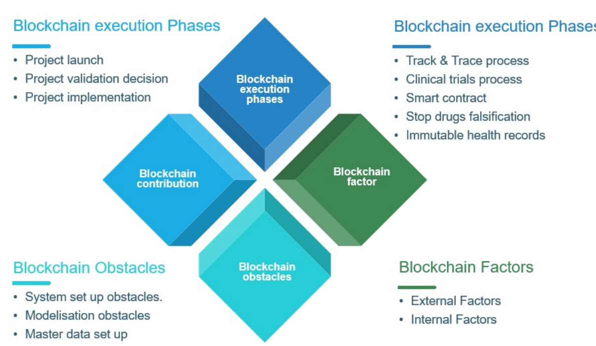

Figure 3: Typology developed for thematic analysis.

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C. Data Examination

Descriptive and thematic analysis make up the data dissemination and analysis step [29]. The earlier analysis seeks to give a succinct summary of the issue under study that captures its breadth and complexity. Thematic analysis, on the other hand, seeks to offer thorough insights based on the generated themes. In the wake of text mining, similar themes were discovered and developed on several 'clusters'. our SLR provides an in-depth review of the challenges, solutions a future direction of blockchain technology adoption in the pharmaceutical supply chain. The taxonomy of this literature review is shared in Fig. 4

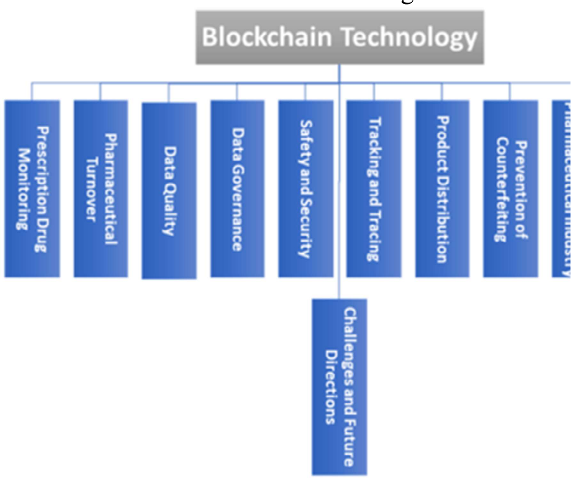

Figure 4: Taxonomy of the systematic literature review.

Figure 3 depicts the "cluster-based" themes that were found and that were the subject of lengthy discussion amongst the authors in order to create a complete typology for the thematic analysis.

- ✓ Implementation phases: This subject aims to summarize changes made during the three stages of blockchain implementation introduction, acquisition, and implementation.
- ✓ Implementation drivers: This subject aims to discover adoption drivers or enablers for blockchain technology in pharmaceutical supply chains.
- ✓ Implementation obstacles: This subject summarizes the implementation issues for blockchain in PSC.
- ✓ Applications phases: This subject encapsulates the deeper uses of blockchain for the pharmaceutical industry. Figures 5 shows the main applications of Blockchain technology.
- ✓

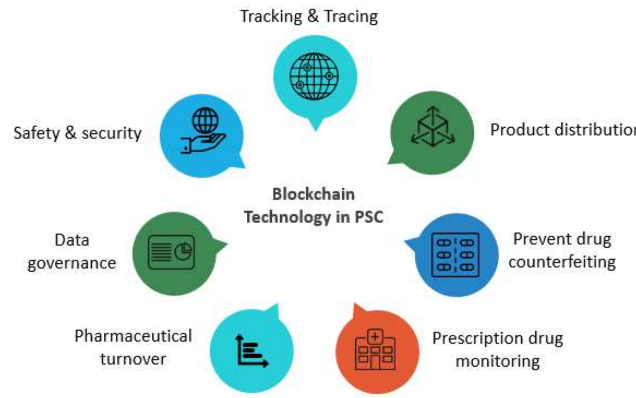

Figure 5 Blockchain applications

D. Data communication

The objective of a systematic literature review is to identify, appraise and synthesize all the empirical evidence that meets pre-specified eligibility criteria to answer a given research question[41]. In this SLR we have identified, evaluated, and synthesized research results related to Blockchain implementation in pharmaceutical supply chain to provide a summary of current evidence that can contribute to evidence-based practice.

3. ANALYTICAL EXAMINATION

An overview of the advancement of Blockchain technology inside PSC is captured by the analytical examination. The previous nine years have seen a substantial increase in Blockchain research within PSC, as evidenced by academic papers published in those years (2014-2022). Although academics have studied blockchain in other industries (including bank, automotive, food, and aeronautics), it is noted that research on blockchain for pharmaceutical supply chain is growing more slowly than study in other industries. Figure 6 depicts the research's exponential rise from 2014.There is undoubtedly an increasing interest in the adoption of Blockchain in PSC, but it is thought that this study is still in its infancy, necessitating greater investigation into the viability of this technology by many supply chain leaders, consultants, top management, and scientific researchers.

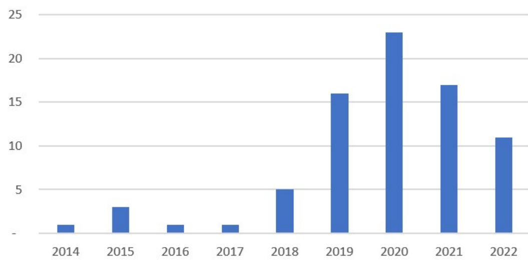

Figure 6: Paper distribution by year of publication.

US and UK were the top two nations for investigating Blockchain in the pharmaceutical industry. Brazil, China, India, the United Arab Emirates, Germany, and other nations also contribute to the expansion of this study area. The growth of Blockchain in the pharmaceutical industry in poorer nations is constrained by subpar healthcare systems and networks, whereas developed countries have better developed use cases or "pilots" for the supply chain for medicines and drugs [42]. This may be the rationale behind why most research is conducted in industrialized nations. Since the epidemic, there has been significant expansion in the pharmaceutical industry in China and India, which may be the cause of the increase in research interest.

Only a tiny number of research have examined the relationship between Blockchain and PSC in a quantitative manner. 41% of papers were focused on literature reviews on the wide subject of Blockchain deployment in various logistics and supply chain disciplines. 16% of papers were dedicated to conceptual and pilot/case study investigations. Conceptual study includes assessing the Blockchain's potential or drawing on current theories of operations and supply chain management to produce fresh ideas. However, Case studies are a successful method for formulating ideas and hypotheses [43]. The adoption of Blockchain for transportation monitoring, data exchange, and integration with supply chain ecosystems has received little attention in conceptual models. To increase efficiency and lower adoption hurdles, these models are frequently integrated with other disruptive technologies from Industry 4.0 [44], such as IoT, Big Data Analytics [45]. For ecosystem security, IoT and Blockchain, for instance, can assist to record supply chain actions. Similar to Big Data Analytics, Blockchain can help with well-informed decision-making. In contrast, proof of concept studies aims to show the functioning of blockchain implementation in SCs and validate the ideas after pilot program[46]. The viability of using blockchain technology, as well as its drivers and hurdles within supply chains, are predominantly studied in business cases and surveys by "early adopters" and blockchain specialists[47]. There is a lack of research aiming to undertake empirical or experimental investigations to establish a connection between Blockchain and PSC. Given the nature of the study, a mixed methodological approach incorporating surveys and modeling may be beneficial. Theories of operations and supply chain management, such as the theory of constraints, system theory, game theory, and transaction costs theory, have all been extensively studied. Additionally, only one-fourth of the chosen research employ a framework or model creation methodology that relies on already-established ideas. This is another proof that the theoretical viewpoints on the blockchain are insufficient and call for additional investigation using either practical experience or new theoretical vision.

4. CONCEPTUAL FRAMEWORK FOR BLOCKCHAIN IMPLEMENTATION

Following a mixed-inductive and mixed-deductive methodology, the analysis offers comprehensive and interpretive study findings [48]. The typology-based evaluation methodology depicted in Figure 3 is followed by the theme assessment. This section examines the stages of blockchain deployment, acceptance factors, roadblocks, and applications within the PSC environment.

A. Blockchain technology implementation phase

Pre-adoption, adoption, and post-adoption stages of the user acceptance and technology acquisition model are how IT innovation adoption works [49], [50]. The effectiveness of the project is impacted by a number of elements throughout the adoption phase, including user approval, organizational and environmental factors. It is noted that the procedure for implementing new technology and related activities inside supply chain and Business models stay constant. According to this general concept and the authors' study [51], the adoption of blockchain in PSC may be roughly divided into three stages: (1) investigation: the company considers various

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aspects of the innovation, (2) Acquisition decision: the company chooses whether and how to implement the innovation, and (3) execution: the company carries out large-scale implementation and incorporates the innovation into its framework.

✓ **Investigation phase**

The knowledge of blockchain and its prospective advantages, including the justification for adoption, are captured in the investigation phase of blockchain [50]. The demand for blockchain adoption is driven by external factors and technological developments. The majority of conceptual studies in the pharmaceutical industry contend that a decentralized, irreversible distributed ledger might encourage a network of pharmaceutical supply chains that is transparent, effective, and free from falsification. Stakeholders won't be ready to take risks to promote implementation of the Blockchain-based solution for the PSC if there aren't uniform technological standards and other pertinent rules. An open government surveillance network by operating with risk benchmark on drug movement in the PSC is recommended [52]. The government and other parties involved in this supply chain may impose inspection of the transaction data in order to safeguard the legitimacy of the pharmaceuticals. The conceptualization of a thriving Blockchain ecosystem for the PSC is supported by the investigation phase, which also contributes to increasing user adoption of this technology.

✓ **Acquisition decision phase**

Organizations must assess their strategic, financial, and technological options before moving from the initiation to the acquisition decision stage [50]. At this stage, resources from different organizations are assessed and allocated to help with technology adoption. Top management support at the acquisition decision stage is crucial in other technology implementation instances like RFID and IoT [48] [49], as this is a strategic level choice that is likely to alter the organizational structure and resource needs. Support from the stakeholders is useful at this level to help organizations create a culture based on blockchain technology and learn relevant information about it. For the stakeholders to fully understand how Blockchain benefits the whole pharmaceutical supply chain financially, a cost model is required [55] [17]. The long-term advantages of blockchain, such as increased supply chain effectiveness, high data security, and the ability to combat medicine counterfeiting, may entice major corporations to participate in the pilot project[56]. In addition, Blockchain platform providers must assist in resolving the technological problems [5] [51]. Blockchain offers interoperable interfaces with many systems and shares medication mobility rather than connecting various healthcare information systems and pharmaceutical firms' ERP systems.

✓ **Execution phase**

To assess the viability of Blockchain in the PSC, it seems logic to launch a pilot project with a small number of supply chain players [58]. The author Van Hoek emphasized that small-scale pilot initiatives can yield significant and worthwhile insights[59]. With the help of 25 top pharmaceutical firms and other members of the pharmaceutical supply chain, the well-known FDA pilot project MediLedger aims to trace medications down to the package level. More stakeholders are interested in this pilot project, which is expected to persuade small enterprises to join the blockchain-based pharmaceutical sector ecosystem. The next step once pilot programs are successful is to scale them up at the supply chain level. However, as previously noted, scaling presents challenges that must be solved, particularly with regard to transaction speed and interoperability across different nodes [60] [61]. If adopted, Blockchain might be widely used and have fewer technological problems and implementation expenses. The expenses associated with using blockchain technology will decrease as the industry becomes more developed[16]. Interestingly, the application of Blockchain is expected to be aided by the pharmaceutical sector, which is anticipated to reach at least $1.6 billion in 2025.

B. Enablers of blockchain implementation

In order to demonstrate the viability of Blockchain-based solutions in the PSC, numerous practitioners, including IBM, have implemented experimental initiatives with pharmaceutical makers, distributors, and hospitals [25], [62], [63]. Driven by both internal and external factors, the PSC can successfully deploy blockchain.

✓ **Internal enablers:**

Three internal enablers were found through thematic assessment during the effective implementation of blockchain in PSC. The improvement of data security, operational efficiency, and transparency were highlighted as the three main drivers for the pharmaceutical supply chain. Figure 7 highlights the features of the Blockchain.

Enhanced trust, transparency, and visibility:
For the purpose of forecasting demand for medications and pharmaceuticals, hospitals, producers, and distributors have disseminated sensitive medical information of individuals. Patients, however, are unable to access the history of the medicine [64]–[66]. As a result, establishing complete transparency and visibility in PSC presents a challenge unlike anything else in the supply chain, but it may also promote cooperation, trust, and efficiency. The immutability, tamper-proofness, and interoperability of Blockchain are motivating factors in solving the aforementioned difficulties [49] [54] [61]. These characteristics make it incredibly appealing to utilize Blockchain to alter personal health records while abiding by data protection laws [2]. PSC members who do this will have access to the transactional data without disclosing it to outside parties. Additionally, it can aid in improved data accuracy, which helps to shorten informational delays. Pharma producers, retailers, and pharmacies recently worked with BlockRx, a pharma ecosystem, to connect their existing information systems, break down information silos, and enable transparency throughout the supply chain [3].

Strengthen data security and integrity end-to-end from drug development to manufacture to distribution:
Electronic medical records may now be stored centrally on the cloud, however this method is subject to cyberattacks and is not recommended for handling distributed data. Each transaction record may be shared over the decentralized distributed ledger by using Blockchain, which groups each record into time-stamped, immutable blocks [68]. Blockchain therefore guards against hacker and cybercriminal attacks on medical and medication data. It's interesting to note that Blockchain for PSC has attracted a lot of interest in medical data management [69]–[71]. Certain pharmaceutical items, including vaccinations, need careful temperature and humidity monitoring while in transit. It is possible to detect any unsuitable environmental conditions for medications during transportation by using IoT devices (such as GPS and temperature sensors) and sending an alarm to the authorized parties on the Blockchain platform [72], [73]. Additionally, patients can control how vaccinations are transported throughout the supply chain [61]. In this process, smart contracts are essential for confirming the legitimacy of items, ensuring compliance with established protocols and standards, terminating contracts, and issuing reimbursements. To manage and trace pharmaceutical product features, including location, chemicals, temperature settings, and product photographs while dealing with international trade, various Blockchain businesses advise Blockchain-based initiatives like "SmartHub"[74]. In a different use case called "LedgerDomain," patients may trace and track their medications using BRUINchain and bar-coding [75], [76]. Other use case “Pharmaledger”, a blockchain-based platform with reference use cases in supply chain, clinical trials and health data. A governance function for sustainability and legal, regulatory and data privacy compliance[77]. The objective is to empower patients, increase digital trust, enable medicine drug traceability and data privacy, and foster a new culture of collaboration in healthcare [58]. In other words, the deployment of Blockchain technology in the PSC is driven by the necessity for drug traceability and security.

Increased efficiency & Enhanced performance in processes:
Using blockchain increases supply chain effectiveness [78], [79]. Blockchain is anticipated to have a favorable influence on emergency response times, payment processing, and pharmaceutical industry predictions [54], [80], [81]. Previous research found that the PSC's notification and medication recall procedures took a lengthy time because of the manual paperwork and disjointed, complicated systems, which resulted in slow reaction times and unsatisfactory healthcare services. Blockchain helps shorten processing times and gives supply chain stakeholders early notice of medication recalls due to the enhanced trust and information transparency among supply chain participants. In addition, smart contracts, where the validation process is conducted within the Blockchain network, can remove additional intermediaries and lower labor expenses. When all predetermined requirements, rights, and duties are met by each party, the self-executed agreement will become enforceable. Blockchain also expands information exchange, which helps the

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pharmaceutical supply chain discover bottlenecks, prevent overstocking, and ultimately achieve improved efficiency[82].

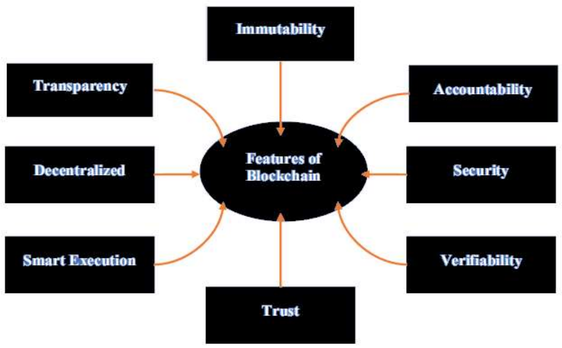

Figure 7. Features of blockchain.

✓ **External enablers**

The external commercial environment such as the macroeconomics and globalization challenges, compliances issues and competitive marketplace push many companies to adopt the new technology breakthrough [83]. Additionally, external settings including suppliers, pharmaceutical regulatory agencies, governments, and patients stimulate external enablers.

Reinforcement by health regulatory authority: Government agencies like the Food and Drug Administration and other non-profit organizations like WHO closely monitor the pharmaceutical sector. Organizations must abide by the rules and act against fake goods. Developed nations are acting more practically than underdeveloped nations in locating fake pharmaceuticals[84]. The blockchain pilot projects, such MediLedger and PharmaLedger, are made to work with hospitals, pharmacies, pharmaceutical distributors, and manufacturers throughout the world to conduct transactions on the distributed ledger. In a same vein, the European Federation of Pharmaceutical Industries and Associations (EFPIA) is working to eradicate unqualified pharmaceuticals and is focusing on finding counterfeit items in the PSC. Blockchain initiatives are also supported by developing nations like India and Brazil to raise the quality of their healthcare services [85].

Patients empowered to take ownership of their data:

Patients are becoming more and more interested in the origins and components of the medications they take in order to check for adverse effects or to adhere to sustainability and quality standards [86]. Additionally, customers were banned from accessing neighborhood pharmacies during the COVID-19 epidemic[87], which fueled a rising tendency for internet medicine shopping. In order to decrease the likelihood of obtaining fake medications, governments sought stringent oversight of internet pharmacies, specifically their legitimacy and authenticity. Recently, My Net Doctor, a licensed online pharmacy, joined MediConnect's Blockchain platform in the UK. The PSC traceability of internet pharmaceuticals, especially prescription drugs, is improved by this partnership. In order to stop prescription drug abuse and overprescribing, sensitive client prescription data and provenance data for medications will be stored on MediConnect's private, permissioned distributed ledger.

C. Obstacles to blockchain application

Three problems are highlighted by prior studies: the system-related adoption obstacle, the conceptualization and regulatory obstacle, and the data security constrain[88].

✓ **System acquisition**

The most frequent problems encountered during installation of technology are technical and operational ones [89], [90]. Scalability, smart contract design, and high adoption costs of Blockchain are regarded as the biggest hurdles to adoption in the multidisciplinary research.

Scalability: To demonstrate the plausibility and viability of new technology adoption, hundreds of market tests are conducted. The use of blockchain in the pharmaceutical sector is still in its infancy, with few successful pilot projects. According to earlier research, expanding the Blockchain to a supply chain network level will require it to handle massive data volumes and thousands of transactions per second [42]. Based on Taiwan's healthcare insurance structure, healthcare and pharmaceutical sector transactions might result in the purchase of 10 billion medications [52]. Time lag for confirming part of the transaction data would be noticeable because the existing Gcoin Blockchain system, a Blockchain-based solution for drug governance, can only execute a million transactions per day. Additionally, the complexity and size of medical supplies as well as the distributed ledger's decentralization make it necessary for numerous nodes to conduct each

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transaction. Scalability is a general problem for larger Blockchain usage, which also applies to PSC.

Smart contract design: Additionally, if there were several permitted parties, self-executive smart contract creation and verification between parties would also be subject to error. For instance, the balance of tensions and advantages among many parties makes the process of converting PSC operations and rules to smart contracts challenging. A failing or incorrect transaction might result from the ambiguous language that was created by the interpretation. Additionally, the earliest smart contracts are limited to simple operations like money transfers, and the verification clauses do not take into account laws and regulations [91]. Smart contracts may be less effective at spotting fake goods as transaction volumes and contractual commitments rise. IBM has created a "crypto-anchor" platform to assure obtaining the proper items through user authentication/certification in order to combat this [92].

Operational cost: The high system adoption (mining) cost as well as associated expenses like system upkeep and specialized consultancy fees are likely to impede the adoption of blockchain technology [93]. Pharmacists are now having difficulty determining if Blockchain's advantages in terms of increased efficiency and cost savings [55] could justify the pharmaceutical company's expensive technological installation expenses. Additionally, the "immature" state of the present Blockchain technology industry may result in expensive system adoption costs and technical difficulties throughout the adoption. Large businesses are anticipated to be "early adopters" of this technology, while medium-sized and small businesses would be hesitant to make the switch owing to the potential financial concerns. In order to get the greatest outcomes, several academics advise combining blockchain technology with other technologies like the cloud, IoT, and RFID [94]. As a result, integrating several systems would be expensive. The use of blockchain at the supply chain level would also require expensive consultants and technical training for staff members[95].

✓ **Blockchain architecture and compliance:**

The success of the implementation is significantly influenced by the top management's support [93]. According to the literature review, the success determinants for blockchain implementation in the pharmaceutical business include leadership commitment and involvement[96]. However, owing to a complicated supply network, pharmaceutical SC players have diverse interests in Blockchain technologies. Therefore, it is difficult for senior management to explain an agreement for a significant expenditure based on judgments based on a few successful pilot projects. However, another major obstacle is the absence of a clear industry governance structure connected to the Blockchain network and standards for information sharing. Although certain government agencies control the sale of fake medications, there are still insufficient rules and regulations pertaining to blockchain, which increases the risks and pressure on managers to implement blockchain in the pharmaceutical and healthcare industries. Clearly, the managerial support and industrial architecture are barriers to PSC's use of blockchain technology.

✓ **Data integrity:**

Cyber hazards will soon pose a greater danger to digital supply chains [45]. A pertinent difficulty for the pharmaceutical sector is data management-related cyber security risks[97]. The cryptography system that will shield a patient's medical data and information about drug transactions from online threats is still in the testing stage. Patients are reluctant to offer useful information for the Blockchain-based solution because they are worried about their privacy being compromised[73]. The patient's trust in data security is eroded by previous occurrences, such as privacy leakage situations like the American Medical Collection Agency data breach in 2018. Furthermore, the absence of private keys stops the verification process, delaying the creation of millions of transaction records, which might harm the entire Blockchain operation [98]. Most crucially, the immutability of Blockchain technology may provide a challenge to the accuracy of data [52]. Though inaccurate data on Blockchain may be fixed in the sense that a subsequent transaction fixes the original. The search in a Blockchain system is now more difficult and time-consuming as a result, though. When serious situations arise, like medicine recalls, such erroneous input data in the Blockchain might be problematic. In addition, misinterpretations of the coding languages may occur throughout the Blockchain's process of confirming and translating codes to text [85].

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D. Blockchain acquisition

Based on the chosen research, the applications of blockchain may be roughly divided into five categories: (1) track & trace process, (2) serialization against drug counterfeiting, (3) improving clinical trials, (4) immutable data and (5) smart contracts. Table 4 displays the pilot projects and use cases identified after the evaluation; use cases like Medichain and BlockRx Pharma track the status of drugs from their initial ingredients to their final users. The probability of counterfeit medications in the pharmaceutical business is decreased by the distributed ledger's real-time tracking of transaction data.

As an illustration, the pharmaceutical corporation Pfizer has utilized the Blockchain pilot project to confirm the legitimacy of their medications. Additionally, blockchain solutions like MeDshare, which Wang et al. (2018) suggested, safeguard patients from cyberattacks and guarantee data security. Additionally, the Blockchain's smart contracts ensure financial transactions while cutting the costs of middlemen.

Technology application	Initiative title	Initiative introduction
Finished Goods Traceability	Pharmaledger (PharmaLedger, 2020)	Leveraging the power of blockchain technology to reduce friction of health data sharing, clinical trials and drug supply chain. This project will serve to demonstrate simple quantity traceability at a batch level
	SmartHub (Ledger Insights 2020)	The pharmaceutical drugs can be traced by 'SmartHub'
	BlockRx (Farouk et al. 2020)	This system ensures information sources. It reinforces current systems and processes and creates an interoperable ecosystem
	MediLedger (MediLedger, 2020)	This initiative highlights important steps to build an interoperable electronic system for all stakholders and follow up sales units at SKU level
	Medi-chain (Schmidt and Wagner 2019)	This project support on medicine movement track & trace process
	IBM Hyperledger (Prada-Delgado et al. 2021)	Hyperledger employs crypto anchor to safeguard SKU ID by linking it with a property that is hard to clone, forge and hard to transfer to another object
Anti-Counterfeiting	Pharmaledger (PharmaLedger, 2020)	Empower patients, increase digital trust among healthcare stakeholders, support medicine drug traceability and data privacy, and build a new culture of collaboration in healthcare. Pharmaledger will design, validate and provide agile delivery of innovative blockchain enabled healthcare applications across the industry, from manufacturers to patients; while creating an innovative governance approach for sustainability
	Innovative drug project (IMI, 2018)	This initiative investigates use cases in falisification medicine detection, supply chain, patient data, and clinical trials
	IBM, KPMG, Merck,Walmart (IBM, 2019)	This project aims to test medicine recalls and enable rapid alerts amongst supply chain actors
	BlockVerify (Radanović and Likić 2018)	This initiative emplyes sensors and identification tags to detect counterfeiting drugs
Enhancing Clinical Trials	Pharmaledger (PharmaLedger, 2020)	This initiative supports with the clinical supply of investigational drugs and traceability of finished products
	Clinical Supply Blockchain (Choudhury et al. 2019)	The objective of this project is to support a digital inventory and event tracking record in the pharma clinical supply chain
Smart Contract	Anti-counterfeit medicine system (Pham, Tran, and Nakashima,2019)	The main contribution of this project is to support on eliminating drug cloning and enancing the applicability of Blockchain-based solutions
	Smart Contract empowred by blockchain (Khatoon 2020)	This initiative generate cost saving & cist avoidance. It facilitates medicine workflow processing
Data management	Healthcare Data Gateway (Khezr et al. 2019)	This solution supports check and share patients' data without impacting their confidentiality and privacy
	Medlock framework (Khezr et al. 2019)	This project helps to avoid segmented databases stored medical records for patients
	MeDShare (Wang et al. 2018)	It gives data source, auditing, and control for shared medical data in cloud lake among healthcare providers
	Blockchain tokens (Queiroz, Telles,2020)	It's a testing Blockchain tokens for a container for enhanced efficiency

Table 4. Potential Blockchain initiatives

5. BLOCKCHAIN TECHNOLOGY FRAMEWORK

The chosen historical studies show that the PSC is still in the early stages of adopting blockchain technology. Large-scale viable Blockchain-based systems for the PSC are difficult to develop because of the lack of empirical knowledge. In addition, practitioners struggle to outline the processes for applying Blockchain technology in the pharmaceutical industry because there is no study establishing a framework for implementation in this particular industry within the context of supply chain management. In light of the theme analysis's conclusions, an attempt is made to develop a conceptual framework for the use of blockchain in the PSC. The suggested structure is probably going to help PSC adopt blockchain successfully. Although hypothetical, it may be evaluated on new initiatives in PSC that are trying to adopt blockchain or retrospectively verified on Blockchain pilot projects inside PSC. In the end, specific research gaps are found, opening the door for new directions in the chosen field of study.

A. Framework evolution

The conceptual architecture that has been built combines many levels to encompass the Blockchain implementation within pharmaceutical supply chain in its entirety. The proposed framework includes four layers, as seen in Figure 7. The implementation process level, the integration process level, the application level, and the ecosystem level. To successfully apply blockchain in PSC and reap the benefits seen in the application level, it is imperative to comprehend the first level and coordinate the second level. A collection of influencing elements (enablers and obstacles) is gathered and displayed in the implementation process level, which is one of the three defined stages of blockchain implementation.

Blockchain development is anticipated to boost technology user adoption and in turn encourage a number of PSC applications. The user integration model, sometimes known as a "sequential type," is dependent on how widely accepted Blockchain

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technology is. Businesses first see the need for Blockchain technology to be introduced in order to address supply chain concerns unique to particular industries. The next step is to identify the resources needed (such as human labor and technical assistance), after the acquisition of knowledge and the determination of whether implementing Blockchain is appropriate for the organization.

Small-scale pilot initiatives with limited actors are suggested during the pre-final stage. Scaling up those successful experiments in a larger setting with more stakeholders, nodes, and transactions being processed is the last stage of Blockchain deployment. As seen in Figure 7, the implementation process level identifies a number of influencing elements for the introduction, adoption, and implementation phases. Obstacles and enablers are categorized according to how well they fit the highlighted stages. The application layer captures many Blockchain applications that benefit the whole pharmaceutical supply chain network. The most frequent uses are locating pharmaceuticals across the PSC and preventing the sale of fake medications. Additionally, smart contracting rules between various players provide secure payment and hasten supply chain operations, increasing supply chain effectiveness. First instances of secure electronic health records, the distribution of unneeded medications, counterfeit prevention, and trustworthy clinical trials have all been witnessed in early adoption activity. In the ecosystem that will be created later, Blockchain technology will link with seven of the most important pharmaceutical supply chain actors and play a critical role in balancing the opportunities & challenges of various supply chain nodes. Because the source of information is visible to vendors and makers, the quality of the medicine's raw materials is ensured[20]. Unqualified raw materials will not be allowed to trade in the PSC with the verification of ingredients, and the pre-set regulations in smart contracts can also cause payment termination to be ambiguous.

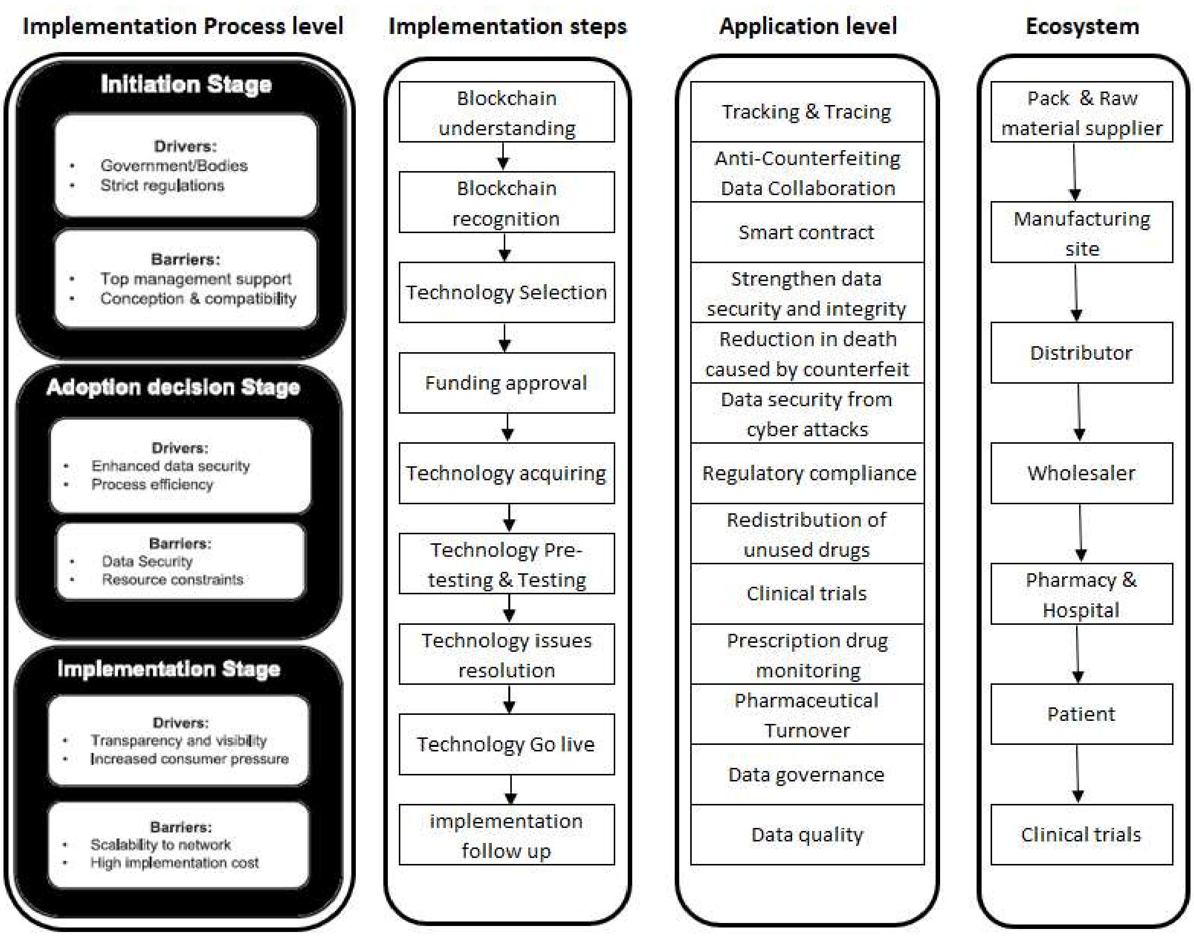

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Figure 7. Framework model for Blockchain deployment in pharmaceutical supply chain.

Additionally, distributors can monitor and trace these pharmaceuticals across the whole PSC with the aid of the identifying codes and serial numbers that are printed on drug packages[10]. Blockchain can help the downstream pharmaceutical supply chain ecosystem (customers/patients, medical institutions, and clinical trials) secure sensitive personal health and medication data. This leveled approach that is being suggested explores the connection between Blockchain and pharmaceutical supply chain to capture different features. Additionally, it allows PSC members to determine whether Blockchain is a good option for their company based on the recognition of influencing elements at every step of deployment and broader PSC uses.

B. Challenges and future research directions

Improving Green supply chain in pharmaceutical supply chain

Deployment of blockchain in the pharmaceutical supply chain is closely related to sustainability in terms of the social and environmental spheres [74], [99]. Through the use of blockchain technology[100], patient privacy and medical data may be protected without sacrificing data accessibility for demand planning and other supply chain operations. As a concrete case, the logistic provider "Ship Chain" created a blockchain to make the transport and logistics more effective, secure and transparent. It uses smart contracts to achieve 100% digital transactions, minimizing the quantity of unnecessary paper[101]. With the usage of blockchain in the pharmaceutical business, future researchers can investigate more environmentally friendly and circular economy techniques[102], such as patient-centered medicine supply and environmentally friendly drug reuse and disposal and explore how to support reverse logistic [80].

- ✓ **Improving medicine reverse logistic**

The blockchain can be used to guarantee drug authenticity, bring transparency and visibility across drug supply chain networks, and provide proactive, efficient drug recall management systems, which are still in demand among supply chain practitioners [4] [103]. Another fascinating area for exploration is the potential application of Blockchain technology in reverse pharmaceutical logistics for recalled or expired medications[104].

- ✓ **Improving Blockchain Governance and compliance requirements**

Due to a lack of effective strategies and clear laws for this digital space, the PSC's Blockchain ecosystem is still in its infancy [71]. The assessment discussed implementation drivers and challenges and clearly recognized and underlined this problem. Pharmaceutical supply chain professionals are concerned about the lack of laws, such as privacy standards protecting sensitive data, which may prevent widespread implementation of blockchain technology. Standardizing Blockchain techniques and Lack of clearly defined PSC laws necessitates more in-depth study.

- ✓ **Reinforce the performance and transaction process**

The Blockchain scalability will be a technical obstacle when thousands of pharmaceutical operations need to be achieved simultaneously [70]. To fulfill high throughput needs, professionals may want to create a more safe and reliable method and practices for smart contract rules.

- ✓ **Enhancing Blockchain compatibility**

Interoperability across blockchains may open up opportunities for cooperation between various blockchain platforms. There are worries that Blockchain interoperability may be difficult in the pharmaceutical sector. Additionally, PSC can improve supply chain traceability by combining Blockchain with other support technologies like IoT and RFID [25], [105], [106]. However, this opportunity has not yet been fully explored. The Blockchain-based IoT system ensures medicine traceability throughout its life cycle. ERP-integrated Blockchain solutions should be built to manage data more effectively. In the future, professionals might look at further options for improving Blockchain compatibility and interoperability with other disruptive technologies.

- ✓ **Implement KPI's dashboard of Blockchain**

Companies may use the performance optimization system of Blockchain to assess their successes and failures and determine whether Blockchain is actually required in this sector [107]. Building a performance monitoring system to gauge the effectiveness of the established Blockchain system is necessary as the number of Blockchain pilot projects in the PSC rises[108]. The performance measurement might make it easier for companies to adhere to benchmarking criteria so they can assess their performance at each step of implementation, ultimately enhancing the supply chain operations as a whole [109]. Research that tries to develop the connection between Blockchain and PSC empirically or experimentally is also shown to be required.

6. CONCLUSION AND FUTURE WORK

With the help of a thorough literature research, this study set out to examine blockchain application in the PSC from all angles and construct a conceptual framework. First, a review of scholarly research conducted by the PSC gave an overview of Blockchain and its potential as a disruptive technology. Insights into the general trend from a geographic and publication viewpoint, as well as modified conceptualization theories, were supplied by the descriptive analysis. Thematic analysis looked at PSC applications, stages of implementation, and important elements (enablers and obstacles). Eventually, the topic analysis-generated insights revealed a conceptual framework and research needs.

In conclusion, it is shown that, in comparison to other industries, blockchain research for pharmaceutical supply chains is growing slowly. The PSC is just beginning to explore blockchain technology, but this trend is expected to increase dramatically in the next years. Blockchain use in the pharmaceutical supply chain is driven by the need for increased transparency, efficiency, traceability, and data security. Additionally, supply chain managers are compelled to use this technology by outside pressure from stakeholders like customers, rivals, and regulators. The most potential Blockchain applications, according to the PSC's current blockchain pilot projects and use cases, are those that address medication falsification, drug recalls, data security, adherence to pharmaceutical standards, and clinical trial dependability. The industry-wide adoption of Blockchain may be hampered by the highlighted hurdles relating to PSC system and technology integration.

This review makes a number of theoretical and practical contributions. First, the SLR gives a general outline of the difficulties PSC has and illustrates how Blockchain might help. We have consolidated and highlighted the best of the authors' knowledge, that tries to examine the possibilities of blockchain in pharmaceutical supply chains. The systematic study offers supply chain leaders and researchers insights on the adoption drivers and hurdles, the latest Blockchain applications, and the various stages of deployment. The conceptual framework based on the stages of adoption for blockchain technology offers guidelines for successfully integrating blockchain into PSC. According to [3], the implementation of Blockchain legislation may make it easier for more small and medium-sized businesses to join the ecosystem. The numerous study possibilities that have been identified offer an excellent place to start when examining the relationship between Blockchain and PSC. Findings can help the government and other policymakers create new norms and regulations for Blockchain-enabled PSCs.

The research does have certain limitations. For the study, only 78 transdisciplinary articles were chosen. The choice of keywords and the screening procedure can be arbitrary and biased, although text mining has been used to help confirm the selection of keywords in an effort to get over this constraint. Additionally, because the research primarily focuses on the pharmaceutical industry, studies that do not have a clear connection to the healthcare industry may be overlooked. Future attention should be paid to the technical elements of Blockchain, such as compatibility, interoperability, and big data sharing before and after deployment, as well as the legal and regulatory problems of PSC, which are not fully considered. Future research will check the suggested conceptual framework's viability in a real-world situation after the empirical investigation.

We may conclude that there is still opportunity for advancement in the application of blockchain technology in the healthcare industry. The findings of this study, which combine theoretical and practical views, may be utilized to suggest future research questions and concerns for adoption. These prospective study areas on blockchain use in the health sector are listed below:

- In order to address the rules for network participant collaboration, data privacy, what data to share, data deletion on patient demand, and ensuring interoperability between various ledgers in blockchain networks, policymakers, blockchain researchers, and developers must collaborate to develop regulatory guidelines.
- When creating blockchains and smart contracts, it is important to consider various data privacy, security, and sharing regulations in light of the international patient mobility.

- Blockchain technology has the potential to produce enormous volumes of private, sensitive health data in the healthcare industry. For the purpose of processing the data gathered in blockchain in a meaningful way, blockchain technology and artificial intelligence may be combined.
- Due to the exponential growth of data in large-scale blockchain usage, data retrieval has performance difficulties. Data retrieval procedures that are suited for such blockchain applications must be created.
- It may be investigated to integrate blockchain technology with current healthcare systems (such electronic health record management systems).
- Data privacy is violated by the transparency of data in the blockchain. Sensitive patient data is transparently stored in the healthcare industry. It is necessary to create additional privacy safeguards, such as keyed hashes.
- Due to the structural properties of blockchain, including contract immutability, the requirement for testing in production settings, and test execution fees, current development life cycle models are not entirely compatible with the development process of blockchain-based apps. As a result, it is essential to create a new model for the blockchain development life cycle that considers its structural attributes and provides guidance for an effective and sustainable blockchain development environment.

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