Heliyon 10 (2024) e29058

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Exploring progress in iron supplement formulation approaches for treating iron deficiency anemia through bibliometric and thematic analysis

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ARTICLE INFO

Keywords:
Iron deficiency anemia
Bibliometric analysis
Thematic analysis
Scopus database

ABSTRACT

Anemia is a severe health issue that affects around one-third of the global population. Therefore, the present study aims to conduct a bibliometric analysis to investigate the research trends regarding advancements on iron formulations in treating iron deficiency anemia via oral or parenteral route. This study adopts thematic and bibliometric methods on existing research on novel iron formulations. It also provides perspective into the existing understanding on treatment strategies for iron deficiency anemia. This study is conducted on 543 papers on various ferrous and ferric formulations used in the treatment of iron deficiency anemia. The study period is from 1977 to 2022, and the papers are identified from the Scopus database. The bibliometric analysis was carried out using the R tool's Bibliometrix package. The study discusses performance analysis, including annual publications, geographic analysis, relevant affiliations, journal analysis, and citation analysis. In addition, the conceptual structure, including the co-occurrence network, thematic map, thematic evolution, intellectual structure highlighting co-citation analysis, and social structure depicting the collaboration network and collaboration world map, are presented. The results showed increased research on formulation strategies for the treatment of iron deficiency anemia from 2010 onwards. The top 5 contributing countries are the USA, Italy, India, Germany, and the UK, and peer-reviewed journals from the area of nutrition. The most trending areas of study are iron deficiency anemia in pregnancy, chronic kidney diseases, inflammatory bowel diseases, and various intravenous formulations used in its treatment. The authors from Europe collaborate the most with authors from other countries. The study concludes that a safer and more effective iron formulation is needed to reduce the prevalence of anemia. The findings of the study are helpful in advancing research on innovative formulations for treating iron deficiency anemia. The insights from the study are helpful to policymakers in designing specific

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https://doi.org/10.1016/j.heliyon.2024.e29058
Received 24 October 2023; Received in revised form 4 March 2024; Accepted 28 March 2024
Available online 4 April 2024

health policies and investing more in research and development of novel formulations for the treatment of iron deficiency anemia.

1. Introduction

Anemia is a severe health concern. According to the Global Burden of [88], anemia affects 24.3% (1.92 billion) of the world [1]. Iron deficiency is the most common cause of anemia [2]. It contributes to around half of the population suffering from anemia [3]. World Health Organization (WHO) defined anemia as a hemoglobin level of ≤13 g/dL in men and ≤12 g/dL in women (≤11 g/dL in pregnancy) [4]. Preschool children and pregnant and non-pregnant women have the highest prevalence of iron deficiency anemia [5]. Likewise, patients with chronic kidney disease (CKD), inflammatory bowel disease (IBD), cancer, and one undergoing bariatric surgery are at high risk of developing iron-deficiency anemia [6–9].

Iron homeostasis is controlled by absorption rather than excretion [10]. The daily iron requirement is approximately 1–2 mg as the body efficiently recycles a significant portion of its iron. The human body recycles 90% of iron by splenic macrophages from the degradation of red blood cells and the rest, 10%, is absorbed from the diet in the duodenum [89]. Hepcidin is a peptide hormone released by hepatocytes. It plays an important role in regulating iron absorption from enterocytes, as it increases iron absorption in conditions of iron deficiency and decreases it when iron levels are sufficient [11]. Hepcidin levels are induced with an increase in hepatic iron storage and increased activity of inhibitory transmembrane protease serine 6 (TMSS 6) and also the reduced level of activator bone morphogenetic protein 6 (BMP 6) [4].

Decreased intake (poverty or malnutrition), increased demand (infants, preschool children, growing age, pregnancy, and mensuration), decreased absorption (IBD, CKD, bariatric surgery, inflammation), and blood loss are among few of the causes of IDA [3,4,12,90]. Inflammation due to chronic diseases such as cancer, cardiovascular diseases, and infectious diseases such as tuberculosis. HIV/AIDS can also be a cause of anemia for which treatment of the underlying cause is required [13,91]. However, this paper focuses on iron deficiency anemia as it is most prevalent. Iron prophylaxis in the area with high malaria, or high ground water iron content is not advisable [14]. Iron is essential for the growth of infectious pathogens also, so, iron withdrawal reduces the growth of pathogens in acute infections [15]. Two treatment options for iron deficiency anemia are oral supplementation and parenteral therapy [16]. The first line of treatment is oral supplementation. In case of severe anemia, intolerance to oral supplementation, rapid iron replenishment, gastrointestinal bleeding, and hereditary decreased iron absorption, patients are shifted to parenteral therapy [4].

Two oral iron supplement forms were traditionally available: ferrous and ferric. Ferrous formulations include ferrous sulfate, ferrous gluconate, ferrous fumarate, and ferrous glycine sulfate [17]. Ferrous formulations have more side effects if not in prolonged-release form. Ferric formulations include iron protein succinylated and iron polymaltose [18]. Novel oral iron formulations include ferric citrate and sucrosomial iron [10]. Ferric citrate consists of ferric citrate coordinate complexes. It is an FDA-approved agent to treat iron deficiency anemia and hyperphosphatemia in patients with Chronic Kidney Disease (CKD) [19]. Sucrosomial iron consists of ferric pyrophosphate coated by a phospholipid bilayer and sucrester matrix, which gives sucrosomial iron high bioavailability and gastrointestinal tolerance [20,21]. Ferric maltol is a non-salt-based iron formulation consisting of a complex of one ferric ion with three maltol (3-hydroxy-2-methyl-4-pyrone) moieties. Ferric maltol is approved for use in the European Union in adults. It is an effective alternative for Inflammatory Bowel Disease (IBD) patients who do not tolerate oral iron salts [22]. Recent studies showed that a low dose of iron and alternative doing is more beneficial.

Parenteral therapy includes intramuscular (IM) injections, intravenous (IV) injections, and infusions. Intravenous iron formulations are colloidal solutions consisting of iron oxide or hydroxide core, and carbohydrate shell, spheroid nano-size particles [23]. Earlier parenteral iron formulations consisted of iron saccharide for IV use and high-molecule weight iron dextran (HMW- ID) for IV and IM. Because of the high molecular weight of dextran in HMW-ID, it was found to cause anaphylaxis in some cases. So, use was discontinued in 1990 [24]. It led to the discovery of two new iron products for use as an IV bolus injection or infusion, including low-molecular-weight iron dextran (LMW-ID) INFeD® and Desferrun® (HMW-ID) in 1992 and 1996, respectively [25]. The second-generation parenteral iron formulation includes iron sucrose and ferric gluconate having a non-dextran carbohydrate shell, so there is a low rate of severe adverse events (SAEs) [26]. However, the limitation is maximum daily dose is restricted to 250 mg for ferric gluconate and 300 mg for iron sucrose, due to concerns of the release of free iron. Novel parenteral iron formulations used in infusion are ferumoxytol, ferric carboxymaltose, and Iron isomaltoside 1000. All these formulations are safer than older ones and can be given rapidly and in large doses [25,26].

Different public health interventions such as daily versus weekly iron supplementation [27], food fortification [28], and directly observed treatment [29] are tried over time. However, the prevalence of IDA is still high. So, to resolve the problem, IDA needs the researcher's attention. This study provides a bibliometric and thematic analysis of iron deficiency anemia in existing studies. We hope to stimulate discussions on iron deficiency anemia research and provide insights from the current understanding of IDA.

The objectives of this article include the following:

- To identify leading scholars and analyze their work on iron deficiency anemia.
- To analyze the volume of research, count on citations, the geography of existing studies, international collaboration among researchers, and author analysis of research on iron deficiency anemia.
- To provide evidence on co-citations, co-occurrences, bibliometric coupling, thematic analysis, and word analysis of existing research on iron deficiency anemia.

- To provide evidence on future research directions on iron deficiency anemia.

2. Materials and methods

The present study applies bibliometric analysis as bibliometric analysis helps identify and investigate existing literature's intellectual structure [12,30]. Aparicio et al. [31] stated that bibliometric analysis helps to examine existing literature on a scientific topic. The bibliometric analysis examines keyword, author, and journal statistics [32,33]. The present study highlights the different approaches to treating IDA associated with different disease conditions. This study attempts to analyze the change in the research trends on the current topic based on disease conditions and requirements over the years. R tool's Bibliometrix [34] is used to analyze the existing literature on IDA [35]. Bibliometrics helps examine co-citations, scientific collaborations, and coupling analysis [36]. The findings of existing literature on iron deficiency anemia are documented in the present study. With the query "TITLE-ABS-KEY ("Iron deficiency anemia" AND "iron supplementation" AND (oral OR parenteral)) AND (LIMIT-TO (SUBJAREA, "MEDI") OR LIMIT-TO (SUBJAREA, "NURS") OR LIMIT-TO (SUBJAREA, "BIOC") OR LIMIT-TO (SUBJAREA, "AGRI") OR LIMIT-TO (SUBJAREA, "PHAR") OR LIMIT-TO (SUBJAREA, "CHEM") OR LIMIT-TO (SUBJAREA, "HEAL")) AND (LIMIT-TO (LANGUAGE, "English"))" 543 articles from Scopus were retrieved at the end of 2022. The Scopus database has a broader and multidisciplinary coverage (Secinaro et al., 2021); [37]. Scopus also has a low likelihood of article omissions compared to other databases [38]. Table 1 provides the primary information on the analyzed article. The 269 articles are scanned from 543 articles to ensure that only articles of interest are selected for bibliometric analysis. Fig. 1 reports the researchers' steps and details in selecting the 269 articles.

3. Results and discussions

3.1. Performance analysis

3.1.1. Annual publications

From Fig. 2, it is clear that annual publications have increased exponentially from 2010 onwards. A marked difference in the number of scientific productions is visible before and after 2010. Sharp peaks can be seen in 2013, 2018, and 2020. The number of articles published in 2009 was nearly three, and it jumped close to nineteen in 2013 and more than thirty in 2020. Fig. 2 shows an increase in interest in Iron Deficiency anemia and its treatment approaches over the last decade. The probable reason behind this trend may be that the World Health Assembly implemented a comprehensive plan on infant, young child, and maternal nutrition, with six global nutrition targets to achieve by 2025. The second policy under this plan is to reduce anemia by 50% in women of reproductive age.

Table 1
Description of data.

Description	Results
Timespan	1977:2022
Sources (Journals, Books, etc.)	191
Documents	269
Average years from publication	9.12
Average citations per document	31.03
Average citations per year per doc	3.123
References	10,948
DOCUMENT TYPES	
Article	180
book chapter	3
conference paper	5
Editorial	1
Letter	2
Note	1
Review	74
short survey	2
DOCUMENT CONTENTS	
Keywords Plus (ID)	2055
Author's Keywords (DE)	435
AUTHORS	
Authors	1261
Author Appearances	1385
Authors of single-authored documents	22
Authors of multi-authored documents	1239
AUTHORS COLLABORATION	
Single-authored documents	25
Documents per Author	0.213
Authors per Document	4.69
Co-Authors per Documents	5.15
Collaboration Index	5.08

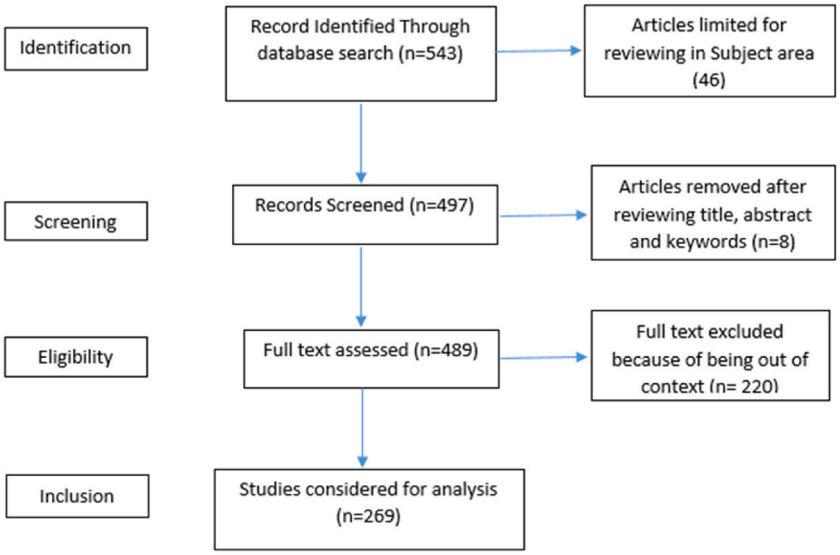

Fig. 1. PRISMA diagram.

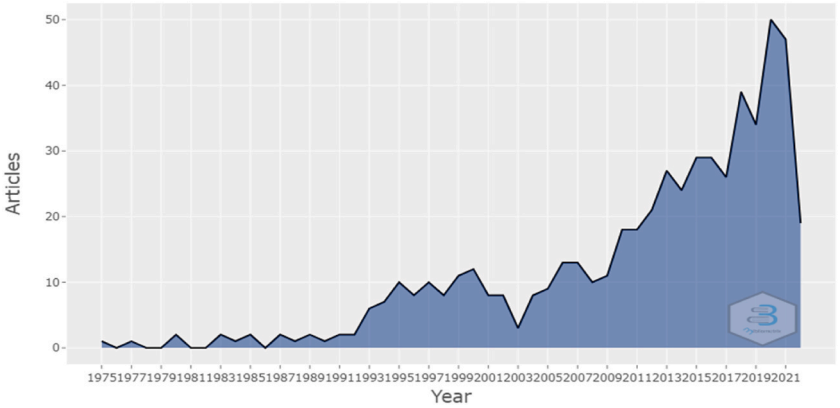

Fig. 2. Annual scientific production (Source: Authors' elaboration using the Bibliometrix R-package).

Fig. 3 shows that the study by Lopez [85] on Iron deficiency anemia is the most cited article. The study has been cited close to 600 times, twice the second or third most cited. The second most cited study is Peña-Rosas [86] on daily oral iron supplementation during pregnancy. The third most cited study is a systematic review and meta-analysis on ferrous sulfate supplementation that causes significant gastrointestinal side-effects in adults by Tolkien et al. [87]. In addition, Table 2 provides author-wise publications count for existing research on iron deficiency anemia.

3.1.2. Geographic analysis

Geographical analysis was conducted based on two aspects. One aspect is the country of production, based on the source of origin of publication, and the second is the country of the author.

Table 3 manifests the country and respective publication frequency. The USA is the country with the highest number of publications. There is a vast difference in publications between top-ranked countries and subsequently-ranked countries. The frequency of publications is not concentrated in one continent but spread over most continents, such as North and South America, Europe, Australia, and Asia. In contrast, no publication in the country belongs to Africa and Antarctica. USA focuses on the novel iron formulation for the treatment of IDA. The research focuses on the potential of various novel active pharmaceutical ingredients (API), such as Ferric Maltol, Ferric carboxymaltose, ferumoxytol, and ferric pyrophosphate citrate, in different disease conditions such as gastrointestinal disorders and chronic kidney disease (CKD) and evaluation of their safety and efficacy.

Table 4 shows that the top most relevant affiliations with research on supplementation for IDA are from the Medical University of Innsbruck, University of Toronto, and Medical University of Graz.

Fig. 4 exhibits the country of the corresponding author concerning single and multiple authors' production. The top three countries are the USA, India, and Italy, with most publications being single-country production. The top three countries confirm the evidence

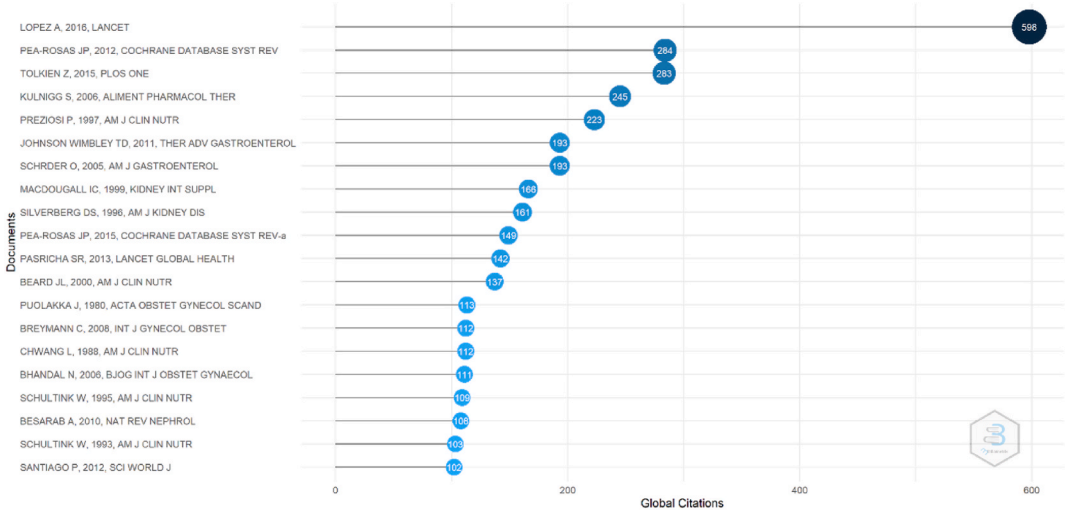

Fig. 3. Global citations (Source: Authors' elaboration using the Bibliometrix R-package).

Table 2
Author-wise frequency of publications.

Authors	Articles	Articles Fractionalized
De-Regil LM	7	2.15
Macdougall IC	7	4.95
Stein J	7	1.68
Gasche C	5	1.38
Pea-Rosas JP	5	1.15
Pereira DIA	5	0.84
Powell JJ	5	0.84
Dowswell T	4	0.95
Geisser P	4	1.31
Gross R	4	0.95
Pasricha SR	4	1.12
Schultink W	4	0.95
Weiss G	4	0.65
Breymann C	3	0.78
Canada RD	3	1.20
Danese S	3	0.29
Dignass A	3	0.39
Dignass AU	3	1.09
Mehta S	3	0.53
Peyrin-Biroulet L	3	0.45

Source: Authors' elaboration using the Bibliometrix R-package.

from the region-wise frequency of publication, shifting to the top two and three ranked countries. These findings are further substantiated by providing evidence of collaboration among researchers from various countries. 1239 authors from multiple countries published research on IDA, while authors published single-authored papers are only 22.

3.1.3. Journal analysis

Table 5 reveals the most relevant source. Nutrients are the most relevant journal of various alternatives available for the management of IDA. American Journal of Clinical Nutrition and the Cochrane Database of Systematic Reviews are also publishing research on IDA closely to Nutrients. Nutrients journal started in 2009, and the most recent volume is 14th Table 6 shows the details of the number of publications on the most studied themes.

Table 5 shows the results of bibliometric analysis using R programming, h-index measures both the productivity and citation impact of a researcher. An author has an h-index of h if h of their papers has been cited at least h times each. g-index is an improvement to the h-index. It takes into account the distribution of citations among a researcher's publications. m index indicates the h-index per year since the first publication, TC is total citations, NP is number of publications, and PY-start- publication year start.

Table 5 provides the information relative to citations and the quality of the source. The top three journals are the American Journal of Clinical Nutrition, Cochrane Database of Systemic Reviews, and Nutrients. The top source of publications supports earlier findings of the corresponding author's country and most relevant source, but essentially in a different order. The top source of publications

Table 3
Region-wise frequency of publications.

Region	Frequency
USA	127
Italy	87
India	63
Germany	58
UK	58
Netherlands	50
Australia	48
Switzerland	36
Canada	35
Spain	30
Austria	27
China	23
France	19
Japan	17
Brazil	16
Denmark	14
Poland	13
Israel	11
Mexico	10
Portugal	10

Source: Authors' elaboration using the Bibliometrix R-package.

Table 4
Most relevant affiliations.

Affiliations	Articles
Medical University of Innsbruck	31
University of Toronto	19
Medical University of Graz	17
Cornell University	15
Huazhong University of Science and Technology	15
Elsie Widdowson Laboratory	14
Istituto Giannina Gaslini	14
University of Manitoba	14
Radboud University Medical Center	13
University of Oxford	13
Magna Graecia University	12
London School of Hygiene and Tropical Medicine	12
Victor Babes University of Medicine and Pharmacy	11
Institute of Food	11
University of Copenhagen	11
University of Melbourne	11
University of Rome La Sapienza	11
Medical University of Vienna	10

Source: Authors' elaboration using the Bibliometrix R-package.

supports that most of the journals publishing on IDA management belong to the area of nutrition. It also reveals that journals publishing about IDA are as old as 1977 and as new as 2020. The difference between the total citations among top-ranked journals and the rest of the journals on the list is immense.

3.1.4. Author and citation analysis

3.1.4.1. Top authors' production over time. Fig. 5 explains the horizontal line signifies the active participation of the author during different periods, while the size of each dot reflects the number of citations received per year. The maximum number of papers contributed by De-Regil and Macdougal who have been the most active researcher since 1997. Peyrin-Biroulet contributed two papers in 2016, with a maximum of 75 citations per year. Gross and SchulTink were the only active contributors from 1993 to 1997. Most authors picked up momentum from 2005 onwards.

3.1.4.2. Three-field plot. Three field plot depicts the connection between country, author, and research keywords. Three field plots in Fig. 6 present the country, author, and research keywords relationship in IDA. Powell and Pereira from the UK contributed the most and studied anemia, Iron deficiency, iron deficiency anemia, iron supplementation, oral iron, and children. De-Regil has contributed in

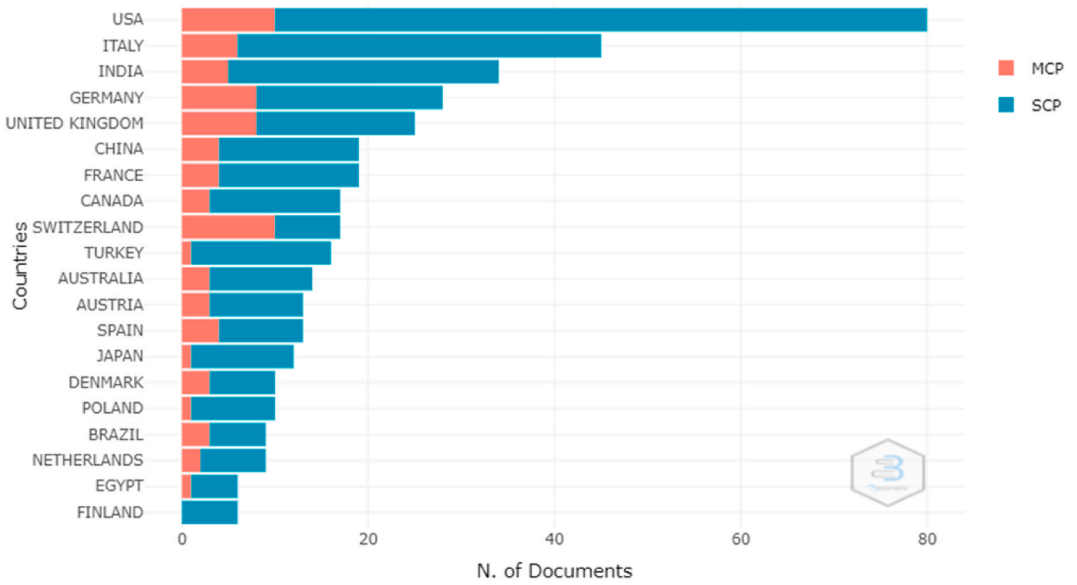

Fig. 4. Corresponding author's country (Source: Authors' elaboration using the Bibliometrix R-package).

Table 5
Most relevant source.

Journal Name	Articles	h-index	g-index	m-index	TC	NP	PY-start
American Journal of Clinical Nutrition	10	9	10	0.257	980	10	1988
Cochrane Database of Systematic Reviews	10	8	10	0.421	477	10	2004
Nutrients	12	6	10	0.750	109	12	2015
Biological Trace Element Research	5	4	4	0.444	24	5	2014
Cochrane Database of Systematic Reviews (Online)	4	4	4	0.308	505	4	2010
Acta Obstetricia Et Gynecologica Scandinavica	3	3	3	0.065	155	3	1977
International Journal of Gynecology And Obstetrics	3	3	3	0.167	141	3	2005
Molecular Aspects of Medicine	3	3	3	1.000	27	3	2020
Pediatrics	3	3	3	0.094	145	3	1991
Swiss Medical Weekly	3	3	3	0.375	89	3	2015
Advances in Therapy	2	2	2	0.667	8	2	2020
Alimentary Pharmacology and Therapeutics	2	2	2	0.118	264	2	2006
American Journal of Gastroenterology	2	2	2	0.111	224	2	2005
American Journal of Hematology	4	2	3	0.286	29	3	2016
Annals of Gastroenterology	2	2	2	0.200	113	2	2013
Annals of Hematology	2	2	2	0.095	28	2	2002
Arzneimittel-Forschung/Drug Research	2	2	2	0.125	19	2	2007
Bmc Gastroenterology	2	2	2	0.222	53	2	2014

Source: Authors' elaboration using the Bibliometrix R-package.

Table 6
Details of the number of publications on the most studied themes.

Type of Study	No. of Paper
Randomized trials	27
Comparative trials	22
Studies involve pregnant women	21
Studies involve children of age group <5	8
Studies involve CKD	14
Studies involve IBD	23

Canada, Switzerland, Australia, and the UK. Author Stein is the most contributing author of Germany, and the key interests of the author include anemia, iron deficiency anemia, oral supplementation, children, and pregnancy. Anemia and IDA are the dominant areas of study in all countries.

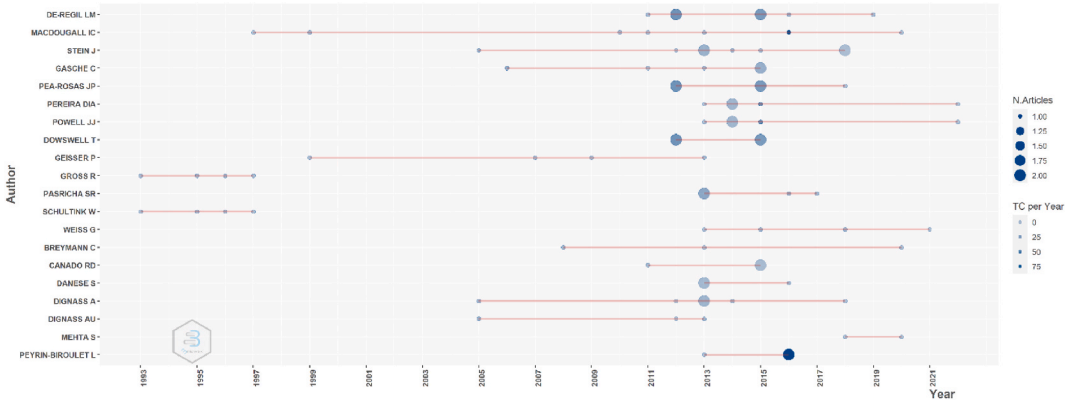

Fig. 5. Selected author's production (Source: Authors' elaboration using the Bibliometrix R-package).

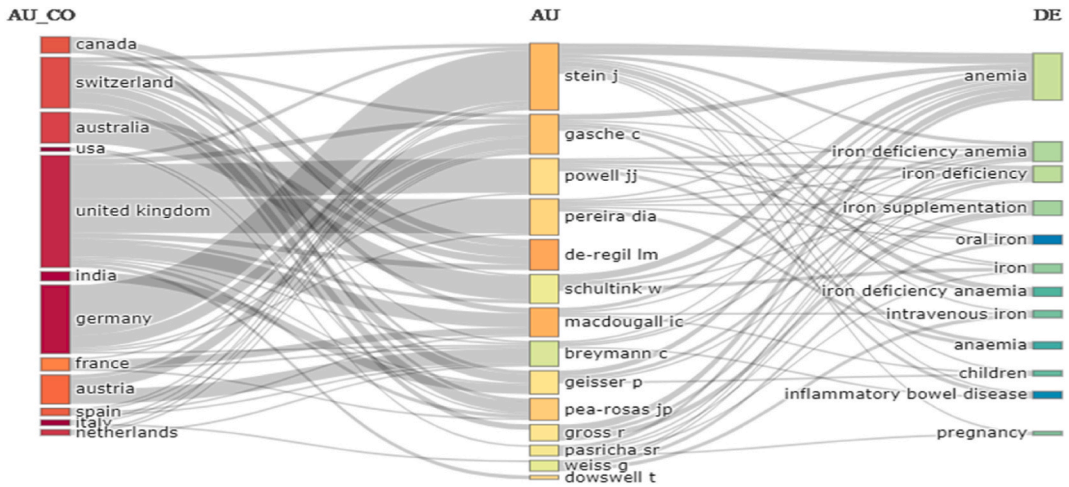

Fig. 6. Three field plots (Source: Authors' elaboration using the Bibliometrix R-package).

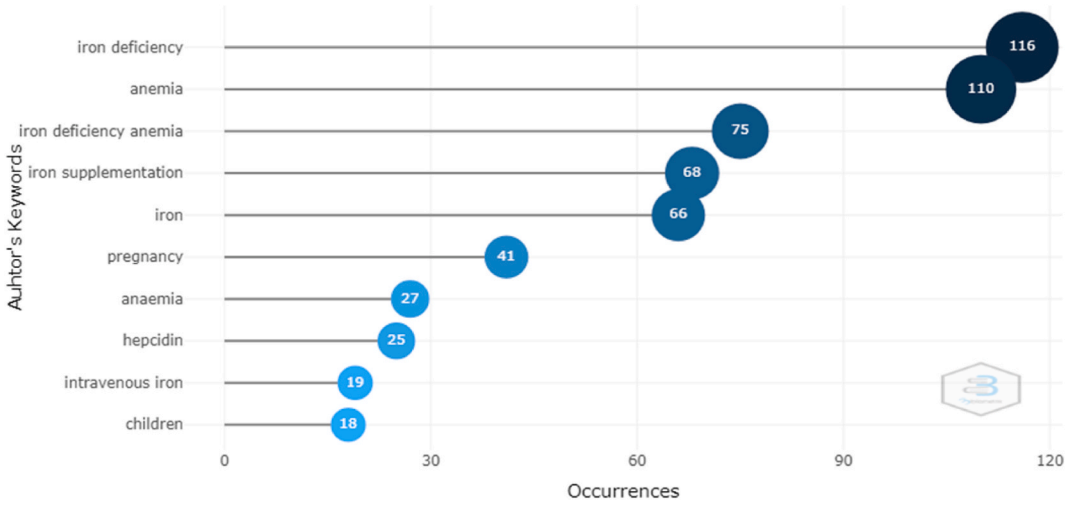

Fig. 7. Most relevant words (Source: Authors' elaboration using the Bibliometrix R-package).

3.1.5. Topic and keyword analysis

Keyword analysis in Fig. 7 depicts that iron is the most frequently used keyword. Other keywords such as female, iron deficiency anemia, anemia, and human are often used. Iron deficiency anemia in females and iron supplementation are the most trending keywords and themes under study.

Fig. 8 depicts the trending topics in IDA and its management. In the early 90s, parenteral therapy with iron sucrose and high molecular weight iron-dextran injection for treating IDA was trending. With Severe Adverse Events (SAEs) with traditional formulation, the trend shifted to other iron formulations, such as iron polymaltose and low molecular weight iron-dextran, in 2011 and 2019, respectively. Various other approaches, such as ferric ion for oral supplementation and dietary supplementation of iron also has been tried to overcome the limitations of traditional treatment. In earlier studies, IDA in chronic kidney disease patients was trending, but research expanded in other areas, such as inflammatory bowel disease, pre-operative care, heart failure, and bariatric surgery. Research in IDA got thrust with the advancement of knowledge regarding the role of protein expression in iron bioavailability and observation of new side effects such as hypophosphatemia via dysregulation of fibroblast growth factor 23 caused by ferric carboxymaltose.

The Word cloud of Fig. 9 expresses that the most prevalent words in the research on IDA are anemia, iron deficiency anemia, children, pregnancy, inflammatory bowel disease, chronic kidney disease, Iron, and intravenous Iron. The most dominating words are anemia and various circumstances leading to iron deficiency anemia. Other words include different treatment options and consequences of disease and treatment.

Fig. 10 expresses word growth over the years. There has been a general trend of increase in growth over the years. The words anemia and anemia have been used interchangeably. It is a sign that iron deficiency anemia is still attracting the interest of authors and publishers.

3.2. Conceptual structure

3.2.1. Co-occurrence network

The co-occurrence network in Fig. 11 presents five clusters. The green cluster is the largest, and it has 15 nodes. The largest node is iron deficiency, followed by intravenous treatment. Iron deficiency is connected to chronic kidney disease, bariatric surgery, inflammatory bowel disease, heart failure, and various treatment options such as oral and intravenous. The green cluster is connected to all the clusters, especially the central nodes of red and blue clusters, which are anemia and iron supplementation.

3.2.2. Thematic map

The thematic map in Fig. 12 is based on density and centrality, with four clusters. Fundamental themes for IDA are anemia, iron deficiency, iron supplementation, pregnancy, and chronic kidney disease. There are no declining themes. Thematic analysis centers on the above-mentioned themes as they represent extensively researched areas. The constant themes are children, oral iron therapy, liposomal iron, iron metabolism, erythropoietin, and anaphylaxis in some cases. Only a few authors are interested in research on anti-anemic drugs.

3.2.3. Thematic evolution

Fig. 13 shows the thematic evolution from 1977 to 2022. The initial research interest from 1977 to 2015 focused on anemia, children, iron deficiency, and iron supplementation. However, from 2016 to 2022, it shifted to iron deficiency anemia and inflammatory bowel disease. Iron deficiency and children are timeless topics that attract the interest of researchers.

3.2.4. Conceptual structure map

A conceptual structure map is a representation map of the research field in that area. Based on the co-occurrence of keywords, the conceptual structure map in Fig. 14 has 10 clusters; the size of the dot is the frequency of occurrence. The main keywords are iron deficiency anemia and iron therapy. Other keywords are related to complications of IDA and iron therapy. Since chronic kidney diseases are one of the most exciting research areas, and the primary treatment option is parenteral therapy, there is a high risk of an anaphylactic reaction in some cases. At the same time, oral therapy is the first line of therapy for other conditions such as pregnancy and blood donation.

3.3. Intellectual structure

3.3.1. Co-citation analysis

Fig. 15 reveals four clusters in the co-citation network. The total number of authors is 36; the green cluster is the largest, consisting of 12 nodes. Studies in this cluster are related to anemia of chronic disease [39], anemia in inflammatory bowel disease [40,88], treatment of IDA [41], the iron requirement in pregnancy [89]. The second cluster, the red cluster, has nines nodes, and most studies are related to anemia in inflammatory bowel disease ([90]; [80]; [42,91]). In the blue cluster are studies on iron deficiency anemia [79] and comparing ferrous and ferric iron formulations for oral delivery [18]. The purple cluster is the smallest one and has studies on managing iron deficiency anemia [92] and intravenous ferric carboxymaltose for treating iron deficiency anemia [43].

Fig. 8. Trending topics (Source: Authors' elaboration using the Bibliometrix R-package).

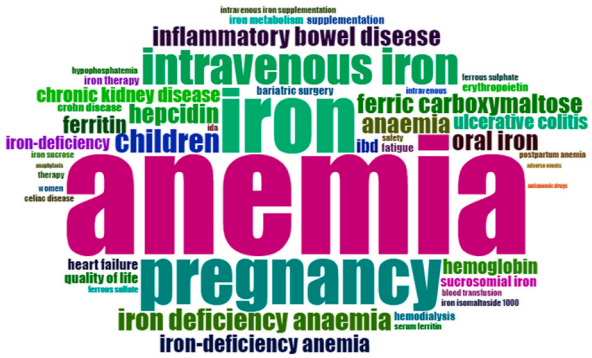

Fig. 9. A word cloud (Source: Authors' elaboration using the Bibliometrix R-package).

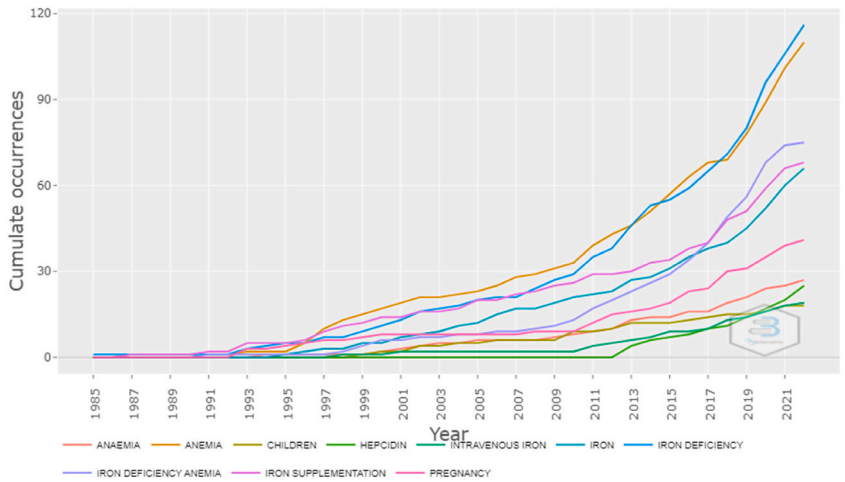

Fig. 10. Word growth (Source: Authors' elaboration using the Bibliometrix R-package).

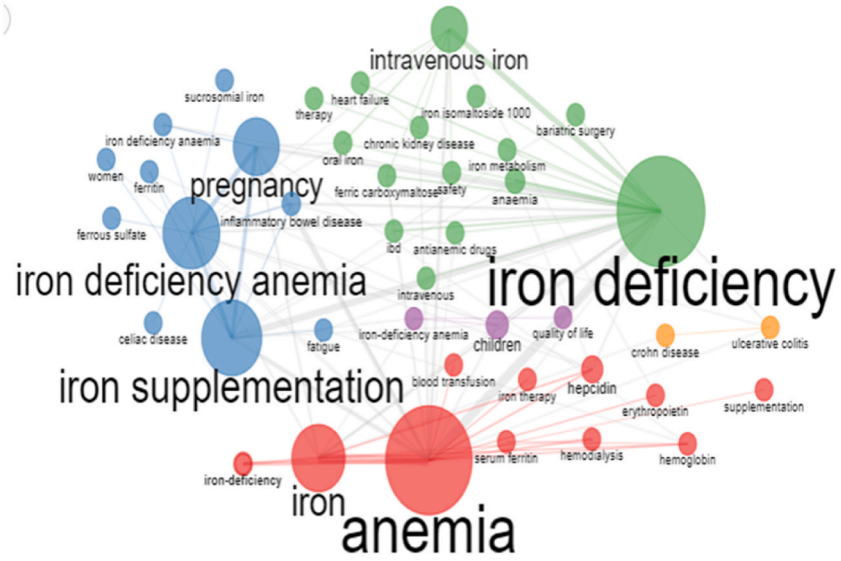

Fig. 11. Co-occurrence network (Source: Authors' elaboration using the Bibliometrix R-package).

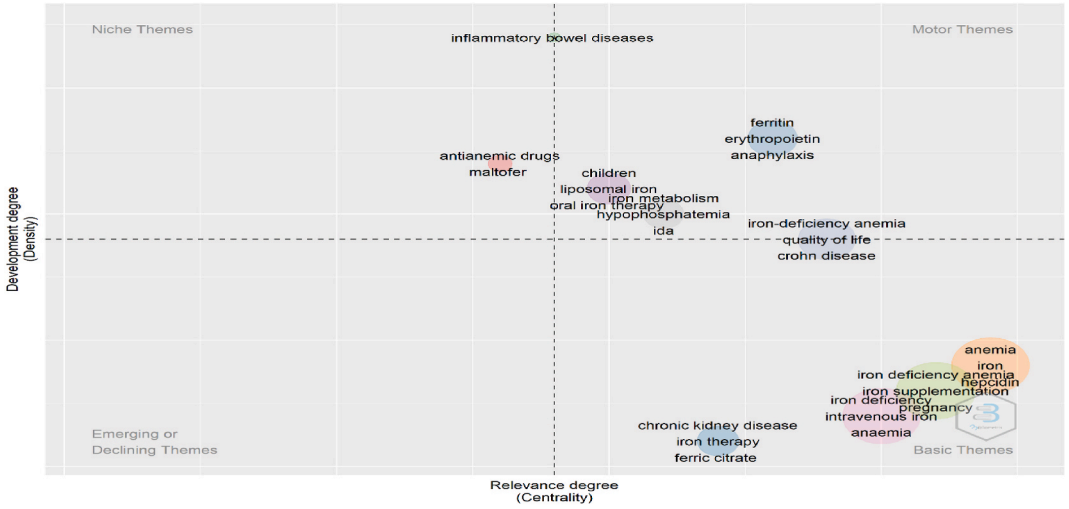

Fig. 12. Thematic map (Source: Authors' elaboration using the Bibliometrix R-package).

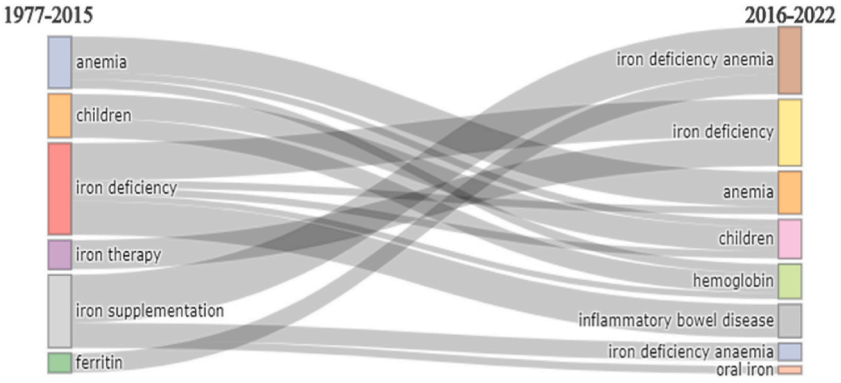

Fig. 13. Thematic evolution (Source: Authors' elaboration using the Bibliometrix R-package).

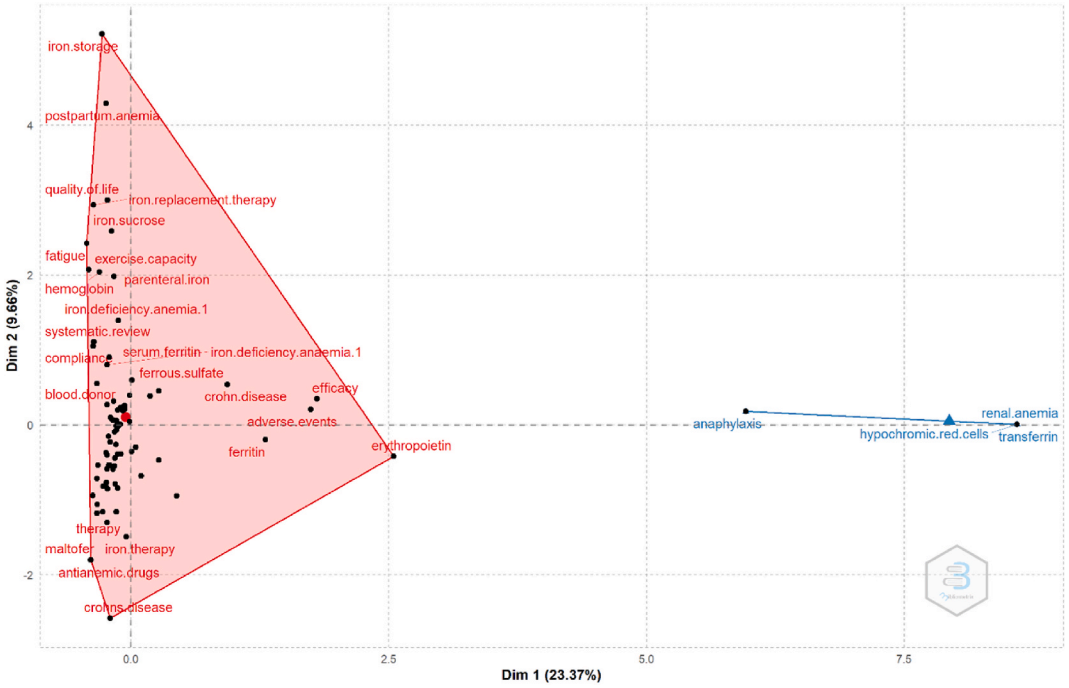

Fig. 14. Conceptual structure map (Source: Authors' elaboration using the Bibliometrix R-package).

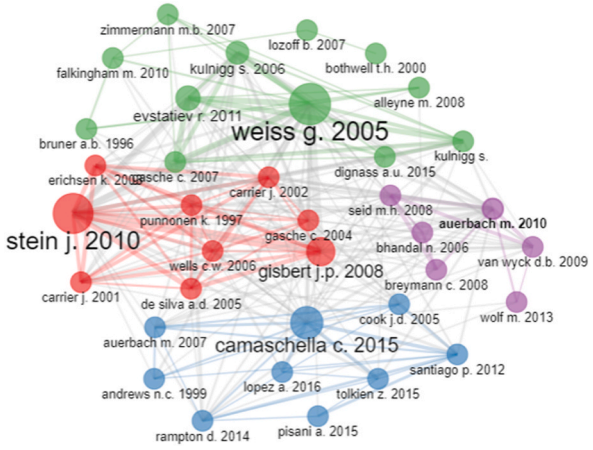

Fig. 15. Co-citation network (Source: Authors' elaboration using the Bibliometrix R-package).

3.4. Social structure

3.4.1. Collaboration network

From Fig. 16, it is clear that ten clusters of collaborations exist in research related to treatment approaches for IDA. The peach and orange color shows the maximum number of collaborations, five in each cluster. Stein collaborated with four other authors. Stein's area of research and aspects of IDA treatment in IBD. De-Regil research interest is the study of various strategies for treating anemia in pregnancy and women of reproductive age. Powell worked on oral iron supplements' bioavailability, safety, and effectiveness.

3.4.2. Collaboration world map

Fig. 17 presents country collaboration among researchers working on IDA. Most researchers are from Austria, Denmark, and Germany. The authors from France and Greece also collaborated. As documented in region-wise contribution, the USA scored the first rank, but surprisingly, collaboration of researchers from the USA with other countries has yet to be observed. Most of the existing collaboration is from among researchers in Europe. Collaboration among researchers from advanced and emerging economies is also

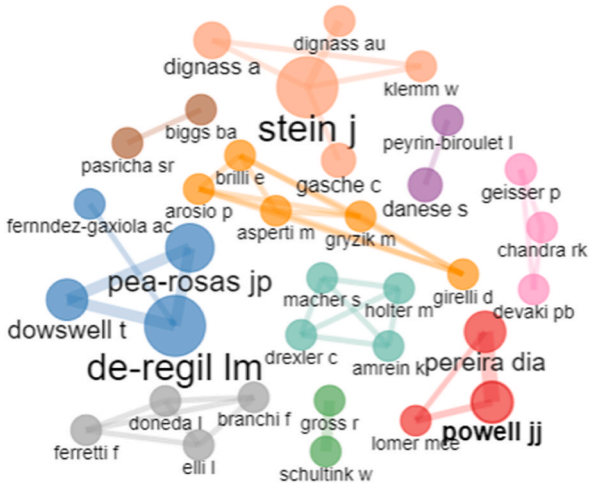

Fig. 16. Collaboration network (Source: Authors' elaboration using the Bibliometrix R-package).

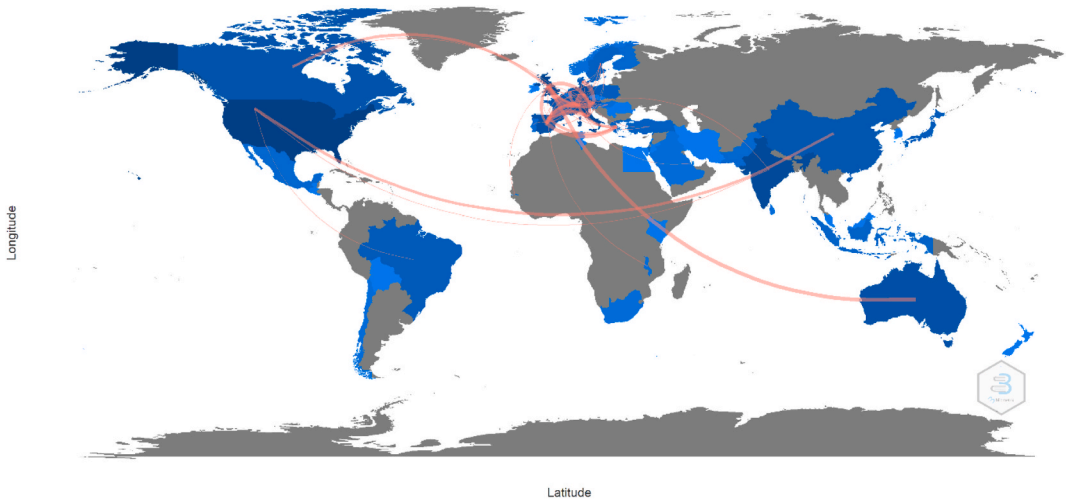

Fig. 17. Country collaboration map (Source: Authors' elaboration using the Bibliometrix R-package).

limited.

4. Thematic analysis

This section presents the thematic analysis of existing iron deficiency anemia (IDA) research. Fundamental themes for IDA are anemia, iron deficiency, iron supplementation, pregnancy, children, inflammatory bowel disease, and chronic kidney disease. There are no declining themes. Thematic analysis centers on the above-mentioned themes as they represent extensively researched areas. Based on the insights from bibliometric analysis, five themes are identified; specifically, these themes focus on studies related to kidney disease, inflammatory bowel disease, IDA in children, IDA in pregnancy, and the treatment of IDA.

4.1. Chronic kidney disease (CKD)

Anemia is a major complication of CKD; the reason may be reduced erythropoietin production, chronic blood loss, or reduced gastric absorption of iron due to inflammation [44]. Oral therapy is ineffective in most cases due to increased hepcidin levels. Therefore, IV iron preparations are required, either alone or along with oral preparations. Iv iron preparations can delay the requirement of erythropoiesis-stimulating agents (ESAs)in non-dialysis patients and reduce the dose of ESAs in dialysis patients [45]. Conventional oral supplements have low efficiency and high gastric side effects. However, new oral iron agents, such as liposomal iron, are claimed to be effective [46]. Ferric citrate, a phosphate binder in CKD, can improve iron status in non-dialysis and dialysis patients. Newer IV iron formulations such as ferric carboxymaltose, ferumoxytol, and iron isomaltisode 1000 can be given in one or two dose

infusions and have a lower incidence of an anaphylactic reaction [47].

4.2. Inflammatory bowel disease (IBD)

Anemia is the most common complication of IBD. In IBD, the patient can suffer from iron deficiency anemia or anemia of chronic diseases (ACD). If anemia is mild and IBD is in a quiescent state, oral supplementation is the preferred treatment. However, iron supplements have low bioavailability and a high rate of gastrointestinal side effects in IBD. Therefore, IV supplementation is the first line of therapy in moderate to severe anemia and active IBD disease states [48]. Intake of an iron-fortified diet is also associated with negative outcomes [49]. Ferric carboxymaltose is also safe and effective and can be given in a single-dose infusion [50]. Iv iron sucrose is well tolerated in children with IBD [51]. Novel oral iron supplements such as ferric maltol, ferrous bis-glycinate chelate, iron (III) poly maltose, and supranormal iron are also reported to be beneficial in IBD [52–54].

4.3. IDA in children

Chwang et al. [55] reported that iron deficiency is associated with low physical growth in infants and children. IDA affects not only physical growth but also intellectual development in children. Treatment with iron resulted in low morbidity and improved growth velocity among children in Indonesia [55]. It has been found that in preschool children, iron supplementation is as effective as daily supplementation in improving iron status [56]. Parenteral iron treatment should be considered in children not responding to oral supplementation to early replenish iron stores [57].

4.4. IDA in pregnancy

There is an increased demand for iron in pregnancy due to increased maternal blood volume and the high fetal iron requirement to meet oxygen delivery and metabolic reaction demands [58]. IDA in pregnant women can cause cardiac insufficiency, increased susceptibility to infection, hemorrhagic shock, preterm delivery, and low birth weight [59]. Apart from traditional ferrous salts such as ferrous sulfate, fumarate, or gluconate, newer oral supplements such as iron hydroxide polymaltose complex and ferrous ascorbate claimed to be more effective and have fewer side effects [60]. Iron absorption varies across the three trimesters of pregnancy, registering at 0.4, 1.9, and 5.0 mg during the first, second, and third trimesters, respectively, when administered in a highly bioavailable form [61]. In cases of moderate to severe anemia during the second and third trimesters of pregnancy, intravenous iron is recommended as it proves to be more effective, rapid replenishment of iron stores, and resolution of anemia. However, various regions may have different hemoglobin (Hb) threshold values for intravenous iron administration. Iron dextran, iron sucrose, ferric gluconate, ferumoxytol, and ferric carboxymaltose are the IV iron formulations that can be used in pregnancy [62].

4.5. Treatment of IDA

4.5.1. Oral supplementation

Iron deficiency, with or without anemia, can reduce exercise capacity and quality of life [63]. Prophylactic daily oral administration of iron effectively prevents anemia and iron deficiency during the second and third trimesters of pregnancy [64]. Oral iron supplementation is the preferred treatment for IDA and iron deficiency in children, adolescents, and non-pregnant and pregnant women [27]. However, it is ineffective in CKD, IBD, cancer, heart failure, and high hepcidin levels [65]. Hepcidin is one of the factors responsible for the failure of treatment response to oral supplementation [11]. Novel oral iron formulations such as sucrasomial iron, Feralgine, and iron (III) hydroxide polymaltose have reduced gastric side effects and improved patient compliance compared to earlier oral iron formulations [66–68].

4.5.2. Parenteral supplementation

Parenteral iron supplementation is recommended when oral supplementation is not well tolerated, ineffective, or rapid response is required. Patients suffering from CKD or IBD require intravenous iron supplementation. New IV iron formulations lack dextran moiety, so there is low a risk of anaphylactic reactions. Novel IV iron formulations include ferumoxytol, ferric carboxymaltose, and iron isomaltoside, which can be given in rapid high doses [47]. Ferric carboxymaltose is associated with hypophosphatemia [69]. Ferumoxytol can alter MRI images for up to 3 months [70].

5. Directions for future research

It is generally accepted that iron in CKD intravenous is superior to oral iron supplements. However, few studies reported the safety and effectiveness of third-generation oral iron supplements such as ferric citrate, liposomal iron, and iron polysaccharides. More clinical trials are required to prove the efficiency of third-generation oral iron salts in CKD [71,72].

Food fortification can effectively eliminate iron deficiency in a vulnerable population considerably. Iron's fate in the body depends on absorption rather than excretion [73]. Unabsorbed iron in the gut can alter gut microflora or cause or precipitate diarrhea [74,75]. Therefore, while developing iron-fortified food, points such as target population requirement, type of food, and amount of iron that will get delivered should be addressed.

IDA in preschool children and pregnant women is life-long [76,77]. And the patients' poor compliance with oral supplementation

[29]. Studies exploring pharmacological and non-pharmacological measures can reduce IDA prevalence in this group.

Few studies claim the effectiveness of oral sucrasomial iron formulations in IBD [68,78]. A study of the safety and effectiveness of oral microsomal iron at intra-individual and inter-individual levels can confirm its actual potential in IBD.

6. Conclusions

Iron deficiency anemia is a global health concern. Iron homeostasis is controlled by absorption, so we need to increase the iron supply in the case of IDA. Various approaches such as diet modification, food fortification for iron deficiency without anemia, and oral or parenteral iron supplementation for treating mild to severe cases of IDA have been used to reach target iron stores and hemoglobin levels. This review provides insight into various iron supplements used in treating IDA using bibliometric analysis and thematic analysis. The research was conducted using 543 articles published in the Scopus database, and 269 articles were selected for bibliometric and thematic analysis. Since research focused on the ferrous and ferric ions used in treating IDA, this paper provides insights into the treatment approaches for IDA. The research on treatment approaches for IDA gained momentum around 2012 after the World Health Assembly implemented a plan to target a 50% reduction of anemia in women. The most contributing country, as well as the country of most contributing authors, is the USA, whereas the most relevant institution is the Medical University of Graz, Austria. The journals writing most about IDA belong to nutrition journals such as Nutrients and the American Journal of Clinical Nutrition. Existing research on IDA is inclined towards IDA in pregnancy, children, CKD, IBD, and intravenous formulations for its treatment. Prior studies focus on IDA in pregnancy, IBD, management of IDA, and intravenous formulations for treating IDA. In the thematic analysis, we discussed the researcher's and clinician's preference for a particular form of iron supplement over the other based on the patient's requirements and the presence of co-morbidities. Because the prevalence of anemia is still high, researchers need an effective alternative for the treatment of IDA, which can overcome the limitations of the existing formulation to reduce it in a great, powerful way.

CRediT authorship contribution statement

Tarnjot Kaur: Writing – review & editing, Writing – original draft, Software, Resources, Methodology, Data curation, Conceptualization. **Jyoti Upadhyay:** Writing – review & editing, Supervision, Software, Resources, Project administration, Funding acquisition, Conceptualization. **Mukesh Nandave:** Writing – review & editing, Supervision, Resources, Conceptualization. **Abdulrhman Alsayari:** Conceptualization, Funding acquisition, Writing – review & editing. **Saad Ali Alshehri:** Writing – review & editing, Resources, Funding acquisition. **Sudeep Pukale:** Writing – review & editing, Writing – original draft, Supervision, Software, Resources, Project administration, Conceptualization, Methodology. **Shadma Wahab:** Writing – review & editing, Methodology, Data curation. **Wasim Ahmad:** Writing – review & editing, Methodology, Data curation. **Summya Rashid:** Software, Writing – original draft. **Mohd Nazam Ansari:** Writing – original draft, Supervision, Resources, Project administration, Funding acquisition, Writing – review & editing.

Declaration of competing interest

The authors declare no conflict of interest. The items expressed in this article are personal and do not represent to Lupin Research Park.

Acknowledgments

The authors extend their appreciation to the Deanship of Scientific Research at King Khalid University for funding this work through large group Research Project under grant number RGP.2/313/44.

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