

Bibliometric analysis of recent research on 5-Fluorouracil (2015–2020)

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ARTICLE INFO

Received on: 27/05/2021
Accepted On: 19/09/2021
Available Online: 05/01/2022

Key words:

5-Fluorouracil, anticancer activity, bibliometric analysis.

ABSTRACT

Cancer is one of the most widespread diseases in the world and causes millions of deaths every year. Currently, there are several anticancer treatments to deal with the different types of cancer reported around the world. However, most of them have both side effects and low selectivity to malignant cells. 5-Fluorouracil (5-FU) is used as first-line treatment against several types of cancer. Recently, hybrid and derivative molecules based on 5-FU have been reported as anticancer with high/modest activity, leading to a new and emerging therapy to treat cancer. The aim of this study was to carry out a bibliometric analysis of studies related to 5-FU in the field of chemistry. Data collection was carried out using the Scopus database, and VOSviewer 1.6.13 was used for data analysis and visualization. “5-Fluorouracil” was the term used in the search during a time span of 2015–2020. A total of 1,025 documents related to 5-FU were indexed in Scopus between 2015 and 2020, both included. Articles and reviews related to 5-FU have increased during the period of 2015–2020, starting and ending with 137 and 241 studies, respectively. The main areas, excluding chemistry, were (i) *Biochemistry, Genetics, and Molecular Biology*; (ii) *Chemical Engineering*; and (iii) *Materials Science*. Within these areas, the studies were focused on drug delivery, synthesis of anticancer compounds and their activity, molecular simulation, treatment of cancer cells, and drug resistance. Finally, the most productive countries on studies related to 5-FU, which also had the most robust collaboration network, were China, India, and the United States.

INTRODUCTION

Cancer disease is one of the primary public burdens and is the second leading cause of death worldwide, with 10 million deaths per year and 70% of them occurring in low-middle-income countries. In 2020, the most common causes of cancer deaths were lung, colon and rectum, liver, stomach, and breast with 1.8, 0.935, 0.830, 0.769, and 0.685 million cases, respectively. In terms of new cases of cancer, and also for 2020, the most common were breast, lung, colon and rectum, prostate, skin (nonmelanoma), and stomach with 2.26, 2.21, 1.93, 1.41, 1.20, and 1.09 million cases, respectively (WHO, 2020). In 2018, 9.6 million people globally

were estimated to have died from cancer (WHO, 2020). Recently, global cancer statistics including incidence and mortality for 36 types of cancer in 195 countries was presented (Sung *et al.*, 2021). Probably because of the high rate of deaths caused by cancer, many researchers have focused on cancer treatment for decades, applying different methodologies with diverse findings. Thus, new alternative therapies against cancer have emerged using compounds that exhibit good anticancer activity. Among those compounds, hybrids and conjugates based on 5-Fluorouracil (5-FU) are highlighted (see review of Cardona-G *et al.*, 2021).

Since the growth and number of studies available on a specific topic, such as cancer, can be considerably high, the task of structuring a comprehensible review with relevant information could become a challenge for researchers. However, bibliometric analysis allows for scientific mapping of large amounts scientific literature, which could provide macroscopic overview of a topic of interest such as antibiotics, emerging contaminant, antivirals, and multidrug-resistant fungus (Gómez-Ríos, López-agudelo,

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and Ramírez-Malule, 2020; Gómez-Ríos and Ramírez-Malule, 2019; Liao *et al.*, 2018; Natalia *et al.*, 2021; Ramírez-Malule, 2018; Ramírez-Malule *et al.*, 2020; Ramírez-Malule *et al.*, 2020; Soosaraei *et al.*, 2018). In the case of cancer treatment, there are several reviews available on cancer of breast (Waks and Winer, 2019), prostate (Nevedomskaya *et al.*, 2018), colon (Banerjee *et al.*, 2017), and even survivorship statistics for different cancers (Miller *et al.*, 2016, 2019). Besides, a recent review based on 5-FU was published (Cardona-G *et al.*, 2021). In that review, the authors reported the synthesis of hybrids and derivatives containing 5-FU and their anticancer activity in different cancer cell lines. However, a bibliometric analysis of 5-FU is still lacking. Thus, the aim of this study was to identify and analyze the studies related to 5-FU in the field of chemistry.

METHODS

Database selection

The Scopus database was used as a tool to retrieve the most relevant documents related to 5-FU in the field of “chemistry.” Data collection was acquired from Scopus on March 2, 2021, and comprised records obtained from a systematic search of documents matching the search terms in the fields of article title, abstract, and keywords. The search was refined to article and review as the document types. The resulting search was as follows:

- Search equation: TITLE-ABS-KEY (“5-Fluorouracil”) AND (LIMIT-TO (DOCTYPE, “ar”) OR LIMIT-TO (DOCTYPE, “re”) AND (LIMIT-TO (SUBJAREA, “CHEM”)).
- Timespan: 2015–2020. 1,025 articles and reviews were retrieved after removing duplicates.

Data export and analysis

The information retrieved from the Scopus database for all records during the search were (i) both citation and bibliographical information, and (ii) abstract and keywords. Retrieved data were downloaded from Scopus and exported to Microsoft Excel®. Later, VOSviewer 1.6.13 was used for visualization and data analysis. Six was set as the minimum number of occurrences of a keyword. After removing the thesaurus terms, 52 of them met the threshold, which led to 9 clusters.

Bibliometric indicators

The following bibliometric indicators were evaluated:

- Volume and growth of publications related to 5-FU studies.
- Subject areas related to 5-FU studies.
- Co-occurring keywords of network visualization.
- Co-occurring keywords of overlay visualization.
- Most active countries.

Results

A total of 1,025 documents related to 5-FU in the field of chemistry were indexed in the Scopus database between 2015 and 2020, both included. Figure 1 shows the evolution of the number of publications in this field. As observed, there is an increase in research outputs starting and ending with 137 and 241 records for 2015–2020, respectively. In this time range, the areas

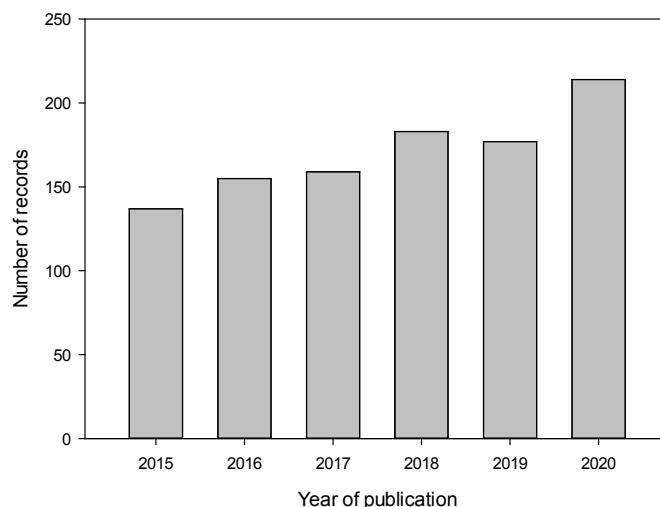


Figure 1. Evolution of published studies related to 5-FU between 2015 and 2020.

of knowledge (excluding chemistry) related to 5-FU studies were (i) *Biochemistry, Genetics, and Molecular Biology*; (ii) *Chemical Engineering*; and (iii) *Materials Science* (Fig 2).

Figure 3a shows the co-occurrence of authors' keywords network, which contains nine clusters easily distinguishable by colors. This figure clearly displays the topic on which the researchers have focused in the last 6 years (2015–2020): (i) drug delivery (blue and purple); (ii) cancer treatment and drug resistance (yellow, orange, and pink); and (iii) anticancer activity (red and blue light) and molecular docking (green). Studies related to drug resistance, chemoresistance, adsorption, mesoporous

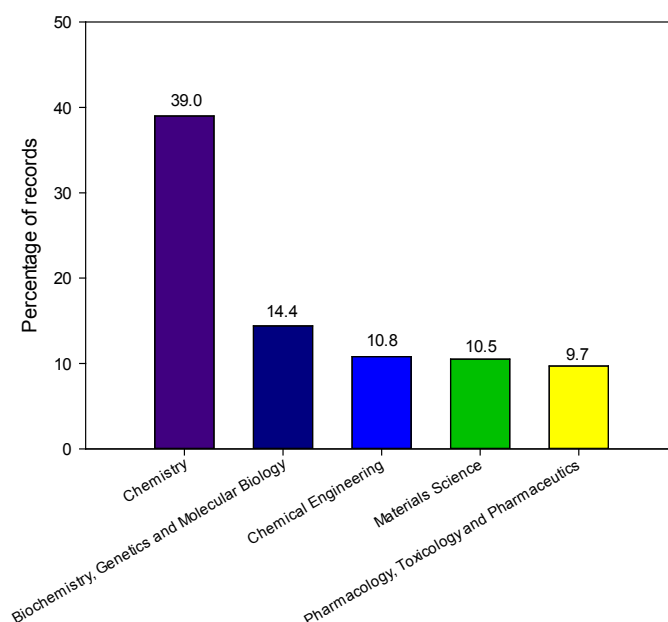


Figure 2. Summary of publications grouped by areas related to 5-FU studies between 2015 and 2020.

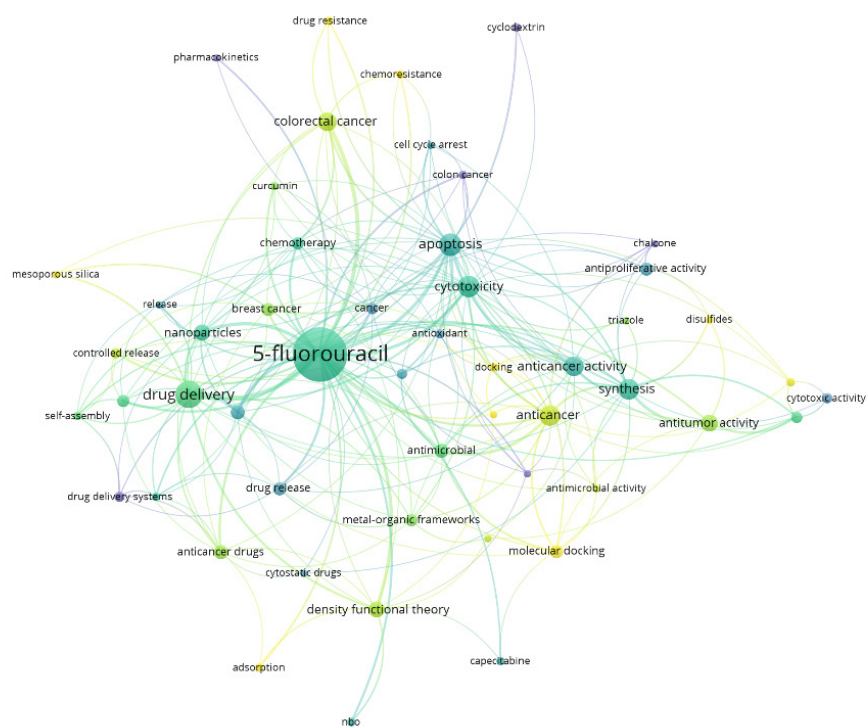
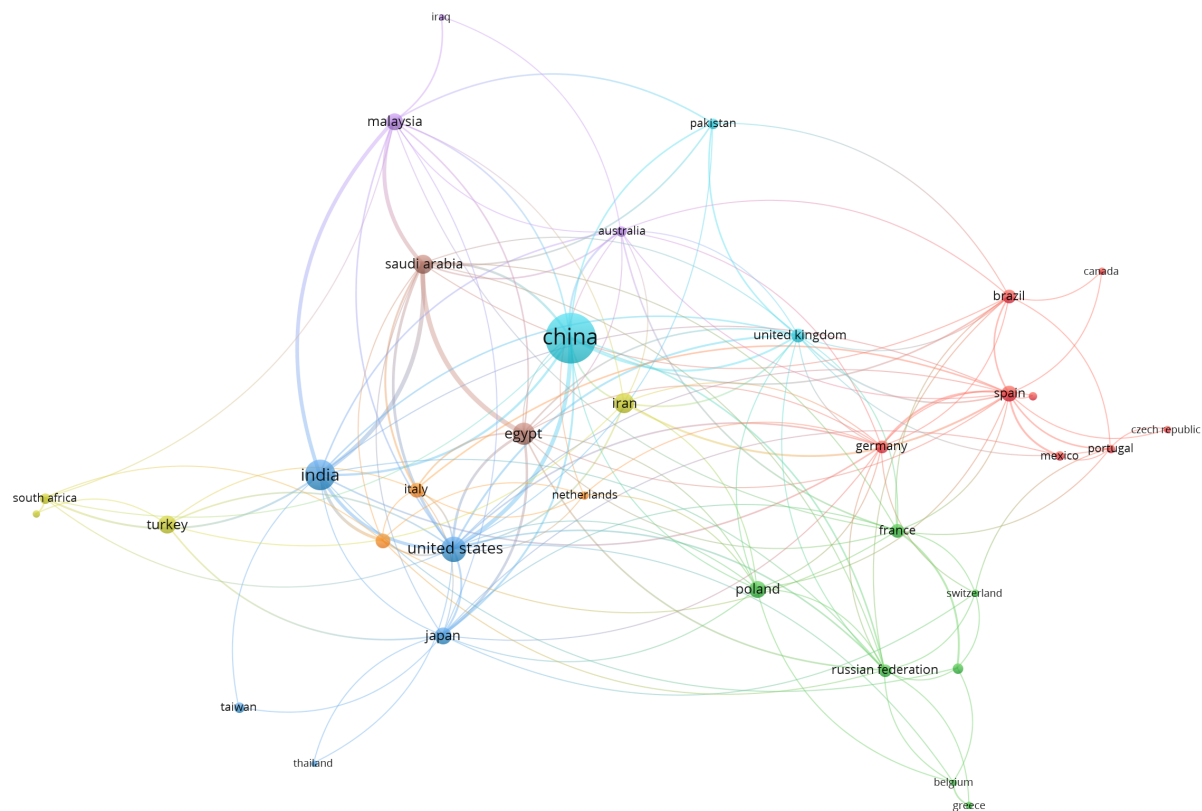
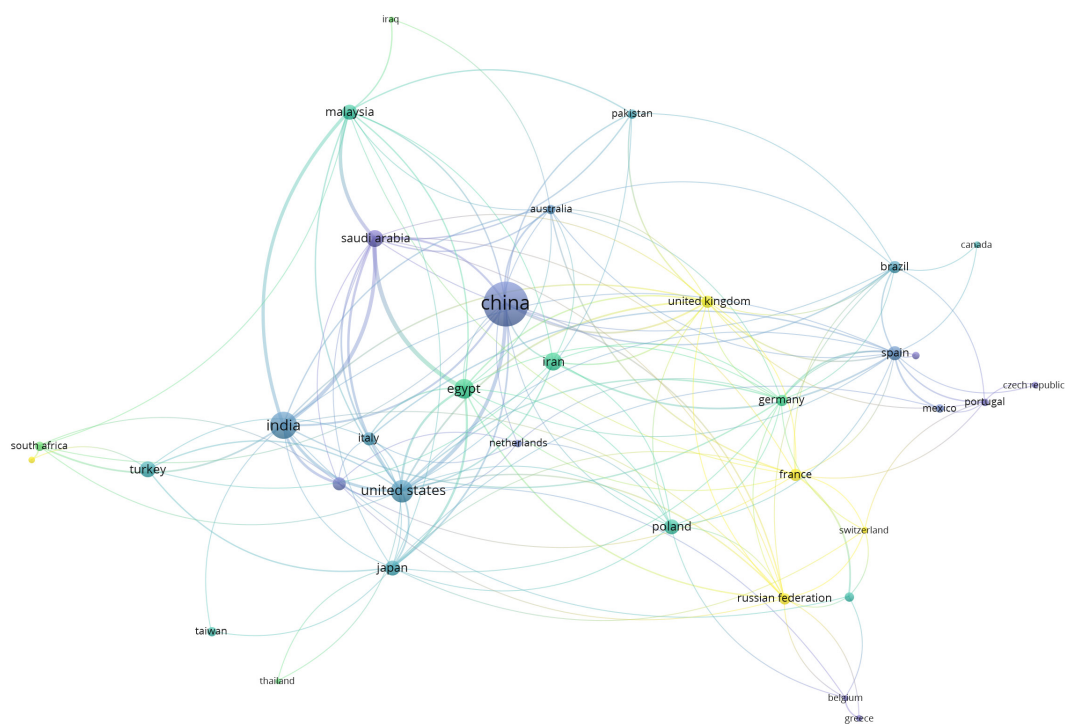


Figure 3. Bibliometric network of studies related to 5-FU between 2015 and 2020. (a) Research topic map. (b) Research topic map with time overlap. Note: minimum number of occurrences of a keyword is six.

a.

VOSviewer

b.

VOSviewer



Figure 4. Countries collaboration network studies related to 5-FU between 2015 and 2020. (a) Network visualization. (b) Overlay visualization. Note: countries contributing with a minimum number of both documents and citations of five.

silica, and molecular docking concentrated the research on 5-FU in 2018 (Fig 3b).

In the collaboration networks of countries researching on 5-FU—in the field of chemistry—and during 2015–2020, China ranked first, followed by India and the United States with 330, 121, and 80 records, respectively (Fig 4a). These countries also have the strongest collaboration network. Nevertheless, countries such as the United Kingdom, France, Switzerland, Germany, Poland, Egypt, and Malaysia concentrated the studies between 2017 and 2018 (Fig 4b).

DISCUSSION

Anticancer activity of hybrids and derivatives based on 5-FU

5-FU (Fig 5) is an antimetabolite of the pyrimidine analog type, which is widely used in the first-line treatment for solid tumors, including colorectal being more effective with regard to others, as reviewed by Ribeiro *et al.* (2016), gastrointestinal tract reviewed by Sara *et al.* (2018) and breast cancer (Tecza *et al.*, 2018). Although 5-FU is effective, it produces undesirable gastrointestinal and neurological side effects, which in many cases

leads to dose limitations or cessation of the anticancer therapy (Rejhová *et al.*, 2018).

In the search to reduce these side effects of 5-FU, two optimization strategies have been proposed: (1) the incorporation of pharmacologically active compounds with anticancer activity (called hybrid molecule) and (2) the functionalization with other groups of compounds (called conjugates). For 5-FU modification and from a synthetic point of view, four important precursors of 5-FU (commonly used in the synthesis of different hybrids or conjugates) have been used: 5-FU acid, 5-FU alkyl bromide, 5-FU-alcohol, and 5-FU alkyne. However, 5-FU acid is the most used (Fig 5).

5-FU colchicine hybrids were obtained via 5-FU acid (Fig 5). These compounds exhibited good cytotoxic activity against four cancer lines cells ($R = \text{SMe}$: 9.5, 7.8, 10.2, and 7.5 μM on A2780, A-549, BEL-7402, and MCF7, respectively; $R = N(\text{C}_2\text{H}_5)_2$: 10.2, 10.6, 10.9, and 9.8 μM on A2780, A-549, BEL-7402, and MCF7, respectively) (Shen *et al.*, 2015). On the other hand, 5-FU-1,3,4-selenadiazole conjugate, which was synthesized from 5-FU acid (Fig 5), displayed good activity over kidney-type

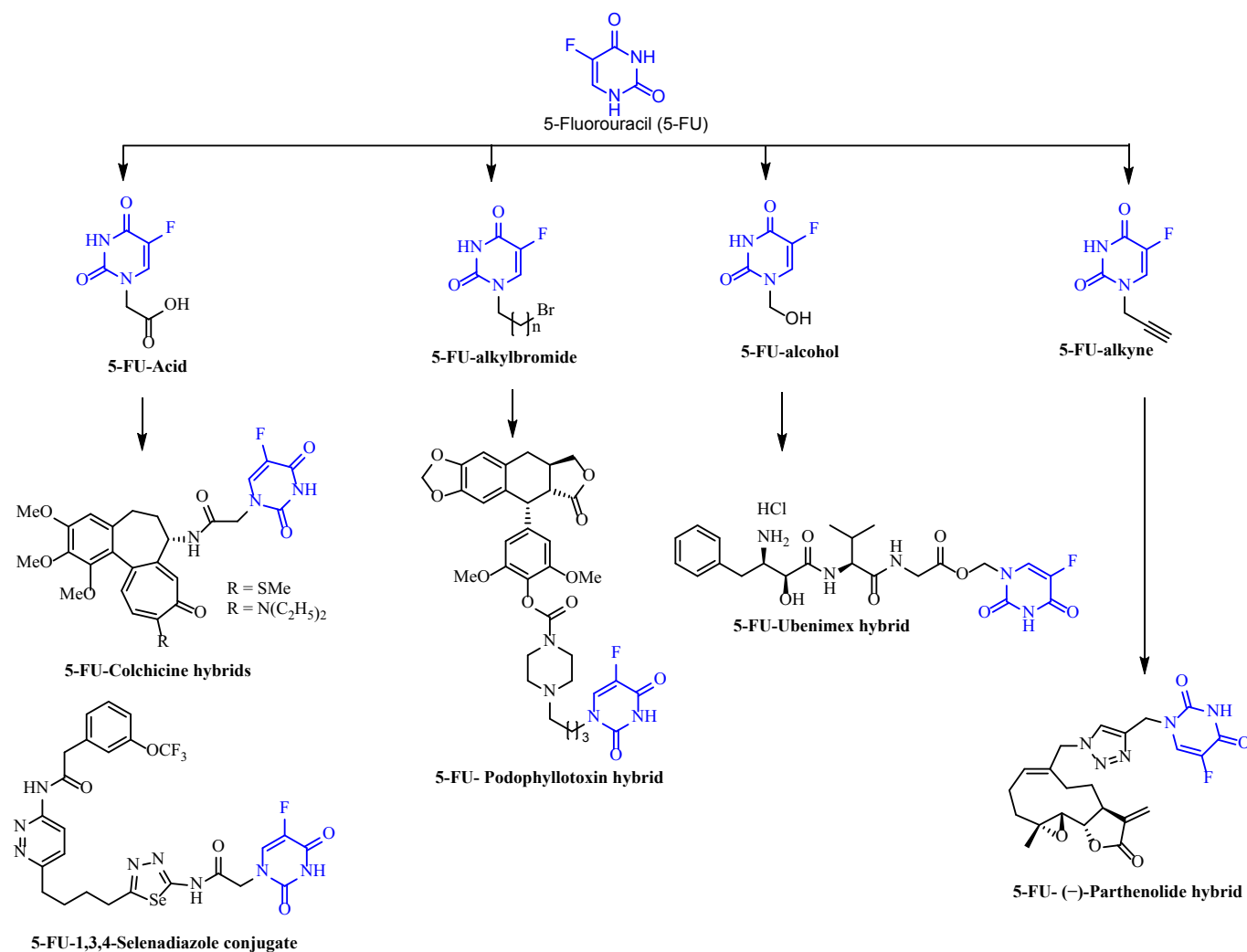


Figure 5. Chemical structures of 5-FU precursors, 5-FU conjugates, and 5-FU hybrids.

glutaminase (KGA) and A549 cell lines with IC_{50} values of 0.02 and 0.46 μ M, respectively (Chen *et al.*, 2019).

5-FU alkyl bromide was used as a precursor to the 5-FU podophyllotoxin hybrid (Fig 5). This compound showed high activity with IC_{50} values of 0.04 μ M against HL-60 and less than 0.01 μ M against A-549 (Guan *et al.*, 2016).

FU alcohol was used in the synthesis of 5-FU-Ubenimex hybrid (Fig 5). This hybrid displayed significant *in vitro* antiproliferation (IC_{50} = 16.52 μ M on PLC/PRF/5), proapoptosis, antimetastasis, antiangiogenesis, and CD_{13}^{+} cell elimination effects. Moreover, it exhibited further potent *in vivo* antimetastasis and lifespan extension effects when compared to the approved 5-FU prodrug capecitabine (Jiang *et al.*, 2018).

5-FU-(–)-parthenolide hybrid was obtained by coupling between 5-FU alkyne and (–)-parthenolide azide derivative (Fig 5). This hybrid displayed IC_{50} values higher than 20 on the two cell lines tested (Bel7402 and Bel-7402/5-FU) (Ding *et al.*, 2019).

Drug resistance of 5-FU-based compounds

Despite the good behavior of 5-FU hybrids and conjugates against diverse types of cancer, there are studies reporting drug resistance to these molecules. In the case of colorectal cancer and using a 5-FU-resistance cell from HTC-8 cells, a high expression of TCF4 and β -catenin indicated an upregulated Wnt pathway. Additionally, the suppression of checkpoint kinase 1 explained the resistance to 5-FU. Both findings led to conclude that the checkpoint kinase 1 pathway was suppressed by the Wnt pathway in 5-FU-resistant cells (He *et al.*, 2018). Kim *et al.* (2018) investigated the role of the AKT pathway on drug resistance to 5-FU in SNU-C5/5-FU cells, which is also 5-FU-resistant human colon cancer cells. They reported that the overactivation of the AKT pathway was responsible for resistance to those drugs. Since the findings suggested that the inhibition of this pathway may overcome the resistance to 5-FU, the authors proposed it as a target for cancer treatment (Kim *et al.*, 2018).

As reviewed by Marjaneh *et al.* (2019), miniRNAs have gained attention as strategies to treat and assess prognosis and reduce 5-FU resistance in colorectal cancer since those miniRNAs have an important role in sensitivity to anticancer drugs and even in tumor resistance induction. Thus, detecting, understanding, and targeting those mechanisms have been explored as a novel therapeutic approach to treat colorectal cancer (Marjaneh *et al.*, 2019). MiniRNAs strategies have been also applied to other cancer types, for example, pancreatic cancer. Wang *et al.* (2016a) reported upregulated miR-320a in 5-FU-resistant pancreatic cancer cells and that its overexpression contributed to the pathogenesis of this cancer. The authors also found that the restoration of PDCD4 expression could in part reduce the function of miR-320a in pancreatic cancer cells, which at the end (by targeting PDCD4) could be an alternative therapeutic (Wang *et al.*, 2016a). 5-FU has been combined with a natural compound such as andrographolide (a bioactive component of the medicinal plant *Andrographis paniculata*) as a potential adjunctive treatment for colorectal cancer. Andrographolide/5-FU cotreatment increased the apoptosis level of HCT116/5-FU cells with a high level of BAX. The authors found that interaction between andrographolide and BAX prevented BAX degradation, which led to enhancing

mitochondria-mediated apoptosis, leading to a reversed 5-FU resistance. On the contrary, BAX silence reduced the 5-FU effect (Wang *et al.*, 2016b).

Delivery systems and molecular simulations of drugs based on 5-FU

In connection with drug delivery, some nanoparticles have been designed to improve 5-FU loading capacity. In this sense, hollow mesoporous silica nanoparticles have been designed and functionalized using silanes, which led to the insertion of the amine of carboxyl, cyano, and methyl groups onto the nanoparticles. Since amine groups have comparable hydrophilicity but reverse charge to the 5-FU, the presence of this group increased the loading capacity of 5-FU by 28.89% (She *et al.*, 2015). Lollo *et al.* (2019) synthesized a lipophilic 5-FU derivative (by using lauric acid). The reaction product (named 5-FU-C12) was encapsulated into lipid nanocapsule and this led probably to increased activity of the 5-FU-C12. Higher cytotoxic effect of 5-FU-C12 (loaded into lipid nanocapsules) on different tumors cell lines [glioma (9L) and human colorectal (HTC-116) cancer cell line] was reported when it was compared with 5-FU-C12 alone or 5-FU (Lollo *et al.*, 2019). Safwat *et al.* (2016) used gold nanoparticles (GNPs) and two thiol-containing ligands, thioglycolic acid (TGA) and glutathione (GSH), to improve the efficacy of 5-FU. In that study, a 5-FU/ligand molar ratio of 1:1 and 2:1 for TGA-GNPs and GSH-GNPs, respectively, led to maximum 5-FU loading (Safwat *et al.*, 2016). 5-FU loading release was pH-dependent, and anticancer effect against colon cancer cells was better for 5-FU/GSH-GNPs when it is compared with free drug.

Molecular simulation approaches have been used to study 5-FU interactions with covalent organic frameworks (COFs) and metal-organic frameworks (MOFs), among others. Safdari *et al.* (2017) studied the interaction of 5-FU with graphene oxide nanosheet using density functional theory (DFT) and molecular dynamics (MD) simulation. MD simulation results showed that hydrogen bonds among different functional groups on graphene oxide and 5-FU molecules were promoted by increasing the temperature to 400 K (Safdari *et al.*, 2017). Hashemzadeh and Raissi (2018) used DFT and MD to study the adsorption behavior of 5-FU on the COF surface. The authors reported that, after the adsorption on the COF surface, 5-FU-COF is protected from degradation. Additionally, 5-FU showed high stability on the COF surface (Hashemzadeh and Raissi, 2018). Both experimental and MD studies on MOFs for 5-FU release have been also conducted and led to pH-triggered control (Wang *et al.*, 2017). All those studies have been focused on the design of 5-FU delivery vehicles for cancers.

CONCLUSION

A clear increase in studies related to 5-FU was observed during 2015–2020, with (i) *Biochemistry, Genetics, and Molecular Biology*; (ii) *Chemical Engineering*; and (iii) *Materials Science* as the main areas (excluding *chemistry*) of this topic. The studies focused mainly on drug delivery, synthesis of anticancer compounds and their activity, molecular simulation, treatment of cancer cells, and drug resistance. China, India, and the United States were the most productive countries on studies related to 5-FU and they also had the strongest collaboration network.

ACKNOWLEDGMENT

Funding: The work has been funded by University of Antioquia, MINCIENCIAS, MINEDUCACIÓN, MINCIT and ICETEX, through the Program Ecosistema Científico Cod. FP44842-211-2018 Project numbers, 58537.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors.

CONSENT TO PARTICIPATE

For this type of study, formal consent is not required.

AUTHORS' CONTRIBUTION

Conceptualization: WCG and HRM; methodology: HRM; formal analysis and investigation: WCG and HRM; writing and original draft preparation: HRM; writing and review and editing: WCG and HRM.

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How to cite this article:

Ramirez-Malule H, Cardona-G W. Bibliometric analysis of recent research on 5-Fluorouracil (2015–2020). *J Appl Pharm Sci*, 2022; 12(01):070–077.