



# Trends in inflammatory bowel disease treatment in the past two decades—a high-level text mining analysis of PubMed publications

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## Abstract

**Aim:** Many therapeutic options for inflammatory bowel disease (IBD) emerged during the last 2 decades, along with the rise in disease prevalence and incidence. We aimed at assessing the published literature on different treatment options in that period. Special attention was attributed to specific medication mechanisms and geographic diversity.

**Materials and Methods:** We have queried PubMed for all available IBD-related entries published during 2000–2020. The following data were extracted for each entry: PubMed unique article ID (PMID), title, publishing journal, abstract text, keywords (if any), and authors' affiliations. Two gastrointestinal specialists decided in consensus on a list of terms to classify entries. The terms belonged to five treatment groups: medical, surgical, dietary, microbiome manipulation, and complementary medicine. The medical and complementary medicine groups were further sub-classified. Annual trends of publications for the years 2000–2020 were plotted for different treatment types. The slopes of publication trends were calculated by fitting regression lines to the annual number of publications.

**Results:** Overall, 77,505 IBD entries were published between 2000 and 2020. Medical treatment showed the highest number of total publications 21,540/77,505 (27.8%), followed by surgical 7605/77,505 (9.8%), microbiome research 5260/77,505 (6.8%), dietary 4819/77,505 (6.2%), and complementary medicine treatment 762/77,505 (1.0%). Interestingly, since 2012 there is a steep rise in microbiome publications that outnumbered surgery in the last 2 years. Trend analysis of medical treatment showed that biologics had the steepest slope (57.5,  $p < 0.001$ ), followed by immunomodulators (4.9,  $p < 0.001$ ), small molecules (3.9,  $p < 0.001$ ), and 5-ASA (3.8,  $p < 0.001$ ).

**Conclusion:** According to our high-level publications trend analysis, the past 2 decades certainly deserve the reference as the “biologic era”, as publications regarding

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biological therapy outnumbered all other treatment options. Interestingly, though very popular among patients, complementary medicine was not studied with correlation to its' acceptance among patients.

#### KEYWORDS

complementary therapies, Crohn disease, drug therapy, inflammatory bowel disease, microbiome, nutrition, surgery, ulcerative colitis

## INTRODUCTION

Crohn's disease (CD) and Ulcerative colitis (UC) are both chronic inflammatory bowel diseases (IBD) that affect the gastrointestinal tract. While CD may affect the whole bowel from mouth to anus, UC mainly affects the large bowel. Both diseases may cause significant morbidity and diminished life quality.<sup>1-5</sup> Disease behavior is usually characterized by periods of exacerbations with active symptomatic disease and periods of remission<sup>6</sup>.

The main goal in IBD treatment is reaching clinical remission as early as possible and maintaining the remission after that. Emerging treatment goals include prevention of disease progression, complications, and permanent structural bowel damage. Achieving complete mucosal healing has been shown to correlate with long-term favorable prognosis, and therefore serves as a surrogate treatment target.<sup>7</sup>

IBD prevalence rises steadily in recent years, with an incidence that has been rising rapidly in Asia, Africa, and South America.<sup>8</sup> Thus, disease burden has a global impact.

Many therapeutic options emerged during the last 2 decades, along with the rise in disease prevalence and incidence. Medical treatment became diverse—with a growing number of different therapeutic options in various mechanisms. Furthermore, herbal treatment and nutritional treatment gained popularity, focusing on restriction diets and medical cannabis. Surgery usually remains a treatment for complications.<sup>9,10</sup>

Current computational power and machine learning development provoked the “text-mining.” technique. This method enables broad-scale data extraction.<sup>11</sup> Text-mining may be employed to characterize trends and examine dynamics in a research field.<sup>12-15</sup>

In the last 2 decades, a major progress was achieved in the field of IBD treatment. Since the introduction and approval of the first biologic treatment for IBD—Infliximab, which was approved by the FDA for CD treatment in August 1998 and for UC in September 2005,<sup>16</sup> many biologic treatments were added to the arsenal, and many more are still in pipeline. This therapeutic advancement influenced deeply treatment options, goals, and decisions in IBD, and actually revolutionized the entire therapeutic approach. We believe that the text mining technique can enlighten and clarify these trends, and point directly at treatment development and tendencies in the last decades and the upcoming years.

#### Key summary

- This work provides a high-level summarization of inflammatory bowel disease treatment related publications from the past 2 decades.
- Trend analysis demonstrates the sharp rise in biologic treatment in the past 2 decades, which overwhelmed other treatment types.
- Microbiome alteration treatment is also rising in the past few years.
- Though popular among patients, complementary medicine was not studied with correlation to its' acceptance among patients.

Therefore, in our current study, we aimed at assessing published literature on treatment options for IBD in the past 2 decades. Special attention was attributed to specific medication mechanisms and geographic diversity.

## MATERIALS AND METHODS

### Data set

The US National Center for Biotechnology Information provides public application programming interfaces (APIs) that allow programmatic access to the PubMed database.

We have used the publicly available PyMed Python package to query the PubMed API.

The following data were extracted for each entry: PubMed unique article ID (PMID), title, publishing journal, abstract text, keywords (if any), and authors' affiliations.

Data lock was performed on April 27, 2021.

### Inclusion criteria

The entire MEDLINE/PubMed database was used as the source for this article. We retrieved all available IBD-related entries. The search

was conducted in entries' titles, abstracts, and keywords using the terms "ulcerative colitis" OR "Crohn" OR "inflammatory bowel disease".

We have limited the entries to publications between 1 January 2000 to 31 December 2020.

### Data processing

The data processing and result visualization were written on Python (Ver. 3.6.5, 64 bits).

For text-mining, each title, study abstract, and authors' affiliations were lowercased.

List of open-access journals was obtained from the Scimago Journal & Country Rank site (<https://www.scimagojr.com/>). The list was merged to the PubMed data using International Standard Serial Numbers.

Two gastrointestinal specialists decided in consensus on a list of terms to classify entries (Table 1). The terms belonged to five treatment groups: medical, surgical, dietary, microbiome manipulation, and complementary medicine (CAM). The medical and CAM groups were further sub-classified. The medical group included biologics, immunomodulators, 5-aminosalicylic acid, and small molecules. Within the CAM group, herbal medicine included cannabis, curcumin, and other herbal medicine (herbal medicine without mention of curcumin and cannabis). Each entry was categorized by querying the title, abstract and keywords for terms belonging to the treatment groups and the sub-classifications.

Following data extraction, all authors' countries were retrieved from the affiliation data. Depending on the affiliations list, entries

could be attributed to more than one country. The total numbers of publications by country were evaluated for different treatment types. Only publications with a country affiliation were utilized in the country-related sub-analysis.

### Statistical analysis

All analyses were conducted with Python (Python software foundation, Version 3.6.5). Statistical significance was established at a two-sided  $p < .05$ . Descriptive statistics were reported using counts with percentages for categorical variables.

Annual trends of the number of journals that published IBD-related publications during 2000–2020 was plotted for overall journals and open-access journals.

Annual trends of publications for the years 2000–2020 were plotted for different treatment types and the medical and herbal medicine sub-classifications. The slopes of publication trends were calculated by fitting linear regression lines to the annual number of publications in the years 2000–2020 (with X being calendar year and Y being annual publications count).  $p$ -values and standard errors (SEs) were calculated for the linear regression lines.

### RESULTS

Out of 31,850,051 PubMed records available, 112,196 (0.4%) were IBD related (Figure 1). 77,505/112,196 (69.1%) of the entries were published between 2000 and 2020. For geographical analyses, 72,067/77,505 (93.0%) entries had a country affiliation. The number of

**TABLE 1** List of terms used to classify entries into five treatment groups: medical, surgical, dietary, microbiome altering, and CAM

Medical	tnf, tumor necrosis factor, anti integrin, anti il-12, anti-il-12, anti il 12, anti il-23, anti-il-23, anti il 23, anti-interleukin 12, anti-interleukin-12, anti-interleukin 23, anti-interleukin-23, vedolizumab, infliximab, adalimumab, ustekinumab, risankizumab, natalizumab, etrolizumab, briakinumab, mirikizumab, golimumab, certolizumab pegol, biologic therapy
	Azathioprine, purinethol, 6 mp, 6-mp, mercaptopurine, thioguanine, methotrexate, tacrolimus, cyclosporine, thiopurine
	5-asa, 5 asa, aminosaliclyic, amino-saliclyic, salazopyrin, sulfasalazine, mesalamine
	s1p1, jak inhibitor, krp-203, fingolimod, ozanimod, etrasimod, amiselimod, tofacitinib, filgotinib, upadacitinib, peficitinib
Surgery	Surgery, surgical treatment, surgical therapy
Dietary	Diet, nutrition
Microbiome	Probiotic, fecal microbiota transplant, microbiome, microbiota
CAM	Curcumin
	Cannabis, marijuana, tetrahydrocannabinol, cannabinol
	Herbal, herbs
	Complementary medicine, alternative medicine, indigo

Note: The medical and CAM groups were further sub-classified. The medical group included biologics, immunomodulators, 5-aminosalicylic acid, and small molecules. Within the CAM group, herbal medicine included cannabis, curcumin, and other herbal medicine.

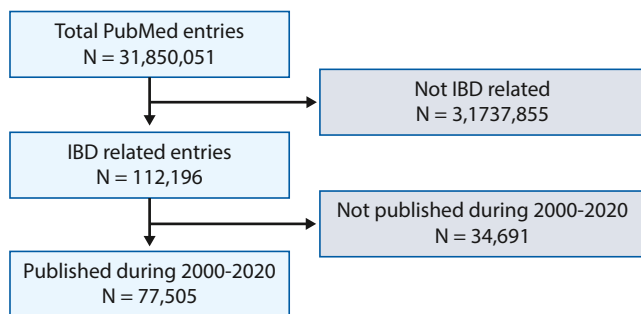
Abbreviation: CAM, complementary medicine.

journals with IBD-related publications during 2000–2020, as well as the growth of open-access journals is presented in Figure 2. Overall, the number of journals grew from 487 in 2000 to 1533 in 2020. The number of open-access journals grew from 34 in 2000 to 366 in 2020.

## Publication trends

Trends of publications by treatment types are presented in Figure 3. Medical treatment showed the highest number of total publications 21,540/77,505 (27.8%), followed by surgical 7605/77,505 (9.8%), microbiome research 5260/77,505 (6.8%), dietary (6.2%), and CAM treatment 762/77,505 (1.0%).

The slope of the trend of medical treatment was also the steepest ( $69.8$ ,  $p < 0.001$ , SE 2.4), followed by microbiome manipulation ( $34.8 \pm 3.0$ ,  $p < 0.001$ ), surgical ( $23.3 \pm 1.0$ ,  $p < 0.001$ ), dietary ( $17.2 \pm 1.4$ ,  $p < 0.001$ ), and CAM treatment ( $4.5 \pm 0.5$ ,  $p < 0.001$ ).



**FIGURE 1** Study inclusion chart. IBD, inflammatory bowel disease

Sub-analysis of the medical treatment group (Figure 4) showed that biologics had the highest number of total publications, 13,874/21,540 (64.4%), followed by immunomodulators 3744/21,540 (17.4%), 5-ASA 2356/21,540 (10.9%), and small molecules 370/21,540 (1.7%).

Trend analysis showed that biologics had the steepest slope ( $57.5 \pm 1.9$ ,  $p < 0.001$ ), followed by immunomodulators ( $4.9 \pm 0.9$ ,  $p < 0.001$ ), small molecules ( $3.9 \pm 0.9$ ,  $p < 0.001$ ), and 5-ASA ( $3.8 \pm 0.3$ ,  $p < 0.001$ ).

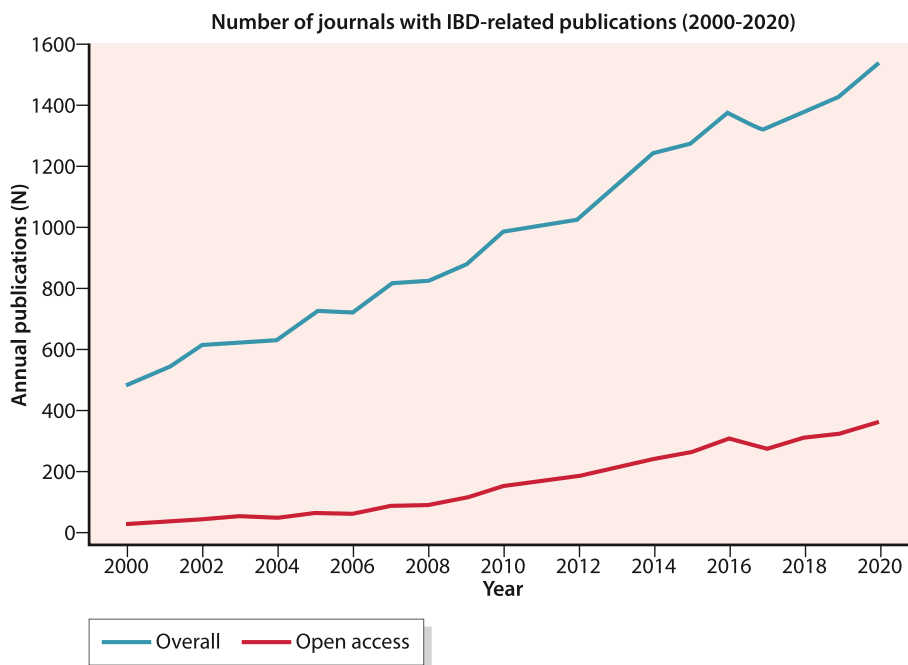
For herbal treatment sub-analysis (Figure 5), other herbal compounds, which include the herbal compounds: indigo, ginseng, astragalus, bupleurum, Lycium barbarum, aloe-vera, aloe-vera gel, andrographis paniculata, artemisia absinthium, barley foodstuff, boswellia serrata, evening primrose oil, Myrrhinil intest<sup>®</sup>, plantago ovata, silymarin, sophora, tormentil (partial list); showed the highest number of publications, with 276/762 (36.2%) of CAM treatment publications, followed by curcumin 198/762 (25.9%) and cannabis 128/762 (16.8%).

Trend analysis showed that other herbal compounds had the steepest slope ( $1.6 \pm 0.3$ ,  $p < 0.001$ ), followed by curcumin ( $1.2 \pm 0.1$ ,  $p < 0.001$ ) and cannabis ( $1.0 \pm 1.6$ ,  $p < 0.001$ ).

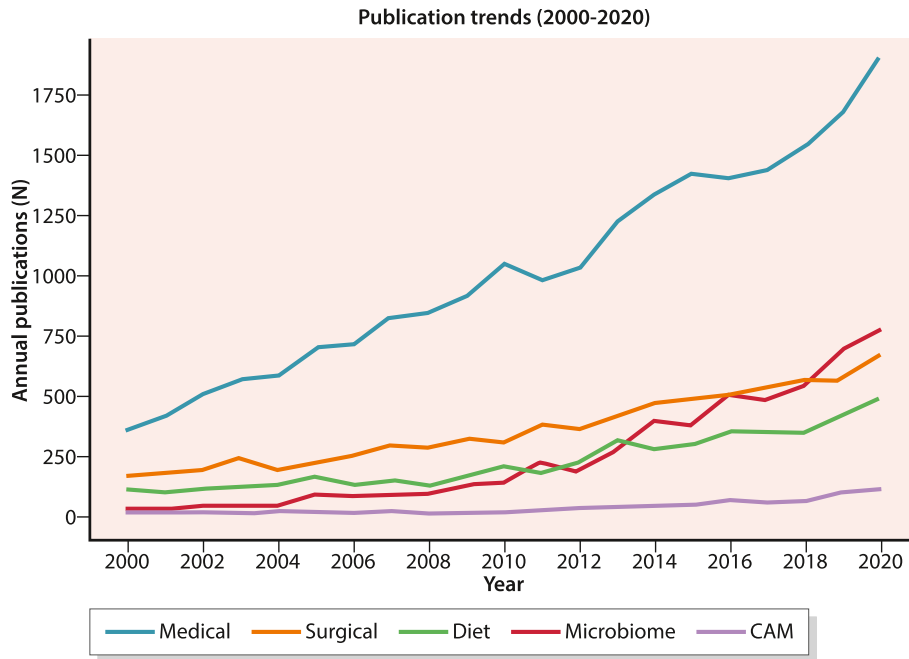
## Geographical analysis

The United States showed the highest proportion of overall publications 18,585/77,505 (24.0%), followed by the United Kingdom 6228/77,505 (8.0%), China 5278/77,505 (6.8%), Japan 4778/77,505 (6.2%), and Italy 4722/77,505 (6.1%).

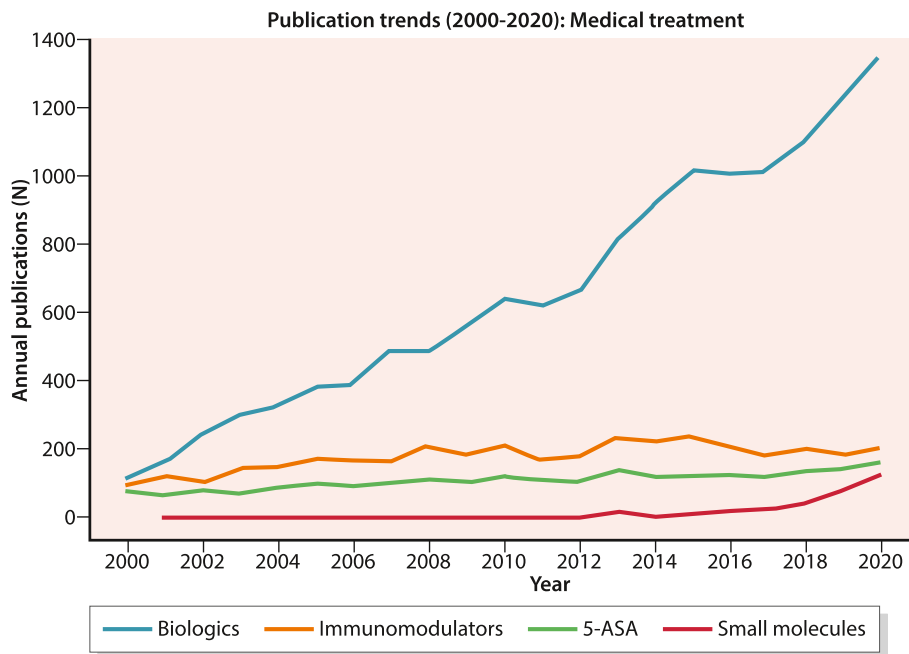
Tables S1–S5 present the geographical distribution of different treatment types. For all treatments other than CAM treatment, the United States had the highest number of publications, while China had the highest CAM treatment publications.



**FIGURE 2** Number of overall and open-access journals with inflammatory bowel disease (IBD)-related publications (2000–2020)



**FIGURE 3** Trends of inflammatory bowel disease publications during 2000–2020, grouped by treatment type: medical, surgical, dietary, microbiome, and complementary medicine (CAM)



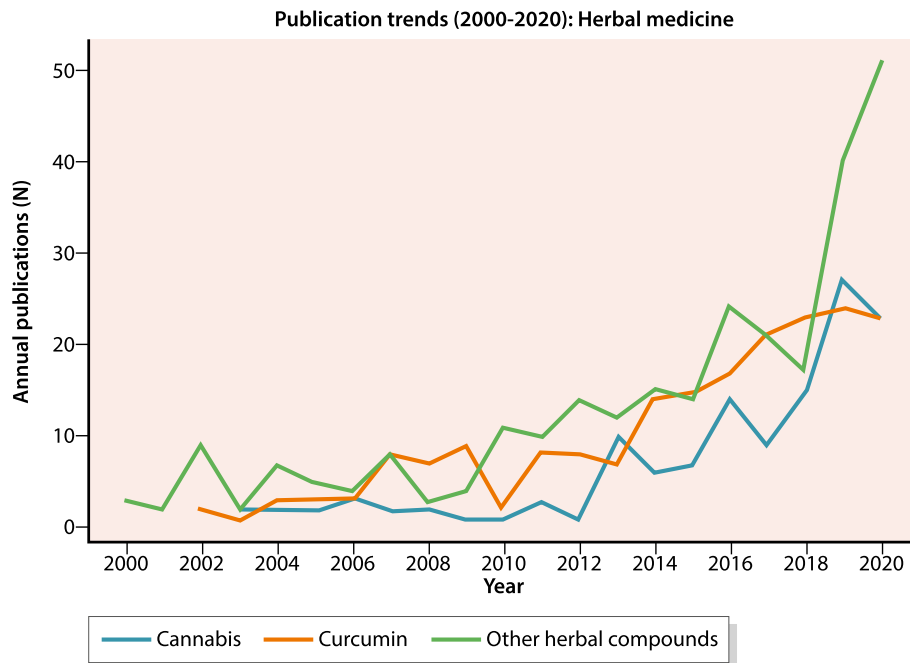
**FIGURE 4** Trends of inflammatory bowel disease medical treatment publications during 2000–2020, grouped into: biologics, immunomodulators, aminosalyclic acid (5-ASA), and small molecules

## DISCUSSION

In the past 2 decades, intensive progress was achieved in the field of IBD treatment. Since the introduction of the first biologic treatment for IBD at the end of the last millennium,<sup>17</sup> other biologics and non-biologic medications with different mechanisms of action were added as therapeutic options, and many more are still

in pipeline.<sup>9</sup> Furthermore, different treatment strategies emerged, focusing on specific restriction diets and herbal medicine.<sup>10,18</sup> Surgical treatment always remains a therapeutic option, though it is usually reserved for complications, with declining rates in the era of biologic therapy.<sup>19</sup>

In our current study, we applied a text mining approach to observe and analyze IBD treatment publications in the past



**FIGURE 5** Trends of inflammatory bowel disease complementary medicine publications during 2000–2020, grouped into: cannabis, curcumin, and other herbal compounds

2 decades, aiming to achieve some comprehensions about treatment trends and development over the years.

Approximately 70% of all IBD-related PubMed publications were issued in the last 2 decades, with an increasing number each year. Medical treatment was by far the most studied treatment, comprising 28% of all treatment publications. Medical treatment was followed by surgical (10%), microbiome manipulation (7%), nutritional (6%), and CAM (1%) therapy. Medical therapy also showed the steepest slope (70,  $p < 0.001$ ), which indicates the most rapid growth in publications rate. These numbers reflect the accelerated rate of new medications development in the IBD field during the last years, probably due to the unmet need arising from the increase in disease prevalence and incidence and the rising global disease burden.<sup>8</sup> Slopes were lower in other treatment strategies, showing a similar slower increase in publications rate over the years. Despite the growing interest in more conservative treatment options, our data shows that between 2000 and 2018 surgical treatment was still the second therapy studied. However, as nutritional therapy and microbiome manipulation therapy strategies are gaining popularity along with a decrease in surgery rates,<sup>19</sup> we notice a change in the trend in the last few years, with more publications focusing on microbiome manipulation than surgical treatment between 2018 and 2020. We suppose this trend will strengthen in the upcoming years.

Sub-analysis of medical treatment showed that almost 65% of publications involved treatment with biologic therapy. Biologics also had the steepest slope, 57.5, which shows the highest increase in publications rate other the years—by far higher than all other treatment options. This data reflects the importance of biologic therapy in the treatment of IBD in the last decades. Essentially,

biologic therapy revolutionized IBD treatment and became the cornerstone of advanced IBD treatment worldwide.<sup>9</sup> Indeed, the last 2 decades are referred now as the biological era.<sup>19</sup> The smallest number of publications was noted for the small molecules—less than 2% of publications to date, but these numbers are about to change as more small molecules will be approved for use in IBD treatment. Currently, only one JAK inhibitor (tofacitinib) was approved and is in clinical use, but there are more JAK inhibitors in the pipeline, and other mechanisms of small molecules as S1P1 inhibitors are about to receive FDA approval and integrate into therapeutic use.<sup>20,21</sup>

In the last years, the popularity of integrative medicine is rising, and according to literature 30%–50% of IBD patients use CAM along their disease course.<sup>22–26</sup> However, clinical data assessing the efficacy and safety of these medications is scarce. Therefore, we chose to perform a sub-analysis of herbal medicine published papers. Among CAM therapies, specific attention is attributed to medical cannabis therapy in IBD and Curcumin treatment in the last years. Both herbal treatments have anti-inflammatory effects.<sup>27–35</sup> Cannabis was also shown to increase appetite<sup>36,37</sup> and serve as a potent analgesic<sup>38</sup>—effects that may further induce symptomatic relief in IBD patients.

Consequently, we separately evaluated cannabis and curcumin and gathered all other herbal compounds in a different group. As a group, and with contradiction to its' high popularity among IBD patients, CAM had the lowest publications numbers—a total of 762 publications over 20 years. A quarter of them addressed curcumin, 17%—cannabis, and the rest were different diverse herbal compounds. These low numbers probably reflect the low interest of the pharma in these compounds. However, as medical cannabis will be

pharmaceutically manufactured, we expect more clinical data assessing its effect in various diseases, including IBD.

Geographic analysis was performed for publication origin for all treatment groups. Not surprisingly, almost a quarter of publications were originated from the United States, and most other publications originated in Europe. This reflects the role of the United States and Europe in clinical research and the high prevalence of IBD in these countries. However, there is a trend of rise in publications from Japan and China.

Interestingly, most CAM publications originated from China. This probably reflects the importance of herbal medicine in this country. Furthermore, in the microbiome manipulation treatments, China publications are only second to the United States. This is also a part of the high recognition traditional medicine is gained in this country.

Our study has a few limitations. This analysis only provides a high-level look at the field. The sheer number of publications prohibits a manual analysis of the records. A list of terms was determined based on current data in the literature and consensus between two senior IBD specialist physicians. However, different terms might have achieved different results. The data was extracted from MEDLINE/Pubmed. Other options as Google Scholar were not included and might have reached different results. The study was limited to PubMed data; thus, we did not have access to the full article texts. A search in full texts data would be broader. Only a search for terms in the articles was conducted, which is not robust and might miss semantical characteristics of the texts.

## CONCLUSION

In our current study, we observed publication trends in IBD treatment over the last 2 decades. According to our findings, these decades certainly deserve the reference as the “biologic era,” as publications regarding biological therapy outnumbered all other treatment options. Interestingly, though very popular among patients, CAM was not studied with correlation to its' acceptance among patients. Most publications originate from the United States and Europe. However, most publications assessing CAM originate from China. A text-mining analysis of IBD treatment contributes to the understanding of treatment options and development trends worldwide.

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## CONFLICT OF INTEREST

The Authors declare that there is no conflict of interest.

## AUTHOR CONTRIBUTIONS

Eyal Klang and Adi Lahat designed and performed the research and wrote the paper; Yiftach Barash, Shelly Soffer and Eyal Shachar contributed to the analysis and revised the paper critically. All authors approved the version to be published.

## DATA AVAILABILITY STATEMENT

Data derived from public domain resources.

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#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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