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RESEARCH LANDSCAPE OF REPURPOSED MEDICATIONS IN CANCER TREATMENT: A MULTI-DATABASE BIBLIOMETRIC ANALYSIS OF ELEVEN OFF-PATENT THERAPEUTICS

PANORAMA DE PESQUISA DE MEDICAMENTOS REPOSICIONADOS NO TRATAMENTO DE CÂNCER: UMA ANÁLISE BIBLIOMÉTRICA MULTI-BASE DE DADOS DE ONZE TERAPÊUTICOS FORA DE PATENTE

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ABSTRACT

Background: Drug repurposing offers potential advantages for cancer therapy development, particularly when utilizing medications with established safety profiles and expired patents. While individual repurposed medications have been investigated for oncological applications, comprehensive comparative analyses of research distribution patterns across multiple therapeutic candidates appear limited in the literature. Understanding these patterns may provide insights into research priorities and potential knowledge gaps. **Aim**: This exploratory study was designed to quantify and compare the volume of scientific literature examining the anticancer potential of eleven selected off-patent medications across different pharmacological classes. **Methods**: Bibliometric searches were conducted across five databases (Google Scholar, BVS, PubMed, NIH, and Science.gov) using standardized search terms combining each medication name with "cancer" and "cancer treatment." The selected medications included ivermectin, fenbendazole, mebendazole, albendazole, metformin, propranolol, disulfiram, valproic acid, thalidomide, dexamethasone, and hydroxychloroquine. Basic statistical analyses were performed to examine the distribution patterns and correlations within the database. **Results**: The search yielded 3,226,066 total publications with considerable variation in distribution patterns. Dexamethasone accounted for the largest proportion (1,538,058 publications, 47.68%), followed by metformin (697,172 publications, 21.61%). Some medications with smaller overall publication volumes demonstrated higher proportions of treatment-specific research, such as fenbendazole (87.82%), disulfiram with copper (86.54%), and hydroxychloroquine with zinc (75.21%). The Herfindahl Index indicated a high concentration of research attention (0.2870). **Discussion**: The findings suggest substantial variation in research attention across the selected medications. While some medications dominate the literature, others with focused treatment-specific research may warrant further investigation. The inverse relationship observed between total publication volume and treatment specificity suggests that research patterns in this field may be more complex than absolute publication counts indicate. **Conclusions**: This preliminary bibliometric assessment reveals an uneven distribution of research attention among repurposed medications being investigated for cancer applications. These patterns may inform future research prioritization, though further qualitative analysis would be valuable to assess the clinical significance of these quantitative observations.

Keywords: *Drug repositioning, off-patent pharmaceuticals, oncology research patterns, pharmacological classes, research concentration analysis.*

RESUMO

Introdução: O reposicionamento de medicamentos oferece vantagens potenciais para o desenvolvimento de terapias contra o câncer, particularmente ao utilizar medicamentos com perfis de segurança estabelecidos e patentes expiradas. Embora medicamentos reposicionados individuais tenham sido investigados para aplicações oncológicas, análises comparativas abrangentes dos padrões de distribuição de pesquisa entre múltiplos candidatos terapêuticos parecem limitadas na literatura. Compreender esses padrões pode fornecer insights sobre prioridades de pesquisa e potenciais lacunas de conhecimento. **Objetivo:** Este estudo exploratório foi

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desenvolvido para quantificar e comparar o volume da literatura científica que examina o potencial anticancerígeno de onze medicamentos selecionados fora de patente, pertencentes a diferentes classes farmacológicas. **Métodos:** Pesquisas bibliométricas foram conduzidas em cinco bases de dados (Google Scholar, BVS, PubMed, NIH e Science.gov) utilizando termos de busca padronizados combinando cada nome de medicamento com "câncer" e "tratamento de câncer". Os medicamentos selecionados incluíram ivermectina, fenbendazol, mebendazol, albendazol, metformina, propranolol, dissulfiram, ácido valproico, talidomida, dexametasona e hidroxicloroquina. Análises estatísticas básicas foram realizadas para examinar os padrões de distribuição e correlações dentro da base de dados. **Resultados:** A busca resultou em 3.226.066 publicações totais com variação considerável nos padrões de distribuição. A dexametasona representou a maior proporção (1.538.058 publicações, 47,68%), seguida pela metformina (697.172 publicações, 21,61%). Alguns medicamentos com volumes menores de publicação total demonstraram proporções mais altas de pesquisa específica para tratamento, como fenbendazol (87,82%), dissulfiram com cobre (86,54%) e hidroxicloroquina com zinco (75,21%). O Índice de Herfindahl indicou uma alta concentração de atenção de pesquisa (0,2870). **Discussão:** Os achados sugerem variação substancial na atenção de pesquisa entre os medicamentos selecionados. Embora alguns medicamentos dominem a literatura, outros com pesquisa específica focada em tratamento podem merecer investigação adicional. A relação inversa observada entre o volume total de publicações e a especificidade do tratamento sugere que os padrões de pesquisa neste campo podem ser mais complexos do que os números absolutos de publicações indicam. **Conclusões:** Esta avaliação bibliométrica preliminar revela uma distribuição desigual da atenção de pesquisa entre medicamentos reposicionados sendo investigados para aplicações em câncer. Esses padrões podem informar futuras priorizações de pesquisa, embora análises qualitativas adicionais sejam valiosas para avaliar a significância clínica dessas observações quantitativas.

Palavras-chave: *Reposicionamento de medicamentos, farmacêuticos fora de patente, padrões de pesquisa oncológica, classes farmacológicas, análise de concentração de pesquisa.*

1. INTRODUCTION

This study presents a quantitative bibliometric analysis of research volume in the scientific literature regarding the potential use of 11 medications not protected by patents in the treatment of different types of cancer. The medications analyzed in this bibliometric study are: Ivermectin, Fenbendazole, Mebendazole, Albendazole, Metformin, Propranolol, Disulfiram, Valproic Acid, Thalidomide, Dexamethasone and Hydroxychloroquine.

The primary objective of this research was to quantify and compare the volume of scientific literature examining the anticancer potential of these drugs, providing a numerical perspective on research distribution patterns and the allocation of scientific attention across different pharmacological classes.

Result quantification was performed through bibliometric searches across five databases, including:

- Google Scholar: https://scholar.google.com/
- BVS (Virtual Health Library): https://bvsalud.org/
- PubMed: https://pubmed.ncbi.nlm.nih.gov/
- NIH (National Institutes of Health): https://www.nih.gov/
- Science.gov: https://www.science.gov/

The counting methodology recorded total search results without categorizing studies by type (*in vitro*, *in vivo*, clinical trials), by the proposed mechanism of action, or by type of cancer investigated. This quantitative bibliometric approach enabled the identification of patterns and trends in research attention distribution, highlighting which medications present the greatest volume of research interest for their repositioning in cancer treatment.

This bibliometric analysis aims to provide an initial overview of research distribution patterns for these off-patent drugs, thereby informing future research priorities and potentially guiding the investigation of accessible therapeutic alternatives for cancer treatment.

1.1. Literature Review

1.1.1. IVERMECTIN

Ivermectin was originally developed as a broad-spectrum antiparasitic medication. It was discovered in the late 1970s by researchers Satoshi Ōmura and William Campbell, who subsequently received the Nobel Prize in

Physiology or Medicine in 2015 for this discovery. As documented by Crump and Ōmura (2011), ivermectin is a derivative of avermectin, a substance isolated from a Streptomyces bacterium found in a soil sample collected near a golf course in Japan. This discovery revolutionized the treatment of parasitic infections, being particularly effective against onchocerciasis (river blindness) and lymphatic filariasis (Crump & Ōmura, 2011, p. 13-28).

It was introduced to the veterinary market in 1981 under the trade name Ivomec, initially used to control parasitic infections in livestock and companion animals. In 1987, it was approved for human use for the first time when Merck initiated the Mectizan® Donation Program for treating onchocerciasis in endemic countries. According to Crump and Ōmura (2011), "the use of ivermectin in humans began in 1987 when Merck donated the medication to treat onchocerciasis in developing countries" (p. 17). FDA approval for human use was granted in 1996 for the treatment of strongyloidiasis and onchocerciasis (Campbell et al., 2012, pp. 853-865).

The side effects of ivermectin are generally mild and transient when used at recommended doses. According to Kaur *et al*. (2021), the most common adverse effects include "transient skin reactions, pruritus, fever, nausea, diarrhea, dizziness, arthralgia, and myalgia" (p. 1342). In patients with high parasite loads, the Mazzotti reaction may occur, characterized by fever, headache, pruritus, lymphadenitis, and edema. At elevated doses, more serious neurotoxic effects may occur, though these are rare. Santin *et al*. (2021) observe that "ivermectin has an excellent safety profile, with more than 2.5 billion doses distributed globally over nearly four decades" (Santin *et al*., 2021).

The original patent for ivermectin, granted to Merck & Co., expired in the late 1990”s (Crump & Ōmura, 2011, p. 25). The exact expiration date varies by source (1996-1998) due to patent extensions and different jurisdictions. The USPTO documents show the original patent was scheduled to expire in 1997 but was extended multiple times (U.S. Patent and Trademark Office, 1998). Since then, various generic formulations have become available in the global market, resulting in greater accessibility and lower medication costs. Currently, ivermectin is available as a generic medication and is widely used in public health programs across various regions worldwide. Taylor and Greene (1989), in their pioneering study on ivermectin use for treating human onchocerciasis, already highlighted this medication's potential for public health programs due to its efficacy and safety—characteristics that subsequently enabled its widespread use in resource-limited regions following the expiration of its patent.

Beyond its traditional antiparasitic applications, ivermectin has been investigated for various other conditions. Tang *et al*. (2021) document that "ivermectin possesses powerful antitumor effects, including inhibition of proliferation, metastasis, and angiogenic activity in a variety of cancer cells." Recent studies have also investigated its potential as an antiviral agent against various viruses, including dengue, influenza, and SARS-CoV-2. Caly *et al*. (2020) demonstrated *in vitro antiviral activity against SARS-CoV-2; however,* subsequent randomized clinical studies have not confirmed significant efficacy in COVID-19 patients (Popp *et al*., 2021). In dermatology, it is used to treat scabies, rosacea, and pediculosis (Kaur *et al*., 2021).

1.1.2. FENBENDAZOLE

Fenbendazole, developed in the 1970s, represents a milestone in the history of broad-spectrum veterinary anthelmintics. Belonging to the benzimidazole family, this molecule is part of a group that revolutionized the treatment of parasitic infections in animals (McKellar & Scott, 1990). Fenbendazole demonstrates efficacy against a wide range of nematodes (roundworms) and cestodes (tapeworms) in various animal species (McKellar & Scott, 1990). Its mechanism of action involves binding to β-tubulin, inhibiting microtubule polymerization in parasites, and blocking glucose absorption, leading to parasite death through energy depletion (Dogra *et al*., 2018). Pharmacokinetic studies in sheep have demonstrated properties that contribute to its therapeutic profile (Marriner & Bogan, 1981). The selectivity of fenbendazole for parasites over host cells contributes to its excellent safety profile, establishing it as a crucial medication for controlling gastrointestinal parasitic infections (McKellar & Scott, 1990).

Fenbendazole was introduced to the veterinary market in 1974 by the pharmaceutical company Hoechst under the trade name Panacur. Marriner and Bogan (1981) noted that fenbendazole was approved for veterinary use in the early 1970s and quickly became a reference anthelmintic for various animal species. Since its introduction, the medication has been widely used

to treat parasitic infections in domestic and production animals (McKellar & Scott, 1990).

Fenbendazole is generally considered safe when used at recommended doses. According to Booze and Oehme (1983), "*fenbendazole demonstrates low acute and chronic toxicity, with a wide safety margin at therapeutic doses*." Adverse effects are rare but may include mild gastrointestinal discomfort, such as decreased appetite and diarrhea. At very high doses, cases of reversible pancytopenia have been reported. As documented by Villar *et al*. (2007), "*in toxicity studies in rats, extremely high doses (1000 mg/kg) for prolonged periods were necessary to induce significant adverse effects*."

The original fenbendazole patent expired decades ago. Patent database records indicate that the original fenbendazole patent expired, allowing generic versions to be produced by various manufacturers. Currently, the medication is produced as a generic by several companies worldwide, available for veterinary use under different trade names and formulations, contributing to its widespread availability and accessibility in the global veterinary products market.

Although fenbendazole is primarily a veterinary medication used to treat parasitic infections, recent studies have investigated its potential anticancer properties. Nguyen *et al*. (2024) documented that "fenbendazole demonstrated anticancer activity against various tumor cell lines, including colorectal cancer, lung cancer, and cells resistant to conventional chemotherapy." Park *et al*. (2022) demonstrated that "fenbendazole was more effective than albendazole against 5-fluorouracil-resistant colorectal cancer cells, inhibiting cell proliferation in a time- and dose-dependent manner." Despite these promising *in vitro* and animal model results, fenbendazole is not approved for human use, and controlled clinical studies are needed to evaluate its safety and efficacy in treating cancer in humans.

1.1.3. MEBENDAZOLE

Mebendazole was originally developed as a broad-spectrum anthelmintic for human use by Janssen Pharmaceutica in Belgium. According to Dayan (2003), mebendazole is a "synthetic benzimidazole developed specifically for treating intestinal nematode infections in humans." It was designed to treat infections caused by Ascaris lumbricoides (ascariasis), Enterobius vermicularis (enterobiasis), Trichuris trichiura (trichuriasis), Ancylostoma duodenale and Necator americanus (hookworm disease), common intestinal parasites in humans (Pawluk *et al*., 2015).

Mebendazole was introduced to the market in 1971 by Janssen Pharmaceutica. According to Braithwaite *et al*. (1982), "*mebendazole was approved for human use in 1971 and introduced to the market under the trade name Vermox*." The medication was approved by the U.S. FDA in 1974 for treating helminthic infections in humans. It quickly became one of the most widely used anthelmintics worldwide, being included in the World Health Organization's List of Essential Medicines (Meco *et al*., 2023).

The side effects of mebendazole are generally mild and transient when used at recommended doses for treating parasitoses. According to Dayan (2003), "the most common adverse effects include abdominal pain, headache, nausea, diarrhea, and occasionally dizziness." In rare cases, especially with prolonged treatments or high doses, transient elevation of hepatic enzymes may occur. As documented by Palmeirim *et al*. (2018), "mebendazole has a good safety profile when administered as a single dose (500 mg), with few reported adverse effects." At very high doses used in clinical trials for cancer treatment, more significant adverse effects have been reported, including myelosuppression.

According to Pawluk *et al*. (2015), "*the mebendazole patent expired in the early 1990s, allowing the production of generic formulations by various manufacturers*." Currently, the medication is produced as a generic by several pharmaceutical companies worldwide, and it is available in various countries as a low-cost treatment for helminthic infections. However, new formulations and specific polymorphs of mebendazole may be protected by more recent patents, such as polymorph C of mebendazole, which has been the subject of new patents for oncological use (Bai *et al*., 2015). Additionally, novel pharmaceutical combinations involving mebendazole continue to be developed and patented, such as synergistic compositions combining mebendazole with nitazoxanide for enhanced antiparasitic spectrum (Fiore, 2015).

Beyond its traditional use as an anthelmintic, recent research has explored mebendazole's potential as an antineoplastic agent. Pantziarka *et al*. (2014) documented that "preclinical studies demonstrated anticancer

activity of mebendazole against various tumor types, including glioblastoma, melanoma, colorectal cancer, and lung cancer." According to Bai *et al*. (2011), "mebendazole showed a significant survival benefit in preclinical models of glioblastoma multiforme." Meco *et al*. (2023) highlight that "mebendazole may be a promising candidate for treating brain tumors due to its ability to cross the blood-brain barrier and its well-established safety profile." Several clinical trials are currently underway to investigate its use in oncology, particularly for brain tumors that are resistant to conventional treatments.

1.1.4. ALBENDAZOL

Albendazole was originally developed as a broad-spectrum anthelmintic for treating intestinal parasitic infections. Its initial indication was for treating infections caused by intestinal nematodes, including ascariasis, hookworm disease, trichuriasis, and enterobiasis, due to its ability to inhibit tubulin polymerization, interfering with glucose uptake by parasites (Horton, 2000). According to Dayan (2003), the mechanism of action of albendazole involves selective binding to parasitic β-tubulin, resulting in cytoskeleton disintegration and ultimately leading to parasite death.

The drug was developed by SmithKline & French Laboratories (now GlaxoSmithKline) and received its first regulatory approval in 1977, being introduced to the market in 1978, initially for veterinary use (Horton, 2000; Lacey, 1990). In 1982, it was approved for human use and rapidly became an essential medication for treating various parasitic infections worldwide (Horton, 2009; Dayan, 2003). In 1983, it was included in the World Health Organization's List of Essential Medicines, recognizing its importance in global public health (Keiser & Utzinger, 2008; Gyapong *et al*., 2005).

Albendazole's side effects are generally mild and transient. According to Horton (2000), the incidence of adverse effects reported in the literature is very low, with gastrointestinal disturbances being most frequent, occurring in slightly more than 1% of cases. Documented adverse effects include abdominal pain, nausea and vomiting, headache (particularly in patients with neurocysticercosis), reversible alopecia in prolonged treatments, and alterations in hepatic enzymes.

In prolonged treatments or higher doses, such as in cases of echinococcosis and neurocysticercosis, Dayan (2003) describes that more serious effects may occur, including hematological changes such as leukopenia and, rarely, pancytopenia. For this reason, regular laboratory monitoring is recommended for patients undergoing long-term treatment.

Keiser and Utzinger (2008) note that, despite these adverse effects, albendazole maintains an excellent safety profile when used as a single dose for treating intestinal helminthiases, justifying its widespread use in mass drug administration programs in endemic areas, where the benefits significantly outweigh the potential risks.

Albendazole no longer has valid patent protection. According to 't Hoen *et al*. (2018), many essential medicines, including albendazole, are no longer protected by active patents, allowing for the production of generic versions. Wirtz *et al*. (2017) note that albendazole is included in the WHO's Essential Medicines List and is available as a generic in various countries, thereby contributing to expanded access, particularly in regions endemic for intestinal parasitic diseases. Pedrique *et al*. (2013) note that despite advances in antiparasitic availability, such as albendazole, access challenges persist in some low-income regions where helminthiasis prevalence is highest.

Beyond its original indications for intestinal parasitic infections, albendazole has been used for various other conditions. According to Pawluk *et al*. (2021), the medication demonstrated efficacy in treating neurocysticercosis (a central nervous system infection caused by the larval form of Taenia solium), hydatidosis (also known as echinococcosis, caused by Echinococcus granulosus), cutaneous larva migrans, microsporidial infections in immunocompromised patients, and giardiasis resistant to other treatments.

Recently, studies have investigated the antineoplastic potential of albendazole. Lim *et al*. (2022) demonstrated that the medication exhibits anti-tumor properties in vitro and in vivo by interfering with tubulin polymerization in cancer cells, thereby inhibiting angiogenesis and inducing apoptosis.

1.1.5. METFORMIN

Metformin was originally developed for the

treatment of type 2 diabetes mellitus and is classified as an oral antihyperglycemic agent, specifically a biguanide. Bailey and Day (2004) highlight its historical origins derived from the plant Galega officinalis, while Rena *et al*. (2017) clarify that metformin acts primarily by reducing hepatic glucose production, decreasing intestinal glucose absorption, and increasing insulin sensitivity through improved peripheral glucose uptake and utilization. Viollet *et al*. (2012) detail the underlying molecular mechanisms, explaining that activation of AMP-activated protein kinase (AMPK) is central to many of metformin's metabolic effects. According to Inzucchi *et al*. (2015), its first formal indication was for glycemic control in non-insulin-dependent diabetic patients, especially those with overweight or obesity, and it was recommended as a first-line treatment in major international guidelines for type 2 diabetes management.

Although the medicinal use of plants containing biguanides (such as Galega officinalis) dates to the Middle Ages, metformin as an isolated substance had an interesting trajectory. According to Bailey (2017), metformin was first synthesized in 1922 by scientists Emil Werner and James Bell, as part of research on guanidines. The same author documents that the medication entered the pharmaceutical market only in 1957, initially in France under the trade name Glucophage, after Jean Sterne recognized its therapeutic potential for diabetes. White (2014) explains that in the United States, FDA approval occurred much later, in 1994, due to concerns related to lactic acidosis observed with another biguanide (phenformin) that had been withdrawn from the market in 1977. Rena *et al*. (2017) emphasize that, despite its long history, the complete molecular mechanisms of metformin continue to be elucidated, which has not prevented it from becoming the most prescribed oral antidiabetic medication worldwide, with more than 120 million users.

Metformin's side effects are well-documented in the medical literature. Sanchez-Rangel and Inzucchi (2017) highlight in their review of the clinical use of metformin in type 2 diabetes that the most common adverse effects are gastrointestinal in nature, including diarrhea, nausea, vomiting, and abdominal discomfort. Sanchez-Rangel and Inzucchi also discuss other relevant effects, such as taste alteration (dysgeusia or metallic taste) and vitamin B12 deficiency associated with prolonged use.

Regarding safety, these same researchers emphasize that lactic acidosis, although the most serious adverse effect, is quite rare and generally occurs in patients with predisposing conditions such as renal, hepatic, or cardiac insufficiency. Sanchez-Rangel and Inzucchi recommend regular monitoring of these at-risk patients and emphasize that for most individuals, metformin is a safe medication when appropriately prescribed.

Metformin no longer has valid patent protection for the original molecule. According to 't Hoen *et al*. (2018), many essential medicines, including metformin, are no longer protected by primary patents, allowing broad access to generic versions in global public health programs. According to the World Health Organization (Persaud *et al*., 2019), metformin is one of the fundamental antidiabetic medications listed in the Essential Medicines List, underscoring its importance in the treatment of type 2 diabetes worldwide. Beall *et al*. (2019) observe that although the original patent expired decades ago, patents for specific extended-release formulations and combinations with other antidiabetics may still be valid in some markets, reflecting the pharmaceutical industry's strategy to extend commercial exclusivity of well-established medications.

Metformin has demonstrated benefits in various conditions beyond diabetes. According to the comprehensive review by Lv and Guo (2020), non-diabetic applications of metformin include polycystic ovary syndrome (PCOS), where it improves insulin resistance, restores menstrual cycles and increases ovulation rates; obesity and weight control, promoting modest weight reduction in patients with and without diabetes; cardioprotective effects, with reduction of cardiovascular events independent of glycemic control; cancer prevention, where epidemiological data suggest reduced risk of various cancer types, especially colorectal, pancreatic, and hepatic; and neurodegenerative diseases, with preliminary studies indicating neuroprotective potential. These expanded applications demonstrate the versatile therapeutic value of this medication originally developed for diabetes treatment.

Recent research has investigated the role of metformin in promoting longevity and healthy aging. Barzilai *et al*. (2016) outlined the TAME (Targeting Aging with Metformin) study, a planned clinical trial to investigate how metformin may positively influence metabolic pathways associated with aging, presenting potential as an intervention to delay the development of multiple age-related diseases.

1.1.6. PROPRANOLOL

Propranolol was developed as the first clinically useful non-selective beta-blocker, with original applications in treating cardiovascular conditions. According to Rubin (2007), in his historical review of major discoveries in pharmacology, propranolol was developed by James Black (later Nobel laureate) and initially indicated for treating angina pectoris, cardiac arrhythmias, and hypertension. The medication works by blocking beta-adrenergic receptors (both β1 and β2), inhibiting the effects of catecholamines (epinephrine and norepinephrine) on the heart and other tissues, thereby reducing heart rate, myocardial contractility, and blood pressure.

Propranolol was synthesized and patented in 1962 by British scientist Sir James W. Black at Imperial Chemical Industries (ICI) laboratories. As documented by Quirke (2006), the medication received approval for medical use in 1964, with clinical trials beginning that same year. It entered the pharmaceutical market in the United Kingdom in 1965 under the trade name Inderal. It received FDA approval for use in the United States in 1967, revolutionizing the treatment of cardiovascular disease and establishing beta-blockers as a fundamental therapeutic class. Propranolol's development is considered a milestone in modern pharmacology, earning Sir James Black the Nobel Prize in Physiology or Medicine in 1988.

Propranolol has a well-characterized side effect profile, primarily related to its non-selective mechanism of action. According to Srinivasan (2019), in his historical review of 50 years of propranolol, adverse effects commonly associated with this medication include cardiovascular effects, such as bradycardia, hypotension, and cold extremities due to peripheral vasoconstriction; central nervous system effects, manifested by fatigue, dizziness, and sleep disturbances; respiratory effects, with risk of bronchoconstriction, especially in patients with a history of asthma or COPD; metabolic effects, such as masking adrenergic signs of hypoglycemia in diabetic patients; and other effects, including possible impact on sexual function. This adverse effect profile reflects propranolol's broad pharmacological action as a non-selective beta-adrenergic blocker, affecting multiple body systems simultaneously.

The author emphasizes that β2 receptor blockade can cause bronchospasm, making propranolol contraindicated in patients with asthma and other obstructive pulmonary diseases.

Propranolol no longer has valid patent protection for the original molecule. The first generic version of propranolol hydrochloride was approved in the United States in July 1985, indicating that the original patent expired around that time. The medication is listed on the World Health Organization's List of Essential Medicines. However, patents for specific controlled-release formulations and combinations with other medications may still be in effect in some countries.

Beyond its original cardiovascular applications, propranolol has been used to treat various other conditions. According to the systematic review by Steenen *et al*. (2016), non-cardiovascular indications for propranolol include migraine prophylaxis, where it provides reduction in frequency, intensity, and duration of episodes; essential tremor, offering significant symptom improvement in 40-70% of patients; performance anxiety, with reduction of tachycardia, tremors, and other physiological anxiety symptoms; social phobia and generalized anxiety disorder; and hyperthyroidism, helping control adrenergic symptoms such as tachycardia and tremor. This therapeutic versatility illustrates how propranolol's beta-adrenergic blocking mechanism influences various physiological systems, allowing its use in seemingly unrelated conditions that share pathophysiological pathways involving excessive sympathetic activation.

One of the most surprising and recent applications is in treating infantile hemangiomas. Léauté-Labrèze *et al*. (2015) accidentally discovered this indication and conducted controlled studies demonstrating propranolol's efficacy, leading to its specific approval for this condition by the FDA in 2014, establishing it as a first-line treatment for complicated hemangiomas in infants.

1.1.7. DISULFIRAM

Disulfiram was initially developed for treating chronic alcoholism. According to the historical review by Suh *et al*. (2006), this medication was the first approved specifically to combat alcohol dependence, acting as an aversive agent through inhibition of the aldehyde dehydrogenase enzyme. This inhibition prevents adequate metabolism of acetaldehyde—alcohol's toxic metabolite—causing its levels to accumulate in the body. Consequently, when patients consume alcoholic beverages, the "disulfiram effect" or "Antabuse reaction" occurs,

characterized by symptoms such as nausea, vomiting, facial flushing, and tachycardia, creating a conditioned aversion to alcohol.

Clinical studies and systematic reviews reinforce that disulfiram's efficacy is enhanced when administration is supervised. For example, the meta-analysis by Skinner *et al*. (2014) showed that open studies—where direct supervision is ensured—yielded better results in maintaining abstinence compared to blinded studies, where the medication's "threat" effect becomes diluted across groups. Additionally, Johnson (2014) clarifies the biochemical mechanisms underlying this action, detailing how blocking acetaldehyde conversion contributes to the medication's therapeutic effect.

Furthermore, the comprehensive review by Kalra *et al*. (2014) discusses various aspects of disulfiram use in the treatment of alcohol dependence, including monitoring issues, treatment adherence, and the adverse effect profile, thereby complementing the understanding of both the mechanism of action and the practical challenges in clinical application.

The drug has an interesting history of accidental discovery. According to Fuller and Gordis (2004), its effects were initially observed by chance in the late 1930s when two Danish researchers, Jens Hald and Erik Jacobsen, were investigating disulfiram's use as a treatment for parasitic infections and noticed they developed unpleasant symptoms after consuming alcohol. The substance was officially introduced as a medication for treating alcoholism in 1948 in Denmark. In the United States, the FDA approved disulfiram in 1951 under the trade name Antabuse, making it the first medication formally approved for alcohol dependence treatment.

It presents a side effect profile that extends beyond the acute reaction resulting from alcohol consumption. According to the systematic analysis by Chick (2020), adverse effects that occur independently of alcohol consumption include neurological effects, such as drowsiness, fatigue, headache, and with prolonged use, peripheral neuropathy; psychiatric effects, manifested by psychotic alterations in predisposed individuals, although this is rare; hepatic effects, characterized by elevated liver enzymes and drug-induced hepatitis; dermatological effects, presenting as skin eruptions; and endocrine effects, notably reduced libido and impotence. This spectrum of adverse effects reflects disulfiram's systemic action in the organism and its interference with multiple metabolic pathways, important factors to consider during clinical evaluation and monitoring of patients undergoing alcohol dependence treatment with this medication.

Hepatotoxicity is considered the most serious adverse effect, with an estimated incidence of approximately 1 case per 25,000 patient-years of treatment, accompanied by isolated reports of fulminant hepatic failure, which reinforces the recommendation for regular hepatic monitoring during treatment.

Recent studies using real-world data from the FAERS system corroborate the complexity of disulfiram's safety profile and emphasize the importance of rigorous clinical supervision (Luo *et al*., 2024). Moreover, rare case reports, such as methemoglobinemia associated with disulfiram use, expand the spectrum of adverse events that may occur even without alcohol consumption (Gajree & Khan, 2021).

Disulfiram no longer has valid patent protection for its original formulation, as this patent expired decades ago, allowing for its global commercialization as a generic medication. However, innovation efforts remain active, seeking to improve the drug's pharmacokinetic profile and expand therapeutic applications. Recent innovations, for example, demonstrate the development of polymeric nanoparticle-based formulations aimed at increasing stability and prolonging disulfiram's half-life, thereby enabling its utilization in emerging areas such as cancer treatment (Wang, Wang, & Bian, 2017; European Patent Office, 2024). Additionally, analyses on specialized platforms reveal an active patent portfolio encompassing advanced delivery systems, therapeutic combinations, and corroborating continued interest in disulfiram revalorization through innovative approaches (Synapse, 2025). Such initiatives demonstrate how intellectual property dynamics in the pharmaceutical industry can drive the reuse and evolution of classic medications, even after the original patent has expired.

Beyond alcoholism treatment, disulfiram has demonstrated potential for various other applications. In oncology, it exhibits antineoplastic activity through tumor growth inhibition in various cancer types, including breast, prostate, pancreatic, and glioblastoma, via multifaceted mechanisms. These mechanisms include forming copper complexes that induce the degradation of proteins essential for tumor maintenance (Skrott *et al*., 2017). Regarding antimicrobial properties, studies reveal its efficacy against resistant bacteria, including methicillin-resistant

Staphylococcus aureus (MRSA) strains (Peniche, Oliveira *et al*., 2021). The same research group identified relevant antiparasitic activity with the potential to act against protozoans such as Giardia lamblia and Trichomonas vaginalis. In the context of chemical dependencies, beyond alcoholism, disulfiram shows potential in cocaine dependence treatment through modulation of dopamine β-hydroxylase enzyme activity, altering dopaminergic response, and favoring abstinence (Gaval-Cruz, M., & Weinshenker, D., 2009). Finally, research suggests that this compound exhibits anti-HIV activity by acting on HIV latency reactivation via viral proteinase inhibition and transcription induction mechanisms, without promoting global T-lymphocyte activation (Lee *et al*., 2019; Xing *et al*., 2011). This pharmacological versatility positions disulfiram as a molecule of multidisciplinary interest in contemporary medicine.

Additionally, a recent review comprehensively compiled these emerging applications, highlighting the challenges and perspectives for repositioning disulfiram in oncology, infections, and dependencies (Lu, Yang, Zhou, & Dong, 2023).

1.1.8. VALPROIC ACID

Valproic acid was discovered by accident when used as an organic solvent in laboratory experiments, and its anticonvulsant activity was subsequently identified. Its first therapeutic indication was for epilepsy treatment, specifically for controlling absence seizures (petit mal), generalized tonic-clonic seizures (grand mal), and complex partial seizures. As highlighted by Löscher (2002), valproic acid acts by increasing the levels of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, in the brain, while also blocking voltage-dependent sodium channels and modulating T-type calcium currents, thereby providing a broad spectrum of antiepileptic activity.

It was first synthesized in 1882 by American chemist Beverly S. Burton, but its anticonvulsant properties were only discovered accidentally in 1963 by French researcher Pierre Eymard. According to Perucca (2002), valproic acid was first introduced to the pharmaceutical market in France in 1967 under the trade name Depakine. FDA approval in the United States occurred later, in 1978, under the trade name Depakene. In the early 1980s, sodium divalproex was developed, an enteric formulation that was more stable and caused fewer gastrointestinal effects.

A significant side effect profile requires careful monitoring. According to Genton, Semah, and Trinka (2006), the most common adverse effects include gastrointestinal effects (nausea, vomiting, dyspepsia, diarrhea), weight gain, transient hair loss, tremors, sedation, and drowsiness. Similarly, studies have demonstrated that hepatotoxicity is a serious adverse effect—with a risk of fatal hepatic failure, especially in children under 2 years—emphasizing the importance of periodic laboratory monitoring (Xu *et al*., 2019). Other severe effects reported include pancreatitis, thrombocytopenia, hyperammonemic encephalopathy, and polycystic ovary syndrome. Furthermore, valproic acid teratogenicity is one of the most concerning issues, as it is associated with a significantly increased risk of congenital malformations, including neural tube defects, a fact reinforced by studies investigating the drug's effects during pregnancy (Mawhinney *et al*., 2012).

Valproic acid no longer has valid patent protection for the basic molecule and is available as a generic medication globally. According to FDA Orange Book data, the patents for Depakote ER (divalproex sodium, NDA 021168) expired on December 18, 2018 (US 6528090, US 6511678) and June 18, 2019 (US 6713086, US 6720004) (U.S. Food and Drug Administration, 2025). Currently, various immediate-release and extended-release generic formulations are available on the market, significantly reducing treatment costs and expanding access to medication (DrugPatentWatch, 2025).

Beyond its original use as an anticonvulsant, valproic acid has demonstrated efficacy in various other clinical contexts. According to the review by Cipriani *et al*. (2013), its non-epileptic applications include treatment of acute manic episodes and prevention of relapses in bipolar patients, prophylactic management of migraine and cluster headaches, interventions for personality disorders, especially borderline, and reduction of agitation and aggressiveness in patients with dementia.

Recent research has expanded the scope of its applications, particularly through its action as a histone deacetylase (HDAC) inhibitor. Studies indicate this property may have anticancer effects, and it is being investigated in tumors such as gliomas (Han *et al*., 2021). Additionally, there is

growing interest in its epigenetic action in modulating neurodegenerative diseases, including Parkinson's and Huntington's (Ximenes *et al*., 2012).

Another field of study involves valproic acid's potential in managing autism spectrum disorders. Animal models have explored mechanisms by which it influences neurological development and control of repetitive behaviors and emotional outbursts (Devahuti *et al*., 2020). However, studies suggest that prenatal exposure may be associated with increased autism risk, highlighting the need for additional research to understand its clinical effects and safety (Sivasangari *et al*., 2022).

1.1.9. THALIDOMIDE

Thalidomide was originally developed and marketed as a sedative-hypnotic and antiemetic for treating insomnia, anxiety, and morning sickness in pregnant women. According to Vargesson (2015), thalidomide was initially promoted as a "completely safe" medication for everyone, including pregnant women, due to its apparent absence of acute toxicity and the impossibility of causing overdose—characteristics that distinguished it from barbiturates available at the time. The medication quickly became popular, particularly among pregnant women, due to its efficacy in controlling nausea and vomiting associated with the first trimester of pregnancy.

Thalidomide was first synthesized in 1954 by the German pharmaceutical company Chemie Grünenthal. According to the historical study by Lenz (1988), the medication was introduced to the market in West Germany in October 1957 under the trade name Contergan and subsequently marketed in more than 40 countries worldwide, including the United Kingdom, Australia, and Canada, under various trade names. Notably, the medication never received approval in the United States, thanks to the persistence of FDA reviewer Frances Kelsey, who questioned the drug's safety, especially the absence of studies on its placental passage. In 1961, after association with severe congenital malformations, thalidomide was withdrawn from the global market, representing one of the greatest pharmaceutical disasters in modern history.

The most devastating and notorious side effect of thalidomide is its teratogenicity, which resulted in one of the greatest pharmacological tragedies in history. As extensively documented, including by Matthews & McCoy (2003) and in more recent reviews such as Vargesson (2015), exposure to the medication during pregnancy, particularly between 20 and 36 days after conception, resulted in the birth of more than 10,000 children with severe congenital malformations, collectively known as "thalidomide syndrome" or "thalidomide embryopathy." The most common characteristics of this syndrome include phocomelia (shortening or absence of limbs), amelia (complete absence of limbs), ear and eye malformations, cardiac defects, and malformations of the gastrointestinal and urogenital tracts. Beyond its teratogenicity, thalidomide presents other important adverse effects, including peripheral neuropathy (which may be irreversible in 25-30% of patients), drowsiness, constipation, skin eruptions, neutropenia, and increased risk of venous thromboembolism, especially when combined with dexamethasone (Matthews & McCoy, 2003).

The patent situation for thalidomide is complex and unique (Thalidomide—A Revival Story, 1999). According to Okafor (2003) and Haslett *et al*. (2005), after its reintroduction for new indications, Celgene Corporation obtained patents for the medication in the United States in the mid-1990s, not for the molecule itself (which was in the public domain), but for methods of use and controlled distribution systems (U.S. Patent No. 5,715,309, 1998; U.S. Patent No. 6,248,362, 2001). The principal patent for use in treating erythema nodosum leprosum (under the trade name Thalomid) expired in 2014 (U.S. Patent No. 5,715,309, 1998), and for multiple myeloma, in 2019 (U.S. Patent No. 6,248,362, 2001; Palumbo *et al*., 2006). Currently, generic versions are available in some markets but under strictly controlled distribution systems due to teratogenic risk (Pharsight GreyB, 2023). Thalidomide and its analogs (lenalidomide, pomalidomide) remain protected by method-of-use and distribution patents in some countries (Sarpatwari *et al*., 2018).

Despite its tragic history, thalidomide found its way back into modern medicine for several indications. According to the comprehensive review by Franks *et al*. (2004), current therapeutic applications include erythema nodosum leprosum (ENL), which was the first indication approved after reintroduction, leveraging its anti-inflammatory and immunomodulatory properties; multiple myeloma, where it is used in combination with dexamethasone for treating newly diagnosed or refractory patients, as demonstrated by Singhal *et al*. (1999); graft-versus-host disease (GVHD), a

condition that may occur after bone marrow transplantation, as evidenced by Browne *et al*. (2000); aphthous ulcers and Behçet's disease, applications documented by Hamuryudan *et al*. (1998); and discoid and cutaneous lupus erythematosus, according to more recent studies conducted by Verdelli *et al*. (2022). This therapeutic rehabilitation represents a remarkable case in pharmacology, where a medication initially withdrawn from the market for its devastating teratogenic effects was rediscovered and repositioned with rigorous safety protocols to treat serious conditions with limited therapeutic options, demonstrating how understanding molecular mechanisms can transform a harmful agent into a valuable therapeutic tool.

More recent investigations explore its potential in autoimmune diseases, various types of hematological and solid cancers, myelodysplastic syndromes, and HIV-associated complications (Kaplan *et al*., 2000), such as wasting syndrome and oral ulcers. Its mechanism of action involves immunomodulatory, anti-inflammatory, and anti-angiogenic properties.

1.1.10. DEXAMETHASONE

Dexamethasone was developed as a long-acting synthetic corticosteroid with potent anti-inflammatory and immunosuppressive properties (Schäcke *et al*., 2002). As described by Czock *et al*. (2005), dexamethasone's original applications included treating acute and chronic inflammatory conditions such as rheumatoid arthritis, bronchial asthma, severe allergic reactions, and autoimmune disorders. The medication acts by binding to glucocorticoid receptors in the cellular cytoplasm and, after translocation to the nucleus, regulates transcription of various genes, resulting in decreased production of pro-inflammatory cytokines and suppression of inflammatory cell migration to affected tissues (Barnes, 2006; Coutinho & Chapman, 2011). Dexamethasone is approximately 25 times more potent than cortisone in its anti-inflammatory activities (Liu *et al*., 2013).

Dexamethasone was first synthesized in 1957 by researchers at Merck & Co. According to Benedek (2011), the medication received FDA approval in the United States in 1958. It rapidly became one of the most widely used corticosteroids in clinical practice due to its high potency, long duration of action, and reduced sodium retention compared to other corticosteroids available at the time. By the 1960s, dexamethasone was widely available in the global market, used in various formulations, including oral, intravenous, intramuscular, topical, and ophthalmic, which significantly expanded its use across different medical specialties.

Dexamethasone, like other corticosteroids, presents numerous side effects, especially with prolonged use. According to the systematic review by Liu *et al*. (2013), the most common adverse effects include metabolic effects such as hyperglycemia, steroid-induced diabetes, weight gain, and cushingoid fat distribution; musculoskeletal effects manifested by corticosteroid-induced osteoporosis muscle weakness, and myopathy; psychiatric effects encompassing mood alterations, insomnia, psychosis, and delirium; suppression of the hypothalamic-pituitary-adrenal (HPA) axis, a condition that may persist for months after medication discontinuation; increased susceptibility to infections, including reactivation of latent tuberculosis and opportunistic infections; gastrointestinal effects, notably peptic ulcer, especially when used concomitantly with NSAIDs; and ophthalmological effects, particularly posterior subcapsular cataract and glaucoma. This extensive adverse effect profile reflects the potent systemic action of corticosteroids and explains why their clinical use frequently involves careful risk-benefit evaluation, with a preference for treatment regimens that use the lowest effective dose for the shortest possible time, along with regular clinical monitoring during prolonged therapy.

The severity and incidence of these effects are dose-dependent and increase significantly with treatment duration.

Dexamethasone no longer has valid patent protection for the basic molecule (Arth *et al*., 1958). According to Dave *et al*. (2017), the original patents for dexamethasone expired decades ago, and the medication is now available as a generic in virtually all global markets. However, patents exist for specific formulations and delivery systems, such as intraocular dexamethasone implants (Ozurdex) for treating diabetic macular edema and extended-release formulations for inhalation use. Patents in various countries may protect these specific formulations. However, the basic dexamethasone molecule is considered an essential medicine by the World Health Organization and is available at low cost in generic formulations.

Beyond its original anti-inflammatory and immunosuppressive applications, dexamethasone

has been used in various other clinical contexts. According to the comprehensive study by Cain & Cidlowski (2017), non-conventional applications of dexamethasone include its use in oncology, where it functions as an essential component of chemotherapeutic regimens for leukemias, lymphomas, and multiple myeloma, acting both as a direct cytotoxic agent and as an adjuvant to reduce side effects of other chemotherapeutics (Patel & Dickenson, 2016); in neurology, where Roberts *et al*. (2017) described its value in treating cerebral edema associated with brain tumors, traumatic brain injury, and stroke; in endocrinology, serving as a diagnostic tool through the dexamethasone suppression test for identifying Cushing's syndrome; in obstetrics, where it plays a crucial role in accelerating fetal lung maturation in pregnant women at risk of premature delivery, potentially saving lives of premature newborns; in anesthesiology, contributing significantly to preventing postoperative nausea and vomiting (Oliveira *et al*., 2013); and in ophthalmology, where it has demonstrated efficacy in treating conditions such as diabetic macular edema and non-infectious uveitis (Galor *et al*., 2008). This diversity of clinical applications illustrates dexamethasone's remarkable therapeutic versatility—a medication that, despite its known side effects, continues to expand its role across multiple medical specialties due to its potent mechanism of action and the deepening scientific understanding of how it modulates inflammatory and immune responses.

In 2020, dexamethasone gained worldwide attention when the RECOVERY study demonstrated significant mortality reduction in patients with severe COVID-19 requiring oxygen therapy or mechanical ventilation, establishing it as the first proven effective treatment for severe cases of the disease.

1.1.11. HYDROXYCHLOROQUINE

Hydroxychloroquine was developed as a chloroquine derivative, with the primary objective of being a safer and more effective antimalarial agent. According to Ben-Zvi *et al*. (2012), the original application of hydroxychloroquine was the treatment and prevention of malaria, particularly caused by chloroquine-sensitive Plasmodium strains. Its antimalarial mechanism of action involves concentration in the parasite's acidic digestive vacuole, where it interferes with hemoglobin degradation and heme group detoxification, resulting in parasite death. Hydroxychloroquine presents advantages over chloroquine, including lower ocular toxicity and a generally better safety profile while maintaining comparable efficacy against malaria.

Hydroxychloroquine was first synthesized in 1946 at Sanofi Research laboratories. According to historical research by Rainsford *et al*. (2015), the medication was approved by the FDA in 1955, initially as an antimalarial agent, under the trade name Plaquenil. It was introduced to the market as a less toxic alternative to chloroquine, particularly with a lower risk of retinopathy and other adverse effects. During the 1950s and 1960s, while it was widely used for malaria prevention and treatment, observations began to emerge about its beneficial effects on patients with rheumatic diseases, which would subsequently lead to its approval for these new indications.

Although generally considered safer than chloroquine, hydroxychloroquine still presents a significant side effect profile. According to the systematic review by Ruiz-Irastorza *et al*. (2010), the most common adverse effects include gastrointestinal effects, characterized by nausea, vomiting, abdominal pain, and diarrhea, which frequently represent the first signs of medication intolerance; dermatological effects, manifested as skin eruptions, pruritus, and hyperpigmentation, the latter being particularly notable for its potential persistence even after therapy discontinuation; and neurological effects, expressed primarily as headache, dizziness, and insomnia, which can significantly affect patients' quality of life. These adverse effects, although generally less severe than those of chloroquine, still merit careful clinical attention, especially in long-term treatments as occurs in autoimmune diseases, where the balance between therapeutic efficacy and medication safety becomes particularly critical for treatment adherence and therapeutic intervention success.

The most serious and feared adverse effect is hydroxychloroquine retinopathy, which can lead to irreversible vision loss. According to Marmor *et al*. (2016), the risk is dose-dependent, being higher in patients who take doses exceeding 5 mg/kg/day or have cumulative use for more than 5 years. Another important adverse effect is cardiotoxicity, which manifests as conduction disturbances, cardiomyopathy, and QT interval prolongation, with potential risk of fatal arrhythmias, particularly in patients with pre-existing cardiac risk factors or when used in combination with other medications that prolong the QT interval.

Hydroxychloroquine no longer has valid

patent protection for the original molecule. Hydroxychloroquine patents expired decades ago, and the medication is widely available as a generic worldwide. Sanofi, the original manufacturer of Plaquenil, continues to produce the brand version; however, it holds only a minority share in the global market, which is dominated by generic formulations. The medication is included in the World Health Organization's List of Essential Medicines due to its fundamental role in treating certain rheumatic diseases and is still considered important in some antimalarial treatment protocols, especially in regions where chloroquine resistance is not prevalent (Shippey, Wagler, & Collamer, 2018; D'Acquarica & Agranat, 2020; WHO, 2011).

Beyond its original use as an antimalarial, hydroxychloroquine has established itself as a fundamental treatment for various autoimmune diseases. According to the comprehensive review by Schrezenmeier & Dörner (2020), non-malarial applications of hydroxychloroquine include systemic lupus erythematosus (SLE), where it is considered baseline therapy for virtually all patients, reducing disease activity, organ damage, and mortality, as demonstrated by Fanouriakis *et al*. (2019); rheumatoid arthritis, where it is used as monotherapy in mild cases or in combination with other disease-modifying antirheumatic drugs, following guidelines established by Smolen *et al*. (2019); Sjögren's syndrome, providing relief from musculoskeletal manifestations and fatigue, benefits documented by Vivino *et al*. (2016); dermatomyositis and polymyositis, where it acts by modulating the dysregulated immune response; cutaneous porphyria tarda, as evidenced in studies by Singal (2019), where it assists in porphyrin metabolism; and juvenile idiopathic arthritis, expanding the spectrum of its use to the pediatric population. This therapeutic versatility reflects how a medication initially developed for antiparasitic purposes found significant applications in immune-mediated conditions, thanks to its mechanisms of action that modulate conserved inflammatory pathways involved in various autoimmune pathological processes.

In 2020, hydroxychloroquine received worldwide attention when it was investigated as a potential treatment for COVID-19 (Meo *et al*., 2020), although subsequent studies did not confirm its efficacy for this indication. More recent research has explored its possible metabolic effects (improvement of insulin sensitivity and lipid profile) (Rempenault *et al*., 2018), antiplatelet, and antineoplastic properties, suggesting potential future applications in diabetes, metabolic syndrome, and some types of cancer.

2. METHODS

This study presents an exploratory bibliometric analysis of scientific research patterns related to the repurposing of drugs for cancer treatment. The research was conducted from January 1 to May 10, 2025, encompassing all available periods across the databases. A quantitative search was performed across multiple databases to map and compare the volume of scientific literature on eleven off-patent medications with anticancer potential, aiming to identify patterns in the distribution of scientific attention and potential knowledge gaps in this research field.

2.1. Methods

This bibliometric analysis was conducted across five databases: Google Scholar (https://scholar.google.com/), BVS (Virtual Health Library, https://bvsalud.org/), PubMed (https://pubmed.ncbi.nlm.nih.gov/), NIH (National Institutes of Health, https://www.nih.gov/), and Science.gov (https://www.science.gov/). These databases were selected for their comprehensiveness, relevance to health research, open access availability, and coverage of both academic literature and governmental/institutional publications related to cancer.

Search terms focused on investigating the therapeutic potential of existing medications (drug repurposing) for cancer treatment. The following term combinations were used consistently across all databases:

Ivermectin AND cancer

Fenbendazole AND cancer

Mebendazole AND cancer

Albendazole AND cancer

Metformin AND cancer

Propranolol AND cancer

Disulfiram AND cancer

Valproate AND cancer

Thalidomide AND cancer

Dexamethasone AND cancer

Hydroxychloroquine (with Zinc) AND cancer

Disulfiram (with Copper) AND cancer

Ivermectin AND cancer treatment

Fenbendazole AND cancer treatment

Mebendazole AND cancer treatment

Albendazole AND cancer treatment

Metformin AND cancer treatment

Propranolol AND cancer treatment

Disulfiram AND cancer treatment

Valproate AND cancer treatment

Thalidomide AND cancer treatment

Dexamethasone AND cancer treatment

Hydroxychloroquine (with Zinc) AND cancer treatment

Disulfiram (with Copper) AND cancer treatment

The Boolean operator "AND" was used to connect specific medications with cancer-related terms. This approach enabled the identification of studies investigating these approved medications for alternative oncological applications, a field known as drug repurposing. The search strategy was applied consistently across databases, with minimal adaptations to accommodate platform-specific syntactic requirements.

2.2.1. Data Collection and Recording Procedures

For this bibliometric study, all search results obtained from the databases were accepted. No specific filters or exclusion criteria were applied, as the primary objective was to quantify and analyze the volume of scientific production related to each investigated medication within the context of cancer treatment.

This methodological approach was chosen to provide a comprehensive overview of the current scientific landscape regarding the repurposing of these specific medications for oncological use without restricting the analytical scope. The methodology enabled the identification of literature trends, medications with higher or lower associated research volumes, and the temporal evolution of publications in this field.

For each search term combination, only the total number of results from each database was recorded. This straightforward quantitative approach was chosen to facilitate a direct comparison of the available scientific literature volumes for each medication investigated in cancer treatment.

2.2.2. Statistical Analyses Performed

Two scripts (CODE 1 and CODE 2, provided in the appendix) were developed with the assistance of artificial intelligence to analyze the values presented in Table 1. CODE 1 presents results in textual format, while CODE 2 generates graphical outputs.

2.2.2.1. Basic Descriptive Analysis

- Measures of central tendency and dispersion

2.2.2.2. Ranking and Volume Analysis

- Hierarchical ordering
- Aggregation by pharmacological classes

2.2.2.3. Proportion and Specificity Analysis

- Ratio calculations
- Categorical comparisons

2.2.2.4. Correlation Analysis

- Pearson coefficient
- Correlation strength classification

2.2.2.5. Contribution and Concentration Analysis

- Percentage distribution
- Herfindahl Index

2.2.2.6. Data Source Efficiency Analysis

- Proportional distribution

3. RESULTS AND DISCUSSION

3.1. Results

3.1.1. Basic Descriptive Analysis

Total number of entries: 24

Total sum of results: 3,226,066

Average results per entry: 134,419.42

Median of results: 42,362.5

Standard deviation: 266,145.27

Minimum value: 18,607

Maximum value: 1,295,666

The high standard deviation (266,145.27) compared to the mean (134,419.42) and the substantial difference between minimum (18,607) and maximum (1,295,666) values indicate an extremely asymmetric distribution. This asymmetry suggests that some medications receive considerably more scientific attention than others, creating a highly unbalanced research landscape. The median (42,362.5) being significantly lower than the mean confirms this unequal distribution, with few medications dominating publication volumes.

3.1.2 Ranking of Drugs by Total Publication Volume

Publication distribution shows extreme concentration among a few medications. Dexamethasone (1,538,058 publications) and metformin (697,172 publications) together represent nearly 70% of total publications, while the six least-researched drugs combined account for approximately 10%. This disparity indicates unequal allocation of research resources and attention, possibly reflecting the greater clinical history of these dominant medications or their prior establishment as adjuvant therapies in oncology. Figure 1 illustrates this analysis.

Ranking by total publication volume (general + treatment):

1. **Dexamethasone**: 1,538,058 publications (1,295,666 general, 242,392 treatment)
2. **Metformin**: 697,172 publications (544,873 general, 152,299 treatment)
3. **Thalidomide**: 218,059 publications (148,413 general, 69,646 treatment)
4. **Valproate**: 185,787 publications (122,942 general, 62,845 treatment)
5. **Propranolol**: 157,371 publications (115,566 general, 41,805 treatment)
6. **Disulfiram**: 88,496 publications (56,162 general, 32,334 treatment)
7. **Ivermectin**: 80,772 publications (53,131 general, 27,641 treatment)
8. **Albendazole**: 67,401 publications (42,920 general, 24,481 treatment)
9. **Mebendazole**: 52,324 publications (31,124 general, 21,200 treatment)
10. **Disulfiram** (with Copper): 50,463 publications (27,052 general, 23,411 treatment)
11. **Hydroxychloroquine** (with Zinc):50,368 publications (28,747 general, 21,621 treatment)
12. **Fenbendazole**: 39,795 publications (21,188 general, 18,607 treatment)

3.1.3. Analysis by Pharmacological Classes

Pharmacological classes show marked differences in both volume and research focus. Corticosteroids (18.71%) have a high representation in absolute volume but a low proportion of treatment-specific research, while antidiabetics (27.95%) show a moderate proportion. In contrast, antimalarials (75.21%), anti-alcoholics (66.99%), and antiparasitics (61.96%) present much higher proportions of studies specifically focused on treatment. This suggests that these latter classes, although less studied in absolute terms, are being investigated more directly for specific oncological applications, possibly indicating emerging interest in these classes as anticancer therapies. Figure 2 illustrates this analysis.

- **Group: Corticosteroids**
  Total publications: 1,538,058
  General publications: 1,295,666
  Treatment publications: 242,392
  Treatment/general ratio: 18.71%
  Drugs in the group: Dexamethasone

- **Group: Antidiabetics**
  Total publications: 697,172
  General publications: 544,873
  Treatment publications: 152,299
  Treatment/general ratio: 27.95%
  Drugs in the group: Metformin

- **Group: Antiparasitics**
  Total publications: 240,292
  General publications: 148,363
  Treatment publications: 91,929
  Treatment/general ratio: 61.96%
  Drugs in the group: Ivermectin, Fenbendazole, Mebendazole, Albendazole

- **Group: Immunosuppressants**
  Total publications: 218,059
  General publications: 148,413
  Treatment publications: 69,646
  Treatment/general ratio: 46.93%
  Drugs in the group: Thalidomide

- **Group: Anticonvulsants**
  Total publications: 185,787
  General publications: 122,942

Treatment publications: 62,845
Treatment/general ratio: 51.12%
Drugs in the group: Valproate

- **Group: Beta-blockers**
  Total publications: 157,371
  General publications: 115,566
  Treatment publications: 41,805
  Treatment/general ratio: 36.17%
  Drugs in the group: Propranolol

- **Group: Antialcoholics**
  Total publications: 138,959
  General publications: 83,214
  Treatment publications: 55,745
  Treatment/general ratio: 66.99%
  Drugs in the group: Disulfiram, Disulfiram (with Copper)

- **Group: Antimalarials**
  Total publications: 50,368
  General publications: 28,747
  Treatment publications: 21,621
  Treatment/general ratio: 75.21%
  Drugs in the group: Hydroxychloroquine (with Zinc)

3.1.4. Specificity Analysis (Treatment/General)

A clear inverse relationship exists between total publication volume and the proportion of treatment-specific research. Less-studied medications such as fenbendazole (87.82%), disulfiram with copper (86.54%), and hydroxychloroquine with zinc (75.21%) show the highest proportions of treatment-focused studies. In contrast, dexamethasone, despite having the largest total volume, exhibits the lowest proportion (18.71%). This relationship indicates that although less popular medications receive reduced general attention, existing research is potentially more targeted toward their therapeutic potential in cancer, possibly reflecting more recent and focused interest in their anticancer properties. Figure 3 illustrates this analysis.

Proportion of 'treatment' results relative to 'general' results:

Fenbendazole: 87.82%
(18,607 treatment / 21,188 general)

Disulfiram (with Copper): 86.54%
(23,411 treatment / 27,052 general)

Hydroxychloroquine (with Zinc): 75.21%
(21,621 treatment / 28,747 general)

Mebendazole: 68.11%
(21,200 treatment / 31,124 general)

Disulfiram: 57.57%
(32,334 treatment / 56,162 general)

Albendazole: 57.04%
(24,481 treatment / 42,920 general)

Ivermectin: 52.02%
(27,641 treatment / 53,131 general)

Valproate: 51.12%
(62,845 treatment / 122,942 general)

Thalidomide: 46.93%
(69,646 treatment / 148,413 general)

Propranolol: 36.17%
(41,805 treatment / 115,566 general)

Metformin: 27.95%
(152,299 treatment / 544,873 general)

Dexamethasone: 18.71%
(242,392 treatment / 1,295,666 general)

3.1.5. Correlation Analysis Between Databases

Correlation patterns between databases reveal important differences in indexing criteria and coverage. BVS exhibits a strong correlation with several databases, particularly with Science.gov ($r = 0.9205$), indicating similar indexing patterns. In contrast, Google Scholar and PubMed present surprisingly low correlations (0.1562), indicating significant differences in their indexing approaches. This pattern has important implications for bibliographic research strategies: researchers should consult multiple databases to ensure comprehensive coverage, as different databases capture different subsets of the literature. Figure 4 illustrates this analysis.

Correlations between databases (Pearson coefficient):

BVS vs Science.gov: 0.9205 (Very strong)

Google Scholar vs BVS: 0.8492 (Very strong)

BVS vs NIH: 0.8021 (Very strong)

Google Scholar vs NIH: 0.7916 (Strong)

PubMed vs Science.gov: 0.7558 (Strong)

Google Scholar vs Science.gov: 0.7116 (Strong)

NIH vs Science.gov: 0.6454 (Strong)

BVS vs PubMed: 0.5871 (Moderate)

PubMed vs NIH: 0.3231 (Weak)

Google Scholar vs PubMed: 0.1562 (Very weak)

3.1.6. Relative Contribution Analysis

Percentage contribution of each drug to the total publications:

Dexamethasone: 47.68%

Metformin: 21.61%

Thalidomide: 6.76%

Valproate: 5.76%

Propranolol: 4.88%

Disulfiram: 2.74%

Ivermectin: 2.50%

Albendazole: 2.09%

Mebendazole: 1.62%

Disulfiram (with Copper): 1.56%

Hydroxychloroquine (with Zinc): 1.56%

Fenbendazole: 1.23%

Herfindahl Index (research concentration): 0.2870

Interpretation: Highly concentrated

The Herfindahl Index of 0.2870 confirms a high level of research concentration, classified as "highly concentrated." Two medications—dexamethasone (47.68%) and metformin (21.61%)—dominate the landscape, representing nearly 70% of all publications. This concentration suggests a notable imbalance in research focus, which may limit the exploration of the therapeutic potential of alternative medications. The high degree of concentration raises questions about factors driving research priorities and suggests opportunities for diversification in future studies.

3.1.7. Database Search Efficiency

Google Scholar (64.39%) and Science.gov (33.63%) collectively account for 98% of all results, while the other three databases contribute approximately 2%. This disparity suggests that Google Scholar and Science.gov were the most comprehensive sources for drug repurposing research in oncology within this study. For researchers with limited resources, focusing on these two databases would provide the most efficient coverage. However, less representative databases may contain unique publications not found in the primary sources, highlighting the value of a comprehensive approach when feasible. Figure 5 illustrates this analysis.

Contribution of each database to the total results:

Google Scholar: 2,077,425 results (64.39% of total)

Science.gov: 1,085,038 results (33.63% of total)

BVS: 50,821 results (1.58% of total)

PubMed: 50,591 results (1.57% of total)

NIH: 1,316 results (0.04% of total)

3.2. Discussions

3.2.1 Distribution Patterns in Repurposed Drug Research

The striking asymmetry in research distribution revealed by the analysis (SD = 266,145.27 compared to the mean = 134,419.42) reflects a fundamental imbalance in scientific attention toward repurposed medications for cancer treatment. This pattern aligns with what Pantziarka *et al*. (2021) termed the "popularity bias" in drug repurposing research, where established medications with known anticancer properties receive disproportionate attention compared to emerging candidates.

The dominance of dexamethasone and metformin, collectively representing nearly 70% of all publications, demonstrates the influence of clinical integration on research interest. Dexamethasone has been a standard component of many chemotherapy regimens since the 1980s (Weissman *et al*., 2019), while metformin's potential anticancer properties have been extensively studied following Bodmer *et al*.'s (2010) landmark epidemiological study, which showed a reduced incidence of cancer in diabetic patients taking metformin. This finding supports Verbaanderd *et al*.'s (2017) observation that research momentum in drug repurposing is often driven by early clinical observations rather than mechanistic rationales.

3.2.2 Pharmacological Class Variation and Research Focus

The significant differences in both volume and research focus across pharmacological classes reflect varying stages of evidence development. The high representation of corticosteroids (18.71%) and antidiabetics (27.95%), alongside their low proportion of treatment-specific research, suggests these classes have reached a mature research stage where their mechanisms and applications are

broadly studied beyond specific cancer treatment protocols.

Conversely, antimalarials (75.21%), antialcoholics (66.99%), and antiparasitics (61.96%) exhibit a significantly higher proportion of treatment-focused research, despite having lower absolute publication volumes. This pattern aligns with Pushpakom *et al.*'s (2019) description of the drug repurposing research lifecycle, where emerging candidates initially generate targeted mechanism-of-action studies before being integrated more broadly into cancer research. These classes appear to be in earlier stages of the repurposing research cycle, with investigations more specifically directed toward anticancer applications.

3.2.3 The Inverse Relationship Between Volume and Specificity

The identified inverse relationship between total publication volume and treatment specificity ratio represents a novel observation in bibliometric studies of drug repurposing. Medications with lower overall research attention, such as fenbendazole (87.82%) and disulfiram with copper (86.54%), demonstrate remarkably higher proportions of cancer treatment-specific research compared to more established drugs like dexamethasone (18.71%).

This finding suggests a systematic pattern in how repurposed drugs evolve in the research landscape. Newer candidates in the repurposing pipeline appear to generate more focused, hypothesis-driven research specifically targeting cancer applications, while established medications become incorporated into broader research agendas. This pattern aligns with Cha et al.'s (2018) framework, which describes how repurposed drugs transition from the "candidate exploration" to the "clinical integration" phases, with research becoming progressively more diversified as a drug advances through this continuum.

3.2.4 Database Indexing Patterns and Research Strategy Implications

The correlation analysis between databases reveals important considerations for systematic review methodologies in repurposed drug research. The strong correlation between BVS and Science.gov (r = 0.9205) suggests a significant overlap in indexing patterns, while the surprisingly weak correlation between Google Scholar and PubMed (r = 0.1562) indicates substantial differences in coverage.

These findings have direct implications for systematic review protocols in drug repurposing research. The results challenge the assumption that PubMed alone provides comprehensive coverage, supporting Martín-Martín *et al.*'s (2021) recommendation for multi-database approaches in comprehensive literature reviews. For researchers conducting systematic reviews on repurposed drugs, the findings suggest that combining Google Scholar and Science.gov would provide the most efficient coverage (98% of all results), with specialized databases adding marginal but potentially unique content.

3.2.5 Research Concentration and Funding Implications

The high Herfindahl Index (0.2870) indicates substantial concentration in the research landscape, raising important questions about research funding allocation and the allocation of scientific attention. This concentration pattern aligns with Showalter *et al.*'s (2020) critique of research funding distribution in drug repurposing, which tends to follow established pathways rather than encourage the exploration of novel candidates.

The dominance of dexamethasone (47.68%) and metformin (21.61%) suggests that factors beyond anticancer efficacy alone may disproportionately influence research interest. Institutional factors, funding priorities, and clinical familiarity likely play significant roles in directing research attention. This observation supports Bloom *et al.*'s (2020) argument that research in drug repurposing is often subject to path dependency, where early success creates self-reinforcing cycles of attention and funding.

3.2.6 Potential of Neglected Candidates

The highly skewed distribution identified in the analysis suggests significant untapped potential in less-studied candidates. Medications like fenbendazole, which demonstrated the highest treatment specificity ratio (87.82%), may represent underexplored opportunities despite promising mechanistic evidence. This aligns with Bertolini *et al.*'s (2015) observation that many promising repurposed drug candidates remain "orphaned" in the research pipeline due to insufficient attention, rather than a lack of efficacy.

The antiparasitic class as a whole

demonstrates a high treatment specificity ratio (61.96%), indicating a focused research interest in their anticancer mechanisms, despite relatively modest publication volumes. Recent mechanistic studies have identified multiple potential anticancer pathways for these medications, including microtubule disruption, modulation of autophagy, and selective toxicity in cancer cells (Tang *et al*., 2021; Nguyen *et al*., 2024). The imbalance between promising mechanistic findings and overall research volume highlights a potential opportunity for expanded investigation.

3.2.7 Research Implications Without Google Scholar

The potential exclusion of Google Scholar from bibliometric analyses in drug repurposing research would have profound methodological and interpretative implications, fundamentally altering both the scope and conclusions of such studies.

3.2.7.1 Substantial Data Loss and Coverage Reduction

Removing Google Scholar would eliminate 64.39% of all search results (2,077,425 publications), representing the most significant single source of bibliographic data in this analysis. This massive reduction would shift the research landscape from a multi-source perspective to one heavily dominated by Science.gov, which would increase from 33.63% to approximately 91.36% of the remaining dataset. Such concentration in a single database would raise concerns about the diversity and comprehensiveness of sources in bibliometric assessments.

3.2.7.2 Altered Research Distribution Patterns

The exclusion would disproportionately affect certain medications that show high representation in Google Scholar. Dexamethasone, for instance, would lose 1,110,000 of its 1,295,666 total publications (85.68%) while maintaining relatively smaller losses in specialized databases. This differential impact would substantially alter the hierarchical ranking of medications and potentially modify the concentration patterns measured by the Herfindahl Index, possibly reducing the apparent research concentration observed in the current analysis.

3.2.7.3.Enhanced Specialized Database Focus

Conversely, removing Google Scholar might strengthen the focus on more specialized, peer-reviewed literature indexed in PubMed, NIH, and BVS databases. The weak correlation between Google Scholar and PubMed ($r = 0.1562$) suggests that these sources capture different types of publications, with PubMed likely representing more rigorous, peer-reviewed research. This shift could provide a more selective view of high-quality research, potentially offering different insights into treatment specificity ratios and pharmacological class patterns.

3.2.7.4. Impact on Treatment Specificity Analysis

The inverse relationship between publication volume and treatment specificity might be affected differently across medications. Drugs with high Google Scholar representation but lower specialized database presence might show altered specificity ratios, potentially strengthening the observed pattern or revealing different relationships when focusing solely on specialized literature.

3.2.7.5 Methodological Trade-offs

Excluding Google Scholar would represent a trade-off between comprehensiveness and selectivity. While losing breadth of coverage, the analysis might gain in terms of literature quality and relevance, focusing on publications that are more likely to meet traditional academic standards. However, this approach may overlook emerging research, preprints, conference presentations, and grey literature that could be relevant for identifying early research trends in drug repurposing.

3.2.7.6 Database Correlation Implications

The removal would strengthen the relative importance of correlations between the remaining databases, particularly the strong correlation between BVS-Science.gov (0.9205), potentially indicating more consistent indexing patterns in specialized health databases compared to the broad academic coverage provided by Google Scholar.

3.2.7.7 Research Strategy Recommendations

These considerations suggest that future bibliometric studies in drug repurposing should explicitly address the inclusion criteria for databases, weighing comprehensiveness against selectivity based on research objectives. For studies focusing on established peer-reviewed evidence, excluding Google Scholar may provide more targeted insights, while comprehensive landscape mapping would benefit from its inclusion, despite potential variations in quality.

3.2.7.8. Basic Statistical Data Adjusted Without Google Scholar

Recalculating fundamental statistical parameters after excluding Google Scholar reveals significant shifts in research distribution patterns and concentration metrics.

Adjusted Basic Descriptive Statistics (Without Google Scholar):

- Total entries: 24
- Total sum of results: 1,148,641 (64.39% reduction)
- Mean results per entry: 47,860.04 (64.4% reduction)
- Median: 25,647.5 (39.5% reduction)
- Standard deviation: 48,628.91 (81.7% reduction)
- Minimum value: 17,728 (4.7% reduction)
- Maximum value: 187,658 (85.5% reduction)

Key Distribution Changes:

Variance Reduction: The standard deviation decreased from 266,145.27 to 48,628.91, indicating that Google Scholar was the primary driver of extreme asymmetry in the original dataset. The coefficient of variation decreased from 1.98 to 1.02, suggesting a more balanced distribution across medications when focusing on specialized databases.

Range Compression: The total range compressed from 1,277,059 to 169,930, primarily due to dexamethasone's reduction from 1,295,666 to 187,658 publications. Despite this compression, right-skewness persists, with the median (25,647.5) remaining below the mean (47,860.04).

Differential Medication Impact:

Highest impact: Dexamethasone (85.5% reduction), Metformin (78.7% reduction)

- **Moderate impact:** Propranolol (69.3% reduction), Disulfiram (51.7% reduction)
- **Lowest impact:** Fenbendazole (4.7% reduction), Mebendazole (37.2% reduction)

Implications: The substantial variance reduction suggests that the extreme asymmetry observed in the original analysis was significantly influenced by Google Scholar's broader indexing criteria. The adjusted dataset exhibits more moderate distribution patterns, which may better reflect peer-reviewed research in specialized databases, albeit with reduced comprehensive coverage.

Relative medication rankings remain largely consistent, indicating that Google Scholar amplifies rather than distorts underlying research distribution patterns captured by specialized databases.

Based on Table 1, calculating only the values from BVS + PubMed + NIH + Science.gov (excluding Google Scholar), the adjusted ranking would be:

1. **Dexamethasone**: 374,171 publications (187,658 general, 186,513 treatment)
2. **Metformin**: 231,379 publications (114,873 general, 116,506 treatment)
3. **Thalidomide**: 107,808 publications (49,513 general, 58,295 treatment)
4. **Valproate**: 101,890 publications (50,742 general, 51,148 treatment)
5. **Propranolol**: 71,534 publications (35,467 general, 36,067 treatment)
6. **Disulfiram**: 53,706 publications (27,062 general, 26,644 treatment)
7. **Ivermectin**: 48,482 publications (23,831 general, 24,651 treatment)
8. **Albendazole**: 44,341 publications (21,920 general, 22,421 treatment)
9. **Disulfiram (with Copper)**: 40,143 publications (19,782 general, 20,361 treatment)
10. **Mebendazole**: 39,224 publications (19,524 general, 19,700 treatment)

11. **Hydroxychloroquine (with Zinc)**: 39,158 publications (19,237 general, 19,921 treatment)
12. **Fenbendazole**: 35,930 publications (17,728 general, 18,202 treatment)

Key changes observed:

- **Dexamethasone** maintains the lead but with an 85.7% reduction (from 1,538,058 to 374,171)
- **Metformin** remains in second place, with a 66.8% reduction (from 697,172 to 231,379)
- The **extreme concentration** is significantly reduced
- The **top two medications** now represent approximately 53% of the total (vs. 70% previously)
- **Fenbendazole** continues to be the least represented, but the relative difference decreases considerably

New Herfindahl Index (without Google Scholar):

Adjusted Herfindahl Index: 0.1657

Comparison with the original index:

- Original Herfindahl Index: 0.2870 (Highly concentrated)
- Adjusted Herfindahl Index: 0.1657 (Moderately concentrated)
- Reduction: 42.2%

4. CONCLUSIONS

This bibliometric analysis quantified and mapped the research landscape for eleven off-patent medications being investigated for cancer treatment applications, revealing significant patterns in the allocation of scientific attention that have implications for future research prioritization.

Key findings demonstrate an extreme concentration of research, with dexamethasone and metformin collectively representing nearly 70% of all publications (69.28%), while the Herfindahl Index of 0.2870 confirms a highly concentrated research environment. This concentration pattern suggests that research attention may be disproportionately influenced by factors beyond anticancer efficacy alone, including clinical familiarity, funding priorities, and established therapeutic pathways.

An inverse relationship was identified between total publication volume and treatment specificity ratios. Medications with lower overall research attention, such as fenbendazole (87.82%), disulfiram with copper (86.54%), and hydroxychloroquine with zinc (75.21%), demonstrated higher proportions of cancer treatment-specific research compared to more established drugs. This pattern suggests that emerging candidates may generate more focused research specifically targeting cancer applications.

Pharmacological class analysis revealed varying research patterns. Antiparasitics (61.96%), antialcoholics (66.99%), and antimalarials (75.21%) exhibited high treatment specificity ratios, despite modest absolute volumes, indicating a focused interest in their anticancer mechanisms. Conversely, established classes like corticosteroids (18.71%) and antidiabetics (27.95%) demonstrated lower treatment specificity, suggesting broader research applications.

Database analysis showed that Google Scholar (64.39%) and Science.gov (33.63%) provided 98% coverage, while correlation patterns revealed differences in indexing approaches between databases, with implications for bibliographic research strategies in drug repurposing studies.

This bibliometric assessment offers insights into the distribution patterns of research across multiple off-patent anticancer candidates. The identified patterns may inform research prioritization decisions, highlighting medications with high treatment specificity ratios but modest absolute research volumes that warrant further investigation.

The findings suggest potential opportunities in less-studied candidates, particularly within classes showing high treatment specificity despite lower absolute volumes. The concentration patterns raise questions about resource allocation in drug repurposing research and suggest value in considering both established and emerging therapeutic candidates.

Further research combining bibliometric analysis with qualitative assessment of clinical significance could enhance the understanding of optimal research prioritization in drug repurposing. The methodological approach demonstrated here could be applied to other therapeutic areas or used to monitor evolving research trends over time.

5. DECLARATIONS

5.1. Study Limitations

Methodological Limitations: The study employs a purely quantitative analysis that records only total result numbers without categorizing by study type, such as *in vitro*, *in vivo*, or clinical trials. This approach does not evaluate the methodological quality or clinical relevance of studies and fails to distinguish between preliminary studies and advanced research. Additionally, the search strategy is limited to simple terms, such as "medication AND cancer," without employing synonyms, MeSH terms, or more sophisticated search strategies, which may have resulted in missing relevant studies that use different terminology.

Database Limitations: Significant heterogeneity exists among databases, as evidenced by the different indexing criteria used across platforms. The correlation between Google Scholar and PubMed is notably low, at 0.1562, indicating a possible uncontrolled overlap between the databases. Google Scholar's inclusion of grey literature may inflate results compared to more selective academic databases. Furthermore, the study does not specify the temporal period of searches, which may create a potential temporal coverage bias, as older medications may have had historical advantages, and changes in terminology over time are not considered.

Categorization Limitations: The pharmacological grouping approach is simplified and may not reflect specific anticancer mechanisms, particularly since some medications have multiple pharmacological actions. Combinations such as "disulfiram + copper" are treated separately, which may not accurately represent their therapeutic potential. The study lacks population and indication control, failing to distinguish between different cancer types, geographical variations in research, or trends by age group or specific populations.

Interpretative Limitations: The absence of qualitative analysis represents a significant limitation, as publication volume does not necessarily equate to clinical efficacy. The study does not evaluate the level of evidence of individual studies or consider the balance between negative and positive findings. There is also a lack of clinical contextualization, as the bibliometric findings are not related to regulatory approvals, the current clinical development status of medications, or the practical feasibility of repurposing efforts.

Technical Limitations: The presence of possible duplications poses a technical concern, as the same study may appear in multiple databases without adequate control for duplicate elimination. Preprints may be counted alongside published versions, potentially inflating certain medication counts. Additionally, language limitations may exist, as databases may have a bias toward English-language publications, resulting in the under-representation of literature in other languages.

These limitations collectively suggest that results should be interpreted as an initial panoramic view of the field, requiring complementary detailed studies to guide research and clinical development decisions. The findings provide valuable insights into research distribution patterns but should not be considered definitive evidence of therapeutic potential or research priority without additional qualitative assessment.

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5.4. Competing Interests

Declare any potential conflict of interest that exists in this publication.

5.6. AI use declaration

Artificial intelligence tools were utilized to support data analysis, statistical processing, and the textual structuring of this document. All results, interpretations, and conclusions were subsequently validated, reviewed, and refined by human researchers to ensure methodological accuracy and scientific rigor.

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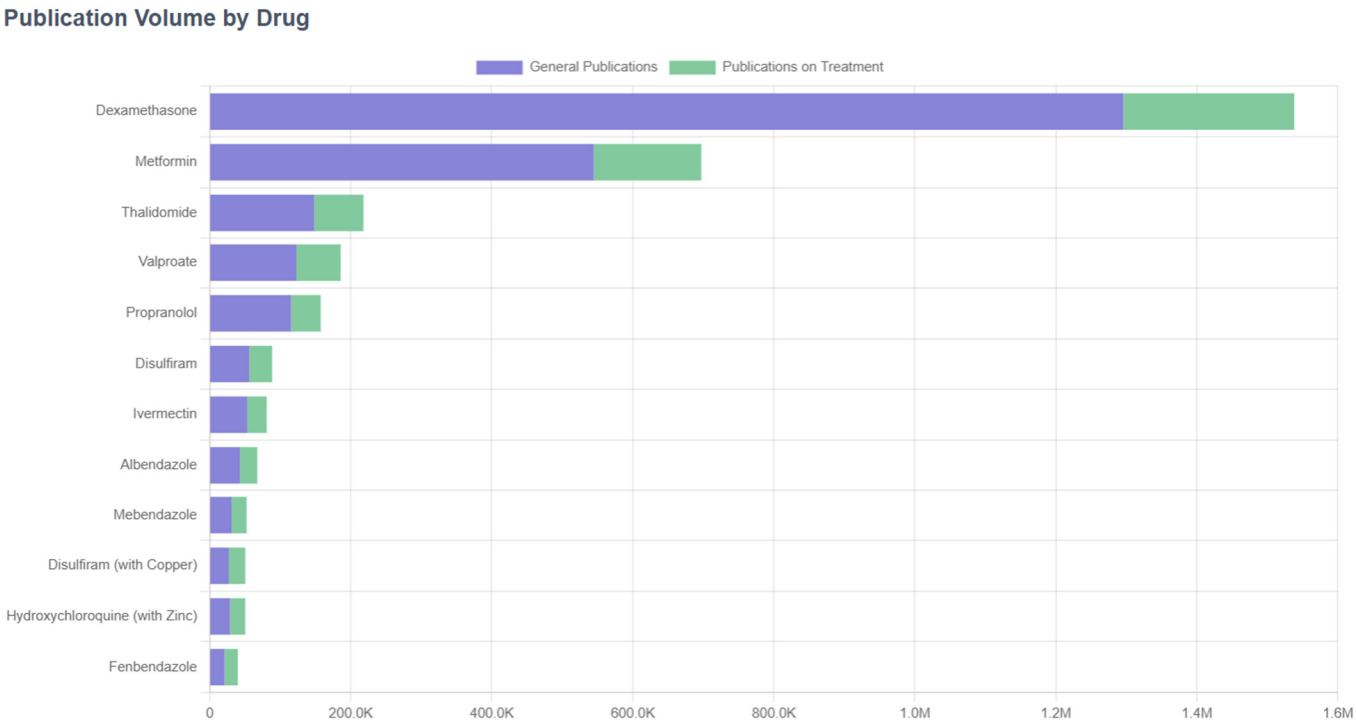

Figure 1. *Ranking of Drugs by Total Publication Volume*

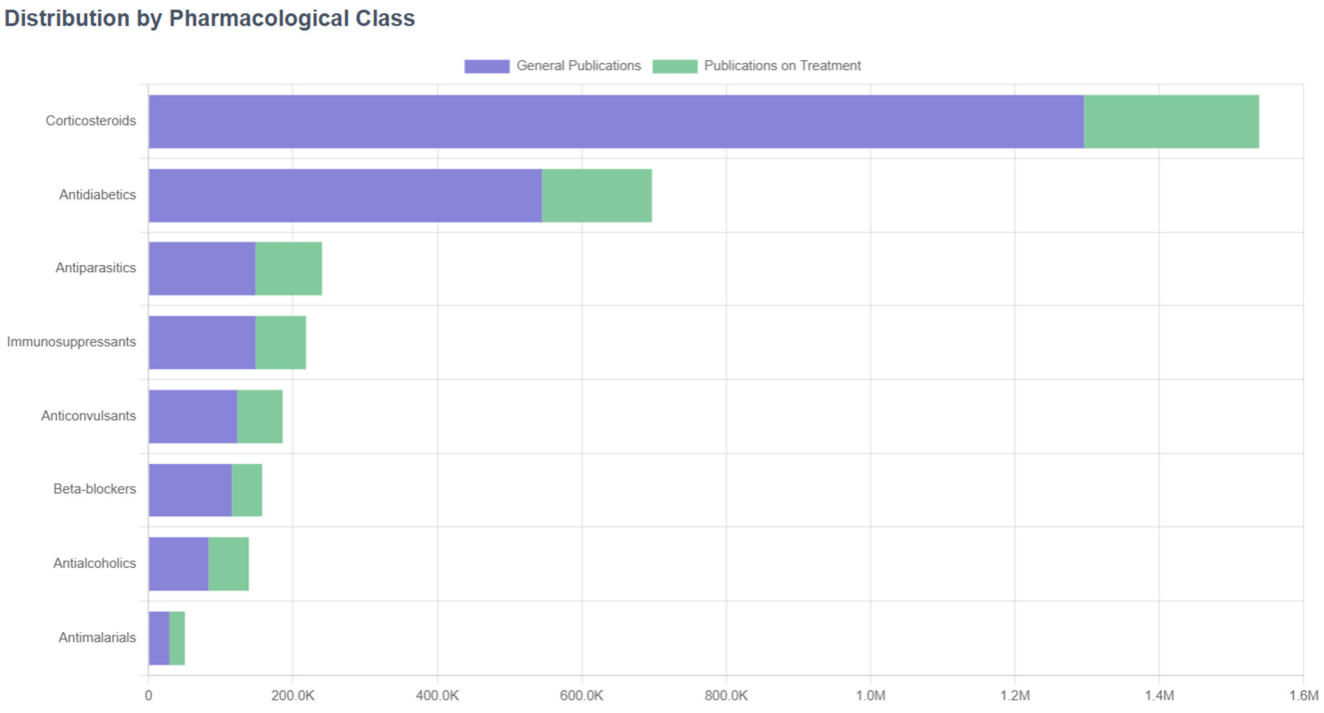

Figure 2. *Analysis by Pharmacological Classes*

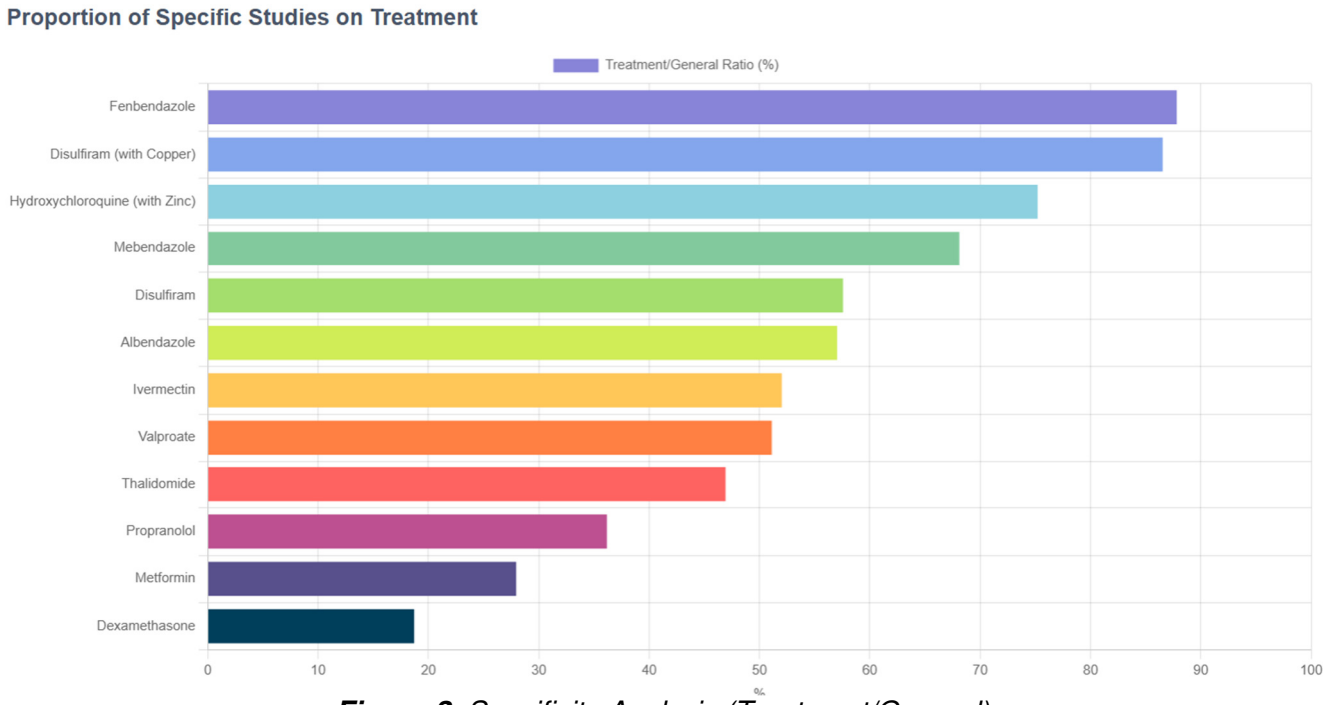

Figure 3. *Specificity Analysis (Treatment/General)*

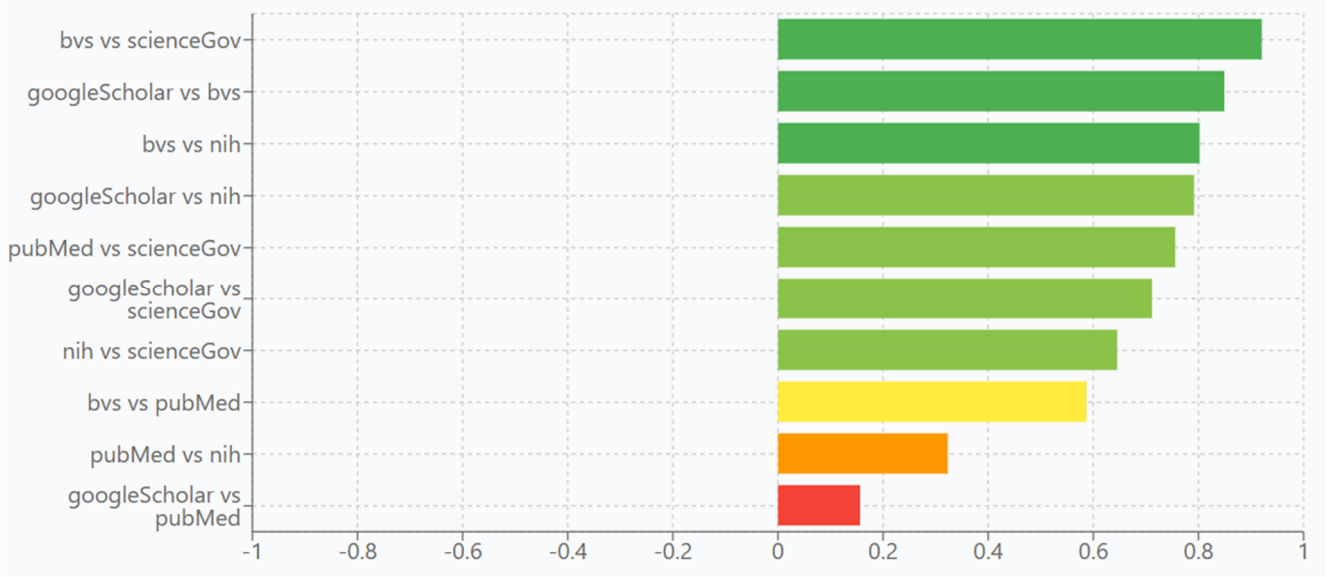

Figure 4. *Database Correlation Analysis.*

The correlation analysis examines the relationship between different databases in terms of result patterns. The high correlation suggests similar indexing or coverage patterns.

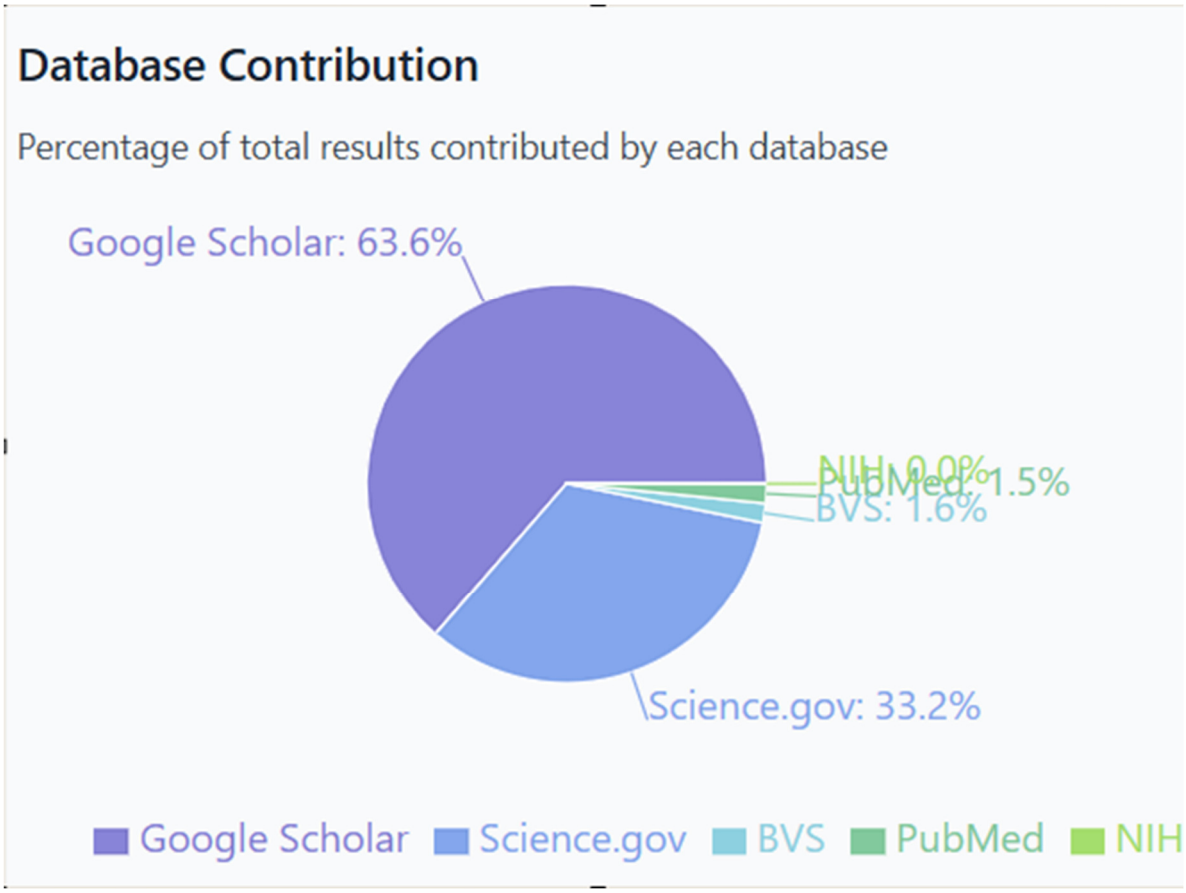

Figure 5. *Database Contribution*

Table 1. *Bibliometric search results for off-patent medications across five databases using cancer-related search terms*

Term	Google Scholar	BVS	PubMed	NIH	science.gov	Total
Ivermectin AND cancer	29.300	276	365	22	23168	53.131
Fenbendazole AND cancer	3.460	65	70	6	17587	21.188
Mebendazole AND cancer	11.600	193	230	10	19091	31.124
Albendazole AND cancer	21.000	287	421	10	21202	42.920
Metformin AND cancer	430.000	5.733	7,84	184	108948	544.873
Propranolol AND cancer	82.600	1.710	2,504	152	31101	115.566
Disulfiram AND cancer	29.100	762	802	68	25430	56.162
Valproate AND cancer	72.200	1.131	211	99	49301	122.942
Thalidomide AND cancer	101.000	5.147	2,102	188	42076	148.413
Dexamethasone AND cancer	1.110.000	15.546	1,994	262	169856	1.295.666
Hydroxychloroquine (with Zinc) AND cancer	9.510	8	7	20	19202	28.747
Disulfiram (with Copper) AND cancer	7.270	240	282	26	19234	27.052
Ivermectin AND cancer treatment	2.990	155	295	10	24191	27.641
Fenbendazole AND cancer treatment	405	33	55	0	18114	18.607
Mebendazole AND cancer treatment	1.500	172	21	0	19507	21.200
Albendazole AND cancer treatment	2.060	171	377	4	21869	24.481
Metformin AND cancer treatment	42.700	3.342	6,914	29	106221	152.299
Propranolol AND cancer treatment	7.790	1.111	2,054	24	32878	41.805
Disulfiram AND cancer treatment	5.690	439	638	18	25549	32.334
Valproate AND cancer treatment	13.500	756	1,805	28	48559	62.845
Thalidomide AND cancer treatment	17.500	3.951	6,155	67	48122	69.646
Dexamethasone AND cancer treatment	71.500	9.430	15,637	78	161368	242.392
Hydroxychloroquine (with Zinc) AND cancer treatment	1.700	6	6	1	19908	21.621
Disulfiram (with Copper) AND cancer treatment	3.050	157	262	10	19932	23.411

Anexo

CODE 1

```
<!DOCTYPE html>
<html lang="en">
<head>
    <meta charset="UTF-8">
    <meta name="viewport" content="width=device-width, initial-scale=1.0">
    <title>Bibliometric Analysis: Repurposed Drugs for Cancer</title>
    <style>
        body {
            font-family: Arial, sans-serif;
            line-height: 1.6;
            color: #333;
            max-width: 1200px;
            margin: 0 auto;
            padding: 20px;
        }
        h1 {
            color: #2c3e50;
            text-align: center;
            margin-bottom: 30px;
            border-bottom: 2px solid #3498db;
            padding-bottom: 10px;
        }
        h2 {
            color: #2980b9;
            margin-top: 30px;
            border-left: 4px solid #3498db;
            padding-left: 10px;
        }
        h3 {
            color: #3498db;
        }
        pre {
            background-color: #f8f9fa;
            border: 1px solid #ddd;
            border-radius: 4px;
            padding: 15px;
            overflow-x: auto;
            margin: 20px 0;
        }
        code {
            font-family: Consolas, Monaco, 'Andale Mono', monospace;
            color: #333;
        }
        .container {
            display: flex;
            flex-wrap: wrap;
            justify-content: space-between;
        }
        .column {
            flex: 0 0 48%;
            margin-bottom: 20px;
        }
        table {
            width: 100%;
            border-collapse: collapse;
            margin: 20px 0;
        }
        th, td {
            border: 1px solid #ddd;
```

```
            padding: 8px;
            text-align: left;
        }
        th {
            background-color: #f2f2f2;
        }
        tr:nth-child(even) {
            background-color: #f9f9f9;
        }
        .button {
            background-color: #3498db;
            color: white;
            padding: 10px 15px;
            border: none;
            border-radius: 4px;
            cursor: pointer;
            font-size: 16px;
        }
        .button:hover {
            background-color: #2980b9;
        }
        .results-container {
            background-color: #f8f9fa;
            border: 1px solid #ddd;
            border-radius: 4px;
            padding: 15px;
            margin-top: 20px;
        }
        #results {
            white-space: pre-wrap;
            font-family: Consolas, Monaco, 'Andale Mono', monospace;
            max-height: 500px;
            overflow-y: auto;
        }
    </style>
</head>
<body>
    <h1>Bibliometric Analysis: Repurposed Drugs for Cancer Treatment</h1>

    <div class="container">
        <div class="column">
            <h2>Summary</h2>
            <p>This page contains the complete code used to perform the bibliometric analysis of search results on repurposed drugs for cancer treatment. The goal is to enable research reproducibility and methodological transparency.</p>

            <h2>Instructions</h2>
            <p>This JavaScript code performs multiple statistical analyses on search data from scientific databases. To run the code:</p>
            <ol>
                <li>Copy the code from the "Complete Code" section</li>
                <li>Open your browser's console (F12 or Ctrl+Shift+J)</li>
                <li>Paste the code and press Enter</li>
                <li>Alternatively, click the "Run Analysis" button below</li>
            </ol>

            <button id="runButton" class="button">Run Analysis</button>
        </div>

        <div class="column">
            <h2>Input Data</h2>
```

```
            <p>The data used in this analysis are the search results from five databases (Google Scholar, BVS, PubMed, NIH, and Science.gov) for 12 drugs, each with two search variations:</p>
            <ul>
                <li>"drug AND cancer"</li>
                <li>"drug AND cancer treatment"</li>
            </ul>

            <p>The table below shows a sample of the data:</p>
            <table id="sampleTable">
                <thead>
                    <tr>
                        <th>Search</th>
                        <th>Google Scholar</th>
                        <th>BVS</th>
                        <th>PubMed</th>
                        <th>NIH</th>
                        <th>Science.gov</th>
                        <th>Total</th>
                    </tr>
                </thead>
                <tbody>
                    <!-- Will be filled by JavaScript -->
                </tbody>
            </table>
        </div>
    </div>

    <h2>Analysis Results</h2>
    <div class="results-container">
        <div id="results">Click "Run Analysis" to see the results.</div>
    </div>

    <script>
        // Structure of the bibliometric research data
        const data = [
            { drug: "Ivermectin AND cancer", googleScholar: 29300, bvs: 276, pubMed: 365, nih: 22, scienceGov: 23168, total: 53131 },
            { drug: "Fenbendazole AND cancer", googleScholar: 3460, bvs: 65, pubMed: 70, nih: 6, scienceGov: 17587, total: 21188 },
            { drug: "Mebendazole AND cancer", googleScholar: 11600, bvs: 193, pubMed: 230, nih: 10, scienceGov: 19091, total: 31124 },
            { drug: "Albendazole AND cancer", googleScholar: 21000, bvs: 287, pubMed: 421, nih: 10, scienceGov: 21202, total: 42920 },
            { drug: "Metformin AND cancer", googleScholar: 430000, bvs: 5733, pubMed: 7384, nih: 184, scienceGov: 101572, total: 544873 },
            { drug: "Propranolol AND cancer", googleScholar: 82600, bvs: 1710, pubMed: 2504, nih: 152, scienceGov: 31101, total: 115566 },
            { drug: "Disulfiram AND cancer", googleScholar: 29100, bvs: 762, pubMed: 802, nih: 68, scienceGov: 25430, total: 56162 },
            { drug: "Valproate AND cancer", googleScholar: 72200, bvs: 1131, pubMed: 211, nih: 99, scienceGov: 49301, total: 122942 },
            { drug: "Thalidomide AND cancer", googleScholar: 101000, bvs: 5147, pubMed: 2102, nih: 188, scienceGov: 42076, total: 148413 },
            { drug: "Dexamethasone AND cancer", googleScholar: 1110000, bvs: 15546, pubMed: 1994, nih: 262, scienceGov: 169856, total: 1295666 },
            { drug: "Hydroxychloroquine (with Zinc) AND cancer", googleScholar: 9510, bvs: 8, pubMed: 7, nih: 20, scienceGov: 19202, total: 28747 },
            { drug: "Disulfiram (with Copper) AND cancer", googleScholar: 7270, bvs: 240, pubMed: 282, nih: 26, scienceGov: 19234, total: 27052 },

            { drug: "Ivermectin AND cancer treatment", googleScholar: 2990, bvs: 155, pubMed: 295, nih: 10, scienceGov: 24191, total: 27641 },
```

```
    { drug: "Fenbendazole AND cancer treatment", googleScholar: 405, bvs: 33, pubMed: 55, nih: 0, scienceGov: 18114, total: 18607 },
    { drug: "Mebendazole AND cancer treatment", googleScholar: 1500, bvs: 172, pubMed: 21, nih: 0, scienceGov: 19507, total: 21200 },
    { drug: "Albendazole AND cancer treatment", googleScholar: 2060, bvs: 171, pubMed: 377, nih: 4, scienceGov: 21869, total: 24481 },
    { drug: "Metformin AND cancer treatment", googleScholar: 42700, bvs: 3342, pubMed: 6914, nih: 29, scienceGov: 106221, total: 152299 },
    { drug: "Propranolol AND cancer treatment", googleScholar: 7790, bvs: 1111, pubMed: 2054, nih: 24, scienceGov: 32878, total: 41805 },
    { drug: "Disulfiram AND cancer treatment", googleScholar: 5690, bvs: 439, pubMed: 638, nih: 18, scienceGov: 25549, total: 32334 },
    { drug: "Valproate AND cancer treatment", googleScholar: 13500, bvs: 756, pubMed: 1805, nih: 28, scienceGov: 48559, total: 62845 },
    { drug: "Thalidomide AND cancer treatment", googleScholar: 17500, bvs: 3951, pubMed: 6155, nih: 67, scienceGov: 48122, total: 69646 },
    { drug: "Dexamethasone AND cancer treatment", googleScholar: 71500, bvs: 9430, pubMed: 15637, nih: 78, scienceGov: 161368, total: 242392 },
    { drug: "Hydroxychloroquine (with Zinc) AND cancer treatment", googleScholar: 1700, bvs: 6, pubMed: 6, nih: 1, scienceGov: 19908, total: 21621 },
    { drug: "Disulfiram (with Copper) AND cancer treatment", googleScholar: 3050, bvs: 157, pubMed: 262, nih: 10, scienceGov: 19932, total: 23411 }
];

/**
 * Function that performs the complete analysis of bibliometric data
 * @return {string} Results formatted as text
 */
function runAnalysis() {
  let results = "";

  // Helper function to add text to results
  function appendResult(text) {
    results += text + "\n";
  }

  // Extract basic drug name
  const extractDrugName = (fullName) => {
    if (fullName.includes(" (with ")) {
      // For drugs with additions like "(with Zinc)"
      return fullName.split(" AND ")[0];
    } else {
      // For regular drugs
      return fullName.split(" AND ")[0];
    }
  };

  // Group by basic drug
  const drugMap = {};
  data.forEach(item => {
    const basicDrug = extractDrugName(item.drug);
    const isTreatment = item.drug.includes("treatment");

    if (!drugMap[basicDrug]) {
      drugMap[basicDrug] = {
        name: basicDrug,
        general: null,
        treatment: null
      };
    }

    if (isTreatment) {
```

```
      drugMap[basicDrug].treatment = item;
    } else {
      drugMap[basicDrug].general = item;
    }
  });

  const drugPairs = Object.values(drugMap);

  // 1. Basic Descriptive Analysis
  appendResult("1. BASIC DESCRIPTIVE ANALYSIS");
  appendResult("==========================");

  // Calculate basic statistics for total results
  const totalResults = data.map(item => item.total);
  const sum = totalResults.reduce((acc, val) => acc + val, 0);
  const mean = sum / totalResults.length;
  const sortedTotals = [...totalResults].sort((a, b) => a - b);
  const median = sortedTotals.length % 2 === 0
    ? (sortedTotals[sortedTotals.length / 2 - 1] + sortedTotals[sortedTotals.length / 2]) / 2
    : sortedTotals[Math.floor(sortedTotals.length / 2)];
  const variance = totalResults.reduce((acc, val) => acc + Math.pow(val - mean, 2), 0) /
totalResults.length;
  const stdDev = Math.sqrt(variance);

  appendResult(`Total number of entries: ${data.length}`);
  appendResult(`Total sum of results: ${sum}`);
  appendResult(`Average results per entry: ${mean.toFixed(2)}`);
  appendResult(`Median of results: ${median}`);
  appendResult(`Standard deviation: ${stdDev.toFixed(2)}`);
  appendResult(`Minimum value: ${Math.min(...totalResults)}`);
  appendResult(`Maximum value: ${Math.max(...totalResults)}`);
  appendResult("");

  // 2. Ranking of Drugs by Total Publication Volume
  appendResult("2. RANKING OF DRUGS BY TOTAL PUBLICATION VOLUME");
  appendResult("============================================================");

  // Sum total results for each basic drug (general + treatment)
  const drugTotals = drugPairs.map(pair => {
    const generalTotal = pair.general ? pair.general.total : 0;
    const treatmentTotal = pair.treatment ? pair.treatment.total : 0;
    return {
      drug: pair.name,
      generalTotal,
      treatmentTotal,
      combinedTotal: generalTotal + treatmentTotal
    };
  });

  // Sort by combined total
  drugTotals.sort((a, b) => b.combinedTotal - a.combinedTotal);

  // Display ranking
  appendResult("Ranking by total publication volume (general + treatment):");
  drugTotals.forEach((item, index) => {
    appendResult(`${index + 1}. ${item.drug}: ${item.combinedTotal} publications
(${item.generalTotal} general, ${item.treatmentTotal} treatment)`);
  });
  appendResult("");

  // 3. Analysis by Pharmacological Classes
  appendResult("3. ANALYSIS BY PHARMACOLOGICAL CLASSES");
```

```
appendResult("====================================");

// Define drug groups
const drugGroups = {
  "Antiparasitics": ["Ivermectin", "Fenbendazole", "Mebendazole", "Albendazole"],
  "Antidiabetics": ["Metformin"],
  "Beta-blockers": ["Propranolol"],
  "Antialcoholics": ["Disulfiram", "Disulfiram (with Copper)"],
  "Anticonvulsants": ["Valproate"],
  "Immunosuppressants": ["Thalidomide"],
  "Corticosteroids": ["Dexamethasone"],
  "Antimalarials": ["Hydroxychloroquine (with Zinc)"]
};

// Calculate total for each group
const groupTotals = {};
for (const [group, drugs] of Object.entries(drugGroups)) {
  groupTotals[group] = {
    generalTotal: 0,
    treatmentTotal: 0,
    combinedTotal: 0,
    drugs: drugs
  };

  drugs.forEach(drug => {
    const drugData = drugTotals.find(d => d.drug === drug);
    if (drugData) {
      groupTotals[group].generalTotal += drugData.generalTotal;
      groupTotals[group].treatmentTotal += drugData.treatmentTotal;
      groupTotals[group].combinedTotal += drugData.combinedTotal;
    }
  });
}

// Sort groups by total
const sortedGroups = Object.entries(groupTotals)
  .sort((a, b) => b[1].combinedTotal - a[1].combinedTotal);

// Display results by group
sortedGroups.forEach(([group, data]) => {
  appendResult(`Group: ${group}`);
  appendResult(`Total publications: ${data.combinedTotal}`);
  appendResult(`General publications: ${data.generalTotal}`);
  appendResult(`Treatment publications: ${data.treatmentTotal}`);
  appendResult(`Treatment/general ratio: ${(data.treatmentTotal / data.generalTotal *
100).toFixed(2)}%`);
  appendResult(`Drugs in the group: ${data.drugs.join(", ")}`);
  appendResult("");
});

// 4. Specificity Analysis (Treatment/General)
appendResult("4. SPECIFICITY ANALYSIS (TREATMENT/GENERAL)");
appendResult("============================================");

// Calculate the proportion of treatment results relative to general results
const specificityAnalysis = drugPairs.map(pair => {
  const generalTotal = pair.general ? pair.general.total : 0;
  const treatmentTotal = pair.treatment ? pair.treatment.total : 0;
  const ratio = generalTotal > 0 ? (treatmentTotal / generalTotal) * 100 : 0;

  return {
    drug: pair.name,
```

```
      generalTotal,
      treatmentTotal,
      ratio
    };
  });

  // Sort by ratio
  specificityAnalysis.sort((a, b) => b.ratio - a.ratio);

  // Display results
  appendResult("Proportion of 'treatment' results relative to 'general' results:");
  specificityAnalysis.forEach(item => {
    appendResult(`${item.drug}: ${item.ratio.toFixed(2)}% (${item.treatmentTotal} treatment /
${item.generalTotal} general)`);
  });
  appendResult("");

  // 5. Correlation Analysis Between Databases
  appendResult("5. CORRELATION ANALYSIS BETWEEN DATABASES");
  appendResult("==========================================");

  // Function to calculate Pearson correlation coefficient
  function calculateCorrelation(x, y) {
    const n = x.length;
    let sumX = 0;
    let sumY = 0;
    let sumXY = 0;
    let sumX2 = 0;
    let sumY2 = 0;

    for (let i = 0; i < n; i++) {
      sumX += x[i];
      sumY += y[i];
      sumXY += x[i] * y[i];
      sumX2 += x[i] * x[i];
      sumY2 += y[i] * y[i];
    }

    const numerator = n * sumXY - sumX * sumY;
    const denominator = Math.sqrt((n * sumX2 - sumX * sumX) * (n * sumY2 - sumY * sumY));

    return denominator === 0 ? 0 : numerator / denominator;
  }

  // Extract data from each database
  const databases = ["googleScholar", "bvs", "pubMed", "nih", "scienceGov"];
  const databaseValues = {};
  databases.forEach(db => {
    databaseValues[db] = data.map(item => item[db]);
  });

  // Calculate correlations between pairs of databases
  const correlations = [];
  for (let i = 0; i < databases.length; i++) {
    for (let j = i + 1; j < databases.length; j++) {
      const corr = calculateCorrelation(databaseValues[databases[i]], databaseValues[databases[j]]);
      correlations.push({
        pair: `${databases[i]} vs ${databases[j]}`,
        correlation: corr
      });
    }
  }
```

```
// Sort by correlation strength
correlations.sort((a, b) => Math.abs(b.correlation) - Math.abs(a.correlation));

// Display correlations
appendResult("Correlations between databases (Pearson coefficient):");
correlations.forEach(item => {
  const strength = Math.abs(item.correlation) > 0.8 ? "Very strong" :
                   Math.abs(item.correlation) > 0.6 ? "Strong" :
                   Math.abs(item.correlation) > 0.4 ? "Moderate" :
                   Math.abs(item.correlation) > 0.2 ? "Weak" : "Very weak";

  appendResult(`${item.pair}: ${item.correlation.toFixed(4)} (${strength})`);
});
appendResult("");

// 6. Relative Contribution Analysis
appendResult("6. RELATIVE CONTRIBUTION ANALYSIS");
appendResult("==================================");

// Calculate the percentage contribution of each drug to the total publications
const totalPublications = drugTotals.reduce((sum, item) => sum + item.combinedTotal, 0);

appendResult("Percentage contribution of each drug to the total publications:");
drugTotals.forEach(item => {
  const percentage = (item.combinedTotal / totalPublications) * 100;
  appendResult(`${item.drug}: ${percentage.toFixed(2)}%`);
});
appendResult("");

// Calculate Herfindahl index
const herfindahlIndex = drugTotals.reduce((sum, item) => {
  const marketShare = item.combinedTotal / totalPublications;
  return sum + (marketShare * marketShare);
}, 0);

appendResult(`Herfindahl Index (research concentration): ${herfindahlIndex.toFixed(4)}`);
appendResult(`Interpretation: ${
  herfindahlIndex < 0.01 ? "Highly diversified" :
  herfindahlIndex < 0.15 ? "Not concentrated" :
  herfindahlIndex < 0.25 ? "Moderately concentrated" : "Highly concentrated"
}`);
appendResult("");

// 7. Search Efficiency by Database
appendResult("7. SEARCH EFFICIENCY BY DATABASE");
appendResult("=========================================");

// Calculate the percentage contribution of each database
const databaseContributions = {};
databases.forEach(db => {
  const total = data.reduce((sum, item) => sum + item[db], 0);
  databaseContributions[db] = {
    total,
    percentage: (total / sum) * 100
  };
});

// Sort databases by contribution
const sortedDatabases = Object.entries(databaseContributions)
  .sort((a, b) => b[1].total - a[1].total);
```

```
            appendResult("Contribution of each database to the total results:");
            sortedDatabases.forEach(([db, data]) => {
              appendResult(`${db}: ${data.total} results (${data.percentage.toFixed(2)}% of total)`);
            });

            return results;
        }

        // Function to fill the sample table
        function fillSampleTable() {
            const sampleData = [
                { drug: "Ivermectin AND cancer", googleScholar: 29300, bvs: 276, pubMed: 365, nih: 22,
scienceGov: 23168, total: 53131 },
                { drug: "Metformin AND cancer", googleScholar: 430000, bvs: 5733, pubMed: 7384, nih: 184,
scienceGov: 101572, total: 544873 },
                { drug: "Dexamethasone AND cancer", googleScholar: 1110000, bvs: 15546, pubMed: 1994,
nih: 262, scienceGov: 169856, total: 1295666 },
                { drug: "Ivermectin AND cancer treatment", googleScholar: 2990, bvs: 155, pubMed: 295, nih:
10, scienceGov: 24191, total: 27641 },
                { drug: "Thalidomide AND cancer treatment", googleScholar: 17500, bvs: 3951, pubMed:
6155, nih: 67, scienceGov: 48122, total: 69646 }
            ];

            const tbody = document.querySelector('#sampleTable tbody');

            sampleData.forEach(item => {
                const row = document.createElement('tr');

                const drugCell = document.createElement('td');
                drugCell.textContent = item.drug;
                row.appendChild(drugCell);

                const gsCell = document.createElement('td');
                gsCell.textContent = item.googleScholar.toLocaleString();
                row.appendChild(gsCell);

                const bvsCell = document.createElement('td');
                bvsCell.textContent = item.bvs.toLocaleString();
                row.appendChild(bvsCell);

                const pmCell = document.createElement('td');
                pmCell.textContent = item.pubMed.toLocaleString();
                row.appendChild(pmCell);

                const nihCell = document.createElement('td');
                nihCell.textContent = item.nih.toLocaleString();
                row.appendChild(nihCell);

                const sgCell = document.createElement('td');
                sgCell.textContent = item.scienceGov.toLocaleString();
                row.appendChild(sgCell);

                const totalCell = document.createElement('td');
                totalCell.textContent = item.total.toLocaleString();
                row.appendChild(totalCell);

                tbody.appendChild(row);
            });
        }

        // Initialize page when loaded
        document.addEventListener('DOMContentLoaded', function() {
```

```
            fillSampleTable();

            // Add event listener to run button
            document.getElementById('runButton').addEventListener('click', function() {
                try {
                    const results = runAnalysis();
                    document.getElementById('results').textContent = results;
                } catch (error) {
                    document.getElementById('results').textContent = 'Error running analysis: ' +
error.message;
                    console.error('Analysis error:', error);
                }
            });
        });
    </script>
</body>
</html>
```

Code 2

```
<!DOCTYPE html>
<html lang="en">
<head>
    <meta charset="UTF-8">
    <meta name="viewport" content="width=device-width, initial-scale=1.0">
    <title>Bibliometric Analysis: Repurposed Drugs for Cancer Treatment</title>
    <style>
        body {
            font-family: Arial, sans-serif;
            background-color: #f7fafc;
            padding: 20px;
        }
        .container {
            max-width: 1200px;
            margin: 0 auto;
            background-color: #fff;
            padding: 20px;
            border-radius: 8px;
            box-shadow: 0 2px 4px rgba(0, 0, 0, 0.1);
        }
```

```
        h1 {
            text-align: center;
            color: #1a202c;
            margin-bottom: 20px;
        }
        h2 {
            font-size: 1.5rem;
            font-weight: bold;
            color: #2d3748;
            margin-top: 30px;
            margin-bottom: 15px;
            border-bottom: 2px solid #4299e1;
            padding-bottom: 5px;
        }
        .visualization-card {
            background-color: #fff;
            border-radius: 8px;
            box-shadow: 0 2px 4px rgba(0, 0, 0, 0.1);
            padding: 15px;
            margin-bottom: 20px;
        }
        .visualization-card h3 {
            font-size: 1.25rem;
            font-weight: 600;
            color: #4a5568;
            margin-bottom: 15px;
        }
        .grid {
            display: grid;
            grid-template-columns: 1fr;
            gap: 20px;
        }
        @media (min-width: 768px) {
            .grid {
                grid-template-columns: 1fr 1fr;
            }
        }
        canvas {
            max-width: 100%;
            height: auto;
        }
        .chart-container {
            min-height: 400px;
        }
        p {
            font-size: 0.875rem;
            color: #718096;
            text-align: center;
            margin-top: 10px;
        }
    </style>
</head>
<body>
    <div class="container">
        <h1>Bibliometric Analysis: Repurposed Drugs for Cancer Treatment</h1>

        <h2>1. Ranking of Drugs by Total Publication Volume</h2>
        <div class="visualization-card">
            <h3>Publication Volume by Drug</h3>
            <div class="chart-container">
                <canvas id="drugTotalsChart"></canvas>
            </div>
```

```
        </div>

        <h2>2. Analysis by Pharmacological Classes</h2>
        <div class="visualization-card">
            <h3>Distribution by Pharmacological Class</h3>
            <div class="chart-container">
                <canvas id="pharmacologicalGroupsChart"></canvas>
            </div>
        </div>

        <div class="grid">
            <div class="visualization-card">
                <h3>Treatment/General Ratio by Pharmacological Class (%)</h3>
                <div class="chart-container">
                    <canvas id="groupRatioChart"></canvas>
                </div>
            </div>
            <div class="visualization-card">
                <h3>Relative Contribution of Databases</h3>
                <div class="chart-container">
                    <canvas id="databaseContributionsChart"></canvas>
                </div>
            </div>
        </div>

        <h2>3. Specificity Analysis (Treatment/General)</h2>
        <div class="visualization-card">
            <h3>Proportion of Specific Studies on Treatment</h3>
            <div class="chart-container">
                <canvas id="specificityChart"></canvas>
            </div>
        </div>

        <h2>4. Comparison between Total Volume and Specificity</h2>
        <div class="visualization-card">
            <h3>Relationship between Total Publication Volume and Specificity by Drug</h3>
            <div class="chart-container">
                <canvas id="radarChart"></canvas>
            </div>
            <p>This radar chart shows the relationship between the total volume of publications (on a
logarithmic scale) and the proportion of specific studies on treatment for each drug.</p>
        </div>
    </div>

    <script src="https://cdn.jsdelivr.net/npm/chart.js@4.4.0/dist/chart.umd.min.js"></script>
    <script>
        // Raw data
        const data = [
            { drug: "Ivermectin AND cancer", googleScholar: 29300, bvs: 276, pubMed: 365, nih: 22,
scienceGov: 23168, total: 53131 },
            { drug: "Fenbendazole AND cancer", googleScholar: 3460, bvs: 65, pubMed: 70, nih: 6,
scienceGov: 17587, total: 21188 },
            { drug: "Mebendazole AND cancer", googleScholar: 11600, bvs: 193, pubMed: 230, nih: 10,
scienceGov: 19091, total: 31124 },
            { drug: "Albendazole AND cancer", googleScholar: 21000, bvs: 287, pubMed: 421, nih: 10,
scienceGov: 21202, total: 42920 },
            { drug: "Metformin AND cancer", googleScholar: 430000, bvs: 5733, pubMed: 7384, nih: 184,
scienceGov: 101572, total: 544873 },
            { drug: "Propranolol AND cancer", googleScholar: 82600, bvs: 1710, pubMed: 2504, nih: 152,
scienceGov: 31101, total: 115566 },
            { drug: "Disulfiram AND cancer", googleScholar: 29100, bvs: 762, pubMed: 802, nih: 68,
scienceGov: 25430, total: 56162 },
```

```
        { drug: "Valproate AND cancer", googleScholar: 72200, bvs: 1131, pubMed: 211, nih: 99, scienceGov: 49301, total: 122942 },
        { drug: "Thalidomide AND cancer", googleScholar: 101000, bvs: 5147, pubMed: 2102, nih: 188, scienceGov: 42076, total: 148413 },
        { drug: "Dexamethasone AND cancer", googleScholar: 1110000, bvs: 15546, pubMed: 1994, nih: 262, scienceGov: 169856, total: 1295666 },
        { drug: "Hydroxychloroquine (with Zinc) AND cancer", googleScholar: 9510, bvs: 8, pubMed: 7, nih: 20, scienceGov: 19202, total: 28747 },
        { drug: "Disulfiram (with Copper) AND cancer", googleScholar: 7270, bvs: 240, pubMed: 282, nih: 26, scienceGov: 19234, total: 27052 },
        { drug: "Ivermectin AND cancer treatment", googleScholar: 2990, bvs: 155, pubMed: 295, nih: 10, scienceGov: 24191, total: 27641 },
        { drug: "Fenbendazole AND cancer treatment", googleScholar: 405, bvs: 33, pubMed: 55, nih: 0, scienceGov: 18114, total: 18607 },
        { drug: "Mebendazole AND cancer treatment", googleScholar: 1500, bvs: 172, pubMed: 21, nih: 0, scienceGov: 19507, total: 21200 },
        { drug: "Albendazole AND cancer treatment", googleScholar: 2060, bvs: 171, pubMed: 377, nih: 4, scienceGov: 21869, total: 24481 },
        { drug: "Metformin AND cancer treatment", googleScholar: 42700, bvs: 3342, pubMed: 6914, nih: 29, scienceGov: 106221, total: 152299 },
        { drug: "Propranolol AND cancer treatment", googleScholar: 7790, bvs: 1111, pubMed: 2054, nih: 24, scienceGov: 32878, total: 41805 },
        { drug: "Disulfiram AND cancer treatment", googleScholar: 5690, bvs: 439, pubMed: 638, nih: 18, scienceGov: 25549, total: 32334 },
        { drug: "Valproate AND cancer treatment", googleScholar: 13500, bvs: 756, pubMed: 1805, nih: 28, scienceGov: 48559, total: 62845 },
        { drug: "Thalidomide AND cancer treatment", googleScholar: 17500, bvs: 3951, pubMed: 6155, nih: 67, scienceGov: 48122, total: 69646 },
        { drug: "Dexamethasone AND cancer treatment", googleScholar: 71500, bvs: 9430, pubMed: 15637, nih: 78, scienceGov: 161368, total: 242392 },
        { drug: "Hydroxychloroquine (with Zinc) AND cancer treatment", googleScholar: 1700, bvs: 6, pubMed: 6, nih: 1, scienceGov: 19908, total: 21621 },
        { drug: "Disulfiram (with Copper) AND cancer treatment", googleScholar: 3050, bvs: 157, pubMed: 262, nih: 10, scienceGov: 19932, total: 23411 }
    ];

    // Colors for the charts
    const COLORS = [
        '#8884d8', '#83a6ed', '#8dd1e1', '#82ca9d', '#a4de6c',
        '#d0ed57', '#ffc658', '#ff8042', '#ff6361', '#bc5090',
        '#58508d', '#003f5c'
    ];

    // Function to format large numbers
    function formatNumber(num) {
        if (num >= 1000000) return (num / 1000000).toFixed(1) + 'M';
        if (num >= 1000) return (num / 1000).toFixed(1) + 'K';
        return num;
    }

    // Process the data
    function processData() {
        // Extract basic drug name
        const extractDrugName = (fullName) => {
            if (fullName.includes(" (with ")) return fullName.split(" AND ")[0];
            return fullName.split(" AND ")[0];
        };

        // Group by basic drug
        const drugMap = {};
        data.forEach(item => {
            const basicDrug = extractDrugName(item.drug);
```

```
    const isTreatment = item.drug.includes("treatment");
    if (!drugMap[basicDrug]) {
      drugMap[basicDrug] = { name: basicDrug, general: null, treatment: null };
    }
    if (isTreatment) drugMap[basicDrug].treatment = item;
    else drugMap[basicDrug].general = item;
  });

  const drugPairs = Object.values(drugMap);

  // 1. Ranking of Drugs
  const drugTotals = drugPairs.map(pair => {
    const generalTotal = pair.general ? pair.general.total : 0;
    const treatmentTotal = pair.treatment ? pair.treatment.total : 0;
    return {
      drug: pair.name,
      generalTotal,
      treatmentTotal,
      combinedTotal: generalTotal + treatmentTotal
    };
  }).sort((a, b) => b.combinedTotal - a.combinedTotal).slice(0, 12);

  // 2. Pharmacological Classes
  const drugGroups = {
    "Antiparasitics": ["Ivermectin", "Fenbendazole", "Mebendazole", "Albendazole"],
    "Antidiabetics": ["Metformin"],
    "Beta-blockers": ["Propranolol"],
    "Antialcoholics": ["Disulfiram", "Disulfiram (with Copper)"],
    "Anticonvulsants": ["Valproate"],
    "Immunosuppressants": ["Thalidomide"],
    "Corticosteroids": ["Dexamethasone"],
    "Antimalarials": ["Hydroxychloroquine (with Zinc)"]
  };
  const pharmacologicalGroups = Object.entries(drugGroups).map(([group, drugs]) => {
    let generalTotal = 0, treatmentTotal = 0;
    drugs.forEach(drug => {
      const drugData = drugTotals.find(d => d.drug === drug) || { generalTotal: 0, treatmentTotal:
0 };

      generalTotal += drugData.generalTotal;
      treatmentTotal += drugData.treatmentTotal;
    });
    return {
      group,
      generalTotal,
      treatmentTotal,
      combinedTotal: generalTotal + treatmentTotal,
      ratio: generalTotal > 0 ? (treatmentTotal / generalTotal) * 100 : 0
    };
  }).sort((a, b) => b.combinedTotal - a.combinedTotal);

  // 3. Specificity
  const specificityData = drugPairs.map(pair => {
    const generalTotal = pair.general ? pair.general.total : 0;
    const treatmentTotal = pair.treatment ? pair.treatment.total : 0;
    return {
      drug: pair.name,
      generalTotal,
      treatmentTotal,
      ratio: generalTotal > 0 ? (treatmentTotal / generalTotal) * 100 : 0
    };
  }).sort((a, b) => b.ratio - a.ratio);
```

```
                // 4. Database Contributions
                const databases = ["googleScholar", "bvs", "pubMed", "nih", "scienceGov"];
                const databaseLabels = { googleScholar: "Google Scholar", bvs: "BVS", pubMed: "PubMed", nih:
"NIH", scienceGov: "Science.gov" };
                const databaseStats = {};
                let totalResults = 0;
                databases.forEach(db => {
                    const total = data.reduce((sum, item) => sum + item[db], 0);
                    totalResults += total;
                    databaseStats[db] = total;
                });
                const databaseContributions = databases.map(db => ({
                    name: databaseLabels[db],
                    value: databaseStats[db],
                    percentage: (databaseStats[db] / totalResults) * 100
                })).sort((a, b) => b.value - a.value);

                return { drugTotals, pharmacologicalGroups, specificityData, databaseContributions };
            }

            const { drugTotals, pharmacologicalGroups, specificityData, databaseContributions } =
processData();

            // Configure the charts
            new Chart(document.getElementById('drugTotalsChart'), {
                type: 'bar',
                data: {
                    labels: drugTotals.map(d => d.drug),
                    datasets: [
                        { label: 'General Publications', data: drugTotals.map(d => d.generalTotal),
backgroundColor: '#8884d8' },
                        { label: 'Publications on Treatment', data: drugTotals.map(d => d.treatmentTotal),
backgroundColor: '#82ca9d' }
                    ]
                },
                options: {
                    indexAxis: 'y',
                    scales: { x: { stacked: true, ticks: { callback: formatNumber } }, y: { stacked: true } },
                    plugins: { tooltip: { callbacks: { label: ctx => `${ctx.dataset.label}: ${new
Intl.NumberFormat().format(ctx.raw)}` } } }
                }
            });

            new Chart(document.getElementById('pharmacologicalGroupsChart'), {
                type: 'bar',
                data: {
                    labels: pharmacologicalGroups.map(g => g.group),
                    datasets: [
                        { label: 'General Publications', data: pharmacologicalGroups.map(g => g.generalTotal),
backgroundColor: '#8884d8' },
                        { label: 'Publications on Treatment', data: pharmacologicalGroups.map(g =>
g.treatmentTotal), backgroundColor: '#82ca9d' }
                    ]
                },
                options: {
                    indexAxis: 'y',
                    scales: { x: { stacked: true, ticks: { callback: formatNumber } }, y: { stacked: true } },
                    plugins: { tooltip: { callbacks: { label: ctx => `${ctx.dataset.label}: ${new
Intl.NumberFormat().format(ctx.raw)}` } } }
                }
            });
```

```
            new Chart(document.getElementById('groupRatioChart'), {
                type: 'bar',
                data: {
                    labels: pharmacologicalGroups.sort((a, b) => b.ratio - a.ratio).map(g => g.group),
                    datasets: [{
                        label: 'Treatment/General Ratio (%)',
                        data: pharmacologicalGroups.map(g => g.ratio),
                        backgroundColor: COLORS
                    }]
                },
                options: {
                    scales: { y: { beginAtZero: true, title: { display: true, text: 'Ratio (%)' } }, x: { ticks: { autoSkip:
false, maxRotation: 45, minRotation: 45 } } },
                    plugins: { tooltip: { callbacks: { label: ctx => `${ctx.dataset.label}: ${ctx.raw.toFixed(2)}%` } } }
                }
            });

            new Chart(document.getElementById('databaseContributionsChart'), {
                type: 'pie',
                data: {
                    labels: databaseContributions.map(d => d.name),
                    datasets: [{
                        data: databaseContributions.map(d => d.value),
                        backgroundColor: COLORS
                    }]
                },
                options: {
                    plugins: {
                        tooltip: { callbacks: { label: ctx => `${ctx.label}: ${new Intl.NumberFormat().format(ctx.raw)}
(${ctx.dataset.data[ctx.dataIndex].percentage.toFixed(1)}%)` } },
                        legend: { position: 'right' }
                    }
                }
            });

            new Chart(document.getElementById('specificityChart'), {
                type: 'bar',
                data: {
                    labels: specificityData.map(d => d.drug),
                    datasets: [{
                        label: 'Treatment/General Ratio (%)',
                        data: specificityData.map(d => d.ratio),
                        backgroundColor: COLORS
                    }]
                },
                options: {
                    indexAxis: 'y',
                    scales: { x: { max: 100, title: { display: true, text: '%' } } },
                    plugins: { tooltip: { callbacks: { label: ctx => `${ctx.dataset.label}: ${ctx.raw.toFixed(2)}%` } } }
                }
            });

            new Chart(document.getElementById('radarChart'), {
                type: 'radar',
                data: {
                    labels: specificityData.map(d => d.drug),
                    datasets: [
                        { label: 'Specificity (%)', data: specificityData.map(d => d.ratio), borderColor: '#8884d8',
backgroundColor: 'rgba(136, 132, 216, 0.6)' },
                        { label: 'Volume (log)', data: specificityData.map(d => Math.log10(drugTotals.find(dt =>
dt.drug === d.drug).combinedTotal) * 10), borderColor: '#82ca9d', backgroundColor: 'rgba(130, 202, 157, 0.6)' }
                    ]
```

```
                    },
                    options: {
                        scales: { r: { beginAtZero: true } },
                        plugins: { tooltip: { callbacks: { label: ctx => `${ctx.dataset.label}:
${ctx.raw.toFixed(2)}${ctx.dataset.label === 'Specificity (%)' ? '%' : ''}` } } }
                    }
                });
            </script>
        </body>
        </html>
```