# Technological monitoring perspective: zebrafish as a model in alcohol-related disease research

Perspectiva de monitoramento tecnológico: o zebrafish como modelo em pesquisas sobre doenças relacionadas ao álcool

Perspectiva de monitoreo tecnológico: el zebrafish como modelo en la investigación de enfermedades relacionadas con el alcohol

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## ABSTRACT

**Objective:** To collect and analyze patent documents related to zebrafish as an animal model for alcohol-related diseases (liver diseases, heart diseases, cancer, and Fetal Alcohol Spectrum Disorders - FASD) based on WHO definitions. **Methods:** A descriptive, quantitative, and qualitative technological monitoring study was conducted using national and international patent databases. The documents were analyzed by alcohol-affected organ, animal model, legal status, type of applicant, and temporal and geographic distributions, presented by figures and tables. **Results:** Out of 2,166 patents identified, 13 met the inclusion criteria. Of these, 54% were in the application stage, and 46% had been granted. Most patents were filed by companies, with dominant IPC codes A61K (medical preparations) and A61P (therapeutic activities). Liver diseases accounted for 71.43% of the patents, followed by FASD (21.43%) and liver cancer (7.14%). Zebrafish was the primary model in 11 patents; two used rats but mentioned zebrafish as an alternative. **Conclusion:** Zebrafish use in alcohol-related disease research is emerging, primarily focused on liver diseases.

**Keywords:** Zebrafish, Alcohol-related diseases, Patents, Technological monitoring.

## RESUMO

**Objetivo:** Coletar e analisar patentes relacionadas ao zebrafish como modelo animal para doenças relacionadas ao consumo de álcool (hepáticas, cardíacas, câncer e transtornos do espectro alcoólico fetal - TEAF) com base nas definições da OMS. **Métodos:** Um monitoramento tecnológico descritivo, quantitativo e qualitativo foi realizado utilizando bancos de patentes nacionais e internacionais. As patentes foram analisadas quanto ao órgão afetado pelo álcool, modelo animal, status legal, tipo de depositante e distribuição temporal e geográfica, apresentados por meio de figuras e tabelas. **Resultados:** Das 2.166 patentes identificadas, 13 atenderam aos critérios de inclusão. Desses, 54% estavam em estágio de depósito e 46% foram concedidos. A maioria das patentes foi depositada por empresas, com os códigos IPC dominantes A61K (preparações médicas) e A61P (atividades terapêuticas). Doenças hepáticas representaram 71,43% das patentes, seguidas por TEAF (21,43%) e câncer hepático (7,14%). Zebrafish foi o modelo primário em 11 patentes; duas usaram ratos, mas mencionaram o zebrafish como modelo alternativo. **Conclusão:** O uso de zebrafish na pesquisa de doenças relacionadas ao álcool está emergindo, com foco principal em doenças hepáticas.

**Palavras-chave:** Peixe-zebra, Doenças relacionadas ao álcool, Patentes, Monitoramento tecnológico.

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**RESUMEN**

**Objetivo:** Colectar y analizar patentes relacionadas con el pez cebra como modelo animal para enfermedades relacionadas con el consumo de alcohol (hepáticas, cardíacas, cáncer y trastornos del espectro alcohólico fetal - TEAF) según las definiciones de la OMS. **Métodos:** Se llevó a cabo una vigilancia tecnológica descriptiva, cuantitativa y cualitativa utilizando bases de datos de patentes nacionales e internacionales. Las patentes fueron analizadas en cuanto al órgano afectado por el alcohol, modelo animal, estado legal, tipo de depositante y distribución temporal y geográfica, presentados mediante figuras y tablas. **Resultados:** De las 2.166 patentes identificadas, 13 cumplieron con los criterios de inclusión. De estas, el 54% estaban en etapa de depósito y el 46% fueron concedidas. La mayoría de las patentes fueron depositadas por empresas, con los códigos IPC dominantes A61K (preparaciones médicas) y A61P (actividades terapéuticas). Las enfermedades hepáticas representaron el 71,43% de las patentes, seguidas por TEAF (21,43%) y cáncer hepático (7,14%). El pez cebra fue el modelo primario en 11 patentes; dos utilizaron ratones, pero mencionaron el pez cebra como modelo alternativo. **Conclusión:** El uso del pez cebra en la investigación de enfermedades relacionadas con el alcohol está emergiendo, con un enfoque principal en enfermedades hepáticas.

**Palabras clave:** Pez cebra, Enfermedades relacionadas con el alcohol, Patentes, Vigilancia tecnológica.

## INTRODUCTION

The consumption of alcoholic beverages is a widespread practice across various cultures worldwide, yet its impact on public health is both significant and alarming. According to the World Health Organization (WHO, 2018), excessive alcohol consumption is directly linked to the development of several severe diseases, including liver diseases such as cirrhosis, cardiovascular diseases, and certain types of cancer. Additionally, Fetal Alcohol Spectrum Disorder (FASD) - a condition affecting babies exposed to alcohol during pregnancy, needs special attention due to the increasing number of cases and results in major consequences for development, resulting in physical, cognitive, and behavioral changes (POPOVA S, et al., 2019).

The symptoms of alcohol-related diseases range from cellular damage and chronic inflammation to severe functional impairments. Current treatments involve multidisciplinary approaches, including pharmacological interventions and lifestyle changes, such as adopting a healthy diet and engaging in regular physical activity. As a result, it is estimated that more than 3 million deaths annually are related to alcohol consumption (WHO, 2024).

In scientific research, animal models play a crucial role in understanding the mechanisms behind alcohol-related human diseases. Murine models are already well-established animal models in research and are used due to their susceptibility and ability to replicate key aspects of these diseases, but the zebrafish (*Danio rerio*) is increasingly used in alcohol-related disease research due to its unique advantages as a model organism.

Its genetic similarity to humans, combined with its transparent embryos and rapid development, allows researchers to observe the effects of alcohol exposure in real-time at various developmental stages (SYED J, et al., 2023). In addition, zebrafish are highly versatile for studying genetics (MANIKANDAN P, et al., 2022), neurotoxicology (CHATTERJEE D, et al., 2014), behavioral impacts, and FASD (CADENA PG, et al., 2020a; CADENA PG, et al., 2020b, and Marrs JA, et al., 2010), making them a powerful tool for understanding these diseases and testing potential therapeutic interventions.

The use of zebrafish as a model in scientific research offers significant bioethical advantages, aligned with the 10 Rs encompassing animal welfare, scientific principles, and conduct. By adding 7 more Rs (registration, reporting, robustness, reproducibility, relevance, responsibility, and respect) to the classic 3 Rs (replacement, reduction, and refinement), researchers not only promote the integrity and relevance of experiments but also ensure the well-being of zebrafish at all stages of development (CANEDO LP, et al., 2022).

This comprehensive approach supports ethical research practices, adherence to standards, and advancements in human and animal health. Patents related to animal experimental models are crucial for

protecting scientific innovations and granting exclusive rights over discoveries, research methods, and therapeutic applications developed from these models. By patenting these models, research institutions and companies can secure a competitive advantage, attract investments, and drive scientific advancement by turning discoveries into marketable products, such as new treatments or diagnostic methods.

According to Milewski CS, et al., (2024), a search on Orbit revealed 1,681 patent families globally involving zebrafish in technological research. Of these, 44.68% have been granted, 24.87% are pending, and 18.86% have expired. This shows the increasing interest in using zebrafish as an animal model in scientific innovation including health sciences. Technological monitoring is an essential tool for mapping the development of new technologies and innovations.

In this perspective, consulting patent databases becomes particularly relevant, as patents offer an extent to recent innovations even before they are published in scientific articles. Using patent databases thus provides a broader and more up-to-date view of new technologies and trends in treating alcohol-related diseases. Based on this, we will now proceed to the methodology, where we will detail the process of data collection and analysis from patent databases (ALVES RL, et al., 2023; LARA-BERTRAND CH, et al., 2022). In this framework, the objective of this study was to carry out technological monitoring of the zebrafish experimental model for alcohol-related diseases.

## METHODS

Descriptive, quantitative, and qualitative technological monitoring was carried out, using main national and international patent databases. First, patent documents related to zebrafish as an animal model for the main alcohol-related diseases (heart diseases, hepatic diseases, and cancer) according to the World Health Organization (2018; 2024), and Fetal Alcohol Spectrum Disorders (FASD) were collected and analyzed. Second, technological monitoring was conducted to study these data.

### Patent Search

We conducted a thorough investigation of various patent databases such as Espacenet (European Patent Office), Patentscope (Platform to WIPO - World Intelectual Property Organization), The Lens, and INPI (Platform to Brazil - Instituto Nacional de Propriedade Industrial). These databases were selected, and the order of search followed this sequence. In addition, Google Patents was used as a support searching tool.

First, was the development of a previous search to find the most relevant keywords based on terms found in WHO documents (2018, 2024) and papers about alcohol-related diseases with the best concatenation with the objective. Each carried search was adapted for each patent database, resulting in search equations. Moreover, the International patent classifications (IPC code) A61K49 (Preparations for testing in vivo) was identified in all patents of interest and included in all subsequent searches.

The filters "Patent Family" (Espacenet and Patentscope) and "Simple Families" (The Lens) were applied to avoid duplicate documents. Finally, based on the described information above, the main keywords with boolean operators used were "zebrafish" AND "alcoh*" AND "A61K49" AND "liver"; "heart*"; "card*"; "Cancer"; "FAS"; "FASD" or "fetal". To Espacenet, Patenscope, and The Lens the search was carried out using the tool "Advanced Search", and to INPI "Simple Search" also used terms in the Portuguese language.

The inclusion criteria in the selected patents involved treatment and/or prevention of FASD, heart and liver diseases, and cancer, and: a. that used zebrafish as an animal model; b. that suggest the possibility of using zebrafish as an animal model; c that disease was induced by alcohol and d. that disease wasn't induced by alcohol, but with a clear explaining the possibility of can be induced by alcohol.

### Data Analysis

Relevant results of each platform were determined, the inclusion criteria described above were applied and the selected patents were analyzed, compared, and discussed to the following information: number of patents, legal status (applicated or granted stage), year of application, IPC codes, type of applicant (Individual

inventors, companies and universities), geographic distribution (country and priority country), alcohol-affected organ/disease, and type of animal model. The results were presented in the form of charts, tables, and figures developed by the software OriginPro® Academic 2015 and CanvaPRO.

## RESULTS

Based on the described information in the methodology, a first search was performed, and the main search equation for each platform was defined and detailed in (**Table 1**).

**Table 1-** Collection of search equations with relevant keywords for each Patent databases.

| Patent databases | Search equation |
|---|---|
| Espacenet | ftxt = "zebrafish" AND nftxt = "alcoh*" AND cl = "A61K49" AND nftxt = alcohol-related disease |
| Patentscope | EN_ALLTXT:( zebrafish AND alcoh* AND alcohol-related disease) AND A61K49 |
| The Lens | zebrafish AND alcoh* AND alcohol-related disease |
| INPI | Zebrafish AND Álcool |

**Source:** Santos-Magnabosco AR and Cadena PG, 2024.

The term "alcohol-related disease" described above has been replaced by liver, heart, cancer, fetal, FAS, or FASD in searches. Thus, the total number of patents identified amounted to 2,166 documents. This result was derived by combining the results from all the search strategies developed and detailed above.

The search equations resulted in 1.187 documents (Espacenet), 790 documents (Patentscope), and 189 documents (The Lens). Based on this, 36, and 17 e 0 were considered relevant results, respectively. In short, after reading and checking the criteria, 13 patents were analyzed. In the INPI platform were not found results. These results are described in (**Figure 1**).

**Figure 1-** Results of search strategy and classification of documents for each patent databases.



**Source:** Santos-Magnabosco AR and Cadena PG, 2024.

In **Figure 2**, we described details about the 13 selected patents. The number of applicated patents (A status) and granted patents (B status) are similar, being approximately 54% A status, and 46% B status (**Figure 2A**). The temporal distribution of these patents started in 2004 (1 Chinese document), and peaked in 2018 (3 documents, 2 of Chinese origin). Their application dates are distributed between the years 2004 to 2022 (**Figure 2B**). In addition, IPCs codes most observed are included in A status category (Human Necessities).

The high number is A61K (Preparations for medical, dental, or toiletry purposes) – 12 documents, followed by A61P (Specific therapeutic activity of chemical compounds or medicinal preparations) – 5 documents.

In G category (Physics) the high number observed was G01N (investigating or analyzing materials by determining their chemical or physical properties) – 3 documents (**Figure 2C**). Finally, among the applicants, companies stand out with the highest number of patents (**Figure 2D**).

**Figure 2-** Compilation of patent information. **A:** Patent status that A - Applicated and B- Granted; **B:** Temporal distribution of applications founded on patent databases Espacenet, Patentscope, The Lens, and INPI between the years 2004-2022; **C**: International Patent Classification - IPC codes. Human necessities (A): A61K - Preparations for medical, dental, or toiletry purposes; A61P - Specific therapeutic activity of chemical compounds or medicinal preparations; A01K - Animal husbandry; aviculture; apiculture; pisciculture; fishing; rearing or breeding animals, not otherwise provided for; new breeds of animals. Chemistry (C): C12N - Microorganisms or enzymes; compositions thereof; propagating, preserving, or maintaining microorganisms; mutation or genetic engineering; culture media; C01D - Compounds of alkali metals, i.e. lithium, sodium, potassium, rubidium, cesium, or francium; C09K - Materials for miscellaneous applications, not provided for elsewhere; C07D - Heterocyclic compounds; C07K – Peptides. Physics (G): G01N - investigating or analyzing materials by determining their chemical or physical properties, **D:** Classification of the type of applicant between individual inventors, companies, and universities.
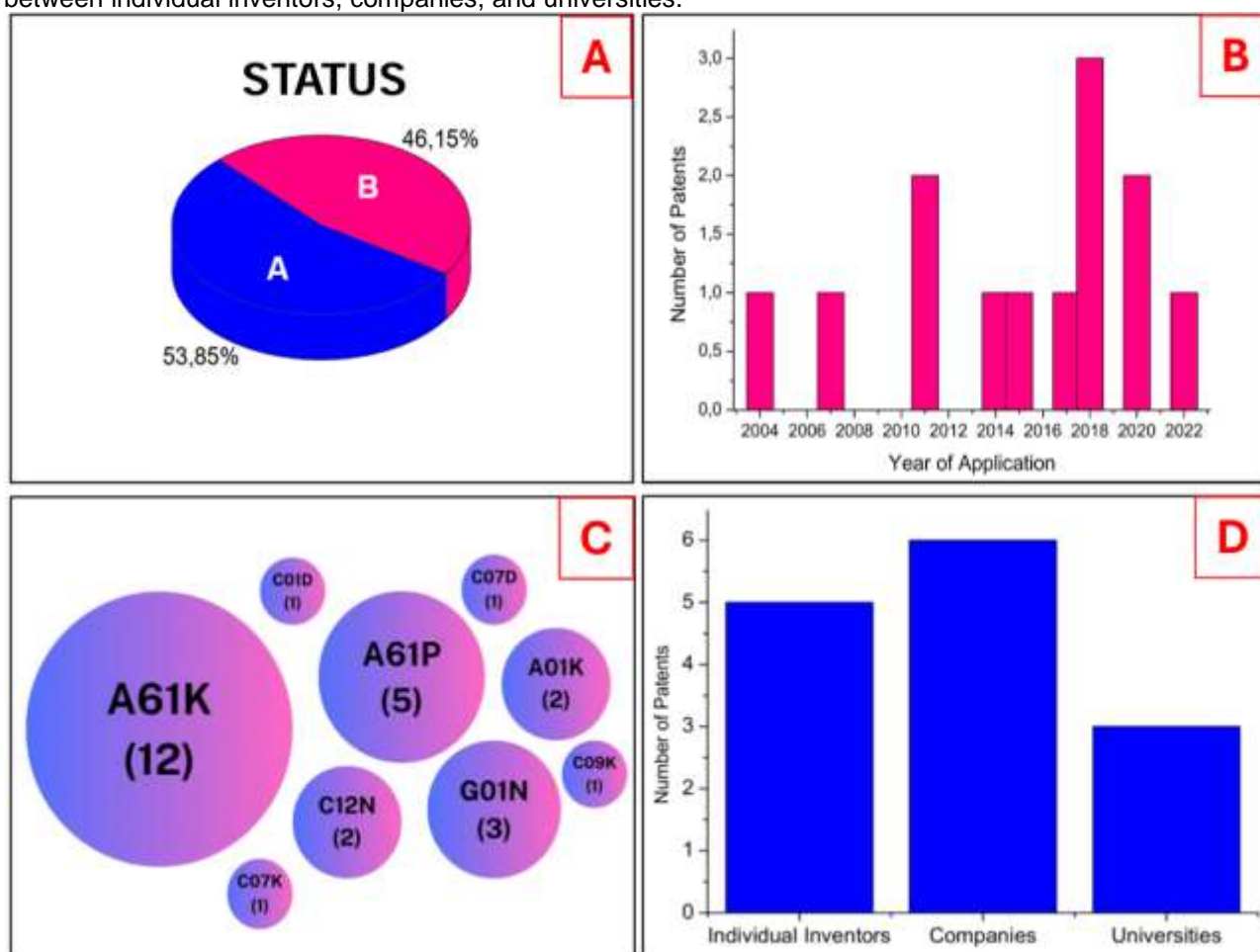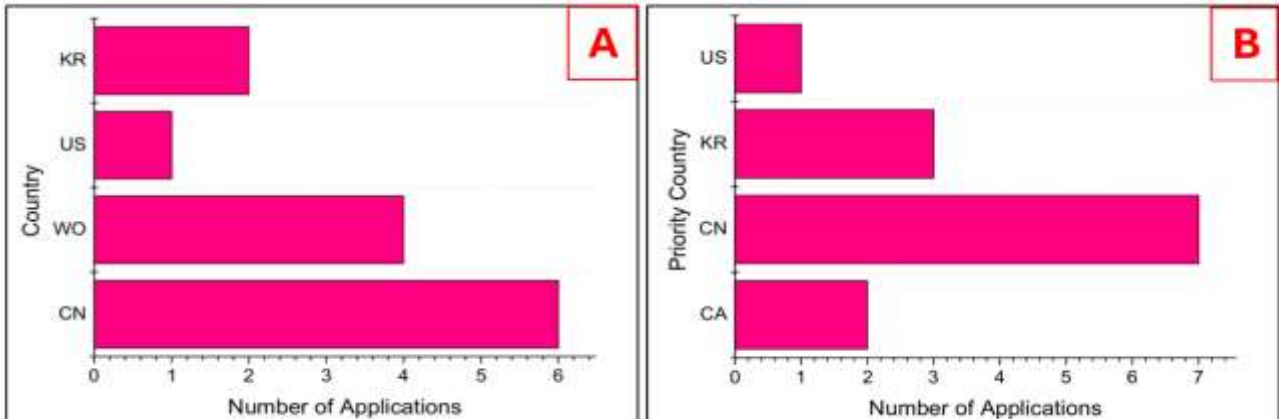


**Source:** Santos-Magnabosco AR and Cadena PG, 2024.

In the analysis of the countries involved in this research, China was identified as the leading country in patent filings for this topic, with 6 documents representing 78% of the total (**Figure 3A**).

When examining the country of origin, China's share increased to 7 out of the 13 documents selected in this technological monitoring (**Figure 3B**).

**Figure 3- A:** Distribution of patent applicants filed by country (Geographic distribution). **B:** Distribution of priority countries. WO- World Patent, KR – Korea, US – United States, CN- China, CA- Canada.



**Source:** Santos-Magnabosco AR and Cadena PG, 2024.

We observed in **Figure 4** that most of the selected patents covered alcohol-related liver diseases (71,43%), followed by FASD (21,43%) and Cancer (7,14%). Only one document reported studies on cancer, which was liver cancer. In this search, no documents on heart diseases were found.

**Figure 4-** Alcohol-related diseases described in patents found after the search strategy, according to the World Health Organization (2018; 2024).



**Source:** Santos-Magnabosco AR and Cadena PG, 2024.

Analyzing in detail the content of the patents, it was possible to verify that most of the obtained results used zebrafish as an animal model, or at least cited the possibility of using it for the purpose described in the document. As a result, 11 documents use zebrafish as an animal model, while only 2 use the murine model, but cite zebrafish as an alternative animal model. The number of each patent is described in (**Figure 5**).

**Figure 5-** Patents found that described zebrafish and mice as animal models for the main alcohol-related diseases (heart diseases, hepatic diseases, and cancer), and Fetal Alcohol Spectrum Disorders (FASD), according to the World Health Organization (2018; 2024).
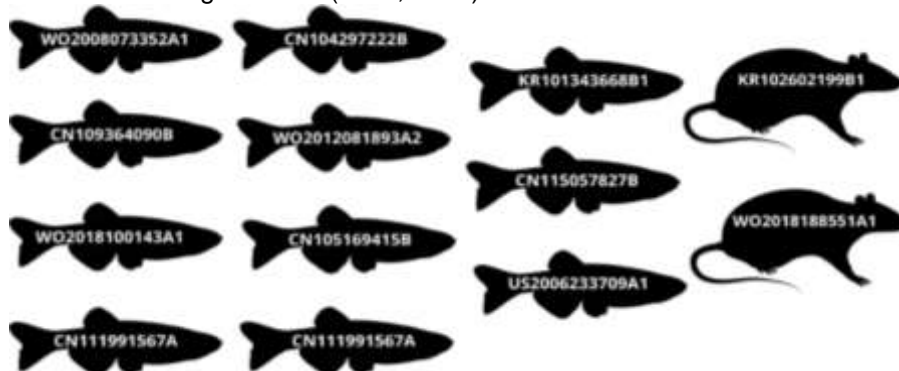


**Source:** Santos-Magnabosco AR and Cadena PG, 2024.

## DISCUSSION

Alcohol-related diseases have been attracting attention from the health system and global organizations. Although alcohol consumption is widely accepted and socially prevalent worldwide, it is important to emphasize that alcohol is a psychoactive substance with depressant effects on the Central Nervous System (CNS) and is directly or indirectly associated with over 200 comorbidities and injuries. This significantly contributes to the global burden of disease, according to the most recent report from the World Health Organization (WHO, 2018).

The zebrafish model, despite not having as many documents in comparison to the murine model, can express characteristics of alcohol-related diseases with great similarity to humans. The zebrafish genome has been completely sequenced (Howe et al., 2013) and the zebrafish embryotoxicity test has earned strong scientific recognition, particularly in the field of toxicological evaluations (BRAGA APA, et al., 2024). In addition to corroborating the 3Rs (refine, replace, and reduce), making it possible to reduce the use of higher vertebrates, is showing itself to be an emerging animal model in this type of research with biomedical importance (BRAGA APA, et al., 2024; CANEDO LP, et al., 2022). Based on the results shown above, we have important findings to discuss.

In technological monitoring, analyzing the status, filing trends, and IPC codes of patents is crucial for understanding innovation dynamics and technological progress within a specific area (LARA-BERTRAND CH, et al., 2022, and SILVA MLSC, et al., 2022). Evaluating the status of patents reveals whether technologies are still protected or have become publicly accessible, which can offer strategic insights for development. The analysis of the 13 selected patents reveals a balanced distribution between applicated patents (54% in A status) and granted patents (46% in B status), with companies dominating as the primary applicants (**Figure 2A**).

As observed, nearly half of the patents identified in our research have been granted, indicating that the interest in this type of animal model for studies associated with alcohol-related diseases is not recent. It is important to note that before a patent is granted, numerous evaluations are conducted, and the backlog process can often take several years. On the other hand, there were no significant peaks in the number of patent filings over the years (**Figure 2B**), which may explain the consistency of patents in Status A.

The analysis of IPC codes provides valuable perspectives into how patents are categorized by technology, allowing for a clearer understanding of specific areas such as the use of zebrafish in alcohol-related disease research. This classification aids in strategic research and development decisions and strengthens competitive positioning in evolving industries. Most of the selected patents are concentrated in the Human Necessities category, particularly under IPC codes A61K (medical preparations) and A61P (therapeutic activities), as shown in (**Figure 2C**).

This focus highlights the importance of these innovations in addressing human health issues, especially alcohol-related diseases like liver diseases, FASD, and cancer. These patents play a key role in advancing therapeutic approaches and developing new medical treatments, which are crucial for public health improvements. The zebrafish model, widely used in these studies, provides an effective method for exploring the biological impacts of alcohol, offering valuable insights into disease mechanisms and potential therapies. The prominence of patents in the Human Necessities category underscores the essential nature of these developments in reducing the global health impact of alcohol-related diseases. Among the applicants, companies stand out with the highest number of patents (**Figure 2D**).

Out of the 13 patents identified in this study, 5 are held by individual inventors, 6 by companies, and 3 by universities. However, we considered 14 patents in total, as one patent (WO2018100143A1) represents a university-company partnership. It is evident that most research initiatives are driven by private entities. When combining patents from individual inventors, companies, and the university-company collaboration, 12 patents, or approximately 86% of the total, are of private origin, underscoring the significant role of the private sector in advancing research in this area. During the analysis of the countries involved in this research, it was found that China, with 6 documents (78% of the total), leads in the number of patent filings on this topic (**Figure 3A**).

Moreover, when considering the country of origin, the number of documents from China rises to 7 out of the 13 selected in this technological monitoring (**Figure 3B**). The Asian country, which tops the global patent filing ranking, saw a notable increase in filings starting in 2015, surpassing the United States in 2018, which is currently in second place according to data from the World Intellectual Property Organization (WIPO, 2022). According to data from The National Bureau of Asian Research (NBR, 2020; 2023) and the WIPO Patent Landscape Report (2024), China has a robust innovation ecosystem and policies that encourage innovation. In accordance with Li S, et al. (2022), excessive alcohol consumption poses significant risks, endangering not only the drinker's life but also the lives of others.

In China, where per capita alcohol consumption in 2016 was 12.5% higher than the global average, this issue is particularly worrying, especially in regions inhabited by ethnic minorities, which have seen a recent increase in consumption, encouraging the creation of public policies to reverse this scenario including innovations as found in our work. In contrast, research involving animal models in Brazil, including the use of fish such as zebrafish, is legally supported by several regulatory frameworks that ensure ethical and sustainable animal use.

Law No. 11,794/2008, known as the Arouca Law, regulates the scientific use of animals in Brazil, aligning with Article 225 of the Federal Constitution. It is supported by Decree No. 6,899/2009, which provides specific guidelines for the care, breeding, and use of animals, including fish, in research. The law also established the Brazilian National Council for the Control of Animal Experimentation, which oversees and ensures ethical animal use in scientific studies. CONCEA's Regulatory Resolution No. 30/2016 outlines best practices for fish research, particularly relevant in alcohol-related disease studies.

Additionally, Instruction No. 10/2020 from the Brazilian Ministry of Agriculture, Livestock, and Supply enforces sustainable practices for handling fish, applicable to research environments. Brazil also has Law No. 13,123/2015, which governs genetic heritage, ensuring that genetic resources used in research are accessed and utilized in a way that respects national regulations and promotes fair and equitable benefit-sharing. Despite these robust regulations, Brazil's technological progress in zebrafish-related patents remains in its early stages.

However, our study did not find any Brazilian patents related to the use of zebrafish as an animal model. While Brazil has established strong legal frameworks, such as the Arouca Law and CONCEA regulations as described above, the practical application in terms of patent development is lacking. Despite having the necessary legal and ethical guidelines in place, our findings suggest that Brazil has yet to translate these into significant technological advancements or patent filings in this area.

According to the study of Milewski CS, et al. (2024), patent prospecting involving zebrafish in Brazil is limited and mostly dominated by foreign companies. However, the presence of foreign entities suggests a potential opportunity for the entry of other companies, including Brazilian ones, which could contribute to the advancement of research and development in zebrafish use. The study also reveals that no national companies have filed patent applications related to zebrafish in Brazil.

This demonstrates a significant gap in technological innovation and the exploitation of zebrafish as a model in scientific research. While foreign companies aim to commercialize the technology or block competitors from entering the Brazilian market, national institutions have yet to take a prominent role in this area. This situation highlights a significant opportunity for Brazil to enhance its role in this field through greater investment in research and development, particularly within public institutions, universities, and research centers.

Currently, Brazil trails behind, with no patents found in this study and most of the scientific work is still centered in academic settings. With only one patent involving a university-company collaboration, it raises the question: Could increased funding for universities help foster stronger scientific innovation and better integrate academia with industry? Among the related diseases, hepatopathies are the most frequently mentioned and have the highest number of cases. These results were observed in our technological monitoring (**Figure 4**). According to the WHO (2018), liver diseases are the leading cause of death associated with alcohol consumption, which justifies the high number of patents involving zebrafish in this context.

The correlation between the commercial interest in using this animal model and the prevalence of alcohol-related liver disease deaths highlights the potential of zebrafish to contribute to the development of new therapies and diagnostics. A chronic condition that stands out is liver cirrhosis, caused by various types of inflammatory lesions and cell death in the liver. Eventually, cirrhosis can progress to liver failure, severely impairing liver function (GINÈS P, et al., 2021).

Furthermore, fatty liver is a highly relevant disease and has been observed with great recurrence in technological monitoring. It can occur because of poor diet as well as excessive alcohol consumption. The most interesting thing is that, when using zebrafish in this research, this induction can be done by gene manipulation (WO2018188551A), by exposure to alcohol (US2006233709A1) or both (KR101343668B1, and WO2012081893A2). The discussion on FASD, reveals a critical issue of underdiagnosis, as highlighted by Pan American Health Organization - PAHO (2020, 2022).

The zebrafish model has emerged as an essential tool for FASD research, being the only animal model used in the FASD patents that met the criteria of this study. This model provides a valuable platform for understanding the effects of alcohol exposure during pregnancy and for testing new interventions. These observations are crucial for developing more accurate diagnostic strategies and more effective treatments, enabling early and personalized intervention. In conclusion, the use of zebrafish as a model for studying FASD offers significant advantages over murine models.

Given that FASD is an embryonic disease, zebrafish provide a clear benefit due to the transparency of their eggs and embryos (SYED J, et al., 2023), allowing for in vivo observation without the need to sacrifice the mother, as would be necessary with murine models. This approach not only reduces animal suffering but also aligns with the principles of the 3Rs (Replacement, Reduction, Refinement) in scientific research (CANEDO LP, et al., 2022). By enabling live observation of embryonic development, zebrafish demonstrate their value as an efficient and ethical model for understanding and researching FASD, potentially leading to more effective interventions and treatments.

## CONCLUSION

In closing remarks, this study highlights the substantial potential of zebrafish as a model organism for researching alcohol-related diseases. Our analysis reveals that liver diseases, the most prevalent alcohol-related condition, are the most frequently studied in patent databases. While zebrafish is gaining recognition in scientific research, its application in patented technologies is still in its early stages, with murine models currently more prevalent. In Brazil, research in this domain remains underdeveloped, and China leads in patent activity. The growing number of patents involving zebrafish reflects a rising global interest in this model. The findings suggest significant opportunities for expanding research on alcohol-related diseases using zebrafish, especially in Brazil, where such advancements could have substantial implications for healthcare.

## ACKNOWLEDGMENTS

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