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# BIBLIOMETRIC ANALYSIS: THE USE OF STREPTOZOTOCIN (STZ) IN DIABETIC ANIMAL MODEL

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## ABSTRACT

**Introduction.** Bibliometric analysis is a relatively new tool in healthcare and therefore does not yet make full use of its potential. This statistical tool analyzes scientific publications which further describe trends in academic literature and research in various fields.

**Research Methods.** This study focused on the development of diabetes research using animal models induced by streptozotocin (STZ), a diabetogenic molecule that triggers DNA damage in pancreatic beta cells and causes extreme oxidative stress. 1090 related articles published between 2017-2022 were obtained from the Scopus-Elsevier database using specific keywords “streptozotocin or STZ, animal models, diabetes, intraperitoneal”.

**Results and Discussion.** Statistical analysis showed 1.67% Annual Growth Rate of publication with 10.66 citation rate per document. Co-occurrence analysis also successfully visualized the main topics related to the mechanism of action of streptozotocin such as oxidative stress, inflammation, rats, diabetic nephropathy, diabetic cardiomyopathy, hyperglycemia, antioxidants, and insulin.

**Conclusion.** An important finding in this study indicated the diabetes research development was not in line with the main problem using animal models that remain unsolved, especially in diabetes research related to pancreatic beta cell proliferation. The result also provided valuable insights of research trends that involved diabetic animal models. The latest research data are significantly important since it can be used for future research development. Further, more comprehensive information could be achieved by using other databases such as Web of Science (WOS) and Dimension in bibliometric analysis.

**Keywords:** Streptozotocin; Animal Models; Diabetes; Bibliometric

## 1. INTRODUCTION

Streptozotocin (STZ) is a compound widely used in diabetes research (Saliu et al., 2022) to induce diabetic state of type I and type II animal models which are important in many experimental studies, such as testing the protective and curative effectiveness of natural substances that believed containing antioxidant or antidiabetic properties (Matowane et al., 2023). STZ induced-diabetic animal models are crucial for investigating how diabetes affects the damage to different tissues using different biomarkers. An early indication that STZ has been extensively used in experimental research comes from the existence of published scientific evidence. However, the extent to which this research has developed is a significant concern. There is a lack of studies that map the use of STZ, particularly in the development of diabetic animal models. Further, studies including the use of experimental animals and the contribution of "outcome research" may be uneven. Keep in mind that "sacrificing" experimental animals is a common practice in STZ research. This makes it important to assess the progression of diabetes research using STZ as an induction agent. Therefore, the role of bibliometrics is necessary to map the development of STZ research in the field of diabetes. Moreover, bibliometrics can broaden one's perspective, give an understanding of the state of the art and research opportunities (T. Rahman et al., 2023).



## 2. METHODS

Structured prototypes and guidelines were implemented, including formulation of Research Question (RQ), defining the keywords, and searching in database. This principle has been applied in many bibliometric studies (Segura-Robles et al., 2020). The list of stages is as follows:

1. Creation of RQ (research question)
2. Determination and formulation of keywords
3. Establishment and use of databases and filters
4. Data retrieval, storage, and preparation
5. Visualization and optimization
6. Interpretation and Concept Validation

This study suggested several significant problems sets (RQs). The study's RQs were designed to offer solutions and were related to the background of the study. Segura et al. also proposed textual RQs in their study (Segura-Robles et al., 2020). Of course, in the proposal, strategies will be carried out in order to maximize in finding the pattern of mapping of knowledge in streptozotocin research and then analyzing it. Finding this pattern is crucial for measuring the advancement of science (van Raan, 2019). The following is a complete list of problem formulations proposed in this study.

1. RQ1: How many cluster domains are there in the study?
2. RQ2: What are the current trends in the study?
3. RQ3: How are the topics related in the study?
4. Is there a conformity in the field of research in contextual and factual visualization?

This study involved the creation of keywords and boolean operators. The following are the operators used in Scopus. Target Keywords: Streptozotocin, (STZ), Animal Models, and Diabetes. The two boolean operators that are employed were AND and OR, which have become the primary search operators (Segura-Robles et al., 2020; van Raan, 2019). In full it is written as follows:

**( TITLE-ABS-KEY ( "Streptozotocin" OR "STZ" ) AND TITLE-ABS-KEY ( "Animal Models" ) AND TITLE-ABS-KEY ( "Diabetes" ) AND TITLE-ABS-KEY ( "intraperitoneal" ) ) AND PUBYEAR > 2017 AND PUBYEAR < 2023 AND LANGUAGE ( english )**

In bibliometric analysis, it is crucial to filter and utilize high-quality databases. This filter is used as a way to find documents relevant to the study goal. The database is used as an official source to obtain document metadata legally. This filtering approach in bibliometrics has been widely applied, with comparative analysis studies being one example (Velez-Estevez et al., 2023). The amount of 1,090 documents were found in the scopus database as a consequence of the above-mentioned search employing keywords and boolean operators.

The following are the filter criteria in maximizing document search in the database.

1. Last 5 years range: 2018-2022
2. Language: English
3. Article Search on: title, abstract, keywords
4. Database: Scopus

Cleaning and replacement techniques were used in the data preparation process. Openrefine application tools were used in the cleaning or deletion process by activating the "facet filter" feature. This step allowed users to view data on cells where there are discrepancies (Velez-Estevez et al.,



2023) such as acronyms or terms that could cause repetition in the calculation of the term "double counting". Details of the improvements as shown in Table 1.

Table 1. Improvement of terms and phrases in data preparation.

No.	Before	After	Improvement
1	Streptozotocin (STZ)	Streptozotocin	Deletion, Acronym & Punctuation
2	streptozotocin (STZ)-induced diabetic rats	Streptozotocin Induced Diabetic Rats	Deletion, Acronym & Punctuation
3	Streptozotocin-treated	streptozotocin treated	Punctuation deletion

Note:

In this process the *sensitive case* was not activated so in the Co-occurrence analysis the upper- and lower-case letters were ignored. The clustering and re-clustering processes were also completed at this point. The objective was to group meaningful terms together and separate meaningless words or sentences. Sensitive case reduction procedures, including capitalization reduction, happened automatically in this process. This re-clustering stage will maximize the term of visualization later.

### 3. RESULTS AND DISCUSSION

#### 3.1 Research Development

The amount of research and studies on STZ is expanding. This can be seen in the annual growth, citation level, and number of documents produced. According to Bibliometrix-Biblioshiny, 4831 authors have published their works throughout a five-year period. The growth rate is greater than 1.67%, with 10.66 citations per document. The statistical quantification displayed is an integral part of bibliometric analysis (Duan & Zhao, 2023).



Figure 1. Summary of data from streptozotocin studies in experimental diabetic animal models.

#### 3.2 Co-occurrence visualization

Co-occurrence analysis is particularly useful in bibliometric analysis (Khuram et al., 2023). This approach enables us to analyze and find new insights into mapping of terminology (Rahmawati & Subardjo, 2022). This mapping was principally constructed based on whether or not there is a relationship between the use of "occurrence" or co-occurrence in an article (Khuram et al., 2023). Based on the mapping of diabetes research publications using streptozotocin, topic clusters of varying sizes were obtained. The members of each cluster also show variations and in general have "topic members".

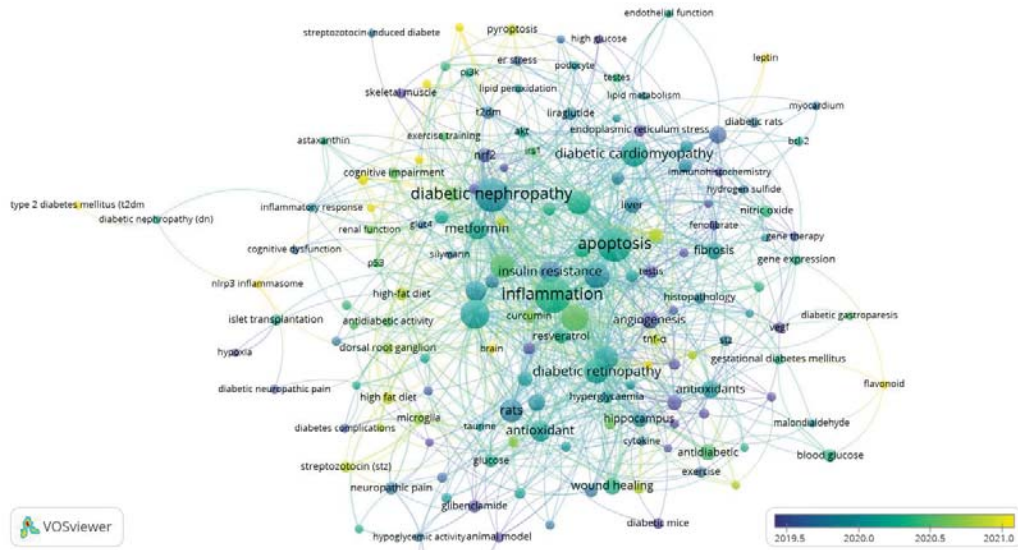


Figure 2. Initial mapping of research topics with a Co-occurrence analysis approach using the Vosviewer application.

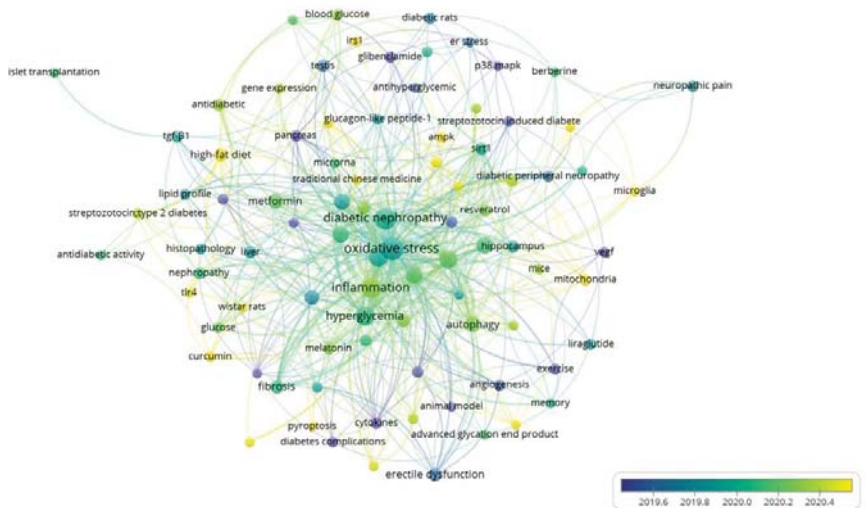


Figure 3. Initial mapping of research topics with a Co-occurrence analysis approach using the Vosviewer application and re-clustering optimization.





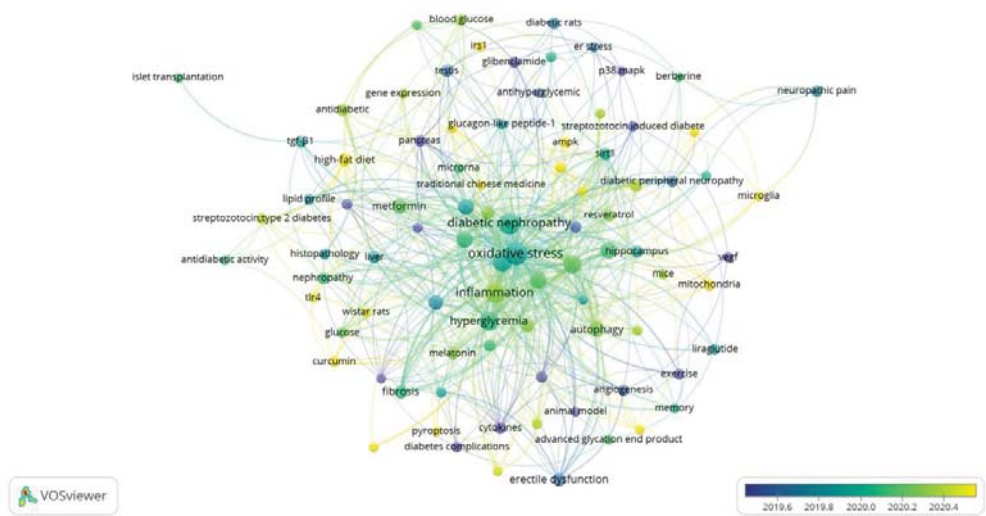


Figure 4. Mapping research topics with a Co-occurrence analysis approach using the Vosviewer application and optimization of re-clustering and LinLog / Modularity.

Co-occurrence analysis of 1090 documents was used to visualize the data, and it was clear that the distribution of subjects has expanded. The variety and volume of papers from diabetes research utilizing STZ reflected this. There is growth in high citation. All documents in the main profile have an average of 10.66 citations. In bibliometric analysis that employs mathematical techniques, quantification of this statistic is crucial (Duan & Zhao, 2023).

This visual data depicted the development of research using STZ-induced animal models to date. Additionally, it is clear that numerous studies have been undertaken on the topic of "ROS inhibition" prevention. This is consistent with the strong nature of STZ as an extremely potent producer of "oxidants" free radicals (Bikri et al., 2022). This study also demonstrated the evolution of type 1 and type 2 diabetes biomarker research. Interleukins, which are closely related to inflammatory processes, IL-6 is an example of the wide variety of these biomarkers (Baig et al., 2022, Li et al., 2021). Research trend indicators can be seen from the color spectrum. The brighter the yellow meaning the research topic is in a trending position.

### 3.3 Streptozotocin Mechanism

Sterptozotocin (STZ) is a diabetogenic molecule which indicates that it can induce diabetes in experimental animals when administered at the proper dose. STZ penetrates the nucleus and damages the DNA of pancreatic beta cells causing ATP depletion and severe oxidative stress, which further results in pancreatic beta cells damage and death (Al Hroob et al., 2018). This mechanism was successfully illustrated in bibliometrix-biblioshiny mapping and co-occurrence mapping using vosviewer.

By looking at how streptozotocin works and the impact of its use, several main topics will emerge including insulin, diabetic nephropathy, diabetic cardiomyopathy, rats, oxidative stress, inflammation, hyperglycemia, and antioxidants. Each of these subjects demonstrates the characteristics of STZ and how systemic harm manifested itself in the STZ induced-animals.

As a classical symptom of diabetes, hyperglycemia has become a major topic. It is identified by glucose levels above normal limits, usually in in-depth examination matched with the results of a complete examination with HbA1c, while another study discovered an association between biomarkers and abdominal circumference anthropometry (M. N. Rahman et al., 2019).

### 3.4 Key findings

Through this bibliometric investigation, important indications of discrepancies in the estimation of research outputs was discovered. This was due to the absence of proliferation phrases and their derivatives. The primary focus of the visualization should be the word proliferation. Insulin, HOMA, and pancreatic beta cells are the derivatives. The other derivative words have not been seen, whereas insulin has only made a very slight appearance as a node. These three components are significant because they show how pancreatic beta cells behave physiologically. We need to remember that only pancreatic beta cells produce insulin, the primary factor allowing glucose to enter the cell, thus it is crucial from a scientific perspective to support and improve this ability. Thus from the visualization above where insulin only appeared slightly, meaning not many publications discussing this derivative, then research on *the caring capacity* of natural materials for pancreatic beta cell proliferation is very low. Important findings in this study indicate that there are research developments that are not in line with the main problem in animal models (*unsolved main problem*). Particularly in diabetes research related to pancreatic beta cell proliferation. The overall concept is depicted in Figure 5.

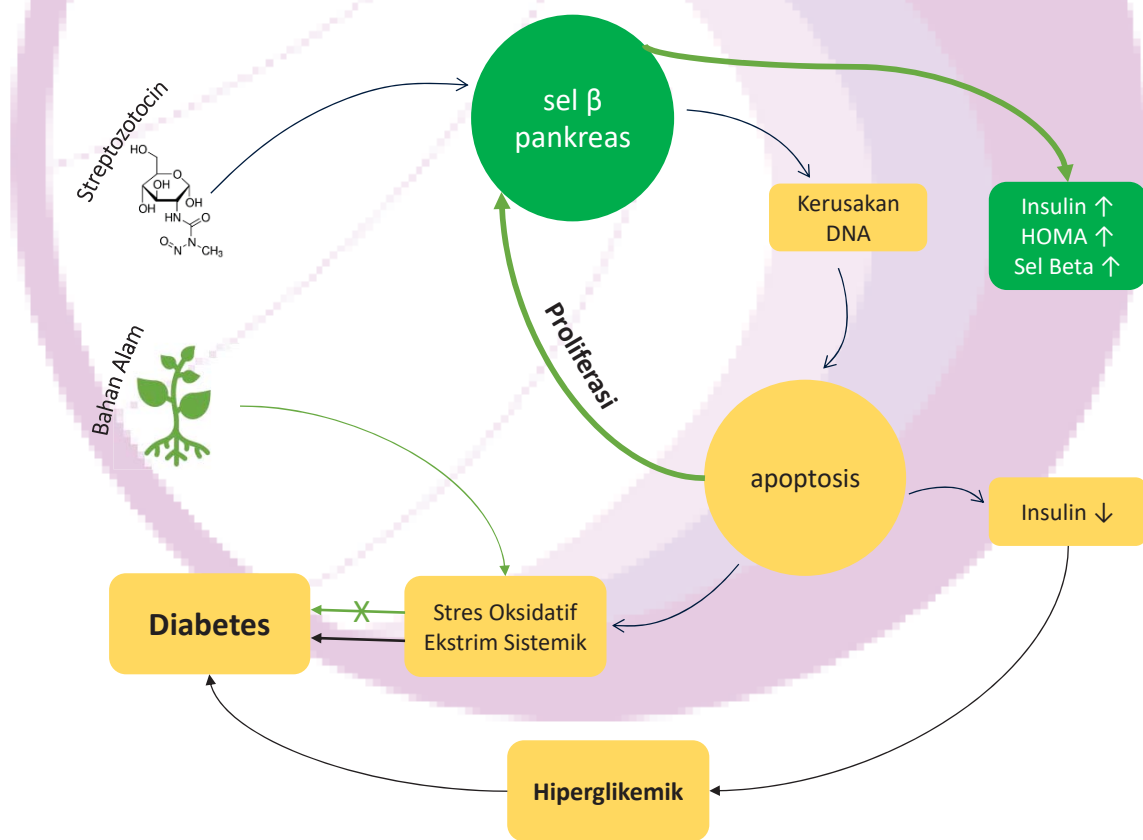


Figure 5. The role of proliferation in the prevention of diabetes progression.

### 3.5 Research Challenges

Research employing STZ often seeks to identify any anti-diabetic or antioxidant properties. There are numerous substances containing flavonoids that have been tested including curcumin, onions, honey, and moringa. However, it is also known that STZ-induced diabetic animal models are prone to high mortality rates. Therefore, the researchers have narrowed down the duration of STZ exposure.

Many studies of experimental animal models of diabetes use a simple biomarker that is easy to measure and interpret such as glucose level. Other biomarkers such as insulin, GLUT, and interleukin have been studied at the molecular level and are relatively more complex. On the other hand, investigation of pancreatic beta cell proliferation on STZ-induced diabetic animals has not been optimally explored, which might be due to high cost, time consuming, and high mortality rate factors.

## 4. CONCLUSION

Bibliometric analysis was performed by selecting articles published between 2017-2022 derived from the Scopus-Elsevier database using specific keywords “streptozotocin or STZ, animal models, diabetes, intraperitoneal”. 1090 articles obtained and statistical analysis showed 1.67% Annual Growth Rate of publication with 10.66 citation rate per document. Co-occurrence analysis also successfully visualized the main topics reflected as big nodes in the vos viewer and those are related to the mechanism of action of streptozotocin such as oxidative stress, inflammation, rats, diabetic nephropathy, diabetic cardiomyopathy, hyperglycemia, antioxidants, and insulin. An important finding in this study indicated the diabetes research development was not in line with the main problem using animal models that remain unsolved, especially in diabetes research related to pancreatic beta cell proliferation. This study suggested to include other databases such as WOS and Dimension to increase the amount of data in order to enhance the main visual nodes and their derivatives, so more comprehensive information can be achieved.

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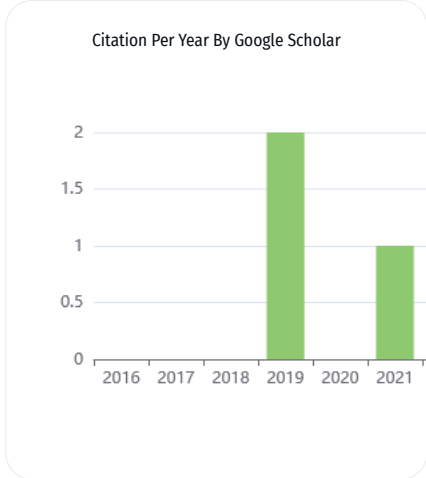
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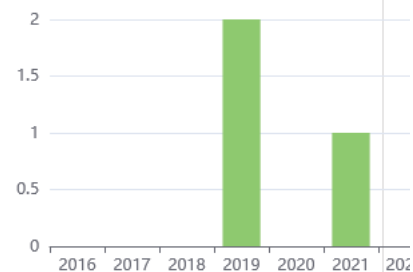
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