El-Hayah

JURNAL BIOLOGI
Journal Homepage: http://ejournal.uin-malang.ac.id/index.php/bio/index
e-ISSN: 2460-7207, p-ISSN: 2086-0064

Original research article

Contribution of Drosophila Climbing Assay in Studying Biology and Diseases

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DOI: 10.18860/elha.v9i4.24210

Article Info

Article history:
Received 30 November 2023
Received in revised form 29 January 2024
Accepted 23 March 2024

Key Word:
Climbing assay Drosophila melanogaster Systematic literature review

Abstract

The Drosophila Climbing Assay (DCA) is an essential assay for disease and other biological studies. This systematic literature review (SLR) aims to analyze DCA's distribution, treatment, and contribution during the 21st Century. VOS Viewer was also involved in analyzing the bibliometric and gap analysis in related studies. By using the Scopus database and limiting document types to journal articles, a total of 183 documents have been successfully collected in this SLR. After going through a selection process based on inclusion and exclusion criteria and eligibility assessment through the PRISMA procedure, 163 articles remain that can be analyzed. Behaviour, model, activity, expression, lifespan, and disease are terms that often equate to studies involving the DCA procedure. The U.S., China, and India are the three countries that most frequently report DCA. DCA has been involved intensively in behaviour, Parkinson's, and nervous system research. The co-occurrence analysis resulted in 5 clusters, and the DCA procedure to study the impact of nutrient stress and nanoparticles resulted from the identified gap analysis.

1. INTRODUCTION

Drosophila melanogaster, or the fruit fly, has become pivotal in advancing biological science [1], [2]. Its small size, short life cycle, high reproductive rate, and ease of observing traits in this organism have made *D. melanogaster* a favoured subject in biological experiments [3]. These insects have helped researchers study various concepts in the field of genetics [4]–[6] and development [7]. This model organism has also been involved in uncovering various complex biological phenomena in physiology [8] and neurobiology [9].

Until the last decade, Drosophila has continued to establish itself as one of the most popular model organisms in various

laboratories in many countries [1], [2], [4]–[6]. Along with the development of bioinformatics and molecular biology techniques, researchers can condition Drosophila to become an organism capable of modelling various biological conditions [7], [10], [11]. Moreover, because its genome is similar to the human genome, this insect has significantly contributed to studying various human diseases [4]. To study various biological phenomena and diseases, researchers have developed various assays whose data can be used as essential indicators of various specific biological conditions.

One of the assays that was developed and is often involved in research involving Drosophila is the Drosophila Climbing Assay (DCA) [12], [13]. This assay involves placing the flies in a vial and observing their ability to climb upward against gravity. Despite its simplicity, this assay informs about the locomotor function of the tested Drosophila and provides data related to their behaviour. Furthermore, this assay can serve as an indicator of the condition of the Drosophila nervous system. Given its cost-effectiveness and simplicity, along with its significance as a vital health indicator, the DCA has been incorporated into various biological research studies up to the present day.

Although the DCA has been extensively documented in various scientific publications, these reports primarily consist of laboratory-based experimental research and methodological development related to the DCA. On the other hand, comprehensive reviews assessing the utilization of DCA up to the present time are scarce. Given the multitude of studies incorporating DCA into their research designs, there is a compelling need for a systematic literature review (SLR) focused on using this assay. Therefore, this paper initiates an SLR specifically targeting the DCA. This SLR aims to provide a holistic perspective on the application, variations, and outcomes of DCA testing in studies conducted across different countries. It has the potential to unearth existing gaps, facilitate discussions concerning standardized protocols that researchers can adopt, and guide the direction of future DCA research.

2. MATERIALS AND METHODS

This SLR adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, the process of which is outlined in Figure 1. The primary research question posed in this SLR is, "How does the Drosophila Climbing Assay (DCA) contribute to the study of various biological conditions and diseases?" The selected database for this study is Scopus. All publications gathered encompass studies in which DCA is utilized as one of its data sources. The search query employed is presented in Table 1, and the inclusion and exclusion criteria are detailed in the same table. After collecting the relevant papers, the screening process commences by selecting papers based on the predefined inclusion and exclusion criteria (Table 1).

Table 1. Search query, inclusion criteria, and exclusion criteria used

Components	Description
Search query	TITLE-ABS-KEY ("climbing ability" OR "climbing behaviour" OR "climbing assay" OR "negative geotaxis" OR "wall climbing") AND ALL ("drosophila" OR "fruit fly") AND ALL ("imago" OR "adult")
Inclusion criteria	articles that were published before 2023, classified as journal articles, in the final publication stage, sourced from journals, written in English, and available as open access.
Exclusion criteria	paper reviews, full papers that were inaccessible, non-original article

Based on Figure 1, 331 publication titles emerged as search results using the search query provided in Table 1. Since no duplicate papers were identified, all papers proceeded to the screening stage. During this stage, papers published before 2023, categorized as journal articles, in the final publication stage, sourced from scientific journals, written in English, and open access in nature were retained, resulting in 183 titles. Furthermore, five full papers remained inaccessible, leaving 176 papers eligible for evaluation. Among these, five papers merely demonstrated or introduced methods, assays, or tools, and eight papers did not involve Drosophila as the subject of their research. Consequently, 163 papers remain for analysis in this systematic literature review (SLR).

Data extraction was conducted on the remaining 163 papers during the data analysis phase. Based on the research questions posed in this systematic literature review (SLR), several key points were scrutinized in each paper, including the positioning of Drosophila as a model organism, the biological topic underlying the research problem, and the specific DCA techniques designed by the researchers. Data analysis was performed using a qualitative approach, and the results served as the foundation for data synthesis. Additionally, a bibliometric analysis was conducted to elucidate the relationships between concepts across all the collected publications.

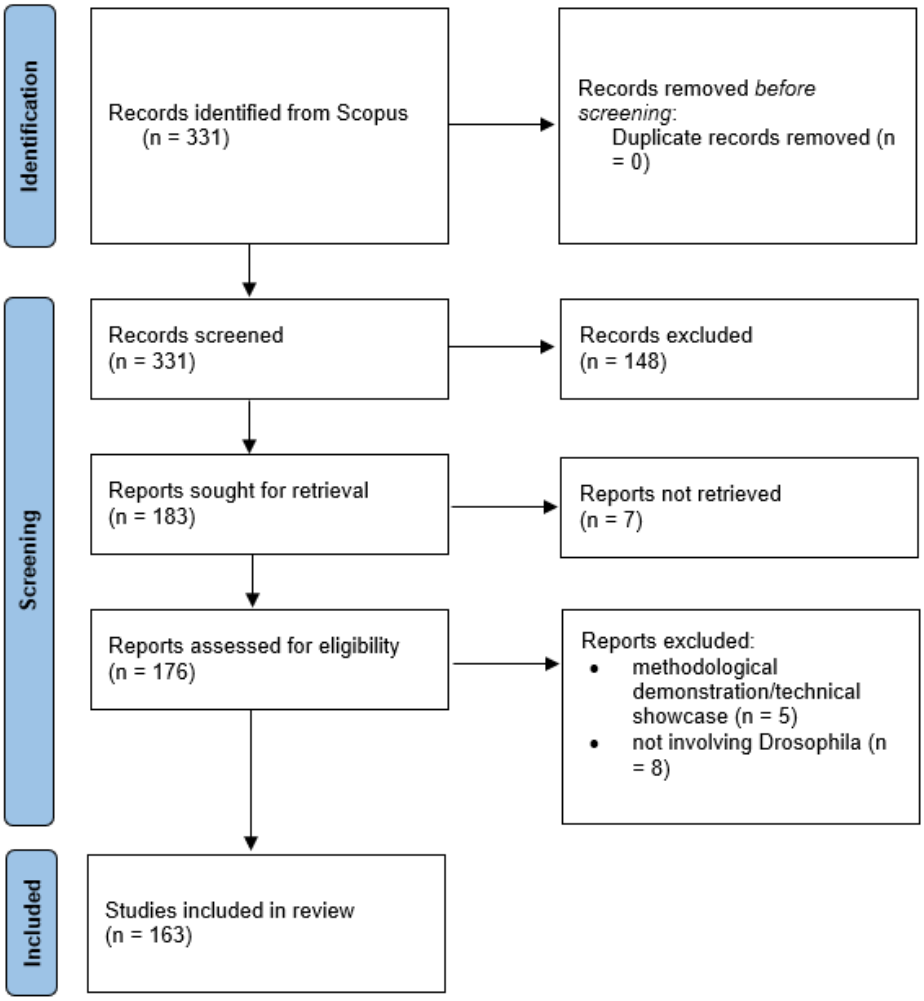

Figure 1. PRISMA steps in this SLR study

3. Results and discussion

Based on the PRISMA-based selection process, out of the 183 papers obtained from the Scopus database, 163 papers remained eligible for further analysis. The first theme used for data extraction in this SLR pertains to the role of Drosophila as a model organism in the reviewed research. The results of this extraction are presented in Table 2. As indicated in Table 2, it is evident that Drosophila has been the subject of research modelling various conditions, spanning from modelling diverse diseases to exposure-related conditions and ageing processes.

Table 2. Data extraction for the model organism theme

Model Organism	Reference
Disease	Parkinson's Disease [14], [15], [24]–[33], [16], [34]–[38], [17]–[23], Alzheimer's Disease [39], [40], [49]–[54], [41]–[48], Huntington's disease [55]–[57], neurodegenerative disease (general) [58]–[60], Autism [61], Barth syndrome [62], Amyotrophic lateral sclerosis [63], Creutzfeldt-Jakob Disease [64], diastolic cardiac defects [65], galactosemia [66], Gerstmann–Straussler–Scheinker syndrome [11], Hereditary spastic paraplegias [55], Myotonic Dystrophy [67], spinocerebellar ataxias [68], FARS2 deficiency [7], Sepsis [69], myopathy [70], diabetes [71]
Medical condition	Brain function [72], depression [73], Mitochondrial diseases [74], gene mutation [75]–[78], neurodegeneration [79], retinal degeneration [80], NT5C2 knockdown [81], Obesity [82], Oxidative stress condition [83], sensorineural hearing loss [84], Traumatic injuries [85]–[88], Obesity [71], Autophagy down expression [89], other [90]–[92]
Aging	age-dependent neurodegeneration [93], age-related behaviour [94], age-related locomotor impairment [95], age-related muscle [10], aging (general) [96]–[100]
Substance exposure	acute exposure to ethanol [101], nanoparticle exposure [102]–[107], Chemotherapy [108], [109], stimulant drug consumption [110], toxicity and heavy metal exposure [111]–[114], herbicide exposure [115], [116], pest [117], pollutant exposure [118], [119], quercetin consumption [120]
Alternative medicine consumption	medical plant substance/traditional medicine evaluation [121]–[125], other [126]
Diet	Dietary restriction [127], [128], Dietary supplementation [129], dietary protein [130], AKG consumption [131], High Fat Diet [132]–[136], high-salt diet [137], MSG consumption [138], non-caloric artificial sweeteners consumption [139], probiotic expose [140]
Physical activity	Exercise training [141]–[144]
Physical condition	Electromagnetic/geomagnetic field effect [145], [146], hypergravity [147], radiation exposure [148], [149], oxygen deprivation [150]
Social condition	male presence [151], predation exposure [152], Social space variation [153]
Other	Other conditions [5], [6], [162]–[171], [154]–[161]

Drosophila is capable of modelling various human diseases primarily due to the high degree of genetic conservation between this organism and humans [172], [173]. Numerous fundamental cellular and molecular pathways are highly conserved in Drosophila, enabling researchers to investigate various human diseases' genetic and physiological mechanisms [174], [175]. This genetic similarity, combined with the simplicity and well-characterized genome of Drosophila, has facilitated researchers in identifying and manipulating specific genes relevant to various human disease conditions. Additionally, developing various molecular techniques, such as gene knockout, overexpression, and downregulation, has allowed researchers to condition Drosophila to model the health conditions under investigation [176].

In addition to modelling diseases, the short lifespan of Drosophila makes it easy for researchers to study the aging process in this organism [93], [94]. Researchers also easily observe various processes and conditions related to aging more quickly than other model organisms. Apart from that, because the generation time is short, but the number of derivatives is significant, researchers will be more efficient in carrying out drug testing on genetic screens on a large scale.

Based on Table 2, the DCA has also been involved in studies positioning Drosophila to model the effects of physical activity [141]–[144], physical factors [145]–[147], social factors [151]–[153], and dietary conditions [132]–[136]. Drosophila has innate locomotor abilities that are needed in studies where treatment involves physical activity. Apart from that, Drosophila also has various complex behaviours that certain physical activities can influence. Furthermore, Drosophila is also sensitive to various environmental conditions, including physical factors [145]–[147]. Because of the small size of the culture, researchers can easily manipulate various physical factors in their laboratories. Furthermore, their social behaviours, including courtship, aggression, and mating, are thoroughly documented and can be manipulated to explore the influence of social factors on gene expression, neurobiology, and overall health [177], [178]. These studies illuminate how social environments can shape biological outcomes. Lastly, Drosophila's responsiveness to dietary conditions is a consequence of their dietary adaptability and the ease of dietary control in laboratory settings [127], [128], [132]–[136]. Researchers can precisely tailor the composition of their food, simulating various dietary scenarios. This adaptability facilitates investigations into the effects of diet on metabolism, aging, and susceptibility to diseases.

In the second theme, the SLR analysis was directed toward mapping the biological topics underpinning the research issues reported in the reviewed articles. Based on the extraction results, the Drosophila Climbing Assay (DCA) was most frequently involved in studies related to the nervous system [14], [15], [24]–[33], [16], [34]–[43], [17], [44]–[53], [18], [54], [58]–[60], [19]–[23]. This climbing assay, a straightforward yet powerful behavioural test, provides researchers with valuable insights into the functional status of the nervous system and its modifications under various conditions or diseases. In this context, the primary role of the nervous system is to control motor activity. On the other hand, DCA serves as a robust indicator for assessing Drosophila's motor skills.

Additionally, the DCA exhibits high sensitivity, making it suitable for detecting subtle changes in motor function. Furthermore, its non-invasive nature and capacity for high-throughput testing make it an attractive option for simultaneously assessing large groups of individuals or conditions, thereby minimizing stress on experimental subjects. Returning to Table 2 and correlating with the result of data extraction in the second theme, Drosophila frequently models Parkinson's Disease [14], [15], [24]–[33], [16], [34]–[38], [17]–[23] and

Alzheimer's Disease [39], [40], [49]–[54], [41]–[48], both of which are neurodegenerative diseases. The decline in negative geotaxis observed in aging flies or those modelling neurodegenerative diseases closely mirrors motor deficits seen in Parkinson's and Alzheimer's patients.

The next theme extracted through this SLR pertains to researchers' application of the DCA. The extraction results reveal that various DCA designs have been reported in the methodology sections of the analyzed articles. The wide range of climbing assay designs and data collection methods in Drosophila studies can be attributed to the assay's adaptability to different research questions and experimental contexts. The diversity in assay formats and collected metrics underscores the flexibility of the climbing assay in assessing various aspects of locomotor behaviour. Researchers select different assay designs and metrics based on the specific objectives of their studies. Several studies designed a simple climbing assay with a basic procedure that involves recording the number of flies that successfully climb a specific height for a particular duration of time [11], [14], [136]. Some other studies involve more complex procedures and equipment, such as the RING assay [69], [108]. RING assay could capture nuanced aspects of climbing, such as the distance climbed or the speed of ascent, making it well-suited for studies focused on the genetic or molecular mechanisms underpinning climbing behaviour. Furthermore, the adaptability of the climbing assay lends itself to a broad spectrum of research areas beyond neurobiology, including toxicology, drug screening, and aging studies. This versatility proves particularly valuable for scientists seeking to comprehend the impacts of various factors, such as substance exposure, diet, or physical activity, on locomotor performance.

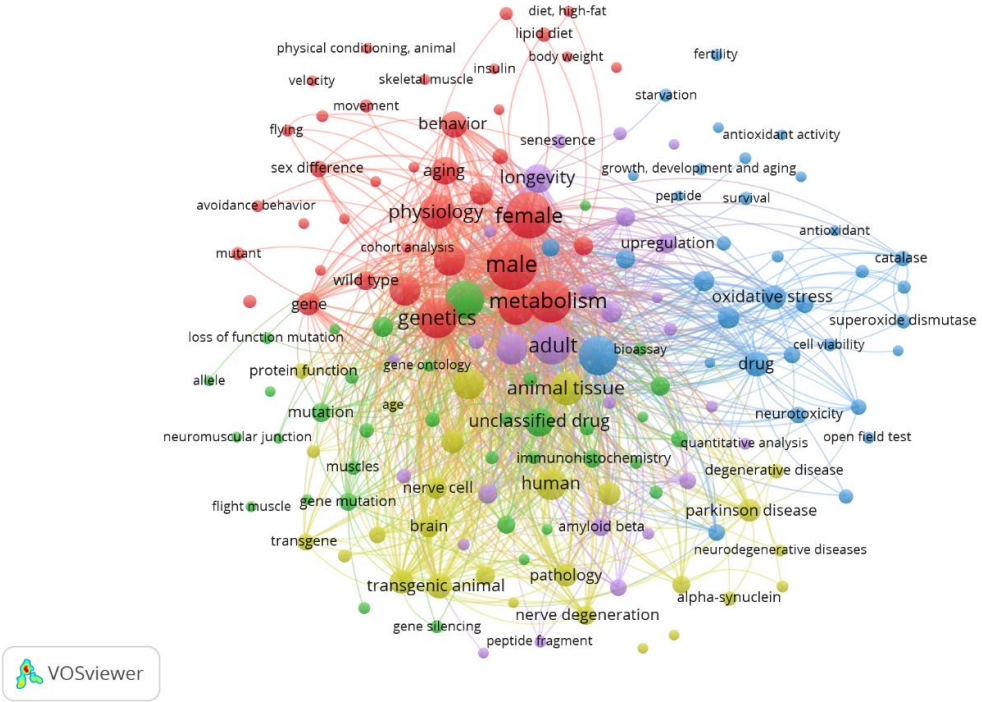

Figure 2. Results of co-occurrence analysis of index keywords

In addition to the systematic literature review (SLR), this paper also presents the results of bibliometric analysis conducted on the reviewed papers. With the assistance of

VOS Viewer, a co-occurrence analysis of index keywords within these papers was visualized (Figure 2). "Male" and "female" emerged as the keywords with the highest occurrence values. This finding indicates that the research encompasses aspects related to gender differences in the context of Drosophila. It underscores the significance of understanding how gender factors influence various biological conditions and bodily responses. Keywords such as "metabolism," "genetics," "model," and "protein" also stand out, signifying that the reviewed research is closely linked to an understanding of genetic and metabolic aspects within the Drosophila model. Additionally, keywords such as "locomotion," "physiology," "lifespan," and "phenotype" suggest that much of the research in the context of Drosophila is focused on comprehending movement, physiological function, lifespan, and related phenotypes. Keywords like "transgenic animal" and "genetically modified," with a high co-occurrence count, indicate that many studies in this review may involve genetic manipulations in Drosophila to create models relevant to the studied conditions.

Meanwhile, keywords with lower total link strength, such as "body weight," "physical conditioning," "physiological stress," "sucrose," and "velocity," may indicate that research in the context of Drosophila may not explicitly encompass these aspects or may not yet have a substantial body of research to establish strong connections. The disparities in occurrence rates and total link strength between keywords reflect the research focus and trends within the reviewed Drosophila behavioural studies. Keywords with high occurrence rates mirror crucial aspects often serving as the primary research focus. In contrast, keywords with lower total link strength may reflect aspects that have not been fully explored or are not the primary focus of the research.

4. CONCLUSION

The systematic literature review (SLR) and bibliometric analysis offer valuable insights into the diverse research landscape surrounding Drosophila behaviour assays. These findings underscore the adaptability of Drosophila as a model organism capable of investigating a broad spectrum of topics, including neurodegenerative diseases, aging, genetic modifications, and the influence of various environmental factors. Notably, the analysis highlights keywords such as "male" and "female" with high occurrence, emphasizing the significance of considering gender differences in Drosophila research. Furthermore, keywords related to genetics, metabolism, and modelling take centre stage, reflecting the organism's pivotal role in genetic and metabolic studies.

Conversely, keywords with lower total link strength, such as "body weight" and "physiological stress," may suggest areas within Drosophila behaviour research warrant further exploration. As a suggestion for future research, prioritizing investigations into the long-term and transgenerational effects of Drosophila behaviour assays is recommended, as these aspects still need to be explored. Gaining insights into how behaviours and phenotypes can be inherited across generations could yield valuable information about Drosophila's intricate interplay of genetic, environmental, and epigenetic factors and potentially shed light on broader biological phenomena

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