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IN SILICO CHARACTERIZATION OF BRAIN-DERIVED NEUROTROPIC FACTOR

CARACTERIZAÇÃO IN SILICO DO FATOR NEUROTRÓPICO DERIVADO DO CÉREBRO

CARACTERIZACIÓN IN SILICO DEL FACTOR NEUROTRÓPICO DERIVADO DEL CEREBRO

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ABSTRACT

BDNF acts as a modulator of synaptic plasticity, influencing both the central and peripheral nervous systems, in addition to regulating neurotransmitters and neuronal excitability. The main objective of this work is to evaluate the in silico characterization of Brain-Derived Neurotrophic Factor (BDNF) for structural, functional and molecular interactions analyses, to understand its role in neurobiological processes, neurodegenerative and psychiatric diseases. And as specific: to analyze the three-dimensional structure of BDNF; to study the molecular interactions between BDNF and its receptors (mainly TrkB); to identify potential mutations or variants that may affect BDNF function; to explore the relationship between BDNF and neurodegenerative diseases; to evaluate the viability of BDNF modulators as possible therapeutic targets. The theme “IN SILICO CHARACTERIZATION OF BRAIN-DERIVED NEUROTROPIC FACTOR: an integrative review” determined the construction of the PICO strategy, which represents an acronym for Patient (P), Intervention (I), Comparison (C) and Outcomes (O-*outcomes*), which generated the guiding question of this integrative literature review: “How can the *in silico* characterization of Brain-Derived Neurotrophic Factor (BDNF) contribute to the understanding of its structure, function and molecular interactions, as well as its implications in the development of neurodegenerative and psychiatric diseases, and in the direction of potential therapies?”. Some therapeutic strategies to increase BDNF are aerobic physical exercises and resistance training that increase BDNF, a diet rich in flavonoids (e.g.: blueberries, green tea) and omega-3 can modulate the expression of BDNF, TrkB agonists and gene therapy are promising, but still in clinical studies and deep brain stimulation (DBS) can restore neuronal plasticity via BDNF. There is a great need for more studies in the area, few articles were observed in the area and mainly in Brazil, on the subject.

Keywords: Brain-derived Neurotropic Factor. Neurology. Health. Medicine.

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RESUMO
O BDNF atua como um modulador da plasticidade sináptica, influenciando tanto o sistema nervoso central quanto o periférico, além de regular neurotransmissores e a excitabilidade neuronal. O trabalho tem como objetivo principal avaliar a caracterização in silico do Fator Neurotrófico Derivado do Cérebro (BDNF) para analises estruturais, funcionais e interações moleculares, para compreensão do seu papel em processos neurobiológicos, doenças neurodegenerativas e psiquiátricas. E como específicos: analisar a estrutura tridimensional do BDNF; estudar as interações moleculares entre o BDNF e seus receptores (principalmente o TrkB); identificar potenciais mutações ou variantes que possam afetar a função do BDNF; explorar a relação entre BDNF e doenças neurodegenerativas; avaliar a viabilidade de moduladores do BDNF como possíveis alvos terapêuticos. O tema "CARACTERIZAÇÃO IN SILICO DO FATOR NEUROTRÓPICO DERIVADO DO CÉREBRO: uma revisão integrativa", determinou a construção da estratégia PICO, que representa um acrônimo para Paciente (P), Intervenção (I), Comparação (C) e Desfechos (O-*outcomes*), que gerou a questão norteadora desta revisão integrativa da literatura: "Como a caracterização *in silico* do Fator Neurotrófico Derivado do Cérebro (BDNF) pode contribuir para a compreensão de sua estrutura, função e interações moleculares, bem como suas implicações no desenvolvimento de doenças neurodegenerativas e psiquiátricas, e no direcionamento de potenciais terapias?". Algumas Estratégias Terapêuticas para Aumentar BDNF são os Exercícios físicos aeróbicos e treinamentos de resistências que aumentam BDNF, uma dieta rica em flavonoides (ex.: mirtilos, chá-verde) e ômega-3 pode modular a expressão do BDNF, agonistas de TrkB e terapia gênica são promissoras, mas ainda em estudos clínicos e estimulação cerebral profunda (DBS) pode restaurar a plasticidade neuronal via BDNF. Existe uma grande necessidade de mais estudos na área, foi observado poucos artigos na área e principalmente no Brasil, com relação ao tema.

Palavras-chave: Fator Neurotrópico Derivado do Cérebro. Neurologia. Sáude. Medicina.

RESUMEN
El BDNF actúa como modulador de la plasticidad sináptica, influyendo tanto en el sistema nervioso central como en el periférico, además de regular los neurotransmisores y la excitabilidad neuronal. El principal objetivo del trabajo es evaluar la caracterización in silico del Factor Neurotrófico Derivado del Cerebro (BDNF) para análisis estructural, funcional e interacciones moleculares, para comprender su papel en procesos neurobiológicos, enfermedades neurodegenerativas y psiquiátricas. Y como específico: analizar la estructura tridimensional de BDNF; estudiar las interacciones moleculares entre BDNF y sus receptores (principalmente TrkB); identificar posibles mutaciones o variantes que podrían afectar la función del BDNF; explorar la relación entre BDNF y enfermedades neurodegenerativas; evaluar la viabilidad de los moduladores del BDNF como posibles dianas terapéuticas. El tema "CARACTERIZACIÓN IN SILICO DEL FACTOR NEUROTROPICO CEREBRAL: una revisión integrativa", determinó la construcción de la estrategia PICO, que representa un acrónimo de Paciente (P), Intervención (I), Comparación (C) y Resultados (O-*outcomes*), lo que generó la pregunta orientadora de esta revisión integrativa de la literatura: "¿Cómo puede la caracterización *in silico* del Factor Neurotrófico Cerebral Derivado del Cerebro (BDNF) contribuir a la comprensión de su estructura, función e interacciones moleculares, así como sus implicaciones en el desarrollo de enfermedades neurodegenerativas y psiquiátricas, y en la dirección de terapias potenciales?". Algunas estrategias terapéuticas para aumentar el BDNF son ejercicios físicos aeróbicos y entrenamiento de resistencia que aumentan el BDNF, una dieta rica en flavonoides (por ejemplo: arándanos, té verde) y omega-3 puede modular la expresión del BDNF, los agonistas de TrkB y la terapia génica son prometedores, pero aún en estudios clínicos y la estimulación cerebral profunda (DBS) puede restaurar la plasticidad neuronal a través del BDNF. Hay gran necesidad de más

estudios en el área, se observaron pocos artículos en el área y principalmente en Brasil, sobre el tema.

Palabras clave: Factor Neurotrópico Derivado del Cerebro. Neurología. Salud. Medicamento.

1 INTRODUCTION

Neurotrophic factors are endogenous soluble proteins that play crucial roles in the regulation of survival, growth, morphological plasticity and synthesis of new neurons, being fundamental for neuronal functionality. Among these proteins, neurotrophins stand out for their similar functionality and structure, and Brain-Derived Neurotrophic Factor (BDNF) is one of the most relevant. With a structure of 27 kDa, BDNF is the most abundant neurotrophin in the brain, essential for the development and maintenance of the neuronal system (Santos, 2024).

BDNF acts as a modulator of synaptic plasticity, influencing both the central and peripheral nervous systems, as well as regulating neurotransmitters and neuronal excitability. This factor binds to two main types of receptors: the high-affinity receptor tyrosine kinase (trk) and the low-affinity receptor p75NTR. NGF binds to the trkA receptor and BDNF to the trkB receptor (Ramos, 2024).

Produced predominantly in the cell bodies of sensory neurons and also in the postsynaptic dendrites of the hippocampus, BDNF plays a crucial role in synaptic and nociceptive modulation by influencing the release of neurotransmitters such as glutamate and GABA. Studies show that physical exercise, especially aerobic exercise, can increase BDNF concentrations, promoting synaptic plasticity, axonal growth, and dendritic remodeling, as well as contributing to the survival of neurons in the Central Nervous System (Haas, 2024).

Motor impairment and lack of coordination can interfere with learning, indicating the need for a curriculum that values both cognitive and motor development (Chen, 2020).

Brain-Derived Neurotrophic Factor *(BDNF*) is an essential protein in neuronal development, maintenance, and plasticity, in addition to being directly related to cognitive processes, such as learning and memory. Studies show that changes in BDNF levels are associated with several neurological and psychiatric conditions, including depression, Alzheimer's, and schizophrenia.

With advances in bioinformatics, *in silico* techniques allow the detailed study of proteins, their structures and functions, in a faster and more efficient way, opening new perspectives for the investigation of therapeutic targets and the development of drugs. The *in silico* characterization of BDNF allows an in-depth analysis of its three-dimensional structure, its molecular interactions and potential modifications that may influence its biological function.

In view of the increasing incidence of neurodegenerative diseases and psychiatric disorders, there is an urgent need to understand in more detail the role of BDNF in these pathological processes. In *silico* characterization can provide valuable information for the

discovery of new treatments that modulate this protein in a therapeutic way. In this way, this study will not only contribute to the expansion of scientific knowledge about BDNF, but may also open doors for neurology and psychiatry with both the most effective clinical interventions.

With this, the following problem arises: how can the *in silico characterization* of Brain-Derived Neurotrophic Factor (BDNF) contribute to the understanding of its structure, function, and molecular interactions, as well as its implications in the development of neurodegenerative and psychiatric diseases, and in the direction of potential therapies?

The main objective of this work is to evaluate the *in silico* characterization of Brain-Derived Neurotrophic Factor (BDNF) for structural, functional and molecular interactions, to understand its role in neurobiological processes, neurodegenerative and psychiatric diseases. And as specific: to analyze the three-dimensional structure of BDNF; to study the molecular interactions between BDNF and its receptors (mainly TrkB); to identify potential mutations or variants that may affect the function of BDNF; to explore the relationship between BDNF and neurodegenerative diseases; to evaluate the feasibility of BDNF modulators as possible therapeutic targets.

2 METHODOLOGY

The present study was a bibliographic research of the integrative literature review type. This procedure was chosen because it enables the synthesis and analysis of the scientific knowledge already produced on the theme "IN *SILICO* CHARACTERIZATION OF BRAIN-DERIVED NEUROTROPIC FACTOR: an integrative review". This review used the methodology proposed in the study by Oliveira et al. (2016).

According to Ercole, Melo and Alcoforado (2014), the integrative literature review is a method that aims to synthesize results obtained in research in a systematic, orderly and comprehensive way, through different methodologies. It is called integrative because it provides broader information on a subject, constituting a body of knowledge and can be directed to the definition of concepts, review of theories or methodological analysis of studies. This method provides the combination of data from the theoretical and empirical literature, providing a greater understanding of the topic of interest. Its elaboration is structured in six distinct stages presented in figure 1.

Figure 1

Stages of construction of an integrative review

Source: Paulo Sérgio da Silva, 2022 (Adapted).

2.1 STAGES OF THE INTEGRATIVE LITERATURE REVIEW

2.1.1 Identification of the theme and selection of the research question

The theme "IN *SILICO CHARACTERIZATION* OF BRAIN-DERIVED NEUROTROPIC FACTOR: an integrative review", determined the construction of the PICO strategy, which represents an acronym for Patient (P), Intervention (I), Comparison (C) and Outcomes (O-outcomes), which generated the guiding question of this integrative literature review: "How does *in silico* characterization Can the use of Brain-Derived Neurotrophic Factor (BDNF) contribute to the understanding of its structure, function, and molecular interactions, as well as its implications in the development of neurodegenerative and psychiatric diseases, and in the targeting of potential therapies?".

To locate the relevant studies that answered the research question, indexed and non-indexed descriptors (keywords) in Portuguese, English and Spanish were used. The descriptors were obtained from the Medical Subject Headings (MESH), the Health Sciences Descriptors (DeCS) and the CINAHL titles.

The VHL (Virtual Health Library) databases, coordinated by BIREME and composed of bibliographic databases produced by the VHL Network, such as LILACS, in addition to the

Medline database and other types of information sources, were consulted by means of descriptors and keywords; and Scielo – Scientific Electronic Library Online.

Element C of the PICO strategy was not addressed in this research because it does not aim to compare interventions. The terms used during the search were classified and combined in the databases, resulting in specific strategies for each database.

2.1.2 Establishment of inclusion and exclusion criteria

The inclusion criteria were studies available in their entirety, published in the last five years, from 2020 to 2024, in Portuguese, Spanish, and English. Book chapters, abstracts, incomplete texts, theses, dissertations, monographs, technical reports, and other forms of publication other than complete scientific articles were excluded from the initial search.

2.1.3 Identification of pre-selected and shortlisted studies

The analysis for the selection of studies was carried out in two phases, namely:

In the first, the studies were pre-selected according to the inclusion and exclusion criteria and according to the operating strategy and search of each database.

Three thousand, one hundred and fifty (3,150) studies were found as a general search in the VHL, and limiting the search to full-text articles carried out with humans in the last five years, brain-derived neurotrophic factor one hundred and five (105) studies, of which titles and abstracts were analyzed where only twelve (12) studies were consistent with the question of this research.

In the Scielo database, as a total search, one thousand, one hundred and fifty (1,150) studies were found, applying in the search the filter that limits by full text of the last five years with humans, brain-derived neurotrophic factor fifty (50) studies, of which titles and abstracts and the influence of exposure to allergens as the final result of ten (10) studies were analyzed.

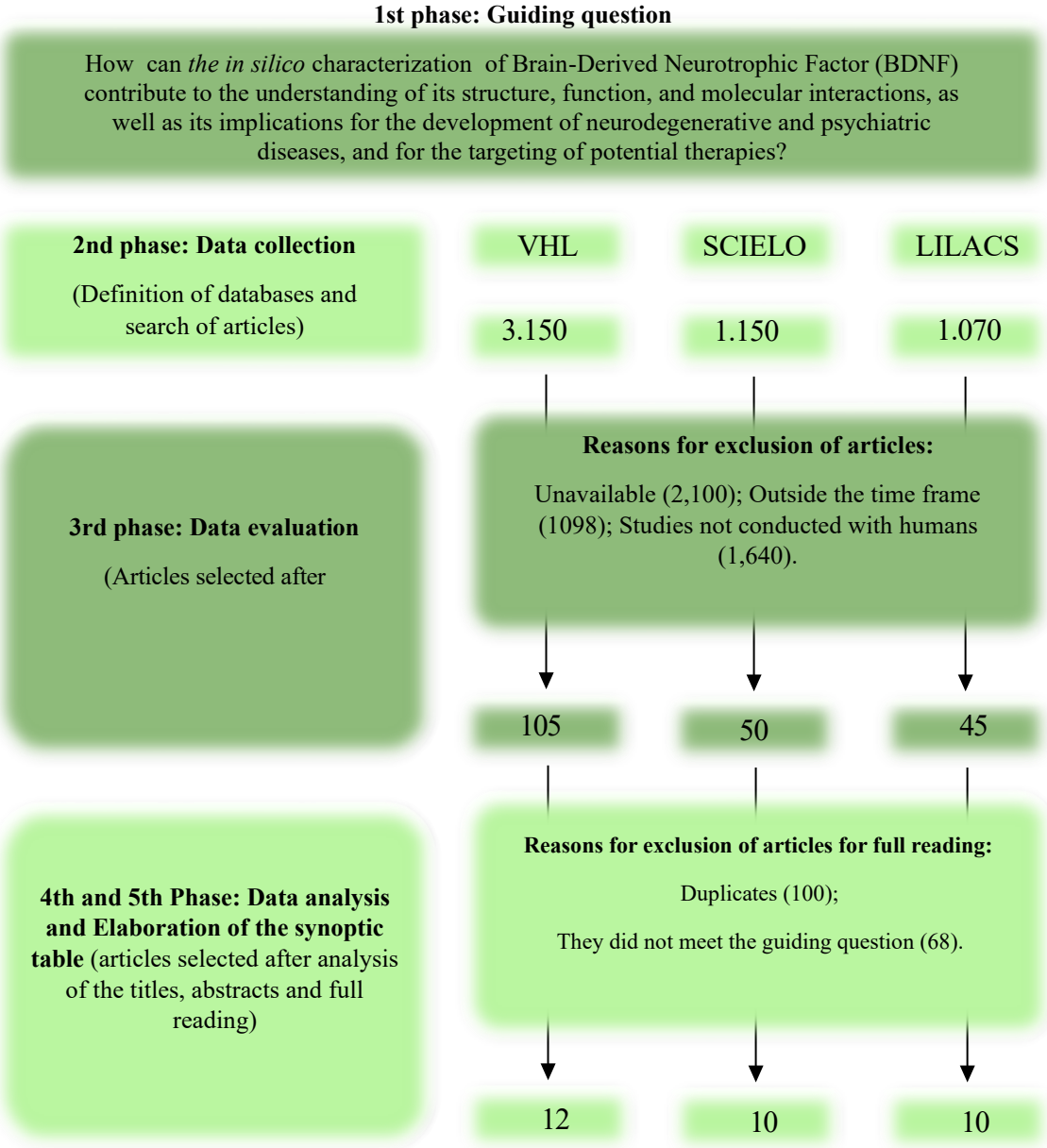
In Lilacs, one thousand and seventy (1,070) studies were obtained as a general search, and limiting the search to full-text articles carried out in the last five years with humans, brain-derived neurotrophic factor forty-five (45) studies, ten (10) of which were consistent with the question of this research after the analysis of the titles and abstracts.

In the second phase, the studies were analyzed regarding the potential for participation in the study, evaluating compliance with the research question, as well as the type of investigation, objectives, sample, method, outcomes, results, and conclusion, resulting in thirty-two (32) articles.

In the end, thirty-two (32) articles met the guiding question and were added to the study.

Figure 2

FlowTable of the selection process of studies for integrative review - Teresina, PI, Brazil, 2025



Source: Databases, 2025.

2.1.4 Analysis and interpretation of the results

In this stage, the information collected in the scientific articles was analyzed and analytical categories were created, which facilitated the ordering and summarization of each study. This categorization was performed descriptively, indicating the most relevant data for the study.

The research took into account the ethical aspects of the research regarding the citations of the studies, respecting the authorship of the ideas, concepts and definitions present in the articles included in the review.

It was decided to analyze in statistical and text form, using mathematical calculations and inferences, which will be presented in tables and tables to facilitate visualization and understanding.

3 RESULTS

The results of this study were structured in two stages. The first stage consists of the characterization of the studies employed, while the second part addresses the objectives of the research, directed to the analysis of scientific productions capable of elucidating the central question investigated. This methodological approach allows for a systematic and rigorous organization of the findings, facilitating the understanding and interpretation of the results obtained.

3.1 CHARACTERIZATION OF THE STUDIES COVERED

The characterization of the included studies (N=32) revealed that most of them consisted of quantitative research. The analysis of the studies obtained was characterized by online databases, showing a homogeneous predominance of the VHL database. As for time, the arrangement pointed to the growing publication of studies in the year 2020. There was a predominance of studies with the English language (31). Therefore, the descriptive analysis of the scientific productions addressed is described in table 1.

Table 1

Representation of the data analyzed

VARIABLES	**No.**	**%**
TYPE OF RESEARCH		
Quantitative	15	47%
Qualitative	5	16%
Randomized	3	9%
Meta Analysis	6	19%
Experimental	4	12%
ONLINE SOURCES		
Bireme/VHL	12	38%
PubMed	10	31%
Scielo	10	31%
TEMPORAL DISTRIBUTION		
2024	0	0
2023	6	19%
2022	7	22%
2021	8	25%
2020	11	34%
LANGUAGE		
Portuguese	1	96%

English	**31**	**4%**

Source: Authors.

Most of the studies evaluated the three-dimensional structure of BDNF. Where they reported the best ways, most used methods, even within other titles always addressing the preventive way, among other similar topics, as shown in the table below.

Table 2

Distribution of the articles included in this literature review according to the year of publication, author and title

YEAR	AUTHOR	TITLE
2022	FERNÁNDEZ-RODRÍGUEZ, Rubén et al	Immediate effect of high-intensity exercise on brain-derived neurotrophic factor in healthy young adults: A systematic review and meta-analysis
2023	DADKHAH, M et al	Experimental and Clinical Evidence of Physical Exercise on BDNF and Cognitive Function: A Comprehensive Review from Molecular Basis to Therapy
2023	CEFIS, M et al	Molecular mechanisms underlying physical exercise-induced brain BDNF overproduction
2022	BABIARZ et al.	Effects of strength training on BDNF in healthy young adults.
2023	FELICE, G. et al	Can Brain-Derived Neurotrophic Factor Be Considered a Biomarker for Bipolar Disorder? An Analysis of the Current Evidence
2022	RENTERÍA, I. et al	The molecular effects of BDNF synthesis on skeletal muscle
2021	PUHLMANN, Lara MC et al.	Association between hippocampal structure and serum Brain-Derived Neurotrophic Factor (BDNF) in healthy adults: A registered report.
2023	LIANG, Zhiqiang et al.	Effects of a Single Bout of Endurance Exercise on Brain-Derived Neurotrophic Factor in Humans: A Systematic Review and Meta-Analysis of Randomized Controlled Trials
2020	GOMUTBUTRA, Patama et al	The effect of mindfulness-based intervention on brain-derived neurotrophic factor (BDNF): a systematic review and meta-analysis of controlled trials
2021	GARCÍA-SUÁREZ Patricia Concepción et al	The effects of interval training on peripheral brain derived neurotrophic factor (BDNF) in young adults: A systematic review and meta-analysis
2021	PETERSEN, N. A.; NIELSEN, M. Ø.; COELHO, K. et al.	Brain-derived neurotrophic factor levels in newly diagnosed patients with bipolar disorder, their

		unaffected first-degree relatives and healthy controls.
2020	NASSAN, M. et al.	Methylation of Brain Derived Neurotrophic Factor (BDNF) Val66Met CpG site is associated with early onset bipolar disorder.
2022	MARIN, M. E. M. et al.	Association between obesity and the brain-derived neurotrophic factor gene polymorphism Val66Met in individuals with bipolar disorder in Mexican population.
2023	MARIANO, I. M. et al.	Exercise training improves blood pressure reactivity to stress: a systematic review and meta-analysis.
2020	LIN, C. C.; HUANG, T. L.	Brain-derived neurotrophic factor and mental disorders.
2021	KARTHIKEYAN, S. et al.	Inflammatory markers, brain-derived neurotrophic factor, and the symptomatic course of adolescent bipolar disorder: A prospective repeated-measures study.
2020	SUGA, Y.; YOSHIMOTO, K.; NUMATA, S. et al.	Structural variation in the glycogen synthase kinase 3β and brain-derived neurotrophic factor genes in Japanese patients with bipolar disorders.
2021	TENG, Z.; WANG, L.; LI, S. et al.	Low BDNF levels in serum are associated with cognitive impairments in medication-naïve patients with current depressive episode in BD II and MDD
2020	TUNÇEL, Ö. K. et al.	Neurotrophic factors in bipolar disorders patients with manic episode.
2021	BAYKARA, B. et al.	Brain-derived neurotrophic factor in bipolar disorder: Associations with age at onset and illness duration.
2022	BOSCUTTI, A.; PIGONI, A.; DELVECCHIO, G. et al.	The Influence of 5-HTTLPR, BDNF Rs6265 and COMT Rs4680 Polymorphisms on Impulsivity in Bipolar Disorder: The Role of Gender
2021	RIBEIRO, Daniel et al.	The impact of physical exercise on the circulating levels of BDNF and NT 4/5
2023	SUN, Bing-xin et al.	Neuroprotection of exercise: P2X4R and P2X7R regulate BDNF actions.
2022	WANG, Ya-Hai et al.	The effect of physical exercise on circulating brain-derived neurotrophic factor in healthy subjects: a meta-analysis of randomized controlled trials.
2020	TROMBETTA, Ivani Credidio et al.	Serum BDNF levels in cardiovascular protection and in response to exercise.
2020	YOU, Tongjian; OGAWA, Elisa F.	Effects of meditation and mind-body exercise on brain-derived neurotrophic factor
2022	ZHOU, Bojun et al.	Effects of different physical activities on brain-derived neurotrophic factor: A systematic review and bayesian network meta-analysis.

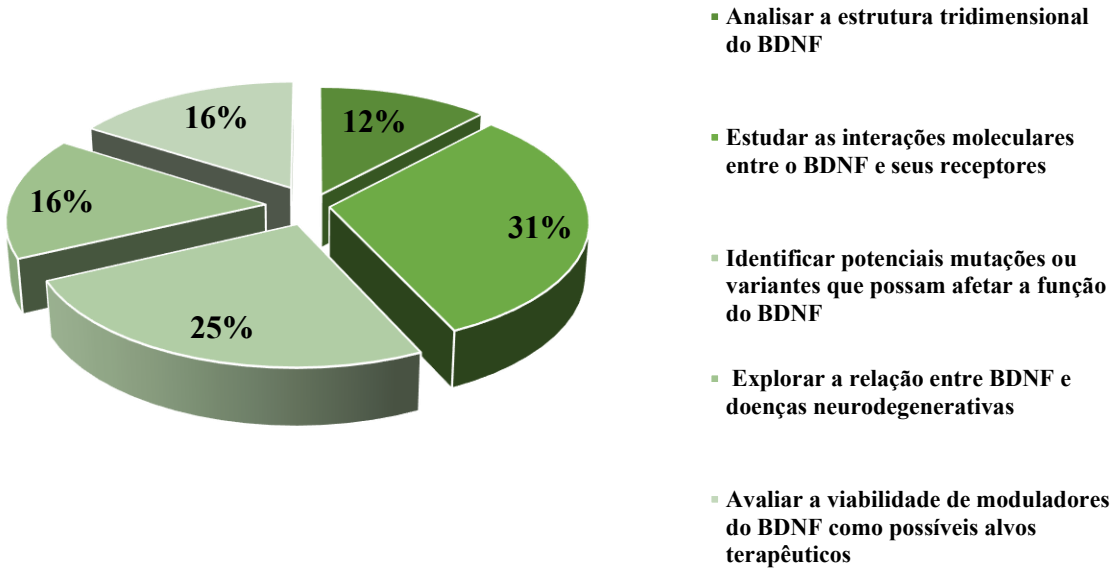
2021	Xiao L, Yan J, Feng D, Ye S, Yang T, Wei H, Li T, Sun W, Chen J.	Critical Role of TLR4 on the Microglia Activation Induced by Maternal LPS Exposure Leading to ASDLike Behavior of Offspring.
2020	Elsabbagh M.	Linking risk factors and outcomes in autism spectrum disorder: Is there evidence for resilience?
2020	Haddad FL, Patel S V., Schmid S.	Maternal Immune Activation by Poly I:C as a preclinical Model for Neurodevelopmental Disorders: A focus on Autism and Schizophrenia.
2020	SPELLMAN, T., & Liston, C.	Toward Circuit Mechanisms of Pathophysiology in Depression.
2020	Liao X, Yang J, Wang H, Li Y.	Microglia mediated neuroinflammation in autism spectrum disorder

Source: Authors.

After analyzing the bibliographies studied, it was observed a predominance and similarity of content in certain themes, and the studies were grouped into the following thematic categories: Category 1 - to analyze the three-dimensional structure of BDNF (12%), Category 2 - to study the molecular interactions between BDNF and its receptors (mainly TrkB) (31%), Category 3 - to identify potential mutations or variants that may affect the function of BDNF, (25%) Category 4 - explore the relationship between BDNF and neurodegenerative diseases (16%) and Category 5 - evaluate the feasibility of BDNF modulators as possible therapeutic targets (16%).

Figure 3

Thematic distribution of the material analyzed



Source: Authors.

4 CHARACTERIZATION OF THE STUDIES ANALYZED

4.1 ANALYSIS OF THE THREE-DIMENSIONAL STRUCTURE OF BDNF

The three-dimensional structure of Brain-Derived Neurotrophic Factor (BDNF) is crucial for its biological function, especially in the interaction with its high-affinity receptor, TrkB (Tropomyosin receptor kinase B). The general structure of BDNF, active form and dimerization, interaction with TrkB, structure resolved by crystallography (Fernández-Rodríguez, 2022).

BDNF belongs to the family of neurotrophins, which also includes NGF, NT-3 and NT-4/5, its structure follows the "cysteine-knot" pattern, a characteristic of neurotrophins that guarantees structural stability and is formed by antiparallel beta sheets and disulfide bonds, essential for its stability. It typically exists as a dimer in its active form, its dimerization is critical for TrkB receptor activation, initiating intracellular cascades that promote neuronal survival and plasticity (Dadkhah, M et al, 2023).

Interaction with TrkB binds to the extracellular domain of TrkB, inducing its dimerization and autophosphorylation. This interaction activates intracellular pathways such as: MAPK/ERK → promotes neuronal growth, PI3K/Akt → protects against apoptosis, and PLC-γ → regulates synaptic plasticity (Cefis, M et al, 2023).

X-ray crystallography studies have revealed that BDNF interacts asymmetrically with TrkB, promoting conformational changes necessary for receptor activation and some of these structures are available in the Protein Data Bank (PDB), such as PDB ID: 1B8M, which contains details of BDNF conformation (Babiarz et al., 2022).

4.2 EXPLORE THE RELATIONSHIP BETWEEN BDNF AND NEURODEGENERATIVE DISEASES

Brain-Derived Neurotrophic Factor (BDNF) plays a key role in neuronal survival, synaptic plasticity, and neurogenesis, making it a critical target in the study of neurodegenerative diseases. Reduced BDNF levels are associated with the progression of several neurodegenerative conditions, including Alzheimer's, Parkinson's, Amyotrophic Lateral Sclerosis (ALS), and Huntington's (Felice, G. et al, 2023).

In Alzheimer's disease, there is a reduction in BDNF levels in the hippocampus and cortex of patients with the disease. BDNF protects against beta-amyloid (Aβ) toxicity and hyperphosphorylated protein accumulation. The Val66Met Variant may increase the risk of AD due to impaired BDNF secretion. Therapies aimed at increasing BDNF include physical exercise, a diet rich in polyphenols, and TrkB agonists (Rentería, I. et al, 2022).

In Parkinson's disease, it regulates the survival of dopaminergic neurons in the substantia nigra. Patients with PD have reduced levels of BDNF in the cerebrospinal fluid and striatum. The loss of BDNF aggravates the degeneration of dopaminergic neurons. Therapeutic strategies include exogenous neurotrophins and deep brain stimulation (DBS), which can increase BDNF (Puhlmann, Lara MC et al., 2021).

In Amyotrophic Lateral Sclerosis, BDNF protects motoneurons against degeneration. Patients with ALS have decreased levels of BDNF in the cerebrospinal fluid. The p75NTR receptor can be more activated than TrkB, inducing apoptosis. BDNF-infused therapies or TrkB analogues are being studied (Liang, Zhiqiang et al., 2023).

In Huntington's disease, the mutation in the HTT gene reduces the production of BDNF in the striatum. The lack of BDNF contributes to neuronal death and motor and cognitive symptoms. BDNF stimulation via physical exercise and gene therapy may slow the progression of HD (Gomutbutra, et al, 2020).

BDNF is a crucial factor in protecting against neurodegeneration and brain plasticity. Strategies to increase their levels are essential in the development of therapies for diseases such as Alzheimer's, Parkinson's, ALS, and Huntington's. It has been widely studied in patients with mental disorders due to its role in regulating mood, cognition, and stress response. Research indicates that altered levels of Brain-Derived Neurotrophic Factor may be involved in the pathophysiology of several mental disorders, including depression, bipolar disorder, schizophrenia, anxiety disorder, and PTSD, among others (García-Suárez et al, 2021).

Patients with depression often have reduced levels of BDNF in their blood and brain. Treatment with antidepressants may increase BDNF levels, suggesting a role in neuronal recovery (Petersen, N. A.; Nielsen, M. Ø.; Coelho, K. et al., 2021).

In bipolar disorder During depressive or manic episodes, BDNF levels tend to be low. Stabilizing mood with lithium or other stabilizers can restore mood levels (Nassan, M. et al., 2020).

Individuals with schizophrenia have reduced BDNF levels, which can contribute to cognitive deficits and structural changes in the brain. Some antipsychotic medications may influence BDNF regulation (Marin, M. E. M. et al., 2022).

In Anxiety Disorder and PTSD , chronic stress and trauma can decrease BDNF levels, impairing neuronal adaptation. Strategies such as cognitive behavioral therapy and physical exercise can help restore your levels (Mariano, I. M. et al, 2023).

4.3 STUDY THE MOLECULAR INTERACTIONS BETWEEN BDNF AND ITS RECEPTORS (MAINLY TRKB)

The study of the molecular interactions between BDNF (Brain-Derived Neurotrophic Factor) and its main receptor, TrkB (Tropomyosin receptor kinase B), is essential to understand how this system regulates neuronal survival, growth, and plasticity (Lin, C. C.; Huang, T. L, 2020).

BDNF belongs to the neurotrophin family and has a dimer structure stabilized by disulfide bonds. It contains a structural "cysteine-knot" motif, typical of neurotrophins, providing stability and high affinity for receptors (Karthikeyan, S. et al., 2021).

TrkB is a receptor tyrosine kinase composed of: extracellular domain (Contains two immunoglobulin (Ig) repeats that interact directly with BDNF), transmembrane domain (Responsible for anchoring the receptor to the membrane) and intracellular domain (Has tyrosine kinase activity, essential for signal transduction) (Suga, Y.; Yoshimoto, K.; Numata, S. et al., 2020).

BDNF binds to two TrkB molecules, promoting their dimerization and activation. The interaction is asymmetric, i.e., a region of BDNF binds with greater affinity to one of the TrkB monomers. BDNF binding causes conformational changes that approximate the intracellular TrkB domains. This leads to the autophosphorylation of tyrosine residues (e.g., Tyr515, Tyr705, Tyr706) in the intracellular domain of the receptor (Teng, Z.; Wang, L.; Li, S. et al., 2021).

The Activation of Intracellular Signaling Pathways TrkB phosphorylation triggers intracellular cascades essential for neuronal function: PI3K/Akt → promotes cell survival and neuroprotection, MAPK/ERK → stimulates neuronal growth and differentiation, and PLC-γ → regulates synaptic plasticity and calcium release (Tunçel, Ö. K. et al., 2020).

BDNF also interacts with the p75NTR receptor, which can have pro-apoptotic or pro-survival effects, depending on the cellular context. The co-expression of TrkB and p75NTR can modulate BDNF's affinity for TrkB, increasing signaling efficiency (You, Tongjian; Ogawa, Elisa F., 2020).

The crystallographic structure of TrkB-bound BDNF is available in the Protein Data Bank (PDB ID: 1HCF). Molecular dynamics studies and techniques such as molecular docking help predict how mutations in TrkB or BDNF may affect their interaction and function (Baykara, B. et al.et al., 2022).

Understanding this interaction is essential for the development of neuroprotective therapies, such as: BDNF mimetics (small peptides that activate TrkB), TrkB agonist molecules for the treatment of neurodegenerative diseases (e.g., Alzheimer's, Parkinson's) and specific inhibitors to modulate altered signaling pathways in psychiatric disorders (Boscutti, A.; Pigoni, A.; Delvecchio, G. et al., 2022).

4.4 IDENTIFY POTENTIAL MUTATIONS OR VARIANTS THAT MAY AFFECT BDNF FUNCTION

The identification of mutations or variants in BDNF is essential to understand its impact on neuroplasticity and its relationship to neurological and psychiatric disorders. Here are some of the main aspects: main variants and mutations in the BDNF gene in the variant Val66Met (rs6265) the substitution occurs: Valine (Val) → methionine (Met) in position 66 of the pro-BDNF. The main effect is to reduce the activity-dependent secretion of BDNF, affecting synaptic plasticity. Leading to a higher risk of depression and anxiety, deficits in memory and cognition, and altered response to stress and antidepressants (Ribeiro, et al., 2021).

In the C270T Variant (rs56164415), the cytosine (C) → Thymine (T) is replaced in the promoter region. Its effect is: reduction of BDNF expression. Its association leads to schizophrenia and increased vulnerability to mood disorders (Sun, et al., 2023).

In the R92H and P75L mutations, point substitutions occur in the mature BDNF structure. Where its main effect is the possible impact on dimerization and binding to the TrkB receptor. The Val66Met variant impairs the transport of pro-BDNF in secretory vesicles by decreasing release into the synaptic cleft. This affects long-term potentiation (LTP), which is crucial for learning and memory (Wang, et al., 2022).

Some mutations can modify the structure of BDNF, affecting the binding and activation of TrkB. This may reduce the activation of the PI3K/Akt and MAPK/ERK pathways, impairing neuroprotection. Pro-BDNF has a high affinity for the p75NTR receptor, which can induce apoptosis. Mutations can increase the activation of this pathway, leading to greater neuronal death under stress conditions (Trombetta, et al., 2020).

Table 3

Mutations and Neurological/Psychiatric Diseases

Mutation	Molecular Effect	Related Diseases
Val66Met	Reduces BDNF secretion	Depression, Anxiety, Schizophrenia, PTSD, Alzheimer's
C270T	Decreases BDNF expression	Schizophrenia, Bipolar Disorder
R92H/P75L	Affects dimer structure	Possible impact on cognition and neurodevelopment

Source: Authors.

TrkB agonists may compensate for the reduction in BDNF in individuals with harmful mutations. Physical exercise, a diet rich in omega-3 and flavonoids help modulate BDNF levels. Studies investigate gene editing (CRISPR) to correct deleterious variants (Zhou, al., 2022).

4.5 EVALUATION OF THE FEASIBILITY OF BDNF MODULATORS AS THERAPEUTIC TARGETS

Brain-Derived Neurotrophic Factor (BDNF) modulation is a promising approach to treat neurodegenerative diseases, psychiatric disorders, and neurological injuries. However, challenges such as bioavailability, selectivity, and safety need to be overcome (Xiao L, Yan J, Feng D, Ye S, Yang T, Wei H, Li T, Sun W, Chen J., 2021).

In recombinant BDNF therapy, the use of exogenous BDNF to compensate for its deficiency in the brain. Tested in Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis (ALS) models. The main challenges are low penetration of the blood-brain barrier (BBB), short half-life and rapid enzyme degradation, and invasive administration (e.g., intracerebral or intrathecal injection) (Elsabbagh M., 2020).

Small molecules that directly activate the TrkB receptor, mimicking the effects of BDNF. The main compounds studied are 7,8-Dihydroxyflavone (7,8-DHF) – crosses the BBB and activates TrkB and LM22A-4 – selective for TrkB, but with limited efficacy. Main Challenges are the Specificity for TrkB without activating p75NTR (a receptor that can induce apoptosis) and the Development of molecules with better pharmacokinetics and lower toxicity (Haddad FL, Patel S V., Schmid S., 2020).

HDAC inhibitors (Histone Deacetylase Inhibitors) increase transcription of the BDNF gene. Physical exercise and a diet rich in polyphenols (resveratrol, curcumin, flavonoids) increase the expression of BDNF. Gene therapy via viral vectors (e.g., AAV-BDNF) is in trials for neurodegenerative diseases (Spellman, T., & Liston, C., 2020).

Transcranial Magnetic Stimulation (TMS) and Deep Brain Stimulation (DBS) can increase BDNF in the brain. Studies show that TMS in the prefrontal cortex increases synaptic plasticity in patients with depression (Liao X, Yang J, Wang H, Li Y., 2020).

5 CONCLUSION

TrkB Agonists are promising**,** but they need better selectivity. Epigenetic modulation and neuroprotective diet are viable complementary approaches. In gene therapy and

neurostimulation they have potential, but require more safety studies. However, combined approaches may be the key to increasing the effectiveness of treatments. Understanding the structure of BDNF helps in the development of drugs that modulate its activity**.** Small peptides or mimetic molecules of BDNF are studied to treat neurodegenerative diseases and psychiatric disorders**.**

Aerobic exercise and resistance training that increases BDNF, a diet rich in flavonoids (e.g., blueberries, green tea) and omega-3s can modulate BDNF expression, TrkB agonists, and gene therapy are promising, but still in clinical studies and deep brain stimulation (DBS) can restore neuronal plasticity via BDNF. There is a great need for more studies in the area, few articles were observed in the area and especially in Brazil, regarding the theme.

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