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Summary

Experience Report

Critical Review

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Letter to the Editor

Inácio de Barros Melo Neto

We are convinced that the year 2023 consolidated the Faculty of Medicine of Olinda (FMO) as an educational institution committed to Social Responsibility. We advanced several aspects aligned to what is expected from a higher education institution that seeks to offer comprehensive training to their members. We had a lot to celebrate in the first semester of 2023, including the re-accreditation with the highest score from the Ministry of Education and the recognition of our course.

First, we would like to highlight the quick rise of our journal, Anais da Faculdade de Medicina de Olinda-Responsabilidade Social, which received several indexations in a short period of time, reflecting the quality of the publications and the Institution's interest in constantly promoting research. Initially, the journal was indexed in Diadorim, Google Scholar, and LivRe. We kept working and we were quickly indexed in Latindex, ROAD, Miguilim, Oasisbr, and DOAJ, officially becoming part of the Global Directory of Open Scientific Journals. In addition, the journal received the Qualis B4 stratum in the 2017/2020 quadrennial evaluation conducted by CAPES (Coordination for the Improvement of Higher Education Personnel), which was a source of pride for us, our academic community, and the journal's dedicated editorial board, highlighting the brilliant performance of our academic director Professor Dr. Paulo Goes, PhD and editorial board.

The journal indexing process is constant and must be valued by higher education institutions. The journal indexing is important for academic training since publication is a requirement for students to obtain their degrees, such as the Medical Residency Program.

Pursuing our aspirations, the Maria Alcoforado de Barros Melo Institute was created with the goal to be a center of reference and excellence in teaching, research, service, and assistance for children with Down syndrome. The Institute's mission is to serve underprivileged children from Olinda and other cities in the state of Pernambuco, stimulating their physical and psychological skills as much and as early as possible, always targeting autonomy and inclusion in various social environments: school, sports activities, groups of friends, and work. The Institute also offers expanded and effective care to people with Down syndrome using technical competence, qualified listening, empathy, and bonding in a welcoming environment. It is in this direction that the Institute aims to build a new relationship with children with Down syndrome and their families. We are confident that the outputs of this intervention will result in many publications to this journal.

Finally, our semester was crowned with the 1st FMO International Marathon, which brought together more than 1,500 runners from different parts of the country and the world, carrying the message of FMO's commitment to social responsibility and reinforcing our commitment with the city of Olinda. All these initiatives encourage us to continue in the incessant search to train doctors in a humanistic approach, with a strong anchor in the inseparable principles of teaching, research, and service.

Anais da Faculdade de Medicina de Olinda
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Cannabidiol interactions in the voltage-gated calcium channel by molecular docking: its role in the neuronal inhibitory mechanism

Interações do canabidiol no canal de cálcio dependente de voltagem por docking molecular: papel no seu mecanismo inibitório neuronal

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Abstract

Objective: to analyze cannabidiol (CBD) interactions on $Ca_V3.2$ channels using molecular docking. **Methods:** this in silico study considered CBD and gabapentin (GBP) as testing drugs and the $Ca_V3.2$ channel as the target protein. The molecular docking was performed on Dockthor®. Simulations were classified according to the highest affinity to the channel. Binding energies were compared using the t-test (GraphPad Prism); values were significantly different when $p < 0.05$. **Results:** The spatial positions into CBD or GBP and $Ca_V3.2$ were 1,000,000 conformers. The binding energies of CBD and GBP on $Ca_V3.2$ were -6.493 ± 0.07 and -6.842 ± 0.19 kcal/mol, respectively; they were not significantly different ($p = 0.08$). This finding suggests that both drugs presented similar affinity with the channel despite their different positionings. **Conclusions:** the CDB binds to the Ca V 3.2, blocking this channel. These data highlight the analgesic effect of CBD via the neuronal inhibitory pathway.

Keywords: Cannabidiol; Analgesic; Drug modeling; Voltage-gated calcium channel.

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Resumo

Objetivo: analisar as interações do canabidiol (CBD) nos canais $Ca_V3.2$ utilizando docking molecular. **Métodos:** este estudo in silico considerou o CBD e a gabapentina (GBP) como drogas de teste e o canal $Ca_V3.2$ como proteína alvo. O docking molecular foi realizado no Dockthor®. As simulações foram classificadas de acordo com a maior afinidade com o canal. As energias de ligação foram comparadas usando o teste t (GraphPad Prism); os valores foram significativamente diferentes quando p <; 0,05. **Resultados:** As posições espaciais em CBD ou GBP e $Ca_V3.2$ foram de 1.000.000 confórmeros. As energias de ligação de CBD e GBP em Ca v 3.2 foram -6,493 ± 0,07 e -6,842 ± 0,19 kcal/mol, respectivamente; não foram significativamente diferentes (p = 0,08). Esse achado sugere que ambas as drogas apresentaram afinidade semelhante com o canal, apesar de seus posicionamentos diferentes. **Conclusão:** o CDB liga-se ao $Ca_V3.2$, bloqueando este canal. Estes dados destacam o efeito analgésico do CBD através da via inibitória neuronal.

Palavras-chave: Canabidiol; Analgésico; Modelagem de medicamentos; Canal de cálcio dependente de voltagem.

INTRODUCTION

Pain is an uncomfortable emotional and sensitive experience that may be associated with potential or real tissue lesions.[1-2] Patients with pain experience consequences, such as limited health activities, social life, and workday.[3] In addition, disorders related to pain present high prevalence, and its effective handling is a challenge.[4]

A putative analgesic is cannabidiol (CBD), a Phytocannabinoid found in Cannabis sativa. CBD acts without psychoactive and does not reduce cognition, ensuring its safety.[5,6] CBD has been applied in many diseases involving membrane excitability, targeting channels, such as voltage-gated sodium (Na_v), voltage-gated potassium (K_v), voltage-gated calcium (Ca_v), and transient receptor potential (TRP).[7-11]

The low Ca_v channel family is important in the peripheral processing of nociceptive signals because they control neuronal excitability.[12] Three subtypes of Ca_v channels have been identified: $Ca_v3.1$, $Ca_v3.2$, and $Ca_v3.3$.Previous studies demonstrated that the $Ca_v3.2$ subtype is predominantly found at sites responsible for pain transmissions.[13,14] Therefore, blockers of CaV3.2 may be used for treating chronic and acute pain.[15-19] CBD was able to abolish full conductance via Ca 3.1, 3.2, and 3.3 T-type channels using patch clamp electrophysiology; however, mechanism molecular details of CBD on Ca_V are still being determined.[9] Therefore, molecular docking allows an understanding of the function-structure relation in a pharmacological target and its ligand-protein binding.[20]

GBP is a synthetic analog of the neurotransmitter gamma- aminobutyric acid that blocks CaV channels, resulting in anticonvulsant activity. This drug has also become a popular alternative

to opioids for pain and is widely used for treating neuropathic pain.[21,22] GBP presents molecular formula $C_9H_{17}NO_2$ and weigth of 171.24 g/mol, while CBD presents $C_{21}H_{30}O_2$ and 314.5 g/mol.[23]

This study aimed to analyze CBD interactions in the $Ca_V3.2$ channel using molecular docking, and to compare the GBP.

METHODS

This quantitative and experimental study was conducted *in silico*. The chemical structures of CBD (CID: 644019) and GBP (CID: 3446) were downloaded from the PubChem database, and the 3D structure of $Ca_V3.2$ from the PDB database (ID: 6N4I). The channel protein and drugs were molecularly docked by Dockthor®, and classified according to the highest affinity with the channel.[24] Simulations were processed from the grid box coordinates (x = 178,5415, y = 169,6810, and z = 193,3300). The docking poses were selected, and H-bonding was visualized by UCSF Chimera®. The binding energy was compared using the t-test by GraphPad Prism®; values were significantly different when $p < 0.05$.

RESULTS AND DISCUSSION

The spatial positions into CBD or GBP and CaV3.2 were 1,000,000 conformers. The top three were selected, and the binding energy of each drug and the channel was calculated and shown in Table 1. The molecular docking is more stable when it presents lower biding energy.[25] The binding energies of CBD and GBP on $Ca_V3.2$ were -6.493 ± 0.07 and -6.842 ± 0.19 kcal/mol, respectively (Table 1). These values were not significantly different, suggesting that both drugs bind similarly to $Ca_V3.2$. Moreover, the binding energies were < −5 kcal/mol, determining the spontaneous binding of the ligand and receptor.[26]

Table 1. Docking binding energy of CBD and GNP in the $Ca_V3.2$.

Ligand	Affinity (kcal/mol)
CBD	- 6.493 ± 0.07
GBP	- 6.842 ± 0.19

Being: $p = 0.08$.

* CBD: cannabidiol; GBP: gabapentin

The best positions of CBD and GBP were presented in Fig. 1, which may correspond to the blocked channel (Fig. 1B). Visualizing the 3D structures, both drugs connected at distinct sites of $Ca_V3.2$; however, they exhibited similar binding energy (Table 1). Similarly, CBD and carbamazepine showed the same energy on Na1.7.[27] Other phytocannabinoids (e.g., cannabigerolic acid and cannabidivarin) inhibited $Ca_V3.2$ using whole-cell patch clamp recordings.[28]

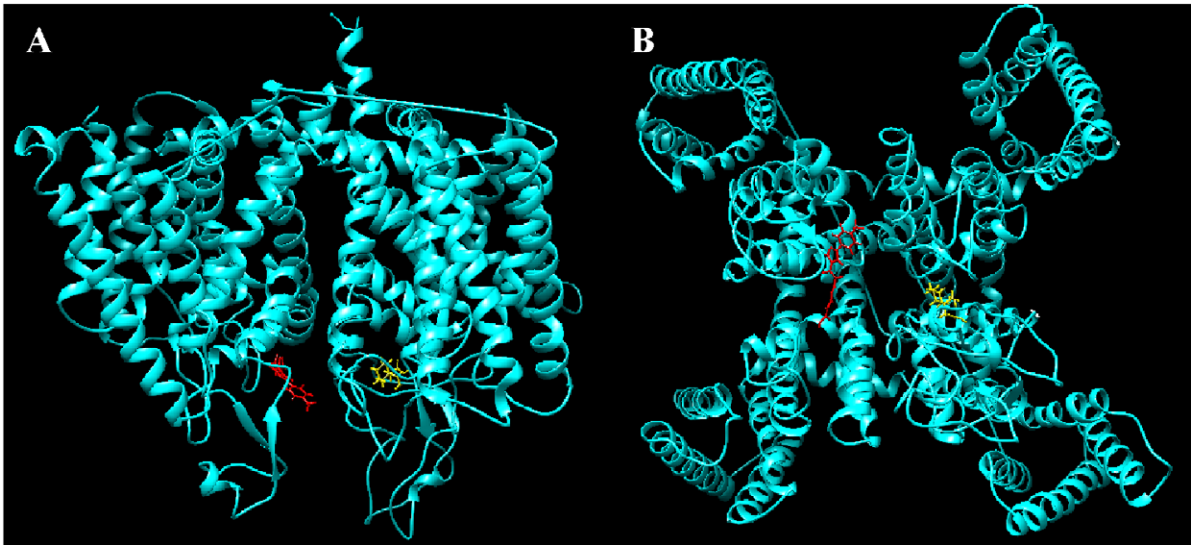

Figure 1 – CBD and GBP sites in the $Ca_V3.2$. Being: CaV3.2 shown from the side (A) and cytoplasmic (B) view. CBD' (red) and GBP' (yellow) conformation inward protein 3D (cyan).

The helices of CaV3.2 and CBD binding sites are presented in Figure 2A. Specifically, the CDB makes an H-bond with ASP690, ASP421, and LYS423 residue (Fig. 2B), whose distances were 2.38, 1.42, and 1.88 Å, respectively. However, GBP did not present H-bond with residue (data not shown), suggesting that it presents less stability than CBD in CaV3.2. The CBD binding site and other channels have been different. For instance NaV1.7 channel involves the THR180, while the bacterial NaV channel involves the M175 residue.[10,27]

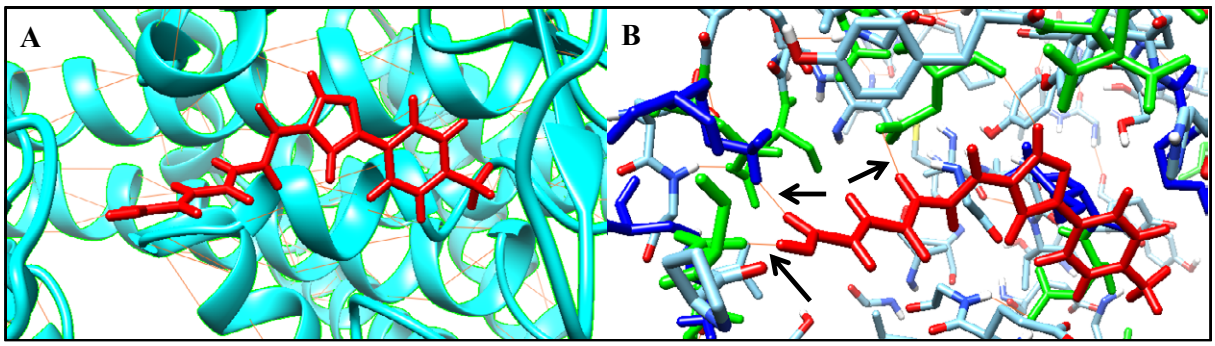

Figure 2 – Sight of CBD binding sites in CaV3.2. Being: CBD' (red) interactions (A); H-bond and ASP690, ASP421 (green), or LYS423 (blue) are presented orange (black arrow) (B).

GBP blocks neuronal Ca_V, and it is a recommended first-line agent for treating neuropathic pain; however it presents a low efficacy rate and a high risk of adverse effects.[29,30] On the other hand, the present study suggest that the CBD mechanism in CaV3.2 may be an analgesic alternative. The binding can block the calcium entry into the neuronal terminal, preventing neurotransmitter exocytosis and the conduction of the painful stimulus.

CONCLUSIONS

The CBD interacted with $Ca_V3.2$, blocking this channel, while GBP interacted with other residues. These findings highlight that the neuronal inhibition promoted by CBD may be an alternative drug to treat neuropathic pain. This result can be used as a reference for further research.

CONFLICT OF INTERESTS

Not applicable

AUTHOR CONTRIBUTIONS

GEJA, **GJSJ**, **NNM**, and **GNM**: scientific Initiation students who developed the article. **AEAC**: the collaborating professor who reviewed the article. **LCLF** and **JLVS**: advisors who designed and reviewed the article.

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Toxicological screening of *Lippia microphylla* extract on *Artemia salina*

Triagem toxicológica de extrato de *Lippia microphylla* frente à *Artemia salina*

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Abstract

Objective: to verify the acute toxicity of crude extracts from the leaves of *Lippia microphylla* on *Artemia salina*. **Methods:** The extracts of *L. microphylla* at 1, 10, 100, and 1,000 µg/mL were used in the acute toxicity tests in triplicates using the microcrustacean *A. salina* (n = 10), incubated for 24 h and 48 h. The number of dead nauplii larvae was quantified, and the mean lethal concentration (CL50) was calculated using nonlinear regression. **Results:** The extract of the *L. microphylla* during the 24-hour incubation produced toxicity ($p < 0.05$) only at the highest concentration of the extract (1,000 µg/mL). On the other hand, the median lethal concentration (LC50) was 246.7 ± 27.85 µg/mL after 48 h of exposure, indicating moderate toxicity. **Conclusion:** The leaves of *L. microphylla* have active ingredients that may not be fully metabolized by *A. salina* after 48 h, causing moderate toxicity on this microcrustacean.

Keywords: Medicinal plant; Plant extract; Toxicity.

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Resumo

Objetivo: Verificar a toxicidade aguda de extrato etanólico bruto das partes aéreas desta espécie vegetal frente a *Artemia salina*. **Métodos**: O extrato das partes aéreas da *Lippia microphylla*, nas concentrações de 1,0, 10,0, 100,0 e 1.000,0 µg/mL, foi utilizado nos ensaios de toxicidade aguda utilizando o microcrustáceo *Artemia salina* (n = 10), incubados por um período de 24 e 48 horas, realizados em triplicata. O número de náuplios mortos foram quantificados e a CL_{50} foram calculadas por regressão não-linear. **Resultados**: O extrato da *Lippia microphylla* durante incubação por 24h promoveu toxicidade ($p < 0,05$) apenas na maior concentração do extrato (1.000 µg/mL). Já na exposição por 48h, mostrou CL_{50} de 246,7 ± 27,85 µg/mL, apresentando toxicidade moderada. **Conclusão**: As folhas de *Lippia microphylla* possuem princípios ativos, os quais, provavelmente, não conseguem ser totalmente eliminados pelo metabolismo da *Artemia salina* durante 48h, causando-lhes toxicidade moderada.

Palavras-chave: Planta medicinal; Extrato vegetal;Toxicidade.

INTRODUCTION

Scientifically tested plants in pharmaceutical forms have been widely used for treating and preventing diseases.[1,2,3] Medicinal plants have several biological activities (e.g., antifungal, antimicrobial, anti-inflammatory, antiallergic, antitumor, analgesic, and antioxidant).[4] In addition, medicinal plants are a natural, low-cost resource that is usually cultivated by users of public health services, making them accessible and contributing to treatment adherence and the health-disease process.[5]

Lippia species are widely distributed in Brazil and present relevant medicinal importance due to therapeutic activities; many are used to treat respiratory and gastrointestinal disorders. In addition, several pharmacological activities have been reported in studies with these species, including anticancer, antiradical, spasmolytic, acetylcholinesterase inhibition, antibacterial, and pathogenic microorganism elimination. However, reports on their toxicity are scarce.[6,7,8] On the other hand, the extract of the leaves of *Lippia microphylla in vitro* presented relaxing activity on isolated aorta and trachea from rats.[9]

Studies related to the efficacy of plant extracts of the genus *Lippia* showed good results on the chemical constitution and antioxidant properties of *Lippia* essential oil. This benefit is related to the presence of thymol and carvacrol, isomers considered promising in the study of therapeutic alternatives for infections.[10]

Despite the various benefits, some plants can cause adverse reactions, affecting the cardiovascular, respiratory, gastrointestinal, neurological, skin, and mucous membranes, and in some cases, death. Patients with risk factors (e.g., heart problems) may present severe poisoning after using low-toxicity plants.[11,12] These adverse effects occur during inappropriate, single, or chronic use or are associated with conventional medications, other plants, or herbal medicines, highlighting the need for more toxicological studies.[13]

Artemia salina is a small halophilic crustacean from a family that plays an important role in saltwater and marine ecosystems. They are highly valued for detecting toxicity and used in ecology, physiology, ecotoxicology, aquaculture, and genetics In addition, the lethality test with *Artemia* is fast, convenient, and low-cost.[14,15]

The absence of studies testing or reporting the toxicity of *L. microphylla* motivated the verification and comparison of acute toxicity of the leaves of this plant species on *A. salina*.

METHODS

The leaves of the *L. microphylla* were macerated in ethanol (95%), and the crude extract was obtained after solvent elimination in a rotary evaporator. This extract was provided by the *Programa de Pós-Graduação em Produtos Naturais e Sintéticos Bioativos da Universidade Federal da Paraíba*, Brazil. The crude extract was obtained by solubilization with cremophor (0.1%) and was diluted in distilled water to obtain a stock concentration (10 mg/mL). At the time of the experiment, they were serially diluted to obtain adequate concentrations for the tests. The *A. salina* method was used to determine acute toxicity.[16]

Cysts of *A. salina* (0.3 g) were kept in synthetic marine water (neutral pH) and incubated for 24 and 48 hours under artificial lighting, a temperature of 22°C, and no feeding. After hatching, ten nauplii were collected for each group: four test tubes containing the extract solution (1, 10, 100, and 1,000 µg/mL) and control (saline solution). The preparations were made in triplicates. After 24 and 48 hours, survivors and deaths were counted. They were considered dead when no active movement was observed for about 20 seconds. The median lethal concentration (LC_{50}) of the extract was obtained by nonlinear regression of the number of viable nauplii for each concentration; the test was performed in triplicates for each concentration. All results were expressed as mean ± standard error of the mean and analyzed using the t-test; $p < 0.05$ was considered significant. Analyses were performed in the GraphPad Prism.

RESULTS

The toxicity of *L. microphylla* in different concentrations is presented in Figure 1 for 24 h (Figure 1A) and 48 h (Figure 1B). Only the highest concentration of the extract (1,000 µg/mL) significantly induced death ($p < 0.05$) after 24 h incubation compared with the control. Therefore, LC_{50} was not determined since it did not have a concentration-response ratio in at least two different concentrations (the higher the concentration, the higher the effect). At 48 h incubation (Figure 1B), 10 and 1,000 µg/mL concentrations were toxic to *A. Salina* compared with the control group. Thus, LC_{50} was calculated and presented a 246.7 ± 27.85 µg/mL value, representing moderate toxicity ($100 < LC_{50} \leq 500$ µg/mL).

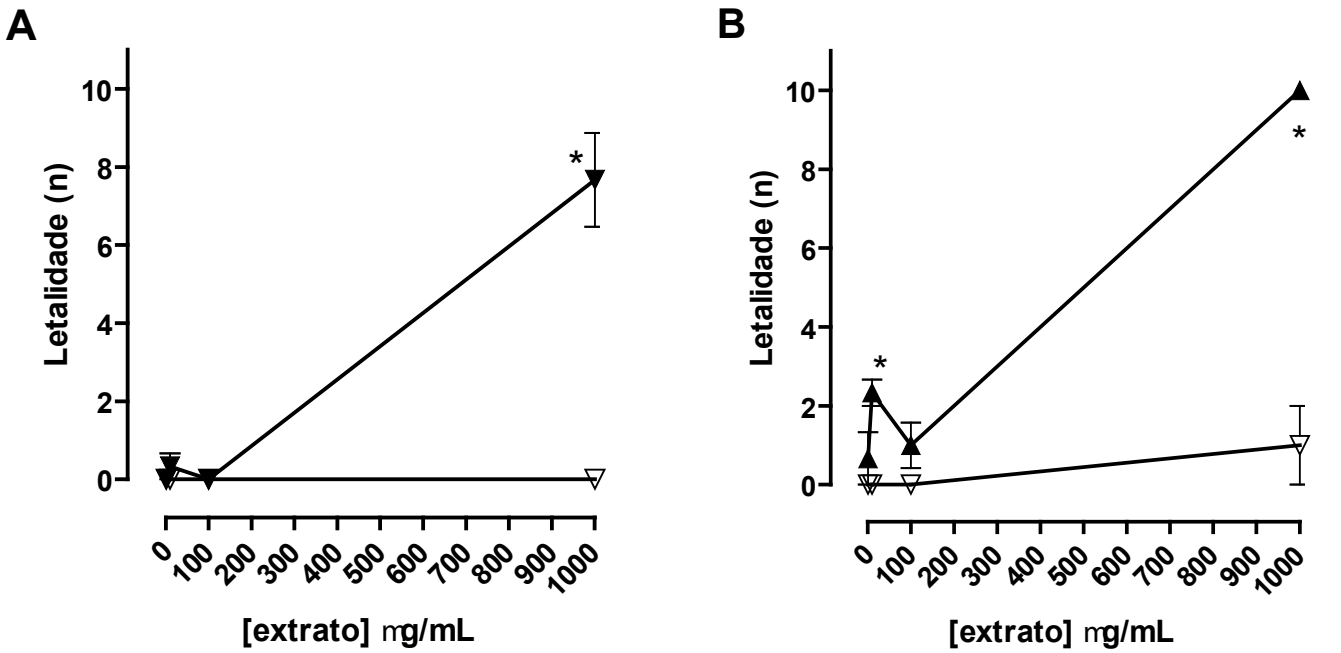

Figure 1 – Effect of the presence (q) and absence (s) of the crude extract of *Lippia microphylla* on *Artemia salina* after 24 h (A) and 48 h (B), n = 10. * The tracings correspond to the concentration-response curves, and the vertical bars represent the standard error of the mean. **p < 0.05; t-test (extract vs. control).

DISCUSSION

The scientific community uses this bioassay because it is quick, easy, and low-cost. Considering the dose per unit of body surface area, the toxic effects in humans are considerably within the same limits as those observed in laboratory animals, and possible human risks can be discovered.[17]

The species of *Lippia* present many bioactive substances with economic potential for local communities. Specifically, *L. microphylla* is an endemic species from the Brazilian vegetation that is little explored; however, the species has medicinal properties that are gaining attention from the scientific community. Despite the interest from scientists, few studies analyzed its toxicity. Natural products, especially medicinal plants, may be an important source of new agents against infectious diseases, cardiovascular diseases, cancer, and immunomodulation,[18] highlighting the importance of toxicological studies.

In the present study, the *Lippia* species presented moderate toxicity, revealing that the microcrustacean could not metabolize (i.e., detoxify) potentially toxic active ingredients in two concentrations after 48 h, and in 1,000 µg/mL in 24 h. The literature indicates several factors interfering with toxicity, including the concentration of the sample tested.[19] Similar results were obtained with the stem extract of *Pepper pseudocaryophyllus*, which showed toxicity on *A. salina*

after 48 h incubation.[18] However, an *in vivo* toxicity study with the same extract of *L. microphylla* did not show toxicity in mice.[20]

The same method was used in a toxicological study of the leaves of *Myosotis sylvatica*, extracts from leaves (Csf), and stem (Csc) of *Cinnamomum stenophyllum* on *A. salina*, which obtained LC_{50} = 38.1 µg/mL and Csf with indeterminate LC_{50}, and Csc with LC_{50} = 8.7 ± 0.7 µg/mL, respectively. As a result, *M. sylvatica* was classified as potentially toxic and Csc as highly toxic (CL < 100 µg/mL).[21-22]

The results obtained in this study also corroborate with a study conducted to evaluate the toxicity of *Lippia alba, Cymbopogon citratus,* and *Rosmarinus officinalis* on *A. salina* at different concentrations (100 ppm, 500 ppm, and 1,000 ppm). All three extracts showed biological activity, concluding that these plants were toxic if used in high concentrations.[23]

Similar results were also found in a study that evaluated the possible toxic, cytotoxic, genotoxic, and mutagenic effects of the leaves of the *Lippia sidoides* at different concentrations on the cell cycle of the *Allium cepa.*The cytotoxicity was verified by the decreased cell division using optical microscope analysis after tissue staining and fixation.[24]

A study evaluating the acute toxicity of essential oils on *A. salina* showed that all essential oils tested manifested high acute toxicity at low concentrations. Some of these oils that showed high lethality included species of *Lippia*, which were *C. citratus* (CL_{50} = 1,212 µg/ml) > *Lippia rotundifolia* (CL_{50} = 1,256 µg/ml) > *Lippia origanoides* (CL_{50} = 1,267 µg/ml) > *C. citratus* lemongrass (CL_{50} = 1,284 µg/ml).[25]

CONCLUSION

The leaves of *L. microphylla* have active ingredients that *A. salina* did not fully metabolize after 48 h and at the highest concentration (1,000 µg/ml) in 24 h, causing moderate toxicity.

Therefore, the toxicity observed for this plant extract should be considered a relevant use characteristic in cytotoxicity studies, providing more robust evidence of properties and effects.

Different environmental conditions can influence the effects of toxic agents on microcrustaceans. Therefore, these findings highlight the need for new tests for safety in the use of this species in developing new studies, and specialized clinical trials and consumption by the population.

CONFLICT OF INTERESTS

Nothing to declare.

AUTHOR CONTRIBUTIONS

GGA, **NSF,** and **AJSVS**: preparation and writing of the manuscript. **TKBO**: conception, elaboration, and writing of the article. **JLVS**: data analysis and final writing of the manuscript. All

authors proofread and approved the final version of the manuscript.

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afmo.emnuvens.com.br ISSN: 2674-8487 Case Report

Relationship between coronary artery disease and rheumatoid arthritis: case report

Relação entre doença arterial coronária e artrite reumatoide: relato de caso

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Abstract

Rheumatoid arthritis (RA) is an inflammatory disease that affects the joints, causing tissue destruction, pain, and deformities. Inflammation accelerates the process of atherosclerosis, progressing to coronary artery disease (CAD). We reported the case of a 64-year-old patient who presented RA for 25 years. The patient evolved with persistently active disease and inflammation markers above the normal value, and was diagnosed with a luminal reduction in the anterior descending artery. He underwent coronary angioplasty. The prevalence of CAD with the risk of premature death increases in these patients due to the chronic inflammatory process. Therefore, annual cardiovascular assessment is essential for patients with RA.

Keywords: Rheumatoid arthritis; Inflammation; Coronary atherosclerosis; Angioplasty.

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Resumo

Artrite Reumatoide (AR) é uma doença inflamatória que afeta as articulações, levando a destruição tecidual, dor e deformidades. A inflamação acelera o processo de aterosclerose ocasionando o desenvolvimento da doença arterial coronariana (DAC). Relatamos o caso de um paciente de 64 anos, portador de AR há 25 anos, que evoluiu com a doença persistentemente ativa e com marcadores de inflamação acima do valor de normalidade, sendo diagnosticado com redução luminal na artéria descendente anterior e submetido à angioplastia coronária. A prevalência de DAC com risco de morte prematura é aumentada nesses pacientes devido a cronificação do processo inflamatório. Logo, a avaliação cardiovascular anual é imprescindível nos portadores de AR.

Palavras-chaves: Artrite reumatoide; Inflamação; Aterosclerose coronária; Angioplastia.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects the synovial tissue of the joints, causing tissue destruction, pain, and deformities.[1] This disease is related to an increased risk of coronary artery disease (CAD) because the chronic inflammation accelerates the process of atherosclerosis. As a result, patients with RA have larger coronary plaque than those without RA.[2] Moreover, the clinical manifestations of CAD start earlier and silently in patients with RA, unlike the general population.[3]

The degree of inflammation and the risk of cardiovascular events are directly related.4 Pro-inflammatory cytokines (e.g., tumor necrosis factor and interleukin-6) impair endothelial function in patients with RA, accelerating atherosclerosis.[3] Other risk factors may be associated, such as age, sex, hypertension, diabetes mellitus, dyslipidemia, obesity, and smoking, influencing the early onset of atherosclerosis.[3]

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are inflammatory markers that may be associated with cardiovascular risk in RA when elevated.[5] Evidence demonstrates that higher CRP is associated with an increased risk of subclinical atherosclerosis and increased incidence of cardiovascular events.[5] Cardiovascular risk increases by 1% for each 20 mg/L increase of CRP.[5] Therefore, persistent inflammatory markers may identify individuals with RA at increased risk for early CAD.[6]

CASE REPORT

The patient (man, 64 years old) with RA for 25 years, presenting systemic arterial hypertension and dyslipidemia, evolved with persistently active RA, with inflammatory markers (CRP and ESR) four-fold above the upper limit of normal. He presented injuries in the wrist and knees and pain in the hip. He reported the use of non-hormonal anti-inflammatory drugs and glucocorticoids. Blood

pressure was controlled using an angiotensin II receptor blocker, and dyslipidemia was controlled with statin.

In 2013, he reported control of low-density lipoprotein and fasting glucose. The patient underwent myocardial perfusion scintigraphy (MPs) with pharmacological stress that did not reveal electrocardiographic, clinical, or perfusion abnormalities; the left ventricular ejection fraction was normal. On the same occasion, a coronary angiotomography (CT angiography) revealed that the coronary calcium score was zero, and coronary arteries were normal (i.e., no obstructive arterial disease).

After six years (November 2019), he reported atypical chest discomfort unrelated to exertion, attributing it to RA. Due to the persistent inflammatory activity, he underwent a new evaluation with CT angiography and calcium score (figure 1), resulting in a score = 98 (65 percentile) and a severe non-calcified lesion in the proximal third of the anterior descending artery (AD), with significant luminal reduction. A coronary angiography confirmed that the right coronary artery presented a severe lesion (80%) in the proximal third and moderate lesion in the middle third. He underwent coronary angioplasty with drug-eluting stent implantation in the proximal third of the AD.

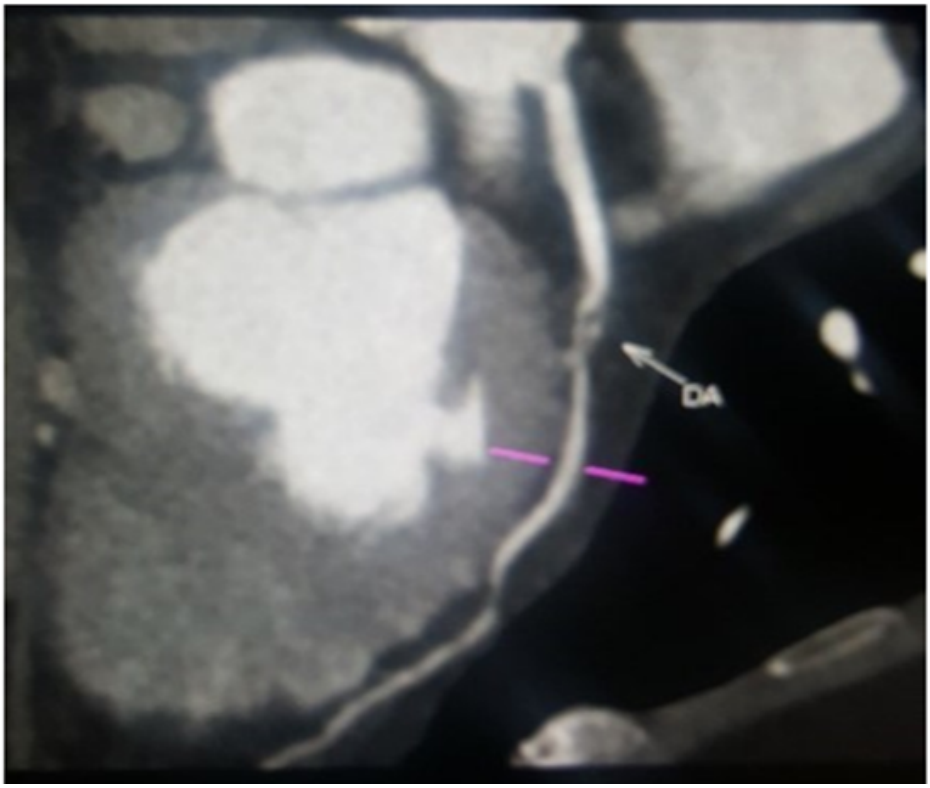

Figure 1 – Angiotomography performed in 2019; 2D reconstruction of the anterior descending coronary artery (AD). According to the white arrow, we note a severe mixed atherosclerotic plaque with severe luminal reduction, predominantly not calcified in the proximal third of the AD. Lilac stripes: a marker for axial cutting of the coronary artery. **Source:** Authors.

DISCUSSION

The prevalence of CAD with the risk of premature death increases in patients with chronic inflammatory diseases (e.g., RA).6 This risk is mainly due to cardiovascular disease, particularly CAD.[6]

The reported incidence and prevalence of CAD in patients with RA varies according to the specific manifestations of the disease, the population evaluated, and the screening and diagnostic methods.[7] A meta-analysis of 24 observational studies (n = 111,758 patients) concluded that the mortality risk from CAD was 59% higher in patients with RA than in the general population.[8] The risk may increase when symptoms develop and before patients meet the formal classification criteria for the RA diagnosis.[9]

A Swedish cohort study involved 1,135 patients with RA and acute coronary syndrome identified in a national database. They experienced more sudden cardiac death, acute myocardial infarction (AMI) with ST-segment elevation, higher troponin levels, and complications when hospitalized than the general population.[10]

It is unclear why patients with RA and CAD are less likely to report chest pain before or during a cardiovascular event.[11] Possible explanations include that patients with active arthritis or structural joint damage may be less physically active, less likely to increase heart demand enough to trigger angina, and more likely to attribute pain to RA. In addition, nonsteroidal anti-inflammatory drugs, glucocorticoids, or disease-modifying antirheumatic drugs may change the pain perception.[12]

Patients with and without RA share some underlying mechanisms of atherosclerosis pathogenesis.[2] Among the general population, inflammation plays a significant role in the development of CAD, and the innate and adaptive immune systems influence the onset and progression of atherosclerosis.[3]

Inflammation contributes to acute myocardial infarction in patients with RA.[2,6] Chronic inflammation may accelerate the progression of atherosclerosis through cytokines, abnormal functions of T lymphocytes, macrophages, and dendritic cells, immune complexes, coagulation abnormalities, oxidative stress, or a combination of these factors.[3]

The approach to diagnosing CAD is similar in patients with and without RA.[2] Given the higher incidence of CAD, it is suggested to perform an annual cardiovascular assessment focused on history, physical examination, and electrocardiogram in patients older than 50 years.[6] Also, because of the low threshold to proceed to exercise, pharmacologically stressed MPs in those with electrocardiographic symptoms or findings suggestive of CAD may be an option.[10] The evaluation of the coronary calcium score in patients with chronic inflammatory diseases is needed even if they are not in an intermediate risk range.[13] The reassessment of the coronary calcium score, if initially zero, should be shorter; however, previous studies did not indicate the ideal time.[13] A score

greater than 100 increases the probability of myocardial ischemia in the face of a CPM of stress and rest, where the prevalence of myocardial ischemia reaches 40%.[10]

In conclusion, chronic inflammatory diseases, including RA, have an intense and continuous inflammatory activity that accelerates the atherosclerotic process, requiring a systematic approach to detect CAD and myocardial ischemia.

CONFLICT OF INTEREST

No comment.

CONTRIBUTIONS OF THE AUTHORS

DBL principal investigator, research elaboration, schedule elaboration, literature survey, data collection and analysis, article writing, article writing correction, final version approval, article submission and procedures; **FAP** co-advisor, research elaboration, schedule elaboration, article writing, article writing correction, and final version approval; **MAF** collaborator investigator, article writing, article writing correction and final version approval; **ARSC** collaborator investigator, article writing, article writing correction and final version approval; **GSSM** collaborator investigator, article writing, article writing correction and final version approval; **LSS** collaborator investigator, article writing, article writing correction and final version approval; and **ELP** advisor, article writing correction and final version approval.

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Heyde syndrome: a diagnosis to consider

Síndrome de Heyde: um diagnóstico a se considerar

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Abstract

Aortic valve stenosis is a frequent clinical condition, especially in older people. Also, these patients often have anemia.This hematological change may be caused by the Heyde syndrome, which presents anemia, intestinal angiodysplasia, and loss of high-molecular-weight multimers of von Willebrand factor, treated by correcting the aortic valve stenosis. In this sense, the Heyde syndrome should be part of the differential diagnosis in patients with anemia and severe aortic valve stenosis.

Keywords: Aortic valve stenosis; Angiodysplasia; Transcatheter aortic valve replacement; Type-2 von Willebrand disease; von Willebrand factor.

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Resumo

A estenose aórtica valvar (EAo) calcificada é uma entidade clínica frequente, particularmente em idosos. Muitos desses pacientes apresentam quadro clínico associado de anemia. Entre as possibilidades para essa alteração hematológica encontra-se a Síndrome de Heyde, que é uma anemia associada a angiodisplasia intestinal e perda de multímeros de alto peso molecular (MAPM) do fator de *von Willebrand* (FvW). A resolução da síndrome ocorre com a correção da estenose aórtica. A Síndrome de Heyde deve fazer parte do diagnóstico diferencial entre pacientes com anemia e portadores de estenose valvar aórtica severa.

Palavras-chaves: Estenose da valva aórtica; Angiodisplasia; Substituição da valva aórtica transcateter; Doença de von Willebrand Tipo 2; Fator de von Willebrand.

INTRODUCTION

Acquired von Willebrand syndrome (AvWS) is a rare bleeding disorder caused by a change in the structure, function, or concentration of von Willebrand factor (vWF) and associated with an increased risk of bleeding[1].

The most common causes of AvWS are congenital and acquired cardiac disorders (e.g., severe aortic stenosis or other valve diseases and congenital heart disease or mechanical heart devices in adults)[1,2]. Other causes include solid tumors, autoimmune disorders, certain medications, lymphoproliferative disorders, myeloproliferative neoplasms, hypothyroidism, hemoglobinopathies, and diabetes[2-4].

Symptomatic AvWS usually presents unexplained mucocutaneous bleeding, and its prevalence in patients with active bleeding is about 2% to 3%. Heyde syndrome includes gastrointestinal bleeding due to angiodysplasia in patients with AvWS caused by aortic valve stenosis (AS)[5-6]. The cardiac causes of this syndrome can be treated by correcting heart defects, including removing the left ventricular assist device and replacing the stenosed aortic valve[4].

Laboratory evidence of AvWS has been found in some patients with AS. Also, the aortic valve may become susceptible to serum proteases due to shear stress from the blood and changes in vWF, resulting in loss of high-molecular-weight multimers (HMWM) and AvWS type-2A, which regresses when the aortic valve is replaced[7].

In this sense, the study aimed to report a case of Heyde syndrome corrected by percutaneous transcatheter aortic valve implantation (TAVI).

CASE REPORT

An 84-year-old female patient sought medical care due to non-radiating oppressive precordial pain, sweating, paleness, and dyspnea on daily activity. The patient had no syncope, fainting, or melena. She presented a history of systemic arterial hypertension and dyslipidemia. The

patient was eupneic on physical examination, with mild paleness and no edema or jugular stasis. Her heart rate and blood pressure were 58 bpm and 140/70 mmHg, respectively. Cardiovascular examination suggested regular heart rhythm and intense ejection systolic murmur in the aorta irradiating to the furcula. The resting electrocardiogram revealed sinus rhythm, normal cardiac axis, left ventricular overload, and secondary changes in ventricular repolarization. Hemoglobin (Hb) was 10 g/dL, hematocrit was 30%, and creatinine was 1.7 mg/dL. The patient underwent pharmacological stress myocardial perfusion imaging, revealing a mild inferobasal ischemia (< 5%). The transthoracic echocardiogram showed mild dilation of the left ventricle, left atrial enlargement, and AS with a mean left ventricle-aorta (LV-AO) systolic gradient of 60 mmHg. She was referred for coronary angiography, revealing a severe bifurcation lesion of the right posterior descending coronary artery. Thus, a percutaneous coronary intervention (PCI) was performed using a stent implant, and a manometer confirmed the mean LV-AO systolic gradient of 60 mmHg. Although angina was reduced months after PCI, dyspnea on daily activity persisted, and anemia progressed (reaching an Hb of 8.3 g/dL), leading to more than one transfusion. The symptoms persisted without clinical signs of gastrointestinal bleeding. Fecal occult blood test for anemia was positive, and immunoelectrophoresis revealed monoclonal peaks in kappa and lambda. The patient was referred to hematology, which identified a monoclonal gammopathy of undetermined significance with no parameters for treatment. The colonoscopy showed regular results. A clinically significant anemia was recurrent (Hb reaching 7-8 g/dL), with hypotension and no clinical evidence of melena or enterorrhagia. The fecal occult blood test remained positive. Considering the severity of symptomatic AS, we performed TAVI due to the high surgical risk. The diagnostic hypothesis of Heyde Syndrome was formulated considering the clinically relevant and recurrent anemia with evidence of microscopic gastrointestinal bleeding in a patient with severe calcified AS.

The patient underwent percutaneous aortic endoprosthesis implantation. Although the procedure had no intercurrence, a stent was implanted in the right iliac artery due to dissection caused by removing the sheaths at the end of the procedure, which was successfully performed. The hematological parameters were monitored during the immediate postoperative period and in the sixth month, with regular Hb (11.6 g/dL) and no signs of bleeding. She has no symptoms, angina, or dyspnea complaints. The transthoracic echocardiogram on the fifth postoperative month showed regular functioning of the prosthesis, with a mild periprosthetic leak without hemodynamic repercussions and a maximum transprosthetic gradient of 14 mmHg (mean of 7 mmHg).

DISCUSSION

In 1958, E. C. Heyde, a general practitioner from Washington (United States), sent a letter to the New England Journal of Medicine to report the possible association of calcified AS with gastrointestinal bleeding[8]:

> "(...) In the past ten years, I have seen at least 10 patients with calcific aortic stenosis who had massive gastrointestinal bleeding for which we could discover no cause. They were nearly all elderly people, ranging from sixty to eighty, and most of them had classic signs of calcified aortic stenosis, with harsh systolic murmurs transmitted widely into neck or back and palpable systolic thrills. I have not found any reference to this association in the literature, and thought that a letter to a prominent journal might elicit some response about the matter. I suppose these people bleed from sclerotic vessels, but I would certainly be interested in hearing from some of your readers concerning their observations. It seems to me that people with this disease have gastrointestinal hemorrhage considerably more often than comparable age groups without it. I would appreciate your printing this letter, and hope it may stimulate some replies or statistical studies."[8].

Many years later, submucosal angiodysplasia was identified as the source of gastrointestinal bleeding in these patients[9]. King et al.[10] conducted a critical study to clarify this association, demonstrating a cease of bleeding in 14 patients with AS after valve replacement. Also, other groups have reported the loss of HMWM of vWF in patients with AS[11]. Considering these factors, Warkentin et al.[12] hypothesized that the syndrome described by Heyde was a type-2A von Willebrand syndrome with an acquired HMWM deficiency. These HMWM are essential to maintain platelet-mediated hemostasis and suffer proteolysis under high shear stress when passing through the stenotic valve. Recent studies have shown that patients with severe AS had decreased HMWM, which was normalized in all patients after valve replacement on the first postoperative day[13].

Regarding the prevalence of angiodysplasia in these patients, severe AS may be associated with decreased gastrointestinal perfusion, resulting in hypoxia-induced fixed vasodilation and angiodysplasia[14]. vWF disease is rare and has been described in patients with multiple myeloma or monoclonal gammopathy of undetermined significance, which has been associated with gastrointestinal angiodysplasia and bleeding. Also, lambda light chain-induced monoclonal gammopathy with deficiency of HMWM of vWF has been reported[15].

In this clinical case, although angiodysplasia was not observed using colonoscopy, fecal occult blood test was positive and persistent, and recurrent anemia was reported. The patient had monoclonal gammopathy and severe calcified AS with a systolic gradient of 60 mmHg. More than 60 years have passed since the original letter of Heyde to the editor appeared in the New England Journal of Medicine. His direct clinical report of an association between AS and gastrointestinal bleeding helped us understand a fundamental biological mechanism underlying a complex aspect of hemostasis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

DBL (main investigator): research and schedule elaboration, literature review, data col-

lection and analysis, manuscript writing, review, and final approval, and submission procedures. **FAP** (co-supervisor): research and schedule elaboration, manuscript writing, review, and final approval. **MLCP** (collaborating researcher): manuscript writing, review, and final approval. **FRON** (collaborating researcher): manuscript writing, review, and final approval. **MCC** (collaborating researcher): manuscript writing, review, and final approval. **MAF** (collaborating researcher): manuscript writing, review, and final approval. **ELP** (supervisor): manuscript review and final approval.

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Common genetic aspects between Autism Spectrum Disorder and Attention Deficit Hyperactivity Disorder: integrative review

Aspectos genéticos comuns entre o Transtorno do Espectro Autista e Transtorno do Déficit de Atenção e Hiperatividade: revisão integrativa da literatura

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Abstract

Objective: The selected studies were analyzed descriptively regarding the common genetic etiology of autism spectrum disorder and attention deficit hyperactivity disorder, allowing for observing, describing, and classifying the data. **Methods:** We performed a review of the literature on Pubmed and Virtual Health Library (VHL) databases. The search descriptors (Autistic Disorder) OR (Autism Spectrum Disorder) AND (Deficit Disorder) of Attention with Hyperactivity) AND (Genetic Association Studies) OR (Genetics) OR (Heredity) were used in VHL; and ((“Autism Spectrum Disorder” AND “Attention Deficit Disorder with Hyperactivity”) AND (“Genetic Association Studies” OR “Genetics OR Heredity”)) were used in PubMed. **Results:** A total of 75 studies were identified, 54 in the VHL and 21 in the PubMed. Of these, 18 remained after screening for title and abstract. After full text reading, nine studies were included in this review. **Discussion**: De novo genic mutations contribute to autism spectrum disorder, and some studies support they might also be determinant for attention deficit hyperactivity disorder. The RFX3, RFX4, and RFX7 genes found in cells of the cerebral cortex of fetuses and adults contribute to linking important regions related to cognition and social behavior. **Conclusion:** The included studies indicate a correlation between genetic etiologies of autism spectrum disorder and attention deficit hyperactivity disorder.

Keywords: Autism Spectrum Disorder; Attention Deficit Hyperactivity Disorder; Mutations; Genes.

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Resumo

Objetivo: Os estudos selecionados foram analisados descritivamente quanto à etiologia genética comum do transtorno do espectro autista e do transtorno de déficit de atenção e hiperatividade, permitindo observar, descrever e classificar os dados. **Métodos:** Foi realizada revisão da literatura nas bases de dados Pubmed e Biblioteca Virtual em Saúde (BVS). Os descritores de busca (Autistic Disorder) OR (Autism Spectrum Disorder) AND (Deficit Disorder) of Attention with Hyperactivity) AND (Genetic Association Studies) OR (Genetics) OR (Heredity) foram utilizados na BVS; e ((“Autism Spectrum Disorder” AND “Attention Deficit Disorder with Hyperactivity”) AND (“Genetic Association Studies” OR “Genetics OR Heredity”)) foram usados no PubMed. **Resultados:** Foram identificados um total de 75 estudos, 54 no BVS e 21 no PubMed. Destes, 18 permaneceram após a triagem para título e resumo. Após a leitura do texto completo, nove estudos foram incluídos nesta revisão. **Discussão:** Mutações gênicas de novo contribuem para o transtorno do espectro do autismo, e alguns estudos apoiam que elas podem também ser determinante para o transtorno de déficit de atenção e hiperatividade. Os genes RFX3, RFX4 e RFX7 encontrados em células do córtex cerebral de fetos e adultos contribuem para ligar regiões importantes relacionadas à cognição e ao comportamento social. **Conclusão:** Os estudos incluídos indicam uma correlação entre fatores genéticos

Palavras-chave: Transtorno do Espectro Autista; Transtorno de Déficit de Atenção e Hiperatividade; Mutações; Genes.

INTRODUCTION

Neurodevelopment disorders encompass multiple conditions affecting cognitive development. Two of the most common neurodevelopmental disorders are autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD)[1]. The ASD leads to deficits in social interaction and communication and is associated to repetitive behaviors and restricted interest to specific topics[2]. In turn, ADHD is characterized by hyperactivity, lack of attention, and impulsivity 3 . In some situations, the two disorders present clinical and genetic overlap, including attention deficit, impulsiveness, delay in language development, communication problems, and difficulties in understanding the thoughts and feelings of other people, accomplishing tasks every day, coping with emotional aspects, and adapting to environments like schools[4].

The ADHD prevalence in children at age school is about 5%, whereas the ASD prevalence varies from 1% to 2%[5]. Both disorders are hereditary, more frequent in males, and associated with lower quality of life[2]. ADHD might occur simultaneously with ASD in 22% to 83% of cases, while ASD might occur simultaneously with ADHD in 30% to 65% of cases. Approximately 20% of ASD diagnoses happen after three years of ADHD diagnosis[4].

Although ASD and ADHD are genetically heterogeneous disorders, a person with both disorders may show alterations in independent genes or common genetic mutations[6]. Common genetic mutations usually present allelic forms of risk shared in non-coding areas of the genome, affecting gene expression regulation[4]. However, de novo genetic variants (i.e., new genes not inhe-

rited from the parents due to various etiologies) culminating in haploinsufficiency are reported as contributors to this comorbidity[2]. An example includes the deleterious variants in the RFX genes, specifically RFX3, RFX4, and RFX7, involved in central nervous system development and ciliogenesis[7]. Another possible etiology for this comorbidity encompasses changes in the SLC9A9 gene, a gene involved in many cellular functions and associated with several human diseases. The main role of the SLC9A9 gene is to maintain the late endosomes recycling, sustaining the surface and the pool of signaling receivers. This gene is also important for cellular survival and neurological development[6].

This review investigated common genetic etiology between ASD and ADHD. The included studies were analyzed descriptively, allowing for observing, describing, and classifying the extracted data.

METHODS

A literature review was conducted in Virtual Health Library (VHL) and PubMed databases. The descriptors and booleans operators (Disorder Autistic) OR (Disorder of Spectrum Autistic) AND (Disorder of Deficit in Attention with Hyperactivity) AND (Studies in Association genetics) OR (Genetics) OR (Heredity) were used to search in the VHL database. The inclusion criteria were: main subject ASD or ADHD, and studies about disorder etiology, published in the last five years in English, Spanish, or Portuguese.

For PubMed database, the following descriptors and boolean operators were searched: ((“Autism Spectrum Disorder” AND “Attention Deficit Disorder with Hyperactivity”) AND (“Genetics Association Studies” OR “Genetics” OR “Heredity”)). The inclusion criteria were MEDLINE database, human species, classic articles, systematic review, and study with twins, published in the last five years in English, Spanish, or Portuguese. The exclusion criteria in both databases encompassed studies not addressing genetic aspects.

RESULTADOS

Initially, 75 studies were identified, 54 from the VHL and 21 from PubMed. Of these, 57 were excluded after screening for title and abstract. From the remaining 18 studies, nine were selected after full text reading to be included in this review, as described in Figure 1.

Relevant findings were rigorously interpreted, and the main themes were selected and 38 transformed into a table with the summary of the analyzed criteria (Table 1).

Figure 1. Flow diagram for this integrative review.

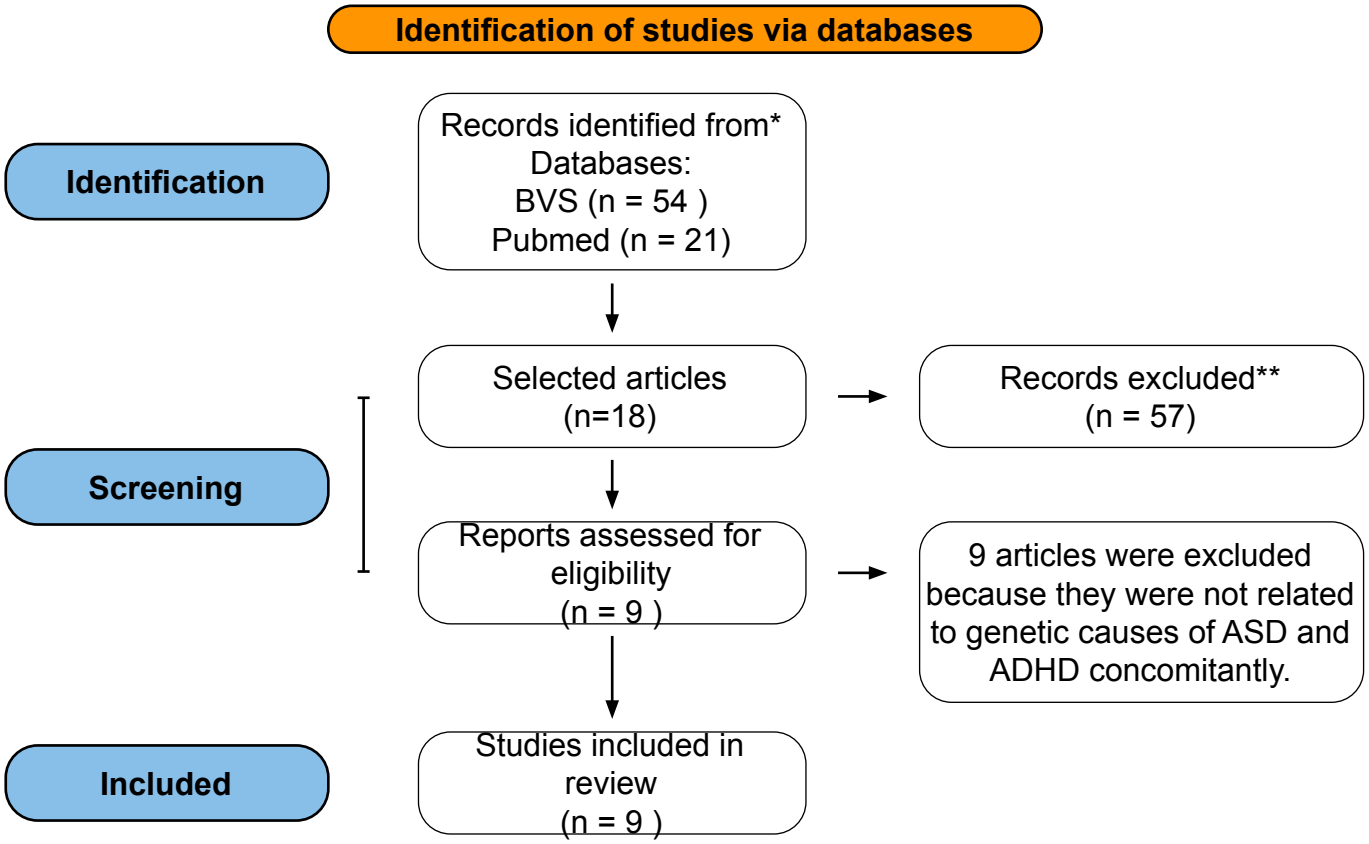

Table 1. Summary of the main findings from the included studies

Title	Author/ Year	Objective	Results	Conclusion
Early environmental risk factors for neurodevelopmental disorders - a systematic review of twin and sibling studies.	Carlsson T. et al., 2021.	To summarize the evidence from studies with twins and family members about the role of environmental risk factors for developmental disorders, defined both dimensionally and categorically, controlling for familial confusion to inform research and funding agencies in preclinical and applied areas of developmental disorders, and guide clinical management.	A total of 140 studies were identified for inclusion. The search resulted in 7,315 unique citations. Two additional studies were identified from reference lists of published articles. After screening the abstracts, 7,061 citations were excluded.	Beyond familial confusion, advanced paternal age, low birth weight, complications at birth, perinatal hypoxia, and respiratory stress are consistently associated with the diagnosis of ASD; low birth weight, gestational age, and low family income or transient decline in income during childhood are associated with ADHD, both categorically and dimensionally.

Disruption of *RFX* family transcription factors causes autism, attention-deficit/hyperactivity disorder, intellectual disability, and dysregulated behavior.	Harris HK., et al. 2021	To describe a new neurobehavioral phenotype in ASD, deficiency intellectual, or ADHD associated with deleterious de novo variants or inherited in genes RFX family members	These individuals share neurobehavioral characteristics, including ASD, intellectual disability, or ADHD. Other common features include hypersensitivity to sensory stimuli and sleep problems. RFX3, RFX4, and RFX7 are strongly expressed in the developing and adult human brain, and X-box binding motifs are enriched in the cis-regulatory regions of known risk genes for ASD, similar to RFX ChIP-seq peaks.	The results establish a role of deleterious variation in RFX3, RFX4, and RFX7 in deficiency intellectual monogenic, ADHD, and ASD. These genes can act as critical transcriptional regulators in neurobiological pathways associated with the pathogenesis of neurodevelopmental disease
Attention Deficit/ Hyperactivity Disorder and risk for non-affective psychotic disorder: The role of ADHD medication and comorbidity, and sibling comparison.	Björkenstam. et al, 2020.	To include a paired cohort composed of all people born in Sweden between 1987 and 1991.	The paired cohort included 18,139 individuals with ADHD and 72,437 without exposure. Parents of individuals with ADHD had more history of psychiatric disorders and less favorable socioeconomic characteristics than control parents. A total of 26% of individuals with ADHD had comorbid substance abuse (but only 5% in controls), of which the most common was alcohol-related disorders (11.9% of individuals with ADHD versus 3.3% in control).	Individuals with ADHD have a markedly increased risk for non-affective psychotic disorder, and the risk is partially explained by comorbid ASD and or both substance abuse. Among individuals with ADHD, using stimulant or non-stimulant medications is associated with an increased risk of NASD, indicating that the clinical symptoms that lead to medication treatment in ADHD may also increase the risk of NAPD.
Examining the autistic traits in children and adolescents diagnosed with attention-deficit.	Okyar E., Görker I., 2020.	To examine the symptoms of ASD in children diagnosed with ADHD and their parents. Also, to investigate the parental risk factors that increase ASD characteristics in children. Lastly, the risk factors related to pregnancy, birth, and development history were examined.	More symptoms of autism were found in children diagnosed with ADHD than in the control group. More autistic symptoms were perceived in males, and the presence of oppositional defiant disorder (ODD). Although more ADHD symptoms were observed in parents of children diagnosed with ADHD, it did not differ from parents in the control group.	ASD and ADHD have high levels of comorbidity. The etiology remains uncertain. Both ADHD and ASD show strong hereditary transitions. Maternal and paternal ADHD symptoms predicted autism in children with ADHD. However, more studies are needed to reveal the etiology.

Early-life antibiotic use and risk of attention-deficit hyperactivity disorder and autism spectrum disorder: results of a discordant twin study.	Slob Em., et al. 2021.	To evaluate the association between the use of antibiotics at the beginning of life and the risk of developing ADHD or ASD, controlling genetic and environmental factors shared in a project of discordant twins.	The use of antibiotics at the beginning of life was associated with an increased risk of developing ADHD [OR = 1.10, 95%CI:1.02-1.17] and ASD (OR = 1.15, IC 95%:1.06 - 1.25) in a project case-control.	The findings suggest that the association between early-life antibiotic use and the risk of ADHD and ASD may be confounded by shared family environment and genetics.
Sodium hydrogen exchanger 9 NHE9 (*SLC9A9*) and its emerging roles in neuropsychiatric comorbidity.	Patak J., Faraone Sv., Zhang-James Y., Et Al. 2020	To summarize the current literature regarding the structure, function, and disease associations of SLC9A9, and provide a comprehensive analysis of the role of SLC9A9 in human pathology.	We examined the structure of the SLC9A9 protein by homology-based comparison and summarized the biochemical mechanism that drives Na+/H+ exchange in homologs with the most conserved sequences.	The SLC9A9 is a multifunctional protein that, by its regulatory function of endosomes and its protein-protein interaction network, may modulate signaling axes, such as the PI3K pathway.
Cis-effects on gene expression in the human prenatal brain associated with genetic risk for neuropsychiatric disorders.	Hall Ls., Et Al. 2021	To define the genetic predictors of gene expression in the fetal human brain in studies analyzing wide association of ADHD, ASD, bipolar disorder, depression disorder, and schizophrenia Transcriptome.	Identify the effects of prenatal cis-regulatory in 63 genes and 166 individual transcribed associated with the genetic risk for these conditions.	The findings support that altered gene regulation in the prenatal brain increases the susceptibility to several neuropsychiatric disorders and prioritizes potential risk genes for further neurobiological investigation.

Mutations associated with neuropsychiatric conditions delineate functional brain connectivity dimensions contributing to autism and schizophrenia.	Moreau Ca., et al. 2020	To characterize the functional connectivity (FC) signatures of four high-risk neurodevelopmental copy number variants (CNV), explore whether the FC signatures of CNV represent dimensions observed in idiopathic ASD, schizophrenia, or ADHD, and investigate the relationship between gene expression level deletions and FC.	The 16p11.2 deletion showed an overall increase in FC compared to controls with a mean deviation = 0.29 z-scores ($p = 0.048$). 88 significantly altered connections (FDR, $q < 0.05$), and all but one were hyperconnected with beta values ranging from 0.76 to 1.34 z- scores. Hyperconnectivity involves the frontal, somatomotor, ventral attention, and basal ganglia networks AD neuropathology and an increased prevalence of amyloid angiopathy brain (AAC). The phenotypic features of DS do not appear to occur in individuals with dup-APP. Although almost all individuals with DS have AD neuropathology, the variability in the prevalence of dementia is more pronounced in DS than in dup-APP, while AAC is less prevalent in DS than in dup-APP. These differences between DS and dup-APP phenotypes provide a better understanding of the roles genes on chromosome 21, other than APP, may have in the pathogenesis of AD.	Individuals with greater similarity to functional connectivity deletion signatures exhibit worse cognitive and behavioral symptoms. Exclusion similarities identified at the connectivity level may be related to the redundant associations observed across the genome between spatial patterns of gene expression and signatures of functional connectivity. The results may explain why many CNV affect a similar range of symptoms in neuropsychiatrics.
Polygenic risk scores for major psychiatric and neurodevelopmental disorders contribute to sleep disturbance in childhood: Adolescent Brain Cognitive Development (ABCD) Study.	Ohi K., et al. 2021.	Investigated whether polygenic characteristics of psychiatric and neurodevelopmental disorders are associated with sleep disorders during childhood.	ADHD symptoms were weakly to modestly correlated with sleep disturbance scales ($p < 0.001$), particularly sleep initiation and maintenance disorders and excessive sleepiness disorders. Preliminarily performed genome-wide association studies using sleep disturbance scale total scores in children of European ancestry and children of trans ancestry.	The findings further confirmed that genetic vulnerabilities to ADHD, major depressive disorder, and anxiety disorders positively correlate with sleep disorders in childhood.

Legend: OD, odds ratio; ASD, autism spectrum disorder; ADHD, attention deficit hyperactivity disorder; NAPD, non-affective psychotic disorder; ODD, oppositional defiant disorder; DD, developmental disorders; AAC, amyloid angiopathy brain; CNV, Copy Number Variants; FC, functional connectivity; CI, confidence interval; GWAS, genome-wide association studies; FDR, False Discovery Rate; p, p-value; APP, amyloid precursor protein; DS, Down syndrome; MDD, major depressive disorder.

DISCUSSION

Autism spectrum disorder and attention deficit hyperactivity disorder are neurodevelopmental disorders that may coincide clinically and genetically. Both disorders may originate from independent genes or the same genetic mutation[1,4].

De novo genic mutations contribute to ASD, and some evidence demonstrates its contribution to ADHD[2]. The RFX transcription factors demonstrated regulatory function in genes involved with several cellular processes related to human development, e.g., cellular cycle, DNA repair,and cellular differentiation[7]. The RFX3, RFX4, and RFX7 genes are found in the cerebral cortex cells of fetuses and adults and contribute to communicating important regions for cognition and social behavior. In adults, the RFX3 and the RFX7 are expressed in neurons from the layer glutamatergic 2/3 and in inhibitory and excitatory neurons, respectively, whereas the RFX4 was mostly described in astrocytes[2]. In contrast with the RFX genes, the SLC9A9 gene is a member of the genetic family expressing proteins that are Na+/H+ exchangers. This gene has 16 exons in the long arm of chromosome 3 (AUTS16 locus), and its dysfunction leads to diseases including cancer and neuropsychiatric disorders, such as ASD and ADHD. Due to its role in regulating the pHj of the endosomal system and assisting with the transport of iron, proteins, and synaptic regulation, a dysfunction impacts several cellular functions[6].

One study published in 2021 and conducted with 38 individuals diagnosed with intellectual disability (ID; ASD and or both ADHD) from 33 families revealed the presence of different deleterious de novo mutations among participants, except for one parent. This parent transmitted the de novo mutation RFX3 to his three children and three other homozygous brothers who shared the same gene for one missense variation of RFX4. Of the 18 individuals carrying RFX3 variants, 72% had ASD, and 56% had ADHD. Fourteen individuals carrying variants RFX7 also presented ASD (36%) and or both ADHD (29%). The conclusion was that the neurobehavioral phenotypes of all individuals were very similar, reinforcing the previous evidence that RFX3 is a risk gene for ASD. Furthermore, this conclusion was extended to other genetic families, such as RFX7. This genetic family was not previously associated with human diseases and can possibly contribute to ADHD[2].

The SLC9A9 is likely related to autistic phenotypes due to the strong correlation to changes in synapses genetic expression. An analysis performed in rats showed that mutations in this

gene increased the interaction of the SLC9A9 protein with the macromolecule calcerin homolog, revealing a potential involvement in the production of inattentive phenotypes similar to those in rats with ADHD. In another study with rats, using C57/BI6 genetic models inducted to delete the exon 2 of the reported gene, results indicate the interruption of translation protein. As a result, similar traits to ASD were observed, such as reduced preference for social novelties, reduced vocalization ultrasonic, and increased time in self-cleaning. The centric inversion of chromosome 3 (p14:q21) could also terminate the expression of DOCK3 and SLC9A9 genes, responsible for phenotypes such as ID, inattention, and low intelligence coefficient. Therefore, the loss of the SLC9A9 function occurs frequently in ASD and ADHD[6].

One study analyzed the copy number variation (CNV), i.e., deletions or duplications of DNA segments representing an important basis for genetic heterogeneity, of 16p11.2 and 22q11.2. The authors found that CNV confers high risk for ASD, schizophrenia, and ADHD, as they affect functional connectivity, with twelve CNV individually associated with ASD and eight with ADHD. Although CNV has major impacts on neurodevelopment, their effect does not lead to a diagnosis. In this sense, the CNV knowledge may facilitate the identification of the main dimensions contributing to idiopathic conditions[8].

The SLC9A9 dysfunction in individuals diagnosed with ASD causes a pH reduction of astrocytic endosomes, physiologically changing the pan- receptor recycling and increasing the glutamate in the synapse. At the same time, a decrease in the uptake action of the GLAST transporter damages the excitatory and inhibitory system, predisposing to seizures and epilepsy, which are common in ASD[6]. Patterns of generalized subconnectivity were frequently demonstrated, except for the superconnectivity in cortico-subcortical connections, particularly involving the thalamus. This shared characteristic between ASD and ADHD appears to encompass several continuous dimensions related to the genetic commonalities between diagnoses, documented for common and rare variants, including the CNV of 16p11.2 and 22q11.2[8].

Genome-wide association studies with human fetuses of second quarter gestation demonstrated the main genes and transcripts with effects cis- regulatory (perform regulatory functions in genic expression at the same chromosome in determined sequence) of the most common neuropsychiatric illnesses. These studies highlight 63 genes and 166 individual transcripts for these conditions. For ADHD, expression predictors are associated with the expression of three genes and four individual transcripts in the fetal brain, whereas for ASD, 17 genes and 29 individual transcripts[9].

The literature shows that ASD is a clear risk factor for non-affective psychotic disorder, including schizophrenia. Differently is observed in the few studies relating ADHD to risk factors. A study of a paired cohort associated comorbid ADHD with ASD and explained the risk for non-affective psychotic disorder in individuals with ADHD. The study concluded that individuals with

ADHD had a higher risk of presenting non-affective psychotic disorder than controls. However, when individuals with ADHD were compared to those with ASD and ADHD comorbidity, the risk of developing non-affective psychotic disorder was smaller in individuals with comorbidity, although the result was quite significant[3].

CONCLUSION

According to the included studies, there is a genetic etiological relationship between ASD and ADHD. The dysfunction of the RFX and SLC9A9 genes was responsible for the association between ASD and ADHD. In contrast, the CNV in 16p11.2 and 22q11.2, in addition to other genes and their transcripts with cis-regulatory effects, appear to contribute individually to these disorders. This review findings contribute to understanding the genetic aspects impacting the pathophysiology of ASD and ADHD. However, additional studies are needed to allow advances in diagnosis and treatments.

CONFLICT IN INTERESTS

None.

CONTRIBUTIONS OF THE AUTHORS

MMLM: main author; **JSM** and **JMSD**: co-authors; **HEEV** and **AESM**: Advisors.

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Anatomical variations of the transverse sinus and clinical-surgical repercussions: an integrative literature review

Variações anatômicas do seio transverso e suas repercussões clínico-cirúrgicas: uma revisão integrativa da literatura

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Abstract

Introduction: The dural venous sinuses drain the blood and cerebrospinal fluid circulating through the brain toward the internal jugular veins. The transverse sinuses are bilateral structures in the posterior portion of the skull that originate at the confluence of sinuses. Such cerebral venous structures have a complex anatomy and are marked by variations. Thus, a complete understanding of the morphology and variations of these anatomical structures is essential for clinical and surgical practice. This study summarized the literature on the anatomical organization of the transverse sinuses, variations, and potential clinical-surgical repercussions. **Objective:** To review the anatomy, variations, and possible clinical-surgical implications of the transverse sinuses. **Methods:** This integrative literature review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis. Studies published in English in the last 15 years were retrieved from PubMed, Virtual Health Library, and MEDLINE databases, based on the following descriptors: transverse sinuses, anatomy, and anatomic variation. **Results:** Of the 48 studies identified after duplicate removal, 10 met the eligibility criteria and were included in the synthesis. Conclusion: Hypoplasia of the left transverse sinus is the most common anatomical variation and is more frequent in adult men over 60 years old.

Key words: Transverse sinus; Anatomy; Literature; Review.

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Resumo

Introdução: Os seios venosos da dura-máter são canais venosos que drenam o sangue e o líquido cefalorraquidiano que circulam pelo cérebro em direção às veias jugulares internas. Os seios transversos, os quais iniciam-se na confluência dos seios estão presentes na porção posterior do crânio, sendo estruturas bilaterais. As estruturas venosas cerebrais, como o seio transverso, possuem uma complexa anatomia e são marcadas por variações. O entendimento completo acerca da morfologia e variações dessas estruturas anatômicas é essencial na prática clínica e cirúrgica. O presente estudo visa sumarizar as informações contidas na literatura sobre a organização anatômica dos seios transversos, suas variações e possíveis repercussões clínico-cirúrgicas. **Objetivo:** Revisar a anatomia, variações e possíveis repercussões clínico-cirúrgicas do seio transverso. **Métodos**: Trata-se de uma revisão integrativa da literatura redigida baseada nas recomendações do PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-Analyse*), a qual analisou estudos publicados na língua inglesa publicados nos últimos 15 anos tendo como referência as bases de dados PubMed (Public Medline or Publisher Medline), BVS (Biblioteca Virtual em Saúde) e MEDLINE empregando os seguintes descritores padronizados: Transverse Sinuses, Anatomy, Anatomic Variation. **Resultados**: Dos 48 estudos identificados após a remoção de duplicatas, 10 atingiram os critérios de elegibilidade e foram incluídos na síntese. **Conclusões:** Hipoplasia do seio transverso esquerdo é a variação anatômica mais comum dessa estrutura anatômica, geralmente mais frequente em homens e na faixa etária acima dos 60 anos.

Palavras chaves: Seios transversos; Anatomia; Literatura; Revisão.

INTRODUCTION

The dural venous sinuses are channels without muscle tissue that drain the blood and cerebrospinal fluid in the brain toward the internal jugular veins. The main venous sinuses include the superior and inferior sagittal, straight, occipital, sigmoid, and transverse[1,2].

The transverse sinuses are mostly bilateral and originate at the confluence of sinuses, which comprise the superior sagittal, straight, and occipital sinuses. These structures are present in the posterior portion of the skull adjacent to the margins of the tentorium cerebelli. The transverse sinuses receive blood from the temporal-lateral surfaces, the basal surface, and temporal and occipital lobes that reach the petrous portion of the temporal bone and flow into the sigmoid sinus. Each transverse sinus receives tributaries from the cerebral and cerebellar hemispheres[1-3].

Cerebral venous structures have complex anatomy and are marked by variations; thus, a complete understanding of the morphology and variations of these structures is essential in clinical and surgical practice (e.g., diagnosing and treating dural venous sinus diseases and neurovascular surgical interventions)[4]. Therefore, this study aims to summarize the literature on the anatomical organization of the transverse sinuses, variations, and possible clinical and surgical repercussions.

METHODS

This integrative literature review combined studies with different methodologies that critically analyzed the morphological aspects, anatomical variations, and clinical-surgical repercussions of the transverse sinuses. The guiding question of this research was, “What are the anatomical variations of the transverse sinuses and their possible clinical-surgical repercussions?”.

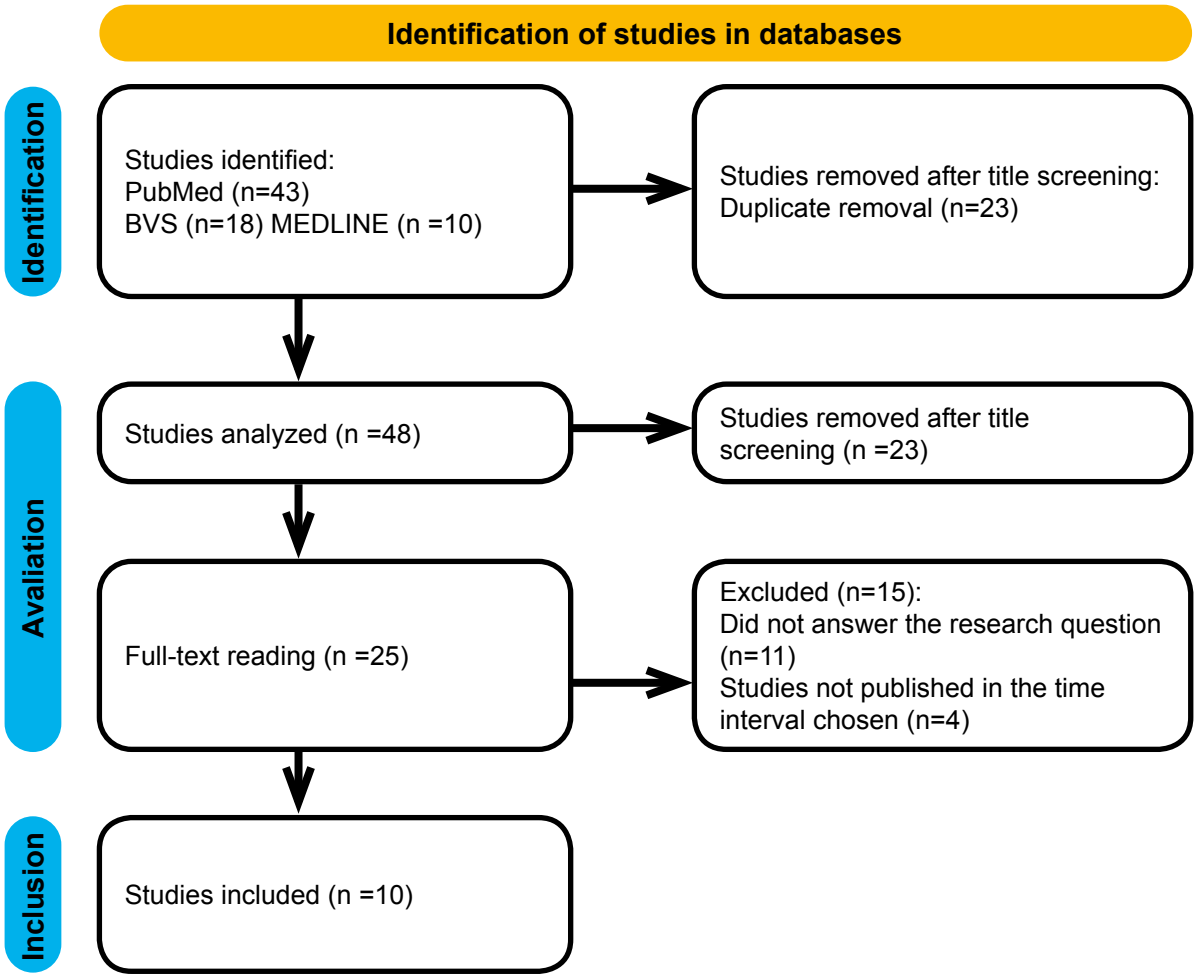
The integrative method was chosen to (1) broaden the possibilities for analyzing the literature without losing the methodological rigor of systematic reviews and (2) combine information from the theoretical literature to define concepts, identify gaps, review theories, and methodologically analyze studies. This method also allows combining and synthesizing studies into a single article, improving the accessibility of results.

This review was developed and written based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes5. Two independent and blinded researchers conducted the search from June 1, 2022 to September 4, 2022 in PubMed, BVS, and MEDLINE databases. The following MeSH terms were combined using the Boolean operator “AND”: transverse sinuses, anatomy, and anatomic variation.

First, titles and abstracts were screened. Studies not meeting the topics regarding anatomy, anatomical variations, and clinical-surgical repercussions of transverse sinuses in humans were not included. Second, two independent reviewers conducted a preliminary full-text reading to select articles for qualitative synthesis according to the eligibility criteria. Last, articles were explored, the relevant content was coded, and results were presented based on categories identified in the material.

Inclusion criteria were original studies using different designs; studies on anatomical aspects, variations of the transverse sinuses, and clinical-surgical repercussions of this venous sinus; studies available in English; and studies published in the last 15 years. Studies not addressing the research question, duplicates, letters to the editor, editorial or opinion articles, preprints, incomplete articles, and those unavailable for access were excluded. Figure 1 shows the flowchart of study selection.

Figure 1. Flowchart of study selection



Source: Authors

RESULTS

After duplicate removal, 43 studies were identified in PubMed. Of these, 23 were removed after title and abstract screening, 20 were analyzed in full, and 8 met the eligibility criteria. Of the 18 studies identified in the BVS, 14 duplicates were removed, none were removed after title and abstract screening, 4 were analyzed in full, and 1 met the eligibility criteria. Regarding MEDLINE, 10 studies were identified: 9 were duplicates and 1 met the eligibility criteria.

Many studies highlighted the clinical and surgical importance of understanding the anatomy and anatomical variations of the dural venous sinuses. The studies shown in Table 1 provided various perspectives for discussing the anatomical aspects, variations, and possible clinical repercussions of the transverse sinus.

Table 1. Characteristics of included studies

Nº	Short title	Objectives	Conclusion
1º	Variations of the transverse sinus	Report an unusual abnormality of the transverse sinus and review and discuss its anatomical variation and clinical repercussions[1]	Understanding the anatomy and variations of the transverse sinus in diseases, such as venous sinus thrombosis, is important[1]
2º	Association between transverse sinus hypoplasia and cerebral venous thrombosis	Perform a case-control study to identify relationships between transverse sinus hypoplasia and cerebral venous thrombosis[6]	Hypoplasia of the transverse sinus may predispose ipsilateral cerebral venous thrombosis, although possibly without functional impact[6]
3º	Different normal anatomical variations of the transverse dural sinus in magnetic resonance venography (MRV)	Conduct a retrospective study on the normal anatomy and variations of the transverse sinus in venograms and assess the relationships between these variations, age, and gender[3]	Hypoplasia of the left transverse sinus is the most common variation and is more frequent in men. Knowledge regarding the anatomy of the dural venous sinuses is important to avoid over-diagnosing[3]
4º	Anatomical variations of the transverse-sigmoid sinus junction intracranial hypertension	Conduct a cadaveric study to analyze variations in the transverse-sigmoid sinus junction and their implications in the endovascular treatment of idiopathic intracranial hypertension[4]	The importance of knowing these structures for surgical procedures was highlighted, with a good understanding of pathological processes in the venous sinuses, which may be related to the structures studied[4]
5º	Anatomical variations of cerebral MR venography	Identify anatomical variations in magnetic resonance venography and analyze gender-related alterations[7]	Hypoplasia of the transverse sinus was the most common anatomical variation identified and is more prevalent in men. Other anatomical variations of the dural venous sinuses did not vary significantly according to gender[7]
6º	Intracranial MR venography using low-field magnet	Analyze the normal venous anatomy and variations in intracranial magnetic resonance venography in a Nepalese population[8]	Flow gaps were an important anatomical variation observed. The visualization of veins with reduced dimensions (e.g., the vein of Labbe) was lower than in other studies[8]
7º	Cranial venous sinusdominance	Analyze the circulation in cerebral venous sinuses, emphasizing morphological and angiographic aspects[9]	A dominance pattern of the cerebral venous sinus was observed, which was not influenced by age and gender[9]

8º	The evaluation of cerebral venous normalanatomy and variations	Evaluate the anatomical variations and normal anatomy of the cerebral venous system using magnetic resonance venography with contrast[10]	The right vessel chain (transverse sinus, sigmoid sinus, and internal jugular veins) prevailed over the left side[10]
9º	Evaluation of dural venous sinuses and confluence of sinusesvia MRI venography	Determine anatomical variations in the superior sagittal sinus, confluence of sinuses, transverse, straight, and occipital sinus[11]	The prevalence of hypoplasia and agenesis of the transverse sinus was higher than in other studies. A total of 49% and 17.53% of the left and right sinuses, respectively, were hypoplastic[11]
10º	Normal variations in cerebral venous anatomy and their potential pitfalls on 2D TOF MRV examination	Assess normal cranial venous anatomy and possible anatomical variations[12]	Knowledge of the physiological anatomy of venous drainage is imperative in surgical practice and when interpreting magnetic resonance venography[12]

Regarding the design of the ten included studies, six were retrospective studies based on data derived from cerebral magnetic resonance venograms, one retrospective study analyzed cerebral angiographies, one was a cadaveric study that conducted statistical analyses, one was a case report with literature review, and one was a case-control study.

Massrey et al.[1] conducted a case report and literature review of a rare variation of the transverse sinus in a male human skull. The authors provided and discussed some of the best-documented variations in literature. Aplasia and hypoplasia of the transverse sinus were two of the most frequent variations, while agenesis of the transverse sinus was one of the most significant. The transverse sinus can sometimes originate from a bifurcation of the distal segments of the superior sagittal sinus and assume small dimensions. The study also highlighted the importance of understanding the anatomy and variations of the transverse sinus in diseases, such as venous sinus thrombosis.

The retrospective case-control study of Arauz et al6. analyzed records of patients with cerebral venous thrombosis to identify relationships between hypoplasia of the transverse sinus and cerebral venous thrombosis. One of the main sites of cerebral venous thrombosis is the transverse sinus, with a prevalence between 38% and 86% of cases. The results suggested that hypoplasia of the transverse sinus was associated with ipsilateral thrombosis, although thrombosis with these characteristics has no functional impact.

Tantawy et al.[3] retrospectively analyzed the transverse sinus of 363 patients who performed magnetic resonance venography. The right and left transverse sinuses differed greatly in size (asymmetry), and hypoplasia of the left transverse sinus was the most frequent variation. A total

of 123 patients (33.9%) presented asymmetry, but no statistically significant differences were observed between gender. Hypoplasia of the right transverse sinus (i.e., caliber lower than half the caliber of the superior sagittal sinus) was observed in 29 patients (8%), whereas 80 patients (22%) presented this variation in the left transverse sinus. Aplasia of the right and left transverse sinus (i.e., structures not identified on venogram) was found in 6 (1.7%) and 13 patients (3.6%), respectively.

McCormick et al.[4] conducted a study in which 36 sigmoid and transverse sinuses of cadaveric heads from the Applied Learning Center of the Wake Forest University were dissected to identify anatomical variations of the transverse-sigmoid sinus junction. Approximately 72.2% of the sinuses contained a variation in the lumen, such as septations or blind pouch. The difference between these luminal variations was based on blood flow, in which the blind pouch was characterized by blood flow blockage.

Goyal et al.[7] conducted a retrospective study that analyzed data from magnetic resonance venography and noted the importance of knowledge about the morphological aspects and anatomical variations of the transverse sinus. Lack of this knowledge may lead to false positive diagnoses of thrombosis in the transverse venous sinus. Regarding the influence of gender, women presented a higher prevalence of symmetry of the transverse sinuses (69.2% of cases compared with 62% in men), whereas men had a higher prevalence of hypoplasia of the left transverse sinus (24.9% of cases compared with 19.4% in women).

Sharma et al.[8] also conducted a retrospective study analyzing 100 Nepalese patients using brain magnetic resonance venography. Dominance of the right transverse sinus and flow gaps were found in 73% and 47% of the population studied, respectively; 91% of flow gaps occurred on the non-dominant side. Also, hypoplasia and aplasia were mostly identified in the left transverse sinuses.

Kitamura et al.[9] retrospectively analyzed 100 cerebral angiographies to analyze circulation in the cerebral venous sinuses. The authors highlighted the importance of neurosurgeons and radiologists understanding these structures, especially for planning and treating of neurological diseases. In the population studied, no significant differences associated with age, gender, or dominance of the circulation were reported. Sinuses appeared to be larger in men and were significantly larger on the right than the left side (6.5 ± 1.84 to 5.1 ± 1.72 mm). Right-sided dominance was observed.

Doğan et al.[10] developed a retrospective study to analyze the anatomy and variations of 136 cerebral magnetic resonance venograms. Right transverse sinus dominance was found in 38.23% of cases, left transverse sinus dominance was identified in 27.95% of cases, and co-dominance accounted for 32.35%. In women, transverse sinus co-dominance rates (36.04%) were higher than in men (32%). Understanding the dominance of the cerebral venous systems is crucial for surgical

procedures, such as radical neck dissections and excisions of invasive tumors in the dural venous sinuses and jugular veins.

Bayaroğulları et al.[11] highlighted the importance of knowledge about cerebral venous anatomy in a retrospective analysis of 211 patients using cerebral resonance venography. Due to the high incidence of anatomical variations in the dural venous sinuses, knowledge of these structures is crucial for neurosurgeons, neurologists, and radiologists, who may avoid several complications and iatrogenesis. The study also showed high rates of hypoplasia of the transverse sinus compared to data obtained in the literature.

Ahmed et al.[12] conducted a retrospective study assessing magnetic resonance venograms of patients between 2 and 75 years to determine the normal anatomy and variations in the cerebral venous system. The study divided venous drainage anomalies into intra- and extracranial, which can also be characterized as intra- and extraluminal. Abnormal valves, septal flaps, and vessel plexuses were considered intraluminal diseases, whereas extraluminal pathologies included reduced vessel caliber. The study also highlighted that arachnoid granulations may appear isolated in the transverse sinus and cause venous obstruction and hypertension.

DISCUSSION

The dural venous sinuses are positioned between the inner lamina and the outer layer of the dura mater, which are considered margins and microanatomical points in neurosurgery. These sinuses are references for accessing lesions located in the parenchyma of the region and lesions located in the cerebral ventricles[13].

Variations in the venous vessels of the brain are important when planning a surgery, especially when dissecting the cerebral planes, because these structures present many variations that may complicate surgical procedures. For example, venous vessels may vary between the hemispheres of the same individual; thus, they are relevant structures in neurosurgery. Adequate knowledge regarding the morphofunctional anatomy of these structures is needed to reduce post-operative neurological deficits[13].

The cerebral venous system is divided into superficial and deep. The superficial system comprises the sagittal sinuses and the superior superficial cerebral veins, which drain the medial surface and the upper half of the superolateral surface of each hemisphere. This system also comprises the basal and transverse sinuses and the inferior superficial cerebral veins, which drain the inferior surface and the lower half of the dorsolateral surface of each hemisphere. The deep system includes the straight sinus and great cerebral vein (formed by the confluence of the internal cerebral and basal veins), which are responsible for the venous drainage of the corpus striatum, internal capsule, diencephalon, and part of the medullary white center. Both systems drain into the internal jugular veins[2].

The confluence of sinuses, also reported as torcular Herophili, is the main drainage site for venous blood from the brain, meninges, and calvaria. This structure is defined as the union of the superior sagittal sinus, transverse sinuses, and straight sinus. In 60% of cases, the superior sagittal sinus originates in the right transverse sinus, justifying some drainage patterns[2,14].

The right transverse sinus is generally larger and receives most blood drained from the superior sagittal sinus. Therefore, the right transverse sinus, sigmoid sinus, and internal jugular vein contain more blood from the superficial parts of the brain. On the other hand, the left vessels contain blood mainly from the deeper parts, drained from the internal cerebral basal and great cerebral veins[2].

A vascular mesh in the transverse sinus was one of the variations identified in the literature. In almost all variations, the transverse sinus was smaller on the side of the anatomical variation. When hypoplasia or aplasia of the transverse sinus occurs, the internal jugular system increases its capacity. The superior sagittal and straight sinuses drain more blood into the right and left transverse sinuses, respectively. Fenestrations of the transverse sinus, a rare anatomical variation of this structure, are not well documented in the literature[1].

Age may influence the prevalence of some variations in the transverse sinus. The highest prevalence of transverse sinus hypoplasia was found in patients over 60 years old, while the lowest prevalence was identified in individuals aged 20 to 29 years. The prevalence of transverse sinus aplasia was similar in both age groups[3].

During embryological development, as the telencephalon enlarges, the confluence of sinuses is positioned inferiorly in the craniocaudal direction. This process is probably associated with an inclination of the lateral portions of the transverse sinuses, which become less prominent. The region of the confluence of sinuses undergoes an increase and subsequent decrease in the caliber of the venous structures. This characteristic may predispose to hypoplasia, irregularities, or even the absence of structures in this region, mostly in the lateral portion of the transverse or sigmoid sinus[8].

A venous sinus is dominant when its measurement is greater than 50% of the contralateral side, and the ratio between the measure of the right and left sides is greater than 1.5 (right dominant) or less than 0.67 (left dominant). Sinuses are classified as symmetrical when the ratios are equal or between 1.5 and 0.67 for the right and left sinus (i.e., between the limit of 50%), respectively. An important repercussion of variations in the transverse sinus is the absence or isolated hypoplasia of part or all this structure, which can be distinguished from sinus occlusion due to lack of dilation of collateral veins and absence of associated parenchymal hemorrhage[9].

One of the clinical and surgical repercussions of the transverse sinus is the possible relationship with idiopathic intracranial hypertension. Stenosis of the junction between the

transverse and sigmoid sinuses generates a change in venous flow, favoring the development of idiopathic intracranial hypertension. Thrombosis, stenosis, and occlusion of the venous sinuses are also relevant to these anatomical structures. Anatomical changes interfering with the flow of the venous system (e.g., septum and spaces in the sinus walls) may be associated with the etiology of venous sinus diseases. Understanding these variations is essential to diagnose and treat neurosurgical diseases[4].

In this review, evidence on the topic was scarce, especially for the Brazilian population. Therefore, some of the included studies may present outdated information.

CONCLUSION

Knowledge about the morphological aspects of the transverse sinus is relevant to clinical and surgical practice. Most studies discussed the morphological aspects and anatomical variations of the transverse sinus using cadaveric studies and brain magnetic resonance venography. Hypoplasia of the left transverse sinus is the most common anatomical variation of this structure and is more frequent in men over 60 years old. Although these variations are important to be considered in surgical procedures, few studies were conducted in Brazil to identify the incidence and factors (e.g., age and gender) interfering with their prevalence.

CONFLICTS OF INTEREST

None.

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Therapeutic applications of *Hypericum perforatum* (St. John's wort) for treating anxiety and depression: integrative review

Aplicações terapêuticas do *Hypericum perforatum* (erva-de-são-joão) no tratamento da ansiedade e depressão: revisão integrativa

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Abstract

Hypericum perforatum, known as St. John's wort, is a popular medicinal plant recommended in traditional Chinese medicine and prescribed for depression in European countries. However, conflicting data were observed regarding its benefits and risks. This study aimed to evaluate phytopharmaceuticals containing *Hypericum perforatum* extracts for anxiety and depression treatment. An integrative review was performed by searching Literatura Latino-Americana e do Caribe em Saúde (LILACS), Scientific Electronic Library Online (SciELO), and Publisher Medline (PubMed) databases and included studies in Portuguese, English, and Spanish from 2017 to 2022. Randomized clinical trials confirmed the efficacy of the *Hypericum perforatum* extracts compared with placebo on mild and moderately severe depression. Further randomized controlled studies demonstrated similar efficacy to conventional antidepressants for anxiety and mild to moderate depression. The study concludes the need for more studies to evaluate the efficacy of *Hypericum perforatum* extracts, especially concerning adverse effects, risks, and drug interactions.

Keywords: Anxiety; Depression; Phytopharmaceuticals; *Hypericum perforatum*.

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Resumo

O *Hypericum Perforatum*, também conhecido como erva de São João é uma planta medicinal popular recomendada pelos praticantes da medicina tradicional chinesa e amplamente prescrita para a depressão em muitos países europeus. No entanto, existem dados conflitantes sobre seus benefícios e riscos. O objetivo deste estudo foi avaliar os benefícios e riscos dos fitoterápicos contendo *Hypericum perforatum*. no tratamento da ansiedade e depressão. Realizou-se uma revisão integrativa a partir de artigos publicados em nas bases científicas Literatura Latino-americana e do Caribe em Saúde (LILACS), *Scientific Electronic Library Online* (SciELO) e *Publisher Medline* (PubMed) entre os anos de 2017 a 2022 nos idiomas português, inglês e espanhol. Evidências de ensaios clínicos randomizados confirmaram a eficácia dos extratos de *Hypericum Perforatu.* em relação ao placebo no tratamento da depressão leve a moderadamente grave. Outros estudos randomizados controlados forneceram algumas evidências de que os extratos da planta são tão eficazes quanto alguns antidepressivos convencionais na ansiedade e depressão leve a moderada. Conclui-se que há a necessidade de mais estudos para avaliar a eficácia dos extratos de *Hypericum Perforatum,* principalmente no que se refere aos eventos adversos, possíveis riscos e interações com outros medicamentos.

Palavras-chave: Ansiedade; Depressão; Medicamento fitoterápico; *Hypericum perforatum*.

INTRODUCTION

Medicinal plants are vegetable species culturally used for nutrition and medicinal therapies.[1] Several societies demonstrated the importance of using medicinal plants and accumulated experiences and knowledge regarding their use, action mechanisms, and treatment effects for physical and psychoemotional illnesses.[2, 3]

Evidence points to the use of medicinal plants throughout human history, starting from Neanderthal men in the Paleolithic period who relied on nature to provide resources for survival.[4, 5] Medicinal plants were also used by the Babylonic civilization, which had an extensive collection of plant- and animal-based drugs as solutions, enemas, suppositories, ointments, and pills. Moreover, a traditional Indian system of medicine named Ayurveda has been using these compounds for over five thousand years.[6]

The knowledge of medicinal plants properties has been used to produce phytopharmaceuticals, which are natural or synthetic medicines obtained exclusively from the raw material of active plants.[7] Ethnopharmacological surveys, technical-scientific documentation, or clinical evidence validated the efficacy, safety, risks, and quality of phytopharmaceuticals.[8] Medicines with isolated active substances, regardless of origin, and the association of isolated substances with plant extracts are not considered phytopharmaceutical.[9]

The easier accessibility to medicinal plants in communities reinforced phytopharmaceuticals as essential resources for treating different pathologies, in addition to possibly reduced costs

and significant benefits compared with allopathy (i.e., conventional medicine treatment for illness symptoms).[10]

The *Hypericum perforatum* (St. John's wort or hypericum) has a high medicinal potential.[11,12] The species from the *Hipericaceae* family presents organic and aqueous extracts vastly used for treating mild, moderate, and severe unipolar depression.[13] The indications for its use were based on empirical studies[14] followed by clinical trials and anxiolytic and anti-depressive assessments, confirming that aqueous extracts were as effective as conventional antidepressants and led to fewer side effects.[15]

The phytopharmaceutical produced with *Hypericum perforatum* is one of the few natural antidepressants influencing dopamine and norepinephrine brain levels and is considered an efficient alternative for depression treatment.[16] In Brazil, *Hypericum perforatum* is commercialized in street markets and was recently added as a component in industrialized products indicated for anxiety and depression treatment.[17]

This study was motivated by the increased interest in medicinal plants and the high consumption of phytopharmaceuticals. Our results may contribute to the knowledge on the benefits and risks of the *Hypericum perforatum*, especially as a therapeutic recommendation for anxiety and depression. Thus, this study aimed to evaluate the benefits and risks of phytopharmaceuticals containing Hypericum perforatum for anxiety and depression treatment.

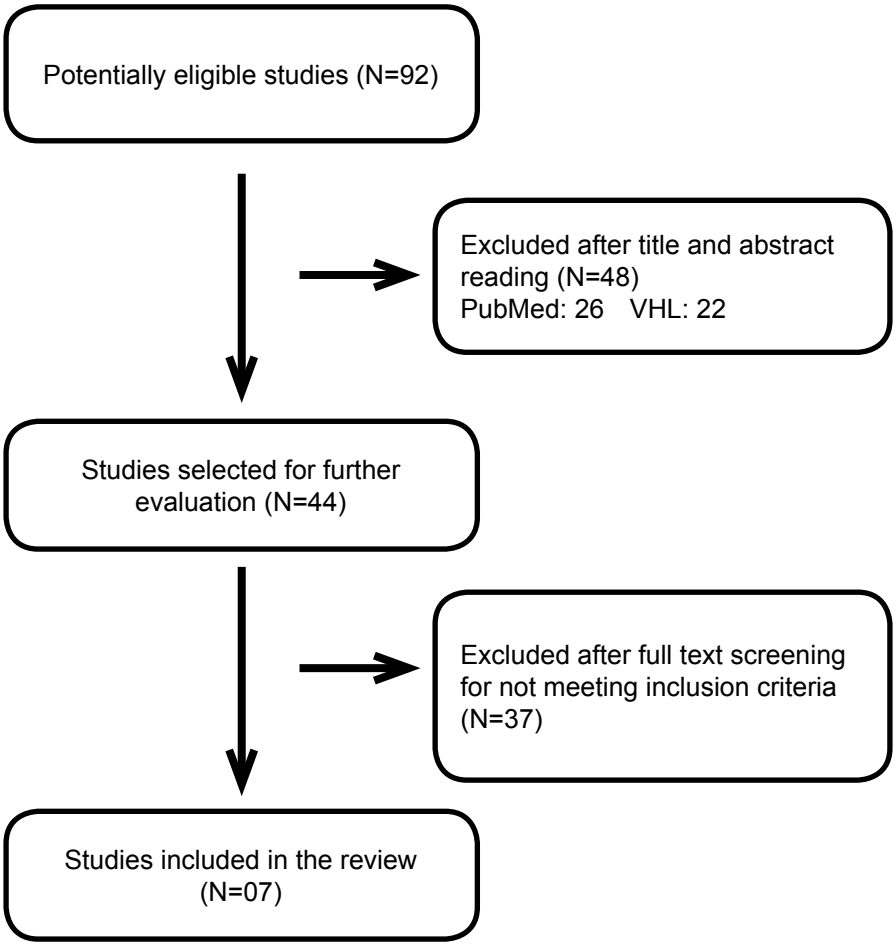
METHODS

This study was an integrative review using data from indexed articles searched on the Scientific Electronic Library Online (SciELO), Latin American and Caribbean Literature in Health Sciences (LILACS), and Publisher Medline (PubMed) databases. Inclusion criteria were studies from 2017 to 2022 published in Portuguese, English, or Spanish (Figure 1). Health sciences descriptors were used in the searches: anxiety, depression, phytopharmaceuticals, and *Hypericum*. Searches were performed with isolated and combined descriptors. Book chapters, monographs, thesis, dissertations, editorials, and publications that did not meet the study criteria were excluded.

RESULTS

After checking for inclusion and exclusion criteria, the characteristics of the selected articles are described in Table 1.

Figure 1. Flowchart of the process for study selection



PubMed: Publisher Medline; VHL: Virtual Health Library

Table 1. Characterization of the included studies

Author/ Year	Title	Aim	Main findings
Apaydin et al. (2017)	A systematic review of St. John's wort for major depressive disorder.	To evaluate the use of St. John's wort for major depressive disorder (MDD) treatment.	St. John's wort monotherapy for mild to moderate depression was superior to placebo for improving depression symptoms and did not show a significantly difference from conventional antidepressants.[18]

Moreno et al. (2017)	*Hypericum perforatum* versus fluoxetine in the treatment of mild to moderate depression: a randomized double-blind trial in a Brazilian sample	To evaluate the efficacy and safety of *Hypericum perforatum* compared with fluoxetine.	*Hypericum perforatum* was less effective than fluoxetine and placebo. Both drugs were safe and well tolerated.[19]
Ng & Venkatanarayanan (2017)	Clinical use of *Hypericum perforatum* (St John's wort) in depression: A meta-analysis.	Review of clinical trials comparing St. John's wort and selective serotonin reuptake inhibitors (SSRIs) in patients with depression.	St. John's wort showed efficacy and safety similar to SSRIs for patients with mild to moderate depression.[20]
Soleymani et al. (2017)	Clinical risks of St John's wort (*Hypericum perforatum*) co-administration.	To evaluate pharmacokinetic changes of conventional medications used concomitantly with St. John's wort preparations.	St. John's Wort preparations showed clinical interactions with several classes of conventional medicine.[21]
Eatemadnia et al. (2019)	The effect of *Hypericum perforatum* on postmenopausal symptoms and depression: A randomized controlled trial.	To test the effects of *Hypericum perforatum* in heatwaves, menopause symptoms, and depression in women with postmenopause.	*Hypericum perforatum* treatment reduced heatwaves, menopause symptoms, and depression in women with postmenopause.[22]
Zirak et al. (2019)	*Hypericum perforatum* in the treatment of psychiatric and neurodegenerative disorders: Current evidence and potential mechanisms of action.	Review of *in vitro*, *in vivo,* and clinical evidence on the efficacy, safety, and action mechanisms of St. John's wort and its active compounds in treating psychiatric and neurodegenerative disorders.	St. John's wort showed potent anti-depressive effects and demonstrated to be an effective and safe treatment.[23]
Adibelli et al. (2022)	St. John's wort (*Hypericum perforatum*)- Related Acute Kidney Injury	To report the case of an acute kidney injury (AKI) in a patient who used *Hypericum perforatum* infusion as treatment for sleeping disorder.	The patient developed acute kidney injury (AKI) after ingesting infused tea of *Hypericum perforatum*.[24]

Studies showed the therapeutic efficacy of *Hypericum perforatum* for treating depression. Ng and Venkatanarayanan analyzed 27 clinical trials with a total of 3,808 patients comparing

the use of St. John's wort with selective serotonin reuptake inhibitors (SSRI).[20] St. John's wort presented a similar response, remission of symptoms, and significantly less discontinuation (i.e., abandonment) compared with standard SSRI treatments. The authors concluded that the long-term efficacy and safety of *Hypericum perforatum* are limited since studies lasted four to twelve weeks.[20]

Apaydin et al. demonstrated similar results when evaluating St. John's wort in adults with depression,[18] showing greater efficacy and safety than placebo and standard antidepressants. These findings were valid even with varying effects according to the depression severity. St. John's wort monotherapy for mild and moderate depression was superior to placebo, significantly improving the symptoms of patients.[18]

However, Moreno et al. observed different results evaluating the efficacy and safety of St. John's wort compared with fluoxetine in an eight-week double-blind study including patients with mild to moderate depression.[19] Seventy-two outpatients were randomly selected to take 900 mg/day of St. John's wort phytopharmaceutical, 20 mg/day of fluoxetine, or placebo. The analysis did not show differences between the average scores of the three groups. Patients who received the phytopharmaceutical had the lowest remission rates (12%) compared with fluoxetine (34.6%) and placebo (45%). The study concluded that St. John's wort was less efficient than fluoxetine and placebo, and all drugs were safe and well tolerable.[19]

A randomized-controlled study by Eatemadnia et al. tested the effect of *Hypericum perforatum* on depression in 80 women with post-menopause, aged 45 to 60 years.[22] Groups received 270 to 330 µg of *Hypericum perforatum* (n = 40) or placebo (n = 40) tablets three times a day for two months. Questionnaires were collected two, four, six, and eight weeks after intervention. Results from 70 women showed that *Hypericum perforatum* treatment reduced menopause symptoms and depression in women with post-menopause.[22]

Zirak et al. reviewed *in vitro*, *in vivo*, and clinical evidence regarding the efficacy, safety, action mechanisms, and active compounds of St John's wort, for the treatment of psychiatric and neurodegenerative disorders.[23] Controlled trials using antidepressants showed that *Hypericum perforatum* and its active compounds, hypericin and hyperforin, presented antidepressant properties similar to tricyclic antidepressants and SSRIs but with fewer and milder side effects. However, clinical evidence on *Hypericum perforatum* efficacy in other psychiatric and neurodegenerative disorders was not robust.[23]

The study of Soleymani et al. evaluated pharmacokinetic changes of conventional medications concomitant with St John's wort formulas.[21] St John's wort formulas presented clinical interactions with several classes of conventional medication, such as immunosuppressants, anticancer agents, cardiovascular medication, oral contraceptives, and lipid-reducing agents, causing life-threatening events. The information label on products with the plant compound must provide

information about interaction risks. Hyperforin seems to be the main ingredient responsible for inducing the activity of Cytochrome P450 and P-glycoprotein by St John's wort. Therefore, products without hyperforin may be candidates to decrease medication interactions of St John's wort.[21]

Phytopharmaceutical products were reported as nephrotoxic due to different mechanisms. Adibelli et al. reported a study case of an acute kidney injury (AKI) in a patient who ingested tea infusions of *Hypericum perforatum* as a treatment for sleep disorders.[24] The patient developed acute renal failure and underwent hemodialysis. The kidney function was reestablished after a week and showed regular function upon hospital discharge.[24]

Clinical guidelines for anxiety and depression treatment in several countries omit *Hypericum perforatum* or advise against its use due to its unknown therapeutic effects.[18, 19] The lack of knowledge from patients and professionals about using this medicinal plant is concerning, especially considering the potential interactions between *Hypericum perforatum* and conventional medicine.[23, 24]

Nowadays, despite the evidence on the efficacy of standard extracts of *Hypericum perforatum*, authorized products hold a "low level" label indication for "slightly low mood symptoms and mild anxiety".[20, 21] This occurs due to loose regulatory structures for phytopharmaceuticals that only authorizes products for self-treatment addressing lower and auto-limited conditions, which is not appropriated for depression.[22, 23, 24]

CONCLUSIONS

The *Hypericum perforatum* chemical composition has been studied, and its pharmacological activities include antidepressant, antiviral, and antibacterial effects, providing supporting evidence for its traditional uses. Most pharmacologic activities are attributed to hypericin and hyperforin, the main components responsible for the anxiolytic and anti-depressive activities.

Safety and tolerability studies showed that *Hypericum perforatum* preparations have better profiles than synthetic antidepressants, being indicated for anxiety and mild or moderate depression. We highlight the need for further studies to evaluate the efficacy of *Hypericum perforatum* extracts, especially regarding adverse effects, risks, and interactions with other drugs.

CONFLICT OF INTERESTS

Nothing to declare.

AUTHOR CONTRIBUTIONS

ALSC, **HGQM**, **KRBS**, **LCDN**, **LCPG**, and **PGPM**: study design, article writing, and final version approval; **MLCP** and **TKC**: supervisor, proofreading, and final version approval.

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afmo.emnuvens.com.br ISSN: 2674-8487 Experience Report

Rescue of the Hiperdia in a Basic Health Unit in the state of Pernambuco: experience report

Resgate do Hiperdia em uma Unidade Básica de Saúde no estado de Pernambuco: relato de experiência

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Abstract

Objective: Diabetes mellitus and systemic arterial hypertension are characterized as a global epidemic. This study aimed to report the experience of students regarding the return of activities of the Hiperdia program created by the Brazilian Ministry of Health. This descriptive study (experience report) with a critical and reflective approach regarding a theoretical and practical activity was conducted in May 2022 at a Basic Health Unit from Igarassu (Pernambuco, Brazil). A health education action was performed to inform the Basic Health Unit users on the importance of healthy eating habits, practicing physical activity, and therapeutic and drug monitoring to control and treat diabetes mellitus and systemic arterial hypertension. Thus, we observed that the population had poor knowledge regarding these diseases.

Keywords: Systemic arterial hypertension; Diabetes mellitus; Health promotion and primary care.

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Resumo

O Diabetes mellitus e a Hipertensão Arterial Sistêmica se caracterizam como uma epidemia global. Objetivou-se relatar a experiência de acadêmicos em relação ao retorno das atividades do grupo Hiperdia, programa criado pelo Ministério da Saúde. Trata-se de um estudo descritivo, tipo relato de experiência, de abordagem crítico reflexiva de uma atividade teórico-prático realizada em maio de 2022, na Unidade Básica de Saúde, Igarassu, Pernambuco. Através de uma ação de educação em saúde, orientou-se acerca da importância de hábitos alimentares saudáveis, aumento da prática de atividade física e do acompanhamento terapêutico e medicamentoso para o controle e/ou tratamento dessas doenças crônicas. Por fim, constatou-se um déficit em relação ao entendimento das patologias em questão.

Palavras-chave: Hipertensão arterial sistêmica; Diabetes mellitus; Promoção da saúde e atenção básica.

INTRODUCTION

According to the Brazilian Ministry of Health, Brazil is the fifth country in the incidence of diabetes mellitus (DM) worldwide (16.8 million people aged 20 to 79 years) after China, India, United States, and Pakistan. Also, its incidence is estimated at approximately 21.5 million until 20301. The guideline of the Brazilian Diabetes Society highlights that the classification of DM allows its adequate treatment and development of strategies for screening comorbidities and chronic complications. Type 2 is the most common DM and is often associated with obesity and aging. It has an insidious onset and is characterized by insulin resistance or partial secretion deficiency by ß-pancreatic cells (or both) and changes in cretin secretion[1].

According to the International Diabetes Federation[2], 6.7 million people died worldwide in 2021 due to DM. In Brazil, more than 214,000 people aged between 20 and 79 years died from this disease, representing 2.8% of deaths of people aged under 60 years in the country. Maeyama et al.[3] described DM as a metabolic disorder with a permanent increase in blood glucose caused by different etiologies (e.g., deficiency in insulin secretion or action or long-term excess consumption of carbohydrates). In this sense, pharmacological (hypoglycemic drugs) and non-pharmacological treatments (physical activity and nutritional diet) are effective for this disease[3].

Systemic arterial hypertension (SAH) affects 30% to 40% of people worldwide, ranging from 22.3% to 43.9% in Brazil[4]. The Mortality Information System of the Brazilian Ministry of Health (2017)[5] reported 141,878 deaths due to SAH or related causes, and most deaths could have been prevented since about 37% of these occurred prematurely. Dantas et al.[6] highlighted that SAH is a multifactorial clinical condition and requires controlling measures to avoid possible complications, such as hypertensive heart disease, heart failure, and cerebrovascular changes.

Primary health care is the main gateway to the Brazilian Unified Health System (SUS) and ensures the autonomy of care, integrality, and longitudinality, essential for monitoring people with

chronic diseases (e.g., SAH and DM)[7]. In this context, Santos et al.[8] emphasized the importance of this health care for people with DM and the follow-up and monitoring as efficient measures to avoid possible complications or interferences in their well-being. Also, DM and SAH should be periodically monitored through monthly consultations with a multidisciplinary team of the Family Health Strategy (FHS)[9].

In this sense, the Brazilian Ministry of Health created the Plan for the Reorganization of Attention to SAH and DM (Hiperdia) in 2002[10]. The program registers and monitors patients with these diseases at the primary health care through health professionals. Based on these data, the Brazilian Ministry of Health develops health promotion strategies to expand actions for preventing, diagnosing, and treating SAH and DM.

The Hiperdia meetings were suspended due to the COVID-19 pandemic in 2020, returning only in late 2021 and early 2022 due to greater flexibility of health actions. According to Almeida and Neto[11], the Ministry of Health recognized that this scenario directly impacted the Hiperdia functioning and user assistance. Thus, FHS services needed to be restructured to fight against the pandemic and maintain primary health actions[12].

In this sense, this study aimed to describe the experience of students in contributing to the return of activities of the Hiperdia with the FHS team and guide and monitor users registered in this program at a Basic Health Unit from Igarassu (Pernambuco, Brazil).

METHODS

This descriptive study (i.e., experience report) occurred during theoretical and practical activities of the curricular subject of teaching-service-community integration in May 2022. This activity aimed to reestablish the Hiperdia in a Basic Health Unit from the municipality of Igarassu, Pernambuco.

The following descriptors were initially selected in the Health Sciences Descriptors (DeCS) database for a theoretical basis: systemic arterial hypertension, diabetes mellitus, health promotion, and primary care. Next, relevant literature reviews and scientific researches published between 2018 and 2022 in Portuguese and English were analyzed using the Virtual Health Library, Lilacs, and Scielo databases.

RESULTS

The activities partially reestablished the Hiperdia and improved the health of the Basic Health Unit users by changing eating habits, physical activity, therapeutic and drug monitoring, and adherence to the Hiperdia meetings, which had been suspended for two years due to the COVID-19 pandemic. These activities also helped estimate the percentage of people with DM and SAH in the covered area and allowed users to be protagonists in the health-disease process

by understanding the disease severity.

Users were asked about the definition of SAH and DM (Figure 1). Next, these diseases were briefly explained, including the main aspects, risk factors, diagnosis, treatment, and possible consequences (Figure 2).

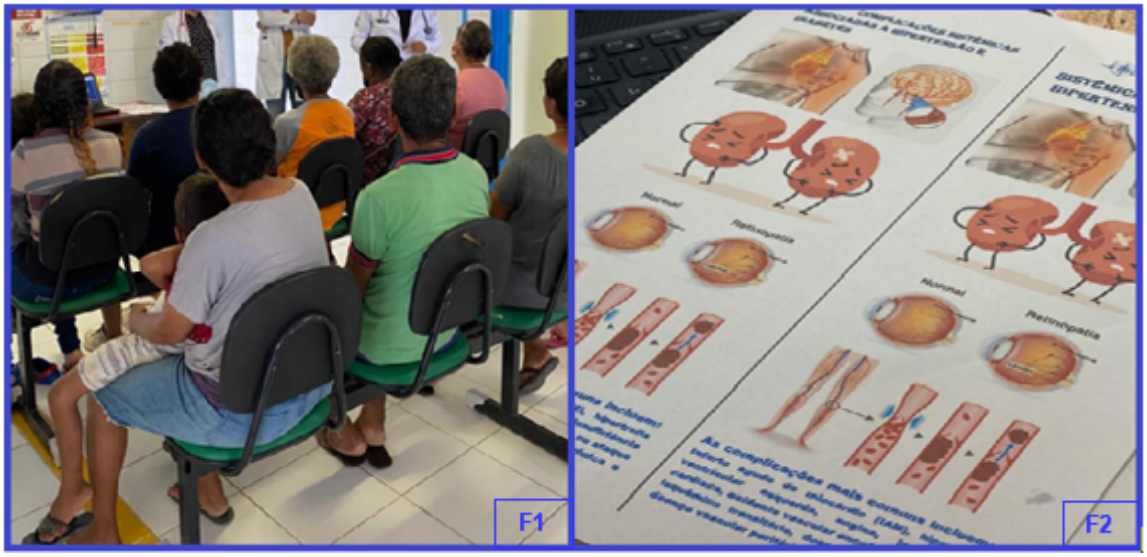

Figure 1 – Health education action for users of the Hiperdia. Source: personal archive.

Figure 2 – Pamphlet developed by the students on the main aspects of systemic arterial hypertension and diabetes mellitus. Source: personal archive.

Users received individual care to verify difficulties in controlling comorbidities, and doubts about the ideal time to use their main medications and side effects were clarified. Most users also questioned the technique for insulin administration and its storage. Considering that the multidisciplinary team and students observed poor knowledge about these diseases and treatments, the doubts were explained to all users to ensure a clear understanding.

CONCLUSION

Actions for users registered in the Hiperdia should occur as a preventive measure and individual monitoring based on existing comorbidities. Also, a lack of knowledge was observed on SAH and DM aspects, such as possible risk and protective factors, impacts on systemic health, and treatment adherence. Some limitations included several uncovered micro-areas due to insufficient community health agents, high replacement of physicians, and lack of support from the multidisciplinary team of the Expanded Family Health Center (e.g., nutritionist, psychologist, and physical education professional), which would be crucial for the Hiperdia actions. Despite the efforts of the Basic Health Unit team and municipal management, the Hiperdia still needs to be fully reestablished with activities planned and executed periodically.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHORS CONTRIBUTIONS

CNGM: supervised the article development and participated in the writing of the final version; **LFO**: participated in developing the theoretical basis of the study and writing the final version of the abstract; **FAA**: participated in writing the results, conclusion, and abstract; **KMRS** and **WBCN**: participated in developing the study methodology and structuring the abstract and references. All authors approved the final version of the article.

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afmo.emnuvens.com.br ISSN: 2674-8487 Experience Report

Follow-up of patients with Autistic Spectrum Disorder and Down Syndrome in a medical genetics outpatient clinic: experience report

Acompanhamento de pacientes com Transtorno do Espectro Autista e Síndrome de Down em ambulatório de genética médica: relato de experiência

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Abstract

Early diagnosis of Autistic Spectrum Disorder (ASD) and/or Down Syndrome (DS) in children and their outpatient follow-up are essential for their development and maintenance of quality of life. The objective of this study is to report the experience of students of the Academic League of Medical Genetics in the outpatient follow-up of these patients in the city of Olinda, Pernambuco, between March and November 2022. The students were able to improve their care, especially in Medical Genetics, making it more humanitarian and comprehensive, due to the growing demand of these patients who, due to their comorbidities, need to be referred to other specialties, in order to provide regular and specialized follow-up.

Keywords: Autism Spectrum Disorder, Trisomy 21, Heredity.

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Resumo

O diagnóstico precoce do Transtorno do Espectro Autista (TEA) e/ou Síndrome de Down (SD) em crianças e o seu acompanhamento ambulatorial são essenciais para o seu desenvolvimento e manutenção da qualidade de vida. O objetivo deste trabalho é relatar a experiência dos discentes da Liga Acadêmica de Genética Médica no acompanhamento ambulatorial desses pacientes no Município de Olinda, Pernambuco, no período entre março e novembro de 2022. Os ligantes puderam aperfeiçoar o seu atendimento, especialmente na Genética Médica, tornando-o mais humanitário e integral, devido à crescente demanda desses pacientes que necessitam, pelas suas comorbidades, do encaminhamento para outras especialidades, de forma a proporcionar um acompanhamento regular e especializado.

Palavras-chave: Transtorno do Espectro Autista, Trissomia do 21, Hereditariedade.

INTRODUCTION

Autism spectrum disorder (ASD) is a multifactorial condition related to genetic, environmental, immunological, and neurological factors, but with no pathognomonic sign, hindering diagnosis.[1] In this sense, ASD is related to the behavior and the difficulties in normal social interaction, intensification of standardized repetition, and sometimes aggressive attitudes.[2]

Thus, it is fundamental to dedicate attention to the service of children with ASD because the number of diagnosed cases increased. For this reason, the expansion of follow-up outpatient and their criteria for a safe diagnosis, which is based on clinical aspects legitimized by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).[1]

Down Syndrome (DS) is a more common chromosomal disorder related to intellectual deficits in the neurodevelopment of the child, such as difficulties in learning and communicating, and long-term complications (e.g., heart disease, visual problems, and endocrinopathies). The early treatment at the follow-up of these children often includes therapies, such as physical therapy and speech therapy, which are essential for adequate growth and promoting the maintenance of their quality of life.[3] Therefore, children with DS live with several barriers to specialized care.[4]

Thus, it is necessary to have adequate follow-up since these populations require targeted attention, mainly due to the demands caused by comorbidities, which impair communication and neurodevelopment in the long term. Therefore, medical genetics outpatient is fundamental for mitigating the harmful effects of these conditions.[5]

METHODS

This experience report described the follow-up of patients with ASD and DS performed by students from the Medical Genetics League, under the supervision of the geneticist, during their outpatient services from March 2022 to November 2022.

The data collection was based on discussions with the genetics preceptor doctor from the clinic and the biweekly meetings of the Medical Genetics League aimed at ASD and DS.

RESULTS

The follow-up began with the emergence of genetics outpatient focused on children and adolescents with ASD and DS aged over 16 years. To better organize this activity during all follow--up periods, the students were divided to ensure the presence of at least one of them at each turn to achieve the greatest number of medical appointments. Meetings were directed at students, focusing on cases, seminars, and the genetic mechanisms related to these conditions.

Besides the knowledge obtained in the meetings, the responsible geneticist explained these topics, emphasizing the medical genetics outpatient clinic of this specialty. Questions related to the anamnesis were also addressed to help confirm the diagnosis, such as food aspects, triggers factors of irritability and aggressiveness, practice in physical activity, and family relationships. Furthermore, the main prescribed medications were exposed, aiming to treat certain signs and symptoms, such as difficulty concentrating and learning, and aggressive behavior; the latter is most common in patients with ASD. The most used medication for aggressive behavior is risperidone, an antipsychotic that blocks serotonin and may cause adverse effects in the long term, such as antipsychotic-induced weight gain, metabolic syndrome, and hyperprolactinemia.[6]

During the appointments, the students had the opportunity to perform the physical examination and distract the children with the toys of the clinic, while their parents were in the medical appointment. Despite their simplicity, these actions made it possible to improve the medical care and perspective of students, mainly in the completeness and equity of the health service of patients with ASD and DS, respecting their particularities.

CONCLUSION

The genetics outpatient clinic may be beneficial for students, especially at the follow-up of patients with ASD and DS due to their growing demand. Moreover, these patients present comorbidities that requires genetics support, other specialties.

Although it is not a compulsory internship, the genetics outpatient clinic becomes an important complementary teaching tool for students. The experience improves their perception of integral care for patients with ASD and DS, making them future professionals more humanitarian.

CONFLICT IN INTERESTS

None.

CONTRIBUTIONS OF THE AUTHORS

TJMBS: preparation of the abstract, introduction, experience report, and final considerations; **HEEV** and **ANF**: preparation of the abstract, introduction, experience report, and final considerations; **HCPO** and **LLRS**: preparation of the introduction, experience report, final considerations, and references formatting; **AESM** and **PSCA**: guidance, correction of the writing and approval of the final version. All the authors approved the final version of the report.

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The potential of dialogic health education in secondary care: experience report at the school clinic

As potencialidades da educação em saúde dialógica na atenção secundária: relato de experiência na clínica-escola

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Abstract

Introduction: Health education practices are important in different Brazilian health contexts since the difficult access to knowledge hinders understanding the health disease process. **Objective:** To describe the impacts observed in a health action about monkeypox. **Methods:** Discussions and interactive dialogues were conducted with people in the waiting room of a university clinical center in Pernambuco, Brazil. **Results:** The population was receptive to discussions that directly impacted daily living, contributed to the dialogue, and exposed pre-existing ideas and questions. **Final considerations:** Health discussions turn the individual into the protagonist of the health disease process, stimulating the search for well-being via autonomy.

Keywords: Health education; Secondary health care; Monkeypox.

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Resumo

Introdução: As práticas de educação em saúde no Brasil são importantes nos diferentes contextos de saúde, uma vez que a dificuldade de acesso ao conhecimento dificulta a compreensão do processo saúde-doença. **Objetivo:** Descrever os impactos observados em uma ação de saúde sobre a varíola dos macacos. **Métodos:** Foram realizadas discussões e diálogos interativos com pessoas na sala de espera de um centro clínico universitário em Pernambuco, Brasil. **Resultados:** A população se mostrou receptiva às discussões que impactaram diretamente no cotidiano, contribuiu para o diálogo e expôs ideias e questionamentos pré-existentes. **Considerações finais:** As discussões em saúde tornam o indivíduo protagonista do processo saúde-doença, estimulando a busca pelo bem-estar por meio da autonomia.

Palavras-chave: Educação em saúde; Atenção secundária à saúde; Varíola dos macacos.

INTRODUCTION

Health promotion is a broad topic composed of personal, sociocultural, historical, economic, and political factors, with an emancipatory perspective focused on the social determinants of health. Consequently, this term is understood as a strategy to face the determinants of the health disease process and facilitate the individual protagonism in the search for better health conditions. Health promotion is also a transversal policy that surpasses the limits of the health sector in the search for social participation and autonomy and is contrary to individual practices focused on the imposition and control of individuals[1].

Therefore, health education is an important tool for promoting well-being. From a dialogical perspective, educational practices seek an emancipatory approach and promotion of autonomy, valuing knowledge as a process of collective creation. In this sense, individuals are actors in the health construction process, regardless of the level of care or complexity[2,3].

This conception is aligned with popular health education, a concept guided by principles of the popular education of Paulo Freire[3]. The Brazilian Ministry of Health recognizes popular health education, through the National Policy of Popular Health Education, as a political-pedagogical reference needed for the integrality of care, qualification of participation, social control, and training of professionals in the area[4].

In this context, strategies are needed to stimulate the implementation of health education actions at all levels of care. Among these levels, secondary care stands out with specialized services at outpatient and hospital levels and intermediary technological density between primary and tertiary care (i.e., procedures of medium complexity)[5].

In secondary care, university clinical centers are important learning environments for professionals to strengthen health education by favoring comprehensive, dialogical, and humanizing care. This care is mediated by qualified listening, defined as the ability to attentively listen to

narratives of individuals and perceive all the involved biopsychosocial factors. Hence, university clinical centers allow horizontal dialogues between professionals and users that contribute to the emancipation and promotion of individual and collective health[6].

Thus, proposing health education within secondary care is challenging since it may intervene with the paradigm of care historically constructed based on passive information, prescriptions, and indications regarding behavior change. The path of health education needs dialogical and meaningful relationships, with health interventions based on ways of experiencing the health and disease process and influenced by gender, socioeconomic status, and race[7].

Accordingly, health education is an important strategy to combat health disinformation by constructing general knowledge based on scientific and popular knowledge. In 2022, an outbreak of monkeypox, a disease with high transmissibility, started in non-endemic countries. Thus, the orientation of the population regarding this disease was fundamental to reducing its incidence[6,7].

OBJECTIVE

This case report aims to describe the impacts of a health education action regarding monkeypox.

METHODS

The health action regarding monkeypox was conducted in a university clinical center in Pernambuco (Brazil) as a clarification activity mediated by academics from the Academic League of Family and Community Medicine and the Academic League of Infectious Diseases.

The topic was chosen due to the contemporary nature of monkeypox and the lack of debate in television news and social networks. To guide the population, the academics explained key points of the disease, such as risk factors, symptoms, prevention care, and places to seek medical care. Resources used in the action included the oratory and distribution of informative pamphlets to enable the community as knowledge propagators.

Furthermore, the group chose the topic based on the methodology of problematization proposed by Maguerez8. This method consists of five steps:

1. Observation of reality and definition of the problem: after contacting users of the university clinical center, doubts concerning the prevention and identification of monkeypox symptoms were identified, mainly because this was a new topic.
2. Key points: the problem identified by academics may have occurred due to several factors, including the dissemination of incorrect information and anguish of the population with the emergence of a new disease.
3. Theorizing: after identifying the problem, a theoretical deepening of the topic in reliable databases was conducted to materialize basic aspects of monkeypox.

4. Solution hypotheses: to clarify the importance of monkeypox prevention practices to strengthen the knowledge of the population on the topic.
5. Application of reality: five days of health education activities were conducted at different times in September 2022 to reach a greater community. The focus was on users in the waiting room of the university clinical center and information sharing about monkeypox without medical jargon (i.e., accessible communication).

The health action was also based on liberating education[9], which recognizes dialogue and problematization as intrinsic processes to constructing knowledge, besides the need to stimulate curiosity and critical reflection about what was said. Thus, problematizing implies asking, an act that indicates human existence since the person of knowledge self-transforms and modifies the object or reality when problematizing[10,11].

Associated with the knowledge from meetings, the responsible medical geneticist explained these topics by highlighting the outpatient clinic and addressing questions related to the anamnesis (e.g., dietary aspects, factors that trigger irritability and aggressiveness, physical activity practice, and family relationships) to help confirm the diagnosis. The geneticist also explained the main medications to treat signs and symptoms, such as difficulty concentrating and learning and aggressive behavior. Aggressive behaviors are more common in young people with autism spectrum disorder, and one of the most used drugs is risperidone, a serotonin and dopamine--blocking antipsychotic that may cause long-term side effects, such as weight gain, metabolic syndromes, and hyperprolactinemia[6].

The problematization occurs through dialogue, defended by Freire[9] as a dialectical-problematizing process, and enables a look at the world and existence in society as a process since reality is constantly changing. In this context, dialogue is a tool that fosters solidarity since people involved reflect and act towards the transformation and humanization of the world.

RESULTS

Health education is a tool of great impact on disease prevention and health promotion; however, it is mostly used in primary care and rarely applied in secondary care services. Thus, this study evidenced that health education may be an effective strategy in secondary care by enhancing the integrality of health care. In addition, it is noteworthy the perspective of Paulo Freire in defending education as active people sharing knowledge and contributing to constructing an autonomous individual that thinks and criticizes health-disease processes[9,10].

During the health action, the waiting room of the university clinical center was considered a favorable environment for horizontal dialogues and knowledge sharing with the potential to promote autonomy and empower the users. Therefore, these spaces may be used to ensure the use of light technologies in secondary care (e.g., reception, bonding, and accountability) to share

information about health and care9. This scenario also contributed to reinforcing the change from the biomedical (focused on the cure of the disease, transmitted vertically, and centered on the figure of the physician) to the biopsychosocial model of health, which covers all spheres of life, has a participatory atmosphere, and is centered on the user[12].

People in the waiting room were receptive to discussions on issues that directly impacted daily living. During the dialogues, users presented limited knowledge about the monkeypox outbreak. Users also presented their previous knowledge and doubts about the topic, which were clarified and helped them recognize signs of monkeypox in acquaintances and spread information beyond that space. This dialogical practice corroborates Freire[9], who stated that teaching required openness, curiosity, and inquiry during speaking or listening to allow users to assume themselves as epistemologically curious.

The health education activity benefited the assisted users and academics, who became aware of different realities and learned from the reports and statements of users; thus, contributing to the formation of a humanized professional. The relationships between the medical student and patient must transcend the formal and technical aspects and involve respect, responsibility, and bonding[13].

To promote humanized care and health education in health services, especially at the secondary level, the professional must use qualified listening for integral care. This tool surpasses listening to a report and is characterized by paying attention to gestures, expressions, and marks that help understand the individual biopsychosocial aspects.

Thus, according to the principles of Paulo Freire, health education (mediated by horizontal dialogue and qualified listening) becomes a fundamental instrument for health promotion if the professional perceives the assisted user as a person of rights, with limitations, and protagonist of the own history[9,10,15].

FINAL CONSIDERATIONS

Health education actions are essential in the health care of the individual, especially in Brazil, which is a country with inequalities that negatively influence the physical, mental, and social well-being and the context of illness of the population. Thus, health promotion is a tool to transform the reality of people by changing from passive listening to inciting questions and criticisms in daily living. Hence, the meeting during the health action stimulated the autonomy of users, an important precept to the liberating education defended by Paulo Freire[9].

Therefore, this case report evidenced the importance of informative actions to elucidate and empower listeners concerning monkeypox, promote health education, and contribute to the consolidation of medicine based on scientific evidence and dissemination of a humanized approach to health.

Different health services have the potential to promote educational activities in health to change the verticalization of knowledge by highlighting the value of empowering the person who seeks continued health care in primary, secondary, and tertiary sectors.

Moreover, assisted users who recognize themselves as main agents in promoting health and conducting prevention and care activities may provide collective development and well-being and help the functioning of the health system and social life.

CONFLICT OF INTEREST

None to declare.

CONTRIBUTIONS OF THE AUTHORS

AAS: elaboration of methods, references, and review of the entire article. **APRC** and **AJPB**: preparation of final considerations, references, and review of the entire article. **LMSE** and **JMFRJ**: preparation of results, references, and review of the entire article. **JRCS**: guidelines, suggestions, and review of the entire article. **JFS**: preparation of the introduction, references, and review of the entire article.

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Health education strategy for the prevention of sexually transmitted infections: experience report

Estratégia de educação em saúde na prevenção das Infecções Sexualmente Transmissíveis: relato de experiência

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Abstract

The incidence of sexually transmitted infections reaches several groups and presents multiple etiologies, symptoms, and complications that can be prevented, diagnosed, and treated early using health education in primary care. This study described the health education experienced by students in primary care according to the methodology of education defended by Paulo Freire. The population accepted the proposal and showed interest in exchanging knowledge, actively participated throughout the process, and were grateful for the space offered.

Keywords: Disease prevention; Sexually Transmitted Infections; Primary health care; Health education

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Resumo

A incidência de infecções sexualmente transmissíveis atinge diversos grupos e apresenta múltiplas etiologias, sintomas e complicações que podem ser prevenidas, diagnosticadas e tratadas precocemente por meio da educação em saúde na atenção primária. Este estudo descreveu a educação em saúde vivenciada por estudantes da atenção básica segundo a metodologia de educação defendida por Paulo Freire. A população aceitou a proposta e demonstrou interesse em trocar conhecimentos, participou ativamente de todo o processo e agradeceu o espaço oferecido.

Palavras-chave: Prevenção de doenças; Infecções Sexualmente Transmissíveis; Atenção primária à saúde; Educação em saúde.

INTRODUCTION

Among public health policies, sexually transmitted infections (STIs) are one of the most addressed in primary care (PC), encompassing promotion, prevention, and early diagnosis and treatment[1]. Given the advance of science for preventing and treating STIs, the global incidence of these infections is worrisome since they reach several groups and present multiple etiologies, symptoms, and complications when not treated or treated inappropriately[2]. Thus, health education is crucial for disease prevention, quality of life, self-care, healthy sex life, and changes in risky behaviors among young people, adults, and older adults[3].

Given the historical context of the Brazilian public health policies, the term health education started to be used from the expansion of preventive medicine in the 20th century, considering authoritarian, biologist, and technicist strategies of the Public Health Service Foundation. In addition, the influence of the Ottawa Charter and the creation of a Unified Health System (SUS) led health education to acquire new strategies aimed at health promotion, disease prevention, early diagnosis and treatment, autonomy, and active participation in individual and collective care[4].

Since health education is inserted in community care, this strategy is used in several public policies in PC. However, the knowledge is transmitted from the health professional to the individual (i.e., vertically), and the latter does not have contextualization of reality and critical reflection, which Paulo Freire defines as banking education[5].

Thus, health education needs to be taught, built, and practiced from the dialogical construction of knowledge, considering the population and popular knowledge as an adjunct for understanding the causes of diseases and how to prevent and overcome them[6, 7]. This process must aim at exchanging of knowledge, guidance, clarification, listening, and reception in the Basic Health Unit (BHU) waiting room, individual care, public squares, schools, home visits, and other

spaces of care intervention in PC[8, 9].

To practice health education, we must focus on the future health professionals working on SUS, as they are current students who are experiencing the service routine during the training process and can create horizontal spaces for health education[10, 11]. Thus, this study aimed to report the successful experience of health education on STIs conducted by students along with the health professionals and population in a BHU in Olinda, Pernambuco.

EXPERIENCE REPORT

Based on the reality experienced during the practical activities of the Course Integration Academy, Service, and Community (IASC) in the BHU, the group of students identified some frequent doubts among the population (i.e., men and women aged between 18 and 60 years) during the rapid tests for syphilis, hepatitis, and Human Immunodeficiency Virus (HIV). They accessed the service by calling Community Health Agents to the target audience of STIs. After accessing the profile of the community, the students discussed with the BHU health professionals the possibility of conducting a health education activity using horizontal dialogue and actions with didactic materials and ludic resources.

Thus, a dynamic presentation was initiated with the audience in the waiting room, followed by a general discussion on the topic and the main methods of prevention against STIs to perceive their prior knowledge. Then, the students asked a rhetorical question to the population about the human papillomavirus (HPV), followed by a brief explanation addressing the form of transmission, symptoms, diagnosis, prevention, and treatment. The focus of the discussion was to inform about HPV vaccination, the age group indicated, the importance of performing the preventive examination, and where to perform it. In addition, other STIs (syphilis and gonorrhea) were addressed, focusing on instruction about the early signs and symptoms and the importance of seeking medical help even in the absence of signs of greater discomfort, such as pain. In addition, some forms of transmission of HIV and how to prevent them were explained, demystifying the idea that the only transmission route would be sexual. Also, the importance of HIV testing was discussed, aiming at a more effective therapy and the consequent increase in the survival of people with this virus. The “Balloon dynamics” was performed in the later stage, which consisted of inviting participants to pop a balloon containing myths or truths about STIs and prevention methods. Next, they discussed how STIs can have negative consequences on the sexual health and reproductive health of adolescents, which impair their physical and emotional development and social behavior, affecting school dropouts. At the end of the intervention, participants could perform rapid testing for the main STIs, such as syphilis, hepatitis B and C, and HIV.

RESULTS OBSERVED

The population accepted health education. They showed interest in exchanging knowl-

edge, actively participating throughout the process, and expressing gratitude for the space offered. The mother of a young pregnant woman also participated, who seized the moment of clarification and reported her puerperium, which was marked by insecurities because of a previous diagnosis of syphilis. The group believes this result was obtained due to the educational materials and dynamics that allowed the speech of popular knowledge. Also, dialogues between the various types of knowledge stimulated reflections, problematization of the theme, and collective construction. Moreover, service professionals (i.e., community health agents and the nursing team) were motivated to build other moments of health education using the proposals presented by students.

FINAL CONSIDERATIONS

The participation of students in this project allowed them to genuinely experience the daily life of a primary care health professional by performing a relevant action for the local community. In addition, the knowledge exchange promoted by the “conversation circle” allowed the ratification of the importance of this dynamic, with the purpose of health education, mainly in expanding knowledge and sharing information about this theme in different age groups. Thus, this practice, along with the dissemination of knowledge to the general population, was relevant for the academic training of future physicians, as it promoted reflection on the value of dialogues and discussions in PC. The practice also favored the expansion of integrative experiences with society, as proposed by the current ideology of SUS.

CONFLICT OF INTEREST

No comment.

CONTRIBUTIONS OF THE AUTHORS

ANF: preparation of the summary, introduction, experience report, and final considerations; **GTMC**: preparation of summary, introduction, experience report, and observed results; **HEEV:** preparation of the introduction, experience report, final considerations, and references; **PGFL** and **SRD**: writing of the experience report; **JRCS:** searching for references, construction of the introduction, standards guidance, and file correction.

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Critical review

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Marsh H. Do No Harm: Stories of Life, Death, and Brain Surgery. São Paulo, SP: Nversos, 2017.

Henry Marsh, a renowned British neurosurgeon approaching the end of a long career, shared the triumphs and tragedies of his professional and personal life in "Do No Harm: Stories of Life, Death, and Brain Surgery." In terms of textual production, this is a surprisingly simple and extraordinarily intimate memoir that recalls some of the author's cases in an elegantly brief work, unraveling the myths that patients have in relation to doctors, unmasking the human and fallible face of neurosurgeons, and the ethical dilemmas and emotional exhaustion that these health professionals go through throughout their careers. The starting point of each chapter is a real-life vignette. He registered the stories of patients with a variety of tumors including glioblastoma, medulloblastoma, pineocytoma, and choroid plexus papilloma (diagnosed in the author's son).

The narratives are simple yet enlightening and disarming. Many depict situations that can assume seismic proportions. This work tells stories of success and failure involving complex neurosurgical procedures, and attitudes of heroism and feelings of hurt experienced by doctors and patients.

Marsh makes us reflect on the pressure that neurosurgeons are under, as they need to make quick decisions and are surrounded by the constant risk of making mistakes as when he writes "the problem is that when doctors such as myself make mistakes the consequences can be

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catastrophic for our patients."

The title of the book itself speaks to the duality that neurosurgeons need to deal with in their daily lives. "Do No Harm" refers to the principle of non-maleficence set out in the Latin expression "Primum non nocere", usually attributed to the Hippocrates of Kós. This principle is often lost when performing neurosurgical procedures. This constant duality experienced by neurosurgeons, sometimes considered superhuman, sometimes villains responsible for usurping the lives of their patients, imposes considerable emotional burden and anguish that makes readers re-signify the prevalent romanticized idea that society has about what medicine is.

Marsh's maturation over the years is notable, from an arrogant young surgeon to a caring older guru (idealism giving way to pragmatism). Although Marsh has become an extremely pragmatic and rational professional, it is precisely this characteristic that allows him to develop a touching and deep involvement with his patients. It is very easy to write a book just with stories of success and happiness, but it takes a lot of self-confidence and courage to face the failures that are inevitable in the course of anyone's life.

Marsh's book is often a lyrical mystery, as when he writes of the brain as "the mysterious substratum of all thought and feeling, of all that was important in human life—a mystery, it seemed to me, as great as the stars at night and the universe around us."

"Do No Harm" will attract admirers of Atul Gawande, Jerome Groopman, and other medical authors who write expressively on subjects pertinent to the medical profession. Those who have felt the ups and downs in their own lives will relate to the book.

"Do No harm", in addition to providing an idea of how some neurosurgeries are conducted, offers incredible lessons and touching stories, inviting a deep analysis of medical ethics. Furthermore, Marsh constructs a literary experience of great importance for medical education, as it can be seen as a reality check to support the decision of students who are still uncertain about the career they want to pursue. In fact, the writing style adopted by the author, unlike traditional academic writings, makes the book extremely accessible, light, and pleasant. His engaging writing makes this work an instrument of scientific dissemination that can be used as complementary reading in undergraduate and postgraduate courses and scientific initiation in the area of health sciences.