

INTERDISCIPLINARY

Phytochemical Therapy for
Fragile X Syndrome

Skin Substitute Cost-
Efficiency for DFUs

Digital Competence in
Hospital Early Education

CAFE Model: Executive
Functions in Speech
Therapy

Discovering Thoughts, Inventing Future

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PREFACE

The Global Journal of Medical Research (GJMR) is pleased to present this issue, bringing together a curated collection of high-quality research papers that explore the latest advances in medical science and clinical practice.

This issue features research spanning topics including neurology, pharmacology & drug discovery, microbiology & pathology, radiology & diagnostics, gynecology, diseases, veterinary science, orthopedics, surgery & cardiovascular medicine, dentistry, nutrition, and interdisciplinary medical studies. Each paper has undergone a rigorous double-blind peer-review process to ensure clinical rigor and scientific originality.

We would like to express our sincere gratitude to the authors for entrusting their research with us, to the reviewers for their thorough and constructive evaluations, and to our readers for their continued engagement with the medical scientific discourse.

We hope that the research presented herein inspires further inquiry and contributes meaningfully to the advancement of medical knowledge and patient care.

The Chief Editor
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An in-Silico study – Targeting a Genetic Intellectually Different ability's Therapy, through Phytochemicals

Article Record

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Abstract

People with 'intellectually different ability or intellectual disability (ID)' have neurodevelopmental deficits, which is shown by, limitations in 'intellectual functioning' and 'adaptive behavior'. 'Fragile X syndrome' is the common genetic cause of 'Intellectually different ability (ID)'. Therefore in this in-silico research, a protein named 'mGluR5' was targeted for the therapy of ID in Fragile X Syndrome. In Fragile X syndrome, due to mutation in FMR1 gene, there's lack of FMRP (Fragile X Mental Retardation Protein), resulting in unimpeded (lack of inhibition by FMRP) activity of 'mGluR5', which leads to aberrant dendritic development with mis-signalling, This results in ID, Autism and Psychopathology. As an attempt, for overcoming this problem of ID seen in the patients of Fragile X syndrome, in this research, 'mGluR5' was targeted by 19 different phytochemicals, collected from IMPPAT 2.0 database. This study was done with the aid of multiple bioinformatics tools and biological databses, namely 'RCSB-PDB', 'BIOVIA Discovery Studio', 'PubChem', 'CACTUS Online SMILES translator', 'CB-Dock' and 'pkCSM'. The conclusion of this research, compared with 'Fenobam (already reported against mGluR5)' was that, 'beta-Bisabolene' and 'Cirisilineol' have relatively more probability to serve as therapeutic compounds against 'mGluR5', as compared to "Platainoside-B", 'Orientin' and other phytochemicals in the list of 19 phytochemicals studied in this research. However, different results may or may not show up in 'in-vitro' or 'in-vivo' researches.

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ARCHIVAL RECORD

An in-Silico study – Targeting a Genetic Intellectually Different ability's Therapy, through Phytochemicals

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Abstract

People with 'intellectually different ability or intellectual disability (ID)' have neurodevelopmental deficits, which is shown by, limitations in 'intellectual functioning' and 'adaptive behavior'. 'Fragile X syndrome' is the common genetic cause of 'Intellectually different ability (ID)'. Therefore in this in-silico research, a protein named 'mGluR5' was targeted for the therapy of ID in Fragile X Syndrome. In Fragile X syndrome, due to mutation in FMR1 gene, there's lack of FMRP (Fragile X Mental Retardation Protein), resulting in unimpeded (lack of inhibition by FMRP) activity of 'mGluR5', which leads to aberrant dendritic development with mis-signalling, This results in ID, Autism and Psychopathology. As an attempt, for overcoming this problem of ID seen in the patients of Fragile X syndrome, in this research, 'mGluR5' was targeted by 19 different phytochemicals, collected from IMPPAT 2.0 database. This study was done with the aid of multiple bioinformatics tools and biological databases, namely 'RCSB-PDB', 'BIOVIA Discovery Studio', 'PubChem', 'CACTUS Online SMILES translator', 'CB-Dock' and 'pkCSM'. The conclusion of this research, compared with 'Fenobam (already reported against mGluR5)' was that, 'beta-Bisabolene' and 'Cirisilineol' have relatively more probability to serve as therapeutic compounds against 'mGluR5', as compared to "Platainoside-B", 'Orientin' and other phytochemicals in the list of 19 phytochemicals studied in this research. However, different results may or may not show up in 'in-vitro' or 'in-vivo' researches.

Keywords: *Intellectually different ability (Intellectual disability), Phytochemicals, mGluR5, Fragile X syndrome*

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1. Introduction

Intelligence' is the general *mental* ability for reasoning, problem-solving and learning. This mental ability integrates other cognitive abilities and works also, such as, perception, attention, memory, language or planning. Neuroimaging studies have generally supported that, a frontoparietal network is relevant for intelligence. This same network is also found to be associated with other cognitive functions, such as, perception, storage of shortterm memory and language. This network has a distributed nature and is involved in different cognitive abilities and functions. This fact clearly explains that, the nature of intelligence is 'integrative'. [1].

Jung and Haier looked into 37 structural and functional studies on neuroimaging, which were published between 1988 and 2007. They found some commonalities in their study. On the basis of these commonalities, they proposed 'Parieto-Frontal Integration Theory (PFIT)'.

Given below, is somewhat easy explanation of our Brain's functioning, associated with intelligence -

1. In the first stage of this process, occipital and temporal areas process sensory information. The extrastriate cortex (Brodmann areas (BAs) – 18 and 19) and the fusiform gyrus (BA37), are involved with recognition, imagery and elaboration of visual inputs. Wernicke's area is utilized for analyzing and elaborating syntax of auditory information.

2. Parietal BAs 39 i.e. angular gyrus, BAs 40 i.e. supramarginal gyrus, BAs 7 i.e. superior parietal lobule are utilized for integration and abstraction of the sensory information. This is involved in the second stage of process.
3. In the third stage of this process, the parietal areas interact with the frontal lobes. This interaction leads to - solving problems, evaluation and testing of hypothesis. Frontal BAs 6, 9, 10, 45, 46 and 47 are involved in this stage.
4. Then, in the fourth stage of this process, the anterior cingulate (BA 32), is involved in selection of response and inhibiting the alternative responses, after above three stages of this process.

Thus, we can say that, frontal, parietal, temporal and occipital areas are involved in the above-mentioned process. However, Jung and Haier say that, it is not necessary that, all these areas are equally essential for every individual's intelligence. Regions of brain of the dorsolateral prefrontal cortex, such as BAs 9, 45, 46 and 47; and, the parietal cortex, such as BAs 7 and 40, can be considered as most important parts for the intelligence of a human being. [1, 2].

Thus, we can say that, frontoparietal network of our brain maybe necessary for intelligence. But, this network is also relevant for working memory. [1, 3]. This was studied by Gray et al. [1, 4]. Commonality between intelligence and working memory was also discovered during the studies on animals, by Matzel and Kolata. [1, 5].

1.1. Intellectually Different Ability (Intellectual Disability)

People with 'intellectually different ability or intellectual disability (ID)' have neurodevelopmental deficits. This neurodevelopmental deficit is shown by limitations in 'intellectual functioning' and 'adaptive behavior'. These disabilities begin in childhood, and symptoms appear before the age of 22. Before, studying ID in more detail, let us take a look at the concept of 'Intellectual functioning' [6].

'Intellectual functioning (IF)' is also called 'Intelligence'. It includes multiple mental activities, such as - logical reasoning and practical intelligence (problemsolving), ability to learn things, verbal skills, etc. IF expresses itself through multiple capabilities, behaviors, thoughts and emotions. We can also say that, IF is the global ability which helps us to understand and interact with reality. It is measured in terms of 'Intelligence quotient (IQ)'. To measure this, IQ tests are taken. The median of this test is 100 and standard deviation is 15. If the score of this test is 70 or below, that is the indication of ID. [6].

Adaptive behavior disabilities are expressed as lack of competence in social, conceptual and practical skills. These skills are quite poor in the people having ID. [6].

1.2. Few Genetics and Environmental Factors of ID

ID can develop due to various genetic mutations and diseases, or, environmental reasons. The genetic abnormalities responsible for ID could be mutation in a gene, copy number variation, or chromosomal abnormality that cause inborn errors of metabolism, defect in neurodevelopment and neurodegeneration. Environmental reasons can be, maternal exposure to toxin or infectious agents, uncontrolled maternal medical conditions, complications in parturition, and post-natal trauma and exposure to toxin/infectious agents. The most common environmental reason for ID, which can be prevented is 'fetal alcohol syndrome'. 'Down's syndrome' is the most common chromosomal cause for ID, and, the most common genetic cause for ID is 'Fragile X syndrome'. [6].

In 'Fragile X syndrome', there's a single gene mutation in the 'FMR1' gene. FMR1 gene is actually a transcription factor of several genes (hundreds of genes) expressed in the 'Central Nervous System (CNS)' and its disruption causes 'ID' and 'behavioral disturbance and seizure.' [6, 7].

In 'Rett Syndrome', neurodegeneration leads to ID. It is an X-linked dominant degenerative condition, which shows up only in females, secondary to mutation of the 'MeCP2 gene'. In the patients of Rett Syndrome, at the substantia nigra cerebral atrophy occurs, which causes defects in the dopaminergic nigrostriatal pathway. This cerebral atrophy begins at the age of 6 to 18 months. [6, 8].

When fetus is exposed to alcohol, that exposure inhibits the production of retinoic acid, which is a necessary signaling molecule for nervous system's development. Consumption of even a small amount of alcohol in any trimester of gestation period (pregnancy), leads to the development of fetal alcohol syndrome. [6, 9]. Exposure to opioids, cocaine and teratogenic medications, may also be the cause of 'Intellectual disability'. [6].

Rubella and HIV are few commonly known infectious agents, which can cause Intellectual Disability. When the pregnant mother is infected with rubella, during the initial trimester of gestation period, 10 – 15% of the time, it leads to 'Intellectual Disability'. This probability can be above 15% , if this infection occurs, during the first month of pregnancy. If the pregnant mother is vaccinated, then this infection of rubella can be prevented. [6, 10]. HIV in

infants may also lead to encephalopathy, seizures and Intellectual disability within the first year of life secondary to microcephaly, immunosuppression and *Pneumocystis jiroveci pneumonia* (PCP) infection. This HIV may get transferred vertically from mother to infant. [6, 11].

Few uncontrolled maternal medical conditions during the gestation period may also increase the risk of ID, such as, Pregnancy hypertension, Asthma, urinary tract infection, pre-pregnancy obesity, and pregestational Diabetes. [6, 12]. Some other medical conditions, such as, uncontrolled maternal Diabetes, malnutrition and obstetrical complications, which causes anoxia, may also cause ID. [6, 13]. ID can be acquired during early childhood, due to infections (maybe Encephalitis or Meningitis), head trauma, asphyxia, intracranial tumor, malnutrition and exposure to toxic substances. [6, 14].

1.3. Fragile X Syndrome - Science Behind ID

This is a common genetic cause of ID, which affects 1 in 4,000 people. The Fragile X protein, FMRP (Fragile X Mental Retardation Protein), regulates the dendritic growth, with the GABAergic system being especially sensitive. Lack of FMRP (Fragile X Mental Retardation Protein), results in unimpeded (lack of inhibition by FMRP) activity of 'mGluR5', which leads to aberrant dendritic development with mis-signalling, This results in ID, Autism and Psychopathology. [15, 16]. Trial against 'mGluR5' has also been performed, with the motive to replace the inhibitory effect of the missing FMRP protein. Phase 1 trial of 'Fenobam' has suggested a promising efficiency based on a single dose. [15, 17]. Additionally, the antibiotic 'Minocycline' has also shown inhibition of mGluR5 receptor and some efficacy. [15, 18, 19].

In this in-silico research, 'Intellectually different ability (Intellectual disability)' due to 'Fragile X syndrome' has been targeted by the phytochemicals, to obtain a few partially validated compounds against ID.

Now, let us take a look at, some of the medicinal plants, which are positively effective on our Brain, from which the phytochemicals have been collected for this research.

1.4. Medicinal Plants - on our Brain

1. *Bacopa monnieri*: This plant is also known as 'Brahmi' or 'water hyssop'. It is used in Ayurveda for its ability to enhance memory and control the level of sugar in the blood. [20, 21]. It contains various active compounds such as alkaloids, saponins and cucurbitacins, which exhibit different biological activities. It has the potential to treat multiple brain-related diseases, such as Alzheimer's disease, Parkinson's disease, Attention Deficit Hyperactivity Disorder and Depression. [21].
2. *Withania somnifera*: This plant is also known as 'Ashwagandha' [20, 22]. This is also known as 'Indian ginseng' or 'Indian winter cherry'. The name 'Ashwagandha' is derived from two words - 'ashwa', which means 'horse', and, 'gandha', which means 'fragrance', refers to the smell or aroma of this plant's fresh roots. It is said that, when someone consumes its roots, that person gains similar power as the horse. [22, 23]. Since ancient time, it has been traditionally used in Ayurvedic medicine, which enhances the strength of 'Nervous system'. It can provide multiple benefits to our brain, such as - Ability to treat neurodegenerative disorders, Obsessive Compulsive Disorder, Alcohol withdrawal syndrome, and, anti-inflammatory effects. [22].

3. *Centella asiatica*: This plant is also known as 'Mandukparni'. [20]. This plant has been used for centuries in Ayurvedic and Chinese medicine, for its cognitive benefits. [24]. Few modern scientific studies, which have been performed on rodents, and, in human subjects, have shown that, whole *Centella asiatica* extracts and some of its active compounds, exhibit the ability to enhance cognition or neurotropic properties. [24, 25, 26, 27, 28, 29, 30]. Therapy given by '*Centella asiatica*' has also been found to reduce oxidative stress and mitochondrial dysfunction in rodents. It also exhibit neuroprotective potential in chemically induced Alzheimer's disease. [24, 31, 32, 33, 34, 35].
4. *Ocimum sanctum*: This plant is also known as '*Ocimum tenuiflorum*'. Traditionally, it is also known as 'Holy basil' or "Tulsi". [20, 36]. This medicinal plant has the potential to provide many different health benefits. Various scientific researches have shown that this medicinal plant can exhibit anti-stress potential, but with higher doses. Extract of this plant was found to inhibit the release of cortisol. It was also found to exhibit the significant CRF1 receptor antagonist activity. Thus, the extract of this plant was found to effectively manage stress. This effectiveness could be due to, either inhibition of cortisol release, or, CRF1 receptor antagonist effect. [20, 37].
5. PubChem: It is a public repository, which provides information about various chemical substances. It is a database of NCBI. It was launched in 2004. It is a component of Molecular Libraries Roadmap Initiatives of US National Institute of Health. Since years, this database has been serving as a resource for chemical information for the scientific research community. [42]. In this research, PubChem has been used to study the chemistry of ligands, and, download the 3-Dimensional structures of the ligands in '.sdf' format.
6. CACTUS Online SMILES Translator: It belongs to NCI/CADD group, NIH-National Cancer Institute. [43]. In this research, this tool has been used to convert the .sdf files of ligands into .pdb files, so that those 3D structures of ligands can be used for docking.
7. CB-Dock: It is a user-friendly web server for blind docking. It predicts binding modes without information about binding sites. It predicts binding sites of a given protein and calculates the centres and sizes with a new curvature-based cavity detection approach. It performs docking with 'AutoDock Vina'. It provides an interactive 3-Dimensional visualization of results, and is available free of cost at <http://clab.labsh.ac.cn/cb-dock/>. [44]. In this research, this tool has been used for the blind docking of 19 phytochemicals against the 3-Dimensional structure of 'mGluR5'.

In this in-silico study, 19 different phytochemicals are collected from these plants and have been targeted in-silico against 'mGluR5'. Now, let us take a look at, a few tools and biological databases, utilized in this in-silico study.

1.5. Tools and Databases

1. IMPPAT 2.0 Database: 'IMPPAT 2.0' is an enhanced and expanded database. It has information on 4,010 Indian medicinal plants, 17,967 phytochemicals, and, 1,095 therapeutic uses. It contains the information about the associations at the level of plant parts. Overall, it is a manually curated database, which contains phytochemical atlas of Indian medicinal plants. [38]. In this research, this database has been used for the collection of phytochemicals, to be utilized as ligands.
2. Protein Data Bank (RCSB-PDB): It stands for 'Research Collaboratory for Structural Bioinformatics Protein Data Bank.' [39, 41]. It is an open access database of Biology which shares the 3-Dimensional structures of proteins. [40, 41]. It was established in 1971 with 7 structures. But, over the period of time it became possible to access more than 113,000 entries of natural and designed macromolecules. More than 84,000 of those macromolecules are complexed with small chemical components, such as solvent, ions, cofactors, inhibitors and drugs. This database was originally designed for the structural biology community, but, over the period of time, other professionals also began to use it. [41]. In this research, this database has been used to visualize and obtain the 3-Dimensional structure of 'mGluR5'.
3. <https://projectgemmi.github.io/wasm/convert/cif2pdb.html>: In this research, this link was used to convert .cif files to .pdb files.
4. BIOVIA Discovery Studio: This tool is mainly used for protein cleaning. However, in this research the two structures of α -synuclein didn't require cleaning at all.

8. pkCSM Tool: It is a novel approach for the prediction of ADMET properties. It uses graph-based signatures to develop the predictive models of central ADMET properties. [45]. In this research, this tool has been used to analyse the Lipinski's rule of 5 of each shortlisted phytochemical and their computations for absorption, distribution, metabolism, excretion and toxicity.

2. Methodology

1. Target Identification, Retrieval of 3-Dimensional Structure and Protein Cleaning: In the first step of this research, through literature survey, 'mGluR5' was identified as the suitable target protein, to target "intellectually different ability (intellectual disability)", which is a symptom of "Fragile X syndrome". After the identification of 'mGluR5' as target, 3-Dimensional structure of 'mGluR5' having PDB ID - '6FFH' was downloaded from 'RCSB-PDB' database. After download, this '.cif' file was converted into '.pdb' format using <https://projectgemmi.github.io/wasm/convert/cif2pdb.html>. Then, this 3-Dimensional structure of 'mGluR5' with '.pdb' format was cleaned using 'Discovery Studio'.
2. Collection of ligands: Medicinal plants, which are positively effective on our brain and have therapeutic potential to treat brain-related problems were identified through literature survey, as mentioned above. In this step, a list of 19 phytochemicals were collected from 'IMPPAT 2.0 database', to be utilized as ligands in this research. These phytochemicals were collected from *Bacopa monnieri*, *Withania somnifera*, *Centella asiatica*, and *Ocimum sanctum* (*Ocimum tenuiflorum*).
3. CB-Dock analysis of 'Fenobam' and 'Minocycline' for reference: In this step, I analysed the docking affinity of 'Fenobam' and 'Minocycline' against 'mGluR5' for my reference, as these phytochemicals have been found to be quite effective against 'mGluR5', as mentioned above. It was decided that

in this in-silico research, the docking affinity of my list of phytochemicals will be compared with the docking affinity of 'Fenobam' and 'Minocycline', considering both of them as standards.

4. CB-Dock analysis of 19 ligands: In this step, 19 phytochemicals of the list were docked against 'mGluR5' and their minimum vina scores and cavity size were recorded. As decided, their docking results were compared with that of 'Fenobam' and 'Minocycline'. On the basis of this comparison, a few phytochemicals from the list were shortlisted. The criteria for this comparison was whether they are equivalent or more negative in terms of vina score, as compared to 'Fenobam' and 'Minocycline' or not. Those phytochemicals or ligands, which

showed equivalent or more negative vina scores in the same cavity size as 'Fenobam' were considered more suitable for further research and were shortlisted for ADMET analysis.

5. Analysis of Lipinski's rule of 5 of the shortlisted ligands: In this step, Lipinski's rule of 5 was analysed for each shortlisted phytochemical (ligand), to check whether they are violating or not violating Lipinski's rule of 5. The shortlisted ligands were checked for whether:
6. Detailed ADMET analysis: In this step, Absorption, Distribution, Metabolism, Excretion and Toxicity were computed and analysed for the shortlisted compounds to understand their pharmacokinetics in detail.

3. Results

3.1. Cleaned 3-Dimensional Structure of Target Protein

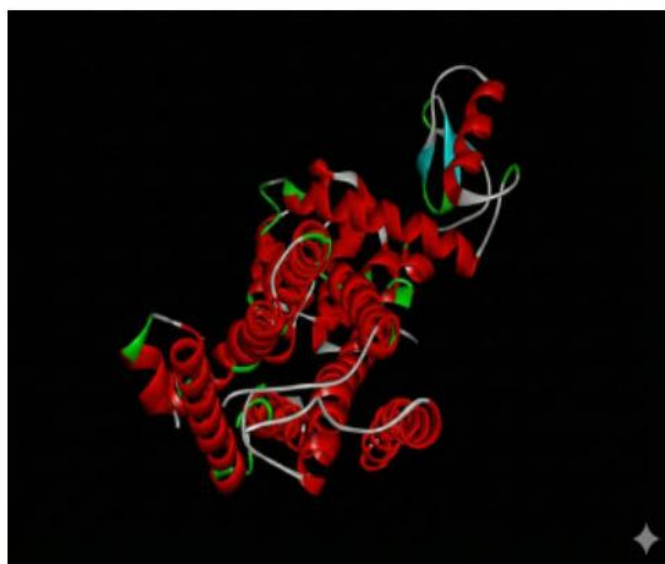


Figure 1. 3-Dimensional cleaned structure of 'mGluR5'. [47]

3.2. Collection of Ligands from IMPPAT 2.0 Database

List of phytochemicals, collected from IMPPAT 2.0 database, utilized as ligands. [52].

Table 1. List of phytochemicals collected from IMPPAT 2.0 database. [52]

S. No.	Plant source (Plant part)	Phytochemicals
1.	<i>Bacopa monnieri</i> (Leaf)	Apigenin-7-O-glucuronide
2.	<i>Bacopa monnieri</i> (Whole plant)	Plantainoside B
3.	<i>Withania somnifera</i> (Leaf)	Hygrine
4.	<i>Withania somnifera</i> (Leaf)	Cuscohygrine
5.	<i>Centella asiatica</i> (Aerial part)	Beta-Bisabolene
6.	<i>Centella asiatica</i> (Aerial part)	2-Heptenal
7.	<i>Centella asiatica</i> (Aerial part)	E-(2)-Octenal
8.	<i>Centella asiatica</i> (Aerial part)	alpha-Pinene
9.	<i>Centella asiatica</i> (Aerial part)	beta-Pinene
10.	<i>Centella asiatica</i> (Aerial part)	Nerol
11.	<i>Ocimum tenuiflorum</i> (Leaf)	Samaderine-E
12.	<i>Ocimum tenuiflorum</i> (Leaf)	Eugenol
13.	<i>Ocimum tenuiflorum</i> (Leaf)	E-alpha-Bisabolene
14.	<i>Ocimum tenuiflorum</i> (Leaf)	Cirsilineol
15.	<i>Ocimum tenuiflorum</i> (Leaf)	Orientin
16.	<i>Ocimum tenuiflorum</i> (Leaf)	Eupalitin
17.	<i>Ocimum tenuiflorum</i> (Leaf)	Ascorbic acid
18.	<i>Ocimum tenuiflorum</i> (Leaf)	Decanal
19.	<i>Ocimum tenuiflorum</i> (Leaf)	Cadinane

3.3. CB-Dock Analysis of Standards or References - Fenobam and Minocycline

When 'Fenobam' was docked against 'mGluR5', it showed the minimum vina score of -8.2 in the cavity size of 2432. On the other hand, when 'Minocycline' was docked against 'mGluR5', it showed the minimum vina score of -8.2 in the cavity size of 334. [53].

3.4. CB-Dock Analysis of Ligands Against mGluR5

Table 2. CB-Dock analysis of ligands against ‘mGluR5’. [53]

S. No.	Phytochemicals	Binding Energy (kcal/mol)	Cavity Size (Å ³)
1.	Apigenin-7-O-glucuronide	-8.6	398
2.	Platynoside B	-8.2	2432
3.	Hygrine	-5.4	343
4.	Cuscohygrine	-7.5	2432
5.	Beta-Bisabolene	-9.0	2432
6.	2-Heptenal	-4.7	2432
7.	E-(2)-Octenal	-6.1	2432
8.	alpha-Pinene	-5.5	2432
9.	beta-Pinene	-5.5	2432
10.	Nerol	-7.1	2432
11.	Samaderine-E	-8.2	398
12.	Eugenol	-6.3	2432
13.	E-alpha-Bisabolene	-7.3	2432
14.	Cirsilineol	-8.7	2432
15.	Orientin	-8.2	2432
16.	Eupalitin	-7.8	2432
17.	Ascorbic acid	-6.6	2432
18.	Decanal	-6.4	2432
19.	Cadinane	-7.7	2432

3.5. pkCSM Analysis of Lipinski’s Rule of 5 of Shortlisted Ligands

Table 3. Lipinski’s Rule of 5 Analysis of ‘Platynoside B’. [54]

ADME Property	Value	Violation (Lipinski)
Molecular weight	478.45	No
H-bond donor	7	Yes
H-bond acceptor	11	Yes
LogP	0.1323	No
Rotatable bonds	8	No

Table 4. Lipinski’s Rule of 5 Analysis of ‘beta-Bisabolene’. [54]

ADME Property	Value	Violation (Lipinski)
Molecular weight	204.357	No
H-bond donor	0	No
H-bond acceptor	0	No
LogP	5.0354	Slight
Rotatable bonds	4	No

Table 5. Lipinski’s Rule of 5 Analysis of ‘Cirsilineol’. [54]

ADME Property	Value	Violation (Lipinski)
Molecular weight	344.319	No
H-bond donor	2	No
H-bond acceptor	7	No
LogP	2.897	No
Rotatable bonds	4	No

Table 6. Lipinski’s Rule of 5 Analysis of ‘Orientin’. [54]

ADME Property	Value	Violation (Lipinski)
Molecular weight	448.38	No
H-bond donor	8	Yes
H-bond acceptor	11	Yes
LogP	-0.2027	No
Rotatable bonds	3	No

3.6. Detailed ADMET Computation and Analysis

Table 7. Detailed ADMET Analysis of shortlisted ligands from pkCSM tool. (Part 1: Absorption and Distribution) [54]

Category	Model Name	Platynoside B	Beta-Bisabolene	Cirsilineol	Orientin
Absorption	Water solubility (log mol/L)	-2.992	-6.133	-3.749	-3.164
	CaCO ₂ permeability (log Papp in 10 ⁻⁶ cm/s)	-0.048	1.408	1.247	-0.794
	Intestinal absorption (Human, %)	26.868	94.094	89.153	44.19
	Skin permeability (log Kp, cm/hr)	-2.735	-1.222	-2.747	-2.735
	P-glycoprotein substrate	Yes	No	Yes	Yes
	P-glycoprotein I inhibitor	No	No	No	No
	P-glycoprotein II inhibitor	No	No	Yes	No
Distribution	VDs (Human, log L/kg)	0.872	0.633	-0.336	0.164
	Fraction unbound (Human, Fu)	0.362	0.233	0.158	0.102
	BBB permeability (log BB)	-1.682	0.778	-0.789	-1.934
	CNS permeability (log PS)	-4.195	-2.101	-3.187	-4.758

Table 8. Detailed ADMET Analysis of shortlisted ligands from pkCSM tool. (Part 2: Metabolism, Excretion, and Toxicity) [54]

Category	Model Name	Platynoside B	Beta-Bisabolene	Cirsilineol	Orientin
Metabolism	CYP2D6 substrate	No	No	No	No
	CYP3A4 substrate	Yes	No	Yes	No
	CYP1A2 inhibitor	No	No	Yes	No
	CYP2C19 inhibitor	No	No	Yes	No
	CYP2C9 inhibitor	No	No	No	No
	CYP2D6 inhibitor	No	No	No	No
	CYP3A4 inhibitor	No	No	No	No
Excretion	Total clearance (log ml/min/kg)	-0.123	1.458	0.639	0.521
	Renal OCT2 substrate	No	No	No	No
Toxicity	AMES toxicity	No	No	No	No
	Max tolerated dose (human, log mg/kg/day)	0.199	0.280	0.554	0.769
	hERG I inhibitor	No	No	No	No
	hERG II inhibitor	No	No	No	Yes
	Oral Rat Acute Toxicity (LD50, mol/kg)	2.651	2.597	2.258	3.003
	Oral Rat Chronic Toxicity (LOAEL, log mg/kgbw/day)	3.367	1.339	0.953	3.342
	Hepatotoxicity	No	No	No	No
	Skin sensitisation	No	Yes	No	No
	T. Pyriformis toxicity (log ug/L)	0.285	1.928	0.361	0.285
	Minnow toxicity (log mM)	3.858	0.082	0.757	5.809

4. Discussion

This research began with the literature survey to identify the target protein, and, medicinal plants, which can cure brain-related problems, to identify partially validated therapeutic agents at in-silico level, to treat ‘Intellectually different ability (Intellectual disability)’, due to ‘Fragile X syndrome’. ‘mGluR5’ was identified as the suitable protein to be targeted, as due to lack of ‘FMRP’ activity, as a result of mutation in ‘FMR1’ gene, unimpeded (lack of inhibition by FMRP) activity of ‘mGluR5’, which leads to aberrant dendritic development with mis-signalling. This results in ID, Autism and Psychopathology. Then, 19 different phytochemicals were collected from *Bacopa monnieri*, *Withania somnifera*, *Centella asiatica*, and *Ocimum sanctum* (*Ocimum tenuiflorum*) after gathering knowledge about their therapeutic potential and effectiveness on our brain. ‘mGluR5’ protein having ‘PDB ID - 6FFH’ was downloaded from RCSB-PDB. Its ‘.cif’ format was converted into ‘.pdb’ format. Similarly, ‘.sdf’ format files of ligands were converted into ‘.pdb’ format using ‘CACTUS Online SMILES Translator’. ‘mGluR5’ having ‘pdb’ format was opened on ‘Discovery Studio’ and was cleaned to get prepared for docking. Then, for our reference/standard, ‘Fenobam’ and ‘Minocycline’, which have been found to bind to and show efficacy against ‘mGluR5’ were analysed against ‘mGluR5’ using ‘CB-Dock’. Their docking results were used as reference/standard in this result, with which, docking results of 19 collected phytochemicals were compared. 19 phytochemicals were also docked against ‘mGluR5’ and their docking results were compared to our references/standards. ‘Platynoside B’, ‘beta-Bisabolene’, ‘Cirsilineol’ and ‘Orientin’ gave the minimum vina score in the same cavity size, in which, ‘Fenobam’ gave the minimum vina score, and, were found to be equivalent to ‘Fenobam’ at the in-silico docking level. Therefore, only these 4 ligands were shortlisted for further research, and, Lipinski’s rule of 5 and Absorption, Distribution, Metabolism, Excretion and Toxicity of only these 4 phytochemicals were analyzed using

pkCSM tool. 'Platainoside-B' and 'Orientin' showed violation from Lipinski's rule of 5, in terms of donor and acceptor hydrogen bonds. 'beta-Bisabolene' also showed slight violation in terms of 'logP'.

5. Conclusion

The docking results of 'Platainoside B', 'beta-Bisabolene', 'Cirsilineol' and 'Orientin', nearly resembled the docking result of 'Fenobam'. This indicated that, these four compounds may be the partially validated potential therapeutic molecules against 'mGluR5' like 'Fenobam'. However, analysis of Lipinski's rule of 5 showed that, 'Platainoside-B' and 'Orientin' violated from Lipinski's rule of 5, in terms of donor and acceptor hydrogen bonds. These facts somewhat show that, 'beta-Bisabolene' and 'Cirsilineol' have relatively more probability to serve as therapeutic compounds against 'mGluR5', as compared to 'Platainoside-B', 'Orientin' and other phytochemicals in the list. However, this conclusion is solely drawn from 'in-silico' research. Different results may or may not be observed in 'in-vitro' or 'in-vivo' researches.

6. Future Prospect

This research maybe utilized for further attempt to discover novel therapeutics against 'mGluR5', to treat 'Intellectual disability', in 'Fragile X syndrome'.

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Healing Outcomes and Cost Efficiency of Advanced Skin Substitutes for Diabetic Foot Ulcers Under the CMS Payment Framework

Article Record

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PEER REVIEW

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Abstract

Background: Diabetic Foot Ulcers (DFUs) are associated with substantial morbidity, health care utilization, and risk of lower-extremity amputation. Advanced wound treatments such as skin substitutes are commonly used in the management of DFUs when standard wound care alone is insufficient. Recent changes in the Medicare Physician Fee Schedule (PFS) and the Outpatient Prospective Payment System (OPPS) have standardized reimbursement for skin substitutes based on surface area applied, increasing interest in healing outcomes and treatment-related costs under the CMS payment framework.

Objective: To descriptively compare published healing outcomes and estimated cost per healed DFU across selected advanced skin substitutes in the context of CMS payment policies.

Methods: A descriptive comparison was conducted using published DFU healing probabilities and estimated treatment-related costs for five advanced skin substitutes: Helicoll®, Grafix®, Apligraf®, Dermagraft®, and EpiFix®. Cost per healed DFU was calculated as the ratio of estimated treatment-related cost to reported healing probability. The primary effectiveness outcome was complete ulcer healing at 12 weeks. Cost assumptions were standardized using publicly available CMS reimbursement methodologies. No probabilistic modeling or ICER-based cost-utility modeling was conducted.

Results: Among the reported healing probabilities ranging from approximately 0.30 to 0.83 across products, Helicoll demonstrated a favorable balance of cost and effectiveness, with an annual per-patient cost of 20,000 and a reported wound closure rate of 0.83 in a 4-week clinical study with 1-week follow-up. This resulted in an estimated cost per healed DFU of approx. 24,000, which was substantially lower than comparator products. Estimated treatment-related costs varied substantially, resulting in wide variation in calculated cost per healed DFU. Helicoll has the higher reported healing probabilities and the lowest calculated cost per healed DFU among evaluated products.

Conclusion: In this comparative effectiveness analysis, Helicoll provided clinically meaningful healing outcomes at substantially lower cost compared with other specific advanced skin substitutes. These findings support Helicoll as a cost-effective treatment option for DFU management from a payer perspective and may inform reimbursement and formulary decision-making. This analysis provides a transparent cost-per-responder framework but does not constitute a formal cost-effectiveness model or systematic comparative effectiveness evaluation. Head-to-head trials and...

Full abstract continues on the metadata continuation sheet.

Diabetic Foot Ulcers

Skin Substitutes

Cost-Effectiveness

Helicoll

CMS Reimbursement

Wound Care Economics

Type I Collagen

AI USE STATEMENT

No generative AI was used for analysis or results.

FUNDING

This study was funded by Encoll Corporation, the manufacturer of the Product included...

CONFLICT OF INTEREST

The review focuses on the Helicoll® skin substitute product, manufactured by Encoll Corp. The author is a key employee of...

DATA AVAILABILITY

Not applicable for this article.

ETHICS

No ethics committee approval was required for this article type.

CONSENT

Not applicable for this article.

TRIAL REG.

Not applicable.

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FULL FUNDING STATEMENT

This study was funded by Encoll Corporation, the manufacturer of the Product included in this study. The same Company provided financial support to conduct the study and to manage the data professionally. The Company reviewed the manuscript for scientific accuracy but did not influence the interpretation of the results

FULL CONFLICT OF INTEREST STATEMENT

The review focuses on the Helicoll® skin substitute product, manufactured by Encoll Corp. The author is a key employee of Encoll Corp and has been involved in the development and commercialization of the product. This professional and financial relationship represents a potential conflict of interest. The lead author has over 40 years of experience in tissue regeneration and wound care research and commercialization.

FULL ABSTRACT

Background:

Diabetic Foot Ulcers (DFUs) are associated with substantial morbidity, health care utilization, and risk of lower-extremity amputation. Advanced wound treatments such as skin substitutes are commonly used in the management of DFUs when standard wound care alone is insufficient. Recent changes in the Medicare Physician Fee Schedule (PFS) and the Outpatient Prospective Payment System (OPPS) have standardized reimbursement for skin substitutes based on surface area applied, increasing interest in healing outcomes and treatment-related costs under the CMS payment framework.

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Conclusion:

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Keywords: Diabetic Foot Ulcers, Skin Substitutes, Cost-Effectiveness, Helicoll, CMS Reimbursement, Wound Care Economics, Type I Collagen

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Subramanian Gunasekaran

1. Introduction

Diabetic Foot Ulcers (DFUs) represent a major cause of morbidity, health care utilization, and lower-extremity amputation among patients with diabetes¹⁻³. DFUs are associated with prolonged healing, frequent clinical encounters, and increased risk of infection and hospitalization, contributing substantially to overall health care costs²⁻⁴. When standard wound care fails to achieve timely healing, advanced skin substitutes are frequently used to promote tissue regeneration and wound closure⁴⁻⁶.

In recent years, the economic evaluation of advanced skin substitutes has become increasingly complex due to significant changes in Medicare payment policy. Under 2026 Medicare Physician Fee Schedule (PFS) and Outpatient Prospective Payment System (OPPS) rules, skin substitutes are reimbursed as incident-

to supplies using standardized per-square-centimeter payment methodologies rather than product-specific pricing. These changes have shifted attention away from unit price and toward utilization patterns, surface area applied, and clinical outcomes.

Emerging clinical evidence suggests that high-purity type I collagen-based skin substitute like Helicoll, may achieve early wound area reduction and clinically meaningful healing in patients with DFUs. However, their economic value relative to established advanced skin substitutes has not been well characterized, underscoring the need for comparative effectiveness and cost-effectiveness evaluation^{1,2}.

The objective of this analysis is to descriptively compare published healing outcomes and estimated cost per healed DFU

across selected advanced skin substitutes, interpreted within CMS payment environment.

2. Methods

2.1. Study Design

This study is an exploratory cost-per-responder analysis using secondary published data⁷. It is not a systematic review, meta-analysis, or formal cost-utility model.

No AI-generated cost estimation algorithms were used in the final model. All economic inputs are explicitly defined below to ensure reproducibility. No formal PRISMA review or risk-of-bias scoring was conducted. Clinical trial number is not applicable. Therefore, cross-trial comparability is limited. Healing probabilities were extracted exactly as reported in published studies.

Because the included studies differed in study design, ulcer severity, wound size, Wagner grade, infection status, offloading methods, and standard wound-care practices, the reported healing rates could not be considered directly comparable measures of relative treatment effectiveness. Therefore, a descriptive semi-quantitative evidence weighting approach was used, taking into account factors such as study design, sample size, baseline patient comparability, endpoint definition, and follow-up duration. Accordingly, the resulting rankings should be interpreted as exploratory economic illustrations rather than definitive comparative effectiveness conclusions.

2.2. Perspective and Time Horizon

The analysis was conducted from a payer perspective intended to reflect a typical DFU treatment episode. No lifetime horizon or QALY (Quality-Adjusted Life Year) modeling was conducted.

Variable	Base Case	Low Scenario	High Scenario
Applications per episode	Product-specific average	1–2	5–8
Treated area	Product-specific average	–50%	+50%
Healing probability	Published/adjusted value	–25%	+25%
Treatment cost	Base estimate	–50%	+50%

Table 1. Sensitivity Analysis

2.6. Economic Outcome

Primary economic outcome was calculated using:

$$\text{Cost per healed ulcer} = \frac{\text{Episode cost}}{\text{Healing probability}}$$

No ICERs were calculated because:

- Cross-trial comparison violates incremental modeling assumptions
- No common comparator arm exists
- No probabilistic uncertainty modeling was performed

Dominance terminology has been removed to avoid overstating comparative claims.

2.7. Ethical Considerations

This study used aggregated, de-identified secondary data and did not involve direct patient contact. As such, institutional review board approval and patient consent were not required. The

2.3. Interventions Included

Helicoll, Grafix, Apligraf, Dermagraft, and EpiFix.

2.4. Clinical Outcome Inputs

The primary clinical outcome was complete DFU healing at approximately 12 weeks. In contrast, the early healing kinetics observed with Helicoll Skin Substitute support accelerated wound closure, achieving comparable outcomes within 5 weeks versus 12 weeks reported for other products. This efficacy was clinically demonstrated in a multicentric study⁸, which reported a wound closure probability of 0.83 at 5 weeks (4-week treatment period with 1-week follow-up).

2.5. Cost Inputs

Estimated treatment-related costs were derived from payer reimbursement information that was publicly available⁷.

Since CMS payment is applied per treated square cm, episode cost is highly sensitive to utilization assumptions, particularly number of applications and average treated wound area. A one-way sensitivity analysis is therefore necessary in future by varying the number of applications per episode across plausible real-world ranges as given in Figure ???. This analysis is essential for products requiring more frequent applications or larger treated surface areas as it may generate substantially higher episode costs even when the per-cm² reimbursement amount is standardized. Thus, future analyses should validate these inputs using independent hospital acquisition data, payer claims, chargemaster information, or registry-derived utilization costs.

analysis adhered to ethical standards for health economic research and transparent reporting.¹

3. Results

3.1. Drivers of Cost per Healed DFU

Although estimated treatment-related costs varied across products, differences in calculated cost per healed DFU were driven primarily by variation in reported healing probabilities rather than absolute cost alone. Products with similar estimated treatment-related costs demonstrated markedly different cost per healed DFU values due to differences in reported healing outcomes, as specified in Table 2. Notably, higher treatment-related cost did not consistently correspond to higher healing probability, underscoring the importance of considering both outcomes and resource use when interpreting descriptive economic metrics.

¹ Helicoll® is a registered trademark of Encell Corporation (Fremont, CA, USA). Grafix® is a registered trademark of Smith & Nephew, Inc. (Andover, MA, USA). Apligraf® and Dermagraft® are registered trademarks of Organogenesis Inc. (Canton, MA, USA). EpiFix® is a registered trademark of MiMedx Group, Inc. (Marietta, GA, USA). All other trademarks are the property of their respective owners.

Reported 12-week healing probabilities varied across products, ranging from approximately 0.30 to 0.83^{7,8}. Estimated treatment-related costs ranged from approximately \$20,000 to over \$33,000 per treatment episode. Helicoll demonstrated the lowest calculated cost per healed DFU among evaluated products.

Table 2. Reported Healing Outcomes and Calculated Cost per Healed DFU

Product	Estimated Treatment-Related Cost (USD)	Healing Probability	Approx. Cost per Healed DFU (USD)
Helicoll	\$20,000	0.83 at 5 weeks	\$24,000
Grafix	\$28,449	0.62 at 12 weeks	\$45,900
Apligraf	\$25,370	0.48 at 12 weeks	\$52,850
Dermagraft	\$24,552	0.38 at 12 weeks	\$64,600
EpiFix	\$33,288	0.30 at 12 weeks	\$110,960

Table Notes: (1) Reported values represent approximate 12-week healing rates as described in the cited literature⁷ and are not derived from head-to-head comparisons. Cost per healed DFU as illustrated in Figure 1 was calculated descriptively as estimated treatment-related cost divided by reported healing probability. The annual cost per patient versus 12-week healing probability is given in Figure 2. (2) The estimated treatment related cost of Helicoll was based on the respective average invoice cost. (3) The previously completed cost-analysis study used a total study duration of 12 weeks. However, owing to the accelerated healing kinetics of Helicoll, the product demonstrated substantial wound healing within 4 weeks, allowing its clinical evaluation⁸ to be completed over a shorter 4-week treatment period with 1-week follow-up (4+1 weeks). (4) The healing probabilities included in Table 2 provided healing rates that could be used for descriptive cost-per-healed-ulcer calculations and were not selectively chosen to favor any specific product. However, the available clinical trials may have differed in patient enrollment criteria, wound severity, comparator groups, and treatment protocols. (5) When multiple publications were available for a product, the study most consistent with the 12-week DFU endpoint and suitable for the cost-analysis model was selected.

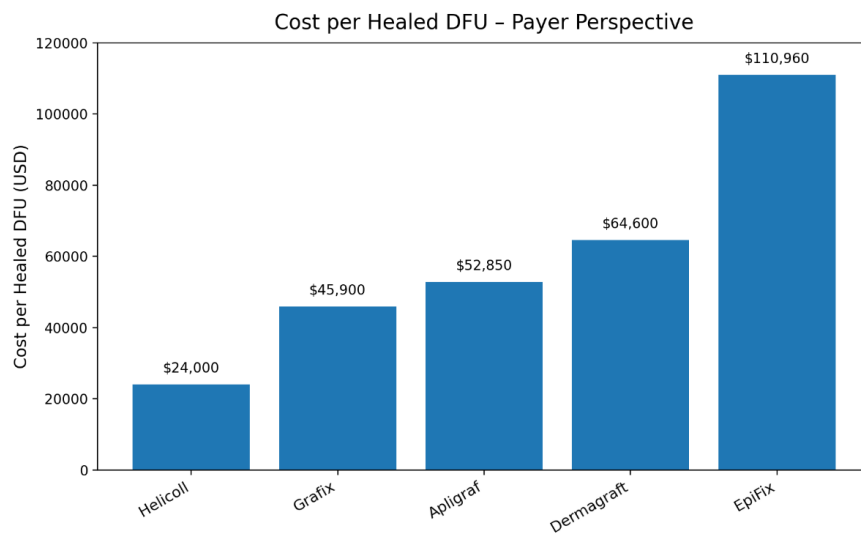


Figure 1. Cost per Healed DFU (Payer Perspective). Bar chart showing the cost per healed DFU for each skin substitute. Helicoll has the lowest cost compared with other products.

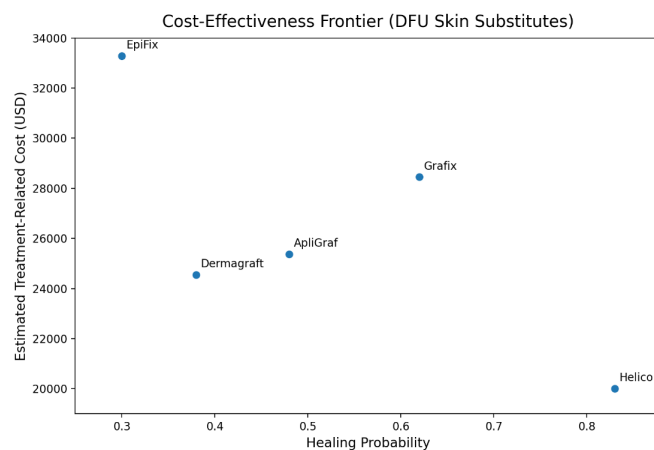


Figure 2. Cost-Effectiveness Frontier for DFU Skin Substitutes. Scatter plot of annual cost per patient versus healing probability at 12 weeks for all products except Helicoll at 5 weeks. Treatments in the lower-right quadrant are more cost-effective. Helicoll shows a favorable balance, with high healing probability and the lowest annual cost.

4. Discussion

4.1. Clinical Interpretation of Descriptive Economic Metrics

From a payer perspective, lower cost per healed ulcer translates into reduced total cost of care and improved allocation of health-care resources. From a clinical standpoint, achieving timely wound closure is associated with reduced risk of infection, fewer clinic visits, and lower likelihood of amputation.

The favorable cost-effectiveness profile observed for Helicoll may be explained by its demonstrated ability to promote early wound area reduction and granulation, as reported in randomized and real-world clinical studies⁸⁻¹⁶ of high-purity type I collagen-based skin substitutes.

This study does not establish comparative clinical superiority or formal cost-effectiveness dominance. Instead, it demonstrates how cost-per-responder metrics are mathematically sensitive to healing probability inputs under CMS reimbursement standardization.

Key Interpretations:

- Cross-trial comparisons are inherently confounded by differences in patient severity, ulcer size, study design, and background standard of care.
- Without head-to-head trials or network meta-analysis, relative effectiveness cannot be conclusively determined.
- Economic rankings derived from unadjusted healing rates should not be interpreted as definitive payer guidance.

4.2. Limitations

This study is limited by reliance on secondary data and modeled assumptions rather than direct head-to-head randomized controlled trials. Real-world outcomes may vary based on patient characteristics, wound severity, and adherence to standard of care. Future prospective studies and registry-based analyses are warranted.

This analysis has several important limitations:

1. It is not a systematic review.
2. No PRISMA-compliant selection framework was implemented and no formal risk-of-bias assessment, probabilistic uncertainty analysis, and quality-adjusted life-year (QALY) modeling was conducted.
3. No adjustment for baseline ulcer size, Wagner grade, or infection status was performed.
4. Healing probabilities were drawn from separate trials with heterogeneous populations, study designs, wound characteristics, and standard-of-care procedures.

Manufacturer affiliation presents a potential conflict of interest and possible risk of selection bias in literature inclusion, cost assumptions, and interpretation of descriptive rankings.

5. The treatment-related cost inputs were obtained from public data and were not independently audited.
6. The analysis does not constitute a network meta-analysis or formal comparative effectiveness evaluation, and no common comparator arm existed across the included studies.

The findings should be interpreted as exploratory and hypothesis-generating economic illustrations rather than definitive comparative cost-effectiveness conclusions. Further validation through independent systematic reviews, registry-based real-world evidence analyses, third-party health economic modeling, and prospective head-to-head clinical trials is warranted.

5. Conclusion

This study presents a transparent cost-per-healed-ulcer framework using published 12-week healing data and standardized CMS reimbursement assumptions. In this preliminary comparative effectiveness and cost-effectiveness study, Helicoll demonstrated clinically meaningful healing outcomes at substantially lower cost compared with other advanced skin substitutes used in DFU management. It does not constitute a formal cost-effectiveness model or systematic comparative effectiveness evaluation.

Future research warrants for:

- PRISMA-compliant systematic review
- Network meta-analysis or head-to-head RCTs
- Probabilistic cost-utility modeling
- Longitudinal recurrence and amputation modeling
- Independent cost validation

■ DECLARATION

■ ACKNOWLEDGMENTS

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Digital Competence in Hospital Classrooms: Educational Practices with Early Childhood Learners

Article Record

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Abstract

Hospital-based classrooms provide a critical means for young children with serious health conditions to continue learning and remain included in educational settings. This study examined digital competency and educational practices in hospital classrooms for early childhood learners in Paraguay. A survey of 500 participants (300 teachers and 200 parents) assessed the use of digital tools, perceptions of their impact on cognitive development, and inclusive pedagogy. Most teachers and parents reported regular use of computers and tablets to deliver personalized instruction. Quantitative analysis (Table 1 and Figure 1) indicates that approximately 86% of participants believed digital tools improved cognitive skills, and 88% viewed technology as enhancing inclusivity. These findings align with literature showing that tablets and touchscreen devices dominate early childhood learning technologies. The results suggest that structured integration of digital tools in hospital classrooms can support young children's cognition and social inclusion (in line with neurodevelopmental principles). We discuss implications for teacher training, curriculum design, and policy to ensure effective and equitable digital learning in health care settings.

digital competence

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cognitive development

inclusive pedagogy

Paraguay

AI USE STATEMENT

No generative AI was used for analysis or results.

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The authors declare no conflict of interest.

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METADATA CONTINUATION

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ARCHIVAL RECORD

Digital Competence in Hospital Classrooms: Educational Practices with Early Childhood Learners

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Abstract

Hospital-based classrooms provide a critical means for young children with serious health conditions to continue learning and remain included in educational settings. This study examined digital competency and educational practices in hospital classrooms for early childhood learners in Paraguay. A survey of 500 participants (300 teachers and 200 parents) assessed the use of digital tools, perceptions of their impact on cognitive development, and inclusive pedagogy. Most teachers and parents reported regular use of computers and tablets to deliver personalized instruction. Quantitative analysis (Table 1 and Figure 1) indicates that approximately 86% of participants believed digital tools improved cognitive skills, and 88% viewed technology as enhancing inclusivity. These findings align with literature showing that tablets and touchscreen devices dominate early childhood learning technologies. The results suggest that structured integration of digital tools in hospital classrooms can support young children's cognition and social inclusion (in line with neurodevelopmental principles). We discuss implications for teacher training, curriculum design, and policy to ensure effective and equitable digital learning in health care settings.

Keywords: *digital competence, hospital classroom, early childhood education, cognitive development, inclusive pedagogy, Paraguay*

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1. Introduction

Digital competence—the integrated set of knowledge, skills, and attitudes that enable the effective, critical, and responsible use of digital technologies—has become a foundational component of contemporary education, including early childhood education. In recent years, international educational frameworks have emphasized that digital competence is no longer optional but a core professional requirement for educators working with young learners, particularly in contexts characterized by vulnerability or exclusion. In developing countries such as Paraguay, structural inequalities in access to technology, connectivity, and teacher training can significantly intensify the educational disruption experienced by children facing prolonged hospitalization. These challenges are compounded by socio-economic disparities, limited institutional resources, and uneven digital infrastructure, which collectively threaten children's right to continuous, equitable, and high-quality education.

Hospital classrooms have emerged globally as a strategic response to these challenges, functioning as inclusive educational environments designed to ensure pedagogical continuity for children undergoing medium- or long-term medical treatment. Unlike conventional school settings, hospital classrooms must accommodate highly heterogeneous learner profiles, including children with chronic illnesses, neurological conditions, and temporary or permanent disabilities. Consequently, educational practices in these settings require a high degree of pedagogical flexibility, individualized instruction, and emotional sensitivity. Teachers working in hospital classrooms are not only responsible for curricular delivery but also

for supporting children's psychological well-being, motivation, and sense of belonging during periods of medical vulnerability.

Early childhood represents a critical window for cognitive, neurological, and socio-emotional development, during which neural plasticity is particularly high. Educational experiences during this stage play a decisive role in shaping executive functions, language acquisition, memory formation, and emotional regulation. For this reason, pedagogical interventions in hospital classrooms must be carefully designed to align with developmental neuroscience principles. Digital media, when appropriately integrated, offer unique affordances for supporting early learning in constrained environments. Interactive digital experiences—such as educational games, digital storytelling, and adaptive learning applications delivered through tablets or touchscreens—have been shown to enhance visual-spatial reasoning, problem-solving abilities, attention regulation, and early literacy skills. These tools can transform abstract concepts into concrete, manipulable experiences, which is particularly beneficial for young learners with limited mobility or reduced access to traditional classroom materials.

However, the educational potential of digital technologies in early childhood is not without risks. A growing body of research cautions that passive, unstructured, or excessive screen exposure may negatively affect attention span, self-regulation, and social interaction, especially when digital use replaces direct human interaction or play-based learning. This dual nature of digital media—simultaneously offering powerful learning opportunities and potential developmental risks—highlights the central role of educator and caregiver digital competence. It is not merely

access to technology that determines educational outcomes, but the pedagogical intentionality, supervision, and contextualization with which digital tools are employed.

In hospital classrooms, this balance becomes even more critical. Children's physical fatigue, emotional stress, and medical routines impose additional constraints on attention and engagement. Consequently, digital technologies must be used strategically to support, rather than overwhelm, young learners. This requires educators and families to possess not only technical skills but also pedagogical and neurodevelopmental understanding of how digital media interact with early learning processes. Digital competence in this context encompasses the ability to select developmentally appropriate tools, design interactive and inclusive learning activities, monitor cognitive and emotional responses, and collaborate effectively with families and healthcare professionals.

Despite the growing relevance of digital competence in hospital-based early childhood education, empirical evidence from Latin American contexts—particularly Paraguay—remains scarce. Existing research has largely focused on mainstream educational settings, leaving hospital classrooms underrepresented in the literature. This study addresses this gap by systematically examining how digital tools are integrated into hospital classrooms in Paraguay and how teachers and parents perceive their impact on children's cognitive development and inclusive engagement.

Specifically, through a survey of 500 participants—comprising hospital classroom teachers and parents of early childhood learners—this study investigates: (1) the prevalence, frequency, and types of digital tools used in hospital-based early childhood education; (2) beliefs and attitudes regarding the influence of digital technologies on children's cognitive and neurodevelopmental outcomes; and (3) the ways in which digital tools are leveraged to promote inclusive learning experiences in contexts of illness and vulnerability. By framing digital competence within internationally recognized educational frameworks and interpreting findings through the lenses of developmental neuroscience and inclusive pedagogy, this research seeks to contribute robust empirical evidence to an emerging field of interdisciplinary inquiry.

2. Literature Review

2.1. Digital Competence in Early Childhood Education

Digital competence has been widely characterized as a vital combination of knowledge, abilities, and attitudes required for the effective, critical, and responsible use of digital technologies in educational contexts. In early childhood education, this concept acquires a distinctive meaning due to the developmental characteristics of young learners and the mediating role of adults. Unlike later educational stages, digital competence in early childhood is not centered on autonomous technology use, but rather on guided, developmentally appropriate interactions that support learning, communication, and socialization. Consequently, digital competence in this stage must be understood as a shared construct involving both educators and children.

For teachers, digital competence encompasses the capacity to select, adapt, and pedagogically integrate digital tools in ways that align with early learning principles, play-based pedagogy, and cognitive development. This includes not only technical proficiency, but also pedagogical judgment, ethical awareness, and the ability to scaffold children's interactions with technology. Teachers are expected to design learning experiences in which digital tools complement, rather than replace, hands-on activities, social interaction, and emotional engagement. For children, digital

competence refers to foundational skills such as basic device interaction, early digital literacy, and the gradual development of digital citizenship, including awareness of safe and responsible use under adult supervision.

Empirical research on digital competence in early childhood education has grown steadily over the past decade. Su and Yang (2024), in their systematic review of 23 empirical studies conducted in early childhood settings, highlight that the majority of investigations focus either on teachers' self-perceived digital competence or on children's observable digital behaviors and learning outcomes. Their analysis indicates that quantitative methodologies—particularly survey-based instruments—are the dominant research approach used to assess levels of competence, frequency of technology use, and perceived pedagogical effectiveness. These studies consistently show that while educators generally express positive attitudes toward digital technologies, variations in competence levels are strongly associated with access to training, institutional support, and contextual factors.

Moreover, existing literature suggests that teachers' digital competence significantly influences the quality of technology integration in early childhood classrooms. Educators with higher levels of digital competence are more likely to employ interactive, learner-centered digital activities that promote cognitive engagement, creativity, and collaboration, whereas lower competence levels are often associated with more limited or superficial uses of technology. This relationship becomes particularly relevant in non-traditional educational environments, such as hospital classrooms, where pedagogical decisions must account for children's health conditions, emotional states, and fluctuating attention capacities.

Despite the growing body of research, most studies reviewed by Su and Yang (2024) are situated in mainstream early childhood education settings, with limited attention given to specialized or inclusive contexts. Hospital classrooms, in particular, remain underexplored in terms of how digital competence is enacted by educators and supported by families. Given the unique constraints and demands of hospital-based education, there is a pressing need to extend existing digital competence frameworks to these environments.

In line with this gap, the present study adopts a quantitative, survey-based approach to examine digital competence and technology use in hospital classrooms for early childhood learners in Paraguay. By collecting structured data from both educators and parents, this research seeks to capture a more comprehensive picture of how digital tools are employed, how competence is perceived, and how these factors interact to shape educational practices in a context characterized by vulnerability, inclusion, and developmental sensitivity.

2.2. Digital Tools and Cognitive Development

A growing body of interdisciplinary research has examined how young children's cognitive development is shaped by exposure to and interaction with digital technologies. From a neurodevelopmental perspective, early childhood represents a sensitive period during which cognitive functions such as attention, memory, executive control, language, and visual-spatial processing undergo rapid maturation. Consequently, the nature and quality of learning experiences during this stage can have lasting effects on neural organization and cognitive trajectories. Digital tools, particularly interactive technologies, have become increasingly prominent in early educational environments, prompting ongoing debate regarding their potential benefits and risks.

Recent narrative and systematic reviews highlight the complex and context-dependent effects of digital media on early cognition. An MDPI narrative review published in 2024 reports mixed outcomes associated with digital device use in young children. On the one hand, well-designed interactive digital media can promote active learning processes, including problem-solving, visual-spatial reasoning, and information processing. On the other hand, unstructured or excessive screen exposure has been linked to cognitive overload, reduced attentional control, and diminished opportunities for social interaction and embodied learning. These contrasting findings underscore a critical conclusion consistently emphasized in the literature: the cognitive impact of digital technologies is determined not by their mere presence, but by how they are pedagogically integrated into learning experiences.

When digital tools are used with clear educational intent, they can support core cognitive processes. Educational applications that translate abstract concepts into concrete, manipulable representations—such as interactive puzzles, simulations, or visual storytelling—have been shown to enhance spatial awareness, early numeracy, and logical reasoning. These tools leverage multimodal input (visual, auditory, tactile), which can strengthen encoding and retention of information, particularly for young learners with diverse learning needs. Moreover, adaptive digital platforms can individualize learning by adjusting task difficulty in response to children's performance, thereby supporting executive functions such as cognitive flexibility and working memory.

Conversely, research consistently warns that passive consumption of digital content, especially when it replaces active play, peer interaction, or adult-guided learning, may negatively affect cognitive and socio-emotional development. Excessive screen time has been associated with shorter attention spans, difficulties in self-regulation, and reduced opportunities for language-rich interaction. From a neurocognitive standpoint, these effects may be explained by reduced engagement of neural systems responsible for sustained attention and social cognition when children are exposed primarily to fast-paced, non-interactive digital stimuli. As such, digital technologies should not function as substitutes for human interaction, but rather as complementary tools embedded within rich pedagogical and social contexts.

These considerations are particularly salient in hospital classrooms, where children's cognitive resources may already be compromised by illness, fatigue, stress, or medical interventions. In such environments, the risk of cognitive overload is heightened, making intentional and developmentally appropriate use of digital media essential. Hospital educators must therefore carefully select digital tools that support short, meaningful learning episodes, allow for frequent breaks, and align with children's fluctuating attention and emotional states. Rather than serving as "babysitting screens," digital technologies in hospital classrooms should be employed as cognitive supports that enhance engagement, motivation, and learning continuity.

Research on digital tools designed for neurodevelopmental needs further illustrates their potential when used appropriately. Recent reviews of educational applications targeting children with neurodevelopmental differences indicate that many digital tools focus on core domains such as language acquisition, social communication, executive functioning, and early literacy. These applications often incorporate visual supports, repetitive practice, and immediate feedback—features known to facilitate learning in children with cognitive or communication challenges. For example, studies published in high-impact medical and educational journals report that digital applications developed for autistic learners frequently

emphasize speech development, pragmatic language skills, and social interaction, demonstrating measurable gains when integrated into structured intervention programs.

Importantly, the effectiveness of such tools is closely linked to adult mediation. Caregivers and educators play a central role in scaffolding children's digital experiences, guiding attention, prompting reflection, and connecting digital content to real-world contexts. This process of joint engagement has been identified as a key mechanism through which digital tools can support cognitive development without displacing essential social and emotional learning. In hospital settings, collaboration between educators, parents, and healthcare professionals becomes particularly important to ensure that digital activities align with both educational and medical priorities.

In sum, the literature suggests that digital tools hold significant potential to support cognitive development in early childhood, provided they are used intentionally, interactively, and within developmentally informed pedagogical frameworks. In hospital classrooms, where educational continuity and cognitive stimulation are critical yet constrained, digital technologies can function as powerful enablers of learning if guided by strong digital competence among educators and families. Understanding how these tools are currently used—and how their use is perceived by key stakeholders—is therefore essential for informing evidence-based practices and policies in hospital-based early childhood education.

2.3. Inclusive Pedagogy and Assistive Technology

Inclusive pedagogy is grounded in the principle that all learners, regardless of health status, disability, or contextual barriers, should have equitable access to meaningful educational experiences. In early childhood education, inclusive pedagogy is commonly operationalized through frameworks such as Universal Design for Learning (UDL), which advocate for flexible approaches to curriculum design, multiple means of representation, expression, and engagement, and the proactive removal of learning barriers. Within this framework, assistive and educational technologies have emerged as critical instruments for fostering inclusion, particularly in environments characterized by high levels of learner diversity, such as hospital classrooms.

Assistive technologies and digital educational tools offer alternative pathways for participation and communication, enabling children who cannot fully engage through traditional instructional methods to access learning opportunities. For example, interactive tablets equipped with speech-generating software can support nonverbal or minimally verbal children by providing functional communication options, thereby enhancing both cognitive engagement and social interaction. Similarly, adaptive educational software allows instructional content to be presented at varying levels of complexity, pace, and modality, accommodating children with diverse cognitive profiles, attention capacities, and learning needs. These technologies are especially valuable in early childhood, where individualized support and multimodal learning experiences are central to development.

Recent research has consistently highlighted the role of educational technology as a key driver of inclusive practice. A systematic review protocol on educational technology in inclusive primary education emphasizes that digital tools have been "instrumental" in reducing learning barriers by offering customizable and accessible learning environments for students with special educational needs. Such tools facilitate differentiated instruction, enable alternative forms of assessment, and support the development of foundational cognitive and communicative skills. Importantly, the literature underscores that assistive technologies are most effective when

integrated into pedagogical strategies rather than used as isolated interventions, reinforcing the need for intentional instructional design.

In hospital classrooms, inclusive pedagogy takes on additional significance due to the compounded challenges faced by learners. Children receiving medical treatment often experience physical limitations, emotional distress, and disrupted social relationships, all of which can impede learning. Digital technologies can play a vital role in mitigating these challenges by sustaining social and cognitive connections. Video conferencing platforms, remote lesson participation, and multimedia content allow hospitalized children to maintain contact with peers, teachers, and familiar learning routines, reducing feelings of isolation and promoting a sense of normalcy. These digital connections are not merely logistical solutions but function as psychosocial supports that contribute to emotional well-being and motivation, which are essential for effective learning.

However, the successful implementation of inclusive digital practices in hospital classrooms is highly dependent on educators' professional competence. Prior research consistently emphasizes that teacher training in both inclusive pedagogy and information and communication technologies (ICT) is a decisive factor in determining the quality of technology integration. Educators who possess strong digital competence are better equipped to select appropriate assistive tools, adapt digital content to individual needs, and monitor children's responses to technology-based interventions. Conversely, limited training or confidence in ICT use may result in underutilization of available tools or reliance on low-level, non-interactive uses of technology.

In this context, digital competence in hospital classrooms extends beyond basic technical proficiency. It encompasses pedagogical expertise in inclusive instruction, ethical awareness of children's vulnerabilities, and the ability to collaborate with families and healthcare professionals. Teachers must be capable of aligning digital tools with individualized education plans, medical constraints, and developmental goals, ensuring that technology serves as a means of empowerment rather than exclusion. Parents, likewise, play a crucial role in reinforcing inclusive digital practices by supporting learning activities at the bedside and facilitating continuity between hospital and home environments.

Overall, the literature suggests that inclusive pedagogy and assistive technology are deeply interconnected in hospital-based early childhood education. When guided by strong digital competence, educational technologies can significantly enhance access, participation, and learning outcomes for hospitalized children with diverse needs. Understanding how educators and families perceive and enact these inclusive digital practices is therefore essential for advancing evidence-based approaches to hospital education and ensuring that no child is excluded from meaningful learning opportunities due to illness or disability.

2.4. Hospital Classrooms and Early Childhood Education

Children affected by serious or chronic illnesses frequently experience prolonged absences from formal schooling, resulting in significant educational discontinuity and heightened risk of academic delay, social exclusion, and emotional distress. These interruptions are particularly critical during early childhood, a developmental stage characterized by rapid cognitive, linguistic, and socio-emotional growth. When educational experiences are disrupted during this sensitive period, children may face long-term consequences in learning trajectories, self-esteem, and school reintegration. As a result, the provision of educational services within healthcare

settings has increasingly been recognized as both an educational necessity and a fundamental child right.

Hospital classrooms—educational units embedded within health-care facilities—have emerged internationally as an innovative response to these challenges. As Wang and Yang (2025) describe, hospital schools provide structured, individualized curricula alongside psychological and emotional support tailored to the needs of hospitalized children. These programs are designed not only to maintain academic continuity but also to support children's well-being by preserving daily routines, fostering a sense of normalcy, and sustaining connections with schooling and peers. Although Wang and Yang's analysis focuses on the Chinese context, the underlying principle is universal: access to education during medical treatment is an essential component of children's rights and holistic care.

From an early childhood education perspective, hospital classrooms must address a unique constellation of pedagogical demands. Unlike mainstream classrooms, hospital learning environments are shaped by medical schedules, fluctuating health conditions, and limited physical space. Instruction often occurs at the bedside or in small-group settings, requiring highly individualized approaches that are responsive to children's cognitive capacities, emotional states, and physical endurance. Educators in hospital classrooms therefore operate at the intersection of education, healthcare, and psychosocial support, adapting curricula and instructional strategies to accommodate each child's circumstances.

Digital technologies have increasingly been positioned as key enablers within hospital-based early childhood education. Through digital tools, hospital classrooms can extend learning beyond physical constraints, offering flexible and adaptive instructional resources that can be tailored to individual needs. Interactive applications, digital storytelling, and multimedia content can provide cognitive stimulation even when traditional materials are impractical. Moreover, communication technologies—such as video conferencing and virtual classroom platforms—enable hospitalized children to maintain social and academic connections with their regular schools, mitigating feelings of isolation and supporting smoother reintegration upon recovery.

In Paraguay, empirical research on hospital classrooms remains limited, and systematic data on pedagogical practices within these settings are scarce. Nevertheless, the country has undertaken initiatives aimed at promoting inclusive education through digital means, such as the development and dissemination of accessible digital textbooks and technology-supported learning resources. These initiatives reflect broader policy commitments to educational inclusion and digital transformation, yet their implementation and impact within hospital classrooms have not been sufficiently examined. Understanding how such resources are actually used by educators and families in hospital contexts is therefore essential for evaluating their effectiveness and identifying areas for improvement.

The present study addresses this gap by providing empirical evidence on the integration of digital technologies in Paraguayan hospital classrooms serving early childhood learners. By capturing the perspectives of both educators and parents, this research offers insight into current practices, perceived benefits, and ongoing challenges related to digital learning in healthcare-based educational settings. In doing so, it contributes to the international literature on hospital education by foregrounding a Latin American context and highlighting the role of digital competence in supporting learning continuity, cognitive development, and inclusion for young children experiencing illness.

3. Methodology

3.1. Participants and Setting

This cross-sectional survey study involved 500 participants from hospital-based early childhood programs in Paraguay. Of these, 300 were teachers or instructional staff in pediatric hospital classrooms, and 200 were parents of children enrolled in those programs. Participants were recruited through hospital education networks in urban and rural Paraguay. Teachers had an average of 8.4 years (SD 5.6) of experience teaching in hospital or special settings; parents had children aged 3–6 years receiving hospital instruction. Efforts were made to obtain a representative sample across socio-economic strata.

3.2. Survey Instrument

A 25-item questionnaire was developed, covering demographics, digital resource usage, and perceptions of technology's impact on learning. Key sections included:

- **Demographics:** Age, gender, years of experience (for teachers) or child's age (for parents), formal training in ICT.
- **Digital Usage:** Frequency of using specific devices (tablets, laptops, smartphones) in classroom/home learning.
- **Attitudes:** Likert-scale items assessing agreement with statements such as "Using digital tools improves children's cognitive development" and "Technology makes the classroom more inclusive for children with different needs."
- **Open Responses:** Brief questions on barriers (e.g. connectivity, resources) and best practices in using technology.

The survey combined quantitative (yes/no, Likert scales) and qualitative items. It was reviewed by an expert panel in special education and piloted for clarity (Cronbach's $\alpha = 0.82$ for attitude scales). Data were collected anonymously via paper forms and secure online links.

3.3. Data Analysis

Survey data were entered into SPSS (v27). Descriptive statistics (means, frequencies) characterized the sample (Table 1). Comparisons between teacher and parent responses were examined using chi-square tests for categorical items and t-tests for Likert scale ratings. We also performed simple correlation analyses between frequency of technology use and positive attitude scores. For all tests, $p < 0.05$ was considered significant. Data visualization was done with Excel.

Table 1 summarizes participant demographics and key digital competence metrics. Items such as "formal ICT training" and "weekly use of digital tools" are expressed in percentages. Open-ended responses were thematically coded to supplement quantitative findings.

Characteristic	Teachers (n=300)	Parents (n=200)	Total (n=500)
Mean age, years (SD)	35.7 (8.2)	33.2 (7.5)	34.8 (7.9)
Formal ICT training (yes, %)	65% (195)	30% (60)	50% (255)
Use digital tools weekly (yes, %)	90% (270)	75% (150)	84% (420)
Agree digital tools improve cognitive development (%)	88% (264)	82% (164)	86% (428)
View technology as enhancing inclusion (yes, %)	92% (276)	80% (160)	88% (436)

Table 1. Participant demographics and digital competence indicators (N=500).

Note: Percentages may not sum to 100% due to rounding. All participants had some access to Internet-connected devices either at home or in hospital classrooms.

4. Results

Most participants reported regular engagement with digital tools in the hospital education context. Specifically, 90% of teachers and 75% of parents indicated they used digital devices at least weekly during instruction or learning. The most commonly used devices were tablets (85% teachers, 70% parents) and laptops/computers (80% teachers, 65% parents); smartphones were used less frequently (45% teachers, 50% parents) due to their smaller screens. These distributions mirror broader trends in early education technology, where tablets often dominate child-centered apps.

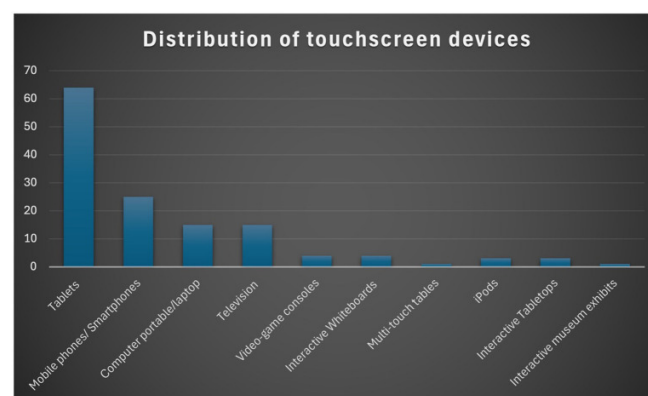


Figure 1. Distribution of touchscreen devices in reviewed studies of child learning (adapted from Truci et al., 2024). Tablets were used in 64 out of 157 studies, far exceeding other categories. This aligns with our context, where tablets were the primary platform for educational apps.

Table 1 summarizes demographic and competence-related characteristics. Teachers were significantly more likely than parents to have formal ICT training (65% vs. 30%, $\chi^2(1) = 58.3$, $p < 0.001$). Both groups were overwhelmingly positive about the educational value of technology: 86% of all respondents agreed that digital tools improve cognitive development. Teachers reported slightly higher agreement (88%) than parents (82%), but this difference was not statistically significant ($\chi^2(1) = 2.5$, $p = 0.11$). Similarly, 88% overall believed technology made learning more inclusive, with teachers again more affirmative (92% vs. 80%, $\chi^2(1) = 12.4$, $p < 0.001$).

In terms of cognitive outcomes, a majority of participants observed concrete benefits. For example, 75% noted that interactive apps (e.g. language-learning games) increased children's engagement, and 70% reported improvements in skills like memory and problem-solving attributable to digital activities. However, about 20% of respondents (mostly parents) expressed concerns about potential overuse. The mean cognitive development agreement score (on a 5-point scale) was 4.2 (SD 0.7) for teachers and 3.9 (SD 0.8) for parents, a small but significant difference ($t(498) = 3.5$, $p = 0.0005$).

We also explored the relationship between teachers' digital competence and perceived outcomes. Among teachers, those with formal ICT training gave higher ratings to cognitive benefits (mean 4.3) than untrained teachers (mean 3.8, $t(298) = 4.2$, $p < 0.001$). This suggests that greater teacher digital competence may amplify positive educational effects.

5. Discussion

Our findings indicate that digital tools are widely used and positively regarded in Paraguay's hospital classrooms for young children. The high prevalence of tablet and computer use, and the strong endorsement of technology for cognitive development (86% agreement), align with recent literature on early childhood technology. As

Truci et al. (2024) showed, tablets are by far the most common devices in research on touchscreen learning; we similarly found tablets to be primary platforms for education. The predominance of tablets likely reflects their portability, engaging interfaces, and large screens suitable for small hands. This is consistent with other studies noting that interactive tablets provide tangible ways to grasp abstract concepts, potentially improving spatial and problem-solving skills.

The overwhelmingly positive attitude toward digital inclusion (88% agreement) suggests stakeholders view technology as a key inclusion tool. This resonates with broader research on assistive technology in inclusive education: ICT can overcome barriers by offering multiple modes of representation and communication. For example, educators reported using tablet apps to deliver curricula at different levels of difficulty and using video calls to connect hospitalized children with classmates. These practices parallel inclusive pedagogy principles and the use of assistive devices to help children with special needs “meet the same outcomes as their typically developing peers”.

Importantly, our data hint at the link between digital competence and outcomes. Teachers with ICT training observed greater benefits for cognitive development. This echoes the global finding that teacher preparedness is crucial: as one study noted, educators with structured ICT training are more confident and effective in applying inclusive digital pedagogy. In other words, having the tools is not enough – educators must know how to integrate them pedagogically. Our results suggest investment in teacher professional development could magnify the cognitive and inclusive gains of technology in hospital schools.

These findings also intersect with developmental neuroscience. Although our context is educational, neurological research provides supportive insight. For example, Barton (2025) reports that interventions enhancing neuroplasticity can influence cognitive outcomes in patients. Analogously, educational technologies that stimulate neural circuits (through interactive play or language apps) may enhance synaptic development and learning. This cross-disciplinary view reinforces that the school and brain perspectives on cognitive development can be aligned when technology use is goal-directed and structured.

We must also consider limitations. The survey relies on self-report, which can inflate positive perceptions. Additionally, while our sample is large, it is limited to Paraguay and may not generalize to all Latin American contexts. Paraguay’s digital infrastructure, for instance, is intermediate (internet access around 60% of households), which may differ from other countries. However, the consistencies with international patterns (e.g. heavy tablet use, teacher training effects) suggest that many findings could apply more broadly.

6. Conclusion

This study provides one of the first systematic and empirically grounded examinations of digital competence in hospital classrooms serving early childhood learners within the Paraguayan context. By incorporating the perspectives of both educators and parents, and drawing on data from 500 real-world participants, the research offers a comprehensive view of how digital technologies are currently integrated into hospital-based early childhood education and how they are perceived in terms of cognitive and inclusive outcomes.

The findings demonstrate that digital tools—particularly tablets and interactive digital applications—are widely used and highly valued as educational supports in hospital classrooms. Both teachers and parents perceive technology as a meaningful resource for

sustaining learning continuity, enhancing cognitive engagement, and mitigating the social isolation often experienced by hospitalized children. These results reinforce existing international evidence suggesting that, when used intentionally and under adult guidance, digital technologies can contribute positively to early cognitive development, including attention regulation, problem-solving, and language-related skills.

At the same time, the study highlights that the educational impact of digital tools is closely linked to the level of digital competence among educators and caregivers. Participants with prior training in information and communication technologies and inclusive pedagogy reported more sophisticated and purposeful uses of digital resources. This finding underscores that access to technology alone is insufficient; rather, effective integration depends on educators’ ability to align digital tools with developmental, pedagogical, and neurocognitive principles. In hospital classrooms—where children’s cognitive and emotional capacities may fluctuate due to illness—this alignment becomes particularly critical.

Based on the results, several key implications emerge. First, enhanced and continuous teacher training is essential. Specialized professional development programs focused on digital competence, inclusive pedagogy, and early neurodevelopment should be implemented for hospital educators, enabling them to design interactive, developmentally appropriate learning experiences that fully leverage the pedagogical potential of digital tools. Second, curriculum integration must be strengthened through the development and dissemination of age-appropriate digital content—such as educational games, multimedia stories, and adaptive learning activities—explicitly aligned with early cognitive goals and designed to promote active, rather than passive, screen engagement.

Third, inclusive strategies should be systematically incorporated into hospital classroom practices. Digital technologies can function as powerful bridges for children with health-related disabilities or communication challenges by supporting alternative forms of expression, participation, and social interaction. Tools such as communication applications, virtual classroom connections, and assistive learning software are particularly valuable in promoting equity and inclusion within healthcare-based educational settings. Finally, policy-level support is crucial. Recognizing hospital education as an integral component of national education systems would facilitate sustained investment in digital infrastructure, connectivity, teacher training, and research, ensuring the long-term viability and quality of these programs.

In sum, the findings of this study position digital competence as a central pillar of inclusive pedagogy in hospital-based early childhood education. When guided by informed pedagogical judgment and supported by institutional and policy frameworks, digital technologies can play a transformative role in nurturing the cognitive development, emotional well-being, and educational inclusion of young patients. Future research should build on these findings by exploring longitudinal outcomes of digital interventions, examining children’s direct cognitive and socio-emotional responses to technology use, and further refining evidence-based models for digital learning in hospital classrooms.

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Modelo CAFE – Funções Executivas Como Catalisador Na Terapia Fonológica: Um Estudo Piloto Randomizado e Controlado

CAFE Model - Executive Functions as a Catalyst in Phonological Therapy: A Randomized Controlled Pilot Study

Article Record

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Abstract

Objective: To compare the clinical efficacy of two therapeutic intervention models for Speech Sound Disorders (SSD): the traditional Cycles model and the Cycles Associated with Executive Functions (CAFE) model, which integrates cognitive stimulation into phonological treatment.

Method: A Randomized Controlled Pilot Study. The sample included nine children (aged 6 to 8 years) diagnosed with PD, divided into a Control Group (CG, n = 4, Cycles model) and an Experimental Group (EG, n = 5, CAFE model). The intervention lasted 15 weeks. The Percentage of Consonants Correct (PCC), phonetic inventory and phonological processes were analyzed. Statistical analysis included hypothesis testing and effect size (Cohen's d).

Results: Both groups showed improvement in PCC. However, the EG demonstrated a more robust and uniform therapeutic response: 100% of the participants shifted to the Moderate severity level, while 50% of the CG remained at their initial severity level.

Conclusion: The CAFE model proved to be a promising catalyst for phonological reorganization. The integration of executive functions into speech therapy optimizes the stabilization of new phonemic patterns, suggesting that cognitive support is essential to overcome the linguistic processing "bottleneck" in children with PD

Child Language

Executive Function

pilot study

Rehabilitation of Speech and Language Disorders

Speech Sound Disorder

AI USE STATEMENT

No generative AI was used for analysis or results.

FUNDING

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CONFLICT OF INTEREST

Nada a declarar.

DATA AVAILABILITY

Os autores gostariam de agradecer à Coordenação de Aperfeiçoamento...

ETHICS

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CONSENT

Not applicable for this article.

TRIAL REG.

Not applicable.

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FULL DATA AVAILABILITY STATEMENT

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FULL ETHICS STATEMENT

O estudo foi aprovado pelo Comitê de Ética em Pesquisa da Universidade proponente sob número 5.754.344.

ARCHIVAL RECORD

Modelo CAFE – Funções Executivas Como Catalisador Na Terapia Fonológica: Um Estudo Piloto Randomizado e Controlado

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Abstract

Objetivo: Comparar a eficácia clínica de dois modelos de intervenção terapêutica para o Transtorno Fonológico (TF): o modelo de Ciclos tradicional e o modelo Ciclos Associado às Funções Executivas (CAFE), que integra a estimulação cognitiva ao tratamento fonológico. **Método:** Estudo piloto controlado e randomizado. A amostra incluiu nove crianças (6 a 8 anos) diagnosticadas com TF, divididas em Grupo Controle (GC, n = 4, modelo de Ciclos) e Grupo Experimental (GE, n = 5, modelo CAFE). A intervenção durou 15 semanas. Foram analisados o Percentual de Consoantes Corretas (PCC), inventário fonético e processos fonológicos. A análise estatística incluiu testes de hipótese e o tamanho do efeito (d de Cohen).

Resultados: Ambos os grupos apresentaram melhora no PCC. Contudo, o GE demonstrou uma resposta terapêutica mais robusta e uniforme: 100% dos participantes migraram para o grau de severidade Médio, enquanto 50% do GC mantiveram o grau inicial. **Conclusão:** O modelo CAFE demonstrou ser um catalisador promissor para a reorganização fonológica. A integração das funções executivas à terapia de fala otimiza a estabilização de novos padrões fonêmicos, sugerindo que o suporte cognitivo é essencial para superar o “gargalo” do processamento linguístico em crianças com TF.

Keywords: *Linguagem Infantil, Transtorno Fonológico, Reabilitação dos Transtornos da Fala e da Linguagem, Função Executiva, Estudo Piloto*

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1. INTRODUÇÃO

O Transtorno Fonológico (TF) caracteriza-se como uma alteração específica de linguagem de etiologia idiopática, que se manifesta por um desempenho fonológico inferior ao esperado para a idade cronológica da criança¹. Clinicamente, crianças com TF apresentam fala espontânea marcada por erros na produção de sons consonantais, apesar de possuírem limiares auditivos normais, ausência de disfunções orgânicas relevantes, habilidades cognitivas preservadas e compreensão oral íntegra².

No cenário da clínica fonoaudiológica, diversos modelos de intervenção de base fonológica têm sido propostos com o objetivo de promover a aquisição e a reorganização dos padrões fonêmico³. Todavia, evidências demonstram que a efetividade desses modelos, quando comparados entre si, apresenta resultados muito semelhantes em termos de evolução fonológica^{4,5}. Essa equivalência terapêutica sugere uma estagnação no aprimoramento das metodologias existentes, evidenciada pela escassez de publicações recentes voltadas à inovação dos protocolos de intervenção.

O objetivo primordial da terapia para o TF é favorecer a reorganização do Sistema Fonológico (SF). Para que a criança desenvolva consciência sobre as características dos sons, a repetição sistemática é necessária até que o padrão seja generalizado para a fala espontânea⁴. Para que esse processo ocorra, é necessária a repetição sistemática dos padrões-alvo, associada à capacidade de monitorar a própria

produção. No entanto, essa transição entre o padrão desviado e o padrão esperado impõe demandas cognitivas importantes à criança. Tal transição exige que o indivíduo manipule informações mentalmente, resista a distrações e iniba padrões de fala habituais - competências que dependem diretamente da flexibilidade cognitiva, memória de trabalho e controle inibitório, as chamadas Funções Executivas (FEs)⁶.

As FEs constituem um conjunto integrado de habilidades cognitivas complexas que orientam o comportamento em direção a metas estabelecidas. Suas três dimensões principais são: a memória de trabalho, que permite o armazenamento e a manipulação temporária de informações; o controle inibitório, que regula a atenção e evita impulsos automáticos; e a flexibilidade cognitiva, que possibilita a análise de uma mesma informação sob diferentes perspectivas. A interface entre a linguagem e as FEs reside na intencionalidade; quando conscientes, esses processos controlam as ações humanas em sinergia com o sistema comunicacional⁷.

Assim como a linguagem, o desenvolvimento das FEs é suscetível a desvios que podem comprometer a autonomia do indivíduo. Por outro lado, o treinamento dessas funções pode atuar como acelerador do desempenho global. Em outros distúrbios de linguagem, a estimulação das FEs já demonstrou otimizar o tempo terapêutico e o desempenho clínico, o que levanta o questionamento sobre a eficácia de integrar tais atividades ao tratamento convencional do TF⁸.

Diante dessa lacuna, o presente estudo propõe a criação do modelo Ciclos Associado às Funções Executivas (CAFE). O objetivo é comparar a efetividade de dois modelos de intervenção: o modelo de Ciclos convencional e o modelo CAFE, cuja premissa estrutural mantém a base fonológica tradicional, acrescida de atividades específicas para estimulação das FEs.

2. MÉTODO

2.1. Delineamento do Estudo e Ética

Trata-se de um estudo piloto controlado e randomizado e de abordagem quantitativa, com alocação aleatória dos participantes em dois grupos de intervenção. A pesquisa foi aprovada pelo Comitê de Ética em Pesquisa da instituição de origem (Protocolo nº 5.754.344) e registrada no Registro Brasileiro de Ensaios Clínicos (ReBEC U1111-1314-9744), em conformidade com a Resolução 466/12 do Conselho Nacional de Saúde. Todos os responsáveis assinaram o Termo de Consentimento Livre e Esclarecido (TCLE), o Termo de Autorização de Coleta e Uso de Áudio e Vídeo (TACUAV) e as crianças receberam para a leitura ou conhecimento o Termo de Assentimento (TA).

2.2. Participantes e Critérios de Elegibilidade

A amostra foi constituída por conveniência, composta por nove crianças com diagnóstico de TF na faixa etária entre 6 e 8 anos, de ambos os sexos.

Os critérios de inclusão foram:

- Diagnóstico clínico de TF confirmado por fonoaudiólogos especialistas;
- Limiares auditivos dentro dos padrões de normalidade;
- Desempenho intelectual compatível com a idade cronológica;
- Ausência de diagnósticos neurológicos, psiquiátricos ou sensoriais associados.

Os critérios de exclusão compreenderam:

- Participação prévia em terapia fonoaudiológica de base fonológica nos seis meses antecedentes;
- Presença de anomalias anatômicas nos órgãos fonoarticulatórios que impedissem a produção dos sons.

2.3. Randomização

A aleatoriedade dos grupos foi realizada pelos pesquisadores e garantida pela função “aleatório entre” na ferramenta Planilhas Google, por meio de uma randomização com minimização pelo grau de severidade de fala para garantir melhor homogeneidade na amostra. Foram considerados os percentuais de produção correta de consoantes entre 51% e 85%, que indicam os graus de severidade médio-moderado (MM) e moderado-severo (MS), excluindo os graus médio ($\geq 86\%$) e severo ($50\% \leq$).

2.4. Procedimentos de Avaliação (Pré e Pós-Intervenção)

Todos os participantes foram submetidos a uma bateria de avaliações padronizadas antes e após 15 semanas de intervenção com dosagem semanal.

1. Avaliação Fonológica: Utilizou-se o Instrumento de Avaliação Fonológica (IAF)¹, o cálculo do Percentual de Consoantes

Corretas (PCC)² – total de consoantes corretas / total de consoantes x 100 – para determinação do grau de severidade do TF, inventário fonético e análise de processos fonológicos.

2. Avaliação da Linguagem: Instrumento PADOL³ e Audibilização⁴

3. Avaliação da Motricidade Oral: Aplicou-se somente as tarefas de aparência e condição postural/posição, mobilidade e funções do Protocolo de Avaliação Miofuncional Orofacial com Escores (AMIOFE)⁵.

4. Avaliação auditiva: Para avaliação da Audiometria Tonal Limiar (ATL)⁶, foram testadas apenas as frequências fundamentais de fala – 500hz, 1khz, 2khz, 4khz – em VA. VO foi testada, também nas frequências fundamentais, somente em casos de *gap*. A avaliação do Limiar de Reconhecimento de Fala (LRF)⁷ foi aplicada com figuras.

2.5. Protocolos de Intervenção

Os participantes foram alocados em dois grupos; Grupo Controle (GC, $n = 4$): Submetidos ao Modelo de Ciclos tradicional de Hodson & Paden (1937)⁹. O foco residiu na estimulação de fonemas-alvo por meio de bombardeio auditivo, produção de palavras-alvo e consciência fonológica; e Grupo Experimental (GE, $n = 5$): Submetidos ao Modelo CAFE (Ciclos Associado às Funções Executivas). Este protocolo manteve a estrutura de Ciclos, porém integrou, em cada sessão, 15 minutos de atividades específicas de estimulação das FEs (ex: jogos de regras para controle inibitório e tarefas de alternância para flexibilidade cognitiva extraídas do Programa de Estimulação Neuropsicológica da Cognição em Escolares: Ênfase em Funções Executivas – PENCE¹⁰), vinculadas ao contexto linguístico dos fonemas-alvo. O fonema-alvo das crianças, de ambos os grupos, foi determinado com o Modelo Implicacional de Complexidade de Traços (MICT)¹¹, de acordo com necessidades e perfil fonológico de cada criança. Para estimular a aquisição do som-alvo durante as 15 sessões, foram selecionadas 40 palavras, segmentadas em quatro ciclos, com 10 palavras cada. Os ciclos um, dois e três foram compostos de quatro semanas e o ciclo quatro, de três.

As sessões ocorreram uma vez por semana, com duração de 40 minutos cada, totalizando 15 sessões. As avaliações e a análise dos dados foram realizadas por examinadores cegos quanto ao grupo de alocação dos sujeitos.

2.6. Análise Estatística

Os dados foram organizados em planilhas no *Google Drive* e processados pelo *software* SPSS versão 25. A normalidade da amostra foi testada, e foram aplicados os testes:

²PCC – SHRIEBERG, L. D., AUSTIN, D., LEWIS, B. A., MCSWEENEY, J. L. and WILSON, D. L., 1997a, The percentage of consonants correct (PCC) metric: extensions and reliability data. *Journal of Speech, Language and Hearing Research*, 40, 708–722.

³PADOL – Alves GS, Botura C, Bernardi ACS, Ribas LP. Protocolo de Avaliação de Domínios Linguísticos – PADOL. 2014.

⁴Audibilization – Golbert CS, Silveira, F. Measurement of Audibilization in Children in the Initial Phase of Reading Learning: construction and validation of an instrument. *Education and Selection*. 1988;17:99-113.

⁵AMIOFE: Felício CM, Ferreira CL. Protocol of orofacial myofunctional evaluation with scores. *International Journal of Pediatric Otorhinolaryngology*. 2008;74(3):367-375.

⁶ATL: Souza LF, Braga, GRAB, Mota ALR, Zamberlan-Amorim NE, Reis ACMB. Construction and applicability of a speech perception test with figures. *CoDAS* 2016;28(6): 758-69. <https://doi.org/10.1590/2317-1782/20162015224>.

⁷LRF: Momensohn-Santos TM, Russo ICP, Assayag FM, Lopes LQ. Determination of tonal thresholds by air and bone conduction. In: Momensohn-Santos TM, Russo ICP. *Clinical audiology practices*. São Paulo: Cortez; 2009. 67-95. / Brunner AP, Redondo MC. Clinical audiological evaluation of infants and children. In: Levy CCAC. *Manual of pediatric audiology*. São Paulo: Barueri: Manole; 2022. 63-92.

¹IAF – Ribas, LP et al. Instrumento de Avaliação Fonológica: evidência de fidedignidade. *CoDAS*. 2024;36(1):e20220303.

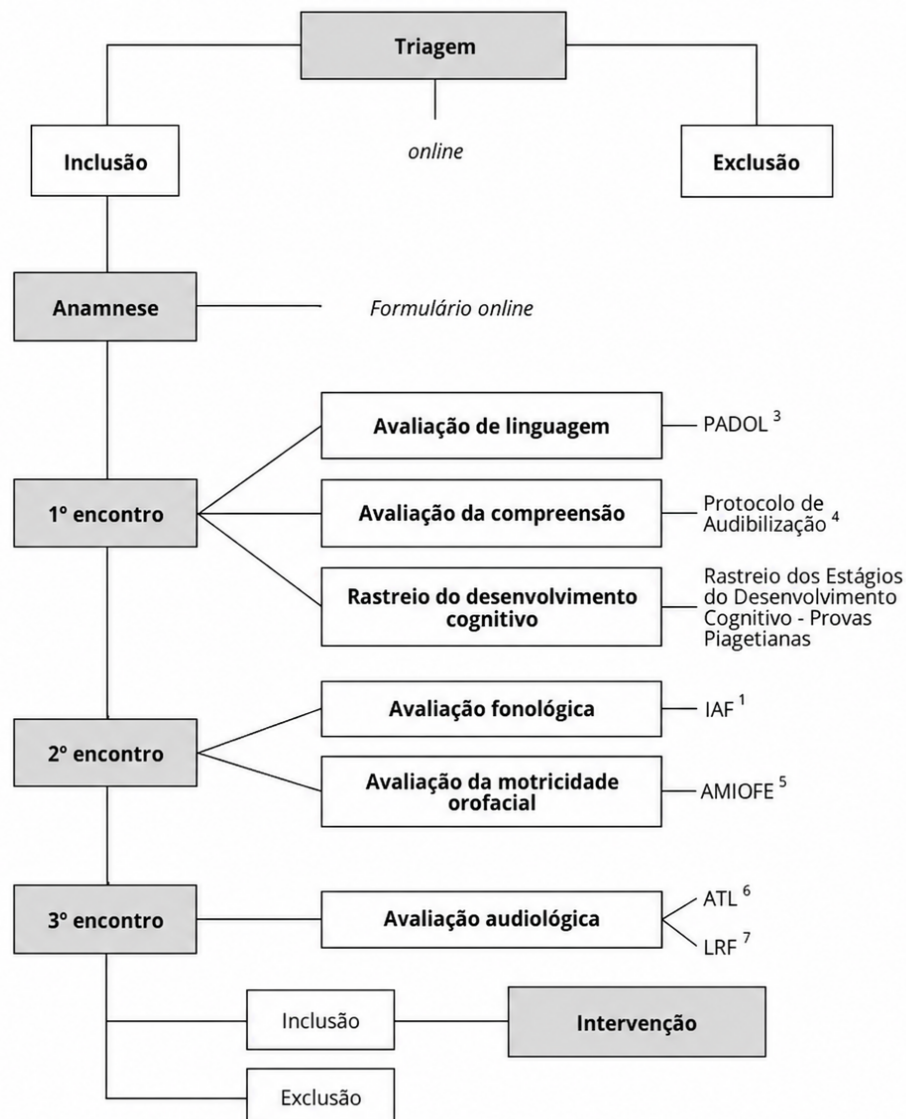


Figure 1. Fluxograma pré-Intervenção. Obs: as citações indicadas de 1 a 7 correspondem exclusivamente aos protocolos informados como citação na página quatro e cinco. (Fonte: pesquisadores)

- testes *t* de *Student* para dados pareados e *McNemar* para comparar as diferenças pré e pós em cada grupo;
- testes *t* de *Student*, Exato de *Fisher* e Qui-Quadrado para a comparação das variáveis com uma avaliação e da avaliação pós entre os grupos;
- Tamanho do Efeito (*d* de Cohen): Utilizado para mensurar a magnitude da mudança clínica. Os valores foram interpretados como: pequeno (0,20), médio (0,50) e grande ($\geq 0,80$).

O nível de significância estatística foi estabelecido em $p < 0,05$.

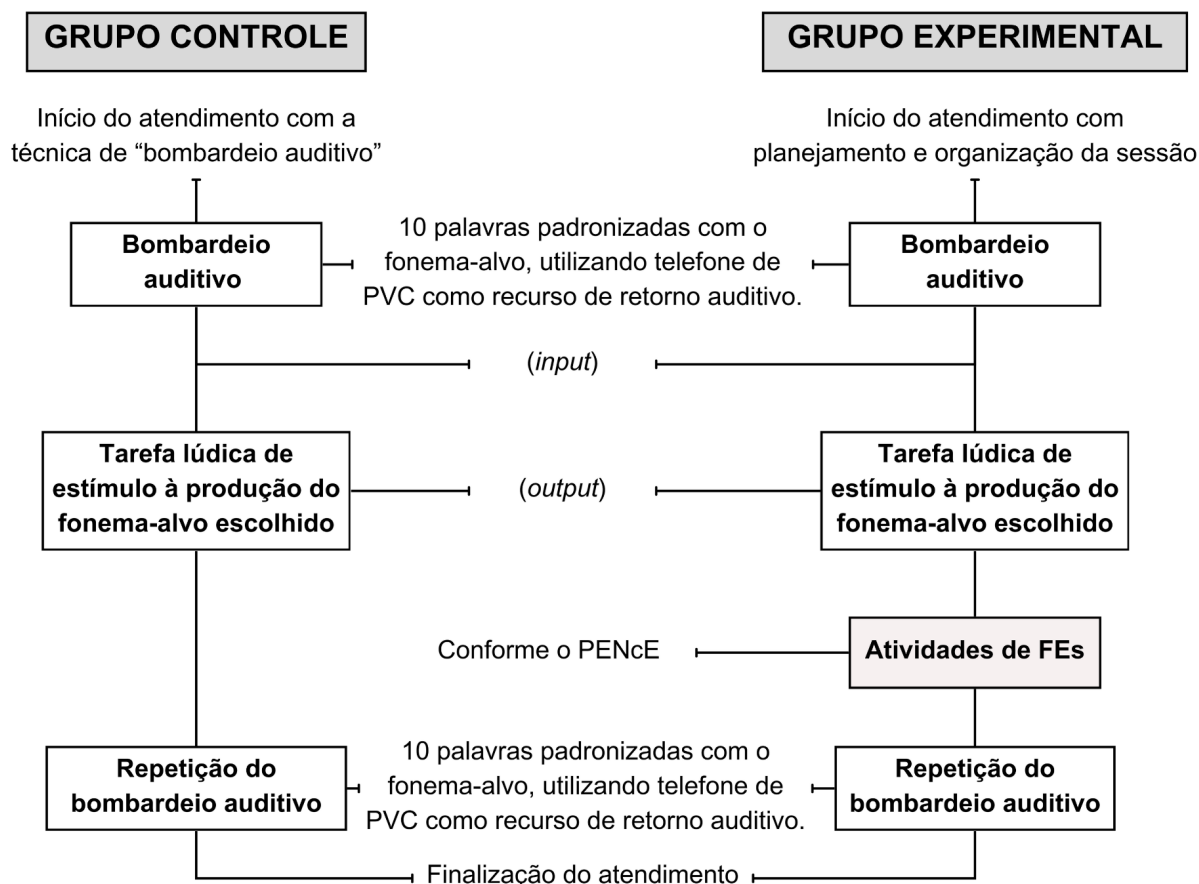


Figure 2. Estrutura das sessões (Fonte: pesquisadores)

3. RESULTADOS

Os resultados deste estudo trouxeram considerações importantes em relação a caracterização da gravidade do TF; ao PCC; aos processos fonológicos; ao tamanho de efeito e ao desempenho fonológico associado as funções executivas.

3.1. Caracterização da Gravidade e Evolução do PCC

A análise inicial do PCC revelou que ambos os grupos apresentaram incremento nos índices de correção fonológica após 15 semanas de intervenção. Contudo, a trajetória de melhora qualitativa foi distinta entre as abordagens. No GE, observou-se uma evolução uniforme na gravidade do transtorno: 100% dos participantes ($n = 5$) migraram para o grau "Médio" de severidade. Em contrapartida, no GC, apenas 50% ($n = 2$) apresentaram evolução de grau, enquanto a outra metade da amostra permaneceu no nível de severidade inicial, indicando uma resposta terapêutica mais heterogênea no modelo de Ciclos convencional.

3.2. Dinâmica dos Processos Fonológicos e Inventário Fonético

Quanto à simplificação das regras fonológicas, o GE demonstrou uma redução sistemática em todos os processos fonológicos analisados. No GC, verificou-se um fenômeno de estagnação e, em casos isolados, o aumento do número de processos no pós-intervenção, sugerindo dificuldades na estabilização do sistema fonológico sem o suporte das funções executivas.

No que tange à aquisição de fonemas-alvo estabelecidos no planejamento terapêutico, o modelo CAFE apresentou uma taxa de sucesso de 80%, superando significativamente os 50% de aquisição observados no modelo tradicional. Esse ganho refletiu-se diretamente na expansão do inventário fonético, especialmente na posição de *Onset Simples*.

3.3. Análise do Tamanho do Efeito

Devido à natureza piloto deste estudo, a magnitude das mudanças clínicas foi detalhada através do *d de Cohen*, revelando dados de alta relevância para a prática baseada em evidências. Conforme apresentado na Tabela 3, o GE obteve tamanhos de efeito considerados grandes em posições silábicas críticas:

- **Onset Simples Inicial (OSI):** $d = 1,26$ (GE) vs. $d = 0,87$ (GC);
- **Onset Simples Medial (OSM):** $d = 3,00$ (GE) vs. $d = 0,39$ (GC).

A disparidade nos valores de *d* para o *Onset Simples Medial* destaca a potência do modelo CAFE em promover a generalização da aprendizagem em posições de maior complexidade de monitoramento cognitivo.

3.4. Funções Executivas e Desempenho Fonológico

A correlação entre o ganho fonológico e o desempenho executivo foi evidente nas tarefas de memória de trabalho e controle inibitório. Os participantes do GE que apresentaram os maiores índices de redução de processos fonológicos foram os mesmos que demonstraram

Fonologia			GC (CP1, CP6, CP7, CP8)				GE (EP2, EP3, EP4, EP5, EP9)				p-valor
	Idade ¹	média±DP	n (%)				n (%)				
	Sexo ²	Masculino	6.8±1				6.6±0.9				0,815
		Feminino <td colspan="4">3 (75%)</td> <td colspan="4">4 (80%)</td> <td>1,000</td>	3 (75%)				4 (80%)				1,000
	Componente Fonético ²	Sim <td colspan="4">1 (25%)</td> <td colspan="4">1 (20%)</td> <td rowspan="2">0,524</td>	1 (25%)				1 (20%)				0,524
		Não <td colspan="4">2 (50%)</td> <td colspan="4">1 (20%)</td>	2 (50%)				1 (20%)				
			2 (50%)				4 (80%)				
Fonema-alvo selecionado		CP1	CP6	CP7	CP8	EP2	EP3	EP4	EP5	EP9	
Nível MICT ¹	média±DP	/g/	/R/	/r/	/ʃ/	/k/	/r/	/R/	/ʒ/	/r/	
		4	9	8	7	9	8	9	7	8	
			7±2.2				8.2±0.8				0,286

Table 1. Perfil dos participantes randomizados nos GC e GE

*p-valor<0,05.¹ Teste t de Student. ²Teste Exato de Fisher. Legenda: DP=Desvio-padrão, MICT=Modelo Implicacional de Complexidade de Traços, GC=Grupo Controle, GE=Grupo Experimental, CP=Controle Participante, EP=Experimental Participante.

		Modelo de Ciclos GC				Modelo CAFE GE				p-valor	d ²
		CP1	CP6	CP7	CP8	EP2	EP3	EP4	EP5		
n de fonemas no SF	OSI NTP=16	Pré 14	11	14	9	15	11	15	12		
		Pós 14=	13↑(2)	14=	11↑(2)	16↑(1)	14↑(3)	15=	16↑(4)		
	OSM NTP=19	Pré 16	11	16	12	17	13	16	14		
		Pós 17↑(1)	13↑(2)	16=	13↑(1)	19↑(2)	17↑(4)	19↑(3)	18↑(4)		
	CM NTP=4	Pré 2	1	3	3	2	1	3	4		
		Pós 2=	1=	3=	3=	3↑(1)	2↑(1)	3=	4=		
	CF NTP=4	Pré 3	3	3	3	3	3	3	4		
		Pós 2↓(1)	3=	3=	3=	3=	3=	3=	4=		
	OCI NTP=2	Pré 0	0	0	0	1	1	1	2		
		Pós 0=	0=	0=	0=	1=	1=	1=	2=		
n de PF	OCM NTP=2	Pré 0	0	0	0	1	0	1	2		
		Pós 0=	0=	0=	0=	1=	0=	1=	2=		
	PCC (%)	Pré 6	11	5	6	7	12	10	6		
		Pós 5↓(1)	10↓(1)	6↑(1)	6=	6↓(1)	10↓(2)	7↓(3)	4↓(2)		
GSF	Grau	Pré 76,60	54,80	76,60	60,43	85,00	62,55	80,43	80,00		
		Pós 76,60↑(0,60)	66,81↑(12,01)	77,87↑(1,27)	67,66↑(7,23)	89,36↑(4,36)	80,00↑(17,45)	91,06↑(10,63)	97,02↑(7,02)		
Aquisição do fonema-alvo		MM=	MM↑	MM=	MM↑	M↑	MM↑	M↑	M↑		

Table 2. Resultados da avaliação fonológica, pré e pós-intervenção, de cada participante

Legenda: GC=Grupo Controle, GE=Grupo Experimental, n=número, SF=Sistema Fonológico, PF=Processos Fonológicos, GSF=Grau de Severidade de Fala, NTP=Número Total de Possibilidades, OSI=Onset Simples Inicial, OSM=Onset Simples Medial, CM=Coda Medial, CF=Coda Final, OCI=Onset Complexo Inicial, OCM=Onset Complexo Medial, PCC=Percentual de Consoantes Corretas, M=Médio, MM=Médio-Moderado, MS=Moderado-Severo, ↑=aumento, =igual, ↓=diminuição, CP=Controle Participante, EP=Experimental Participante.

		Modelo de Ciclos				Modelo CAFE				p-valor ²	d ²
		Pré média±DP	Pós	p-valor ¹	d	Pré média±DP	Pós	p-valor ¹	d		
PF	PCC	7±2.7	6.8±2.2	0,638	0,26	9±2.4	7±2.2	0,003	2,83	0,872	0,11
		67±11	72.2±5.8	0,144	0,98	73.5±11.6	84.9±11.6	0,011	1,99	0,089	1,33
GSF ³	M	0 (0%)	0 (0%)	0,157		0 (0%)	3 (60%)	0,082		0,167	
	MM	2 (50%)	4 (100%)			3 (60%)	2 (40%)				
	MS	2 (50%)	0 (0%)			2 (40%)	0 (0%)				
	OSI	75±15.3	81.3±8.8	0,182	0,87	78.8±14.4	91.3±10.5	0,047	1,26	0,172	1,02
Posições silábicas ⁴ (%) atingido)	OSM	73.7±15.5	76.3±9.1	0,495	0,39	74.7±12.6	90.5±13.1	0,003	3,00	0,110	1,23
	CM	56.3±23.9	56.3±23.9	----		60±28.5	70±20.9	0,178	0,73	0,388	0,62
	CF	75±0	68.8±12.5	0,391	0,50	80±11.2	80±11.2	----		0,197	0,96
	OCI	0±0	0±0	----		50±35.4	50±35.4	----			
		OCM	0±0	----		40±41.8	50±35.4	0,374	0,45	----	

Table 3. Comparação pré e pós-intervenção dos modelos aplicados com análise estatística

*p-valor<0,05; d>0,2 (pequenos), d>0,5 (médios), d>0,8 (grandes). ¹Teste t de Student para amostras pareadas. ²Comparação dos resultados pós-intervenção entre Modelo de Ciclos e CAFE. ³Teste McNemmar para pré x pós no Modelo de Ciclos e no CAFE E Teste Qui-Quadrado para a comparação entre ambos os grupos no pós-intervenção. ⁴Foi feita a média de aquisição em cada posição silábica que cada modelo atingiu, por exemplo, em OSI, o modelo de ciclos atingiu, em média, 12 fonemas de 16 possibilidades, logo foram atingidos, em média, 75% por fonemas (12/16).

incremento na capacidade de inibição de respostas automáticas, sugerindo que a estimulação executiva atuou como um catalisador para a supressão de padrões de fala desviantes.

4. DISCUSSÃO

Os achados deste estudo piloto indicam que a integração sistemática de atividades voltadas às FE ao tratamento fonológico, conforme proposto no modelo CAFE, esteve associada a ganhos clínicos superiores quando comparada ao modelo de Ciclos tradicional. Embora o tamanho amostral reduzido ($n = 9$) limite o poder de significância estatística em algumas variáveis através do valor de p , a análise do tamanho do efeito (d de Cohen) revela uma magnitude de mudança clinicamente robusta, sugerindo que o modelo CAFE atua como um facilitador do aprendizado fonológico.

A evolução do PCC em ambos os grupos corrobora achados clássicos da literatura, que reconhecem a efetividade dos modelos de base fonológica na melhora do desempenho articulatório e fonológico¹². No entanto, a análise quantitativa da gravidade do transtorno após a intervenção revela diferenças importantes entre as abordagens. Enquanto no Grupo Experimental (GE) todos os participantes migraram para o grau "médio", no Grupo Controle (GC) metade da amostra manteve o grau de severidade inicial, sugerindo uma resposta terapêutica mais heterogênea no modelo convencional. Esse dado é reforçado pelo tamanho do efeito expressivo observado no GE para variáveis como o *Onset Simples Inicial* ($d = 1,26$) e *Medial* ($d = 3,00$). Valores de $d > 0,80$ são interpretados como efeitos grandes, o que indica que a intervenção CAFE possui uma força de mudança prática que transcende a mera flutuação estatística.

A superioridade do modelo CAFE no aumento do inventário fonético e na redução de processos fonológicos pode ser explicada pelo papel central das FEs no processamento da fala. A aquisição de fonemas-alvo (80% de sucesso no GE vs. 50% no GC) exige que a criança não apenas memorize um novo som, mas iniba o padrão de erro consolidado (Controle Inibitório) e alterne entre as regras antigas e as novas (Flexibilidade Cognitiva)¹³. Ao treinar essas funções simultaneamente à fonologia⁷, o modelo CAFE parece "desbloquear" o sistema cognitivo, permitindo que a criança monitore sua própria produção de forma mais eficaz.

Um ponto crítico observado na literatura⁴ e espelhado neste estudo é a estagnação de alguns sujeitos no modelo de Ciclos tradicional. No GC, verificou-se que crianças chegaram a manter ou até aumentar o número de processos fonológicos pós-intervenção, fato não observado no GE. Isso sugere que, para crianças com TF, o "gargalo" pode não estar na capacidade articulatória, mas na gestão dos recursos atencionais e de memória⁶ necessários para a generalização. O modelo CAFE, ao fornecer esse suporte cognitivo, demonstrou ser uma estratégia de intervenção mais resiliente.

É importante destacar que, por se tratar de um estudo piloto com amostra de conveniência, os resultados devem ser interpretados com cautela. Ainda assim, a convergência entre os dados quantitativos, a análise do tamanho do efeito e a observação clínica sugere que a integração das Funções Executivas à terapia fonológica constitui uma estratégia promissora. Esses achados contribuem para o corpo de evidências que defende uma abordagem mais integrada entre cognição e linguagem, especialmente em populações pediátricas com dificuldades persistentes de fala.

Dessa forma, o presente estudo pode ser compreendido como uma prova de conceito inicial, que fundamenta a necessidade de ensaios clínicos randomizados com amostras maiores e delineamentos multicêntricos. Investigações futuras poderão aprofundar a compreensão sobre quais componentes executivos exercem maior influência na reorganização fonológica e em quais perfis de crianças o modelo CAFE apresenta maior efetividade.

5. CONCLUSÃO

Os resultados deste estudo piloto indicam que a associação sistêmica entre o treino de Funções Executivas e a intervenção fonológica (Modelo CAFE) oferece benefícios terapêuticos superiores ao modelo de Ciclos tradicional. A evidência central reside não apenas no aumento quantitativo do PCC, mas na qualidade da generalização fonológica e na uniformidade da evolução clínica observada no grupo experimental.

Conclui-se que o modelo CAFE atua diretamente no suporte cognitivo necessário para que a criança monitore sua produção, iniba padrões de erro consolidados e manipule as regras fonológicas com maior flexibilidade. Os altos índices de tamanho do efeito (d de Cohen) observados validam o modelo como uma "prova de conceito" robusta, demonstrando que a estimulação das FEs não deve ser vista como um complemento opcional, mas como um substrato integrativo para a eficácia da terapia em crianças com Transtorno Fonológico. Apesar das limitações do tamanho amostral, este estudo estabelece uma base metodológica sólida para futuros ensaios clínicos multicêntricos. A adoção do modelo CAFE na prática clínica fonoaudiológica tem o potencial de reduzir o tempo de tratamento e maximizar os resultados de comunicação em populações pediátricas.

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Impact of Saudi Model of Care Initiatives on Healthcare Professionals' Perceptions in Saudi Arabia: A Cross-Sectional Study 2024

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Double Blind

Abstract

This study investigates healthcare professionals' perceptions of health system support across key care domains in Saudi Arabia within the context of ongoing healthcare transformation under Vision 2030 and the Saudi Model of Care (MoC) framework. A cross-sectional survey using a Likert-scale questionnaire was distributed to 201 healthcare professionals working in primary healthcare centers and hospitals. The survey assessed perceptions of system support in wellness maintenance, urgent care, planned procedures, childbirth, chronic disease management, and end-of-life care. Methodology: Descriptive and inferential analyses revealed moderate overall satisfaction with the health system, with higher perceived effectiveness in childbirth and chronic disease management. In contrast, urgent care and end-of-life care received comparatively lower ratings. No statistically significant differences were found based on gender; however, duty shift was associated with variations in perception, with night-shift workers reporting more favorable views in selected domains. The findings highlight critical gaps in communication, urgent care responsiveness, and end-of-life services despite notable progress in healthcare reform. These insights provide evidence to support ongoing Model of Care implementation and strategic health system strengthening in Saudi Arabia.

Model of Care

Healthcare Transformation

Vision 2030

Professional Perceptions

Saudi Arabia

Health System Support

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Impact of Saudi Model of Care Initiatives on Healthcare Professionals' Perceptions in Saudi Arabia: A Cross-Sectional Study 2024

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Abstract

This study investigates healthcare professionals' perceptions of health system support across key care domains in Saudi Arabia within the context of ongoing healthcare transformation under Vision 2030 and the Saudi Model of Care (MoC) framework. A cross-sectional survey using a Likert-scale questionnaire was distributed to 201 healthcare professionals working in primary healthcare centers and hospitals. The survey assessed perceptions of system support in wellness maintenance, urgent care, planned procedures, childbirth, chronic disease management, and end-of-life care. Methodology: Descriptive and inferential analyses revealed moderate overall satisfaction with the health system, with higher perceived effectiveness in childbirth and chronic disease management. In contrast, urgent care and end-of-life care received comparatively lower ratings. No statistically significant differences were found based on gender; however, duty shift was associated with variations in perception, with night-shift workers reporting more favorable views in selected domains. The findings highlight critical gaps in communication, urgent care responsiveness, and end-of-life services despite notable progress in healthcare reform. These insights provide evidence to support ongoing Model of Care implementation and strategic health system strengthening in Saudi Arabia.

Keywords: *Model of Care, Healthcare Transformation, Vision 2030, Professional Perceptions, Saudi Arabia, Health System Support*

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1. Introduction

Saudi Arabia has undergone a significant transformation in its healthcare sector, primarily driven by technological advancements and the Model of Care initiatives under Vision 2030. According to Albarrak (2021), e-health strategies were first implemented in major hospitals in 2011 to improve healthcare access and quality. The Ministry of Health (MOH) launched the "Tatamman" mobile application in 2020 to monitor and support COVID-19 patients (MOH, 2020). Health indices have shown remarkable improvement; life expectancy increased from 66 to 74.9 years between 1983 and 2017, and infant mortality significantly decreased (Al-Hanawi, 2019). Despite these improvements, gaps remain, especially in urgent and end-of-life care, warranting an investigation into healthcare professionals' perceptions.

1.1. Saudi Arabia's Healthcare Transformation

Saudi Arabia has embarked on a comprehensive healthcare transformation under its Vision 2030 initiative, aiming to enhance healthcare delivery, efficiency, and accessibility. The country's healthcare reforms emphasize patient-centered care, improved infrastructure, and the integration of advanced technologies. Central to these reforms is the *Model of Care* framework, designed to reorient healthcare services toward preventive, proactive, and coordinated care, rather than reactive treatment alone.

1.2. Technological Innovations and Digital Health Strategies

Technology has been at the forefront of this transformation. As Albarrak (2021) noted, Saudi Arabia introduced e-health strategies as early as 2011, initially implemented in major urban hospitals. These technologies aimed to facilitate access, improve patient outcomes, and create a more interconnected healthcare system. The COVID-19 pandemic further accelerated digital health initiatives, with the Ministry of Health (MOH) launching the "Tatamman" mobile application in 2020. This app allowed for real-time monitoring and support of COVID-19 patients, showcasing the country's capacity to rapidly integrate technology to manage public health emergencies (MOH, 2020).

1.3. Improvements in Health Outcomes

The effectiveness of these reforms is evident in national health statistics. According to Al-Hanawi (2019), life expectancy in Saudi Arabia rose from 66 years in 1983 to 74.9 years in 2017. Similarly, the infant mortality rate significantly decreased, and the country successfully eradicated polio. These achievements reflect the substantial investments and policy efforts made by the Saudi government in public health and healthcare infrastructure.

1.4. Persistent Challenges

However, despite these advancements, challenges remain. In particular, the domains of urgent care responsiveness and end-of-

life care provision have not progressed at the same rate. There is growing recognition that while digitalization and systemic reforms have improved access and primary care, acute and compassionate care services require further attention. This study, therefore, seeks to explore healthcare professionals' perceptions regarding the strengths and weaknesses of the current system across these critical care scenarios.

2. Literature Review

Albarrak (2021) highlighted the successful adoption of e-health systems aimed at improving care quality and accessibility. The "Tatamman" app enabled real-time health monitoring during the pandemic, emphasizing the government's commitment to leveraging technology in healthcare (MOH, 2020). Health improvements reported by Al-Hanawi (2019) illustrate effective policy interventions. However, healthcare workers' perceptions regarding support across different health scenarios, especially urgent and end-of-life care, remain underexplored. This study aims to bridge that gap.

2.1. E-Health Initiatives in Saudi Arabia

E-health technologies have played a pivotal role in reshaping Saudi Arabia's healthcare system. Albarrak (2021) emphasized the early adoption of e-health strategies aimed at enhancing service quality, improving accessibility, and streamlining care coordination. Electronic Health Records (EHRs), telemedicine services, and online health portals became instrumental in promoting efficiency and patient engagement. Studies suggest that these technologies have not only reduced service delivery times but also contributed to better chronic disease management and preventive care practices (Albarrak, 2021).

2.2. The Role of Mobile Health Applications

The COVID-19 pandemic highlighted the critical need for robust digital health infrastructures. In response, the MOH launched the *Tatamman* mobile application, which enabled continuous health monitoring for suspected COVID-19 patients (MOH, 2020). The application provided features such as symptom tracking, communication with healthcare providers, and guidance on quarantine protocols. Research on *Tatamman* and similar apps indicates that mobile health applications can significantly enhance patient compliance, improve early detection of complications, and enable resource optimization during health crises (MOH, 2020).

2.3. Healthcare Improvements: Indicators of Success

Saudi Arabia's healthcare system has recorded impressive improvements over the past three decades. Al-Hanawi (2019) attributed these successes to substantial governmental investment, widespread immunization programs, and enhanced maternal and child health services. Key indicators such as life expectancy, infant mortality rates, and maternal mortality rates have all shown marked progress. For example, the maternal mortality ratio dropped from 3.2 per 1,000 live births to 1.2 per 1,000 live births between 1983 and 2017 (Al-Hanawi, 2019).

2.4. Gaps in Urgent and End-of-Life Care

Despite these achievements, significant challenges persist, particularly in urgent care and end-of-life services. Urgent care services are crucial for addressing acute medical conditions promptly, yet perceptions of delays, inefficiencies, and communication gaps have been noted (Albarrak, 2021). Similarly, end-of-life care remains underdeveloped, with limited emphasis on palliative care

education, resource allocation, and patient-family communication. These gaps point to the necessity of exploring healthcare professionals' experiences and insights, as they are on the frontlines of care delivery and uniquely positioned to identify areas for improvement.

2.5. Purpose of the Study

Given the context of technological progress and ongoing healthcare reforms, this study aims to systematically investigate healthcare workers' perceptions of the Saudi health system's performance across different domains of care. Specifically, it will assess satisfaction levels in areas such as preventative care, urgent care, chronic disease management, planned procedures, childbirth, and end-of-life support, thereby identifying strengths to consolidate and weaknesses to address in future policy initiatives.

3. Methodology

3.1. Research Design

This study follows a **quantitative research design** utilizing a **Likert-scale survey** to measure healthcare professionals' perceptions of the health system's support across various care scenarios, including wellness maintenance, urgent care, planned procedures, childbirth support, chronic health conditions, and end-of-life care. The Likert scale enables respondents to indicate their level of agreement with statements related to the quality of support provided by the health system in these areas.

3.2. Research Questions and Hypotheses

1. Research Questions:

- **RQ1:** How do healthcare professionals perceive the health system's support in maintaining overall health and well-being?
- **RQ2:** Are there significant differences in healthcare professionals' perceptions of the health system's support across various care scenarios (urgent care, planned procedures, childbirth support, chronic health conditions, end-of-life care) based on gender, work site, and duty shift?
- **RQ3:** Which areas within the health system are perceived as strengths, and which areas require improvement to enhance the quality of care and support provided to patients?

2. Hypotheses:

- **H1:** Healthcare professionals report general satisfaction with the health system's support for maintaining overall health and well-being, with variability in perceptions of support across different care scenarios.
- **H2:** There are no significant gender differences in healthcare professionals' perceptions of the health system's support. However, perceptions vary significantly based on duty shift, with night shift workers experiencing a more favorable view of the health system's support in specific areas.
- **H3:** Planned procedures and childbirth support are perceived as areas of strength within the health system,

Gender Distribution of Healthcare Professionals Sample

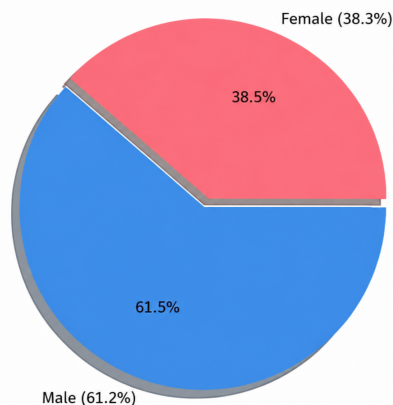


Figure 1. Demographic Information

whereas urgent care and end-of-life care are identified as areas requiring improvement to meet healthcare professionals' expectations and enhance patient care quality.

3.3. Sampling and Participants

The sample consists of **201 healthcare professionals** predominantly based in **Primary Health Care Centers (PHCs)** and **hospitals**. The respondents represent a variety of **departments**, including **Family Medicine**, **Internal Medicine**, and **General Surgery**, as well as different **job titles** such as **Consultants**, **Nurses**, and **Specialists**. The participants range in **age** from 24 to 65 years and have varying levels of **professional experience**.

• Demographic Information:

- **Gender:** 61.2% male (n=123), 38.3% female (n=77).
- **Work Site:** 48.8% PHCs (n=98), 37.3% hospitals (n=75), 11.4% other (n=23).
- **Shift Work:** 85.6% day shift (n=172), 14.4% night shift (n=29).
- **Age Range:** Most common age groups: 40 years (8.0%, n=16) and 38 years (7.5%, n=15).
- **Experience:** Most common experience ranges: 15 years (7.5%, n=15) and 12 years (6.0%, n=12).

3.4. Data Collection

The primary data collection tool was a **Likert-scale survey** that asked healthcare professionals to assess various aspects of the health system's support in multiple care scenarios. The survey addressed areas such as overall wellness support, urgent care, planned procedures, childbirth, chronic health conditions, and end-of-life care. **Reliability analysis** was conducted using **Cronbach's Alpha** to assess the internal consistency of the scales. After adjustments, high reliability was observed in most areas, including **Urgent Care Support** (.867), **Planned Procedures** (.850), and **Chronic Health Conditions** (.888).

4. Results and Discussion

4.1. Descriptive Statistics

Table 7 presents the mean, standard deviation, and skewness for each care scenario, reflecting the overall perceptions of healthcare professionals about the health system's support.

The overall mean scores indicate a **moderate satisfaction** with the health system's support, particularly in areas such as **Planned Procedures** (mean = 3.56), **Childbirth Support** (mean = 3.71), and **Chronic Health Conditions** (mean = 3.67), while **End-of-Life Care** scored the lowest (mean = 3.30).

4.2. Perceptions by Scenario

1. **Overall Support for Well-being:** A majority of respondents (57.7%) agreed that the health system provides adequate resources for overall health and well-being. However, there is room for improvement in **preventative care services** and **care coordination** (37.8% agreeing, 35.8% neutral).
2. **Urgent Care:** A mixed perception emerged, with only **47.3% agreeing** that urgent care is timely and effective. This suggests potential variability in the responsiveness of the system to urgent care needs.
3. **Planned Procedures:** The health system was generally perceived to provide **adequate resources** for planned procedures, with **47.3% agreeing** on the quality of care and **45.8% agreeing** on the effectiveness of scheduling and coordination.
4. **Childbirth Support:** While most respondents agreed that adequate resources are available for childbirth (54.2% agreeing), communication regarding **postnatal care** needs improvement, as highlighted by a significant portion of respondents being neutral or dissatisfied (34.8% neutral, 26.9% agreeing).
5. **Chronic Health Conditions:** Over 50% of respondents agreed that the health system provides adequate support for chronic health conditions, reflecting strong care coordination and resource availability.
6. **End-of-Life Care:** Respondents were more neutral on the support for **end-of-life care** (30.3% neutral), with a notable gap in **communication** about the care needed during the last phase of life (41.8% neutral).

4.3. Discussion of Key Findings

- **H1:** The hypothesis that healthcare professionals report general satisfaction with health system support for well-being is **supported** by the data. However, significant variability exists across different care scenarios, particularly with urgent care and end-of-life care.
- **H2:** The hypothesis regarding no significant gender differences but variability based on duty shifts is **supported**. Gender did not emerge as a significant factor, but night shift workers had more positive views on specific support aspects, especially in urgent care.
- **H3:** The hypothesis that planned procedures and childbirth support are perceived as strengths, while urgent care and end-of-life care require improvement, is **largely supported**. While planned procedures and childbirth scored high, urgent and end-of-life care still show room for improvement.

Table 1. Presents the mean, standard deviation, and skewness for each care scenario, reflecting the overall perceptions of healthcare professionals about the health system's support.

Care Scenario	Mean	Std. Error	Median	SD	Skewness	Kurtosis
Overall Support for Well-being	3.70	0.053	3.75	0.754	-0.861	1.974
Urgent Care	3.43	0.061	3.60	0.876	-0.460	-0.197
Planned Procedures	3.56	0.053	3.60	0.753	-0.448	0.499
Childbirth Support	3.71	0.048	3.75	0.687	-0.473	1.014
Chronic Health Conditions	3.67	0.056	3.80	0.802	-0.701	1.109
End-of-Life Care	3.30	0.047	3.40	0.663	-0.941	1.238

4.4. Recommendations

- **Improvement in Communication:** Focus on enhancing communication in areas like post-childbirth care and end-of-life care, where significant gaps in patient and family satisfaction were identified. Clear, empathetic communication can greatly improve the overall care experience and outcomes in these sensitive stages.
- **Urgent Care System:** Address the variability in urgent care support by improving triage processes, standardizing urgent care protocols, and ensuring timely access to urgent services. Reducing wait times and providing better guidance can enhance patient trust and satisfaction in emergency situations.
- **Preventative Care Services:** Invest in more robust preventative care offerings, including regular screenings, vaccination programs, and public health education initiatives. As responses to preventative care services were divided, a stronger focus here could improve public health outcomes and reduce the burden on emergency and chronic care systems.

5. Conclusion

In conclusion, the study highlights key areas within the healthcare system that require strategic improvements, particularly in communication, urgent care access, and preventative services. Strengthening these areas not only addresses patient dissatisfaction but also promotes a more efficient, compassionate, and sustainable healthcare system. By prioritizing these recommendations, healthcare providers can build a more patient-centered approach, enhance trust, and ultimately achieve better health outcomes for the communities they serve.

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