ISSN: **2764-4006** | www.revistacientificaipedss.com

THERAPIES BASED ON PEPTIDES IN MODERN MEDICINE: CLINICAL APPLICATIONS AND CHALLENGES IN STABILITY AND BIOAVAILABILITY - SYSTEMATIC REVIEW

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Publication date: 27 July 2026
DOI: http://doi.org/10.55703/27644006060301

ABSTRACT

Peptide-based therapies have high pharmacological selectivity and a broad ability to modulate receptors, enzymes, and signaling pathways, but their clinical development is limited by enzymatic degradation, low permeability across biological membranes, rapid clearance, and reduced bioavailability. This study aimed to analyze contemporary clinical applications of therapeutic peptides and evaluate the strategies used to enhance their molecular stability, half-life, absorption, and tissue distribution. A systematic review was conducted in accordance with the PRISMA 2020 recommendations. The main search was carried out in PubMed/MEDLINE, from the start of indexing to July 20, 2026, with additional verification in PubMed Central, Crossref, and official journal records. Original clinical, pharmacokinetic, translational, and preclinical studies related to therapeutic-purpose peptides were included. In the end, 50 studies published between 2001 and 2025 were included and organized into five thematic axes. The results demonstrated that amino acid substitutions, lipidization, albumin binding, conformational restriction, PEGylation, depot formulations, implants, and absorption promoters increased stability and prolonged pharmacological exposure. Semaglutide, tirzepatide, and other incretin agonists showed significant benefits in glycemic control, weight loss, and reductions in cardiovascular events. Relevant applications were also observed in genetic obesity, achondroplasia, short bowel syndrome, osteoporosis, neuroendocrine tumors, drug-resistant HIV infection, hereditary angioedema, pruritus, refractory pain, and erythropoietic protoporphyria. However, oral absorption remained variable and dependent on administration conditions, whereas ingestible devices and other delivery technologies showed predominantly preclinical evidence. Negative results with cilengitide and NLY01 demonstrated that prolonging half-life and molecular plausibility do not ensure efficacy when tissue distribution or
target engagement are insufficient. It is concluded that peptide therapies constitute a versatile therapeutic platform, the success of which depends on the integration of molecular engineering, stability, bioavailability, targeting to the intended tissue, safety, and clinical applicability.

Keywords:peptides; bioavailability; drug stability; drug delivery systems.

ISSN: **2764-4006** | www.revistacientificaipedss.com

INTRODUCTION

Peptides constitute a class of biologically active molecules involved in the regulation of essential physiological processes, including energy metabolism, glycemic homeostasis, growth, nociception, gastrointestinal motility, immune response, cardiovascular signaling, and neuroendocrine communication. Their high affinity for specific receptors, the ability to modulate protein–protein interactions, and the possibility of reproducing or modifying endogenous sequences give these molecules a high pharmacological potential. Unlike many small-molecule compounds, peptides can act on highly selective targets and reproduce complex physiological mechanisms, enabling targeted therapeutic interventions and, in certain contexts, aligning with the principles of precision medicine.

The development of peptide therapies evolved from formulations based on natural hormones to structurally modified molecules, long-acting analogs, multireceptor agonists, cyclic peptides, radioconjugates, and controlled-release systems. This evolution significantly expanded its clinical applicability. Peptide analogs similar to glucagon type 1, such as semaglutide, and combined agonists of the GLP-1 receptor and glucose-dependent insulinotropic polypeptide, such as tirzepatide, have shown significant benefits in glycemic control, in reducing body weight, and in preventing cardiovascular events in selected populations (16–28). More recently, molecules with simultaneous agonism of the GLP-1, GIP, and glucagon receptors, such as retatrutide, have come to represent a new generation of metabolically active peptides, although their efficacy and safety still need to be confirmed in clinical trials of longer duration (29).

The expansion of peptide therapies, however, is not limited to metabolic diseases. Selective activation of the melanocortin 4 receptor by setmelanotide enabled clinically relevant reductions in weight and hyperphagia in rare forms of genetic obesity associated with alterations in pro-opiomelanocortin pathways, the leptin receptor, and Bardet-Biedl syndrome (30,31). In achondroplasia, vosoritide, a C-type natriuretic peptide analog,

demonstrated an increase in annual growth velocity in children through modulation of signaling related to the fibroblast growth factor receptor 3 (32). In short bowel syndrome, teduglutide increased intestinal absorptive capacity and reduced dependence on parenteral support, while linaclotide and plecanatide showed that peptides with predominantly luminal activity can produce gastrointestinal benefits without significant systemic exposure (33–35). Therapies based on fragments or analogs of parathyroid hormone also promoted increased bone mineral density and reduced fracture risk in patients with osteoporosis (36,37).

In oncology, long-acting somatostatin analogs, such as lanreotide, have delayed the progression of neuroendocrine tumors that are positive for specific receptors, while conjugating a peptide analog to a radionuclide, represented by ^ 177Lu-DOTATATE, has enabled ionizing radiation to be directed to tumor cells with high somatostatin receptor expression (38,39). In infectious diseases, enfuvirtide has shown that a synthetic peptide can directly block the fusion of the human immunodeficiency virus with the cell membrane, reducing viral load in patients with multidrug-resistant infection (41,42). Other examples include icatibant in hereditary angioedema, difelikefalin in pruritus associated with hemodialysis, ziconotide in refractory pain, bremelanotide in hypoactive sexual desire disorder, and afamelanotide in erythropoietic protoporphyria (43–45,47,49). These findings highlight the diversity of receptors, physiological pathways, and clinical conditions that may be potentially modulated by peptide-based drugs.

Despite this broad therapeutic potential, the clinical use of peptides remains conditioned by limitations pharmaceutical and relevant pharmacokinetics. The presence of peptide bonds susceptible to protease action, low permeability across biological membranes, high polarity, limited transcellular diffusion, rapid systemic clearance, and the possibility of renal elimination contribute to shorter half-lives and low bioavailability. In the gastrointestinal tract, these limitations are intensified by gastric acidity, enzymatic degradation, the mucous layer, and poor passage across the intestinal epithelium. As a result, many peptides require subcutan-

eous, intravenous, intramuscular, or intrathecal administration, which can reduce therapeutic convenience, increase dependence on technical training, and compromise adherence in long-term treatments.

Different molecular engineering strategies have been developed to overcome these barriers. Substituting amino acids susceptible to degradation, acylation with lipid chains, and reversible binding to albumin have made it possible to increase proteolytic stability, reduce renal clearance, and prolong systemic exposure to GLP-1 analogs, enabling weekly administration regimens (6,7). Conformational restriction, cyclization, dimerization, and PEGylation can also protect vulnerable regions of the molecule, alter its hydrodynamic volume, and modify tissue distribution (8,15,50). Depot formulations, subcutaneous implants, and peptide-radionuclide conjugates represent additional approaches to control release, prolong the action, and target the active principle to tissues that express specific receptors (38–40,49).

Oral administration remains one of the main challenges in development of peptide-based medicines. The association of semaglutide with sodium salcaprozate, known as SNAC, showed that the localized increase in pH and the temporary promotion of gastric permeability can protect the peptide from degradation and promote its transcellular absorption in the stomach (1). However, systemic exposure to oral semaglutide has been shown to depend on the fasting period, the amount of water, the interval between administration and eating, tablet erosion, and the presence of other medications administered simultaneously (2–5,12). These findings indicate that the feasibility of an oral formulation does not eliminate pharmacokinetic variability or the need for specific conditions of use.

Other technologies aim to physically or chemically bypass gastrointestinal barriers. Ionic liquids have been investigated to protect insulin from proteolysis and to increase its passage through the intestinal epithelium, while ingestible, self-orienting devices and microneedle systems have been developed to introduce macromolecules directly into the gastric or intestinal wall (9–11). Although these strategies have produced promising prec-

linical results, their clinical incorporation depends on demonstrating mechanical safety, biocompatibility, performance reproducible, tolerability in repeated administrations, and large-scale production viability. Oral octreotide, in turn, showed that converting a parenteral treatment to an oral formulation may preserve biochemical control in part of the patients, but also evidenced variability in response and loss of therapeutic control in a relevant proportion of the individuals treated (13) .

Extending the half-life or increasing systemic exposure also does not, on its own, ensure clinical benefit. Cilengitide, a cyclic peptide integrin inhibitor, did not improve survival in glioblastoma patients when associated with standard treatment, despite biological plausibility and preliminary results that supported its development (46) . Similarly, NLY01, a pegylated GLP-1 agonist, showed no significant clinical benefit in patients with early Parkinson's disease, suggesting that plasma stability may not correspond to adequate exposure in the central nervous system or effective modulation of the pathological target (50) . These negative results are fundamental to understand that the success of a peptide therapy depends on the integration between target affinity, structural stability, bioavailability, tissue distribution, duration of the presentation, population selection, and relevance of the pathophysiological mechanism.

Although the literature demonstrates substantial advances, the evidence is distributed across studies in medicinal chemistry, experimental pharmacology, drug delivery systems, pharmacokinetic research, and clinical trials conducted in distinct therapeutic areas. This fragmentation makes it difficult to achieve an integrated understanding of the relationships among the structural properties of peptides, the strategies used to enhance their stability and bioavailability, and the results actually obtained in patients. In addition, the concentration of studies in certain classes—especially incretin agonists—may obscure specific challenges observed in oncology, infectious diseases, neurology, gastroenterology, rare diseases, and therapies with local action.

Against this background, this systematic review aimed to analyze conte-

mporary clinical applications of peptide-based therapies and critically assess the strategies used to overcome limitations related to molecular stability, enzymatic degradation, half-life, permeability, distribution, and bioavailability. In addition, we sought to identify the main therapeutic benefits, pharmacokinetic limitations, translational challenges, and technological perspectives associated with the development of peptide-based medicines in modern medicine.

METHODOLOGY

This is a systematic literature review intended to analyze contemporary clinical applications of peptide-based therapies and the strategies used to overcome limitations related to molecular stability, enzymatic degradation, half-life, permeability, distribution, and bioavailability. The preparation and presentation of the review were guided by the recommendations ofthe *Preferred Reporting Items for Systematic Reviews and Meta-Analyses*-PRISMA 2020 (51). Due to the breadth of the topic and the inclusion of clinical, pharmacokinetic, translational, and preclinical studies, the review was structured into two complementary evidence domains. The first included studies that assessed efficacy, safety, pharmacokinetics, and clinical applications of peptide drugs, while the second brought together investigations

related to molecular engineering, proteolytic stability, extending half-life, absorption, permeability, systems of release and bioavailability. No prospective protocol registration was carried out on a public platform; however, the research question, eligibility criteria, outcomes of interest, and synthesis procedures were defined before the final sample was consolidated.

The guiding question of the review was: what are the main clinical applications of peptide-based therapies in modern medicine, and what strategies have been used to overcome challenges related to stability molecular and to the bioavailability of these molecules? To account for the heterogeneity of the studies, adapted PICOS structures were used. In the clinical setting, considered individuals were subjected to treatment with

medicines peptide, regardless of the clinical condition, with interventions including therapeutic peptides, peptide analogs, multi-receptor agonists, peptide conjugates, or formulations containing peptides. The comparators included placebo, active treatment, standard therapy, different doses, different formulations, or baseline condition. The primary outcomes were clinical efficacy, therapeutic response, safety, adverse events, pharmacokinetics, pharmacodynamics, systemic exposure and bioavailability. Randomized clinical trials were eligible, non-randomized clinical studies, pharmacokinetic studies, bioequivalence studies, and clinical trials of phases l, 2, or 3.

In the translational and preclinical domain, cellular systems, biophysical models, ex vivo tissues, and animal models were considered. The interventions included structural modifications of peptides, absorption promoters, pharmaceutical formulations, and delivery systems. The comparators included unmodified peptides, conventional formulations, negative controls, experimental placebos, or reference parenteral routes. Outcomes related to resistance to proteolysis, structural stability, half-life, binding to albumin, permeability, plasma concentration, area under the curve, maximum concentration, relative or absolute bioavailability, and the performance of release systems were evaluated. In this domain, mechanistic studies were included, experimental, pharmacological, and translational studies with original results.

The main bibliographic search was conducted in PubMed/MEDLINE, from the start of database indexing up to July 20, 2026. Complementary searches were performed by reference tracking of eligible articles, consultation of related publications, and verification of records in Crossref and on the official journal websites. PubMed Central was used to access full texts when available. Title, authorship, journal, year, volume, pagination, PMID, and DOI were verified in the official records. Studies with inconsistent metadata were re-evaluated before inclusion. Targeted searches were also carried out using the names of the molecules identified during screening, with the aim of locating key clinical trials, molecular development studies, and pharmacokinetic investigations that might not have been fully retrieved by the generic search strategy.

The search strategy combined controlled descriptors from *Medical Subject Headings*- MeSH - and free-text terms related to therapeutic peptides, clinical applications, stability, and bioavailability. The baseline strategy used in PubMed/MEDLINE included combinations of the terms *"*Peptides*"*, *"*therapeutic peptide*"*, *"*therapeutic peptides*"*, *"*peptide-based therapy*"*, *"*peptide drug*"*, and *"*peptide drugs*"*, associated with *"*Drug Stability*"*, *"*stability*"*, *"*proteolysis*"*, *"*degradation*"*, "half-life", "Bioavailability", "absorption", *"*permeability*"*, *"*pharmacokinetics*"*, and *"*drug delivery*"*. These terms were combined with filters and expressions referring to clinical, pre-clinical, translational, human, and animal studies. Additional combinations involving *"*oral delivery*"*, *"*lipidation*"*, *"*albumin binding*"*, *"*PEGylation*"*, "conformational restriction*"*, *"*cyclic peptide*"*, *"*depot formulation*"*, *"*microneedle*"*, *"*gastric delivery*"*, *"*intestinal delivery*"*, *"*peptide conjugate*"*, *"*receptor agonist*"*, *"*efficacy*"*, *"*safety*"* and *"*randomized trial*"*.

The general search was complemented by specific searches involving the names of the peptides and therapeutic classes identified during the selection process, including semaglutide, tirzepatide, retatrutide, setmelanotida, vosoritida, teduglutida, linaclotide, plecanatide, teriparatide, abaloparatide, lanreotide, octreotide, pasireotide, enfuvirtide, icatibant, difelikefalin, ziconotide, cilengitide, bremelanotide, exenatide, afamelanotide, and NLY01. Boolean operators AND and OR were used to combine the concepts, and the strategies were adapted according to the characteristics of each complementary search.

Peer-reviewed original studies were included that involved peptides used or developed for therapeutic purposes. Randomized or non-randomized clinical trials, studies pharmacokinetic studies,

pharmacodynamic or bioequivalence studies, pre-clinical and translational investigations directly related to stability, absorption, permeability, half-life, or bioavailability, and molecular engineering studies that assessed modifications intended to increase enzymatic resistance, systemic exposure, or pharmacological duration. Research on oral, gastric, intestinal, subcutaneous, intrathecal delivery systems, whether via implants or depot formulations, was also included. Quantitative or

qualitative results sufficient to characterize the intervention and its main outcomes were required, in addition to identification bibliographic and traceability confirmed by PMID, DOI, or official journal record. Studies published in English, Portuguese, or Spanish were accepted, with no initial year limit, which allowed the inclusion of fundamental historical studies and contemporary research.

Narrative reviews, systematic reviews, meta-analyses, scoping reviews, editorials, letters, comments, opinions, book chapters, and scientific news were excluded. Protocols without results, conference abstracts without full publication, preprints, duplicate studies, secondary publications without new relevant results, research that only mentioned peptides without directly evaluating a therapeutic intervention or a property related to stability and bioavailability, studies exclusively nutritional or cosmetic, research involving supplements without purpose pharmacologically defined, with investigations into proteins or antibodies without a clearly delimited peptide component. Articles with insufficient methodological data, retracted publications, and studies submitted under an editorial alert or a statement of concern that would compromise the reliability of the results were also excluded. When different publications presented results from the same population or from the same clinical trial, the main report or the publication with the more complete data was prioritized, avoiding duplication of participants in the synthesis.

The retrieved records were initially organized and compared by title, author, DOI, and PMID, with duplicates removed. Selection took place in two stages. In the first stage, titles and abstracts were examined to identify studies potentially related to peptide therapies, their clinical applications, or their pharmacological challenges. Records clearly incompatible with the research question were excluded. In the second stage, potentially eligible articles were assessed in full text or through the complete records available in the official databases. Final eligibility was determined by the match between population or experimental model, intervention, design, outcomes, and predefined criteria. The reasons for exclusion in the full-text screening stage were organ-

ized for later presentation in the PRISMA flow diagram. At the end of the process, 50 original studies met the eligibility criteria and were included in the synthesis.

The data were organized into a standardized matrix developed specifically for this review. For each study, information was extracted regarding the reference number, first author, year of publication, country or multicenter context, methodological design, sample size or experimental model, clinical condition or pharmacological purpose, peptide or technology assessed, characteristics of the intervention, dose, route of administration, comparator, duration of follow-up, primary and secondary outcomes, pharmacokinetic parameters, efficacy results, adverse events, methodological limitations, source of funding, potential conflicts of interest, and the study's contribution to stability, bioavailability or clinical application. In pharmacokinetic studies, the following were prioritized: area under the curve, maximum concentration, time to maximum concentration, half-life, bioavailability, systemic exposure, and interindividual variability within-subject or between-subject. In clinical trials, the results corresponding to the main therapeutic outcomes were extracted, including metabolic changes, weight loss, hormonal control, tumor progression, viral load,

The methodological assessment was conducted according to the design of each study. The randomized clinical trials were assessed using the RoB 2 instrument, considering domains related to the randomization process, deviations from the intended interventions, missing data, outcome measurement, and selection of the reported results (52). Non-randomized clinical studies were analyzed using ROBINS-I, which considers bias arising from confounding, selection of participants, classification of interventions, deviations from the intended interventions, missing data, outcome measurement, and selection of the reported results (53). Experimental animal studies were assessed using the SYRCLE instrument, covering generation and concealment of the sequence, baseline similarity, allocation, blinding, outcome assessment, incomplete data, and selective reporting (54).

In studies exclusively involving cells, biophysics, or medicinal chemistry, for which there is no single instrument applicable to all designs, predefined methodological domains were examined, including description of the experimental model, presence of groups or control conditions, number of repetitions, validation of analytical methods, reproducibility of experiments, completeness of outcomes, coherence among methods, results, and conclusions, funding, and conflicts of interest. No overall numerical quality score was calculated, since the sum of distinct methodological items can conceal specific sources of bias. Judgments were used to weight the interpretation of results, without automatically excluding studies solely due to isolated limitations.

The data were synthesized in a descriptive, thematic, and stratified manner. The studies were organized into five axes: molecular engineering, stability and bioavailability; metabolic and cardiometabolic applications; rare diseases, gastroenterology, and bone health; oncology, infectious diseases, pain, and other clinical applications; and neurology, therapeutic translation, and studies with negative results. Effect measures were presented as reported in the original studies, including mean differences, proportions, risk ratios,*hazard ratios*, percentage changes, pharmacokinetic parameters, and their corresponding confidence intervals.

A global meta-analysis was not conducted due to high clinical and methodological heterogeneity across molecules, populations, experimental models, comparators, routes of administration, follow-up periods, and outcomes. The quantitative combination of studies that are so different would produce an effect estimate without valid clinical interpretation. The synthesis without meta-analysis was guided by the recommendations of the *Synthesis Without Meta-analysis*- SWiM (55). The results were grouped by pharmacological mechanism and therapeutic purpose, taking into account the direction and magnitude of effects, consistency across studies, precision of the estimates, biological plausibility, clinical applicability, risk of bias, the stage of development of the intervention, and the existence of confirmatory or negative results.

Preclinical and clinical studies were not combined as if they represented the same level of evidence. Experimental

results were used to explain mechanisms of stability, absorption, and distribution, while clinical trials supported conclusions about efficacy and safety in humans. A single certainty classification was not assigned to the entire body of evidence, since the studies addressed different questions and had designs incompatible with a comprehensive assessment. The strength of the conclusions was weighed separately according to the study design, risk of bias, consistency of the findings, precision, and the correspondence between the outcome analyzed and the proposed clinical application.

Because it used exclusively previously published data available in scientific sources, this systematic review did not involve participant recruitment, direct intervention, access to identifiable personal information, or the collection of biological material. Accordingly, there was no need to submit to an Ethics Committee for Research, in accordance with the applicable principles for literature review studies.

RESULTS

The application of the eligibility criteria resulted in the inclusion of 50 original studies published between 2001 and 2025. The sample showed high methodological diversity, including medicinal chemistry studies, mechanistic and biophysical investigations, cellular and animal experiments, pharmacokinetic studies, studies of bioequivalence and randomized clinical trials in phases 2 and 3. This heterogeneity reflected the scope of peptide-based therapies, ranging from the structural development of the molecules and the delivery systems to the assessment of efficacy and safety under different clinical conditions.

Of the studies included, 15 primarily investigated molecular engineering strategies, stability, absorption, pharmacokinetics and Bioavailability (1–15). The other 14 evaluated metabolic and cardiometabolic applications of peptidic receptor agonists of GLP-1, GIP, and glucagon (16–29). Eight studies analyzed therapies used in rare diseases, gastroenterology, and bone health (30–37); ten investigated applications in oncology, infectious diseases, angioedema, pruritus, pain, and sexual health (38–47); and three evaluated neurological applications or other rare cond-

ISSN: **2764-4006** | www.revistacientificaipedss.com

itions treated with peptidic analogs (48–50). The synthesis

The theme of the included studies is presented in Table 1.

Table 1. Thematic Synthesis of the Studies Included in the Systematic Review

Thematic axis	References	Predominant types of studies	Key results	Main limitations
Molecular engineering, stability, and bioavailability	1–15	Mechanistic, pharmacokinetic, preclinical, bioequivalence studies and early clinical phases	Lipidization, amino acid substitution, albumin binding, conformational restriction, and PEGylation increased resistance to degradation and half-life. SNAC, ionic liquids, oral formulations, and ingestible devices increased absorption or systemic exposure.	Small samples, predominance of preclinical models, high pharmacokinetic variability, and limited assessment of long-term safety.
Metabolic and cardiometabolic applications	16–29	Randomized clinical trials of phases 2 and 3 and cardiovascular studies	Semaglutide, tirzepatide, and retatrutide reduced glycated hemoglobin and body weight. Semaglutide also reduced cardiovascular events in people with obesity and established cardiovascular disease.	Predominance of incretin agonists, gastrointestinal events, industrial funding, and uncertainty about maintaining benefits after discontinuation.
Rare diseases, gastroenterology, and bone health	30–37	Randomized clinical trials and phase 3 studies	Setmelanotide reduced weight in genetic obesity; vosoritide increased growth rate; tedugutide reduced parenteral support; teriparatide and abaloparatide reduced fractures.	Reduced samples in rare diseases, surrogate endpoints, heterogeneous responses, and the need for prolonged or parenteral administration.
Oncology, infectiology, pain, and other applications	38–47	Randomized clinical trials, comparative studies, and receptor-targeted therapies	Lanreotide and ^177LuDOTATATE delayed tumor progression; enfuvirtide reduced viral load; difelikefalin and ziconotide reduced itching and pain. Cilengitide did not improve survival.	Invasive routes, local reactions, specific toxicities, subjective outcomes, and failures of clinical translation.
Neurology and other conditions	48–50	Phase 2 and 3 randomized clinical trials	Exenatide showed an exploratory signal in Parkinson's disease; NLY01 did not demonstrate efficacy; afamelanotide increased tolerance to sun exposure.	Small samples, lack of confirmation of neuroprotection, possible insufficient brain exposure, and risk of unblinding.

Source: prepared by the author based on the studies included.
Note: the numerical references correspond to the bibliography list presented at the end of the article

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Molecular Engineering, Stability, And bioavailability

The studies related to development molecular

demonstrated that increasing stability and duration of pharmacological action was achieved mainly through structural modifications aimed at reducing proteolysis and systemic clearance. The development of semaglutide included substitution of amino acids susceptible to degradation by dipeptidyl peptidase-4 and acylation with a lipid chain capable of promoting reversible binding to albumin. These modifications reduced renal clearance and prolonged systemic exposure, enabling weekly administration (6) . Biophysical studies confirmed that binding to albumin played a predominant role in the prolonged circulation of lipidized incretin peptides, while oligomerization was of greater relevance at the high concentrations used during formulation (7) .

The association between lipiderization and conformational restriction also increased resistance to degradation and prolonged the hypoglycemic activity of GLP-l analogs in experimental models (8). The development of ecnoglutide incorporated targeted modifications to prolong its half-life and to achieve preferential signaling via the cyclic adenosine monophosphate pathway. In the initial clinical evaluations, the molecule

showed an approximate half-life between l24 and l38 hours, consistent with once-weekly administration (l5).

Oral administration was investigated mainly in studies involving semaglutide associated with sodium salcaprozate, called SNAC. The mechanistic analysis demonstrated that absorption occurred predominantly in the stomach, near the eroding tablet. SNAC temporarily increased

the pH of the local microenvironment, reduced proteolytic degradation, and promoted transcellular transport of semaglutide across the gastric epithelium (l).

The systemic exposure was influenced by dosing conditions. Fasting, the lowest volume of water, and the longest interval between dosing and food increased the absorption of oral semaglutide

(4). A pharmacoscintigraphic evaluation showed that slower tablet erosion and the longer period of contact with the gastric mucosa were associated with higher plasma exposures (12). Despite these strategies, absorption showed considerable intraindividual and interindividual variability.

The concomitant use of omeprazole did not clinically significantly reduce exposure to semaglutide, although a small inconclusive increase in the area under the curve and in the maximum plasma concentration was observed (2). In contrast, the simultaneous administration of several tablets reduced by approximately 34% exposure to semaglutide. The association between oral semaglutide and levothyroxine also increased total thyroxine exposure by approximately 33%, indicating potential for interactions clinically relevant pharmacokinetic interactions (3).

The bioequivalence study showed that lower doses of a second-generation formulation produced exposure similar to the corresponding doses of the original oral semaglutide formulation, while keeping pharmacokinetic parameters within the conventional bioequivalence limits (5). In participants with different degrees of renal impairment, including individuals on hemodialysis, no consistent relationship between renal dysfunction and exposure to oral semaglutide was identified (14).

Oral octreotide was evaluated in patients with acromegaly previously controlled by injectable somatostatin analogs. Approximately 65% maintained biochemical control after the transition to the oral formulation. However, a relevant proportion lost the response previously achieved with parenteral administration, demonstrating individual variability in absorption and therapeutic exposure (13) .

Other technologies were evaluated predominantly in preclinical models. An insulin formulation with an ionic liquid composed of choline and geranate increased protection against enzymatic degradation, enhanced intestinal permeability, and promoted sustained reduction of blood glucose in animals (9) . The ingestible self-orienting SOMA system enabled the insertion of insulin directly into the gastric wall and produced systemic exposure comparable to subcutaneous administration under experimental

conditions (10) . The LUMI device, consisting of an intestinal injector with dissolvable microneedles, introduced macromolecules into the mucosa and promoted rapid systemic absorption in animal models (11) .

Metabolic and cardiometabolic applications

Peptidic agonists related to incretins were the most represented class among the included clinical studies. In the PIONEER trials, oral semaglutide reduced glycated hemoglobin and body weight in different populations with type 2 diabetes.

In PIONEER 1, conducted in patients initially treated only with diet and physical activity, doses of 3, 7, and 14 mg promoted dose-dependent glycemic reductions. The estimated difference versus placebo reached approximately _1.1 percentage points in glycated hemoglobin with 14 mg, accompanied by an additional reduction in body weight (16) .

In PIONEER 2, oral semaglutide showed a greater reduction in glycated hemoglobin than empagliflozin in patients not controlled with metformin, with an additional advantage regarding weight reduction in later assessments (17) . In direct comparison with subcutaneous liraglutide, oral semaglutide was noninferior for glycemic control and demonstrated a greater weight reduction in certain analyses (18) .

In patients with moderate renal impairment, oral semaglutide reduced glycated hemoglobin by approximately 0.8 percentage point and body weight by about 2.5 kg in addition to placebo (19). Among participants using insulin, with or without metformin, dose-dependent reductions in glucose and weight were observed, with a difference of up to approximately _1.2 percentage point in glycated hemoglobin compared with placebo (21).

In the PIONEER cardiovascular trial 6, major cardiovascular events occurred in 3.8% of participants treated with oral semaglutide and in 4.8% of those who received placebo. The *hazard ratio* was 0.79, demonstrating cardiovascular noninferiority, although

the study was not powered to confirm superiority (20).

In obesity, the 2.4 mg subcutaneous semaglutide produced an average reduction of 14.9% in body weight in the STEP 1 study, compared with

2.4% in the placebo group. Approximately 86% of the treated participants achieved a minimum loss of 5% of the initial body weight (22). In STEP 3, the association between semaglutide and intensive behavioral intervention resulted in an average loss of nearly 16.0%, compared with 5.7% in the placebo group subjected to the same behavioral program (23).

The SELECT study included 17,604 people with overweight or obesity, established cardiovascular disease, and no diabetes. Major cardiovascular events occurred in 6.5% of participants treated with semaglutide and in 8.0% of those who received placebo, corresponding to a *hazard ratio* of 0.80 (24).

Tirzepatide, a dual agonist of the GIP and GLP-1 receptors, showed clinically relevant reductions in blood glucose and weight. In SURPASS-1, the 5, 10, and 15 mg doses reduced glycated hemoglobin hemoglobin in by approximately 1.9% to 2.1%, with weight losses between 7 and 9.5 kg (25). In SURPASS-2, the reductions in glycated hemoglobin were approximately 2.01%, 2.24%, and 2.30%, depending on the dose, compared with 1.86% with semaglutide 1 mg. Tirzepatide also produced greater reductions in body weight (26).

In SURPASS-4, in patients at high cardiovascular risk, tirzepatide showed a greater reduction in glycated hemoglobin and body weight, and a lower frequency of clinically significant hypoglycemia than insulin glargine (27). In SURMOUNT-1, the mean weight reductions were approximately 15.0%, 19.5%, and 20.9% with doses of 5, 10, and 15 mg, respectively, compared with 3.1% in the placebo group (28).

Retatrutide, an agonist of the GLP-1, GIP, and glucagon receptors, was investigated in a phase 2 trial. After 48 weeks, the highest doses produced mean reductions in body weight close to 23% to 24%. The predominant adverse events were gastrointestinal, and a dose-dependent increase in heart rate was observed (29).

Rare Diseases, Gastroenterology and Bone Health

Setmelanotide was evaluated in monogenic and syndromic forms of obesity. In studies involving POMC/PCSK1 deficiency or LEPR deficiency, 80% of patients with alterations in the POMC/

PCSK1 pathway and 45% of those with LEPR deficiency achieved a minimum reduction of 10% in weight after approximately one year of treatment. Reductions in hunger and hyperphagia were also observed (30).

In Bardet-Biedl syndrome, approximately 32.3% of eligible patients achieved a minimum reduction of 10% in body weight after 52 weeks of setmelanotide. The number of participants with Alström syndrome was insufficient to draw conclusions that are consistent. Hyperpigmentation and injection-site reactions were among the most frequent adverse events (31).

In children with achondroplasia, vosoritide increased annual growth velocity. The adjusted difference versus placebo was approximately 1.57 cm per year after 52 weeks of treatment (32).

In short bowel syndrome with intestinal failure, teduglutide reduced the need for parenteral support. Approximately 54% of treated patients were able to reduce at least one weekly infusion day, compared with about 23% in the control group (33).

Peptidic agonists of guanylate cyclase-C showed efficacy in functional gastrointestinal disorders. Linaclotide increased the frequency of complete spontaneous bowel movements and reduced abdominal pain in patients with irritable bowel syndrome with constipation. Diarrhea was the main treatment-related adverse event (34). Plecanatide produced a complete and durable response in 21.0% of participants who received 3 mg and in 19.5% of those treated with 6 mg, compared with 10.2% in the placebo group (35).

In osteoporosis, teriparatide reduced the occurrence of new vertebral fractures. These fractures were observed in approximately 14% of participants in the placebo group, 5% of those treated with 20 μg, and 4% of those who received 40 μg. There was also an increase in bone mineral density and a reduction in non-vertebral fractures (36). Abaloparatide reduced the occurrence of new vertebral fractures to approximately 0.58%, compared with 4.22% in the placebo group, along with an increase in bone mineral density (37).

Oncology, Infectious Diseases, Pain, and Other Applications

ISSN: 2764-4006 | www.revistacientificaipedss.com

In the CLARINET study, long-acting lanreotide reduced progression of somatostatin receptor-positive enteropancreatic neuroendocrine tumors. The estimated progression-free survival at 24 months was 65.1% with lanreotide and 33.0% with placebo (38).

In the NETTER-1 trial, ^177LuDOTATATE, which consists of a somatostatin analog conjugated to a radionuclide, produced an estimated progression-free survival of approximately 65% at 20 months, compared with 11% in patients treated with high-dose octreotide. Objective tumor response was also superior with radioligand therapy (39).

In acromegaly, long-acting pasireotide achieved biochemical control in approximately 31.3% of patients, compared with 19.2% of those treated with octreotide. However, the greater hormonal efficacy was accompanied by a higher frequency of hyperglycemia and diabetes (40).

In patients with multidrug-resistant HIV-1, enfuvirtide associated with optimized antiretroviral therapy produced a greater reduction in viral load than optimized therapy alone. In the TORO 1 study, the mean reduction was approximately _1.70 log10 copies/mL with enfuvirtide and _0.76 log10 in the control group (41). In TORO 2, the reduction was approximately _1.43 log10 and _0.65 log10, respectively. Injection site reactions were observed in most participants (42).

In the FAST trials, icatibant significantly reduced the time to relief of hereditary angioedema compared with tranexamic acid. However, in the placebo-controlled study, the primary endpoint did not reach statistical significance, and differences in the use of rescue medication made direct comparison difficult (43).

Difelikefalin reduced itching in patients undergoing hemodialysis. A minimal decrease of three points on the intensity scale occurred in 49.1% of treated participants and in 27.9% of those who received placebo, along with improvement in measures related to quality of life (44).

Intrathecal administration of ziconotide in patients with refractory pain associated with cancer or acquired immunodeficiency syndrome produced an approximate mean reduction of 53.1% in pain intensity, compared with 18.1% in the placebo group. Clinical response occurred in approximately 50% and 17.5% of

participants, respectively (45).

Cilengitide did not demonstrate benefit in newly diagnosed glioblastoma. The median overall survival was 26.3 months both among patients who received the peptide associated with standard treatment and among those who underwent only conventional treatment, with a *hazard ratio* of 1.02 (46) .

In studies with bremelanotide, were observed an increase statistically significant increases in sexual desire scores and a reduction in distress related to low desire in premenopausal women. The effect on the number of satisfactory sexual events was less consistent, and nausea was reported in approximately 40% of treated participants (47) .

Neurology and Other Clinical Conditions

Weekly exenatide was evaluated in patients with Parkinson's disease in a phase 2 clinical trial. After 48 weeks of treatment and an additional withdrawal period, the adjusted difference in motor score was approximately _3.5 points in favor of exenatide. The result represented an exploratory signal of possible persistence of the effect, but the study did not have statistical power to demonstrate modification of disease progression (48) .

In erythropoietic protoporphyria, subcutaneous implants of afamelanotide increased the pain-free duration of sun exposure, reduced the frequency of phototoxic reactions, and improved quality of life. In the United States, the median pain-free sun exposure was approximately 69.4 hours with afamelanotide and 40.8 hours with placebo. In the European population, the medians were 6.0 and 0.8 hours, respectively (49).

NLY01, a pegylated GLP-1 receptor agonist, did not significantly improve the primary outcome in patients with early, untreated Parkinson's disease. None of the doses evaluated produced consistent benefits in the main motor or non-motor outcomes after 36 weeks (50).

Safety and Tolerability

Adverse events varied according to the pharmacological class and route of administration. Nausea, vomiting, diarrhea, constipation, decreased appetite, and other gastrointestinal symptoms predo-

minated among GLP-1, GIP, and glucagon receptor agonists (16–29). The frequency of these events generally increased with dose and during dose-escalation periods, although most had mild or moderate intensity.

Subcutaneous therapies were associated with local reactions, particularly frequent with enfuvirtide and also observed with setmelanotide and bremelanotide (30,31,41,42,47) . Cutaneous hyperpigmentation was characteristic of the melanocortin agonists setmelanotide and afamelanotide (30,31,49) . Pasireotide showed a higher frequency of hyperglycemia compared with octreotide, while ziconotide was associated with neurological and neuropsychiatric events clinically relevant (40,45) .

In studies involving ingestible devices and ionic liquids, safety was assessed predominantly in animal models and over shorter periods. Although extensive perforations or acute toxicities that would prevent the experiments described were not identified, it was not possible to adequately evaluate chronic inflammation, mechanical failures, cumulative toxicity, or safety after repeated administrations (9–11) .

Methodological Assessment and Risk of Bias

The large randomized, double-blind, placebo-controlled trials generally presented procedures suitable of randomization, baseline comparability, and standardized outcome measurement. This characteristic was identified mainly in the PIONEER, STEP, SELECT, and SURMOUNT programs and in studies of vosoritide, teriparatide, abaloparatide, lanreotide, difelikefalin, ziconotide, and afamelanotide (16, 19– 25,28,32,36–39,44,45,49) .

Greater possibility of bias was observed in open-label trials or trials without a parallel control group, such as studies of oral octreotide, semaglutide versus empagliflozin, tirzepatide versus semaglutide, tirzepatide versus insulin glargine, setmelanotide in monogenic obesity, enfuvirtide, and cilengitide (13, 17,26,27,30,41,42,46) . In these studies, knowledge of the intervention could influence adherence, concomitant management, symptom reporting, or therapeutic decisions, although the use of laboratory outcomes or objective endpoints partially reduced this risk.

Investigations into rare diseases have shown limitations related to small sample sizes and the lack of power to detect unusual events or differences between subgroups. Pharmacokinetic studies were mainly limited by the low number of participants, the selection of healthy volunteers, and the high variability of oral absorption. In preclinical studies, the main limitations were the lack of evaluation in humans, anatomical and physiological differences between animal models and patients, the short duration of the experiments, and incomplete information about blinding, allocation, and reproducibility.

Overall Summary of Results

The results showed that structural modifications and pharmaceutical technologies were able to increase stability, extend half-life, and enable new modes of administration for different peptides. Lipidation and albumin binding showed results consistent for prolongation of systemic exposure, while absorption enhancers, oral formulations, implants, depot systems, and ingestible devices expanded the possibilities for administration (1–15) .

Clinical trials have demonstrated therapeutic benefits in type 2 diabetes, obesity, cardiovascular diseases, genetic obesity, achondroplasia, short bowel syndrome, osteoporosis, neuroendocrine tumors, drug-resistant HIV, hereditary angioedema, pruritus associated with hemodialysis, refractory pain, hypoactive sexual desire disorder, and erythropoietic protoporphyria (16–45,47,49).

However, the negative results with cilengitide and NLY01 showed that stability molecular, prolongation of half-life, and biological plausibility do not guarantee clinical efficacy when exposure in the target tissue, receptor selection, or the relationship between the pharmacological mechanism and pathophysiology are insufficient (46,50).

DISCUSSION

The findings of this systematic review demonstrate that peptide-based therapies have moved beyond a limited role in hormone replacement or the treatment of specific endocrine conditions, and have become a therapeutic platform applicable to metabolic, cardiovascular, genetic, gastrointestinal, oncological, infectious, neurological, and pain-related dis-

eases. Analysis of the 50 studies showed that the clinical progress of this class was not driven solely by the identification of new biological targets, but mainly by the ability to modify the structure, formulation, and route of administration of the molecules to overcome enzymatic degradation, short half-life, rapid clearance, low permeability, and inadequate tissue distribution.

The high specificity of peptides for receptors and signaling pathways is one of their main pharmacological advantages. This feature makes it possible to replicate physiological mechanisms, block specific molecular interactions, or target therapeutic agents to tissues that express certain receptors. However, biological selectivity alone is not enough to ensure clinical success. The molecule must remain stable during production, storage, and administration, reach the bloodstream or the compartment of action at an adequate concentration, and maintain exposure for the time necessary to produce a therapeutic response. The analyzed results therefore indicate that the clinical efficacy of peptides depends on the integration of pharmacodynamics, pharmacokinetics, pharmaceutical technology, and the appropriate selection of the target population.

Stability molecular and prolongation of exposure

Lipidization and the reversible binding to albumin were the most established strategies for prolonging the systemic exposure of peptides. The development of semaglutide showed that substituting amino acids vulnerable to degradation, coupled with acylation with a lipid chain, can increase resistance to dipeptidyl peptidase-4 and simultaneously reduce renal and proteolytic clearance (6). The demonstration that binding to albumin plays a predominant role in the prolonged circulation of lipidized incretin peptides reinforces that extension of half-life depends not only on direct protection of cleavage sites, but also on modification of the distribution and availability of the free fraction of the molecule (7).

In this context, albumin functions as a circulating reservoir, reducing glomerular filtration and immediate exposure to proteolytic enzymes. This strategy made it possible to transform peptides originally associated with a short duration of action into drugs administered once weekly. The

clinical success of semaglutide and tirzepatide shows that reducing dosing frequency can coexist with high pharmacological potency and relatively predictable control of exposure (22–28).

Conformational restriction and other structural modifications also showed the ability to increase stability. By reducing molecular flexibility and making it harder for proteases to access vulnerable regions, these modifications can prolong the peptide's integrity and, in certain cases, alter its affinity or selectivity for receptors. Preclinical results with modified GLP-l analogs demonstrated increased duration of hypoglycemic activity, although translating these findings to humans remains dependent on assessments of immunogenicity, toxicity, and pharmacokinetic behavior (8) .

PEGylation, exemplified by NLY0l, represents another strategy to increase hydrodynamic volume, slow clearance, and prolong plasma half-life. However, the negative clinical outcome of this drug in Parkinson's disease shows that prolonged systemic exposure does not necessarily mean adequate concentration in the central nervous system or effective interaction with the relevant pathological mechanism (50) . Plasma stability should therefore be distinguished from bioavailability in the target tissue. A molecule may remain in circulation for extended periods without crossing biological barriers, reaching specific cells, or achieving concentrations
pharmacologically active in the compartment of interest.

The development of ecnoglutide added another dimension to peptide engineering by combining pharmacokinetic prolongation with preferential signaling through certain intracellular pathways (l5). Biased agonism aims to promote responses associated with efficacy and reduce mechanisms related to desensitization or adverse effects. Although biologically plausible, this strategy still requires clinical evidence that differences observed in cellular models translate into measurable therapeutic advantages. The preference for a signaling pathway should not be automatically interpreted as clinical superiority.

ISSN: **2764-4006** | www.revistacientificaipedss.com

Oral Administration and Bioavailability Challenges

Oral administration remains one of the main frontiers of peptide therapies. Degradation by gastric pH and digestive proteases, high molecular mass, polarity, and limited passage through the intestinal epithelium naturally make oral bioavailability reduced. Oral semaglutide showed that these barriers can be partially overcome by means of an absorption promoter capable of temporarily modifying the gastric microenvironment and promoting transcellular transport (1) .

The localized mechanism of association with SNAC represents an important pharmaceutical innovation, but pharmacokinetic studies showed that absorption continues to depend on strict conditions. The fasting period, the volume of water, the interval until feeding, the time for tablet erosion, and the concomitant administration of other medications influenced systemic exposure (2– 4, 12) . These results indicate that the oral formulation reduces the need for injections, but transfers part of the complexity to patient behavior.

The requirement for administration while fasting and for an interval before ingesting food or other medications may affect adherence, especially in patients with polypharmacy, irregular routines, or changes in gastric motility. In addition, the reduction in exposure to semaglutide when multiple tablets were administered simultaneously suggests that the physical presence of other products in the stomach may interfere with erosion, mucosal contact, or the microenvironment produced by the absorption promoter (3). Therefore, the oral bioavailability of peptides should be understood as the result of the interaction between the molecule, excipients, dosage form, and physiology gastroi ntestinal and use behavior.

Bioequivalence achieved with a second-generation formulation of semaglutide shows that pharmaceutical improvements can reduce the amount of active ingredient needed to achieve similar exposure (5). This result has industrial and environmental implications, considering that peptide formulations may require relatively large quantities of the molecule to compensate for the low fraction absorbed. However, bioequivalence does not prove greater adhere-

nce, less clinical variability, or therapeutic superiority, and should be interpreted within its specific pharmacokinetic objective.

Experience with oral octreotide showed that converting a parenteral regimen to an oral formulation can preserve biochemical control in some patients, but not all (13) . This result demonstrates that the average exposure observed in a population does not eliminate individual variability. Differences in anatomy, motility, gastric secretion, use of medications, adherence to instructions, and disease characteristics may determine loss of response after changing the route of administration.

Technologies based on ionic liquids and ingestible devices aim to overcome gastrointestinal barriers through distinct mechanisms. Ionic liquids combine protection against degradation with increased epithelial permeability, while the SOMA and LUMI devices functionally transform oral administration into a parenteral application performed internally in the stomach or intestine (9–11) . These approaches have shown promising preclinical results, but they also present their own challenges, including mechanical safety, positioning accuracy, risk of injury, anatomical variability, performance in patients with gastrointestinal diseases, and efficacy after repeated administrations.

The incorporation of these technologies into clinical practice will depend on evidence that the benefit of avoiding external injections outweighs the complexity, cost, and risks of the devices. It will also be necessary to assess large-scale production, stability during transport, compatibility with different peptides, and the possibility of release failures. The preclinical results provide relevant proof of concept, but they still do not demonstrate clinical equivalence to conventional parenteral systems.

Dominance and Success of Incretin Therapies

The high representation of GLP-1, GIP, and glucagon agonists in the background reflects the rapid development of this class and the consistency of the clinical results obtained over the past decades. Oral semaglutide reduced glycosylated hemoglobin and body weight at different stages of type 2 diabetes, including patients on monotherapy, using metformin, with

renal impairment or treated with insulin (16–21) . The observed efficacy despite low oral bioavailability demonstrates that a small absorbed fraction may be sufficient when the molecule has high potency, prolonged half-life, and a dose adjusted to compensate for gastrointestinal losses.

The results with subcutaneous semaglutide showed benefits of greater magnitude in obesity, with clinically relevant weight reductions and improved cardiovascular outcomes in patients with established cardiovascular disease (22–24) . The SELECT study expanded the relevance of this class by demonstrating a reduction in cardiovascular events in people with overweight or obesity without diabetes, indicating that the benefits are not limited to glycemic control (24) .

Tirzepatide represented the progression from simple agonism to combined hormonal agonism. Simultaneous activation of the GIP and GLP-1 receptors produced greater reductions in glycated hemoglobin and weight compared with placebo, insulin glargine, and semaglutide 1 mg across different trials (25–28) . These results suggest that integrating multiple metabolic pathways within a single molecule can increase the magnitude of the therapeutic response.

Retatrutide extended this principle through agonism of the GIP, GLP-1, and glucagon receptors, producing significant weight losses in a phase 2 study (29). However, the inclusion of glucagonergic activity may also introduce additional physiological effects, such as increased heart rate, changes in energy expenditure, and possible hepatic or cardiovascular. The magnitude of weight loss observed in early studies does not replace the need for long-term safety assessment, maintenance of results, and impact on lean mass, body composition, and clinical outcomes.

The benefits of incretin-based therapies must be weighed against the high frequency of gastrointestinal effects and the possibility of stopping treatment. Nausea, vomiting, diarrhea, constipation, and reduced appetite occurred recurrently and were dose- and titration-related. Although often mild or moderate, these events can compromise adherence and persistence with treatment.

Another relevant aspect is maintaining results after discontinuation. The trials analyzed demonstrated efficacy during the period of use, but they did not establish that weight loss or metabolic benefits are permanently preserved without ongoing therapy. This characteristic brings pharmacological obesity treatment closer to the management of other chronic diseases, in which stopping the medication may allow recurrence of pathophysiological mechanisms.

Precision Medicine and Rare Diseases

Studies with setmelanotide demonstrate the most direct application of precision medicine in peptide therapy. Efficacy was observed in patients with specific genetic alterations in the melanocortin pathway, in which pharmacologic activation of the MC4R receptor can partially restore compromised signaling (30,31). The differential response between POMC/PCSK1 deficiency, LEPR deficiency, and Bardet-Biedl syndrome shows that the presence of severe obesity, by itself, is not sufficient to indicate treatment. Molecular diagnosis and the location of the defect in the signaling pathway determine the likelihood of a response.

The small samples of these studies are an inevitable consequence of the rarity of the conditions. In this context, the strength of the evidence cannot be assessed by the number of participants alone. Effect magnitude, biological coherence, reproducibility, reversibility of the response, and the absence of therapeutic alternatives must be considered together. However, the small number of individuals limits the identification of rare adverse events, differences between genetic variants, and the durability of benefits.

Vosoritide also represents a targeted peptide therapy directed at a defined molecular alteration. By modulating the pathway related to FGFR3, the C-type natriuretic peptide analog increased growth velocity in children with achondroplasia (32). Nonetheless, growth velocity is an intermediate endpoint. The impact on adult height, functionality, foramen magnum stenosis, spinal cord compression, mobility, and quality of life requires prolonged follow-up.

Afamelanotide has shown that long-acting peptide implants can provide be-

nefit in rare diseases characterized by an environmental triggering exposure (49). Increasing pain-free sun exposure time and reducing phototoxic reactions are clinically relevant outcomes. However, the tanning induced by the medication can reveal allocation and influence participants' behavior and reporting.

Gastrointestinal Applications and Local Action

Studies with teduglutide, linaclotide, and plecanatide have shown that not all peptide therapies require high systemic bioavailability. Teduglutide uses a structural modification to resist degradation and prolong the intestinotrophic action of GLP-2, resulting in greater absorptive capacity and reduced parenteral support in short bowel syndrome (33).

By contrast, linaclotide and plecanatide were developed to act predominantly in the intestinal lumen and on the apical surface of the epithelium, with minimal systemic absorption (34,35). This feature reduces exposure of other organs and limits systemic adverse effects. Diarrhea, the main adverse event, results from the very mechanism of increasing intestinal secretion.

These examples show that low systemic bioavailability is not always a limitation. When the pharmacological target is located in the gastrointestinal tract, luminal residence may be desirable. The development of the peptide should be guided by the location of the target, rather than by an indiscriminate search for higher plasma concentrations.

Bone health and dependence on intermittent exposure

Teriparatide and abaloparatide demonstrated benefits in preventing fractures and increasing bone mineral density (36,37). These therapies illustrate the importance of the temporal pattern of exposure. Intermittent administration of parathyroid hormone receptor agonists favors anabolic bone activity, whereas continuous exposure may produce distinct physiological effects.

The need for daily subcutaneous administration represents a potential barrier to adherence. However, the magnitude of the fracture reduction demonstrates that parenteral routes may remain

clinically acceptable when benefits are relevant and alternatives are limited. Developing longer-lasting formulations or less invasive administration devices may increase convenience without compromising
the necessary signaling standard.

Oncology and Receptor-Based Targeting

Oncologic applications showed contrasting results. Prolonged-release lanreotide delayed the progression of neuroendocrine tumors, confirming that activation of somatostatin receptors can exert antiproliferative effects beyond hormonal control (38) . The depot formulation was essential to maintain sustained exposure and reduce the frequency of administration.

The ^177Lu-DOTATATE represents a more complex strategy, in which the peptide acts as a molecular recognition vector and directs a radionuclide to tumor cells that express somatostatin receptors (39) . The significant benefit in
progression-free survival demonstrates the potential of peptide conjugates for selective delivery of cytotoxic or radioactive agents.

The effectiveness of this approach depends on receptor expression, internalization of the complex, tumor distribution, and protection of non-target tissues. Patient selection based on molecular imaging is an essential part of the treatment and reinforces the integration between diagnosis and therapy.

In contrast, cilengitide did not improve overall survival in glioblastoma, despite its rationale as an integrin inhibitor and preliminary results that supported clinical development (46). Failure may be related to low exposure in tumor tissue, the complexity of angiogenesis, redundancy of molecular pathways, or inadequacy of the dosing regimen. This result demonstrates that target affinity under experimental conditions does not guarantee sufficient modulation in a heterogeneous tumor microenvironment.

The inclusion of negative studies is essential to reduce overly optimistic interpretations and to understand the determinants of translational failure. The lack of benefit with cilengitide and NLY01 shows that the development of peptides should incorporate exposure markers in the target tissue, confirmation of receptor

engagement, and biologically driven participant selection criteria.

Infectiology, Pain, and Other Indications

Enfuvirtide showed that peptides can directly block essential processes in viral entry. The reduction in viral load in patients with multidrug-resistant HIV represented an important breakthrough during a period of limited therapeutic options (41,42). However, twice-daily subcutaneous administration and the high frequency of local reactions reduced its convenience. The case of enfuvirtide demonstrates that significant biological efficacy can be limited by low stability, lack of an oral formulation, and the burden of administration.

Icatibant, in turn, showed rapid action as a bradykinin B2 receptor antagonist in attacks of hereditary angioedema (43). The inconsistency among the comparators reinforces the need to interpret the overall body of studies, considering rescue medication, subjective outcomes, and characteristics of the acute episode.

Difelikefalin demonstrated that restricting distribution to the peripheral compartment can be used as a safety strategy. Due to limited penetration into the central nervous system, the κ-opioid receptor agonist was developed to reduce pruritus with a lower risk of central effects typical of opioids (44).

Ziconotide represents the opposite situation, in which the blood-brain barrier prevents effective systemic administration and requires intrathecal application (45). The analgesic benefit was significant in patients with refractory pain, but the complexity of the route and neuropsychiatric events limit its use to selected situations. This contrast shows that distribution can be deliberately constrained or directly circumvented depending on the target location and the desired safety profile.

Bremelanotide produced a statistically significant improvement in measures of desire and distress; however, the absolute effects were modest and nausea was frequent (47). For conditions assessed using subjective outcomes, clinical relevance should be evaluated beyond statistical significance, considering magnitude, tolerability, patient preferences, and the possibility of unmasking.

Neurology and barrier blood-brain barrier

The neurological results were heterogeneous. Exenatide showed an exploratory signal of a motor benefit in Parkinson's disease, but the study was small and not sufficient to prove a disease-modifying effect (48). Persistence of the difference after the withdrawal period led to the hypothesis of neuroprotection; however, changes in clinical scales may be influenced by variability, residual symptomatic effects, and baseline characteristics.

The study with NLY01 did not confirm benefit in patients with early disease (50). The discrepancy between the results may be related to molecular differences, dose, population, duration, disease stage, or brain penetration. It is also possible that GLP-1 modulation does not produce a clinically relevant effect in all Parkinson's subgroups.

These studies demonstrate the difficulty of developing peptides for diseases of the central nervous system. In addition to plasma stability, it is necessary to cross the blood-brain barrier, reach specific cells, preserve activity in the brain environment, and produce a measurable effect in slowly progressive diseases. Future studies should incorporate biomarkers of central exposure and target engagement to distinguish pharmacodynamic failure from distribution failure.

Safety, Tolerability, and Adherence

The safety profile varied widely among the classes. Incretin agonists showed a predominance of gastrointestinal events, generally related to the dose and the dose-escalation period. the therapies melanocortin–based therapies were associated with hyperpigmentation, while somatostatin analogs showed distinct metabolic effects depending on the receptor affinity profile.

Reactions at the injection site were particularly relevant for enfuvirtide and also occurred with setmelanotide and bremelanotide. These events show that local tolerability and frequency of administration can influence the clinical usefulness of a therapy, even when its efficacy is demonstrated.

The route of administration should be considered a component of the therapeutic benefit, not just a technical characteristic. Weekly formulations, implants, and depot systems can reduce the frequency of administration, whereas intrathecal routes or frequent injections restrict

treatment to specific settings. Convenience should be assessed together with efficacy, safety, cost, training, and follow-up capacity.

Methodological quality and interpretation of evidence

The large randomized trials provided robust evidence for several indications, particularly diabetes, obesity, cardiovascular prevention, osteoporosis, and neuroendocrine tumors. However, much of the clinical development was financed by manufacturers, which requires careful attention to the selection of comparators, the choice of doses, the definition of endpoints, and the reporting of secondary analyses.

Open-label trials presented a greater possibility of bias related to knowledge of the intervention, adherence, concomitant management, and event reporting. Still, the use of objective endpoints, such as glycated hemoglobin, viral load, fractures, radiological progression, and mortality, partially reduced this limitation.

Preclinical studies provided essential information about mechanisms, but they should not be given the same weight as clinical trials. Anatomical, metabolic, and immunological differences may affect absorption, distribution, and toxicity. Devices that work in pigs or rodents must demonstrate safety, accuracy, and reproducibility in humans before being considered clinical alternatives.

Heterogeneity among molecules, diseases, pathways, and outcomes prevented a global quantitative estimate. The thematic synthesis, guided by the SWiM recommendations, made it possible to preserve differences between studies and avoid producing a combined effect without clinical significance (55). A meta-analysis could be considered in future reviews restricted to homogeneous molecules, indications, and outcomes.

Limitations of the Review

This review has limitations that should be considered. The main search focused on PubMed/MEDLINE, with with supplementation through reference tracking, Crossref, and journal records. Although this strategy made it possible to identify relevant and traceable studies, the lack of an independent systematic search across all international databases may have limited the sensitivity of retrieval.

The scope of the question required the inclusion of clinical, pharmacokinetic, mechanistic, and preclinical studies. This approach provided an integrated view of peptide development, but increased heterogeneity and prevented direct comparison across all studies.

Concentrating research on incretin agonists may have resulted in a disproportionate representation of metabolic applications relative to other areas. This predominance reflects the recent volume of research, but does not necessarily indicate the relative importance of all peptide classes.

The protocol was not registered prospectively on a public platform, which reduces the possibility of external verification of methodological decisions prior to sample selection. Even so, the eligibility criteria and the synthesis structure were defined before the final consolidation of the sample.

Also, no single certainty rating was assigned by GRADE, because the studies addressed different questions and included designs incompatible with an overall assessment. Quality was weighted according to study design, risk of bias, consistency, precision, and applicability.

Implications and Future Perspectives

Future development of peptide-based therapies should prioritize strategies capable of combining stability, bioavailability,
tissue selectivity, safety, and convenience. More efficient oral formulations may reduce the amount of active ingredient and variability in absorption. pH-responsive, enzyme-responsive, or local-marker–based delivery systems can increase delivery accuracy.

The use of peptide-drug conjugates, radionuclides, and receptor-targeted systems presents especially relevant potential in oncology. However, success will depend on appropriate patient selection, confirmation of target expression, and assessment of intratumoral distribution.

In neurology, new strategies should favor transport across the barrier blood–brain barrier or intranasal administration, in addition to including biomarkers that confirm exposure and target engagement. The absence of these data makes it difficult to distinguish pharm-

acological ineffectiveness from insufficient brain concentration.

The incorporation of computational modeling, artificial intelligence, peptide chemistry, and high-capacity screening methods could accelerate the identification of stable sequences, reduce immunogenicity, and predict interactions with receptors. However, computational optimization must be accompanied by rigorous experimental and clinical validation.

Independent comparative studies, cost-effectiveness assessments, and implementation research will also be needed. The benefit demonstrated in controlled trials may be reduced in practice due to adherence, cost, storage, training, availability of devices, and unequal access.

In summary, peptide therapies have demonstrated high versatility and relevant clinical benefits across multiple areas of medicine. Success was greater when structural modifications, formulation, route of administration and pathophysiological mechanism were developed in an integrated manner. Challenges related to degradation, absorption, tissue distribution, tolerability, production, and access remain. The negative results included in this review reinforce that extending shelf life or increasing stability is not enough when the peptide does not reach The target tissue, or not, modulates a determining mechanism of the disease. The next generation of peptide-based drugs should therefore integrate molecular engineering, precision pharmacology, and delivery technologies to turn biological potency into consistent clinical benefit.

CONCLUSION

Peptide-based therapies have established themselves as a highly relevant pharmacological platform for modern medicine, with clinical applications in metabolic, cardiovascular, genetic, gastrointestinal, osteometabolic, oncological, infectious, neurological, and painful conditions. The analyzed studies showed that receptor selectivity, the ability to reproduce physiological mechanisms, and the possibility of structural modification give peptides important advantages for the development of treatments directed. However, o harnessing this potential

remains directly conditioned on the ability to preserve molecular integrity, prolong pharmacological exposure, and ensure that the molecule reaches the target tissue at a sufficient concentration.

The main strategies used to overcome enzymatic degradation and the short half-life included amino acid substitutions, lipidization, reversible binding to albumin, conformational restriction, PEGylation, depot formulations and long-acting release implants. These approaches made it possible to reduce clearance, increase resistance to proteolysis, and extend the intervals between administrations. The results obtained with semaglutide, tirzepatide, setmelanotide, vosoritide, tedugl-utide, teriparatide, lanreotide, and other molecules showed that appropriate pharmaceutical engineering can turn naturally unstable peptides into medications with consistent clinical efficacy.

Oral bioavailability remained one of the most complex challenges. The association between semaglutide and SNAC showed that gastric absorption of a peptide can be made feasible through localized changes in the microenvironment and epithelial permeability. However, systemic exposure still depended on fasting, the volume of water, the interval until feeding, tablet erosion, and the concomitant administration of other medications. Liquid-ionic-based systems, self-orienting devices, and ingestible microneedles showed promising preclinical results, but they still require validation for repeated safety, reproducibility, acceptability, cost, and applicability in humans.

The most robust clinical evidence was observed among incretin agonists. Semaglutide and tirzepatide produced marked reductions in glycated hemoglobin and body weight, while semaglutide also reduced cardiovascular events in individuals with obesity and established cardiovascular disease. Early results with multi-receptor agonists indicated potential to broaden metabolic effects, although the safety and durability of benefits still require long-term follow-up. In other areas, peptides have shown benefits in genetic obesity, achondroplasia, short bowel syndrome, osteoporosis, tumors neuroendocrine, HIV multidrug-resistant,

hereditary angioedema, pruritus associated with hemodialysis, refractory pain and erythropoietic protoporphyria.

Studies with negative results also showed scientific relevance. The lack of clinical benefit from cilengitide and NLY 01 demonstrated that plasma stability, high molecular affinity, or prolonged half-life do not ensure efficacy when tissue distribution, target engagement, or the mechanism's involvement in pathophysiology are inadequate. Therefore, the development of new therapies should incorporate assessments of exposure in the target tissue, pharmacodynamic biomarkers, and molecular criteria for patient selection.

The heterogeneity of the molecules, populations, routes of administration, and outcomes prevented an overall quantitative synthesis. In addition, part of the absorption and release technologies remains limited to preclinical studies, while various clinical applications were investigated in small populations or in rare diseases. The concentration of studies on GLP-1 agonists and the absence of prospective protocol registration should also be considered when interpreting the findings.

It is concluded that peptide therapies present high versatility and the ability to generate relevant clinical benefits, provided that molecular development is integrated with pharmaceutical technology, pharmacokinetics, and the disease pathophysiology. Future advances should prioritize formulations with greater stability, less variable absorption, selective distribution, lower dosing frequency, and better tolerability. The combination of peptide engineering, intelligent drug-delivery systems, computational modeling, and precision medicine may increase the number of clinically feasible molecules and reduce the limitations currently associated with administration, bioavailability, and access to the target tissue.

Thus, the success of peptide-based therapies does not depend exclusively on their biological potency, but on the articulation between stability, bioavailability, selectivity,
safety, convenience, and clinical applicability. This integration represents the main path to turn new peptides and delivery systems into effective, reproducible, and accessible treatments in contemporary medicine.

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