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Review Article

Pharmacogenomics and Toxicogenomics of Bioactive Peptides: Special Focus on Therapeutic Peptides

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Abstract

Bioactive peptides and peptide-based therapeutics have emerged as a rapidly expanding class of pharmacological agents used to treat metabolic diseases, cancer, infectious diseases, and cardiovascular disorders. Advances in peptide engineering, structural optimization, and delivery technologies have accelerated the clinical translation of peptide drugs. Concurrently, pharmacogenomics and toxicogenomics are transforming precision medicine by enabling individualized prediction of drug efficacy, adverse reactions, and toxicological responses. Pharmacogenomics examines how genetic variability influences pharmacokinetics and pharmacodynamics, whereas toxicogenomics integrates transcriptomics, proteomics, metabolomics, and systems biology to characterize molecular toxicity pathways. This study comprehensively reviews the intersection of pharmacogenomics and toxicogenomics in bioactive peptides, with emphasis on therapeutic peptides and peptide drugs. We also discuss genomic determinants of peptide drug response, toxicogenomic biomarkers, omics-based safety evaluation, regulatory perspectives, computational approaches, and future directions for precision peptide therapeutics.

Keywords: Pharmacogenomics, Toxicogenomics, Bioactive Peptides, Drug Peptides.

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Introduction

Bioactive peptides are short amino acid sequences with impressive biological and pharmacological effects in living organisms. These small molecules regulate various physiological functions by interacting with receptors, enzymes, ion channels, and complex signaling pathways inside cells (1). Because of their unique structures and functions, bioactive peptides are gaining attention in biomedical science, pharmaceutical research, and new therapy development. They can target specific molecules while generally causing fewer side effects than many traditional medications (2-4).

These peptides can originate from a variety of natural and synthetic sources. Many are produced naturally, such as hormones, neurotransmitters, or signaling molecules that help to regulate cellular processes such as metabolism, immune responses, growth, and communication between nerve cells. Notable examples include peptide hormones like insulin and glucagon-like peptide analogs such as semaglutide, which are commonly used to manage diabetes and obesity. Bioactive peptides can also be derived from food proteins found in milk, fish, soy, eggs, and plants. They often show antioxidant, antimicrobial, antihypertensive, and anti-inflammatory effects. Additionally, some peptides are extracted from animal venoms and microbial products and display powerful biological activities that can be harnessed for medical purposes (5, 6).

Advances in pharmacogenomics and toxicogenomics have enabled researchers to identify biomarkers associated with peptide drug response and safety profiles. These discoveries support precision medicine strategies, allowing clinicians to select the most effective therapy for each patient. Consequently, the study of pharmacogenomics, toxicogenomics, and genomic determinants has become increasingly important in improving the clinical success of peptide-based therapeutics.

Therapeutic peptides stand between traditional small-molecule drugs and larger biologic therapies like monoclonal antibodies. Their smaller size allows them to interact effectively with biological targets, while their specific amino acid composition helps to minimize toxicity. Compared with many synthetic drugs, therapeutic peptides generally have a better safety profile (7-9). Based on their therapeutic potential, therapeutic peptides can be categorized into various classes (Figure 1). This study explores how genomic variations influence responses to therapeutic peptides, enabling personalized efficacy prediction and toxicity risk assessment for safer peptide-based drug development. Below, some of the most important and major classes of these molecules have been described:

Hormonal peptides (insulin, GLP-1 agonists)

Hormonal peptides are a major class of therapeutic peptides that regulate signaling processes in homeostasis and metabolism. Pharmacogenomics investigates how genetic variations influence the pharmacokinetics and pharmacodynamics of these peptides, thereby

affecting efficacy, safety, and individual patient responses. Insulin represents a well-established example, as polymorphisms in genes involved in insulin signaling, glucose transport, and metabolism (e.g., INS, INSR, and SLC2A4) can contribute to interindividual variability in glycemic control and therapeutic outcomes among patients receiving insulin therapy. Variations in genes such as transcription factor 7 like 2 (TCF7L), potassium inwardly rectifying channel subfamily j member 11 (KCNJ11), and peroxisome proliferator-activated receptor gamma (PPARG) can affect beta-cell function, which in turn affects blood sugar control. Changes in the insulin receptor (INSR) gene can alter how insulin binds to its receptor, sometimes requiring dosage adjustments. Regarding glucagon-like peptide-1 (GLP-1) agonists like liraglutide and semaglutide, certain single nucleotide polymorphisms (SNPs) in the GLP1R gene, such as rs6923761, are associated with less effective receptor activation and a weaker ability to lower glucose levels. Moreover, genetic variations in dipeptidyl peptidase 4 (DPP4) can influence peptide turnover and affect efficacy (10-12).

Toxicogenomics, by contrast, describes the pathways that lead to adverse outcomes. While insulin is generally safe, higher doses can lead to severe hypoglycemia, especially for those with genetic traits that dampen the body's counter-regulatory hormone responses, like variants in glucokinase (GCK) and ABC transporter subfamily C member 8 (ABCC8), which can worsen neuroglycopenic toxicity. Additionally, genetic differences in genes that control pancreatic ductal differentiation, such as PDX1 and HNF1A, might shed light on the rare occurrences of acute pancreatitis. By incorporating pharmacogenomic testing, treatments can be tailored to enhance their effectiveness while reducing genetic risks. Monitoring for toxicogenomic effects, particularly related to thyroid and pancreatic health, is crucial to ensuring the long-term safety of these peptide hormones in precision medicine (13-15).

Anticancer peptides

Anticancer peptides (ACPs) are small, positively charged peptide molecules with unique structures that allow them to target and disrupt cancer cell membranes specifically. Recent advances in peptide engineering have facilitated the development of sophisticated hybrid platforms, including peptide–drug conjugates that selectively deliver cytotoxic agents to cancer cells and multivalent peptides capable of simultaneously targeting multiple molecular pathways, thereby enhancing therapeutic efficacy and specificity (16). From a pharmacogenomic perspective, ACP effectiveness hinges on the specific genetic and epigenetic changes found in tumors. For instance, loss of the PTEN gene (phosphatase and tensin homolog) can increase phosphatidylserine on the outside of the cell, which boosts ACP binding. Conversely, too much ATP11B (a gene that helps flip lipids) can make the cell membrane less negatively charged, which can lead to resistance to ACPs. Additionally, variations in protease-related genes, such as CTSL (Cathepsin L1), that

activate or break down ACPs can affect individuals' responses to these treatments. Certain pharmacogenomic markers, such as microsatellite instability or the methylation status of O6–methylguanine–DNA methyltransferase (MGMT), may help predict ACP effectiveness in glioblastoma or colorectal cancer patients (17, 18). From a toxicogenomic standpoint, while ACPs are designed to protect normal cells, off-target toxicity remains possible. High-throughput transcriptomic and epigenomic profiling has shown that ACPs can actually ramp up the expression of pro-inflammatory genes like interleukin-6 (IL6), tumor necrosis factor (TNF), and nuclear factor kappa B (NFKB1) in kidney and liver tissues, which can lead to serious side effects like nephrotoxicity and hepatotoxicity (19, 20). Additionally, SNPs in complement regulatory genes, such as CD59, have been associated with hemolytic adverse reactions. Also, when ACPs cause mitochondrial membrane permeabilization, they trigger the expression of apoptosis-related genes, such as Bcl-2-associated X protein (BAX) and Cytochrome P450 1A1 (CYP1A1), which can contribute to cardiotoxicity (21, 22). Toxicogenomic signatures, including changes in miRNA profiles like miR-122 linked to liver injury, act as early indicators of organ damage caused by ACPs. Tumor heterogeneity also plays a significant role in both pharmacogenomic resistance and toxicogenomic vulnerability. By integrating next-generation sequencing of both germline and tumor genomes, dosing can be optimized to minimize toxicity while enhancing the anticancer effects. Current toxicogenomic research using Clustered regularly interspaced short palindromic repeats (CRISPR-Cas9) screens is uncovering genetic factors that influence the safety of ACPs, paving the way for safer peptide-based cancer treatments (23, 24).

Antimicrobial peptides

Antimicrobial peptides (AMPs) are a diverse group of naturally occurring or synthetic molecules that play a crucial role in innate immunity and represent promising alternatives to conventional antimicrobial agents. In recent years, pharmacogenomic and toxicogenomic investigations have provided important insights into the mechanisms underlying the therapeutic efficacy and toxicity of AMP-based drugs. These peptides exert their antimicrobial activity primarily by disrupting microbial cell membranes (25, 26). Due to their cationic and amphipathic structures, AMPs interact electrostatically with negatively charged bacterial membranes, leading to pore formation, membrane destabilization, and ultimately microbial cell death. Beyond direct membrane disruption, some AMPs also modulate intracellular targets by interfering with nucleic acid synthesis, protein translation, and enzymatic activity. Moreover, AMPs exhibit potent antibacterial activity by selectively disrupting bacterial cell membranes, representing a promising strategy for combating antibiotic resistance (27). In addition, AMPs have immunomodulatory properties by regulating inflammatory signaling pathways. Genes involved in toll-like receptor (TLR) signaling, nuclear

factor kappa B (NF-κB), mitogen-activated protein kinase (MAPK), and cytokine production are critically involved in AMP-mediated immune responses (28, 29). Key genes such as TLR4, NFKB1, IL6, TNF-α, and Beta-defensin 1 (DEFB1) have been associated with variability in AMP activity and host susceptibility to infection (30).

Pharmacogenomic studies indicate that genetic polymorphisms affecting immune regulation, membrane composition, and peptide transport can influence therapeutic response to AMP drugs (31, 32). Simultaneously, toxicogenomic analyses have revealed that excessive AMP exposure may induce oxidative stress, mitochondrial dysfunction, apoptosis, and inflammatory tissue injury (33). Mitochondrial toxicity represents an additional mechanism of AMP-induced cellular damage. Because mitochondrial membranes share structural similarities with bacterial membranes, some AMPs may act in mitochondria and impair mitochondrial integrity. This can result in excessive reactive oxygen species (ROS) generation, disruption of ATP production, loss of mitochondrial membrane potential, and activation of apoptosis pathways (34, 35). Hemolysis is another important safety concern in AMP-based therapeutics. Certain amphipathic peptides can disrupt erythrocyte membranes through pore formation or detergent-like effects, leading to red blood cell lysis and hemoglobin release. Structural characteristics including peptide charge, hydrophobicity, and helicity strongly influence hemolytic activity. Genetic variability in erythrocyte membrane proteins and oxidative defense pathways may contribute to differential sensitivity among individuals. Genes associated with oxidative stress pathways, including Superoxide dismutase (SOD1), Cysteine Aminotransferase (CAT), Glutathione peroxidase 1 (GPX1), and BAX, are implicated in AMP-induced cytotoxicity (36, 37). Understanding these molecular pathways may facilitate the development of safer and more effective AMP-based therapeutics and support the advancement of precision antimicrobial medicine.

Immunomodulatory peptides

Immunomodulatory peptides (IMPs) are biologically active molecules capable of regulating innate and adaptive immune responses and have emerged as promising therapeutic agents for inflammatory, infectious, autoimmune, and malignant disorders. Recent advances in pharmacogenomics and toxicogenomics have enhanced understanding of the molecular mechanisms governing the efficacy and safety of these peptides. Unlike conventional immunosuppressive drugs, IMPs can either stimulate or suppress immune activity depending on the physiological context and target pathways involved (38). The mechanisms of action of immunomodulatory peptides involve interaction with immune cell receptors, modulation of cytokine release, and regulation of intracellular signaling cascades. Many IMPs activate TLRs, leading to downstream activation of NF-κB, Janus kinase/signal transducer and activator of transcription (JAK/STAT), and MAPK pathways. Through these mechanisms,

IMPs influence the production of inflammatory mediators such as IL-6, TNF-α, interferon-gamma (IFN-γ), and transforming growth factor-beta (TGF-β). Genes including TLR2, TLR4, NFKB1, signal transducer and activator of transcription 3 (STAT3), IL10, and TNF play essential roles in determining cellular responses to immunomodulatory peptides (39).

Pharmacogenomic studies suggest that genetic polymorphisms within immune-related genes may significantly affect patient responsiveness to peptide-based immunotherapies. Variations in cytokine genes, receptor expression, and signaling molecules can alter therapeutic efficacy and susceptibility to adverse reactions. Toxicogenomic investigations have additionally demonstrated that excessive immune activation by certain peptides may induce oxidative stress, mitochondrial injury, apoptosis, and cytokine imbalance (40). Genes associated with oxidative defense and apoptosis regulation, including B-cell lymphoma 2 (BCL2), BAX, Caspase 3 (CASP)3, SOD1, and GPX1, are involved in peptide-induced cellular toxicity (41). Understanding these molecular and genetic interactions may contribute to the development of safer, more targeted immunomodulatory peptide therapies and facilitate the advancement of personalized medicine approaches.

Cell-penetrating peptides

Cell-penetrating peptides (CPPs) are short bioactive peptides that can cross biological membranes and deliver a wide range of therapeutic cargoes, including nucleic acids, proteins, nanoparticles, and small-molecule drugs, into intracellular compartments. Due to their remarkable translocation capacity, CPPs have attracted significant attention as drug delivery systems in cancer therapy, gene therapy, and precision medicine (42). The mechanisms of CPP cellular uptake are complex and may occur through direct membrane translocation or energy-dependent endocytic pathways. CPPs commonly interact with negatively charged membrane phospholipids and glycosaminoglycans, facilitating membrane destabilization and internalization. Several uptake mechanisms have been proposed, including macropinocytosis, clathrin-mediated endocytosis, caveolae-dependent endocytosis, and pore formation (43). Intracellular trafficking and endosomal escape are critical determinants of therapeutic efficiency. Genes involved in membrane transport, vesicle trafficking, and cytoskeletal organization, including Caveolin-1 (CAV1), CLTC, Ras-related C3 botulinum toxin substrate 1 (RAC1), Ras homolog family member A (RHOA), and dynamin1 (DYN1) play essential roles in CPP uptake and intracellular distribution (44).

Pharmacogenomic investigations indicate that genetic variations affecting membrane receptors, transporter proteins, and endocytic signaling pathways may influence the cellular response to CPP-based therapeutics. Moreover, toxicogenomic analyses have demonstrated that excessive CPP exposure can induce membrane damage, oxidative stress, mitochondrial dysfunction, and inflammatory responses. Genes

associated with apoptosis and cellular stress pathways, such as BAX, BCL2, caspase 3 (CASP3), tumor protein p53 (TP53), and SOD1, have been implicated in CPP-induced cytotoxicity. In some cases, CPPs may also alter immune signaling pathways through activation of NF-κB and inflammatory cytokine production (45).

Peptide-drug conjugates

Peptide-drug conjugates (PDCs) are an emerging class of targeted therapeutic systems designed to improve drug selectivity, enhance intracellular delivery, and reduce systemic toxicity. These conjugates consist of three principal components: a biologically active peptide, a cytotoxic or therapeutic payload, and a chemical linker that connects the two molecules (46). Owing to their high specificity and favorable biocompatibility, PDCs have gained considerable attention in cancer therapy, antimicrobial treatment, and precision medicine. PDCs primarily act through receptor-mediated targeting. The peptide moiety selectively binds to overexpressed receptors on the target cells, facilitating cellular uptake through endocytosis. Following internalization, enzymatic or chemical cleavage of the linker releases the active drug within intracellular compartments. Several receptors involved in PDC targeting include integrins, somatostatin receptors, and growth factor receptors. Genes such as integrin beta-3 (ITGB3), somatostatin receptor 2 (SSTR2), epidermal growth factor receptor (EGFR), and Erb-B2 Receptor Tyrosine Kinase 2 (ERBB2) are critical to receptor expression and therapeutic responsiveness. Additionally, intracellular trafficking and lysosomal degradation pathways regulated by genes including Rab5 (RAB5), lysosome-associated membrane protein 1 (LAMP1), and Clathrin Heavy Chain (CLTC) influence drug release efficiency and therapeutic outcomes (47-49).

Pharmacogenomic studies suggest that variability in genes encoding cytochrome P450 enzymes, ATP-binding cassette transporters, and cellular uptake proteins can influence pharmacokinetics and treatment efficacy. Toxicogenomic analyses have also demonstrated that some PDCs may induce oxidative stress, mitochondrial injury, apoptosis, and inflammatory responses in non-target tissues. Genes associated with cellular stress and apoptosis pathways, including TP53, BAX, CASP3, SOD1, and GPX1, are implicated in PDC-related toxicity (49).

Radiolabeled peptides

Radiolabeled peptides are specialized peptide-based molecules conjugated with radioactive isotopes for diagnostic imaging and targeted radionuclide therapy. These compounds have become increasingly important in nuclear medicine because of their high specificity, favorable tissue penetration, and ability to selectively bind cellular receptors that are overexpressed in tumors and other pathological tissues. The mechanism of action of radiolabeled peptides is primarily based on receptor-mediated targeting. After systemic administration, the peptide component binds selectively to specific cell-surface receptors, followed by receptor-mediated internalization into target cells. The

attached radionuclide emits ionizing radiation that induces DNA damage, oxidative stress, and apoptosis in diseased cells. Commonly targeted receptors include somatostatin receptors, gastrin-releasing peptide receptors, and integrins. Genes such as SSTR2, gastrin-releasing peptide receptor (GRPR), integrin alpha-V (ITGAV), and EGFR are critically involved in receptor expression and treatment responsiveness (50). Furthermore, genes associated with DNA repair pathways, including Breast Cancer gene 1 (BRCA1), ataxia-telangiectasia mutated (ATM), and TP53, influence cellular sensitivity to radiation-induced injury.

Pharmacogenomic studies indicate that genetic variability in receptor expression, radionuclide transport, and DNA repair mechanisms may significantly affect individual responses to radiolabeled peptide therapy. Variations in these genes can alter therapeutic efficacy, radiation sensitivity, and treatment outcomes. Toxicogenomic investigations have additionally demonstrated that exposure to ionizing radiation may induce mitochondrial dysfunction, oxidative stress, inflammatory responses, and damage to non-target tissues such as the kidneys and bone marrow. Genes related to oxidative defense and apoptosis regulation, including SOD1, CAT, GPX1, BAX, and CASP3, are closely associated with radiotoxicity (51, 52).

Other bioactive peptides

Bioactive peptides are short sequences of amino acids that exert beneficial physiological and pharmacological effects through interactions with specific molecular targets. These peptides have attracted considerable attention in biomedical and pharmaceutical research because of their diverse biological activities, including antimicrobial, antihypertensive, antioxidant, immunomodulatory, anticancer, and anti-inflammatory properties.

Food-derived peptides are generated through enzymatic hydrolysis, fermentation, or gastrointestinal digestion of dietary proteins. Milk, soy, fish, egg, and plant proteins are major sources of bioactive food peptides. These peptides exhibit various health-promoting effects, including antioxidant, antihypertensive, antimicrobial, and immunomodulatory activities (53). Many food-derived peptides exert their effects by inhibiting angiotensin-converting enzyme (ACE), modulating inflammatory cytokines, or regulating oxidative pathways. Genetic variability in metabolic enzymes and transporters may influence peptide absorption, bioavailability, and therapeutic efficacy. Genes associated with antioxidant defense, such as SOD1, CAT, and GPX1, are often involved in cellular responses to these peptides (54).

Venom peptides are isolated from animal venoms, including those of snakes, scorpions, spiders, and cone snails. These peptides possess highly specific biological activities and are increasingly explored for drug development in pain management, cardiovascular disorders, and cancer therapy. Their mechanisms commonly involve modulation of ion channels, neurotransmitter release, and membrane receptors (55). Examples include ziconotide, a peptide derived from cone snail venom used to

treat severe pain. However, venom peptides may also induce neurotoxicity, cytotoxicity, and immune reactions. Toxicogenomic studies have implicated genes involved in ion transport, apoptosis, and inflammatory signaling pathways in venom peptide-induced toxicity (56).

Synthetic peptides are artificially designed molecules developed to enhance stability, selectivity, and therapeutic efficiency. Advances in peptide engineering have enabled the production of peptides with improved pharmacokinetic properties and reduced immunogenicity. These peptides are widely used in antimicrobial therapy, targeted drug delivery, and cancer treatment (57). Recombinant peptides, produced through genetic engineering technologies, are synthesized using microbial or mammalian expression systems. Recombinant insulin, interferons, and growth factors are important examples widely used in clinical medicine. Genetic factors affecting receptor signaling, immune regulation, and protein metabolism may significantly influence the efficacy and safety of recombinant peptide therapeutics.

Overall, classifying bioactive peptides by source provides valuable insight into their biological mechanisms, therapeutic applications, pharmacogenomic variability, and toxicological characteristics, supporting the development of safer, more personalized peptide-based therapies.

Bioactive peptides can also be classified by pharmacological function, as different peptides exert distinct biological activities through interactions with specific molecular targets and signaling pathways. These functional peptides have gained increasing importance in pharmaceutical and biomedical research because of their therapeutic potential in cardiovascular, metabolic, infectious, neurological, immunological, and oncological disorders (58). Accordingly, some major subgroups of bioactive peptides based on their pharmacological functions are as follows:

Antihypertensive peptides primarily reduce blood pressure by inhibiting angiotensin-converting enzyme (ACE), decreasing angiotensin II production and reducing vasoconstriction. Many of these peptides are derived from milk, fish, or plant proteins. Genes associated with the renin-angiotensin system, including ACE, AGT, and AGTR1, may influence individual responses to antihypertensive peptides. Toxicogenomic studies also suggest that excessive modulation of vascular signaling pathways may contribute to oxidative stress and endothelial dysfunction (59).

Neuroactive peptides function as neurotransmitters or neuromodulators in the central and peripheral nervous systems. They regulate neuronal communication, cognition, stress responses, and pain perception through receptors associated with dopamine, serotonin, and G protein-coupled signaling pathways. Genes such as Dopamine receptor D 2 (DRD2), Solute Carrier Family 6 (SLC6A4), and Catechol-O-Methyltransferase (COMT) are implicated in neuropeptide responses. Dysregulation of these pathways may contribute to neurotoxicity and mitochondrial impairment (60).

Opioid peptides, including endorphins and enkephalins, modulate pain transmission through interaction with opioid receptors. Variations in the mu-opioid receptor gene l (OPRM1) and related signaling genes may alter analgesic response and addiction susceptibility. Chronic activation of opioid pathways may also induce oxidative stress and inflammatory toxicity (61, 62). Immunomodulatory peptides regulate innate and adaptive immune responses through cytokine signaling and activation of pathways such as JAK/STAT, MAPK, and NF-κB. Genes including IL6, TNF, STAT3, and TLR2 play major roles in determining therapeutic efficacy and inflammatory responses. Toxicogenomic studies have demonstrated that excessive immune activation may lead to cytokine imbalance, apoptosis, and tissue injury (38).

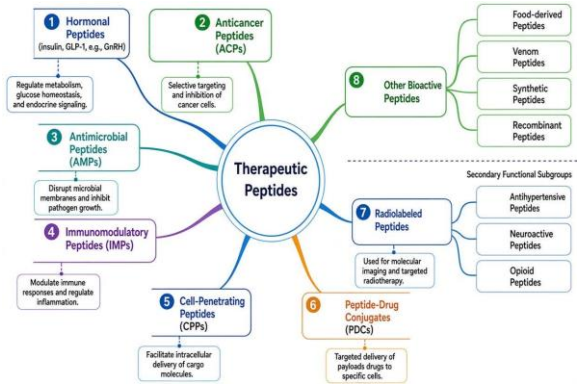


Figure 1. Some major classes of biologically active peptides.

Characteristics of peptide drugs

Peptide drugs possess several favorable characteristics that make them attractive therapeutic agents in modern medicine. Peptides are short chains of amino acids that can mimic the functions of naturally occurring proteins in the body. Due to their high specificity and selectivity, peptide drugs can effectively target specific receptors or biological pathways, reducing the risk of unwanted side effects compared with many conventional small-molecule drugs. Another important advantage of peptide drugs is their generally low toxicity. Since they are composed of naturally occurring amino acids, they are usually well-tolerated by the human body and are less likely to accumulate in tissues. Furthermore, peptide therapeutics often demonstrate strong biological activity even at low concentrations, making them highly effective in treating various diseases (31).

Peptide drugs also play a significant role in the treatment of conditions such as diabetes, cancer, metabolic disorders, and infectious diseases. Advances in biotechnology and peptide synthesis have improved their stability, bioavailability, and half-life, overcoming some limitations of earlier peptide-based therapies. In addition, peptides are biodegradable and break down into harmless amino acids after exerting their therapeutic effects. This characteristic contributes to their safety profile and reduces environmental concerns. Overall, the unique combination of efficacy, safety, specificity, and biocompatibility makes peptide drugs a promising class of pharmaceuticals for current and future medical applications (2, 63).

Genomic determinants of peptide drug response

Pharmacogenomics investigates how genetic variability influences individual responses to therapeutic agents by affecting drug absorption,

distribution, metabolism, excretion, target interaction, intracellular signaling, and susceptibility to adverse reactions. In the context of bioactive peptides, pharmacogenomic principles are particularly important because peptide-based therapeutics interact with highly specific receptors and signaling pathways that may vary considerably among individuals. Understanding these genomic differences is essential to optimize therapeutic efficacy, minimize toxicity, and advance personalized medicine strategies (64).

Genetic factors strongly influence the absorption and distribution of peptide therapeutics by regulating membrane transporters, endocytic pathways, and vascular permeability. Variations in ABC transporter genes, including ATP binding cassette subfamily B member 1 (ABCB1) and ABC subfamily G, isoform 2 (ABCG2), may alter peptide uptake, intracellular trafficking, tissue distribution, and consequently therapeutic outcomes. Similarly, polymorphisms in transport-related genes involved in endocytosis and vesicular transport, such as CLTC, CAV1, RAB5, can affect the delivery efficiency of CPPs and PDCs (65). Metabolism and excretion of bioactive peptides are also affected by genomic variation in proteolytic enzymes and metabolic pathways. Unlike many small-molecule drugs, peptides are primarily degraded by peptidases and proteases rather than hepatic cytochrome P450 enzymes. Polymorphisms in genes encoding neprilysin, DPP4, aminopeptidases, and matrix metalloproteinases may significantly influence peptide stability, half-life, and bioavailability (66). For example, genetic differences in DPP4 activity may alter the therapeutic response to GLP-1-based antidiabetic peptides. Additionally, variations in renal transport and filtration genes may influence peptide elimination and systemic exposure.

Target engagement represents another critical component of peptide pharmacogenomics. Many bioactive peptides exert their effects through highly selective interactions with membrane receptors or intracellular signaling proteins. Receptor polymorphisms may alter ligand-binding affinity, receptor activation, and downstream biological responses. Variations in genes such as GLP1R, EGFR, SSTR2, OPRM1, and TLR4 have been associated with altered responsiveness to antidiabetic peptides, anticancer peptides, opioid peptides, and immunomodulatory peptides (66, 67). In radiolabeled peptide therapies, receptor density and genomic variability significantly affect targeting efficiency and radiation sensitivity. Downstream intracellular signaling pathways also contribute to pharmacogenomic variability. Peptide therapeutics frequently regulate pathways such as PI3K/AKT, JAK/STAT, MAPK, and NF-κB, which are involved in cell proliferation, metabolism, apoptosis, inflammation, and immune responses. Genetic polymorphisms in signaling genes including AKT2, STAT3, NFKB1, IRS1, and MAPK1 may influence both therapeutic efficacy and cellular toxicity (68, 69). Altered signaling activity can additionally contribute to drug

resistance or exaggerated inflammatory responses (Figure 2).

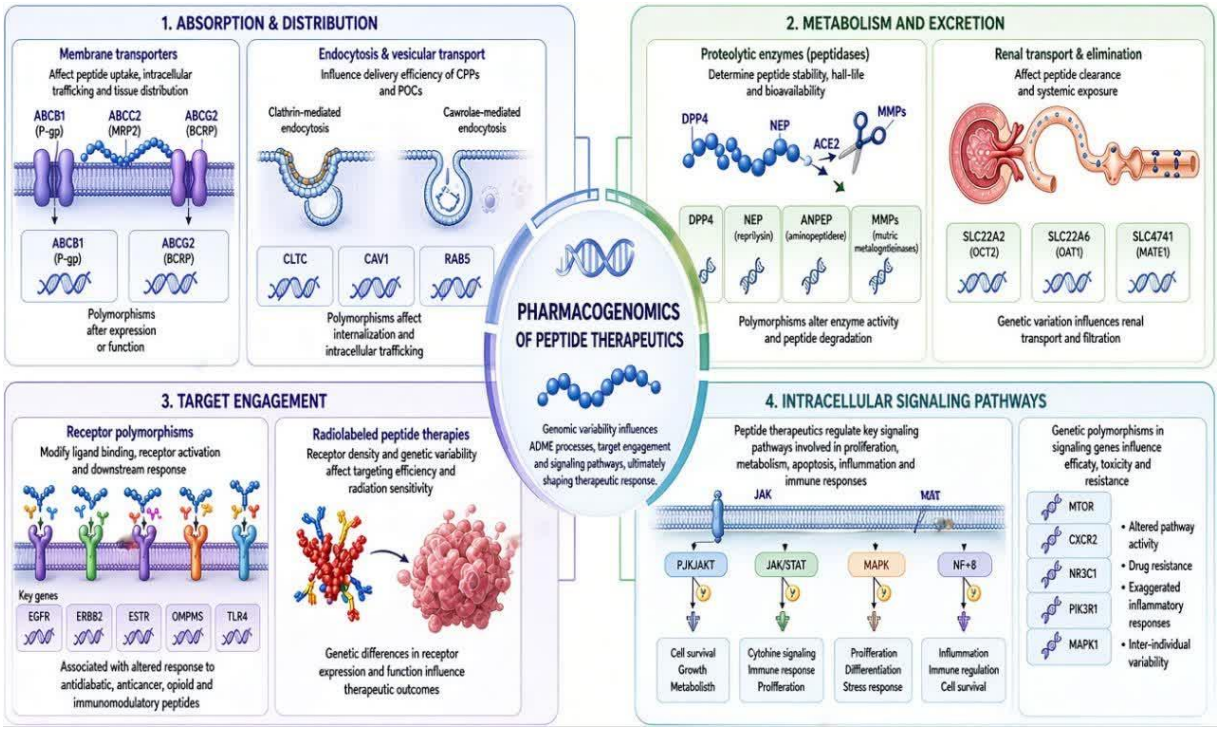


Figure 2. Pharmacogenomics of individual response to peptide drug

In addition, genetic differences in enzymes responsible for peptide degradation may affect drug stability and circulation time in the body. Certain individuals may metabolize peptide drugs more rapidly than others, requiring adjustments in dosage or treatment schedules. Genomic factors can also influence the likelihood of adverse drug reactions by affecting immune responses or cellular sensitivity to treatment. Advances in genomic technologies, including next-generation sequencing and genome-wide association studies, have enabled researchers to identify biomarkers associated with peptide drug response. These discoveries support precision medicine strategies, allowing clinicians to select the most effective therapy for each patient. Consequently, studying genomic determinants has become increasingly important for improving the clinical success of peptide-based therapeutics (70, 71).

Receptor gene polymorphisms

Receptor gene polymorphisms are genetic variations in the genes that encode cellular receptors. These variations can significantly influence the way individuals respond to drugs, including peptide therapeutics. Since receptors are primary targets for many medications, alterations

in receptor structure or expression may affect drug binding, signal transduction, and overall therapeutic outcomes. SNPs are among the most common forms of receptor gene variations. These genetic differences can modify receptor function by changing amino acid sequences, altering receptor density on cell surfaces, or influencing gene expression levels (72, 73). As a result, patients with different receptor gene variants may respond differently to the same treatment.

In peptide therapeutics, receptor gene polymorphisms are particularly important because peptide drugs often act through highly specific receptor-mediated mechanisms. For example, variations in genes encoding hormone receptors, growth factor receptors, or G protein-coupled receptors may lead to differences in drug sensitivity and effectiveness. Some polymorphisms can enhance receptor activity, while others may reduce receptor responsiveness, potentially requiring individualized dosing strategies.GLP-1 receptor agonists such as semaglutide, liraglutide, and exenatide represent one of the most successful peptide drug classes. Also, Specific polymorphisms such as rs6923761 have been associated with altered therapeutic responses in diabetic patients (74, 75). Somatostatin analogues including octreotide and lanreotide exhibit variable efficacy in acromegaly and neuroendocrine tumors (76).

Opioid peptide receptors are important molecular targets involved in pain regulation, reward pathways, and various physiological functions. Endogenous opioid peptides, such as endorphins and enkephalins, exert their effects primarily through μ-opioid receptors encoded by the OPRM1 gene (77). Genetic variations in OPRM1 can significantly influence receptor function and individual responses to opioid-based therapies. One of the most extensively studied polymorphisms is A118G, which alters receptor expression and ligand-binding properties. This variant has been associated with differences in pain sensitivity, analgesic efficacy, and susceptibility to opioid dependence (78).

Genetic factors in peptide metabolism

Genetic polymorphisms affecting enzymes involved in peptide metabolism can alter enzyme activity, expression levels, or substrate specificity, which may lead to substantial interindividual differences in drug exposure and therapeutic outcomes. As a result, some patients may experience rapid degradation of peptide drugs, reducing their effectiveness, while others may have prolonged drug exposure and an increased risk of adverse effects. These differences are particularly important for peptide hormones, growth factors, and therapeutic analogs designed to mimic endogenous peptides. Advances in pharmacogenomic research have enabled the identification of genetic biomarkers associated with peptide metabolism, which can be used to predict treatment response and optimize dosage regimens (79, 80).

Genetic and epigenetic factors may substantially influence the metabolism, activity, and toxicity of bioactive and therapeutic peptides by regulating gene expression and molecular signaling

pathways. Recent evidence demonstrates that bioactive compounds can modulate miRNAs, including miR-145, miR-200a, and miR-223-3p, as well as genes involved in metabolic and reproductive pathways. These findings support the integration of toxicogenomic and pharmacogenomic approaches to investigate interindividual variability in peptide responses. Characterizing gene-expression profiles and regulatory networks may therefore help predict peptide efficacy, toxicity, metabolism, and patient-specific responses, facilitating safer and more personalized development of peptide-based therapeutics (81-83).

DPP-4 is a key enzyme involved in the metabolism of incretin peptides, particularly GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). These hormones play essential roles in glucose homeostasis by stimulating insulin secretion and suppressing glucagon release following food intake. DPP-4 rapidly degrades incretin peptides, thereby limiting their biological activity and duration of action. Genetic variations in the DPP4 gene may influence enzyme expression and activity, potentially affecting the effectiveness of incretin-based therapies used in the treatment of type 2 diabetes. Individuals carrying certain genetic variants may exhibit differences in incretin degradation rates, insulin responses, and glycemic control. Such variability may contribute to differences in clinical outcomes among patients receiving DPP-4 inhibitors or GLP-1 receptor agonists (70, 84).

Pharmacogenomic studies have suggested that DPP4 polymorphisms could serve as biomarkers for predicting therapeutic response (84). Understanding these genetic influences may help clinicians select the most appropriate treatment strategy and optimize patient care. Furthermore, research on DPP-4 and incretin peptides provides valuable insights into the mechanisms underlying metabolic diseases.

Transporter polymorphisms

Transporter polymorphisms refer to genetic variations in membrane transport proteins that regulate the absorption, distribution, and cellular uptake of drugs. Although peptide drugs often rely less on classical transport systems than small-molecule medications, transporter proteins can still influence their pharmacokinetic behavior and therapeutic effectiveness. Variations in transporter genes may alter protein expression, transport capacity, or substrate recognition. Members of transporter families such as ABC transporters and solute carrier (SLC) transporters have been investigated for their potential roles in peptide drug disposition (85). Polymorphisms in these transporters can affect tissue penetration, drug clearance, and intracellular concentrations. Consequently, individuals with different transporter genotypes may exhibit variable responses to the same peptide therapy. Transporter polymorphisms may also contribute to differences in drug toxicity and treatment outcomes. Reduced transporter activity can increase systemic exposure to a peptide drug, whereas enhanced transport may lower circulating

concentrations and decrease therapeutic efficacy. Identifying these genetic factors can improve the prediction of patient responses and support individualized dosing strategies.

Toxicogenomics of peptide-based therapeutics

Toxicogenomics has emerged as a valuable field for understanding the safety profile of bioactive peptides and peptide-based therapeutics. By integrating genomic data with toxicological outcomes, toxicogenomics helps identify genetic factors that contribute to interindividual variability in drug toxicity. Although peptide drugs are generally considered safer than many conventional small-molecule drugs due to their high target specificity and biodegradability, adverse reactions may still occur in susceptible individuals. The mechanisms underlying peptide drug toxicity are often multifactorial. One important mechanism involves excessive activation or inhibition of target receptors, leading to unintended physiological effects. In addition, some peptide therapeutics may trigger immune responses, resulting in hypersensitivity reactions or the formation of anti-drug antibodies that alter treatment efficacy and safety. Off-target interactions, although less common than with small molecules, may also contribute to toxicity under certain conditions. Toxicogenomic variations can significantly influence toxic responses. Genetic polymorphisms may alter drug exposure and tissue sensitivity, and patients with specific genetic variants may be more susceptible to adverse events despite receiving standard therapeutic doses. Reported adverse effects associated with peptide drugs vary depending on the therapeutic class and route of administration. Commonly observed reactions include injection-site irritation, gastrointestinal disturbances, nausea, headache, and mild immune-mediated responses (86). Toxicogenomics may partially explain why these events occur in only a subset of treated individuals.

Advances in toxicogenomic and pharmacogenetic research provide opportunities to identify biomarkers associated with toxicity risk before treatment initiation. Such approaches support the development of personalized therapeutic strategies, enabling clinicians to optimize drug selection, adjust dosing regimens, and minimize adverse effects. Ultimately, integrating genomic information into peptide drug development and clinical practice may improve both safety and therapeutic effectiveness.

Transcriptomics in peptide toxicity assessment

Transcriptomics plays an important role in the assessment of peptide drug toxicity by examining changes in gene expression patterns following exposure to bioactive peptides. This approach provides a comprehensive view of cellular responses and helps identify molecular pathways associated with toxic effects before clinical symptoms become apparent. By analyzing mRNA profiles, alterations in genes involved in inflammation, oxidative stress, apoptosis, immune regulation, and cellular metabolism can be detected. In peptide toxicity studies, transcriptomic technologies such as RNA sequencing and microarray analysis are widely used to identify

biomarkers that predict adverse reactions. These biomarkers can reveal early signs of tissue injury and provide insights into the mechanisms underlying toxicity (87, 88). Furthermore, transcriptomic data can help distinguish between adaptive biological responses and harmful toxic effects. When combined with pharmacogenomic information, transcriptomics offers a powerful tool for personalized medicine. Genetic differences among individuals may influence gene expression responses to peptide therapies, contributing to variability in safety outcomes. Therefore, transcriptomic analysis enhances the prediction, monitoring, and prevention of peptide-induced toxicity while supporting the development of safer and more effective therapeutic peptides.

Epigenomics

Epigenomics is the study of genome-wide epigenetic modifications that regulate gene expression without altering the underlying DNA sequence. These modifications include DNA methylation, histone modifications, and non-coding RNA activity (89). In peptide drug research, epigenomic analysis helps researchers understand how therapeutic peptides influence gene regulation and cellular function. Epigenetic changes can affect drug response, toxicity, and disease susceptibility. Exposure to bioactive peptides may alter epigenetic patterns, leading to changes in the expression of genes involved in metabolism, immune function, inflammation, and cell survival (90). Furthermore, individual epigenetic profiles may contribute to variability in therapeutic outcomes among patients. Combining epigenomic data with pharmacogenomics provides a more comprehensive understanding of drug responses and adverse effects. As a result, epigenomics is becoming an increasingly important tool in evaluating the safety and efficacy of peptide therapeutics (91).

Challenges and Limitations

Despite their therapeutic potential, bioactive peptides face several challenges and limitations that can restrict their clinical application. One major obstacle is their poor oral bioavailability, as many peptides are rapidly degraded by digestive enzymes and exhibit limited absorption across biological membranes. Consequently, numerous peptide drugs require parenteral administration, which may reduce patient compliance. Another challenge is their relatively short half-life in circulation due to enzymatic degradation and rapid clearance. Although chemical modifications and advanced delivery systems have improved peptide stability, these strategies may increase development costs and manufacturing complexity. In addition, large-scale peptide production often requires sophisticated synthesis and purification processes, making peptide therapeutics more expensive than many conventional drugs. Variability in patient responses also remains a concern. Genetic, epigenetic, and environmental factors can influence treatment efficacy and safety, highlighting the need for personalized approaches. Furthermore, some peptide drugs may induce immunogenic reactions or lose effectiveness over time. Addressing these

limitations through advances in drug delivery, peptide engineering, and precision medicine will be essential for expanding the successful clinical use of bioactive peptides.

The introduction of new medicines, particularly protein-based and other biopharmaceutical products, into the pharmaceutical market is a complex and highly regulated process requiring careful consideration of scientific, clinical, regulatory, manufacturing, and economic factors. These products must undergo extensive laboratory and preclinical investigations followed by well-designed clinical trials to establish their quality, safety, efficacy, and therapeutic value before marketing authorization. Moreover, regulatory requirements, approval delays, manufacturing complexity, supply-chain vulnerabilities, and limited availability of essential materials may restrict timely market access, particularly in developing countries. Therefore, successful commercialization requires effective risk management and economic evaluation to ensure that innovative therapies are clinically valuable, accessible, and financially sustainable (92-95).

Conclusion

Bioactive and therapeutic peptides represent one of the fastest-growing therapeutic modalities in modern medicine. Pharmacogenomics and toxicogenomics of therapeutic peptides provide critical frameworks for understanding variability in efficacy, safety, and toxicity among individuals. Genetic polymorphisms affecting receptors, signaling pathways, proteolytic enzymes, and immune responses significantly influence peptide drug outcomes. Simultaneously, toxicogenomic technologies including transcriptomics, proteomics, metabolomics, and systems biology are revolutionizing predictive toxicology and precision medicine. The integration of pharmacogenomics with toxicogenomics offers enormous potential for optimizing peptide therapeutics, minimizing adverse reactions, and enabling individualized treatment strategies. Continued advances in omics technologies, computational biology, and systems pharmacology will further accelerate the development of safer and more effective peptide-based medicines.

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Use of Artificial Intelligence

The authors declare that no generative AI tools were used in the writing of this manuscript. The layout of Figure 2 was initially generated by AI; however, substantial modifications, refinements, and scientific details were subsequently added by the author for

minimizing the original AI-generated content and ensuring scientific accuracy.

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