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Sustainable Peptide synthesis and design: Integrating green synthesis and computational tools

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Abstract

Peptides play an important role in biological systems and are applicable in different sectors such as therapeutics, biomaterials, drug delivery systems, etc. However, they also face issues pertaining to stability and oral bioavailability. Moreover, the costs involved in conventional peptide design can get very high. Novel peptide synthesis approaches have emerged as an effective and sustainable method for peptide design in addition to computational strategies. The current review explores this landscape of peptide synthesis and design; it discusses the key green metrics used in evaluation of the process of peptide synthesis and mentions important breakthroughs in sustainable peptide synthesis methods while also highlighting the computational tools and methods enabling such processes. It also mentions the recent innovations that have enhanced the process of sustainable peptide synthesis and design. The review underscores the importance of combining computational predictions with experimental validation to optimize peptide sequences for various applications, including drug development and diagnostics.

1 Introduction

Peptides are essential in biological systems, facilitating major protein-protein interactions (PPIs) and contributing to crucial cellular processes like transport and signaling. Their remarkable binding specificity makes them promising therapeutic candidates, providing unique advantages that position them between small molecules and large biologics as drugs. Peptides can be chemically synthesized, facilitating large-scale production and allowing precise modifications at specific sites. Additionally, they exhibit low immunogenicity and can achieve effective tissue and cellular penetration when appropriately modified (1). Due to the aforementioned reasons, peptides have emerged as a promising category of drugs, with nearly 20 new peptide-based clinical trials initiated each year. The financial impact of these advancements is evident, as the peptide drug market has grown at a compound annual growth rate (CAGR) of 9.1% from 2016 to 2024, largely driven by improvements in computational methodologies (1, 2).

However, peptide-based drugs also face significant challenges, primarily their instability in vivo and poor membrane permeability. Their susceptibility to proteolytic degradation in serum shortens their half-life and reduces bioavailability, necessitating frequent dosing to sustain therapeutic effectiveness (1). Peptide chemical synthesis also has inherent limitations compared to small molecules due to its iterative nature. The peptide bond formation requires activation of the acid moiety in protected amino acids, which restricts efficiency (2).

Additional challenges in industrial peptide production involve scalability, optimizing yield, addressing bitterness that affects sensory performance, uncertainties in molecular mechanisms, and ensuring the sustainability of materials used for large-scale manufacturing (3). Despite the shortcomings and challenges associated with peptide-based therapeutic design, recent technological advances in drug delivery, formulation, and chemistry have generated a lot of interest in peptide therapeutics (4). The

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current review focuses on the different tools and synthesis methods for peptide design highlighting the new innovations that have led to the improvement in the process, making it more sustainable over time. It also covers the importance of computational interventions such as peptide databases in detail along with the current advances in peptide design due to the impact of Machine Learning (ML) and Deep Learning (DL) tools.

2 Evaluation of Sustainable Peptide Synthesis

The American Chemical Society's Green Chemistry Institute (ACS GCI) promotes sustainable chemistry through initiatives like the Pharmaceutical Roundtable (ACS GCI-PR), which, though initially focused on small molecules, has increasingly addressed peptides. As peptides gain prominence, sustainable practices must balance environmental goals with cost-efficiency. For new chemical entities (NCEs), high profit margins lessen API cost concerns, but in the generics market, price competition makes cost-effective, green synthesis essential. Intellectual property and cost remain key barriers to broader adoption of sustainable methods (5).

2.1. Green Metrics Used in Peptide Synthesis

As mentioned earlier, the iterative nature of peptides makes it difficult to synthesize. The fact that the formation of the peptide bond is always performed by activating the acid moiety of the protected amino acid, make green metrics like Trost's atom economy, Wender's step count, and Baran's ideality factor unsuitable for assessing sustainability of peptide synthesis. Alternative green metrics such as Sheldon's complete environmental factor (cEF) and process mass intensity (PMI) provide better comparisons by accounting for all chemicals, including water, used in the process (2).

2.1.1. Complete Environmental Factor (cEF)

The Complete E-Factor (cEF) is an extension of the traditional E-Factor concept, which quantifies the total mass of waste generated per unit mass of product. The cEF includes not only process-related waste but also waste associated with the production of raw materials and reagents, offering a more comprehensive view of a process's environmental impact. Since cEF accounts for all process materials including solvents and water and assumes no recycling, it is more appropriate for total waste stream analysis (6, 7).

2.1.2. Process Mass Intensity (PMI)

First put together by ACS GCI-PR to correctly assess sustainability efforts in peptide synthesis, the property Mass Intensity (PMI) is currently the most comprehensive assessment metric for synthetic peptide environmental metrics. It is defined as the overall mass of all materials utilized—such as raw materials, reactants, and solvents—to generate a given amount of product. However, it's important to note that PMI does not consider the environmental impact associated with the production of starting materials and reagents. Another limitation of PMI is that it overlooks the types of materials used and excludes other important factors such as energy consumption, transportation logistics, environmental impact, and the complexity of starting materials (7).

$$cEF = \frac{\Sigma m \text{ (raw material inputs)} - m(\text{products})}{m(\text{products})}$$

$$PMI = \frac{\Sigma m \text{ (raw material inputs)}}{m(\text{products})}$$

3 Methods in Sustainable in Peptide Production

Traditional methods for peptide synthesis typically involve processes such as classical solution peptide synthesis (CSPS), and Solid phase peptide synthesis (SPPS). CSPS was the earliest method developed for peptide synthesis. This approach enables the

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use of minimal reagent excess, which is beneficial both economically and environmentally. However, CSPS is labor-intensive and extremely time-consuming, particularly when synthesizing peptides for research purposes or producing medium to long peptides on a large scale. In this method, each intermediate is typically isolated and often characterized, which can lead to high-quality crude products but at the cost of significant time and manual effort (8). The introduction of solid-phase peptide synthesis (SPPS) by Merrifield in 1963, led to the transformation in the previously dominant liquid-phase methods, making peptide synthesis significantly easier, more efficient, and more accessible. Moreover, further improvements in the SPPS methods in the following decades lead to the introduction of the Fmoc-based strategy which marked a significant advancement in SPPS, offering a safer and more advantageous alternative to earlier methods that involved the use of hazardous hydrofluoric acid. This improvement in reaction conditions greatly enhanced the efficiency of peptide synthesis and enabled the development of automated synthesis techniques. Despite these advancements, synthesizing peptide chains with "difficult sequences" containing more than 50–60 amino acids remains a considerable challenge, even with automation. While microwave-assisted synthesis can improve overall yields, its effectiveness is limited when dealing with such complex sequences (9–11). Additionally, SPPS has several disadvantages, including the need for large excess of reagents and substantial volumes of solvents such as dichloromethane, dimethylformamide etc. at each step of the synthesis and also relies heavily on organic solvents which are classified as hazardous under REACH regulations (12). From a green chemistry standpoint, reducing these quantities is highly desirable (8).

Bioactive peptides can also be extracted via processes such as enzymatic hydrolysis, microbial fermentation and recombinant production. The simplest and most widely used method for producing bioactive peptides is enzymatic hydrolysis, particularly using digestive enzymes (13). However, conventional enzymatic hydrolysis is often limited by the availability of raw materials and the challenge of incomplete protein breakdown, highlighting the need for alternative approaches (14). Microbial fermentation uses bacterial enzymes to break down proteins into smaller peptides. This process, a form of enzymatic hydrolysis, relies on microbes with strong proteolytic activity—common in many industrial starter cultures. Both starter and non-starter bacteria used in fermented foods can generate bioactive peptides (15). Bioactive peptides produced through microbial fermentation can be purified without the need for hydrolysis, making the process more cost-effective than enzymatic methods (16). In recombinant peptide production, genes encoding the desired peptides are expressed using either in vivo or in vitro systems. In in vivo systems, the peptide gene is often fused to a carrier protein to aid purification, enabling large-scale production—used for drugs like desirudin (17), typically expressed in yeast. The more advanced in vitro (cell-free) system conducts peptide synthesis outside of living cells using essential transcription and translation components. While faster, its high cost limits use to research or specialized peptides. Currently, many therapeutic peptides are also produced using a mix of chemical synthesis and recombinant methods (15). Utilization of biological recombinant methods can reduce reliance on hazardous reagents and lower production costs over time. One such method is the molecular farming approach which refers to the use of genetically engineered plants and plant-based systems to produce high-value peptides and proteins, mainly for antimicrobial peptides (AMPs) production (18). A key advancement in this field has been the use of viral vectors. The viral genome after undergoing removal of “unnecessary”

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sequences to create appropriate vectors are called 'deconstructed' vectors. These vectors are then used for large scale peptide production. For example, the pEAQ-HT vector, by Chaudhary et al., produced peptides at concentrations of 0.07 mg/g of leaf tissue, demonstrating the system's potential for industrial-scale synthesis (19). To address plant toxicity issues associated with AMP expression, unique strategies have been employed. These include inducible promoters that activate peptide production only when triggered externally, and sequestration methods that direct peptides to inert compartments like the apoplast. Techniques such as fusing AMPs with SUMO tags or expressing them as tandem repeats have further improved peptide stability and reduced toxicity, enabling successful large-scale expression (18, 20).

Liquid-Phase Peptide Synthesis (LPPS) is a modern approach to peptide production that merges the strengths of CSPS and SPPS. It emerged as a response to the growing demand for peptides in therapeutics, as well as the need for more efficient, scalable, and environmentally friendly production methods. LPPS addresses the issues pertaining to solvent reliance and labor intensiveness faced by CSPS and SPPS by performing reactions in solution (like CSPS) while using a soluble tag to support the growing peptide chain. This tag enables easier separation and purification without the need for excessive solvent use or chromatography. Unlike SPPS, which uses large, solid polymers, LPPS relies on small, well-defined molecules or soluble polymers, drastically reducing solvent consumption and chemical waste. From a sustainability perspective, LPPS is a major advancement as it offers lower solvent and reagent use, reduced energy consumption, lower labor requirements. high scalability (from research scale to tons of product), adequate automation potential and overall lower production costs and environmental footprint (Figure 1) (8).

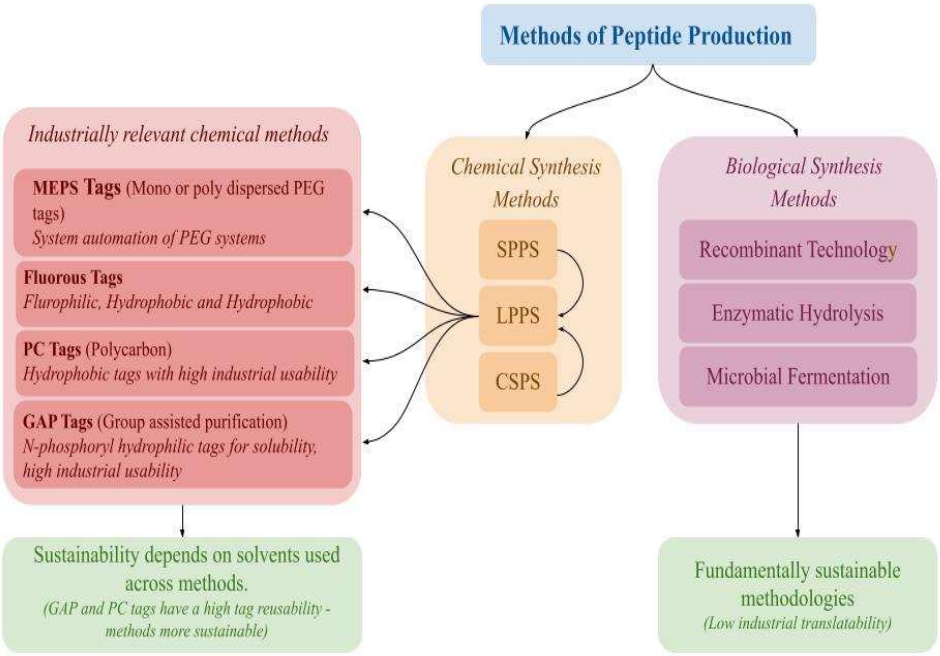

Fig. 1: Methods in peptide synthesis: role of LPPS

Sustainable Peptide Synthesis and Design

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3.1. Advancements in peptide synthesis approaches

Recent years have witnessed a growing interest in alternative peptide synthesis methods. Some of the earlier green peptide synthesis approaches involved usage of water-dispersible amino acid nanoparticles, eliminating the need for traditional organic solvents. In solid-phase synthesis, Fmoc-protected amino acids formed nanoparticles that efficiently reacted with resins in water. During the solution-phase synthesis, Boc-protected amino acids were used similarly with water-soluble reagents like 4-(4, 6-dimethoxy-1, 3, 5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM). This nanoparticle approach boosted reaction efficiency by increasing surface area and dispersion, reducing both reaction time and solvent waste, while maintaining high yield and purity (21). More recently, Mattelone et al., proposed a green solution-phase peptide synthesis (GSolPPS) via a continuous protocol using propylphosphonic anhydride T3P® as the coupling reagent and N-benzyloxycarbonyl-protecting group (Z), which is easily removed by hydrogenation. Here, the dimethylformamide (DMF) is replaced by EtOAc and the complete protocol has achieved a PMI of 30, one of the lowest in the peptide synthesis. This protocol was instituted in achieving significantly less levels of PMI thereby synthesizing increasingly sustainable peptides (22).

Continuous-flow peptide synthesis is a method that allows for the continuous and efficient assembly of peptides by flowing reactants through a packed column bed. Peptide synthesis under continuous-flow conditions offers several benefits over traditional batch and discontinuous microwave SPPS methods. For instance, continuous flow through a packed column enables faster, more cost-effective, and efficient removal of excess reagents compared to batch washing. Moreover, this approach significantly reduces the typical excess of coupling agents and solvents required in standard SPPS processes (23). Recently, Ruhl et al, used a 10-amino acid sequence from a known PCSK9 inhibitor as a model, and demonstrated that continuous flow-SPPS offers significant advantages over traditional batch-mode SPPS, including faster optimization, reduced waste, shorter timelines, and streamlined scale-up. To support larger production, they designed a hydraulically controlled continuous flow-SPPS prototype that efficiently translates small-scale optimizations into scalable peptide synthesis (24). The Sustainable Ultrasound-assisted Solid-Phase Peptide Synthesis (SUS-SPPS) method also significantly reduces solvent consumption, time, washing and reagent use compared to conventional manual SPPS by leveraging ultrasound at each synthesis stage and work-up, reducing the process to two steps- the initial step integrates Fmoc-amino acid coupling, capping of any unreacted amines, and Fmoc group removal into one streamlined process, followed by a second step involving a single wash procedure. This process not only reduced solvent use per coupling cycle by 83–88%, but also was compatible with various resins (Rink-amide, Wang, Cl-Trt) and enabled efficient production of peptides, including 20-mers and difficult sequences. It improved reaction rates, yields, and purity while minimizing waste and side reactions like racemization. Furthermore, the SUS-SPPS approach was validated by synthesizing biologically relevant and aggregation-prone peptides, which are traditionally challenging to synthesize due to incomplete couplings and steric hindrance thus demonstrating its potential as a greener alternative for peptide production (25). Other approaches in green peptide synthesis include the Microwave-assisted peptide synthesis (MW-SPPS) that leverages dielectric heating to drastically reduce reaction times, improve yields, and minimize waste. Unlike conventional heating methods, microwave irradiation enables rapid and uniform heating, which enhances reaction kinetics and solubility, particularly in polar, environmentally friendly solvents such as water, alcohols, DMSO, or acetone. MW-SPPS also minimizes common side reactions like aspartimide formation and racemization, leading to higher purity products. Its adaptability allows

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integration with other sustainable techniques, such as using green solvents or alternative coupling agents. Initially limited to small-scale synthesis, recent advances in scalable microwave reactors have enabled multigram to kilogram peptide production under GMP conditions (26). For example, Collins et al. demonstrated that MW-SPPS could reduce waste by up to 90% and cut reaction time from 60 minutes to 4 minutes per cycle, while increasing purity and yield across a diverse set of peptides (27).

Chemo-enzymatic peptide synthesis (CEPS) proposed by Pawlas *et al.*, is an effective approach for sustainable peptide manufacturing which involves ligation of chemically synthesized peptides using enzymes. The process involved synthesis of antidiabetic peptide, exenatide using SPPS, and enzymatic ligation, while optimising synthesis and scalability. Two fragments of exenatide namely, 1-21 and 22-39 were synthesized chemically and thereafter the two were ligated using Omniligase-1. Enzymatic ligation with Omniligase-1 replaced traditional chemical coupling agents, avoiding hazardous reagents and allowing milder reaction conditions while using acetonitrile as a greener co-solvent. The process was further optimized to lower waste (cEF) and carbon intensity (CI), ensuring high yields with minimal environmental impact. By assessing economic feasibility, the study successfully integrated green chemistry principles without significantly raising production costs, promoting a more sustainable and scalable approach to therapeutic peptide manufacturing (28). Recently, mechanochemical methods have been reported by Wehbe et. al. for N-acylation of silk sericin lipopeptide. Sericin is a hydrophilic peptide composed of serine, aspartic acid and glycine and has antibacterial, antioxidant and anticoagulant properties. A one-pot, two-step process involving 1, 1′-carbonyldiimidazole for fatty acid activation and optimization of acylation was performed using mechanical methods of vibrational and planetary ball mills. Ethylacetate, an FDA approved food additive, was chosen as the liquid-assisted grinding agent (LAG), which contributed to an increase in the acylation rate. This method was then applied to graft hydrophobic chains onto silk sericin hydrolysates using fatty acids with 10–14 carbon atoms, resulting in acylation rates of 48–51%. The resulting lipopeptides exhibited good surface activity and significantly reduced surface tension. Importantly, green metrics analysis demonstrated this method's environmental advantages over the traditional Schotten–Baumann approach, making it a compelling sustainable alternative for peptide modification (29).

3.2. Choice of raw materials

As evident from the previous examples pertaining to the innovations in green peptide synthesis, the choice of raw materials play a pivotal role in reducing the environmentally hazardous effects. As of now, and likely continuing through 2030, peptides are primarily produced through chemical synthesis. This trend is largely driven by the types of production facilities used by pharmaceutical companies and CDMOs. Among chemical methods, liquid-phase and solid-phase synthesis are the most common, accounting for 39% and 41% of use, respectively (2). However, to ensure more sustainable peptide synthesis practices, it is imperative to switch to other 'greener' raw material alternatives.

3.1.1. Solvents

Commonly employed solvents in peptide synthesis such as DMF, diethyl ether, dichloromethane and N- methyl-2-pyrrolidone (NMP) account for most of the waste produced in chemical processes, which is particularly significant in SPPS methods (2). Consequently, studies have reported various substitutes for such solvents, providing more sustainable alternatives. Some examples of green solvent used in SPPS methods include 2-MeTHF (2-methyltetrahydrofuran) (30), γ-Valerolactone (31, 32), Propylene carbonate (33), Anisole (methoxybenzene) and Dimethyl Carbonate (DMC) (34), Dimethyl Sulfoxide

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(DMSO) – Ethyl Acetate (EtOAc) (2, 35), Rhodiasolv (PolarClean) (36), Triethyl phosphate (TEP) – dimethylsulfoxide (DMSO) (37), and Anisole/N-octylpyrrolidone (NOP) (38) (Figure 2).

3.1.2. Coupling Agents

Despite being one of the most common transformations in the pharmaceutical industry, amide bond formation still lacks broadly applicable and reliable catalytic methods. The majority of current amide coupling methods in peptide synthesis rely on benzotriazole-based derivatives such as uronium/aminium salts, phosphonium salts and carbodiimide combinations. The main challenge posed by usage of such benzotriazole-based derivative coupling agents is the explosive properties of the structure. (26). Initial strides toward incorporating sustainable coupling agents in peptide synthesis saw the introduction of OxymaPure® (ethyl cyano(hydroxyimino) acetate) in 2009. This compound emerged as a viable substitute for traditional benzotriazole-based reagents, offering better compatibility with environmentally friendly solvents and demonstrating a favorable combination of reactivity, solubility, and stability in different solvent systems (39). This was followed by introduction other green coupling agents based on the OxymaPure® scaffold these included- COMU (a uronium-type coupling reagent) (40), PyOxyma, Oxyma B, Oxyma T, TOMBU, and COMBU. However, these coupling reagents did not offer significant advantages over earlier reagents like

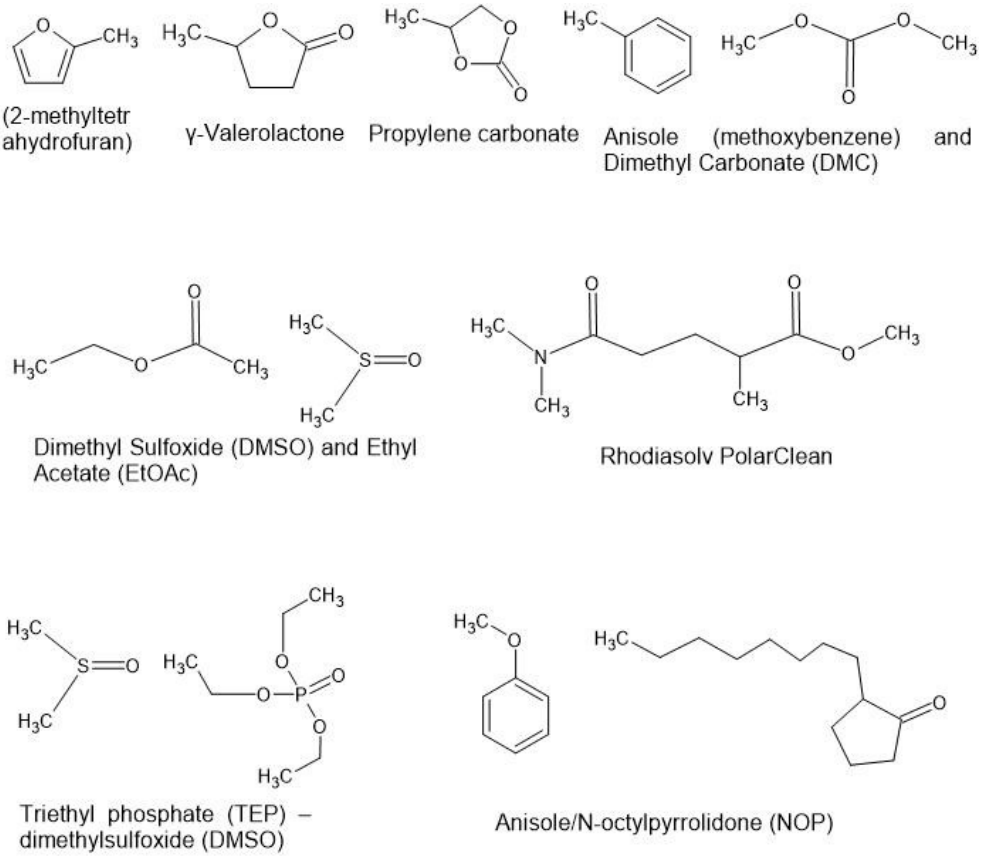

Fig. 2: Green solvents in SPPS

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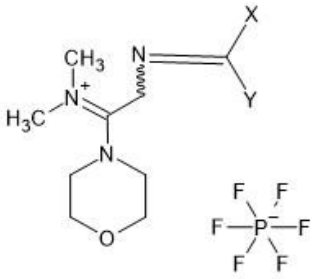
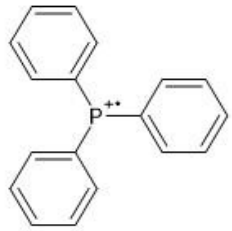
OxymaPure and COMU in terms of green chemistry, since they were required in stoichiometric amounts, resulting in substantial waste generation (26). While a universal green method for forming amide bonds in peptide synthesis, particularly for longer peptides, has yet to be developed (5), Mattelone et al. reported the use of propylphosphonic anhydride, T3P® as a green coupling reagent (22) Another notable contribution includes the usage of triphenylphosphine (Ph3P) as green coupling agent by Nagahara et al., (41) where, even though the process of amide bond formation generated triphenylphosphine oxide as a stoichiometric byproduct it can be recycled and reused, making the approach more sustainable (42, 43). Figure 3 shows the structures of a few greener coupling reagents.

3.1.3. Resins

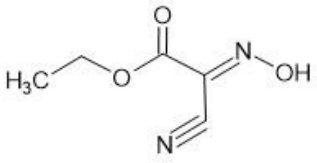
Resins play a crucial role as solid supports for peptide synthesis, particularly in the solid-phase peptide synthesis (SPPS) process. The choice of resin affects the efficiency, swelling capacity, and compatibility with greener solvents, which are key factors in developing more sustainable protocols (44). For instance, ChemMatrix (CM) resins, which are fully PEG-based, were found to be more compatible with greener solvent alternatives like acetonitrile (ACN), tetrahydrofuran (THF), and 2-MeTHF compared to traditional polystyrene (PS)-based resins. This compatibility is important because it allows the full use of bio-derived and less toxic solvents, reducing reliance on hazardous substances such as DMF and NMP (2). Compatibility of resin with green



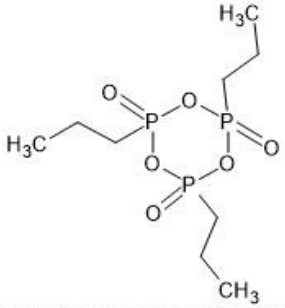
uronium-type coupling reagents



triphenylphosphine



OxymaPure® ethyl cyano(hydroxyimino)acetate)



propylphosphonic anhydride T3P®

Fig. 3: Green coupling agents for peptide synthesis

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solvents is also highly important. Recent studies indicate that the poly-ε-lysine resin SpheriTide is less compatible with green solvents than polyethylene glycol-based resins even though it offers high loading capacity, is biodegradable, and is produced from renewable starting materials (45). Resins that are compatible with green solvents enhance the green potential of peptide synthesis by supporting the use of renewable, biodegradable, and low-toxicity solvents such as γ-valerolactone (GVL) and N-formylmorpholine (NFM) (32). Another major challenge in usage of PEG-based resins is that they are too costly for practical use in large-scale manufacturing of therapeutic peptides and also show excessive swelling during TFA-mediated cleavage of peptides from the polymer support. As a result, recent years have seen numerous studies exploring the use of greener SPPS solvents in combination with industrially practical polystyrene (PS)/divinylbenzene (DVB) resins (8).

3.3. Choice of peptide purification methods

Irrespective of the methods employed in the process of peptide synthesis/extraction, the main objective is to obtain viable yield with minimal impurities, thereby reducing the need for extensive downstream purification and lowering the overall PMI. As a result, careful monitoring of the most frequent side reactions in peptide synthesis is essential (2). Usually, this process is the major bottleneck in the manufacturing process (5). Consequently, it is important for the peptide purification process to give practically viable yields in an economically feasible manner. The efficient chemical synthesis and purification of longer peptides (exceeding 30 amino acids) is often challenging and heavily influenced by the specific sequence of the peptide (46).

Certain peptide synthesis methods enhance the purification by virtue of the method itself, therefore reducing the reliance on specialised purification methods. For instance, the use of Fmoc/tBu solution-phase peptide synthesis using benzyl-type group-assisted purification (GAP) protecting group as a a solution-phase alternative retains the purification advantages of solid-phase synthesis while eliminating the need for chromatography and recrystallization (47). modifying the benzyl protecting group by incorporating a diphenylphosphine oxide moiety, which provided the necessary solubility characteristics for GAP chemistry. This modification allows peptides to be selectively precipitated from reaction mixtures, simplifying purification and reducing solvent use. Using this method, Seifert et al., successfully synthesized over 1 gram of thymopentin, an immunostimulant peptide, with an 83% overall yield and 99% purity. More interestingly, the GAP protecting group enabled efficient purification without chromatography or recrystallization, which are typically required in peptide synthesis. Additionally, this approach allowed for mild deprotection protocols, making it compatible with the widely used Fmoc/tBu strategy. This was particularly important because conventional solution-phase synthesis struggles with the removal of N-fluorenylmethylpiperidine (NFMP), a side product that is difficult to eliminate without polymer support (48).

Some of the common peptide purification processes include Reversed-Phase Liquid Chromatography (RPLC), Membrane Filtration (MF), Isoelectric Focusing (IEF), Magnetic Nanoparticles (MNPs), Hydrophilic Interaction Liquid Chromatography (HILIC), Mixed-Mode Chromatography (MMC) and Sub/Supercritical Fluid Chromatography (SFC) (49). Out of these, the RPLC is the most commonly employed method.

SFC is an environmentally friendly method that enhances peptide solubility and separation efficiency while minimizing waste. It uses supercritical CO◘ as the primary mobile phase, reducing organic solvent consumption. Peyrin and Lipka have highlighted how preparative-scale

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supercritical fluid chromatography (SFC) acts as a green analytical method that aligns with all six principles of green analytical chemistry. By using carbon dioxide as the primary solvent, SFC significantly reduces solvent consumption, avoids toxic and flammable substances, and minimizes energy use due to the absence of heating or cooling cycles typical in traditional liquid chromatography. It also limits the need for chemical derivatization and enables real-time analysis, reducing potential pollutants. Additionally, the non-flammable nature of CO◘ lowers the risk of accidents, making SFC a safer, more sustainable alternative for chromatographic separations (49, 50). Moreover, specialised SFC methods such as ultra-high performance supercritical fluid chromatography (UHPSFC) have been reported to be capable of simultaneously separating highly polar and less polar peptides within the same run, making it a valuable technique (51).

An emerging approach to improve peptide purification in reversed-phase liquid chromatography (RPLC) involves the use of umbrella sampling, a molecular dynamics (MD) technique designed to calculate free energy profiles of molecular interactions. Introduced by Scrosati et al., in this method, peptides are computationally restrained at various distances within a simulated C18-lined stationary phase, allowing the determination of binding free energy (ΔG) under different mobile phase conditions. Unlike traditional MD, which may show poor correlation with experimental retention times, umbrella sampling offers more accurate predictions by capturing the thermodynamic aspects of peptide-stationary phase interactions. These ΔG values can be directly correlated with experimental retention behavior, making the technique a valuable tool for method development in peptide purification—especially when empirical data are scarce or when dealing with novel peptide sequences or chromatographic conditions (52).

4 Role of Computational Methods in Sustainable Peptide Synthesis

Pharmaceutical manufacturing is known to generate significant waste, especially from solvents, contributing to greenhouse gas emissions and environmental pollution. This necessitates methods enabling estimation and monitoring of constituents used in the process of synthesis CAMPD (Computer-Aided Molecular and Process Design) is a sustainability-focused approach that integrates molecular design with process optimization in pharmaceutical manufacturing. Instead of treating molecules and processes separately, CAMPD allows for a holistic view, leading to smarter solvent and material choices, improved energy efficiency, and reduced environmental impact. By minimizing waste, lowering greenhouse gas emissions, and supporting the use of safer chemicals, CAMPD helps pharmaceutical companies make their operations more sustainable without compromising on efficiency or product quality (53).

4.1. Peptide Databases and Virtual Screening

Peptide structural databases have been instrumental in advancing computational approaches for peptide design, allowing researchers to study a wide range of peptides while minimizing redundancy. These databases are therefore a valuable asset for researchers saving time and money allowing virtual assessment of large volumes of peptide data. (54). Various specialized computational approaches in virtual screening (VS), molecular docking and molecular dynamics (MD) simulations have been dedicated towards rational peptide design. These methods have been particularly impactful in designing cyclic peptides, peptide inhibitors of protein-protein interactions (PPIs), and peptide-based nanomaterials, offering new avenues for drug discovery and biomaterial development. For instance, Saha et al., developed a computational approach to create an annotated gigalibrary containing more than 2 billion composite peptidic macrocycles. By combining their experimentally developed synthesis methodologies with algorithms and software tools like Composite Peptide Macrocycle Generator (CPMG) and ConfBuster++, they

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were able to generate virtual libraries of three-dimensional macrocycle structures. Such extensive libraries contribute to sustainability by reducing the need for physical experimentation, thereby conserving laboratory resources such as chemicals and energy. Their methodology improves drug-like properties, which can lead to effective therapeutic solutions while minimizing waste (55).

VS offers substantial economic and sustainability benefits over traditional high-throughput screening (HTS) methods in drug discovery. By employing *in silico* techniques to evaluate extensive chemical libraries, VS significantly reduces the reliance on physical reagents and consumables, leading to cost savings and decreased environmental impact. The integration of cloud computing and high-throughput virtual screening as a service (HiTViSc) further enhances the accessibility and scalability of VS, enabling researchers to efficiently utilize distributed computational resources without substantial capital investment in dedicated hardware (56). This approach not only streamlines the drug discovery process but also promotes a more sustainable research environment by minimizing laboratory waste and energy consumption. Moreover, advancements in machine learning and molecular docking algorithms have improved the accuracy and speed of VS, reducing the need for extensive experimental validation and thereby conserving additional resources. Consequently, the adoption of computational VS methodologies can lead to significant cuts in computational costs. For instance, in a study by Graff et al., employing a directed-message passing neural network enabled them to pinpoint 94.8% or 89.3% of the top 50, 000 ligands within a 100-million-member library by examining only 2.4% of candidate ligands through an upper confidence bound or greedy acquisition strategy, respectively (57).

4.2. Role of Simulations

Peptide simulations are highly crucial to understand how peptides behave over time in a simulated environment, thus enabling the assessment of novel peptides without extensive use of resources. These simulations however, typically involve complex computation which can rely on extensive power supply for optimal performance. Power consumption remains a significant challenge in computational peptide design, particularly as the complexity of simulations increases, necessitating substantial energy resources. GPU-based computing offers a viable solution to this issue by enhancing computational efficiency while reducing energy consumption. Modern GPU architectures leverage parallel processing capabilities to optimize performance, significantly accelerating simulations compared to traditional CPU-based approaches. By distributing workloads across thousands of cores, GPUs achieve higher throughput per watt, thereby improving energy efficiency. According to recent findings, optimized GPU-accelerated computations can reduce power consumption by up to 53%, demonstrating their potential for sustainable high-performance computing in scientific research (58). These advancements not only minimize energy demands but also contribute to the broader goal of environmentally sustainable computational methodologies.

4.2. Role of Artificial Intelligence

The rapid growth in documented peptide sequences has spurred interest in using computational biology to analyze peptides, predict their biological activities, calculate their properties, and aid in peptide design (59). AI accelerates the identification and optimization of therapeutic peptides, reducing the time and resources required for research and development. This efficiency not only lowers financial expenditures but also minimizes the environmental footprint associated with traditional laboratory experiments. AI-driven approaches can also predict the pharmacokinetics and toxicity of peptide candidates, decreasing reliance on resource-intensive animal testing and further conserving environmental resources. Additionally, AI aids in optimizing peptide synthesis processes, promoting the adoption of sustainable manufacturing methods that reduce the use of hazardous chemicals and waste generation.

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5 Conclusion

Peptide synthesis is undergoing a significant transformation, driven by the growing need for sustainability, efficiency, and cost-effectiveness. Traditionally hampered by challenges such as instability, low bioavailability, and high production costs, peptide production has been revitalized through advancements in synthesis methods, purification processes, and computational tools. A key component of this shift is the focus on environmental impact, with metrics like Process Mass Intensity (PMI) enabling optimization of yield while minimizing ecological burden. Innovative synthesis techniques, such as Liquid-Phase Peptide Synthesis (LPPS), continuous-flow systems, and ultrasound-assisted solid-phase peptide synthesis (SUS-SPPS), have enhanced scalability and reduced solvent usage. The adoption of greener solvents (e.g., γ-Valerolactone, 2-MeTHF), eco-friendly coupling agents like OxymaPure, and biodegradable resins further contributes to more sustainable practices. Peptide purification, a critical step in production, has also evolved, with alternatives like supercritical fluid chromatography (SFC) significantly lowering solvent consumption compared to traditional reversed-phase liquid chromatography (RPLC). Computational modeling has refined purification strategies by improving retention predictions, while AI-driven simulations, peptide databases, and GPU-accelerated computing have streamlined design and minimized resource use. Looking ahead, continued integration of green chemistry and computational technologies—including AI-assisted design, enzymatic synthesis, and recombinant production—is expected to further reduce the environmental footprint of peptide manufacturing. As these sustainable innovations become standard, the field is moving decisively toward scalable, cost-effective, and environmentally responsible peptide synthesis, aligning scientific advancement with ecological stewardship.

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