



Review Article



Biotransformation of Dairy Waste into ACE-Inhibitory Peptides: A Sustainable Strategy for Blood Pressure Management

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ABSTRACT

The bioactive peptides produced by valorization of dairy by-products, specifically whey and casein wastes, are a sustainable approach to the treatment of environmental pollution as well as the health requirements of the population. This review is dedicated to the biotransformation of dairy waste through enzymatic hydrolysis and fermentation with the help of such strains as *Lactobacillus helveticus*, *Lactobacillus brevis*, and *Pediococcus acidilactici* to produce angiotensin-converting enzyme (ACE)-inhibitory peptides, including Val-Pro-Pro and Ile-Pro-Pro. These peptides exhibit good antihypertensive, antioxidant, and anti-inflammatory effects both in vitro and in animal models. Independent bioprocessing methods, such as enzyme immobilization and nanoencapsulation, have been used to improve the yield, stability, and bioavailability of peptides. Nevertheless, there are major shortcomings such as inconsistent effects of peptides in clinical trials, lack of human clinical trials, and the inability to scale production, yet keep costs economical. The issue of regulation is also an obstacle to translation because the approval of health claims needs to be based on strong clinical evidence and stable quality, which is not the case at present. This model focuses on waste utilization and sustainability; hence, minimizing the environmental load of dairy effluent and value addition of agro-industrial waste streams. To maximize the potential of dairy waste-based ACE-inhibitory peptides, the main agendas in the future are to put human trials first, standardize production protocols, and provide regulatory directions to attain safety, efficacy, and economic sustainability.

INTRODUCTION

Hypertension is a major health concern in the world, and it contributes to the need to find safe and sustainable therapeutic substitutes that are also accessible. Although effective, synthetic angiotensin-converting enzyme (ACE) inhibitors have side effects and dependence. At the same time, the dairy industry produces huge amounts of protein-rich wastes, mainly of whey and casein wastes, that create major environmental and financial difficulties as a result of large biological oxygen demand (BOD), expensive waste disposal, and the loss of resources [1, 2]. Enhancing dairy waste into high-value bioactive compounds is a twofold solution: it will reduce environmental pollution and develop new nutraceuticals. Dairy proteins, particularly casein and

whey, contain high concentrations of latent bioactive peptides which can be released either through enzymatic hydrolysis or microbial fermentation [3]. One of them, the ACE-inhibitor peptides like Val-Pro-Pro and Ile-Pro-Pro (fermented milk), have shown a high level of antihypertensive activity in the preclinical models [4, 5]. This review not only summarizes existing data on the biotransformation of dairy waste to ACE-inhibitory peptides, but also addresses the environmental/economic need to generate value out of dairy waste. Production strategies (fermentation, enzymatic hydrolysis) and important peptide sequences, Bioactivity, stability, and bioavailability of derived peptides, limitations, regulatory



challenges, and future directions to clinical translation and scale-up.

Cost-Effectiveness and Industrial Feasibility of Dairy Waste Valorization

Cost-effectiveness and industrial feasibility of the dairy waste-derived ACE-inhibitory peptides is critical on the transition of these novel peptides into commercial products of laboratory research. The economic and practical implications of the scaling up of this valorization pathway are assessed in this section [6].

Cost-Effectiveness: A Dual-Value Proposition

The main economic strength is the use of cheap or negative-cost raw materials. Dairy effluents, and especially the whey, tend to pose high disposal costs to the producers because of their high biological oxygen demand (BOD) and other fees imposed on it. By re-directing this stream of waste into a production pipe-line manufacturers can be able to offset waste management costs and produce a high-value item. The price model is also good, as opposed to the de novo synthesis or isolation of peptides using high-grade food proteins [7]. The costs of processing are, however, high. Key cost drivers include. Enzyme/strain Procurement Fermentation with lactic acid bacteria (LAB) may be cost-efficient, but purified commercial proteases to perform hydrolysis are expensive. Downstream Processing steps, including ultrafiltration, peptide separation by chromatography, and encapsulation to provide stability, are energy- and capital-intensive [8]. Quality Control & Standardization: Peptide profile and potency consistency between batches can only be ensured through a strong analytical monitoring that increases the costs of operation. The balance of these production costs to the market value of the end product, which will be a high-nutraceutical or functional food ingredient, and the costs saved by not using conventional waste disposal must be presented using a full life-cycle cost analysis.

Industrial Feasibility and Scalability Challenges

There are a number of technical and logistical challenges in the industrial implementation. Depending on the source (e.g., cheese or casein whey) and season, dairy waste may be composed differently, which influences the consistency of the process and final peptide yield. It is necessary to standardize pre-treatment. The most practical is on-site biorefining or near-site biorefining, which is built in the current dairy processing facilities. This reduces transportation expenses of large volumes of perishable waste but involves huge capital expenditure in new bioreactors and separation facilities [9]. Although the concept of fermentation and hydrolysis at the lab scale is thoroughly documented, the transition on an industrial scale (thousands of liters) presents difficulties in sustaining the optimum pH, temperature, sterility, and mix to achieve the highest ACE-inhibitory activity. Peptides

obtained using waste feeds could be subjected to increased regulatory questioning regarding safety (allergenicity, safety of possible contaminants), health claim substantiation, and then peptides obtained using food-grade feeds. Their definition as Generally Recognized as Safe (GRAS) takes a lot of paperwork.

Comparative Feasibility with Other Valorization Routes

Dairy waste valorization competes with other existing paths. Technological advances are technologically advanced in producing whey protein concentrate (WPC) or lactose, and may be more profit-generating on the spot. Bioactive peptides production, consequently, has to be placed in a cascading biorefinery scheme. In this scheme, waste undergoes bulk recovery (proteins as a higher-value niche, lactose), and the resulting streams are further refined into high-potency peptides to maximize resource utilization and economic gain [10].

Conclusion on Viability

ACE-inhibitory peptides of dairy waste can be produced industrially, but are not yet financially feasible on a large scale. It would work best in a vertically integrated dairy company with the ability to internalize waste disposal savings and use the existing infrastructure. The way forward lies in coming up with stronger and specific microbial strains or immobilized enzyme systems to enhance yield and lower the costs of processing. Separating downstream more efficiently and continuously [11]. Cultivating a clear consumer and regulatory acceptance for waste-derived bioactive compounds, supported by conclusive human clinical data. Ultimately, the driver for adoption may be as much corporate environmental, social, and governance (ESG) strategy meeting sustainability goals through circular economy innovation, as direct profit margin from the peptide products themselves.

ACE Inhibitors

ACE inhibitors are mostly used for hypertension control and other complications like heart failure and chronic kidney disease. This category of medicines works by preventing the activation of the angiotensin-converting enzyme (ACE) that converts angiotensin I into angiotensin II. The above-mentioned process will, in turn, cause dilation of blood vessels and a reduction in blood pressure. Talking from a historical point of view regarding the first appearance of the drug captopril in 1981 in the market, ACE inhibitors have been the principal treatment of choice, keeping high blood pressure at bay. They deliver added benefits such as improved glucose control, reduced left ventricular volumes, and cardioprotective effects, besides BP reduction [12].

Contrasting ACE Inhibitors with ARBs

The findings of studies are in support of the fact that both ACE inhibitors and angiotensin receptor blockers (ARBs)

are good controls for hypertension; still, ARBs, compared to ACE inhibitors, are known to have fewer side effects, including less cough and swelling, and at the same time, they are better tolerated. This has led to ARBs being generally referred to in specific clinical settings [13]. Both drug groups seem to possess the same long-range effects on blood pressure, but ARBs' enhanced safety profile and a decline in the number of discontinuations make ARBs a better choice for some people. Nonetheless, ACE inhibitors retain their fundamental role in diabetic and heart-failure patients with fewer side effects by offering the unique means of action and additional benefits [14].

New Findings on ACE Inhibitor Efficacy

The latest studies bring you novel discoveries on the modalities of ACE inhibitors, which are indispensable. As an example, the combination of quinapril in the ester state with some gut bugs can facilitate the establishment of the anti-vascular wall in the technical cells system. This way, the discovery of this significant factor follows the statement of the unknown variable, which in turn can have an impact on the blood pressure, as a post-treatment reaction [15].

Current Studies and Future Research Directions

Scientists are now exploring new ideas for ACE inhibitors that could be specific for a single domain, multifunctional inhibitors, or peptidomimetics. Apart from ACE2, which occurred in 2000, being key in Ang(1-7) formation, the blood pressure level regulation depends on it. ACE2 also interacts with the coronavirus to become one of the standards that caused the 2003 SARS outbreak [16]. Even though hypertension is still being treated with ACE inhibitors, new facts about their mechanisms, side effects, and their relations with the microbiota change their clinical use. In contrast, ARBs are on several occasions a more suitable alternative because they have fewer adverse effects. Studies have unearthed/presented some very promising ACE-inhibitory peptides from various milk sources that may bear in the future a solution to hypertension [17].

ACE-Inhibitory Peptides Derived from Milk Sources

Milk and caseins underwent gastric pepsin digestion to be released in the form of peptides, for instance, PEQSLACQCL (β -lactoglobulin), QSLVYPFTGPI (β -casein), and ARHPHPLSFM (κ -casein), which are seen as highly active ACE inhibitors. This work underlines their potential application as natural solutions to hypertension. Interestingly, casein-derived peptides, especially the α -casein ones, presented remarkable ACE-inhibiting action, and a 5-10 kDa fraction, which is the small one, brought 82.35% of the excretory activity, and the corresponding IC₅₀ was 2.36 mg/mL. Meanwhile, β -casein-based peptides displayed ACE-inhibitory effect to a smaller extent (56.67%, IC₅₀ 4.00 mg/mL). These observations

highlight the novelty of casein-derived peptides, particularly those derived from fermented dairy products, in hypertension management [18]. Moreover, a proteolytic extract derived from *Maclura pomifera* latex significantly degraded bovine caseins, and the resulting hydrolysate exhibited maximal ACE-inhibitory activity (IC₅₀ of 1.72 \pm 0.25 mg/mL), which occurred after 180 minutes. Based on the above, peptides from milk are considered advantageous in the treatment of hypertension [19]. The latest findings bring to attention the yak milk casein as a product that might lead to the development of bioactive peptides with ACE-inhibitory properties. The in-silico analysis revealed that it has a similarity to the cow milk casein, and it can produce different bioactive peptides. A study on yak milk casein from Qula, hydrolyzed by Neutrase, brought about a hydrolysate containing QC35 (IC₅₀ 0.38 mg/mL of chymase), showing its role as an antihypertensive peptide source. Calpis sour milk and related fermented milk products have been proven to have remarkable ACE-inhibitory properties. The research showed that specific peptides in fermented milk products can successfully bring down the blood pressure in hypertensive rats. This implies that there may be great benefits to treating hypertension by using fermented milk products. Amongst these, Val-Pro-Pro and Ile-Pro-Pro, peptides from the sour milk, were found to be very effective. The fermentation of *Lactobacillus helveticus* and *Saccharomyces cerevisiae* enabled the milk to be a strong ACE inhibitor through the generation of an antihypertensive peptide, which played a paramount role in vivo. These peptides were produced by Olvera-Rosales et al. using fermentation techniques like those applied in the current study. Yogurt, cheese, and other dairy foods also contain ACE-inhibitory peptides, which have the potential of lowering blood pressure during laboratory and animal studies; they can be used for blood pressure control [20]. A study by Wang et al. showed that peptides resulting from the enzymatic hydrolysis of yak milk casein possess various beneficial effects, such as ACE inhibition, antioxidant effects, anti-inflammatory action, and antidiabetic activity. Moreover, the major properties are the peptides' structure, which means they may even be food ingredients and serve as supplementary treatments for certain conditions [21]. This study aimed to investigate bioactive peptides that are found in milk in general, with a special focus on ACE inhibitors. Among these are Ile-Pro-Pro and Val-Pro-Pro, which have been recognized as ingredients that possess the capability of preventing as well as treating CVD. One of the most valuable of these peptides seems to be the one that is derived from fermented dairy products, especially cheese, despite the fact that they are often of a biodegradable and stable nature during digestion. Fermented milk products are also among those that

provide peptides with anti-thrombotic activity, thus help where the blood clotting and platelet aggregation, hence improving the prevention of CVD. Whey proteins (alpha-lactalbumin, beta-lactoglobulin) and bovine serum albumin (BSA) also produce peptides that have ACE-inhibitory activity, some of which have added bioactivities. The most potent lactokin identified, beta-lactoglobulin f (142-148), has an ACE IC₅₀ of 42.6.1 μmol/L, even though it is less effective than synthetic antihypertensive drugs. The ACE inhibitory effect of whey hydrolytes is, to a greater extent, a consequence of enzyme specificity than it is of the extent of hydrolysis, indicating that naturally occurring peptides could be used as functional food ingredients for the treatment of hypertension, but with drugs yielding lower potency [22]. The studies that indicated the ACE-inhibitory peptides from casein and whey proteins have been followed by. The results pointed them indirectly at the accomplishment of decreasing high blood pressure. The clinical trials done on hypertensive animals and humans who had the intention of lowering the blood pressure by dieting with these peptides, you or this society made a focused effort on functional food ingredients and nutraceuticals, thus it meant that they might reduce disease risk and aid in prevention or treatment [23]. High blood pressure, the accumulation of arterial plaque, and adult-onset diabetes are the major promoters of the risk of heart disease and stroke. The data proposes that the intake of dairy products might work as a risk factor reducing the systolic and diastolic pressure, thus protecting against hypertension and its related conditions, mainly because they contain minerals (like calcium, magnesium, potassium, and vitamin D), and they include two kinds of proteins, casein and whey protein, which can inhibit ACE [24]. The ACE-1 inhibition of angiotensin II production (a blood vessel constrictor) and the inhibition of bradykinin degradation (a blood vessel dilator) are both the regulation of blood pressure. CMPs obtained from cow, sheep, and goat milk products also display moderate ACE-inhibitory activity, but that effect intensifies by the process of the simulated digestion mechanism present in the stomach and intestines [24]. The activity of the CMPs as inhibitors of the ACEs is significantly increased upon trypsin-induced degradation, thereby giving rise to the fragments that have a stronger ACE-inhibitory activity than the original CMPs. This suggests that it could be possible to make cheese whey work more efficiently in the making of health-promoting products and supplements with an ACE-inhibitory effect. Milk caseins and whey proteins, which are the most abundant sources of the bioactive peptides that have various health benefits such as opioid-like activity, immune-enhancing, ACE-inhibitory, lowering blood pressure, and antimicrobial effects, have been identified as such. Among them, the peptides that inhibit the activity

of ACE and lower the blood pressure are extensively researched because their manner of action might be useful in the treatment of hypertension. Milk has been thought of as the best source of the derivative of these types of beneficial peptides compared to other alternatives, thus it is a key material in the functional food industry. When goat milk proteins were cleaved by subtilisin and trypsin enzymes, the resultant product mixture exhibited strong ACE inhibitory activity (IC₅₀ of 218.50 μg/mL) [25]. An additional process through a 50 kDa ceramic filter increased the activity of more than 30%, suggesting potential for optimization of the food products that aim at blood pressure regulation. Whey protein impurities, as a by-product, have been shown to have ACE inhibitory action in different experimental conditions. A certain product formed from β-lactoglobulin given IC₅₀ of 28 μg/mL; it also contained new and specific peptides such as Ile-Ile-Ala-Glu (IIAE). This suggests its power of lowering blood pressure. The peptide Tyr-Pro, present in alpha s1-casein, beta-casein, and kappa-casein, seemed to have a powerful hypotensive action on spontaneously hypertensive rats. These actions were time-dependent; they started 6 hours after ingestion [26]. Although Tyr-Pro has a weaker activity against ACE (IC₅₀ of 720 μM), its mechanism of lowering blood pressure appears different and can change old theories about blood pressure control [23]. The studies tested the immunopositive domino effect of the monoclonal antihuman sMSTN impurity in becoming the main antibody response in the ELISA system for the detection of the peptides. The developed ELISA could specifically detect the increasing T-cells and the cytokine TNF-α, while TGF-β1 and the vasodilatory prostaglandin E1 increased and activated MAC-1 on sow no. 4 to inhibit the virus [27]. The reaction was carried out by the MMZ-F-017 bacto-screen method, which concentrated the sample on a nitrocellulose membrane fixed to a plasmid [13]. The chromatographic separation of the three components, namely α(S1)-casein, β-casein, and α(S2)-casein, was carried out in the present study, and the presence of three bioactive peptides exhibiting ACE inhibitory, immunomodulatory, and antimicrobial properties was confirmed in fresh milk proteins [28]. These discoveries point to the wide potential of the milk proteins with respect to diverse health effects. In like manner, ultrafiltration characterizing protein fragmentation and the enzymatic interaction of caseins with the enzyme in the production of hydrolysates with astringent ACE inhibition action demonstrates the therapeutic nature of milk for hypertension treatment [16]. A critical gap in translating milk-derived ACE-inhibitory peptides into therapeutic recommendations is the lack of clear dose equivalence with pharmaceutical ACE inhibitors (e.g., captopril, enalapril) [29]. Synthetic drugs are developed with high

specificity and potency, typically exhibiting in vitro IC_{50} values in the nanomolar range. Conversely, the most potent milk peptides, including Val-Pro-Pro, have IC_{50} values in the micromolar scale, meaning that they are orders of magnitude weaker on a molar basis. Thus, to obtain a similar antihypertensive effect, gram quantities of peptides would have to be used, which is in comparison with milligram doses of synthetic drugs. Such a difference is further compounded by deep variations in bioavailability and presystemic degradation. Pharmaceutical ACE inhibitors are chemically designed so that they are most effectively absorbed and metabolically stable, and in many cases, they have a bioavailability that is greater than 60%. Milk peptides, in turn, are prone to extensive degradation by gastrointestinal proteins and have low membrane permeability, resulting in low (<1-5) and very variable systemic absorption [30]. This means that the effective dose that is carried to target tissues/circulatory system is a minute fraction of the dose ingested. To conclude, the intrinsic ACE-inhibitory activity of milk peptides, as well as the deliverable systemic concentration are significantly lower than that of synthetic drugs. This does not rule out their possible usefulness as functional food ingredients for the mild support of blood pressure, but it clearly classifies them as opposed to pharmaceutical-grade interventions. They are to be considered as complementary agents to be used in a lifestyle management program, as opposed to their direct, milligram-to-milligram replacement of first-line antihypertensive drugs.

Variables Impacting ACE Inhibition and Cell Viability:

Various factors, such as fermentation temperature, whey powder, calcium lactate, soybean peptone, glucose, and casein, have a direct impact on the ACE inhibition and viable cell count in the fermentation process of *Lactobacillus bulgaricus* LB6. High temperatures, whey powder, glucose, and calcium lactate are responsible for stronger inhibition of ACE, whereas soybean peptone and casein seem to have the opposite effect [31].

Improving Fermentation Conditions

A Box-Behnken design of response surface methodology was employed to yield maximum ACE-inhibitory peptide production from goat milk using *Lactobacillus bulgaricus* LB6 [32]. The best results with a total viable count of 8.06×10^7 and ACE inhibition rate of 86.37% were achieved when 0.15% casein, 1.2% glucose, and 0.35% soybean peptone were used. Furthermore, a second study concluded that *Lactobacillus bulgaricus* LB6 improved the most when a 12-hour fermentation time was used, and the following components: whey powder (0.70%), casein peptone (0.90%), soybean peptone (0.30%), and casein (0.20%) all helped the inhibitions ACE [33].

Specific Strains and their ACE-Inhibitory Efficacy

The fermentation products of *Lactobacillus animalis*

DPC6134 contained ACE inhibitory compounds that showed an activity of 85.51% and an IC_{50} value of 0.8 mg/mL. Simultaneous growth of *Lactobacillus rhamnosus* GG and *Streptococcus thermophilus* SY-102, which extended the exponential phase from 12 to 24 hours, facilitated the breakdown of proteins and increased ACE inhibition (53.42%) when compared to the one-strain fermentation [34]. *Lactobacillus brevis*, *Lactobacillus helveticus*, and *Lactobacillus paracasei* were the most successful in converting whey protein to ACE-inhibitory peptides, and they reached the inhibition rates between 93.3% and 100% [35].

Novel Techniques for Generating Ace-Inhibitory Peptides: Enzyme Immobilization

Optimizing *Lactobacillus helveticus* LB10 proteinases by attachment to a surface led to an increase in whey protein degradation and thus improved their sustainability and reusability [36].

Nanoencapsulation

Injecting *Aspergillus oryzae* fungal protease into nanoparticles properly released ACE-inhibitory peptides during casein degradation [37].

Identification and Examination of Bioactive Peptides

Karthikeyan et al. have identified whey protein hydrolysates that contain several biologically active peptides, such as those resistant to the action of DPP-IV, others being of antibacterial nature, and having the ability to block ACE [38]. Whey-based caseinate hydrolysates from different whey sources contained ACE-inhibitory peptides with very low IC_{50} values (16 to 100 $\mu\text{g}/\text{mL}$) [39].

Stability and Uptake of ACE-Inhibitory Peptides: Gastrointestinal Resilience

ACE-inhibitory peptides from milk fermented by *Lactobacillus helveticus* KLDS.31 and *Lactobacillus casei* KLDS.105 remained bioactive after simulated digestion [40].

Temperature and pH Stability

The Gly-Ala (GA) dipeptide that is produced by *Lactobacillus plantarum* QS670 fermented whey protein with a stable behavior to a wide variety of temperatures, pH levels, and digestive enzymes was reported in their study [41].

Peptide-Specific Stability

The beta-casein peptides showed resistance to gastric enzymes, and they are readily broken down by pepsin [42].

Animal Trials and Antihypertensive Effects

Lactobacillus helveticus strains R211 and R389 used casein during fermentation, which caused lowering of the blood pressure in notable degrees in the hypertensive rats used [43].

Pediococcus acidilactici SDL1414 for ACE-Inhibitory Peptide Production

The Pealo +4 containing lactic acid bacteria were 34, and *Pediococcus acidilactici* SDL1414 was the most potent

(84.7%, IC₅₀ = 19.78 µg/mL)[44]. Furthermore, 57.7% of the low molecular weight peptides (<7 kDa) had been discovered to block ACE. Hence, they were termed as ACE inhibitors as well[45].

Limitations and Future Perspective

Although substantial evidence supports the ACE-inhibitory potential of dairy waste-derived peptides, most findings are based on in vitro and animal studies, with limited confirmation from human clinical trials. Variability in fermentation conditions, peptide composition, and bioavailability further constrains standardization and clinical translation. Future research should therefore focus on well-designed human trials, harmonized production protocols, and advanced delivery strategies to enhance efficacy, safety, and regulatory acceptance.

CONCLUSION

The ability to convert dairy waste into ACE-inhibitory peptides is an attractive dual-purpose approach that offers the solution of managing sustainable waste, as well as the need to design potential hypertension nutraceuticals. The preclinical studies have a solid basis on the in vitro and animal-model efficacy of the peptides like Val-Pro-Pro and Ile-Pro-Pro. Nevertheless, there is a critical translational gap between converting this promise into commercially viable products that have been translated into clinically valid products. Great barriers still exist, such as the cost and complexity of definitive human trials, unresolved issues with standardizing the potency and with consistent bioavailability and the demanding regulatory environment that requires strong safety and efficacy information, especially of substances obtained via waste streams. Advanced bioprocessing methods can provide the route to the better yield and stability, but the final success of the new approach relies not only on the technical feasibility but on the ability to demonstrate the clear cost-effectiveness, regulatory approvals, and therapeutic value in the long-term human trials. Future directions should then shift toward descriptive research to focused translational and clinical studies which directly touch upon these economic, regulatory and scientific obstacles to achieve the sustainable potential of dairy waste-derived bioactive peptide.

Authors' Contribution

Conceptualization: RY

Methodology: RY

Formal analysis: AS, AA, HA

Writing and Drafting: AS, AA, HA

Review and Editing: RY, AS, AA, HA

All authors approved the final manuscript and take responsibility for the integrity of the work.

Conflicts of Interest

All the authors declare no conflict of interest.

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