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Systematic Review

The Pharmaceutical Potential of α- and β-Amyrins

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Abstract

Plant-derived pharmaceuticals represent a highly compelling area of research and continue to attract significant interest from countries, regions, scientific communities, and pharmaceutical companies worldwide. Among these, α- and β-amyrins have been identified as high-value triterpenoid compounds with a broad spectrum of potential therapeutic properties, including anti-inflammatory, antidiabetic, antiatherosclerotic, analgesic, antigout, neuroprotective, anti-Parkinsonian, anticancer, antibacterial, and anti-HIV activities. Relevant information and data were obtained through comprehensive searches of major scientific databases, including Web of Science, Elsevier, and the National Library of Medicine. This study highlighted the pharmaceutical potential of α- and β-amyrins, supported by specific evidence from in vivo, in vitro, and clinical trials. Various extraction methods for α- and β-amyrins are discussed, followed by recommendations for future directions in the development of these compounds as pharmaceutical agents and functional food ingredients. This review highlights the therapeutic of α- and β-amyrin compounds in the prevention and treatment of various serious diseases worldwide, potentially opening new opportunities and directions for the pharmaceutical industry.

Keywords: α- and β-amyrins; anti-inflammatory; antidiabetes; antiatherosclerosis; antinociceptive; antigout; positive effects on nerves; anti-Parkinsonian; anticancer; antibacterial; anti-HIV

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1. Introduction

Pharmaceuticals are commodities of high social significance [1] and an eternal need of the world [2]. The role of pharmaceuticals in treating, preventing, and improving health, and prolonging and enhancing the quality of life of billions of people worldwide is indisputable [3,4]. The global demand for pharmaceuticals is growing rapidly [5]. The global demand for pharmaceuticals is increasing rapidly, necessitating the expansion and advancement of production capabilities [6]. The global herbal medicine market was valued at approximately USD 230.03 billion in 2021 and is projected to grow to USD 430.05 billion by 2028, reflecting a compound annual growth rate (CAGR) of 11.32% [7].

The rapid growth of the global population, along with increasing environmental pollution, has driven rising pharmaceutical demand and profoundly affected pharmaceutical consumption patterns worldwide [8]. In recent decades, the research and development of pharmaceuticals has received significant attention from governments, scientists, companies, individuals, and organizations around the world [9]. According to global standards for evaluating living conditions, access to medicine for healthcare is considered a vital benchmark. For this reason, the development of pharmaceuticals is consistently prioritized by world leaders as a critical element of both social security and national development [10]. Following the COVID-19 pandemic and predictions of future natural disasters that may lead to the emergence of new diseases, the role and importance of the pharmaceutical industry have become more critical than ever. As a result, this field is increasingly attracting scientific research focused on analyzing viral variants and pathogens to develop effective strategies for combating more dangerous and complex diseases [11]. If the position of the pharmaceutical industry is destabilized, it could lead to shortages of essential medicines, causing widespread anxiety and disruption within society, and potentially impacting socio-political stability [12]. Moreover, against the backdrop of rapid population growth, persistent conflicts, and the emergence of epidemics, the demand for medicines continues to escalate, further complicating the global healthcare landscape [13]. There is a growing global trend toward the use of natural products such as raw materials in the production of medicines, health supplements, cosmetics, functional foods, nutritional products, and herbal beverages, all designed to promote and safeguard human health [14].

Triterpenoids are a class of terpenes composed of six isoprene units with the molecular formula $C_{30}H_{48}$. They can also be considered as consisting of three terpene units. Triterpenoids are a group of naturally occurring chemical compounds found in various animal and plant species [15,16]. Triterpenoids fulfill diverse functions in chemistry, acting as key precursors in the biosynthesis of various compounds such as steroids and saponins [17]. Triterpenoids are considered essential bioactive components in traditional medicine throughout many countries, such as China, Japan, Korea, and Vietnam [18]. Triterpenoids are compounds found in numerous plants, belonging to the isoprenoid group. These compounds are often present in plants as glycosides and saponins. Due to their diverse bioactivities and abundant availability, triterpenoids are considered a promising source of raw materials for the pharmaceutical industry [19].

Within the class of triterpenoid acids, α-amyrin (characterized by an ursane skeleton) and β-amyrin (characterized by an oleanane skeleton) are two structurally related compounds, both belonging to the triterpenoid acid group [20]. Among these, ursane-type triterpenes, derived from α-amyrin, are the most common triterpenes, while oleanane-type triterpenes are derived from β-amyrin [21]. Amyrins occur in the surface wax of tomato fruit and dandelion coffee. Particularly, these two compounds have been extensively researched and were successfully extracted by the authors in significant quantities (10.75 g/kg) from the leaves of *Celastrus hindsii* [22].

α-Amyrin and β-amyrin are two representative compounds within the triterpenoid group. These compounds have similar chemical formulas but differ in the molecular structure of the α- and β-forms. In α-amyrin, the (CH3-29) group is attached at carbon position C19 facing forward, while the (CH3-30) group is attached at carbon position C20 facing backward. In β-amyrin, both the (CH3-29) and (CH3-30) groups are attached at carbon position C20 and face forward (Figure 1) [20,21,23]. α-Amyrin and β-amyrin are commonly found in plants, and previous research has successfully extracted them from *Celastrus hindsii*. However, the pharmaceutical values of these compounds are not widely known, and their isolation remains challenging. Therefore, this study clarified the therapeutic potential and biological activities of the two compounds. It served as a

comprehensive summary of their value, aiming to maximize the inherent potential of this compound mixture as a foundation for the development of future pharmaceutical products.

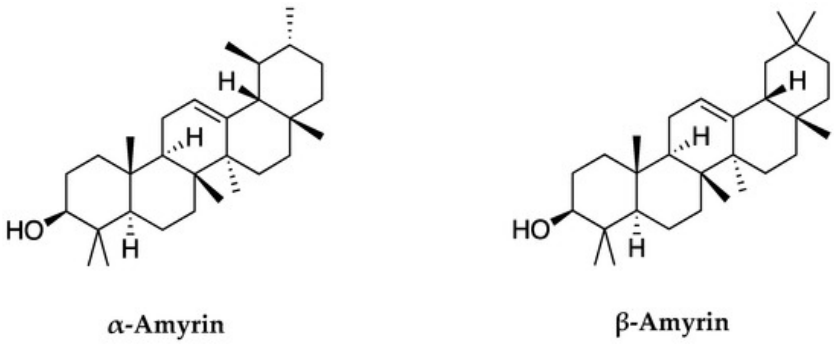


Figure 1. Molecular structure of α-amyrin and β-amyrin [23].

2. Materials and Methods

This study was carried out based on a comprehensive review of 550 scientific articles concerning α- and β-amyrins. Among these, 400 articles were screened and identified as relevant to the objectives of this research. From these, 350 articles with content most closely aligned with the research objectives were selected. Subsequently, 108 articles were excluded due to limitations in transparency, inadequate language clarity, or lack of indexing within the Science Citation Index (SCI) system. Ultimately, 242 articles containing the most comprehensive and clearly presented content and data were selected to serve as the foundation for this research project (Figure 2). This article integrates knowledge from reputable global sources. The information and data were derived from authoritative indexing systems, including the Science Citation Index (SCI), Science Citation Index Expanded (SCIE), and the Institute for Scientific Information (ISI), all of which cover high-quality research published in a vast number of peer-reviewed journals worldwide. The foundation of this research is a rigorously selected database of 242 scientific articles sourced from reputable academic publishers, including Springer, Elsevier, Wiley-Blackwell, Taylor & Francis, Oxford University Press, Cambridge University Press, the University of Chicago Press, InderScience Publishers, and Edward Elgar Publishing, covering the period from 1999 to 2025. Furthermore, the study integrates the authors' expertise, informed by two prior research publications in MDPI-indexed journals.

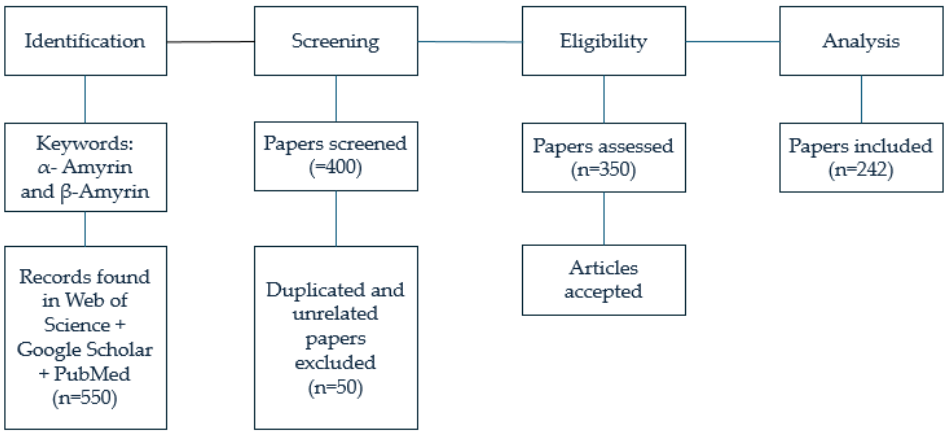


Figure 2. PRISMA flow diagram of the literature included in the review.

3. Results

3.1. Anti-Inflammatory Potential of α- and β-Amyrins

The anti-inflammatory properties of α- and β-amyrins were assessed in a rat model of acute periodontitis, in which the condition was induced by ligating the upper right second molar. Two hours prior to ligature placement, rats received intraperitoneal injections of α- and β-amyrins at doses of 5–10 mg/kg. Lumiracoxib and dexamethasone were used as positive controls, while a placebo group served as the negative control. Six hours after induction, plasma levels of tumor necrosis factor-α (TNF-α) were measured. After 24 h, the rats were sacrificed, and gingival tissues were analyzed using myeloperoxidase (MPO) activity and thiobarbituric acid reactive substance (TBARS) assays. The results showed that α- and β-amyrins, particularly at the 5 mg/kg dose, significantly reduced markers of inflammation. While lumiracoxib produced variable effects on the measured parameters, α- and β-amyrins demonstrated notable efficacy in mitigating acute inflammation. These results underscore the potential of α- and β-amyrins as promising therapeutic agents for managing inflammation associated with periodontal disease, and they highlight the need for further research into their efficacy in preventing chronic bone loss [24].

The anti-inflammatory and analgesic effects of α- and β-amyrin were assessed in experimental models involving the activation of cannabinoid receptor type 1 (CB1) and type 2 (CB2) signaling pathways. The findings demonstrated that both compounds markedly inhibited the production of pro-inflammatory cytokines and downregulated the expression of nuclear factor-kappa B (NF-κB) binding protein and cyclooxygenase (COX) enzymes. These results indicated that α- and β-amyrins may exert their anti-inflammatory effects, at least partially, through modulation of the endocannabinoid system, thereby highlighting their potential as therapeutic candidates for the treatment of inflammation and pain-related disorders [25].

The anti-inflammatory properties of α- and β-amyrin were evaluated in a TNBS-induced murine model of colitis, with the compounds administered in a 1:1 ratio. Following the induction of colitis via rectal administration of trinitrobenzene sulphonic acid (TNBS), the animals were monitored for 72 h to assess clinical and biochemical parameters. Systemic treatment with α- and β-amyrin (3 mg/kg, intraperitoneally) was compared to treatment with dexamethasone and to a vehicle-treated control group. Disease progression was evaluated through both macroscopic and microscopic assessments of colonic lesions, along with measurements of myeloperoxidase (MPO) activity and cytokine levels. Immunohistochemical analysis was performed to assess the expression of cyclooxygenase-2 (COX-2), vascular endothelial growth factor (VEGF), phosphorylated NF-κB (phospho-p65), and phosphorylated cAMP response element-binding protein (phospho-CREB). TNBS-induced colitis was characterized by severe tissue damage, marked neutrophil infiltration, and elevated levels of pro-inflammatory mediators. Treatment with α- and β-amyrin led to notable improvements in colonic tissue morphology, a significant reduction in polymorphonuclear cell infiltration, decreased levels of interleukin-1β (IL-1β), and restoration of the anti-inflammatory cytokine interleukin-10 (IL-10) in the colon. Furthermore, α- and β-amyrin markedly suppressed the expression of vascular endothelial growth factor (VEGF), cyclooxygenase-2 (COX-2), phosphorylated NF-κB (phospho-p65), and phosphorylated CREB (phospho-CREB). These findings highlight their potent anti-inflammatory activity in TNBS-induced colitis and underscore their potential as therapeutic candidates for the treatment of inflammatory bowel disease (IBD) [26].

α- and β-Amyrin exhibit potent anti-inflammatory activity, notably through modulation of the endocannabinoid system. In a murine model of colitis induced by dextran sulfate sodium (DSS), administration of these compounds significantly attenuated the severity of colonic lesions. This therapeutic effect was associated with decreased activity of

inflammatory enzymes, including myeloperoxidase (MPO) and *N*-acetylglucosaminidase. Administration of the triterpenes also significantly reduced levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and various chemokines, while enhancing the expression of the anti-inflammatory cytokine interleukin-4 (IL-4). Moreover, α- and β-amyrin downregulated the mRNA expression of several adhesion molecules involved in leukocyte recruitment and inflammation, including intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), platelet endothelial cell adhesion molecule-1 (PECAM-1), β2-integrin, CD68, and P-selectin. Importantly, these compounds also inhibited cannabinoid receptor type 1 (CB1), suggesting a role in modulating cannabinoid-mediated signaling. Additionally, they suppressed the expression of endocannabinoid-degrading enzymes such as monoglyceride lipase (MGL) and fatty acid amide hydrolase (FAAH), thereby enhancing endocannabinoid tone. Collectively, these findings support the therapeutic potential of α- and β-amyrin as novel agents for the treatment of inflammatory diseases, particularly those involving dysregulation of the cannabinoid system [27].

α- and β-amyrin have demonstrated considerable therapeutic potential in the treatment of acute pancreatitis. In a model of pancreatitis induced by L-arginine, treatment with these triterpenes significantly reduced the elevated pancreas wet weight to body weight ratio, an established marker of inflammation and edema. Furthermore, administration of α- and β-amyrin led to substantial decreases in serum amylase and lipase levels, which are key biochemical indicators of pancreatic injury. The compounds also markedly lowered concentrations of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). In pancreatic tissues, treatment with α- and β-amyrin reduced the activity of inflammation and oxidative stress markers, including myeloperoxidase (MPO), thiobarbituric acid reactive substances (TBARSs), and nitrate/nitrite levels. Immunohistochemical analysis further confirmed decreased expression of tumor necrosis factor-alpha (TNF-α) and inducible nitric oxide synthase (iNOS), reinforcing the observed anti-inflammatory effects. Collectively, these findings indicate that α- and β-amyrin exert both antioxidant and anti-inflammatory actions, highlighting their potential as therapeutic agents for the management of acute pancreatitis [28].

3.2. Antidiabetes Potential of α- and β-Amyrins

α- and β-amyrins have demonstrated significant antidiabetic and hypolipidemic properties in experimental models. Oral administration of these compounds resulted in marked reductions in blood glucose levels, total cholesterol, and serum triglycerides. At a dose of 100 mg/kg, α- and β-amyrin not only normalized blood glucose levels but also exhibited strong lipid-lowering effects. During oral glucose tolerance tests, elevated glucose concentrations were significantly reduced, indicating improved glucose metabolism. Additionally, plasma insulin levels and histopathological analysis of pancreatic tissue supported the beneficial role of α- and β-amyrin in preserving pancreatic function. Rats administered α- and β-amyrin at doses of 10, 30, and 100 mg/kg demonstrated dose-dependent improvements in lipid profiles. Notably, treatment at 100 mg/kg led to a substantial decrease in very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) cholesterol levels, accompanied by an increase in high-density lipoprotein (HDL) cholesterol. These findings underscore the potential of α- and β-amyrin as therapeutic agents for managing hyperglycemia and dyslipidemia. Moreover, their efficacy in reducing risk factors associated with atherosclerosis suggests their promise as lead compounds in the development of novel treatments for diabetes and cardiovascular diseases [29].

β-amyrin, extracted from the roots of *Hemidesmus indicus*, has demonstrated notable antidiabetic activity in experimental models. Its derivative, β-amyrin palmitate, exhibited

significant antihyperglycemic effects in glucose-loaded rats. Remarkably, this compound showed potent antidiabetic activity in both alloxan-induced and streptozotocin-induced diabetic rat models, even at a very low dose of 50 μg/kg body weight. The primary mechanism of action of β-amyrin palmitate appears to involve inhibition of intestinal glucose absorption, thereby reducing postprandial hyperglycemia. These results suggest that β-amyrin and its derivatives have strong potential as lead compounds for the development of future antidiabetic therapeutics [30].

β-amyrin has been shown to possess significant antibacterial and antidiabetic properties through its enzymatic inhibitory activity. At a concentration of 24.24 μg/mL, β-amyrin effectively inhibited violacein production, with inhibit percentages ranging from 22.9 ± 1.2% to 42.1 ± 1.0%, suggesting its potential as an antiquorum sensing agent. Furthermore, β-amyrin exhibited notable α-amylase inhibitory activity, achieving inhibition rates between 49.8 ± 0.3% and 69.3 ± 1.0% at a concentration of 10 μg/mL. In addition, β-glucosidase inhibition assays further confirmed the compound's effectiveness in targeting key carbohydrate-metabolizing enzymes. These findings highlight β-amyrin's dual functionality in both antimicrobial and antidiabetic roles, supporting its potential development as a multifunctional therapeutic agent [31].

α-Amyrin has demonstrated significant hypoglycemic activity in murine models and has been shown to exert dual effects on peroxisome proliferator-activated receptors (PPARδ and PPARγ) in 3T3-L1 adipocytes, highlighting its potential for the management of type 2 diabetes. Mechanistically, α-amyrin activates both PPARδ and PPARγ, along with adenosine monophosphate-activated protein kinase (AMPK) and protein kinase B (Akt). These signaling pathways are crucial for the translocation of glucose transporter 4 (GLUT4), which plays a pivotal role in enhancing insulin sensitivity and combating insulin resistance. Studies suggest that α-amyrin acts as an allosteric activator of AMPK, promoting GLUT4 translocation and improving glucose uptake in target tissues. Given these multiple mechanisms, α-amyrin is considered a promising bioactive molecule for the development of novel, multi-target therapeutic strategies aimed at addressing diabetes and its associated metabolic complications [32].

β-Amyrin has been identified as a promising antidiabetic compound with beneficial effects on preventing renal failure. In vivo, streptozotocin-induced diabetic rats were used as a model for diabetic nephropathy (DN), while in vitro, high glucose (HG)-stimulated human proximal tubular HK-2 cells served as an experimental model. β-Amyrin demonstrated its ability to alleviate renal injury in diabetic rats and reduce both the inflammatory response and apoptosis in HG-stimulated HK-2 cells. Mechanistically, β-amyrin induced the upregulation of miR-181b-5p, which was found to interact with high mobility group box 2 (HMGB2), as confirmed by luciferase reporter assays. Furthermore, β-amyrin promoted the downregulation of HMGB2 expression. Overexpression of HMGB2 was shown to reverse the protective effects of miR-181b-5p on the inflammatory response and apoptosis of HG-treated HK-2 cells, suggesting that β-amyrin exerts its nonprotective effects through the miR-181b-5p/HMGB2 axis. These findings underscore β-amyrin's potential as a therapeutic agent for managing diabetic nephropathy and preventing renal damage in diabetes [33].

β-Amyrin has demonstrated significant antidiabetic potential, as evidenced by its α-amylase inhibitory activity in vitro, with an IC_{50} of 19.50 μg, which is comparable to the standard antidiabetic drug acarbose (IC_{50}: 11.25 μg). Further computational studies revealed that β-amyrin exhibits high binding affinity to four key targets involved in diabetes regulation: glucagon-like peptide-1 (GLP-1), glycogen synthase kinase (GSK), glucokinase (GK), and insulin receptor tyrosine kinase (IRTK). Additionally, β-amyrin was found to possess favorable physicochemical properties, including high stability and bioactivity, a

smaller energy gap, lower hardness, and higher softness, all of which contribute to its potential as a promising lead compound for antidiabetic drug development [34].

3.3. Antiatherosclerosis Effect of α- and β-Amyrins

α- and β-Amyrins, isolated from a 95% ethanol extract of the fruits of the wild species *C. scabrifolia*, were evaluated for their lipid-lowering potential. Comprehensive spectroscopic and biochemical analyses were conducted to characterize the compounds. Their lipid-lowering activity was assessed using an in vitro HepG2 cell model. Results from molecular docking studies further supported the findings, indicating that both α- and β-amyrins exhibit strong potential as lipid-lowering agents [35].

α- and β-Amyrins were isolated from the stem and leaf extracts of *Rhus sylvestris* Siebold. Spectroscopic analysis confirmed the identity of the compounds, and cytotoxicity assays indicated that they were non-toxic at concentrations ranging from 0 to 1.0 μM. The compounds were further evaluated for their immunomodulatory properties, particularly their ability to inhibit cytokine secretion. In vitro studies using the murine macrophage cell line RAW264.7 demonstrated that α- and β-amyrins significantly reduced lipopolysaccharide (LPS)-induced secretion of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). Notably, TNF-α secretion was inhibited even at a low concentration of 0.01 μM. These findings suggest that α- and β-amyrins hold promise as potential therapeutic agents for TNF-α-related inflammatory conditions, including transplant rejection, type II diabetes, and atherosclerosis [36].

α- and β-Amyrins, isolated from *Protium heptaphyllum*, have demonstrated significant antiatherosclerotic potential and hepatoprotective effects. Using a mouse model of non-alcoholic fatty liver disease (NAFLD), male Swiss mice were fed a high-fat diet (HFD) for 15 weeks to induce fatty liver pathology. Histological analysis of liver tissue sections using hematoxylin and eosin (H&E) staining, along with biochemical evaluations, revealed that administration of α- and β-amyrins significantly attenuated hepatic steatosis and inflammation. Further mechanistic insights were obtained through RT-qPCR and Western blotting, which showed that these compounds reversed the expression of key signaling pathways associated with lipid accumulation and inflammatory responses. These findings support the potential of α- and β-amyrins as therapeutic agents for the prevention and treatment of NAFLD [37].

α- and β-Amyrins, isolated from *Euphorbia hirta* L., have demonstrated potent anti-inflammatory effects, particularly in the context of vascular inflammation. In vitro assays were conducted using endothelial cells (SVEC4-10 cell line) treated with a medium composed of 50% lipopolysaccharide (LPS)-activated macrophage culture supernatant (RAW medium). Treatment with α- and β-amyrins significantly inhibited the expression of the endothelin-1 (ET-1) gene, a known pro-inflammatory and vasoconstrictive marker. Furthermore, α- and β-amyrins restored the mRNA expression of endothelial nitric oxide synthase (eNOS), which was otherwise suppressed by RAW medium exposure. These findings suggest that α- and β-amyrins may serve as effective therapeutic agents in the prevention of vascular disorders associated with chronic inflammation [38].

The effects of α- and β-amyrins on angiogenesis and the underlying molecular mechanisms were investigated using cultured human umbilical vein endothelial cells (HUVECs). Treatment with α- and β-amyrins was found to be non-cytotoxic to HUVECs. These compounds promoted angiogenic activity by enhancing tube-like structure formation and increasing cell migration. Moreover, α- and β-amyrins significantly stimulated the phosphorylation of Akt and endothelial nitric oxide synthase (eNOS), resulting in elevated nitric oxide (NO) production. These results suggest that α- and β-amyrins promote neovascularization in endothelial cells through an Akt-eNOS signaling-dependent mechanism.

Therefore, α- and β-amyrins may represent promising therapeutic agents for the treatment of vascular diseases [39].

The effects of α- and β-amyrins (20 mg/kg for 15 days) on vascular reactivity were evaluated in a mouse model of diet-induced obesity. Mice were fed a high-fat diet (HFD) for 15 weeks to induce obesity. The contractile responses of isolated thoracic aorta to potassium chloride (KCl) and phenylephrine, as well as endothelium-dependent and -independent vasodilation induced by acetylcholine and sodium nitroprusside, respectively, were assessed. Treatment with α- and β-amyrins prevented HFD-induced vascular dysfunction by restoring the attenuated contractile response to phenylephrine and improving vasodilatory responses to both acetylcholine and sodium nitroprusside. Furthermore, α- and β-amyrin administration reversed impaired K^+ channel activation and restored the inhibitory effects of tetraethylammonium on vasodilation. These findings suggest that α- and β-amyrins exert significant vascular protective effects in the context of obesity-associated endothelial dysfunction [40].

3.4. Antinociceptive Effect of α- and β-Amyrins

The analgesic activity of α- and β-amyrins, extracted from *Protium heptaphyllum*, was evaluated using a murine model of oral pain induced by formalin or capsaicin. Mice were administered α- and β-amyrin intraperitoneally at doses of 10, 30, and 100 mg/kg. Morphine (5 mg/kg, subcutaneously) and vehicle (3% Tween 80) served as controls. Pain was induced by injecting 20 µL of formalin (1.5%) or capsaicin (1.5 g) into the orofacial region. α- and β-Amyrins significantly reduced facial rubbing behavior in both pain models. Notably, at 30 mg/kg, α- and β-amyrins potentiated the second phase of the formalin response in a naloxone-sensitive manner, indicating involvement of peripheral opioid pathways. In the capsaicin-induced pain model, α- and β-amyrins exhibited a pronounced analgesic effect at the 100 mg/kg dose. These findings suggest that α- and β-amyrins exert antinociceptive effects through mechanisms at least partially mediated by peripheral opioid receptors [41].

The antinociceptive properties of α- and β-amyrins, extracted from *Protium kleinii*, were evaluated in rat models of visceral and inflammatory pain. Visceral pain was induced by intravenous injection of acetic acid, and the compounds were administered via both intraperitoneal and oral routes. The treatment provided rapid and effective pain relief. Further, α- and β-amyrins were assessed in central nervous system pain pathways through formalin injections into the hind paw, examining nociceptive responses at the level of the cerebral cortex and ventricles. The compounds effectively inhibited both the neurogenic and inflammatory phases of nociception. Moreover, α- and β-amyrins significantly reduced nociceptive responses induced by 8-bromo-cAMP (8-Br-cAMP), 12-O-tetradecanoylphorbol-13-acetate (TPA), and glutamate, suggesting a broad-spectrum analgesic profile. Notably, these antinociceptive effects appeared to be independent of classical opioid, α-adrenergic, serotonergic, or nitrergic pathways. Furthermore, α- and β-amyrins significantly reduced mechanical hyperalgesia triggered by inflammatory mediators such as carrageenan, capsaicin, bradykinin, substance P, prostaglandin E2, 8-Br-cAMP, and TPA. These results suggest that α- and β-amyrins exert robust peripheral, spinal, and supraspinal antinociceptive effects, supporting their potential as novel agents for treating inflammatory and visceral pain [42].

The analgesic potential of α- and β-amyrins was demonstrated in the acetic acid-induced writhing test, where these compounds exhibited significant activity in reducing nociceptive responses. When administered orally, α- and β-amyrins effectively decreased the number of abdominal constrictions induced by acetic acid, indicating strong peripheral analgesic properties. Furthermore, in the formalin-induced pain model, α- and β-amyrins

attenuated the behavioral responses associated with both the neurogenic and inflammatory phases of pain. These findings underscored the role of α- and β-amyrins in modulating pain perception and support their potential as therapeutic agents for the management of inflammatory and visceral pain [43].

Pharmacological activation of cannabinoid receptors CB1 and CB2 were a promising therapeutic strategy for the treatment of chronic pain and inflammation. In this context, α- and β-amyrins were investigated as bioactive compounds and demonstrated significant inhibition of persistent neuropathic pain and inflammation in murine models through oral administration. These triterpenes exerted their effects via both CB1 and CB2 receptor pathways. Notably, α- and β-amyrins exhibited strong inhibitory activity against the hydrolysis of 2-arachidonoyl glycerol (2-AG) in porcine brain homogenate, suggesting an indirect cannabimimetic mechanism. Rather than binding directly to cannabinoid receptors, α- and β-amyrins appear to enhance endocannabinoid signaling by preventing the enzymatic degradation of 2-AG. These findings position α- and β-amyrins as potential lead compounds for the development of novel analgesic and anti-inflammatory therapies targeting the endocannabinoid system [44].

3.5. Antigout Effect of α- and β-Amyrins

α- and β-Amyrin extracted from *Celastrus hindsii* were shown to possess antigout potential by inhibiting the activity of the xanthine oxidase (XO) enzyme, with an IC_{50} value of 258.22 μg/mL [23]. Compounds α- and β-amyrins, isolated from *Tabebuia roseoalba* leaves and identified in ethanol extracts by HPLC analysis, were shown to reduce serum uric acid concentrations and inhibit the inflammatory process associated with gout. The study evaluated their antihyperuricemic, hepatic xanthine oxidoreductase inhibitory, and anti-inflammatory activities in hyperuricemic rats and monosodium urate crystal-induced paw edema models [45]. β-Amyrin significantly reduced serum uric acid levels in hyperuricemic rats by inhibiting hepatic xanthine oxidase activity and effectively reduced monosodium urate crystal-induced paw edema. These findings suggest that β-amyrin is a promising agent for the treatment of gouty arthritis, hyperuricemia, and related inflammatory conditions [46].

α- and β-Amyrin were isolated from the pericarp, heartwood, and seed of *Garcinia subelliptica*. Structural identification of these triterpenoids was confirmed through spectroscopic analysis, including techniques such as NMR and mass spectrometry. Both compounds demonstrated a notable inhibitory effect on xanthine oxidase (XO), an enzyme involved in purine metabolism and a key contributor to uric acid production. This suggests their potential antigout and antioxidant applications. Flow cytometric analysis revealed that treatment of NTUB1 cells with compound 1, either alone or in combination with cisplatin, resulted in cell cycle arrest and a significant increase in apoptotic cell death after 24 h of exposure. These data suggested that the induction of cell cycle arrest and apoptosis in NTUB1 cells treated with compound 1 or with a combination of compound 1 and cisplatin for 24 h is mediated by an increased production of reactive oxygen species (ROS) [47].

3.6. Positive Effects of α- and β-Amyrins on Nerves

α- and β-Amyrins were studied for their pharmacological effects on sleep in mice. The sleep was induced using pentobarbital, and the mice were then administered α- and β-amyrin at concentrations of 1, 3, or 10 mg/kg. The results showed that α- and β-amyrins significantly extended the sleep duration in mice. This suggests that α- and β-amyrins have potential anti-insomnia effects, likely through the activation of the GABAergic neurotransmitter system in the brain [48]. α- and β-Amyrins isolated from *Protium heptaphyllum* have demonstrated anticonvulsant, sedative, and anxiolytic properties. In the study, rats

were treated with α- and β-amyrins at concentrations of 2.5, 5, 10, and 25 mg/kg (i.p. or orally). The results showed a significant increase in barbiturate-induced sleep duration, confirming the sedative effect. Additionally, the study found that tyrosine levels increased by 89%, while levels of GABA and glutamate decreased by 72%, 55%, and 60%, respectively. Furthermore, excitatory amino acids were reduced, and inhibitory amino acids were increased, suggesting a shift towards a more inhibitory neurotransmitter profile [49].

α- and β-Amyrins extracted from *Protium heptaphyllum* were evaluated for their ability to reduce capsaicin-induced analgesia in mice. The results demonstrated that orally administered α- and β-amyrins (doses ranging from 3 to 100 mg/kg) effectively inhibited pain sensation induced by capsaicin applied to the plantar (1.6 µg) and colon (149 µg). Notably, α- and β-amyrins did not alter sleep duration, nor did they impair walking, locomotion, or cause any observable abnormalities. Additionally, these compounds significantly blocked the hyperthermic response induced by capsaicin (10 mg/kg). These findings suggest that α- and β-amyrins may be potential compounds for analgesia, likely involving the vanilloid receptor (TRPV1) and opioid mechanisms [50].

The isolation of α- and β-amyrin from *Lobelia inflata* leaves was studied for its effects on the central nervous system in mice. The results showed that α- and β-amyrins significantly reduced the immobility time of mice in a dose-dependent manner (5, 10, and 20 mg/kg). These compounds also dose-dependently reduce locomotor activity and potentiated methamphetamine-induced locomotor antagonism. Unlike imipramine, α- and β-amyrins did not affect haloperidol-induced rigidity, tetrabenazine-induced ptosis, or apomorphine-induced stereotypy. They also had no effect on the 5-hydroxytryptophan-induced head-clonic reaction. Additionally, α- and β-amyrins (5, 10, and 20 mg/kg) had a stronger effect on pentobarbital sodium-induced delirium than imipramine (10, 20, and 40 mg/kg). These findings suggest that α- and β-amyrins exhibit sedative and antidepressant-like effects, comparable to the activity of meandering [51].

α- and β-Amyrin, components found in the waxy surface of tomatoes and dandelion coffee, have been shown to improve memory impairment caused by cholinergic dysfunction. These compounds act as PI3K inhibitors, which help reduce long-term potentiation (LTP) impairment. In studies on Aβ-injected mouse models of Alzheimer's disease, α- and β-amyrin were found to improve object recognition memory deficits. Furthermore, α- and β-amyrin treatment helped restore neurogenesis impairment induced by Aβ. These findings suggest that α- and β-amyrin are promising candidates for the treatment of Alzheimer's disease [52]. The isomer mixture of α- and β-amyrin found in the resin of *Protium heptaphyllum* has demonstrated potential as an anti-inflammatory agent. Additionally, these compounds have been shown to have a protective effect on both the central and peripheral nervous systems, helping the brain respond to various effects on the central nervous system [53].

3.7. Anti-Parkinsonian Effects of α- and β-Amyrins

α- and β-Amyrins have been shown to offer protective effects on dopaminergic neurons by reducing 6-hydroxydopamine (6-OHDA)-induced cell damage. These compounds exhibit strong antioxidant activity, reducing intracellular reactive oxygen species (ROS) in *C. elegans*. α- and β-Amyrins significantly decrease α-synuclein aggregation in the NL5901 transgenic strain, upregulate LGG-1 mRNA expression, and increase the number of localized LGG-1 dots in the DA2123 transgenic strain. These results suggest that α- and β-amyrins could be beneficial in the treatment and slowing of Parkinson's disease progression [54]. The use of α- and β-amyrins has been explored as a potential treatment to prevent Parkinson's disease by targeting misfolded proteins and damaged organelles. These effects have been tested through mechanisms related to LGG-1, suggesting that

α- and β-amyrins may play a role in mitigating the underlying causes of Parkinson's disease [55]. Autophagy has been recognized as a promising therapeutic approach for preventing Parkinson's disease, as it plays a crucial role in eliminating misfolded proteins and damaged organelles, which are key contributors to the disease's progression [56]. During the process of autophagosome formation, LGG-1 plays a crucial role in structural maintenance, making it a valuable marker for monitoring autophagic activity [57].

α- and β-Amyrins have been shown to participate in the LGG-1-related autophagy pathway by enhancing LGG-1 expression and increasing the number of localized LGG-1 spots. These compounds have demonstrated the ability to protect dopaminergic neurons by reducing cell damage and preventing α-synuclein aggregation, both of which are associated with Parkinson's disease symptoms [58]. Anti-Parkinsonian activities are closely linked to the regulation of cholesterol metabolism, as sterol-mediated cholesterol metabolism plays a significant role in neurological diseases. Low levels of LDL-C are often associated with a higher incidence of Parkinson's disease. α- and β-Amyrins have been shown to regulate cholesterol metabolism, supporting their potential antineurological and antidementia effects. This suggests that α- and β-amyrins could be promising agents for the treatment of Parkinson's disease [59].

3.8. Anticancer Potential of α- and β-Amyrins

Because of constant demand to develop new, effective and affordable anticancer drugs, the traditional medicinal system is a valuable and alternative resource for identifying novel anticancer agents. A study investigated the inhibitory activity of the compounds in methanolic bark extract of *Shorea robusta* on hepatocellular carcinoma by molecular docking studies on isolated α- and β-amyrins compounds. These compounds are used for docking on human oncogene protein. Docking studies of designed compounds were carried out using molecular docking servers. The recorded for alpha and beta amyrin binding with human Ras protein was −9.36 kcal/mol and −8.90 kcal/mol, respectively. Frontier singly occupied molecular orbitals (SOMO) were studied by density functional theory (DFT) and time dependent-DFT calculations. Among the calculated band gap energies, the β-MOs of α- and β-amyrin compounds have a very narrow band gap (−1.057 eV). These findings explain the anticancer activities of alpha and beta amyrin from *Shorea robusta* [60].

Another study aimed to evaluate the chemical composition of *P. heptaphyllum* resin and cytotoxicity on a breast cancer cell line (MCF-7). The chemical composition of the resin was determined by gas chromatography coupled with a mass spectrometer. Cytotoxicity was evaluated using an MTT assay. Annexin V-FITC, caspase-3, Angiotensin Converting Enzyme activity, and Tumor Necrosis Factor alpha (TNF-α) assays were performed to evaluate apoptosis and inflammatory events. The resin consisted of triterpenes, such as α- and β-amyrin. Cytotoxicity was only observed in fractions enriched with α- and β-amyrin. The resin and fractions elicited antiproliferative activity, increased activity of caspase-3 and ACE, and decreased the TNF-α level. Altogether, the resin and fractions enriched with α- and β-amyrin promoted cytotoxicity and apoptosis [61].

α- and β-Amyrins have been studied to exhibit significant pharmacological properties. One study was conducted to investigate the anticancer and pro-apoptotic effects of β-amyrin against HepG2 liver cancer cells. The antiproliferative potential of α- and β-amyrins was evaluated using the MTT assay. Apoptosis was assessed through DAPI staining, and DNA damage was analyzed using the comet assay. Cell cycle analysis was performed using flow cytometry, and protein expression levels were assessed by Western blotting. β-Amyrin exhibited significant anticancer activity against Hep-G2 liver cancer cells, with an IC_{50} value of 25 μM. The anticancer effects of α- and β-amyrins were attributed to the induction of apoptosis and G2/M phase cell cycle arrest in a dose-dependent manner. Based on the

results of the study, α- and β-amyrins may represent a promising lead compound for the treatment of liver cancer [62].

The anticancer activity of α- and β-amyrins have been evaluated in various therapeutic combinations against colon cancer, aiming to identify the key mechanisms involved in mitigating nickel-induced carcinogenesis. To evaluate the ligand–protein interactions of four selected compounds with Vascular Endothelial Growth Factor (VEGF), Matrix Metalloproteinase-9 (MMP-9), and Interleukin-10 (IL-10), a molecular docking approach was employed using the PyRx bioinformatics tool. Ten rats, each weighing between 160 and 200 g, were administered intraperitoneal injections of nickel at a dose of 1 mL/kg once per week for three months. Following this exposure, the rats were treated with β-amyrin at a dose of 100 mg/kg body weight for one month. Correlation analysis was performed using Pearson's correlation matrix. All parameters were significantly elevated in the positive control group, indicating pronounced inflammation. The study concluded that α- and β-amyrins are potent anticancer agents capable of targeting cancer biomarkers and hold future promise as a superior therapeutic approach against colon cancer [63].

Natural α- and β-amyrins were isolated from the endemic Brazilian plant *Esenbeckia grandiflora* Mart., and eight synthetic derivatives were subsequently obtained through esterification with bromoacetate, followed by treatment with various amines. The structures of all compounds were confirmed through analysis of ^{1}H and ^{13}C nuclear magnetic resonance (NMR), Fourier-transform infrared spectroscopy (FTIR), and high-resolution mass spectrometry (HRMS) data. The synthetic derivatives were evaluated for their cytotoxic activity against human tumor cell lines, including PC3 (prostate carcinoma), HCT-116 (colon carcinoma), and HL60 (leukemia). The HCT-116 and PC3 cell lines exhibited weak tumor growth inhibition, with inhibition ranges of 13.9–25.4% and 10.3–28.8%, respectively. In contrast, the derivatives demonstrated moderate cytotoxic activity against the HL60 leukemia cell line, with inhibition ranging from 13.6% to 59.0% [64].

α- and β-Amyrins were found to be highly active and non-toxic compounds against tumor cells. Their inhibitory effects were tested on four human tumor cell lines (HL-60, MDAMB-435, SF-295, and HCT-8), as well as on normal peripheral blood mononuclear cells (PBMCs). The results demonstrated that α- and β-amyrins exhibited significant anticancer activity while showing minimal toxicity to normal cells, making them promising candidates for further exploration in cancer therapy [65].

HeLa cells were treated with β-amyrin, and the cells were pretreated with 100 μM *N*-acetyl-L-cysteine for 1 h before treatment. The efficacy of β-amyrin was evaluated through antiproliferative activity measured by the MTT assay, genotoxicity using the micronucleus assay, and the determination of reactive oxygen species (ROS), nitric oxide (NO), and caspase-3 levels using fluorescence spectrophotometry and a colorimeter. Protein expression was assessed via immunoblotting. β-Amyrin (10–200 μM) inhibited the growth of cancer cells, with IC_{50} values ranging from 10 to 100 μM. Western blot analysis revealed that β-amyrin induced apoptosis-related proteins, including Bcl-2, caspase-3, caspase-9, phospho-p38 mitogen-activated protein kinase (MAPK), and phospho-Jun N-terminal kinase (JNK) in cancer cells. Genotoxic effects were observed following β-amyrin treatment, and HeLa cells exhibited a significant increase in total ROS. Protein expression analysis showed that β-amyrin upregulated MAPK-p38, phospho-JNK, and growth arrest and DNA damage-inducible β (GADD45β) in HeLa cells. These results suggest that β-amyrin induces apoptosis through a ROS-mediated mechanism by activating p38 MAPK and JNK pathways via the transcription factor GADD45β, which plays a major role in suppressing the growth of cervical cancer cells [66].

The mixture of α-amyrin and β-amyrin demonstrated anticancer potential against the MCF-7 breast cancer cell line with an IC_{50} value of 28.45 μg/mL. Importantly, this com-

pound was not cytotoxic to normal cells, suggesting a selective action against cancer cells. These findings position α- and β-amyrin as promising candidates for developing treatments for breast cancer, with potential for fewer side effects due to their selective cytotoxicity [67].

The mixture of α-amyrin and β-amyrin, isolated from dichloromethane extract, exhibited significant antitumor activity against several cancer cell lines, including KB-oral, and NCI-H187, with IC_{50} values of 18.01 and 18.42 μg/mL, respectively. Additionally, α-amyrin and β-amyrin demonstrated strong antibacterial activity against *Escherichia coli*, with a minimum inhibitory concentration (MIC) of 31.25 μg/mL. These findings highlight the dual potential of α- and β-amyrin as both anticancer and antibacterial agents [68,69].

The study on α-amyrin and β-amyrin from *Mesua ferrea* stem bark demonstrated their significant in vitro anticancer activity against human colon cancer HCT116 cells. The compounds were tested using the MTT assay, which revealed their toxicity against various cancer cell lines, while also indicating their selective action, as they did not show similar toxicity to normal cell lines. This further supports the anticancer potential of α-amyrin and β-amyrin as promising therapeutic agents for cancer treatment [70].

α-Amyrin- and β-amyrin-loaded nanocapsules for intestinal delivery were evaluated, preliminarily, for their cytotoxic ability against leukemic cells. Nanocapsule formulations were designed by the solvent displacement–evaporation method. The cytotoxic potential of the nanocapsules was evaluated in vitro using different leukemic lineages. Nanocapsules coated with Kollicoat® Mae 100 P presented the smallest particle size (130 nm), the lowest zeta-potential (−38 mV), and the narrowest size distribution (PdI = 0.100). The entrapment efficiency was 65.47%, while the loading capacity was 2.40%. Nanocapsules release 100% of α-amyrin in 40 min (pH 7.4) by using a possible mechanism of swelling–diffusion. The formulation showed excellent on-shelf physicochemical stability for one year. Additionally, nanocapsules produced a selective cytotoxic effect on a human leukemia lineage Kasumi-1, an acute myeloid leukemia cell line, and produced cell death by apoptosis. α-Amyrin-loaded nanocapsules appear to be a promising nanoformulation that could be used against leukemia [71].

3.9. Antibacterial Potential of α- and β-Amyrins

The mixture of α- and β-amyrins isolated from *Protium heptaphyllum* demonstrates significant antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* strains, including multidrug-resistant strains. Additionally, these compounds effectively inhibit efflux resistance mechanisms in *S. aureus* strains 1199B and K2068, which carry the NorA and MepA efflux pumps. α- and β-Amyrins showed a higher affinity for these efflux pumps (NorA and MepA) compared to commonly used antibiotics like ciprofloxacin and norfloxacin. This suggests that α- and β-amyrins may enhance antibiotic activity by inhibiting efflux pumps, thus preventing bacteria from expelling the antibiotics. These findings support the potential of α- and β-amyrins as promising antibacterial agents, especially when combined with conventional antibiotics, to combat multidrug-resistant infections [72].

A study demonstrated that the mixture of α- and β-amyrin isolated from *Morinda lucida* leaves exhibited strong antibacterial activity against multidrug-resistant strains of Enterobacteriaceae, including *Klebsiella*, *Pragia*, *Serratia*, *Enterobacter*, *Providencia*, and *E. coli*. The compound mixture showed inhibition zones ranging from 15 to 18 mm at a concentration of 0.093 μg/mL. These results suggest that α- and β-amyrins from *M. lucida* could be potent agents for treating infections caused by antibiotic-resistant bacteria. This supports the traditional use of *M. lucida* in herbal medicine, and these compounds may offer alternative or complementary treatment for infectious diseases that are resistant to conventional antibiotics [73].

Another study demonstrated that the α- and β-amyrin fraction (3.4 mg/mL) from *C. trichotomum* exhibited significant antibacterial activity against *E. coli*, *S. aureus*, and *H. pylori*. The compounds showed inhibition zones of 12 mm against *E. coli* and 13 mm against *H. pylori*, indicating their potential as antibacterial agents. At a lower concentration of 1.7 mg/mL, α- and β-amyrins still showed inhibition against *H. pylori*, with inhibition zones of 10 mm and 11 mm, respectively. These findings suggest that α- and β-amyrins from *C. trichotomum* could serve as promising therapeutic agents against infections caused by these bacterial strains, offering a potential alternative to traditional antibiotics [74].

3.10. Anti-HIV Potential of α- and β-Amyrins

The potential of α- and β-amyrins in combating HIV has been studied with promising outcomes. These compounds were extracted from the stems and roots of *Kadsura lancilimba*. Their structures and stereo chemistries were identified primarily from mass and NMR spectral data. α- and β-Amyrins inhibited HIV replication with an (IC_{50}: 1.4 μg/mL). α- and β-Amyrins have shown antiviral activity, particularly against HIV, making them a significant discovery in the pursuit of treatments for this "disease of the century." Their therapeutic potential could be a step forward in developing alternative treatments for HIV, especially given the ongoing need for more effective antiviral drugs [75]. This underscores the urgent need for safer, more effective drugs to combat resistant strains and advance acquired immunodeficiency syndrome (AIDS) therapeutics. α- and β-Amyrins were identified from *Uncaria rhynchophylla* hooks. These compounds exhibited potent inhibition of HIV-1 protease (PR), one of the essential enzymes in the virus's life cycle, with 3β-hydroxy-27-p-Z-coumaroyloxyurs-12-en-28-oic acid (8) showing the most potent inhibitory activity.In a study using in silico docking, triterpene ester 8 demonstrated conventional hydrogen bonding with specific amino acid residues, Asp29B, Lys45B, and Asn25A, interacting with the aromatic hydroxyl group at position 7 and the carboxylic acid at position 28. Additionally, these interactions occur via π–anion and π–alkyl and alkyl hydrophobic interactions, which are responsible for the compound's mode of action. These molecular docking studies strongly confirmed an excellent SAR. The study suggests that triterpene esters from *U. rhynchophylla* could represent a new class of potent HIV-1 PR inhibitors with less toxicity, suitable for combination antiretroviral therapy for AIDS [76]. The isolation of α- and β-amyrins, along with 10 other triterpene compounds from dried stems of *Stauntonia obovatifoliola* Hayata subsp, represented a significant step in the search for potential anti-HIV agents. Through the analysis of high-resolution EI/FAB-MS spectral data and 1D and 2D NMR spectra, the structures of these compounds were elucidated. Notably, α- and β-amyrins, along with other compounds from this plant, demonstrated HIV-1 protease inhibitory activity in the studies. This discovery highlighted the potential of these triterpenes as promising candidates for the development of novel anti-HIV therapies. Further, these results emphasize their importance in addressing the ongoing global HIV/AIDS epidemic [77]. α- and β-Amyrins, isolated from the leaves and twigs of *Gardenia carinata*, were structurally characterized using spectroscopic methods. These triterpenoids exhibited notable biological activities, specifically antitopoisomerase IIα and anti-HIV-1 properties. Remarkably, α- and β-amyrins were found to be completely non-cytotoxic, indicating their potential as safe therapeutic agents. The ability of these compounds to inhibit topoisomerase IIα, an enzyme critical in DNA replication and transcription, alongside their anti-HIV-1 activity, positions them as promising candidates for further research in the development of novel treatments for cancer and HIV, with minimal toxicity [78].

α- and β-Amyrins are triterpenoids that were isolated from *Cassine xylocarpa* stem and *Maytenus cuzcoina* root bark and studied for their anti-HIV potential. The structures of these compounds were elucidated using 1D and 2D NMR techniques. To enhance their anti-

HIV activity, derivatives of triterpenoids were synthesized through chemical modification of parent compounds. These modified derivatives exhibited inhibitory effects on HIV replication, with IC_{50} values (4.08, 4.18, 1.70 μM) in the micromolar range. This indicates their strong potential as anti-HIV agents. The findings support the idea that α- and β-amyrins, both in their natural form and as modified derivatives, could be developed as valuable therapeutic agents for the treatment of HIV [79]. α- and β-Amyrin derivatives have demonstrated potent anti-HIV activity, with the derivatives being specifically characterized based on their C-3 configuration. This study aimed to explore how modifications to the C-3 position and the overall triterpene backbone influence their anti-HIV effectiveness. The results provided valuable insights into the structure–activity relationship of α- and β-amyrins, highlighting how changes in the chemical structure can enhance their ability to inhibit the growth of HIV cells. This research further identifies α- and β-amyrins, particularly their modified derivatives, as promising candidates for the development of anti-HIV therapies. The study emphasizes the importance of structural modifications in improving the efficacy of natural compounds in combating complex diseases like HIV [80].

3.11. The Isolation α- and β-Amyrins

The extraction of α- and β-amyrins from *C. hindsii* has proven highly effective, yielding a remarkable amount of 10.75 g/kg dry weight. This highlighted *C. hindsii* as a valuable source of raw material for α- and β-amyrins extraction. The identification and structural elucidation of the isolated compounds were carried out using advanced techniques such as gas chromatography–mass spectrometry (GC-MS), electrospray ionization–mass spectrometry (ESI-MS), and nuclear magnetic resonance (NMR). These methods enabled accurate characterization of the compounds and confirmed the effectiveness of the extraction process, thereby reinforcing *C. hindsii* as a promising source of bioactive triterpenoids [23].

4. Discussion

The world is currently facing a significant burden of disease. According to statistics from the World Health Organization, the global demand for pharmaceuticals increased steadily at an annual rate of 5.8% between 2014 and 2017 [81]. The demand for pharmaceuticals is expected to increase steadily at an annual rate of 9 to 11.6% in the coming years [82]. Antibiotic consumption accounted for the largest share, increasing by 16.3% from 29.5 to 34.3 billion defined daily doses (DDDs) between 2016 and 2023 [83]. Cardiovascular drugs rank second, followed by anticancer drugs in third place and anti-infectives in fourth. The fifth largest segment of the pharmaceutical market includes treatments for metabolic disorders such as diabetes, together with thyroid and pituitary diseases [84]. The demand for cholesterol-lowering drugs increased nearly fourfold, the use of antidepressants doubled, and the consumption of antihypertensives and antidiabetics nearly doubled between 1999 and 2012 [85,86]. In recent years, medications for the treatment of diabetes, hypertension, acquired immunodeficiency syndrome (AIDS), malaria, and tuberculosis have ranked among those with the highest global demand [87]. The demand for pharmaceuticals is increasing not only in quantity but also in the need for higher quality and greater variety. In particular, the COVID-19 pandemic in 2020 starkly highlighted the urgent need for effective pharmaceuticals [88]. Pharmaceutical consumption is increasing rapidly worldwide due to an aging population and the growing need for clinical management [89]. Global population growth is a major factor contributing to the increased demand for pharmaceuticals [90]. As society develops, the demand for pharmaceuticals, healthcare, and protection is increasingly focused on addressing more complex needs [91]. Therefore, the pharmaceutical industry is becoming increasingly vital, and natural compounds continue to serve as a crucial source of raw materials for drug development [92]. The discovery of natural com-

pounds with potent biological activity has opened promising avenues for the development of new drugs [93]. The pharmaceutical industry always requires strict standards for all input materials to ensure safety, efficacy, and quality in the development of therapeutic products [94]. Therefore, the research and development of compounds such as α- and β-amyrin to serve the global pharmaceutical industry is of great importance.

Figure 3 illustrates the synthesis of α- and β-amyrin activities that have been studied, aiming to clarify the potential contributions of these compounds to the pharmaceutical industry. The pharmacological activities of the α- and β-amyrin mixture have been extensively studied both in vitro and in vivo to support future medicinal applications. Research has demonstrated that α- and β-amyrin possess a wide range of therapeutic properties, including analgesic, anti-inflammatory, anticonvulsant, antidepressant, gastroprotective, hepatoprotective, antipancreatitis, antihyperglycemic, and hypolipidemic effects [95]. α- and β-Amyrin have also been shown to exhibit anticancer and anti-inflammatory properties, and beneficial effects in cardiovascular disease, diabetes, and arthritis [96]. Notably, these compounds have been shown to be non-toxic to normal cells [97]. Therefore, α- and β-amyrin represented a promising source of raw materials for the development of future medicinal products.

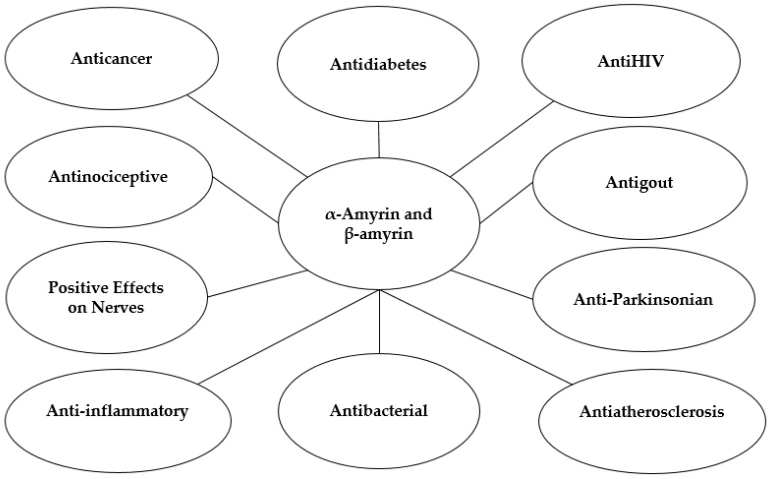


Figure 3. The summary diagram of α- and β-amyrins's pharmaceutical potential.

Inflammation is the body's biological response to external or internal agents [98]. Dangerous inflammatory conditions include hepatitis, appendicitis, colitis, gastritis, encephalitis, and nephritis [99]. One of the most serious inflammatory diseases is pneumonia, which is closely linked to coronavirus disease [100]. Periodontal disease leads to gum recession and deterioration of the bone structure that supports teeth [101]. Inflammation can negatively affect bone health by disrupting bone growth and accelerating bone loss [102]. Inflammation is also associated with depression, contributing to symptoms such as mood swings, loss of appetite, and sleep disturbances [103]. Inflammation can activate immune cells to respond to bacteria already present in the digestive system, leading to chronic inflammation, inflammatory bowel disease (IBD), Crohn's disease, and ulcerative colitis [104]. Arthritis is associated with inflammation and an increased risk of cardiovascular problems [105]. Inflammation is also associated with cardiovascular disease leading to atherosclerosis in the arteries, increasing the risk of cardiovascular disease [106]. Chronic inflammation is associated with an increased risk of many types of cancer, including lung, esophageal, cervical, and gastrointestinal cancers. When immune cells initiate an inflammatory response, the regulatory ability of the immune system is impaired, creating a favorable environment for cancer cells to thrive [107,108]. Inflammation can negatively affect sleep, causing difficulty falling asleep or leading to excessive sleepiness [109]. Therefore, inflam-

mation is not only the body's response to harmful agents, but also at the core of many serious diseases. This study demonstrated that the anti-inflammatory potential of α- and β-amyrin (Table 1) has opened many opportunities for the development of adjuvant drugs for the treatment of related conditions.

Table 1. The anti-inflammatory activities of α- and β-amyrins.

Disease	Cell Line (Receptors)	Duration	Doses of α- and β-Amyrins	Assay	References
Periodontal	TNF-α	24 h	5–10 mg/kg	Vivo	[24]
Persistent Inflammatory and neuropathic hyperalgesia	CB1, CB2	12 h	30 mg/kg	Vivo	[25]
Colitis	COX-2, VEGF, NF-κB	72 h	3 mg/kg	Vivo	[26]
Colitis	ICAM-1, VCAM-1, PCAM-1, β2-integrin, CD68, P-selectin	0–7 days	1, 3, and 10 mg/kg	Vivo	[27]
Acute pancreatitis	(TNF-α), (IL-6)	24 h	10, 30, and 100 mg/kg	Vivo	[28]

Documents quoted from Science Citation Index (SCI) journals system.

Diabetes is a chronic disease that affects the body's ability to produce or use insulin, a hormone that helps convert glucose into energy [110]. The effects of diabetes are significant on the endocrine system. It causes both acute and chronic complications associated with diabetes [111]. Diabetes causes a buildup of ketones that can lead to ketoacidosis if not detected and treated promptly, which can lead to loss of consciousness or even death [112]. Diabetes can lead to kidney damage [113]. Diabetes can cause irreversible damage that can lead to kidney failure [114]. Hyperglycemic hyperosmolar syndrome (HHS) occurs in patients with type 2 diabetes. If left untreated, HHS can lead to serious complications such as heart attack, stroke, or infection [115]. Diabetes is the leading cause of gastroparesis [116]. High blood sugar, oxidative stress, and inflammation from diabetes can lead to hardening of the blood vessels [117]. Diabetes can lead to paralysis of the limbs, leaving the individual unaware of injuries or infections [118]. One of the harmful effects of diabetes is an increased risk in developing infections or diabetic foot ulcers [119]. Diabetes increases the risk of high blood pressure, which puts additional stress on the heart [120]. Diabetes can lead to various skin problems, including dry skin and skin infections [121]. Diabetes can damage peripheral nerves, impairing the patient's ability to perceive heat, cold, and pain [122]. Diabetics are more likely to develop cataract at an earlier age than those without diabetes [123]. In 2015, approximately 422 million people worldwide were living with diabetes. The number of diabetic patients has been steadily increasing over the years, and each year around 1.5 million people die from diabetes-related complications [124]. Diabetes results in many serious consequences and poses a significant challenge to global health. Studies conducted both in vivo and in vitro have demonstrated the antidiabetic potential of α- and β-amyrin (Table 2). These findings highlight the considerable value of α- and β-amyrin and suggest numerous opportunities for developing antidiabetic drugs.

Table 2. Studies on the antidiabetes potential of α- and β-amyrins.

Disease	Cell Line (Receptors)	Duration	Doses of α- and β-Amyrins	Assay	References
Diabetes, Cardiovascular	Beta cell	12 h	10, 30, and 100 mg/kg	Vivo	[29]
Diabetes	Beta cell	24 h	50 µg/kg	Vivo	[30]
Diabetes	-	-	10 µg/mL	Vitro	[31]
Diabetes	3T3-L1	24 h	1,10, and 100 µg/mL	Vivo	[32]
Diabetes	HK-2	24 h	100 µg/kg	Vivo	[33]
	-	-	19.50 µg/mL	Vitro	[34]

Documents quoted from Science Citation Index (SCI) journals system; (-): Not yet determined.

Atherosclerosis causes blockages caused by plaque, which consists of fats, cholesterol, calcium, and other substances that build up on the walls of arteries [125]. Atherosclerosis disrupts blood flow, preventing oxygen and nutrients from reaching vital organs and tissues, contributing to the development of cardiovascular disease. If an atherosclerotic plaque ruptures and forms a blood clot, it can lead to a heart attack or stroke [126]. Patients with coronary atherosclerosis may experience angina and myocardial infarction, which can lead to heart failure [127]. Atherosclerosis can progress to a stroke, causing sudden weakness or numbness in one arm or leg, slurred or difficult speech, temporary loss of vision in one eye, or drooping eyelid [128]. Atherosclerosis increases the risk of stroke, heart attack, and gangrene, which can lead to amputation [129]. Atherosclerosis can lead to chronic kidney disease, preventing the kidneys from effectively removing toxins and excess fluid from the blood [130]. Atherosclerosis has been extensively studied as a cause of many dangerous complications. The strong antiatherosclerotic potential of α- and β-amyrin is documented in Table 3, opening new opportunities and directions for the development of pharmaceutical products. These findings highlight the value of α- and β-amyrin in supporting and treating diseases related to atherosclerosis.

Table 3. Studies on the antiatherosclerosis potential of α- and β-amyrins.

Disease	Cell Line (Receptors)	Duration	Doses of α- and β-Amyrins	Assay	References
Atherosclerosis	HepG2	-	200 µmol/L	Vitro	[35]
Type II diabetes, and atherosclerosis	IL-6, TNF-α	-	0.01 µM	Vitro	[36]
Nonalcoholic fatty liver	Lipid levels	15 weeks	10, 20, 50 mg/kg	Vivo	[37]
Vascular disorders	SVEC4-10	-	0.6 và 0.3 µM	Vitro	[38]
Vascular	HUVECs	24–72 h	0.025–10 µM)	Vitro	[39]
Obesity	PHE, ACh, SNP	15 days	20 mg/kg	Vivo	[40]

Documents quoted from Science Citation Index (SCI) journals system. (-): Not yet determined.

Nociception is the process by which noxious stimuli are encoded by the sensory nervous system. A series of events and processes are required for an organism to detect a painful stimulus, which is then converted into a molecular signal. This signal is recognized and processed to activate the appropriate response [131]. Nociception causes discomfort and may indicate that tissues are being damaged. To alleviate this, antinociceptive treatments are often used. While these treatments may not eliminate pain, they provide relief, helping the patient feel more comfortable [132]. Antinociception drugs are effective in the treatment of headaches, colds, and flu [133]. Antinociception drugs are used for muscle pain [134], joint pain [135], and back pain due to disc herniation or spinal stenosis [136]. Antinociception is applied to treat physical trauma [137], surgery [138], or childbirth [139]. Non-steroidal anti-inflammatory pain relievers (NSAIDs) comprise a group of drugs that includes meloxicam, piroxicam, aspirin, diclofenac, indomethacin, etc. This group of drugs is used to treat fever, headaches and pain, colds, and sinusitis [140]. Non-steroidal anti-inflammatory pain relievers (NSAIDs) have been studied and shown to provide a novel mechanism for antinociception [141]. Paracetamol pain reliever is the most popular drug and is the basic pain reliever in treating mild to moderate pain, especially fever reduction [142]. Paracetamol pain reliever is a kind of antinociception [143]. Thus, α- and β-amyrin have been proven to possess antinociceptive properties (Table 4). This indicates that α- and β-amyrin hold significant value, comparable to many other pharmaceuticals, in treating various diseases and complications related to nociception. α- and β-Amyrin were considered valuable discoveries in the development of effective pharmaceutical treatments.

Table 4. Studies on the antinociceptive potential of α- and β-amyrins.

Disease	Cell Line (Receptors)	Duration	Doses of α- and β-Amyrins	Assay	References
Antinociceptive	Capsaicin, naloxone	10–20 min	10, 30, and 100 mg/kg	Vivo	[41]
Antinociceptive	Protein kinase A, protein kinase C	-	0.1–100 mg/kg	Vivo	[42]
Visceral pain	KBr pellets, Bruker AC	-	45–90%	Vitro	[43]
Novel analgesic	CHO-K1 cell, Cannabinoid CB1 and CB2 receptors	-	>10 µM	Vitro	[44]

Documents quoted from Science Citation Index (SCI) journals system. (-): Not yet determined.

Gout is a common form of arthritis characterized by sudden and severe pain in the joints, particularly in the toes, fingers, and knees. The affected joints become red, swollen, and extremely painful, often making it difficult for patients to walk [144]. Gout occurs in individuals who have elevated levels of uric acid in their blood. It can form sharp, needle-like crystals that accumulate in the joints, causing intense pain and inflammation [145]. Uric acid crystals can accumulate in the tubes that carry urine from the kidneys to the bladder, leading to the formation of kidney stones [146]. Tophi are deposits of urate crystals that form around joints in people with long-term gout. These crystals appear as nodules, bulging underneath the skin in areas such as the feet, knees, wrists, fingers, and heel tendons [147]. The areas surrounding the tophi are often hot, soft, swollen, and painful. This swelling can limit joint movement, reduce the range of motion, and cause significant difficulty in daily activities [148]. Chronic gouty arthritis can result in permanent joint damage, leading to deformity and stiffness [149]. High uric acid levels in the body can lead to kidney stones [150]. Gout can lead to kidney failure, increasing the risk of kidney damage, potentially causing scarring that impairs kidney function [151]. Complications of gout can also include bone fractures, which weaken bones, increase the risk of osteoporosis, and make patients more susceptible to fractures [152]. Although gout does not directly cause cardiovascular disease, studies show that people with gout are twice as likely to have a heart attack or stroke as people without the disease. Cardiovascular complications associated with gout are particularly dangerous because patients are twice as likely to die from heart failure as people without gout [153]. Many people with gout have sleep disturbances because gout attacks often flare up at night. Gout can cause fatigue, stress, and a host of other health problems associated with insomnia [154]. Decreased bone density is a common complication of gout, due to bone damage and impaired bone function. This increases the risk of other bone and joint diseases, including osteoporosis, osteoarthritis, and fractures [155,156]. The impact of gout on human life and health is of great concern. The discovery of the antigout potential of α- and β-amyrin (Table 5) is considered a breakthrough in the development of pharmaceuticals that can effectively treat this condition. The harmful effects of gout on human life and health are concerning. The discovery of the antigout potential of α- and β-amyrin (Table 5) is considered a significant breakthrough in the development of pharmaceuticals that can effectively treat this condition.

Table 5. Studies on the antigout potential of α- and β-amyrins.

Disease	Enzyme (Receptors)	Duration	Doses of α- and β-Amyrins	Assay	References
Gout	XO	-	258.22 µg/mL	Vitro	[23]
Gout	XO, Urate crystals	-	-	Vivo	[45,46]
Gout	NTUB1	24 h	-	Vitro	[46]

Documents quoted from Science Citation Index (SCI) journals system; (-): Not yet determined.

Sedatives work by slowing down brain activity, helping to calm and regulate the nervous system. These drugs have a direct effect on the central nervous system, either stimulating or inhibiting nerve activity to prevent and treat various conditions [157]. Insomnia is a type of sleep disorder that manifests in various forms, including difficulty falling asleep, trouble staying asleep, waking up too early despite not obtaining enough rest, and being unable to return to sleep after waking [158]. Insomnia can be a symptom of underlying mental health conditions [159]. The positive effects of α- and β-amyrin on the nervous system, including sedation and promoting better sleep, are considered among its greatest values (Table 6). These findings have shown the promising potential of this compound in the development of pharmaceuticals and functional foods aimed at sedatives, sleeping aids, and supporting or stimulating the nervous system.

Table 6. Studies on the positive effects of α- and β-amyrins on nerves.

Disease	Cell Line (Receptors)	Duration	Doses of α- and β-Amyrins	Assay	References
Insomnia	GABAergic	12 h	1, 3, or 10 mg/kg	Vivo	[48]
Convulsant, Sedative, Anxiolytic	Glutamate, Aspartate, Taurine	12 h	2.5; 5; 10; 25 µg/mL	Vitro	[49]
Analgesia	TRPV1, Opioid	12 h	3–100 mg/kg	Vivo	[50]
Sedative, Depressant	TRPV1, Ruthenium red	15 h	5, 10, 20 mg/kg	Vivo	[51]
Alzheimer	pPI3K, PI3K, pAkt, Akt	24 h	4 µg/mL	Vitro	[52]
Protective central and peripheral nervous systems	Triglycerides	-	2000 mg/kg	Vivo	[52]

Documents quoted from Science Citation Index (SCI) journals system; (-): Not yet determined.

Parkinson's disease is a neurological disorder that typically occurs when a group of brain cells degenerate, impairing the brain's ability to control muscle movements. This leads to difficulties in walking, slow leg movements, and hand tremors. As the disease progresses, it can affect nerve cells, leading to a deficiency of dopamine, a key neurotransmitter involved in motor control [160]. Progressive Parkinson's disease can increase the risk of death, particularly as symptoms, such as hallucinations, cognitive decline, worsening motor disability, comorbidities, and prolonged disease duration, become more severe [161]. Individuals with advanced Parkinson's disease may experience falls, pressure ulcers, difficulty swallowing, and weakness. These complications are associated with an increased risk of early death [162]. Thus, finding effective pharmaceuticals to treat Parkinson's disease is an urgent need. The results demonstrating the potential of α- and β-amyrin in treating Parkinson's disease (Table 7) offer promising opportunities to develop pharmaceuticals that can support and treat this condition.

Table 7. Studies on the anti-Parkinsonian potential of α- and β-amyrins.

Disease	Cell Line (Receptors)	Duration	Doses of α- and β-Amyrins	Assay	References
Parkinson	6-OHDA	72 h	5, 10, 15, 30 µM	Vitro	[54]
Parkinson	LGG-1	12 h	5–30 µM	Vitro	[55]
Parkinson	LGG-1	-	-	Vitro	[57]
Parkinson	LGG-1	-	-	Vitro	[58]
Parkinson	LDL-C	-	-	Vitro	[59]

Documents quoted from Science Citation Index (SCI) journals system; (-): Not yet determined.

Cancer is a group of diseases that can originate in various organs and tissues throughout the human body. These cells grow beyond the normal regulatory boundaries of the body and can invade nearby tissues. When cancer spreads to other parts of the body through the bloodstream or lymphatic system, a process known as metastasis, it leads to complex

complications and is a major cause of death [163]. Cancer is recognized as the leading cause of death worldwide, posing a major challenge to global public health. In 2020 alone, there were approximately 18 million new cancer diagnoses and 10 million cancer-related deaths. According to the World Health Organization (WHO), cancer is the second leading cause of death after cardiovascular diseases in 112 countries and territories [164]. As shown in Table 8, the global cancer burden remains alarming, characterized by a substantial number of new diagnoses and deaths. Lung cancer leads in mortality, followed sequentially by colorectal, liver, female breast, and stomach cancers [165].

Table 8. New cases and deaths in 2022 from 20 cancers and all cancers combined.

Cancer Deases	Incidence		Mortality	
	Rank	New Cases	Rank	Deaths
Lung	1	2,480,301	1	18,171,722
Female breast	2	2,308,897	4	665,684
Colorectum	3	1,926,118	2	903,859
Prostate	4	1,466,680	8	396,792
Stomach	5	968,350	5	659,853
Liver	6	865,269	3	757,948
Thyroid	7	821,173	24	47,485
Cervix uteri	8	661,021	9	348,189
Bladder	9	613,791	13	220,349
Non-Hodgkin	10	553,010	11	250,475
Esophagus	11	510,716	7	445,129
Pancreas	12	510,566	6	467,005
Leukemia	13	486,777	10	305,033
Kidney	14	434,419	16	155,702
Corpus uteri	15	420,242	19	97,704
Lip, oral cavity	16	389,485	15	188,230
Skin	17	331,647	22	58,645
Ovary	18	324,398	14	206,839
Brain	19	321,476	12	248,305
Larynx	20	188,960	18	103,216

Data quoted from the research conducted [165].

The overall incidence of cancer is expected to be two to three times higher in some countries. Globally, the cancer burden is projected to reach 28.4 million cases by 2040, representing a 47% increase from 2020 [166]. The world is currently confronted with significant challenges arising from the increasing burden of cancer. Consequently, the discovery and development of effective cancer therapies has become an urgent global priority [167]. α- and β-Amyrins have demonstrated strong anticancer activities (Table 9), making them highly valuable compounds. These research findings played an important role in the development of pharmaceuticals and functional foods aimed at supporting and treating various types of cancer.

Bacteria are responsible for numerous human diseases and can be transmitted via ingestion (fecal oral route), inhalation (airborne or droplet transmission), or close contact with an infected person or contaminated surface. Once bacteria infect the host, a compromised immune system due to factors such as age, chronic illness, or immunosuppression can enable bacterial proliferation and progression to clinical disease [168]. The detrimental effects of bacteria can be extremely serious, as they can thrive and multiplying rapidly in diverse environments. Moreover, their microscopic size makes them invisible to the naked eye, rendering detection and control more challenging. These characteristics emphasize the critical importance of studying bacterial infectious diseases and implementing effective preventive measures to safeguard human health [169]. Since the discovery of bacteria, it has

become clear that they pose a significant danger to humans, causing and spreading various diseases. There is no part of the human body that is immune to bacterial infection [170]. Bacteria can multiply in the body and release toxins that can damage the body's tissues, leading to sickness [171]. Sore throats, staphylococcal infections, cholera, tuberculosis, and food poisoning are all caused by bacteria [172]. Bacteria are extremely dangerous causes of diseases and health problems in humans [173]. Any organ or part of the body can be susceptible to bacterial infections. If left untreated, these infections may progress rapidly and potentially lead to fatal outcomes [174].

Table 9. Studies on the anticancer potential of α- and β-amyrins.

Disease	Cell Line (Receptors)	Duration	Doses of α- and β-Amyrins	Assay	References
Liver cancer	Hepatocellular	-	−9.36 and −8.90 kcal/mol	Docking	[60]
Breast cancer	MCF-7, ATCC-HTB22	72 h	2.35–2.48 µg/ml	Vitro	[61]
Liver cancer	Hep-G2	-	25 µM	Vitro	[62]
Colon cancer	VEGF, MMP-9, IL-10	30 days	100 mg/kg	Vivo	[63]
Prostate Carcinoma	PC3, HL60	72 h	13.9–25.4%	Vitro	[64]
Leukemia cancer	HL-60, MDAMB-435, SF-295, HCT-8	-	1.8–3 µM	Vitro	[65]
Cervical cancer	HeLa	-	10–200 µM	Vitro	[66]
Breast cancer	MCF-7	-	28.45 µM	Vitro	[67]
Skin cancer	KB-oral	-	18.01 µM	Vitro	[68]
Lung cancer	NCI-H187		18.42 µM	Vitro	[69]
Colon cancer	HCT116	-	-	Vitro	[70]
Leukemia cancer	Kasumi-1	1 year	-	Nano	[71]

Documents quoted from Science Citation Index (SCI) journals system. (-): Not yet determined.

Table 10 shows that bacteria are responsible for numerous serious diseases in humans, as they can invade and damage nearly any part of the body. Consequently, the identification of effective pharmaceutical agents to combat and treat bacterial infections is of great importance. The antibacterial potential of α- and β-amyrins, as demonstrated in Table 11, highlight their promise as potential pharmaceutical candidates for the development of effective products aimed at the prevention and treatment of bacterial infections.

Table 10. Groups of diseases caused by bacteria.

Related Diseases	Type of Bacteria	Reference
Respiratory	*Staphylococcus*	[175]
	Pneumococcus	[176]
	Diphtheria	[177]
	Streptococcus	[178]
	Bacillus	[179]
Gastrointestinal	*E. coli*	[180]
	Salmonella	[181]
	Shigella	[182]
	Vibrio cholerae	[183]
	Listeria monocytogenes	[184]
Genital	*Neisseria gonorrhoeae*	[185]
	Treponema pallidum	[186]
	Haemophilus ducreyi	[187]
	Chlamydia trachomatis	[188]
	Mycoplasma genitalium	[189]
Blood	*Staphylococcus aureus*	[190]
	Neisseria meningitidis	[191]
	Pseudomonas aeruginosa	[192]
	Salmonella typhi	[193]
	Yersinia pestis	[194]
	Staphylococcus epidermidis	[195]

Documents quoted from Science Citation Index (SCI) journals system.

Table 11. Studies on the antibacterial potential of α- and β-amyrins.

Bacterial	Receptors	Doses of α- and β-Amyrins	Assay	References
Escherichia coli, *Staphylococcus aureus*	NorA, MepA	-	Docking	[72]
Klebsiella, *Pragia*, *Serratia*, *Enterobacter*, *Providencia*, *E. coli.*	Inhibition zones	0.093 µg/ml	Vitro	[73]
E. coli, *S. aureus*, *H. pylori*	Inhibition zones	3.4 mg/mL	Vitro	[74]

Documents quoted from Science Citation Index (SCI) journals system; (-): Not yet determined.

Human Immunodeficiency Virus (HIV) is the virus that causes immunodeficiency in humans [196]. It attacks the immune system, specifically CD4 white blood cells, which play a crucial role in helping the body fight off infections and diseases [197]. Over time, HIV gradually weakens the immune system, making the body more vulnerable to serious infections and cancers that it would normally be able to resist [198]. This includes opportunistic infections such as pneumonia, tuberculosis, encephalitis, and oral thrush, caused by bacteria, viruses, fungi, or parasites [199]. If left untreated, HIV progresses to its final stage: AIDS (Acquired Immunodeficiency Syndrome), which significantly increases the risk of death [200]. HIV can also affect the brain and nervous system, leading to memory loss, poor concentration, depression, dementia, and potentially severe neurological complications such as meningitis and encephalitis [201]. Additionally, it raises the risk of heart attacks [202], liver cirrhosis [203], kidney failure [204], pneumonia [205], chronic diarrhea [206], weight loss [207], and malabsorption [208]. By late 2024, an estimated 40.8 million individuals worldwide were living with HIV, among them approximately 1.4 million children under the age of 15. That same year saw around 1.3 million new HIV infections and nearly 630,000 deaths resulting from AIDS-related conditions [209]. Given the alarming global impact of HIV, the discovery of α- and β-amyrins's anti-HIV properties, as presented in Table 12, represents a meaningful contribution toward efforts to combat this disease of the century.

Table 12. Studies on the anti-HIV potential of α- and β-amyrins.

Disease	Research Subject (Receptors)	Doses of α- and β-Amyrins	Assay	References
HIV	NMR spectral-	1.4 µM	Vitro	[75]
HIV	SAR of HIV-1 PR inhibitors	0.34 µM	Vitro	[76]
HIV	HR-EI/FAB-MS and 1D and 2D NMR	-	Vitro	[77]
HIV	A549	0.6–4.8 µM	Vitro	[78]
HIV	1D and 2D NMR	4.08, 4.18, 1.70 µM	Vivo	[79]
HIV	C-3 pharmacophore	0.0006 µM	Vitro	[80]

Documents quoted from Science Citation Index (SCI) journals system. (-): Not yet determined.

Table 13 illustrates the mechanisms underlying the pharmaceutical activities of α- and β-amyrin. Additionally, the bioactivities of α- and β-amyrins can be explained as follows: From a molecular structural perspective, α- and β-amyrins are triterpenoids, a class of compounds composed of six isoprene units [40]. They exhibit physical properties such as a relatively high molecular weight, typically ranging from 400 to 500 Daltons, which enables them to interact with other large molecules in biological environments [210,211]. Chemically, α- and β-amyrins are triterpenoids with acidic characteristics. Consequently, they demonstrate notable antioxidant activity, allowing them to effectively scavenge free radicals [212].

Table 13. Mechanism of formation of pharmaceutical potential of α- and β-amyrins.

Pharmaceutical Potentials	Mechanisms
Anti-inflammatory	- Reduction of tumor necrosis factor alpha (TNF-α) and Interleukin-6 (IL-6), and helps decrease inflammation and tissue degeneration [213] - Inhibition of nuclear factor kappa B (NF-κB), cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS) reduces the production of prostaglandins and nitric oxide (NO) [214] - Antioxidant activity (via thiobarbituric acid reactive substances (TBARSs) inhibition) helps reduce oxidative stress [215] - Activation of cannabinoid receptor (CB1/CB2) contributes to anti-inflammatory and analgesic (pain-relieving) effects [216]
Antidiabetic	- Enhancing secretion and protecting β-cells helps lower blood glucose and preserve pancreatic islets [217] - Activation of activated protein kinase (AMPK) and Glucose Transporter type 4 (GLUT4) pathway helps reduce peripheral blood glucose levels [32] - Inhibition of intestinal glucose absorption helps lower postprandial glucose spikes [218] - Anti-inflammatory and antioxidant effects help improve insulin resistance [219]
Antiatherosclerotic	- Reduction in adhesion molecules vascular cell adhesion molecule 1 (VCAM-1), and intercellular adhesion molecule 1(ICAM-1) helps prevent leukocyte infiltration [27] - Activation of the phosphoinositide 3-kinase (PI3K/Akt), endothelial nitric oxide synthase (eNOS), and nitric oxide (NO) pathway promotes vasodilation and reduces inflammation [39] - Improvement of blood lipid profiles (low-density lipoprotein (LDL)/very low-density lipoprotein (VLDL), high-density lipoprotein (HDL) helps reduce plaque buildup [220] - Anti-inflammatory and antioxidant effects help limit endothelial inflammation [221]
Antinociceptive	- Inhibition of monoacylglycerol lipase (MAGL), which breaks down 2-arachidonoylglycerol (2-AG), helps reduce pain through cannabinoid-like mechanisms [222] - Inhibition of PKA and PKC helps reduce pain signal transmission [42] - Inhibition of nuclear factor kappa B (NF-κB) and cyclooxygenase-2 (COX-2) contributes to anti-inflammatory and analgesic effects [223] - Multilevel effects enable action on both peripheral and central pain pathways [25]
Antigout	- Inhibition of Xanthine Oxidase (XO) helps reduce uric acid production [23] - Antioxidant effects help protect joints and kidneys, reduce inflammation [224] - Reduction of inflammation and sensitivity to crystals and acute pain helps relieve swelling and pain during gout attacks [225] - Inhibition of NF-κB, COX-2, and pro-inflammatory cytokines helps stabilize arthritis and protect tissues [226]
Positive Effects On Nerves	- Reduces oxidative stress and neuroinflammation [227] - Stabilizes mood and the hypothalamic–pituitary–adrenal (HPA) axis [228] - Modulates neurotransmission (GABA, serotonin) [48] - Protects and regenerates neurons [229]
Anti-Parkinsonian	- Activation of autophagy (via LGG-1) and enhanced degradation of α-synuclein help reduce accumulation and protect cells [54] - Antioxidant activity reduces ROS, helping to alleviate cellular stress [66] - Reduction of central inflammation (microglia) and inhibition of cytokines, along with polarization, helps protect dopaminergic neurons [230] - Reduced α-synuclein accumulation, combined with autophagy and antioxidant effects, helps improve neurological function [54]
Anticancer	- Activation of the MAPK pathway (p38 and JNK) induces oxidative stress and triggers apoptosis [66] - Inhibition of cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX) reduces inflammation and suppresses cancer cell growth [231] - Selective anticancer activity without cytotoxicity to normal cells [71] - Inhibition of NF-κB and COX-2 reduces cancer cell proliferation and metastasis [232]
Antibacterial	- Generation of reactive oxygen species (ROS) causes oxidative stress leading to cell death via an apoptosis-like mechanism [233] - Disruption of ion balance and mitochondria causes mitochondrial damage and DNA fragmentation [234] - Inhibition of adhesion and biofilm formation reduces the ability of bacteria to adhere and form biofilms [235] - Inhibition of drug efflux pumps helps enhance the effectiveness of antibiotics when combined [95]

Table 13. *Cont.*

Pharmaceutical Potentials	Mechanisms
Anti-HIV	- Inhibition of HIV-1 reverse transcriptase (RT): α-amyrin strongly binds to the HIV-1 RT enzyme (PDB ID 1JLB), forming two hydrogen bonds with residues Cys181 and Gln182 at the allosteric site, with a binding energy of −7.33 kcal/mol; RT inhibition is dose-dependent, with an IC_{50} of approximately 26 μg/mL, close to that of nevirapine (IC_{50} ~21 μg/mL). At the maximum concentration tested (200 μg/mL), α-amyrin achieved 82% inhibition, while nevirapine achieved 92% [236] - Acts as a non-nucleoside reverse transcriptase inhibitor (NNRTI) by binding non-competitively at the allosteric site, inducing conformational changes in RT that block DNA synthesis from viral RNA and inhibit viral replication; inhibits HIV-1 integrase enzyme, which plays a crucial role in integrating viral DNA into the host genome [237]

Documents quoted from Science Citation Index (SCI) journals system.

Table 14 summarizes studies investigating the pharmaceutical potential of α- and β-amyrins. Most of this research has been carried out at the in vitro and in vivo levels. Furthermore, significant attention has been given to non-cytotoxicity assays to evaluate the safety profile of α- and β-amyrins. However, clinical trials specifically assessing these compounds have yet to be conducted or reported. Consequently, the absence of clinical studies represents both a challenge and a promising opportunity for future research on α- and β-amyrins. Notably, a specialized extraction method detailed in Table 15 has yielded the highest reported global quantities of α- and β-amyrins. These findings collectively highlight and reinforce the significant value of these compounds for pharmaceutical development.

Table 14. α- and β-Amyrins's pharmaceutical potential research level accreditation.

Level Studies / Activities	In Vivo	In Vitro	In Clinical	Not Cytotoxicity
Anti-inflammatory	✔	✔	-	✔
Antidiabetic	✔	✔	-	✔
Antiatherosclerotic	✔	✔	-	✔
Analgesic	✔	✔	-	✔
Antigout	✔	✔	-	✔
Neuroprotective	✔	✔	-	✔
Anti-Parkinsonian	✔	✔	-	✔
Anticancer	✔	✔	-	✔
Antibacterial	✔	✔	-	✔
Anti-HIV activities	✔	✔	-	✔

(✔: Researched); (-: Not Researched).

Table 15. The source quantification of α- and β-amyrins.

Source of Extraction	Extraction Efficiency (g/kg Dry Weight)	References
Protium kleinii	2.40	[238]
Symplocos cochinchinensis	1.70	[221]
Swertia longifolia	2.0	[239]
Melastoma malabathricum	0.60	[240]
Swertia longifolia	1.00	[241]
Canarium tramdenum	1.52	[242]
Celastrus hindsii	10.75	[23]

Documents quoted from Science Citation Index (SCI) journals system.

5. Conclusions

The global demand for pharmaceuticals continues to rise steadily. The identification of the pharmacological potential of α- and β-amyrins including anti-inflammatory, antidiabetic, antiatherosclerotic, receptor-modulating, antigout, neuroprotective, anti-Parkinsonian, anticancer, anti-infective, and anti-HIV activities without significant cytotoxicity represents a valuable advancement. Numerous studies have demonstrated the efficacy of α- and β-amyrins at both in vitro and in vivo levels, thereby opening promising avenues for future clinical investigations. Owing to their diverse and adaptable biochemical response mechanisms, coupled with a unique molecular structure, α- and β-amyrins exhibit notable bioactivities. This study further corroborates the significance of our previous research by achieving the highest reported extraction yield of α- and β-amyrins worldwide, reaching 10.75 g/kg. These findings serve as an important reference for subsequent studies exploring the application of α- and β-amyrins, while also laying a foundational basis for the development of pharmaceuticals and functional foods derived from these valuable compounds.

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