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REVIEW

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Soy-derived materials: a sustainable resource and their applications in medicine and tissue engineering

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Abstract

As the trend of 'green medicine' has emerged robustly over the past decades, an expanding demand for sustainable development of biomaterials has led scientists to shift their attention to more sustainable alternatives such as plant-derived products, especially soybean-derived products. The cultivation of soy farms, if performed responsibly, can generate fewer greenhouse gases than synthetic or animal-derived materials can generate, leading to a lower environmental footprint. In this narrative review, first, we briefly summarize the history of soy-based materials, how they have been used in different cultures worldwide for thousands of years, and their bioactive components, including proteins, isoflavones, lecithin, and other minerals. Our review will also discuss the sustainability of these biomaterials in greater depth, with a focus on their biodegradability, biocompatibility, renewable nature and multiple applications in current medicine and tissue engineering areas. While soy products have been proven to be promising, eco-friendly alternatives in these fields, much more effort and further research are needed to optimize their performance and scalability before they can be fully applied in clinical settings in the future.

Keywords Soy-based products, Sustainable, Tissue engineering

Histories of soybeans and their components

Soybeans (*Glycine max* L.) have been consumed in China and Southeast Asia for more than 5,000 years. They are now recognized globally as valuable sources of high-quality protein and healthy oils [1]. Soybean cultivation originated in the Yellow River watershed of China and subsequently expanded to neighboring Asian regions. By the first century AD, soybeans had become a staple food in these areas because of their versatility and superior nutritional value. Today, soybeans are cultivated worldwide, with major production centers in the United States, Brazil, Argentina, China and India [2]. Recently, there has been a surge in consumer interest in the health benefits of soybeans and soy-based products, driven not only by their high protein and oil contents but also by their beneficial phytochemicals. In their life cycle, soybeans go through various phases, from germination, and seedling to plant and fruition (Fig. 1). To maximize the yield of soy production, cultivation and crop maintenance such as watering, drainage, and disease control are critical according to the different vegetative and reproductive stages of the bean [2].

Soy-based products have also been employed across various cultures throughout history, particularly in Asian regions. Soy foods such as tofu, miso, and natto made from soybeans have a long history of being valued for their nutritional benefits and role in promoting

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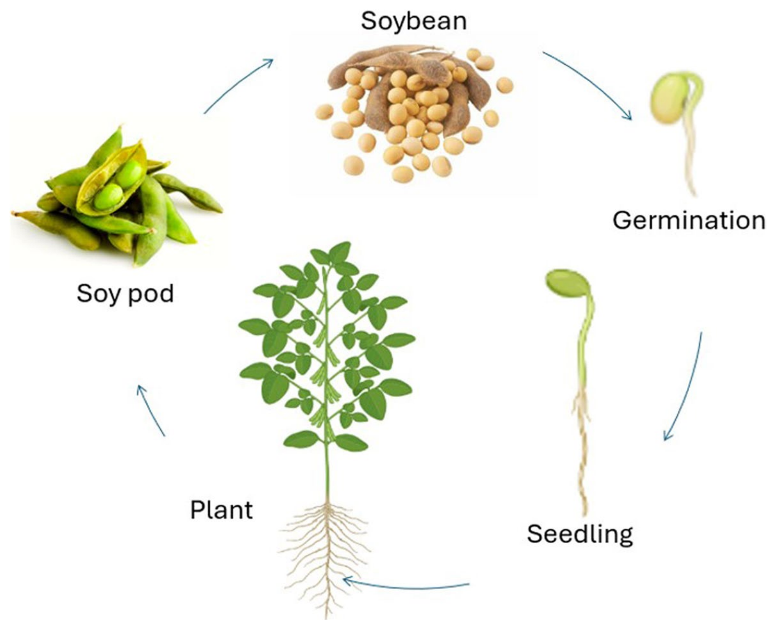

Fig. 1 A schematic image to represent the life cycle of soybean

health, especially in China, Japan and Korea [3]. In addition to their culinary uses, soybeans have found applications in a wide range of non-food industries (Fig. 2). In recent years, soybean-based materials have garnered global attention as sustainable alternatives, with soy-derived bioplastics emerging as a promising substitute for petroleum-based plastics [4]. Furthermore, soybeans are utilized as a feedstock for bioenergy production. The technology for converting soybean oil into biodiesel has made significant progress, particularly in soybean-producing countries such as the United States and Brazil, where it is gaining increasing recognition as a viable alternative to fossil fuels [5]. Soybean cultivation is expected to produce lower greenhouse gas (GHG) emissions compared to animal-based products, thereby reducing environmental impacts [6]. As a plant, soybeans absorb carbon dioxide (CO_2) through photosynthesis and release oxygen during growth, contributing to the reduction of greenhouse gases. Furthermore, while livestock production requires large expanses of

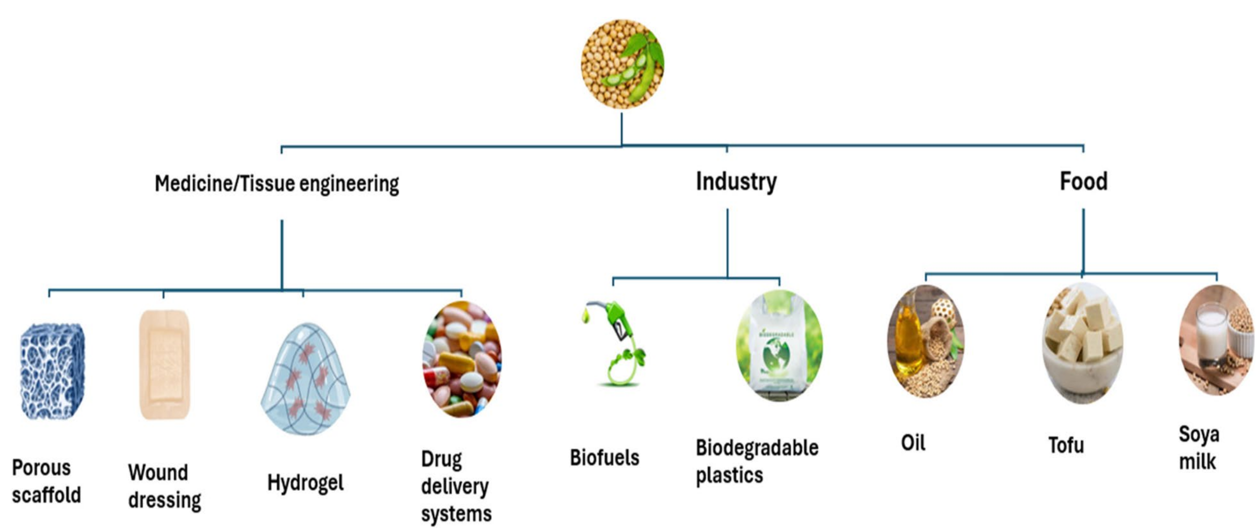

Fig. 2 Major applications of soybeans in daily life

land and can lead to increased GHG emissions through deforestation and the clearing of pasturelands, soybeans can be grown on relatively smaller plots of land. This allows for more efficient use of agricultural land, thereby minimizing the environmental burden [7].

Dry soybeans contain approximately 36–38% protein, 19% oil, 33–35% carbohydrates (of which 17% are dietary fibers), and 5% vitamins, minerals, and trace elements [1, 8]. Over the past 25 years, rigorous scientific research has demonstrated the substantial health benefits of soybeans, particularly in preventing lifestyle-related diseases [9–11]. For example, emerging evidence indicates that soybeans can decrease the risk of coronary heart disease and certain cancers, such as gastrointestinal cancer and lung cancer [12–15]. Soybeans are also recognized for alleviating symptoms of menopausal hot flashes and depression, as well as having a positive impact on renal function and skin health [16, 17]. Among the 36% protein content in soybeans, approximately 90% consists of two storage globulins: 11S glycinin and 7S β-conglycinin [8]. These proteins supply all the essential amino acids necessary for human nutrition, making soy products comparable to animal protein sources but with lower levels of saturated fat and no cholesterol. According to the U.S.A. Food and Drug Administration (FDA), soybeans not only provide a wealth of nutrients but also play a preventive role in coronary heart disease, including myocardial infarction and angina pectoris [18]. Furthermore, soy proteins are conducive to improving insulin resistance and mitigating the risk of type 2 diabetes [19, 20].

Isoflavones, classified as both phytoestrogens and selective estrogen receptor modulators, belong to the heterocyclic plant phenolic category known as flavonoids. Soybeans are the most abundant natural source of isoflavones, containing up to 3.5 mg/g dry weight [21]. Although isoflavones are not essential nutrients, they confer various health advantages. Notably, isoflavones play crucial roles in maintaining bone mineral density and reducing the risk of osteoporosis and subsequent fractures associated with decreased estrogen levels, especially in postmenopausal women [22]. In addition, isoflavones possess potent antioxidant properties and hormonal regulatory effects, which contribute to the elimination of free radicals, the prevention of aging, and the effective reduction of risks relevant to cardiovascular disease and hormone-dependent cancers [23, 24]. Soybeans surpass cereals as a source of B vitamins, although they lack vitamin B12 and vitamin C. Soybean oil is also rich in tocopherols, which serve as potent natural antioxidants [25]. Moreover, soybeans contain ferritin, a multimeric iron storage protein that provides a good source of iron [26]. Iron from soybean ferritin is now as easily absorbed and bioavailable as iron from animal products [26].

Soybean as a sustainable biomaterial

What is sustainability?

The term 'sustainable development' was originally defined as development that meets the needs of the present without compromising the ability of future generations to meet their personal needs, as published in the Burtland Report by the United Nations in 1987 [27]. As recognized by the European Union in 2001, sustainability policy evolved holistically to encompass multiple dimensions, such as economic, environmental, and social aspects. [28]. The year 2015 marked a milestone, as the United Nations member states adopted the United Nations Sustainable Development Goals (SDGs) by establishing 17 SDGs [27, 28]. These SDGs were incorporated as practically achievable guides aimed at better healthcare, eradicating poverty, managing climate and environmental changes, conserving energy, and achieving a greener globe by 2030 [27, 28]. Among the 17 defined SDGs, 13 categories of sustainable materials, biomaterials and nanotechnology have been recognized [28]. A study has elaborated on certain sustainable ideologies adaptable within a laboratory establishment to match the SDGs [29]. The authors proposed using greener materials, a policy of reuse, and a reduction in energy, water consumption, and solid waste as a few achievable steps that will enable laboratories to implement an optimal resource management system with impactful environmental practices [27, 29].

Soy-based biomaterials are gaining prominence due to their sustainability, versatility, and eco-friendly properties. Derived from renewable plant sources, soy proteins and soy derivatives like lecithin are biodegradable and exhibit excellent biocompatibility, making them ideal for biomedical applications such as tissue engineering scaffolds, drug delivery systems, and wound dressings [30, 31].

Sustainable healthcare

Green healthcare or sustainable healthcare is the practice of providing medical care via an eco-friendly approach with the goal of improving community health and public health. The Alliance for Natural Health defined sustainable healthcare in 2008 as a complex system amalgamating approaches to the restoration, management, and optimization of human health with an ecological base that is environmentally, economically, and socially viable indefinitely and that functions harmoniously both with the human body and the nonhuman environment and that does not result in unfair or disproportionate impacts on any significant contributory element of the healthcare system [32]. The Royal College of Physicians reported that sustainable healthcare is essential to ethically provide high-quality healthcare, augmenting related economic, social and environmental aspects [33]. Recently, it has been summarized the features of a green healthcare system to incorporate multiple factors, including leadership, safer chemical substitutions, waste disposal practices, energy efficiency, renewable energy generation, transportation strategies, food, green buildings, safer pharmaceuticals, and purchasing [34].

Green medicine refers to the application of sustainable, eco-friendly, and biodegradable resources in healthcare, including the development of pharmaceuticals, medical devices, and tissue engineering materials [35]. This emphasizes the development of materials that are sustainable, biodegradable and derived from renewable resources. Thus the medical applications of soy-derived materials also align with basic principles of green medicine; such as sustainability and renewable source (utilizing soy, a renewable plant-based material, aligns with green medicine principles by reducing reliance on non-renewable resources like petroleum-based polymers), biocompatibility and biodegradability (soy-derived materials are often biocompatible and biodegradable, making them suitable for medical applications, including tissue engineering scaffolds that can degrade safely in the body), and low environmental impact (the production and processing of soy-derived biomaterials typically have a lower environmental footprint compared to synthetic counterparts) [36]. These aspects support the use of soy as a green material for medical applications, emphasizing the ecological and health benefits while promoting sustainable innovation in healthcare.

Sustainable materials/biomaterials in research

The Association for the Advancement of Sustainability in Higher Education defines sustainable research as a study that directly addresses the idea of sustainability, deepens our understanding of the interactions of ecological and social/economic systems, or focuses primarily and explicitly on a significant sustainability concern [37]. Quantifying the demand for sustainable biomaterials involves a multifaceted approach, combining market trend analysis, evaluation of policies, research activity and technological innovations, and environmental impact studies [38, 39].

Tissue engineering is the field of research that applies the concepts of life sciences, material sciences, and engineering in mimicking physiologic and/or pathological tissue microenvironments in terms of structure and function [40]. To encourage cell development in the tissue microenvironment, this multidisciplinary approach exploits the characteristics of a porous, biocompatible, and biodegradable material in the form of a two- or three-dimensional scaffold or template. When put closely into a functioning system, a natural or synthetic material, or a mixture of similar materials, may replace and regenerate the body's tissues on its own and is referred to as a biomaterial [40].

Green chemistry refers to the utilization of safe and clean resources to minimize hazardous outcomes in scientific research [41]. Thus, it employs safe energy or reduces waste materials via a variety of commercial and experimental synthetic techniques. Reducing the harmful impacts of pollution on the environment and human health is a key objective of green technologies and practices [41]. Green technology is used to generate eco-friendly biomaterials derived from other biological sources. Many biomaterials have been researched and produced as viable alternatives to conventional materials and have proven promising in various biological domains [42]. Biomaterials are generally intrinsically noncytotoxic, nonimmunogenic and minimally proinflammatory, biocompatible, bioactive, biodegradable, and cost-effective and may be employed in cutting-edge techniques such as bioprinting and nanotechnology [42, 43]. Therapeutic biomaterials are broadly classified into two major categories: (a) living material derived from human or animal origin and (b) plant-based biomaterials and biocompatible synthetic materials [43, 44].

Soy proteins, with their natural origin and functional versatility, offer a sustainable alternative to synthetic materials in biomedical and tissue engineering applications where biocompatibility and biodegradability are critical. They also have comparable mechanical strength due to enhanced crosslinking and blending ability, are hydrophilic, allow chemical modifications, enabling the incorporation of bioactive molecules, and also contribute less to environmental pollution [45].

Plant-based biopolymers in research

Recently, biopolymers have garnered significant attention as biodegradable and sustainable materials in research [46]. The development of drug delivery strategies to increase the activity of bioactive substances is still crucial for achieving disease treatment, and progress in the fields of additive manufacturing, nanotechnology, and tissue engineering has been enormous. Natural biological sources of biopolymers include bacteria, plants, animals, and agricultural wastes [46, 47]. Plant- and animal-based proteins are plentiful, biocompatible, and biodegradable and are inexpensive and sustainable green sources of biopolymers [42, 46]. Plant-based proteins can be manufactured in large quantities and have minimal greenhouse gas emissions, typically because they rely on renewable resources. Soybean cultivation not only results in lower greenhouse gas emissions compared to animal-based and synthetic materials, but it also further reduces environmental impact by minimizing the use of pesticides and synthetic fertilizers. Soybeans are nitrogen-fixing crops, with symbiotic bacteria (Rhizobium) in their roots that capture atmospheric nitrogen and convert it into a form usable by plants [48]. This process significantly reduces the need for synthetic fertilizers, which are responsible for substantial greenhouse gas emissions during production. In addition, by maintaining soil health and enhancing carbon storage potential, soybean cultivation contributes to CO_2 emission reduction [48]. Therefore, responsible soybean farming plays a crucial role in achieving sustainable agriculture and mitigating the progression of global warming. Furthermore, plant-based proteins are often not associated with animal-transmitted illnesses and can provide an alternative option for individuals who abstain from animal-derived products because of personal dietary choices, religious or ethical beliefs, or both [42].

The component proteins of these cross-linking plant materials can be made more sensitive to proteolytic breakdown. They are rendered more adaptable and useful for a range of applications by choosing the appropriate solvent. Proteolytic enzymes hydrolyze proteins, and the pace of this breakdown can greatly influence the in vivo performance of protein-based biomaterials. Therefore, the type of plant protein determines how a protein-based material behaves throughout the degradation process and its impact on tissue engineering [42, 46]. Proteins and peptides need to be authorized as safe excipients before biomaterials based on them may receive clinical consent. The FDA has given a few companies permission to sell plant protein-based delivery systems. The plant sources include rice, maize, wheat, sorghum, yams, cassava, potatoes, bananas, tapioca, cotton, barley, and soybean [42, 46].

Soy/soybean as a sustainable plant protein-based biopolymer

The concept of a sustainable biomaterial requires understanding the complete life cycle of the material [42]. This encompasses the favorable and long-lasting physical properties of the material, as well as the ecological consequences of the complete production cycle, from manufacturing through processing, deterioration, recycling, and ultimately disposal of the material [47]. A sustainable biomaterial should be sourced from renewable resources that are grown sustainably and can be manufactured via environmentally friendly processes. These materials are nonhazardous to the environment and can be reused or recycled. Additional crucial factors are the material's economic viability and societal advantages. Innovative environmentally friendly plant protein-based biomaterials are abundant and renewable and fulfill the United Nations' SDG objective for 2030. These proteins are advantageous because they are readily accessible, can be produced via uncomplicated processes, and are compatible with living organisms. Soy/soybean has recently been exploited for its plant protein chemistry and has proven advantageous in the field of tissue engineering [47].

In tissue engineering applications, soybean protein has been widely used as it is non-toxic, highly biocompatible, and biodegradable, allowing for safe absorption by the body [49]. Soy protein also exhibits favorable mechanical properties and elasticity, making it an ideal material for scaffolds in various tissue engineering applications [50]. Figure 3 represents the main compositions of soybean and the amino acid distribution in soy protein, showing the chemical heterogeneity of soy due to its various amino acid components. Since most proteins are capable of dissolving in water, the entire manufacturing process may be carried out with minimal reliance on organic solvents.

Soy-based products and other plant-derived materials such as hemp, algae, and bamboo are increasingly evaluated for their sustainability in various applications, including tissue engineering and medicine. Soy products stand out due to their relatively high protein yield per hectare, low greenhouse gas emissions, and the ability to enhance soil fertility through nitrogen fixation. In comparison, materials like hemp and bamboo may have lower protein extraction efficiencies for medical applications [30, 31]. Soy-based biomaterials are known for their remarkable physical qualities and have the significant advantage of being naturally biodegradable, sustainable, and cost-effective, thereby contributing to the circular economy of source materials [47].

Soy protein in tissue engineering and biomedical applications

Medical application of soybeans

Soy components are extensively utilized in medical and health-related fields across various countries, with numerous scientific reports highlighting their diverse health benefits and applications. For instance, research suggests that compounds found in soybeans, such as saponins and phytoestrogens, may play a role in cancer prevention and immune function enhancement [51]. In particular, within Asian countries, where soybean's nutritional value and health benefits are deeply embedded in traditional culinary practices, there is a strong cultural foundation supporting the integration of soybeans into medical treatment [52]. According to the American Heart Association (AHA), soy proteins effectively prevent stroke and cardiovascular diseases by lowering LDL

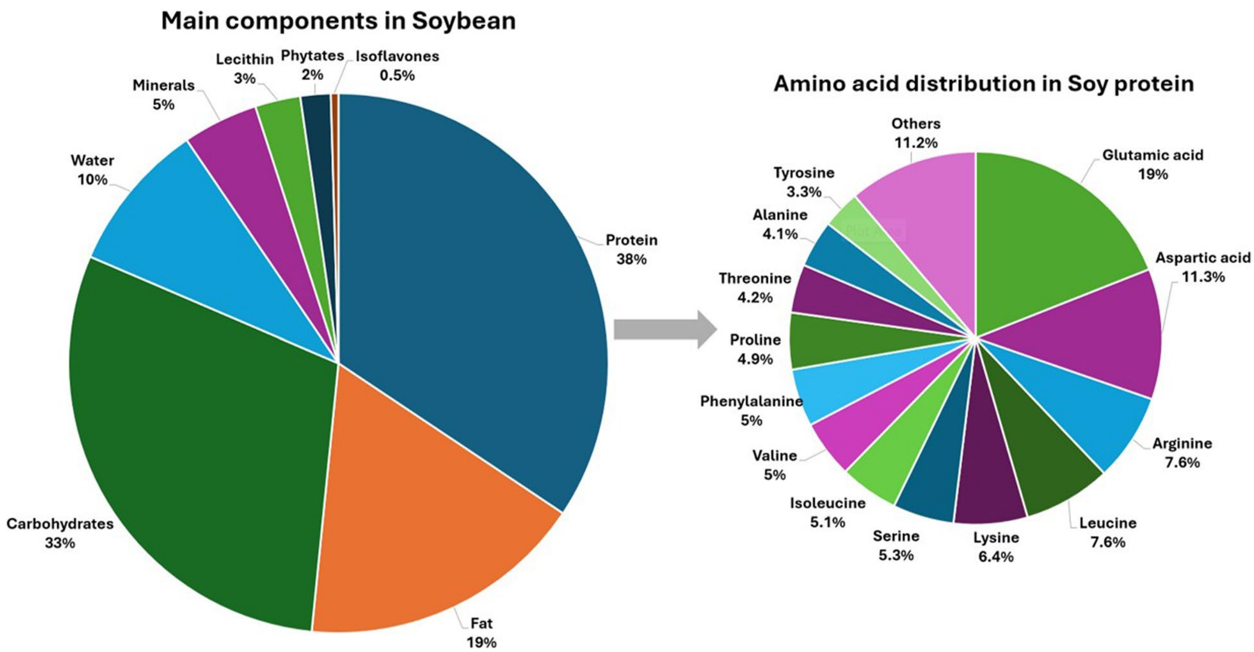

Fig. 3 The main components in soybeans and the amino acid distribution of soy protein

cholesterol levels and controlling blood pressure. [53]. Soy isoflavones have also been investigated as a form of estrogen replacement therapy, especially in the United States, with several studies suggesting that they enhance cognitive function and visual memory in postmenopausal women. [54, 55].

Traditional Chinese medicine (TCM) has a long history of utilizing plant-derived ingredients, including soybeans [56]. The constituents of soybeans such as isoflavones, lecithin and soy proteins have now been thoroughly validated for their therapeutic effects [57–59]. In China, the birthplace of soybeans, these beneficial properties have been recognized and empirically utilized for centuries [60]. In TCM, soybeans and their derivatives are commonly used because of their cooling and moisturizing properties [56]. They are considered to nourish the spleen and stomach, promote digestion, and improve blood circulation. Additionally, soybeans are thought to alleviate swelling and assist with detoxification [56]. Fermented soybean products, made from black soybeans, are employed in some TCM practices to promote respiratory health and treat cold symptoms of coughs and nasal congestion. These products are associated with a multitude of health advantages, such as improved gut health, enhanced immune function, and a reduced risk of chronic diseases, including cardiovascular disease and diabetes mellitus [61, 62]. Soy isoflavones, with their estrogen-like chemical structure, are frequently used in TCM to support the health of menopausal women. In TCM, soy isoflavones are often combined with other herbs to create formulas that address the menopausal symptoms of hot flashes, mood swings, and insomnia. Several studies have revealed that Asian countries with high levels of soy consumption exhibit significantly lower incidences of breast and prostate cancers than Western countries do, particularly those in the Nordic regions [62, 63]. One epidemiological study suggested that in Asian countries with high soy intake, the risk of breast cancer is reduced by approximately one-third in both premenopausal and postmenopausal women [64]. Furthermore, in traditional Indian medicine (Ayurveda), soy components are used to address digestive issues and increase immune function. Fermented soy products and isoflavone-rich soy milk are considered beneficial for overall human health, whereas phytic acid and saponins, known for their potent antioxidant properties, are employed in Ayurveda to prevent aging and manage chronic diseases [65].

Tissue engineering applications of soybeans

Many products derived from soybeans have been employed in multiple biomedical applications because of their versatility, nonanimal origin, biocompatibility and stability for long-term storage [66]. The versatility in the fabrication of plant-based materials has prompted much interest from the scientific community, allowing researchers to tailor the material to diverse applications ranging from scaffolding strategies and cell carriers to drug delivery systems. Regarding biocompatibility, it has been defined by IUPAC that biocompatible materials should contain and release minimal toxic by-products to the host living system [67]. Soy-based materials have been considered biocompatible since it is proven to not cause irritation or immunoreaction to the body in specific applications [68, 69]. Some studies also reported that the material supports cellular functions, inhibits adverse immune reactions, and promotes tissue regeneration, all of which are essential for successful and sustainable tissue repair [70–72]. Biocompatibility is fundamental for the success of soy applications in tissue engineering and regenerative medicine, it can also mean that soy-based biomaterials degrade at a controlled rate, aligning with tissue formation and healing [69]. In assessing the biodegradability of soy-based materials, numerous methods have been proposed. Among these, gravimetric analysis is a primary approach to quantify degradation, which measures the initial weight and then periodic reweigh of the materials after incubation [73]. This method is to keep track of the total mass loss over a certain period. Furthermore, other techniques have also been used to evaluate the biodegradability of soy materials, including mechanical testing, pH and Ion release studies, surface erosion, and morphological changes. The use of these methods collectively can provide researchers with a more profound assessment of the degradation rate of soy-based biomaterials, further adding to their appeal in the field of tissue engineering and regenerative medicine [73]. Table 1 represents numerous soy-based products in tissue engineering that have been investigated extensively over the last decade.

A. Sponges/foams (porous scaffolds)

According to the International Union of Pure and Applied Chemistry (IUPAC), macroporous materials usually contain pores that are greater than 50 nm. The large porous structures are especially useful in certain applications that require extensive surface areas and efficient flow of large particles such as fluid filtration, drug delivery systems for large molecules [88]. Porous soy-based products are usually designed with pore sizes ranging between 100 μm and 300 μm, to meet the requirements of different applications. They can be used as scaffolds in tissue engineering, allowing for cell infiltration, vascularization, nutrient and oxygen transport, as well as waste exchange [66]. There are various techniques used for the fabrication of porous structures, among which the freeze-drying method or lyophilization is one of the most popular. The ice crystals that are formed during the process of freezing can significantly affect the pore sizes and the structure of the scaffolds. The slower the freezing rate is, the larger the pores are at the end of the process, and vice versa [89]. Another method to create porous scaffolds for tissue engineering is three-dimensional (3D) printing. Unlike conventional methods such as freeze drying, 3D printing provides more accurate details of the scaffold structure, morphology and pore size, enabling the creation of complex structures customized for specific applications in tissue engineering [87]. Mass fabrication of 3D soy scaffolds with reproducible results can be performed via 3D bioplotting at room temperature or 37 °C [87]. Human mesenchymal stem cells (hMSCs) can attach to and proliferate well on porous soy protein scaffolds via both freeze-drying and 3D printing methods [70, 87]. The authors also confirmed that the growth and morphology of the cells were considerably influenced by the scaffold degradation rate. Transglutaminase is an enzyme that catalyzes an acyl-transfer reaction between the γ-carboxamide group of glutamine (Q) and the ε-amino group of lysine (K), forming an ε-(γ-glutamyl) lysine bond. This covalent bond is highly stable and resistant to degradation [90]. With the treatment of transglutaminase, the degradation time of the soy scaffolds increased significantly, leading to the improvement of cell attachment and proliferation after several weeks of culture [70]. Hence, the formation of these specific ε-(γ-glutamyl) lysine cross-links after transglutaminase treatment is one of the main modifications that enhance the functional properties of soy proteins.

A European study fabricated an injectable composite bone cement made from soybean, gelatin and hydroxyapatite, which can retain high porosity after injection [91]. Although the achieved compressive strength of the composite scaffolds was just acceptable for bone grafts with non-load or light-load-bearing locations, the incorporation of soy protein led to remarkable improvements in both osteogenic and injectable effects, as well as greater compressive strength while maintaining the same macroporosity. After self-hardening, the sponged scaffolds exhibit favorable characteristics for the adhesion and proliferation of osteoblast-like cells. ALP activity and collagen production assays to test for osteoblastic activity and differentiation also revealed higher values in the soy-incorporated group. Owing to the injectability of the material, this novel composite bone cement has great potential for many clinical applications, such as vertebroplasty and secondary implant fixation procedures, and can minimize invasive surgical trauma for future patients [91].

Another composite scaffold derived from soy protein isolate has been demonstrated to promote nerve regeneration [80]. In this study, hydroxypropyl chitosan/soy protein sponges exhibited highly porous microstructures and high water retention capacities. Compared with those in the other groups, the expression of neural markers, such as TGF-β, Krox20, Zeb2, and GAP43, in RSC96

Table 1 Summary of soy-based applications in tissue engineering over the last 10 years

Year	Application	Soy products	Outcomes
2024	Wound dressing [72]	Soy protein/Collagen/ Sodium Alginate Bilayer dressing	A soy/collagen dressing could inhibit the growth of gram-positive and negative bacteria, and prolong the release of drugs including Cinnamaldehyde, Artemisia absinthium, and oxygen
	Neural repair [74]	Soy protein isolate/collagen hybrid gel	Hybrid materials exhibited a reduction of human astrocytes' proliferation rate and the downregulation of genes encoding ECM components, including HSPG2, LUM, SDC2, COL4A1, COL4A5, COL4A6, FN1, and genes encoding chemokines, including CCL2, CXCL1, CXCL2, CX3CL1, CXCL3, and LIF
2023	Wound dressing [75]	Soy protein isolate matrices	Soy-based cryo-gels showed excellent mechanical properties, immediate shape restoration, a good absorption rate, exceptional cell infiltration, adherence, and proliferation. They also had the dual effect of cell–matrix interaction and excess exudate absorption, leading to homeostasis acceleration and blood clot formation
	Drug carrier for cardiac tissue engineering [76]	Soybean oil/Gelatin nanofibrous scaffolds	Soy-based scaffolds exhibited excellent anticoagulant properties and positive effects on cardio-myoblasts attachment and growth by the controlled release of simvastatin
	Sustained-release Bone Morphogenetic Protein (BMP)- Delivery system [77]	Soybean Lecithin/Calcium Phosphate Silicate Microspheres	Soy Lecithin-loaded microspheres improved the loading rate of BMP, leading to a smoother release of the protein into desired tissues and enhancing the osteogenic effect
2022	Drug delivery system [78]	Soy protein nanoparticles	Soy protein nanoparticles with a ratio of 10:30 (vancomycin: soy) can be a delivery system with low toxicity, controlled release, and potent antibacterial activity
	Bioink for 3D Bioprinting [79]	Soy protein/Soy peptide/Alginate/Gelatin hydrogel	The bio-ink could exhibit excellent shear-thinning behavior and promote cell attachment, spread, migration, and proliferation. They could also promote angiogenesis in animal studies
2021	Peripheral Nerve Regeneration [80]	Hydroxypropyl chitosan/soy protein isolate composite (SPI) sponges	50% SPI sponges promoted the proliferation of cells and the secretion of neuro-related factors (Krox20, Zeb2, and GAP43). The combination of bone marrow mesenchymal stem cells or Schwann cells with the hybrid sponges can promote axonal regeneration and repair sciatic nerve injury in rats
	Bioink for 3D printable platform [81]	Soy protein isolate/Silk fibroin hydrogels	The 3D-printed SPI/SF hybrid hydrogels exhibited a stable isotropic hierarchical structure under printing shear stress, a larger micropore size and better mechanical properties The hydrogel also supported the fibroblast viability, attachment, and proliferation
2020	Bone regeneration [71]	Hydroxyethyl cellulose/soy protein isolate scaffolds with hydroxyapatite (HAp) functionalization coating	Soy-based coated scaffolds exhibited a porous structure with improved mechanical properties, a controllable degradation rate, good cytocompatibility and cell attachment, and proliferation. They also supported the upregulation of osteogenesis-related genes (Col-1, Runx2, OPN, and OCN)
	Retinal pigment epithelium regeneration [82]	Nanofibrous soy protein membrane	The nanofibrous scaffold can exhibit superior mechanical and biochemical properties. They also promote the maturation of retinal pigment epithelium sheets and the potential for in vivo implantation as a functional tissue

Table 1 (continued)

Year	Application	Soy products	Outcomes
2018	Skin regeneration/Wound healing [83]	Soy protein hydrolysate (SPH)/Cellulose acetate nanofiber scaffolds	The nanofibers can mimic the physicochemical properties of skin ECM with high water-retaining capability and promote fibroblast proliferation, migration, and integrin β1 expression. They can also accelerate the re-epithelialization, epidermal thinning process and reduce scar formation and collagen anisotropy
	Neural protection/regeneration [84]	Soy-derived protein Lunasin	Soy Lunasin blocked cell death in retinal neurons and ameliorated Aβ42-mediated neurodegeneration by downregulating JNK signalling, restoring axonal targeting from the retina to the brain
2016	Bioink for 3D bioprinting [85]	Soy protein isolate (SPI)/Polyurethane (PU) hydrogel	The PU/SPI gel could undergo rapid gelation at 37 °C with a modulus of 130 Pa in 1 min. The ink also provided unique rheological properties for direct cell/tissue printing and a biomimetic microenvironment for neural stem cell survival, growth, and differentiation
2014	Management of experimental allergic encephalomyelitis (EAE) [86]	Soy Daidzein	A high dose of oral daidzein after the disease's onset reduced IFN-γ, IL-12 secretion and lymphocyte proliferation, and enhanced IL-10 production, leading to the reduction of demyelination and inhibition of disease exacerbation
2013	Soft tissue engineering/ Wound healing [70, 87]	Soy protein hydrogels	A higher percentage of soy increased the robustness of the hydrogels and reduced the drug release rate Histological staining of injected soy hydrogels into mice subcutaneously showed minimal fibrous capsule formation for 20 days

cells in the 50% soy protein group significantly increased. In vivo results also revealed that composite soy-based sponges incorporated with mesenchymal stem cells and Schwann cells can repair sciatic nerve injury and support axonal regeneration in rats [80]. A recent study confirmed the remarkable potential of soy-based scaffolds as capping conduits for nervous system regeneration. Animal studies have indicated that scar deposition, autotomy scores and the inflammatory response are significantly decreased, whereas myelin thickness and axon diameter are greater in the soy-based conduit group. These authors suggested that the soy-based conduit could act as an optimal physical barrier to prevent the formation of painful neuromas [92].

B. Films/membranes

Although porous soy-based materials have been widely used, numerous applications are more beneficial using non-porous or microporous products (no pores or pore sizes less than 2 nm) such as soy membranes or films for wound dressing or skin grafts, as they can act as barriers against bacteria, virus or moisture, while inhibiting fluid loss from the injury and also promote healing process [93]. The fabrication of soy-based films or membranes usually includes several techniques, such as electrospinning, melt spinning and wet spinning [94]. The electrospinning technique has been widely applied for the manufacturing of soy-based scaffolds in regenerative medicine; however, this method has several shortcomings, such as fragile weak interfiber bonding and inconsistent pore sizes [75]. Numerous methods of physical (thermal treatment or UV light) and chemical cross-linking strategies (glutaraldehyde, carbodiimide) have been employed to enhance the poor mechanical properties of soy protein scaffolds. In some cases, combining electrospinning with other methods can help overcome these challenges, making them more applicable to various bioengineering areas [76, 82]. Moreover, soy protein possesses RGD sequences (arginine, glycine, aspartic acid) and is rich in amino acids such as glycine and proline, which are necessary for cell attachment and proliferation [95, 96]. As glycine is an indispensable component of collagen, this amino acid in soy can promote collagen formation [75]. A study demonstrated that soy-based materials have the capacity to speed up collagen deposition by fibroblasts, facilitating soft tissue repair and the wound healing process. The composite hydroxypropyl chitosan/soy protein film represents excellent water resistance, mechanical behavior and wound healing efficiency. Additionally, the wound repair efficiency of the groups with 30%, 50% and 70% soy protein was greater than that of the control groups, as these scaffolds have more favorable characteristics, such as biocompatibility, blood coagulant effects, and rough surfaces, making the films more conducive to human dermal fibroblast attachment and proliferation [93]. Soy-derived scaffolds have been reported to support the upregulation of many genes related to extracellular matrix (ECM) deposition, such as MMP-10, MMP-1, collagen VII, integrin-α2 and laminin-β3 [97]. Another team of researchers also acknowledged the potential of soy protein in the wound-healing process. They suggested that owing to the anti-inflammatory effect of isoflavones such as genistein and daidzein in soy protein, partial and full-thickness wound healing can be shortened in the presence of these components [98]. These findings suggest that this sustainable protein is a promising system for dermal regeneration. However, further studies are needed to determine the interactions between soy protein and dermal cells and their mechanisms in wound dressing applications.

Furthermore, electrospun soy-based nanofibrous scaffolds have also been applied for the regeneration of retinal pigment epithelium in patients with age-related macular degeneration [82]. Compared with those of the control group, the mechanical properties of the scaffolds were more similar to those of the connective fascia, exhibiting less brittleness and ease of handling, unfolding and stretching, suggesting that these scaffolds are prospective candidates for retinal epithelium implantation. Researchers have reported that lunasin peptides in soy-based sheets are covalently bonded to the structures, making them relatively stable even over a long period of implantation [82]. The soy-based scaffolds also allowed the homogenous expression of ciliogenesis-related genes in induced pluripotent stem cells (iPSCs); however, further phenotypic changes may occur when these scaffolds are translated into clinical applications and transplantation. Hence, future animal studies involving the implantation of soy-derived scaffolds should be performed to further determine the biological behavior of this plant-based protein in vivo [82].

C. Hydrogels

Hydrogel contains a complex network of hydrophilic polymer chains, which can absorb and retain more than 90% of the water relative to their total mass [99]. Soy protein isolates have been employed in multiple hydrogel applications owing to a broader trend toward green and sustainable healthcare. This plant-based component is a renewable resource, offering a harmonious balance between cost, environmental impact and biological performance [79, 100–102].

A group of authors have successfully fabricated hydroxypropyl chitosan/soy protein isolate hydrogels via a chemical crosslinking method for hemorrhage control. When the concentration of soy protein was adjusted, excellent cytocompatibility and hemocompatibility were observed, especially in the 30% soy group. In vivo studies have also shown that this soy-derived hydrogel can effectively facilitate hemostasis and promote blood coagulation in New Zealand rabbits [103]. Another application of soy-based hydrogels that has been developed is as potential carriers for controlled antibiotic delivery, especially in many oral diseases caused by bacterial infections [100]. The soy protein isolate was incorporated with acrylic acid-co-4-(4-hydroxyphenyl) butanoic acid or SPI-g-(AA-co-HPBA) to form a composite hydrogel at pH 7.4. The hydrogel consisted of highly porous structures with nontoxicity, thermal stability and pH-responsive behaviors that could prolong the release of ciprofloxacin over 12 h for bacterial infections in the oral cavity [100]. Another favorable characteristic of soy protein is its capacity for water retention, especially when it is blended with other polysaccharides, and its emulsifying ability [104]. A project has developed an alginate and soy protein microsphere structure as an oil delivery system. The authors reported that an increase in the soy protein concentration led to an increase in the swelling ability of the matrix, viscosity of the gel and longer release of thyme oil in the intestine [104].

Recently, soy-based hydrogels have been used to develop ink for 3D printing and bioprinting techniques, i.e., the addictive manufacturing of 3D constructs, as these hydrogels closely resemble the native extracellular matrix and are highly biocompatible. However, owing to poor mechanical properties, soy protein isolate is often combined with other ingredients, such as alginate, chitosan, polyvinyl alcohol (PVA) and gelatin, to improve structural strength [79, 93, 105]. The soy composite inks subjected to heat treatment exhibited excellent shape fidelity properties during extrusion in the 3D printing process, especially those with 3% alginate and 2–3% gelatin. This study demonstrated that the incorporation of sodium alginate and gelatin together enhanced the self-supporting ability of soy-based inks, increasing their printability [105]. These findings indicate the potential of soy-based proteins as remarkable 3D printing inks. A further study was performed to develop a 3D construct from a soy protein and soy peptide composite hydrogel. The hydrogel could be applied as a cell-laden bioink for bioprinting, i.e., 3D printing [79]. The novel soy-based ink exhibited excellent shear thinning behavior—an important characteristic of the extrusion printing technique—and exceptional cytocompatibility when tested with human umbilical vein epidermal cells (HUVECs). The composite hydrogels can also facilitate neovessel growth in chicken allantoic membrane assays and animal studies. In vivo experiments, soy-based scaffolds were embedded subcutaneously in rats. After two weeks, as the scaffolds started to degrade gradually, the number of inflammatory cells decreased significantly, and blood vessels began to form in these animals. The authors reported that while the newly formed blood vessels in the soy protein group presented a greater sprouting rate, those in the soy peptide group presented more vascular branches. These in vivo results demonstrated that soy-based products can pave the way for the formation of blood vessels or angiogenesis; however, this effect of the soy peptide group is more profound than that of the soy protein and control groups because the lower molecular weight of soy peptide leads to better absorptivity of anti-inflammatory and antioxidizing amino acid subgroups [79]. Overall, both 3D-printed scaffolds in soy protein and soy peptide groups have been reported to have good cytocompatibility and promote angiogenesis, which holds great promise for future applications in tissue and organ engineering.

Future prospects

As awareness of environmental impacts has increased over recent decades, more focus has been placed on the renewability and sustainability of soy-based products in tissue engineering. Compared with other synthetic materials or those derived from nonrenewable sources, soybean has a much lower carbon footprint and a less energy-intensive manufacturing process, making it a readily consistent and eco-friendly supply. Nevertheless, several limitations are associated with the extraction of these proteins from natural sources. These challenges encompass inconsistency in the properties of soy-based materials across batches, the presence of contaminants, thermal instability and moisture sensitivity [106]. Moreover, soy-based counterparts often possess weaker mechanical properties and stability compared to other synthetic materials. Some fabrication methods including ethanol/acid wash, enzyme treatment, and fermentation can help improve soy's performance. Yet, there is a sophisticated balance between optimizing the nutritional value and preserving the bioactive components in soy products [107]. To address these problems, biotechnological methods such as more efficient extraction and processing techniques have been devised to generate larger quantities of protein with enhanced uniformity, improved biological safety, reduced costs and improved scalability [107]. Furthermore, other polymers and nanoparticles have been incorporated into soy materials together with some physical and chemical modifications including blending with synthetic materials or cross-linking chemicals to improve the structural strength of soy, increase the degradation rates for a wider range of bioengineering and medical applications of soy-based materials, including scaffolding, drug delivery systems or cell encapsulation platforms [106].

Although soy-based products are widely used nowadays, many side effects should also be addressed and carefully monitored in patients. One of the undesirable effects of soy products is its impact on thyroid functions [108]. A randomized clinical trial was performed to evaluate three thyroid hormones including T3 (triiodothyronine), T4 (thyroxine) and TSH (thyroid stimulating hormone) with the intervention of soy component. It was reported that the use of soy protein and soy isoflavones could increase the level of TSH by 10%, but no change in T3 and T4 levels. The modest rise of TSH may negatively affect thyroid function and potentially lead to certain medical conditions such as hypothyroidism. However, the results were not significant, especially from the clinical point of view [108]. Another adverse effect of soy products is the risk of allergic reactions. Soy allergy from soy lecithin, soy milk or even soy sauce, can vary from mild to severe symptoms including gastrointestinal discomfort, hives or rashes, respiratory distress and swelling, and sometimes even anaphylaxis [109, 110]. Some soy components can be found not only in food but also in pharmaceutical products, which may not be apparent to patients. However, some experts have mentioned that it is not necessary for individuals to completely avoid medications containing soybean oil or soy lecithin. It is still debatable about the safety of the drugs, hence, some medicines containing soy lecithin have been reassembled and soy components have been removed from the formula [111]. In addition, clear labelling and instruction are crucial for the accessibility of public use, especially for those with previously diagnosed soy allergies [109]. Researchers have tried to modify soy proteins by enzymatic hydrolysis to break down allergenic epitopes, reducing their immunogenicity or experimenting with advanced purification techniques such as ultrafiltration and chromatography to separate and remove allergenic agents in soy. These efforts have been made extensively to minimize the risk of soy-based immunoreactions, making them safer and more suitable for clinical applications [112].

Soybean provides a complete protein source for humans with all essential amino acids, making it an ideal alternative to animal protein. It can help address global protein demands, especially in regions facing food insecurity or high rates of malnutrition [113]. This shift can help lower greenhouse gas emissions and also reduce heavy pressure on land and water resources, which contributing greatly to carbon offset initiatives when cultivated sustainably [7]. Several new technologies have been employed such as Life Cycle Assessment (LCA) or Carbon Footprint Quantification to evaluate the long-term impact of soy cultivation worldwide [6, 38, 114]. In the process of sustainable development, government policies play a critical role in promoting the adoption and incorporation of sustainable soy-based biomaterials. Through supportive regulations, tax incentives, and funding, they can encourage both private and public sectors to invest in sustainable plant-based alternatives to petroleum-based materials [115]. For example, more subsidies or tax incentives can be adjusted to favor farmers who adopt eco-friendly practices to grow soybeans, such as crop rotation, organic farming, or soil health improvements. Also, the government can also help pharmaceutical or biotechnology companies to accelerate advancements in soy-based biomaterials by funding research into new applications, greater production efficiency and material performance [115, 116].

Recently, owing to the state-of-the-art development in research, soy-based products have been employed in the development of 3D printing and bioprinting to fabricate complicated structures and scaffolds. However, there is still a great need for more in vivo and clinical studies before fully establishing and commercializing soy-derived products on the market. Perhaps, the trend could also be shifted toward the application of soy-based inks for 4D printing technology—a more advanced method to fabricate dynamic 3D constructs that are stimuli-responsive, with the integration of time in the process considered the fourth dimension. In addition, studies in other aspects of soy-based products can be further investigated including multiple clinical trials on cardiovascular health, bone density, cancer prevention and menopausal therapies. Future clinical trials as well as studies into patient outcome, acceptability and perceptions of soy products can be beneficial for both patients and clinicians [11, 53]. Understanding patient and clinician perspectives on soy biomaterials, especially in terms of safety concerns and perceived benefits, can guide better patient-centered design in future clinical settings [11]. Whatever the future directions might be, the process of developing this plant-based biomaterial that has less impact on the environment but can also match the complicated requirements of multiple bioengineering applications is still an endless journey for scientists.

Conclusion

In summary, soybeans and its derivatives, such as soy protein isolate and soy isoflavones, have gained significant attention in the fields of biomedical sciences and tissue engineering because of their therapeutic effects, biocompatibility, biodegradability, and abundance in nature. Furthermore, their products typically have lower environmental impacts, and reduced costs associated with pollution such as greenhouse gas emissions or petrochemical production. Developed countries seeking to meet sustainability targets may provide grants, subsidies, and tax incentives for companies working on soy-based biomaterial innovations, further driving investment and industry growth. The transition to soy-based biomaterials presents a lot of opportunities for economic growth, offering the potential for job expansion, supply chain stability, and reduced environmental expenses. However, it requires careful management of agricultural land use and water exploitation.

Due to its potential as a nutritious, versatile, and low-impact alternative to other conventional sources, the global community can harness soy as a key resource to address many international issues such as food security, environmental impacts, and economic opportunities as well as to build a resilient, sustainable, and equitable food system worldwide. Hopefully, the favorable characteristics of soy products can pave the way for the implementation of green biomaterials in medicine, which can address some of the current medical challenges and improve the quality of life of patients in many upcoming years.

Authors' contributions

U.M.N.C., S.D.T., and J.I. designed and conceptualized the review. U.M.N.C., J.I., and R.K. collected the information from the literature and wrote the manuscript. U.M.N.C., J.I., R.K., and S.D.T. reviewed and edited the manuscript. S.D.T. and Y.S. supervised the paper. All authors have read and agreed to the published version of the manuscript.

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Declarations

Competing interests

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