"Fabrication of Bioactive Polyphenolic Biomaterials for Bone Tissue Engineering"

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Abstract

Bone disorders constitute a major problem for public health worldwide. Bone tissue engineering (BTE), which involves the fabrication of a bioactive bone scaffold has provided an effective solution for this global issue. Polyphenolic compound (PPC) as a bioactive molecule can be incorporated into the bone scaffold to promote the bone recovery process. This is because PPCs are recognized as having the potential to enhance the proliferation, migration, and differentiation of bone cells and hydroxyapatite (HA) mineralization for bone formation. In addition, PPCs possess antioxidant, anti-inflammatory, and antibacterial properties, making them effective biomolecules for bone tissue regeneration. Furthermore, the presence of PPCs in easily available and low-cost food and agricultural wastes, with desirable biological characteristics has promoted an increasing interest in their isolation and further exploitation in tissue engineering. food and agricultural wastesThis review discusses the effective applications of PPCs for the fabrication of different polyphenol-functionalized scaffolds for BTE applications. Furthermore, fruit wastes' potential for the extraction of PPCs with various biological activities is discussed. It is anticipated that this review will help to improve the design and preparation of the next generation of bioactive bone scaffolds, using the fruit waste-derived PPCs.

Keywords: Polyphenolic compounds; bone tissue engineering; polyphenol-functionalized bone scaffold; biological activity; fruit waste

List of Abbreviations

Abbreviation	Definition	Abbreviation	Definition
BTE	Bone tissue engineering	PLE	Pressurized liquid extraction
PPC	Polyphenolic compound	$SCCO_2$	Supercritical carbon dioxide

HA	Hydroxyapatite	ECM	Extracellular Matrix
BMPs	Bone morphogenetic proteins	AgNPs	Silver nanoparticle
ROS	Reactive oxygen species	COL	Collagen
Qu	Quercetin	TA	Tannic acid
GA	Gallic acid	GEL	Gelatin
FAO	Food and Agriculture Organization	CHS	Chitosan
GP	Grape pomace	PBS	Phosphate buffer saline
ORAC	Oxygen radical absorbance capacity	ALP	Alkaline phosphatase
UAE	Ultrasound-assisted extraction	PLLA	Poly(L-lactide)
MAE	Microwave-assisted extraction	PDA	Polydopamine
$ABTS^+$	Cationic radical scavenging activity	SF	Silk fibroin
PHWE	Pressurized hot water extraction	DC COL	Duck's feet collagen
SWE	Subcritical water extraction	MSCS	Calcium silicate calcium sulfate
HUVECs	Human umbilical vein endothelial cells	PC	Polycaprolactone
hMSCs	Human Bone Marrow Stromal cells	EGCG	Epigallocatechin gallate
PA	Proanthocyanidins	PVDF	Poly vinylidene fluoride
AP	Apple pomace	POSS	Polyhedral oligomeric silsesquioxane
NEPPs	Non-extractable polyphenols	NG	Naringin
SFE	Supercritical fluid extraction	CUR	Curcumin
GMs	Gelatin microsphere	GIN	Ginger
SA	Sodium alginate	SS	Silk sericin
IC	Icariin	ß-GP	ß-glycerophosphate
OPA	Oligomeric proanthocyanidins	MC3T3-E1	Mouse osteoblast cell
PCA	Protocatechualdehyde	MSCs	Mesenchymal stem cells
CA	Cellulose acetate	BMSCs	Bone marrow stromal cells
SIS	Intestinal submucosa	BMMSCs	Bone marrow mesenchymal stromal cells
SM-MSCs	Synovial membrane mesenchymal stem cells	hADSCs	Human adipose-derived stem cells
WJMSCs	Jelly mesenchymal stem cells	SrF2	Strontium fluoride

1. Introduction

BTE is a well-recognized and successful strategy for treating bone tissue problems such as bone loss and defects that may occur due to trauma, cancer, accidents, and congenital malformation [1]. In most of these bone problems, normal healing and regeneration of bone tissue do not happen which negatively affects the quality of life, with BTE highlighted as capable of addressing bone tissue difficulties and challenges via its ability to facilitate the development of a biological construct (scaffold) to act at the molecular and cellular level to not only repair the bone tissue but also promote the organ function [2, 3]. Bone tissue-engineered scaffold requires some characteristics to be actively applied in BTE such as its possession of a 3D structure with interconnecting pores to provide structural integrity, cell penetration, transportation of nutrients, and neovascularization as well as biocompatibility and biodegradability [4]. Moreover, osteoconductivity, osteogenicity, and osteoinductivity are other important properties that can be achieved by the addition of bioactive compounds to the bone scaffold through their effective influence on cell signaling procedures [5]. PPCs, which are characterized by multiple functional phenolic groups, are among the bioactive compounds identified mostly in plants with unique antioxidant activity, antimicrobial activity, and antiviral and anti-inflammatory properties

[6, 7]. Indeed, the ingestion of polyphenol-rich diets composed of fruits, vegetable, and whole grains have received tremendous attention among nutritionist and consumers because of their health effects and their key roles in human health with a reduced risk of many diseases such as cancer, cardiovascular diseases, neurodegenerative diseases, Alzheimer disease, and chronic inflammation [8, 9]. Over the past few decades, PPCs have been employed in developing various kinds of bioactive biomaterials with applications in tissue engineering [10].

Waste-derived biocompounds, including PPCs, have demonstrated remarkable characteristics such as biodegradability and biocompatibility, when integrated with biopolymers to produce bioactive composites for tissue engineering applications [11, 12]. Furthermore, besides their roles in environmental sustainability through decreasing the waste disposal and greenhouse gas emissions, their utilization increases the availability of cheap sources while reducing manufacturing costs [13, 14]. From the standpoint of extracting PPCs from waste sources, the extraction process introduces certain costs. However, a comprehensive techno-economic assessment study would allow for an accurate analysis of extraction-related costs, taking into consideration the various parameters that influence the process while simultaneously increasing the yield of PPCs [15-18]. This optimization can contribute to mitigating the overall extraction-related costs.

In the context of bone regeneration, autologous bone grafts and bone allografts have demonstrated several disadvantages such as limited availability, morbidity at the donor site, and reduced osteoinductivity [19]. To address these issues, various growth factors as bioactive compounds such as bone morphogenetic proteins (BMPs) can be incorporated into bone grafts, but their application has been restricted due to their high cost and the possibility of negative side effects [20]. The potential of PPCs can then become significant. A tissue-engineered scaffold fortified with PPCs presents a multifaceted advantage due to the low-cost of such fortified scaffolds, rapid recovery times, and diminishing associated risks such as multiple surgeries, infection, and immune rejection. This stands in stark contrast to conventional therapies [21].

The incorporation of PPCs into the bone scaffolds contributes to their bioactivity through their roles in cell proliferation, attachment, and differentiation, thereby enhancing the healing process of bone tissue. Additionally, PPCs offer a range of beneficial properties, including antioxidative, anti-inflammatory, and antibacterial effects [22]. The need for additional compounds to confer such benefits is obviated by infusing these properties into the scaffold. Therefore, the incorporation of PPCs, particularly from wastes, into the bone scaffold, gives useful properties to the scaffolds which can be economical and cover the fabrication costs.

This review aims to focus on the effective functions of PPCs in BTE in the context of a polyphenol-functionalized bone scaffold. The description of PPCs, their classifications, and their natural sources is initially provided. Next, the review presents the importance of agricultural wastes for the extraction of PPCs and discusses the biological potential of extracted PPCs from fruit wastes. This review then explores the conventional and various green extraction procedures of PPCs from different fruit wastes

after which the role of PPCs in tissue engineering is briefly discussed. The different functionalities of PPCs in BTE applications such as crosslinker, drug, and surface modifiers are also comprehensively discussed. We believe that this review can provide an overview of future trends and predictions for the development of bone scaffolds functionalized with bioactive PPCs derived from fruit wastes with existing challenges and strategies that can be resolved to promote their proposed clinical BTE applications.

The literature search for this review was carried out in the 'Google Scholar' search engine and included articles published in the last 25 years (from 1998 to 2023). The search strategy was based on using a wide range of keywords and terms as follows: 'bone tissue engineering', 'polyphenol and bone tissue regeneration', 'polyphenol extraction, 'polyphenol and green extraction', 'polyphenol and classification', 'polyphenol extraction and waste', 'fruit waste polyphenol', 'apple waste polyphenol', 'grape waste polyphenol', 'polyphenol and tissue engineering'. To investigate the research trend of PPCs utilization in BTE, we obtained data from the National Library of Medicine (PubMed®) database considering available relevant journals and books. Fig. 1. displays the publication trend of PPCs application in BTE captured in the last 10 years and shows that ~ 17000 publications have been published from 2013 to date (2023). The growing research interest in this area is illustrated by the ~50% and ~35 % increase in the number of publications in year 2021 and 2022 respectively, compared to the reference year 2013, with the improved knowledge of the importance of PPCs and its impact in BTE for improving human health contributing to this increased interest.

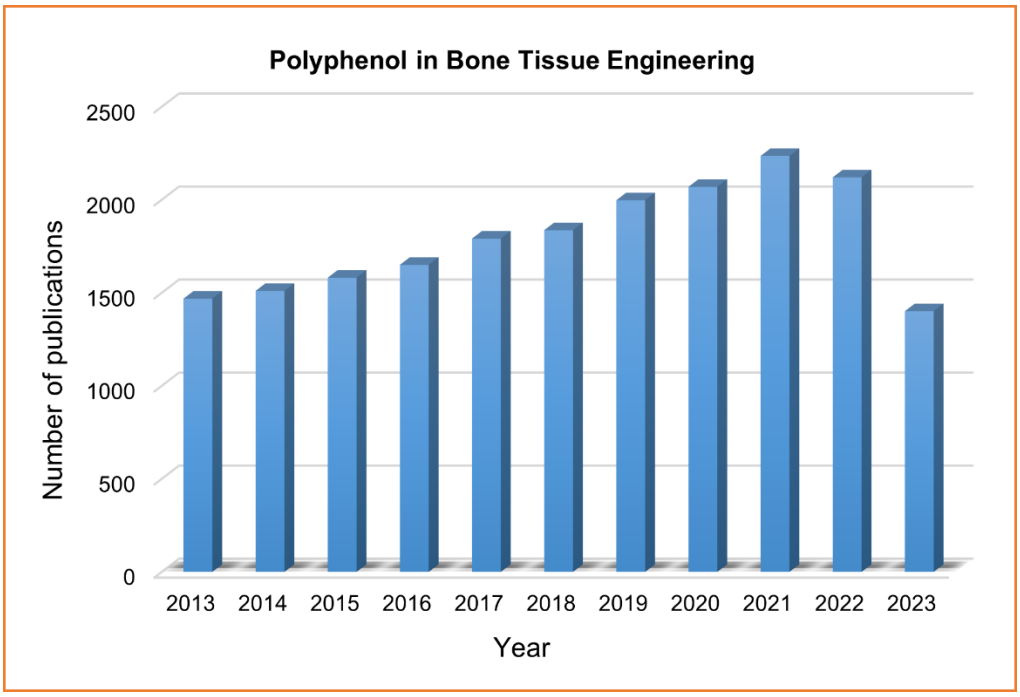

Fig. 1. Trends in research in polyphenol applications in bone tissue engineering in the past ten years. Source: PubMed

2. Polyphenols, classification, and their natural sources

PPCs constitute a broad range of bioactive compounds that are mainly found in plant materials; however, the presence of phenolic amino acid, recognized in crustaceans and mollusks is the exception [23]. Over 8000 polyphenol molecules, characterized by a common structure based on hydroxyl groups on an aromatic ring have been identified [24]. PPCs are secondary metabolites including small and simple molecules such as phenolic acids containing one to three hydroxyl groups complex molecules with higher content of hydroxyl groups such as tannins with molecular weight (MW) ranging from 200-5000 Da and polymerized compounds with MW > 30000 Da [23, 25, 26]. PPCs can also exist as complexes in combination with carbohydrates, proteins, and other insoluble PPCs such as anthocyanins [25].

PPCs, which have been identified as strong antioxidants, via inhibiting the creation and deactivation of active species and precursors of free radicals, can scavenge the formation of free radicals [8, 27]. The unique chemical structure consisting of an aromatic ring with multiple hydroxyl groups has provided the antioxidant activity for PPCs which are capable of donating hydrogen or electrons for neutralization of reactive oxygen species (ROS) and free radicals [28]. Besides the antioxidant potential of PPCs, polyphenolic-rich extracts of fruits such as grape, blueberry, blackberry, and elderberry have exhibited wide-spectrum antibacterial effects by controlling pathogenic bacteria, particularly antibiotic-resistant bacteria [29]. Generally, PPCs are classified into two main groups of flavonoids and non-flavonoids (Fig. 2), which have been distributed in fruits, vegetables, legumes, and whole grains as well as other products including tea, chocolate, and wine [24, 30]. Interestingly, PPCs with beneficial biological activities have also been found in different fruit wastes with potential medicinal and therapeutic applications [31].

2.1 Flavonoids

The largest group of PPCs is flavonoids comprised of a wide variety of polyphenolic molecules with low molecular weight identified by common diphenyl-propane (C6-C3-C6) skeleton which accounts for the main PPCs in human diets [32]. According to Wang et al. [33], flavonoids are aromatic keto-compounds characterized by their anti-inflammatory, antioxidant, antiviral, anti-aging, and anticancer features leading to well-known therapeutic properties [34]. Quercetin (Qu), catechin, naringenin, cyanidin glycoside, and daidzein are the commonest flavonoids [25]. In addition to their common occurrence in diverse vegetables and fruits, other foods and products such as nuts, seeds, grains, spices, tea, wine, and beer as well as various medicinal plants contain flavonoids [35]. Different fruit wastes containing peel, pomace, and seed have also been reported to contain flavonoids. The pomace of apple, grape, strawberry, and olives, peel of fruits such as oranges, watermelon, banana, mango, and pineapple were reported as flavonoid sources. The seed/kernel of some fruits including apricot, date, mango, and avocado also contained different content of flavonoids [31]. Regarding the structural differences, flavonoids are categorized into six main groups including anthocyanidins (cyanidin, malvidin), flavanols (epicatechin, catechin), flavones (apigenin, luteolin), flavonols (Qu, myricetin, kaempferol), flavanones (naringenin, hesperetin) and isoflavones (genistein, daidzein) [36].

One important subclass of flavonoids is anthocyanidins which are widely distributed in plants and principally are in the conjugated form, anthocyanins. Anthocyanins have been widely studied and appear as different important pigments in nature that are responsible for the colors (purple, red, pink, or cyan) of fruits. Anthocyanins exist in different chemical structures, such as aglycone, glycosylated with glucose, and esterified with different organic acids and polyphenolic acids [37]**.** The rich source of anthocyanins in fruits are cherries and berries with red, blue, and purple colors such as raspberry, blackberry, blueberry, chokeberry, and bilberry. The health-promoting effect of anthocyanins has been proven by exhibiting different beneficial nutraceutical and pharmaceutical effects such as anticancer, antidiabetic, neuroprotective, angiogenesis, antimicrobial, and antioxidant activities [38]. Other polyphenol molecules such as phenolic amino acids, phenolic acids, stilbene, tannins, lignans, and curcuminoids are classified into the non-flavonoids group [24].

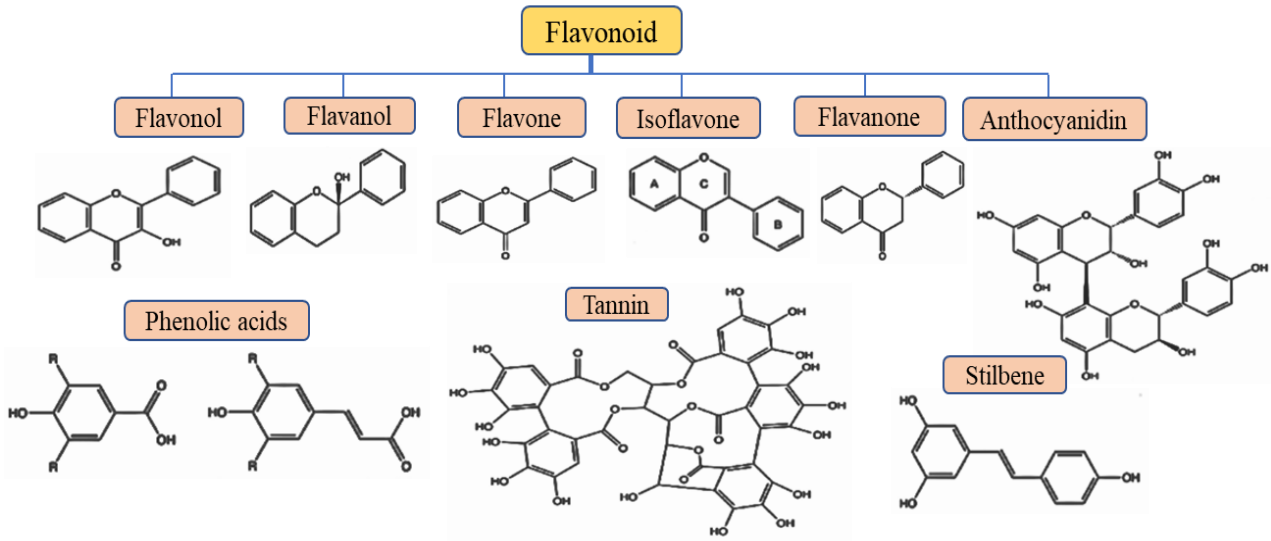

Fig. 2. Main classes of flavonoids, phenolic acids, tannin, stilbene, and their chemical structure. Reproduced with permission from [39]. Copyright 2021, Elsevier.

2.2 Phenolic acids

Phenolic acids are among the most important non-flavonoid PPCs which constitute one-third of the dietary PPCs existing in three configurations of conjugated-soluble, free, and insoluble-bound [40]. Phenolic acids are considered a precursor in the synthesis of lignin and other PPCs such as hydrolyzable tannins [41]. According to Robbins, phenolic acid can be classified into two distinct carbon structures of hydroxycinnamic and hydroxybenzoic in which the position and number of the hydroxyl groups on the aromatic ring characterize these groups. These phenolic acids may be found in all food groups and are known to exert antioxidant activity by scavenging several radials such as the hydroxyl radical, several organic radicals, superoxide radical anion, etc. [42]. In addition to their antioxidant activity, phenolic acids have been known for their anti-inflammatory, antitumor, antihypertensive, antimicrobial, antiaging, cardioprotective, and neuroprotective properties [43].

Different phenolic acids including gallic acid (GA), protocatechuic acid, vanillic acid, p-hydroxybenzoic acid, syringic acid, and ellagic acid, with the common structure of C6-C1, are classified in the hydroxybenzoic acids category. On the other side, the most common representatives of hydroxycinnamic acids are caffeic acid, p-coumaric acid, ferulic acid and sinapic acid possessing the (C6-C3) structure [6, 44]. Hydroxycinnamic and hydroxybenzoic in addition to their occurrence in fruits, also constitute the major phenolic acids of grains, legumes, and oil seeds [45]. Ellagic acid is mainly present in fruits and nuts and has been identified in high amounts in extracts of red raspberry leaves or seeds and pomegranates. Caffeic acid is predominantly found in fruits, cereals, coffee, and vegetables, and coffee beans have been placed as one of the richest sources of chlorogenic acids [25, 35]. Phenolic acids have also been found in fruit wastes such as gallic acid, ellagic acid, and vanillic acid [43]. For example, the peels of mango, pomegranate, watermelon, apple, pawpaw, orange, pineapple, and banana contained a large amount of phenolic acids. Moreover, pomace of blueberry, raspberry, strawberry, grapes, citrus, apple, peach, kiwi fruit, pear, plum, and seed/kernel of avocado, pomegranate, mango, papaya, orange, date palm, and apple were reported as sources of phenolic acids [31].

2.3 Tannins

Tannins are high molecular weight PPCs that mostly exist in the polymeric structure and are found in a broad range of plant sources of fruits such as strawberries, raspberries and blackberries, cereal grains, and legume seeds [46]. There are two main classification groups of tannins: condensed tannins or pro-anthocyanidins and hydrolyzable tannins. Hydrolyzable tannins which are the esters of GA or ellagic acid and commonly referred to as gallotannins and ellagitannins are widely found in grapes and wines contributing to the organoleptic qualities of these foods [47]. Peels of several fruits such as banana, mango, apple, orange, watermelon, kiwi, the pomace of orange, apple, pineapple, sweet lemon, apricot, and seeds of black plums, apple, tamarind, watermelon and, guava are among the fruit waste sources of tannins [31].

2.4 Stilbenes

Different kinds of PPCs of the stilbenes class have been identified in several plant species including peanut, sorghum, grape wine, and many medicinal plants [48]. The main representative of stilbenes is resveratrol which has attracted attention because of its anti-carcinogenic, anti-inflammatory, and cardioprotective properties and is found in the peel of red grapes as a dietary source [49]. Another important polyphenolic molecule is pterostilbene which has primarily been recognized in bilberries, blueberries, grapes, and juice residues. Grape pomaces, solid residues of wine and juice production, have been reported to contain abundant stilbene compounds. Moreover, the bark waste of conifer trees contains considerable amounts of different stilbene compounds such as piceatannol, pinosylvin, and *trans*-resveratrol [50].

2.5 phenolic amides

Phenolic amides are composed of functional substituents containing nitrogen which are essentially conjugates of aromatic amines to phenolic acids, and include compounds of avenanthramides and capsaicinoids that can be found in oats and chili peppers, respectively [51, 52]. phenolic amides are reported to have antioxidant and anti-inflammatory properties which are presented as modulating the system of cell oxidative defense and inhibitor of the oxidation of low-density lipoprotein [52]. Regarding the presence of PPCs in different fruit wastes, the next section discusses the importance of the isolation of PPCs from fruit wastes particularly apple and grape wastes which can be potentially applied in biomedical applications.

3. Polyphenols from fruit waste

Food and agriculture waste is now recognized as a global issue because of its associated negative production and ethical, economic, social, and environmental consequences, which has created a growing concern [53, 54]. Annually about 1.3 billion tons of food waste including fruits, vegetables, meat, fish, seafood, dairy, and bakery products are wasted before and after consumption during various phases of the food supply chain [55]. Regarding the FAO (Food and Agriculture Organization) report, fruit and vegetable wastes constitute up to 60% of horticulture production, and the contribution of the fruit and vegetable processing industry in the production of wastes accounts for 25-30% of the agricultural product loss [56]. Only in European countries, 100 million tons of waste and by-products are produced annually in which drink industries, and fruit and vegetable processing companies contribute to 26% and 14.8 % of the waste production, respectively [57]. Among different food wastes generated around the world, fruits, vegetables, and cereal products constitute major wastes including pulp, seed, peel, rind, pomace, husk, bran, and germ which are not commonly consumed and discarded in the landfills and cause environmental issues [58]. Wide ranges of high-value compounds such as bioactive compounds have been identified in various kinds of wastes with well-known biological activities such as antimicrobial, anti-inflammatory, antioxidant, and anti-immunomodulatory properties that can have significant roles in human health [55, 59]. Crucially, fruit waste as a source of thousands of valuable compounds have been considered to be employed in diverse industries such as food, cosmetics, nutraceutical, pharmaceuticals, biochemicals and biofuel [57, 60, 61]. Substantial quantities of polyphenolic-rich wastes are generated from agricultural and industrial residues of fruit and vegetable, and it has been confirmed that some of these wastes are a good source of polyphenolic antioxidants which have exhibited antioxidant activities comparable to synthetic antioxidants when investigated in food products such as edible oil, fish, meat and poultry products [62]. Among fruit wastes, the well-known sources of PPCs are citrus fruits, apples, grapes, berries, banana, mango, and pomegranate pomaces (Fig. 3), and polyphenolic-rich wastes of vegetables have been recognized in onion, tomato,

potato, carrot, red beet, pumpkin, artichoke, brassica crops (cauliflower, cabbage, and broccoli), lettuce and chicory as well as asparagus [35]. These valuable wastes are typically used for animal feed and fertilizer which is not economically attractive or disposed of in landfills or incinerate causing land and water pollution and eventually a risk to public health [55, 63]. Therefore, the valorization of wastes by applying eco-friendly and cost-effective technologies has attracted considerable attention toward zero-waste production, design, and production of new bio-based materials [64]. In this regard, numerous investigations are being carried out for the recovery of PPCs from largely available, and low-cost wastes which can be potentially utilized in producing high-value bioactive compounds with food, pharmaceuticals, cosmetics, and biomedical applications [62, 64, 65]. In the subsequent subsections, the recovery of PPCs from two main fruit wastes of apple and grape with reported diverse biological activities is discussed.

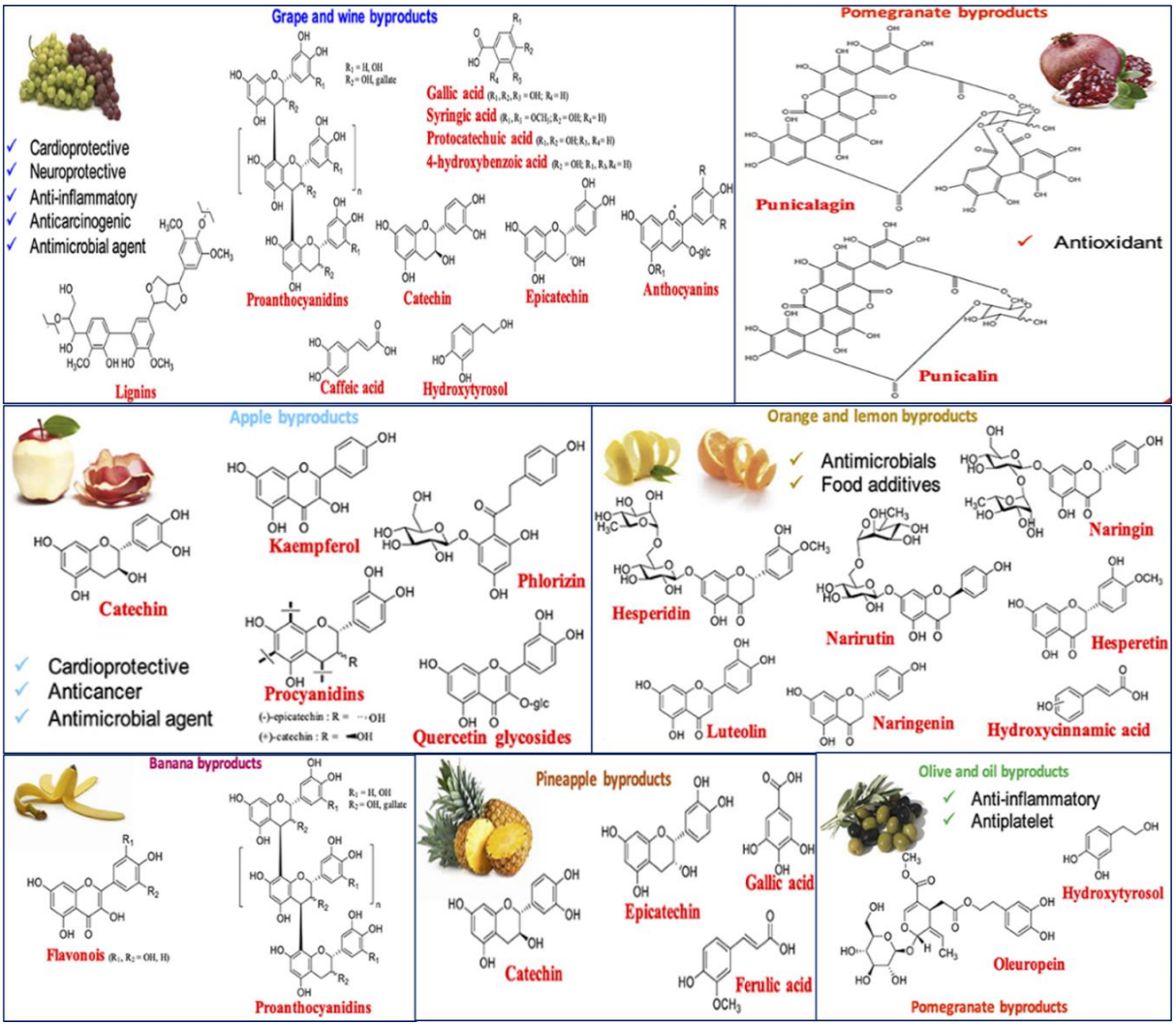

Fig. 3. Fruit wastes and their main PPCs with reported bioactivities [66].

3.1. Grape waste PPCs

Grape winemaking is an important industry that consumes 80 % of global grape production. This industry also produces huge amounts of residues; millions of tons of grape pomace (GP) [67], constituting mainly seeds (38-52 wt.% on a dry matter basis), skin, stem, and leaves in which large quantities of PPCs remain in GP during the production of wine [35, 68]. Indeed, 1 kg of GP has been estimated to be generated from the production of 6 L of wine [69], and 5-9 million tons of GP annually discarded creating economic and environmental problems [70]. Therefore, the efficient exploitation of GP characterized by the high level of PPCs as a rich and cheap source would be of great importance and can be effectively utilized in the cosmetic, food, and pharmaceutical industries [71]. Various kinds of PPCs including anthocyanins, phenolic acids, catechins, flavonol glycosides, and stilbenes constitute major PPCs in GP [72]. Numerous research studies have been carried out to efficiently recover PPCs from GP that have shown various biological activities. For instance, in a study by Diandra Pintać et al., different classes of PPCs from GPs of diverse varieties containing skin, seeds, pulp, and stem were efficiently extracted using six different solvent compositions. Rich polyphenolic extracts from diverse classes containing flavone, flavanol, stilbenes, flavanones, phenolic acids, and coumarins were obtained using ethyl acetate. Anthocyanins and ursolic acid were extracted using methanol and acetone solvents, respectively; while PPCs with the highest yield which is the interest of industries, were achieved with 80% v/v methanol [73]. In another study, the antioxidant activity of PPCs extracted from different winery pomace from red and white grapes using solvents of acidified ethanol (0.1% HCl), 80% ethanol, 50% ethanol, and acetone was investigated. The highest content of total PPCs and DPPH radical scavenging activity was achieved using ethanol (0.1% HCl) and 80% ethanol which could be ascribed to the GA and catechin, the main PPCs of ethanolic extracts. Moreover, diverse PPCs such as catechin, rutin, rosmarinic acid, chlorogenic acid, caffeic acid, vanillic acid, and coumaric acid were identified with different values based on the utilized solvent [74]. PPCs extracted from red GPs obtained from the Portuguese red wine industry exhibited high antioxidant properties of iron chelating capacity and oxygen radical absorbance capacity (ORAC) for ethanol/water extracts from three red pomaces. PPCs such as GA, syringic acid, caffeic acid, (−)-epicatechin, and (+)-catechin, and were identified in the extracts. Moreover, the highest total PPCs (142.4 ± 1.1 mg GAE g^{-1} dry residue), scavenging capacity against DPPH (1.12 ± 0.04 mmol TE g^{-1} dry residue), and ORAC (1579 ± 244 mol TE g^{-1} dry residue) were achieved in one of the GPs variety [75]. Caldas et al. compared different extraction methods of PPCs from grape skin, and the results revealed the better performance of ultrasound-assisted extraction (UAE) followed by microwave-assisted extraction (MAE) and ethanol extraction. Main PPCs of Qu, malvidin-3-O-glucoside, rutin, catechin, and epicatechin were found to show antioxidant properties of cationic radical scavenging activity ($ABTS^{+}$) and ORAC [76]. Strong cytotoxicity on HL-60 cancer cells was observed in polyphenolic extracts of GP using green technology of pressurized hot water extraction (PHWE) at the highest tested concentrations, particularly in the extract treated at 200 ºC [77]. A study by Pedras et al. showed antibacterial activity of polyphenolic extract of GP obtained from white wine recovered with subcritical water extraction (SWE) at 210 °C with higher DPPH radical scavenging

activity compared to ethanol extraction [78]. The protection potential of polyphenolic extract from GP obtained from winery waste against oxidative cell death was investigated by Posadino et al. Various anthocyanin molecules such as peonidin-3-O-glucoside, malvidin, and malvidin-3-(6-acetyl)-glucoside, were detected in the polyphenolic extract which was cytocompatible towards human umbilical vein endothelial cells (HUVECs) and protected the cells from oxidative death induced by hydrogen peroxide (H_2O_2) due to the strong antioxidative property of the polyphenolic extract [79]. Polyphenolic extracts of GP from two different types including Croatina, a red grape variety, and Arneis, a white grape were tested for their influence on cell (Human Bone Marrow Stromal cells (hMSCs)) responses. Proanthocyanidins (PA), flavonoids (flavonols and flavones), and hydroxycinnamic acids were identified in Croatina GP, while phenolic and hydroxycinnamic acids were the major PPCs of Arneis GP. PPCs of two GPs could activate and increase different gene expressions such as BMP2 and Runx2 of hMSCs cells, resulting in enhanced osteoblast activity and differentiation which could be applicable for the fabrication of a biomaterial for bone regeneration [80].

3.2. Apple waste PPCs

Another main fruit waste is apple pomace (AP) generated in considerable amounts mainly from the fruit juice processing industry [81]. This residue, which comprises different parts of an apple such as pulp, peel, seed, core, and stem, accumulates mostly in landfills creating environmental pollution [82]; however, this industry by-products has been reported to contain important bioactive molecules of PPCs [83]. Thus, numerous researchers have investigated the recovery of PPCs from AP and evaluated their biological properties for useful applications in the food, pharmaceutical, and biomedical sectors. For instance, in a study by Bai et al., six fractions of PPCs from industrial AP were purified, and Qu chlorogenic acid, caffeic acid, syringic acid, cinnamic acid, procyanidin B2, (−)-epicatechin and coumaric acid, were the main PPCs of the AP fractions. All the polyphenolic fractions displayed antioxidant activity, however, one fraction had the strongest antioxidant activities of ABTS radical inhibition rate, DPPH radical scavenging rate, and the reducing power with values 89.78% ± 6.54%, 90.96% ± 10.23%, and 8.30 ± 0.71 µmol Trolox equivalents kg^{-1} dry AP, respectively which could be ascribed to the highest amount of total PPCs with highest antioxidant potential in this fraction compared to other fractions [84]. Non-extractable PPCs (NEPPs) such as PA, which are in the cell wall of fruits and attached to the fibers and proteins, have not been extensively the focus of the literature studies. However, these groups of PPCs can provide interesting biological activities. For instance, a study by Tow et al., demonstrated that NEPPs of AP containing PA exerted high DPPH radical scavenging activity (89.76 ± 0.93%) and antiproliferative activity against different human cancer cells including HeLa, HepG2, and HT-29. The inhibitory effect of NEPPs on cancer cells was obtained at 46.2% to 95% showing a higher value compared to 3.9% to 22.2% achieved for extractable PPCs containing (+)-catechin, (−)-epicatechin, chlorogenic acid, and Qu [85].

Another research exhibited the anticancer effects of different polyphenol fractions from industry-sourced AP extracted with ethanol, methanol, and acetone which were then partitioned with ethyl acetate. PPCs of phloridzin, quercitrin, Qu, and phloretin were identified in different extracts and showed toxic effects against different human cancer cell lines such as colorectal adenocarcinoma (HT-29), cervical squamous cell carcinoma (SiHa) and oral carcinoma (KB). Moreover, the anti-inflammatory potential of PPCs was detected through their inhibitory effect on NO synthesis [86]. The antiviral effect of acetonic and ethanolic extract of AP against two viruses of HSV-1 and HSV-2 was assessed in research by Suárez et al. The results showed that quercetin glycosides such as hyperin and avicularin and dihydrochalcones including phloridzin and phloretin-2´-xyloglucoside were the main PPCs that could contribute to the reduction of viral replication levels of HSV-1 and HSV-2 viruses as two human pathogens [87]. Ethyl acetate extract of AP contained phlorizin and phloretin in higher concentration along with procyanidin B2, gallic acid, hyperin, quercetin-3-O-rthamnoside, chlorogenic acid, syringing, querecetin-3-O-pentoside, and Qu exhibiting antibacterial activity against *E. coli* and *S. aureus*, with higher inhibition effect against the growth of *S. aureus* [88]. Our previous study on the extraction of PPCs from four different fractions of industry-sourced AP exhibited that phloridzin, chlorogenic acid, and Qu constituted the major PPCs of all the fractions, and the DPPH radical scavenging activity of the polyphenolic extract of peel fraction could be comparable to ascorbic acid. Furthermore, the polyphenolic extracts were cytocompatible towards two human cell lines of human fibroblast (3T3-L1) and salivary gland acinar cells (NS-SV-AC) highlighting the efficiency of the polyphenolic extract in biomedical applications [89]. Considering the importance of fruit waste PPCs, the next section discusses different methods of extraction of PPCs.

4. Extraction of PPCs from fruit waste

A review of the literature shows extraction techniques for PPCs may be categorized into conventional extraction methods i.e. Soxhlet, percolation, and maceration [90], and modern green extraction techniques including UAE, MAE, PHWE, supercritical fluid extraction (SFE) and pressurized liquid extraction (PLE) [90, 91]. These extraction methods are discussed in the subsequent subsections.

4.1. Conventional extraction methods

4.1.1 Soxhlet, percolation, and maceration

These conventional extraction methods of Soxhlet, percolation, and maceration are quite similar, employing solvents directly to enable the isolation of compounds from a solid matrix [92]. In the maceration process, the ground sample from which the PPCs are to be extracted is placed in a closed container under atmospheric pressure conditions and room temperature which contains the solvent, and is allowed to stand for a long period (~3 days) with agitation imposed till the PPCs are extracted [93] (Fig. 4A) [94]. In the percolation extraction method, a percolator which is a narrow and cone-shaped vessel is commonly used. The ground sample is initially moistened using the solvent and kept for about

4 h. Additional solvent is then added and the mixture is macerated for ~24 h, finally, the percolator's outlet is opened and the solution containing solvent and the extracted PPCs are recovered [95]. Regarding the constant replacement of saturated solvent with fresh solvent and continuous extraction process, the percolation extraction method has been recognized as more efficient than the maceration technique (Fig. 4B) [96, 97].

In the Soxhlet extraction method, a Soxhlet extraction apparatus is typically used. In this technique, the ground sample interacts consistently with a fresh solvent, for enhanced recovery of the target PPCs via the displacement of the mass transfer equilibrium of the solvent-extract system [98]. Soxhlet extraction occurs by applying heat to the distillation flask under atmospheric pressure conditions to enable some level of extraction cavity for enhanced leaching of the target compounds (Fig. 4C) [99]. These conventional extraction methods are characterized by several limitations which include, long extraction times and large masses of solvent consumption. Crucially, the large masses of solvent consumption resulted in associated negative environmental impacts leading to the need to explore 'greener' extraction methods which are discussed in the subsequent sections [100, 101].

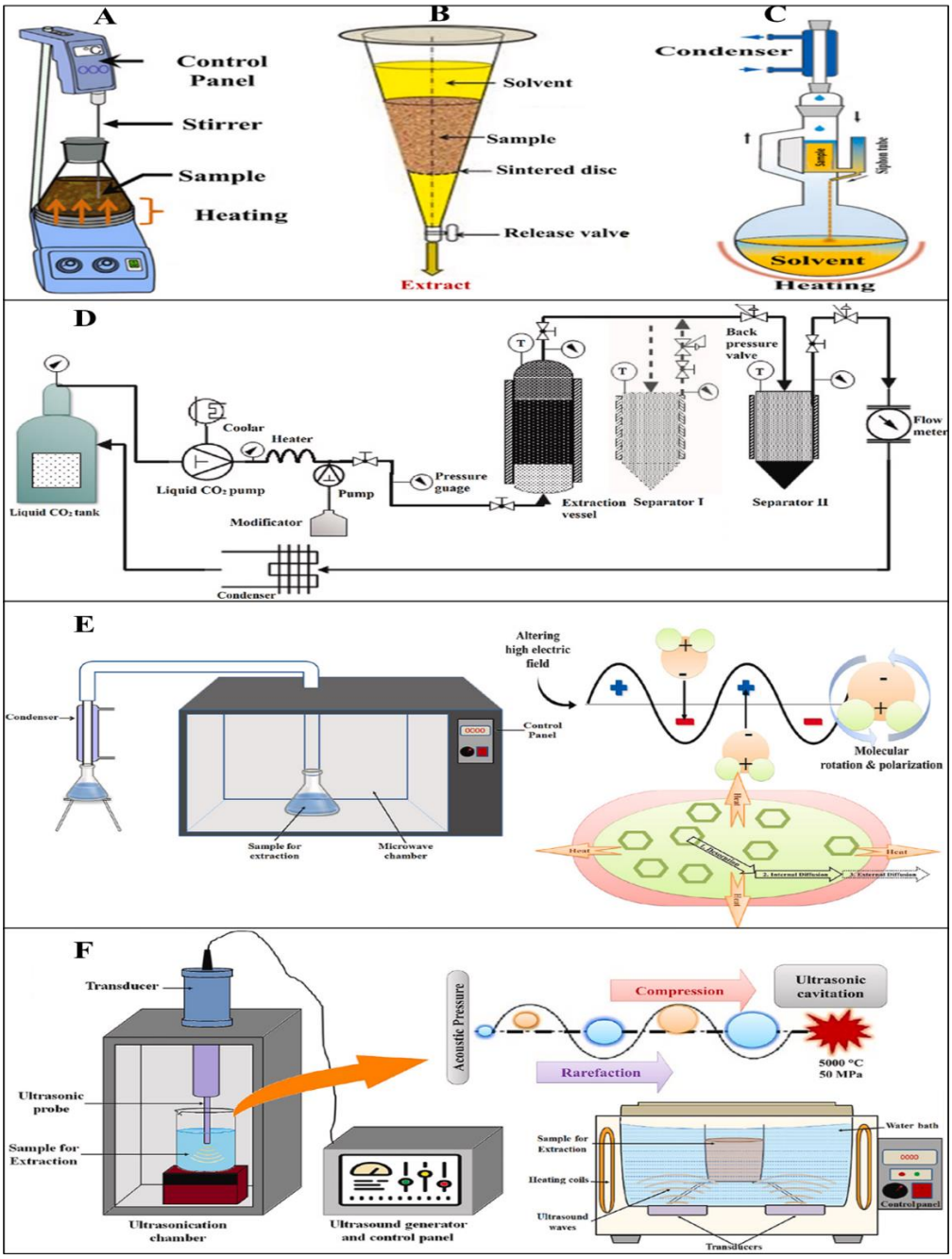

Fig. 4. Schematic illustration of conventional and green extraction methods of PPCs; (A) Maceration, infusion (without heating), and decoction (with heating); (B) Percolation; (C) Soxhlet extraction; (D) SFE; (E) MAE; (F) UAE. Reproduced with permission from [102]. Copyright 2022, Elsevier.

4.2. Green extraction techniques

4.2.1 Supercritical fluid extraction

SFE is characterized by several advantages over other conventional extraction methods and is recognized as an environmentally friendly technique. Typically, in the SFE extraction method, carbon dioxide (CO_2) constitutes a frequently employed supercritical fluid since it is non-toxic and requires lower temperature and relatively low pressure [103, 104]. The use of CO_2 as a solvent while under

conditions above its critical temperature and pressure of 304.1 K and 73.8 bar [105] enables the supercritical carbon dioxide ($SCCO_2$) to present both gas-like viscosity and liquid-like density thus enabling the $SCCO_2$ to be able to penetrate into small pores that are typically inaccessible to liquids (Fig. 4D) [106]. Due to the aforementioned advantages, SFE is recognized as preferred to conventional techniques in the extraction of PPCs as demonstrated in the literature [103, 107]. Crucially, however, the application of SFE while using CO_2 as the solvent may be undesirable when polar PPCs are to be extracted since CO_2 is considered a weak solvent since it is a nonpolar lipophilic compound [108]. To circumvent this issue, to some extent, it has been proposed to add polar co-solvent to the SFE-CO_2 system to enhance the solubility of polar PPCs, for improved yields. [109]. In a study by Kupnic et al., SFE of PPCs from pomegranate (*Punica Granatum L.*) peel, in which ethanol was used as a co-solvent, showed its high efficiency in the extraction of different flavonoids and phenolic acids, particularly ellagic acid with antioxidant activity and antimicrobial activity against fungi and various species of Gram-negative, Gram-positive bacteria [110]. Another research also demonstrated the potential of SFE in the extraction of phenolic acids and flavonoids from papaya seed with high antioxidant activity against DPPH radical and lipid oxidation [111].

4.2.2 Microwave-assisted extraction

MAE is a technique that combines microwave, i.e. a wavelength from 0.001 m to 1 m (i.e. with a frequency from 3 × 1011 Hz to 3 × 108 Hz) and traditional solvent extraction via heating the solvent using microwave energy, resulting in a process that is more rapid than conventional Soxhlet, while also reducing solvent consumption [112, 113]. Thus, in simple terms in MAE, polar molecules in the extraction solution interact with microwaves, such that heat is generated leading to an increase in the internal pressure of the sample for enhanced release of PPCs while enhancing the breakage of weak hydrogen bonds [114]. MAE works according to two main principles of dipole rotation and ionic conduction with a full description of these mechanisms extensively discussed elsewhere (Fig. 4E) [115]. Multiple factors have been identified to influence the efficiency of the MAE including the structure of the solvent and sample matrix, the type of solid sample to be extracted, and the dielectric constants of the sample and solvent [116]. MAE, therefore, enhances the reduced retention of the PPCs by the matrix, although there is an increased risk of PPCs degradation at higher temperatures in certain applications [112]. Due to the several advantages, the application of MAE technology for the recovery of PPCs from fruit wastes has been explored significantly in the literature. For example, in the work of Carbone et al., the utilization of MAE in the extraction of PPCs with high antioxidant potential from kiwi fruit pomace was demonstrated [117]. Another study compared the efficiency of the MAE of phenolic acids from peels of citrus mandarin with the UAE and rotary extraction. MAE could recover a higher yield of phenolic acid with higher antioxidant activity within the shortest extraction time compared to other methods [118]. The added benefit of this extraction technique is that it is reported to be more suitable in the recovery of polar and moderately polar PPCs than the previously described SFE technique [119].

4.2.3 Ultrasound-assisted extraction

UAE technique employs ultrasounds to facilitate the formation of cavitation bubbles in the mixture of solvent and sample from which the PPCs are to be extracted [120]. When these cavitation bubbles collapse, localized temperature and pressure changes occur thus enhancing PPCs release from the sample by increasing its mass transfer rate [121]. Since the UAE technique functions based on the cavitation phenomena and mechanical mixing effect for increased extraction efficiency compared to the increase in temperatures that characterizes the MAE extraction technique, heat-sensitive PPCs are not thermally decomposed (Fig. 4F) [122]. The UAE technique is reported to be simpler, less prone to contamination, and occasionally, faster than MAE [123]. The UAE has been employed in previous works such as the extraction of PPCs particularly flavanones from the peel of orange (*Citrus sinensis L.*) with high total polyphenolic content (275.8 mg of GAE/100 g sample) [124]. In another study, UAE was employed in the recovery of PPCs from pineapple skin [125]. PPCs with antioxidant activity were extracted from the peel and pulp of apricot using the UAE method [126]. A study by Pingret et al. exhibited that UAE could extract PPCs with a 30% increase in yield and enhanced antioxidant activity from AP compared to the conventional maceration method. Furthermore, ultrasound-assisted extracts were richer in phenolic acids, dihydrochalcones, and flavonols [127]. Crucially the UAE technique may be significantly influenced by the particle size compared to the MAE technique with additional risks of reduced extraction efficiencies reported due to the aging of the ultrasonic probe surface [123].

4.2.4 Pressurized liquid extraction

The PLE technique employs elevated temperature and pressure on organic solvents, above their normal boiling points to achieve fast and efficient extraction of compounds such as PPCs from the solid matrix [128]. In PLE, a solid sample is introduced into a stainless steel extraction cell, and PPCs are extracted using a suitable solvent at high temperature and pressure (and typically for short periods (5-15 min). The extracted PPCs are subsequently purged into a collection vial using a compressed gas [129]. The use of the PLE technique in the extraction of PPCs has been widely explored in the literature and recognized as an excellent substitute for conventional extraction methods [130]. Examples of studies that have explored the PLE method include the work of Tamkutė et al. where the extraction of PPCs from cranberry pomace using pressurized ethanol and water was investigated. PLE extraction with two solvents could effectively recover six anthocyanin glycosides that exhibited antioxidant activity [131]. In another study by Alonso-Salces et al., PLE was optimized for the extraction of different PPCs from Golden Delicious apple peel and pulp [132].

4.2.5 Pressurized hot water extraction

PHWE technique may be considered as a subset of the previously discussed PLE method with liquid water employed as the extraction solvent at temperatures higher than the atmospheric boiling temperature of water (i.e. 100°C) but lower than the water critical temperature (374°C) [133]. The

PHWE technique exploits the unique ability of water to present a polarity close to alcohol under various conditions of temperature and pressure and thus can be applied for the extraction of low polarity PPCs in a wide range of mediums [134, 135]. The main privilege of PHWE is, therefore, the consumption of non-toxic water instead of organic solvents with readily recycled or even disposed of without significant negative environmental outcomes [134, 136]. One example of PHWE utilization in the extraction of PPCs from fruit waste is our previous study, where the optimization study of PPCs from food industry AP was investigated, and higher content of total PPCs (39.08 ± 1.10 mg GAE/g db) from PHWE extract was achieved compared to the conventional extraction with ethanol (10.78 ± 0.94 mg GAE/g db) [89]. In another research, a higher content of total PPCs (63.14 mg GAE/g) with higher antioxidant activities towards DPPH, FRAP, and ABTS from red pitaya (*Hylocereus polyrhizus*) seeds was obtained at an optimized point compared to conventional extraction (organic solvent) [137]. Table 1 displays fruit waste potential for the extraction of diverse PPCs with different methods.

Table 1. Extracted PPCs from different fruit wastes with different extraction approaches.

Fruit waste	Extraction method	polyphenolic compounds	Reference
AP	solvent extraction	catechin, epicatechin, chlorogenic acid, phloretin, phloridzin, quercetin	[138]
Apple seed	UAE	chlorogenic acid, phloridzin, Qu, hyperin, (−)-epicatechin, protocatechuic acid, caffeic acid, (+)-catechin	[139]
Apple seed, skin, core, AP	UAE	Qu, quercetin glycosides, catechin, epicatechin, phloridzin, phloretin, caffeic acid, ferulic acid epigallocatechin, chlorogenic acid, isoferulic acid,	[140]
AP	PHWE	chlorogenic acid, phloridzin, procyanidin B2, epicatechin, quercetin glycosides, protocatechuic aldehyde	[141]
Mandarin peel	PHWE	hesperidin, narirutin, rutin, chlorogenic acid	[142]
Citrus peel	solvent extraction	naringin, hesperidin, hesperetin, neohesperedin, narirutin, rutin	[143]
Citrus pomace	solvent extraction	GA, chlorogenic acid, hesperetin, vanillin, quercetin, rosmarinic acid, hesperidin, ellagic acid, catechin, p-coumaric acid, trans-ferulic acid	[144]
Lime pomace	UAE/PLE	narirutin, hesperidin	[145]
Kinnow peel	solvent extraction/UAE	ferulic acid, hesperidin, GA, caffeic acid epicatechin, chlorogenic acid, naringenin, coumaric acid, Qu, catechin	[146]
Grape pomace, skin, seed	solvent extraction	GA, catechin, vanillic, syringic, caffeic acid, chlorogenic acid, resveratrol, rutin trihydrate, kaempferol-3-glucoside, quercetin, caftaric	[147]
Blackcurrant pomace	UAE	protocatechuic acid, caffeic acid, naringenin, apigenin, chlorogenic acid, isoquercitrin, cyanidin-3-O-glucoside, cynaroside, narirutin, naringenin-O-diglucoside, quercetin 3-O-diglucoside	[148]
Apricot pomace	UAE	delphinidin, chlorogenic acid, malvidin 3-O-glucoside, kaempferol-O-glucoside, caffeic acid-O-glucoside, catechin, naringenin, caffeic acid, 3,4-dimethoxybenzoic acid	[148]
Cranberry pomace	PFE	cyanidin 3-galactoside, cyanidin 3-glucoside, cyanidin 3-arabinoside, peonidin 3-galactoside, peonidin 3-glucoside, peonidin 3-arabinoside	[149]
Blueberry pomace	UAE	malvidin, delphinidin, petunidin, cyanidin	[150]

Melon seed	solvent extraction	caffeic acid, protocatechuic acid, GA, rosmarinic acid, luteolin-7-*O*-glycoside, naringenin, apigenin, oleuropein, lignans, pinoresinol, amentoflavone	[151]
Pomegranate peel	UAE/PLE	α punicalagin, β punicalagin, pedunculagin I, ellagic acid, ellagic acid pentoside, ellagic acid hexoside, ellagic acid deoxyhexoside,	[152]
Pomegranate peel	PLE	ellagic acid, GA, punicalagin B, punicalagin A,	[153]
Sour cherry pomace	MAE	vannilic, epicatechin, syringic, gentisic, quercitrin	[154]
Kiwifruit pomace	PHWE	(+)-catechin, protocatechuic acid, chlorogenic acid, caffeic acid, p-coumaric acid,	[155]
pineapple peel	solvent extraction	catechin, epicatechin, gallic acid, ferulic acid	[156]

5. Polyphenols in tissue engineering

Millions of people around the world suffer from tissue loss or organ failure [157] with the general treatment approach being tissue or organ transplantation therapy. This treatment is however limited by the number of donor resources and a myriad of issues associated with tissue or organ recovery such as organ rejection [158]. To address this issue, an acceptable alternative therapy, tissue engineering, has been recognized for the repair and replacement of injured, lost, and diseased tissues in the past decades [159, 160] via the construction of new tissue or organs by integrating the components of proteins, cells and scaffold to help the restoration of structure and functionality of the tissue [161]. Fabrication of bioactive scaffold is the key element in tissue regeneration because it performs a role similar to the function of the Extracellular Matrix (ECM) in natural tissues. Nanomaterial including nanoparticles can be employed to develop an inorganic/organic scaffold that can be a substitute for fabricating a novel biomaterial for bone tissue regeneration [162, 163]. For example, silver nanoparticle (AgNPs) has highlighted their effective role in the regeneration process by enhancing biocompatibility osteoinductivity, and antibacterial activity when coated or combined with polymers, however, the safety of AgNPs which are influenced by the synthesis methods can be deleterious for biological systems [163, 164]. Recently, the utilization of biological synthesis (green synthesis) for the fabrication of AgNPs has attracted attention where a study by Ahmadov et al. showed the successful synthesis of AgNPs by a plant extract containing different PPCs which could be utilized as nanoparticle-antioxidant as nano-drugs for tissue regeneration [165].

Bioactive scaffold regulates the function of cells in the structure, their accumulation, and growth while also supporting their attachments, proliferation, and differentiation [166]. Different kinds of biomaterials have been employed for the fabrication of a scaffold that endows this important bioactive characteristic, however, due to the limitations such as weak hydrophilicity, lack of cell binding sites, and biological signals recognized in the ECM, when common synthetic polymeric biomaterials are used,

novel bioactive compounds such as PPCs, that may be incorporated with the scaffold, have generated significant interest [10, 167, 168].

PPCs are considered potential compounds for the fabrication of a bioactive scaffold since they have shown to reduce oxidative stress by quenching excessive ROS in the inflammatory stage and also reduce the inflammatory responses owing to their antioxidant property [169, 170]. They also possess multiple functional groups that can be employed as cross-linker agents, which interact efficiently with various biomolecules through covalent and non-covalent interactions [171]. Fig. 5 depicts the covalent and non-covalent interactions of polyphenol-functionalized biomaterial and antioxidant mechanisms. Understanding the interactions that exist between PPCs and biomaterial constitutes an important criteria when the structure and properties of the biomaterial are designed and modified for tissue engineering applications [172]. Due to the need to decipher these interactions, previous works have proposed the utilisation of computational modeling approaches to enable the precise identification the nature of intermolecular interactions between PPC and biomaterials [172-174]. For instance, computational docking simulations showed the interaction of tannic acid (TA) with COL through hydrogen bonding and hydrophobic interaction which could provide thermal and enzymatic stability for COL [172].

PPCs can therefore participate in improving the scaffold's mechanical and biological properties, and enzymatic resistance as well as acting as a stabilizer for fixing bioactive molecules in the scaffold as demonstrated in the literature [175-178]. For instance, in the research by Kim et al., a composite film of gelatin (GEL) and chitosan (CHS) was crosslinked by PA. The results indicated enhanced in biological and mechanical properties of the film when PA was incorporated. The mechanical properties improved due to the interactions between the functional hydroxyl group of PA and the carboxyl groups of GEL to form multiple covalent ester linkages. The PA/GEL/CHS film also displayed improved thermal and water stability (pH of 4 and 7), low degradation rate by digestive enzymes, enhanced elasticity, flexibility, and stiffness as well as increased fibroblast cell adhesion and proliferation suggesting it as a bioactive promising biomaterial for tissue engineering applications [175].

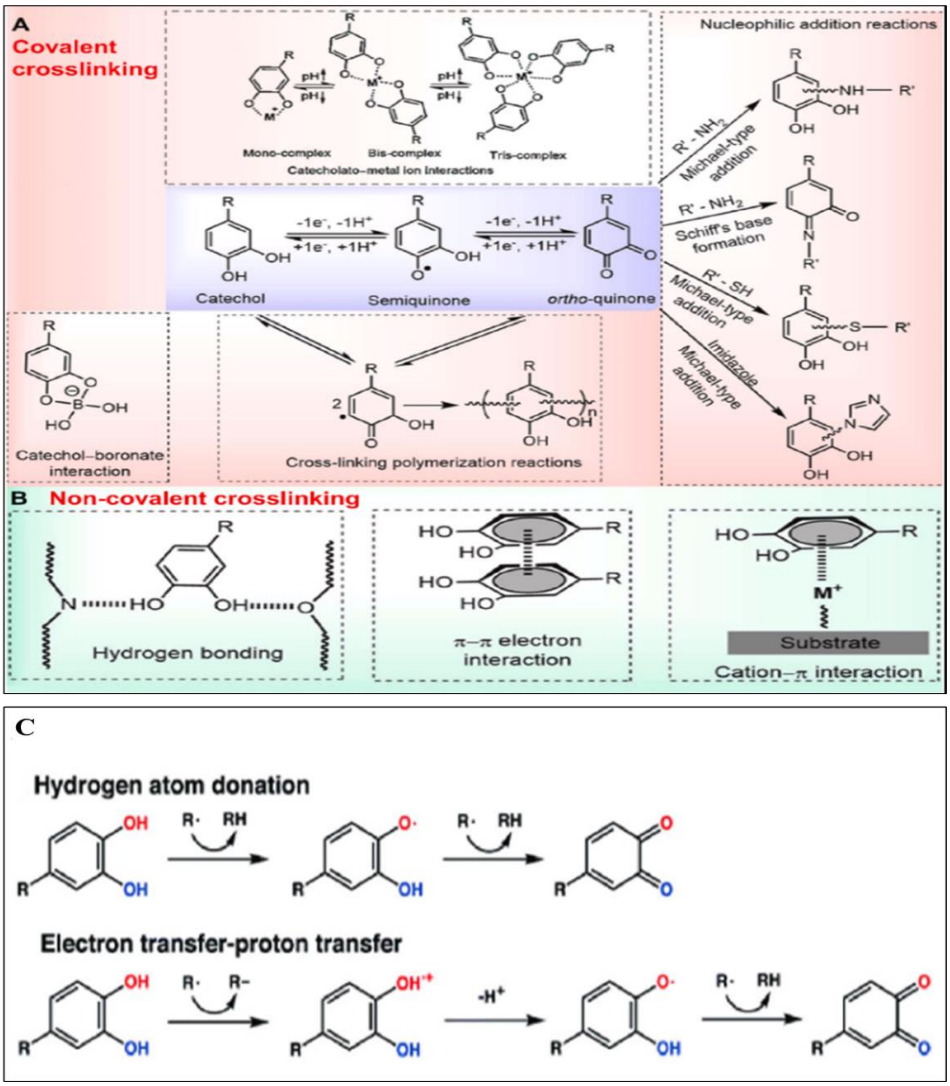

Fig. 5. Schematic illustration of (A) covalent and (B) non-covalent crosslinking interactions in polyphenol-functionalized materials. (C) Schematic representation of two mechanisms of polyphenols' free radical scavenging activity: hydrogen atom donation and electron transfer-proton transfer. R•: free radical [179].

The unique structure enables the PPCs to participate in various signal transduction pathways necessary for tissue regeneration processes [180]. Therefore, besides the mentioned advantages, as well as antimicrobial, bio-adhesive activities, biocompatibility, and a wide range of available sources, PPCs have been applied as a favorable bioactive agent for the fabrication of different types of biomaterials for tissue regeneration applications such as wound, bone, nerve, vascular and heart valve repair (Fig. 6) [22, 39, 181-183]. In a study by Riccucci et al., polyphenol extract from GP (skin and seed) was grafted on the CHS-coated HA to investigate its release in two aqueous biological media of phosphate buffer saline (PBS) and simulated inflammatory condition (H_2O_2). The results showed that the release behavior of the PPC was influenced by the pH of the solution which release of PPC initiated when the polyphenol-grafted scaffold was introduced to a simulated inflammatory media at a pH of 4.5. The CHS-HA grafted PA scaffold also exhibited antioxidant activity of ~ 86% and ~73% after soaking in PBS and H_2O_2,

respectively, and 78% without immersion in media, indicating the presence of the outermost layer of the grafted PPCs on the surface of the sample. It was found that the polymeric structure and pH could affect the release of PPCs and the antioxidant activity degree of a polyphenol-functionalized scaffold. Indeed interaction of PPCs with the polymeric structure can be useful for the reduction of inflammatory risks [184]. Regarding the prominent effect on bone healing, the following sections discuss the different roles of PPCs when they participate in the fabrication of polyphenol-functionalized scaffolds for BTE applications.

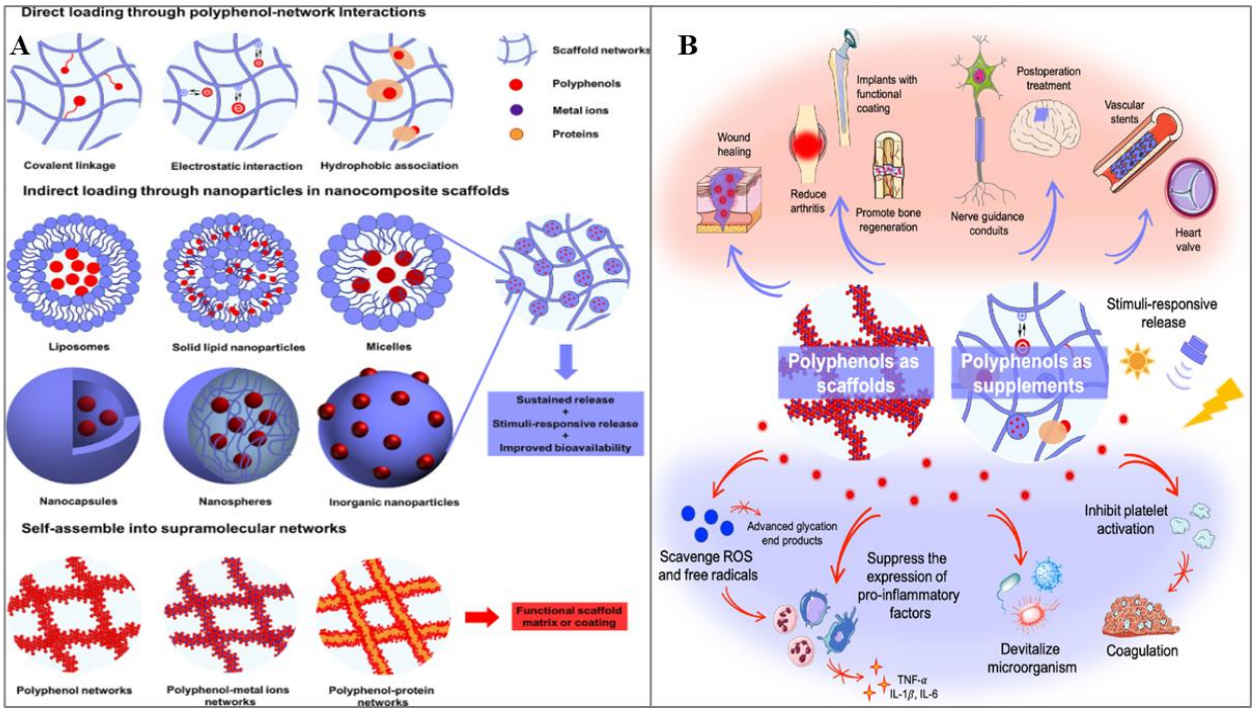

Fig. 6. (A) Schematic illustration of PPCs delivery approaches in tissue engineering. (B) The role of PPCs in modulating microenvironment through different functions and their wide applications in tissue engineering. Reproduced with permission from [39]. Copyright 2021, Elsevier.

6. Polyphenol-functionalized scaffold for BTE application

Bone is a vascularized connective tissue with unique biological and mechanical properties. It is mainly composed of a collagen (COL) matrix with nanocrystals of HA which are settled into the pores of the COL matrix [185, 186]. Remodeling of bone tissue continuously promotes the retention of the structural integrity of bone [187]. This vital process is undertaken through the action of different bone cellular systems including osteoblasts-bone forming cells which are responsible for the storage of minerals, coating of the bone surfaces and synthesis of organic matrix and its secretion, osteoclasts-bone resorbing cells with the action of collagenases and hydrolases enzymes and hydrogen ions which digest the bone structure and dissolve the calcium crystals and osteocytes cells [187, 188].

However, the normal process of bone tissue remodeling, which is a balance between formation and resorption processes, is disrupted in the presence of different bone tissue defects which may occur due to congenital malformations, trauma, infections, and surgery [189]. Although autologous and allogeneic bone grafts are functional when utilized in filling the voids in critical-sized bone defects, their use has been limited due to several issues such as the increased risk of infection, slow biointegration, and risk of immune reactions [190]. Therefore, in an effort to find a suitable solution for bone defects, bone scaffolds have been developed. Bone scaffolds have shown their efficiency in bone tissue regeneration by providing a porous structure for cell activities such as cell attachment, migration, and proliferation which are also biodegradable and biocompatible with suitable mechanical properties [191, 192].

Bioactive phytochemicals such as PPCs are incorporated in bone scaffolds to improve the bioactivity properties of the scaffold [22, 183, 193]. These compounds have shown their proficiency in enhancing new bone formation through various actions such as their influence on different cell signaling pathways [194]. For example, Qu has shown its positive effect on bone health via different mechanisms including the promotion of osteogenesis, angiogenesis, antioxidant expression, adipocyte apoptosis, and osteoclast apoptosis as well as inhibition of oxidative stress, inflammatory response, osteoclastogenesis, and osteoblast apoptosis [195]. In this section, we discuss the utilization of PPCs for designing the bioactive scaffolds for BTE applications which are also summarized in Table 2.

Table 2. Summary of studies of the influence of polyphenol-functionalized scaffolds on bone tissue regeneration.

Polyphenol	Scaffold	Structure	Fabrication method	Outcomes	Reference
Qu	GEL/tragacanth/HA/Qu	Polyphenol-coated sponge	Loading of 50 µM Qu solution on the freeze-dried scaffold	Sustained release of Qu, increased viability, proliferation, differentiation, ALP activity, and expression of different osteogenic genes of hBMSCs cells	[196]
Qu	Decellularized goat lung tissue/HA/Qu	Polyphenol-crosslinked sponge	Crosslinking of the scaffold by adding 10 µM Qu solution to the scaffold	Enhanced the growth, proliferation, differentiation, and mineralization of BMMSCs cells	[197]
Qu	PLLA/PDA/Qu	Polyphenol-coated 3D printed scaffold	FDM 3D printing of PLLA scaffold, functionalized with PDA and coated with 100, 200, and 400 µM Qu solution	Promoted the proliferation, osteogenic differentiation, and mineralization of MC3T3-E1 cells, increased hydrophilicity of PLLA, enhanced cell affinity and adhesion	[198]
Qu	SF/HA/Qu	Polyphenol-incorporated sponge	Mixing Qu solution (0.03, 0.05, 0.1 wt %) with 3 wt % SF solution, freeze-dried and coated with HA	Increased adhesion, proliferation, ALP activity, osteogenic differentiation of BMSCs cells, improved closure of bone defect	[199]
Qu	DC COL/HA/Qu	Polyphenol-incorporated sponge	Mixing Qu solution (0, 25, 50, 100 µM) with 2%	Increased adhesion, proliferation, ALP activity, osteogenic differentiation of BMSCs cells, improved closure of bone defect	[200]

			COL solution, freeze-dried and coated with HA		
Qu	MSCS/PCL/Qu	Polyphenol-incorporated 3D printed scaffold	3D printing of Qu/MSCS/PCL solution with 0:50:50, 1:49:50, and 2:48:50 ratios	Improved adhesion, proliferation, and mineralization of WJMSCs cells, HA crystal formation on the scaffold surface	[201]
TA	POC/HA/TA	Polyphenol-coated film	Mixing of TA/HA particles with POC	Improved compression strength of the scaffold, enhanced proliferation, adhesion of hMSCs cells, HA crystallization, enhanced formation of new bone	[202]
TA	SF/HA/TA	Polyphenol-incorporated hydrogel	Mixing of TA/HA complex solution with SF solution	Strong toughness of the hydrogel, new bone formation, antibacterial activity	[203]
TA	SF/E7 peptide/TA	Polyphenol-incorporated hydrogel	Mixing SF, TA, and E7 solution, enzymatic crosslinking	Enhanced viscosity, hydrophilicity, and decreased weight loss of the hydrogel increased the release time of E7, enhanced DPPH radical scavenging activity, increased cell viability, enhanced new bone formation	[204]
EGCG	GEL/EGCG	Polyphenol-incorporated sponge	Mixing of Gel with EGCG and chemical agent - Chemical and non-chemical modified methods	More retention of EGCG in the modified chemical sponge, new bone formation	[205]
EGCG	SIS fibers/ EGCG	Polyphenol-crosslinked fiber	Crosslinking of fiber by immersing in EGCG solution	Enhanced mechanical and hydrophilicity of the fiber, improved osteogenic differentiation of MC3T3-E1 cells, new bone formation	[206]

			(0.1, 0.25, 0.5, 1, 2 wt%)		
EGCG	PVDF/POSS/EGCG	Polyphenol-incorporated electrospun nanofibers	Electrospinning of mixed solution of PVDF and POSS-EGCG conjugate	Enhanced osteoblast cell survival, proliferation, differentiation, ALP activity, calcium deposition, and decreased production of the inflammatory cytokine IL-6	[207]
EGCG	DC COL/HA/EGCG	Polyphenol-incorporated sponge	Mixing of EGCG (1, 5, 10 μM) solution with 2% COL solution, freeze-dried and coated with HA	Enhanced mechanical strength of the sponge, improved cell viability, osteoinductivity, and mineralization of BMSCs cells	[208]
GA	PCL/SrF2/GA	Polyphenol-incorporated electrospun nanofiber	Electrospinning of PCL solution with SrF2 NPs, grafting nanofiber with GA by immersing in GA solution	Increased water absorption capacity, facilitated the release of Sr^{2+}, promoted adhesion, penetration, and proliferation of hMSCs cells, improved HA formation, ALP activity, and antibacterial activity	[209]
NG	SF/HA/GMs/NG	Polyphenol loaded into GMs - encapsulated in SF/HA scaffold	Adding NG to the crosslinked lyophilized GMs, Mixing HA, GMs/NG, and SF solutions	Enhanced proliferation, adhesion, osteogenic differentiation, and mineralization of BMSCs cells, enhanced new bone formation	[210]
NG	SA/HA/NG	Polyphenol-incorporated 3D printed scaffold	Preparation of ink with the mixing of HA with NG, the addition of SA to the HA/NG	Continuous releases of NG, improved proliferation and osteogenic differentiation of BMSCs cells, HA formation, enhanced new bone formation	[191]

			solution, the printing of the SA/HA/NG ink		
IC	CHS/HA/IC	Polyphenol-incorporated scaffold	Mixing IC solution and CHS, addition of $Ca(NO_3)_2$ and KH_2PO_4 to the CHS/IC solution	Promoted adhesion, osteogenic differentiation, and ALP activity of the MSCs cells, no alteration in mechanical and morphological properties of the scaffold	[211]
OPA	COL/OPA	Polyphenol-crosslinked film	Addition of different concentrations of OPA solution to the COL solution	Enhanced mechanical property and decreased degradability of the film, new bone formation, enhanced growth of L929 and MG-63 cells	[67]
Catechin	PCL/catechin	Polyphenol-coated nanofiber	Immersion of PCL nanofiber in catechin solution	Enhanced attachment, spreading, and proliferation of hADSCs cells, increased osteogenic differentiation of cells and mineralization, enhanced new bone formation	[212]
PCA	CA/Zn^{2+}/PCA	Polyphenol-coated membrane	Addition of $ZnCl_2$ to the PCA solution, immersion of CA membrane to the PCA/$ZnCl_2$ solution	Enhanced DPPH and PTIO radical scavenging activity, increased expression of osteogenesis genes, improved calcium deposition and ALP activity	[213]
CUR and GIN	COL/HA/CUR COL/HA/GIN	Polyphenol-incorporated scaffold	Addition of HA to the COL solution, mixing of GIN or CUR with the COL/HA solution	Increased viability and osteogenic differentiation of SM-MSCs cells and HA formation, reduced inflammation, enhanced mechanical strength of the scaffolds	[214]

Longan seed polyphenolic extract	CHS/SS/ß-GP/polyphenolic extract	Polyphenol-incorporated hydrogel	Mixing of CHS and SS solutions, the addition of ß-GP to the CHS/SS mixture, the addition of polyphenolic extract to the CHS/SS/ß-GP solution	Improved attachment and viability of MC3T3-E1 cells	[215]

ALP: alkaline phosphatase, PLLA: poly(L-lactide), PDA: polydopamine, SF: silk fibroin, DC COL: duck's feet collagen, MSCS: calcium silicate calcium sulfate, SIS: intestinal submucosa, PCL: polycaprolactone, EGCG: epigallocatechin gallate, PVDF: poly (vinylidene fluoride), POSS: polyhedral oligomeric silsesquioxane, NG: naringin, GMs: gelatin microsphere, SA: sodium alginate, IC: icariin, OPA: oligomeric proanthocyanidins, PCA: protocatechualdehyde, CA: cellulose acetate, CUR: curcumin, GIN: ginger, SS: silk sericin, ß-GP: ß-glycerophosphate.

6.1 Polyphenols as a drug for BTE

Oxidative stress has been recognized as one of the reasons for bone mass loss [216]. Phytochemicals such as PPCs with potent antioxidant activity have demonstrated their potential in the treatment of bone mass losses due to their positive influence on different osteoblast cell mechanisms, which are responsible for new bone tissue formation [186]. Therefore, the utilization of various PPCs as a potential drug for the fabrication of a polyphenol-functionalized scaffold has been investigated. For instance, in Madani et al.'s study, a GEL/tragacanth/HA scaffold was fabricated and loaded with Qu to examine its biological activities and impact on bone regeneration. Sustained release of Qu was obtained in which 93% was released after 120 h. Qu-loaded scaffold showed higher hBMSCs cell viability, proliferation, differentiation, and ALP activity compared to the control (culture plate), Qu-only, and non-Qu loaded scaffolds. Moreover, Qu increased the expression of different osteogenic genes of hBMSCs cells resulting in improved osteogenic activity and cell differentiation in the Qu-loaded scaffold compared to the unloaded scaffold [196].

In another study, a thermosensitive hydrogel containing CHS, SS, and ß-GP was developed, and polyphenolic extract from Longan (*Dimocarpus longan Lour*.) seed containing high content of GA (~13 mg/g) and ellagic acid (~26 mg/g) was then loaded into the hydrogel. The research exhibited that the cumulative release of PPCs depended on the hydrogel's structure and its degradation behavior, and the incorporation of SS increased the percentage of the drug release. Moreover, the improved attachment of the mouse osteoblast cell (MC3T3-E1) on the hydrogel surface loaded with polyphenolic extract and high cell viability of more than 70% also highlighted the promising potential of the polyphenol-functionalized thermosensitive hydrogel for bone tissue repair [215].

Honda et al. prepared two types of vacuum-heated EGCG/GEL sponges such that one was chemically modified with 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4 methylmorpholinium chloride (DMT-MM) and N-methylmorpholine (NMM) and the other one was not modified, to assess their potential for bone defect formation. The results showed that EGCG in non-chemical modified GEL sponge was released quickly within 1 hour; however, the chemically modified sponge could retain 75 % of EGCG for up to 24h. The critical-sized defects (9 mm) of rat calvaria could be completely covered with newly formed bone within 4 weeks after implantation of chemically modified EGCG/GEL sponge in the defect, and its effect was greater than the non-chemical modified sponge. Interestingly, the new-formed bone showed similar bone quality (the mineral density of bone and maturation of COL) in two groups of EGCG/GEL sponges [205].

Another study showed that IC, a plant-derived flavonol glycoside, could promote bone regeneration when loaded into a CHS/nano HA (IC/CHS/HA) composite. The release of IC happened in a continuous and controlled way based on the degradation kinetics of both CHS and HA. The presence of IC in the composite promoted the adhesion, osteogenic differentiation, and ALP activity of the seeded

Mesenchymal stem cell **(**MSCs) without considerably altering the composite's mechanical strength and morphological (porosity) properties [211]. NG, a polymethoxylated flavonoid, is another PPC that was reported to promote bone regeneration when loaded into GMs that are encapsulated in SF/HA (SF/HA) composite scaffold. The NG/GM/HA/SF scaffold provided higher proliferation, adhesion, osteogenic differentiation, and mineralization of rat bone marrow stromal cells (BMSCs) (Fig. 7) and resulted in greater bone formation in lumbar vertebrae critical size defect of osteoporotic rats likely due to the continuous release of NG [210].

Another study by Liang et al. showed that a 3D-printed SA/HA hydrogel loaded with NG (SA/HA/NG) was an effective drug for bone tissue repair, with mineral formation observed on the scaffold surface accompanied by continuous and stable releases of NG. The SA/HA/NG scaffold was cytocompatible and improved the osteogenic differentiation and proliferation of BMSCs. It also had higher potential in bone tissue repair of full-thickness defects in the calvarial bone of the beagle compared to the SA/HA scaffold, highlighting the enhanced osteogenesis and osteointegration of the NG-loaded scaffold [191].

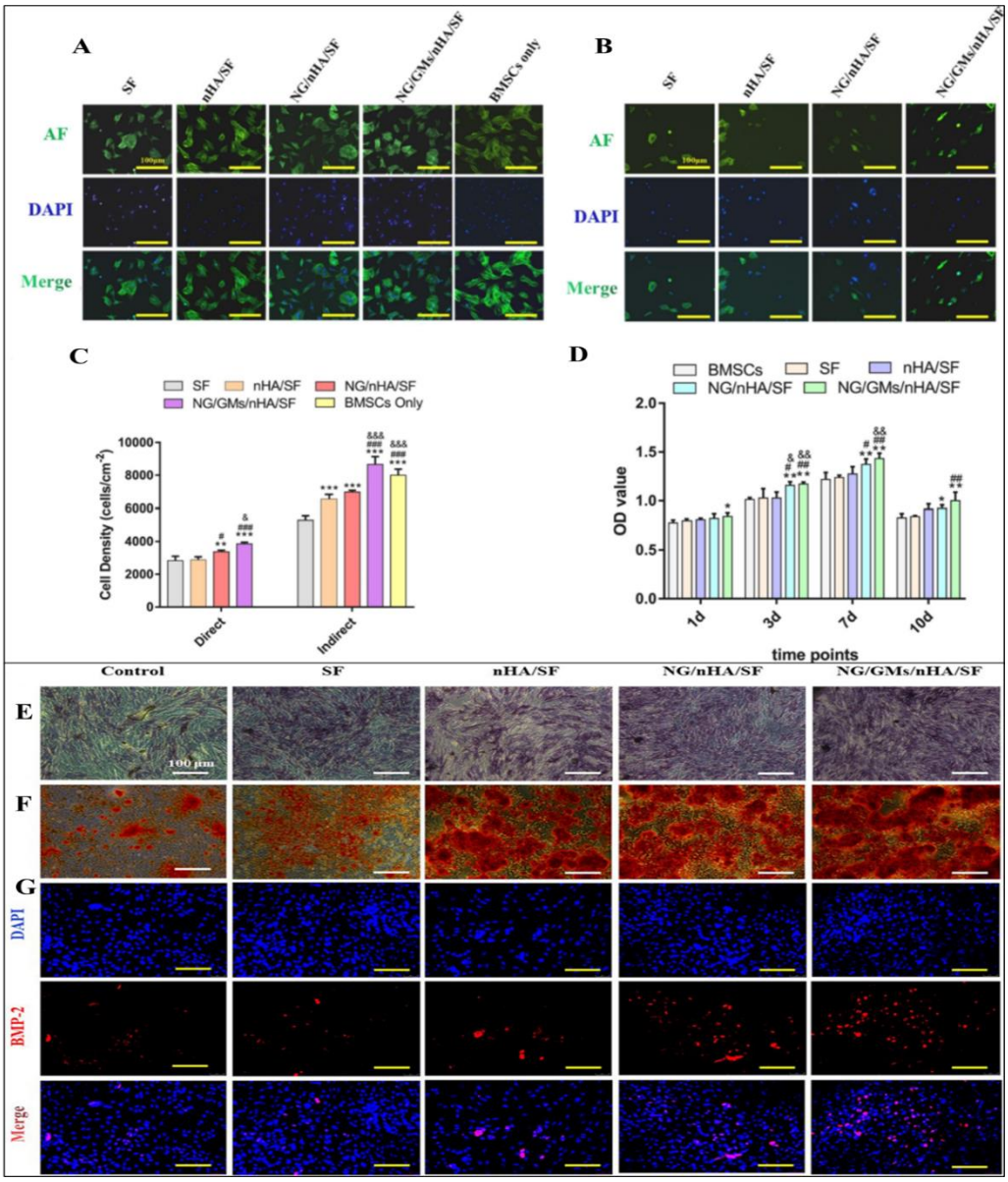

Fig. 7. Schematic representation of the immunofluorescence images showing the (A) indirect cell adhesion around the scaffolds and (B) direct cell adhesion on the scaffolds' surfaces. (C) Analysis quantitively of the cell numbers adhered directly and indirectly in the scaffolds. (D) Results of BMSCs proliferation on the scaffolds tested at different time points. (E-G) Schematic representation of osteogenesis of BMSCs affected by the scaffold composition determined by different analyses including (E) ALP staining at 7 days, (F) Alizarin Red staining at 14 days, and (G) BMP-2 protein expression at 14 days by immunofluorescence assays. Blue (DAPI) and red staining were employed for the detection of the nucleus and BMP-2, respectively. Reproduced with permission from [210]. Copyright 2021, Elsevier.

6.2 Polyphenol as a crosslinker and surface modifier for BTE

Crosslinking is an effective approach for modifying the various properties of the biomaterial. PPCs have been successfully applied as a crosslinking agent to improve several properties of the materials such as mechanical properties [206, 217]. Thanks to the presence of functional groups of pyrogallol and

catechol, PPCs can make different covalent interactions including polyphenol-metal coordination and Michael addition/Schiff-base reaction, and non-covalent interactions such as π-π interactions, cation-π interaction and hydrogen bonding with various kinds of molecules [179]. For instance, Gou et al. demonstrated that EGCG could be employed for the crosslinking of SIS fibers to improve its mechanical and biological properties while enhancing hydrophilicity for better cell adhesion. Indeed, the study showed that EGCG-crosslinked fibers presented an improved osteogenic differentiation of MC3T3-E1 cells and accelerated bone healing in a rat critical skull defect (5 mm) [206].

In another study by Chen et al., OPA employed to crosslink GEL/tricalcium phosphate porous scaffold could enhance the stability of the scaffold and improve the rates of MG-63 cell proliferation. Additionally, a BMSCs-seeded scaffold could successfully fill the rat calvarial bone defect and form the new bone after 8 weeks [218]. Gupta et al. fabricated a scaffold from decellularized goat lung tissue and then crosslinked it with Qu. *In silico* docking and binding study confirmed the crosslinking of COL molecules of decellularized goat lung tissue with Qu through hydrogen and hydrophobic bonds between the Qu and COL structure. The addition of Qu enhanced the growth, proliferation, differentiation, and mineralization of bone marrow mesenchymal stromal cells (BMMSCs) cells compared to other tested scaffolds without HA or Qu, indicating the synergetic effect of Qu and HA on the metabolic activity of the cells highlighting its potential for the regeneration of bone [197]. OPA were utilized for crosslinking COL type 1 film in a study by Li et al. Among different COL films, 10% OPA crosslinked film, demonstrated better mechanical and biological properties and remained stable after 50 days. Moreover, two different cell lines of L929 and MG-63 could well spread and expand on the surfaces of 10% OPA-crosslinked COL film. New bone formation was also detected in a rat calvarial bone defect [67].

Surface modification has been considered an important strategy for enhancing the functionality of the biomaterial applied in tissue engineering [212, 219]. Surface properties is an important parameter that affects the biological characteristic of a biomaterial. Physical properties such as hydrophobicity, hydrophilicity, elasticity, surface roughness, surface structure and geometry, and chemical properties of a biomaterial surface influence cellular functions such as cell attachment, migration, differentiation, and proliferation [220]. Surface modification through bioactive coating has attracted great attention because of its influence on regulating biological processes, modulating cell behavior, and effective interaction with biomolecules [221].

PPCs due to their catechol and galloyl groups can form a successful coating on the surface of a material through crosslinking and covalent and noncovalent interactions [222] that can interact with cell surface molecules, serum proteins, and immobilized bioactive molecules resulting in enhanced cell adhesion and proliferation [223]. For instance, PCL nanofibers were surface functionalized with catechin hydrate in which two catechin molecules were self-assembled physically with Na^+ ion through cation-π interaction. Catechin coating enhanced the attachment and spreading of human adipose-derived stem

cells (hADSCs) resulting in improved cell proliferation. PCL/catechin nanofiber treated with H_2O_2 (oxidative reagent) could promote cell viability due to the catechin potential in scavenging ROS (reduction of oxidative stress of the cells) which increased osteogenic differentiation of cells and improved mineralization. Furthermore, the PCL/catechin scaffold exhibited the highest volume of new bone regeneration with the greatest mineral density and COL deposition compared to uncoated PCL and in mouse calvarial bone defect after 8 weeks (Fig. 8A) [212].

In a study by Guo et al. TA and HA nanoparticles were employed to functionalize POC polymer. TA was covalently bonded to the citrate-based polymer (POC) which was coated on the surface of HA. The improved compression strength of citrate-based tannin-bridged composite was observed indicating the effective role of TA in making successful interactions between organic (POC) and inorganic (HA) phases. Moreover, HA crystallization (biomineralization), hMSCs cell proliferation, and adhesion were enhanced when TA composites were utilized compared to the control (without TA). Favorable osteoconductivity and osteoinductivity of the TA composite also resulted in the enhanced formation of new bone, fibrous tissue in-growth, and cartilage tissue in the lumbar fusion defect model of rabbit [202]. In a study by Bai et al. TA was utilized to fabricate a bone adhesive hydrogel comprising SF and HA (SF/HA). SF/TA/HA hydrogel showed strong toughness which could be attributed to the metal-phenol complex between TA and Ca^{2+} ions of HA and the cross-linking of SF molecule with TA (Fig. 8B). The new bone with higher bone volume and bone mineral density was formed in a critical-sized femoral defect of a rat model when SF/TA/HA hydrogel was utilized compared to the control. Moreover, SF/TA/HA hydrogel demonstrated antibacterial activity against *E. coli* and *S. aureus* which could relate to the antimicrobial activity of the TA [203].

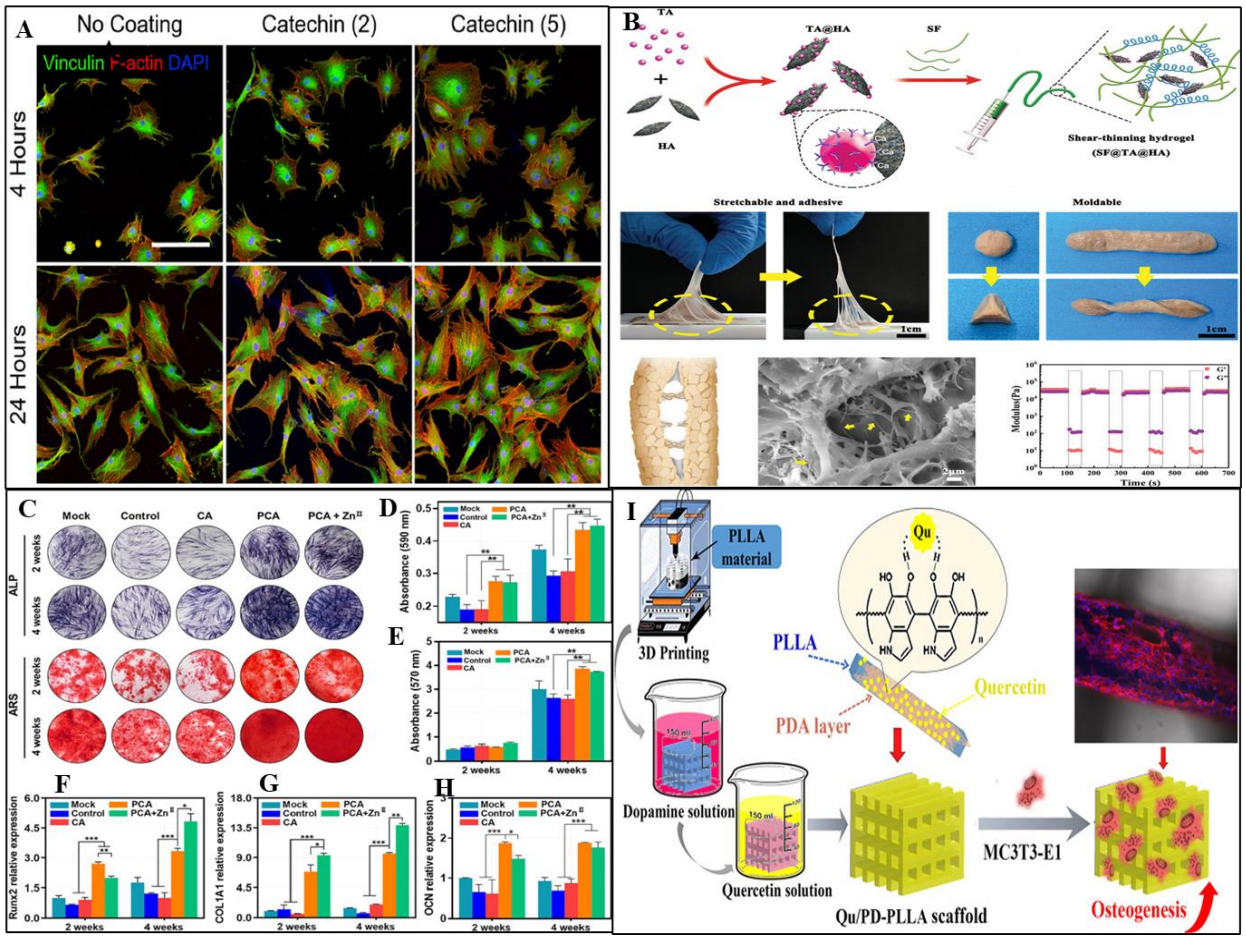

Fig. 8. (A) Schematic description of immunofluorescent staining test for the evaluation of viability and proliferation of hADSCs on uncoated and catechin-coated (2 and 5 mg/mL) scaffolds. Reproduced with permission from [212]. Copyright 2017, American Chemical Society. (B) Schematic illustration of an adhesive SF/TA/HA hydrogel for bone fracture repair showing the shapeable and moldable behaviors, mineralized COL fibrils interconnected by glue filaments, and rheological behavior of the hydrogel. Reproduced with permission from [203]. Copyright 2019, John Wiley and Sons. (C) Schematic illustration of ALP and ARS staining of PCA/CA and PCA/CA/Zn^{2+} membranes (D-E) quantitative analysis of PDLSCs cells cultured by conditioned medium; (F-H) expression of different osteogenesis-related genes of PDLSCs after 2 and 4 weeks of incubation. Reproduced with permission from [213]. Copyright 2023, Elsevier. (I) Schematic illustration of fabrication procedure of the 3D printed PLLA/PDA/Qu scaffold. Reproduced with permission from [198]. Copyright 2019, American Chemical Society.

To improve the bioactivity of the CA membrane for bone healing application, PCA in combination with Zn^{2+} was utilized to modify the surface of the polymer membrane. PCA/CA membrane showed slow release (< 20%) of PCA during 5 days, and DPPH and PTIO radical scavenging activity of the PCA/CA and PCA/CA/Zn^{2+} membranes were higher than the CA membrane. Moreover, PCA/CA/Zn^{2+} membranes could induce considerable anti-inflammatory properties by decreasing the level of the inflammatory cytokine genes. Calcium deposition and ALP activity showed improved levels in modified membranes compared to unmodified which was attributed to the increased osteogenesis-associated gene

expression such as BMP-2, OCN, and Runx2 in cells on PCA-modified membranes (Fig. 8C-H) [213]. Chen et al. fabricated a 3D-printed PLLA scaffold which was surface functionalized with different concentrations of Qu with the aid of a PDA layer. Qu could be immobilized successfully on the scaffold by the formation of covalent and noncovalent interaction with PDA. Increase in MC3T3-E1 cell proliferation, osteogenic differentiation, and mineralization was observed in a dose-dependent manner when PLLA/PDA/Qu scaffold was employed. The hydrophilicity of the PLLA scaffold was also increased when loaded with Qu and PDA leading to the enhancement in cell affinity and adhesion to the scaffold (Fig. 8I) [198].

6.3 Miscellaneous function of polyphenols for BTE

PPCs in addition to their mentioned properties for BTE, have demonstrated other effective roles such as anti-inflammatory, antioxidant, antibacterial, and promotion of mechanical properties when they are incorporated into a bone scaffold material. For example, TA was incorporated into SF to fabricate a polyphenol-functionalized scaffold (SF/TA) to evaluate its potential to suppress oxidative stress to enhance osteochondral defect regeneration. SF/TA hydrogel was also loaded with a therapeutic molecule (E7, EPLQLKM) as a BMSC-specific affinity peptide. TA enhanced the viscosity and hydrophilicity of the SF/TA hydrogel due to the hydrogen bond interactions between TA and water. The weight loss of SF/TA after 88 days was about 15% which was comparable to the SF weight loss (~16%). TA increased the release time of E7 which was 43.84% after 21 days. Moreover, SF/TA hydrogel showed higher DPPH radical scavenging activity (76.34%) compared to SF hydrogel (35.86%). Higher cell viability (more than 95%) and superior efficiencies in repairing cartilage and subchondral bone defect was observed in using SF/TA and SF/TA/E7 hydrogels compared to SF hydrogel which could relate to the alleviation of ROS oxidative stress of cells (Fig. 9A-I) [204].

The extract of GIN and CUR were utilized to enhance the functionality of the COL/HA scaffold. The bioactivity of the scaffold was improved when 10% CUR and 5% GIN were added to the scaffold, leading to increased sedimentation of HA crystals compared to scaffolds without CUR and GIN. In addition, CUR and GIN extracts exhibited their potential in increasing the viability and osteogenic differentiation of synovial membrane mesenchymal stem cells (SM-MSCs) in GIN/COL/HA and CUR/COL/HA scaffolds, surpassing the performance of the COL-only scaffold. Implantation of CUR/COL/HA and GIN/COL/HA scaffolds in a rat animal model resulted in reduced inflammation compared to the control scaffold over an 8- to 12-week period. Moreover, the CUR/COL/HA exhibited enhanced mechanical strength, as evidenced by improved modulus, tensile strength, and elongation properties. (Fig. 9J-K) [214].

In two studies, Qu was incorporated into SF/HA [199] and DC COL/HA sponges at different concentrations [200]. The results demonstrated the dose-dependent potential of Qu in promoting bone tissue recovery. Qu stimulated the osteogenic differentiation of BMSCs cells, leading to enhanced

adhesion, proliferation, ALP activity, and closure of bone defects in the Qu-functionalized scaffolds (Fig. 9L-N). Another study by Huang et al. showed that when Qu was incorporated into a 3D printed scaffold of PCL/MSCS, the adhesion, proliferation, and mineralization of jelly mesenchymal stem cells (WJMSCs) was improved, with apatite crystal formation observed on the scaffold surfaces. (Fig. 9O) [201]. Pishva et al. developed a PCL electrospun nanofiber scaffold functionalized with GA and loaded with strontium fluoride (SrF2) nanoparticles. The incorporation of GA promoted the adhesion, penetration, and proliferation of hMSCs by increasing water absorption capacity and facilitating the release of Sr^{2+}. Additionally, the GA/Sr^{2+}/PCL nanofiber scaffold exhibited improved apatite formation, ALP activity, biomineralization, and antibacterial activity against *P. aeruginosa* [209].

In another study, electrospun nanofibers of PVDF were fabricated with different concentrations of POSS–EGCG [207]. The incorporation of EGCG enhanced osteoblast cell survival, reduced osteoblastic apoptosis, and promoted cell proliferation, differentiation, ALP activity, calcium deposition, and decreased production of the inflammatory cytokine IL-6. The scaffold with the highest concentration of EGCG demonstrated the most pronounced effects, indicating its effectiveness in bone tissue regeneration. Kook et al. also utilized EGCG with different concentrations of 1 μM, 5 μM, and 10 μM to prepare a composite sponge of EGCG/DC COL/HA. The incorporation of EGCG led to the enhanced mechanical strength of the sponges, achieved through the formation of more compact and dense pores, resulting in higher compressive strength. The EGCG concentration of 5 μM promoted superior cell viability, osteoinductivity, and mineralization of BMSCs compared to other EGCG-loaded and DC COL/HA sponges [208].

Dziadek et al. fabricated a composite biofilm with PCL/bioactive glass functionalized with extracted PPCs from sage (*Salvia officinalis L.*) for bone tissue repair. The incorporation of sage PPCs altered multiple properties of the biofilm, including antioxidant and bacterial inhibitory effects against Gram-positive (*S. aureus*) and Gram-negative (*P. aeruginosa*) bacteria. The lowest concentration of PPCs exhibited cytocompatibility, enhanced ALP activity, and expression of bone extracellular matrix proteins. The PPCs also improved the biofilm's apatite-forming ability and plasticizing characteristics. [224]. These studies highlight the potential of PPCs, such as TA, CUR, GIN, Qu, GA, and EGCG, for improving the properties and functionality of scaffolds applied in BTE.

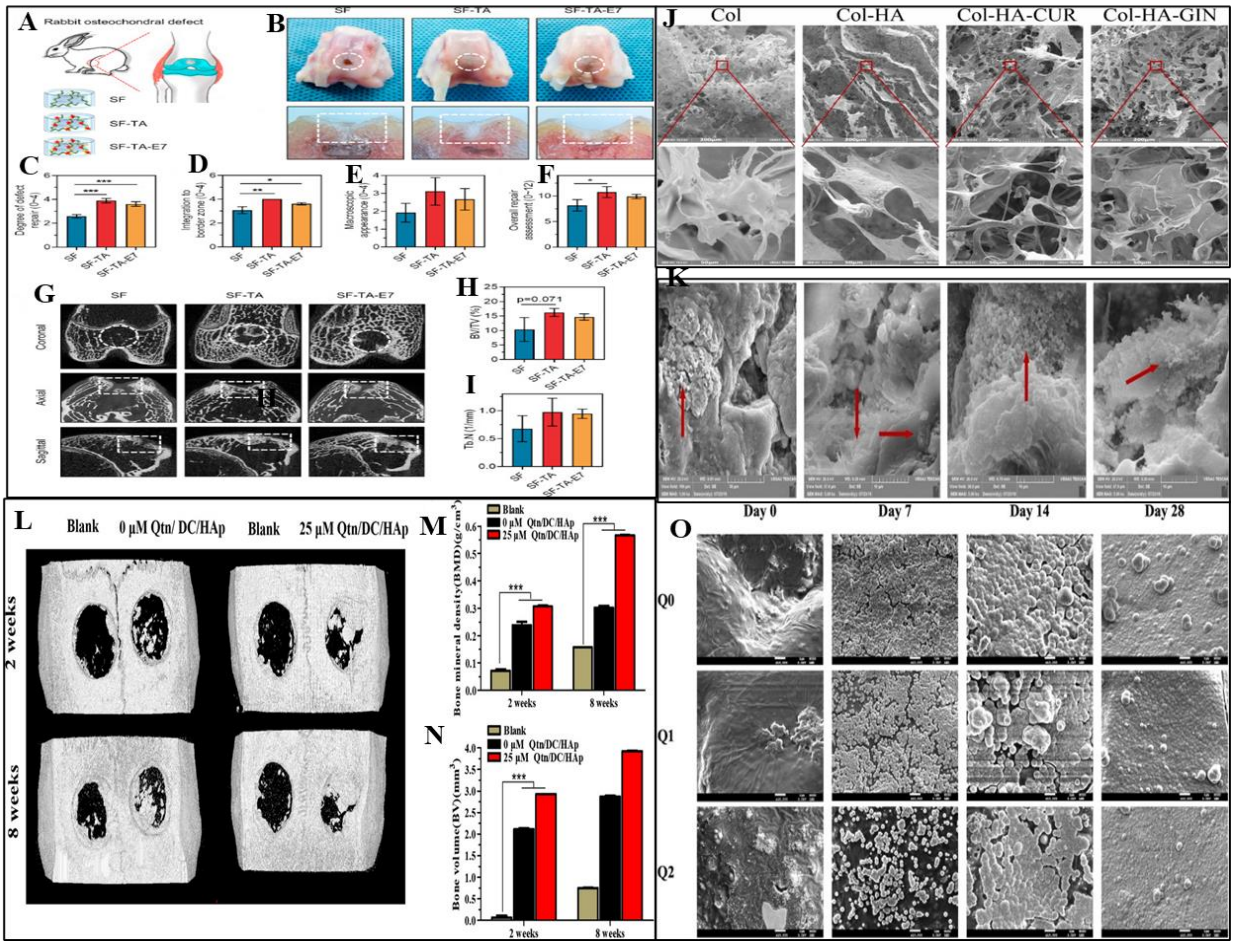

Fig. 9. (A) Schematic illustration of implantation of SF, SF/TA, and SF/TA/E7 hydrogels into the osteochondral defect of rabbit. (B) Images of osteochondral repair by showing gross morphology of joint samples and cross-sectional views after 12 weeks of implantation of three groups of hydrogels. (C-F) Quantitative sub-item scores of hydrogels according to the ICRS scoring system. (G) Images of coronal, axial, and sagittal planes taken by micro-CT (H-I). Quantitative analysis of the repaired subchondral bone defect using micro-CT method by investigating (H) BV/TV (%) and (I) Tb. N parameters. Reproduced with permission from [204]. Copyright 2022, Elsevier. (J-K) Schematic illustration of SEM images obtained (J) before and (K) after immersion of COL, COL/HA, CUR/COL/HA, and GIN/COL/HA scaffolds in SBF solution during 4 weeks for assessing the biomineralization potential of scaffolds (HA crystals were indicated in red arrows). Reproduced with permission from [214]. Copyright 2022, Elsevier. (L) Schematic illustration of formed new bone in SD-Rat cranial defect after implantation of Qu/DC/HA scaffold during 2 and 8 weeks analyzed by micro-CT analysis. (M-N) Micro-CT quantitative analysis of the repaired bone, including (M) bone mineral density (BMD) and (N) bone volume. Reproduced with permission from [200]. Copyright 2020, John Wiley and Sons. (O) Schematic representation of FE-SEM images of formed HA crystals on the surface of Qu/MSCS/PCL scaffold after immersion in SBF solution during different time points. Reproduced with permission from [201]. Copyright 2021, Elsevier.

7. Conclusion and future perspectives

The fabrication of a bioactive tissue-engineered scaffold has attracted considerable attention due to its potential as an alternative approach compared to autografts, allografts, and synthetic materials for repairing tissue or organ defects. This is because bioactive tissue-engineered scaffolds are endowed with different favorable characteristics such as antioxidant, antibacterial, and anti-inflammatory properties. PPCs, well-known for their inherent favorable biological properties, can be incorporated into the scaffold to fabricate these bioactive scaffolds. Indeed, numerous studies have demonstrated the positive influence of PPCs on healing rates in tissues or organs. In this review, the vast array of the roles of PPCs for bone tissue regeneration, ranging from participating in different bone healing mechanisms, such as influencing cell process (proliferation, differentiation, migration, etc.) to acting as crosslinking agent, antioxidant, anti-inflammatory and antibacterial properties, were discussed. Moreover, this review provided an overview of the potential of fruit waste-derived PPCs in bone tissue regeneration because of their uniquely favorable biological activities, biocompatibility, etc.

A review of the literature exhibited that commercial PPCs were mainly employed for the fabrication of a polyphenol-functionalized bone scaffold, and PPCs that can be recovered from wastes have not been comprehensively explored. However, multiple studies have reported that agricultural wastes, particularly fruit wastes are comprised of various PPCs, with desirable properties that provide a promising basis for their implementation in tissue engineering. These waste sources are readily available and constitute cost-effective sources for the extraction of PPCs, with desirable biological activities that can be applied for the fabrication of a bioactive bone scaffold. In recent decades, waste-derived biomaterials have gained their place for application in tissue engineering while they showed their effective role in agricultural waste management thus helping the environmental sustainability.

However, several challenges may limit the use of polyphenol-derived fruit wastes in tissue regeneration such as safety issues and toxicity of the extracted PPCs, waste collection, extraction, and purification complexities as well as low yields. It is proposed that these obstacles can be solved via the integration of green extraction approaches and process optimization strategies for enhanced recovery while also employing in vitro and in vivo experiments to establish safe cytotoxicity limits for waste-derived PPCs for tissue support and microenvironment for cell differentiation. Therefore, further efforts are essential to develop a cost-effective technology to transform fruit waste sources to the commercial value polyphenol-functionalized scaffold with high quality and performance. It is predicted that the future utilization of freely available fruit waste for the recovery of PPCs in future research for bioactive scaffold fabrication will mitigate environmental issues caused by significant fruit waste generation challenges, while simultaneously providing a therapeutic solution for bone tissue regeneration. In summary, the polyphenol-functionalized bone tissue-engineered scaffold constitutes a promising research direction, with more research in the area required. It is therefore anticipated that the review will

inspire further investigations in the development of polyphenol-functionalized bone tissue-engineered scaffolds.

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Conflicts of Interest

The authors declare no conflict of interest.

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