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Prospects of Polycaprolactone-Based Nanocomposite Porous Scaffolds for Sustained Release of Flavonoids in Bone Tissue Engineering

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Abstract: ***Current therapeutic limitations of bone graft substitutes drive the development of multifunctional grafts where the bioactive flavonoids with osteogenic potential can be incorporated into three-dimensional porous bone regeneration scaffolds. The aim of this review is to explore the possibility of fabricating nanocomposite scaffolds incorporated with widely available and non-toxic flavonoid formulation for repair and regeneration of bone tissue. This review summarizes different bone regeneration strategies based on porous scaffolds and provides an overview of the most widely preferred methods for obtaining porous polycaprolactone scaffolds. Further, we intend to outline flavonoids and their classification, and have listed a few of them used for in vitro bone tissue engineering applications. Finally, we aim to show the prospects of flavonoids to be incorporated into nanocomposite porous scaffolds based on polycaprolactone for sustained release of flavonoids to enhance bone regeneration.***
Keywords: ***Nanocomposite scaffolds, Polycaprolactone, Flavonoids, Bone tissue engineering, Drug delivery, Porous scaffolds***

I. INTRODUCTION

Bone is a mineralized connective tissue that performs numerous important functions in the body including hematopoeisis, vital organs protection, mineral homeostasis and musculoskeletal mechanical support [1], [2]. The bone's self-renewal capability allows spontaneous scar-free healing [3], [4]. For patients with critical size bone defects, intrinsic bone self-healing ability is limited and invasive surgical procedures are needed to restore the structural integrity of the damaged bone [4]–[6]. Autografts (from the person's own body) and allografts (from human cadavers or living donors) are widely used to treat large bone defects, but they show the following drawbacks, such as donor-site morbidity and limited availability, and the risk of disease transmission [7]–[10]. Metallic implants (joint prostheses, plates and screws) commonly used to provide structural and mechanical assistance for joint arthroplasties and long bone and spine fractures, but these are limited due to non-degradability, poor host tissue integration, high rigidity, extrusion and infection [11]. In order to overcome conventional implant limitations, bone tissue engineering (BTE) has emerged as a promising strategy for bone reconstitution [12], [13]. BTE strategies include either the use of scaffold alone, or a combination of scaffold and bioactive molecules, or a combination of scaffold and harvested cells (stem cells are harvested from various types of tissues), or a combination of scaffold, harvested cells and bioactive molecules, or a combination of scaffold and differentiated cells (differentiated osteoblasts from harvested cells), or a combination of scaffold, differentiated cells and bioactive molecules (Fig. 1) [2], [6], [14]–[18].

II. POLYCAPROLACTONE (PCL): A BIOMATERIAL FOR BTE APPLICATIONS

PCL is synthetic biodegradable aliphatic polyester approved by the Food and Drug Administration, used as scaffolds or as bone tissue supports in medical applications [19]–[21].

III. SYNTHESIS OF PCL

PCL can be synthesized either by polycondensation of 6-hydroxyhexanoic acid (forms low molecular weight PCL) or by radical ring-opening polymerization of 2-methylene-1,3-dioxepane (forms amorphous PCL) or by ring-opening polymerization (ROP) of ε-caprolactone (forms high molecular weight PCL with low polydispersity) (Fig. 2) [22]–[24]. High molecular weight PCL is needed for scaffolds and implants to maintain the material's stability for months or years; hence, ROP is the preferred method of synthesizing PCL with high molecular weight and low polydispersity [25], [26]. The ROP process includes four general mechanisms (anionic, cationic, monomer-activated and coordination-insertion), each affecting the resulting molecular weight and its distribution, the end group composition and the copolymer structure [26]. Different catalytic systems, such as metal, organic and enzymatic, support the mechanisms involved in ROP, where stannous (II) 2-ethylhexanoate is the most frequently used catalyst with high efficacy and low toxicity in ROP [20], [23].

IV. PHYSICOCHEMICAL CHARACTERISTICS AND BIODEGRADATION OF PCL

PCL, a biodegradable and biocompatible polymer with a glass transition temperature of around –60ºC and a melting point of 59ºC–64ºC [27], [28]. At ambient temperature, PCL is soluble in dichloromethane, chloroform, benzene, carbon tetrachloride, toluene, 2-nitropropane and cyclohexanone; slightly soluble in ethyl acetate, acetone, 2-butanone, acetonitrile and dimethylformamide; and insoluble in water, alcohols, diethyl ether and petroleum ether [23]. Depending on molecular weight, degree of crystallinity and conditions of degradation, PCL degrades within several months to several years [20], [29]. From the degradation studies reported in the literature it can be inferred that PCL undergoes a two-stage degradation process, (i) non-enzymatic hydrolytic breakdown of ester bonds in the amorphous region results in mass loss and subsequent increase in crystallinity; (ii) intracellular degradation occurs when the molecular weight of PCL is low (less than 3000) and highly crystalline [20], [30]. The biodegradation of polymer leads to fragmented materials by the action of living organisms until the complete decomposition to carbon dioxide and water [31].

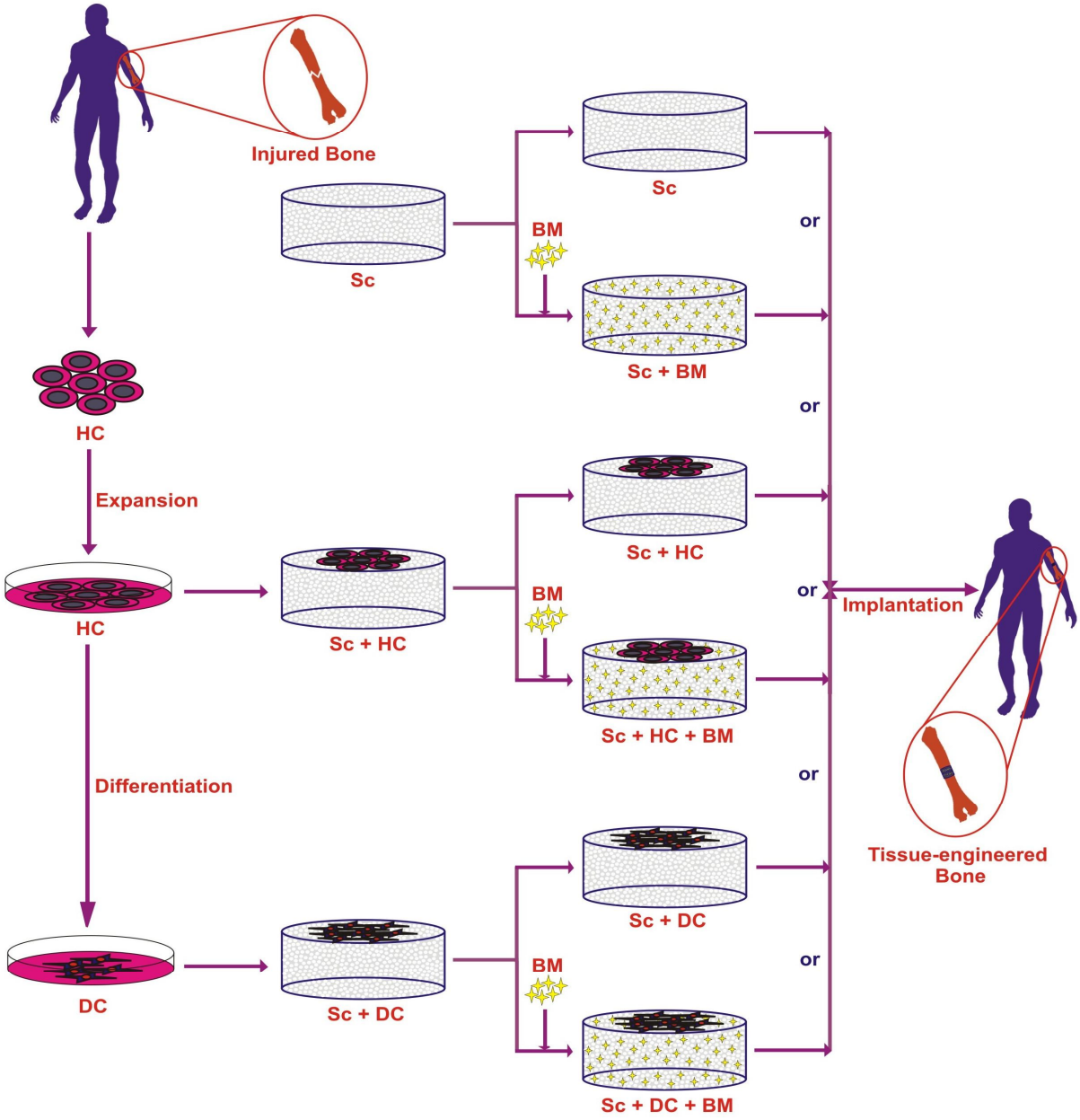

Fig. 1 Schematic illustration of porous scaffold-assisted different bone tissue engineering strategies. Where, Sc – Scaffold; HC – Harvested cells; DC – Differentiated cells; BM – Bioactive molecules.

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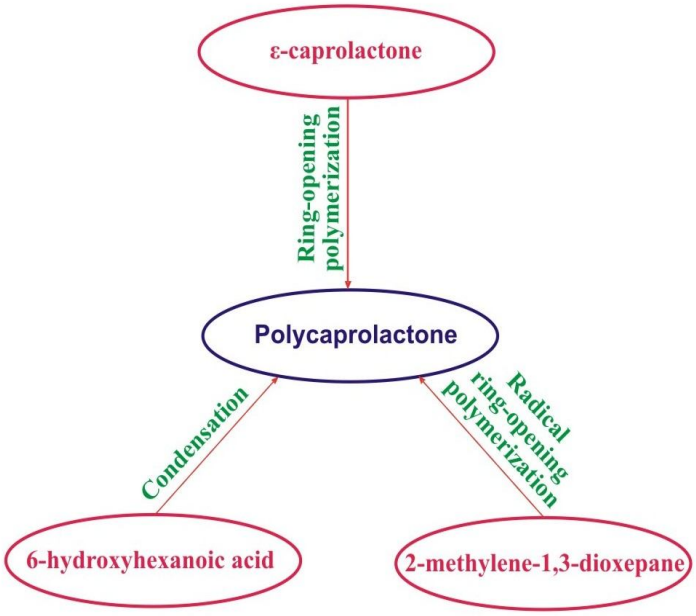

Fig. 2 Schematic showing methods of polycaprolactone synthesis.

V. POROUS PCL SCAFFOLD FABRICATION METHODS

Different methods have been reported for preparing porous PCL scaffolds [32], and Fig. 3 shows few commonly used fabrication methods.

A. Solvent Casting and Particulate Leaching

Solvent casting and particulate leaching is one of the most common techniques used for the preparation of porous PCL scaffolds [33]. This technique consists of four steps, (i) homogeneous dispersion of porogens in a polymer solution; (ii) pouring the mixture obtained into the mold; (iii) removal of the solvent from the solution by evaporation; and (iv) immersion of the polymer/porogen composite into water or a suitable solvent to leach porogens [34]. Scaffold pore size and porosity can be controlled by the size and amount of porogens used [35]–[37]. In addition to its simplicity, some challenges are associated with solvent casting and particulate leaching method, such as the solvent removal mechanism may lead to dimensional shrinkage or solvent trapping inside the samples [34].

B. Gas Foaming and Particulate Leaching

Gas foaming technique allows to fabricate solvent-free porous scaffolds, and pores are formed by gas expansion in a polymer [36], [38]. Carbon dioxide, a low-toxic and non-flammable gas used as a porogen gas [36]. In this method, there are three basic steps, (i) polymer plasticization because of the diffusion of carbon dioxide into the polymer matrix with increasing pressure; (ii) nucleation of gas bubbles due to depressurization and supersaturation; and (iii) nucleation growth because of the diffusion of gas from the surrounding polymer [39]. However, interconnectivity remains limited and is mostly combined with particulate leaching to increase porous interconnectivity [38].

C. Freeze Extraction

Freeze extraction, a simple and energy-efficient process does not require special equipment to prepare the scaffolds and allows modification of certain factors affecting the structure [40], [41]. This process involves three basic steps, (i) pour the polymer solution prepared into a mold and freeze; (ii) immerse the frozen polymer solution into a suitable pre-cooled extractive solvent (a polymer non-solvent) at a temperature equal to or less, to extract the solvent used to dissolve the polymer; (iii) after extraction, dry the scaffold obtained at room temperature to eliminate the extractive solvent [42]–[45]. By modifying the polymer concentration, solvent / non-solvent ratio, freezing temperature and time, and the cooling rate may lead to porous structures with distinctive morphologies adapted to the target application [43], [46], [47].

D. Extrusion-based Cryogenic 3D Printing

Extrusion-based cryogenic 3D printing is considered an advanced 3D printing process for fabricating BTE scaffolds with the capability to deliver biomolecules [48]. There are three basic steps in this method, (i) prepare the printing ink by dissolving the polymer in a suitable solvent and loading it into a syringe; (ii) fix the polymer solution loaded syringe with motor-driven piston in the extrusion chamber to adjust flow rate (BTE scaffolds can be printed and stabilized by adjusting the processing parameters (extrusion velocity, platform speed, cryogenic substrate temperature and nozzle diameter)); (iii) lyophilize the printed scaffold to eliminate the residual solvent and to obtain dried scaffolds [48], [49].

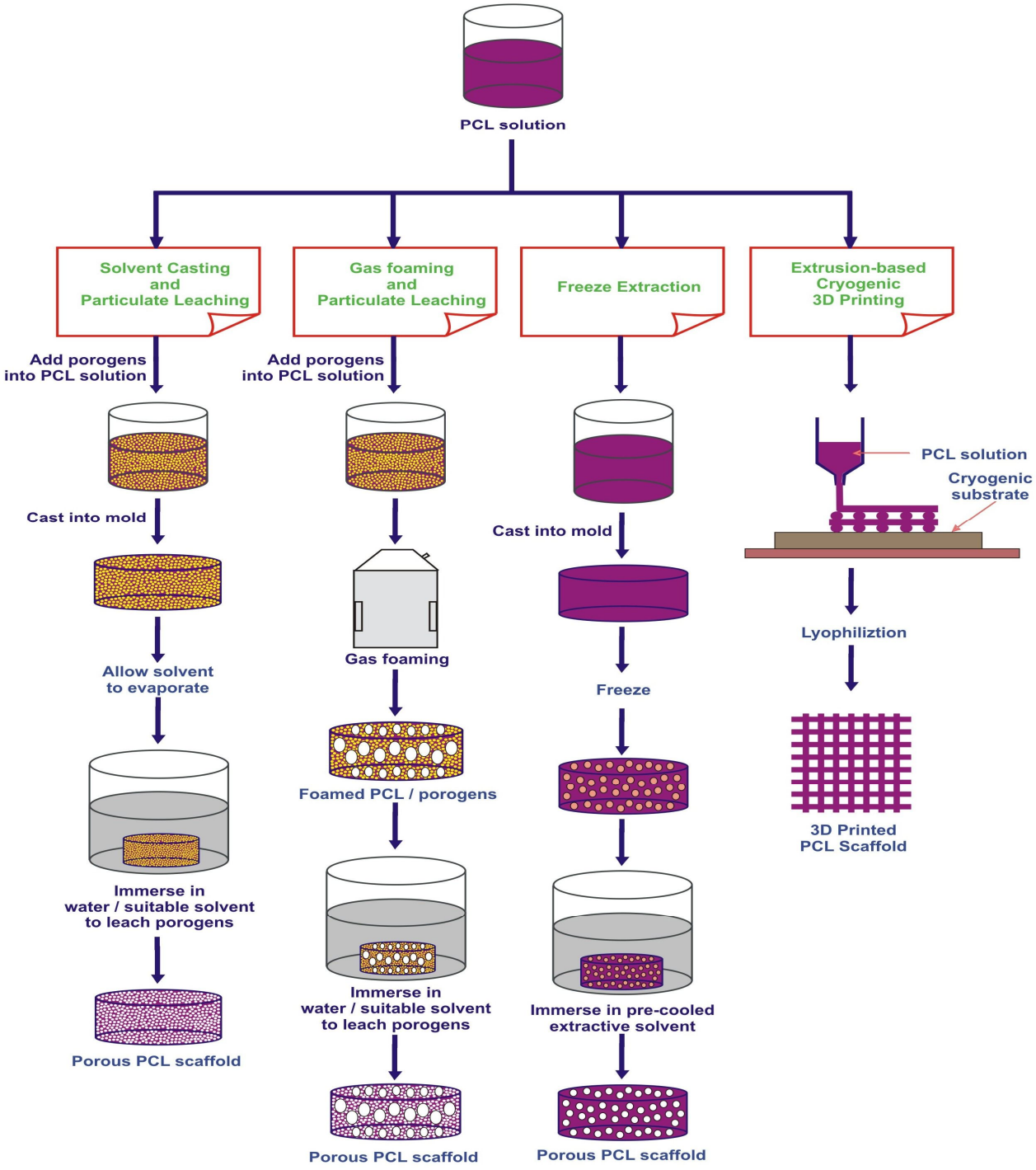

Fig. 3 Scheme of various methods to fabricate porous polycaprolactone scaffolds. Where, PCL – Polycaprolactone.

VI. FLAVONOIDS

Flavonoids are naturally available biologically active compounds that are an excellent source for drug discovery [50], [51]. The basic structure of flavonoids consists of two benzene rings (ring A and ring B), linked by three-carbon-ring (ring C) [52], [53]. Flavonoids are classified into different subclasses (Fig. 4), such as flavanones (naringin, hesperetin and naringenin), flavonols (quercetin, myricetin and kaempferol), flavones (apigenin, luteolin, chrysin and rutin), flavanols (catechin, epicatechin and epigallocatechin), isoflavones (genistein and daidzein) and anthocyanidins (cyanidin and delphinidin) [54]–[56]. Concerns regarding their wide-ranging bioactive benefits including anti-oxidant, anti-inflammatory, anti-viral/bacterial, anti-cancer, cardioprotective, anti-aging, anti-diabetic, have long been gained increasing attention and well-supported by several studies [52], [57], [58]. Table 1 lists a few flavonoids used for *in vitro* BTE applications.

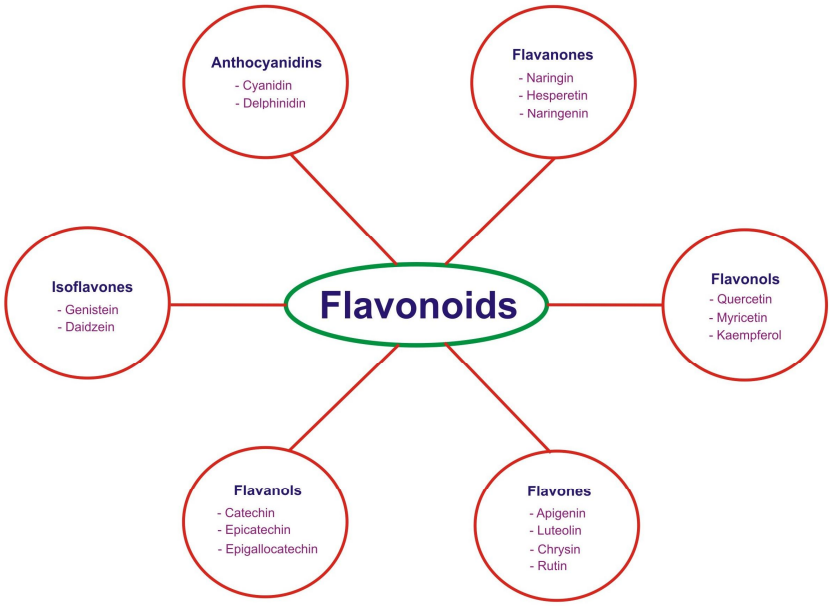

Fig. 4 Scheme showing classes and subclasses of flavonoids.

TABLE I
List Of A Few Flavonoids Used For *In Vitro* Bone Tissue Engineering Applications

Flavonoids	Cell line	References
Naringin	Human amniotic fluid-derived stem cells	[59]
	Human periodontal ligament stem cells	[60]
	Human bone marrow mesenchymal stem cells	[61], [62]
Hesperetin	Primary rat osteoblasts	[63]
	Human mesenchymal stem cells	[64]
Quercetin	Rat bone marrow-derived mesenchymal stem cells	[65]
	human adipose tissue-derived stromal cells	[66]
	Mouse adipose-derived stem cells	[67]
	Mouse bone marrow mesenchymal stem cells	[68]
	Mouse bone marrow derived mesenchymal stem cells	[69]
Myricetin	MG-63, hFOB	[70]
	Human bone marrow stromal cells	[71]
	Human periodontal ligament stem cells	[72]
Kaempferol	Human mesenchymal stromal cells	[73]
	Rat bone marrow stromal cells	[74]
	MC3T3-E1	[75]

Apigenin	Human fetal bone marrow-derived mesenchymal stem cells	[76]
Chrysin	MC3T3-E1	[77]
Rutin	Mouse bone marrow derived mesenchymal stem cells	[69]
	Periodontal ligament stem cells	[78]
Catechin	Human mesenchymal stem cells	[79]
Genistein	MG-63	[80]
	Human bone marrow cells	[81]
	Rat calvarial osteoblasts	[82]
Daidzein	Human mesenchymal stem cells	[83]
	MG-63	[84]

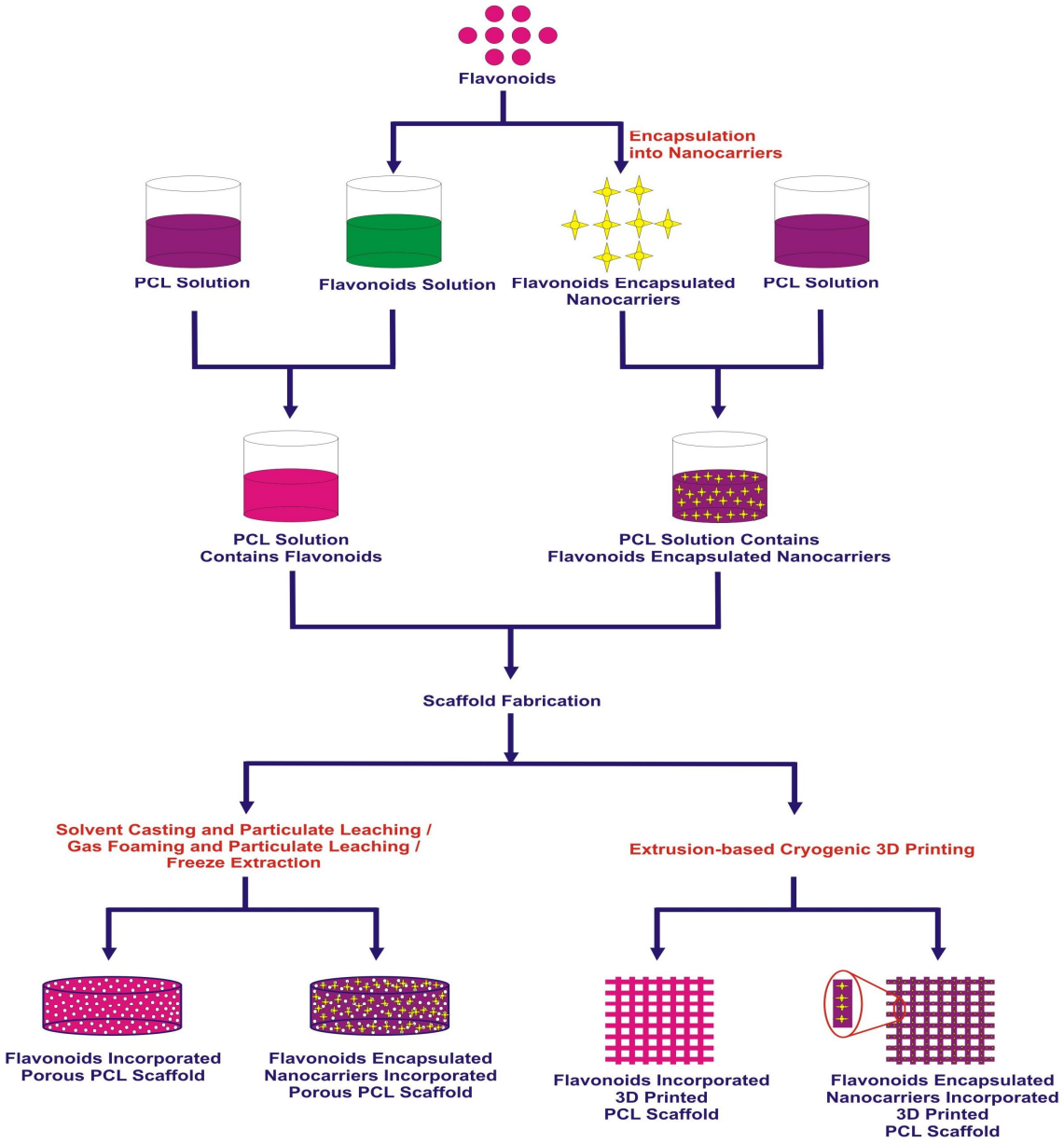

Fig. 5 Schematic showing the prospects of flavonoids to be incorporated into polycaprolactone porous scaffolds for sustained flavonoids release. Where, PCL – Polycaprolactone.

VII. PROSPECTS OF FLAVONOIDS RELEASE FROM POLYCAPROLACTONE-BASED NANOCOMPOSITE POROUS SCAFFOLD

The porous scaffolds fabricated using various methods could provide physical support for proliferation and differentiation of the cells, however, physical support alone is not adequate for ideal BTE applications [85]. A new generation of tissue engineering scaffolds strives to further enhance tissue regeneration by delivering bioactive molecules locally that are essential for natural bone formation [86]. The incorporation of bioactive flavonoids in porous scaffolds enables site-specific controlled drug delivery, which could further enhance bone repair or regeneration efficiency [85], [87]–[89].

Flavonoid delivery methods can rely on the incorporation of flavonoids within the scaffold or the use of nanoparticles as flavonoid reservoirs (Fig. 5) [86]. Drug delivery systems using various types of nanocarriers could improve the bioavailability, solubility, pharmacokinetics and site-specific controlled delivery of the encapsulated drugs [90]–[92]. Nanotechnology approaches in BTE help to overcome some of the limitations associated with inadequate mechanical strength of scaffolds [93]. The incorporation of nanoparticles into scaffolds has shown improvements in the mechanical strength of scaffolds [94], [95]. The encapsulation of flavonoids within nanoparticles, which then get delivered by scaffolds, would allow effective control of their release and achieve the sustained, long-term release profiles required for BTE applications [86], [96], [97].

VIII. CONCLUSION

Designing scaffolds that can mimic the extracellular matrix's three-dimensional structure and deliver bioactive molecules which favorably influence and regulate the cell response is of great importance in BTE applications [98], [99]. The use of porous scaffolds has become a more important aspect for treating bone defects [100]. Porous scaffold based on PCL have been extensively used for BTE applications due to its biodegradability, cost efficacy, tissue compatible and so on [101]. In this review, we highlighted different strategies based on porous scaffolds used for BTE. We also outlined flavonoids and its classification, and listed a few of them used in BTE applications. A growing interest has recently emerged in evaluating the potential of flavonoids to enhance bone repair or regeneration [82]. Further, we have attempted to show the possible ways for sustained flavonoids release from PCL-based nanocomposite porous scaffolds to enhance bone regeneration. The PCL porous scaffold with flavonoids encapsulated nanoparticles could be used in BTE applications as a promising bone grafting material.

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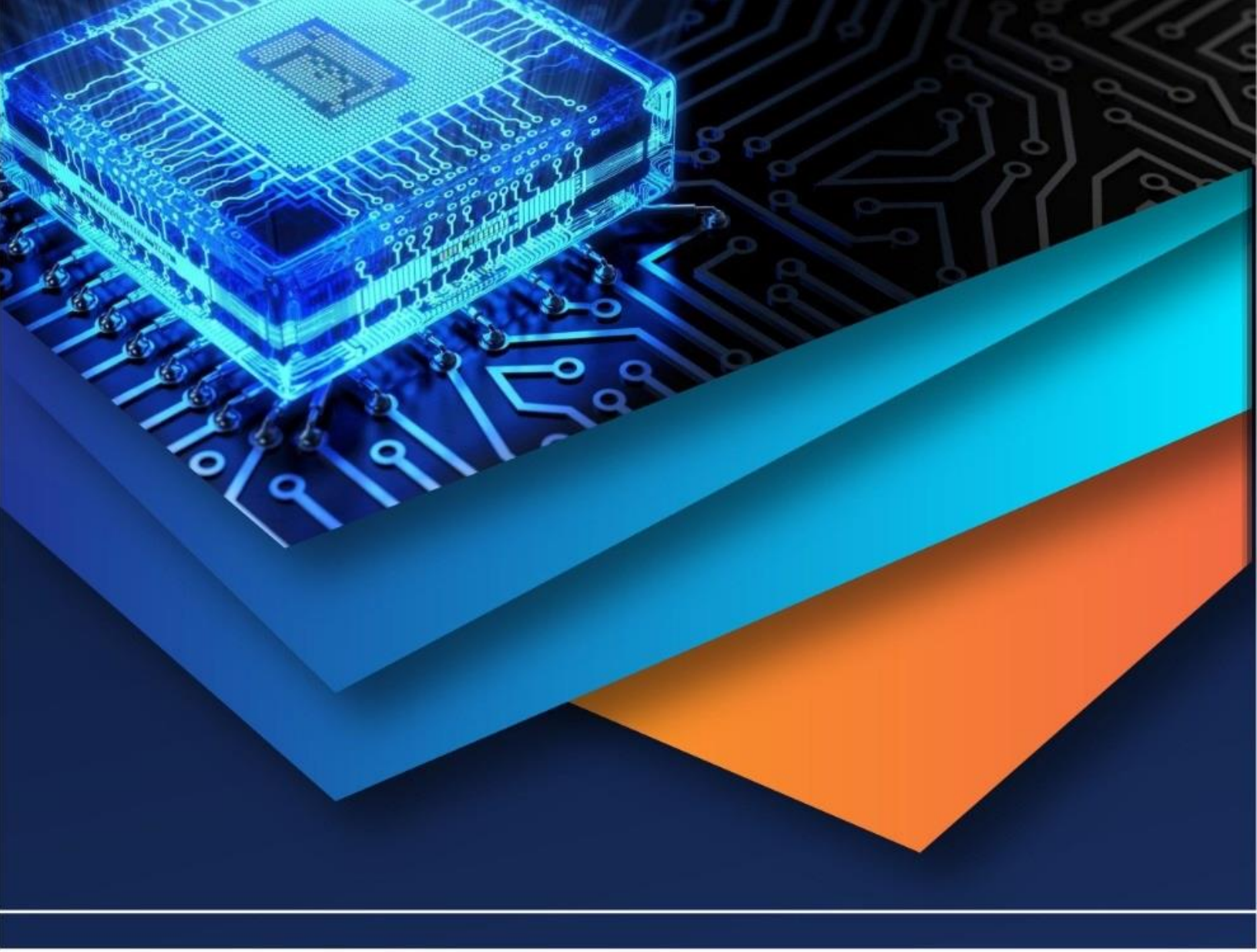

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