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Pharmacokinetics of bioactive plant-derived polysaccharides for enhanced drug release, stability, bioavailability and target specificity

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19.1 Introduction

Polysaccharides are the most naturally abundant macromolecular biopolymers, which exhibit significant biological and pharmaceutical functions and can be found in living organisms ranging from plants (pectin and gums) to algae (alginate), animals (chitosan), and microorganisms (dextran) [1–3]. They can be used as antioxidants/anticoagulants, antiviral/antimicrobial, antitumor/antidiabetic, antihypoglycaemic, immune regulatory, and immunomodulatory biological and pharmaceutical materials [4,5] which make them highly promising candidates for biotechnological, biomedical, and pharmaceutical applications [6,7]. Their vast physicochemical features, makes them susceptible to physical/chemical modifications which helps to improve their inherent properties toward ensuring high compatibilities for diverse applications such as in food packaging, energy, wood processing, paper production, textiles, fiber-manufacture, and petroleum production [8,9]. Due to the potential of polysaccharides, they are fast replacing traditional and conventional therapies for several diseases-applications. In spite of the aforementioned advantages of polysaccharides, some challenges associated with their nonmodified forms include low target-specificity, poor in vitro stability, low bifunctionality, poor absorption, and short-term storage in tissues. Hence, there is the need to modify them in order to enhance their worths. This informs why they are sometimes combined with other biomolecules, such as nucleotides, proteins, and nucleotides, as a means of improving their activities, in terms of their cell–cell communications, adhesion, and immune-related molecular recognitions [10]. Polysaccharides have also been reported to play significant roles in several tumor metastasis and physiological processes [11]. Their other functions include the provision of structural support, binding, protection, adhesion, responsiveness to stimuli, immune-boost, aversion of parthenogenesis, fertilization, blood clotting, fertilization, and therapeutics [12]. Polysaccharides such as pectin, amylose, inulin, guar gum, chondroitin sulfate and dextran

have also been reported to exhibit some forms of potency in colon-specific drug release (i.e., as prodrugs and tablet coatings) [13,14] alongside their tendencies to serve as pharmaceutical excipients [15].

Despite the widespread/bioavailability of polysaccharides, the intent of this discourse is on bioactive plant-derived polysaccharides, their drug release potential, target-specificity, and their pharmacokinetics.

19.2 Some bioactive plant-based polysaccharides, their bioavailability, stability, drug release, and target specificities

Plants, a treasure trove of many valuable chemicals, consisting of a variety of bioactive polysaccharides/biologically active materials. In lieu of the fact that 80% of the world's rural dwellers rely on primary healthcare systems [16], the use of medicinal plants for the treatment of human diseases and sicknesses is a present reality owing to the nonassociated side effects of these bioactive plant derivatives. Approximately 50% of drug prescriptions in Europe and America have their origin in plants and their derivatives such as polysaccharides [17,18]. Plants consist of over 200,000 phytochemicals [19] and about 25% of modern medicine (antimicrobial and antitumoral drugs) are directly/indirectly sourced from higher plants [20–22]. Also, of the 250,000–500,000 abundant plant species, only 1%–10% have been investigated for their chemical and pharmacological medicinal attributes [23], which then suggests that more work needs to be done to explore the potential of other plants as storage systems of useful medicinal bioactive components. Plant-derived bioactive materials present an attractive source of affordable natural materials/polysaccharides [24]. The sustenance/maintenance of good health is feasible owing to the possibility of integrating phytochemicals/bioactive plant-derived polysaccharides in the food chain. These biochemicals can also be used in the treatment of health disorders and diseases for which the world still struggles to find synthetic replacements of similar potency and pharmacological specificity. Also, the high cost of procuring nonorthodox drugs has caused the persistent wane in their demand, thus shifting reliance to traditional/orthodox bioactive plants with such potential. The potency of plant-based medicine relies on the quantitative bioavailability of bioactive compounds that can be targeted at specific organs or sites. Some bioactive plant-based polysaccharides for pharmacological/medicinal applications are detailed in the following sections.

19.2.1 2,3,5,4'-Tetrahydroxy-stilbene-2-O- β -D-glucoside

2,3,5,4'-Tetrahydroxy-stilbene-2-O- β -D-glucoside (THSG) is a bioactive polyhydroxystilbene sourced from *Polygonum multiflorum* Thunb [25,26]. It is a well-known edible tonic plant and a famous anti-aging dietary supplement [27] that is used to invigorate the kidneys/liver as well as expel toxins from the human blood [28–30]. THSG also offers antiinflammatory, antineurodegenerative, antiangiogenesis, hepatoprotective, antiatherogenic, antidiabetic, and neuroprotective effects [31,32]. Despite its therapeutic potentials, its poor stability (under constant irradiation, alkaline pH, high temperature, metal ions) [33,34], poor intestinal absorption, and poor durability/short-term storage in tissues are some of the challenges associated with the biopolymer [34]. When sourced from herbal plants, they

can be used as medicines/drugs or plant supplements in foods. However, owing to the need to improve their activities/performances, they are often coadministered with other active ingredients, although, their effects are yet to be studied or revealed by the current body of literature. Sun et al. [35] studied the effects of hybrid polymer composite of *Ophiopogon japonicus* polysaccharides (OJPs) blended with THSG. The results revealed that the OJPs significantly improved the solubility of THSG in aqueous solution and its biostability, however, they recorded a slight decrease in the permeability of the THSG. Fig. 19.1 illustrates the structural orientation of the THSG-OJP conjugate system, while Fig. 19.2 shows the different solubilities exhibited by the THSG-OJP conjugates in different proportions; the trend-wise increase in solubility is enhanced by the increased concentration of the polysaccharide with the 1:20 THSG:OJP giving the highest solubility in aqueous solution.

Furthermore, the time (T_{\max}) taken to attain maximum concentration (C_{\max}), as well as the area under the concentration–time curve (AUC_{0-t_n}) were found to be 3.5-, 1.45-, and 2.32-fold higher for the THSG-OJP relative to the pristine THSG, thus implying that OJPs have the potential to enhance biopharmaceutical characteristics and sustain the pharmacological influence of THSG when used as a drug. Table 19.1 contains data on kinetic parameters obtained for the influence of THSG-polysaccharide conjugate from *O. japonicus* on 2,3,5,4'-tetrahydroxy-stilbene-2-O- β -d-glucoside in vitro and in vivo.

Table 19.2 gives the pharmacokinetic parameters of the THSG-OJP conjugates in terms of maximum time, maximum concentration, and the areas under the concentration–time curve at 0– t_n to 0– t_∞ as well as their corresponding residence times.

Figs. 19.3A–D are kinetic illustrations of $\ln(c_t/c_0)$ versus time at different pH of the medium and irradiation, where c_t = concentration at time $t = t$, while c_0 = concentration at $t = 0$; these were used in generating the k -values indicated in Table 19.1.

19.2.2 Epigallocatechingallate

Epigallocatechingallate (EGCG) is a plant-based polysaccharide that has several health benefits owing to its ability to serve as an antioxidant, antitumorigenic, antiinflammatory, and antiangiogenic

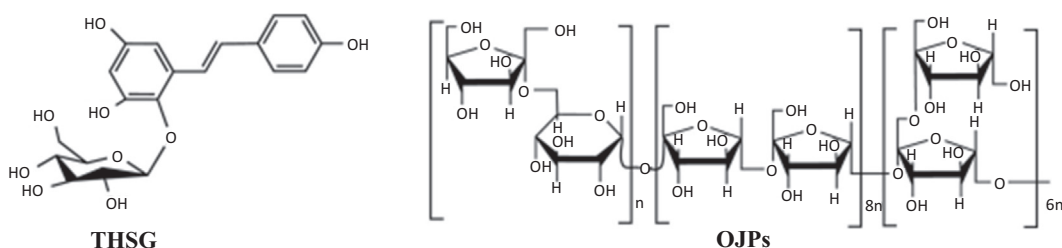


FIGURE 19.1

Structural view of 2,3,5,4'-tetrahydroxy-stilbene-2-O- β -D-glucoside-*Ophiopogon japonicus* polysaccharide conjugate.

Adopted from Sun L-L, Wang M, Zhang H-J, You G-J, Liu Y-N, Ren, X-L, et al. The influence of polysaccharides from *Ophiopogon japonicus* on 2,3,5,4'-tetrahydroxy-stilbene-2-O- β -d-glucoside about biopharmaceutical properties in vitro and pharmacokinetics in vivo. *Int J Bio Macromol* 2018 [35] with reprint and copyright permission from Elsevier.

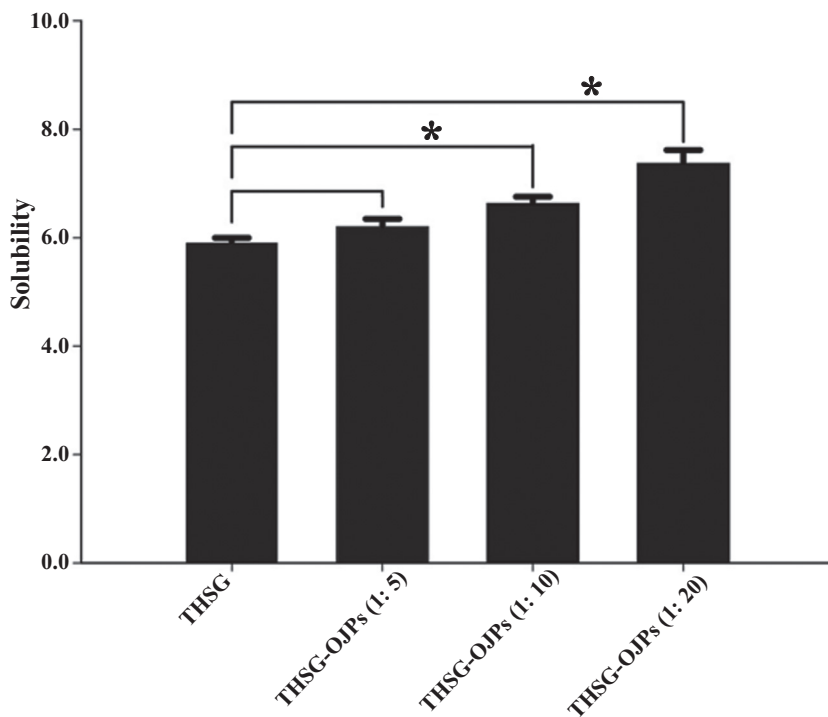


FIGURE 19.2

Solubilities of the conjugates for varying proportions of *Ophiopogon japonicus* polysaccharide.

Adopted from Sun L-L, Wang M, Zhang H-J, You G-J, Liu Y-N, Ren, X-L, et al. The influence of polysaccharides from *Ophiopogon japonicus* on 2,3,5,4'-tetrahydroxy-stilbene-2-O- β -D-glucoside about biopharmaceutical properties in vitro and pharmacokinetics in vivo. *Int J Bio Macromol* 2018 [35] with reprint and copyright permission from Elsevier.

agent [36]. It is the most available bioactive catechin in green tea, that is of every 25%–55% green tea, about 8%–15% is catechins. EGCG can be partly/completely isolated as nanoparticulates, thus enhancing its stability, In aqueous solutions of acids, EGCG is stable, however, it is easily degraded in the blood/body fluid at an alkaline pH of 7.4 [37]. In addition, there is also evidence of the low absorptivity of EGCG in the human body and animals [38,39].

19.2.3 Alginate–fucoïdan/curcumin/oligonucleotide/rhodamine

Alginate is a natural/integrin-rich biocompatible polymer-extract of brown seaweed that has found extensive use in the monitoring of integrin signals in the extracellular matrix of ECM, while fucoïdan, a sulfated-polysaccharide, can be found in brown algae/brown seaweeds (mozuku, kombu, bladderwrack, wakame, and hijiki). Alginate can serve as a 3D culture-matrix because it aids cellular growth and provides an anchor for cells and cartilages. Cartilages complement the functionalities of bones by providing them with adequate mechanical support and balance. Hence, an apt

Table 19.1 Kinetic parameters for 2,3,5,4'-tetrahydroxy-stilbene-2-O- β -D-glucoside-*Ophiopogon japonicus* polysaccharide-conjugates.

pH	THSG: OJPs	Kinetic model	Correlation coefficient (<i>r</i>)	Rate constant k_{obs} (h^{-1})	Retention time, $t_{0.9} * 10^2$ (h)	Retention time $t_{0.5} * 10^2$ (h)
1.2	1:0	$y = -7.78 * 10^{-4} x$	0.996	$7.78 * 10^{-4}$	1.35	8.91
	1:5	$y = -5.53 * 10^{-4} x$	0.991	$5.53 * 10^{-4}$	1.91	12.53
	1:10	$y = -5.16 * 10^{-4} x$	0.995	$5.16 * 10^{-4}$	2.04	13.43
	1:20	$y = -4.63 * 10^{-4} x$	0.997	$4.63 * 10^{-4}$	2.28	14.98
6.8	1:0	$y = -1.20 * 10^{-2} x$	0.984	$1.20 * 10^{-2}$	0.088	0.58
	1:5	$y = -9.95 * 10^{-3} x$	0.975	$9.95 * 10^{-3}$	0.11	0.70
	1:10	$y = -8.23 * 10^{-3} x$	0.977	$8.225 * 10^{-3}$	0.13	0.84
	1:20	$y = -5.98 * 10^{-3} x$	0.962	$5.98 * 10^{-3}$	0.18	1.16
8.3	1:0	$y = -1.96 * 10^{-1} x$	0.998	$1.96 * 10^{-1}$	0.0054	0.035
	1:5	$y = -1.74 * 10^{-1} x$	0.997	$1.74 * 10^{-1}$	0.0061	0.04
	1:10	$y = -1.53 * 10^{-1} x$	0.995	$1.53 * 10^{-1}$	0.0069	0.045
	1:20	$y = -1.24 * 10^{-1} x$	0.987	$1.24 * 10^{-1}$	0.0085	0.056

THSP, 2,3,5,4'-tetrahydroxy-stilbene-2-O- β -D-glucoside; OJP, *Ophiopogon japonicus* polysaccharide.
Adapted from Sun L-L, Wang M, Zhang H-J, You G-J, Liu Y-N, Ren, X-L, et al. The influence of polysaccharides from *Ophiopogon japonicus* on 2,3,5,4'-tetrahydroxy-stilbene-2-O- β -D-glucoside about biopharmaceutical properties in vitro and pharmacokinetics in vivo. *Int J Bio Macromol* 2018 [35].

reconfiguration of collagen is an imperative for the correction of structural deformities. In the study conducted by Karunanithi et al. [40], a fucoidan–alginate hydrogel made via ionic gelation, was used to evaluate the potential of the plant-based bioactive polymer in the blend, as a promoter of cartilage repair. The hydrogel was seen to have enhanced in vitro chondrogenesis. However, the delayed transition of the mesenchymal stem cells and increased production of glucosamino-glycans, were ascribed to the presence of fucoidan in the biocomposite/hydrogel. As a way of infusing photocross-linking characteristics in fucoidan, methacrylic anhydride was used to synthesize methacrylated-fucodan (mF) [41]. Spheres of the mF were anchored on hydrophobic surfaces under the influence of visible light. After 3 days, the mF-spheres were seen to have a good measure of compatibility with L929 cells, as observed from the cell proliferation assay (MTS assay); the L929 cells were also seen to have remained on the spheres for 14 days. Cell-migration was prominent at the surface through to the interior of the spheres. As a way of examining the potential of

Table 19.2 Pharmacokinetic parameters of 2,3,5,4'-tetrahydroxy-stilbene-2-O- β -D-glucoside-*Ophiopogon japonicus* polysaccharides conjugates.

Variable	THSG	THSG-OJP conjugate
t_{\max} (h)	0.5 \pm 0.0021	1.75 \pm 0.27**
C_{\max} (mg/L)	0.35 \pm 0.15	0.51 \pm 0.12**
AUC _{0-t_n} (mg/L.h)	0.51 \pm 0.29	1.18 \pm 0.32**
AUC _{0-t_∞} (mg/L.h)	0.64 \pm 0.35	1.28 \pm 0.32**
MRT _{0-t_n} (h)	1.34 \pm 0.39	2.28 \pm 0.38**
MRT _{0-t_∞} (h)	3.08 \pm 0.79	3.42 \pm 0.72*

THSQ, 2,3,5,4'-tetrahydroxy-stilbene-2-O- β -D-glucoside; OJP, *Ophiopogon japonicus* polysaccharide
* $P < .05$; ** $P < .01$; mean \pm SD, $n = 6$.
Adapted from Sun L-L, Wang M, Zhang H-J, You G-J, Liu Y-N, Ren, X-L, et al. The influence of polysaccharides from *Ophiopogon japonicus* on 2,3,5,4'-tetrahydroxy-stilbene-2-O- β -d-glucoside about biopharmaceutical properties in vitro and pharmacokinetics in vivo. *Int J Bio Macromol* 2018 [35].

fucoidan in stimulating cardiac tissue differentiation in human embryonic stem cells (hESC), a synthetic/chemically cross-linked macroporous polysaccharide scaffold, comprising dextran, fucoidan, and pullan, was produced using sodium trimetaphosphate. The idea behind the use of fucoidan was to aid cell proliferation as well as embryonic-stem cell adhesion. According to Hamidi et al. [42], gene regulation of NKX2.5, GATA4, and MEF2C in hESC cells supported on fucoidan-scaffolds, can be achieved using the qPCR procedure, but the subsequent upward regulation of the genes by fucoidan-scaffolds is the height of utmost projection of the cardiogenic differentiation which is contributed by the highly emphasized atrial natriuretic factor of the embryonic cardiac differentiation induced by the fucoidan scaffolds, thus indicating the potential application of the polysaccharide for cardiac tissue regeneration [42].

Alginate in curcumin is another polysaccharide composite/conjugate that helps to speed up the solubility of curcumin in aqueous solutions; the conjugate also has anticancer characteristics [43]. In another study, Na-alginate conjugated with cisplatin was produced and embedded in a liposomal cell system, in which the surfaces of the liposomes were activated using epidermal growth factor in order to enhance target-specificity and delivery [44]. An alginate–oligonucleotide conjugate has also been investigated for its potency in human cells, where the linked polysaccharide molecules were seen to assume the form of a time-response/intermittent drug replenishing system, such that the complementary nucleotide drug-sequence-conjugate locates the alginate cell system in order to refill its drug bank/depot after releasing its constituents [45,46]. An alginate–rhodamine polysaccharide composite was revealed to possess self-identifying characteristics of alginate-based mercury ions (Hg^{2+}) and chromium III ions (Cr^{3+}) scavenger [47]; the authors also discovered that Ca^{2+} -rhodamine-conjugated alginate-beads can identify and scavenge the aforementioned toxic metals when consumed by humans. Fig. 19.4A–C are sample illustrations of the chemical structure of poly(ϵ -caprolactone)-(dimethylamino)ethyl methacrylate tangled with indomethacin, showing the evident interactions between carboxyl and tertiary amine functional groups as well as the method of synthesis of drug-loaded micelles and sodium alginate beads as potential material for drug delivery.

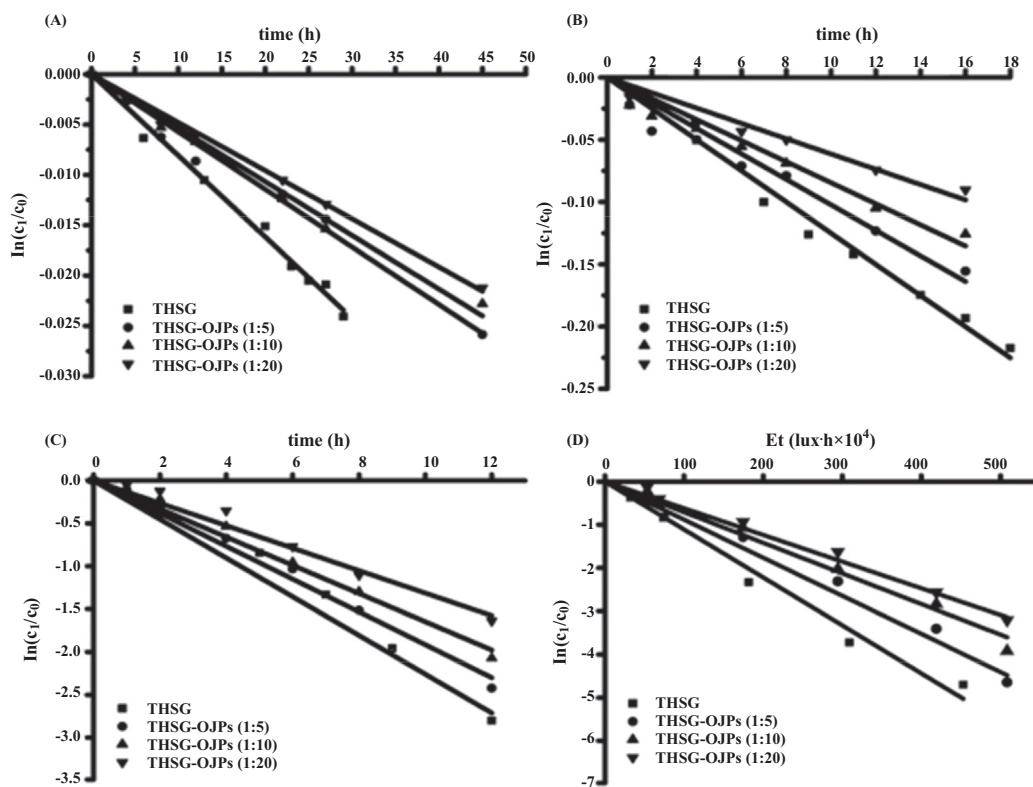


FIGURE 19.3

$\ln(c_1/c_0)$ versus time for pristine and conjugate 2,3,5,4'-tetrahydroxy-stilbene-2-O- β -D-glucoside at pH: (A) 1.2; (B) 6.8; (C) 8.3; (D) irradiation.

Adopted from Sun L-L, Wang M, Zhang H-J, You G-J, Liu Y-N, Ren, X-L, et al. *The influence of polysaccharides from Ophiopogon japonicus on 2,3,5,4'-tetrahydroxy-stilbene-2-O- β -d-glucoside about biopharmaceutical properties in vitro and pharmacokinetics in vivo.* *Int J Bio Macromol* 2018 [35] with reprint and copyright permission from Elsevier.

19.2.4 Carrageenan

Carrageenan being a sulfated polysaccharide, has its origin in red seaweeds that are edible. Three groups have been identified, namely, the ordinary carrageenan, kappa (κ)-carrageenan, and lambda (λ)-carrageenan. In terms of structure, κ -carrageenan has some semblance with dermatan sulfate and chondroitin-4-sulfate, found in native extracellular matrices such as glycosaminoglycans. Carrageenan is gel-like under thermal/ionic conditions, which influences its ability to be blended with other materials. The hydrogel's viscosity decreases with temperature and the gel's viscosity is a measure of its carrageenan concentration, whereas its gelation occurs at low temperature. In extrusion-based bioprinting, the young modulus of the polymer gel is a function of carrageenan concentration, where 1% and 3% (w/v) concentration of carrageenan correspond to Young's

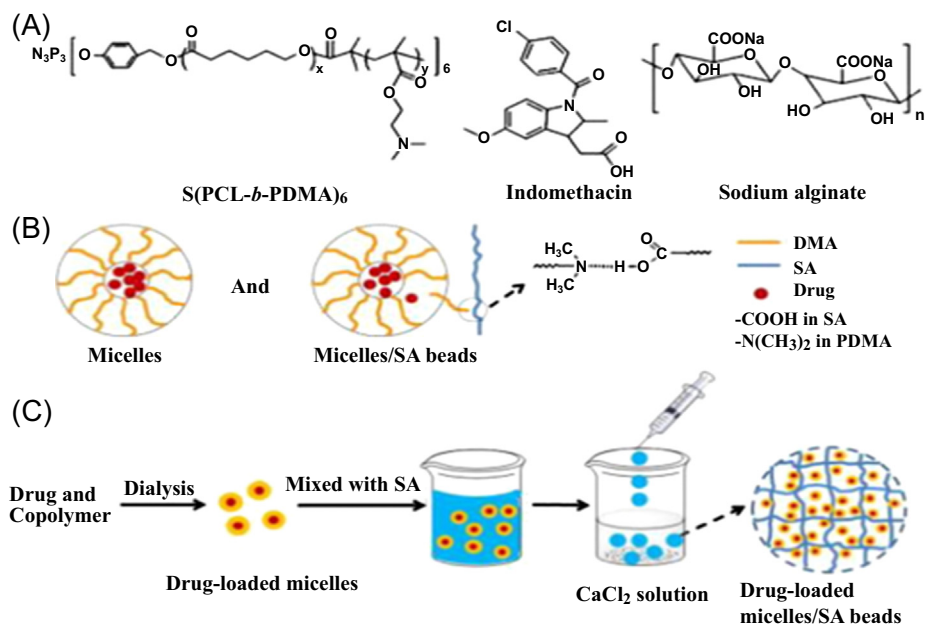


FIGURE 19.4

(A) Polymer conjugates of poly(ϵ -caprolactone)-(dimethylamino)ethyl methacrylate tangled with indomethacin; (B) comingling of carboxyl and tertiary amine functional groups; (C) method of synthesis of drug-loaded micelles and sodium alginate beads.

Reproduced from Alvarez-Lorenzo C, Blanco-Fernandez B, Puga AM, Concheiro A. Crosslinked ionic polysaccharides for stimuli-sensitive drug delivery. *Adv Drug Deliv Rev* 2013;65(9):1148–1171 [48] with reprint permission of Elsevier.

modulus of 0.1 and 0.66 MPa. Carrageenans have also been reported to have high tensile strength in the region of 39.34–0.51 MPa, hence their suitability for bioprinting [49]. According to Rhim [50], the progressive integration of carrageenan in agar films enhances their contact angle, solubility in water/water vapor barrier properties, as well as their swelling ratios. Carrageenan has been successfully converted to several hydrogels including gradient, photocross-linked, floating, and micropatterned hydrogels [51], which can be used to provide some specific mechanical/physical properties. The exhibition of superior gel properties and the ability of carrageenan to infuse mechanical strength during ionic cross-linking, increases their chances of being employed in tissue engineering [52]; this is due to the fact that carrageenan is a thermoresponsive polymer characterized by a fibrillary network for the construction of scaffolds of different sizes and shapes. Its tunable mechanical properties, make it viable for bioink formulations. Bioinks sourced from alginate and carrageenan have recorded improved rheological behavior, mechanical strength, and printability without jeopardizing the cell's viability [53]. Multicomponent stoma cells obtained from the human skin (i.e., skin-derived multicomponent stoma cells—SDMSCs) have been found to be compatible with carrageenan hydrogel scaffolds. The fast-healing potential of the aforementioned scaffolds supported by extracellularly deposited matrix were examined using several loadings of the SDMSC

carrageenan hydrogels incorporated in murine [54]. Hybrid-alginate + k/L-type carrageenan, shaped as beads/fibers have been explored as cell delivery systems. The addition of κ -carrageenan produced beads of smoother surfaces and higher thermal stabilities when CaCl_2 was used as the gelling-agent has been investigated [55]. Improved mechanical properties such as compressive and tensile strengths were documented for the κ -carrageenan relative to those comprising the L-carrageenan fiber-hydrogels owing to the lower composition of sulfate groups in the k-carrageenan bead-hydrogels. In lieu of the insignificant impact of the hydrogel's surface on ATDC5 chondrocytes, the κ -carrageenan entrained hydrogels have yet been seen to display more improved viability than the hydrogels containing the ι -carrageenan fiber-hydrogels.

19.2.5 Pectin

Pectin, a well-known acidic heteropolysaccharide-extract of the cell walls of citrus fruits, comprises D-galactosyluronic acid, bonded with α -1 \rightarrow 4-glycosidic bonds. It is classified as either a high- or low-methoxy pectin based on the degree of esterification undergone by its residual galacturonic acid. Viscoelastic moderation/fine-tuning of the properties of pectin can be achieved via increasing the concentration of the polymer/cross-linkers such that they assume the forms of natural tissues [56]. Due to the presence of hydroxyl and carboxyl groups in pectin, it readily undergoes cross-linking with other carboxylic compounds in the presence of Ca^{2+} ions, which induce bridges within its homogalacturonic polymer chains. It is affordable, less toxic, and easily degraded by protease/amylase, which is the reason for its high degradability and biocompatibility, hence it has gained tremendous application in biomedical science/engineering. Pectin-chitin derivatives + CaCO_3 -scaffolds have also found significant use in tissue engineering; the resulting scaffolds were reported to also serve as inducements for cell-proliferation of the human dermal fibroblasts, L929-, as well as the NIH3T3-cells. According to Kumar et al. [57], the inclusion of pectin in scaffolds has also improved their hydrophobicity with an unusual reduction or restriction to the degradation of the polymer matrix, which provides the sustainable release of some loaded bioactive ingredients such as Fosamax that help to moderate bone functionality. Owing to its high compatibility, pectin has been grafted with polyhydroxybutyrate (PHB) via chemical modification as a way of improving its function; the grafted polymer composite was seen to be more hydrophilic relative to the individual components that make up the composite, thus resulting in the improvement of its biocompatibility with human retinal pigmented epithelial (ARPE-19) cells. Also, synthetic scaffolds + increased concentrations of pectin-PHB composite and pristine PHB were electrospun and investigated in order to ascertain their prospective application in retinal tissue engineering. Increased concentrations of the composite in the scaffold gave rise to improved adhesive strength and proliferation of the in vitro ARPE-19 cells, thus confirming the potential for retinal regeneration [58]. The inducement of a spongy-like structure in pectin is made possible by cross-linking it with matrix-forming polymers, after which it is lyophilized. Silk-fibroin cross-linked with amidylated-oxypectin was made by the addition of CaCl_2 to the functionalized pectin; this helped to induce porous 3D-scaffolds for the proliferation and adhesion of skin fibroblast cells within the cell's architecture [59]. A report also indicates that a carbodiimide cross-linked collagen-pectin hybrid was used to synthesize porous scaffolds of about 130 μm pore size, which were biocompatible with myoblasts cells without any alteration to the cell's architecture [60]; the attained pore size has been affirmed

to be the required optimum for the successful implementation of such pectin-based scaffolds in soft tissue/skin and muscle engineering.

19.2.6 Ulvan

Ulvan is a thermoresponsive hydrophilic biodegradable biopolysaccharide which consists of sulfated xylose/rhamnose and iduronic/glucuronic acids that can be sourced from green algae (i.e., *Ulva rotundata*, *Ulva lacuta*, etc.) for tissue engineering applications. Its unique sulfate-containing sugar residues infuse morphological characteristics that have the same semblance as glycosaminoglycans of the mammalian origin (i.e., chondroitin/heparin chondroitin sulfate) [61]. Ulvan solutions are either shear thickeners or thinners depending on the algal source or the method adopted during its isolation. In vitro cytotoxicity tests on ulvans (soaked in DMEM supplemented with Na_2CO_3) mixed with fibroblast cells were tested using MTS assay in order to understand the contribution of the fibroblasts or hyaluronic acid to the metabolic activities exhibited by the ulvans. Ulvans in concentrations of 15 mg/mL were seen to be nontoxic, and hence can be applied in biomedicine in the manufacture of scaffolds/hydrogels that can mineralize apatite with the aim of improving osteoconductive and osteoinductive activities [62].

19.3 Pharmacokinetics of polysaccharides during drug release

Pharmacokinetics is the study of the rate of adsorption/absorption, distribution, metabolism, and excretion of pharmaceutical chemicals ingested or transmitted to the body via intravenous, oral, or other means [63]. The modification of hydroxypropyl cellulose was done by Xu et al. [63] using cationic poly((2-dimethyl amino)ethyl methacrylate) as vector for the effective delivery of plasmid DNA with low cytotoxicity in HEK293 cells. The 3,4-hydroxyl-modification of the polysaccharide was aided by acetal bonding, after which the modified saccharide was hydrolyzed in a pH-regulating medium, thus providing the required support for linkers/diamines with the aim of ensuring the release of siRNAs [64]. Colistin, an antibiotic, has been conjugated with succinylated dextran. The colistin – dextran hybrid extended drug release without any significant effect on its antimicrobial activity [65]. The performance of a dual gene-chemotherapy poly(β -amino) ester and pullulan-conjugated methotrexate has been reported to be very useful for drug and chemotherapeutic deliveries respectively, in which the genetic material serves as the inner core complex with the carrier (cationic carrier), while the outer shell consists of pullulan-conjugated methotrexate [66].

The work of Alvarez-Lorenzo et al. [48] is a review on cross-linked ionic/anionic cross-linked polymers/polysaccharides as delivery systems for the regulation of drug release as induced by changes in pH, nature of ions/concentration, light intensity and wavelength, redox potential, temperature, electric/magnetic field intensity, redox potential, molecules of enzymes/illness-markers, etc. According to the authors, the anionic functional group in sodium carboxymethylcellulose (Na-CMC), with a pka of approximately 4.8, makes it an apt compound for the synthesis and application of hydrogels in shrinkable interpenetrating networks (IPNs) within acidic pHs where they shrink, whereas they swell at neutral/alkaline pHs, especially at low ionic strengths. IPN-CMC

microspheres and PVA cross-linked with glutaraldehyde, have shown increased/rapid release of diclofenac/5-fluorouracil at a higher pH of 7.2 relative to that seen at a pH of 1.2; the slow-release rate at the lower pH was ascribed to the inherent hydrogen bonds existing between the CMC and PVA. The anionic behavior of CMC gains reinforcement by the grafting of acidified-acrylic-based polymer composites i.e., CMC-g-poly(sodium acrylate)/clay (CMC-g-PNaA/clay), as well as CMC-g-poly(acrylic acid)/polyvinylpyrrolidone (CMC-g-AAc/PVP) cross-linked with N,N-methylenebis-acrylamide, help to control the on and off switch-swelling of the polymer-composite at pHs of 7.2 and 1.2, respectively. CMC-hydrogels have demonstrated a high potential for drug-release regulation in a reverse manner as compared to their swelling/absorptive behavior. Cross-linked CMCs with epichlorohydrin cause cationic molecules to be expunged at a rapid pace at a pH of 4, especially in situations where the inherent zero-charge carboxylic groups exhibit weak interactions from the hydrogels toward the cationic drug. When the pH = 4.6, stronger attractive forces are initiated, released, and sustained up to a pH of 9. At still higher pHs, there is a corresponding rise in ionic concentration, which weakens the attractive forces and accelerates drug-/epichlorohydrin-release [10]. Ionic cross-linking can revert the behavior of microgels of CMC and a polymeric β -cyclodextrin cross-linked with 2-hydroxyethyl trimethylammonium chloride benzoate. The cross-linker comingles with cyclodextrin and CMC to form ionic complexes. Upon loading the cross-linked polymer with calcein, 100% release of codextrin was noticed at a pH of 3 and this was ascribed to the protonation of carboxylic groups which cut off any progressive interaction with the cross-linker, thus leading to the disintegration of the microgels. At an alkaline pH (i.e., a pH of 8), the density of the cross-linked molecules was highest with a corresponding drug-release of 23% after 24 hours, whereas there was a remarkable decrease in the density of the cross-linked molecules at a pH of 11 which resulted from the screening of the ionic interactions, which in turn stimulated the further release of the drug.

According to Svenson et al. [67], cyclodextrin conjugates, comprising cyclic oligosaccharides of hydrophilic and hydrophobic exterior and interior parts, were conjugated using a nanoformulation of cyclodextrin, that is CRLX101/IT-101, via covalent bonding of camptothecin with a hybrid polymer (β -cyclodextrin-PEG); although this modified drug is currently undergoing the second phase of its clinical trials in order to ascertain its efficacy for the treatment of ovarian cancer [68], its preclinical/clinical data have confirmed patients' improvement over challenges that hinder the administration of camptothecin, in terms of toxicity, formulation, solubility, and pharmacokinetics/pharmacodynamics (adsorption, distribution and metabolism). Young et al. [69] have also reported the enhanced pharmacodynamics and efficacy of camptothecin.

Falk et al. [70] mentioned that amphotericin B, an antifungal hydrophobic drug with low bio-availability, was oxidized to produce an oxy-arabinogalactan conjugate, which helped to improve its solubility in aqueous media. The conjugate was seen to have significant influence on the pharmacokinetics of the drug, thus reducing its toxicity whilst retaining its antifungal characteristics [71]; the toxicity of amphotericin can be ascribed to the presence of free aldehydes in the antibiotic [72]. Conjugation of drugs with polymers by tosylation [73] have also been conducted where the pharmacokinetic studies on this conjugate revealed that the pharmacokinetics of the conjugated drug is largely influenced by the macromolecular moiety and molecular weight of the bioactive ingredient/polysaccharide molecule [74–76]. Also, a scale-up procedure for arabinogalactan amphotericin B conjugate has been reported for its potency in the treatment of leishmania [77,78] as well as several other parasites [79].

Table 19.3 Mpeg-receptor tyrosine kinase–like orphan receptor (ROR) conjugates and their properties.

Conjugates	Average molecular weight ($\times 10^4$)	Molecular weight (normal) ($\times 10^4$)	Peak molecular weight ($\times 10^4$)	Polydispersity index	Degree of grafting	Designation
Radix ophiopogonis polysaccharide	0.17	0.21	0.199	1.18	—	—
30 KDa Mpeg-NH ₂	3.08	3.31	3.45	1.06	—	—
40 KDa Mpeg-NH ₃	3.49	4.14	4.80	1.19	—	—
Mpeg _{30k} -ROP	3.24	3.49	3.47	1.08	0.99	^{0.99} P _{30k} -R
Mpeg _{40k} -ROP	3.57	4.27	4.95	1.2	0.98	^{0.98} P _{40k} -R

Adapted from Lin X, Wang Z-J, Huang F, Liang S, Shen L, Feng Y, et al. Long-circulating delivery of bioactive polysaccharide from radix ophiopogonis by PEGylation. Int J Nanomed 2011;6:2865–2872 [81].

The conjugation of folic acid and methotrexate (MTX) with AG (AG-folic acid-MTX) was initiated as a means to differentially supply a cargo of the cytotoxic conjugate to cells with overexpressed folate receptors. The linkage between the MTX and AG-folic acid was achieved via an endosome cleaved to peptides in order to stimulate/activate the target-release mechanism. The resulting drug conjugate exhibited increased cytotoxicity to cells overexpressed by the folate receptor [80]. Table 19.3 shows the results of characterization of several conjugates comprising methoxy-polyethylene glycol (mPEG) and amines/bioactive radix ophiopogonis polysaccharide (ROP). Information on the weights and dispersion indices of the samples are also contained therein, with the Mpeg_{30k}-ROP, 30 KDa Mpeg-NH₂, and pristine MOP samples showing lower dispersion indices relative to that of the Mpeg_{40k}-ROP sample.

Pulsatilla chinensis is one traditional medicine that is known for its long-use-history in the treatment of amoebic diseases, bacterial infections, and vaginal trichomoniasis. In recent times, attention has been given to its antitumor activities. In the work of Huang et al. [82], several formulations of the pharmacokinetic profile of pulchinenosides were studied to improve the oral bioavailability of the saponin extracts (triterpene glycosides) of *Pardanthus chinensis*, an ornamental plant species also known as *Iris domestica*/blackberry lily/leopard flower or leopard lily, which was used to prepare PRS-Na salt, PRS-HP β CD (hydroxypropyl- β -cyclodextrin complex), PRS oil-water emulsion, and micronized PRS-silica, respectively. A noncomplex/durable liquid chromatography mass spectrophotometry (LC-Ms/MS), was used to quantitatively and simultaneously analyze the five saponin formulations (i.e., pulsatilla saponin D, B7, B10, B11 and saponin PD). From the results, for four of the saponin extracts, the order of decreasing oral bioavailability of the saponins is PRS-HP β CD > PRS-silica > PRS-O/W > PRS-Na, which is a confirmation of the water-soluble capacity of pulchinenosides to improve the solubility of saponins, and enhance their bioavailability. Considering the pharmacokinetics of the absorbed saponins, the inclusion of the hydroxypropyl- β -cyclodextrin complex was seen to be the best means of promoting the saponin absorption, thus elevating the estimated F values or bioavailability 20 times more. This further confirms that

saponin molecules of *P. chinensis* can be gradually released via emulsion and micronization, which in turn abates any tendency for its abundance up to the maximum limit/maximum concentration (C_{\max}) in HP β CD as judged from its pharmacokinetics profile. However, of the four saponin extracts, PRS-Na, had the lowest F value/bioavailability.

In terms of specificity, the identification of the analytes and IS using MRM was highly selective with zero-interference. Sample-chromatograms of the blank plasma and the blank plasma + each of the analytes and IS, were monitored after 8 hours of administration at a constant dose-rate of 0.30 g/kg. From the results, the retention times of the pulsatilla sapoin D, B7, B10, B11, PD, and dioscin (IS) were estimated to be approximately 5.65, 6.89, 7.47, 7.71, 6.36, and 8.39 minutes, respectively. Also, the estimated concentrations of the analytes as determined from the calibration curve were 1.66 ng/mL (B11), 2.0 ng/mL (pulsatilla sapoin D, B10, and sapoin PD), and 4.0 ng/mL (B7). It is worthy to note that one major drawback experienced in the use of ESI is that it is prone to matrix effects, thus the co-eluting matrix-components stimulate ionic-suppression. From 0 to 5 minutes, the observed matrix effects for each of the analytes were in the range of 3.5%–10.8% (pulsatilla sapoin D), 1.6%–12.1% (sapoin PD), 2.3%–5% (B7), 3.4%–6.7% (B10), and 3.7%–11.2% (B11), which are indicative of insignificant matrix-effects on the ionization potential of the analytes [82].

The administration of drugs to the human body is necessitated by the need to enjoy good health and wholeness, hence it becomes essential to understand the absorption pathways of drugs when delivered by polysaccharides sourced from bioactive plants. These polysaccharides are then transported and absorbed in the intestine. A Caco-2 cell mobility model was used to examine the transmembrane activity of *Gastrodia/Grifola frondosa* (Dicks) polysaccharides; the observed polysaccharides were found to be stable without undergoing any form of degradation. Investigations on their absorption pathways, showed that the polysaccharide-uptake via the small intestinal cells was largely enforced by the heavy clathrin chain-endocytosis [83]. Wang et al. [84] also observed that oral doses of ASP were absorbed via the large cell-drinking path, as well as the clathrin/small concave (lipid raft) endocytosis before entering the blood for circulation.

Based on reports from clinical trials, lung cancer-infected rats were treated using *Scleromitron diffusum* (Willd.) R.J. Wang (syn. *Hedyotis diffusa* Willd.) SDP polysaccharide consisting of galactose to mannose to glucose ratio of 1:1:2. High doses of the SDP showed some measure of tumor-inhibition rates that are similar to those of cisplatin [85]. Upon treating the mice with *Citrus aurantifolia* (Christm.) Swingle polysaccharides (CAs) transplanted within the H22 cells of the mice, a high tumor-suppression rate of about 58.9% was recorded [86]. However, with *Polygonatum sibiricum* Redouté polysaccharide, the antitumor effect was highly significant in the H22 tumor-cells of the examined mice [87]. For the case of other polysaccharides [i.e., *Saccharina japonica* (J.E. Areschoug) (syn. *Laminaria japonica*)], there was an enhancement in the immunomodulatory response with corresponding reduction in the weight of the tumor-cells of the H22-mice carriers. According to Zhu et al. [88], the rate of tumor-suppression can sometimes get as high as 59.67%. Considering the use of *Achyranthes bidentata* Blume-type polysaccharide (ABP), tumor growth in the rats was a function of the polysaccharide dosage. For doses of 100 and 50 mg/kg of ABP, the levels of inhibition of the Lewis cancer of the mouse were 5.36% and 40.06%, respectively, although there were mediations of the anticancer effect of ABP by induced cell-cycle-arrest, such that high ABP-doses enhanced tumor growth along with NK cell dysfunction/upregulation of IL-6 and TNF- α [89].

According to some authors, the pharmacokinetics of several bioactive plant-derived substances including polysaccharides may be affected by the host's pathological status [90,91] which can be

informed by conditions such as stroke, diabetes, liver injury, rheumatoid arthritis, cancer, fever, heart or neurodegenerative diseases, which greatly impart on the metabolism of these compounds [33,92–99]. Parenchymal liver-cells (hepatocytes) enhance the excretion/expulsion of xenobiotics via urine/feeces by the induced structural modifications of the phase I xenobiotic oxidation/hydrolysis, which is followed by glucuronidation, sulfation, and acetylation/glutathione conjugation during the second stage metabolism. Since the cytochrome P450 enzyme is found in the pericentral part of liver lobules, high expression of glutathione peroxidase is therefore very evident in the periportal zone [100], and hence high drug-metabolism then ensues in the liver when polysaccharide-liver drug conjugates are absorbed by this organ. This goes further to suggest that liver lesions can alter the liver–drug pharmacokinetics [101]. Also, the interactions exhibited by dl-Praeruptorin A (PA), an active component of *Peucedanum praeruptorum* Dunn, which contains coumarins, and CYP 450 isozymes 3A1/3A2 of clinical rats were examined. The pharmacokinetic study was based on liver cirrhosis in affected and normal rats for one-time dose of the intravenous drug in order to monitor the variability of PA in situations of hepatic damage. Slow hepatic elimination was ascribed to PA for the PA-induced rats and this they ascribed to the low flow of hepatic blood and CYP450 isoform-levels in the liver cirrhosis-infected rats [102], thus confirming the influence of the host rats' status on their pharmacokinetics and responses to drug doses induced by the carriers/bioactive-plant derive polysaccharides.

Polysaccharide-protein extracts from Longan Pulp/*Dimocarpus longan* Lour, a fruit used as a Chinese traditional medicine/agent were used for the promotion of blood metabolism, soothing of nerve cells, insomnia relief, and amnesia prevention [103]. The extracted, purified, structural, and bioactive components of the extracts have also been studied [104,105] and the complexes were seen to significantly improve the immune tendencies of lab mice against chicken red blood cells owing to the secretion of antibodies, macrophage phagocytosis, proliferation of ConA-induced splenocyte, and cytotoxicity against YAC-1 lymphoma-cells/secretion of cytokine in the serum [106]. Since the mechanisms underscoring the pharmacokinetics of longman pulp polysaccharide extract is still unclear, its pharmacochemistry is often discussed in relation to it being a carrier moiety of micromolecular drugs. The lack of a proper understanding of the in vivo mechanism is caused by the lack of actual microassay techniques [107]. However, on the contrary, most pharmacokinetics/tissue distribution studies of the longman pulp polysaccharide as a bioactive plant are based on its use in fluorescence labeling alongside chromatography [108], spectrophotometry [109], isotope labeling, fluorospectrophotometry [110], and biological assay determination [111]. Hence, the need to test the efficacy of combined tools as done by Min et al. [112], where high-performance size-exclusion chromatography (HPSEC) was combined with the fluorescent fluorescein isothiocyanate (FITC) prelabeling technique for the identification/microanalysis of protein complexes and detection of the effect of the longman pulp polysaccharide. The pulp-polysaccharides were fractionated via gel-filtration chromatography and the mean molar weight/degree of FITC substitution of the bioactive-extracts was estimated to be 39.01 kDa/0.20%. The linearity of the HPSEC-FD calibration graph was seen within 1–200 $\mu\text{g/mL}$ polysaccharide concentration in the plasma, lung, and spleen samples of the mice with a correlation coefficient of 0.995. The inter-/intraday accuracy of the measurements were within 6.9%, with relative recoveries of 93.7%–106.4%. For 40 mg/kg body weight of each mouse, the concentration–time graph of the polysaccharide from intravenous administration obeyed a two-compartment model and plasma elimination of the saccharide was within half lives of $t_{1/2\alpha} = 2.23$ minutes and $t_{1/2\beta} = 39.11$ minutes with mean retention times of $\text{MRT}(0) t = 1.15$ hours, $\text{MRT}(\infty) = 1.39$ hours; the concentration–time profile of the saccharide

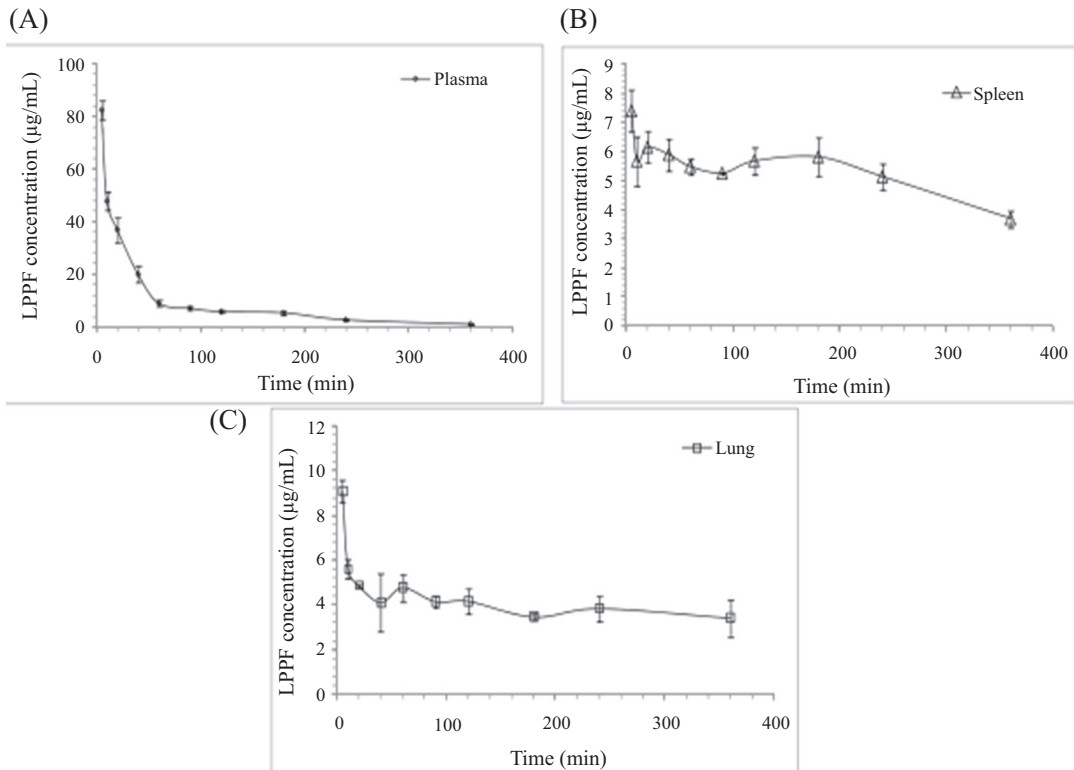


FIGURE 19.5

Concentration-time profile of the distribution of longman pulp polysaccharide in the: (A) plasma cell, (B) spleen, and (C) lung of 40 mg/kg weighted mice.

Adopted from Min T, Sun J, Yi Y, Wang H-X, Hang F, Ai Y-W, et al. *Microanalysis, pharmacokinetics and tissue distribution of polysaccharide-protein complexes from longan pulp in mice*. *Int J Mol Sci* 2015;16:24403–24416 [112] with reprint and copyright permission from Elsevier.

in the plasma cells is as illustrated in Fig. 19.5A. In 5–360 minutes, the saccharide concentration reduced from 7.41–3.68 $\mu\text{g/mL}$ and 9.08–3.04 $\mu\text{g/mL}$ in the spleen (Fig. 19.5B) and lung (Fig. 19.5C) homogenates, respectively, thus confirming the ease with which they are easily distributed within tissues for healing of cells/release of antibodies against blood-related diseases.

19.4 Conclusion

Plant-based bioactive polysaccharides are unique components that offer excellent properties when used in fabricating polymeric matrices for use in biomedical applications including tissue engineering, cancer treatment, and drug delivery. The recent upsurge in the use of plant-derived bioactive polysaccharides in the biomedical sciences is due to their plausible replacement as alternatives to

their man-made counterparts owing to their relative abundance/bioavailability, cost-effectiveness, as well as their biocompatibility/biomedical properties. Bioactive plant-derived polysaccharides are known to impart mechanical strengths to scaffolds in tissue engineering due to their characteristic charge densities, molecular weights, solubilities, viscosity, stability, etc., which make them easily adaptable to human cells with high target-specificities. These modified/hybrid/conjugate-bioactive plant-based polysaccharides can also serve as replacements for essential oils that help to heal wounds as a result of their high antimicrobial features. It is also worthy to note that these bioactive polysaccharides provide a good measure of cross-linking of polymers that constitute the framework for scaffold-assembly. The molecules of these polysaccharides attach to active cell-sites, which in turn stimulate their rates of absorption, distribution, and cell metabolism owing to the imparted stability, target specificity, and improved drug delivery as compared to their pristine forms. Hence there is a need to consider the adaptation of bioactive plant-based polysaccharides for regenerative purposes. Furthermore, ionic/anionic polysaccharides can be used to influence the sensitivity of hydrogel networks within a set of internal/external tissues/organs which may in turn enhance the on and off switching of drug release via several mechanisms in the human body. Polysaccharide–polymer hybrids and their composites can be grafted to enforce some measure of reinforced responsiveness with a widened range of stimuli, to which bioactive plant-based polysaccharides are sensitive. Also, there is substantive evidence that several cross-linked networks of ionic bioactive plant-derived polysaccharides are suitable building blocks for the development and advancement of some externally activated/feedback modulated drug delivery systems ranging from anticancer to antiviral, hypoglycemic, anticoagulant, ulcer healing, and immunomodulatory.

Furthermore, since the cost of treating cancer is quite exorbitant and laborious, the burdens associated with it are usually high for the affected individuals, communities, families, and the prospective healthcare systems [113–115]. The existence and growth of cancerous cells is usually caused by the changes occurring in the genome and epigenome [116], which cause the cells to proliferate and avoid undergoing apoptosis, thus resulting in the disruption of tissue-cells' homeostasis [117]. The promotion of cancer cell apoptosis (the mechanism for chemo/radiotherapy) helps in the effective treatment of cancer [118–121]. Most of the existing drugs for curing cancer are known to induce normal cell apoptosis, which subsequently results in serious physical damage including cardiotoxicity, myelosuppression, nephrotoxicity, hepatotoxicity, and gastrointestinal toxicity [122–124]. However, nature's isolates obtained from plants such as bioactive plant-derived polysaccharides are known to offer some measure of safety and efficiency when used as alternatives [125–127]. Bioactive plant-derived polysaccharides are active constituents of plants with low levels of toxicities and high efficacy/potency in treating cancer [128,129], especially those of the genera *Schisandra*, *Giseng*, *Astragalus*, *Ginseng*, etc. which have proven to be highly selective for cytotoxic tumor cells. Hence, they can terminate cancer cells without any known side reactions/effects; this is achieved by the prevention of cell proliferation of the cancer cells via induced apoptosis in vivo/in vitro.

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