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Review article

Hydrogels as promising therapeutic strategy for the treatment of skin cancer

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ABSTRACT

Skin cancer, such as melanoma and non-melanoma, is the most common malignancy in white populations. The local therapy strategy plays an important role in skin cancer treatment, and hydrogels can act as perfect platforms. Recently, hydrogels have been investigated in medicine and pharmacy due to their desirable biocompatibility and physicochemical properties, including softness, high water content, and flexibility. Hydrogels can be formed from synthetic, semi-, and natural polymers chemically or physically cross-linked. Their resemblance to living tissue can find enormous biomedical applications. The principal problem with common melanoma chemotherapy is the strong side effects, because neoplastic factors do not recognize cancer cells from healthy cells. For example, some of the side effects of treating melanoma cancer with chemotherapy and immunotherapy include nausea, vomiting, kidney toxicity, fatigue, cellular depression, abdominal pain, dermatitis, hepatitis, and infection. The side effects of conventional therapies encourage the search for novel therapies for cancer cells. Recently, hydrogel has been applied for tissue engineering scaffolds, wound dressings, and drug delivery systems. These percutaneous drug delivery systems are emerging as a promising alternative strategy for carrying anti-neoplastic agents to prevent side effects. The purpose of this study is to describe some of the latest developments (2019–2021) in the use of hydrogels for the treatment of skin cancer.

Abbreviation: (AgNPs), silver nanoparticles; (Alg/HA/Gel), alginate/hyaluronic acid/gelatin; (AIBN), 2,2-azo-isobutyronitrile; (ARX), arabinoxylan; (AV), arteriovenous; (B16), melanoma B16 cells; (BCC), basal cell carcinoma; (BGN@PDA), bioactive glass nanoparticles @ Polydopamine; (BMH), bio-inspired MnO_2 hybrid; (BSA/AgNP), bovine serum albumin (BSA)-coated silver nanoparticles; (CA), citric acid; (CD), cyclodextrin; (CDs), cyclodextrins; (CDT), chemodynamic treatment; (Ce6), chlorine e6; (CFMG), an injectable multi-responsive micelle/nanocomposite hybrid hydrogel; (CMARX), carboxymethylarabinoxylan; (CMC), carboxymethylcellulose; (CS-DA), chitosan-grafted-dihydrocaffeic acid; (2D), two-dimensional; (3D), three-dimensional model; (DexMA), dextran methacrylate; (DNA), deoxyribonucleic acid; (Dox), doxorubicin; (DS), degree of substitution; (DTX), docetaxel; (ECM), extracellular matrix; (EGR1), early growth response gene 1; (FAK), focal adhesion kinase; (FCB), F: FEPL; C:, F127-Phe-CHO; B:, BGN@PDA; (FS), β-$FeSi_2$; (FS/SA), β-$FeSi_2$-incorporated sodium alginate hydrogel; (FTIR), fourier-transform infrared; (5FU), 5-Fluorouracil; (GelMA), gelatin methacryloyl; (GOx), glucose oxidase; (GPDF), a multifunctional bioactive therapeutics-repair-enabled citrate-iron hydrogel scaffold; (H_2O_2), hydrogen peroxide; (HPCCC), high-performance counter current chromatography; (HP-β-CD), Hydroxypropyl-β-cyclodextrin; (HUVECs), human umbilical vein endothelial cells; (ICG), indocyanine green; (MCS), Mn-doped calcium silicate; (MCSA), manganese-doped calcium silicate nanowire-incorporated alginate hydrogels; (MDR), multidrug-resistant; (MNs), microneedles; (mRNA), messenger ribonucleic acid; (NCH), nanocomposite hydrogel; (NCimiq), Imiquimod-loaded polymeric nanocapsules; (NC $(PhSe)_2$), $(PhSe)_2$-supported polymeric nanocapsules; (NIR), near-infrared; (NLC), nanostructured lipid carriers; (NMSC), non-melanoma skin cancer; (NPs), nanoparticles; (OH), hydroxide; (3OMQ), 3-*O*-Methylquercetin; (OPC), oligomeric proanthocyanidins; (PAD), poly (acrylamide-co diallyldimethylammonium chloride); (PCD), polycitrate-dopamine; (PCHG), plumbagin loaded α-chitin hydrogel; (PCHG-TP), when 1% tween-80 and 1% PEG was incorporated into PCHG; (PEC-imiq), pectin-based hydrogel containing the drug; (PEC-NCimiq), pectin containing the drug-loaded nanocapsules; (PEDOT/PSS), poly(3,4-ethylenedioxythiophene)/poly(styrenesulfonate); (PEG), polyethylene glycol; (PEGDA), PEG-diacrylate; (PEGMC), poly (ethylene glycol-maleate-citrate); (PF-127), pluronic® F-127; $(PhSe)_2$, diphenyl diselenide; (PLGA), poly lactic-co-glycolic acid; (PTT), photothermal therapy; (PTT and CDT), photothermal treatment and chemodynamic therapy; (PTX), paclitaxel; (PTX-Gel), paclitaxelloaded micelles-embedded hydrogel; (PTX-M), paclitaxel-loaded micelles; (rGO), reduced graphene oxide; (RNA-Seq), RNA sequencing; (SCC), squamous cell carcinoma; (SCOD), polysaccharide hydrogels; (SEM), scanning electron microscope; (SF), silk fibroin; (SFMA), SF methacrylate; (SFMA-Ce6), SF methacrylate- chlorine e6; (SK-MEL-28), the cell line; (SK-MEL-28 and MV-3), two melanoma tumor cell lines; (TAMs), the tumor microenvironment contains abundant pro-tumorigenic tumor-associated macrophages; (TEOS), tetraethyl orthosilicate; (TME), tumor microenvironment; (TNFα), tumor necrosis factor α; (UV), ultraviolet; (VNR), vinorelbine; (Yb-CS Hydrogel), [Yb $(NO_3)_3$]-containing chitosan hydrogel.

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1. Introduction

In recent years, skin cancer has been considered as the most common diagnosed cancer in developed and developing countries and is divided into two main groups namely melanoma and non-melanoma [1]. Also, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are classified as nonmelanoma skin cancer (NMSC) [2]. These cancers are most common in white patients [3]. American Academy of Dermatology Association reports that about 9500 people in the United States get skin cancer every day [4], and research estimates that nonmelanoma skin cancer (NMSC) affects more than 3 million Americans a year [5]. There are several risk factors, including increased occupational and recreational UV light exposure and being older populations, exposure to certain chemicals and smoking are associated with skin cancer [6]. Surgery, chemotherapy, and radiotherapy are standard cancer treatment methods. However, drug resistance in chemotherapy, high toxicity, and systemic side effect are the biggest challenges in cancer treatment [7–9]. Therefore, the local therapy strategy has great potential for skin cancer because of their advantages over routine therapy ways. It has the capacity of delivering high concentrations of the pharmaceutical compounds on tumor sites. Among different drug delivery systems, hydrogels have been considered as typical and ideal platforms for local therapy. Hydrogels are hydrophilic polymers with a three-dimensional (3D) lattice that can maintain a great amount of water. They can be prepared with various kinds of biocompatible synthetic or natural polymers [10]. Hydrogels are named physical gels if molecular entanglements and second forces including H-bonding, ionic bonding, and hydrophobic force play an important role in making the network. However, in chemical gels, the network of covalent bonds is formed by cross-linking in solution or dry state [11].

Chemical hydrogels are usually provided in two various methods: (1) synthesis of hydrogels using three-dimensional (3D) polymerization (Fig. 1A) [12], (2) synthesis of hydrogels using crosslinking of water-soluble ready-made polymers (Fig. 1B) [12]. Polymerization commonly begins with free radical scavenging compounds like benzoyl peroxide, 2,2-azo-isobutyronitrile (AIBN), ammonium peroxodisulphate or by UV-, gamma- or electron beam-radiation. 3D polymerization further results in materials that contain exceptional levels of residual monomers, so the treatment of these materials must be complete because unreacted monomers are usually toxic and can be permanently removed from hydrogels. Purification of hydrogels comprising residual monomers is usually done by extracting excess water and may take several weeks to complete [12–14]. Water-soluble polymers like poly (vinyl alcohol), poly (vinyl pyrrolidone), poly (acrylic acid), poly (ethylene glycol), polyacrylamide, and some polysaccharides are the most available systems utilized to form hydrogels. These polymers are non-toxic and are broadly used in different pharmaceutical, and biomedical usages and so do not need to be removed from the system and eliminate the need for filtration. Radiation cross-linking, such as the aqueous solution of hydrophilic polymers with gamma beams, permits hydrogels to form simultaneously and sterilize. Nowadays, the development of nanomaterials has attracted widespread attention in hydrogel formulation due to their individual properties such as effectual target delivery, tunable functional modification, and high surface area [9,15,16]. This review focuses on the latest articles (2019–2021) on the preparation of hydrogels to supply insight into the rational synthesis of these formulations that can be used in skin cancer therapies.

2. Methods

This paper is a recent overview of the involvement of the formulation of hydrogel in skin cancer. The literature search is accomplished in the Web of Science, PubMed, Google, Scopus, and the Google Scholar databases. The following keywords were used: Hydrogel* AND skin cancer, Hydrogel * AND melanoma, Hydrogel * AND squamous cell carcinoma, Hydrogel * AND basal cell carcinoma, and Hydrogel * AND chemoprevention. The results were screened based on their titles, abstracts, and full-text availability. All non-English publications were removed from the present review. Filter restrictions (such as article availability, article type, and release date) were not applied (Fig. 2).

3. Types of hydrogels based on polymer origin

Hydrogels are hydrophilic, cross-linked and adsorbent polymers that do not dissolve in water but retain specific structures. These attributes underlie many applications, mainly in biomedicine [17,18]. The crosslinks that bind the polymers of a hydrogel are divided into two general groups of physical and chemical. Chemical hydrogels have covalent bonds, while physical hydrogels have non-covalent bonds [19]. In general, hydrogels based on polymer origin are divided into natural, synthetic, and hybrid types. The chemical composites and fibrous structures of natural hydrogels are similar to natural extracellular matrix (ECM). They are usually highly compatible [20]. Natural polymers for the preparation of hydrogels include chitosan, hyaluronic acid, heparin, Matrigel, fibrin, and alginate [21]. They are used in biomedical studies for different targets such as three-dimensional cell culture, microfluidic platforms, biodegradable implants, and the discovery of preclinical medicines [20]. More straightforward chemical modification and more controllable mechanical properties than natural hydrogels are the advantages of hydrogels made with synthetic polymer. Usually, synthetic polymers include polyethylene glycol, polyvinyl alcohol, sodium polyacrylate, acrylate polymers, and their copolymers [17]. Although natural and synthetic hydrogels are commonly utilized, one type of hydrogel may not meet all the needs of biomedical usage. Thus, researchers have constructed new hybrid hydrogels that can combine some of the benefits of a system to reduce batch variability, adjust response, and more accurately summarize native ECM (Fig. 3).

4. A brief background on the hydrogel system for the management of skin cancer

Novel shapes of treatment are needed to attack cancer cells while reducing the side efficacies of healthy cells [22,23]. To prevent side effects, percutaneous drug delivery systems are emerging as a favorable alternative strategy for transporting anti-neoplastic factors [24,25]. Hydrogels can absorb large amounts of water, biological liquids or molecules [12]. Another significant feature of hydrogels is their ability to distend and dissolve in water [26]. According to this, the strategies have been developed in recent years on the hydrogel system for the management of skin cancer (Table 1).

4.1. Review of the latest articles on the use of hydrogels for the treatment of skin cancer

4.1.1. Natural hydrogels

Kappelmann-Fenzl et al. [37] compared gene expression templates in melanoma cells cultured in three-dimensional alginate with two-dimensional culture. Three-dimensional cell culture models help to affect the heterogeneity and flexibility of tumor cells in melanoma. Alginate is an easy-to-use material, and because of its desirable properties, it is generally used as a biomaterial in cell capsule growth and biosynthesis. In this work, changes in transcripts were analyzed based on RNA-Seq data by

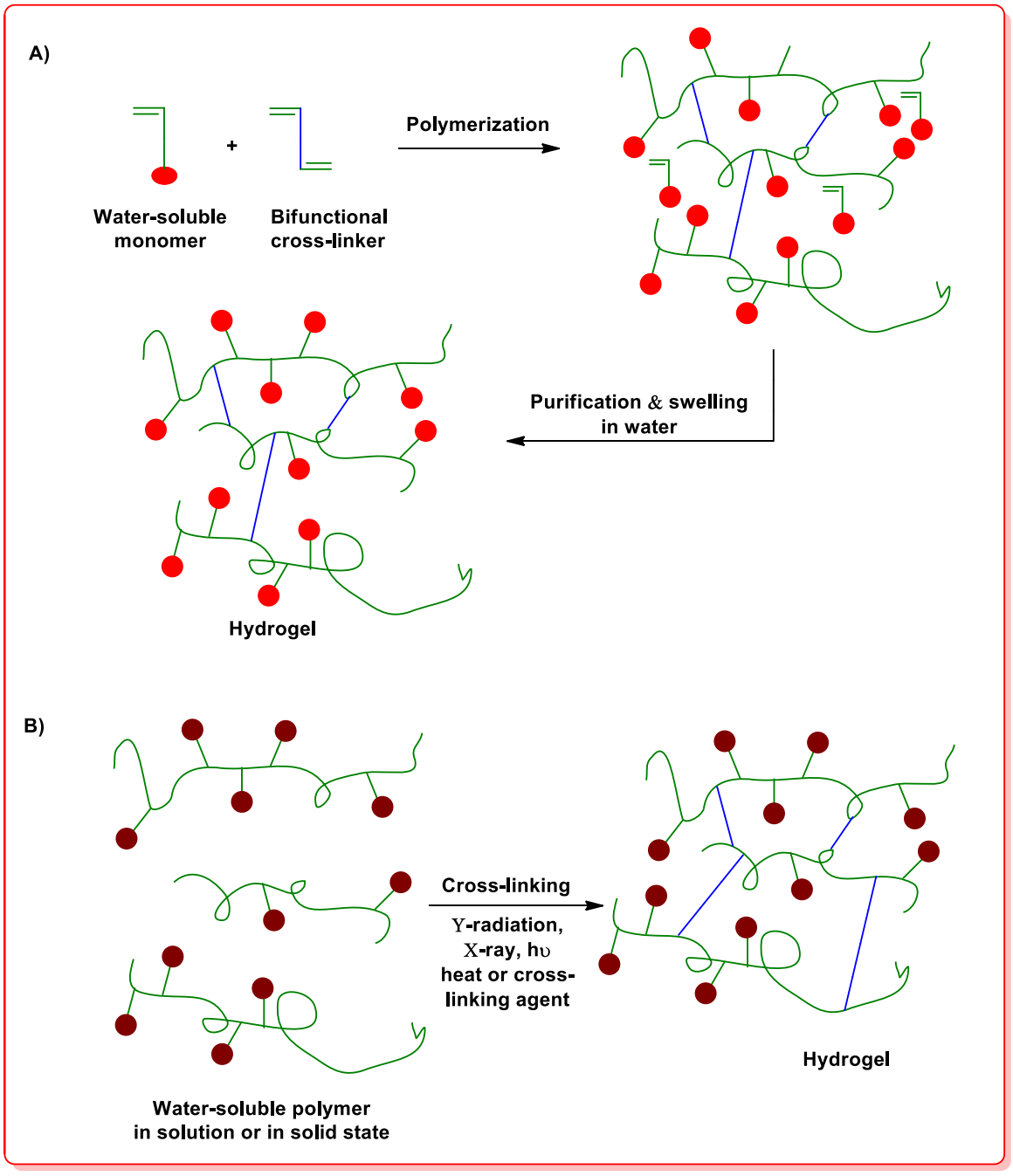

Fig. 1. Synthesis of hydrogels by: (**A**) three-dimensional polymerization; (**B**) cross-linking of ready-made water-soluble polymers [12].

culturing melanoma cells in three-dimensional alginate and showing significant modifications compared to cells cultured on conventional two-dimensional tissue culture plastics. Using deep analysis of changes in transcripts, EGR1 was identified as having an essential role in melanoma plasticity. The three-dimensional correlation of cell phenotype with the study of gene expression in tumor samples, mostly with future single-cell RNA-Seq, helps to reconcile 3D models to unique *in vivo* settings in the future. These models are also available for therapeutic studies. It makes it very notable with higher potential correlation compared to 2D cultures due to *in vivo* status. Three-dimensional culture of tumor cell lines in hydrogels such as alginate used in this study is more suitable due to the management and complexity of the model compared to patient-specific organoid models [38] that draw more attention to three-dimensional models of cancer.

A three-dimensional collagen hydrogel pattern was expanded and identified for B16.F10 melanoma tumors by Heller et al. [39]. Cells in this three-dimensional medium showed less multiplication than cells in a regular two-dimensional culture medium. In particular, the primary expression level of many genes differs from that of customarily grown cells. In this study, cells compared in these surroundings showed diversities in multiplication, basal and induced gene expression, protein expression, and transfection surfaces. A remarkable number of melanoma cells in each growth medium were transfected by plasmid electroporation (electrotransfer), although expression was only detectable on the level of three-dimensional structures. The cellular responses to plasmid entrance, as indicated by regulation of chemokine involvement and proinflammatory cytokines vary based on growth medium like mRNA levels. Multiple receptors detect specific DNA patterns (DNA sen-

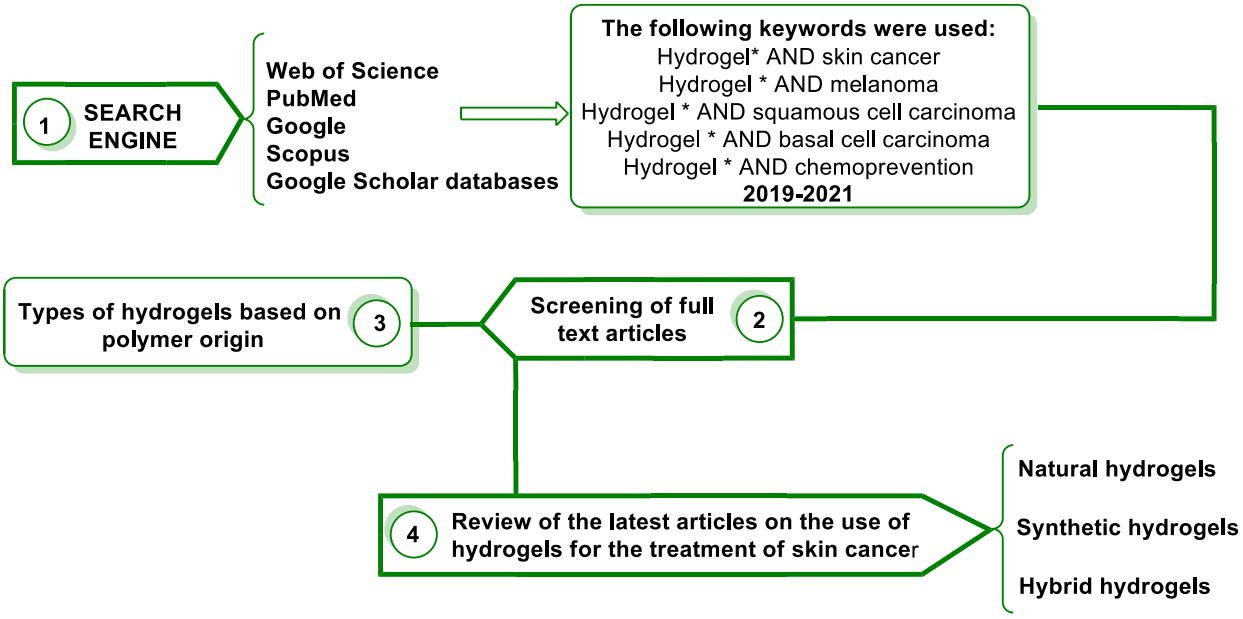

Fig. 2. Chart related to the content provided in this review.

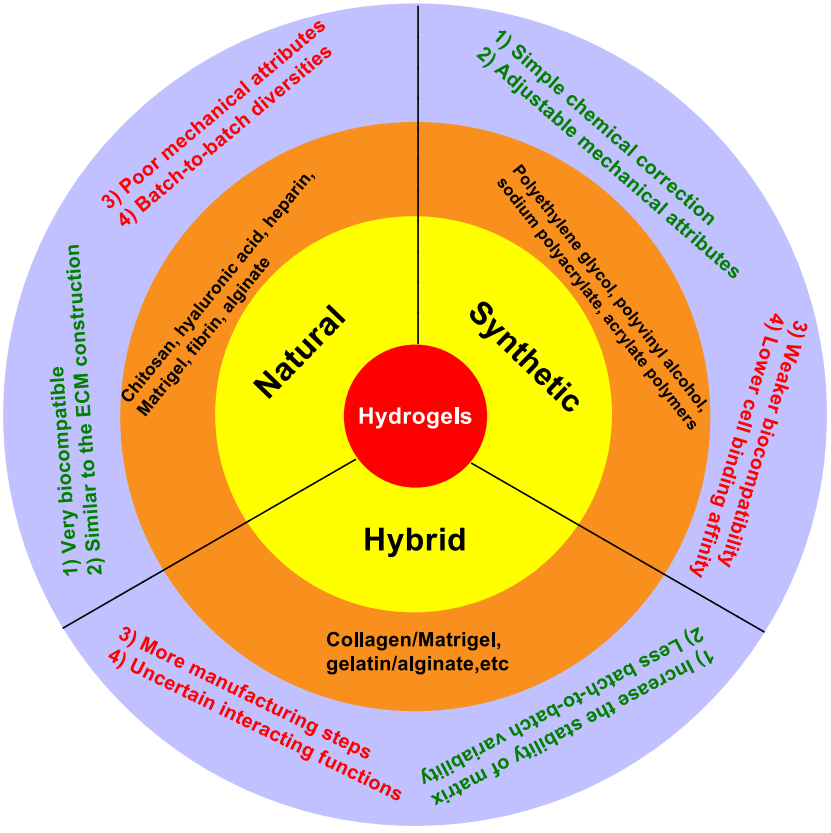

Fig. 3. Benefits and drawbacks of hydrogels from various origins (benefits are highlighted in green and drawbacks are marked in red).

sors). Since the plasmid DNA was surrendered when the cells were connected in two-dimensional or three-dimensional media, the mRNAs of the p204 DNA sensor and the inflammatory mediator TNFα were regulated only in the cells receiving the pulse. The Nucleic acid is an evident need for gene treatment. Activation of nucleic acid PRRs may cause associated inflammation with viral [40] and non-viral [41] gene therapy. This result is generally useful in inducing vaccine immunization or enhancing cancer therapies. However, it may be harmful to other therapies, such as protein replacement therapy or gene modification. In general, this research shows that there are scrutable diversities between cells in different environments and in their biological replies, which makes distributions more inaccurate from *in vitro* to the *in vivo* test environment.

A α-chitin polysaccharide-based hydrogel comprising anticancer drug plumbagin (0.3%) was expanded by Nair et al. [42] (To reduce the systemic side effects). Alpha-chitin hydrogel loaded with

Table. 1
A brief history of the hydrogel system for skin cancer management.

Type of cancer	Cell	Polymer (hydrogel)	Crucial results	Year	Refs.
Skin	HEK 293T normal cells and A375 melanoma cancer cells	Carboxymethylcellulose polymer with anticancer drug doxorubicin	Modulate cytotoxicity and drug release, with moderate effect	2018	[27]
Skin	Cell lines. B16.F10 mouse melanoma cells	PTX-CTs-embedded hydrogel(PTX-CTs/Gel)	Reduction of tumor growth in combination with the systemic chemotherapy by Taxol	2018	[28]
Skin	Cell lines. B16.F10 mouse melanoma cells	DOX, IL-2 and IFN-γ based on poly(γ-ethyl-L-glutamate) poly(ethylene glycol) poly (γ-ethyl-L-glutamate) (PELG-PEG-PELG) hydrogel	Improving therapeutic efficacy against B16F10 melanoma- xenograft without clear side effects	2018	[29]
Skin	Mouse melanoma cells B-16 and skin fibroblast cells L929	lanthanum-doped chitosan-(La-CS) hydrogels	Prevention of proliferation of B-16 melanoma cells and reduction toxic side effects for L929 skin fibroblast cells	2018	[30]
Skin	Radial growth phase human melanoma cells (WM35) and metastatic A375 cells	PEG–peptide hydrogels	3D spherical models decreased drug sensitivity in cells compared to two-dimensional ones	2017	[31]
Skin	Mouse myoblast cells (C2C12) and Human liver cells (HL7702)	Sericin/dextran composite- hydrogels	Substantial suppression of tumor growth using hydrogel loaded with Doxorubicin	2016	[32]
Skin	$CD8^+$ T cells in a mouse model	Chitosan hydrogel	Equal effect of vaccination with chitosan hydrogel compared to dendritic cell vaccination in tumour protection	2015	[33]
Skin	Human cell lines derived from radial growth phase (WM35) and metastatic melanoma (A375)	PEG hydrogels	Reduction of cytotoxic effects of PLX4032 on more compliant substrates by Metastatic A375 cells that led to decreased proliferation more than an increase in apoptosis	2014	[34]
Skin	Cell line – B16-F10	Hydrogels of curcumin and its inclusion complexes of hydroxypropyl-ß-cyclodextrin	Transdermal effect and cytotoxicity on B16-F10 cells	2014	[35]
Skin	Cell line M14 ADR2	Nanohydrogels (NHs) based on cholesterol-graft-hyaluronic acid (HA-CH)	BSAO immobilized on injectable NHs based on HAcholesterol derivative is a new instrument in the treatment of melanoma cancer cells	2013	[36]

plumbagin (PCHG) was chemically and physically specified. The liberation of plumbagin from the PCHG displayed a low and stable release of 33.8% in six days. Porcine skin penetration experiments *In vitro* showed skin penetration of plumbagin from Plumbagin loaded α-chitin hydrogel was 35.05 $\pm$ 0.73% after 48 h. The existence of 1% polyethylene glycol (PEG) and 1% Tween-80 acts as special boosters in the PCHG formula, which increases the penetrance of the plumbagin skin. The anti-cancer activity of PCHG was confirmed *in vitro*, containing 1% tween 80 and 1% PEG against the A375 melanoma cell line. Preliminary results of these studies revealed that PCHG-TP could be utilized as a topical hydrogel to treat different types of skin cancer. The anti-cancer activity of Plumbagin has been demonstrated *in vitro* on several cancer cell lines such as lung, ovarian, colon, breast, and so on. Further researches showed that Plumbagin successfully induces paraptosis using inducing extensive cytoplasmic vacuum and cell death in some cancers [43–45].

From *Achyrocline satureioides*, there was isolated 3-*O*-Methylquercetin (3*O*MQ), a natural 3-*O*-methylflavonoid, which was purified by high-efficiency reverse flow chromatography on a semi-preparative measure. The results showed that significant purity 3*O*MQ (98%) can be acquired using HPCCC (high-performance counter current chromatography) in semi-preparative action from Achyrocline satureioides. Isolated 3*O*MQ was appraised as opposed to the A375 human amelanotic melanoma cancer cell tiers with varying degrees of aggression (A375-A7, A375-G10, and A375-PCDNA3). The studies revealed that 3*O*MQ decreased the cell livability in all strains and showed dose- and time-related responses. To acquire hydrogels for the topical therapy of melanoma was utilized 3*O*MQ. Therefore, 3*O*MQ was inserted into hypromellose hydrogels with/without various cyclodextrins (CDs). HPMC hydrogel contains HP-β-CD, a formulation suitable for 3*O*MQ skin delivery, and can target melanoma cell proliferation sites. *In vitro*, this hydrogel displayed a release of 3OMQ (Franz cell model) of about 100%. In general, these results indicate that 3OMQ can be separated from Achyrocline satureioides using HPCCC on a semi-preparative measure and showed cytotoxic activity as opposed to melanoma cells [46].

For the treatment of melanoma, a pectin-based hydrogel comprising nano-capsules was described by Gazzi et al. [47]. The first goal of this study was to appraise the efficacy of imiquimod nanoencapsulation on melanoma. Imiquimod nanoencapsulation presented a higher cytotoxic result than the free drug as opposed to SK-MEL-28. Imiquimod-loaded nano-capsules (NCimiq) displayed a notable time-related reduction in cell livability after therapy at 3 μmol/L (79% viable cells in 24 h and 55% in 72 h), which was not seen in drug-treated cells (IMIQ) (99% viable cells in 24 h and 91% in 72 h). The second aim was to expand the hydrogel, including the drug-containing nano-capsules (PEC-NCimiq). *In vitro* studies exhibited that 63% of imiquimod after 2 h was liberated from the pectin-supported hydrogel comprising the drug (PEC-imiq), while 60% of the drug was liberated after 8 h from PEC-NCimiq. In the penetration study, 2.5 μg of imiquimod penetrated the skin during 8 h after the primary tangency of PEC-NCimiq, while only 2.1 μg of drug penetrated after 12 h of contact since PEC-imiq was evaluated. Pectin-relying hydrogels activate the drug perme-

Table 2
Combination (% w/w) of VNR gel formulations.

VNR		Propylene glyco	PF-127 aqueous solution			
			15% (w/w)	20% (w/w)	23% (w/w)	25% (w/w)
G15	0.5	29.5	70.0	—	—	—
G20	0.5	29.5	—	70.0	—	—
G23	0.5	29.5	—	—	70.0	—
G25	0.5	29.5	—	—	—	70.0

PF-127: Pluronic® (F-127), Vinorelbine (VNR).

ation in all layers of skin, mostly the dermis (PEC-NCimiq = 6.8 μg and PEC-imiq = 4.3 μg). In the adhesion study, PEC-NCimiq revealed the most adhesiveness compared to PEC-imiq (42% removed from the skin than 71% removed from the skin, respectively). As a result, the nanoencapsulation showed greater cytotoxic efficacy of imiquimod in SK-MEL-28, and the integration of drug-containing nano-capsules into pectin-based hydrogels displayed higher adhesion and deeper permeation of the drug into the skin.

Oligomeric proanthocyanidins (OPC) having hydrogel trellises can act as an average, photothermal factor for treating melanoma and bioactive substances for wound healing. With grapeseed extracts, OPC was investigated as a photothermal factor and supplied excellent and controlled photothermal capability to the hydrogel lattices. The rheological character of the hydrogel lattices responded to Near Infrared (NIR) laser ability density, OPC quantities, and irradiation time. The high temperature induced by OPC comprising hydrogels under Near Infrared laser irradiation could successfully destroy melanoma cells and repress the tumor growth. Multiplication and relocation of human dermal fibroblasts (HDFs) and human umbilical vein endothelial cells (HUVECs) are supported by OPC containing hydrogels and boost angiogenesis and skin repair in tumor and severe wounds. Overall, the OPC-containing hydrogels exhibited controlled photothermal, rheological, and compressive mechanical properties under NIR laser stimulation, and exhibited excellent biocompatibility for melanoma treatment and wound healing [48].

4.1.2. Synthetic hydrogels

De Melo Fonseca et al. [49] constructed hydrogels with VNR solubilized in the drug vehicle propylene glycol in combination with the copolymer PF-127, and these hydrogels were selected based on their better penetration index than some other examined vehicles. The target of this research was to expand Pluronic® F-127 (PF-127) hydrogels, including vinorelbine (VNR), for percutaneous injection route. G20 and G23 formulations showed excellent VNR penetration profiles between the PF-127 hydrogels appraised VNR and propylene glycol. Diffusion profiles and their influence on VNR in a Franz diffusion cell were investigated. Their rheological manner, optical perspective during storage, and divination in VNR silicon adsorption were assessed by GastroPlus®. Then, they provided identical release profiles with skin-compatible pH. Formulas G20 and G23 revealed similar release and diffusion profiles to G20, which showed higher diffusion of VNR at 8 h ($p < 0.05$). The cumulative infiltration rate was 495.2 ± 46.7 μg/cm^2 at 24 h. In addition, their activity was examined on melanoma SK-MEL28 and MV-3 cell lines to assess survival and cell multiplication. In addition, their movement was investigated on melanoma SK-MEL28 and MV-3 cell lines to assess survival and cell multiplication. Although multiplication profiles were identical, at VNR concentrations of 75 and 100 μg / ml, the cell livability of both melanoma cells in the attendance of G20 was less than G23 after 24 h of treatment. Since incorporated with a pharmacokinetic model *in silico*, the evidence shows that dermal VNR administration can be a promising alternative to intravenous injection, and that the G20 formula is a favorable candidate for direct use on melanoma. Table 2 displays the combination of the VNR gel formulation containing the drug at an ultimate concentration of 5 mg /g. For preparing the solution formulation, 5 mg VNR per gram of vehicle was added and dissolved by magnetic stirring. Azone® (5% (w / w), NetQem® - Durham, North Carolina, USA) was added to the propylene glycol solution as a penetration enhancer. For gel formulations, aqueous solutions of Pluronic® F-127 (PF-127, Sigma Aldrich®, St Louis, USA) in polymers of 15, 20, 23 and 25% (w / w) were dissolved overnight in refrigerated water [50]. Then, a solution of propylene glycol containing VNR was slowly added to various aqueous solutions of PF-127 at 4°C for 30 min under magnetic stirring. In next step, the gels are formed at ~25 °C from The corresponding formulations G15, G20, G23 and G25.

Tang et al. [51] developed a silk-inspired *in situ* gelation structure comprising chlorine e6 and methacrylated silk fibroin (SF), which displayed boosted antitumor results and precipitated wound healing. SFMA-Ce6 hydrogel is permitted to create at wound sites by Light-induced gelation. Due to the adsorption valence of SF hydrogel macrophages, favorable anti-tumor immune responses can be activated by near-controllable infrared irradiation to attain a compound of photodynamic treatment for considerable assuagement of melanoma relapse. In addition, the impressive photodynamic antibacterial property of this bioactive system with light-modulating macrophage phenotype capacity enhances significant tissue growth by regenerating hair follicles to repair Staphylococcus aureus-infected wounds. This multi-purpose hydrogel system, as an optimal wound dressing, supplies a novel substrate for the promising therapy of melanoma and skin reconstruction.

Injectable brush biopolymers hydrogels as supported drug-delivery vehicles were planned for the therapy of melanoma by Shukla et al. [52]. Polyurethane bonding on linear dextrin was synthesized to qualify hydrophilic-hydrophobic equilibrium for delivery of the adjusted drug. The slow increase in molecular weight along with the contact angle shows a variation from a hydrophilic to a hydrophobic and brush-like complex structure. The properties of bond copolymers are regulated by bond density. The created links are stable and potent (thermally and mechanically). An injectable hydrogel is made by embedding drug-charged brush copolymers in methylcellulose to control long-term release, more significantly by keeping the drug liberation at a constant speed. Cellular studies have shown that the biocompatible nature of the brushes, co-polymerized with the controlled and gradual release of the drug, has a significant cytotoxic effect on cancer cells. Drug-labeled contrast factor endocytosis reflects the more extensive transmission of biologically active substances within the cell as observed through cell uptake studies. Research on melanoma mice shows the actual effect of controlled drug liberation from injectable hydrogels with notable assuagement of melanoma without any side results compared to the intense toxic efficacies discovered in conventional chemotherapy. The particular use of drug-containing hydrogels below the tumor makes this sys-

tem extremely efficient through confinement. Therefore, injectable copolymer brush hydrogels are a good tool for controlling drug release for cancer therapy in the future.

Nazir et al. [53] synthesized nanodrug with loading chemotherapeutic factor, Fluorouracil (5FU), onto the reduced graphene oxide (rGO). The synthesized nanodrug was loaded by eliciting of arabinoxylan (ARX) from the shell of *Plantago Ovata* and Conversion into carboxymethylarabinoxylan (CMARX). The researchers have combined CMARX / nano-drug with various amounts of tetraethyl orthosilicate (TEOS) to prepare the rGO-5FU-CMARX nanocomposite hydrogel system for the care and treatment of melanoma skin cancer. These rGO-5FU-CMARX nanocomposite hydrogel systems have shown various chemical and physical attributes. These attributes were investigated by SEM, FTIR, swelling in different media, biodegradation in PBS media, and water contact angle. Based on diverse crosslinking, the nanocomposite hydrogels showed various anticancer and antimicrobial activities. A patented rGO-5FU-CMARX nanocomposite hydrogel drug delivery system was extended for the treatment of virulent melanoma skin cancer after bacterial infections. The surface area of rGO provides a significant amount of drug loading and liberation under the effect of photothermal. By humidity and thermal shock, developed nanocomposite hydrogels can provide lasting release of drug shipments.

Hwang and Jin [54] recommended the use of a binding hydrogel for the treatment of melanoma, which allows the size and number of indocyanine green (ICG) to be controlled for photothermal treatment (PTT). In this study, a hydrogel with the ability to connect called (poly (acrylamide-co diallyldimethylammonium chloride); PAD) containing ICG as a near-infrared (NIR) absorbing was constructed using a biocompatible polymer. The temperature of PAD-ICG is increased by 808 nm laser irradiation. ICG is protected as opposed to decomposition by hydrogel. As a result, PAD-ICG can be reused for Photothermal Therapy. Binding of PAD-ICG to a zone with melanoma in mice successfully eliminated melanoma by irradiation using NIR laser. Therefore, the data showed that PAD-ICG is an intelligent substance that can treat the target of choice against melanoma in humans. High resistance, good biocompatibility, and controlled drug liberation are main benefits of this hydrogel as a vehicle for the delivery of anticancer medicines and hydrophobic PTT factors.

Huang et al. [55] synthesized photocrosslinkable dextran methacrylate (DexMA), for the earliest time, utilized DexMA hydrogel to expand a novel kind of Microneedles (MNs) for continual skin prescription. Microneedles technology has many benefits as well. It is an ideal local transdermal drug delivery way. Dextran methacrylate hydrogel (30 %) has low viscosity, excellent mechanical resistance, constancy, and is biologically immune (According to the specification of DexMA hydrogels). This prepared hydrogel can interpenetrate the epidermal substrate and attain stable drug release. Trametinib (Tra) and Doxorubicin (DOX) are anticancer medicines accepted by FDA. In addition, Trametinib can inverse P-gp-mediated multidrug stability to successfully prevent the doxorubicin efflux by P-gp. In this research, MNs were utilized for simultaneous loading of Tra and DOX, and synergistic was obtained in B16 cell xenograft nude mouse model. The DexMA hydrogel Microneedles can increase the dermal delivery of tiny molecule drugs and decrease systemic toxicity and side effects. The depth of drug transfer can reach at least 600 micrometers (μm). The best inhibitory efficacy is obtained by MNs loaded with Tra and DOX (Fig. 4).

The objective of this research was to further evaluate the antitumoral efficacy of $(PhSe)_2$-supported polymeric nanocapsules (NC $(PhSe)_2$) opposed to a cell line of persistent melanoma (SK-Mel-103) and fabrication of a hydrogen gel based on xanthan gum for dermal application of NC $(PhSe)_2$. For laboratory assessment, cells were incubated with the release $(PhSe)_2$ or NC $(PhSe)_2$ (0.7–200 μM), and after 48 h, the MTT experiment, propidium iodide perception (necrosis marker) and nitrite surfaces were evaluated. The hydrogels were made by $(PhSe)_2$ solution with xanthan gum or thickness of the NC $(PhSe)_2$ suspension. They were determined polydispersity indicator, average diameter, pH, spreadability, drug amount, rheological profiles, and *in vitro* penetration in human skin. The researches revealed that NC $(PhSe)_2$ had higher antitumoral efficacy than free $(PhSe)_2$ and increased the nitrite extent. Total hydrogels exhibited pH values of about 7, drug extent close to the theoretical quantities (5 mg/g), and average diameter in the nanometric span. In addition, formulations were arranged as non-Newtonian flow with the behavior of pseudoplastic and appropriate spread-capability factor. Skin permeation research revealed that the composition extent for nano-based hydrogels was greater in the dermis layer, indicating its higher penetration, which is obtained by encapsulation of the composition. Therefore, this prepared hydrogel may be a special adjuvant therapy for melanoma treatment and help to improve the effectiveness of current intravenous drugs for melanoma treatment [56].

Xu et al. [57] expanded a wide range of nanocomposite hydrogel (Gel/PF127) with high mechanical attributes, hemostasis, and antibacterial activity. It was utilized for the dual diffusion system based on micelles and hydrogels used to maintain long-term release of paclitaxel (PTX) at the wound spot after melanoma surgery, thereby killing remaining tumor cells and superior repairing tissue faults. The outcomes displayed which PF127 nano micelles could successfully load PTX and liberate it in the tumor environment. In addition, quaternary ammonium gel lattice revealed excellent growth inhibition for *S. aureus* and *E. coli* and (inhibition rate up to 98%). Experimental results have shown that such nanocomposite hydrogels can quickly stop bleeding, prevent wound infection, apoptose tumor cells, and effectively prevent a recurrence. It, therefore, shows that building an *in-situ* chemotherapy platform that combines trauma repair and tumor inhibition significantly boosts relapse and trauma repair of melanoma. This efficient strategy might also supply a new idea for other postoperative cancer wounds and tissue reparation.

In this study, a nanocomposite hydrogel based on self-healing, injectable and antibacterial bioactive polypeptide was fabricated for skin cancer treatment, skin restoration, and *in vitro* and *in vivo* anti-infection. The multipurpose hydrogel was successfully prepared using a combination of bioactive single-dispersed polypopamine (BGN @ PDA) glass nanoparticles in an antibacterial hydrogel F127-ε-Poly-L-lysine. FCB hydrogel displayed a useful self-healing and shear-thinning manner with good injectable valence. FCB hydrogel (F: F127-ε-Poly-L-lysine; C: F127-Phe-CHO; B: BGN@PDA) has a fast photothermal function *in vitro* by successfully killing cancer cells with minimal cytotoxicity. In addition, FCB hydrogel showed great antibacterial ability against *E. coli, S. aureus*, and MRSA. The critical point is that FCB hydrogel can notably repress the tumor growth and disconnect the tumor by effective photothermal reply. FCB hydrogels can also significantly increase wound healing by stimulating collagen formation and angiogenesis. This indicates that FCB hydrogel is a favorable candidate for disinfection, tumor treatment, and wound healing [58].

In other study, Poly [(*R*)-3-hydroxybutyrate-(*R*)-3-hydroxyhexanoate] (PHBHx) has been copolymerized with poly (ethylene glycol) (PEG) and polypropylene glycol (PPG) oligomers to supply a sequence of new PHBHx containing polyurethanes (PHxEP). The synthesized PHxEP copolymers have displayed good thermal resistance and miscibility. All of them can form hydrogels at specific concentrations and temperatures, and the PHxEP-2 copolymer has the best gelling performance, which can be gelled at 8% (w / v) and 36 °C. The rheological results of PHxEP-2-based thermogels revealed its rapid gelation effect with increasing temperature and high resistance to increasing strain, frequency,

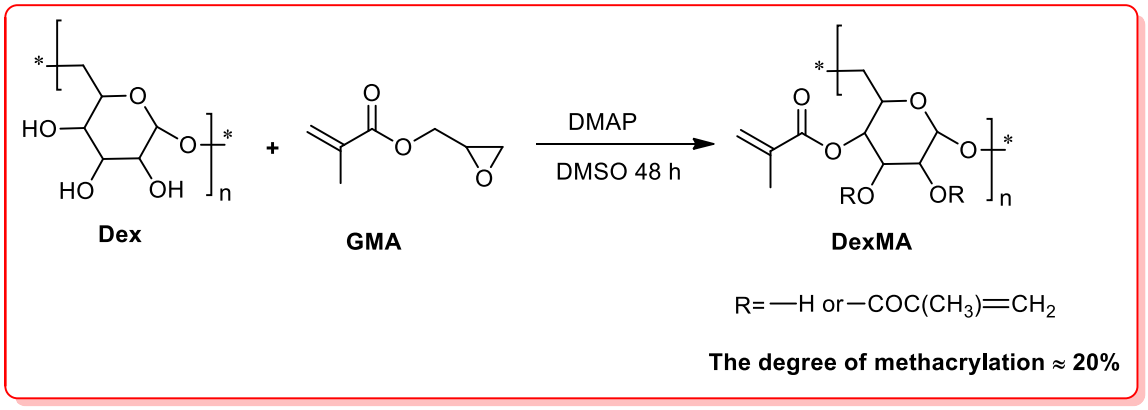

Fig. 4. Dex and GMA transesterification reaction equation to DexMA [55].

and high temperature. It also showed stable DTX release and had no effect on DTX effectiveness. After an initial assessment, a study was performed to inhibit tumor growth *in vivo*, DTX-loaded thermogels exhibited an improved therapeutic result on melanoma tumors, and no great tissue damage was observed in mice. The studies have shown that PHxEP-based thermogels can be a promising drug carrier for the ongoing delivery of anticancer medicines [59]. The anti-cancer drug Docetaxel (DTX), has good remedial results on a wide range of tumors. DTX is more cost effective and has better anti-tumor efficacy than the costly paclitaxel [60,61].

4.1.3. Hybrid hydrogels

Cattand et al. [62,63] developed a sprayable FS/SA composite hydrogel with possible usage for the treatment of skin tumor and ulcer healing and β-$FeSi_2$ (FS) extensively investigated as a thermoelectric material (due to its semiconductor properties). They revealed that FS, in addition to optimal photothermal function, could induce a Fenton reaction at the tumor site due to released iron ions. The cast iron ions can produce excess H_2O_2 in the tumor microenvironment and OH in acidic states. In addition, sodium alginate hydrogel combined with β-$FeSi_2$ (FS / SA) was prepared as immediate gelation following spraying *in situ*, which provides timely repair of tumor-induced skin wounds and effective suppression of tumors through photothermal treatment and chemodynamic therapy (PTT and CDT). Also, FS / SA hydrogel, due to the presence of FS can effectively kill tumor cells (up to 95%). The *in vivo* tumor growth of SA-10FS + NIR group was well suppressed with the benefit of high efficiency of synergistic CDT and PTT. Moreover, sprayable FS / SA hydrogels can enhance migration, endothelial cell differentiation, and angiogenic capacity *in vitro* and burn ulcers by releasing a definite quantity of Si and Fe ions, which is undoubtedly beneficial for wound healing. For the first time in this research, FS was used as bioactive materials, which enormously expanded the usage of FS excluding semiconductor materials. In addition, sprayable hydrogels have shown the benefits of simplicity, excellent yield, and timeliness in treating emergency wounds (e.g, burn wounds). In general, by integrating FS into FS / SA sprayable hydrogel, the composite hydrogel had the double role of tumor treatment and skin wound healing.

In this study, polysaccharide hydrogels (SCOD) were generated locally using oxidized dextran and *N*-succinyl chitosan by Schiff-base establishment for doxorubicin (Dox) delivery. According to rheological data, SCOD hydrogels include significant self-healing ability and injectable shear-shinning assets. It can also be widely broken down into body fluids by lysozyme. SCOD hydrogels were quickly loaded with Dox into precursor solutions, and the drug was released in a pH-dependent manner within one week. By *in vitro* evaluations, the ability of SCOD hydrogels loaded with Dox to prevent the growth of human A375 and murine B16 melanoma was confirmed. Polarization of TAMs towards M1 phenotype is efficiently induced by Dox-loaded SCOD hydrogels, which advocates an anti-tumorigenic tumor microenvironment. According to the experiments, SCOD hydrogels with local Dox loading showed significant anti-tumor activity against melanoma and performed better than the Dox at doses equivalent to intravenous transfusion. Overall, the self-healing polysaccharide and injectable hydrogels are a favorable procedure to improve locoregional control in melanoma [64].

Luo et al. [65] described a citrate-iron hydrogel scaffold (GPDF) active multipurpose therapy with healing ability to effectively treat postoperative skin cancer. This hydrogel is made with injectable, self-healing, biodegradable, antioxidant, UV protection, and photothermal function to prevent tumor recurrence and simultaneous wound healing. GPDF was built with a dual network by photo-crosslinking gelatin in the presence of Fe^{3+} ions and polycitrate-dopamine (PCD), where PCD can chelate with Fe^{3+} ions to form a dynamic coordination bond that results in hydrogel injection and self-healing performance. PCD-Fe^{3+} revealed an enhanced photothermal response and extremely high efficacy in inhibiting tumor recurrence after surgery (100%). PCD activated the apparent antioxidant function of GPDF, which by reducing the inflammatory response and improving angiogenesis, greatly enhanced wound healing and regeneration. This work demonstrated that the expansion of multipurpose hydrogel with precise functions designed was very favorable for complex treatment of wound repair and healing.

Wu et al. [66] have produced photothermal-efficient manganese doped calcium silicate (MCS) nanowires to incorporate into an alginate hydrogel to create a dual-purpose bioactive hydrogel (MCSA) integrating reverse heat treatment and wound healing proceedings. Due to the combination of calcium silicate nanowires as the *in situ* crosslinker factors and bioactive parts, the offered MCSA hydrogel had controllable gelling attributes, superior bioactivity, and rational stability. High photothermal effects of the eradication of melanoma under near-infrared (NIR) radiation have been obtained by Manganese doping in calcium silicate nanowires. However, the composite hydrogel (Mn^{2+} and SiO_4^{4-}) precipitated the wound healing procedure. Observations indicated that the expanded MCSA dual-purpose hydrogels are superior candidates for integrated photothermal treatment of melanoma and wound healing processes. Silicate bioceramics can leisurely liberate divalent metal ions by gently acidic conditions [67,68]. As a result, the compilation of manganese-doped calcium silicate in SA hydrogels can lead to a controllable gelling procedure to produce homogeneous hydrogels.

In this research, a hydrogel was made for biological construction, which is appropriate for mimicking the tumor microenvironment *in vitro* and further research is being evaluated as an *in vivo* novel model of vascular melanoma. The alginate/hyaluronic acid/gelatin (Alg/HA/Gel) bioink demonstrates good fidelity and wide cell survival speed. This proposed hydrogel was able to successfully do the cultivation of melanoma cells and *in vitro* fat-derived stem cells and cell distinction. In combination with the arteriovenous (AV) ring (*In vivo*), this is an inimitable model for studying the progression of melanoma, vascular, and finally metastasis that is very similar to human pathophysiology in a controlled and isolated environment. These outcomes reveal that this three-dimensional model (3D) is beneficial for molecular research and treatment expansion [69].

BSA/Silver nanoparticles (NPs) and their loaded hydrogel layers have been developed and recognized by Amatya et al. [70]. Then, its application (bioadhesive, mechanical, photothermal, and swelling attributes) has been evaluated for topical photothermal treatment (PTT) of skin cancer. The results showed that the BSA/Silver nanoparticles have an excellent photothermal property, and their light-to-heat transformation valency was well maintained when formulated as gel layers. The significant point is that adequate tumor temperature above 45 °C (necessary for tumor ablation) can be obtained *in vivo* with a low laser potency of 0.6 watts, and impressive inhibition of tumor growth can be achieved with one treatment. In general, the outcomes of this research revealed that BSA/AgNP- containing hydrogel layers might act as a successful but secure topical PTT factor for the therapy of skin cancer.

Gonsalves et al. [71] described an *in situ* nanocomposite hydrogel (NCH) comprising poly lactic-co-glycolic acid (PLGA)-carboxymethyl chitosan nanoparticles (186 nm) for topical treatment of skin cancer and ulcer healing. This reported hydrogel, consisting of a polymer backbone derived from citric acid, was gelled within 5 min and showed superior swelling (283% dry weight) and pressing ability of about 5.34 MPa (PEGMC polymer based on citric acid, PEGDA, and pH-responsive PC-2.5 NPs). PC-2.5 nanoparticles showed notably the superior release of chemotherapeutic drugs encapsulated at acidic pH, which confirms their pH-responsive conduct. PC-2.5 NPs were relatively evenly distributed throughout the system. The NCH also showed higher mechanical attributes and swelling. The integration of nanoparticles had no considerable efficacy in the hydrogel properties. NCH effluents were compatible with human skin fibroblasts at a concentration of 500 µg / ml and showed favorable pH-dependent medicine release and therapeutic influence on skin cancer cells G361 and A431. Multiple inhibition regions were seen in cultures of *Staphylococcus aureus and E. coli* in NCH treatment, which confirms its antibacterial attributes. These studies suggest that pH-reactionary NCH can be utilized as an adjunctive therapy in skin cancer and wound healing (Fig. 5).

In this study, a hybrid hydrogel (HGel- NLC_{DTX}) was synthesized with anesthetic and antineoplastic effects by de Moura et al. [72]. This hydrogel was constructed of docetaxel (0.5%) loaded in nanostructured lipid carriers (NLC) and a polymeric matrix of xanthan-chitosan comprising lidocaine (2%). CryoEM accuracy of the hybrid hydrogel showed the preservation of the nanoparticle construction even after placement in the polymer matrix. This system also demonstrated the false properties of plastic as desired for stable hydrogels. Cell livability experiments have shown that the cytotoxicity of free docetaxel (DTX) decreases after encapsulation in the hybrid formulation, resulting in continuous drug release. *In vivo* evaluation showed that hybrid hydrogels could inhibit tumor growth equivalent to conventional therapy (free DTX). In addition, treatment with hybrid hydrogels did not show any side effects in biochemical, histopathological, and physical parameters. These outcomes confirm that loaded NLC related to lidocaine-in-hydrogel can be a substitute and favorable biocompatible formulation for the therapy of melanoma. The observations also showed the significant effects of lidocaine (analgesic and anti-tumor) on the treatment of melanoma.

Zheng et al. [73] reported a multifunctional nanocomposite/micelle hybrid hydrogel (CFMG) for photothermal and bioenzyme boosted chemodynamic treatment (CDT) of both skin cancer and bacterial incursion. The multipurpose hybrid hydrogel was constructed by combining MoS_2@$MnFe_2O_4$ nanocomposites in a chemical cross-attached hydrogel of chitosan-linked-dihydrocaffeic acid (CS-DA) and aldehyde Pluronic F127 (F127-CHO) micelles loaded with glucose oxidase (GOx). Stable GOx-induced release using the pH-reactive bio decomposition of the hybrid hydrogel could constantly use inside the tumor glucose, generate H_2O_2, and raise acidity. Meantime, the quick liberation of catalytic Fe ions from MoS_2@$MnFe_2O_4$ nanocomposites in the slowly increased acidic environment catalyzed the dissociation of H_2O_2 into extremely toxic •OH through Fenton-like reaction to induce cell death. The CFMG hydrogel showed a skin tumor with a synergistic enhancement in bioenzyme and photothermal. It displayed almost perfect appeasement of the tumor both *in vivo* (97.6%) and *in vitro* (98.8%) using incorporating spatially and temporarily controlled photothermal hyperthermia. In addition, due to cationic chitosan and increased OH production, CFMG hydrogel also showed an impressive bacterial eradication (≥99%) *in vitro* and *in vivo*. Overall, CFMG hydrogel showed significant potential for treating skin cancer and antibacterial infection simultaneously.

For impressive multidrug-resistant (MDR) bacteria, infected-wound healing and melanoma photothermo-chemotherapy were expanded an injectable redox and light reactionary bio-inspired MnO_2 hybrid (BMH) hydrogel by Wang et al. [74]. BMH hydrogels were innovatively constructed by non-covalent self-assembly, and MnO_2 nanosheets were created for the first time by covalent oxidative polymerization of catechol-functionalized chitosan. This hydrogel showed superior injectable, shear-thinning, sticky, redox/light reactive, and contact-active antibacterial abilities. Well-designed BMH hydrogels can significantly reduce hypoxic tumor microenvironment (TME) by breaking down endogenous H_2O_2 to O_2, releasing the anticancer drug DOX simultaneously. Enhancing the local usability of O_2 increased the DOX cytotoxicity as opposed to melanoma in a highly site-particular way. This study showed almost complete tumor suppression in both *in vitro* (98.6%) and large solid tumors *in vivo* (96.2%) with further combination with a spatially and temporarily controlled photothermal hyperthermia. In addition, BMH hydrogels can significantly enhance the healing of MDR-infected wounds *in vivo* by effectively eradicating bacterial invasion and permanently improving the oxidative and inflammatory wound microenvironment. Overall, BMH hydrogels showed great therapeutic potential for tissue engineering and cancer treatment.

Xu et al. [75] planned ibuprofen-modified methoxy poly (ethylene glycol)-poly (ethylene imine) polymer to create paclitaxel-supported micelles (PTX-M) and Carbopol 940 hydrogel comprising PTX-M (PTX-Gel) to correct skin paclitaxel delivery for the positional melanoma therapy. The PTX-M showed healthy performance in the skin permeation and preservation study. According to FT-IR analysis, this evidence was obtained that PTX-M or PTX-Gel mainly modified the spatial structure of skin lipid and keratin. Therefore, the fluidity of lipid molecules in the stratum corneum increased, and the polymer had a positive charge to increase skin penetration and deposition. The positive charge also increases the cellular uptake of PTX-M into melanoma B16, which leads to better cytotoxicity of PTX-M to B16 cells Taxol®. The Taxol® plus PTX-M/Gel group displayed superior anticancer properties than Taxol® alone (against B16 cells solid tumor experiment).

Capanema et al. [76] synthesized and reported hybrid hydrogels made of silver nanoparticles (AgNPs) placed in the carboxymethyl-

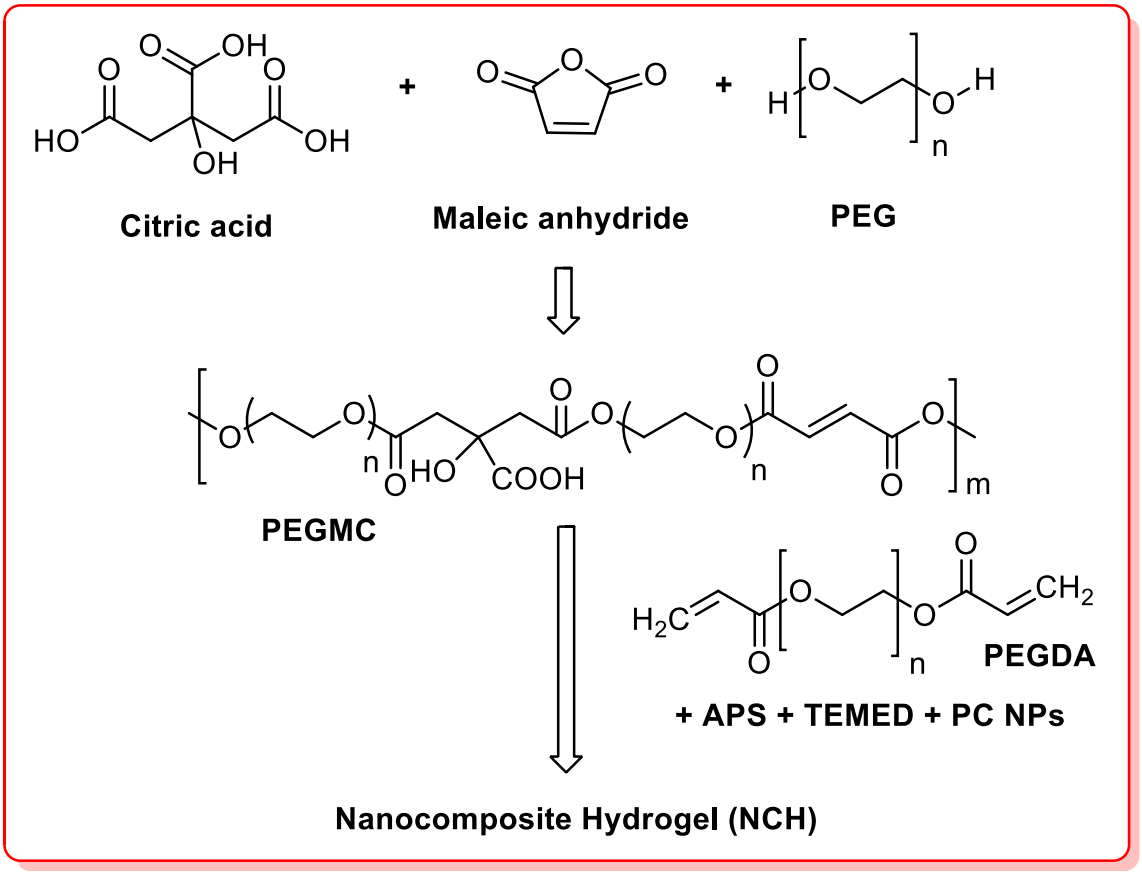

Fig. 5. Schematic representation of the synthesis and use of PEGMC polymer to create the NCH system [71].

cellulose (CMC) polymer reciprocal lattices connected to doxorubicin (DOX) the anticancer medicine. This system was synthesized by one-pot *in situ* reductions of Ag^{+} using carboxymethylcellulose polymer, pursued by the electrostatic conjugation with doxorubicin, to create colloidal nanocomplexes in aqueous media. These nanoconjugates bonded to citric acid (CA) under mild temperature and pH states. The observations showed the successful nucleation and fixation of spheral AgNPs nanocolloids, with the same size dispensation (d∼10 nm). The physicochemical attributes of the hybrid nanocomplexes (AgNP@CMC-DOX) were influenced by the grade of carboxymethylation (DS = 0.8 and 1.2) of CMC linked to the progress supramolecular nanocolloidal diffusions. These nanohybrids were mainly fixated using electrostatic interplays among carboxylate groups and amino groups, and formed vesicle-like nanosystems. In conclusion, these hybrids exhibited *in vitro* regulated DOX intracellular kinetics, indicating a synergistic efficacy with AgNPs to kill melanoma cancer cells. In addition, these hybrid nanocomposites showed antibacterial activity as opposed to gram-positive and gram-negative bacteria. Therefore, an innovative platform based on nanoparticle-polysaccharide-drug nanostructures was designed and developed to produce anti-cancer and anti-bacterial hybrid hydrogels to be used as an arsenal against skin cancer through topical drug chemotherapy.

Oktay and Alemdar [77] reported electro-responsive hydrogels using integration of poly(3,4-ethylenedioxythiophene)/poly(styrenesulfonate) (PEDOT/PSS) into the gelatin methacryloyl (GelMA) using photopolymerization method. Cytotoxicity experiments were accomplished using L929 cell series to assess cell adaptability. Inflation tests were performed to evaluate the water absorption capacity of the hydrogels. 5-Fluorouracil (5-FU) was chosen as the pattern medicine because it is realized as a topical drug for some types of skin cancer therapy. 5-FU release from the hydrogel was efficiently presented and bridled at emulated skin cancer (pH = 5.5) and below 0 and 1.5 V. The *in vitro* simulated medicine delivery tests performed showed that the drug release was higher when voltage was applied to the hydrogels. All observations indicate that GelMA-based PEDOT / PSS hydrogels with advanced electrical attributes could be a possible candidate as an electrically penetrable drug carrier for the therapy of skin cancer in future requests.

Shukla et al. [78] reported an injectable hydrogel that modulates drug release by assembling different progeny of cyclodextrin (CD) followed by a hydrophobic layer, which has long relied on a drug delivery vehicle for drug release, thus enabling impressive cancer treatments. The efficiency of the vehicle for its stable emission following non-Fickian kinetics is a controlled emission process. The extended substance is biocompatible, so long as the embedded drug supernatant shows better cell killing yield (75%) than pure medicine at the same time and concentration. *In-vivo* researches by albino mice intelligibly show the effectiveness of complete tumor healing within one month without any side factors, as is commonly seen in conventional chemotherapy.

Miao et al. [79] synthesized a new antitumor $Yb^{3+}[Yb(NO_3)_3]$-comprising chitosan hydrogel (Yb-CS hydrogel) using dissolution Yb $(NO_3)_3$ and chitosan in acetic acid solution and creating composite hydrogels with a freeze-drying procedure after adding sodium hydroxide to the reaction mixture. *In vitro* research has shown that Yb^{3+} creates cell death induction in Yb-CS hydrogels. In addition, the Yb-CS hydrogel prevented from a focal adhesion kinase (FAK)-related signaling route and induced B-16 cell anoikis although the Yb-CS hydrogel was less efficient in the normal skin cells of L929 mice. *In vivo* observations have shown that the Yb-

CS hydrogel prevents melanoma relapse in a nude xenograft tumor model in mice. In general, Yb-CS hydrogels could be utilized in anti-melanoma, mainly in preventing melanoma relapse. Lanthanides reveal anticancer results using overcoming cell multiplication and inducing cell apoptosis at higher concentrations, and promote cell development at down concentrations [80]. So, preserving proper concentrations of Yb^{3+} ion is the way to achieve therapeutic effects.

5. Conclusions

Recently, hydrogels have been used as a drug carrier for skin cancer drug delivery. A hydrogel drug carrier was considered due to great biodegradability, good biocompatibility, and low toxicity. The development of a drug delivery system for effective cancer treatment in which we can track *in vivo* activity non-invasively is highly desirable, primarily with the aim of avoiding or reducing side effects. One of the major benefits of developing a drug delivery system for targeted treatment of melanoma skin cancer is that it is easier to access than other cancers. For this reason, there will be the possibility of several progresses in this region (drug delivery system with the melanoma cancer model). Also, there are several studies that have planned drug delivery systems with various anti-neoplastic factors that are used to investigate various kinds of cancer, including colon cancer, breast cancer, and ovarian cancer. The previously mentioned methods can also be tested in melanoma skin cancer. The use of hydrogel-based formulations in melanoma skin cancer as an anti-proliferative delivery system has several benefits compared to other conventional drug delivery systems and treatments. This formulation of hydrogel caused lower side effects than synthetic chemotherapy. It can be very effective in the treatment of skin cancer. They can be synthesized from natural, semi, and synthetic polymers by physically or chemically cross-linking. In pried of cancer treatment, the hydrogel can load drugs with poor solubility or stability, and they act as a carrier for drugs. In conclusion, comprehensive research is needed to advance the clinical translation of hydrogel-based drug delivery systems.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request. We have presented all data in the form of figures.

Declaration of Competing Interest

The authors declare that they have no competing interests.

CRediT authorship contribution statement

Mahrokh Marzi: Writing – original draft, Writing – review & editing. **Mahsa Rostami Chijan:** Writing – review & editing. **Elham Zarenezhad:** Conceptualization, Visualization, Writing – original draft, Writing – review & editing.

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