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REVIEW ARTICLE

Therapeutic compression materials and wound dressings for chronic venous insufficiency: A comprehensive review

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Abstract

Chronic venous insufficiency (CVI) is a common disorder worldwide. Related pathophysiological mechanisms reportedly involve venous pooling and reduced venous return, leading to heaviness, aching, itchiness, tiredness, varicosities, pigmentation, and even lower limb ulceration. Approaches adopted to manage CVI at various stages of clinical-etiology-anatomy-pathophysiology include compression therapy, pharmacological treatment, ultrasound treatment, surgery, electrical or wireless microcurrent stimulation, and pulsed electromagnetic treatment. Among these, polymer-based therapeutic compression materials and wound dressings play increasingly key roles in treating all stages of CVI because of their unique physical, mechanical, chemical, and biological functions. However, the characteristics, working mechanisms, and effectiveness of these CVI treatment materials are not comprehensively understood. The present systematic review examines the structures, properties, types, and applications of various polymer-based compression materials and wound dressings used in prophylaxis and treatment of CVI. Existing problems, limitations, and future trends of CVI treatment materials are also discussed. This review could contribute to the design and application of new functional polymer materials and dressings to enhance the efficiency of CVI treatments, thereby facilitating patients' self-care ability and long-term health improvement.

KEYWORDS

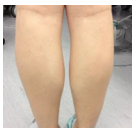
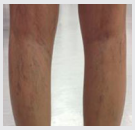
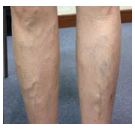
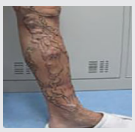
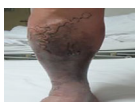
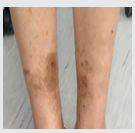
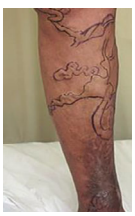
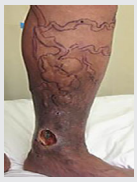
chronic venous insufficiency, prophylaxis, therapeutic compression materials and textiles, treatment, wound dressings

1 | INTRODUCTION

Chronic venous insufficiency (CVI) is a common medical problem where blood pooling hinders venous return, resulting in itchiness, tiredness, varicosities, and even ulceration of the lower limbs (Howlader & Coleridge Smith, 2003). CVI affects not only the legs but also one's physical and psychological wellbeing, leading to impaired body control and depression. In the Western adult population, CVI affects 10% of young adults, and its prevalence is as high as 77% in seniors aged over 70 years (Serra et al., 2017). In China, 8.9% of the population suffer from venous disorders of the lower extremities, with an annual illness rate of 0.5–3.0%, of which leg ulcerations account approximately 1.5% (Liu, Guo, Lao, & Little, 2016). The prevalence of CVI is generally far higher in women than in men (Özdemir & Surmeli, 2017), exhibits a consistent global increase, owing to the growing aging population and increasing prevalence of risk factors, such as diabetes, smoking, cancer, obesity, and arthritis (Pires, Nogueira, & Navarro, 2017).

The clinical-etiology-anatomy-pathophysiology (CEAP) classification is commonly adopted to categorize the stages and severity of CVI according to clinical assessment (Table 1) (Padberg, 2005). The spectrum of CVI includes (a) the primary stage (classes C_1–C_2, for example,

TABLE 1 Functional compression materials (devices) and wound dressings commonly used in prophylaxis and treatment of CVI according to CEAP classification (Padberg, 2005)

Classification	Symptoms	Modalities used	Function	Illustration
C_0	No clinical or functional sign, heavy, pains, and pruritus	• Elastic compression stocking (Ibegbuna, Delis, Nicolaides, & Aina, 2003)	• Improve blood circulation • Reduce leg tiredness • CVI prevention	
C_1	Telangiectasia or reticular veins	• Elastic compression stocking (Hague, Pherwani, & Rajagopalan, 2017; Liu, Guo, Lao, & Little, 2017; Partsch, 2012)	• Improve blood circulation • Prevent venous oedema	
C_2	Visible and palpable varicose veins	• Elastic compression stocking (Jakobsen, 1979; Rutgers & Kitslaar, 1994)	• Relieve varicose veins • Hide or cover for cosmetic purposes	
C_3	Venous oedema	• Compression garments (stocking and bandages) (Hardy, 2010) • Intermittent pneumatic compression (Mosti & Partsch, 2011)	• Reduce venous hypertension • Antiedema and skin dry • Relieve discomfort	
C_{4a}	Pigmented purpuric dermatitis	• Crepe bandage (Jain & Cifu, 2016) • Silver-containing dressing (Haug et al., 2006)	• Relieve or prevent itching	
C_{4b}	Lipodermatoscleosis or athrophie blanche	• Compression stockings (Middleton, 2007) • Bandages (Barron, Jacob, & Kirsner, 2007)	• Minimize allergic symptoms	
C_5	Healed venous leg ulcer	• Alginates dressings (Nilforoushzadeh et al., 2017) • Hydrocolloid (Gloviczki, 2017) • Hydrogel (Palfreyman, Nelson, Lochiel, & Michaels, 2006) • Collagen (Rath, Hussain, Chauhan, Garg, & Goyal, 2016)	• Adsorb exudates • Help wound healing • Reduce inflammation	
C_6	Venous leg ulcer	• Silver releasing foam dressing (Knetsch & Koole, 2011) • Honey-impregnated dressings (Gloviczki, 2017; Moore, 2008; Senet, Bause, Jørgensen, & Fogh, 2014)	• Adsorb exudates • Help wound healing • Reduce inflammation • Alleviate pain • Remove odour	

Abbreviations: CEAP, clinical-etiology-anatomy-pathophysiology; CVI, chronic venous insufficiency.

telangiectasia, reticular veins, and varicose veins); (b) the secondary stage with additional features (class C_3, e.g., edema), and (c) severe leg skin changes (class C_4, e.g., hyperpigmentation, eczema, and lipodermatosclerosis), and leg ulceration (classes C_5–C_6) (Engelhorn et al., 2017). Diverse modalities and techniques have been employed to manage CVI, including compression therapy (Hague et al., 2017), pharmacological treatment (Word, 2010), surgery (Word, 2010), and other adjunctive therapies (e.g., ultrasound (Maher et al., 2014;

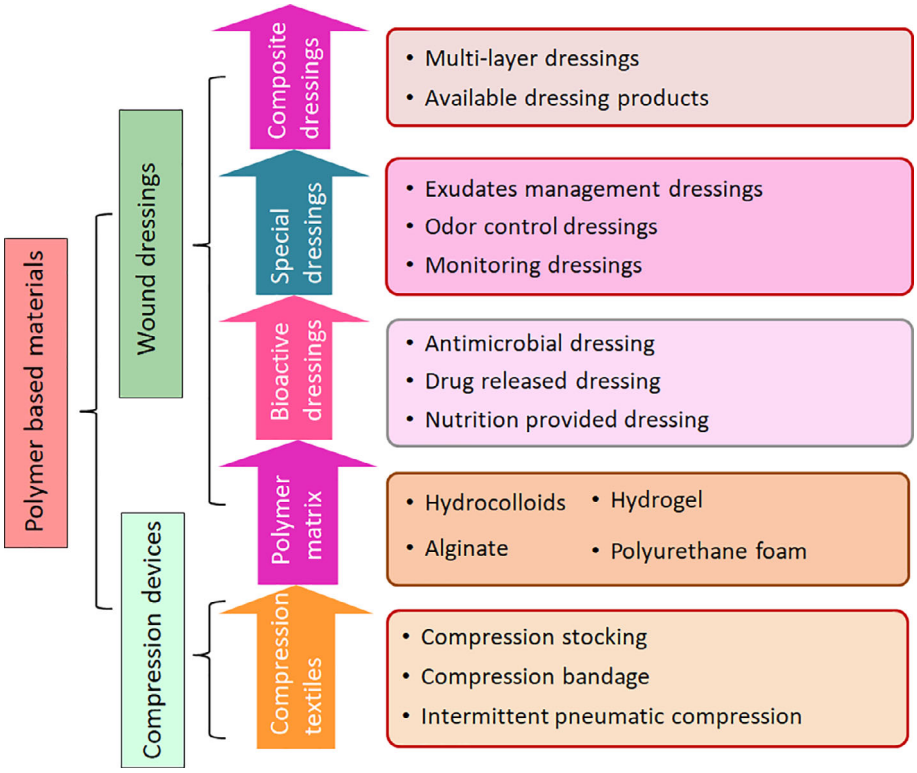


FIGURE 1 Summary of the different types of polymer-based compression materials (devices) and wound dressings for prophylaxis and treatment of CVI

Peschen, Weichenthal, Schöpf, & Vanscheidt, 1997), pulsed electromagnetic fields (Aziz, Cullum, & Flemming, 2013; Kwan et al., 2015), and electrical or wireless microcurrent stimulation).

As a critical treatment medium, polymer-based functional materials are widely applied to treat various stages of CVI because of their unique physical, mechanical, chemical, and biological properties (Cornish, 2017; Pang, Ibrahim, Bulstrode, & Ferretti, 2017). These materials are mainly fabric-based compression devices (e.g., compression stockings (Hobson et al., 2017), compression bandages (Wiklander, Andersson, & Källman, 2016), and intermittent pneumatic pump) used to treat CVI with C_1–C_6 symptoms, and functional wound dressings (e.g., scaffolds (Dickinson & Gerecht, 2016), pads (Brown, 2016), and sutures (Masood et al., 2017)) to facilitate primary treatment of leg ulceration (i.e., classes C_5–C_6) (Figure 1).

Conventional polymer materials such as naturally sourced polymers (e.g., cotton, silk, and wool) and modified natural polymer materials (e.g., cellulose, collagen, polylactic acid, chitin, and chitosan) (Alamgir, 2017; Boateng & Catanzano, 2015) have been applied to treat CVI at different stages based on CEAP classification; however, these materials have limitations, including those of mechanical properties (Mele, 2016), water uptake (Baghaie, Khorasani, Zarrabi, & Moshtaghian, 2017), and anti-infection properties (Sandreschi, Piras, Batoni, & Chiellini, 2016), related to potential infection or maceration of wounds (Dufresne, 2017). With advances in materials science, textile technology, and medicine and clinical diagnosis techniques, various advanced functional polymers (e.g., hydrocolloid, hydrogel, alginate, and polyurethane foam) have emerged and been applied in CVI treatment. These advances may not only provide wound prevention and tissue support and promote cleaning and healing, but also control exudates and odors, and increase tactile comfort. Figure 1 illustrates the categories of polymer-based functional materials used in CVI management. In practice, these new functional polymers can be used alone or in combination with compression fabrics, adhesive padding, foams, films, bioactive agent-based dressings, or composite dressings. However, to date, comprehensive understanding of the characteristics and effectiveness of these polymers remain insufficient, and thus the development of new functional compression materials (devices) and wound dressings to cater for diverse uses is limited.

This review integrates studies on materials science, medicine, physiology, biomechanics, and textile engineering to clarify five aspects of polymer-based compression materials and wound dressings in prophylaxis and treatment of CVI, including (a) material classification, (b) material characteristics, (c) working mechanisms, (d) material selection, and (e) future development. The research objectives were to enhance our understanding of polymer-based functional materials applied in CVI prophylaxis and treatment of lower extremities, and to facilitate cooperation among parties working in different fields from material fabrication to clinical medicine.

2 | POLYMER-BASED THERAPEUTIC COMPRESSION MATERIALS (DEVICES)

Compression therapy is a gold-standard conservative approach and cornerstone for prophylaxis and treatment of CVI. Its working principle (Figure 2) is to facilitate venous flow return from the lower limbs to the heart through pressure externally controlled by a compression

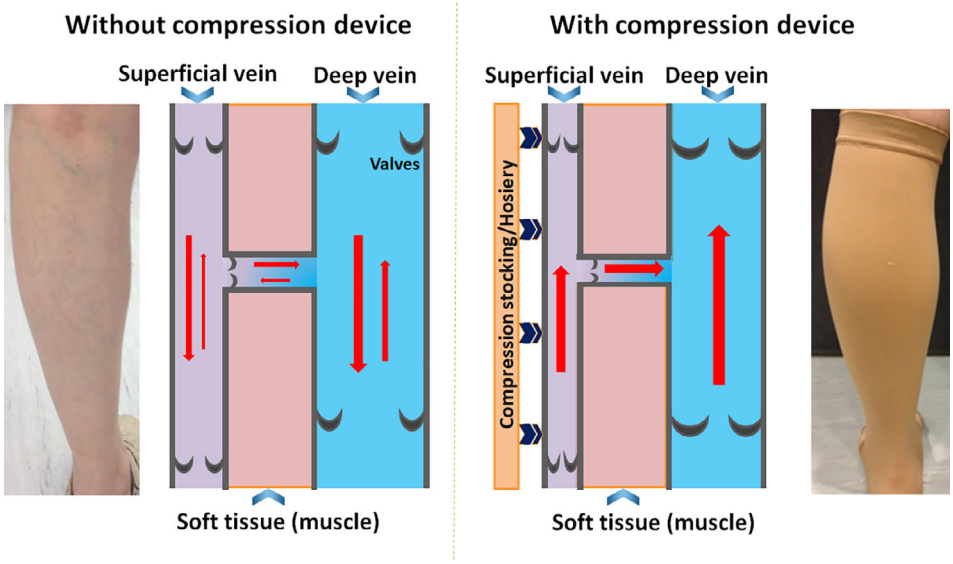


FIGURE 2 The action of mechanism of elastic fabric compression device

device (Lim & Davies, 2014). The highest compression is exerted distally (e.g., on the ankle), and the pressure decreases proximally up to the knee or thigh. Compression therapy can reverse venous hypertension (Van Bemmelen, Beach, Bedford, & Strandness, 1990), augment the skeletal muscle pump (Miller, Pegelow, Jacques, & Dempsey, 2005), and promote venous return (Sochart & Hardinge, 1999) and lymphatic drainage (Chan, Duffield, & Watsford, 2016). It also triggers sophisticated physiological and biochemical effects on blood vessels, soft tissue, and lymphatic systems (Lim & Davies, 2014). Depending on severity and the affected sites, fabric-based functional compression devices have been employed in the form of socks, boots, knee, or thigh-high elastic compression stockings (ECSs), pantyhose, elastic or inelastic bandages, and intermittent pneumatic compression (IPC) pumps (Andriessen et al., 2017; Liu, Guo, et al., 2017).

Among the aforementioned device forms, the ECSs are the most widely applied to treat all stages of CVI, largely because of its low profile, cost-effectiveness, and sustained mobile pressure delivery (Cullum, Nelson, Fletcher, & Sheldon, 2001; Nelson, Bell-Syer, Cullum, & Webster, 2000). Four compression classes that adhere to the RAL-GZ 387/1 standard are commonly employed, that is, light (Class I: 18–21 mmHg), medium (Class II: 23–32 mmHg), strong (Class III: 34–46 mmHg), and very strong (Class IV: 49+ mmHg) (Mosti & Partsch, 2011), as indicated by ankle skin pressure. The "pressure gradient", which reflects the proportion of pressure varying from distal to proximal leg, is designed to counteract the force of gravity. In general, ECSs with lower pressure (<21 mmHg) are associated with higher user tolerance and compliance than those with higher pressure (>30 mmHg) (Aghassi, Aurigemma, Folland, & Tighe, 2005). However, those with higher pressure are more clinically effective for preventing lower leg ulcer recurrence (Kapp, Miller, & Donohue, 2013) and promoting leg wound healing when fewer exudates and less swelling are presented in the legs (Fletcher, Cullum, & Sheldon, 1997). High noncompliance with sustained external compression has been reported by numerous clinical studies. In addition, compression therapy is invariably ineffective for treating chronic leg ulcers in the ankle, which tend to exhibit frequent critical relapse resulting in stiffening from *dermatofibrosis* (Asaf, Salim, & Tuffaha, 2018; Milic, Zivic, Bogdanovic, Karanovic, & Golubovic, 2009).

To date, myriad polymer-based compression devices have been fabricated by applying knitting, weaving, heat press, and high-frequency welding techniques and by different polymer materials (e.g., plastic and rubber) and yarns. The mechanical function of ECSs depends on the tensile strain behavior, shear, bending, thickness, and friction coefficient of compressive materials, as well as the fabrication techniques adopted (i.e., seamless circular knitting, flat-bed knitting, and warp knitting) (Liu, Liu, Lao, Ying, & Wu, 2018; Ng, Collins, & Tate, 2017). Heterogeneous compression fabric materials can be produced by core-spinning, core-twisting, air-covering, single-covering, and double-covering yarns in the form of various yarn blending and knitting structures (Figure 3). Core-sheath composite elastomeric materials are mostly used to construct compression shells by wrapping single or double polymer-based filament fibers (e.g., cotton, polyester, nylon, and viscose) around an elastic core stream of fibers (e.g., polyurethane and polypropylene). Elastomers with higher linear densities (e.g., 120–400 denier) serving as ground yarns are commonly interlaced with yarns with lower linear densities (e.g., 40–90 denier) to generate controlled pressure magnitudes and gradient proportions of ECS shells. The classification of bandages can be determined by four critical compression parameters: elasticity, layers, pressure, and component properties (Partsch et al., 2008). The exerted pressure of a bandage depends on the mechanical properties of a fiber type, and dynamic elasticity plays a prominent role in interface pressure variation over time. Highly elastic bandages are usually applied in multiple layers and can deliver consistent high compression in the lower leg. By contrast, bandages with low elasticity deliver higher operational pressure when the user is mobile but considerably lower resting pressure when the user is static (Dale et al., 2004; Venkatraman & Tyler, 2015). Bandages are generally supplied in kit form and are predominantly used by community nurses in patients'

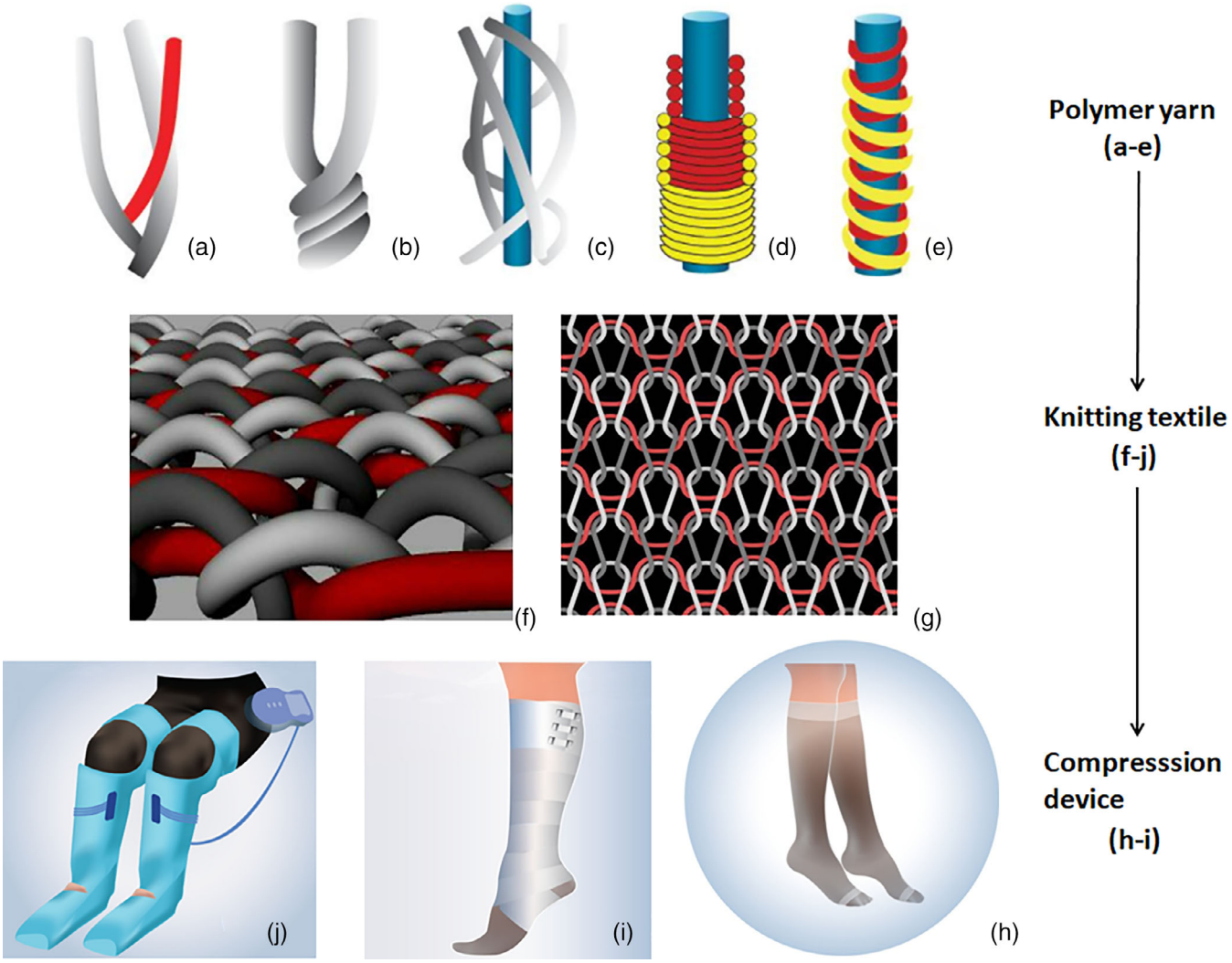


FIGURE 3 Functional polymer-based compression devices and commonly used fabrication techniques and polymer yarns. (a) Core spinning yarn. (b) Core twisting yarn. (c) Air-covering yarn. (d) Single and (e) double covering yarn. (f and g) Knitting structures. (h) Elastic compression stocking. (i) Bandages. (j) IPC. IPC, intermittent pneumatic compression

homes. Use of compression bandages should be subject to holistic assessment after application, including vascular diagnosis by physicians with training in assessment and application. Inappropriate application of bandages to lower limbs where circulation is compromised can result in disastrous consequences, including ischemia requiring amputation of the affected limbs (Brown, 2016).

An IPC pump is an inflating and deflating device that employs an air pump to control single- or multipolymer-based bladder(s) positioned around the affected lower limb; the bladder mimics the leg muscle's contractions and accelerates venous flow and lymphatic drainage (Gimmelreich, Karsilnikov, Litman, & Rosenblum, 2016; Young, Chok, & Wilkes, 2017). IPC can be applied for prophylaxis to treat deep vein thrombosis (DVT) and heal chronic leg ulcerations (Dunn & Ramos, 2017; Xiao, Xu, Zhu, & Sun, 2014). Studies investigated the effects of inflation modes and times, pressure levels, and multichamber versus one chamber IPC on physiological parameters in healthy individual and those with health problems (Allsup, 1994). The results indicated that multichamber IPC with higher pressure resulted in faster venous blood flow than did one chamber IPC with lower pressure. Differences in the trial results are related to differences in protocol design, testing techniques, and the sample population. Moreover, insufficient knowledge of the physiological mechanism of CVI and applied IPC process rendered these research results difficult to explain (Berliner, Ozbilgin, & Zarin, 2003).

3 | POLYMER-BASED FUNCTIONAL WOUND DRESSINGS FOR TREATING CVI

3.1 | Leg ulcer healing mechanism

Venous ulcers are a severe complication of CVI, that commonly appear when varicose veins become extensive in the lower limbs (Brown, 2016); these ulcers are responsible for more than 50% of all leg ulcerations (Nelzen, Bergqvist, & Lindhagen, 1994). Management of excess exudates relies on skilled assessment and comprehensive knowledge of the available adjuvant dressing options (Societies,

2007). The healing of leg ulceration is a long-term and complex process of epithelium restoration after injury, involving interactions among skin layers, cells, growth factors, vessels, and the extracellular matrix (Barrientos, Brem, Stojadinovic, & Tomic-Canic, 2014). The stages of chronic venous wound healing in the legs follow the organic processes of hemostasis, inflammation, proliferation, and maturation (Qing, 2017). Cytokines (e.g., vascular endothelial growth factor, and transforming growth factor-beta) promote ulcer healing through multiple routes, including facilitating the regeneration of various components in the matrix, preventing skin dehydration, and forming granulation tissue (Dorai, 2012). However, the healing process may be affected by various local and systemic factors, such as pain, hypothermia, radiation, infection, aging, inadequate nutrition, vitamin and mineral deficiency, and the overall health status of an individual. Local application of medications, surgery, and alternative wound dressings is common treatment options for leg ulcers (Dabiri, Damstetter, & Phillips, 2016). Among these options, wound dressings are the most effective for symptom control and optimization of the local wound environment. For example, an occlusive dressing provides moisture to a leg ulcer wound to promote growth factor synthesis, decrease the wound bed pH value, and prevent wound infection. However, no single adjuvant dressing is suitable for all stages of venous leg ulcers. Appropriate wound dressing can be applied in conjunction with compression device therapy in practice.

3.2 | Advanced polymer matrix for wound dressings

Wound dressings are usually divided into passive and interactive modes (e.g., bioactive dressings). Passive dressings are nonocclusive and are usually fabricated using woven and nonwoven cotton or polyester in modalities of gauzes and bandages. Several sterile gauzes are used to remove excess fluid and protect leg wounds by using fibrous materials. However, these dressings must be changed regularly, are often moistened from wound exudation, and tend to adhere to wounds, resulting in pain following removal (Souliotis, Kalemikerakis, Saridi, Papageorgiou, & Kalokerinou, 2016). Therefore, these traditional adjuvants are more commonly applied to cover and clean wounds with few exudates. By contrast, rather than serving merely as coverage, interactive dressings not only provide an ideally controlled environment (in terms of pH and temperature) to prevent wound dehydration but also interact with wound bed components (e.g., through absorb extrudes, *target*-based *sterilization*, and an improvement in tissue regeneration) to further promote ulcer healing. During the mid-1990s, polymer matrices used for interactive dressings were developed into various types, including hydrocolloids, hydrogels, alginates, polyurethane, and other polymer-based materials (Figure 4) (Saco, Howe, Nathoo, & Cherpelis, 2016; Zarrintaj et al., 2017).

3.2.1 | Hydrocolloids dressings

Hydrocolloids are fabricated by combining adjuvants (e.g., elastomers and adhesives) and gel (e.g., carboxymethyl cellulose, gelatin, and pectin) as agents. These materials allow moisture transference and are impermeable to bacteria. Hydrocolloid-based polymer materials are occlusive and absorbent and mostly applied as secondary dressings. They comprise a matrix layer (hydrocolloid layer) bonded onto a permeable layer with or without adhesive border and are used to treat shallow and cavity wounds, particularly leg wounds (Kumar, 2018). Their desirable characteristics are promotion of autolytic debridement of necrotic tissue and absorption of wound exudates. When a hydrocolloid dressing comes into contact with wound exudates, a gel layer is formed near the wound to facilitate rehydration in ulcers with low or moderate exudation (Límová & Troyer-Caudle, 2002). Laboratory study revealed that 3M Tegasorb hydrocolloid dressing (3M Health Care) exhibited higher permeability of moisture vapor and greater exudates-handling capacity than another dressing product, namely Duoderm CGF (ConvaTec) (Límová & Troyer-Caudle, 2002).

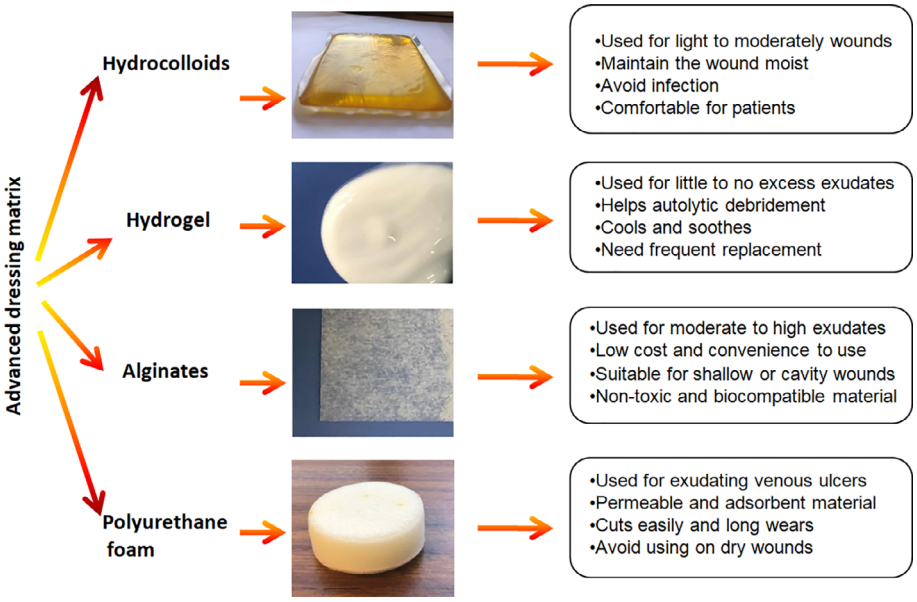


FIGURE 4 Different types of advanced polymer matrix for wound dressings

3.2.2 | Hydrogel dressings

Hydrogels are a type of hydrophilic materials that can be synthesized by poly (methacrylates) and polyvinyl pyrrolidine, both of which provide an ideal environment to facilitate tissue dehydration and exudate absorption from leg wounds. These materials have three-dimensional (3D) structure of hydrophilic polymers composed of 70–90% of water to donate fluid in order to facilitate autolytic debridement of devitalized tissue. Hydrogel dressings are usually formed through two pathways, namely 3D polymerization and direct cross-linking of water-soluble copolymers (Caló & Khutoryanskiy, 2015). In 3D polymerization, hydrophilic monometers are polymerized by using a cross-linking agent. Polymerization is often initiated by a free-radical catalyst (e.g., azo-bis (isobutyronitile)) combined with ammonium peroxodisulphate or through various radiation methods (e.g., gamma radiation, ultraviolet radiation, and electron beam radiation) (Lian & Ye, 2015). Gamma radiation cross-linking (Mozalewska et al., 2017) was employed to obtain sterile hydrogel materials for wound treatment. Hydrogel dressings are available as films with or without adhesive borders or amorphous gels; they are nontoxic and nonreactive with biological tissue. Kendall, DermaGauze, and Intrasite gel are commercial available hydrogel dressings.

3.2.3 | Alginates dressings

Alginate is a natural anionic polysaccharide heteropolymers (Figure 5) (Bruchet & Melman, 2015; Sun & Tan, 2013) that can be extracted from brown algae—a nontoxic, biodegradable, and highly biocompatible material (Sari-Chmayssem et al., 2016). Brown algae is widely applied in drug delivery and tissue regeneration because of its unique gel-formation property. Alginate comes in three main forms: sponge, hydrogel, and fibre (Thomas, 2000). After making contact with exudates, the polymer forms a gel to promote rehydration in wounds with many exudates, thereby enhancing autolytic debridement (Dabiri et al., 2016). Alginate adjuvant contains calcium salts and sodium salts of alginic acid, and the soluble calcium–sodium alginate is produced after alginate dressing has been applied to a moist leg wound to maintain the moist environment and promotes autolytic debridement (Alavi et al., 2016). Cutimed, Tegaderm Biatain, and Kaltostat are commercially available alginate dressings that conform to the shape of a wound to avoid the occurrence of periwound skin and delayed healing.

3.2.4 | Polyurethane foam dressings

Polyurethane foam dressings are fabricated from polyisocyanates and polyol in the presence of a catalyst with or without external heating of the reactor (Gokarneshan, Rachel, Rajendran, Lavanya, & Ghoshal, 2015; Landrock, 1995). The reaction mechanism of polyurethane materials is based on the occurrence of two processes: polymer formation and gas generation. Polyurethane foams or sheets are widely used as medical adjuvant dressings because of their high oxygen permeability, ability to transmit water vapor and carbon dioxide, and favorable biological properties. The mechanical features of polyurethane foams can be adjusted by molecular weight, equivalent weights of polyols, and type of isocyanate. They are highly flexible in that they can assume any size and shape without additional tapping. Their fluid absorption capacity varies with foam thicknesses (Figure 6), and they are easy to apply and remove. Polyurethane foam dressings can be employed as primary dressings in combination with hydrogel to reduce overgranulation in wounds with moderate to high quantities of fluid (Liu, Niu, Chen, & Chen, 2017; Sood, Granick, & Tomaselli, 2014).

3.3 | Bioactive wound dressings

Bioactive wound dressings generally comprise antimicrobial dressings (Alavi et al., 2016; Marston, Tang, Kirsner, & Ennis, 2016), drug-released dressings (Jull et al., 2016; Stana et al., 2017), and nutrition-providing dressings (Ray & Kalia, 2017). Recently, Hussain et al. systematically reviewed and reported a number of convincing evidences for bioactive materials embedded polymer-based chronic wound healing modalities, as well as the latest and innovative therapeutic strategies for management of chronic nonhealing wounds (Hussain, Thu, Shuid, Katas, & Hussain, 2017; Shao et al., 2017). Related studies also introduced technical solutions in development of different biomaterials used in wounds healings (Mir et al., 2018; Murray, West, Cowin, & Farrugia, 2019; Pop & Almquist, 2017). Figure 7 illustrates the classification of bioactive agent-based dressings applied to treat CVI.

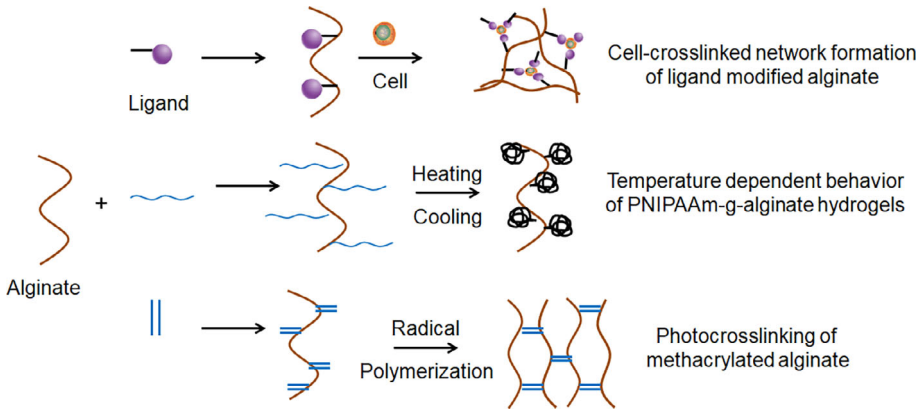


FIGURE 5 Schematic illustration of the preparation of different alginate dressing materials (image reproduced from 84 with permission)

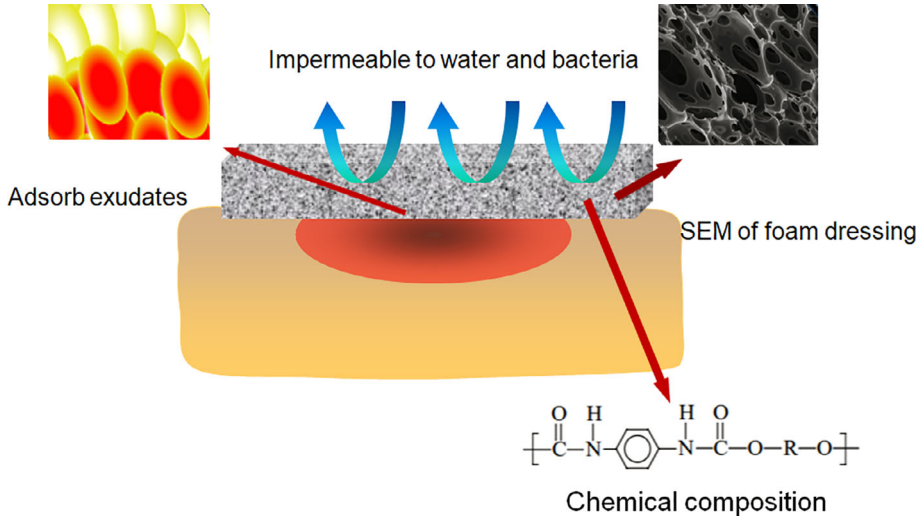


FIGURE 6 The structure and property of polyurethane foam dressings

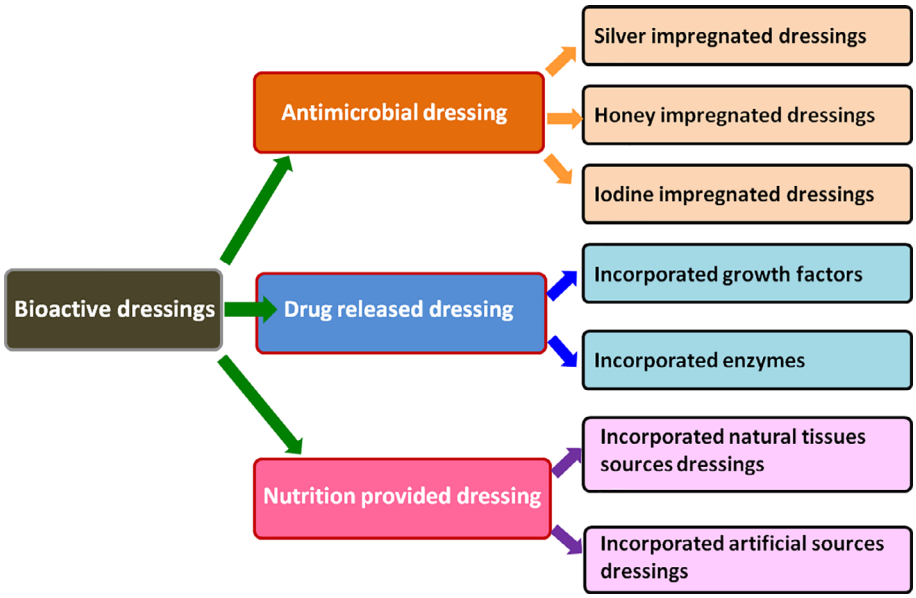


FIGURE 7 Different types of bioactive wound dressings used in CVI treatment. CVI, chronic venous insufficiency

3.3.1 | Antimicrobial dressings

Antimicrobial dressings are those that incorporate various antiseptic agents without antibiotics. Silver-, honey-, and iodine-based antimicrobial dressings are commonly used to prevent and treat infections in leg ulcers (Boateng & Catanzano, 2015) during management of CVI (Fronzo, 2016). Silver was commonly applied as an antibacterial agent at the beginning of the 20th century; however, its application in antimicrobial adjuvant dressings to treat chronic wounds is relatively new (Carter, Tingley-Kelley, & Warriner Iii, 2010). Silver-ions or silver-nanoparticles in dressings can react with and destroy the bacteria organisms contained in exudates. Studies have demonstrated that the silver dressings can reduce healing time and thus lower treatment costs (Sun & Tan, 2013; Woodward, 2005). Figure 8 displays the working mechanisms of silver foam dressings (Allevyn Ag) (Knetsch & Koole, 2011), which comprise three processes: (a) the dressing attracts bacteria while absorbing exudates (Figure 8a); (b) antimicrobial silver is released and activated (Figure 8b); and (c) silver particles attack bacterial cell wall and disturb cell metabolism through multiple methods to destroy bacteria (Figure 8c). Honey-impregnated dressings have antimicrobial and anti-*inflammatory properties*, *because honey* act as a catalyst for the growth of blood vessels, fibroblasts, and epithelial cells (Alam, Islam, Gan, & Khalil, 2014; Oryan, Alemzadeh, & Moshiri, 2016; Ousey, Roberts, & Leaper, 2016; Reimer et al., 2000; Watson & Hodgkin, 2005; Winter, 2017), all of which can be used to treat leg ulcers in modalities of pure medical-grade honey or honey mixed with other components (Norman, Dumville, Westby, Stubbs, & Soares, 2017). Medihoney and Activon Tulle are examples of commercial honey-impregnated dressing products. Iodine-based antimicrobial dressings can release free iodine after making contact with ulcer exudates. These dressings are usually formed of two structures, namely, iodine and concentrated cadexomer iodine paste injected into a dressing substrate (Zhou, Nahm, Badiavas, Yufit, & Falanga, 2002). In addition, gauze-based and ointment-impregnated dressings exhibit favorable antibacterial characteristics in practice, for example, Bactigras gauze dressing (Smith & Nephew).

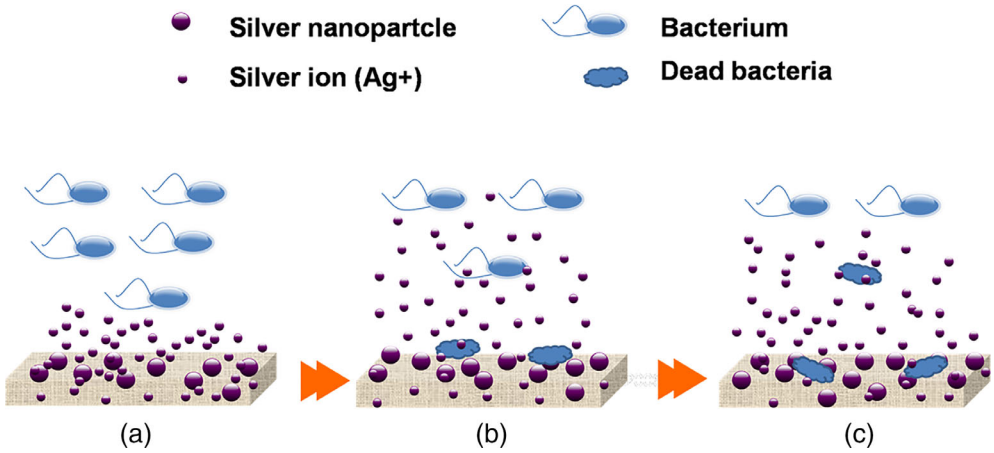


FIGURE 8 The antimicrobial mechanism of silver in an adjuvant dressing

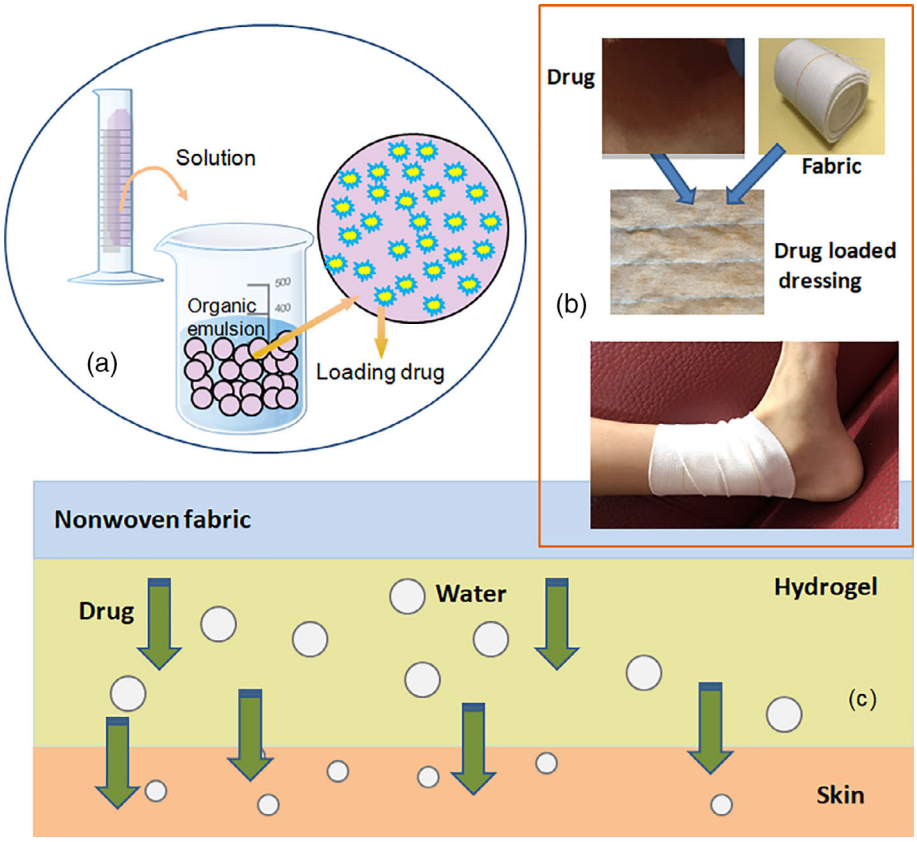


FIGURE 9 Schematic procedure of drug loaded polymer matrix and dual functional delivery system of drugbased dressings. (a) Drug loaded with the polymer. (b) Applying the drug-loaded fabrics to patient's wound. (c) Working mechanism of the dual functional delivery system of drug-based dressings

3.3.2 | Drug released dressings

Drug-released dressings play an increasingly key role in infection prevention and tissue regeneration in leg ulcer healing through direct or indirect removal of necrotic tissues. Drug molecules or particles can be dispersed in alginate microspheres by using an emulsified *solvent* diffusion *method*. Figure 9a illustrates the procedure for preparing drug-loaded polymer matrix (Dhivya, Padma, & Santhini, 2015). Alginate-based capsules can promote drug transportation and release to protect against degradation (Zhang, Huang, Zhao, & Jin, 2017). In addition, alginate-related microspheres and injectable scaffold (Zhao, Weir, & Xu, 2010; Zhou & Xu, 2011) can be employed as cell microcarriers (Bian et al., 2011; Gröhn, Klöck, & Zimmermann, 1997) for tissue engineering. Figure 9b,c presents a schematic diagram of drug released dressings with dual delivery systems (i.e., water molecules and drug supply) for ulcer management. The incorporated drugs are commonly enzymes (Singer, Tassiopoulos, & Kirsner, 2017) and various growth factors (Park, Hwang, & Yoon, 2017). Normal tissue regenerations are controlled by cellular activities of various growth factors intrinsically involved in human body. Exogenous introduction of the growth factors benefits the wound healing process, which has been demonstrated by numerous experimental studies (Ho, Walsh, Yue, Dardik, & Cheema, 2017; Wang et al., 2016; Westby et al., 2017).

3.3.3 | Nutrition-providing dressings

Nutrition-providing dressings are generally derived from natural or artificial resources, such as collagen (González, 2016), elastin (Chouhan, Chakraborty, Nandi, & Mandal, 2017), chitosan (Abdel-Mohsen et al., 2016; Singh, Shitiz, & Singh, 2017; Szymonowicz et al., 2017), and hyaluronic acid (HA) (Roehrs et al., 2016), all of which are well known for their biodegradability, biocompatibility, and nontoxic characteristics. These polymers are commonly used alone or in combination with various growth factors or other agents to promote ulcer healing in CVI treatment. As a main structural protein, collagen is used to initiate fibroblast regeneration and promote endothelial migration following contact with wound tissue (Rath et al., 2016). Chitosan is a highly molecular copolymer with *acetyloglucosamine and glucosamine* units in its chain; it is beneficial for wound healing because of enhanced formation of granulation tissue by active groups, including hydroxy- and amino groups, during the ulceration healing process. An example is Chitopack C (Zhou et al., 2017). HA, as a major component of extracellular matrix, plays an important role in regulating tissue injury, stimulating tissue regeneration, accelerating tissue formation, as well as remodeling extracellular matrix and promoting ulcer healing (Schneider & Landsman, 2019; Shaharudin & Aziz, 2016). Hussain et al. systematically reviewed the studies on therapeutic efficacy of HA-based wound dressings on treatment of chronic wounds and tissue regeneration (Chan et al., 2018; Hussain, Thu, Katas, & Bukhari, 2017). HA scaffolds, antiadhesive sheets, sponge-like hydrogels and thin films have demonstrated their favorable effectiveness in wounds treatment of skin, articular cartilage, and tympanic membrane. Generally, bioactive dressings are superior to other substances largely because of their hemostatic, antimicrobial, rapid wound healing, and tissue regeneration features.

3.4 | Other functional wound dressings for CVI management

3.4.1 | Exudates management dressings

Patients with venous leg ulcers with high exudation levels are recommended to use compression bandages with an integrated absorbent padding layer. However, the efficacy of bandage dressings could be influenced by reduced moisture vapor transmission. Adjuvant dressings with advanced absorption contain a permeable backing layer to absorb more fluid and remove exudates from the wound through evaporation via the bandage fabric; this ensures a moist but not wet microenvironment. Figure 10 displays a basic absorption dressing mechanism for absorbing moderate to large quantities of exudates into the adjuvant dressings matrix designed in one flat layer or cavity structure. Vacuum-assisted closure and wound-drainage container bags have been developed in recent studies to collect large quantities of exudates (Ellis, 2016; Orsini, 2017).

3.4.2 | Odor control dressings

Most deodorizing polymer-based dressings are composed of deodorizing-agent-related materials (e.g., carbon, metronidazole, and oil) that absorb gas molecules (Akhmetova et al., 2016; Tsai, Hsu, & Lin, 2014). Studies have proved that charcoal-related materials are powerful deodorizers (Bennett-Marsden, 2010a; Morris, 2008) for the management of leg ulcers because of their ability to absorb small gas molecules and bacterial spores. Such odor-controlled products (e.g., Actisorb (White, 2013), and Clinisorb (Milne, 2017; Vijay et al., 2017)) have been used as primary and secondary dressings to treat infected and malignant leg ulcers (Akhmetova et al., 2016; Murphy, 2016). The deodorizing mechanisms of deodorants differ considerably in terms of physical and chemical interactions (Castro & Santos, 2015). One or multiple removal mechanisms (e.g., hydrophobic interactions, electrostatic interactions, $\pi - \pi$ bonds, and hydrogen bonds) could be involved in physical adsorption and chemical reactions. Carbon materials, such as activated carbon, carbon fiber, carbon aerogel, carbon nanotube, and graphene are microporous material with relatively complex Brunauer–Emmett–Teller surface area structure. Small gas molecules and bacterial spores can be adsorbed into the micropore surfaces of carbon-related materials during deodorization, thereby enabling a powerful deodorization process to occur that removes unpleasant smells (Castro & Santos, 2015; Morris, 2008). Metronidazole is a nitroimidazole derivative and a topical antibiotic featuring antiprotozoal medication and bactericidal activity. Metronidazole-based wound dressings can achieve a deodorizing effect by inhibiting redox reaction of the amoeba protozoa to break nitrogen chain of the protozoa.

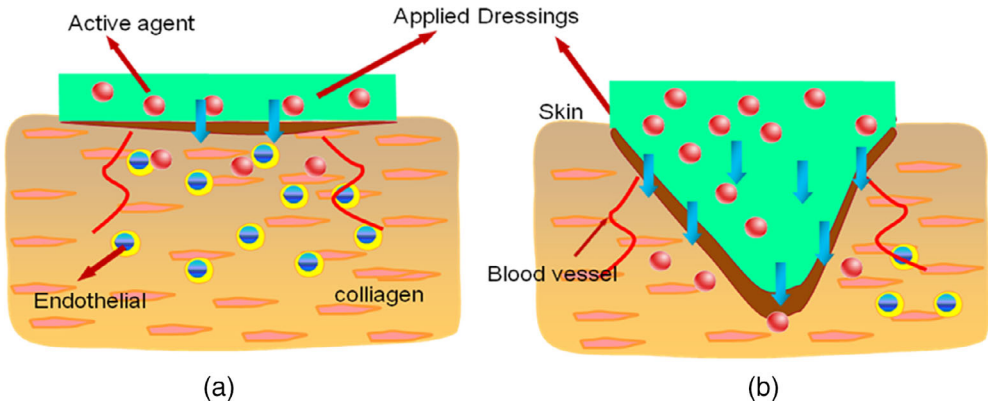


FIGURE 10 The basic mechanism of absorption wound dressing. (a) Flat layer dressing matrix. (b) Cavity structure dressing matrix

3.4.3 | Monitoring dressings

Reportedly, 50% of ulcerations can heal within 4 months, whereas 20% remain unclosed even after 24 months and approximately 8% remain vigorous after 60 months (Nicolaides, 2000; Salvo et al., 2015). One approach to improving wound management is through real-time monitoring to provide potential biomarkers from the onset of a biochemical reaction. Real-time monitoring can provide objective measurements of the wound status and timely feedback regarding treatment effectiveness. Some biological and physiological parameters, such as pH value, temperature, moisture level, and tissue oxygenation, can be considered indicators of wound healing status (Khan, Ansari, & Ali, 2015). These indicators are associated with infection, inflammation, tissue regeneration, microbial multiplication, and various skin conditions. Temperature and pH sensors are currently incorporated into wound dressings for daily monitoring of the health status of wounds. Usually, healthy leg skin is weakly acidic (pH 4–6), whereas the PH value of CVI patient's skin can be higher than 7.3. Monitoring a patient's pH value is an effective means of understanding their wounds-healing status. Recently, Liu et al. developed a novel smart alginate-polyacrylamide hydrogel patch dressing, incorporating a pH indicator for real-time detection of wound healing. As the pH value gradually increases, the patch color transitions from yellow (pH 5–7) to orange (pH 7.4–8), and finally to red (pH 9). The observed transitional color pattern matches the pH range of venous wounds (Figure 11). This functional dressing composed of nanocomposites involving multiwall carbon nanotubes embedded in poly(styrene-b-[ethylene-co-butylene]-b-styrene) was developed to measure tissue temperature ranging from 20 to 50°C through electric resistant change (Liu et al., 2017; Matzeu, Pucci, Savi, Romanelli, & Di Francesco, 2012).

3.5 | Composite and mixed multifunctional dressing

Composite and mixed polymer dressings usually combine multiple functional components or any two or more adjuvant materials into a single product to serve as primary or secondary adjuvant dressing for various wound-healing procedures (De Francesco et al., 2017). These dressings act as bacterial barriers to prevent infection and maintain suitable moisture conditions around wounds. In addition, they feature multilayer structures (Figure 12), including but not limited to (a) a wound contact layer, (b) an adsorption (foam) layer, (c) a spreading (distribution) layer, (d) a retention layer, (e) an adhesive (binding) layer, and (f) a protective backing layer (Benbow, 2015; Ousey, Atkin, & White, 2013; Wiegand & Hipler, 2013). Their main functions are to (a) absorb and retain exudates to protect against fluid strikethrough, (b) maintain size and volume to avoid becoming bulky, (c) keep the outer layer dry, (d) provide a healing environment, and (e) promotes user comfort (McCarthy & Donovan, 2016). The available composite and mixed functional dressing products applied to treat CVI are listed in Table 2.

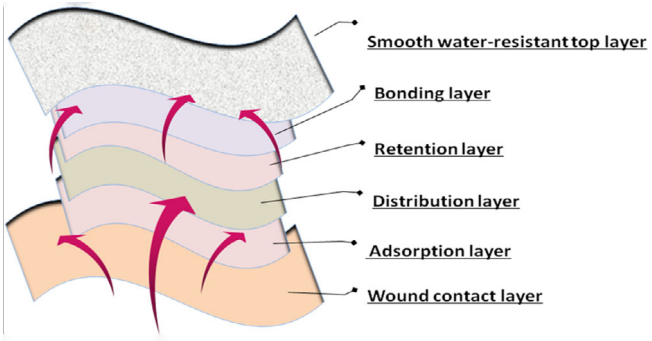


FIGURE 12 Multilayer structure of composite and mixed dressing

4 | SELECTION OF POLYMER-BASED COMPRESSION DEVICES AND DRESSINGS IN CVI TREATMENT

The functions of polymer-based compression devices (e.g., compression stockings and bandaging, and pneumatic pressure pump) and wound dressings (with film, padding, and foam) have been demonstrated by several clinical studies and are summarized in the next section. Any decisions made to improve a device and dressing

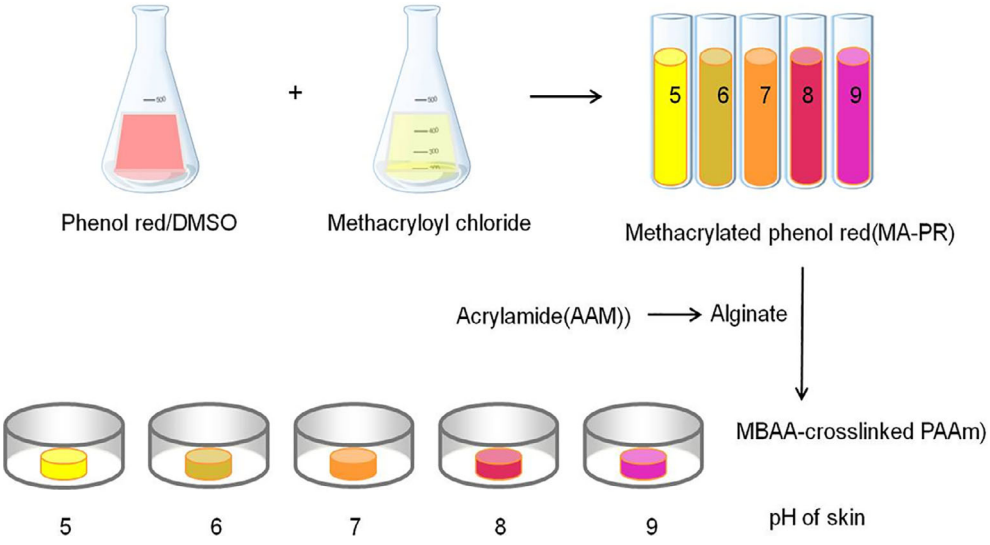


FIGURE 11 Preparation of alginate/Polyacrylamide (PAAm) hydrogel wound patch and its colorimetric display

TABLE 2 Functional polymer-based composite wound dressings used in CVI treatment

Product	Manufacturer	Construction	Application
MPM multilayered composite dressing	MPM medical	• Gaseous exchange top layer • Center absorb layer • Nonadherent bottom layer	• For heavy draining wounds; deep partial or full thickness draining wounds • Maintains moist environment and promotes healing
COVADERM PLUS® composite wound dressing	Deroyal	• Conformable adhesive-coated fabric tape • Second breathable semi-occlusive polyurethane barrier layer • Soft padding layer • Protective nonadherent contact layer	• For leg ulcers healing • Maintains moist environment with protection from outside contaminants • Drainage absorption above on skin
COVADERM PLUS® thin composite wound dressing	Deroyal	• Absorbent padding • Rounded corners • Nonadherent pad bottom layer	• For various wound and sizes • Prevent drainage strike and wound trauma • Prevent from lifting off prematurely
DermaDress™ waterproof composite dressing	Dermarite	• Semi-occlusive layer • Nonwoven adhesive tape • Low adherent contact layer	• For partial and full-thickness leg ulcers • Flexible and conformable • Low to heavy exuding ulcers
Tegaderm™ + pad composite dressings	3 M	• Waterproof bacterial and viral barrier layer • Unique, nonadherent absorbent pad layer	• For light to moderately draining chronic leg ulcers • Prevent infection • Easy to put on and off • Adapts to body contours
Opsite post-Op visible dressing	Smith& Nephew	• Patented waterproof bacterial barrier film • Lattice shaped hydrocellular absorbent foam pad • Low adherent wound contact layer	• For low to moderately exuding wounds • Provides impermeable barrier against bacteria • Provide optimal balance between wound exudate and fluid for moist wound healing. • Prevent blistering
Telfa™ plus island dressing	Covidien (medtronic)	• Soft nonwoven backing layer. • A super absorbent Telfa pad	• For absorption of moderate amounts of fluid • Provide comfort • Provide barrier to fluid and bacteria • Used as primary or secondary dressing
Kliniderm® foam silicone	Klinion-apotheek	• Vapor permeable polyurethane top film • Absorbent foam • Silicone adhesive bottom layer	• Minimizes fluid strike-through and protect the surrounding skin • Reduces the risk of maceration • Flexible and conformable for increased patient comfort • Provides up to 7 days wear time
AQUACEL® Ag foam dressing	ConvaTec	• Waterproof polyurethane layer • Multilayered absorbent pad • Hydrofiber® contact layer • Silicone adhesive border	• Lock in exudates and maintain a moist environment • Reduce risk of maceration • Kill microorganisms • Rapid, effective, and sustained antimicrobial action (up to 14 days)
Mextra® superabsorbent dressing	Mölnlycke Health Care	• Nonwoven, polypropylene membrane • Core absorbent layer • Polyester and viscose nonwoven distribution • Polypropylene spun-bonded nonwoven wound contact layer	• Outstanding absorption and retention • Reduce of maceration and leakage • Protect against fluid strike through • Remain dry and comfortable for the patient

Abbreviation: CVI, chronic venous insufficiency.

regimen must consider users' CEAP stages, concomitant conditions, psychosocial status, and personalized demands.

1. Compression devices for stages of C_0–C_6 of CEAP (Brennan & Miller, 1998; Partsch, 1991) reduce venous hypertension, augment muscular pumping action, improve blood flow, lessen pain, and discomfort in lower limbs, and reduce chances of DVT.
2. Wound dressings for stages of C_5–C_6 of CEAP (Bennett-Marsden, 2010b; Dhivya et al., 2015) provide or maintain a moist environment, absorb leg ulcer exudate, control ulcer odors, protect ulcer

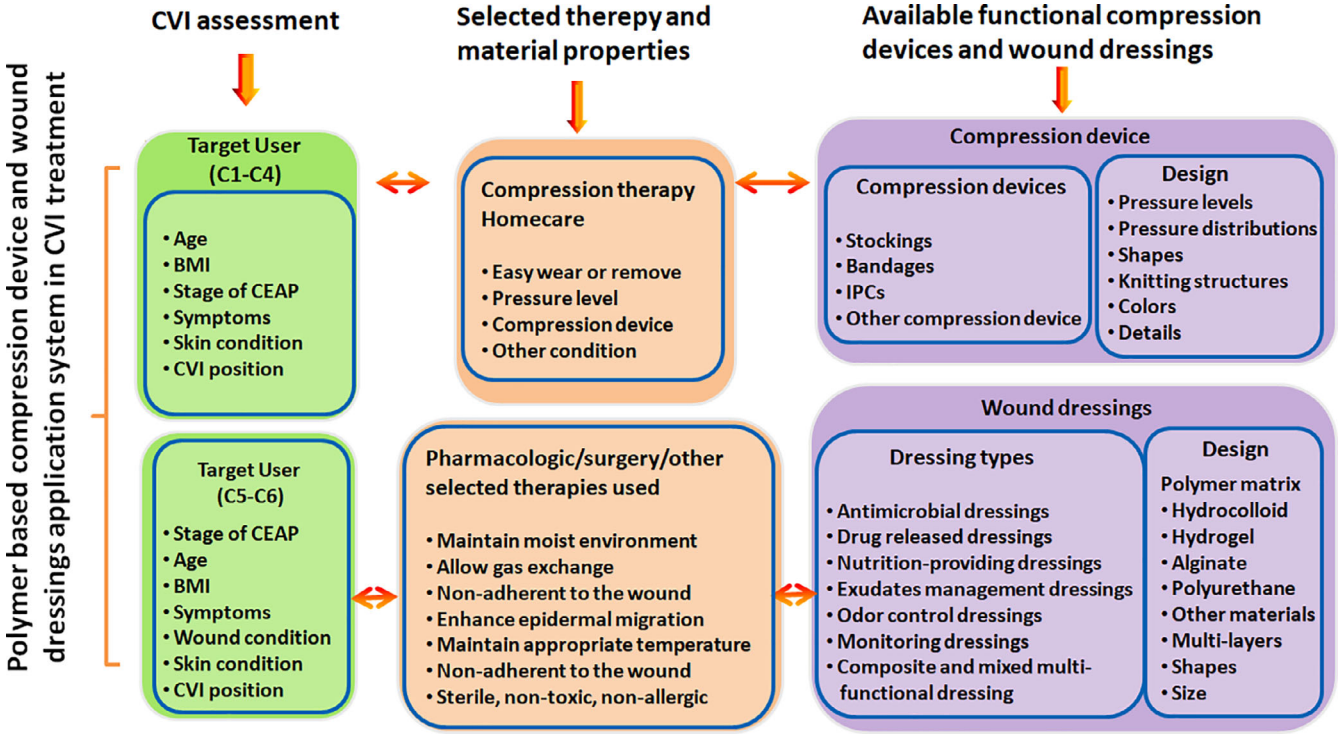


FIGURE 13 Selection of the suitable compression devices and wound dressings in management of CVI

from bacteria, enhance epidermal or leucocytes migration, promote soft tissues synthesis, help gas exchange between leg tissues and environment, maintain ideal temperature to enhance blood flow, improve epidermal regeneration, keep optimal pH value, and monitor wound healing process.

5 | DEVELOPMENTAL TRENDS OF COMPRESSION DEVICES AND WOUND DRESSINGS FOR CVI TREATMENT

Clinical studies have indicated that not all users tolerate higher pressures (>30 mmHg), which can sometimes cause pain and discomfort (Shepherd, 2016; Weiss & Duffy, 1999) when applied in elastic compression modalities (e.g., socks and stockings). Rigid compression bandages are appropriate for treating severe CVI (C_3–C_6), but do not adapt to the changing volume of a leg as edema decreases (Collins & Seraj, 2010) (e.g., these bandages can be used only for 48 hours when used alone). Although IPC *pumps are effective for treating* CVI (C_3–C_6), they are bulky and tedious in practice and may lead to lymphatic congestion in the upper thigh and pelvic region, thereby hindering lymphatic return (Allen & Cheng, 2016; Wild et al., 2017). Existing compression devices and wound dressings still require improvements in terms of aspects such as pressure comfort, intelligent management, low profiles, safety, and cost-effectiveness to provide more benefits to end users.

Advanced smart compression shells are promising for application in implemented or embedded electronic sensors or conductive materials to detect vital signs from blood vessels and skeletal muscles, as well as physiological parameters (e.g., temperature, hormone levels, and blood pressure), through users' skin (Felkowitz, 2004). Nanoparticles (e.g., silver, silica, gold, and platinum) have demonstrated various biological effects (e.g., antibacterial action, tissue regeneration, and cell culture (Revell, 2006)) and thus are key materials for treating diverse diseases because of their notable antimicrobial characteristics and high ratio of surface area to volume (Abdallah et al., 2016). In addition, polymers such as polyvinyl alcohol, chitosan, and starch have excellent biocompatible and biodegradable properties (Daeschlein et al., 2016; Morganti, Del Ciotto, Carezzi, Nunziata, & Morganti, 2016), and are increasingly used in drug delivery, leg ulcer healing, and artificial cartilage materials because of these sought-after renewable biological properties. Recently, new polymer manufacturing techniques have exhibited potential for application in fabricating advanced wound dressings through processes such as 3D printing and electrospinning.

Although numerous polymer-based dressings are available in the adjuvant market for CVI management, few effective evaluations on their clinical effectiveness have been conducted in clinical trials (especially large-scale randomized controlled trials). Furthermore, the working mechanisms behind the use of compression devices and wound dressings in CVI management require further in-depth research at both the primary and advanced stages of CEAP classification system.

6 | CONCLUSION

Increasing population aging and a rise in number of people with diabetes and obesity contribute to the increasing number of patients with

CVI and ulceration. Treating and managing CVI is a long and costly process both in terms of time and the medical resources required. Advanced polymer-based products provide an improved care environment, safety, and user compliance to CVI treatment. New development of polymer-based compression materials and wound dressings requires multidisciplinary cooperation among material scientists, fabrication engineers, product designers, clinicians, and public health practitioners. Moreover, continued clinical-evidence-based research is required to optimize the design and application of compression materials for the various CEAP stages. Figure 13 summarizes the use of polymer-based therapeutic compression materials (devices) and wound dressings guided by CVI assessment through clinical diagnostic techniques to evaluate personal conditions and symptom status. Advances on nanotechnology and biocompatible and biodegradable functional composite polymers in adjuvant dressings would contribute to substantial development of novel compression devices and wound dressings for CVI treatment. In addition, using wearable electronic technologies in compression devices could enable timely monitoring, diagnosis, and therapy for prophylaxis and treatment of venous disorders.

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