https://doi.org/10.31925/farmacia.2023.4.3 **REVIEW**

AN UP-TO-DATE ON POVIDONE-IODINE WITH FOCUS ON WOUND MANAGEMNT: CURRENT AVAILABLE DATA AND NEW APPROACHES

ALINA CHELMUȘ-BURLACU [1]*, LENUȚA PROFIRE [2], DRAGOȘ PIEPTU [1,3]

[1] *"Grigore T. Popa" University of Medicine and Pharmacy of Iași, Faculty of Medicine, 16 Universității Street, Iași, Romania*
[2] *"Grigore T. Popa" University of Medicine and Pharmacy of Iași, Faculty of Pharmacy, 16 Universității Street, Iași, Romania*
[3] *Plastic Surgery Department, Regional Oncology Institute, 2-4 General Henri Mathias Berthelot Street, Iași, Romania*

**corresponding author: alina.c.chelmus@d.umfiasi.ro*

Manuscript received: April 2022

Abstract

Wound care, mainly chronic wounds and burns with difficult bioburden control and at high risk of infection or biofilm development, remains a challenge. Between antiseptics, as a good option for wound management, povidone-iodine (PVI) is one of the most commonly used. Although with a broad spectrum and efficacy including on biofilms, the available data is controversial, especially regarding its effects on wound healing. Thus, the aim of this paper was to evaluate recent publish data, including original research papers and case reports. Literature search was conducted in PubMed, using a key terms strategy for papers published from 2021 up to present. Out of 101 results, based on inclusion and exclusion criteria, 24 papers were selected for in depth analysis and divided in three categories: reviews, original research and case reports. Out of the selected papers, 6 (25%) were reviews, including two systematic reviews on clinical trials and 3 (12.5%) case reports, out which one reported a significant adverse effect. A total of 15 (62.5%) original research papers were included, that reported heterogeneous results in regards with povidone-iodine effects but similar antimicrobial efficacy. The recent data is focused on comparing antiseptics, including PVI, and proposing algorithms for wound management. Although there is heterogeneity between experimental designs, there is a shift towards more complex models. Thus, is emphasising the need for standardized antiseptic tests and clinical guidelines.

Rezumat

Tratamentul plăgilor continuă să fie o provocare, mai ales în cazul celor cronice și al arsurilor, unde controlul încărcăturii microbiene este dificil de obținut, iar riscul de a dezvolta infecții este ridicat. Iod povidona (PVI) este cel mai frecvent antiseptic folosit pentru tratarea plăgilor. Deși are un spectru larg de acțiune, cu eficacitate inclusiv în cazul biofilmelor, datele actuale sunt contradictorii, în special cu privire la impactul asupra procesului de vindecare. Prin urmare, scopul prezentei lucrări a fost evaluarea ultimelor date publicate pe acest subiect. A fost efectuat un studiu de literatură în baza de date PubMed, folosind o combinație de termeni în limba engleză pentru a identifica publicațiile din 2021 până în prezent. Din 101 rezultate generate, au fost selectate, folosind criterii de includere și excludere, 24 de publicații care ulterior au fost împărțite în trei categorii: *review*-uri, articole originale de cercetare și raportări de cazuri. Publicațiile selectate, 6 (25%) au fost *review*-uri, dintre care două *review*-uri sistematizate despre studii clinice și 3 (12,5%) cazuri raportate, dintre care raportarea unui efect advers semnificativ. Un total de 15 (62,5%) publicații originale din domeniul cercetării incluse, raportează rezultate heterogene cu privire la efectele toxice ale iod-povidonei, deși eficiența antimicrobiană este similară. Datele recente pun accent pe compararea eficacității antisepticelor, inclusiv a iod- povidonei și propun algoritmi pentru utilizarea lor în tratamentul plăgilor. Deși există heterogenitate în privința design-ului experimental, modelele utilizate tind să fie complexe. Astfel se subliniază necesitatea utilizării testelor antimicrobiene standardizate, cât și ghidurilor clinice.

Keywords: antiseptics, povidone-iodine, wound management

Introduction

Wound care remains a clinical challenge and wound healing process can be impaired by multiple factors [1, 2]. One major factor is the bioburden, as critical colonization, infection or biofilm formation; and infection is the main mortality cause in severe burns [2, 3]. Although antiseptics are frequently used and considered a key component in wound management, their use in infected wound treatment or prevention is under debate [1, 2]. This controversy arises due to conflictual reports, mainly from *in vitro* data, that antiseptics display a cytotoxic effect that could negatively reflect on the wound healing process. Also, there are some concerns regarding efficacy, due to different conditions of *in vivo* wound microenvironment, such as proteins that could inactivate the antiseptic [3, 4].

One of the most commonly used antiseptics is povidone-iodine (PVI), an iodophor, composed of iodine and a water soluble synthetic polymer called polyvinyl-pyrrolidone, that acts as a carrier. Within an aqueous solution, the iodine is released from the complex and

binds to the cell membrane, and also, affects the electron transport chain [5-7].

Although having a broad-spectrum activity and a widely use, PVI in wound management remains disputed and controversial [8]. Thomas *et al.* reported that PVI decreases fibroblasts migration and proliferation in a dose-dependent manner [9]. In an *in vivo* study, Wang *et al*. evaluated the effect of topical 0.5% PVI on excisional wounds and suggested that PVI could promote wound healing through TGFβ modulation even in the absence of infection [10]. Moreover, in a study on patients with chronic ulcers, the authors found that topical PVI did not impaired micro vessels or cell density within the wounds [11]. Currently, most *in vitro* studies demonstrated various degrees of PVI cytotoxicity, while most *in vivo* studies do not report a significant wound healing impairment, especially at low concentrations [5].

As research advances in wound care with emerging stem cell-based therapies or new technologies to shift healing process towards a foetal wound healing phenotype, it is important to further evaluate the role of antiseptics in wound management [12, 13]. Kim *et al.* demonstrated, using freshly isolated adipose derived stem cells, that PVI significantly decreases proliferation, differentiation ability and down regulates stem cell markers [14].

Considering the diversity and heterogeneity of existing data regarding PVI in the context of new emerging therapies to improve wound healing, the aim of the herein literature review is to evaluate current published data in an attempt to identify the reasoning behind the divergent reports between *in vitro* and *in vivo*.

Materials and Methods

For the literature review, literature search was conducted in PubMed, using the following key terms strategy: (wound) and (povidone iodine) and (burn) and (povidone iodine) from 2021 up to present. Due to difficulties in accessing papers without free full text link and the amount of papers in veterinary filed, additional two filters were used: free full text and human species. The search revealed 101 papers, which were screened by title and chosen according to subject relevance. Case reports considered relevant to the subject or reporting side effects were included. Papers regarding using PVI for skin decontamination, preoperatively and postoperatively surgical site infection prevention, as control group in testing non-approved active substances or used in experimental setups as proof of concept for other subject areas, were excluded. Thus, 31 papers were selected for abstract screening and in depth evaluation. Further, 7 papers were excluded based on the exclusion criteria mentioned above. The algorithm used for this literature review is summarized in Figure 1. The 24 selected papers were dived in three categories for evaluation: reviews, case reports and original research.

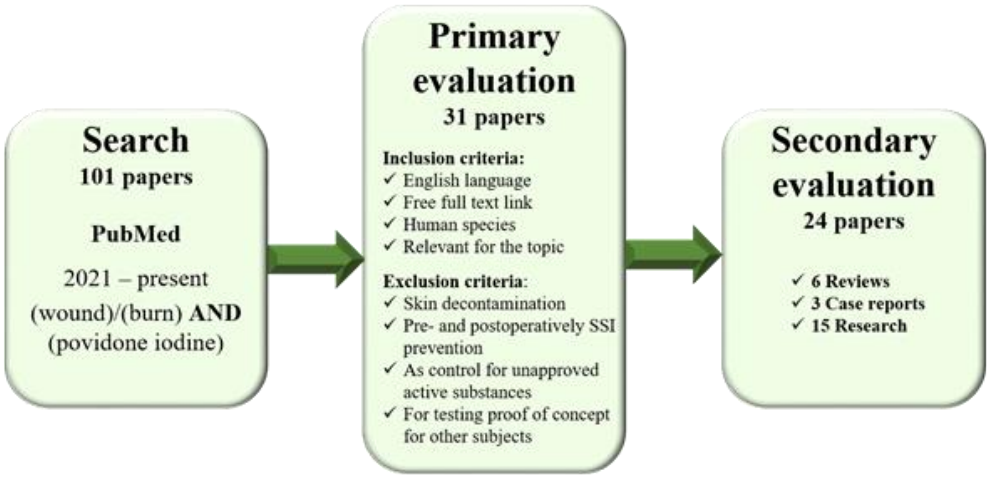

Figure 1.
Algorithm for literature search and selection

Results and Discussion

The selected papers were grouped in the three mentioned categorizes. Out of 24 papers, 6 (25%) were reviews, which reviewed not only PVI. Type of review, topic and main results on regards with PVI were evaluated and summarized in Table I.

Only one paper compared cadexomer iodine ointment with PVI, recommending cadexomer especially for chronic wound care with increased exudate [15]. Other three papers evaluate antiseptics roles, including PVI, in wound management in different contexts such as European guidelines, critical colonization and/or biofilm and nursing homes [2, 16, 17]. There were only two systematic reviews on clinical trials regarding antiseptics in chronic wounds management [18, 19].

Table I

Reviews on PVI in wound management

Author, year	Type of study	Topic	Main outcomes
Gupta *et al*., 2023	Narrative review	Cadexomer *vs.* PVI	Cadexomer recommended over PVI for wounds with increased exudate [15]
Alves *et al*., 2021	Narrative review	AS in chronic wounds with critical colonization and/or biofilm	Algorithm to guide PVI usage in wound care [16]
Alves *et al*., 2022	Narrative review	AS in chronic wound treatment and prevention in nursing homes	PVI recommended for wounds with critical colonization and/or biofilm [17]
Babalska *et al*., 2021	Review	AS in the context of European Guidelines for wound care	PVI is one of the five AS recommended for wound treatment, but not for chronic wounds [18]
Barrigah-Benissan *et al*., 2022	Systematic review	6 clinical trials regarding AS in chronic wounds	Only one clinical study on PVI No significant differences regarding healing rate between PVI *vs* NS [18]
Cwajda-Białasik *et al*., 2022	Systematic review	29 clinical trials regarding AS in chronic wounds	Two clinical trials on venous leg ulcers and PVI [19] Good results for PVI and compression therapy [19] Improved healing when using PVI and hydrocolloid dressing [19]

AS – antiseptics; NS – normal saline; PVI – povidone-iodine

Three case reports (12.5%) were selected, two of them because of the chosen treatment method and a reported acute kidney injury, a rare side effect of PVI usage [20-22]. Although it did not occur following soft tissue wound care, the case reporting the acute kidney injury was selected because, it was considered relevant due to possible risk when using high amounts of PVI in large wound surfaces. The cases were evaluated for their topic and main results in using, as display in Table II.

Table II

Case reports summary

Author, year	Topic	Main outcomes
Papadopoulos *et al*., 2022	PVI-induced acute kidney injury following postoperative uterine instillation	50 mL of 10% PVI diluted 1:10 POD 8 h – anuria POD 32 h – continuous venous-venous haemodialysis POD 48 h – iodine levels of 136.9 mcg/L (normal range 40 - 100 mcg/L) [20]
Hihara *et al*., 2022	Left sole diabetic ulcer with osteolytic lesions at the 2nd MTPJ and MRSA treated with daily foot bath in carbonated water and 3% PVI sugar ointment	Wound closed in 6 months following incision and drainage and daily treatment with bone and joint remodelling At 1.5 years without recurrence [21]
Ismail *et al*., 2021	PVI used as a sclerosing agent for a recurrent type 1 Morel-Lavallée lesion	Percutaneous irrigation and compression therapy No recurrence over 5 months [22]

MRSA - Methicillin-resistant *Staphylococcus aureus*; MTPJ – metatarsophalangeal joint; POD – postoperative days; PVI – povidone-iodine

A total of 15 (62.5%) original research papers were selected and divide in three categories based on aim: antimicrobial activity evaluation; effects on wound healing and cytotoxicity (safety profile) and development of bioactive dressings using PVI. Furthermore, methods, such as experimental design, PVI concentrations, micro-organism stains used and main results were evaluated, with summary presented in Table III. PVI seems to maintain high efficacy on different bacterial, fungal and viruses strains [23]. When efficacy was tested in different setups mimicking wound microenvironment, it maintained its efficacy [24]. Although broad spectrum activity reported, it seems that on biofilms with *Acinectobacter baumannii* antibiotic-resistant strains isolated from patients, PVI was reported less effective [25]. Moreover, when synergy between antibiotics and antiseptics was evaluated, PVI displays an antagonist effect with meropenem and synergy with gentamicin [26].

Most *in vitro* research papers reported that PVI display a cytotoxic effect on cells, with impact on cell viability, proliferation, migration and *in vivo*, on murine models, PVI delayed wound healing [27-30]. Brown *et al*. reported that PVI modulates i*n vitro* inflammation both at transcriptome and proteomic levels [31]. In clinical studies, Zhao *et al*. demonstrated improved healing rates with decreased inflammatory cytokines when PVI was used in combination with recombined human epidermal growth factor, although Gupta *et al*. reported better outcomes on regards to wound healing when using cadexomer compared with PVI [32, 33].

Out of the selected papers, four described bioactive dressing development, such as carboxymethyl chitosan, bacterial cellulose and biodegradable pectin@carboxy-methyl pullulan hydrogel loaded with PVI, especially for obtaining controlled release within the wound microenvironment [34-37].

Table III

Original research papers summary

Author, year	PVI used	Experimental design	Main outcomes
In vitro Antimicrobial activity evaluation			
Tan *et al*., 2021	Multiple concentrations (80%, 40%, 20%, 8% and 1 mg/mL for solid products) and wound antisepsis PVI products (solution, ointment, cream, powder, liposomal hydrogel)	Bacteria (13 strains) Fungal (2 strains) Viruses (2 strains)	PVI highly effective in 30 - 60 seconds, regardless of concentration [23]
Severing *et al*., 2022	PVI 10%	Human acute/chronic exudate to mimic wound microenvironment Bacteria (2 strains)	PVI maintained efficacy regardless of protein levels, stain or exposure time [24]
Pietsch *et al*., 2021	Multiple concentrations (range between 120 and 350 μg/mL)	AB and AS synergy *Pseudomonas* strain	PVI – antagonism with meropenem and synergy with gentamicin [26]
Denysko *et al*., 2022	PVI 10% PVI 2%	MDR *A. baumannii* isolated from patients	PVI maintained effect on planktonic cultures, with less efficacy on biofilms [25]
Effects on wound healing and cytotoxicity (safety profile)			
a. *In vitro*			
Rueda-Fernández *et al*., 2022	PVI 10%	Neonatal fibroblast cell line treated for 1 minute	PVI decreases viability, proliferation, migration Increases apoptosis [28]
Ortega-Llamas *et al*., 2022	PVI 10% PVI 1%	Fresh isolated human fibroblasts and HaCat treated every 48 h for 14 days	PVI 1% affects fibroblasts viability, proliferation, migration PVI 1% impairs HaCat cell growth [27]
García-Valdivia *et al*., 2022	PVI 10%	Bioengineered skin substitute using fresh isolated human keratinocytes and fibroblasts	Decreased cell viability Modulated cytokine levels No effect on epidermal barrier function [30]
Brown *et al*., 2022	PVI 10%	Episkin (3D skin epidermis) co-cultured with complex biofilm treated with AS	Inflammation modulation at both trascriptom and proteomic levels Reduced biofilm efficiency compared with H_2O_2 [31]
b. *In vitro* and *in vivo*			
Zhang *et al*., 2021	*In vivo* 0.05%	Wound model on rats (AS treatment 1/day)	Delayed wound healing with increased inflammatory cells infiltrate [29]
	In vitro multiple concentrations (range from 0.00048% to 0.02%	HaCat cell line	*In vitro* – PVI displays less apoptosis and ROS production dependent on concentration [29]
c. Clinical studies			
Zhao *et al*., 2022	PVI 10% cream and rh-EFG	105 patients with pressure ulcers	Reduced healing time with decreased cytokines [32]
Gupta *et al*., 2022	Cadexomer *vs* PVI 5% oitment	40 patients with ulcers	Cadexomer had better results on wound healing (based on clinical evaluation) [33]
Development of bioactive dressings			
Yu *et al*., 2022	Carboxymethyl chitosan - PVI microspheres	Wound model on diabetic mice	Improved healing time [34]
Dydak *et al*., 2021	AS loaded on bacterial cellulose dressing (7.5% PVI)	Effect assessment on multiple strains	Good antimicrobial activity and the highest on biofilms [35]
Emam *et al*., 2021	Networked Pectin@Carboxymethyl Pullulan Hydrogel loaded with PVI 2%	Bioactivity evaluation on one bacterial strain and one fungal	Controlled release of PVI (57,7% after 6 h) with good bioactivity [36]
Argel *et al*., 2022	Bacterial nanocellulose loaded with AS	Bioactivity, release profile and diffusion evaluation	Slow-release profile with good bioactivity [37]

MDR – *A. baumannii* – multi-drug resistant *Acinectobacter baumannii*; AB – antibiotics; AS – antiseptics; HaCat – keratinocyte cell line; H_2O_2 – hydrogen peroxide; ROS – reactive oxygen species; rh-EFG – recombine human epidermal growth factor

As chronic wound incidence is increasing with important impact on patients' life-quality, it also affects the health-care systems as well as socio-economic burden [13]. Burns also have a high impact on both the patients and the systems. Topical antimicrobials have been key players in burn management, especially in nonsurgical management and preventing patients with severe burns succumbing to infections [38]. Although debates on PVI impact on wound healing is ongoing, it is widely used in both chronic wound management and burns treatment [1, 3].

Our literature search, identify 6 reviews on antiseptics that also included PVI, out of which 3 proposed it in wound care. Alves *et al*. recommend PVI in chronic wound management and also propose a practical algorithm in conjunction with mechanically wash and debridement if necessary [16, 17]. In contrast, Babalska *et al*., although one of the antiseptics to consider in wound care, argues against PVI in chronic wounds, due to cytotoxicity and lack of synergy with silver dressings [2]. The clinical trials, identify in the two systematic reviews included, did not report any strong evidence against PVI. Also, in one study there was no difference regarding the wound healing rate between PVI and normal saline [18, 19].

Furthermore, Hihara *et al*. obtained in 6 months wound closure in a diabetic patient with refractory plantar ulcer and MRSA colonized using PVI ointment in the treatment approach [21]. Ismail *et al*. used PVI a sclerosant agent, in the absence of alternatives, with good results in a recurrent Morel-Lavallée lesion [22]. This suggests that PVI could be used in more clinical settings. One case report described an acute kidney injury following postoperative uterine instillation with 50 mL of 1% PVI (from 10% stock solution, diluted 1:10) [20]. It is known that PVI has a good absorption rate, proportional with the exposure time [39]. Moreover, with dilution the bonds between the polymer carrier and iodine are weakened, leading to free iodine increase in the solution [2].

Regarding research area on cytotoxicity, all *in vitro* studies reported negative impact on cells, including on viability, proliferation and migration. From experimental design point of view, there is shift towards more complex models using human cells, either freshly isolated or cell lines as HaCat and CCD-1064Sk (neonatal fibroblast cell line) [27, 28, 30]. It is known that murine fibroblasts display increased tolerance when exposed to PVI, thus *in vitro* results may not always reflect results than can be translated into clinical settings [4]. Also, studies evaluating PVI bioactivity, experimental designs included testing on models developed using patient wound exudate to mimic the wound microenvironment or complex biofilms co-cultured with 3D skin epidermis [24, 31].

Currently, there is an insufficient standardized testing and evaluation for antiseptics [40]. For antiseptics testing, the DIN-EN-13727 standard is the mostly used, but it was not developed for antiseptic testing in the context of wound microenvironment and allows different test settings [24]. Within the studies evaluated, apart from different testing models used, PVI concentration range variation was from 0.02% up to 80%, which could also explain the current divergent results reported. Zhang *et al*. evaluated *in vivo* antiseptics effects on wound healing, including 0.05% PVI topical application which delayed wound healing with increased inflammatory cells infiltrate [29]. Murine models may not the most appropriate models for evaluating antiseptic effects on wound healing, due to variations of cell tolerance and murine heal mainly through contraction [4, 41].

The evaluated papers also included four studies on designing bioactive dressing using PVI, focusing on the slow release of the antiseptic [34-37]. Zhao *et al*. evaluated the effects of combined PVI 10% cream for 10 minutes followed by topical gel with recombined human epidermal growth factor on 105 patients with pressure ulcers that resulted in reduced healing time and decreased cytokines [32].

The main limitation of the study is the range of time set for the literature search (from 2021 up to present), which was due the large amount published date regarding antiseptics. Also, the study did not include unpublished data or a grey literature search.

Conclusions

The recent data is focused on comparing antiseptics, including PVI, and proposing algorithms for wound management. Thus, emphasising the need for standardized clinical guidelines in the context of divergent existing data with difficult translation results from *in vitro* to clinical settings. Although there is heterogeneity between experimental designs, such as models and PVI concentrations, there is a shift towards more complex models, including using human cells in 3D structures, which may better mimic wound micro-environment.

Acknowledgement

The present paper was written as part of a "Grigore T. Popa" University of Medicine and Pharmacy of Iași PhD program.

Conflict of interest

The authors declare no conflict of interest.

References

1. Vermeulen H, Westerbos SJ, Ubbink DT, Benefit and harm of iodine in wound care: a systematic review. *J Hosp Infect.*, 2010; 76(3): 191-199.
2. Babalska ZŁ, Korbecka-Paczkowska M, Karpiński TM, Wound Antiseptics and European Guidelines for Antiseptic Application in Wound Treatment. *Pharmaceuticals (Basel)*, 2021; 14(12): 1253.

3. Slaviero L, Avruscio G, Vindigni V, Tocco-Tussardi I, Antiseptics for burns: a review of the evidence. *Ann Burns Fire Disasters*, 2018; 31(3): 198-203.
4. Barreto R, Barrois B, Lambert J, Malhotra-Kumar S, Santos-Fernandes V, Monstrey S, Addressing the challenges in antisepsis: focus on povidone iodine. *Int J Antimicrob Agents*, 2020; 56(3): 106064.
5. Bigliardi PL, Alsagoff SAL, El-Kafrawi HY, Pyon JK, Wa CTC, Villa MA, Povidone iodine in wound healing: A review of current concepts and practices. *Int J Surg.*, 2017; 44: 260-268.
6. Ben-Yehuda Greenwald M, Frušić-Zlotkin M, Soroka Y, Ben-Sasson S, Bianco-Peled H, Kohen R, A novel role of topical iodine in skin: Activation of the Nrf2 pathway. *Free Radic Biol Med.*, 2017; 104: 238-248.
7. Marinescu SA, Bejinariu CG, Marinescu B, Boiangiu I, Panche T, Budurca R, Botnaru I, Ciurea M, A new bromelain-enriched proteolytic enzymes concentrate treatment in patients with extensive burns: Romanian consensus. *Farmacia*, 2021; 69(4): 792-798.
8. Kramer SA, Effect of povidone-iodine on wound healing: a review. *J Vasc Nurs.*, 1999; 17(1): 17-23.
9. Thomas GW, Rael LT, Bar-Or R, Shimonkevitz R, Mains CW, Slone DS, Craun ML, Bar-Or D, Mechanisms of delayed wound healing by commonly used antiseptics. *J Trauma.*, 2009; 66(1): 82-91.
10. Wang L, Qin W, Zhou Y, Chen B, Zhao X, Zhao H, Mi E, Mi E, Wang Q, Ning J, Transforming growth factor β plays an important role in enhancing wound healing by topical application of Povidone-iodine. *Sci Rep.*, 2017; 7(1): 991.
11. Fumal I, Braham C, Paquet P, Piérard-Franchimont C, Piérard GE, The beneficial toxicity paradox of antimicrobials in leg ulcer healing impaired by a polymicrobial flora: a proof-of-concept study. *Dermatology*, 2002; 204 Suppl 1: 70-74.
12. O'Kane S, Wound remodelling and scarring. *J Wound Care*, 2002; 11(8): 296-299.
13. Öhnstedt E, Lofton Tomenius H, Vågesjö E, Phillipson M, The discovery and development of topical medicines for wound healing. *Expert Opin Drug Discov.*, 2019; 14(5): 485-497.
14. Kim BS, Ott V, Boecker AH, Stromps JP, Paul NE, Alharbi Z, Cakmak E, Bernhagen J, Bucala R, Pallua N, The Effect of Antiseptics on Adipose-Derived Stem Cells. *Plast Reconstr Surg.*, 2017; 139(3): 625-637.
15. Gupta SJr, Shinde S, Shinde RK, Topical Management of Wound: A Narrative Review of Cadexomer Iodine Ointment *Versus* Povidone Iodine Ointment. *Cureus*, 2022; 14(4): e24598.
16. Alves PJ, Barreto RT, Barrois BM, Gryson LG, Meaume S, Monstrey SJ, Update on the role of antiseptics in the management of chronic wounds with critical colonisation and/or biofilm. *Int Wound J.*, 2021; 18(3): 342-358.
17. Alves PJ, Gryson L, Hajjar J, Lepelletier D, Reners M, Rodríguez Salazar J, Simon A, Role of antiseptics in the prevention and treatment of infections in nursing homes. *J Hosp Infect.*, 2023; 131: 58-69.
18. Barrigah-Benissan K, Ory J, Sotto A, Salipante F, Lavigne JP, Loubet P, Antiseptic Agents for Chronic Wounds: A Systematic Review. *Antibiotics (Basel)*, 2022; 11(3): 350.
19. Cwajda-Białasik J, Mościcka P, Szewczyk MT, Antiseptics and antimicrobials for the treatment and management of chronic wounds: a systematic review of clinical trials. *Postepy Dermatol Alergol.*, 2022; 39(1): 141-151.
20. Papadopoulos P, Iordanou S, Georgiou F, Kalifatidis D, Herodotou E, Timiliotou-Matsentidou C, Povidone-Iodine-Induced Acute Kidney Injury in a 23-Year-Old Woman: The First Clinical Case Report From the Republic of Cyprus. *Cureus*, 2022; 14(4): e24034.
21. Hihara M, Fukui M, Mitsui T, Kakudo N, Kuro A, Osteolytic metatarsal osteomyelitis regenerated by combined treatment of artificial carbon dioxide foot bathing and povidone-iodine sugar ointment: a case report. *J Med Case Rep.*, 2022; 16(1): 434.
22. Ismail A, Nyamuryekung'e M, Rajeev K, Recurrent Morel-Lavallée lesion obliterated with povidone iodine, a case report. *Int J Surg Case Rep.*, 2021; 79: 343-349.
23. Tan EL, Johari NH, Comparative *in vitro* evaluation of the antimicrobial activities of povidone-iodine and other commercially available antiseptics against clinically relevant pathogens. *GMS Hyg Infect Control.*, 2021; 16: Doc05.
24. Severing AL, Borkovic M, Stuermer EK, Rembe JD, Composition of Challenge Substance in Standardized Antimicrobial Efficacy Testing of Wound Antimicrobials Is Essential to Correctly Simulate Efficacy in the Human Wound Micro-Environment. *Biomedicines*, 2022; 10(11): 2751.
25. Denysko TV, Nazarchuk OA, Gruzevskyi O, Bahniuk NÀ, Dmytriiev DV, Chornopyschuk RM, Bebyk VV, *In vitro* evaluation of the antimicrobial activity of antiseptics against clinical *Acinetobacter baumannii* strains isolated from combat wounds. *Front Microbiol.*, 2022; 13: 932467.
26. Pietsch F, Heidrich G, Nordholt N, Schreiber F, Prevalent Synergy and Antagonism Among Antibiotics and Biocides in *Pseudomonas aeruginosa*. *Front Microbiol.*, 2021; 11: 615618.
27. Ortega-Llamas L, Quiñones-Vico MI, García-Valdivia M, Fernández-González A, Ubago-Rodríguez A, Sanabria-de la Torre R, Arias-Santiago S, Cytotoxicity and Wound Closure Evaluation in Skin Cell Lines after Treatment with Common Antiseptics for Clinical Use. *Cells*, 2022; 11(9): 1395.
28. Rueda-Fernández M, Melguizo-Rodríguez L, Costela-Ruiz VJ, de Luna-Bertos E, Ruiz C, Ramos-Torrecillas J, Illescas-Montes R, Effect of the most common wound antiseptics on human skin fibroblasts. Clin Exp Dermatol., 2022; 47(8): 1543-1549.
29. Zhang J, Yan Y, Li Y, Shen C, Zhang Y, Topical effect of benzalkonium bromide on wound healing and potential cellular and molecular mechanisms. *Int Wound J.*, 2021; 18(5): 566-576.
30. García-Valdivia M, Quiñones-Vico MI, Ortega-Llamas L, Fernández-González A, Ubago-Rodríguez A, Sanabria-de la Torre R, Arias-Santiago S, Cytotoxicity, Epidermal Barrier Function and Cytokine Evaluation after Antiseptic Treatment in Bioengineered Autologous Skin Substitute. *Biomedicines*, 2022; 10(6): 1453.
31. Brown JL, Townsend E, Short RD, Williams C, Woodall C, Nile CJ, Ramage G, Assessing the inflammatory response to *in vitro* polymicrobial wound

biofilms in a skin epidermis model. *NPJ Biofilms Microbiomes*, 2022; 8(1): 19.
32. Zhao Z, Lv D, Zhang B, Yong L, Zhang R, Wang X, Efficacy of Human-Recombinant Epidermal Growth Factor Combined with Povidone-Iodine for Pressure Ulcers and Its Influence on Inflammatory Cytokines. *Mediators Inflamm.*, 2022; 2022: 3878320.
33. Gupta S, Shinde RK, Shinde S, Comparison of the Outcomes of Cadexomer Iodine and Povidone-Iodine Ointments in Wound Management. *Cureus*, 2022; 14(5): e24667.
34. Yu J, Wang P, Yin M, Zhang K, Wang X, Han B, Carboxymethyl chitosan-grafted polyvinylpyrrolidone-iodine microspheres for promoting the healing of chronic wounds. *Bioengineered*, 2022; 13(4): 8735-8746.
35. Dydak K, Junka A, Dydak A, Brożyna M, Paleczny J, Fijalkowski K, Kubielas G, Aniołek O, Bartoszewicz M, *In Vitro* Efficacy of Bacterial Cellulose Dressings Chemisorbed with Antiseptics against Biofilm Formed by Pathogens Isolated from Chronic Wounds. *Int J Mol Sci.*, 2021; 22(8): 3996.
36. Emam HE, Mohamed AL, Controllable Release of Povidone-Iodine from Networked Pectin@Carboxymethyl Pullulan Hydrogel. *Polymers (Basel)*, 2021; 13(18): 3118.
37. Argel S, Castaño M, Jimenez DE, Rodríguez S, Vallejo MJ, Castro CI, Osorio MA, Assessment of Bacterial Nanocellulose Loaded with Acetylsalicylic Acid or Povidone-Iodine as Bioactive Dressings for Skin and Soft Tissue Infections. *Pharmaceutics*, 2022; 14(8): 1661.
38. Zanfirescu A, Marineci CD, Păun G, Ungureanu O, Neagu E, Chiriță C, Velescu BȘ, Olaru OT, Negreș S, Chitosan supports containing *Impatiens noli-tangere* and *Symphytum officinale* hydroalcoholic extracts in burns treatment: antimicrobial and healing effects. *Farmacia*, 2021; 69(5): 948-953.
39. Nesvadbova M, Crosera M, Maina G, Larese Filon F, Povidone iodine skin absorption: an *ex-vivo* study. *Toxicol Lett.*, 2015; 235(3): 155-160.
40. Gunasekaran T, Nigusse T, Dhanaraju MD, Silver nanoparticles as real topical bullets for wound healing. *J Am Coll Clin Wound Spec.*, 2012; 3(4): 82-96.
41. Grambow E, Sorg H, Sorg CGG, Strüder D, Experimental Models to Study Skin Wound Healing with a Focus on Angiogenesis. *Med Sci (Basel)*, 2021; 9(3): 55.