3 Biotech (2021) 11:261
https://doi.org/10.1007/s13205-021-02826-4

2021 india
reviewed 7/25/2022
see bookmarks

REVIEW ARTICLE

Incorporation of grape seed extract towards wound care product development

Amita Ajit[1] · **A. G. Vishnu**[1] · **Prashanth Varkey**[2]

Received: 17 February 2021 / Accepted: 4 May 2021 / Published online: 11 May 2021

Abstract

Naturally derived ingredients are becoming more prevalent in therapeutic drug formulations due to consumers' concerns about chemical side effects. In the context of wound care, despite the impressive progress in therapeutic product development, drugs dispensed to treat impaired healing challenged by biofilms; excessive inflammation and oxidation are not yet really effective. Thus, the hunts for improved drug formulations preferably using natural ingredients that are cost-effective in accelerating the wound-healing process are of constant demand. The grape seed extract is extensively studied and is reported to be rich in phenolic compounds, unsaturated fatty acids and vitamins which exhibit numerous therapeutic benefits owing to their anti-inflammatory, anti-microbial, and anti-oxidative properties that support its potential use in the development of wound-healing products. We conducted a literature study using Scopus, PubMed, and Google Scholar including the keywords "grape seed extract" and "wound healing". We also scanned all the references cited by the retrieved articles. Accordingly, this review is aimed to (i) explore the various phytochemical constituents found in grape seed extracts along with their mechanism of action that instigate wound healing, (ii) to highlight the latest pre-clinical and clinical assessments of grape seed extract in wound models, and (iii) to encourage innovation scientists in the field to address current limitations and to effectively develop grape seed extract-based wound care product formulations for commercialization.

Keywords Grape seed extract · Anti-microbial · Anti-inflammation · Wound healing · Wound product development · Tissue regeneration

Introduction

The grape (*Vitis vinifera*) is a fruit crop widely grown all over the world. Grape seed is obtained as a waste by-product of the grape juice and wine processing industry. Global grape production is estimated to be about 75 million metric tons per year (Rajabi Hamedani et al. 2019). Considering the low cost to collect and process the grape seeds in addition to its reported therapeutic phyto-composition that aids cardio protective (Zhang et al. 2016), anti-inflammatory (Lin et al. 2017), anticancer (Kumar et al. 2018; Di Meo et al. 2019), anti-microbial (Fiallos et al. 2020; Memar et al. 2019; Al-Mousawi et al. 2020), anti-oxidant (Kwatra 2020), antiviral (Kwatra 2020), neuroprotective (Zhao et al. 2020), hepatoprotective (Nassiri-Asl and Hosseinzadeh, 2016), and wound-healing properties (Moalla Rekik et al. 2016), it is currently gaining attention for therapeutic use in pharmaceutical industries (Rodríguez-Pérez et al. 2019). Extracts obtained from grape seed contains large quantities of monomeric phenolic compounds such as (−)-epicatechin, (+)-catechins, and (−)-epicatechin-3-o-gallate and dimeric, trimeric, and tetrameric proanthocyanidins (condensed tannins) (Mohammed et al. 2016). These phenolic compounds are recognized to have potential anti-microbial effects that inhibit the growth of pathogenic bacteria (Kandasamy et al. 2016). Previous reports demonstrate and validate the anti-bacterial and anti-microbial effects of grape seed extracts

✉ Amita Ajit
dr.amitaajit@gmail.com

A. G. Vishnu
vishnuag007@gmail.com

Prashanth Varkey
drpvarkey@gmail.com

[1] Research and Development, Zum Heilen Diagnostic and Therapeutics Pvt. Ltd, Office No. 12/1543-C, SB Center, 2nd Floor, Museum Road, Thrissur, Kerala 680020, India

[2] Jubilee Centre for Medical Research, Jubilee Mission Medical College & Research Institute, P.B.No.737, Thrissur, Kerala 680 005, India

using gram-positive bacteria such as *Bacillus subtilis*, *Micrococcus luteus*, *Streptococcus mutans*, *Staphylococcus aureus*, Gram-negative bacteria such as *Escherichia coli* and *Pseudomonas aeruginosa*, as well as against fungi such as *Aspergillus niger* and *Fusarium oxysporum* (Ghouila et al. 2017). Additionally, recent studies also demonstrate the anti-oxidant and anti-inflammatory properties of grape seed extracts (GSE) that favour its use in tissue regeneration (Locilento et al. 2019; Manca et al. 2019). In the context of wound healing, bacterial biofilm (BBF), a membranous tissue composed by bacteria, is known to be an important factor that impairs the healing. The presence of antibiotic-resistant isolates in these biofilms, such as methicillin-resistant *S. aureus*, vancomycin-resistant *Enterococcus*, and multidrug-resistant *Acinetobacter baumannii*, further complicates the effectiveness of available clinical therapy (Percival et al. 2012). This has compelled the current research focus to develop effective combinations of traditional antibiotics or specific anti-BBF agents that either penetrate existing biofilms while maintaining both potential cytotoxicity and anti-bacterial efficacy or prevent the formation of BBF (Wei et al. 2019). Another major hindrance in chronic wounds has been the prolonged inflammatory response, due to excessive infiltration of neutrophils (Irving 2019) which still remains an unmet clinical need for new targeted therapies (Zhao et al. 2016) It is also reported that regulation of oxidation plays an essential role in wound healing. Extreme release of free radicals in response to cutaneous injury devastates proteins, lipids, and extracellular matrix (ECM) elements which leads to impaired healing (Ustuner et al. 2019). As per the retrospective analysis of Medicare beneficiaries in 2018, almost 8.2 million people were established to have infectious or non-infectious wounds with a treatment cost ranging from $ 28.1 to $ 96.8 billion highlighting its impact towards clinical, social, and economic burden (Sen 2019). With these rising numbers, the National Institutes of Health's (NIH) Research Portfolio Online Reporting Tool (RePORT) now lists wounds as a category (Sen 2019). Today, despite ongoing attempts in development of advanced therapeutic approaches, traditional/plant-based compounds are accepted as easily reached treatment alternatives that do away with the side effects associated with modern therapeutic drug formulations (Pereira and Bártolo 2016). The World Health Organization (WHO) also advocates and promotes the use of plant-based treatments, whose safety and effectiveness have been well established (Zhang et al. 2019). We conducted a literature study using Scopus, PubMed, and Google Scholar including the keywords "grape seed extract" and "wound healing". We also scanned all the references cited by the retrieved articles.

Based on the promisingly compelling therapeutic findings on the anti-microbial, anti-inflammatory, and anti-oxidant benefits of grape seed extracts over the years, their implications in addressing current challenges in wound healing are combined in this review with the intention to encourage effective incorporation of GSE in wound product development upon addressing the future considerations.

Bioactive compounds in grape seed extract

Grapes contain abundant pharmacologically important bioactive compounds. Among these components, phenolic compounds form about 70% of the bioactive molecules (Mattos et al. 2017). Phenolic compounds consist of an aromatic ring with one or more hydroxyl substituents and have a range of simple to highly polymerized molecules. They are divided into two main classes: flavonoids, which include anthocyanins like flavan-3-ols, flavonols, flavones and chalcones, and non-flavonoids which include phenolic acids (hydroxycinnamic acids and hydroxybenzoic acids), tannins, stilbenes, neolignans, and coumarins (Niculescu et al. 2018; Mattos et al. 2017). The main phenolic compounds found in grape pomace are flavonols, anthocyanins, hydroxycinnamic acids, hydroxybenzoic acids, and stilbenes. Their composition greatly depends on grape seed variety, vineyard, production techniques, and climatic conditions (Averilla et al. 2019). The anthocyanins are responsible for the pink, violet, red, and blue colour for flowers and fruits. Anthocyanins have essential functions in the plant tissues, such as sun protection, ultraviolet radiation, oxidative damage, and pathogens action. The important anthocyanins present in grape skin are forms of cyanidin, malvidin, and delphinidin, which possess anti-oxidative and antimicrobial properties (Khoo et al. 2017) The Phenolic acids are molecules formed by a single phenolic ring and divided into hydroxycinnamic acids and hydroxybenzoic acids. Hydroxycinnamic acids are abundant in foods than hydroxybenzoic acids and are rarely seen in free form. The major hydroxycinnamic acids are ferulic, *p*-coumaric, and caffeic acids; looking to hydroxybenzoic acids, the important acids are gallic, vanillic, and *p*-hydroxybenzoic (Al-Gubory et al. 2017). Flavonols are phenolic compounds that have a carbonyl group in their structure. They are mainly present in grape seeds, in which the most abundant ones are kaempferol-3-O-glucoside, quercetin-3-O-glucoside, quercetin, and myricetin (Averilla et al. 2019). Stilbenes are commonly seen in the grape seed with anti-fungal action, having two isomeric forms, such as *trans*-resveratrol, *cis*-resveratrol, *trans*-piceid, *cis*-piceid, *cis*-astringin, and *trans*-astringin (Ananga et al. 2017).

Extraction techniques of bioactive compounds from grapes seeds

The targeted isolation, identification, and attainment of maximum yield of bioactive compounds from grape seed largely depends on well standardized extraction procedures which deal with sample pre-treatment, solvent/sample ratio, solvent type, particle sizes, and time and temperature parameters (Lucarini et al. 2018). A comparative economic cum yield assessment study performed on several grape seed varieties showed that it is viable to initiate supercritical fluid extraction (SFE) at 313 K/35 MPa, with an extraction time of 240 min and S/F of 6.6 which delivers the best relationship between cost and yield on process scale up (Prado et al. 2012). Moreover, it is also reported that in SFE process with supercritical CO_2, the yields were between 0.56 and 7.9%; with propane, the yield increased to 10.8% and with SFE modifiers such as *n*-hexane, ethanol, ethane, ethyl acetate, and methanol the yield further increased to 7.8–11.4%. However, the use of these co-solvents, some being toxic, puts concerns in to maintaining the SFE green label (Prado et al. 2012). Another non-conventional method is the ultrasound assisted extraction (UAE) process. Here, the sample is mixed with ethyl acetate and then sonicated in an ultrasound bath. The obtained supernatant is then homogenized and evaporated, and the extracted remnant is dissolved in methanol (Burin et al. 2014). This method has been preferred owing to its large-scale industrial feasibility based on competitive effectiveness, simplicity, easy handling, low cost, high efficiency, lower organic solvent consumption, and reduced extraction time of 10–60 min (Vilkhu et al. 2008). The optimization of this technology could allow retainment of the natural-like quality and prevention of degradation of labile compounds due to high frequencies (Vilkhu et al. 2008). Another available method is the liquid–liquid extraction (LLE) like the ethanolic and Soxhlet extraction process**.** In the ethanolic extraction process, the seeds are lyophilized and grinded to obtain a powder with small particles, which increases the surface contact between the material and the extraction solvent. The powder is dispersed in ethanol, left under constant stirring for 48 h, at room temperature, followed by centrifuging the extractive dispersions. The extracts are then diluted with water, lyophilized and stored under vacuum until use (Manca et al. 2019). In the Soxhlet process, the grape seeds are shade dried and powdered; thereafter extracted successively with ethanol as a solvent for 18–20 h in a Soxhlet extractor and concentrated under reduced pressure and controlled temperature (40–50 °C) in a rotavapor (Garcia-Salas et al. 2010). Though the LLE method is simple, it is limited by its high solvent consumption, long extraction times and yields, exposure risk to organic vapours, and degradation of the target compounds (Jahromi 2019). A detailed review on the latest extraction methods for plant bioactive compounds explaining the pros and cons are reported by *Jahromi et al.,* recommending the apt process to be dependent on the chemistry of the bioactive compound, its attained yield, cost, and safety (Jahromi 2019).

Characterizing the grape seed extract for therapeutic use

It is important to keep in mind that natural products are a complex mixture of many chemical compounds that can also be responsible for the development of adverse reactions on clinical administration. To overcome this potential problem, researchers are advocated to chemically characterize their extracts with respect to their composition. Reports on use of various protocols and spectroscopic techniques such as UV–visible spectroscopy, near-infrared reflectance spectroscopy, nuclear magnetic resonance (NMR), and high performance liquid chromatography (HPLC) and gas chromatography mass spectrometry (GC–MS) for purifications and identifications highlighting their advantages and disadvantages are well established (Jahromi 2019). Recent reports also highlight the effectiveness of FTIR spectroscopy coupled with chemometrics as a valuable tool for monitoring the composition towards optimization of the most suitable extraction process (Lucarini et al. 2018). In vitro cytotoxic potential of extracts could also be performed in several human cell lines to screen irritant potential of formulations and to validate its safety, acceptability, and use in humans (Ustuner et al. 2019). In the context of industrial standard (quality assurance) for botanical analyses, the use of HPLC–UV is much regarded. However, inherent biases of this detector can result in misrepresentation of the compounds that lack a chromophore (e.g., sugars, fatty acids, etc.) leading to biased quantitative information which can be overcome by the use of universal detectors, such as charged aerosol detector (CAD) and the incorporation of gas chromatography–flame ionization detector (GC-FID) and gas chromatography–high resolution mass spectrometry (GC–HRMS) to the ultrahigh-performance liquid chromatography—mass spectrometry (UHPLC-MS) analysis for toxicological safety assessment that would obviate the need for in vitro and in vivo safety analysis (Sica et al. 2018).

Potential of grape seed extracts for wound application

The anti-microbial activity

The abundance overview of predominant chronic wound colonizer species include the *Staphylococcus* (*S. aureus* and *Staphylococcus epidermidis*) at 30.7%, *Corynebacterium* at 14.14%, *Pseudomonas* at 9.71%, and *Streptococcus* at 5.38% (Choi et al. 2019). The potential of grape seed extract as an anti-bacterial agent is well explored in these common clinical and drug-resistant pathogenic isolates. Studies have reported that grape seed alcoholic-based extracts have anti-bacterial activity against *E. coli*, *Proteus*, and *S. aureus* (Mohammed et al. 2016). Ghouila et al. (2017) reported that ethanolic extract of grape seeds show anti-bacterial activity against gram-positive bacteria such as *M. luteus* (ATCC 9341), *S. aureus* (ATCC 29213), Gram-negative bacteria such as *E. coli* (ATCC 25992), *P. aeruginosa* (ATCC 27853) and Fungi such as *A. niger* and *F. oxysporum* (Ghouila et.al., 2017). Another study reports that grape seed extract may be more active than some antibiotics such as Penicillin G at 6 µg, Oxacillin at 5 µg which are not active against *E. coli* (ATCC 25922), and *P. aeruginosa* (ATCC 27853), as well as methicillin at 5 µg against *S. aureus* (ATCC 25922) (Weinstein 2019). Also, a higher concentration of grape seed extract was reported to show potent anti-bacterial effect against *Streptococcus mutans* (Swadas et al. 2016). Another study suggests that grape seed extract is effective against 3 out of 10 strains of Methicillin-resistant *S. aureus* (MRSA) and 2 out of the 10 ESBL at 20 mg/mL concentration (Kandasamy et al., 2020). Similarly another study shows effectiveness of grape seed extract against MRSA (Al-Habib et al. 2010). Su Xiaowei et al. also observed that grape seed extracts at 1 and 5 mg/mL were most effective against two MRSA strains compared to other anti-microbial agents tested (Su et al. 2012). Al-Saleh E et al. reported that the anti-bacterial effect of grape seed extract against MRSA is due to the disruption of bacterial cell wall membrane which was examined using scanning electron microscope (SEM) and scanning electron microscope (TEM) (Al-Habib et al. 2010). Accordingly, GSE is promising for use in the treatment of infected wounds.

The anti-inflammatory activity

During prolonged inflammation in wounds, pro-inflammatory cytokines are activated via downstream cascades. These cytokines include tumor necrosis factor (TNF), interleukin (IL)-1, IL-6, and IL-17 (Xiao et al. 2020). Previous studies have demonstrated the anti-inflammatory potential of GSE on murine macrophage RAW264.7 cells. These studies report that GSE has significant potential to reduce the production of inflammatory markers such as tumor necrosis factor-α (TNFα), inducible isoform of nitric oxide synthase (iNOS), interleukin (IL-6), and nitric oxide (NO). This is achieved by impeding the phosphorylation p38, ERK1/2, JNK, and NF-κB signalling pathways through a synergistic action between the phenolic compounds and flavonoids present in the GSE (Harbeoui et al. 2019). Carullo et al. also reported that GSE containing a good number of carotenoids could display a good anti-inflammatory effects in RAW264.7 cell lines (Carullo et al. 2020). In another study, the effect of GSE on the production of MCP-1, a pro-inflammatory cytokine, was looked into using human umbilical vein endothelial cells. The results demonstrated significant reduction in the mRNA expression of MCP-1 which confirmed the anti-inflammatory property of GSE (Cádiz-Gurrea et al. 2017). Another study on the action of grape seed proanthocyanidin reported the reduction of inflammatory factors such as myeloperoxidase, interleukin (IL)-1β, IL-6, and tumor necrosis factor alpha (TNF-α) in the lung tissue, which further confirms the anti-inflammation activity pf GSE (Chen et al. 2019; Wang et al. 2020). A recent study similarly highlights the underlying mechanisms of GSE against amyloid beta-induced pro-inflammatory events in mouse retinas (Chu et al. 2020). It is also reported that grape seed proanthocyanidin extracts reduced the respiratory syncytial virus infection-induced transcription of pro-inflammatory cytokines in the epithelial airway (Kim et al. 2019). Thus, these reports on GSE seem beneficial for the treatment of inflammation associated with chronic wounds.

The anti-oxidant and anti-scarring activity

It is well established that the wound-healing process can be accelerated by the existence of antioxidants. Various reports describe rich anti-oxidant composition in grape seed extracts with clinically relevant redox-active properties via facilitation of oxidant-induced VEGF expression in keratinocytes (Süntar et al. 2012). Grape seed extract's anti-oxidant property is also reported in prevention of Alzheimer's and cancer (Faki et al. 2019). Another study demonstrated reduction of the bacterial lipopolysaccharide-induced intracellular reactive oxygen species production and mitochondrial superoxide production using GSE via up-regulation of anti-oxidant enzyme genes in human Caco-2 colon cells (Nallathambi et al. 2020). Reports also state that GSE have elevated anti-oxidant potential due to its Carotenoids, leading to anti-atherosclerotic effects, prevention of cellular oxidative damage, and control of anti-oxidant enzyme expression in both human and animal models via inhibition of the NF-κB pathway (Carullo et al. 2020). It is also reported that the grape seed extracts have anti-oxidant and cell regeneration property due to its phenolic content (Manca et al. 2019). Based on these reports, the rich presence of antioxidants in grape seed extract can potentially prevent scarring in wounds. However, additional research is required to establish the anti-scarring effectiveness of GSE in wounds which would facilitate in achieving less scarring and faster healing.

Assessment of grape seed extract in wound healing

For validation of the mentioned potential anti-microbial, anti-inflammatory, and anti-oxidant properties of grape seed extracts in accelerating wound healing, numerous in vitro and in vivo strategies have been demonstrated. A recent study reports that GSE when incorporated with chitosan capped sulfur nanoparticles, as a hydrogel film, it displayed significant anti-bacterial activity against *S. epidermis* and *E.coli* in 3 h of contact. It also showed good biocompatibility when tested on mouse fibroblasts (L929 cell lines). This finding was also further validated in vivo on artificially wounded male Sprague–Dawley rats (Jaiswal et al. 2019). Another study also demonstrated that hydro-alcoholic grape extract when applied on excision wounds in rabbits was effective in wound healing (Derakhshanfar et al. 2019). In another study, electro-spun grape seed extract-loaded silk fibroin mats demonstrated a high potential cytocompatibility, significant proliferation of skin cells, and also prevented damage from tert-butyl hydroperoxide-induced oxidative stress, proving its potential for skin care, tissue regeneration, and wound healing (Lin et al. 2016). Similarly, in an in vitro study using human foreskin fibroblast, addition of grape seed extract in electro-spun polylactic acid, and polyethylene oxide matrix showed significant anti-oxidant property favourable for application in wound healing (Locilento et al. 2019). Studies also show that grape extracts effectively removed the oxidative damage that occur in rat liver tissue during in intraoral wound healing (Erdemli et al. 2018). On assessing the effect of grape seed extract ointment in randomized, controlled clinical trials, incorporating 129 women with complications of the delayed recovery of caesarean section wounds, the results suggest that grape seed extract may have beneficial therapeutic effects in promoting caesarean section wound healing. Based on the results of this study, 5% grape seed extract seemed to be more effective than 2.5% grape seed extract emphasising future research to focus on different concentrations of grape seed extract ointment and a larger cohort of caesarean section and other wounds (Izadpanah et al. 2019). It is also reported that application of 2% hydro-alcoholic grape seed extract aids rabbit wound contraction and closure on topical application in addition to anti-oxidant and anti-inflammatory properties (Hemmati et al. 2011). A previous study evaluated the effect of grape seed extract 2% herbal cream on human skin lesions. Proanthocyanidins present in the grape seed extract triggered the release of vascular endothelial growth factor, resulting in wound closure and contraction through accelerated proliferation areas with shield edges in the epithelium, escalated cell density, and increased accumulation of connective tissue at the wound area (Hemmati et al. 2015). A previous in vitro assay on grape seed extract using human skin fibroblast cells and bacterial isolates determined that graduated dilutions of GSE from 1:1 through the 1:128 concentrations, stayed toxic as well as bactericidal, while at 1:512 dilution, GSE stayed bactericidal, but fully nontoxic. Moreover, the displayed method of anti-bacterial activity dealt with disruption of the bacterial membrane in 15 min of contact even on further dilute concentrations as determined by scanning transmission electron microscopy (Heggers et al. 2002). In another study, to obtain a material with potential for use in tissue engineering, a scaffold of anionic collagen from porcine serosa and bovine tendon and grape seed extract was synthesised. Using differential scanning calorimetry, scanning electron microscopy, and phosphate-buffered saline absorption assay, it was reported that GSE extract increases absorption capacity and decreases the collagen degradation percentage by collagenase (Garcia et al. 2019). This would be a boon for collagen-based skin tissue substitutes or for synthesis of hemostatic scaffolds. Table 1 lists the major bioactive compounds of grape seed extract and their proven bio-application in the context of wound healing.

Considerations for development and manufacture of GSE wound products

Promising data have been obtained upon pre-clinical and clinical assessment of grape seed extracts encouraging its potential use in wound healing as shown in Fig. 1. It is also noteworthy that utilization of grape seeds, an enological by-product, symbolizes the foundation for an 'intelligent' reconversion of waste attained through eco-compatible 'green technologies', guarantees environmental sustainability in the supply chain (Lucarini et al. 2018). Moreover, plant-based therapeutic compounds are known to be easily accessible and removes the commotion associated with modern treatment methods (Savoia 2012). Within this context, World Health Organization (WHO) recommends and encourages the use of plant-based treatments, which have been known as safe and effective (Zhang et al. 2019). For the ease in plant product development and commercialization, based on country to country, a set of regulations are also available for validation of its safety and quality, e.g., the European Parliament under a special category of "traditional herbal medicinal products" has its laid regulations (Ramadoss and Koumaravelou 2019). However, global differences in the standards and regulations of herbal medicinal products create limitations to the manufacturing companies to bring out a standardized herbal product in the market which calls for collaborative efforts by regulatory bodies and the WHO to launch uniform regulations (Ramadoss and Koumaravelou 2019). Moreover, implementation of Good Manufacturing Practices is advocated to ensure product batch consistency with compliance to the laid quality standards. In the context of grape seed extract, being a heterogeneous constituent, it should be crucial to screen individual polyphenols using appropriate characterization and standardization approaches as described earlier to attain reproducible cause–effect relationships on administration. Despite progress in the development of novel extraction methods, purification procedures,

Table 1 List of major bioactive compounds of grape seed extract and their mechanism of action in wound repair

SL. no	Bioactive compounds in Grape seed extract	Mechanism of action in wound repair	References
1.	Cyanidin	Anti-oxidative and anti-microbial properties	(Khoo et al. 2017)
2.	Malvidin		
3.	Delphidin		
4.	Carotenoids	Anti-inflammatory and anti-fungal properties	(Carullo et al. 2020)
5.	Proanthocyanidin	Anti-inflammatory	(Chen et al. 2019; Wang et al. 2020; Kim et al. 2019)
6.	Stilbenes	Anti-fungal	(Ananga et al. 2017)
7.	(+)-catechins		
8.	(−)-epicatechin	Anti-microbial	(Averilla et al. 2019; Mohammed et al. 2016)
9.	Vanillic acid	Anti-oxidant	(Rasheeda et al. 2018)
10.	Dimeric,trimeric and tetrameric proanthocyanidin	Anti-microbial	(Averilla et al. 2019; Mohammed et al. 2016)
11.	(−)-epicatechin-3-o-gallate		
12.	Anthocyanin	Anti-bacterial	(Averilla et al. 2019)
13.	Tanin		
14.	p-coumaric acid		
15.	Gallic acid		
16.	Ferulic acid	Anti-oxidant	(Al-Gubory et al. 2017)
17.	Caffeic acid	Anti-inflammatory	
18.	Hydroxybenzoic acid	Anti-microbial and	(Al-Gubory et al. 2017)
19.	Hydroxycinnamic acid	Anti-oxidant properties	
20.	Flavan-3-ol	Anti-oxidant	(Aslam et al. 2018)
21.	Flavones		
22.	Flavonols		
23.	Chalcones		
24.	Neolignans	Proangiogenic activity	(Buckler et al. 2017)
25.	Caffeic acid	Anti-inflammatory and anti-oxidant property	(Song et al. 2008)
26.	Coumarin	Anti-inflammatory and anti-oxidant property	(Afshar et al. 2020)

quality control assessment, and treatment protocols, the exact mechanisms of action, side effects, and dose-dependent safety of these compounds also demand further research (Pereira and Bártolo 2016). Commercially, patented formulations of resveratrol, a stilbenoid polyphenol of the grape, is sold as a nutritional supplement for the treatment of stomach ache, hepatitis, arthritis, urinary tract infections, fungal diseases or skin inflammation, and cardio-protection, owing to its high anti-oxidant and free radical scavenging activities (Salehi et al. 2018). However, Martins et al. reported that resveratrol irrespective of its wide therapeutic benefits can simultaneously modulate multiple pathways, resulting in diverse and even opposite biological effects, depending on its concentration or period of treatment time (Martins et al. 2014). This projects the pivotal role of dose-dependency and the requirement for further research to address this concern. Additionally, it is reported that resveratrol has limited clinical efficacy due to its poor water solubility and rapid metabolism leading to poor bioavailability. A detailed review by Intagliata et al. on latest technological delivery approaches to address effective clinical bioavailability of resveratrol using liposomes, polymeric and lipid nanoparticles, microemulsions, and cyclodextrins can be referred for needful consideration (Intagliata et al. 2019). Another commercially available brand of grape seed extract is CITRICIDAL™, a broad spectrum anti-microbial compound used in the treatment of burns (Holzner 2002). NutriBiotic® is also a commercially available brand which contains Citricidal in a spray format for treatment of Skin & Wounds (Feng et al. 2020). Today, Citrosept™ branded GSE is a modified formulation of CITRICIDAL™ which eliminates several contaminants thus holding an “organic” designation. However, the loss in anti-bacterial effectiveness in its latest formulation is also reported (Feng et al. 2020). In a similar context on grape seed formulations, a study reports that large variation exists in the constituents of 21 tested commercial GSEs on chemical profiling which urges the need for development of quality control standards specific for GSE for therapeutic use

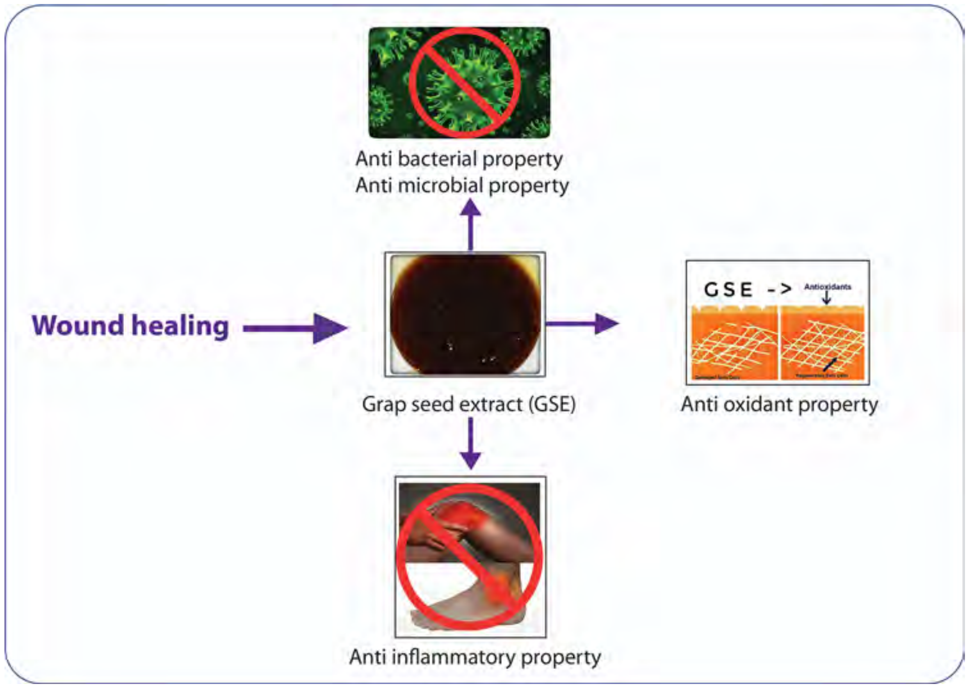

Fig. 1 Therapeutic potential of grape seed extract in wound healing: the rich presence of proanthocyanidins and other phyto-constituents in GSE can synergistically provide anti-inflammatory, anti-oxidant, and anti-microbial effects that can fasten wound healing by addressing concerns of prolonged inflammation, microbial infection, and oxidative stress

(Villani et al. 2015). Based on the considerable anti-oxidant, anti-inflammatory, anti-microbial, and wound-healing properties laid by extensive pre-clinical and clinical assessments, the effective incorporation of grape seed extract in wound products warrants further well-planned studies to uncover dose-dependent responses, ideal grape seed extract reference standards, and identification of suitable GSE delivery approaches for bioavailability on wound application.

Conclusion

Grape seed extract contains pharmacologically important and abundant bioactive compounds whose therapeutic efficiencies are mainly detected by in vitro and in vivo studies, validating anti-inflammatory, anti-microbial, and anti-oxidant properties that favour wound healing. The only reported clinical data on use of grape seed extracts in recovery of complicated caesarean section wounds does give a spark of confidence that the product could be of value. We hope this review sheds light to exploring its potential use as a plant-based therapeutic alternative in the development of wound care products. This review also hopes to encourage innovation scientists to work on addressing the projected gap areas for effective deliverables in the development of GSE products in accelerating wound healing.

Acknowledgements The authors would like to thank Zum Heilen Diagnostic & Therapeutics Pvt. Ltd. for providing facilities and support to complete this work.

Author contributions AA: conceptualization; methodology; investigation; resources; supervision; project administration; validation; visualization; original drafting; review & editing. AGV: Investigation, data acquisition, resources; writing—original drafting. PV: conceptualization, project administration, and review &editing. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed.

Funding The author(s) received no financial support for the research, authorship, and/or publication of this article.

Data availability All data generated or analysed during this study are included in this published article.

Declarations

Conflict of interest No conflict of interest has been declared by the authors; the present review paper is intended for educational purposes only.

Ethical approval This material is the authors' own original work, which has not been previously published elsewhere.

Informed consent The authors grant the Publisher permission to publish the work in Inflammation.

References

Afshar M, Hassanzadeh-Taheri M, Zardast M, Honarmand M (2020) Efficacy of topical application of coumarin on incisional wound healing in BALB/c mice. Iranian J Dermatol 23(2):56–63
Al-Gubory KH, Laher I (eds) (2017) Nutritional antioxidant therapies: treatments and perspectives. Springer, New York

Al-Habib A, Al-Saleh E, Safer A-M, Afzal M (2010) Bactericidal effect of grape seed extract on methicillin-resistant *Staphylococcus aureus* (MRSA). J Toxicol Sci 35:357–364. https://doi.org/10.2131/jts.35.357

Al-Mousawi AH, Al-kaabi SJ, Albaghdadi AJH, Almulla AF, Raheem A, Algon AAA (2020) Effect of Black Grape seed extract (*Vitis vinifera*) on biofilm formation of methicillin-resistant *Staphylococcus aureus* and *Staphylococcus haemolyticus*. Curr Microbiol 77:238–245. https://doi.org/10.1007/s00284-019-01827-0

Ananga A, Obuya J, Ochieng J, Tsolova V (2017) Grape seed nutraceuticals for disease prevention: current status and future prospects. Phenolic Compds-Biol Activity. https://doi.org/10.5772/66894

Aslam MS, Ahmad MS, Riaz H, Raza SA, Hussain S, Qureshi OS, Javed O (2018) Role of Flavonoids as wound healing agent. In: Phytochemicals-source of antioxidants and role in disease prevention. IntechOpen, pp 95–102

Averilla JN, Oh J, Kim HJ, Kim JS, Kim J-S (2019) Potential health benefits of phenolic compounds in grape processing by-products. Food Sci Biotechnol 28:1607–1615. https://doi.org/10.1007/s10068-019-00628-2

Buckler JN, Banwell MG, Kordbacheh F, Parish CR, Santiago FS, Khachigian LM (2017) Developing neolignans as proangiogenic agents: stereoselective total syntheses and preliminary biological evaluations of the four guaiacylglycerol 8-O-4′-coniferyl ethers. ACS Omega 2(10):7375–7388

Burin VM, Ferreira-Lima NE, Panceri CP, Bordignon-Luiz MT (2014) Bioactive compounds and antioxidant activity of *Vitis vinifera* and *Vitis labrusca* grapes: evaluation of different extraction methods. Microchem J 114:155–163. https://doi.org/10.1016/j.microc.2013.12.014

Cádiz-Gurrea MDLL, Borrás-Linares I, Lozano-Sánchez J, Joven J, Fernández-Arroyo S, Segura-Carretero A (2017) Cocoa and grape seed byproducts as a source of antioxidant and anti-inflammatory proanthocyanidins. Int J Mol Sci 18:376. https://doi.org/10.3390/ijms18020376

Carullo G, Sciubba F, Governa P, Mazzotta S, Frattaruolo L, Grillo G, Cappello AR, Cravotto G, Di Cocco ME, Aiello F (2020) Mantonico and Pecorello grape seed extracts: chemical characterization and evaluation of in vitro wound-healing and anti-inflammatory activities. Pharmaceuticals 13:97. https://doi.org/10.3390/ph13050097

Chen F, Wang H, Zhao J, Yan J, Meng H, Zhan H, Chen L, Yuan L (2019) Grape seed proanthocyanidin inhibits monocrotaline-induced pulmonary arterial hypertension via attenuating inflammation: in vivo and in vitro studies. J Nutr Biochem 67:72–77. https://doi.org/10.1016/j.jnutbio.2019.01.013

Choi Y, Banerjee A, McNish S, Couch KS, Torralba MG, Lucas S, Tovchigrechko A, Madupu R, Yooseph S, Nelson KE, Shanmugam VK, Chan AP (2019) Co-occurrence of anaerobes in human chronic wounds. Microb Ecol 77:808–820. https://doi.org/10.1007/s00248-018-1231-z

Chu Z, Ma G, Sun X, Xu Z, Zhang J (2020) Grape seed extracts inhibit the overexpression of inflammatory cytokines in mouse retinas and ARPE-19 cells: potentially useful dietary supplement for age-related eye dysfunction. J Med Food 23:499–507. https://doi.org/10.1089/jmf.2019.4558

Derakhshanfar A, Moayedi J, Derakhshanfar G, Poostforoosh Fard A (2019) The role of Iranian medicinal plants in experimental surgical skin wound healing: an integrative review. Iran J Basic Med Sci 22:590–600. https://doi.org/10.22038/ijbms.2019.32963.7873

Di Meo F, Aversano R, Diretto G, Demurtas OC, Villano C, Cozzolino S, Filosa S, Carputo D, Crispi S (2019) Anti-cancer activity of grape seed semi-polar extracts in human mesothelioma cell lines. J Funct Foods 61:103515. https://doi.org/10.1016/j.jff.2019.103515

Erdemli ME, Ekhteiari Salmas R, Durdagi S, Akgul H, Demirkol M, Aksungur Z, Selamoglu Z (2018) Biochemical changes induced by grape seed extract and low level laser therapy administration during intraoral wound healing in rat liver: an experimental and in silico study. J Biomol Struct Dyn 36:993–1008. https://doi.org/10.1080/07391102.2017.1305297

Faki R, Gursoy O, Yilmaz Y (2019) Effect of electrospinning process on total antioxidant activity of electrospun nanofibers containing grape seed extract. Open Chem 17:912–918. https://doi.org/10.1515/chem-2019-0098

Feng J, Leone J, Schweig S, Zhang Y (2020) Evaluation of natural and botanical medicines for activity against growing and non-growing forms of *B. burgdorferi*. Front Med 7:6. https://doi.org/10.3389/fmed.2020.00006

Fiallos NDM, Cecchin D, de Lima CO, Hirata R Jr, Silva EJNL, Sassone LM (2020) Antimicrobial effectiveness of grape seed extract against Enterococcus faecalis biofilm: a confocal laser scanning microscopy analysis. Aust Endodont J 46(2):191–196

Garcia CF, Martins VC, Plepis AM (2019) Effects of grape seed extract on properties of type I collagen scaffolds. IJAMB 2(2):02–10

Garcia-Salas P, Morales-Soto A, Segura-Carretero A, Fernández-Gutiérrez A (2010) Phenolic-compound-extraction systems for fruit and vegetable samples. Molecules 15:8813–8826. https://doi.org/10.3390/molecules15128813

Ghouila Z, Laurent S, Boutry S, Vander Elst L, Nateche F, Muller RN, Baaliouamer A (2017) Antioxidant, antibacterial and cell toxicity effects of polyphenols Fromahmeur bouamer grape seed extracts. J Fundam Appl Sci 9(1):392–420

Harbeoui H, Hichami A, Wannes WA, Lemput J, Tounsi MS, Khan NA (2019) Anti-inflammatory effect of grape (*Vitis vinifera* L.) seed extract through the downregulation of NF-κB and MAPK pathways in LPS-induced RAW264.7 macrophages. S Afr J Bot 125:1–8. https://doi.org/10.1016/j.sajb.2019.06.026

Heggers JP, Cottingham J, Gusman J, Reagor L, McCoy L, Carino E, Cox R, Zhao J-G (2002) The effectiveness of processed grapefruit-seed extract as an antibacterial agent: II. Mechanism of action and in vitro toxicity. J Altern Complement Med 8:333–340. https://doi.org/10.1089/10755530260128023

Hemmati AA, Aghel N, Rashidi I, Gholampur-Aghdami A (2011) Topical grape (*Vitis vinifera*) seed extract promotes repair of full thickness wound in rabbit. Int Wound J 8:514–520. https://doi.org/10.1111/j.1742-481X.2011.00833.x

Hemmati AA, Foroozan M, Houshmand G, Moosavi ZB, Bahadoram M, Maram NS (2015) The topical effect of grape seed extract 2% cream on surgery wound healing. Glob J Health Sci 7:52–58. https://doi.org/10.5539/gjhs.v7n3p52

Holzner G (2002) U.S. Patent No. 6,479,456. U.S. Patent and Trademark Office, Washington, DC

Intagliata S, Modica MN, Santagati LM, Montenegro L (2019) Strategies to improve resveratrol systemic and topical bioavailability: an update. Antioxidants 8:244. https://doi.org/10.3390/antiox8080244

Irving S (2019) Managing chronic, nonhealing wounds stalled in the inflammatory phase: a case series using a novel matrix therapy, CACIPLIQ20. Br J Community Nurs 24:S33–S37. https://doi.org/10.12968/bjcn.2019.24.Sup9.S33

Izadpanah A, Soorgi S, Geraminejad N, Hosseini M (2019) Effect of grape seed extract ointment on cesarean section wound healing: a double-blind, randomized, controlled clinical trial. Complement Ther Clin Pract 35:323–328. https://doi.org/10.1016/j.ctcp.2019.03.011

Jahromi SG (2019) Extraction techniques of phenolic compounds from plants. In: Plant physiological aspects of phenolic compounds. IntechOpen

Jaiswal L, Shankar S, Rhim J-W (2019) Carrageenan-based functional hydrogel film reinforced with sulfur nanoparticles and grapefruit seed extract for wound healing application. Carbohydr Polym 224:115191. https://doi.org/10.1016/j.carbpol.2019.115191

Kandasamy M, Nasimuddin S, Malayan J, Nithyalakshmi J, Gnanadesikan S, Chandrasekar M (2016) A study on antibacterial effect of grape seed extracts in common clinical and drug resistant isolates. Int J Clin Trials 3(3):165–168

Khoo HE, Azlan A, Tang ST, Lim SM (2017) Anthocyanidins and anthocyanins: colored pigments as food, pharmaceutical ingredients, and the potential health benefits. Food Nutr Res 61:1361779. https://doi.org/10.1080/16546628.2017.1361779

Kim SJ, Lee J-W, Eun Y-G, Lee KH, Yeo SG, Kim SW (2019) Pretreatment with a grape seed proanthocyanidin extract downregulates proinflammatory cytokine expression in airway epithelial cells infected with respiratory syncytial virus. Mol Med Rep 19:3330–3336. https://doi.org/10.3892/mmr.2019.9967

Kumar A, D'silva M, Dholakia K, Levenson AS (2018) In vitro anticancer properties of table grape powder extract (GPE) in prostate cancer. Nutrients 10:804. https://doi.org/10.3390/nu10111804

Kwatra B (2020) A review on potential properties and therapeutic applications of grape seed extract. World J Pharm Res 9:2519–2540

Lin S, Chen M, Jiang H, Fan L, Sun B, Yu F, Yang X, Lou X, He C, Wang H (2016) Green electrospun grape seed extract-loaded silk fibroin nanofibrous mats with excellent cytocompatibility and antioxidant effect. Colloids Surf B 139:156–163. https://doi.org/10.1016/j.colsurfb.2015.12.001

Lin T-K, Zhong L, Santiago JL (2017) Anti-inflammatory and skin barrier repair effects of topical application of some plant oils. Int J Mol Sci 19:70. https://doi.org/10.3390/ijms19010070

Locilento DA, Mercante LA, Andre RS, Mattoso LH, Luna GL, Brassolatti P, Correa DS (2019) Biocompatible and biodegradable electrospun nanofibrous membranes loaded with grape seed extract for wound dressing application. J Nanomater. https://doi.org/10.1155/2019/2472964

Lucarini M, Durazzo A, Romani A, Campo M, Lombardi-Boccia G, Cecchini F (2018) Bio-based compounds from grape seeds: a biorefinery approach. Molecules 23:1888. https://doi.org/10.3390/molecules23081888

Manca ML, Firoznezhad M, Caddeo C, Marongiu F, Escribano-Ferrer E, Sarais G, Peris JE, Usach I, Zaru M, Manconi M, Fadda AM (2019) Phytocomplexes extracted from grape seeds and stalks delivered in phospholipid vesicles tailored for the treatment of skin damages. Ind Crop Prod 128:471–478. https://doi.org/10.1016/j.indcrop.2018.11.052

Martins LAM, Coelho BP, Behr G, Pettenuzzo LF, Souza ICC, Moreira JCF, Borojevic R, Gottfried C, Guma FCR (2014) Resveratrol induces pro-oxidant effects and time-dependent resistance to cytotoxicity in activated hepatic stellate cells. Cell Biochem Biophys 68:247–257. https://doi.org/10.1007/s12013-013-9703-8

Mattos GN, Tonon RV, Furtado AA, Cabral LM (2017) Grape by-product extracts against microbial proliferation and lipid oxidation: a review. J Sci Food Agric 97:1055–1064. https://doi.org/10.1002/jsfa.8062

Memar MY, Adibkia K, Farajnia S, Kafil HS, Yekani M, Alizadeh N, Ghotaslou R (2019) The grape seed extract: a natural antimicrobial agent against different pathogens. Rev Med Microbiol 30:173–182. https://doi.org/10.1097/MRM.0000000000000174

Moalla Rekik D, Ben Khedir S, Ksouda Moalla K, Kammoun NG, Rebai T, Sahnoun Z (2016) Evaluation of wound healing properties of grape seed, sesame, and fenugreek oils. Evid-Based Compl Altern. https://doi.org/10.1155/2016/7965689

Mohammed KAK, Hussein SZ, Noori SI (2016) Chemical analysis and antibacterial activity of grape (*Vitis vinifera*) seed extracts. World J Exp Biosci 4(1):58–61

Nallathambi R, Poulev A, Zuk JB, Raskin I (2020) Proanthocyanidin-rich grape seed extract reduces inflammation and oxidative stress and restores tight junction barrier function in caco-2 colon cells. Nutrients 12:1623. https://doi.org/10.3390/nu12061623

Nassiri-Asl M, Hosseinzadeh H (2016) Review of the pharmacological effects of vitis vinifera (grape) and its bioactive constituents: an update. Phytother Res 30:1392–1403. https://doi.org/10.1002/ptr.5644

Niculescu VC, Paun N, Ionete RE (2018) The evolution of polyphenols from grapes to wines. Grapes Wines-Adv Prod Process Anal Valorization

Percival SL, Hill KE, Williams DW, Hooper SJ, Thomas DW, Costerton JW (2012) A review of the scientific evidence for biofilms in wounds. Wound Repair Regen 20:647–657. https://doi.org/10.1111/j.1524-475X.2012.00836.x

Pereira RF, Bártolo PJ (2016) Traditional therapies for skin wound healing. Adv Wound Care 5:208–229. https://doi.org/10.1089/wound.2013.0506

Prado JM, Dalmolin I, Carareto NDD, Basso RC, Meirelles AJA, Vladimir Oliveira J, Batista EAC, Meireles MAA (2012) Supercritical fluid extraction of grape seed: process scale-up, extract chemical composition and economic evaluation. J Food Eng 109:249–257. https://doi.org/10.1016/j.jfoodeng.2011.10.007

Rajabi Hamedani S, Del Zotto L, Bocci E, Colantoni A, Villarini M (2019) Eco-efficiency assessment of bioelectricity production from Iranian vineyard biomass gasification. Biomass Bioenerg 127:105271. https://doi.org/10.1016/j.biombioe.2019.105271

Ramadoss MSK, Koumaravelou K (2019) Regulatory compliance of herbal medicines—a review. Int J Res Pharm Sci 10:3127–3135. https://doi.org/10.26452/ijrps.v10i4.1609

Rasheeda K, Bharathy H, Fathima NN (2018) Vanillic acid and syringic acid: exceptionally robust aromatic moieties for inhibiting in vitro self-assembly of type I collagen. Int J Biol Macromol 113:952–960

Rodríguez-Pérez C, García-Villanova B, Guerra-Hernández E, Verardo V (2019) Grape seeds proanthocyanidins: an overview of in vivo bioactivity in animal models. Nutrients 11:2435. https://doi.org/10.3390/nu11102435

Savoia D (2012) Plant-derived antimicrobial compounds: alternatives to antibiotics. Future Microbiol 7(8):979–990

Salehi B, Mishra AP, Nigam M, Sener B, Kilic M, Sharifi-Rad M, Fokou PVT, Martins N, Sharifi-Rad J (2018) Resveratrol: a double-edged sword in health benefits. Biomedicines 6:91. https://doi.org/10.3390/biomedicines6030091

Sen CK (2019) Human wounds and its burden: an updated compendium of estimates. Adv Wound Care 8:39–48. https://doi.org/10.1089/wound.2019.0946

Sica VP, Mahony C, Baker TR (2018) Multi-detector characterization of grape seed extract to enable in silico safety assessment. Front Chem 6:334. https://doi.org/10.3389/fchem.2018.00334

Song HS, Park TW, Sohn UD, Shin YK, Choi BC, Kim CJ, Sim SS (2008) The effect of caffeic acid on wound healing in skin-incised mice. Korean J Physiol Pharmacol 12(6):343

Su X, Howell AB, D'Souza DH (2012) Antibacterial effects of plant-derived extracts on methicillin-resistant *Staphylococcus aureus*. Foodborne Pathog Dis 9:573–578. https://doi.org/10.1089/fpd.2011.1046

Süntar I, Akkol EK, Nahar L, Sarker SD (2012) Wound healing and antioxidant properties: do they coexist in plants? Free Radic Antioxidants 2:1–7. https://doi.org/10.5530/ax.2012.2.2.1

Swadas M, Dave B, Vyas SM, Shah N (2016) Evaluation and comparison of the antibacterial activity against streptococcus mutans of grape seed extract at different concentrations with chlorhexidine gluconate: an in vitro study. Int J Clin Pediatr Dent 9:181–185. https://doi.org/10.5005/jp-journals-10005-1360

Ustuner O, Anlas C, Bakirel T, Ustun-Alkan F, Diren Sigirci B, Ak S, Koca-Caliskan U (2019) In vitro evaluation of antioxidant, anti-inflammatory, antimicrobial and wound healing potential of Thymus Sipyleus Boiss. Subsp. Rosulans (Borbas) Jalas. Molecules 24(18):3353

Vilkhu K, Mawson R, Simons L, Bates D (2008) Applications and opportunities for ultrasound assisted extraction in the food industry—a review. Innov Food Sci Emerg Technol Food Innov 9:161–169. https://doi.org/10.1016/j.ifset.2007.04.014

Villani TS, Reichert W, Ferruzzi MG, Pasinetti GM, Simon JE, Wu Q (2015) Chemical investigation of commercial grape seed derived products to assess quality and detect adulteration. Food Chem 170:271–280. https://doi.org/10.1016/j.foodchem.2014.08.084

Wang Y, Wang Y, Shen W, Wang Y, Cao Y, Nuerbulati N, Chen W, Lu G, Xiao W, Qi R (2020) Grape seed polyphenols ameliorated dextran sulfate sodium-induced colitis via suppression of inflammation and apoptosis. Pharmacology 105:9–18. https://doi.org/10.1159/000501897

Wei D, Zhu X-M, Chen Y-Y, Li X-Y, Chen Y-P, Liu H-Y, Zhang M (2019) Chronic wound biofilms: diagnosis and therapeutic strategies. Chin Med J 132:2737–2744. https://doi.org/10.1097/CM9.0000000000000523

Weinstein MP (2019) Clinical and laboratory standards institute. Performance standards for antimicrobial susceptibility testing

Xiao T, Yan Z, Xiao S, Xia Y (2020) Proinflammatory cytokines regulate epidermal stem cells in wound epithelialization. Stem Cell Res Ther 11:232. https://doi.org/10.1186/s13287-020-01755-y

Zhang H, Liu S, Li L, Liu S, Liu S, Mi J, Tian G (2016) The impact of grape seed extract treatment on blood pressure changes. Medicine. https://doi.org/10.1097/MD.0000000000004247

Zhang Q, Sharan A, Espinosa SA, Gallego-Perez D, Weeks J (2019) The path toward integration of traditional and complementary medicine into health systems globally: the World Health Organization report on the implementation of the 2014–2023 strategy. J Altern Complement Med 25:869–871. https://doi.org/10.1089/acm.2019.29077.jjw

Zhao R, Liang H, Clarke E, Jackson C, Xue M (2016) Inflammation in chronic wounds. Int J Mol Sci 17:2085. https://doi.org/10.3390/ijms17122085

Zhao D, Simon JE, Wu Q (2020) A critical review on grape polyphenols for neuroprotection: strategies to enhance bioefficacy. Crit Rev Food Sci Nutr 60:597–625. https://doi.org/10.1080/10408398.2018.1546668