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A POTENTIAL PLANT FOR WOUND DRESSING: EVALUATION OF THE PHARMACOLOGICAL ACTIVITIES OF POLYGONUM COGNATUM MEISSN WITH A 3D CELL CULTURE PERSPECTIVE

YARA GİYSİSİ İÇİN POTANSİYEL BİR BİTKİ: POLYGONUM COGNATUM MEISSN.'IN FARMAKOLOJİK AKTİVİTELERİNİN 3B HÜCRE KÜLTÜRÜ PERSPEKTİFİYLE DEĞERLENDİRİLMESİ

Ufkay KARABAY[1,2] Sıla Aze BAKAN[1] R. Bugra HUSEMOĞLU[3]
Mehtap YUKSEL EGRILMEZ[2]

[1] Izmir Tınaztepe University, Vocational School of Health Services, Department of Pathology Laboratory Techniques, Izmir, Turkey

[2] Dokuz Eylul University, Institute of Health Sciences, Department of Molecular Medicine, Izmir, Turkey

[3] Dokuz Eylul University, Institute of Health Sciences, Department of Biomechanics, Izmir, Turkey

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SUMMARY

A physiologic wound healing is a complex multi-faceted process regulated by the hemostasis/inflammation, proliferation, and remodelling phases. In order to better understand the wound healing mechanism, novel reports are published in the literature with in vitro and in vivo wound models. Tissue repair may progress insufficiently in autoimmune, diabetic, pressure and burn wounds. In this regard, patients with like these wounds may need to be treated with cellular therapy. Regenerative medicine is an interdisciplinary field of study in which life sciences apply engineering principles to heal and repair diseased and injured tissues and restore and maintain normal function. Polygonum cognatum Meissn. (P. cognatum) is an antioxidant and antimicrobial perennial wild edible plant belonging to the Polygonaceae family that is rich in crude protein, vitamin C and E, carotenoids, Zn, Fe and, Mn elements, folic acid. In this review, we aimed to summarize the pharmacological properties of P. cognatum and its potential use as a candidate for 3D scaffolds. The literature search from the database PubMed and Google Scholar was done for the key word "Polygonum Cognatum" and 15 articles were identified. P. cognatum leaves as a 3D tissue scaffold by decellularization may present a unique approach as a skin wound dressing.

ÖZ

Fizyolojik yara iyileşmesi, hemostaz/iltihap fazı, proliferasyon fazı ve yeniden şekillenme fazı tarafından düzenlenen karmaşık, çok yönlü bir süreçtir. Yara iyileşme mekanizmasının daha iyi anlaşılabilmesi için literatürde *in vitro* ve *in vivo* yara modelleri ile ilgili yeni raporlar yayımlanmaktadır. Otoimmün, diyabetik, bası ve yanık yaralarında doku onarımı yetersiz ilerleyebilmektedir. Bu bakımdan bu tür yaraları olan hastaların hücresel terapi ile tedavi edilmesi gerekebilmektedir. Rejeneratif tıp, hastalıklı ve yaralı dokuları iyileştirmek ve onarmak, normal işlevi eski haline getirmek ve sürdürmek için yaşam bilimlerine mühendislik ilkelerinin uygulandığı disiplinler arası bir çalışma alanıdır. *Polygonum cognatum* Meissn. (P. cognatum), ham protein, vitamin C, E, karotenoidler, Zn, Fe ve Mn elementleri, folik asit düzeyleri açısından zengin, antioksidan, antimikrobiyal, idrar söktürücü, antidiyabetik, antelmintik ve antifungal özelliklere sahip Polygonaceae familyasına ait çok yıllık yabani

yenilebilir bir bitki türüdür. Bu derlemede, P. cognatum'un farmakolojik özelliklerini ve 3 boyutlu yapı iskelelerine aday olarak kullanımını incelemeyi amaçladık. “Polygonum Cognatum” anahtar kelimesi için PubMed ve Google Scholar veri tabanından literatür taraması yapılmış ve 15 makale tespit edilmiştir. Hücresizleştirme yoluyla bir 3D doku iskelesi olarak P. cognatum yaprakları, cilt yara örtüsü olarak özgün bir yaklaşım sunabilir.

1. Introduction

The insufficient wound healing process is preceded in the chronic inflammatory microenvironment compared to normal wound healing. There are studies reporting that three dimensional (3D)-printed scaffolds contribute to the regeneration of the target region, with or without cells, in the insufficient healing of skin wounds. In this review, we aimed to summarize the potential use of *Polygonum Cognatum* Meissn. (P. cognatum) plant, which has high vitamin and protein contents, antioxidant and antimicrobial properties, as 3D tissue scaffolds in line with its pharmacological properties. The literature search was done from the database PubMed, Science Direct, and Google Scholar with the keywords “Polygonum Cognatum” and “Polygonum Cognatum Meissn.” separately and 691 articles were identified. These articles were limited according to clinical, *in vivo*, and *in vitro* studies published in English and 15 articles were evaluated for this review. (Figure 1).

2. Physiology of Normal and Inflammation Wound Healing

A physiologic wound healing is a complex multi-faceted process regulated by the hemostasis/inflammation phase, the proliferation phase, and the remodelling phase (1). After a skin injury, the sub-endothelium at injury sites activates the tissue factor platelet aggregation, resulting in degranulation and the release of chemotactic and growth factors to form the clot (2). Neutrophils play a beneficial role in wound healing by cleaning debris and bacteria in the wound site. Subsequently, macrophages accumulate in the wound site, facilitating the

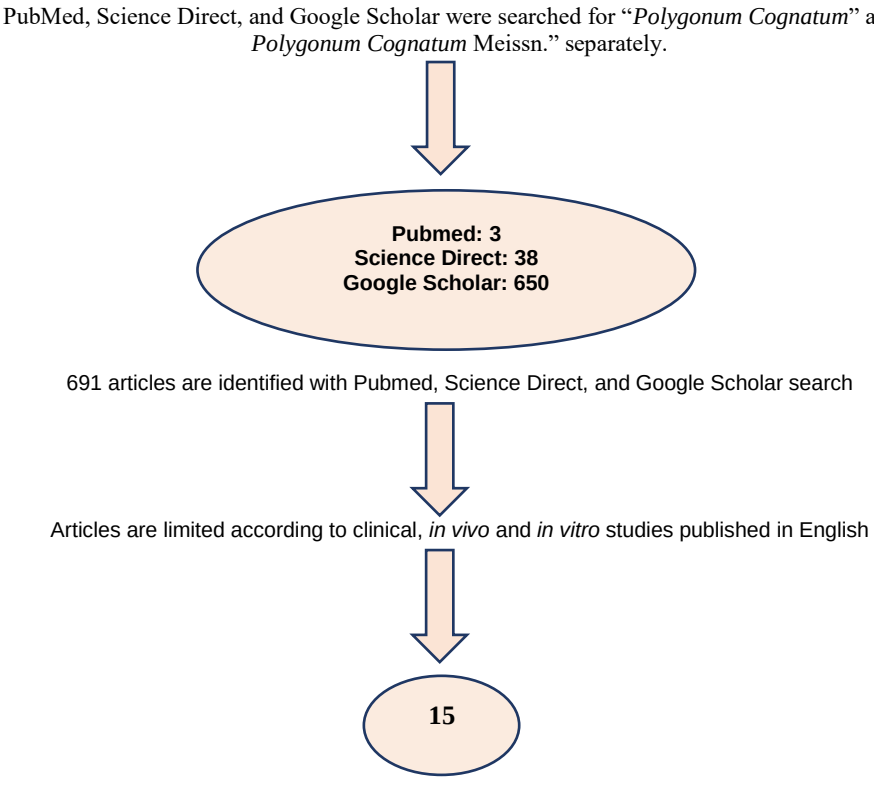

Figure 1. Literature search for the plant *Polygonum cognatum* Meissn.

phagocytosis of bacteria and damaged tissues. Hemostasis and the inflammatory phase are usually occurred 72 h to complete (3). In the proliferative phase, many cells play a role such as fibroblasts, keratinocytes and endothelial cells, and granulation tissue is formed to replace the original clot formation with the production of extracellular matrix (ECM) including hyaluronic acid, proteoglycans, elastin and collagen. Numerous cytokines and growth factors such as the transforming growth factor-β family (TGF-β, TGF-β1, TGF-β2 and TGF-β3), interleukin (IL) family and angiogenesis factors (vascular epidermal growth factor) are produced in the proliferative phase (4). The last phase of wound healing is the remodelling phase, which requires a balance between apoptosis of existent cells and the production of new tissue cells. The gradual degradation of abundant ECM and immature type III collagen produced in the wound site and the formation of mature type I collagen are critical at this stage. Any aberration in this phase can result in excessive wound healing or chronic wound formation (5, 6). In order to better understand the wound healing mechanism, novel reports are published in the literature with *in vitro* and *in vivo* wound models. Fetal wound healing is characterized by the regeneration of the normal dermal architecture, including restoration of the neurovasculature and dermal appendages. Wound healing in fetal skin includes a characteristic growth factor and anti-inflammatory cytokine profile with a potential role of stem cells, and lower inflammatory response and biomechanical stress comparing adult wounds. Also, fetal skin wound healing has an ECM rich in hyaluronic acid and type III collagen. The risk of scar formation in wound healing in adults is higher compared to fetal skin (6-8). The studies reveal the wound healing difference between fetal skin and adult skin. The early stage of adult wound healing is characterized by an inflammatory reaction with the migration of neutrophils and macrophages, but inflammation is not evident in the fetal skin wound. Studies are specified fewer inflammatory cells in the fetal wound than in the adult wound (8). Fibroblasts are cells that play role in the anti-inflammatory phase of wound healing, producing a higher proportion of ECM in the fetal wound. The ratio of collagen type III to collagen type I is higher in the fetal wound. Also, the levels of hyaluronic acid in the ECM are higher in the fetal wound comparing the adult wound. In contrast to adult wounds, myofibroblasts do not appear in fetal wound healing. Therefore, further studies of the underlying mechanisms of fetal wound healing will identify potential drugs that will minimize scar formation. In another study, it is reported that excessive wound healing such as keloid and the hypertrophic scar is related to the pathological process including inflammation (9, 10). Reports have been published stating that excessive ECM deposition occurs through upregulation of fibroblast function in purulent-inflammatory wounds (11). However, tissue repair may progress insufficiently in autoimmune, diabetic, pressure and burn wounds.

3. Applications of Biomaterials in Regenerative Medicine

Regenerative medicine is an interdisciplinary field of study in which engineering principles are applied to the life sciences to heal and repair diseased and injured tissues and restore and maintain normal function. Additive manufacturing (AM), also known as three-dimensional (3D) printing includes various techniques such as stereolithography, fused deposition modelling (FDM) and selective laser sintering (12). FDM is commonly used to process thermoplastic polymers (13). 3D printed tissue scaffolds are biomaterials that provide a new field of application for regenerative medicine which is produced with 3D printing technology by programming pore sizes and shapes. 3D printed scaffolds act as temporary supplements for cells until reconstructed the natural extracellular matrix ECM. In particular, the development of 3D tissue scaffolds and the utilisation of tissue-biocompatible biomaterials facilitate the medical treatments of tissue damaged by trauma or disease. In this context, 3D cell culture provides much better cell-cell and cell-ECM interactions compared to 2D cell culture.

In this regard, patients with such wounds may need to be treated with cellular therapy. Advances in tissue engineering have led to the production of personalized implants in many medical fields. However, host response to implanted biomaterials can cause immune

rejection. In this context, biomaterials used as implants have should be biocompatible, non-toxic, biodegradable and anti-bacterial properties. Patient-specific 3D printed scaffolds can be designed to mimic and heal the damaged tissue microenvironment in medical applications. Natural and synthetic polymers are used to manufacture 3D scaffolds. Tissue scaffolds can be preferred in pure and copolymer form or coated with biological materials. Biomaterials from synthetic polymers such as polylactic acid (PLA), poly-caprolactone (PCL), polyether-ether-ketone (PEEK) and thermoplastic polyurethane (TPU) can be used to mimic the target tissue in tissue engineering.

4. Pharmacological Properties of *Polygonum cognatum* Meissn.

Polygonum cognatum Meissn. (P. cognatum) is a perennial wild edible plant belonging to the Polygonaceae family. In our country, especially at the beginning of April, it spreads over a wide habitat such as roadsides, cliffs, and agricultural areas, especially at 700-3000 m above sea level (14). Young shoots and leaves of P. Cognatum are used in the traditional treatment of various diseases in the central Anatolia region of Turkey. According to the literature search, it has been reported that P. cognatum is rich in crude protein, vitamin C, E, carotenoids, Zn, Fe and, Mn elements, folic acid and has antioxidant, antimicrobial, diuretic, antidiabetic, anthelmintic and antifungal properties (14-24).

Yıldırım et al., reported that the treatment of P. cognatum extract in a rat model of haemorrhoids reduced biochemical and histochemical destruction in plasma and recto-anal tissue (25). In addition, it has been reported that P. Cognatum has protective roles in the rat colitis model by regulating the activities of antioxidant molecules, downregulating colon tissue lesions and oxidative stress (26). In another study, it was reported that P. cognatum decreased cell viability in aggressively progressive Glioblastoma multiforme (GBM) cell lines (U87), one of the most common types of brain tumors and increased the apoptotic activity of doxorubicin (27). Parallel to these results, P. cognatum showed cytotoxic effects on MCF-7 in vitro, whereas these effects were not observed in human epithelial cells (28). The use of extracts from Polygonum Cognatum Meissn in animal and cell models is shown in Table 1.

Table 1. Use of extracts from *Polygonum Cognatum Meissn.* in animal and cell models.

Article	Extract type	Target cell/tissue/animal/ microorganisms	Results	References
Yildirim et al., 2003	Ether, Ethanol and Water	*Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, and *Pseudomonas aeruginosa in vitro*	Ether and ethanol extracts of P. cognatum showed antimicrobial activity against Staphylococcus aureus and Bacillus subtilis, while water extract did not show any antimicrobial activity.	14
Cevik et al., 2014	Maceration wtih saline	Colitis rat model	P. cognatum decreased serum IL-6 and TNF-α, MDA levels, GGT and MPO activities and increased SOD and CAT activities and GSH levels in colitis group.	26
Yildirim et al., 2017	Ethanol	Haemorrhoids rat model	P. cognatum decreased tissue damage and MDA levels and increased GSH, CAT, GPx and SOD activity in haemorrhoids group.	25
Sarac et al., 2018	Water	MCF-7 and HUVEC cells *in vitro*	P. cognatum had strong cytotoxic effects on MCF-7 cells while no cytotoxic effect was observed on human healthy epithelial cells.	28
Dereli et al., 2018	n-hexane, ethyl acetate and methanol	*Syphacia obvelata* and *Aspiculuris tetraptera* infected mice model	P. cognatum extracts were found to decrease the egg numbers of *S. obvelata* and *A. tetraptera*.	18
Pekdemir et al., 2020	Ethanol, methanol, n-hexane and acetone	MKN-45, MCF-7 and PC3 cell lines *in vitro*	All four different extracts of P. cognatum had cytotoxic effects on MKN-45, MCF-7 and PC3 cell lines.	22
Pehlivan et al., 2020	Methanol	U87 cell line *in vitro*	P. cognatum extract decreased the cell viability of U87 cells in a time and concentration-dependent manner.	27

IL-6: interleukin-6, TNF-α: tumor necrosis factor alpha, MPO: myeloperoxydase, CAT: catalase, SOD: superoxide dismutase, GGT: gamma-glutamyl transferase, MDA: malondialdehyde and GSH: glutathione, GPx: glutathione peroxidase

5. Plant-Derived 3D Scaffolds

In recent years, plant-derived natural polymers have been used as an alternative to 3D-printed scaffolds produced with animal-derived natural products (29,30). There are reports that plant polysaccharides including celluloses, hemicelluloses and pectins may serve various biological functions such as cell-cell communication, mitogenesis, and immune recognition, in favour of plant-derived 3D scaffolds (31). In one study, it was shown that the leaf vasculature system can be decellularized and used as a 3D tissue scaffold in bioengineering applications (32). 3D-printed tissue scaffolds produced from plants with anti-inflammatory properties may be preferred, especially in chronic inflammatory diseases such as autoimmunity with insufficient wound healing. P. cognatum, which has high antioxidant content and antimicrobial properties in terms of pharmacological properties, is a candidate plant species that may be used in the production of plant-derived 3D printed scaffolds.

6. Conclusion

In this context, examining the anti-inflammatory properties of P. cognatum leaves as a 3D tissue scaffold by decellularization may present a unique approach as a skin wound dressing. In addition, the use of decellularized P. cognatum leaves as composites with synthetic polymers such as PLA, TPU, PEEK and PCL, which have been reported to have biocompatible and non-toxic properties in many studies, may offer a unique approach to the field of bioengineering. In experimental models with insufficient wound healing due to dermal involvement, such as systemic sclerosis, 3D decellularized wound dressings obtained from P. cognatum leaves are predicted to be candidates for future applications.

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