Wound Healing Improvement by Polymer Surgical Suture Coated with Tannic Acid

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Abstract

A surgical suture is a vital medical device to uphold wounded tissue during surgery. However, the application to improve tissue healing must still be developed. This study offered to solve this problem by incorporating tannic acid (TA) into polydioxanone (PDS) sutures. The PDS suture was immersed in TA complexing with iron (III) solutions in pH 8.0 solution. The engineered suture was successful, as revealed by the OH peak of TA in FTIR spectra. Furthermore, it was confirmed by TA particle appearance under Scanning Electron Microscopy. Contact angle measurement showed better wettability in biological mimicking solutions, such as water, serum, and saline solution. Thereby, it improved *in vitro* wound healing activity. Moreover, our bioinformatics data showed that TA enhanced the wound healing process by addressing multiple targets in the early phase of inflammation. For instance, it induced platelets to reduce bleeding at the early wound healing stage, activated T cells at the inflammation stage, accelerated epidermis cell proliferation, and activated fibroblast as a key player in wound healing. Due to multiple wound healing targets, our suture system was expected to be emphasized in clinical applications.

Keywords: Tannic acid, Wound, Suture, Biocompatibility, Fibroblast

Introduction

A suture is a provisional and the most widely applied biomaterial in trauma or surgery to uphold the tissue, allowing them to heal [1,2]. Suturing ultimately aims to mend the wound healing process of surgery, and the materials must be biocompatible with high tensile strength [2,3]. Based on their degradability, surgical sutures are categorized into non-absorbable and absorbable [2,4]. The absorbable materials are popular in clinical applications because it does not challenge revision surgery, which is particularly complicated in specific tissue anatomy [3-5]. Since suture material has direct contact with the defective tissue, it must be safe, non-toxic, biocompatible, non-allergenic, and could deliver therapeutics agents for specific purposes [1,2,6,7]. Therefore, many attempts were employed to achieve the best platform of the surgical suture in clinical applications.

Some modifications have been investigated to coat surgical sutures with therapeutic proteins or bioactive molecules, such as growth factors, extracellular matrix components, pain relief molecules, or antibiotics [8-14]. Surgical suture modification mainly aims to accelerate tissue healing, prevent infection, minimize immune reactivity, and improve tissue biocompatibility [9]. In the previous study, fibronectin, extracellular matrix (ECM) components, had been successfully coated to the suture surface to improve wound healing and impede bacterial infection [15]. However, the stability of the protein requires cold storage for its structural stability during the distribution. Hence, innovations must overcome this shortcoming.

Like a typically injured wound, a surgical wound is a complex multiple-stage inflammation process, tissue proliferation/formation, and tissue remodeling. Each stage involves multiple proteins at a dynamic cellular level, from keratinocytes endothelial cells to fibroblasts [16,17]. The process includes ECM reorganization, synthesizing, and degradation of the fibrin clots as provision ECM, then replacing it with collagen matrix during tissue formation and remodeling [16]. As the basic understanding of the wound healing process, tannic acid (TA) is a promising candidate to modulate the wound healing process. TA, a polyphenolic compound, consists of poly alloy groups to a glucose core and modulates inflammation in wound healing stages [18]. Moreover, TA promoted wound healing and tissue regeneration and exhibited

antibacterial activity [19-21]. TA coating has multiple potential surface functionalization by complexing TA-iron (III) coordination on various substrates, including polymers and metals and its oxidation form [22-25].

This study proposed to engineer TA-iron (III) coating on polydioxanone (PDS) suture as a platform for an easy, versatile, and effective method to fabricate bioactive suture. PDS is one of the biodegradable polymers commonly used as a surgical suture, instead of non-biodegradable sutures, which need revision surgery to take it out from the surgery site, such as nylon, silk, polypropylene, polyester, and polybutester [26,27]. Instead of the surgical suture, PDS has been employed as a biomaterial for implant, tissue engineering, and gene/drug delivery [28]. However, using PDS in surgery remains some problems related to wound healing, biocompatibility, and bacterial infection [15,19,27].

In this study, the PDS hypothesized that TA would be coated on the PDS suture, as revealed by the OH peak in FTIR spectra and TA particle on the PDS surface in Scanning Electron Microscopy (SEM) data. The engineered suture predicted a higher wettability degree of water, saline, and serum, representing the biological fluid, which was expected to have better biocompatibility and accelerated *in vitro* wound healing. The molecular mechanism of TA in the wound healing pathway was analyzed using bioinformatics to investigate TA's protein targets, possibly facilitating the wound healing process.

Materials and methods

Materials

The surgical sutures applied in this study were purchased from PDSII® (Ethicon, Z346H), whose size met those listed in The United States Pharmacopeia. This study used a size 0 suture with a diameter of 0.350 - 0.399 mm. The suture was cut into the 20-mm length and kept at −20 °C until it was used for experiments. Tannic acid (TA) was purchased from Sigma (W304204), and iron (III) chloride hexahydrate ($FeCl_3.6H_2O$) was obtained from Merck (943103). Phosphate Buffered Saline (PBS) solution was dissolved in PBS powder (Sigma, P-3813) in deionized water and then filtered using a membrane filter (GSWP04700). For cell culture, GFP-human dermal fibroblast neonatal (Angio-proteomic) cultured in 10 % fetal bovine serum (FBS, Gibco 16000044) containing high-glucose media (DMEM) (Gibco, 11965092) and 1 % penicillin-streptomycin (Gibco, 10378016). The cells were detached using trypsin-EDTA 0.25 % (25200056).

Bioinformatics data collecting and processing

NCBI (https://www.ncbi.nlm.nih.gov/) and GeneCards (genecards.org) were used to identify potential target genes (PTG) for wound healing (genecards.org). STITCH v5.0 (https://stitch.embl.de) provided the natural protein reacting with TA (DPTA). Further, indirect proteins reacting with TA (IPTA) were explored in STRING-DB v11.5 (https://string-db.org/). PTG and IPTA were analyzed using a Venn diagram to determine the intercept as probable TA target proteins. The Protein–Protein Interaction (PPI) network was analyzed and displayed using Cytoscape 3.9.1 and STRING-DB v11.5 software) [29,30]. The top 10 genes were chosen using the default settings of the Degree method from the Cyto–Hubba plugin and were classified as hub genes [31].

Crosslinking of TA-coated polydioxanone suture

To create solutions with 10 and 30 mg mL^{-1} TA concentrations, TA and FeCl3.6H2O (0.1 mg mL^{-1}) were combined in deionized water. Adding Fe3+ increases the crosslinking degree of TA on the suture by forming the TA-Fe3+ complex. The pH of the solutions was adjusted to 8 using a NaOH solution (1.0 M). PDS subsequently were immersed in 1.5 mL of TA-Fe3$^+$ solution and sat for 24 h at room temperature. Coated PDS sutures with TA coating were cleaned in deionized water and dried at 65 °C in an oven.

Characterization of the modified suture

Engineered sutures were characterized using Fourier-transform infrared (ATR-FTIR) spectroscopy. Before the test, the fabricated sutures were dried in the air, then measured with attenuated total reflectance using the Agilent Cary 610 system; 64 scans accumulated at the wavenumber range from 600 to 4,000 cm^{-1}. Moreover, the suture was imaged under the SEM to observe the surface profile of the sutures. The air-dried sutures from the previous coating process were fixed in 4 % glutaraldehyde for 20 min, then gently washed under free-ionized water 3 times, 15 min each. The sample was dried at 65 °C overnight, fixed on a silicon wafer, and observed under the Zeiss JSM7100F system for SEM characterization.

Contact angle measurement

PDS and its modifications tested their contact angle in water, FBS, and saline (NaCl 0.9 %). Our homemade, assembled device measured the contact angle based on the previous protocols to minimize systematic and random errors [32]. This study adopted a previous study by Ribe and colleagues (2016) to make a sample holder using a glass slide and align the camera's center. The white background was put behind the sample, and 1 μL solution was dropped on the surface of the suture [33]. The data was then analyzed using a Drop analysis plugin in Image-J.

Scratch wound healing assay

Human neonatal dermal fibroblast cells (HDF, purchased from ATCC® PCS-201-010™) were cultured in 10 % v/v heat-inactivated FBS containing high-glucose DMEM with 1 % (v/v) penicillin-streptomycin at 37 °C in a humidified atmosphere of 5 % CO_2. After the cells were 80 % confluent, the medium was discarded, HDF cells were rinsed with PBS, then detached using 0.25 % trypsin. The scratch assay was designed based on our previous study [15]. Several 3×10^5 cells were seeded on the 35-mm dish after 24 h and were scrapped with yellow tips in 1-mm width. The cells were washed with PBS 3 times to remove the cell debris. The suture was placed between the cells' gaps, and the medium was changed to 0.5 % FBS-containing medium. The wound enclosure was calculated by measuring the wound between the cells' gap at 0 and 24 h.

Results and discussion

Bioinformatics study: Tannic acid protein target and proposed molecular pathway

Recently, advances in bioinformatics made analyzing the multicenter data of the wound healing process possible, which is affected by TA comprehensively. TA, a polyphenol molecule with poly alloy groups present in vascular plants (**Figure 1(a)**), was successfully applied to the surface of polymers. Subsequently, proteins' direct and indirect interactions with TA, called TAP, are recognized. This study shows in the Venn diagram the discovered 60 probable overlapping TAP in wound healing, in which 88 proteins were TAP and 8,713 wounds healing-related protein process (**Figure 1(b)**). Among the 60 wound-healing genes affected by TA, only EVA1 is not connected to the other genes (**Figure 1(c)**). Our study further constructed protein-protein interaction (PPI) network involving epithelial growth factor receptor (EGFR), src family tyrosine kinase (FYN), cluster differentiation 4 (CD4), signal transducer and activator of transcription 3 (STAT3), heat shock protein 90 alpha family class a member 1 (HSP90AA1), a cluster of differentiation 8a (CD8A), protein tyrosine phosphatase receptor type C (PTPRC), src family of protein tyrosine kinase (LCK), mitogen-activated protein kinase-1 (MAPK1), and heat shock protein family A (Hsp70) member 4 (HSPA4) (**Figure 1(d)**). The top 10 genes play crucial roles in wound healing and tissue regeneration in various targets and mechanisms, as listed in **Table 1**.

Fabrication and characterization of modified PDS

This study coated TA, a natural phenolic compound, into the PDS suture by immersing TA and ferric ions in a basic solution. This method offered biocompatible, simple, fast, and cost-effective, which possesses cryoprotecting and stimulates cell proliferation [22,34]. TA coating has been considered a promising surface functionalization by stable TA-iron (III) coordination complexes which interfere with its pH [23,24]. This complex is strongly bound to various substrates, including polymers, metal, and its oxidation form [22,25]. The fabricated sutures were characterized by FTIR analysis and SEM observation, then tested the wound healing activity by *in vitro* scratch assay (**Figure 2(a)**). After immersing in 10 and 30 mg/mL TA using ferrous ion, PDS spectra showed broad OH stretching broad peak from 3,504 to 3,950 cm^{-1} wavenumbers indicating the crosslinking between PDS and TA successfully occurred (**Figure 2(b)**). This data was confirmed under SEM observation in which the TA particle (green) appeared only in engineered PDS, not in the control group. A higher TA concentration (30 mg/mL) increased the probability of TA complexes on the suture than the lower concentration (**Figure 2(c)**).
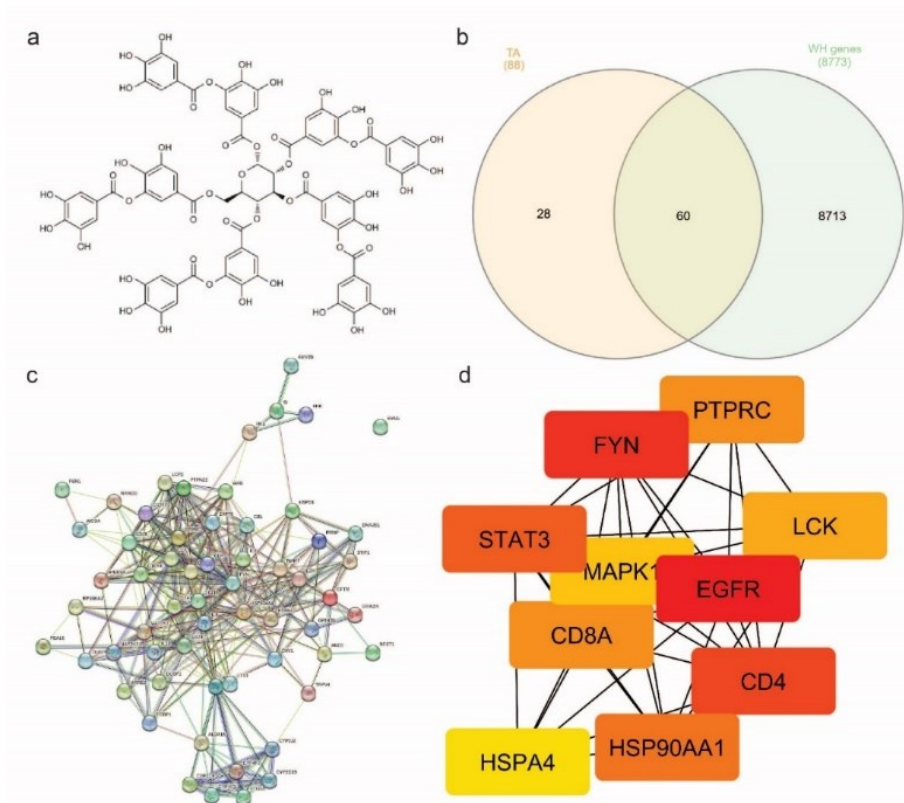
Figure 1 Tannic acid's top protein and target genes are related to wound healing and tissue regeneration; a) Structure of tannic acid, b) Venn diagram of tannic acid and wound healing interfered genes, c) Protein-protein interaction (PPI) network, and d) Top 10 hub genes analyzed with Degree methods.
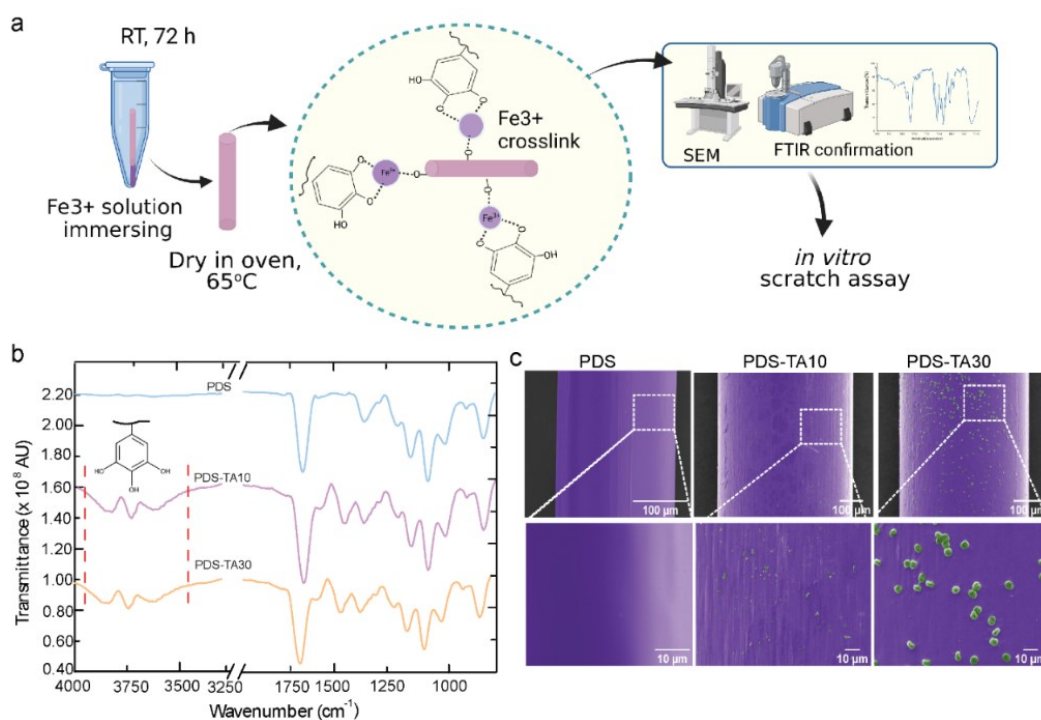
Figure 2 The modification of PDS surface confirmation using FTIR and SEM imaging; a) Scheme of modified PDS fabrication, b) FTIR confirmation of TA-coated PDS, and c) SEM of suture surface of PDS and 10 and 30 mg/mL TA treated PDS.

Contact angle measurement

The capability of a biomedical material *in situ* is commonly tested by its biocompatibility, and contact angle (CA) is a crucial important parameter in evaluating materials' biocompatibility. It indicates wettability, affected by the surface characteristics of the materials [35,36]. PDS originally had hydrophilic surface characteristics, shown by CA 48.19 ± 5.16 °, 53.63 ± 4.72 ° and 50.69 ± 1.64 ° against water, saline (NaCl 0.9 %), and serum. After coating with 10 and 30 mg/mL TA, the suture surface became more hydrophilic due to the CA value dropping to 42.20 ± 1.47 ° and significantly to 32.20 ± 1.37 ° ($p < 0.001$) in water. Moreover, they also decreased significantly to 24.10 ± 2.13 ° ($p < 0.001$) and 22.04 ± 1.28 ° ($p < 0.001$) when it was coated with 10 and 30 mg/mL TA. The same phenomena happened when it was dropped with serum, and the CA decreased to 22.85 ± 2.90 ° and 19.72 ± 1.56 ° (**Figures 3(a) - 3(b)**). Complexing TA on the PDS sutures increased the suture's hydrophilicity, leading to better biocompatibility in a biological system. The hydroxyl group of TA formed hydrogen bonds to the water molecule existing in the representative biological fluid [36]. The higher hydrophilicity and wettability of the PDS surface may strongly correlate with biological activity, such as wound healing. Our previous study had proven higher wettability degree of PDS had better *in vitro* and *in vivo* wound healing activity [15].
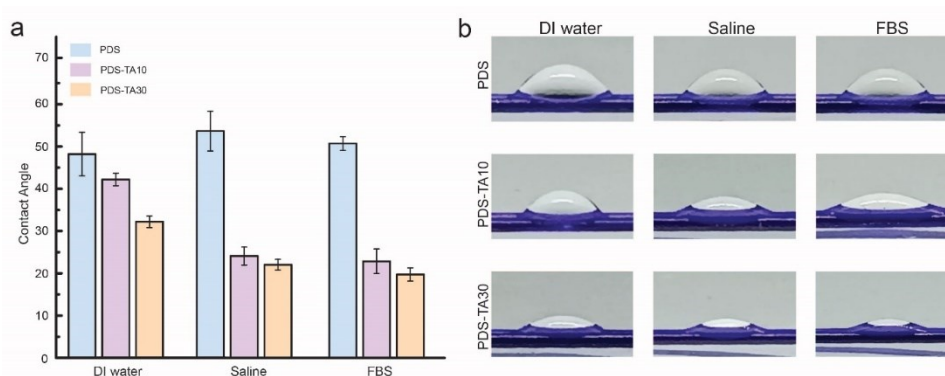
Figure 3 The contact angle of the suture and its modifications' surface with DI water, saline, and FBS; a) Quantitative contact angle measurement of suture surfaces (n = 3), error bars represented the S.D. and b) The image of the PDS surface at each group.

In vitro wound healing assay

Lv and colleagues investigated that TA improved cell adhesion and proliferation [20], preventing scar formation and premature degradation of newly elastic fiber [34,37]. Additionally, since it had attracted and crosslinked collagen, a major ECM having RGD peptide for cell binding [36], PDS-TA was hypothesized to improve wound healing activity. Based on *in vitro* scratch assay, wound enclosure for PDS-TA10 and PDS-TA30 was 38.30 ± 8.18 and 37.52 ± 2.25 %, respectively, which increased significantly (*$p < 0.05$, and ***$p < 0.001$) than those in the pristine group value (22.38 ± 5.81 %) (**Figure 4(a)**). Taken together, TA-coated surgical sutures revealed better wound-healing activity. Further, TA's molecular mechanism pathway to wound healing must be studied.
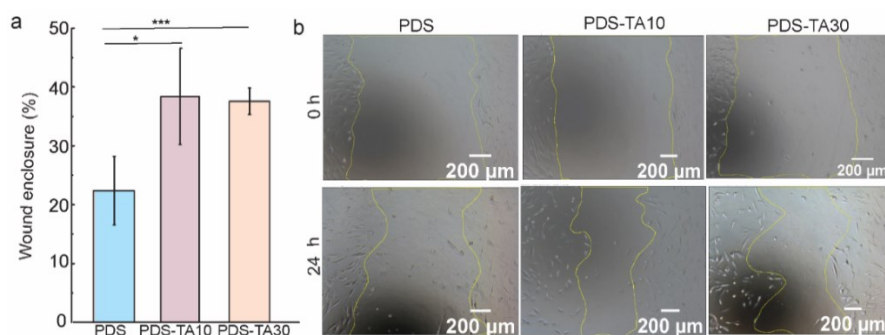
Figure 4 *In vitro* wound healing assay; a) Quantification of wound enclosure percentage of the sutures (n = 3); data revealed in means ± S.D. as error bars; statistical significance was calculated using a one-way ANOVA followed by the Tukey test; *$p < 0.05$ and ***$p < 0.001$. b) cell imaging of PDS and modified ones in the scratch assay at 0 and 24 h.

Proposed molecular mechanism of TA wound healing

Wound healing is a complex process comprising 4 main stages: hemostasis, inflammation, new tissue formation, and remodeling [16]. Our study proposed the molecular mechanisms of TA in the wound healing pathway (**Figure 5**). In the early stages of the wound, TA induces FYN, a member of the Src family of tyrosine kinases, to interact with platelets through glycoprotein IIb-IIIa to elevate platelets' function and reduce the bleeding to hemostasis [38,16]. Thus, platelets are involved in all phases of the wound healing cascade, including coagulation, immune cell recruitment and inflammation, wound healing, vascularization, and remodeling [39]. During the inflammatory stage, TA activates non-inflammatory macrophage through CD8a T cells to suppress bacterial growth and inflammation in the wound site. After an injury, TA showed activated CD4+ cells, an initially activated type of helper T cell, then undergoes proliferation and exhibits crucial function in skin and mucosa wound healing. Even though it is crucial for wound healing, the depletion of CD4 and CD8 seems not to impair the wound healing rate [40,41].

Fibroblast, the key player in the wound healing process, and endothelial cells migrate to the wound site by Hsp90 secreted by keratinocytes in the new tissue formation stage [42]. TA activates PTPRC (CD45 cells) to secrete IL-22, further binding to IL-22Ra in fibroblast binding. As IL-22 induces STAT3 phosphorylation and nuclear translocation, STAT3 expresses ECM [40,42-44]. Furthermore, TA activates STAT3 directly, then stimulates COLIA1 expression as the main ECM fiber and MMP-9 to remodel the provisional matrix in the tissue remodeling stage of the wound healing process [44,45]. TA also induces the ECM production stimulation effect through MAPK-1 activation as a transcription factor in fibroblast [34,46,47] (**Figure 5**).

Taken together, TA engineered suture prepared in this *in vitro* work accelerated fibroblast migration to the wound site. Based on bioinformatics data, it comprehensively supported the wound healing pathway at multiple targets at hemostasis, inflammation, new tissue formation, and remodeling stage. Nevertheless, more *in vivo* study is needed to explore the efficacy of the suture in wound healing processes.

Table 1 The function top 10 genes ranked based on degree method.

No	Gene symbol	Protein name	Degree score	Biological function related to wound healing	Ref.
1	EGFR	Epithelial growth factor receptor	31	Tyrosine Kinase receptor for Epidermal Growth Factor stimulates cell growth and proliferation.	[38,16]
2	FYN	a member of the Src family of tyrosine kinases	29	Interact with glycoprotein IIb-IIIa on platelets to increase platelet function and reduce bleeding	[39,48]
3	CD4	Cluster of Differentiation 4	28	Glycoprotein receptors of T cells initially respond to tissue injury and are critical for successful wound healing.	[43,49]
4	STAT3	Signal transducer and activator of transcription 3	26	Re-epithelialization during wound repair, a transcription factor of interleukin-6 (IL-6), collagen IA1 (COL1A2), modulate (matrix metalloproteinase-9 (MMP-9)	[44,45]
5	HSP90AA1	Heat Shock Protein 90 Alpha Family Class A Member 1	25	Secreted by keratinocytes, then promote re-epithelialization by recruiting fibroblast and endothelial cells into the wound site	[42]
6	CD8A	Cluster of Differentiation 8a	24	Glycoprotein receptors of T cells facilitate non-inflammatory macrophage polarization to turn ECM deposition stimulation and angiogenesis and suppress the inflammation; it also supports wound healing by secreting microbicidal factors that clear the infection.	[40,41]
6	PTPRC	Protein Tyrosine Phosphatase Receptor Type C	24	Known as CD45, releasing IL-22, which binds to the receptor and activates STAT-3 as a transcription factor in fibroblast	[50-52]
8	LCK	Src family of protein tyrosine kinase	23	Phosphorylate T cell receptor to engage and recognize antigenic peptides to major histocompatibility complex	[53]

No	Gene symbol	Protein name	Degree score	Biological function related to wound healing	Ref.
9	MAPK1	Mitogen-activated protein kinase-1	22	Extracellular signal-regulated kinases (ERK-2), fibroblast activation, ECM production, and myofibroblast survival	[54,46,47]
10	HSPA4	Heat Shock Protein Family A (Hsp70) Member 4	21	Upregulating macrophage-mediated phagocytosis, guiding protein folding and translocation	[57,58]
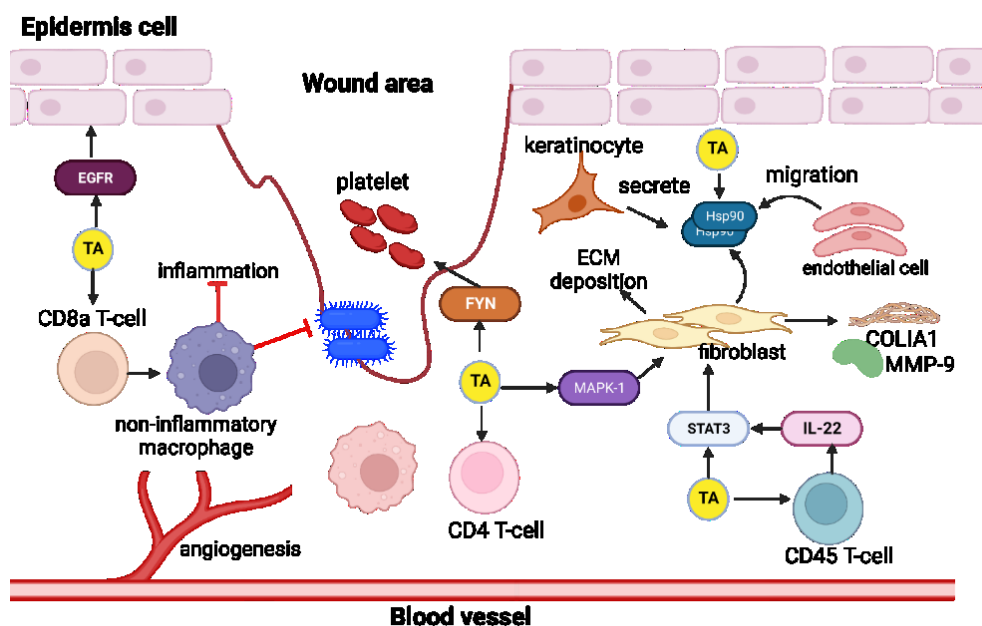
Figure 5 Proposed molecular mechanism of TA in wound healing process; TA: Tannic acid, EGFR: Epithelial growth factor receptor, FYN: A member of the Src family of tyrosine kinases, CD8a: Cluster of differentiation 8a, CD4: Cluster of differentiation 4, STAT3: Signal transducer and activator of transcription 3, MAPK-1: Mitogen-activated protein kinase-1, IL-22: Interleukin-22, COLIA1: Collagen IA1, MMP-9: Matrix metallo proteinase-9. Graphics were prepared using Biorender.

Conclusions

In the present study, we engineered a PDS suture by stable coordination complexing TA with iron (III) on the surface of the surgical suture under basic conditions. Our study concluded that TA coating on the PDS surface was effective in basic pH, as confirmed by the OH peak of TA at 3,504 - 3,950 cm^{-1} in FTIR spectra. Based on our *in vitro* study, it accelerated fibroblast migration to the wound site more than the control. TA supported the molecular pathway of wound healing in multiple targets at inflammation, new tissue formation, and remodeling stages. However, *in vivo* study should be conducted to perform the efficacy test of the suture. The emphasis study on compromised wound healing patients is suggested for future study.

Acknowledgments

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