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Dasatinib as a Potential Targeted Therapy for Chronic Pancreatitis: A Narrative Review of Macrophage-PSC Interactions

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ABSTRACT

Chronic pancreatitis is a long-term inflammatory condition affecting the pancreas, with progression worsening over time. One of the effects of this disease is the formation of scar tissue, which can permanently damage the pancreas and disrupt its functions, both exocrine and endocrine. Chronic pancreatitis can result in various serious complications and even be fatal. In the effort to treat chronic pancreatitis, therapies targeting macrophages have begun to attract attention as an innovative approach. One of the drugs in the spotlight is dasatinib, a tyrosine kinase inhibitor, which has shown the ability to alter the inflammatory response by affecting the macrophage population in the pancreatic microenvironment. This literature review aims to dig deeper into the role of dasatinib in the treatment of chronic pancreatitis and explain the pathophysiology of this disease, especially how macrophage activation contributes to the inflammatory process, as well as the therapeutic effects of dasatinib, we can find new insights to develop more effective treatment strategies.

1. Introduction

Pancreatitis is an inflammation of the pancreas that can be categorized into two main forms: acute pancreatitis and chronic pancreatitis. Acute pancreatitis usually begins with premature activation of pancreatic enzymes (trypsin) before they reach the small intestine. Common causes include gallstones, excessive alcohol consumption, trauma, and infection. Activation of enzymes in the pancreas causes damage to pancreatic tissue, leading to the release of proinflammatory cytokines and inflammatory mediators. This results in inflammation of the pancreatic tissue and edema. If the inflammation is severe, it can lead to pancreatic necrosis, where the pancreatic tissue dies. This can lead to cyst formation, secondary infection, or other organ disorders.[1–4]

Chronic pancreatitis is characterized by repeated and increasing inflammation leading to fibrosis and irreversible damage to pancreatic tissue. Activation of the identical enzymes may transpire, although it is frequently linked to danger variables such as chronic alcohol usage or hereditary diseases. As damage escalates, the pancreas diminishes its capacity to synthesize essential hormones and digestive enzymes, resulting in digestive problems and diabetes mellitus. Chronic pancreatitis is a disorder resulting from recurrent bouts of pancreatic inflammation and subsequent fibrosis, culminating in the impairment of both exocrine and endocrine pancreatic functions. The condition is marked by abdominal pain, diminished quality of life, maldigestion and malabsorption of nutrients, diabetes, and an elevated risk of pancreatic adenocarcinoma.[5]

About 50 out of every 100,000 people have chronic pancreatitis, according to estimates. This number comes from surveys and healthcare system datasets in the US, Japan, China, India, and a few European countries. Chronic pancreatitis frequently arises after repeated instances of non-gallstone-

related acute pancreatitis. The prevalence of acute pancreatitis varies by region since the causes of the disease differ from one area to another. communities exhibiting a higher frequency of gallstone-related acute pancreatitis often show a lower prevalence of chronic pancreatitis. Conversely, communities with an elevated incidence of non-gallstone-related acute pancreatitis, especially due to alcohol abuse, display a higher prevalence. Variability in prevalence estimates can also be caused by discrepancies in the criteria used to diagnose diseases and the methods utilized in epidemiological investigations. There is no definitive cure for chronic pancreatitis at present; nonetheless, advancements in the comprehension of its pathophysiological underpinnings have resulted in substantial improvements in its clinical management.[6–8]

Recent developments in clinical science are continually reshaping our comprehension of chronic pancreatitis (CP), necessitating modifications in its description, diagnosis, and therapeutic strategies. Pancreatic fibrosis is a complicated pathological process that is controlled by the balance between making and breaking down extracellular matrix (ECM). Pancreatic stellate cells (PSCs) are the main cells that fight against different kinds of damage to the pancreas. Activated PSC secretes numerous ECM proteins, including collagen, α-smooth muscle actin (α-SMA), fibronectin, and desmin for tissue repair, as well as a number of cytokines (such as TNF-α, IL-1β, IL-4, etc.) and chemokines (CCL and CXCL) that will aid inflammatory cell infiltration. If the damage causes and inflammatory response remain unaddressed, persistent PSC activation will induce a chronic fibroinflammatory condition and lead to the emergence of pathological fibrosis in the pancreas. Furthermore, some recent studies have demonstrated that the mitogen-activated protein kinase (MAPK) pathway is involved in the regulation of PSC activation and the progression of pancreatic fibrosis. Macrophages are a type of cell that can change shape and are important for host defense and immunity. They are also thought to be important for controlling inflammation and are very important for fibrosis, speeding up wound healing, reducing inflammation, and preventing tumor growth.[9–11]

Dasatinib is an oral inhibitor that targets multiple receptor tyrosine kinases (RTKs).[12] This literature review highlights how Dasatinib may intervene in the pathological processes underlying fibroinflammation in chronic pancreatitis, with a particular focus on its effects on pancreatic stellate cells and macrophage polarity. With its ability to suppress excessive CNS activation and regulate the immune response through its effects on M1 and M2 macrophages. Dasatinib has the potential not only to reduce fibrosis but also to improve the microenvironment that contributes to disease progression.[13] Furthermore, understanding the mechanisms of action of Dasatinib at the molecular and cellular levels provides a solid basis for further research. It will contribute to the development of more effective therapeutic strategies in the management of chronic pancreatitis, which will ultimately improve the quality of life of affected patients. Therefore, further studies are needed to explore the full potential of Dasatinib as a therapeutic agent for chronic pancreatitis and to clarify its safety and efficacy profile in clinical practice.

2. Methods

This narrative review was conducted to explore the role of Dasatinib in chronic pancreatitis, with particular emphasis on its interaction with macrophages and pancreatic stellate cells as potential targets of antifibrotic therapy. A comprehensive literature search was performed using electronic databases including PubMed, ScienceDirect, and Google Scholar. The search strategy combined the following keywords and Boolean operators: *"Chronic pancreatitis" AND "Dasatinib" AND "Macrophages" AND "Targeted therapy"*.

Inclusion criteria were applied to select articles published in the last 10 years (2014–2024), written in English, and available in full-text format. Only peer-reviewed journal articles, including original research, systematic reviews, and high-quality narrative reviews, were considered. Opinion pieces, letters to the editor, and non-peer-reviewed sources (gray literature) were excluded to ensure the credibility and scientific rigor of the evidence.

3. Chronic Pancreatitis

Chronic pancreatitis is a chronic inflammation of the pancreas, progressive, accompanied by scarring, which irreversibly damages the pancreas, resulting in loss of exocrine and endocrine functions of the pancreas.[5] Chronic pancreatitis is divided into three main forms: (1) chronic calculous pancreatitis; (2) chronic obstructive pancreatitis; (3) chronic autoimmune pancreatitis (steroid-responsive pancreatitis). The clinical presentation varies depending on the etiology, but the main symptom is abdominal pain.[14]

Pathogenesis of Chronic Pancreatitis

The pathogenesis of acute and chronic pancreatitis begins with trypsinogen activation in acinar cells due to genetic or environmental factors, leading to cell injury and local inflammation.[5] Animal studies show that chronic pancreatitis involves interactions between activated pancreatic stellate cells (PSCs) and macrophages. The TGF-β/Smad3 signaling pathway plays a central role in fibrosis and pain responses. These intercellular signals are critical for understanding disease progression and represent potential therapeutic targets.[14]

In a healthy pancreas, pancreatic stellate cells (PSCs) are dormant and contain vitamin A-rich lipid droplets. During inflammation, PSCs become activated, producing fibrotic matrix proteins and cytokines that recruit myeloid cells and convert them

into alternatively activated macrophages. These macrophages secrete TGF-β, maintaining PSC activation in a positive feedback loop. PSCs also release IL-4 and IL-13, further promoting macrophage activation and TGF-β secretion. TGF-β plays a key role in fibrosis and pain, acting via SMAD3 signaling in sensory neurons. This cellular cross-talk drives the fibroinflammatory and pain responses in chronic pancreatitis.[14]

Chronic pancreatitis is marked by the formation of a fibrotic stroma infiltrated by granulocytes (e.g., neutrophils, eosinophils), monocytes, macrophages, and pancreatic stellate cells (PSCs). These cells play a crucial role in initiating and sustaining inflammation and fibrosis, a major risk factor for pancreatic cancer. Various inflammatory cytokines and molecular pathways—including TGF-β/SMAD, MAPK, Rho kinase, JAK/STAT, and PI3K—contribute to PSC activation and pancreatic fibrogenesis. This inflammatory response can cause permanent pancreatic damage when uncontrolled. The process begins with PSC activation triggered by factors like alcohol and metabolic stress. While short-term exposure may resolve, repeated insults lead to recurrent acute inflammation and sustained PSC activation. Proinflammatory mediators such as TRAIL and chemokines induce parenchymal injury, ductal obstruction, and fibrosis. Over time, ductal remodeling activates Notch and Hedgehog pathways, promoting acinoductal metaplasia (ADM), pancreatic intraepithelial neoplasia (PanIN), and pancreatic ductal adenocarcinoma. Under IFN-γ influence, acinar cells express death receptors (CD95, TRAIL-R1/R2), making them vulnerable to apoptosis via CD95L and TRAIL produced locally by the CNS. This is further mediated by perforin and granzyme B. Conversely, islet cells resist apoptosis through TRAIL-R4 expression and NF-κB-induced inhibitor of apoptosis proteins (IAPs). The inflammatory, fibrotic, and pain responses in chronic pancreatitis are tightly linked to PSC activation. The CNS also contributes by releasing IL-4 and IL-13, which polarize macrophages into the M2 phenotype. These macrophages maintain PSC activation by secreting TGF-β, which also mediates pain via Smad3 signaling in pancreatic sensory neurons. Cytokines and growth factors are thus central to both the pathogenesis and symptomatology of acute and chronic pancreatitis.[14]

4. Immune Pathways in Chronic Pancreatitis : Focus on Macrophages

Multiple immune cell types—neutrophils, macrophages, T cells, B cells, mast cells—coordinate a complex inflammatory and fibrotic response in CP. Their interaction with PSCs, especially via NF-κB and cytokine signaling, governs disease progression. Macrophages contribute to CP pathogenesis through their dynamic polarization, crosstalk with PSCs, and activation of inflammatory transcriptional pathways. Depending on microenvironmental cues, macrophages polarize into classically activated M1 or alternatively activated M2 phenotypes. M1 macrophages secrete pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, exacerbating pancreatic injury. In contrast, M2 macrophages facilitate fibrosis by producing TGF-β, which activates pancreatic stellate cells (PSCs) to synthesize extracellular matrix proteins.[15–18]

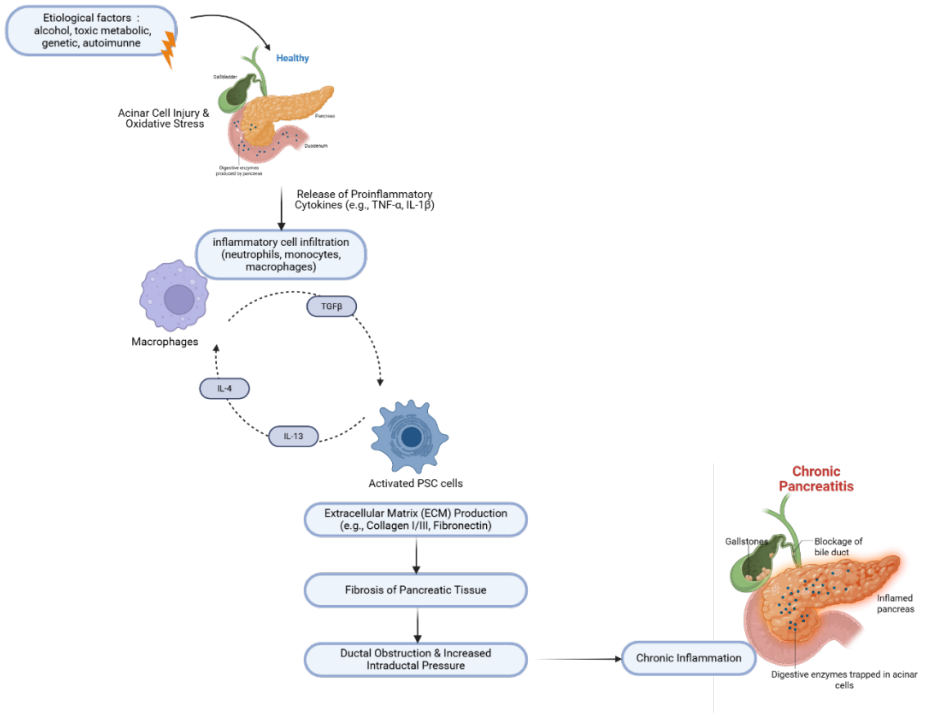

Figure 1. Pathogenesis of chronic pancreatitis[14]

Initially macrophages recruited following neutrophil infiltration, macrophages participate in pathogen clearance via phagocytosis and modulate inflammation by secreting pro-inflammatory cytokines (e.g., IL-1, IL-6, TNF-α) as well as anti-inflammatory mediators such as IL-10.These cells originate from bone marrow–derived hematopoietic stem cells or yolk sac progenitors and are recruited into damaged pancreatic tissue through chemotactic signals. Their phenotypic differentiation is influenced by the microenvironment, a process known as macrophage polarization. Gordon classified polarized macrophages into two major subtypes: classically activated M1 macrophages—induced by IFN-γ and LPS—are pro-inflammatory and cytotoxic, while alternatively activated M2 macrophages—induced by IL-4/IL-13—exhibit anti-inflammatory and profibrotic functions, marked by CD206 expression. Importantly, both M1 and M2 subtypes are implicated in chronic pancreatitis (CP), with M2 macrophages playing a key role in tissue remodeling and fibrosis. M0 macrophages, representing an unpolarized state, have also been associated with poor prognosis in pancreatic ductal adenocarcinoma (PDAC). Chronic pancreatitis models show that macrophages (F4/80+) quickly accumulate in the pancreas, more than neutrophils, and are linked to increased fibrosis and IL-6 levels.[15]

In chronic pancreatitis, M1 macrophages appear early, while M2 dominate later, suggesting phenotype switching. PSCs stimulated by TGF-β1 can induce M2 polarization with increased IL-4, IL-13, and CD206 expression. This polarization promotes fibrogenesis, as shown in IL-4/IL-13 knockout mice, where CP severity, M2 markers, and fibrosis-related proteins (α-SMA, Col1a1) were markedly reduced. Furthermore, M2 macrophages interact with PSCs via autocrine/paracrine mechanisms, reinforcing fibrotic loops. The M2/M1 ratio increases with fibrosis severity, and idiopathic CP shows higher CD68+ macrophage levels than hereditary CP, suggesting immunophenotypic differences. Mechanistically, macrophage-induced fibrosis involves NF-κB activation. NF-κB subunits (RelA, RelB, c-Rel, p50, p52) are activated via IκB degradation, leading to nuclear translocation and transcription of inflammatory genes.[7] Sendler et al. demonstrated that CD68+ macrophages engulf zymogen-containing vesicles and activate NF-κB upon trypsinogen exposure, promoting IL-6, TNF-α, and MCP-1 production. These findings highlight NF-κB's central role in amplifying pancreatic inflammation. Their phenotypic plasticity and profibrotic potential make them critical targets for future antifibrotic therapies. Therapeutic strategies targeting macrophage recruitment and polarization have shown promise. Pharmacological modulation of macrophage signaling pathways (e.g., NF-κB) or promoting M1-to-M2 transition may suppress both inflammation and fibrosis. Depleting macrophages or using nanotechnology-based delivery systems for targeted interventions is also under investigation.[15,18]

5. Dasatinib : A tyrosine kinase inhibitors with antifibrotic potential

Dasatinib, a broad-spectrum tyrosine kinase inhibitor, has shown substantial antifibrotic and anti-inflammatory benefits in caerulein-induced chronic pancreatitis (CP) mice. Its capacity to impede cellular activation and intercellular connections within the inflamed pancreatic milieu indicates a possible role in the management of pancreatic fibrosis. It focused on receptor tyrosine kinases (RTKs), such as Abelson kinase (cAbl), stem cell factor receptor (c-KIT), platelet-derived growth factor receptor (PDGFR), and Src family kinases (SFKs). Transcriptomic and in vitro studies demonstrated that Dasatinib inhibits the proliferation and activation of pancreatic stellate cells (PSCs) through the TKs/GSK3β/β-catenin signaling pathway. It also lessens the polarization of M1 and M2 macrophages and stops them from being recruited and interacting with PSCs.[23] These dual effects on fibroinflammatory cells highlight Dasatinib's potential as a therapeutic option for fibrosis-related diseases, especially CP.[19]

Macrophages, as critical mediators of inflammation and fibrosis, can polarize into M1 (pro-inflammatory) or M2 (pro-fibrotic) phenotypes. M2 macrophages, in particular, secrete cytokines such as TGF-β and PDGF-β, which activate PSCs and contribute to extracellular matrix deposition. Dasatinib attenuates these processes by suppressing M2-associated gene expression (e.g., CD206, Arg1) and downregulating cytokines involved in macrophage-PSC crosstalk.[19]

In PSC cultures, Dasatinib reduced expression of fibrogenic mediators and inhibited Wnt/β-catenin signaling via modulation of GSK3β activity.[23] Specifically, Dasatinib suppressed the phosphorylation of upstream kinases (PDGFR, Src), leading to decreased β-catenin nuclear translocation and fibrogenic gene expression. Interestingly, Dasatinib increased JNK1/2 phosphorylation, suggesting additional regulatory mechanisms that merit further investigation. Dasatinib was also found to inhibit expression of Dkk-1 and Dkk-2 (Wnt antagonists), while promoting phosphorylation of LRP-6, indicating that its effects on GSK3β and β-catenin are mediated independently of canonical Wnt signaling. These findings suggest that Dasatinib regulates PSC activity through inhibition of Src/MAPK and TK-related pathways rather than Wnt itself.[19]

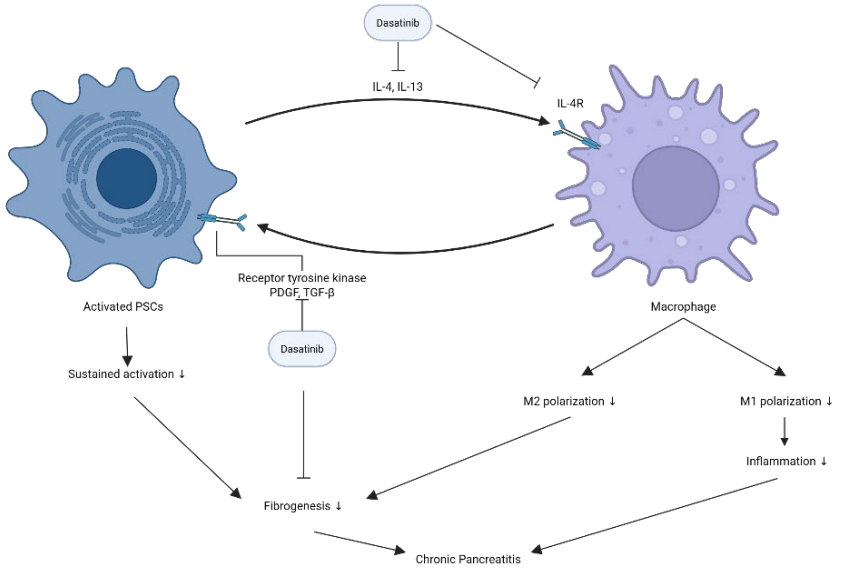

Figure 2. Dasatinib inhibits pancreatic stellate cell activation and macrophage polarity[19]

Furthermore, Dasatinib reduces the number of macrophages infiltrating pancreatic tissue and inhibits both M1 and M2 polarization in RAW 264.7 macrophage models. This contrasts with PP2, a Src inhibitor, which primarily targets M2 polarization, supporting the role of Src in M2 skewing. Studies have linked the IL-4/Src/STAT6 pathway with anti-inflammatory macrophage generation, while the Src/ERK/AP-1 axis contributes to TGF-β1 expression in inflammatory macrophages. Therefore, Dasatinib's capacity to interfere with these pathways underlies its immunomodulatory effects.[19] Collectively, Dasatinib's ability to inhibit PSC activation, modulate macrophage polarization, and disrupt macrophage-PSC interactions presents it as a potential therapeutic candidate for CP. Further preclinical and clinical studies are required to elucidate the full therapeutic potential and safety profile of Dasatinib in pancreatic fibrogenesis.

6. Conclusion

Pancreatitis arises from a combination of factors, encompassing various triggers and a complex pathogenesis. Immune cells are essential in the pathogenesis and severity of pancreatitis, irrespective of its cause. A comprehensive understanding of the interactions between immune cells and the central nervous system may facilitate the development of more effective therapies in the future. A targeted approach is anticipated to enhance progress in the treatment and management of chronic pancreatitis. Current therapies for chronic pancreatitis focus on pain management and the correction of exocrine and endocrine dysfunction. Different immune cell types play a role in influencing CP. Both in vivo and in vitro experiments demonstrate that macrophages facilitate pancreatic fibrosis in CP and influence the progression of CP through their interactions with pancreatic stellate cells. This study examined the effects of Dasatinib on pancreatic fibrosis and inflammation through both in vivo and in vitro methodologies, likely attributable to its antifibrotic and anti-inflammatory characteristics. Dasatinib demonstrated notable inhibitory effects on the proliferation and activation of pancreatic stellate cells via the TKs/GSK3β/β-catenin pathway. Moreover, Dasatinib inhibited the M1 and M2 polarization of macrophages and disrupted the interaction between pancreatic stellate cells and macrophages. The findings indicate that Dasatinib may serve as a therapeutic agent for chronic pancreatitis, with the MAPK/GSK3β/β-catenin pathway representing a viable target for future therapeutic development. Dasatinib may provide a novel strategy for treating pancreatic fibrosis by leveraging the identified molecular mechanisms. Additional research is required to evaluate the clinical efficacy of Dasatinib and to gain a deeper understanding of its mechanism of action in relation to this disease.

7. Author Contribution

A.P. wrote the manuscript with support from S. S also helped supervise the project.

8. Acknowledgements

None

9. References

1. Yuan Q, Pan A, Fu Y, Dai Y. *Anatomy and physiology of the pancreas*. Integrative Pancreatic Intervention Therapy: A Holistic Approach. INC; 2020. 3–21 p.
2. Szatmary P, Grammatikopoulos T, Cai W, Huang W, Mukherjee R, Halloran C, et al. *Acute Pancreatitis: Diagnosis and Treatment*. Drugs. 2022;82(12):1251–76.

3. Walkowska J, Zielinska N, Karauda P, Tubbs RS, Kurtys K, Olewnik Ł. *The Pancreas and Known Factors of Acute Pancreatitis*. J Clin Med. 2022;11(19):1–21.
4. Mihoc T, Latcu SC, Secasan CC, Dema V, Cumpanas AA, Selaru M, et al. *Pancreatic Morphology, Immunology, and the Pathogenesis of Acute Pancreatitis*. Biomedicines. 2024;12(11):1–38.
5. Hart PA, Conwell DL, Krishna SG. *Acute and Chronic Pancreatitis*. In: Loscalzo J, Fauci A, Kasper D, Hauser S, Longo D, Jameson JL, editors. Harrison's Principles of Internal Medicine, 21e. New York, NY: McGraw-Hill Education; 2022.
6. Yadav D, Lowenfels AB. *The Epidemiology of Pancreatitis and Pancreatic Cancer*. Gastroenterology. 2013;144(6):1252–61.
7. Weiss FU, Laemmerhirt F, Lerch MM. *Etiology and risk factors of acute and chronic pancreatitis*. Visc Med. 2019;35(2):73–81.
8. Ul Hassan MS, Mobusher M, Mansoor MH, Ahmad CA, Ahsan I, Hamza M, et al. *Prevalence and Associated Risk Factors of Acute Pancreatitis in Patients With Gallstones: A Cross-Sectional Study*. Cureus. 2025;17(5):4–11.
9. Ramsey ML, Conwell DL, Hart PA. *Complications of Chronic Pancreatitis*. Dig Dis Sci. 2017;62(7):1745–50.
10. Wang Z, Dong S, Zhou W. *Pancreatic stellate cells: Key players in pancreatic health and diseases (Review)*. Mol Med Rep. 2024;30(1):1–18.
11. Abdullah A, Mohd Yunos SNM, Basuno B. A *Comprehensive Review of Recent Advances in Scalar Convection-Diffusion Studies*. J Adv Res Numer Heat Transf. 2024;27(1):14–27.
12. Park NS, Park YK, Yadav AK, Shin YM, Bishop-Bailey D, Choi JS, et al. *Anti-growth and pro-apoptotic effects of dasatinib on human oral cancer cells through multi-targeted mechanisms*. J Cell Mol Med. 2021;25(17):8300–11.
13. Abdalla M, Thompson LA, Gurley E, Burke S, Ujjin J, Newsome R, et al. *Dasatinib inhibits TGFβ-induced myofibroblast differentiation through Src-SRF Pathway*. Eur J Pharmacol. 2015;769:134–42.
14. Manohar M, Verma AK, Venkateshaiah SU, Sanders NL, Mishra A. *Pathogenic mechanisms of pancreatitis.* World J Gastrointest Pharmacol Ther. 2017;8(1):10.
15. Hashimoto A, Karim MR, Kuramochi M, Izawa T, Kuwamura M, Yamate J. *Characterization of Macrophages and Myofibroblasts Appearing in Dibutyltin Dichloride–Induced Rat Pancreatic Fibrosis*. Toxicol Pathol. 2020;48(3):509–23.
16. Mayerle J, Sendler M, Hegyi E, Beyer G, Lerch MM, Sahin-Tóth M. *Genetics, Cell Biology, and Pathophysiology of Pancreatitis*. Gastroenterology. 2019;156(7):1951-1968.e1.
17. Zhang T, Zhang G, Yang W, Chen H, Hu J, Zhao Z, et al. *Lnc-PFAR facilitates autophagy and exacerbates pancreatic fibrosis by reducing pre-miR-141 maturation in chronic pancreatitis*. Cell Death Dis. 2021;12(11).
18. Chang M, Chen W, Xia R, Peng Y, Niu P, Fan H. *Pancreatic Stellate Cells and the Targeted Therapeutic Strategies in Chronic Pancreatitis*. Molecules. 2023;28(14).
19. Zeng XP, Wang LJ, Guo HL, He L, Bi YW, Xu ZL, et al. *Dasatinib ameliorates chronic pancreatitis induced by caerulein via anti-fibrotic and anti-inflammatory mechanism*. Pharmacol Res. 2019;147(May):104357.