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Beyond Pharmaceuticals: A Journey into Herbal Remedies for Pancreatitis

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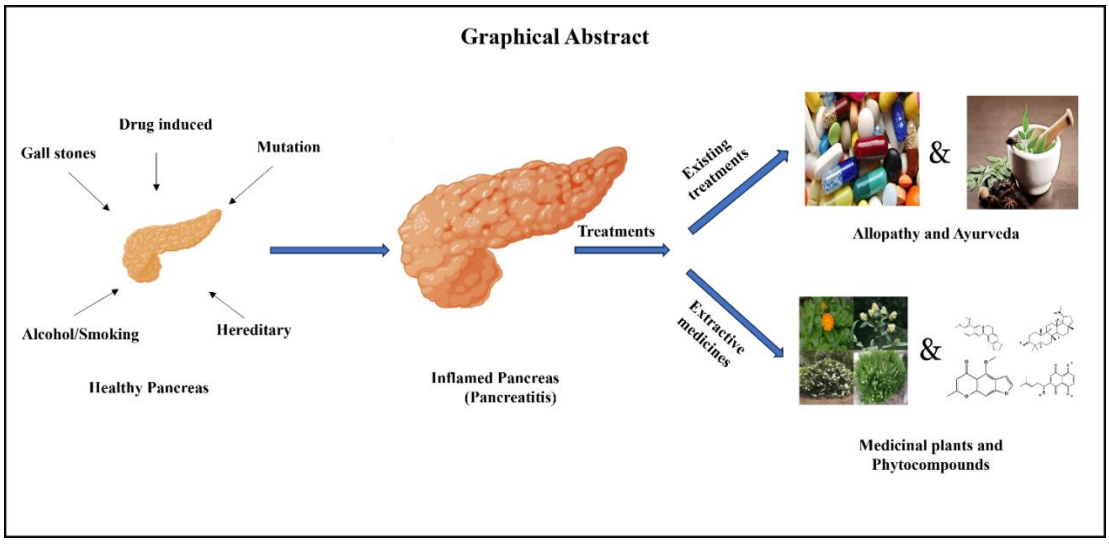
Abstract

Pancreatitis is a multifaceted inflammatory disorder of the pancreas, marked by acute or chronic phases and often linked to severe complications. Alcohol and gallstones are typical causes of acute pancreatitis, which can develop into chronic pancreatitis, which is marked by irreparable damage and malfunction. Genetic mutations, being the major reasons for hereditary, contributing significantly to the pathogenesis, highlighting its complex etiology. Current allopathic treatments focus on symptomatic relief, yet lack curative options, and also few of the allopathic drugs prescribed to cure or to manage various diseases, which in turn inducing pancreatitis as a side effect. In contrast, evidence suggests that Ayurveda has shown promising outcomes in alleviating pancreatitis symptoms and even reversing pancreatic damage based on the case studies of around 625 patients in India. This review explores medicinal plants and bioactive compounds known for their anti-inflammatory and antioxidant properties, emphasizing their potential in combating pancreatitis and advancing therapeutic strategies.

Keywords: Alternative medicine, Ayurveda, Herbal drug, Medicinal plants, Pancreatitis

Introduction

Graphical Abstract:



Pancreas, the complex organ with both exocrine and endocrine functions, located in the upper retroperitoneal cavity and connected to biliary system and the duodenum. The exocrine gland comprises of pancreatic acinar cells which secretes digestive enzymes and duct cells that produces sodium bicarbonate. These are the enzymes which are responsible for digesting and absorbing the food. The endocrine gland consists of various types of glandular cells that produce hormones such as glucagon and insulin who are the major heroes in maintaining glucose homeostasis [1,2]. The [condition of an inflamed pancreas, is referred to as pancreatitis, and is caused by obstruction of the pancreatic duct by gallstones, high consumption of alcohol, mutations, drug-induced, hereditary, autoimmune, and idiopathic reasons. The mechanism behind pancreatitis remains unclear. Mutations that serve as the causative agent for hereditary pancreatitis are PRSS1 (Serine Protease), SPINK1 (Serine Protease Inhibitor Kazal type 1) [3], CFTR (Cystic Fibrosis Transmembrane Conductance Regulator), and CTRC (Chymotrypsin C) [4]. According to a survey conducted in 2002, idiopathic pancreatitis is most common in India. Chronic pancreatitis was found to be higher in South India with a range of 114 to 200 per 1 Lakh

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population [5]. There is no cure for pancreatitis, allopathy medicines are the one which is focusing on symptomatic relief in case of pancreatitis, whereas, Ayurveda treatment have been reported successful reversal of pancreatitis. Apart from these, the awareness towards herbal medicines have been increased and people started to prefer herbal medicine over synthetic ones as it has less or no side effects. The major aim of this review is to focus on the traditional medicinal plants and the phytocompounds which has the ability to reverse pancreatitis.

Classification of Pancreatitis

Pancreatitis is classified into two types based on their severity as; acute and chronic pancreatitis. Acute pancreatitis is an inflammatory condition of the pancreas, which often comes with severe abdominal pain, and elevated serum pancreatic enzymes. It can be further classified into mild and severe acute pancreatitis. In severe acute pancreatitis, the complications like, pseudocysts, organ failure and abscesses are associated and the mortality rate is approximately 15%. The major causes for acute pancreatitis are gallstones and alcohol consumption [6–8]. Chronic pancreatitis is a chronic inflammatory disease of the pancreas defined by gradual and irreversible damage to the pancreas, resulting in permanent loss of exocrine and endocrine function. This condition involves chronic inflammation, acinar atrophy, pancreatic fibrosis and blocked ducts which will lead to exocrine and endocrine insufficiency. It also includes the complications such as gastric and biliary obstruction, pseudocyst formation and in worst case there is a high possibility of developing into pancreatic adenocarcinoma [9–13].

Based on the cause, pancreatitis is classified as, hereditary pancreatitis, Autoimmune pancreatitis, Idiopathic pancreatitis, Alcoholic pancreatitis, and Drug-induced pancreatitis. According to Iannuzzi et al., the rate of incidence of acute pancreatitis in the globe increases by 3.07% per year [14]. This rise can lead to various undesirable conditions in the future, so it is necessary to have a cure for pancreatitis. In this review, we are going to see about the pathways involved in pancreatitis, the available treatments in allopathy, ayurveda, and the natural products and medicinal plants that are effective against pancreatitis.

Hereditary Pancreatitis:

Genetic mutations such as SPINK1 (Serine Protease Inhibitor Kazal type 1) [15], PSSR1 (Serine Protease) [16], and CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) [17], play significant roles in hereditary pancreatitis. PSSR1 mutations, particularly R122H and N29I, affect cationic trypsinogen, enhancing its auto-activation and stability, which leading to pancreatitis [18]. CFTR mutations, notably in cases like N34S PSTI, increase the risk of chronic pancreatitis [19]. SPINK1 mutations disable the inhibition of trypsin production, triggering pancreas autodigestion, commonly seen in idiopathic pancreatitis cases [20].

Other than the above, mutations in CaSR (Calcium Sensing Receptor) [21], CTRC (Chymotrypsin C) [22], and CLDN2 (Claudin 2) [23] may also cause hereditary pancreatitis.

Auto-immune Pancreatitis:

Auto-immune pancreatitis is one of the rare forms of chronic inflammation of pancreas. It is an autoimmune disorder and can be associated with other autoimmune conditions. Autoimmune pancreatitis is of two types: type 1 and type 2. Type 1 autoimmune pancreatitis is associated with IgG4 (immunoglobulin G4) related disease whereas type 2 is not of any such kind. The symptoms of both are the common symptoms of pancreatitis such as, diffuse swelling of pancreas, painless obstructive jaundice. Type 1 autoimmune pancreatitis is common in aged males and usually comes with an elevated level of IgG4. Type 2 autoimmune pancreatitis will not include IgG4 levels and can affect both males and females in their 30s or 40s. Both type 1 and type 2 autoimmune pancreatitis responds fair enough to steroids whereas type 1 alone has higher risk of recurrence [24,25]

Drug-induced Pancreatitis:

Some drugs which were given to treat some other disorders will also induce pancreatitis, 0.1% to 2% of acute pancreatitis are because of drugs [26]. Some of the most common drugs to induce pancreatitis are, calcium channel blockers, valproic acid, corticosteroids etc., [27] A few other drugs are listed in Table 1. [28].

Table 1 Drugs that induced pancreatitis

S. No	Drug-induced	Prescribed For

1.	Azathioprine	Crohn's disease, Immune suppressor, Rheumatoid arthritis, and Ulcerative colitis
2.	Mercaptopurine	Acute lymphocytic leukemia
3.	Dexamethasone	Inflammatory conditions including bronchial asthma, endocrine disorders
4.	Everolimus	Treat various malignancies
5.	Tigecycline	Bacterial infections
6.	Torasemide	Hypertension and edema associated with renal failure, heart failure, or liver disease
7.	Vildagliptin	Type-2 diabetes
8.	Asparaginase	Acute lymphoblastic leukemia
9.	Doxycycline	Bacterial infections
10.	Indapamide	Hypertension and edema due to congestive heart failure
11.	Losartan	Hypertension, diabetic neuropathy, reduces the risk of stroke
12.	Interferonα2a	Hepatitis C and Hepatitis B
13.	Metronidazole	Amebiasis, bacterial infections, inflammatory lesions of rosacea, trichomoniasis, and postoperative infections
14.	Ibuprofen	Moderate pain, fever, and inflammation
15.	Pitavastatin	Reduce the risk of cardiovascular diseases, lower lipid levels,
16.	5- aminosalicylate	Inflammation
17.	Eslicarbazepine	Epilepsy
18.	Dexketroprofen	Anti-inflammatory drug

19.	Levofloxacin [29]	Bacterial infections in the upper respiratory tract, urinary tract, prostate and skin
20.	Propofol [30]	General anaesthesia and sedation

Existing treatments for pancreatitis:

Allopathy:

As per the information gathered from doctors, there is no drug available to cure pancreatitis. However, painkillers, enzyme supplements, vitamins, and insulin were prescribed for the treatment of pancreatitis. These help in maintaining the condition of the patient to not get worse. Nonetheless, these do not offer a cure.

Some of the chemical drugs prescribed are, Roles-D (Domperidone and Rabeprazole), Panlipase-25000 (Pancreatin), Rabichill L, and Lupase 10000.

Apart from these, the antioxidant, and anti-inflammatory effects of two other chemical drugs viz. Captopril and Methylprednisolone were tested by Ashmawy et al., It was found that both these drugs had positive effects on treating pancreatitis [31].

Ayurveda:

Ayurveda is a natural medicine system which has originated from India's ancient Vedic period. In recent times, there has been a positive thought and high awareness towards herbal-based drugs and treatment which has less or no side effects [32]. The ayurvedic drugs prescribed in case of pancreatitis are given in Table 2.

Table 2 Ayurvedic prescriptions for pancreatitis

References	Ayurvedic Prescriptions	Form	Patient details
Kumar Panda et al., [33]	Saubhagya sunthi khanda madakaa	Powder	No. of Patients: **3** Gender: **Male** Age: **20 - 30**
	Sutasekhar Rasa		
	Kamadudha Rasa		
	Siddha Makardwaja		
	Dasamula haritaki		
Sharma et al., [34]	Panchttikat ghrita guggulu	Powder	No. of Patients: **1** Gender: **Male** Age: **40**
	Trikatu churna		
	Kutaki churna		
	Drakshavleha		
	Shankha Bhasma		
	Trivrit churna		
Sawarkar et al., [35]	Arogyavardhini Vati	Tablet	No. of Patients: **1** Gender: **Female** Age: **12**
	Amruttotar Kashayam + Dhanvantara Kashayam	Decoction	
	Chandraprabha Vati	Powder	

	Avipattikar Churna	Powder	
	Triphala Guggulu	Tablet	
	Panchatikta Ghrita + Dhanvantara Ghrita	Powder	
Prakash VB et al., [36]	Amar	Capsule	No. of Patients: **620** Gender: **Male- 516** **Female- 104** Age: **Less than 11 years - 20** **11 to 18 - 63** **19 to 45 -479** **Above 45 years - 58**
	RasonVati	Tablet	
	Prak-20	Powder/Capsule	
	Narikel Lavan	Powder	

Extractive Medicines

"Extractive medicines" refers to medications that are to be extracted for more research but lack a specific establishment as potential therapies. Apart from allopathy, ayurveda, and other kinds of treatments, such as bioactive compounds and medicinal plants are also available which show positive effects against pancreatitis.

Medicinal plants effective against pancreatitis

Table 3: Plants possessing positive effects against pancreatitis

SI.No	Plant	Extract	Animal	Effectiveness
1	*Senna auriculata* [37]	Aqueous extract of leaves	Rats	Lowered the levels of serum amylase, lipase and showed noticeable changes in pancreatic tissue and serum lipid peroxidation
2	*Myrtus communis* [38]	Ethanolic extract of leaves	Wistar albino rats	Noticeable reduction in pancreatic damages
3	*Gardenia jasminoides* [39]	Aqueous extract	C57BL\6 mice	Improved by inhibiting the activation of extracellular signal-regulated protein kinase (ERK) and c-Jun N-terminal kinase (JNK) in Pancreatic Stellate Cells
4	*Mimosa pudica* [40]	Ethanolic extract of leaves	Rats	Improved the condition by modulating diagnostic markers, and also improved TGF-β1 and collagen levels which in turn prevented fibrosis
5	*Calendula officinalis* [41]	Ethanolic extract of flower	Sprague-Dawley rats	Noticeable reduction in pancreatic nitrosative and oxidative stress
6	*Ligustrum Vulgare* [42]	Methanolic extract of berries	Male Sprague-Dawley rats	Reduced the expression of NF-κB/p65 and activation of the inhibitor of p38 MAPKs and NF-κB (IκBα).

Senna auriculata: *Senna auriculata* is a widely-known medicinal plant, that belongs to the family- Fabaceae. It has various pharmacological activities like antidiabetic, antihyperlipidemic, cardioprotective, anti-atherosclerotic, antifertility, cytotoxic, immunomodulatory, nephroprotective, antipyretic, antiviral, anti-helminthic, anti-melanogenesis, antioxidant, antimutagenic, antimicrobial, antiulcer and anti-inflammatory activity [43].

Myrtus communis is a medicinal plant; belongs to the Family- Myrtaceae. It has various pharmacological activities such as anti-inflammatory, analgesic, antioxidative, neuroprotective, antimutagenic, anti-diabetic, antimicrobial, antiparasitic, insecticidal, and anticancer. It also has good effects on skin, gastrointestinal disorders, antiaging, and impotency [44].

Gardenia jasminoides is a Chinese traditional medicinal shrub, that belongs to the family Rubiaceae and is native to China, India, Japan, and Thailand. It has various pharmaceutical activities such as hepatoprotective, anti-inflammatory, anti-depressant, anti-allergic, neuroprotective, anti-thrombin, anti-tumour, and cardioprotective [45]

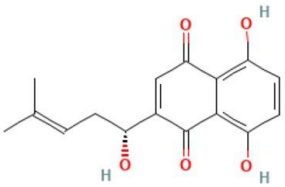
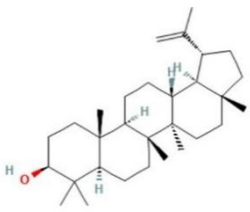
Mimosa pudica - A well-known ornamental plant commonly called Touch Me Not. It has many pharmacological activities such as wound healing activity, anti-inflammatory, antinociceptive, hypolipidemic, antidiabetic, diuretic, antiparasitic, antimicrobial, antioxidant, hepatoprotective, anti-venom, and antifertility. Leaves, roots, and whole plants are used in folk medicine [46].

Calendula officinalis is a medicinal plant belonging to the family Asteraceae, commonly called English marigold or pot marigold. The whole plant and its various parts can be used for the preparation of medicines. *Calendula officinalis* has many pharmacological activities such as anti-diabetic, anti-hyperlipidemic, hepatoprotective, antihelmintic, anti-inflammatory, anticancer, antioxidant, wound healing, anti-bacterial, angiogenic activities and is also effective in treating cardiovascular disorders [47].

Ligustrum vulgare commonly known as wild privet is a fast-growing shrub, native to Southern Europe, Northwest Asia, and North Africa. It is an ornamental plant. The pharmacological activities of this plant include anti-diabetic, immunomodulatory, cardioprotective, anti-bacterial, antioxidant, anti-proliferative, etc., [48].

Identified Natural Drugs - Bioactive compounds:

Table 4 Identified Phytocompounds effective against pancreatitis

SI. No	Phytocompounds	Structure	Effectiveness
1	Shikonin [49]	 [50]	Ameliorates by the inhibition of NF-κB activity
2	Lupeol [51]	 [52]	Showed desirable effects on the diagnostic markers and digestive enzymes and cytokine levels

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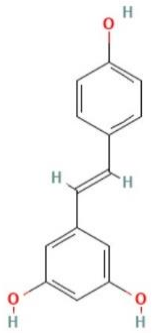
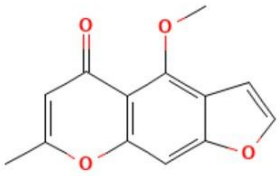
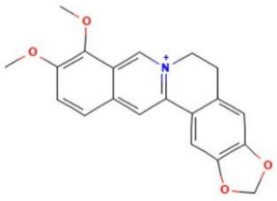
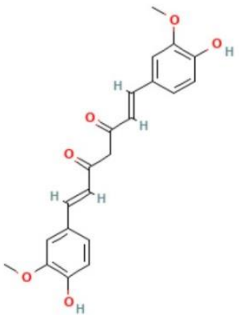
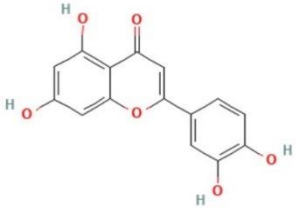
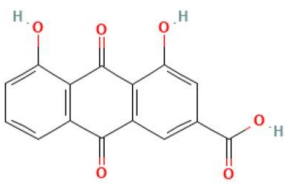
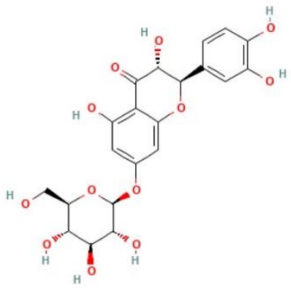
3	Resveratrol [53]	 [54]	Showed increased apoptosis, decreased serum amylase, lipase and cytokine levels.
4	Visnagin [55]	 [56]	Improved antioxidant by improving Nrf2 expression and stopped inflammation by inhibiting NFκB and nitrotyrosine expression
5	Berberine [57]	 [58]	Showed improved effects by inhibiting the activation of c-Jun N-terminal kinase (JNK).
6	Curcumin [59]	 [60]	Reduced the inflammatory response and severity level of acute pancreatitis.
7	Luteolin [61]	 [62]	Showed possible effects by inhibiting the activation of NF-κB pathway.
8	Rhein [63]	 [64]	Reduced key fibrotic markers, extra cellular matrix proteins.

9	(2R,3R)-taxifolin 7-O-β-D-glucopyranoside [65]	 [66]	Showed positive results by the upregulation of Nrf2/ARE antioxidant pathway

Shikonin is a liposoluble naphthoquinone pigment extracted from the roots of a Chinese medicinal herb, *Lithospermum erythrorhizon*. It possesses pharmacological activities such as anti-cancer, anti-inflammatory, wound healing, etc., [67].

Lupeol is a pentacyclic lupine-type triterpene, found in many edible vegetables and fruits such as carrot root, mulberries, red grapes, aloe plants, soybeans, tomato, mango pulp, etc. It has several pharmacological activities such as antioxidant, anti-hyperglycemic, anti-mutagenic, anti-diabetic, anti-asthma, anti-inflammatory, anti-dyslipidemic, cardioprotective, hepatoprotective, anti-arthritic, nephroprotective, anticancer, neuroprotective, etc [68].

Resveratrol is a polyphenolic phytocompound found in various plants such as grapes, jackfruit, berry fruits, peanuts, etc. Also, it has many remarkable pharmacological activities such as anticancer, anti-inflammatory, anti-adipogenic, neuroprotective, cardioprotective, anti-tumour, anti-obesity, antioxidant, anti-ageing, immunomodulatory, anti-microbial and it has promising effects on cell death, atherosclerosis, and inflammation [69].

Visnagin is a phytocompound obtained from the plant, *Ammi visnaga*. *A. visnaga* is an annual or biennial herb origin in the Mediterranean. The major pharmacological activities of this plant include antimicrobial and antispasmodic activities and it is effective against vitiligo, urolithiasis, and cardiovascular diseases [70].

Berberine is a compound derived from plants such as *Curcuma longa, Berberis sp., Mahonia aquifolium, Coptis sp. and Hydrastis canadensis*. It exhibits various pharmacological activities such as antioxidant, anti-inflammatory, anticancer, antidiabetic etc., This has been commonly used in traditional Chinese medicine [71]

Curcumin: is a natural lipophilic polyphenol and it has various pharmacological properties such as, antimalarial effect, anti-inflammatory, antinociceptive, antioxidative, antiparasitic, and also can be used as a wound-healing agent [72].

Luteolin, the main component of Reseda odorata L., which is also widely found in many natural herbs and vege-tables. It possesses a range of pharmacological properties such as; anti-inflammatory, antioxidant, neuroprotective, and analgesic [73].

Rhein is a lipophilic anthraquinone mostly found in medicinal herbs, such as *Rheum palmatum* L., *Aloe barbadensis* Miller, *Cassia tora L*., and, *Polygonum multiflorum* Thunb., It also has many pharmacological activities such as anti-inflammatory, antioxidant, hepatoprotective, anticancer, nephroprotective, and antimicrobial activities [74].

Conclusion:

The whole mechanism of pancreatitis is still unclear. These though knots can be untied by in-depth research of the known biological pathways, mutations and other causative agents such as smoking, alcohol, gall stones, drug induced etc., As discussed in Table 1, many allopathic drugs which are prescribed for various other diseases are acting as a triggering point to induce the onset of pancreatitis. Whereas, there is a very less hope of curing pancreatitis using allopathic drugs, as they are focusing mainly on symptomatic relief, mostly the drugs prescribed for pancreatitis is to maintain the condition than getting it worsen. At the same time, a combination of various ayurvedic herbal formulations has resulted in the cure of pancreatitis. Research on the crude extract of various plants, and a few other Phytocompounds isolated from plants, has shown noticeable results in reversing the damage caused to pancreas, and it is found that anti-inflammation and antioxidant activity of the

plants plays a crucial role in the reversal of pancreatitis. Hence, many other plants which have high level of both antioxidant and anti-inflammatory properties can be used for research and new treatment approaches such as sustained release, targeted drug delivery system may also help in effective reversal of pancreatitis. Still in-depth research should be carried out to find the exact mechanism of pancreatitis which will ease the drug discovery to cure pancreatitis.

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