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Review

Scleroderma: An insight into causes, pathogenesis and treatment strategies

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ABSTRACT

Scleroderma is an autoimmune disorder, characterized by morphological changes in skin followed by visceral organs. The pathogenesis of scleroderma involves immune imbalance and generation of auto antibodies. The major causes of scleroderma include multitude of factors such as immune imbalance, oxidative stress, genetics and environment factors. A constant effort has been made to treat scleroderma through different approaches and necessitates life time administration of drugs for maintenance of a good quality life. It has been reported more in women compared to men. Traditional treatment strategies are restricted by limited therapeutic capability due to associated side effects. Advancement in development of novel drug delivery approaches has opened a newer avenue for efficient therapy. Current review is an effort to reflect scleroderma in provisions of its pathogenesis, causative factors, and therapeutic approaches, with concern to mode of action, pharmacokinetics, marketed products, and side effects of drugs.

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1. Introduction

Scleroderma is an autoimmune rheumatic disease characterized by substantial damage of vascular system, tissue fibrosis and accumulation of collagen in skin. Word 'scleroderma' comes from two Greek words in which SCLERO stands for hard and DERMA for skin. So it is a disease in which hardening of skin and connective tissue occurs either locally or all over the body. Scleroderma has been classified into two types on the basis of level of its occurrence i.e. localized and systemic [1]. Localized scleroderma is limited to skin and muscular levels which are known as morphea and linear type. If it affects larger area of skin and organ then it is known as systemic which further includes limited and diffuse forms [2]. Limited form includes: Calcinosis (skin ulcer with white deposits and mineral crystal deposits); Raynaud's Phenomena (blue coloration of fingers); Esophageal motility (severe heart burn and reflux disorder); sclerodactylia (stiffness and tightening of skin); Telangiectasia (whitening of blood vessels creates flat red mark) [3]. Diffusive form includes: Interstitial Pulmonary fibrosis (damaging heart, dry cough, shortness of breath, reduced ability to exercise); Pulmonary Hyper Tension (narrowing of the pulmonary arteries, chest pain and fatigues); Kidney symptoms (renal crisis, weakness and fatigue); Heart symptom (inflammation, arrhythmias and heart failure) [4].

Crest syndrome involves c-calcinosis (calcium deposits in skin), r- raynauds phenomenon (spasm of blood vessels), e-esophageal dysfunction (acid reflux and decrease in motility of esophagus), s-sclerodactyly (thickening and tightening of skin on fingers and hands), t-telangiectasias (dilation of capillaries) [5]. Scelroderma is also associated with frequent fatigues, depression, sleeping disorders and sexual dysfunction that also lead to disability and a reduced quality of life [6]. Scleroderma is among the auto-immune rheumatic diseases with high disease-related mortality and morbidity with an impaired quality of life. [7]. Women are more frequently affected and especially while pregnant [8]. It is distributed worldwide as 2–10 per million. The prevalence rate of this disease is around 5/100,000 with an incidence of 1/100,000 [9] Higher rates have been reported in USA, Australia, and Eastern Europe and lower rates have been reported in Northern Europe and Japan [10].

1.1. Complications of scleroderma

Marked modulation in scleroderma involve overall immune activation, vascular damage, impaired angiogenesis and excessive accumulation of extracellular matrix with deposition of increased content of structurally normal collagen [11] One of the earliest signs of scleroderma is Raynaud's phenomenon. In this condition numbness of fingers, toes, ear and nose occurs and color of skin changes from pale white to blue on restriction of blood oxygen supply and further on supply of blood color changes to red. The condition is worsened during extreme cold condition, stress or due to change in temperature.This mainly occurs due to capillaroscopic abnormalities (enlarged capillaries and capillary loss with or without peri-capillary hemorrhages), involvement of antibodies like anti-centromere antibodies (ACA) oranti-Scl70, anti-RNA polymerase III, anti-PmScl (rare antinuclear antibodies and is associated with inflammatory myositis and scleroderma) or anti Th/To (antinuclear antibodies and is associated with diffusive scleroderma including pulmonary fibrosis and scleroderma renal crisis) [12–13]. Anticentromereantibodies (approximately 60–80%) are only found in limited systemic scleroderma. Diffuse forms associate with proximal and distal skin thickening, capillary loss, and visceral involvements as pulmonary, renal, myocardial and gastrointestinal damages. These are often associated with anti-topoisomerase I antibodies (30% in diffusive systemic scleroderma) and the absence of ACA. (ACA) or anti-Scl70 is also found in patients having initial stage of Raynauds phenomena. Limited cutaneous forms include a distal skin involvement, systemic vascular disorders like delayed onset of pulmonary arterial hypertension (PAH) and prevalence of ACA. Mainly antinuclear antibodies (ANA) in between range of 60–80% are found positively in patients of scleroderma [5]. The disease reduces the efficiency and quality life of patient due to increased level of sleeping disorders, fatigues, depression, and sexual dysfunction.

1.2. Causes of scleroderma

Immunological imbalance, environmental factors (silica exposure, chlorinated solvents, trichloroethylene, welding fumes for men, aromatic solvents and ketones), genetic factors and oxidative stress play a major role in the pathogenesis of Scleroderma (Fig. 1). Environmental factors and oxidative stress causes immune imbalance effecting both B cells and T cells. Immune imbalance causes generation of antibodies like anti-centromere, anti-topoisomerase-I and anti-RNA polymerase III indirectly suggesting role of B cells which causes vasculopathy and skin fibrosis. Endothelial and fibroblast cells get exposed to autoantibodies inducing production of reactive oxygen species. This collectively promotes fibroblast cells proliferation and fibrosis. Increased risk of pulmonary fibrosis has also been observed due to gene associated expression of signal transducer activator of transcription 4 (STAT4) and interferon-regulatory factor 5 (IRF5) and c-src tyrosine kinase (CSK) which alters signaling through T-cell receptor and their subunits like CD247. The Fig. 1 depicts the causative factor and pathogenesis of scleroderma. Oxidative stress too contributes a lot in pathogenesis of scleroderma. Oxidative stress provokes respiratory burst in inflammatory cells, promotes production of reactive oxygen and nitrites species like superoxides, hydroxyls, peroxynitrites and peroxides [14]. All these collectively trigger generation of ROS (Reactive oxygen species) and RNOS (Reactive nitrogen species) mediated by endothelial and fibroblast cells. Reactive species activates fibroblast proliferation, production of autoantibodies, promotes differentiation to myofibroblast and visceral fibroblast, and stimulates platelet derived growth factor [15]. These factors initiate collagen synthesis, fibrosis and progression of scleroderma [16].

2. Pathogenesis and its causative factors

The pathogenesis of scleroderma includes active involvement of cell mediated and humoral mediated immune response. Major histocompatibility complex formed between dendritic cells and T cells stimulates production of proinflammatory Th2 cells which releases proinflammatory cytokines like IL-4 and IL-13. In turn it stimulates B cells and production of vascular epidermal growth factor (VEGF) [10]. Immune mediated responses have been confirmed by elevated level of cryoglobulins, rheumatoid factors, gammagloubulins, autoantibodies [17]$^{-}$, over-expression of B cell co-receptors CD19, CD21, CD86 and CD95 in memory B cells [18], increased expression of anti-endothelial cell receptor antibodies, anti-angiotensin type 1 receptor antibodies and endothelial cell apoptosis [19]. The pathogenesis have been further manifested by increased level of plasma tumor growth factor-β (TGF-β), INF-γ, colony-stimulating factors, interleukins (IL), interferons, cytokines like IL-1, IL-4, IL-13, Th-2 cytokine, activated TCD8^{+} lymphocytes, increased level of MCP-1 (monocyte chemoattractant protein1) [20], VCAM-1 (vascular cell adhesion molecule-1) cell, platelet derived growth factor (PDGF-R) and the connective tissue growth factor (CTGF) [21–22]. TGF-β plays a major role in fibroblast activation and phenotypical modifications [23]. Overexpression of dendritic cell protein CXCL4, TNFα, IL-6 too induces recruitment of endothelin-1 which promotes the

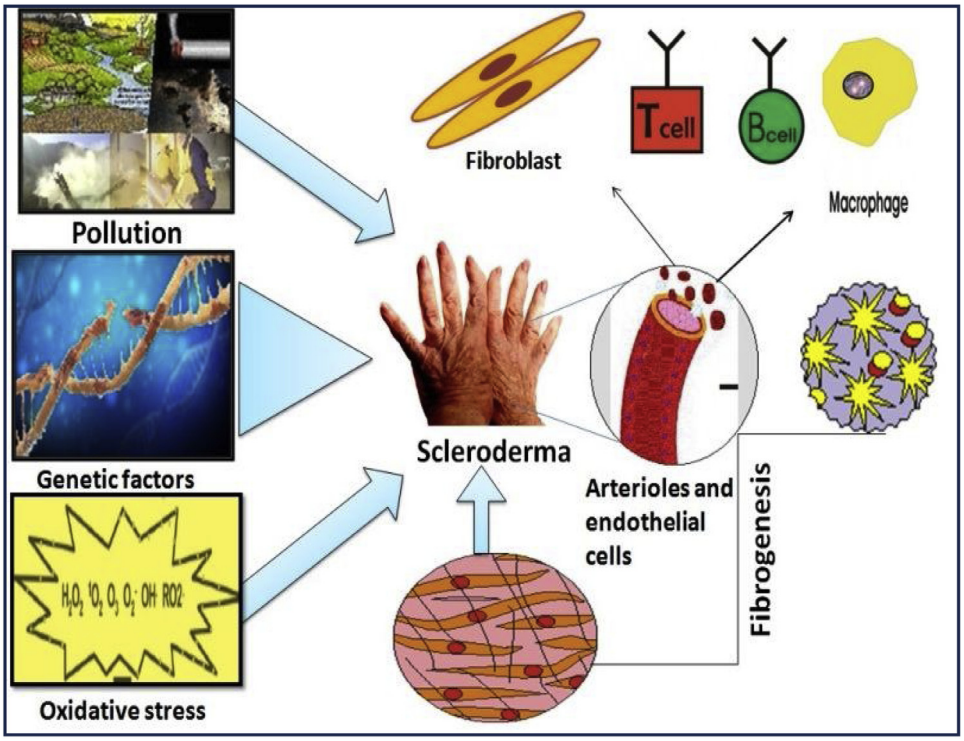

Fig. 1. Causative factors and pathogenesis of scleroderma.
Figure 1 contains all the original images and have not been taken from any other sources.

cause of scleroderma. Endothelin-1 activates release of inflammatory mast cells, cytokines, neutrophils, monocytes and free oxygen radicals. Endothelial-1 also promotes generation of tumor necrosis factor-alpha. Thus enhances fibrosis by promoting fibroblast cell replication, migration and contraction. Collagen and fibronectin synthesis too are stimulated by reducing collagen degradation by inhibiting MMP-1 production thus effects digital arteries and renal arterioles. Collectively these molecular pathogenesis effects many organs and leads tovascular damage, pulmonary fibrosis, and pulmonary hypertension. Thus wide selection of drug is required for treatment of scleroderma [5,6]. Further detail role of macrophages and T cells has been discussed further below.

2.1. Importance of T cell and Macrophage:

Macrophage and T cell are two important cells that are involved in progression of scleroderma. Macrophages activated by lipopolysaccharide (LPS), TNF-α, IFN-γ and IL-12 produces high amounts of the pro-inflammatory cytokines as TNF, IL-1, and IL-6, but little TGF. This is classically activated macrophages that are well-organized at antigen presentation, which activates type 1 T cells and reduces collagen production by fibroblasts. In contrast, macrophages activated by IL-4, TGF and glucocorticoids have an anti-inflammatory, phagocytic, profibrotic phenotype and activate type 2 T cells. These refer as alternatively activated macrophages produces large amounts of TGF, PDGF, and IL-1 receptor antagonist (IL-1ra), but not TNF or IL-1. Alternatively activated macrophages stimulate collagen production by fibroblasts. Thus, alternatively activated macrophages appear to be key player in pathologic processes that are associated with fibrosis [24–27].

In the initial stages of sclerosis, activated T cells, monocytes and macrophages gathers inside lesioned skin and releases pro-inflammatory and pro-fibrotic intermediates like numerous cytokines, chemokines and growth factors mainly TGF-β. These activate fibroblasts and endothelial cells to proceeds further inflammatory cells for initiating the fibrotic response. TGF-β persuades its own production as well as that of other growth factors for cytokine burst that result in augmented cytokine secretion and continued autocrine and paracrine signaling. Variations in the comparative proportions and function of regulatory T cells and T-helper 17 cells, and innate lymphoid cells have been recognized and possibly will play important roles in pathogenesis [28]. Various gene loci like IL12R, STAT4 (Signal Transducer and Activator of Transcription), CD247, PTPN22 (Protein Tyrosine Phosphatase, Non-Receptor Type 22), and TNFSF4(Tumor necrosis factor superfamily Member 4) related with T cell gene function are involved in systemic sclerosis [28]. A slanted balance among T helper, Th1 and Th2 cytokines manifest fibrosis. Th2 cells produce copious amount of IL-4, IL-5, and IL-13, but only low levels of the characteristic Th1 cytokines and IFN-γ. Th2 cytokines straightforwardly encourages collagen synthesis, myofibroblast trans-differentiation, and making of TGF-β, a potent incentive for ECM accumulation, whereas IFN-γ hunk these responses and exerts anti-fibrotic effects [29].

Allograft inflammatory factor-1 (AIF-1) is a lately notorious protein expressed by macrophages and neutrophils. Some study demonstrated increased AIF-1 expression in the infiltrating cells within lesions. It was also seen that AIF-1 encourages T-cell infiltration and persuade the expression types I and III collagen and cytokines by normal dermal fibroblasts [30,31]. Some study reveals increase level of one pro-inflammatory cytokine MIF (Macrophage migration inhibitory factor). It is released from activated T cells, macrophages and promotes production of TNF-α and other cytokines by macrophages and T cells [30].

2.2. Progression of scleroderma

The progression of scleroderma disease includes abnormal multiplication of fibroblast cells and endothelial damage across blood vessels due to immune imbalance. Disease progresses due to abnormal growth of connective tissues causing thickness of skin and

its pigmentation followed by constriction of blood vessels. Clinically disease progression involves cutaneous, vascular systems and organs. Active changes are observed like thickened skin with pigmentation, hair fall and fat loss. The fibrotic phase further causes joint discomfort and restricted motions [5]. Cutaneous system includes limited cutaneous systemic sclerosis that includes calcium deposition, numbness of fingers, color changes, oesophageal dysfunctions, skin tightening, and thickening. Diffusive cutaneous system includes lesion formation over chest, arms, shoulders and abdomen. Vascular conditions are adverse by narrowing of blood vessels, cause of numbness and changes in color. Abnormal fibrosis adversely affects organs includes swelling of hand, joints, muscles pain, chest pain, shorthness of breadth, difficulty in swallowing occurs, heartburns, bloating, and choking occurs pulmonary fibrosis and kidney failure. Its difficult to control fibrosis once it has been established. Thus numerous treatment strategies has been established to control its growth and relapse nature

3. Treatment strategies

Varied categories of drug have been directed for treatment of scleroderma. Treatment requires targeting inflammation, vascular damage, excessive collagen production and fibrosis [32]. The treatment strategies for scleroderma have been discussed in two class i.e. treatment and novel delivery based approach and recent therepies. Treatment based approach includes drugs, herbs, antioxidants and biologics. Novel delivery system based approach generally comprises of vesicular systems, particulate system, self assembled system, eukaryotic and prokaryotic cell carriers. Recent therapy includes targeting cells and genes proliferating the cause of scleroderma.

3.1. Treatment based approach

Treatment based approach has been reclassified into drug based approach, herb based approach, antioxidant approach and biologics which have been discussed below.

3.1.1. Drug based approach

In scleroderma major cause of fibrosis is due to upregulation of inflammatory cytokines, inflammation and dysregulation in blood flow [32]. The immunosuppressant drugs which are preferred includes methotrexate, cyclosporine, mycophenolate and cyclophosphamide [33]. Marrani et al., 2018 investigated the comparative efficacy of Methotrexate or phototherapy (UVA) for treating localized scleroderma and suggested that UVA and methotrexate protocols have both a favorable effect in active lesions of childhood localized scleroderma. However, methotrexate resulted significantly superior to UVA, with or without Psoralen [34]. Vascular damage could be regulated by calcium channel blocker, angiotensin converting enzyme inhibitor and endothelial-1 receptor inhibitor. Endothelin-1 receptor inhibitors like Bosentan/Prostacylins like epoprostenol are highly preferred to regulate blood flow. Collagen production could be reduced with help of anti fibrotic agents like dimethyl sulfoxide, colchicines and p-aminobenzoic acid. Detailed mechanism of action, pharmacokinetics, side effects and marketed product of drugs involved in therapy of scleroderma [35] have been illustrated in (Table 1).

3.1.2. Herbs based approach

Alternative to drug approach herbs have been also used by many researchers to treat scleroderma. Few works have been enlisted below that promises to restrict the proliferation of scleroderma by use of herbs for example:

1 Todisco M et al 2006 reported that when melatonins were administered to 5 patients along with adrenocorticotropic hormone and vitamin E for 3 months no progression of disease was observed [57].
2 Gaby AR et al 2006 revived that para-aminobenzoic acid, vitamin E, vitamin D, evening primrose oil, estriol, N-acetylcysteine, bromelain, and an avocado/soybean extracts can be used for effective treatment of scleroderma [58].
3 Zhou *J* et al 2018 has examined that by taking bath with decoction of Taohong Siwu Decoction along with oral prednisone significantly helps in the treatment of preliminary stage of mild to moderate diffuse cutaneous systemic sclerosis (dcSSc) better effect in patients with systemic sclerosis without serious adverse effect [59].
4 Han L et al 2016 has demonstrated that antiproliferative and pro-apoptotic actions of traditional Chinese medicine as the Wenyang Huazhuo Tongluo formula decoction has been found effective against fibroblasts, down-regulation of mRNA, cyclin D1 and survivin in systemic sclerosis [60].
5 Wu T et al 2014 has reported that Chinese formula Yiqihuoxue decoction effectively down regulates extracellular matrix (ECM) gene expressions and collagen production in systemic sclerosis dermal fibroblasts. Down regulation of TGF-β1-induced NIH/3T3 fibroblasts has been also reported to effectively treat scleroderma [61].

3.1.3. Antioxidant therapy

Antioxidants aid in scavenging peroxyradicals, inhibits lipid peroxidation, gene mutation, free radical generation like superoxides, hydroxyls, peroxides, nitrites. Thus antioxidants minimize the antigen generation and production of autoantibodies. The antioxidants may be supplemented naturally from herbal/dietary sources or synthetically like vitamin E, polyphenols, flavonoids, carotenes, olives, ascorbic acid, elements like zinc and selenium for proper functioning of enzymes [62]. Higher doses of these antioxidants may alleviates/reduces slight oxidative stress, and are only marginally effective in acute conditions including ischemia-reperfusion, inflammation and radiation injury [63]. Other specifically derived natural antioxidants as epigallocatechin, (-)-epicatechin-3-gallate, epicatechin are found to regulate transduction pathway and transcription factors (Nrf2, NF-κB, AP-1). Their usefulness are proved as antifibrotic, anticancer, and anti-inflammatory activities as it regulates both TGF-β and PDGF-induced 1(I) collagen, fibronectin, -smooth muscle actin (-SMA), and proliferation in activated human and rat hepatic stellate cells, rat pancreatic cells, human keloid fibroblasts, and SSc dermal fibroblasts [63]. Therapy with Antioxidant enzymes (AOEs) is an alternative and effective means to target oxidative stress directly. Basic AOEs include administration of Superoxide dismutase (SOD), catalase, glutathione peroxidase, Paraoxonase and Heme-oxygenase-1 [64] and non-enzymatic antioxidants like α-tocopherol, selenium, carotene and ascorbic acid reduces phosphorylation, generation of peroxides in systemic scleroderma and inhibits collagen proliferation [65]. Paraoxonase is an antioxidant extracellular enzyme which posses anti-inflammatory property, SOD causes conversion of superoxides into peroxides and catalase decompose superoxide and H_2O_2 to non toxic molecules. These are more potent antioxidants that are not consumed in reaction with ROS and inhibit generation of free radicals which aids in destruction of DNA bases and leads to development of antigenic molecules [66].

3.1.4. Biologics

Biologics are modified form of recombinant proteins that are preferred to target interleukins and tumor necrosis factor to treat autoimmune disorders. Although many are at clinical levels but

Table 1
List of drugs used for treatment of scleroderma with their marketed formulations.

S.No	Drugs	Mechanism of action	Pharmcokinetics	Side effect	Marketed Formulation	References
1.	**Endothelin Receptor Antagonists (**Improves blood flow and prevents finger ulcers and improving hand function					
a	Bosentan	A specific and competitive antagonist at endothelin receptor types ET_A and ET_B	Absolute bioavailability: 50%. Half-life: 5 hrs. Single dose: 2400 mg	severe headache, nausea, and vomiting, but no serious adverse events	Tracleer	[35]
2.	**Calcium channel Blockers (**Open blood vessels- used for pulmonary artery hypertension and Raynaud's phenomenon**)**					
	Nifedipine	Vasodilator, inhibits the influx of calcium ions through L-type calcium channels,result in an overall decrease in blood pressure.	Rapidly and fully absorbed following oral administration Half Life-2 hrs Protein binding-92-98%	Dizziness, drowsiness, nausea, severe drop in blood pressure, slurred speech, and weakness.	Adalat, Procardia, Nifecard.	[36]
3	**PDE5 Inhibitors**					
	Sildenafil	Inhibits cGMP-specific phosphodiesterase type 5 (PDE5) responsible for degradation of Cgmp. Cyclic GMP causes smooth muscle relaxation and increased blood flow	>90% absorbed with ~40% reaching systemic circulation unchanged following first-pass metabolism	Redness in the face, inability to differentiate between the colors green and blue.	(Rovatio)	[37]
	Tadalafil	Similar to sildenafil	Half life -4 hrs (Cmax) of tadalafil is achieved between 30 minutes and 6 hours	Difficulty inbreathing; swelling of your face, lips, tongue, or throat.	Adcirca	[37,38]
4	**Angiotensin Converting Enzyme (ACE) Inhibitors (**Controlls blood pressure, but appear to be effective for scleroderma patients because of their protective actions in the kidney**)**					
	Captopril	Inhibits enzymatic proteolysis of ATI to ATII. Decreasing ATII levels in the body decreases blood pressure by inhibiting the effects	60-75% in fasting individuals; food decreases absorption by 25-40%. Half life-2 hrs	Dose-dependent rash (usually maculopapular), taste alterations, hypotension, gastric irritation, cough, and angioedema.	(Capoten),	[39]
	Enalapril	Competitivily inhibits Angiotensin Converting Enzyme.	< 2 hours for unchanged enalapril	Gastric irritation, Dry cough, irritation.	(Vasotec),	[40]
	Lisinopril	Lisinopril is competitive inhibitor of angiotensin-converting enzyme (ACE),responsible for conversion of angiotensin I (ATI) to angiotensin II (ATII).	**Half life-** accumulation following multiple dosing is 12 hours.	Headache, dizziness, cough, fatigue hypotension, electrolyte disturbances, and renal failure	(Prinivil, Zestril)	[41]
	Benazepril	Inhibition of ACE results in decreased plasma angiotensin II, decreasesvasopressor activity and decreases aldosterone secretion.	Peak in plasma within 0.5-1.0 hours. Half life: 10-11 hours	Headache, dizziness, fatigue, somnolence, postural dizziness, nausea, and cough.	Lotensin	[42]

Table 1 (*Continued*)

S.No	Drugs	Mechanism of action	Pharmcokinetics	Side effect	Marketed Formulation	References
5	**Angiotensin II Receptor Antagonists (Used similarly as ACE inhibitors)**					
	Losartan	Losartan competitively inhibits binding of angiotensin II to AT1 in many tissues including vascular smooth muscle and the adrenal glands.	Peak concentrations of losartan and its active metabolite are reached in 1 h and in 3-4 h	Hypotension and tachycardia; Bradycardia could occur from parasympathetic (vagal) stimulation,	Cozaar, Hyzaar	[43]
	Candesartan	Antagonizes the renin-angiotensin-aldosterone system (RAAS).	Half life:- 9 hours.		Candesartan Cilexetil	[44]
6	**Prostacyclins (**Open blood vessels and have antibloodclottingproperties- used to treat pulmonary artery hypertension and Raynaud's phenomenon.**)**					
	Iloprost,	Iloprost binds with equal affinity to human prostacyclin and prostaglandin EP1 receptors. Inhibits the ADP, thrombin, and collagen-induced aggregation of human platelets.	Rapidly absorbed with bioavailability of 63%. **Half Life**: 20-30 minutes	Trismus, vasodilatation, increased cough, and flushing. Other side effects include insomnia, and glossalgia.	Ventavis	[45]
	Alprostadil	Causes vasodilation by means of direct effect on vascular and ductus arteriosus (DA) smooth muscle, preventing or reversing the functional closure of the DA that occurs shortly after birth. So has multiple effects on blood flow. This results in increased pulmonary or systemic blood flow in infants.	**Half life:** 5 – 10 minute **Administration:** infused continuously because it is very rapidly metabolized	Apnea, bradycardia, pyrexia, hypotension, and flushing may be signs of drug overdosage	Prostaglandin E1	[46]
	Epoprostenol	Protein kinase A (PKA) causes phosphorylating and inhibiting myosin light-chain kinase which leads to smooth muscle relaxation and vasodilation.	**Half-life**:6 minutes.	Nervousness, chest pain,, hypotension, nausea, flushing. dizziness, bradycardia..	Flolan	[47]
	Treprostinil	Direct vasodilatory effects, also inhibits inflammatory cytokine. As a synthetic analogue of prostacyclin, it binds to prostacyclin receptor, which subsequently induces the aforementioned downstream effects.	**Half-life**: 2 to 4 hours **Protein binding :** 91%	Flushing, headache, hypotension, nausea, vomiting, and diarrhea	Remodulin	[47]

Table 1 (*Continued*)

S.No	Drugs	Mechanism of action	Pharmcokinetics	Side effect	Marketed Formulation	References
7	**Immunosuppressant**					
	Cyclophosphamide	Alkylating agents causes attachment of alkyl groups to DNA bases, resulting in the DNA being fragmented by repair enzymes in their attempts to replace the alkylated bases, preventing DNA synthesis and RNA transcription from the affected DNA, DNA damage via the formation of cross-links and cause mutation.		Neutropenia, febrile neutropenia, fever, alopecia, nausea, vomiting, and diarrhea		[48]
	Azathioprine (AZA)	Azathioprine antagonizes purine metabolism and may inhibit synthesis of DNA, RNA, and proteins. It may also interfere with cellular metabolism and inhibit mitosis. Its mechanism of action is likely due to incorporation of thiopurine analogues into the DNA structure, causing chain termination and cytotoxicity	**Absorption**- Well absorbed following oral administration, Protein binding- 30%. **Halflife**- Approximately 5 hours for the unchanged drug and its metabolites, **Metabolism**- in liver, Excretion- in the urine. 1.5–2.5 mg/kg/day orally	Night sweats, weight loss, tiredness, pale skin, rapid heart rate, nausea, upper stomach pain, itching, loss of appetite, dark urine, clay-colored stools, jaundice	Imuran, Azasan	[49]
	Mycophenolatemofetil	MPA has potent cytostatic effects on lymphocytes. It is inhibitor of inosine monophosphate dehydrogenase (IMPDH), and therefore inhibits the de novo pathway of guanosine nucleotide synthesis without incorporation into DNA.	Rapidly absorb through oral administration Volume of distribution in oral administration is4 ± 1.2 l/kg and in Half-life of mycophenolic acid (the active metabolite) is 8-16 hours	Hematological abnormalities such as leukopenia and neutropenia, and gastrointestinal symptoms such as abdominal pain, diarrhea, nausea and vomiting, and dyspepsia	Cellcept	[50]
8	**Other Immunosuppressant's**					
	Methotrexate	Methotrexate anti-tumor activity is a result of the inhibition of folic acid reductase, leading to inhibition of DNA synthesis and inhibition of cellular replication	Bioavailability- 60%, Protein binding- 50%, Half life- 3-10 hrs, Elimination- 80% to 90% of the administered dose is excreted unchanged in the urine within 24 hours. **Dose-** 15–25 mg weekly (IM/SC/orally)	Overdose include bone marrow suppression and gastrointestinal toxicity.	Rheumatre	[51]
	Sirolimus	Inhibits T lymphocyte activation and proliferation that occurs in response to antigenic and cytokine (Interleukin IL-2, IL-4, and IL-15).	Half life- 57-63 hours	Peripheral edema, hypertriglyceridemia, hypertension, hypercholesterolemia, creatinine arthralgia, thrombocytopenia.	Rapamycin	[52]

Table 1 (*Continued*)

S.No	Drugs	Mechanism of action	Pharmcokinetics	Side effect	Marketed Formulation	References
	Antithymocyte globulin (ATG),	Binds to multiple, T-cell specific antigens leading to T-lymphocyte cell death via complement mediated cytotoxicity or apoptosis.	Average 21.5 and 87 mcg/mL 4–8 hours post-infusion after first and last IV dosesV Half life: 2-3 days	Abdominal pain, Diarrhea, labored breathing, dizziness, feet, and fingers, tightness in chest, unusual weak fee	Grafalon	[52]
	Corticosteroids(**Prednisolone**)	Binds with high affinity to specific cytoplasmic receptors. The result includes inhibition of leukocyte infiltration at the site of inflammation, interference in the function of mediators of inflammatory response	Half life- 2-3 hours, Absorption- readily absorbed by gastrointestinal tract, Protein binding- >90%, Metabolism- in liver, Excretion- in the urine as either free or glucoconjugate. **Dose-** 20–60 mg orally	Anxiety, blurred vision decrease in the amount of urine, swelling trouble thinking, speaking, or walking, weight gain	Ak-Tate, Alphadrol Articulose-50, Co-Hydeltra	[23]
9	**Vitamin D3 analogue**					
	Calcipotriol	It acts by slowing down the production of pro-inflammatory cytokines. as (IL)-8, IL-4 and IL-10.	Bioavailability — 5-6%, metabolism — hepatic,excretion— by biliary	Pruritis, buythmea, hypercalcemiarning, er	Dovonex	[53]
10	**Phototherapy**					
	Ultraviolet B therapy	Interaction between UVB radiations and DNA causes generation of pyrimidine dimers and other photoproducts causing inhibition of DNA synthesis. Inhibition of proliferating lymphocytes and keratinocytes	Not yet defined	Dimers and other photoproducts leading to keratinocytes.	------	[54]
	Psoralen plus ultraviolet A therapy (PUVA) Methoxsalen	Psoralen activated by UV radiation inhibits DNA synthesis. Thus prevents cell proliferation and avoid cells to duplicate their DNA.	Not defined	Skin cancer, mainly squamous cell carcinoma (SCC) and malignant melanoma and premature skin aging	Oxasolaren	[54]
	Light emitting diodes-based ultraviolet A1 phototherapy	Dermal mast cells count in mice with scleroderma was reduced after high and medium dose treatment	Not defined			[55]
11	**Stem Cells**					
	Adipose-derived stem cells	Reduced the skin thickness and the total content of hydroxyproline and significantly lower levels of TGF-β1 and higher levels of VEGF	Subcutaneously injected into the dorsal area in the model treatment group	No		[56]

Table 2
List of biologics targeting inflammatory interleukins.

S.no	Inflammatory interleukins	Biologics targeted	Remark	References
1	IL6 (critical interleukins in systemic sclerosis)	Tocilizumab (humanized anti-IL6 receptor antibody)	Reported to improve skin texture and thickness, reduced lung fibrosis and reduced patient's Global Disease Activity scores	[69]
2	TNF-α (pro-inflammatory cytokine)	Etanercept, Infliximab, Adalimumab, Golimumab	Reduced level of collagen content, TGF-β, hydroxyproline and infiltrating myofibroblasts has been observed	[70]
3	IL-1(role in proliferation and collagen production of fibroblasts)	Rilonacept	Clinical studies reported reduced level of fibroblast proliferation, IL-6 production and procollagen synthesis	[71]
4	IL13 (profibrotic cytokine that interplays with other mediators such as TGF-β)	Tralokinumab	Results are under evaluation in a phase II clinical trial in idiopathic pulmonary fibrosis	[72]
5	IL-17, IL-17 receptor (actvates fibroblast cells and promotes secretion of pro-inflammatory cytokines as IL-6 and IL-8, and increased surface expression of Intercellular Adhesion Molecule.	Ixekizumab and Brodalumab respectively	Benefits in other autoimmune disorders has been observed as in psoriatic arthritis but no such data has been observed in scleroderma	[73]
6	Tumor growth factor-β (central mediator of fibrosis)	Metelimumab,Fresolimumab	No significant results were observed in case of metelimumab but effect has been found in case of fresolimumab, posses capacity to inhibit all isoforms of tumor growth factor.	[74]
7	B Cells	Rituximab	Improves skin score, reduces hyalinised collagen score	[75]
8	B cell activating factor (found elevated and promote fibrosis)	Belimumab	Reduced level of IL6 has been observed	[76]
9	T cells	Abatacept	Found effective in treating established fibrosis. Activated T-cells, B-cells and monocytes infiltrating the skin were reduced, along with IL-6 and IL-10 levels, but its treatment is only limited to inflammatory fibrosis	[77]

Table 3
Novel approaches for treatment of Scleroderma.

S.no.	Carrier system	Drug	Remark	Reference
1.	**Liposomes**			
1.1.	Multilamellar liposomes	Colchicines	Encapsulation in liposomes may reduce the colchicines toxicity.	[79]
1.2.	Dicationic liposomes	interferon γ	It increases the production of IFNγ which increases the lymphatic activity.	[80]
2.	**Particulate system**			
2.1.	IFN-γ nanoparticles	IFN-γ-coding plasmid	Modulate excessive collagen synthesis in scleroderma-affected skin	[81]
2.2.	Carbon-based nanoparticulate	-------	Reported to stimulate cytokine gene expression at a higher extent in SSc keratinocytes versus normal cells	[82]
3.	**Emulsion**			
3.1.	Microemulsion	curcumin	Treating various skin diseases like scleroderma, psoriasis, and skin cancer	[83]

recently tocilizumab has been found to qualify clinical trials and two year stability test. Rituximab and Imatinib has been, recently recommended as a first-line biologic agent for treatment of autoimmune disorders like arthritis [67] and skin fibrosis but no such effect has been observed in fibrotic lesion. Contradictory in case of scleroderma TNF inhibitors such as infliximab failed to show marked positive response. Studies have been demonstrated for tumor growth factor-β1 antibody and oral type I collagen but no statistical benefits have been observed [68]. Some of the studies have shown positive effect in animal model but are still struggling to pass clinical trials. List of many other biologics has been used to target inflammatory interleukins has been represented in Table 2.

3.2. Novel delivery based approach

Novel based therapies are considered to combat disadvantages possessed by conventional therapies. These are advantageous in terms of having long lasting action, improved bioavailability, enhanced patient compliance, dose minimization, improved loading of drug at target site, improved safety, reduced toxicity by reducing dose frequency, highly flexible and versatile, potentially possess targeting property. Novel delivery system provides effective means to control the release of drug for inflammatory diseases and local treatment. These systems are mainly made up of phospholipids and biocompatible polymers for safe homing with controlled release of drug [66]. Novel carrier systems could be classified into vesicular systems, particulate systems, polymer systems, emulsions and cellular carriers [16–17]. The additional benefits can be taken by modifying and exploring cellular carriers, erythrocytes, platelets or by utilizing recombinant technoldelivery of gene. Innovative systems helps to target the actives at site of action, minimizes drug loss, increased drug bioavailability and targeting at site of action. Inflamed skin allows utmost localization and adsorption of vesicular and particulate system allowing them to release drug locally and inhibit its toxicity [78]. Numerous novel approaches opted for therapy of scleroderma has been enlisted with their effects in Table 3.

3.2.1. Recent therapy

Recent studies suggest that plasmacytoid dendritic cells (pDCs) are one of important cells thatcontributes to cause of scleroderma. Normally it secrete interferon to help fight off infections. However, as study revealed, in scleroderma patients these cells are chronically activated and infiltrates at the site of skin causing fibrosis and

Table 4
List of patents associated with scleroderma.

S.N.	Patent no. and Date	Title	Significant	
1.	61/844,983, filed Jul. 11, 2013	Topical treatment of localized scleroderma	Compositions and formulations for topical administration that contain a tyrosin kinase inhibitor, such as imatinib or nilotinib useful in treating scleroderma.	[91]
2.	CN106620353A, 2017-05-10	Medicine for treating systemic scleroderma	The invention aims to treat systemic scleroderma by taking mixture of lots of herbs as mixture of mother of pearl, ephedrine, wolfberries, honeysuckle, calcinied oyster, seaweed, epimedium, hedyotis diffusa, gardenia, hui wheat, forsythia, codonopsia, calcinied turtle, licorice.	[92]
3.	WO 2010/102983 A1 on Sep. 16, 2010	Methods for the treatment or prevention of systemic sclerosis	The invention involves methods to develop for treatment or prevention of fibrosis in patients suffering fromscleroderma, by reducing plasma level of CXCL4.	[93]
4.	WO 2009/061818 Al, date 14.05.2009	Methods of treating scleroderma	The present invention provides compositions and methods of treating scleroderma and the symptoms associated with scleroderma by inhibitinf type I interfern gene expression.	[94]

inflammation. This study also reveals that depleting pDCs in an animal model of scleroderma prevented the disease from forming, and reversing already existing fibrosis [84]. The inflammasome, a central driver of fibrosis is a bulky protein complex that regulates the release of various cytokines like IL-1, IL-18, IL-36 and IL-33 having important role in the fibrotic response. IL-36 also belongs to the IL-1 family of cytokines and is a new comer to this field of research. Recent studies reported that numerous of them play a significant role in skin inflammation and fibrosis and their consequent antagonists (IL-1RA and IL-36RA) can repeal this pathology [85]. IL-22 expression in infiltrated lymphocytes may encourage the up-regulation of type I collagen protein in dermal fibroblasts [86]. Genetic connection for sclerosis lies mainly in the MHC (Major histocompatibility) region, with loci in HLA-DRB1 (Human leukocyte antigens), HLA-DQB1, HLA-DPB1, and HLA-DOA1 being the most replicated. The non- HLA genes linked with sclerosis are involved in a range of functions, with the most robust links including genes for B and T cell activation and innate immunity. Genes, IRF5 (Interferon Regulatory Factor 5), STAT4, and CD247 were replicated most frequently while SNPs rs35677470 in DNASE1L3 (Deoxyribonuclease 1 Like 3), rs5029939 in TNFAIP3, and rs7574685 in STAT4 have the strongest links with sclerosis [87]. Various miRNAs (micro RNA)have been identified in scleroderma patients, like miR-21, miR-29, miR-130b, miR-21-5p, miR-92a-3p, miR-155-5p, and miR-16-5p. These are found to be up-regulated in sclerodermic fibroblasts and dermis involved in the lung proliferation and angiogenesis [88,89,90,91]. These may shed light in new areas for therapeutic development. Few technologies which have been patented have been too enlisted in Table 4.

4. Conclusion and future prospects

The cause of scleroderma includes immune modulation and fibroproliferative condition effecting vital organs of a body. Thus, treatment of scleroderma depends on their indication and effected region through different classes of drugs such as corticosteroids, immunosuppressive, H2 blockers, proton pump inhibitors, endothelin receptor agonists, calcium channel blockers, PDE-5 inhibitors, chelating agents and prostacyclin analogues. But the complete cure of scleroderma is still questionable, making it more difficult to cure due to associated side effects of drugs. Limitations too persist in analyzing their treatment strategies because only few patients are available for their clinical trials. Even drugs that are effective in small groups of patients fails to show its effectiveness on larger groups. Designing of treatment strategies that will improve symptoms of diseased organs without affecting nearby organs is very difficult. So, more research is needed to fulfill the therapeutic demand of scleroderma by use of biologics, targeted and novel approaches. In future, therapeutic regimen could also be extended in field of stem cells research because significant reduction in inflammation and improvement in lung function were observed in patients by means of human stem cell therapy. Similarly significant improvement in Raynaud's syndrome and PAH has been also observed by use of botulinum toxin and Bosentan.

Treatment efficacy could also be improved by actively targeting surface receptors, soluble receptors and signaling pathway which could downregulate the activity of inflammatory cytokines playing crucial role in cause of scleroderma. Biologics imatinib mesylate, a protein tyrosine kinase inihibitor are greatly used to treat fibrosis and vasculopathy in Systemic Scleroderma. Future medicine could include active targeting of inflammatory agents as transforming growth factor -beta, connective tissue growth factor, platelet-derived growth factor and endothelin-1 which collectively promotes fibrosis, vasculopathy and pathogenesis of Systemic Scleroderma.

5. Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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