Antifibrotic Herbs

Indications, Mechanisms of Action, Doses, and Safety Information

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Abstract

Many herbs and their constituents have been shown to interfere with, or prevent, excessive, abnormal fibrosis in a range of diseases. *Glycyrrhiza glabra* (licorice) and *G. uralensis* (gan cao) root, glycyrrhizin, isoliquiritigenin, isoangustone, sho-saiko-to (xiao chai hu tang), *Centella asiatica* (gotu kola) leaf, asiaticoside, madecassoside, madasiatic acid, *Silybum marianum* (milk thistle), silymarin, *Colchicum autumnale* (autumn crocus), colchicine, *Salvia miltiorrhiza* (Chinese sage, dan shen), tanshinones, magnesium lithospermate B, danshensu, and dang gui bu xue tang are reviewed in some depth in terms of their antifibrotic effects. Indications, mechanisms of action, doses, and safety information are given for each remedy.

Introduction

Formation of increased levels of matrix material (collagen and related molecules) in response to injury is a normal part of tissue repair. However, this process can spiral out of control, particularly if the causative insults are not removed. This can lead to permanent fibrosis (which excludes cellular regeneration) and ultimately cirrhosis, with total replacement of normal tissue with fibrotic tissue.

For a list of conditions associated with excessive fibrosis, see Some Fibrotic Conditions. Herbal medicine provides an intriguing pool of potential modulators of this process—these remedies may help prevent fibrosis or resolve existing fibrosis in a healthy manner, and may be able to break down pathologic cirrhotic tissue in some more-advanced cases. An overview of the process of liver fibrosis is provided in Figure 1. Many of the pathways highlighted in this figure are known to be problems in all sorts of other fibrotic conditions.

The reversibility of fibrosis has been proven, without doubt, to be possible, for example, in large trials of interferon treatment of patients who had hepatitis with cirrhosis.[1] Examples from human studies of herbal medicine indicating reversal of existing fibrosis are provided throughout this review. However, because it is always best to prevent a pathogenic process from occurring in the first place, emphasis will be given to research on herbs that can prevent pathologic fibrosis.

There are many more studies of Chinese herbs for fibrotic conditions, compared to studies of European or American herbs, partly because of the epidemic nature of hepatitis B–induced cirrhosis in Asia and the greater support for herbal medicine in general in Asian cultures. This does not necessarily mean that Western antifibrotic herbs are ineffective or unavailable but, rather, means that there has been less focus on them.

Licorice or Gan Cao and Sho-Saiko-To

Whether it is the European/Central Asian species *Glycyrrhiza glabra* (licorice) or the East Asian species *G. uralensis* (gan cao), this is arguably one of the most widespread and important herbal medicines used around the globe. "Licorice" is the term used to refer to both species throughout this review. Among licorice's many actions and benefits are prevention and reversal of fibrosis in many organs, notably the kidneys and liver.

In one long-term open clinical trial of intravenous glycyrrhizin (usually 2 mg per day), the key triterpenoid saponin in licorice combined with glycine, the risk of patients with hepatitis C developing cirrhosis was significantly reduced, compared to untreated controls.[2] The duration of follow-up was 13 years in this trial. In a 12-week randomized trial followed by a 40-week open trial, 67% of patients with hepatitis C who had not improved after a course of interferon and ribavirin had stable or decreased liver fibrosis after 5 injections of glycyrrhizin per week.[3]

Other clinical findings have been published but the methods and results were not available in English for full assessment.[4] Further rigorous trials are warranted, but it appears that injectable glycyrrhizin with glycine may have a significant ability to prevent and treat chronic hepatitis C–induced liver fibrosis. Trials of oral, whole-plant extracts and trials concerning other clinical fibrotic diseases are also urgently needed.

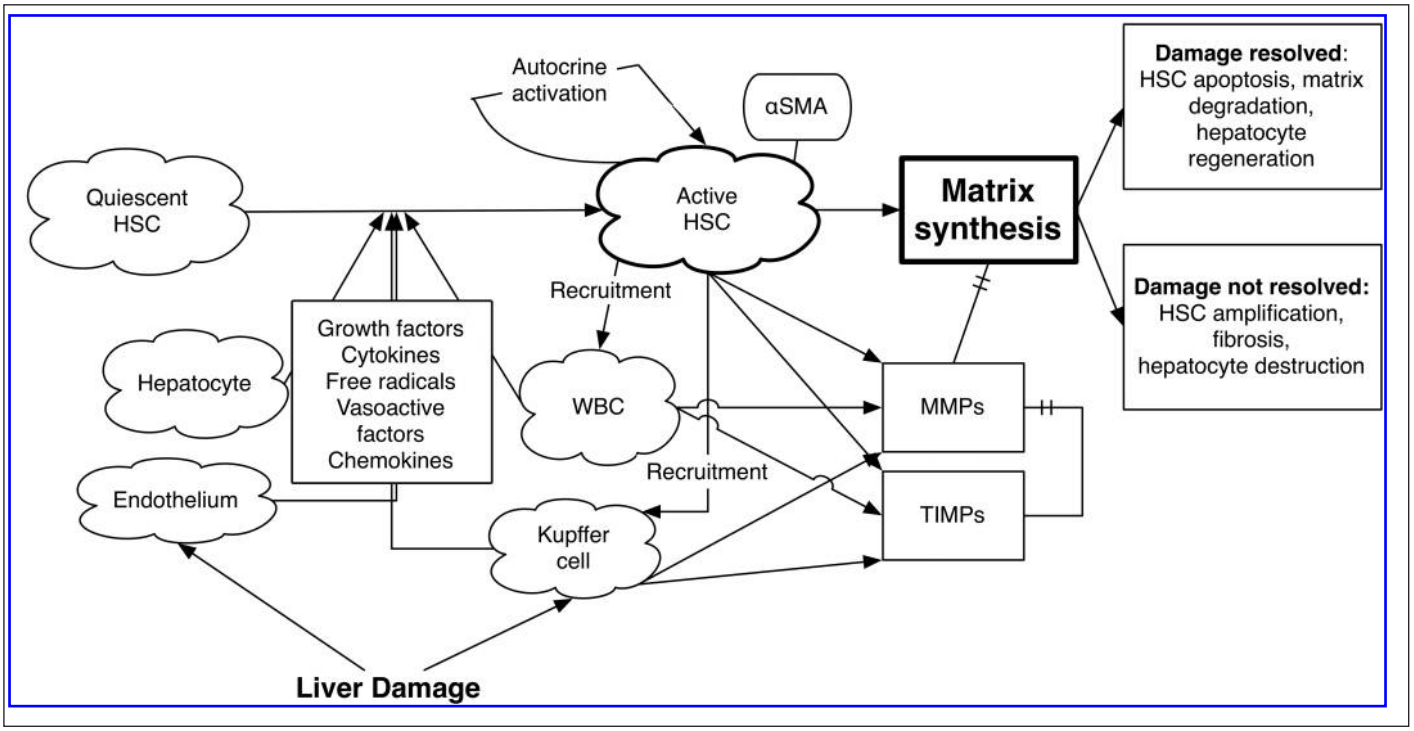


Figure 1. Overview of hepatic fibrosis. A complex network of cells and chemical mediators starts, maintains, and completes the cycle of fibrosis in the liver. HSCs are the prime cellular mediators of fibrosis there. Depending on the exact pathophysiologic process, the HSC-driven fibrosis process can have many outcomes. This diagram also illustrates many of the points where herbal medicines act to promote healthy fibrosis and avoid adverse outcomes. Any line with double lines crossing it indicates inhibition. αSMA, α-smooth muscle actin; HSC, hepatic stellate cell; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinases.

Numerous preclinical studies have evaluated the mechanisms by which licorice and its constituents influence fibrosis, mainly in the liver and kidneys. A glycyrrhizin-containing intravenous product (its other ingredients were not clear) inhibited liver cirrhosis in rats treated with carbon tetrachloride and ethanol.[5] There is evidence that glycyrrhizin interferes directly with transforming growth factor–β (TGFβ), a key driver of hepatic stellate cell–mediated fibrosis.[6]

Further analysis of this relationship showed that glycyrrhetinic acid, the aglycone of glycyrrhizin, inhibited Smad3 accumulation in hepatic stellate cell nuclei.[7] Smad3 is one of the primary transcription factors upregulated by TGFβ and is a key intermediary in the profibrotic effects of TGFβ. Glycyrrhizin also prevents hepatic stellate cell activation and promotes apoptosis by interfering with NFκB, a major profibrotic-signaling molecule.[8]

In a different rodent model in which concanavalin A by injection was used to induce hepatic fibrosis, intraperitoneal glycyrrhizin greatly reduced fibrosis, compared to a saline control.[9] This was found to be the result of inhibiting T-lymphocyte infiltration into the liver and promoting T-helper type 1 cytokine production in the cells that were present.

Constituents other than glycyrrhizin in licorice have also been shown to be antifibrotic, primarily in studies involving diabetes-induced glomerulosclerosis. Isoliquiritigenin, a flavonoid found in licorice root, inhibited renal fibrosis caused by high glucose in vitro, partly by blocking TGFβ.[10] Isoangustone A, a biprenylated isoflavone in licorice root, had similar effects in this model, but also interfered with NFκB.[11] Crude extracts of roasted licorice root, which have elevated levels of the saponin glycyrrhetic acid, were more effective than raw licorice root extracts higher in glycyrrhizin at preventing renal fibrosis caused by high glucose levels.[12] Again, TGFβ inhibition was important for this action. Clearly, more research is needed in this area, given these promising findings.

The typical dose of licorice tincture, glycerite or fluid extract for patients with any manner of fibrotic condition is 1 mL t.i.d. The typical single dose of licorice tea is 1 tsp of root simmered for 15 minutes in 1 cup of water; the total dose is 3 cups per day. Every patient's blood pressure should be measured after 2 weeks of taking licorice, and then monthly thereafter, and all patients should be encouraged to eat a high-potassium diet to avoid pseudohyperaldosteronism.

Various researchers have also looked at licorice and its constituents in combination with other herbs or herbal compounds as antifibrotics. Glycyrrhizin combined with matrine, an alkaloid from the root of *Sophora flavescens* (ku shen), was superior to either compound alone for limiting hepatic stellate cell proliferation and fibrosis in vitro.[13] Extracts of *Salvia miltiorrhiza* (dan shen, Chinese sage), *Ligusticum chuanxiong* (chuang xiong, Szechuan lovage), and licorice were as effective as silymarin and more effective than vehicle for preventing hepatic fibrosis in rats caused by dimethylnitrosamine injection.[14]

The Chinese herbal formula xiao chai hu tang, known as shosaiko-to in Japanese, contains licorice as well as several other herbs: *Bupleurum falcatum* (chai hu, thorowax), *Pinellia ternata* (ban xia), *Zingiber officinale* (ginger), *Zizyphus jujuba* (jujube), *Panax ginseng* (Asian ginseng) and *Scutellaria baicalensis* (Asian skullcap). Clinical trials have shown that this formula can prevent development of hepatocellular carcinoma in patients with

hepatic cirrhosis.[15] The formula's effects on fibrosis in humans are not well-characterized, although at least one study did not find a correlation between the formula's ability to lower serum alanine aminotransferase levels in patients with chronic hepatitis C and decreasing fibrosis seen on liver biopsies.[16] A typical dose of sho-saiko-to granules is 2.5 g t.i.d.

Sho-saiko-to decreased liver fibrosis in rats who were exposed to dimethylnitrosamine, compared with untreated controls.[17] A similar study showed that flavonoids in Asian skullcap were primarily responsible for the antifibrotic effects of sho-saiko-to.[18] A similar study found the antifibrotic effect was limited to animals with milder liver damage, and effects were at least partly caused by inhibition of TGFβ.[19]

In a rat model of Wilson's disease (copper overload–induced hepatitis and fibrosis), sho-saiko-to was as effective as lycopene and more effective than no treatment for reducing liver fibrosis and inflammation.[20] Two studies showed that sho-saiko-to was an effective hepatic antifibrotic in a bile-duct obstruction rat model.[21,22] The utility of sho-saiko-to in so many models is positive, but more-definitive human trials are warranted to determine if this truly is a valuable clinical antifibrotic.

Gotu Kola

Centella asiatica (gotu kola) is originally a South and Southeast Asian (now pantropical) herb of great utility, including use as an antifibrotic. The entire plant is used—leaf, stem, flower (if present), fruit (if present), and root. The herb grows in or next to water, so it is important that this plant be harvested from clean water only. This herb is readily cultivated, so there is little ecologic concern about it. Although the whole plant is used, an extract focusing on three triterpenoid saponins (sometimes referred to as a titrated extract) from gotu kola—asiaticoside, madecassoside, and madasiatic acid—is very commonly used in U.S. and European research.

One early clinical trial showed that a titrated extract reduced inflammatory infiltrates into the livers of patients who had hepatic cirrhosis.[23] A dimethylnitrosamine-induced hepatic fibrosis model in rats showed that a titrated extract of gotu kola

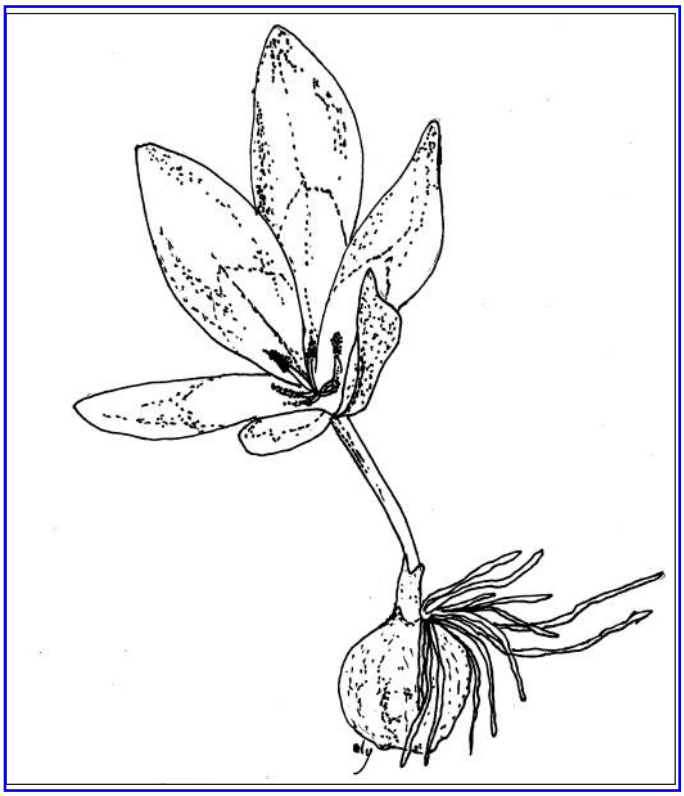
Some Fibrotic Conditions

- Biliary cirrhosis
- Hepatic cirrhosis
- Renal fibrosis (seen in many conditions)
- Scleroderma, localized (morphea)
- Scleroderma, systemic (progressive systemic sclerosis)
- Peyronie's disease
- Dupuytren's contracture
- Keloids
- Hypertrophic scars
- Spinal stenosis
- Oral submucous fibrosis
- Idiopathic pulmonary fibrosis

Table 1. In Vitro and In Vivo Antifibrotic Effects of *Salvia miltiorrhiza*

Model system	Extract	Effect	Reference
Bleomycin pulmonary fibrosis in rats	Unclear	Most effective for reducing fibrosis, compared to *Astragalus mongholicus* (astragalus), *Tripterygium wilfordii* (lei gong teng), hydrocortisone & azathioprine	Dai et al. 2004[a]
Dermal fibroblasts from patients with scleroderma	Tanshinone IIA	More effective than danshensu or lithospermic acid for decreasing fibroblast proliferation & collagen synthesis	Lü et al. 2007[b]
Carbon tetrachloride liver fibrosis in rats	Standardized extract of *Salvia miltiorrhiza* (Chinese sage)	Induces apoptosis in hepatic stellate cells	Parajuli et al. 2013[c]
Dimethylnitrosamine liver fibrosis in mice	Unclear; combined with *Boswellia serrata* (frankincense) extract	Decreases liver fibrosis by inhibiting TGFβ; mostly the result of Chinese sage extract	Sferra et al. 2012[d]
Thioacetamide liver fibrosis in rats	Magnesium lithospermate B	Inhibited hepatic stellate cell collagen secretion & free-radical production	Paik et al. 2011[e]
Isoprenaline cardiac fibrosis in mice	Cryptotanshinone	Prevented fibrosis by upregulating MMP-2	Ma et al. 2012[f]
Chlamydia trachomatis ovary tube fibrosis in mice	Unclear; combined with azithromycin	Combination reduced tubal occlusion better than antibiotic alone	Chen et al. 2007[g]

[a]Dai LJ, Hou J, Cai HR. Experimental study on treatment of pulmonary fibrosis by Chinese drugs and integrative Chinese and Western medicine [in Chinese]. Zhongguo Zhong Xi Yi Jie He Za Zhi 2004;24:130–132; [b]Lü XY, Li M, Weng MW. Inhibition effects of constituents of Radix *Salviae miltiorrhizae* on proliferation and procollagen transcription of dermal fibroblasts in systemic sclerosis [in Chinese]. Zhonghua Yi Xue Za Zhi 2007;87:2426–2428; [c]Parajuli DR, Park EJ, Che XH, et al. PF2401-SF, standardized fraction of *Salvia miltiorrhiza*, induces apoptosis of activated hepatic stellate cells in vitro and in vivo. Molecules 2013;18:2122–2134; [d]Sferra R, Vetuschi A, Catitti V, et al. *Boswellia serrata* and *Salvia miltiorrhiza* extracts reduce DMN-induced hepatic fibrosis in mice by TGF-beta1 downregulation. Eur Rev Med Pharmacol Sci 2012;16:1484–498; [e]Paik YH, Yoon YJ, Lee HC, et al. Antifibrotic effects of magnesium lithospermate B on hepatic stellate cells and thioacetamide-induced cirrhotic rats. Exp Mol Med 2011;43:341–349; [f]Ma S, Yang D, Wang K, et al. Cryptotanshinone attenuates isoprenaline-induced cardiac fibrosis in mice associated with upregulation and activation of matrix metalloproteinase-2. Mol Med Report 2012;6:145–150; [g]Chen MK, Chen ZX, Han JD, Liao QM. Effects of *Salvia miltiorrhiza* on *Chlamydia trachomatis* mice of salpingitis [in Chinese]. Zhongguo Zhong Yao Za Zhi 2007;32:523–525.
TGFβ, transforming growth factor—β; MMP-2, matrix metalloproteinase–2.



Colchicum autumnale (autumn crocus). Drawing © 2013 by Eric Yarnell, ND, RH (AHG).

could greatly reduce induction of fibrosis.[24] Three open trials or case series have reported that oral and topical extracts of gotu kola of various types are helpful for treating localized and systemic progressive sclerosis or scleroderma.[25–27]

Two other preliminary clinical trials found that crude extracts of gotu kola prevented formation of postsurgical adhesions and reduced postsurgical scarring.[28,29] One open trial found that topical titrated extract of gotu kola prevented postburn and postsurgical hypertrophic scars.[30] Interestingly, gotu kola is an excellent vulnerary based on many clinical trials, and it appears that, by promoting healthy wound healing, this herb prevents abnormal scar production in the process.[31]

In one of the most recent of these trials, 170 patients with diabetes with surgery-related chronic foot ulcers were given either gotu kola extract standardized to 100 mg asiaticoside t.id. or placebo.[32] The trial duration was 21 days. Wound healing was superior in the gotu kola group, compared to the placebo group, with limitation of scar formation. This is one of the only trials using oral gotu kola; most others have used topical applications.

Several in-vitro studies have evaluated the mechanisms by which gotu kola prevents hypertrophic scars. In one, madecassoside prevented migration of overactive fibroblasts inside of scars, which was associated with reduced overactivity.[33] Effects on many molecular pathways—such as phosphorylation of cofilin and diminution of F-actin filaments—were shown to account for this effect. Another study showed that asiaticoside suppressed collagen synthesis in scars, at least in part, by blocking TGFβ.[34]

Gotu kola is an extremely safe treatment that is highly recommended for patients with fibrotic conditions. It can be slow to act, so giving it plenty of time (several months for full resolution is not unusual), particularly in chronic, stubborn conditions, is important. The typical dose of glycerite or tincture of fresh plant is 3–5 mL t.i.d. The typical dose of capsules of crude herb is 1–2 g t.i.d. The typical single dose of tea is 1 tbsp of herb/cup, infused for 15 minutes in hot water; and the total dose is 3 cups per day. Standardized extracts can also be used and should be dosed as indicated on the labels of the extracts.

Gotu kola is an extremely safe treatment that is highly recommended for patients with fibrotic conditions.

Milk Thistle and Silymarin

Silybum marianum (milk thistle) is native to Eurasia but is something of an invasive weed in other temperate areas, including North America. The complex, flavonolignan extract from the seeds, known as silymarin, has been widely studied as an antifibrotic, primarily for liver fibrosis and cirrhosis. Despite the strong association of silymarin with the liver, various lines of evidence suggest that this extract may be antifibrotic in other tissues, including the kidney and heart.[35,36]

A meta-analysis of trials of silymarin in combination with antiviral drugs in patients with chronic hepatitis B showed that the extract was significantly more antifibrotic than the drugs by themselves, as assessed by serum levels of TGFβ and other markers as well as by biopsy results.[37] In a year-long double-blinded, randomized trial of silymarin combined with phosphatidylcholine and vitamin E, the combination was more effective than placebo for improving liver histology and reducing liver fibrosis.[38] There were no serious adverse effects. This confirmed the results of a prior open clinical trial on the same product.[39]

Silymarin was not effective when taken for 1 year by patients with biliary cirrhosis, whose conditions were not responding to ursodeoxycholic acid.[40] The extract also was ineffective for halting progression of, or reducing death caused by, severe alcoholic cirrhosis in one clinical trial.[41] However, in patients with early stage alcoholic cirrhosis, mortality was reduced by silymarin compared to placebo according to one meta-analysis.[42]

The usual dose of silymarin is 140 mg t.i.d. It has been posited that some negative clinical trial results were caused by poor absorption of silymarin. Doses of up to 2.1 g of silymarin per day have been shown to overcome this problem to some extent.[43] Various extracts combined with phosphatidylcholine are avail-

able and show greater absorption either at doses of 360 mg q.d. or 120 mg b.i.d.[44] The usual dose of milk thistle seed powder is 1 tbsp b.i.d.–t.i.d. The usual dose of milk thistle tincture or fluid extract is 3–5 mL t.i.d. Despite many concerns, to date, no human clinical trial has clearly demonstrated a clinically relevant, harmful drug–silymarin interaction.[45]

Autumn Crocus and Colchicine

The Eurasian native *Colchicum autumnale*, known as autumn crocus or meadow saffron, contains the potent antifibrotic alkaloid colchicine in the plant's bulb. Interestingly, the plant's ovaries are underground, so it has extremely long (several inches at full maturity) styles stretching up to the aboveground flower. All parts of the plant and its alkaloid are violently poisonous in overdose. Because of their narrow therapeutic windows, they should only be applied in extreme cases or with very careful supervision and clear instructions to patients about the hazards. Colchicine's use for treating acute gout, pericarditis, or familial Mediterranean fever (various nonfibrotic diseases) is still accepted as effective, but this topic is beyond the scope of this article.

The exact mechanisms of action of colchicine or autumn crocus against fibrosis are not fully known. Colchicine interferes with β-tubulin and thus cytoskeleton assembly, which can result in widespread changes in cellular function. The alkaloid interferes with many inflammatory pathways. However, one small human trial in patients with idiopathic pulmonary fibrosis demonstrated that oral colchicine mainly seemed to act by decreasing collagen production and produced minimal to no anti-inflammatory activity.[46]

Unfortunately, isolated colchicine has produced disappointing effects on a range of fibrosing conditions, including hepatic cirrhosis, biliary cirrhosis, and Peyronie's disease.[47–49] It is unclear if the whole plant would be more effective, because it has simply not been studied in modern times. It is also unclear, because of a lack of information, if autumn crocus whole-plant extracts or colchicine combined with other therapies would be more effective.

One hint that this might be the case comes from a retrospective chart review of 14 patients with chronic hepatitis C who were treated with complex naturopathic protocols, including colchicine 1.2 mg q.d. (5 days per week); silymarin; ursodeoxycholic acid; antioxidant vitamins and minerals; and a mixture of *Avena sativa* (oats), *Linum usitatissimum* (flax), lecithin, milk thistle seed, *Prunus dulcis* (almond), *Helianthus annuus* (sunflower) seed, and *Triticum* spp. (wheat) germ for breakfast.[50] No patient's disease progressed; instead, patients reported feeling a better sense of wellness, and the average decline in serum alanine transaminase level was 35 U/L. Further research is needed to determine the synergistic effects of colchicine and autumn crocus with other therapies, and to confirm if they do actually improve the conditions of patients with fibrotic diseases.

The usual dose of autumn crocus bulb tincture is 2–5 gtt b.i.d. The usual dose of colchicine is 0.6–1.2 mg q.d. (although the higher end of this dose is often only given 5 days/week). Patients with severe hepatic or renal disease should be advised not to take these products or should be advised about significant dose reductions. At least quarterly, serum aminotransferases and complete blood count should be checked to spot any colchicine toxicity early.

Colchicine is metabolized by CYP3A4, as are many other drugs. Gastrointestinal absorption of colchicine is also decreased by the P-glycoprotein (P-gp) transmembrane efflux

Table 2. Selected Herbal Antifibrotics: Preclinical Evidence

Herb	Constituent/Extract	Results	Citation
Artemisia iwayomogi (haninjin)	Aqueous extract	Decreased liver fibrosis & damage	Wang et al. 2012[a]
Curcuma longa (turmeric)	Curcumin	Antifibrotic in oral myofibroblasts	Zhang et al. 2012[b]
Olea europaea (olive)	Oleuropein	Decreased liver fibrosis & damage	Domitrović et al. 2012[c]
Rheum palmatum (rhubarb)	Emodin; crude extract	In vitro antifibrotic	Hu et al. 2009[d]
Scutellaria baicalensis (Chinese skullcap)	Baicalein, baicalin; crude extract	In vitro antifibrotic	Hu et al. 2009[d]
Stephania tetrandra (stephania, han fang ji)	Crude extract	Induces HSC apoptosis, thus, reversing liver fibrosis	Chor et al. 2009[e]
Taraxacum officinale (dandelion)	Root tincture	Reverses liver fibrosis	Domitrović et al. 2010[f]
Zanthoxylum piperitum (Japanese prickly ash)	Trihydroxy-α-sanshool	In vitro collagen suppression	Hasegawa et al. 2009[g]

[a]Wang JH, Choi MK, Shin JW, et al. Antifibrotic effects of *Artemisia capillaris* and *Artemisia iwayomogi* in a carbon tetrachloride–induced chronic hepatic fibrosis animal model. J Ethnopharmacol 2012;140:179–185; [b]Zhang SS, Gong ZJ, Li WH, et al. Antifibrotic effect of curcumin in TGF-β 1–induced myofibroblasts from human oral mucosa. Asian Pac J Cancer Prev 2012;13:289–294. [c]Domitrović R, Jakovac H, Marchesi VV, et al. Preventive and therapeutic effects of oleuropein against carbon tetrachloride-induced liver damage in mice. Pharmacol Res 2012;65:451–464; [d]Hu Q, Noor M, Wong YF, et al. In vitro anti-fibrotic activities of herbal compounds and herbs. Nephrol Dial Transplant 2009;24:3033–3041; [e]Chor JS, Yu J, Chan KK, et al. *Stephania tetrandra* prevents and regresses liver fibrosis induced by carbon tetrachloride in rats. J Gastroenterol Hepatol 2009;24:853–859; [f]Domitrović R, Jakovac H, Romić Z, et al. Antifibrotic activity of *Taraxacum officinale* root in carbon tetrachloride–induced liver damage in mice. J Ethnopharmacol 2010;130:569–577; [g]Hasegawa M, Matsushita Y, Horikawa M, et al. A novel inhibitor of Smad-dependent transcriptional activation suppresses tissue fibrosis in mouse models of systemic sclerosis. Arthritis Rheum 2009;60:3465–3475.

HSC, hepatic stellate cell.

pump. Any drugs, herbs or foods that inhibit the P-gp pump or CYP3A4 can cause serious toxicity (in the case of P-gp and CYP3A4 inhibitors, such as grapefruit juice or itraconazole, which increase absorption) or interfere with efficacy (in the case of CYP3A4 inducers such as *Hypericum perforatum*'s [St. John's wort] constituent hyperforin). Colchicine is particularly contraindicated for use with statin drugs because of increased risk of toxicity of the alkaloid and the statins.[51]

Chinese Sage

Salvia miltiorrhiza (Chinese sage, dan shen) root is an important Traditional Chinese Medicine. The herb is widely cultivated, so its use presents no known ecologic risk. It is unknown if other species of the *Salvia* genus would have similar properties to Chinese sage, as, generally, the leaves of other species are used for fairly distinct purposes. Some of the constituents found in Chinese sage root include diterpenoids (tanshinones), caffeic-acid polymers (magnesium lithospermate B), and phenylpropanoids (danshensu).

In 97 patients with chronic hepatitis B, an injectable form of Chinese sage was compared to an injectable form of the Chinese herbal formula shengmai, which contains *Panax ginseng* (Asian ginseng), *Ophiopogon japonicus* (mai men dong), and *Schisandra chinensis* (wu wei zi) fruit.[52] Both treatments reduced symptoms, but the Chinese sage was more effective than the shengmai for actually decreasing liver fibrosis.

Chinese sage was more effective than shengmai for actually decreasing liver fibrosis.

In a randomized trial of 60 patients with oral submucous fibrosis, a precancerous condition associated with chronic abuse of areca nut or chili peppers, prednisolone alone was compared to prednisolone with Chinese sage.[53] After 3 months, patients with the most advanced fibrosis who were given the combination had better reversal of their fibrosis than those who were given prednisolone alone (there were no differences in the results of patients with moderate disease). Adverse effects were lessened in the combination group, compared to prednisolone-alone group.

In 2 patients with localized scleroderma, also known as morphea, application of topical asiaticoside from *C. asiatica* along with oral *S. miltiorrhiza* was effective for reducing lesions, compared to *S. miltiorrhiza* by itself.[54] While hardly definitive, this provides a hint that synergy between antifibrotic herbs might exist and may be quite important.

In preclinical research Chinese sage extracts have been shown to decrease or prevent fibrosis in multiple tissues in multiple models. See Table 1 for a summary of some of these studies.

Dang Gui Bu Xue Tang

The formula dang gui bu xue tang (*Astragalus mongholicus* [astragalus]/dong quai decoction) was first described in writing in 1247 AD (Jin Dynasty) in *Differentiation on Endogenous and Exogenous (Neiwaishang Bianhuo Lun),* an unpublished work by Dongyuan Li. The formula is historically more famous for its use in female reproductive conditions. It has been assessed as an antifibrotic in several preclinical studies.

In a rat model of renal fibrosis, administering a decoction of *Astragalus mongholicus* root and *Angelica sinensis* (dong quai) root, 3 mL per day for 12 weeks, produced an antifibrotic effect.[55] The effect was not a result of inhibition of the renin–angiotensin–aldosterone axis. Instead TGFβ1 and osteopontin were blocked. Osteopontin is a potent chemotactic agent for macrophages, and, accordingly, macrophage infiltration into the kidneys was decreased by these herbs. Fibrosis-producing intrinsic kidney fibroblasts, mesangial cells, and related cells were also inhibited by these herbs. All these effects were significant, compared to no treatment and were similarly effective, compared to enalapril.

A decoction of these same two herbs in a 5:1 ratio (astragalus to dong quai) was tested in a rabbit model of fibrosis induced by schistosomiasis.[56] This ratio was chosen and is used in many other studies as it produces the best results, compared to other ratios.[57] The dose was 50 g/kg of an ethanol-preserved aqueous extract. The extract significantly inhibited hepatic fibrosis, compared to untreated controls. The mechanism of action was not evaluated.

Many other herbs have been assessed in preclinical studies for being antifibrotic. Some of these are reviewed very briefly in Table 2.

Conclusion

Many antifibrotic herbs hold great promise for helping patients with a host of conditions characterized by excessive fibrosis. This article has attempted to highlight some of the herbs that have been best-studied and most-used historically to address fibrotic conditions. More work is needed to be certain of the efficacy of these herbs and their extracts, but, for the most part, they represent safe and novel approaches to consider for fibrotic diseases. ■

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