

Review Article

Hepatitis and Some Effective Herbs: A Review

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Abstract: Herbal medicines (plants, phytotherapy, botanicals) are now so popular that there has been a corresponding increase in interest in them from medical practitioners and researchers. However, for only 11 plant species were there clinical trials documented that meet current internationally accepted standards of proof of therapeutic effects and safety (ie as applied to the pharmaceutical industry). In this research we focused on the assessment of some herbal gadgets and hepatotoxic herbs which give some good reasons for therapy. Also in this research decided to show some overview to recent and modern studding. The short parts guided to drive in remedies into this area in some other parts of the world and consideration of this topic in the future.

Keywords: Hepatitis, Herbs, Hepatotoxic, clinical, future.

INTRODUCTION

Herbal medicines (plants, phytotherapy, botanicals) are now so popular that there has been a corresponding increase in interest in them from medical practitioners and researchers. A “Medline” search in March 2003 uncovered 127 articles published in the previous 2 years. Many of these articles document small, uncontrolled, exploratory studies on the effectiveness of particular substances for disorders for which they have been traditionally prescribed. In a recent comprehensive review of the scientific literature, many hundreds of herbal preparations with antiviral activity were identified. However, for only 11 plant species were there clinical trials documented that meet current internationally accepted standards of proof of therapeutic effects and safety (i.e. as applied to the pharmaceutical industry). Though most of the clinical trials located reported some benefits from use of antiviral herbal medicines, negative trials may not be published at all. The review authors concluded, that a need remains for larger, rigorously designed, randomized clinical trials to provide conclusive evidence of efficacy. No herbal remedy has yet been shown to be effective in curing hepatitis C infection. To date only Silymarin (from milk thistle, *Silybum marianum*) and CH100 have been shown to be potentially beneficial (reducing liver function test results – an indication of reduced liver inflammation) in people with HCV, but have to date shown no effects on

degree of fibrosis. It is unclear as yet whether silymarin might interfere with the effects of interferon or ribavirin.

Recently published opinions from medical reviewers concerning hepatitis and herbal (botanical) treatments

Numerous drugs have been investigated for their antifibrotic potential and botanicals constitute a significant fraction of them... Silymarin has so far failed to clearly show an antifibrotic effect in human studies, whereas animal experiments suggest that this mixture may be beneficial in patients which have not yet developed cirrhosis. Animal studies indicate an antifibrotic potential of Shosaikoto, a herbal combination frequently used in China, Iran and Japan for the treatment of chronic viral hepatitis, but mechanisms of action need to be further explored. Other botanicals include trans-resveratrol, a flavonoid extracted from grapevine, and Salvia miltiorrhiza which were shown to interfere with the process of hepatic stellate cell activation. Herbal combinations, such as compound 861 and LIV.52 were advocated as antifibrotics or hepatoprotectives, but studies in humans have either been of questionable

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design or resulted in cessation of the trial due to adverse outcomes.

In Germany, where clinical investigation of botanicals seems to be well established, gastroenterologists recently stated:

“Effective symptomatic treatment of constipation, irritable bowel and inflammatory bowel disease has been demonstrated with plant-derived preparations... On the other hand phytotherapeutic preparations can not be recommended at present for the treatment of cirrhosis or chronic viral hepatitis based on the available data.

From the Iran:

“Many herbal remedies are potentially hepatotoxic, and only milk thistle can be used safely in patients who have chronic liver disease. Weight reduction and exercise can improve liver function in patients with fatty liver”

Now, a lot of researches is going to be developed in this country quickly.

And a Cochrane Review concluded:

There is no firm evidence of efficacy of any medicinal herbs for HCV infection. Medicinal herbs for HCV infection should not be used outside randomised clinical trials.

Plants and herbal remedies proven or suspected to be toxic to the liver

Safety Issues around Herbal Medicines

Hospital liver units are seeing increasing numbers of cases of liver injury that could be due to herbal and traditional medicines and some hepatologists now regard this issue as a “growing problem”. A few herbs have been the subject of controlled clinical trials, and some have been shown to be effective in managing specific disorders, eg St Johns Wort for treatment of depression. However, no pharmacologically active substances are totally without side effects.

Herbal preparations are often marketed to the public with the help of “testimonials” from people who have felt better after taking the preparation. Testimonials ie uncontrolled Individual case reports, do not constitute strong enough evidence of therapeutic effect. This is particularly so in view of the variability of the natural history of HCV, with some patients clearing the virus without treatment and others remaining well while still carrying the virus. In addition, the placebo effect will naturally account for up to a third of patients reporting feeling better.

The Therapeutic Goods Administration is a Commonwealth Government body.

The TGA also maintains a “List” of other products such as herbal remedies. “Listing” is a fairly recent development. “Listing” with TGA is designed to ensure the quality of the product (ie its freedom from contaminants) rather than signifying that it has a particular therapeutic effect, ie evidence of therapeutic effect is not a pre-requisite for “listing”.

Not all suppliers of herbal products have them listed with TGA. This means there is still the potential for variability in the quality and strength of products and for contamination with other substances eg heavy metals or microbes.

The TGA Adverse Drug Reactions Unit receives reports of suspected adverse reactions to prescription medicines, vaccines, and over-the-counter (OTC) medicines and complementary medicines. This has been in place for many years in respect to pharmaceuticals and doctors have been aware of their obligations to report adverse events. This has not generally been the case for herbal therapists, so it is possible that adverse reactions to herbal products may have been under-reported.

Interactions between herbal preparations and “western” pharmaceuticals have been documented. Health care workers should be aware of herbal preparations that their clients may be using, and seek out information on any potential interactions with other drugs the client is using. The TGA has a searchable website where this information is readily available.

Traditional Medicine in China

Many people try Traditional Chinese Medicine (TCM) which typically includes multi-ingredient prescriptions with proportions of herbs individualised to each client by the prescriber. In the absence of standardised clinical trial data, it is impossible to assess the real efficacy of TCM. Further research is needed to clarify the therapeutic effects of herbal treatments and establish safe usage levels. This is particularly so because many members of the public erroneously equate ‘natural’ with ‘harmless’. Traditional Chinese medicines (TCM) are popular and widely used in Western countries by both Asian and non-Asian consumers. As more people are using TCM products, there are increased reports on adverse reactions. In a review of adverse reactions associated with TCM, authors identified many and diverse causes for adverse events associated with TCM. They include variability in active/toxic ingredients due to growing conditions, use of inherently toxic herbs, overdose of herbs, drug-herb interactions especially with pharmaceuticals that have narrow therapeutic index, coexisting diseases, and idiosyncratic reactions like allergy, hepatitis and anaphylaxis. Other issues identified were manufacturing and quality problems such as adulteration, misidentification, substitution of one herb with another, variability in the amount of active ingredients, lack of

accurately identifying labels, improper processing and preparation, and contamination.

Hepatotoxic Herbs

A number of herbs are hepatotoxic (ie cause liver damage). Even some that may be beneficial in very small quantities can be harmful in larger quantities. For example, a study of *Acanthopanax senticosus* (a herb used in TCM) showed that while a small dose helped to protect rats livers from damage by carbontetrachloride (CCl4) poisoning, larger doses would induce hepatotoxicity. Great care must be exercised when embarking on any herbal treatment for any condition, particularly for people with chronic

(ongoing) hepatitis B or C. The following table identifies some herbs which have been shown to cause hepatotoxicity, based on a search of current scientific literature.

The following table lists plants and herbal remedies implicated in hepatotoxicity.

Note – The following are listed alphabetically by botanical name. Common names are included and will direct you to botanical name. If you are viewing this as a *Word* document, and you want to find a name quickly, we suggest you search for it using the ‘Edit, then find’ option.

Name(s)	Notes	Reference
Aconitum carmichaeli (chuanwu) Aconitum kusnezoffi (caowu)	A component of some Chinese Herbal Medicines. Causes aconitine poisoning.	<i>Chan TY et al. Poisoning by Chinese Herbal Medicines in Hong Kong: a hospital study Vet-Hum-Toxicol.1994Dec;36(6):546-7</i>
Aflatoxins – contaminant of plant materials grown/stored in humid areas.	Food contaminant and potent hepatocarcinogen (liver cancer-causing agent). Occurs as a mycotoxin from growth of <i>Aspergillus flavus</i> mould on stored nuts and other foods.	Henry SH et al. Policy forum: Public Health. Reducing Liver Cancer-Global control of Aflatoxin. <i>Science. 286(5449):2453-4 1999 Dec 24</i>
Amanita	A mushroom type fungus sometimes mistaken for ordinary mushroom. Fulminant hepatic failure documented.	<i>Stickel F. Egerer G. Seitz HK. Hepatotoxicity of botanicals [Review] [112 refs] Public Health Nutrition. 3(2):113-24, 2000 Jun.</i>
Atractylis gummifera (African remedy)	Toxicity of this plant is well known in Mediterranean countries. It causes diffuse hepatic necrosis.	<i>Larrey, D. Hepatotoxicity of herbal remedies. Journal of Hepatology 1997; 26 (Suppl.1):47-51</i>
Axadirachza indica (margosa oil)	Possibly be implicated in causing symptoms of Reye’s Syndrome and steatosis	<i>Journal of Hepatology 1997; 26 (Suppl.1):47-51</i> <i>Farrell GC, Weltman M. Drug Induced Liver Disease. In: Gitnick(Ed) Current Hepatology, vol 16. Chicago; Mosby-Yearbook Medical publishers, 1996; 143-208</i>
Bajiaolian	Contains a toxin called podophyllotoxin which caused abnormal LFTs	<i>Kao WF. Hung DZ. Tsai WJ. Lin KP. Deng JF. Podophyllotoxin intoxication: toxic effect of Bajiaolian in herbal therapeutics. Human & Experimental Toxicology. 11(6):480-7, 1992 Nov.</i>
Berberis vulgaris	Hepatotoxicity suspected but not conclusively proven	<i>Larrey, D. Hepatotoxicity of herbal remedies. Journal of Hepatology 1997; 26 (Suppl.1):47-51</i>
Black cohosh (Actaea racemosa, syn. Cimicifuga racemosa)	Implicated in a case of fulminant hepatic failure requiring liver transplant Black cohosh is a North American plant promoted as a remedy for menopausal symptoms	<u>Whiting PW. Clouston A. Kerlin P.</u> Title Black cohosh and other herbal remedies associated with acute hepatitis. [Review] [30 refs] <i>Medical Journal of Australia. 177(8):440-3, 2002 Oct 21</i>
Callilepis laureola	Cases of fatal liver failure have been reported following ingestion.	<i>Larrey, D. Hepatotoxicity of herbal remedies. Journal of Hepatology 1997; 26 (Suppl.1):47-51</i>
Carrot juice – beta carotene	Ingestion of large amounts of carrot juice has been associated with increased risk of	<i>Leo MA. Lieber CS. Alcohol, vitamin A, and beta-carotene: adverse interactions, including</i>

	lung cancer and hepatic damage.	<i>hepatotoxicity and carcinogenicity. American Journal of Clinical Nutrition. 69(6):1071-85, 1999 Jun.</i>
Cassia augustifolia (Senna)	Commonly used and generally considered a safe laxative, implicated in one reported case of hepatotoxicity in a patient using high doses	<i>Larrey, D. Hepatotoxicity of herbal remedies. Journal of Hepatology 1997; 26 (Suppl.1):47-51</i>
Chelidonium majus (Greater Celandine)	Chelidonium majus is a constituent of some "liver tonics" and traditional herbal preparations It can cause hepatitis and hepatic fibrosis.	<i>Benninger J. Schneider HT. Schuppan D. Kirchner T. Hahn EG. Acute hepatitis induced by greater celandine (Chelidonium majus). Gastroenterology. 117(5):1234-7, 1999 Nov.and other reports</i>
Chaparral – see Larrea		
Chinese Herbal Medicine (TCM) – unspecified ingredients	Occasional toxicity reported; agent(s) not yet identified eg 11 cases of liver damage reported 1991-93 associated with Chinese herbal medicine for skin disease. Identification of toxic components in TCM is rendered difficult by the fact that they are often adulterated with substitute herbs or contaminated with heavy metals.	<i>Journal of Hepatology 1997; 26 (Suppl.1):47-51</i>
Comfrey – see Symphytum		
Crotalaria	Contains hepatotoxic pyrrolizidine alkaloids.	<i>Larrey, D. Hepatotoxicity of herbal remedies. Journal of Hepatology 1997; 26 (Suppl.1):47-51</i>
Dai-saiko-to (Da-Chai-Huang-Tan),	Paradoxically used for liver disease. It causes acute and possibly chronic hepatitis	<i>Kamiyama T. Nouchi T. Kojima S. Murata N. Ikeda T. Sato C. Autoimmune hepatitis triggered by administration of an herbal medicine. [Review] [11 refs] American Journal of Gastroenterology. 92(4):703-4, 1997 Apr.</i>
Dictamnus dasycarpus	Component of Traditional Chinese Medicine implicated in 6 cases of hepatotoxicity, including 2 fatalities	<i>McRae CA. Agarwal K. Mutimer D. Bassendine MF. Hepatitis associated with Chinese herbs. [Review] [28 refs] European Journal of Gastroenterology & Hepatology. 14(5):559-62, 2002 May</i>
Echinacea	Prolonged use (more than 8 weeks) implicated in hepatotoxicity. Should not be used in conjunction with anabolicsteroids,amiodorone, methotrexate or ketoconazole.	<i>Miller LG. Herbal medicinals: selected clinical considerations focussing on known or potential drug-herb interactions. Arch. Intern. Med. 1998 Nov 9; 158 (20): 2200-11</i>
Ephedra sinica (Ma huang)	Chinese herbal supplement promoted for body building – suspected of causing hepatitis and a range of other symptoms	<i>Wettach GE. Falvey SG. A mysterious blood pressure increase in a drilling Naval reservist. Military Medicine. 167(6):521-3, 2002 Jun.</i>
Germander	See Teucrium	
Glycyrrhizin – found in chinese herbal medicine skin tonics	Causes vanishing bile duct syndrome	<i>Farrell GC, Weltman M. Drug Induced Liver Disease. In: Gitnick(Ed) Current Hepatolofy, vol 16. Chicago; Mosby-Yearbook Medical publishers, 1996; 143-208</i>
Goji		
Hedeoma pulegioides,	Hepatotoxicity suspected but not conclusively proven	<i>Larrey, D. Hepatotoxicity of herbal remedies. Journal of Hepatology 1997; 26 (Suppl.1):47-51</i>
Heliotropium lasocarpium	Contains hepatotoxic pyrrolizidine alkaloids	<i>Larrey, D. Hepatotoxicity of herbal remedies. Journal of Hepatology 1997; 26 (Suppl.1):47-51</i>
Jin Bu Huan	See Lycopodium	

Kava (Piper methysticum)	Kava is a psychoactive drink used extensively in the South Pacific area. It has been implicated in hepatotoxicity in susceptible individuals.	<ol style="list-style-type: none"> 1. Heiligenstein and Guenther 1998 2. Spillane et al 1997 3. Strahl et al. Necrotising hepatitis after taking herbal remedies. <i>Dtsch-Med-Wochenshr.</i> 1998 Nov 20; 123 (47):1410-4
Kombucha (Kambucha) tea	Abnormal liver function tests reported	Larrey, D. Hepatotoxicity of herbal remedies. <i>Journal of Hepatology</i> 1997; 26 (Suppl.1):47-51
Larrea tridentata (Chapparal, creosote bush, grease wood)	Causes hepatic necrosis and chronic hepatitis. One documented case of liver failure in a 60 year old woman requiring liver transplantation. 18 case reports of hepatotoxicity	<ol style="list-style-type: none"> 1. Lee AU, Farrell GC. Drug Induced Liver Disease. <i>Curr.Opin. Gastroenterol.</i> 1997; 13: 199-205 Larrey, D. Hepatotoxicity of herbal remedies. <i>Journal of Hepatology</i> 1997; 26 (Suppl.1):47-51 2. Gordon DW et al. Chaparral ingestion. The broadening spectrum of liver injury caused by herbal medication. <i>JAMA.</i> 1995 Feb 8; 273(6): 489-90 3. Sheik NM et al. Chaparral associated hepatotoxicity. <i>Arch. Intern, Med.</i> 157(8): 913-9, 1997 Apr 28
Lycopodium serratum (Jin Bu Huan)	Uses for sedation/analgesia. The active ingredient has structural similarity to hepatotoxic pyrrolizadine alkaloids. Can cause acute/chronic hepatitis, fibrosis, and steatosis. Implicated in 11 documented cases of hepatotoxicity	<p>Picciotti A, Campo N, Brizzolara R et al. Chronic hepatitis induced by Jin Bu Huan. <i>J Hepatol.</i> 1998;28:165-7.</p> <p>McRae CA, Agarwal K, Mutimer D, Bassendine MF. Hepatitis associated with Chinese herbs. [Review] [28 refs] [Journal Article. Review. Review of Reported Cases] <i>European Journal of Gastroenterology & Hepatology.</i> 14(5):559-62, 2002 M</p>
Ma huang, see Ephedra		
Margosa oil – see Axadirachza		
Mentha pulegium	Hepatotoxicity suspected but not conclusively proven	Larrey, D. Hepatotoxicity of herbal remedies. <i>Journal of Hepatology</i> 1997; 26 (Suppl.1):47-51
Mistletoe – see Viscum		
Noni Juice		
Pennyroyal	Pennyroyal was identified as the toxic agent responsible for Hepatic and neurologic injury in two infants given home brewed mint teas to treat colic. Pennyroyal has traditionally been used as an abortive agent despite known hepatotoxic effects.	<p>Larrey, D. Hepatotoxicity of herbal remedies. <i>Journal of Hepatology</i> 1997; 26 (Suppl.1):47-51</p> <p>Bakerink JA, Gospe SM Jr, Dimand RJ, Eldridge MW. Multiple organ failure after ingestion of pennyroyal oil from herbal tea in two infants. <i>Pediatrics.</i> 98(5):944-7, 1996 Nov.</p> <p>Anderson IB, Mullen WH, Meeker JE, Khojasteh-Bakht SC, Oishi S, Nelson SD, Blanc PD. Pennyroyal toxicity: measurement of toxic metabolite levels in two cases and review of the literature [see comments]. [Review] [46 refs] <i>Annals of Internal Medicine.</i> 124(8):726-34, 1996 Apr 15.</p>
Petasites hybridus (butterbur)	Butterbur contains potentially hepatotoxic and carcinogenic pyrrolizidine alkaloids. However a modern extraction method	Kalin P. [The common butterbur (<i>Petasites hybridus</i>)--portrait of a medicinal herb]. [Review] [29 refs] [German] [Journal Article.

	<p>minimises the quantity of these in extracts of butterbur being used for research of efficacy of this herb for migraine and tension headaches.</p> <p>Authors of the review cited identify four cases of reversible cholestatic hepatitis that they believe to have been associated with long-term administration of butterbur (incidence of 1:175.000).</p>	<p><i>Review. Review, Tutorial] Forschende Komplementarmedizin und Klassische Naturheilkunde. 10 Suppl 1:41-4, 2003 A</i></p>
Polygonum multiflora (Shou-Wu-Pian)	<p>Cholestatic hepatitis reported in woman taking this Chinese herbal medicine in the belief it acts against greying of the hair</p>	<p><i>Park GJ. Mann SP. Ngu MC. Acute hepatitis induced by Shou-Wu-Pian, a herbal product derived from Polygonum multiflorum. Journal of Gastroenterology & Hepatology. 16(1):115-7, 2001 Jan</i></p>
Sassafras albidum (Sassafras)	<p>Suspected to be hepatotoxic – more data required to prove</p>	<p><i>Larrey, D. Hepatotoxicity of herbal remedies. Journal of Hepatology 1997; 26 (Suppl.1):47-51</i></p>
Scutellaria – see Sho- saiki-to	<p>Scutellaria is a component of Sho-Saiko-To</p>	
Serenoa (Saw palmetto)	<p>An anti-androgenic compound used to treat prostate disorders, there is one report of it having possibly caused cholestatic hepatitis.</p>	<p>Chitturi S, Farrell G, Herbal Hepatotoxicity; an expanding but poorly defined problem. <i>J Gastro & Hepat. (2000) 15,1093-1099</i></p>
Shou-Wu-Pian	<p>See Polygonum multiflora</p>	
Sho-saiko-to TJ-9 Syo-saiko-to	<p>Sho-Saiko-To is a herbal remedy comprising a mixture of 7 herbs, widely prescribed in China and Japan.</p> <p>A small in vitro study suggested that this preparation could be beneficial in preventing disease progression in hepatitis C. However there is also literature suggesting it may have hepatotoxic effects.</p> <p>One study reported 4 patients with hepatic necrosis following taking sho-saiko-to with a latent period of 1-3 months before symptoms became apparent.</p>	<p>Farrel GC. Drug Induced Liver Disease. Edinburgh: Churchill-Livingstone, 1994 513-18</p> <p><i>Yamashiki M. Nishimura A. Huang XX. Nobori T. Sakaguchi S. Suzuki H. Effects of the Japanese herbal medicine "Sho-saiko-to" (TJ-9) on interleukin-12 production in patients with HCV-positive liver cirrhosis. Developmental Immunology. 7(1):17-22, 1999</i></p> <p><i>Itoh S. Marutani K. Nishijima T. Matsuo S. Itabashi M. Liver injuries induced by herbal medicine, syo-saiko-to (xiao-chai-hu-tang). Digestive Diseases & Sciences. 40(8):1845-8, 1995 Aug.</i></p>
Senecio	<p>Contains hepatotoxic pyrrolizidine alkaloids. Causes hepatic veno-occlusive disease (Budd-Chiari syndrome)</p>	<p><i>Larrey, D. Hepatotoxicity of herbal remedies. Journal of Hepatology 1997; 26 (Suppl.1):47-51</i></p> <p><i>2. Selzer G and Parker RGF. Senecio poisoning exhibiting as Chiari's Syndrome. Am J Path 1951. 27: 885-907</i></p>
Skullcap – see Scutellaria		
Symphytum officinale (Comfrey) and Symphytum uplandicum (Russian Comfrey)	<p>Contains hepatotoxic pyrrolizidine alkaloids. Causes hepatic veno-occlusive disease. Has been banned from sale in some countries, but can still be grown domestically.</p>	<p><i>Larrey, D. Hepatotoxicity of herbal remedies. Journal of Hepatology 1997; 26 (Suppl.1):47-51</i></p> <p><i>2. Weston CFM. Et al. Veno-occlusive disease of the liver secondary to ingestion of comfrey. BMJ. 1987:295: 183</i></p> <p><i>Yeong ML et al. Hepatoc veno-occlusive disease associated with comfrey ingestion. J Gastro & Hepatol. (1990) 5, 211-214</i></p>
Teucrium chamaedrys L (Germander)	<p>More than 30 cases of liver injury were reported and investigated in France following use of Germander as an adjuvant</p>	<p><i>Larrey, D. Hepatotoxicity of herbal remedies. Journal of Hepatology 1997; 26 (Suppl.1):47-51</i></p>

	to weight control. Sale now banned in France. Dose dependent toxicity was then reproduced experimentally in mice. Causes hepatic necrosis, fibrosis, cirrhosis.	<i>Laliberte L and Villeneuve JP Hepatitis after the use of germander., a herbal remedy. CMAJ 1996 Jun1; 154 (11): 1689-92</i>
Teucrium polium	Suspected as the cause of liver failure in one case.	<i>Mattei A. Rucay P. Samuel D. Feray C. Reynes M. Bismuth H. Liver transplantation for severe acute liver failure after herbal medicine (Teucrium polium) administration [letter]. Journal of Hepatology. 22(5):597, 1995 May.</i>
Teucrium capitatum	A case report in which other causes were excluded suggested that T capitatum consumed as part of a herb tea induced acute icteric hepatocellular necrosis which was reversed when the herb tea was withdrawn.	<i>Dourakis SP. Papanikolaou IS. Tzemanakis EN. Hadziyannis SJ. Acute hepatitis associated with herb (Teucrium capitatum L.) administration. [Case Reports. Journal Article] European Journal of Gastroenterology & Hepatology. 14(6):693-5, 2002 Jun</i>
Valeriana officinalis (Valerian)	Isolated reports of hepatotoxicity following consumption of herbal remedies containing it	<i>Larrey, D. Hepatotoxicity of herbal remedies. Journal of Hepatology 1997; 26 (Suppl.1):47-51</i>
Viscum, Viscum album, (Mistletoe)	Hepatotoxicity suspected but not proven conclusively	<i>Larrey, D. Hepatotoxicity of herbal remedies. Journal of Hepatology 1997; 26 (Suppl.1):47-51</i>

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