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REVIEW ARTICLE

Review of plants with hepatoprotective activity evaluated in Mexico

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Abstract Liver diseases represent a major health problem around the world. In Mexico these are the 5th leading cause of death in the economically active population. In Mexico, it is estimated that about 60% of the population uses some medicine from plants to treat their illnesses. The purpose of this work was to search for medicinal plants in Mexico that have been evaluated for their hepatoprotective effect in different models. In this review we found only 13 plants evaluated for hepatoprotective activity: *Amole tuber*, *Cochlospermum vitifolium*, *Heterotheca inuloides*, *Hibiscus sabdariffa*, *Leucophyllum frutescens*, *Prostechea michuacana*, *Psidium Guajava*, *Rosmarinus officinalis*, *Verbena Carolin*, *Centaurea americana*, *Juglans mollis*, *Krameria ramossisima* and *Turnera diffusa*. This study describes the studies conducted in Mexico for each of them and the international literature reports of pharmacological and phytochemical studies.

Introduction

Liver diseases represent a major health problem around the world, receiving special attention from health professionals and scientists. They affect about 10% of the world's population and include fatty liver disease, chronic hepatitis, alcoholic steatosis, fibrosis, cirrhosis and hepatocellular carcinoma.[1] In Mexico, such diseases represent the 5th leading cause of death in the economically active population.[2] Studies on liver disease tendencies and epidemiologic projections in

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Mexico predict an increase in the next 2 years, as a result of the low rate of treatment response which these conditions present.[3-5]

Medicinal plants constitute a viable alternative for the development of phytopharmaceuticals with hepatoprotective activity in order to solve some of these health problems. Civilizations in countries like China, India and Egypt have employed this source for thousands of years. In Mexico, the use of herbal remedies is an ancestral practice, but even though the information about the plant's attributed properties is transmitted from generation to generation, for the most part there is no research supporting the information.[6] It has been established that just 20% of the plants used in traditional medicine have been biologically and scientifically assessed.[7] In Mexico, close to 60% of the population uses some type of remedy based on plants to treat their diseases.[8] The use of medicinal plants has been employed by socially and economically disfavored groups, in addition to the part of the population with cultural and economic resources who generate an increase in the consumption of medical plants.[9]

The purpose of this work was to search for medicinal plants in Mexico that have been evaluated for their hepatoprotective effect in different models.

Materials and methods

In this review, bibliographic research was identified through editorial books, articles and indexed as well as non-indexed journals. The indexed articles were found by searching through PubMed, Medigraphic, Imbiomed, Scifinder and ScienceDirect, using the following terms: plant extract, hepatoprotective plants, hepatoprotective activity in Mexico.

In addition, non-indexed sources were identified through health websites and International Health agency reports. We only considered plants with a detailed description of hepatoprotective activity.

Results

In the present review we found just 13 plants that had been evaluated for hepatoprotective activity in Mexico, mainly through *in vitro* and *in vivo* studies in experimental hepatic damage models. We did not find any report of plant hepatoprotective activity in controlled clinical studies in Mexico. Here is a description of each of the plants which have reported hepatoprotective activity by Mexican research groups in natural products, as well as some reports from international literature of pharmacological and phytochemical studies described for every one of them.

Amole tuber

Agave sp, belongs to the Ruscaceae family, commonly known as Amole. This is an endemic plant of America, distributed in the southeast of the United States and the south of Florida up to the tropical area of South America, including the Caribbean.[10-12] *Amole tuber* (Agave sp.) has been referred to for the treatment of diseases with a bacterial etiology, and against diseases associated with oxidative stress (*i.e.* cancer, diabetes and hypertension).[13-16] On the other hand, antifibrogenic,[17] anti-inflammatory,[18] antihypertensive,[19] inmunomodulator,[20] antiparasitic[21] and antifungal[22] activities have been reported (Table 1). Even our search only found one report on the evaluation of the hepatoprotective effect of *Amole tuber*. In this study, antifibrogenic activity was proven on experimental cirrhosis induced by carbon tetrachloride (CCl_4) in rats, where a reduction in aspartate aminotransferase (AST) in serum was reported, as well as minor centrilobular fibrosis, perihepatocytic fibrosis, and minor collagen in the group of rats taking an aqueous extract of *Amole tuber* compared to the CCl_4-induced cirrhosis group.[17]

Centaurea americana

A species of Centaurea, belonging to the Asteraceae family, commonly known as American Starthistle or American Basketflower is an annual plant, native from the north of Mexico, Coahuila, Nuevo León, Arizona, Arkansas, Kansas, Louisiana, Missouri, New Mexico, Oklahoma and Texas and cultivated in several countries. It has been referred to by "healers" in the treatment of liver diseases.[23] The characterization of this plant has generated the isolation of sesquiterpene, lignans and phytoecdysteroids.[24,25]

There are 4 studies of interest on this species.[23-26] In one of them, antioxidant activity and toxicity were evaluated through the fatality of *Artemia salina* from the hexane, dichloromethane and methanol extract of *Centaurea americana* seeds. Here, the antioxidant activity of methanol extract was good compared to the controls. Regarding toxicity, none of the extract was toxic; however, isolated lignans from total extracts showed considerable toxicity.[24] Antioxidant activity of *C. americana* has also been evaluated through the capture of free radicals 1-1-diphenyl and 1-2-picrylhydrazyl through thin-layer chromatography and spectrophotometry, displaying strong antioxidant activity.[23] The anti-tumor activity of lignans obtained from *C. americana* was evaluated in another study, which showed that at a 50 mg/6 dosage arctigenin was effective in inhibiting the development of colorectal cancer C38 in mice C57Bl/6.[26] Lastly, hepatoprotective activity from the flower and stem/leaf methanol extract of *C. Americana* was evaluated in human hepatoma cells (Huh7) posterior to the damage induced by CCl_4. This damage was measured through cellular viability, AST release and oxidative stress after malondialdehyde (MDA) generation. This study shows that pre-treatment of the Huh7 cells with methanol extract at a 10, 100 and 1000 µg/ml concentration protected the cells from damage induced by the toxic agent.[27]

Cochlospermum vitifolium

A species of *Cochlospermum*, from the Bixaceae family commonly known as "Silk cotton tree". It is a deciduous dry forest tree in Mexico; its bark decoction is used in traditional medicine for the treatment of hypertension, type 2 diabetes mellitus, hepatitis and related diseases.[28] The traditional drink is prepared using 10 g of dried plant in 1 L of water. In this plant's characterization, flavones and flavonoids were isolated, compounds to which biological activity is attributed.[29] There are several pharmacological studies related to this species evaluating the plant's vascular relaxing activity.[30,31]

Table 1 Plants with hepatoprotective activity evaluated in Mexico.

Plant	Effects described	References
Amole tuber		10*, 11*, 12
	Antibacterial, Anti-fibrogenic and hepatoprotective	17*
	Anti-inflammatory	18
	Anti-hypertensive	19
	Immunomodulatory	20
	Antiparasitic	21*
	Antifungal	22*
Centaurea americana	Hepatoprotective	23*, 27*
Cochlospermum vitifolium	Anti-hypertensive and hepatoprotective	28*
Heterotheca inuloides	Treatment of skin damage	36*
	Antimicrobial	37
	Antioxidant	38
	Anti-inflammatory and Analgesic	40
	Hepatoprotective	42*
Hibiscus sabdariffa	Anti-hyperlipidemic	45
	Anti-hypertensive	46
	Diuretic	47
	Hepatoprotective	50*
Juglans mollis	Anti-diarrheic	51
	Anti-inflammatory	52
	Anti-oxidant	53
	Antifungal	55
	Hepatoprotective	27*
Krameria ramosissima	Anti-gastric and intestinal cancer	57
	Not hepatoprotective	27*
Leucophyllum frutescens	Treatment of liver and gallbladder disorders	58*
	Hepatoprotective	60*
Prostechea michuacana	Anti-inflammatory, diuretic, antidiabetic	61*
	Hepatoprotective	63*
Psidium guajava		65*
	Treatment of gastrointestinal and anti-inflammatory disorders	
	Cures jaundice	65*, 66*
Rosmarinus officinalis	Antiseptic	76
	Anti-rheumatic	77
	Anti-inflammatory	78*, 84
	Hepatoprotective	78*, 79
	Antidiabetic	80, 81
	Anti-ulcerogenic	82
	Anti-depressive	83
	Antioxidant	80
Turnera diffusa	Treatment of sexual impotence	87, 89
	Treatment of depression	
	Treatment of inadequate coitus	90
	Antioxidant	
	Hepatoprotective	91
Verbena carolina		23*, 92
		27*
	Treatment of bile disorders	93*, 95*
	Hepatoprotective	

* Studies performed in Mexico.

In another study, we are able to see that the angiotensin II receptor is inhibited by more than 50% by this plant's extract.[32] A 3rd report showed anti-inflammatory activity through cyclooxygenase inhibition.[33] Finally, in a different study antidiabetic, anti-hypertensive and hepatoprotective effects of this plant were reported. Hexane, dichloromethane and methanol extracts were evaluated, and the hexane extract displayed significant relaxation independent of the endothelium in the rat's aorta and the methanol extract produced a relaxation dependent on the endothelium in tissue. In addition, the hexane extract (120 mg/kg dose) showed a significant reduction of glucose levels in rats. On the other hand, the methanol extract (100 mg/kg dose) was also administered in the biliary duct to determine hepatoprotective activity, showing a statistically significant decrease in serum AST and alkaline phosphatase levels.[34]

Heterotheca inuloides

A species of *Heterotheca* which belongs to the Asteraceae family, commonly known as Acáhuatl, Acahual and Arnica. It grows wild in both cold and warm regions of Mexico.[35] Dry flowers of *Heterotheca inuloides* have been used for a long time as a popular medicine in a topical treatment for contusions, bruises and postoperative thrombophlebitis. More frequently this plant has been used externally for skin damage.[36] Moreover, it has been recognized as an antioxidant, for its inhibitor activity against lipid peroxidation and oxidative hemolysis, and for its antimicrobial, anti-inflammatory, analgesic and cytotoxic effects against several solid tumor cellular lines.[37-40]

This plant's cetonic and methanolic extracts had been previously characterized, and it is known to have several constituents such as polyacetylene, cadinales, triterpenes, sterols, sesquiterpenes, flavonoids and glycosylated flavonoids.[41] Its hepatoprotective activity was shown in a toxicity model by CCl_4 in rats. This research proved that animal pretreatment with a methanolic extract of *Heterotheca inuloides* (100 mg/kg of weight) attenuated the increase in AST serum activity, alanine aminotransferase (ALT) and histological changes observed in the damage induced by CCl_4. Additionally, it was linked to the prevention of stress markers (oxidative, 4-hydroxynonenal and 3-nitrotyrosine) as well as activity decrease in several antioxidant enzymes including superoxide dismutase, catalase and glutathione peroxidase.[42]

Hibiscus sabdariffa

A species of *Hibiscus,* belonging to the Malvaceae family, commonly known as Rosella, Red Tea, Southern Tea or "Rosa de Jamaica". This plant is distributed throughout Latin America, southern Asia, India and areas of central Africa.[43] Several parts of the plant, such as leaves, flowers and chalice, have been used as infusions for medicinal purposes.[44] It is commonly used for anti-hyperlipidemic[45] and anti-hypertensive effects;[46] another use for it is as a diuretic.[47] The compounds linked to beneficial effects are polyphenols, anthocyanins, flavonoids and proanthocyanidins.[48,49] This plant's aqueous extract is reported to attenuate hepatic steatosis in obese mice. In a study, treatment with an aqueous extract of *Hibiscus sabdariffa* (administered *ad libitum*) reduced the accumulation of fatty tissue, decreased weight and normalized the glycemic index. It also reduced blood lipid levels in mice compared to the group of obese mice that did not receive treatment. Moreover, the treatment attenuated hepatic steatosis, through the sterol regulatory element binding protein 1C and peroxisome proliferator-activated receptor, interleukin-1 messenger RNA blockade, tumor necrosis factor-alpha, lipid peroxidation and catalase messenger RNA level increment.[50]

Juglans mollis

A species of *Juglans* belonging to the Juglandaceae family, commonly known as Walnut, Walnut Tree or Gallic Nut. The leaves contain hyperoside and other glycosides and flavonoids. Chlorogenic acid, caffeic acid, ferulic acid, sinapic acid, gallic acid, ellagic acid, syringic acid, vanillic acid, catechin, epicatechin, myricetin and juglone have been described in its characterization. Walnut liquor is reportedly used to prevent low-density lipoprotein (LDL) oxidation and total cholesterol and LDL cholesterol reduction without change in high-density lipoprotein (HDL) cholesterol, which reduces cardiovascular risk.

The leaves are used as an antidiarrheal and as a topical healer; it has also been reported that they possess antifungal properties and anti-inflammatory and anti-oxidant properties in mice.[51-55]

In a study, the plant's antioxidant activity was evaluated through different assays such as capture of free radical l-l-dipheny l-2-picrylhydrazyl via thin-layer chromatography and spectrophotometry, xanthine oxidase inhibitory activity and total content of phenols. This study showed that *Juglans mollis* extract displayed a strong antioxidant activity, through all the evaluated assays.

In a different study, the hepatoprotective effect of the plant was evaluated in an *in vitro* model after induced damage by CCl_4. Pre-treatment with methanol extract of the leaf and bark protected human hepatoma cells (Huh7) from damage induced by the toxic agent, because it showed decreased AST activity released at the culture medium and lipid peroxidation in comparison to the damage group.[27]

Krameria ramosissima

A species of *Krameria*, belonging to the Krameriaceae family, it is known as Calderona.[56] It grows in the northeast of Mexico and the root is used for medical purposes. There are reports of its use in stomach and intestinal cancer treatment and it is used as a tea in case of diarrhea and moderate fever. Nornelignans 2-(4-hydroxyphenyl)-5- (E) -propenyl-benzofuran and 2-(2,4,6- trimethoxyphenyl)-5-(E) -propenyl-benzofuran have been isolated from this plant for the medicinal uses previously described.[57] The methanol extract effect of this plant was evaluated in a human hepatoma cell model (Huh7). In this study it was proved that the methanol extract was toxic at the evaluated concentrations (10,100 and 1,000 µg/mL) measured by cellular viability, AST le-vels and MDA production, thus discarding its hepatoprotective activity.[27]

Leucophyllum frutescens

A species of *Leucophyllum*, belonging to the Scrophulariaceae family. It is known as Texas Ranger, Texas Sage, Cenizo, Texas Silverleaf or Ash-bush. This plant was originally grown in Texas, New Mexico and the north of Mexico. Now it is widely grown in Florida and the south of Asia, where it blooms magnificently in tropical weather. It is used to relieve fever, cough, asthma and rheumatic pains. It is also used for gallbladder and hepatic disorders.[58] A phytochemical study revealed the *presence of phytotoxic furofuran lignans called* diayangambin, epiyangambin, diasesartemin, and epiasantin.[59] The hepatoprotective effect has been shown in Wistar albino mice in intoxication with CCl_4. This study reported that methanol extracts of *Leucophyllum frutescens* (100 and 200 mg/kg) administered orally at 2 ml/kg weight twice a week for 50 days, decreased hepatic enzyme levels (AST and ALT) induced by CCl_4 damage. In addition, the study showed maintenance of the hepatocytes membrane's structural integrity after the methanol extract administration at both evaluated doses.[60]

Prosthechea michuacana

A species of *Prosthechea* belonging to the *Orquidaceae* family, commonly known as "Water Sweet Potato" or "Water Lily". It is an orchid species and is used as an anti-inflammatory, diuretic, antidiabetic agent and for hepatic disorders.[61] Characterization studies of this species' constituents have been reported to contain 8-C-(6-deoxy-D-glucopyranoside) apigenin, 1-(3'- hydroxy-5'-methoxyphenyl)-2-(4"-hydroxy-5"-methoxy phenyl) ethanol and malic acid 2-(4-hydroxybenzyl).[62] Hepatoprotective activity was evaluated in a model of hepatic damage induced by CCl_4 and paracetamol in rats. This study showed that pre-treatment in rats with methanol extracts at 200, 400 and 600 mg/kg significantly reduced ALT, AST and alkaline phosphatase levels as well as total bilirubin in a dose-dependent manner in animals treated with paracetamol and tetrachloride.[63]

Psidium guajava

A plant of the genus *Psidium*, which belongs to the Myrtaceae family and is commonly known as guayabo, guayaba or guayabero. This plant is considered native to Mexico, extending through South America, Europe, Africa and Asia. It grows in all the tropical and sub-tropical areas of the world, adapting to the differing climatic conditions but preferring dry climates.[64] Its principal traditional use in Mexico is the treatment of gastrointestinal, respiratory, and inflammatory disorders.[65] The root, bark, leaves and unripe fruits are commonly used for the treatment of gastroenteritis, diarrhea and dysentery. Its leaves are applied to wounds and ulcers; they are also used for rheumatic pain, and chewed they relieve pain in the molars. The decoction in water of the leaves of this plant is used to cure jaundice and reduce glucose levels in diabetics.[65,66]

The antioxidant activity of *Psidium guajava* is due primarily to the presence of caryophyllene oxide, caryophyllene and tannins. It has likewise been characterized to contain constituents such as flavonoids, triterpenes, saponins and monounsaturated fatty acids, which have been reported with multiple biological activites.[67]

The hepatoprotective effect of extracts from this plant has been evaluated in multiple models. In one investigation, the aqueous extract of the leaves of *Psidium guajava* was studied in the hepatic damage induced by CCl_4, monitored by serum transaminases (AST and ALT), alkaline phosphatase, serum cholesterol, total lipids and histopathology. The extract of the leaves at a dose of 500 mg/kg produced significant hepatoprotection.[68] In another report, the hepatoprotective activity of this plant was evaluated in the experimental acute hepatic damage induced by CCl_4 and paracetamol in Balb/c mice. In this study it was reported that the methanolic extracts of the leaves of this plant, at a dose of 250 mg/kg and 500 mg/kg, significantly reduced the serum levels of AST, ALT, alkaline phosphatase and total bilirubin. The high dose of the methanolic extract prevented weight increase of the liver when it was compared with the damage control, while the low dose was inefficient except for the damage induced by paracetamol. The histological evaluation of the hepatic tissues showed a reduction in swelling, degenerative changes and steatosis.[69]

The pre-treatment with Asian acid (a terpenoid extracted from *Psidium guajava* leaves and fruit) at doses of 25 mg/kg, 50 mg/kg or 100 mg/kg significantly hindered the serum AST and ALT increase induced by lipopolysaccharide and D-galactosamine; it also showed a decrease in nuclear condensation, proliferation and lesser lipid deposits.[70]

Rosmarinus officinalis

A plant of the genus *Rosmarinus*, which belongs to the Lamiaceae family, commonly known as Blessed, White Rosemary, Common Rosemary, Coronary Rosemary, Garden Rosemary, Fine Rosemary, Female Rosemary, Male Rosemary, Peregrine Rosemary, Royal Rosemary, Rose of the Sea, Rosmarino or Rumani. It is native to Europe, but is widespread in Mexico and Brazil. This plant is known for its use in foods, but it is acquiring interest for its pharmacological properties. Two groups of compounds are primarily responsible for the biological activity of this plant, the volatile fraction and phenolic constituents like rosmarinic acid[71] and fractions of flavonoids and diterpenes, which are structural derivatives of carnosic acid.[72-75] It has been utilized for medicinal purposes and is known for its antiseptic,[76] anti-rheumatic, anti-inflammatory[77] and anti-spasmodic properties. The extracts obtained from this plant have shown hepatoprotective,[78,79] antidiabetic,[80,81] anti-ulcerogenic,[82] antidepressive,[83] antibacterial, antioxidant[80] and anti-inflammatory effects.[84] Its hepatoprotective effect was evaluated through the induction of acute hepatic damage induced by CCl_4 in rats. In this study the pre-treatment with 200 mg/Kg of *Rosmarinus officinalis* prevented hepatic lipid peroxidation and increase in bilirubin and ALT levels; it also prevented the recovery of the consumption of hepatic glycogen and the increase in glutathione-S-transferase plasma. The histological evaluation showed a partial prevention of inflammation, necrosis and vacuolization induced by CCl_4.[78]

Turnera diffusa

A plant of the genus *Turnera*, which belongs to the Turneraceae family, commonly known as Damiana, Shepherd's Herb,

Venison's Herb and Pastorcita.[85,86] It is a plant native to America and Africa; it has a geographical distribution that extends from Texas to South America; it is wild in the majority of our country, although it is originally from Baja California. It is used in infusions, decoctions, dyes and tobacco. The best form of utilizing this plant has been described as employing 4 g of fresh plant into 120 ml of water and drinking it as a tea after meals. This plant is traditionally utilized for the treatment of various illnesses, including sexual impotency, neurasthenia, diabetes mellitus, urinary retention, malaria, diarrhea, peptic ulcers and alcoholism.[87-89] The natives of the north of Mexico have used it to combat sexual impotency. The Mexican Pharmacopoeia recognizes that the plant acts as a general tonic and diuretic. The British Herbal Pharmacopoeia lists the specific indication of Damiana for anxiety associated with impotence and it includes other indications such as depression, nervous dyspepsia, atonic constipation and inadequate coitus. Phytochemical reports on this plant report the presence of glycosides, phenolic glycosides, flavonoids, carbohydrates and volatile oils.[90,91] A study showed that arbutin, a major constituent, is a powerful antioxidant compound.[92] Different trials have evaluated the antioxidant activity of this plant including the capture of free radicals 1-1-diphenyl-2-picrylhydrazyl by thin-layer chromatography and spectrophotometry, inhibition of xanthine oxidase activity and total phenols content. Throughout all these trials it was shown that the *Turnera diffusa* extract is a strong antioxidant.[23]

The hepatoprotection of this plant was evaluated in an *in vitro* model through the induction of damage by CCl_4. In this study, it was shown that pre-treatment with the methanolic extract of the surface of this plant protected that cells from harm induced by CCl_4 at doses of 10 and 100 µg/ml, measured by the AST released at the culture medium, MDA and the maintenance of cellular viability.[27]

Verbena carolina

A plant of the genus *Verbena*, which belongs to the Verbenaceae family, commonly known as the Saint Joseph's Herb, Saint John's Herb, Verbena, Dog's Verbena, Fieldspike, Black Pennyroyal, Large Wormwood and Chinese Chili.[93,94] Widely distributed in the Valley of Mexico with the exception of the northeast where its occurrence becomes sporadic. It grows from Arizona to El Salvador and Honduras. In traditional Mexican medicine, it is utilized in the treatment of hepatic illnesses, diarrhea, renal problems and dysentery as a purgative. It is also employed in molar pain, headaches, malaria, rheumatism and pyrogenic states; the flowers are infused by impact and the foliage is used as an infusion for bile disorders.[93] The effectiveness of this species was evaluated in a study in the model of hepatic damage induced by CCl_4 in mice. The CCl_4 produced a rise in gamma-glutamyl transpeptidase serum activity, ALT, alkaline phosphatase, MDA and total bilirubin concentration, but it decreased hepatic glycogen. Verbena partially avoided the effect of the CCl_4 in the activity of gamma-glutamyl transpeptidase, but it did not diminish the effect on the other evaluated markers.[95]

Discussion

According to the present revision, there are few plants evaluated for hepatoprotective activity in Mexico. In most studies, hepatoprotective activity has been evaluated in *in vitro* and *in vivo* experimental models with different inductors of hepatic damage.

No controlled clinical studies on the use of extracts of natural products in patients with some type of hepatopathy were found; this contrasts with the many international studies reporting the use of different standard or compound isolated herbal extracts for the treatment of hepatic diseases.

The goal of most plant extract studies is the development of phytopharmaceuticals with hepatoprotective activity for the treatment of diseases such as fatty liver, hepatic diseases caused by alcohol and as a factor in viral hepatitis. In this context, isolation and characterization of the main compounds of the active extract are crucial steps in the development of a new phytopharmaceutical. This is essential to guarantee the active principles within, as well as for the phytopharmaceutical's quality control issues. Even though there are other non-scientific reports describing hepatoprotective activity of several plants in Mexico, there are no *in vitro* or *in vivo* studies which support this activity; thus the importance of the present review where only 13 studies were found among national and international scientific literature of plants with hepatoprotective activity evaluated in Mexico. The need to conduct experimental and clinically-controlled studies for the use of plant extracts with hepatoprotective activity is highlighted as a result of their high consumption among the Mexican population and the secondary effects that may occur, which may cause hepatic damage.

Conflicts of interest

The authors have no conflicts of interest to declare.

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