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Mechanisms of Action of Herbal Cholagogues

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Abstract

Plant secondary metabolic compounds with the cholagogue mode of action are important therapeutic agents for the treatment of cholestasis and hepatobiliary disorders. Herbal cholagogues target different components of the complex bile production and secretion system, and exert their action via diverse routes, such as cholecystokinin-dependent and independent gallbladder contraction, up-regulation of the bile acid synthesis, stimulation of the bile salt export pump, multidrug resistance protein transporter system, and osmotic bile flow.

Herbal Cholagogues and Choleretics

The ancient science of herbal medicine was born many centuries ago and speaks Symptomatic, the language which is cast in magnificent Greek and imperial Latin. Symptomatic describes effects of herbal medicines on the human body at the organismal level, as experienced by a patient and observed by a physician. Numerous herbs have been used in traditional medicines against liver complaints and have been claimed to exert a beneficial action against hepatobiliary diseases and cholestasis, a condition in which the flow of bile from liver to the intestine is reduced or blocked.

Medicinal plants with the hepatobiliary mode of action remain essential therapeutic agents for the treatment of cholestasis. They are denoted as cholagogues (promoting the flow of bile from the liver and gall bladder into the intestines) and choleretics (increasing bile production). Cholagogic and choleretic properties of chamomile (*Chamomilla recutita*) [1], elecampain (*Inula helenium*), dandelion (*Taraxacum officinalis*), St. John's wort (*Hypericum perforatum*) [2], *Artemisia* sp [3, 4], yarrow (*Achillea millefolium*) [5], rosemary (*Rosmarinus officinalis*) [6], (*Chelidonium majus*) [7] and other medicinal plants have been confirmed in animal experiments and clinical studies. Many of these plants, that have been traditionally used to improve digestion and relieve cholestasis, are employed by contemporary European and Asian pharmacopeias.

Aromatic plants are important components in the liver and intestinal herbal formulas for the treatment of hepatobiliary and gastrointestinal disorders. Essential oils have been traditionally employed as carminatives due to their myorelaxant and spasmolytic action on the intestines, and also in the treatment of cholecystitis and cholelithiasis owing to their antispasmodic action on biliary ducts. Choleretic properties have been described for essential oils from peppermint (*Mentha piperita*) [8], *Rosaceae* species, *Anethum graveolens*, *Perovskia abrotanoids*, *Salvia rhytidea*, *Ziziphro afghanica* and *Origanum glaucum* [9]. Notably, some edible plants and spices, such as artichoke [10, 11], licorice [12], coriander, turmeric, red chilli and black pepper, cumin, and onion [13] also possess marked choleretic properties.

Bile Production and Enterohepatic Circulation

Modern biological science speaks the Biochemical and Physiological languages, which are by far more exact and subtle than Symptomatic. The physiological and molecular events involved in bile formation and recycling have been studied in detail in recent decades [14-16]. Bile acids are lipid-soluble compounds that are synthesized in the liver by hepatocytes from blood cholesterol, conjugated to water-soluble glycine or taurine moieties, and released into hepatic bile canaliculi through the bile salt export pump, BSEP. Formation of canalicular bile is driven by an osmotic water flow in response to active solute and ion transport. The efflux of bile components from hepatocytes is also mediated by the members of the multidrug resistance protein (MRP) family transporters. In particular, MRP2 mediates secretion of bilirubin and glucuronidated bile acids from hepatocytes into bile ducts. From the liver duct system, bile is collected in the gallbladder and released into the small intestine by the sphincter of Oddi that opens into the duodenum. In the intestine, bile acids serve as endogenous detergents and facilitate intestinal absorption of lipids, lypophilic nutrients and vitamins, and also act a natural laxative.

Most of the bile acids are recycled from the gastrointestinal tract to the liver by enterohepatic circulation and re-used for digestion multiple times. The process of recirculation begins with active reabsorption of bile acids from the intestine into ileal enterocytes by the sodium-dependent transporter, ASBT, followed by their release into hepatic portal circulation [16, 17]. Once in the bloodstream, bile acids are absorbed from the portal blood into the liver hepatocytes by NTCP and other membrane transporters, and released again into hepatic duct system.

The physiological mechanisms of food digestion involve regulation by cholecystokinin and other peptide hormones of the gastrointestinal system. Cholecystokinin is produced by the mucosal epithelium of the small intestine and duodenum, and released to the bloodstream in response to fat- and protein-rich food [18]. This hormone increases the production of pancreatic enzymes and hepatic bile, stimulates contraction of the gallbladder and relaxation of the sphincter of Oddi, resulting in the release of bile and pancreatic enzymes into the duodenal part of the small intestine. At the same time, cholecystokinin suppresses the feeling of hunger and inhibits gastric acid secretion and gastric emptying, in order to allow more time for intestinal digestion of lipids and proteins.

In addition to aiding in the digestion and absorption of lipids, bile acids serve as signaling molecules that regulate the metabolism

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of hepatocytes [17]. In hepatocytes, bile acids bind to the nuclear receptors FXR, PXR and VDR that activate major signaling cascades controlling hepatocyte metabolism and the detoxication of xenobiotics. FXR plays a central role in the regulation of bile acid synthesis and mediates feedback inhibition of bile production in hepatocytes by bile acids returning to the liver via enterohepatic circulation.

Cholestasis and the subsequent liver injury may develop owing to biliary diskinesia (the gallbladder and sphincter of Oddi motility disorders), a mechanical blockade of bile ducts by gallstones, or metabolic defects that affect formation or recycling of hepatic bile. Bile acids accumulating in the liver in cholestasis affect hepatic physiology and contribute to the development of hepatic disorders through activation of pro-inflammatory signaling pathways in hepatocytes and Kupffer cells. Malfunctioning of hepatic transporters may result in intracellular accumulation of bile acids that trigger apoptosis of hepatocytes through activation of the death receptor signaling cascades [19] and lead to parenchymal injury of the liver.

Choleretically Active Plant Compounds

Choleretic and cholagogic activity has been reported for a number of structurally diverse plant secondary metabolites (Table 1). How can choleretic and cholagogic properties of natural plant substances be translated into the languages of modern science? Although only a limited knowledge of the mechanisms of action exists for herbal cholagogues, a translation is available for selected plant compounds.

Cholecystokinin-dependent Choleresis

Plant oils have been used for centuries as potent natural cholagogues and laxatives. Effects of the oral and intraduodenal administration of olive, sunflower and corn oil were studied on healthy human subjects using real-time ultrasonography in the last years [31-33]. It was shown that choleretic action of plant oils is mediated via the release of cholecystokinin into the blood that stimulates gallbladder contraction and exocrine pancreatic secretion. Gallbladder contraction by plant oils was inhibited with cimetropium bromide, an anticholinergic agent, indicating the involvement of cholinergic hormonal response. Choleretic effects of plant oils strongly depends on the length of carbon chains of fatty acids in the oil triglycerides. Olive, sunflower and corn oils are composed of long-chain triglycerides (with chain length between 16 and 18 carbon atoms) that require the emulsification by bile for digestion by intestinal lipases into free fatty acids and monoglycerides, and for absorption into the gut wall. In the enterocytes of the gut wall, free fatty acids and monoglycerides are re-esterified into triglycerides and released from the gut into circulation via the lymphatic system. In contrast, more hydrophilic medium-chain triglycerides (with a chain length between 6 and 12 carbon atoms) do not require emulsification. They are rapidly hydrolyzed in the gut lumen, absorbed into enterocytes, and diffuse from the intestinal cells into the portal circulation. Unlike long-chain triglycerides, medium chain triglycerides do not cause release of cholecystokinin and pancreatic enzymes, and do not induce contraction of the gallbladder [33].

Some of the secondary metabolic plant compounds also trigger cholecystokinin release. For example, the stimulation of pancreatic secretion in rats by platycodin D, a choleretic saponin from the root of *Platycodon grandiflorum*, triggered the release of cholecystokinine from the duodenum into the bloodstream [34]. The effects of platycodin D were inhibited by loxiglumide, a cholecystokinine receptor antagonist, confirming its action through the receptor.

Cholecystokinin-independent Choleresis

Phytohemagglutinin from red kidney bean (*Phaseolus vulgaris*) employs a different and distinct mode of choleteric action. This stable protein resists enzymatic and bacterial degradation in the gastrointestinal tract. After oral administration, it survives the passage through the gastrointestinal tract and binds to complex glycans on the surface of parietal cells of the stomach, the brush border epithelium of the small intestine, and to the surface membrane of the colon. By this binding, phytohemagglutinin can mimic or inhibit binding of

Compound	Plant species	Reference
Menthol, menthone, isomenthone	*Mentha piperita*	[8]
Eugenol, acetyleugenol	*Syzygium aromaticum*	[9]
Borneol	*Dryobalanops aromatica*	[9]
Zygophillin, quinovic acid	*Zygophyllum coccineum*	[9]
Crocin, crocetin	*Gardenia florida*	[9]
Loganin	*Patrinia villosa*	[9]
Syringopicroside	*Syringa oblate*	[9]
Ferulic acid, caffeic acid	different species	[9]
Caffeine	*Coffea arabica*	[9]
Theophylline	*Camellia sinensis*	[9]
Glycyrrhizinic acid and derivatives	*Glycyrrhiza glabra*	[12]
Liquiritigenin	*Glycyrrhizae uralensis*	[20]
Xanthone glycosides and aglycones	*Gentianopsis barbata*	[21]
Chamiloflan	*Chamomilla recutita*	[22]
Cynarin, cynaropicrin	*Cynara scolumis*, *Saussurea amara*	[23]
Gingerol	*Zingiber officinale*	[24]
Dicaffeoylquinic acids	*Achillea millefolium*	[25]
N-demethyl ricinine	*Ricinus communis*	[26]
Silymarin, silibinin	*Silybum marianun*	[27]
Andrographolide	*Andrographis paniculata*	[28]
Protopine	*Fumaria officinalis*	[29]
Picroliv	*Picrorrhzia kurroa*	[30]
Platycodin D	*Platycodon grandiflorum*	[34]
Geniposide, genipin	*Gardenia fructus*, *G. jasminoids*	[37]
4-Hydroxyacetophenone	*Aster* and *Artemisia* species	[39]
Phloracetophenone	*Curcuma comosa*	[40]

Table 1: Plant secondary metabolic compounds with cholagogue and choleretic activity.

an endogenous lectin, producing local gastrointestinal and systemic effects. Unlike fatty acids, red kidney bean phytohemagglutinin does not increase cholecystokinin levels in the blood, but instead induces potent gallbladder contraction by activating an unidentified cholinergetic pathway [35].

Menthol, menthone and isomenthone from *Mentha piperita* possess choleretic properties and act as myorelaxant on smooth musculature of the gastrointestinal tract [8]. There is no clear understanding of the underlying mechanisms. However, the results of a recent study suggest that the choleretic activity of peppermint oil can be mediated at the molecular level though up-regulation of two genes: cholesterol-7α-hydrolase that is involved in bile acid synthesis, and FXR nuclear receptor that regulates production of bile acids [36].

BSEP- and MRP-dependent Choleresis

Cholestasis often results in systemic accumulation of biliary compounds and jaundice. This condition has been associated with impaired function of the bile export pump and multidrug resistance protein transporters, especially multi-specific organic anion transporter MRP2, which is localized to the hepatocellular plasma membrane and mediates the efflux of a variety of organic anions, including bilirubin, glucuronides, glutathione and bile acid conjugates. Diverse plant choleretics directly affect the hepatic bile secretion system. In recent years, several plant compounds have been identified that target and up-regulate BSEP and MRP2-mediated pathways.

Liquiritigenin, a flavonoid aglycone from licorice (*Glycyrrhizae uralensis*), has a marked choleretic activity. Upon administration in rats, liquiritigenin is rapidly metabolized into choleretically active glucuronide conjugates that induce increased secretion of bile [20]. Administration of liquiritigenin up-regulates expression of BSEP, MRP2 and other transporters, leading to an increase in bile flow rate and the excretion of bile acids, glytathione and bilirubin. At the same time, administration of liquiritigenin led to a significant induction of hepatic detoxication enzymes glucuronosyl-transferase, heme oxigenase, glytathione S-transferase and microsomal epoxide hydrolase, demonstrating that a systemic hepatocellular response to liquiritigenin was orchestrated at the gene expression level.

Gardenia fructus is used by Chinese and Japanese herbal medicines for the treatment of cholestasis and jaundice, a condition which is caused by hyperbilirubinemia. Geniposide, a major iridoid glycoside of *Gardenia fructus*, is converted in the intestine into biologically active metabolite, aglycone genipin. Administration of genipin to rats resulted in a significant increase of the MRP2 content in the bile canalicular areas of the liver [37, 38]. The increase in the MRP2 levels was accompanied with a two-fold rise in the bile flow and biliary excretion of bilirubin conjugates and glutathione. Notably, genipin did not affect BSEP levels and did not increase secretion of bile acids, suggesting that the choleretic activity is mediated via BSEP-independent pathway. The increased biliary secretion was not observed in mutant MRP2-deficient rats, confirming that genipin specifically targets the MRP2-mediated excretion pathway.

The MRP-dependent biliary secretion pathway is also affected by other choleretically active plant compounds. Using similar approaches and experimental animals which have a congenital defect in MRP2 transporter, independent research groups demonstrated that the choleretic action of 4-hydroxyacetophenone from *Aster* and *Artemisia* species [39] and phloracetophenone from *Curcuma comosa* [40] is also mediated via the MRP2 secretory pathway. Results of these and other studies [41, 42] suggest that the osmotic effects and excretion of the biliary electrolytes play important roles in the MRP2-dependent choleresis and may attenuate the cholestatic effects of hepatotoxins undergoing biotransformation in the liver and excretion via the MRP transporter system.

One of the best studied herbal cholagogues is silymarin from milk thistle *Silybum marianun*, which has been empirically used as a hepatic remedy for almost two thousand years, and remains being used as an officinal medicine for many types of acute and chronic liver diseases. Silymarin is a mixture of four isomeric flavonolignans: silibinin (main active component), isosilibinin, silydianin and silychristin [43]. After administration, silibinin is taken up from the bloodstream by hepatocytes and partially glucuronidated. Silibinin is a potent inhibitor of cAMP-phosphodiestrease, an enzyme which catalyzes degradation of cyclic AMP resulting in an increase in cellular cAMP levels, which mediate its biological effects [44]. It acts as a multifunctional hepatoprotective agent through evocation of cAMP-dependent cell signaling pathways, stimulation of synthesis and secretion of bile acids, and activation of biotransformation and detoxication of cholestatic compounds by hepatocytes.

Silymarin induces hepatic output of bile acids and bile acid-dependent choleresis, but does not affect bile acid-independent bile flow [27]. These effects are primarily due to the stimulation of bile acid synthesis and an increase in the endogenous pool of bile acids, and not to elevated reabsorption of bile acids from the intestine. Under hepatocellular cholestasis, silibinin reliefs inhibition of the bile acid synthetic and redirects synthesis towards more hydrophilic and less toxic bile acid species, thus alleviating the metabolic strain on hepatocytes. Silibinin also prevents failure of the bile salt export pump. This is achieved through the protection of the BSEP transport activity by blocking internalization and redistribution of BSEP, which may involve cAMP-induced increase in cytosolic calcium levels. [27, 43, 45].

Conclusion

The complex bile production and secretion system provides many opportunities for the therapeutic correction of cholestasis and hepatobiliary disorders, which are exploited by plant secondary metabolites and natural food components. Results of the recent studies demonstrate that plant secondary metabolites affect choleresis via different routes, such as cholecystokinin-dependent and independent gallbladder contraction, up-regulation of the bile acid synthesis, stimulation of the bile export pump, hepatic MRP transporter systems, and osmotic bile flow. Future elucidation of the molecular mechanisms of herbal cholagogues will advance our knowledge and provide scientific basis for the therapeutic use of the medicinal plants.

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This article was written in a personal capacity and does not represent the opinions of the US Food and Drug Administration, the US Department of Health and Human Services, or the US Federal Government.

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