Apart from their use to provide non-specific support for recuperation and repair, specific phytotherapeutic strategies include the following.

**Treatment of:**
- cholecystitis (biliary infection);
- minor or early cholelithiasis (biliary stones);
- conjugated hyperbilirubinaemia.

**Management of:**
- established cholelithiasis;
- chronic and moderate hepatobiliary diseases.

Because of the use of secondary plant products, particular caution is necessary in applying phytotherapy to:
- biliary carcinoma;
- blocked bile duct;
- acute and severe hepatobiliary diseases.

**BACKGROUND**

**Bile acids/salts and mechanisms of biliary flow**

Whereas cholesterol accounts for more than 90-95% of the sterols in bile, bile acids and their salts are the most important solutes; they are essential in the management of cholesterol levels and themselves help determine the extent of bile flow. Bile acids are synthesized from cholesterol in the liver. There are three groups. Primary bile acids, in humans mainly cholic and chenodeoxycholic acids and their salts, are produced directly. Secondary bile salts are created by the action of intestinal bacteria on primary bile salts with deoxycholate and lithocholate being formed from cholate and chenodeoxycholate, respectively. Tertiary bile salts are the result of modification of secondary bile salts by intestinal flora or hepatocytes; in humans these include the sulphate ester of lithocholate and ursodeoxycholate and the 7-beta-epimer of chenodeoxycholate.1

Bile flow rates and composition are subject to a wide variety of neural, endocrine and paracrine influences. One of the main stimulants of bile flow are bile acids themselves, either in their primary form or reabsorbed as secondary or tertiary forms in the enterohepatic circulation (see below). The chologenic effects of bile acids have led to their prescription in hepatobiliary disorders. One derivative, ursodeoxycholic acid, has been shown in controlled clinical studies to be a useful agent in the management of patients with primary biliary cirrhosis, autoimmune chronic active hepatitis2 and cystic fibrosis.3

**Cholestasis**

Infective conditions may lead to cholestasis or reduced bile flow. This has been attributed to the effects of lipopolysaccharide endotoxins.4 Chronic alcoholics may have hypotonic gallbladder, with increased speed of bile secretion and low biliary levels of cholic acid, cholesterol and bilirubin. Patterns of bile stagnation can occur with increasing severity of alcoholism, especially when associated with cirrhosis.5

In one study serum cholesterol/cholesterol proportions were determined in 79 patients with inflammatory bowel (colonic and ileal) diseases, such as ulcerative colitis and Crohn's disease, and 23 with irritable bowel syndrome as controls. The findings suggested that the increased cholesterol proportion in colonic inflammatory bowel diseases is determined mainly by impaired biliary elimination of this sterol, while in ileal disease the dominating change in sterol balance is activated cholesterol synthesis. Increased serum cholesterol is a novel finding in colonic inflammatory bowel diseases, apparently indicating the presence of subclinical cholestasis in a marked number (20-50%) of inflammatory bowel disease patients.6

Therapeutic stimulation of bile flow could thus be justified in the management and treatment of any of the above circumstances (see below).

It appears that a substantial amount of urate is also eliminated by the biliary route in humans. Gout and other urate-associated conditions linked to decreased renal urate excretion may therefore benefit from measures that increase biliary urate excretion.7

**Toxicity of bile acids**

Because it is known that high concentrations of bile acids are cytotoxic, it has been speculated that their raised presence in serum and tissues in hepatobiliary diseases contributes to the pathological progression of these disorders. Bile acids are a causative factor in chronic gastritis.8 Recent evidence suggests that oral administration of ursodeoxycholate, being a relatively non-toxic bile acid, can replace more hydrophobic hepatotoxic bile acids in the circulating pool and by doing so, ameliorate the harmful effects of the latter.9 Although one further clinical study suggests that beneficial effects are not universal,10 these data highlight the implications for health of the
development or retention of relatively toxic bile metabolites.

**Enterohepatic circulation**

An important aspect of bile acid function and toxicity is the constant reabsorption from the intestine into the portal circulation and back to the liver and biliary system – the enterohepatic circulation. Both primary and secondary bile acids are involved in this recycling. In modern medicine a high degree of recycling is assumed but it is likely that humans living a more primitive lifestyle with much higher levels of fibre intake had lower reabsorption rates. The implications of enterohepatic circulation are best understood with reference to the kinetics of drugs like the morphine alkaloids and digoxin which are largely eliminated from the body through the bile. Increased retention of bile in the enterohepatic circulation is known to increase the half-life of these and other drugs in the body. It is likely, therefore, that the level of bile products (with the formation of tertiary bile acids) and other, potentially toxic metabolites may increase unless the enterohepatic circulation is at as low a level as possible. In practice, this is most likely to follow a relatively fast intestinal transit time, associated with a high-fibre diet.

**Bile and cholesterol**

Although they are generally cholagogic, the presence of bile acids in the enterohepatic cycle acts to decrease the biliary secretion of cholesterol, presumably through a process of negative feedback, and this is likely to control excessive cholesterol secretion in gallstone conditions. As with other hepatic conditions, replacement therapy with bile acids like chenodeoxycholic and ursodeoxycholic acids is promoted as a treatment, leading even to dissolution of existing gallstones.11

Of wider significance is the finding that reduction in the absorption of bile acids from the gut, associated with, for example, diarrhoea, leads to an increase in cholesterol synthesis and cholesterol esterification rate by the liver.12,13

**Effects of bile acids in the intestinal tract**

Both primary and secondary bile acids have secretagogue effects on the intestinal mucosa, changing net fluid transport across the villi from absorption to secretion.14 There is also an atropine-inhibited (i.e. cholinergic) stimulation of intestinal contractions15 and an increased mucosal vasodilation (blood flow increasing by around 50%) which is not inhibited by atropine.16 Secondary bile acids in particular are thought to increase permeability at the zonulae occludentes which bind endothelial cells together at their luminal borders so that normal subepithelial hydrostatic pressure is raised sufficiently to reverse net sodium, chloride and water absorption to net secretion.17

Bile has sometimes been referred to as the body's own laxative or 'endolaxative'. Indeed, it is established that bile acids (especially secondary bile acids – see below) can be responsible for bowel looseness and their effects should be borne in mind in cases of unexplained chronic diarrhoea.18,19

Bile has a wider range of actions on the intestinal mucosa. Where there is clear reduction in bile levels, there is a reduction in thickness of the mucus blanket, reduced numbers of mucus-associated enterocytes (suggesting a reduced endothelial turnover rate) and lymphocytes and increased populations of bacterial organisms. The implication is that normal bile function is a vital part of the body's gut-related defences.20 It has also been demonstrated that bacterial endotoxin absorption is increased in the absence of bile salts from the intestine.21

**Bacterial action on bile acids – consequences and implications**

The generally positive functions of primary bile acids become rather more mixed in their effects once bacterial deconjugation and dehydroxylation occur. Secondary bile acids are produced at a very early age – the process is clearly under way even in month-old infants22 – and are an entirely normal range of metabolites. It is clear that most bacterial deconjugation occurs in the colon23 but in various less ideal circumstances invasive bacterial populations can lead to secondary bile product formation in the small intestine.

Secondary bile acids have a decidedly irritating effect on the intestinal wall. Exposure of the intestinal wall to deconjugated bile acids stimulates local inflammatory mechanisms, accompanied by the release of prostaglandin E2 and leukotriene C4. Such effects are particularly pronounced if there is already latent or active inflammatory disease of the intestinal wall, particularly in small intestinal Crohn’s disease.24 The irritant effect of secondary bile products is especially apparent if their quantities are increased due to stasis in the small intestine. Among a number of ultrastructural alterations to the intestinal mucosa, they increase the numbers of lysosomal vascular structures, fused microvilli and dilated endoplasmic reticulum, which among other implications leads to a reduced
absorption of solutes including glucose and other carbohydrates and, significantly, fluid absorption: diarrhea is thus possible. Secondary bile metabolites substantially increase the absorption rates of urea and oxalates from the gut.

There are more insidious potential effects too. Secondary bile acids and their metabolites increase colonic cell proliferation. The carcinogenic effect is clearly linked to changes in the nature of bacterial populations in the gut rather than to the nature of the bile acids or indeed other starting materials in the gut. However, there is also little doubt that decreased reabsorption of bile acids (for example, as seen with increasing old age) does increase the likelihood that carcinogenic and other pathogenic bile metabolites will be produced.

Dietary factors are known to affect the balance between intestinal flora and bile metabolism. For example, consumption of sugars was shown in nine volunteers on a crossover basis to significantly prolong transit time through the colon and significantly raise the faecal levels of both primary and secondary bile metabolites. On the other hand, the consumption of 16 g of wheat bran a day on a double-blind 6-month crossover basis by ulcerative colitis sufferers in remission was shown to decrease the faecal concentration of bile acids by almost half. No such effect was observed with psyllium seed.

There are some potential benefits in bacterial action on bile acids. Anaerobic bacteria, for example, can produce volatile fatty acids which are known to nonspecifically inhibit pathogenic bacterial populations.

Bile acids in diseases

Disturbed and pathological states can change the dynamics of bile and other intestinal relationships. In malnutrition, for example, morphological changes in the intestinal wall lead to increased sensitivity to the effects of secondary bile acids, poor absorption of fats and other nutrients, all of which is compounded by changes in intestinal flora.

The impact of inflammatory intestinal diseases like Crohn's is even more pronounced. The damage induced by the disease on the intestinal wall leads to reduced bile acid reabsorption and compensatory increased cholesterol synthesis by the liver, a reaction that probably explains the high level of biliary disease like gallstones in sufferers from Crohn's. The link between inflammatory bowel disease and cholestasis has already been mentioned.

Similar negative impact on enterohepatic circulation follows small intestinal resection which has been shown to lead to increased synthesis of both bile acids and cholesterol.

The association between biliary and intestinal functions is further highlighted in the condition primary sclerosing cholangitis, a disease characterized by inflammation and obliterative fibrosis of bile ducts. In 70% of cases it is associated with ulcerative colitis. In about two-thirds, there are circulating IgG antibodies to a peptide shared by epithelial cell walls in both bile ducts and colon. Another suggested cause is portal bacteremia secondary to diseased bowel wall. The addition of bile acids to the gut has been proposed as a treatment.

**PHYTOTHERAPEUTICS**

**Plant constituents, cholesterol and bile function**

In spite of its obvious significance, the dynamics of cholesterol has been little studied. In part, this is because observations are difficult. There is considerable interchange of cholesterol and its metabolites and analogues and it has proved impossible to track cholesterol through the body. A useful insight, however, has been made in studies of the metabolism of plant sterols. Plant sterols are structurally similar to cholesterol but, because of poor intestinal absorption, are ordinarily not present in the liver. However, there does appear to be some competition in the movement of plant sterols and cholesterol. For example, the proportions of plant sterols are significantly lower in cholesterol-rich gallstones than in bile but stones with low cholesterol content are proportionately richer in plant sterols. One sterol studied, sitostanol, parallels the secretion from and distribution of cholesterol in the liver (e.g. both requiring bile salts for secretion in bile) so that it can be used as a physiologic analogue of unesterified cholesterol to trace the transport of sterols through the liver. Such studies, for example, indicate that high-density lipoproteins (HDLs) are necessary along with bile acids for cholesterol elimination in bile. The use of plant sterols (in this case campesterol and sitosterol) as markers of cholesterol absorption and biliary secretion was also seen in a study referred to above, showing subclinical cholestasis as a feature of bowel inflammatory disease.

When serum concentrations and metabolism of cholesterol were studied in human vegetarians, cholesterol absorption was found to be normal and synthesis was slightly enhanced, though without increase in serum cholesterol precursors. The serum concentrations of total and low-density lipoprotein cholesterol were
decreased but in addition to the obvious lower intake of cholesterol itself, it appeared that the higher intake of plant sterols interfered with cholesterol absorption and thus increased endogenous cholesterol synthesis. Thus, cholesterol saturation and bile acid composition of the bile were not changed. Biliary excretion of plant sterols was apparently relatively inefficient.

Interactions between cholesterol transport and plant constituents extend to another major group. Saponins have been implicated in interference with the absorption of cholesterol, bile acids and fats, leading to reduced animal growth, but also have shown potential in the reduction of blood cholesterol levels. There is evidence of interference with the absorption of vitamins A and E. Their cholesterol-lowering effect may also be linked to their binding of bile salts and increasing their faecal excretion, thus increasing bile salt synthesis by endogenous cholesterol. Further studies to investigate the effects of saponins on bile, cholesterol and lipid metabolism are clearly warranted. One steroidal sapogenin that has been studied, diosgenin, is, like the sterols, also similar enough in structure to cholesterol to interfere with its esterification in the liver. This may contribute to a marked increase observed in biliary cholesterol relative to phospholipids when it was fed for 7 days to rats.

The role of dietary plant lipids in cholesterol elimination has also been studied. In rats a sunflower seed oil-enriched diet has been shown to reduce liver cholesterol levels and increase faecal excretion of cholesterol.

There is the prospect of increased retention of bile acids in the body with the use of tannins as bowel astringents. Although this may have some beneficial effects (see above), the chances are that negative or even toxic metabolites may also accumulate and on balance this prospect adds to the usual caution against using large doses of tannins for a long time.

Choleretics and cholagogues

There is a traditional differentiation made between cholagogues and choleretics. The former are agents that stimulate the release of bile that has already been formed in the biliary system. Bile acids are the main endogenous cholagogues; fatty foods the most obvious exogenous factors.

Choleretics stimulate bile production by hepatocytes and must have effective cholagogy properties as well. Cholecystokinin, secretin and some of the other humoral agents are involved endogenously. Bitters and some of the botanical agents referred to below are likely to have choleric activity.

There is very little interest in choleric and chologogue treatments in conventional medicine, at least in the English-speaking world. Among agents incidentally discovered, NSAIDs, especially aspirin (in one study at a level of 100 mg/kg), cause choleresis in animals. Magnesium sulphate (Epsom salts), sometimes used for constipation, has at doses of 500 mg been shown to exert a direct effect on the motor activity of the gallbladder in dogs.

Research on herbal choleretics and chologogues has largely come from Germany and Eastern Europe. It is not comprehensive and most practice in this area is informed by traditional reputation. Given the difficulty in knowing what actually happens in the liver and the potential risks of counterproductive treatments (see below), this is not an ideal situation.

Among the work that has been done, it has been shown that the ethanolic extract of Chelidonium majus (greater celandine) in isolated liver culture significantly caused choleresis by increasing bile acid-independent flow. A survey of the literature shows that Cynara scolymus (artichoke) possesses choleric, diuretic and hypcholesterolaemic properties. The main active components of this plant are mono- and dicaffeylquinic acids, flavonoids and sesquiterpenes. The most suitable raw material is fresh leaves in the plant's first year of growth. Phenolic acids in Mentha longifolia were found to possess significant in vivo choleric and CNS stimulative effects. The potential of Curcuma comosa rhizome as a choleric and hypcholesterolaemic treatment has been supported in experimental studies. This activity was later linked to a phloracetonaphenone glucoside.

CHOLERETICS AND CHOLAGOGUES

Plant remedies traditionally used as choleretics and chologogues

Berberis vulgaris (barberry), Berberis aquifolium (Oregon grape), Chelidonium (greater celandine), Chelone (balmony), Chionanthus (fringe-tree), Dioscorea (wild yam), Euonymus atrapurpureus (wahoo), Taraxacum (dandelion), Veronicastrum (black root), Peumus (boldo).

Indications for choleretics and chologogues

- Non-impacted gallstones
- Moderate cholecystitis (gallbladder infection)
- Conjugated hyperbilirubinemia (jaundice due to decreased excretion of conjugated bilirubin through the bile duct)
Other traditional indications for choleretics and cholagogues

- ‘Bilious’ conditions associated with heaviness in the epigastrium, nausea, susceptibility to alcohol and fats, headaches
- ‘Toxic’ conditions associated with intestinal congestion, especially in skin and autoimmune diseases
- Constipation

Contraindications for choleretics and cholagogues

The effects of choleretic and cholagogue agents may be different in the diseased liver than the response produced in the normal liver. For example, experimental evidence suggests that the use of choleretic agents where hepatobiliary damage (e.g. cholangitis) is caused by obstructive jaundice might further depress hepatic functions.60

The use of choleretics and cholagogues is either contraindicated or at least inappropriate in the following.

- Obstructed bile ducts (due to impacted gallstones, cholangitis or cancer of bile duct or pancreas)
- Unconjugated hyperbilirubinaemia (jaundice following haemolytic diseases, hereditary diseases like Gilbert’s and Crigler-Najjar syndromes)
- Acute or severe hepatocellular disease (e.g. following viral hepatitis, cirrhosis, adverse reactions to drugs, e.g. anaesthetics, steroids, oestrogen, chlorpromazine)
- Septic cholecystitis (where there is a risk of peritonitis)
- Intestinal spasm or ileus
- Liver cancer

Traditional therapeutic insights into the use of choleretics and cholagogues

Stimulating bile flow has been seen as one of the main eliminative strategies in traditional medicine, reflecting the importance attached by even the most primitive cultures to the role of the liver (the name of the organ was often as evocative as it is in English).

However, bile stimulation was often accompanied by vigorous approaches to eliminating it from the gut as well; the almost universal reliance in folk medicine on emetics and purgatives as first-resort approaches to the treatment of acute disease almost certainly had the effect, intended or otherwise (and in the case of emetics it was often intended), of radically removing bile from the body. It is now easy in modern medicine to dismiss the use of such drastic procedures as useless or dangerous but, unlike the use of bleeding, which was often likely to be counterproductive, emesis and catharsis were almost prehuman measures and established themselves over millennia in the most demanding court of efficacy, the survival from acute disease.

Given what is now known of the retentive qualities of the enterohepatic cycle, the certainty that modern diets and lifestyle have significantly lengthened intestinal transit time compared to that of early humans, thus extending enterohepatic recycling further, it is likely that many modern practitioners might look with some envy at their forebears’ ability to get rid of this pool of potentially or actually toxic metabolites. However, emesis and catharsis were seen as an option for the most robust constitutions and apart from the obvious inappropriateness, they are contraindicated in the more chronic and low-vitality conditions most often seen in the modern clinic.

Modern techniques to eliminate the bile pool generally involve dietary and other measures to decrease intestinal transit time combined with the use of choleretics and cholagogues. Some of the latter actually have laxative effects in any case, either because they contain the appropriate constituents or, more often, because their release of more bile is in itself laxative.

Application

Choleretics and cholagogues are best taken before meals, preferably about 30 minutes, but immediately before will suffice. They may, however, have contradictory effects if taken with or after food. As many rely at least in part on the effect of bitter constituents, they should be taken in fluid form.

Long-term therapy is probably not appropriate and clinical experience is that for maximum benefit, they are best applied for short duration, of up to 2 weeks at a time, sometimes much shorter.

Advanced phytotherapeutics

Choleretics and cholagogues may also be usefully applied in some cases (depending on other factors) of:

- constipation (not due to intestinal spasm nor responding to conventional measures);
- migraine;
- acne rosacea;
- inflammatory bowel disease;
- dysbiotic conditions of the gut;
- chronic skin diseases;
- autoimmune diseases (especially where associated with any of the above – see relevant sections).
45. Robins SJ, Fasulo JM. High density lipoproteins, but not other lipoproteins, provide a vehicle for sterol transport to bile. Journal of Clinical Investigation 1997; 99 (3): 380–384