The main health indications of natural bile acids in professional literature¹

Documentation and sources of the following quotations can be found in the referenced literature and on the website www.gallmet.hu and www.gallmed.co.uk

The present information sheet serves the appropriate and detailed information of the consumers and its aim to support the sound and conscious decision making of the consumers by providing a short summary of the scientific literature on the health indications of bile acids.

During the course of drawing up this information sheet we took into account to comply with the provisions of **Directive** 2011/83/EU on consumer rights, Directive on labelling, presentation and advertising of foodstuffs (2000/13/EC) and the Unfair Commercial Practices Directive (2005/29/EC) with respect to the aim of the above regulations to provide the consumers with the most possible detailed information on the product and its substances. The information provided on the ingredients of the product is of educational nature only, not referring to effects related to the product.

See your doctor in case of health problems!

1. THE ROLE OF BILE ACIDS IN DIGESTION AND THE LACK OF THEM AFTER GALL BLADDER SURGERY

<u>Bile acids</u>: The liver, the gall bladder and the bile ducts, the duodenum and the pancreas together form a structural and functional unit of the digestive system. These organs closely interact with each other, well-coordinated cooperation is necessary for the perfect digestion. In the mouth, the food is chewed up into small pieces by the teeth. Even the sight or smell of food, but even more the taste stimulates the secretion of saliva, gastric and other digestive juices as well as a little bile flow. The movements of the stomach help in the proper mixing of food and also help to propel it into the duodenum with a great force but in small portions. On the mechanical or chemical effect of food and drink, more and more cholecystokinin (gastrointestinal hormone, also called gut hormone) is secreted, controlling the emptying of the gallbladder; one hand this opens the common sphincter of the bile and pancreatic duct forming a common pipe system, on the other hand contracts the bladder, so the bile and pancreatic juice flows in the duodenum, where it is mixed with the food pulp, thirdly it simulates increased pancreatic secretions, resulting in greatly increased volume of digestive enzymes. The production of the gut hormone

(cholecystokinin) is triggered by food and drink entering the gut and which causes the bile to be released from the gallbladder. If bile secretion, bile production or enterohepatic circulation are insufficient (resulting in bile deficiency that occurs in 25 % of the population), then the breakdown and the digestion of fats won't be correct. This can be favourably influenced by the administration of bile acids at mealtimes. After cholecystectomy, storage function of the gall bladder is lost. The bile continuously trickles, so, if there is a higher demand for bile (when having a meal containing fats), there isn't any bile to release because of the lack of the bladder. So, the fats are not completely digested (fat metabolism disorder), and when it's getting into the colon, the intestinal flora breaks down the undigested parts along with gas formation, causing abdominal bloating, possibly diarrhoea. Digestive problems after gall bladder surgery - bloating, pale stools, reflux diarrhoea or constipation, etc. - and other resulting illnesses can be positively influenced by taking 1-3 capsules of bile acid daily.

<u>Digestive enzymes:</u> digestive enzymes are essential elements of the digestive process, each responsible for processing different types of nutrients: bile and lipase = fats, amylase = starch, gastric acid, pepsin, protease, bromelain and papain = proteins. A lack of digestive enzymes can lead to a whole range of problems.

Improperly digested nutrients can cause fermentation in the gut, leading to gas production and bloating. They can be replaced by food supplements.

2. GALLSTONE

If a person has bile emptying disorder for a long time, biliary stone formation can start. Initially, bile salt crystals form on the gallbladder wall, and as the stagnant bile fluid builds up on these, small and then larger gallstones form. Biliary problems are often initially asymptomatic. "Thanks to bile acids, cholesterol is constantly dissolved in the gallbladder. If there is insufficient bile acid formation, the cholesterol molecule precipitates and <u>forms the nucleus of the growing gallstone</u>. So, cholesterol stones are formed from bile with a relatively higher cholesterol content and a lower bile salt content. There is evidence that gallstones grow at an average rate of 2.6 mm/year.²

The symptoms of gallstones (bloating, abdominal cramping, bile cramps, pain under the right rib cage, stabbing pain in the back, diarrhoea or constipation) can be reduced by consuming bile acids, as they are caused by the lack of bile.

Bile stone dissolving: by consuming bile acids, a so-called soft cholesterol stone of up to 15 mm can be dissolved in 6-24 months.

Principle: reversing the process of stone formation by restoring the altered ratio of bile composition. Two important bile acids are formed in the liver, whose role is to keep otherwise water-insoluble fats in emulsion. In cases where gallstones are formed from cholesterol crystals, they can be made soluble by taking capsules containing bile acids of high purity.³

3. BILIARY REFLUX

"In addition to a bad lifestyle (e.g. too much sedentary work) and bad eating habits (e.g. late dinners), poor bile function also causes reflux disease. This poor bile function causes a blockage in the small intestine, which prevents food from moving down the gut." ⁴

"The administration of bile acids helps bile secretion to become regular and also triggers the small intestine to function, eliminating the condition that allows food to pass upwards and cause reflux-like symptoms."

Some medicines prescribed for reflux, such as antacids and proton pump inhibitors, can interfere with the activity of enzymes.

In such cases, the inadequate breakdown of food can cause unpleasant abdominal discomfort and heartburn due to increased abdominal pressure, and in such cases, food supplements can be used to replace the missing enzymes.⁵

4. INTESTINAL DISEASES

'If there is a problem with the breakdown of fats (e.g. because of gallbladder surgery), the digestion of fat will be by putrefaction, which will alter the bacterial flora in the colon in an unfavourable manner. This allows microorganisms that don't belong there to colonise and multiply in the intestines.' This can trigger inflammatory processes, causing pain, cramping and the development of IBS and dysbiosis.

'Proper liver function, bile production, bile circulation (enterohepatic circulation) may prevent the listed intestinal diseases. If the bile cycle is not functioning properly or is damaged for whatever reason, bile acid supplementation can help to alleviate the symptoms of these diseases and speed up recovery, as bile acids support the bile cycle, digestion, gut and immune health and help to alleviate their dysfunction.'

Intestinal diseases such as Crohn's disease, irritable bowel syndrome (IBS) or other inflammatory bowel diseases can affect enzyme production or nutrient absorption, which can be compensated by supplements. This is a common phenomenon in cases of gallstones or post-cholecystectomy syndrome, where bile flows from the liver directly into the duodenum.⁶ Extracts of milk thistle (silymarin) have been clinically shown to significantly improve the quality of life of people with various inflammatory bowel diseases.⁷

<u>SIBO:</u> overgrowth of bacteria in the small intestine. Undigested food provides a breeding ground for bacterial overgrowth in the small intestine. <u>Primary endotoxemia:</u> normally the gut barrier effectively prevents endotoxins from entering the bloodstream. However, certain conditions can damage this barrier, allowing endotoxins to leak into the circulation. Some conditions, such as SIBO, dysbiosis, etc., lead to increased endotoxin production and leaky gut syndrome. Endotoxemia leads to inflammatory reactions that can affect the whole body.

5. PSORIASIS AND OTHER SKIN PROBLEMS

Role of bile acids and endotoxins in the pathogenesis and treatment of psoriasis ⁸

"On the basis of their clinical observations (digestive disorders, gallbladder lesions, etc.) authors supposed that the deficiency of

bile acids and the consecutive endotoxin translocation might play a role in the pathogenesis of psoriasis. Bile acids are the basis of (physico-chemical) protection against bacterial endotoxins produced in the gut, and their deficiency allows the absorption (translocation) of endotoxins, which can lead to the release of cytokines. If we prevent endotoxin translocation with bile acid supplementation, then the release of inflammatory cytokines can be blocked."

"Many skin diseases are related to the function of the bile, because if the body persistently excretes insufficient bile and fats are not broken down well, intensive putrefaction processes occur in the intestine, which produce endotoxins (the body's own toxins) that irritate and inflame the intestinal wall and make the intestinal mucosa more permeable to these endotoxins. These can then be released into the lymphatic system and the blood and cause inflammation and allergy-like symptoms on the skin. One skin symptom is psoriasis, but it can also be eczema, allergies, skin rashes, etc. Treating psoriasis is a complex task, which may involve restoring proper bile production and secretion, which can be helped and accelerated by taking bile acids."⁹

Based on literature, 551 patients with psoriasis were treated with oral bile acids for 1-8 weeks. **Of these patients, 434 (78.8%) became asymptomatic.** Of the 249 patients who received conventional treatment, only 62 (24.9%) were asymptomatic during the same period.¹⁰

Undigested proteins due to enzyme deficiencies can trigger immune responses and skin problems such as **eczema** or **acne**. It should be noted that in many cases these skin problems are only a warning sign for deeper underlying problems such as: enzyme deficiency, low enzyme activity, leaky gut syndrome, SIBO, dysbiosis, endotoxemia, etc. Enzymes **essential for protein digestion** can be supplemented with food supplements.¹¹

6. NATURAL IMMUNITY. "The Role of Bile Acids in Physico-Chemical Host Defence^{12,13} Bile acids regulate immunity, according to the latest international research, immunity depends on bile acids.^{12,13}

The important effect of bile acids, what we have discovered (since then others have confirmed the results of our studies) is the special protection of the human body, expressing itself in the bowel system.

We have been inspired by the *in vitro* experiments of an American research group, which observed that the treatment of endotoxin with a bile acid, sodium deoxycholate, resulted in the production of small non-toxic units. On the basis of these findings, we considered the possibility that **bile acids may play an important role** *in vivo* (in the intestines) in the *detoxification of endotoxin*.

Bacterial endotoxin chemically is a lipopolysaccharide molecule, in which the toxic molecy has attached to the envelope rich in fatty acids. On the basis of the above observations, one may suggest that that a sufficient amount of bile and bile acids is required to detoxify endotoxin within the gastrointestinal tract.

We have named this protective process as "physico-chemical host defence". The basis of this defence mechanism is the detergent (fat break down) effect of bile acids.

Max Theiler has observed that the virus of yellow fever and other athropod borne viruses (Flaviviridae-family according to present taxonomy) are inactivated when presented with monkey bile acid.

About the bile acids: Physico-Chemical Host Defence⁵.

In natural conditions, bile acids protect the human body against endotoxins that are always present in the intestines, because they split them into nontoxic parts. It turned out that this defense protects against all agents with lipoid (lipoproteid) structure (e.g. peplon enveloped viruses, so called large viruses). We named this protection system, based on the surfactant (detergent) effect of bile acids "physico-chemical host defence" (Bertók, 2002). Weaker or more severe endotoxaemia due to bile deficiency may play a role in the development of several diseases, such as septic shock, renal failure in patients with jaundice due to bile duct obstruction, intestinal ischaemia, burn shock, radiation sickness, some endocrine diseases, psoriasis, atherosclerosis, etc. Bile acids may have an important role to play in supporting the human body against certain diseases (e.g. kidney failure, psoriasis). It turned out that all the effects that damage the intestinal mucosa, can reduce or completely impossible the production of a peptide, cholecystokinin (CCK). In the absence of the CCK, the gall bladder cannot empty the bile into the intestine. If this process has partially damaged, then the endotoxins, released from the outer membrane of dead Gram-negative bacteria can absorb, get in the bloodstream, causing endotoxemia, a large variety of diseases and triggering shock – in severe cases

Modern methods of investigating, and detailed exploration of the "physico-chemical host defence", that based on the surface-active property of bile acids, can be the developer of a new approach to pathology, because the fundamental issues of cholesterol metabolism are also affected, as bile acids are mostly reusable end products of this process. As all sterane hormones are quantitatively only a fraction of the resulting bile acids, it can be rightly assumed that cholesterol-bile acid conversion can greatly influence the production and destruction of all steroidal hormones, which are important for natural or acquired immunity (Bertók, 2002).

It can be concluded that "physico-chemical host defence", that based on the surface-active property of bile acids is a general defence mechanism of the human body, which is not confined to bacterial endotoxins but refers to all the "agents" (such as some viruses) having lipoid (peplos) or lipoprotein structure on their surface. Therefore, we can add "physico-chemical host defence" to the lineup of general defence mechanisms of the human body, which is provided by bile acids produced in the liver and involved in the enterohepatic circulation..

7. STRESS. The negative effect of stress - on bile production and secretion - can be counteracted by bile acids¹⁵

Stress is a characteristic group of symptoms manifested by the body's response to any harmful (physical or psychological) stimuli, especially in women with more sensitive nervous systems.

Stress has a significant impact on the entire digestive system, including bile production and excretion. The Oddi sphincter spasms under stress and does not open, so the bile produced does not pass from the gallbladder into the duodenum. People who regularly work under stressful conditions or have psychological problems in their private life and notice frequent bloating and abdominal pain should take bile acids to relieve these digestive problems.

It cannot be ignored that stress is a major influence on the whole digestive system, so that on bile production and secretion too. Disorders of bile production and secretion reduce or suspend one of the important protective mechanisms, the "physico-chemical host defence" based on the surface-active (detergent) effect of bile acids, without which the body will become exposed to the attack of some of the toxins in the gut (e.g. endotoxins) and to so-called large viruses (such as the herpes family).

8. HERPES. Herpes and bile acids.¹⁶

"One of the causes of herpes might be the relative deficiency of bile acids. Bile acids can break down some of the viruses, mainly viruses with lipoprotein (peplos) envelops (Sodium - deoxycholate-sensitive viruses: yellow fever virus, herpes viruses, etc.)"

According to the latest international research and scientific literature this includes, for example, the following viruses: influenza, rota, hepatitis B / C / D virus families.¹⁰

"It appears likely that temporary bile acid deficiency may be important, for example in the development of herpes infections after major dietary overloads (e.g., fatty foods at weddings, christenings, etc.). For example, if you eat too much food during a hearty meal, small herpes blisters can appear on your lips within a few days. Normally, bile acid destroys the herpes virus in the digestive tract, but our gall bladder and stomach are not prepared for these stressful meals, so the herpes virus can multiply.

In addition to traditional creams, you should also **take capsules containing bile acid**, because bile acids help the immune system to destroy lipid/fat-coated herpes viruses through their fat-busting action.¹⁷

9. CHOLESTEROL. The cholesterol question: high or low? 18

"Bile acids represent a large group of compounds formed from cholesterol. Bile acids are made by the liver, and in addition to their role in the digestion and absorption of fats, they are also important in detoxification, and meaning the only physiological way of get rid of cholesterol. The role of forming an optimal amount of bile has great importance <u>because low bile acid secretion rate can cause several diseases</u>. Their primary role is to help the human body get rid of excess and dangerous cholesterol. If, for whatever reason, the liver produces and excretes less bile acid, more excess cholesterol remains in the body. The digestion of fats then becomes more imperfect and the resulting absorbed fats raise the cholesterol and triglyceride content of the blood, depositing in the circulatory system on the walls of blood vessels, narrowing their inner lumen and thus creating catastrophic circulatory and infarct-causing situations. Most of the bile acids that enter the gut are reabsorbed, allowing the absorption of fat-soluble vitamins. Then, with the help of bile

acids, circulating in the blood, they take the fat-soluble vitamins to their place of use nearby the cells. Therefore, if there aren't enough bile acid molecules in the intestines, because we don't eat enough choleretic foods (e.g. fats and oils), then the absorption and utilization of fat-soluble vitamins (A, D, E, K vitamins) will be disturbed. Although we get enough fatsoluble vitamins, they are not absorbed because they are poorly utilised, and deficiencies can occur despite apparently adequate vitamin supply.

Approximately 90% of the bile acids that enter the intestines are reabsorbed into the blood and then enter the liver, where they participate in the gut-blood-liver-intestinal cycle, thus fulfilling their physiological functions.

10. THĚ ROLE OF LIPID PROCESSING IN DISEASES. "Bile flow disfunction affects almost all of the diseases ¹⁹

The team of doctors, set up by Dr. Péter Légrády, tried out a new kind of approach and they achieved new results after 8 years of investigation. The circulation of fat, fat-like and fat-soluble substances, or more simply: the dysfunction of the liver and biliary system, was investigated.

Consequently, they studied not only the diseases of the hepatobiliary system (e.g. gallstones), but the diseases, that originate from or rather playing a role in the functional disorders of this system, for example, rheumatic diseases, migraine, functional infertility. The relationship between migraine and biliary tract disorders is a well-known phenomenon too.

They studied and investigated allergic diseases too, and they searched for the role of the hepatobiliary system in the development or in the curability of some-more prolonged or chronic illnesses. This is a new, different approach.

Defects of the bile acid metabolism can be located at 5-7 places. They have observed two thousand patients that means more than five thousand files including control. After 8 years of research, the followings can be clarified from their work: The circulation of fat-like and fat-soluble materials is present at most diseases. And the circulation of bile acids is a crucial part of it."

11. CANDIDA Albicans (candidiasis).

"Candidiasis: real danger or large business²⁰. Candida yeast is a fungus that can produce pseudo hyphae and comes from the fungus family of Saccharomycetaceae. It lives on the human mucosa, on the skin and in the GI tract. The Candida yeasts are also involved in the utilization of degradation products formed in the human body as the other microorganisms living in the intestinal tract. The starting point of candidiasis usually means the point when some of the environmental effects (e.g. antibiotics, poor diet, stress) reduces intestinal immunity, therefore C. albicans fungi can reproduce ourselves. Candida fungi attack our organs from many sides and they do it in a comprehensive manner. If the reproduction of C. Albicans has been started in the cavities of the intestinal, genital and urogenital tract, at the surface of the skin and in the mouth, then it is followed by the break-through of the intestinal wall. In this case, fungi are able to reabsorb and they could get in the blood stream, causing systemic candidiasis (it affects the whole body)."

"Nowadays, by the heightened number of temporarily or permanently immunodeficient patients, importance of fungal infections has significantly increased²¹. Granulocytes and monocytes play main role in antifungal defence, therefore patients with lesser (neutropenia) will be more sensitive for generalized infections.

Aspects of the effect of bile salts on Candida albicans²² "...Cholic acid, chenodeoxycholic acid, deoxycholic acid, glycocholic acid, glycodeoxycholic acid, hyodeoxycholic acid and lithocholic acid as their sodium salts, were fungistatic to the growth of Candida albicans... the bile salts promote formation of the yeast form of Candida albicans."

"Antifungal utility of bile acids²³: ... It has now been found, very surprisingly, that bile acids and their simple derivatives have anti-Candida activity...The discovery that bile acids inhibit the growth of Candida fungus species was surprising in the light of the previous statements.

"Ecology of Candida albicans Gut Colonization²⁴: Secondary bile acids and VFA may have reduced the mucosal association of C. *albicans* by modifying Candida adhesin(s) or mucosal receptor(s), or both, **thus rendering** *Candida* **cells unable to attach to intestinal tissues.**"

12. HEALTH-METABOLISM-DIABETES

"Fountain of Youth in Bile?"25, 2

The human quest for longer life may be one step closer. Concordia University published in the journal Aging, a new study is the first to identify the role of a bile acid, called lithocholic acid (LCA), in extending the lifespan.

"We do know from previous studies, however, that bile acids are beneficial to health and longevity. For example, they have shown to accumulate in the serum of long living mice and play a role in improving rodent liver and pancreatic function. This leads us to believe that bile acids have potential as pharmaceutical agents for the treatment of disorders which are age-related, continues Titorenko. They may indeed offer hope for a healthy aging life."

This is linked to the fact that the production of enzymes naturally declines with age and can be supplemented with food supplements.

"Bile and pancreatic secretions are discharged into the duodenum through the same orifice. If the bile is stagnant, for example because of poor diet, stressful lifestyle, drinking too much coffee, then the enzymes in the pancreas cannot be excreted along with the bile and over time these stagnant enzymes will erode the pancreatic lining and the insulin secreting glands will be damaged. If, in addition to this disorder, someone also eats too many calories over several months, they can develop diabetes."²⁷

"Diabetics complaining of biliary disorders who were given bile acids not only had their bloating and abdominal pains eliminated, but also improved their sugar tolerance, as measured by a drop in blood sugar levels. Bile acid helps glucose to flow into cells, increasing physical performance and reducing blood sugar levels. In diabetics, it is very common for cholesterol to build up in the blood. Bile acids also have a beneficial effect in helping to lower cholesterol."²⁸

13. PANCREATIC INSUFFICIENCY:

When pancreatic insufficiency occurs, the pancreas does not function properly and the production of digestive enzymes, which play a key role in digestion, is disturbed. Chronic pancreatitis, cystic fibrosis and celiac disease can be among the most common causes.

- **14. FOOD DIGESTION PROBLEMS:** Diets lacking essential nutrients or high in processed foods can interfere with enzyme production. Examples include diets that are too high in fat or, conversely, vegan; eating too much sweets or snacking, etc.
- **15. DISBIOSIS:** (symptoms: bloating, diarrhoea or constipation) Partial digestion causes changes in bowel movements, which in itself can cause unpleasant symptoms. In addition, the lack of digestive enzymes means that undigested food is passed to bacteria in the large bowel, so that the individual's unique gut flora composition is disrupted and a condition called dysbiosis develops.²⁹
- 16. NUTRIENTS DEFICIENCIES: If nutrients are left in undigested food, the body cannot absorb them properly, which can lead to deficiencies.
- 17. LIVER PROTECTION: Over the past decade, the effects of bile acids have been widely studied in the treatment of non-alcoholic fatty liver. Studies support a role for bile acids in the treatment of non-alcoholic fatty liver, but the mechanism of action is not yet fully understood.²⁹ For hundreds of years, herbalists have used milk thistle to treat a wide range of liver diseases, including fatty liver disease, hepatitis, cirrhosis and to protect the liver from environmental toxins.³⁰

Silymarin, the active ingredient in milk thistle, protects intact and not yet irreversibly damaged liver cells. In clinical trials in patients with alcoholic or non-alcoholic fatty liver disease, treatment with silymarin was associated with a significant reduction in liver-related deaths.³¹

Artichoke has shown antioxidant, bile stimulant, hepatoprotective and lipid-lowering effects, consistent with its historical use. Ongoing research indicates that artichoke does indeed have medicinal effects, with particular benefits for the liver. In one study, liquid extracts of artichoke roots and leaves were shown to be able to protect the liver and possibly even promote liver cell regeneration.³²

Soya lecithin plays a beneficial role in protecting the liver from damage, preventing liver cirrhosis by reducing inflammation of liver cells. It reduces the accumulation of collagen in the liver, increases choline levels and the activity of an enzyme that helps break down collagen in

the liver. Since lecithin's primary role is to break down and emulsify fat, it may help prevent fatty liver disease. Soy lecithin therefore restores normal liver structure and function, helps liver cells regenerate and protects the liver from damage.³³

Research shows that the enzyme papain reduces fatty liver deposits.³⁴

 NATURAL SOLUTIONS FOR ENZYME REPLACEMENT: While dietary and lifestyle changes – avoiding snacks and eating an unbalanced diet - are often recommended to treat enzyme deficiencies, certain natural substances can provide additional support:
Soy lecithin: This phospholipid contains phosphatidylcholine, which may help fat digestion by emulsifying fats so they can be more easily

2. alpha-amylase: This enzyme specifically targets carbohydrates, breaking them down into simpler sugars for absorption. It may be beneficial

for people with pancreatic insufficiency or those who have difficulty digesting resistant starches.³⁵

3. Lipase: This enzyme is essential for digesting fats. Lipase supplementation may be beneficial for people with pancreatic insufficiency or conditions that adversely affect fat digestion, such as celiac disease.³⁶

4. Papain and bromelain: This plant-based enzyme found in papaya and pineapple has protein-digesting activity ³⁷, meaning it breaks down proteins. Studies have shown potential benefits for digestive complaints ^{38, 39} and inflammation. ^{34, 40}

5. *Silymarin and cinarin:* The active ingredients in artichokes and milk thistle stimulate bile production^{41, 42} and relieve digestive disorders^{43, 44} and IBS symptoms^{45, 46} such as bloating, stomach cramps and constipation. The active ingredients have antioxidant activity and help protect the liver from damage ^{47, 48} and help liver cells regenerate. Both active ingredients can help to normalise cholesterol levels^{49, 50, 51}

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