PURE ANIMAL WELLBEING

By BLACKMORES

LIVER HEALTH

in Dogs & Cats

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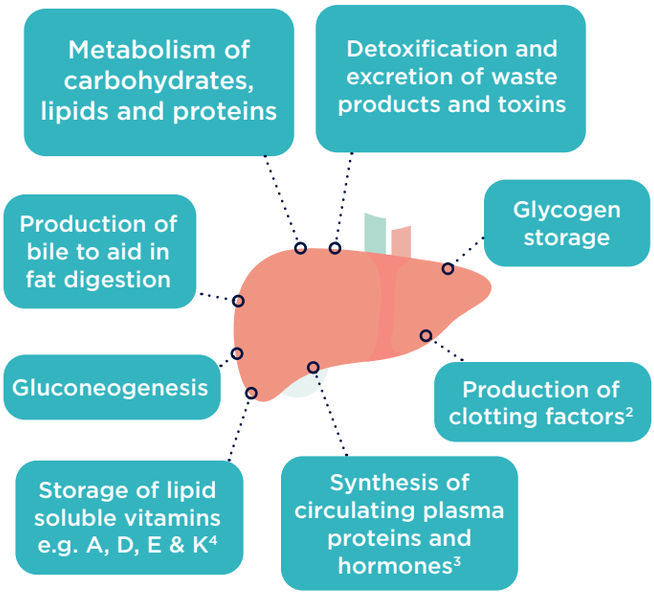
LIVER DISEASE IN DOGS AND CATS

Hepatobiliary disease is an important cause of morbidity and mortality in dogs and cats.[1]

THE LIVER IS A VITAL ORGAN

The liver is critically involved in numerous biological processes that are essential to life.[2] These functions include:



THE LIVER IS UNIQUELY SUSCEPTIBLE TO INJURY

By virtue of its pivotal role in metabolism and detoxification, along with its unique dual blood supply, the liver is particularly susceptible to damage.[5]

of blood flow to the liver arrives from the portal circulation, whereas the hepatic artery supplies the remaining 20%.[6]

In view of the fact that this portal venous blood supply filters the products of digestion from the gastrointestinal tract directly into the liver, hepatocytes are routinely exposed to any toxic intermediates that have been absorbed by enterocytes.[5] The flow on effect of hepatocytes receiving the majority of their blood supply from a venous rather than an oxygen-rich arterial circulation, means that they are also prone to hypoxic injury.[5]

UNDERSTANDING LIVER DISEASE[7,8]

Liver disease relates to any process that results in hepatocyte injury, cholestasis, or both and can be classified as acute or chronic in nature.[9] Liver disease may also arise secondarily to systemic diseases, such as inflammatory bowel disease, pancreatitis and endocrine disorders.

Acute vs chronic hepatitis[8, 10]

Acute hepatitis results in the rapid onset of clinical disease (usually over the timeframe of days). Chronic hepatitis on the other hand, refers to canine hepatic disease lasting over four to six months in duration, and is the most identified canine inflammatory liver disease.

Both acute and chronic hepatitis are characterised histologically by a combination of inflammation (despite differences in the types of inflammatory cells present), hepatocellular apoptosis and necrosis, and varying degrees of regeneration. However, fibrosis is a key feature in the diagnosis of chronic hepatitis because it is the main hallmark of chronicity. Unfortunately, in the majority of acute and chronic hepatitis cases, thorough investigation fails to disclose a definitive underlying cause of disease and as such, they are termed ‘idiopathic’.

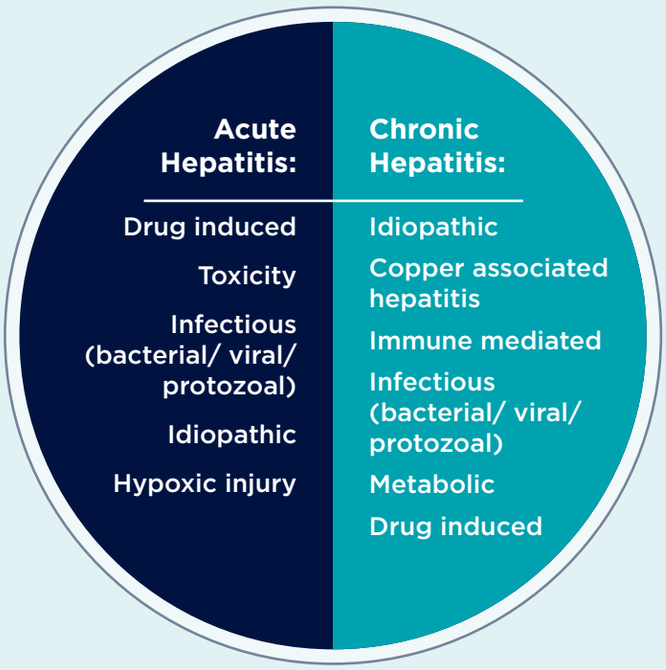
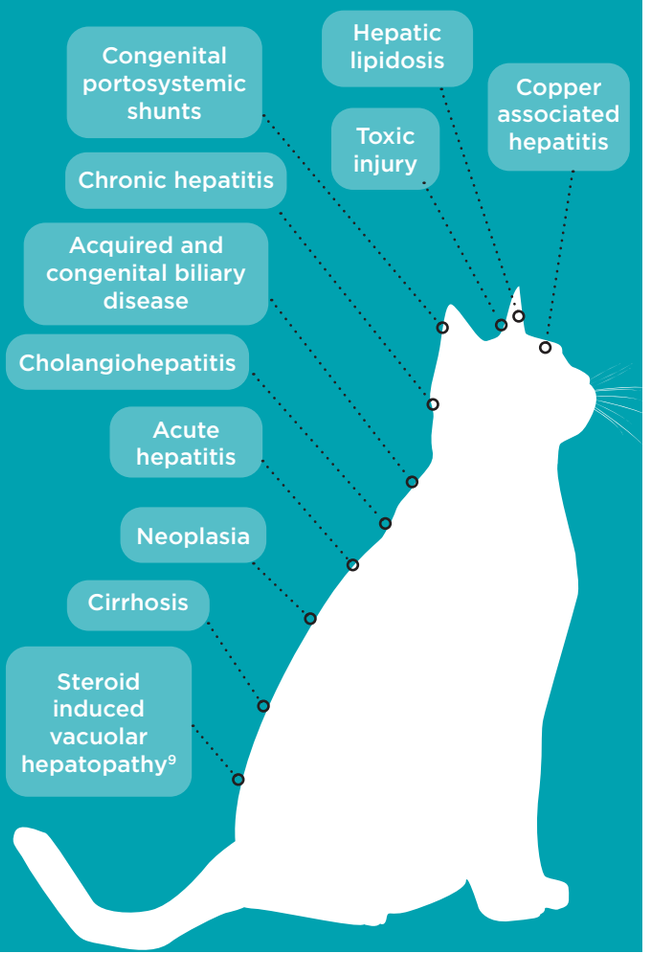
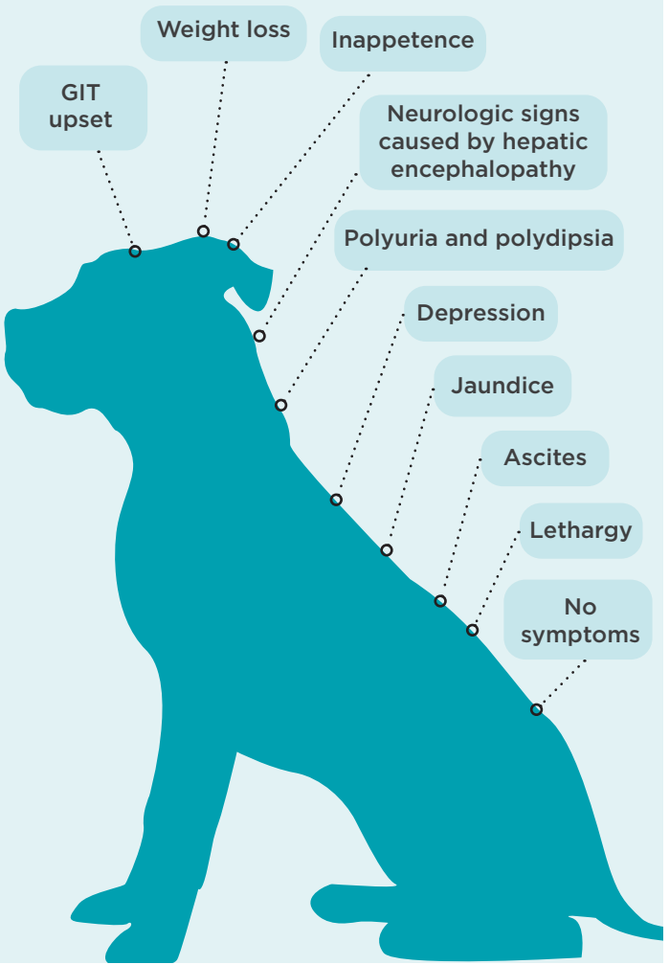


Figure 1. Common causes of acute and chronic hepatitis[10]

LIVER DISEASE ON THE INSIDE:[11]



WHAT WE SEE ON THE OUTSIDE:



LIVER DISEASE DOES NOT ALWAYS RESULT IN LIVER FAILURE[7]

The liver has an impressive reserve capacity, and as such,

70-80% **of the functional hepatic mass must be lost before liver failure (loss of function) occurs.**

Due to the liver's great reserve capacity, clinical signs often only become apparent when the hepatic disease is advanced and tend to be non-specific. As such, liver disease may easily be overlooked by pet parents and can be difficult to diagnose.[9] The signs that are most suggestive of liver dysfunction include jaundice and ascites, occurring in approximately 33% of dogs.[7, 9, 10, 12, 13]

DID YOU KNOW?

Hepatocytes have an enormous regenerative capacity, which means that early diagnosis and therapy offers the best hope of disease resolution in both acute and chronic cases.[16, 18]

PRINCIPLES OF TREATING AND MANAGING LIVER DISEASE

Diagnosis of canine hepatic disease often involves a combination of thorough history taking, clinical examination, clinical pathology and diagnostic imaging. However, definitive diagnosis can only be achieved from histological evaluation of representative liver biopsies.[8, 10, 15]

Once a diagnosis has been achieved, management of the hepatic disease needs to be tailored to each patient's condition, with therapy targeted at the underlying cause.[8,10, 15] In cases of idiopathic hepatopathies, treatment and management is based on supportive and symptomatic therapy, including antifibrotics, glucocorticoids, antioxidants, antibiotics, and dietary changes.[8,16]

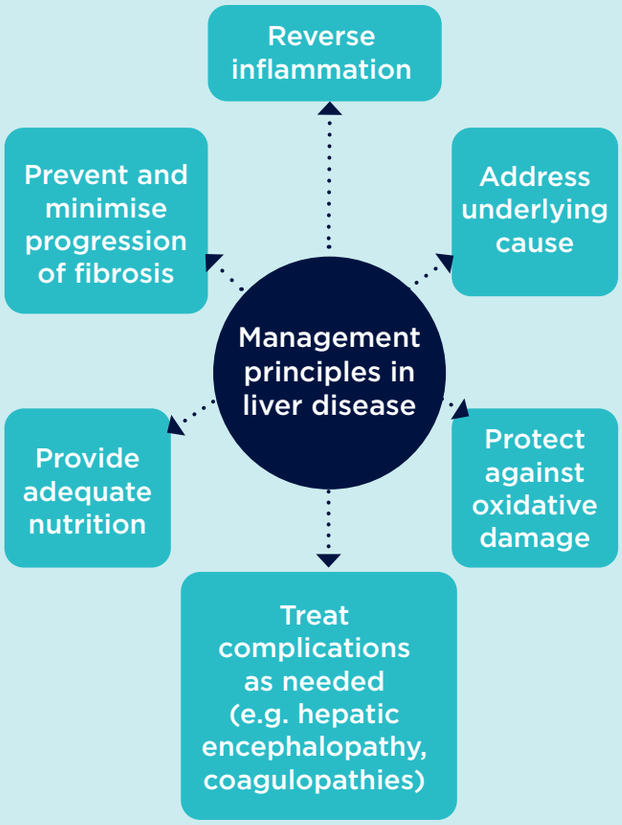


Figure 2. The overarching principles of therapy for the management of hepatobiliary diseases[8, 16, 17, 18]

OXIDATIVE STRESS IN THE LIVER

The healthy liver has an elaborate antioxidant network, including enzymatic and non- enzymatic defences such as glutathione and vitamin E, which enhance natural defence mechanisms against hepatotoxins.[5]

Normally the level of reactive oxygen species (ROS) in cells are kept in a fine balance between their production in metabolic processes and their subsequent elimination via antioxidant systems.[5] However, in hepatobiliary disease, activated inflammatory cells (neutrophils, Kupffer cells), enzymes and damaged mitochondria contribute to the over-production of ROS, leading to oxidative stress.[5]

> Oxidative stress is defined as an imbalance between oxidant and antioxidant systems, such as an excess of ROS or a deficiency in antioxidants in the cell.

Oxidative stress contributes to tissue damage through the peroxidation of cell membranes, activation of pro-apoptotic protein kinases, induction of pro-inflammatory cytokines and modulators of apoptosis, ultimately leading to cell death.[20]

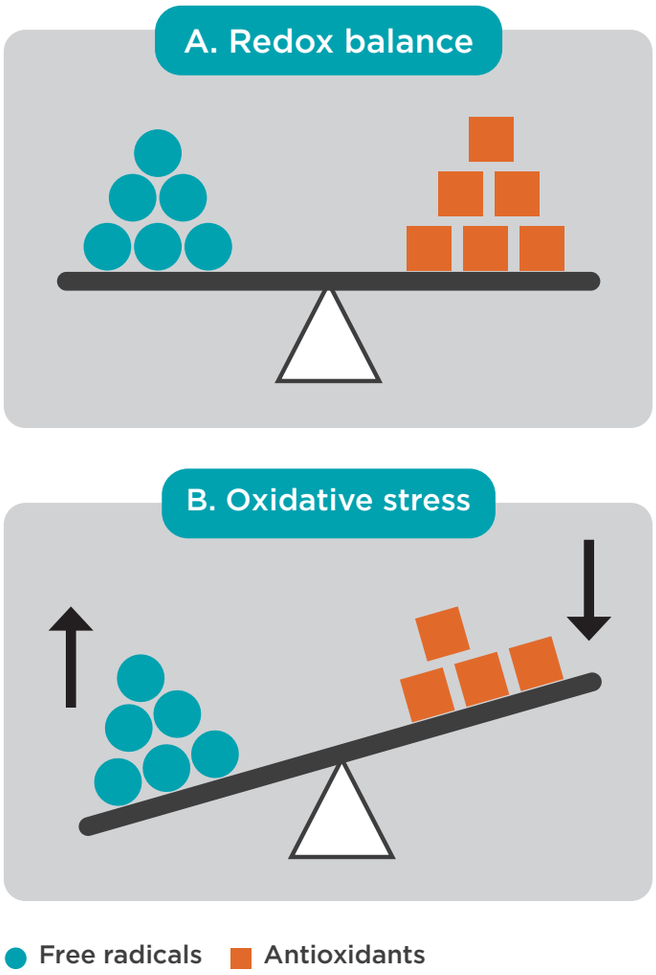


Figure 3. Contrasting oxidative status in health (A) compared to in liver disease (B)

UNDERSTANDING GLUTATHIONE

Glutathione (GSH) is the most abundant and important intracellular antioxidant in the body.[20] Given its unique anatomical positioning between the systemic and portal circulation, the liver is the major source of glutathione for the entire body, with 90% of the systemically distributed glutathione synthesised by hepatocytes.[21, 22]

It exists principally in two forms—a thiol reduced form (GSH) and a disulfide oxidised form (GSSG), which are normally maintained in a 95:1 ratio by GSH redox cycling.[5, 23]

Glutathione is essential for a number of physiological functions including:[10]

- **The management of cell redox status**
- **Detoxification and conjugation reactions**
- **Normal enzyme functions**
- **Protein-structural configurations**
- **Gene expression**

GLUTATHIONE DEFICIENCY IN HEPATIC DISEASE

Given that glutathione is an imperative component of the liver's antioxidant network, it is crucial for optimal liver function. Hepatocytes are protected from oxidative stress primarily due to the liver's capacity to synthesise glutathione.[24] The large supply of glutathione that is synthesised is either utilised locally or flows into the biliary and systemic circulation.[21]

In particular, necro-inflammatory hepatic disease, cholestatic liver disease and hepatic lipidosis in cats is associated with the depletion of liver GSH levels. In view of that, the use of cytoprotective agents with antioxidant properties is justified in the supportive treatment of canine and feline hepatobiliary disease.[10, 18, 21]

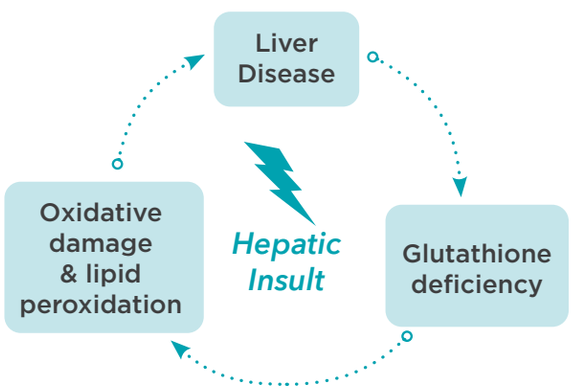


Figure 4. The vicious cycle of hepatic disease and glutathione deficiency

DID YOU KNOW?

Hepatic glutathione concentrations in healthy dogs are inherently lower compared to other species, which predisposes them to oxidative injury.[21]

PUTTING THE SPOTLIGHT ON ANTIOXIDANT THERAPY

It is well established that oxidative stress plays a major role in the pathogenesis of hepatobiliary disease in humans and animals alike.[5, 18, 19] Consequently, therapeutic intervention with antioxidants is of vital importance in supporting acute and chronic liver disease, through the enhancement of natural hepatic defence mechanisms to inhibit inflammation and fibrosis, prevent apoptosis and protect against oxidative injury.[5, 18]

S-ADENOSYLMETHIONINE: A GLUTATHIONE PRECURSOR

The essential roles of SAMe in health and disease

S-adenosylmethionine (SAMe) is an intermediary metabolite that is synthesised from the amino acid methionine and adenosine triphosphate (ATP) in all living cells.[10,25] Considering that SAMe is a glutathione precursor[26], it is of particular importance in hepatocytes and plays a central role in three important biochemical pathways: hepatic transsulfuration (via which glutathione is generated), transmethylation, and aminopropylation[10]. The liver metabolises nearly 50% of dietary methionine, directly converting approximately 80% of this to SAMe. Thus, it serves as the major site of systemic SAMe synthesis.[5, 27, 28]

> Because severe liver injury can downregulate SAMe synthetase (the enzyme controlling methionine transformation into SAMe), SAMe can become a conditionally essential nutrient.[5, 10, 29]

One major consequence of the limited SAMe production in liver disease is reduced glutathione availability, leading to profound consequences on overall health.[10, 20, 27] SAMe supplementation replenishes hepatic glutathione concentrations and consequently decreases production of reactive oxygen species in dogs.[29] Thus, it effectively protects against the risk of hepatotoxicity, particularly in necro-inflammatory and cholestatic diseases.[5, 19, 21]

DID YOU KNOW?

of dogs and cats with liver disease have reduced glutathione concentrations in the blood and liver, supporting the presence of oxidative damage and the consequential need for antioxidant therapy.[15]

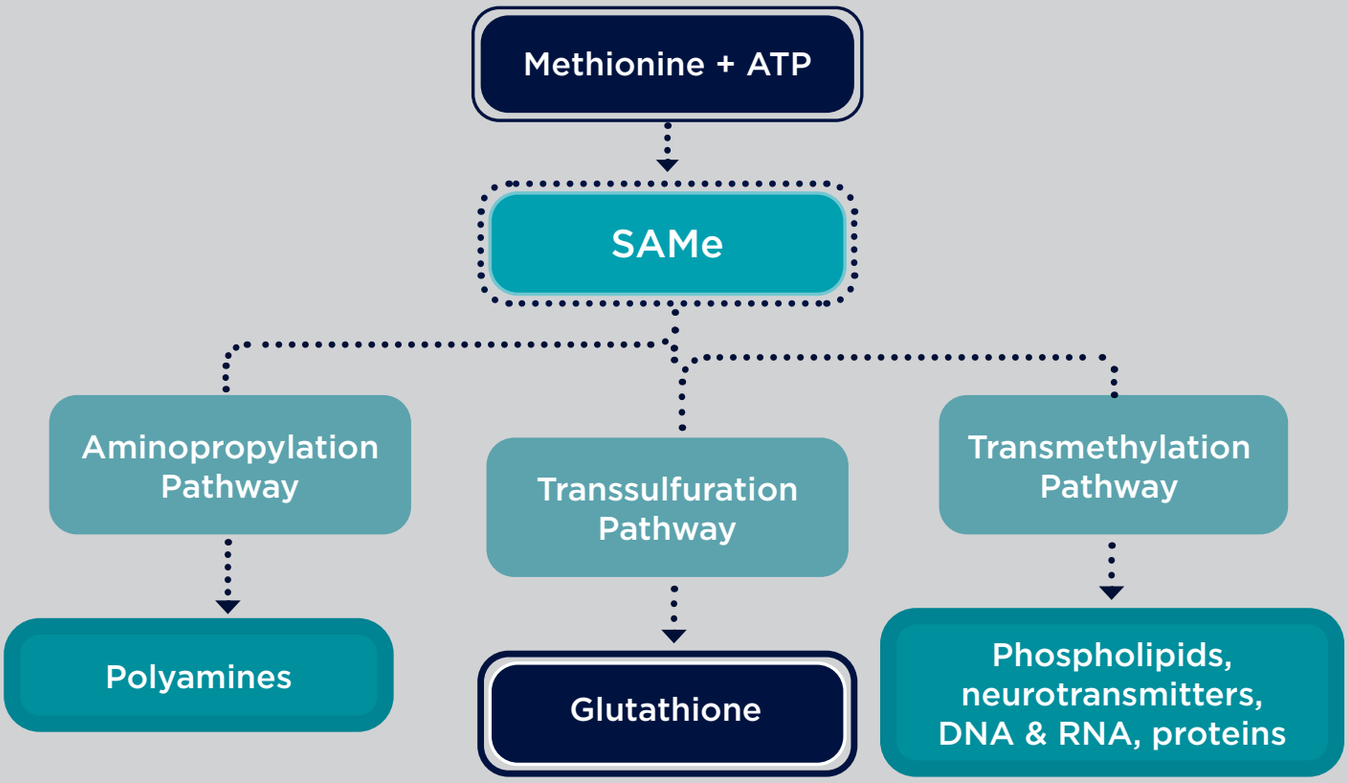


Figure 5. Biochemical pathways of SAMe[27]

DIRECT SUPPLEMENTATION WITH GLUTATHIONE IS INEFFECTIVE

Direct administration of glutathione is without benefit, since it is not readily available for uptake into intracellular sites.[21] As such, supplementation with SAMe is not only highly efficacious, but it also provides a broad spectrum of additional biological effects given its key role in the three metabolic pathways.[22]

NOT ALL SAMe IS THE SAME

The high reactivity and instability of natural SAMe limits its pharmacological potential.[10,30] However, stable synthetic salts, particularly tosylated forms which have a longer half-life, enable the therapeutic use of oral SAMe supplements.[27,31] Caution is advised in selecting a SAMe product because many have unknown bioavailability and vary widely in SAMe content. Prescribe and recommend SAMe products from reputable manufacturers for which bioavailability, pharmacokinetics and product content is known.[29]

SAMe reduces age-related mental decline in senior dogs[25]

Treatment with SAMe reportedly stimulates brain glutathione, thereby reducing oxidative stress, which is increased and strongly implicated in age related cognitive dysfunction.[32]

A randomised, double-blinded, placebo-controlled clinical field trial at five veterinary centres in France, Belgium, and Spain was conducted to determine if oral SAMe supplementation could be useful in the management of cognitive dysfunction in 36 senior dogs.

Seventeen dogs were administered SAMe PO once daily at a mean dose of 18.5 mg/kg, whereas the remaining 19 dogs received placebo tablets according to an identical treatment regimen for a total of two months. Clinical and behavioural evaluations were performed at baseline and then again after four and eight weeks of treatment.

Compared with the placebo group, SAMe supplemented dogs showed a significant improvement in activity and awareness scores (attention to surroundings). Eight out of the 12 behavioural parameters (including disorientation, confusion, learning deficits, change in the sleep-wake cycle and anxiety, amongst others) improved with SAMe supplementation over the study period, compared to 3 out of the 12 parameters in the placebo group.

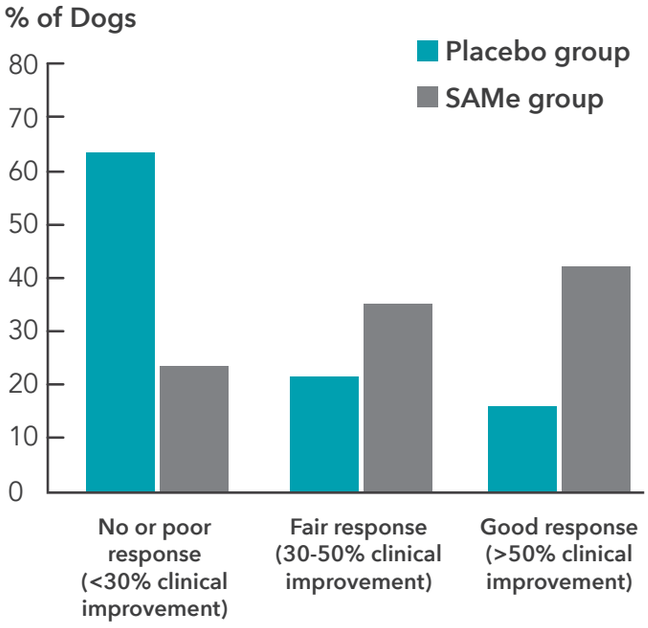


Figure 6. Overall response to treatment as measured on day 60.

SAMe therapy proved to be a safe and effective means of significantly reducing the signs of age- related mental decline in approximately 75% of the treatment cases, resulting in an improved quality of life.

SAME IS PROTECTIVE AGAINST OXIDATIVE INJURY

SAMe reduces haemolysis and increases hepatic glutathione levels in cats with acetaminophen (paracetamol) induced oxidative injury[33]

In a study with 18 cats, three groups of cats were treated according to the following regimes:

- Group ACE: Acetaminophen 90 mg/kg Day 0 as a one-off dose.
- Group ACE-SAMe: Acetaminophen 90 mg/kg Day 0 one-off and then 1 hour later, SAMe 180mg BID Days 0-2, then 90mg BID until Day 14.
- Group SAMe: SAMe 180mg BID for Days 0-2, then 90mg BID until Day 14.

Samples were obtained for PCV, GSH and GSSG evaluation.

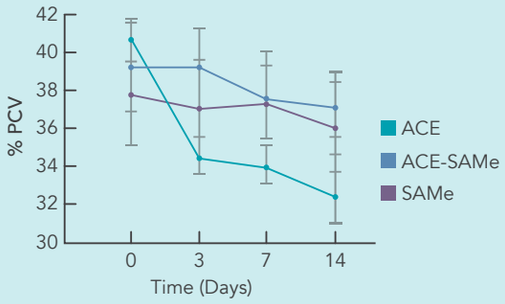


Figure 7. Percentage change in PCV (mean + standard error) with time. SAMe-supplemented groups (ACE-SAMe and SAMe) showed only a 5% and 6% decrease in PCV respectively, in contrast to the ACE only group, which reduced by 20%.

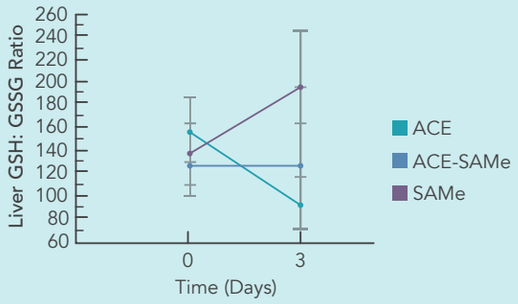


Figure 8. Change ratio of reduced glutathione (GSH) to oxidised glutathione (GSSG) in the liver over time (mean + standard error). Over the first three days, the ratio of 'active' reduced glutathione (GSH) to 'used' oxidised glutathione (GSSG) increased for the SAMe group and was stabilised for the ACE-SAMe group, but reduced markedly for the ACE group, consistent with SAMe mediated protection.

In conclusion, SAMe therapy showed evidence of protecting against acetaminophen-induced oxidative damage through the increase of glutathione levels in the liver and erythrocytes.

The positive impact of S-adenosylmethionine on the redox status of dogs administered prednisolone long term[24]

In a prospective double-blinded, placebo-controlled, crossover trial, S-adenosylmethionine (SAMe) was administered orally to 12 dogs to evaluate its clinicopathologic and hepatic effects induced by long-term administration of prednisolone in dogs.

Dogs were divided into two groups and received prednisolone (2.2 mg/kg) orally once daily for the length of the 84-day trial. One group received SAMe (20 mg/kg/day divided into two doses) for 42 days and then a placebo for 42 days; whilst the other group received treatments in the reverse order.

Administration of SAMe appeared to conserve erythrocyte total glutathione (TGSH) values and significantly increase hepatic TGSH concentration from baseline values, as well as the hepatic tissue GSSG:TGSH ratio.

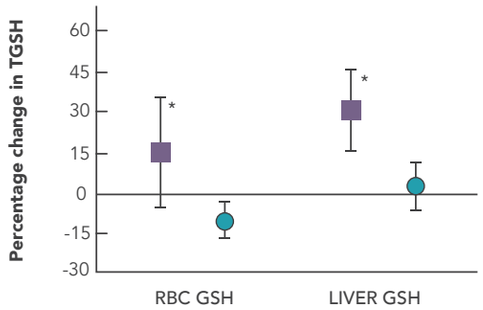


Figure 9. Mean ± SEM percentage change in erythrocyte and liver total glutathione (TGSH) concentrations after 42 days of treatment with SAMe and prednisolone (squares) or placebo and prednisolone (circles) in an 84-day crossover study. *Value significantly different ($P < 0.03$) between treatments.

Although SAMe therapy did not block the development of classic clinicopathologic or histologic features of vacuolar hepatopathy, the results were suggestive that the pro-oxidant influences of prednisolone were counteracted by SAMe through a favourable improvement in RBC and hepatic redox status. Considering that many of the necro- inflammatory and cholestatic liver disorders affecting dogs are treated with high dose glucocorticoids, supportive application of SAMe in this context may be appropriate.

SILYMARIN: ANTIOXIDANT, ANTI-INFLAMMATORY AND ANTIFIBROTIC[5]

What is silymarin?

Silymarin is the major active ingredient of benefit in the milk thistle plant (*Silybum marianum*).[34] A standard milk thistle extract contains approximately 70% of silymarin, which is primarily composed of four flavonoid isomers: silybin A&B, isosilybin A&B, silydianin, and silychristin.[5, 34, 35] Of these, the most abundant and biologically potent is silybin.[28]

Silymarin in liver disease

Silymarin has a wide range of biological effects that are highly beneficial in the treatment of hepatobiliary disease, including antioxidant, anti-inflammatory, and antifibrotic properties. Primarily, silymarin acts as an antioxidant by reducing free radical production and lipid peroxidation. It also scavenges reactive oxygen species and aids in the replenishment of glutathione concentrations.[28, 36]

Additional actions of silymarin include:

- Cell membrane stabilising effects, which are suspected to provide hepatoprotection by inhibiting toxin entry[19, 28]
- Acceleration of hepatic protein synthesis and therefore, hepatocyte regeneration[5, 37]
- Inhibition of leukotriene production and other immunomodulatory effects[18]
- Restoration of the expression and activity of antioxidant enzymes[19]
- Prevention of the conversion of hepatic stellate cells to myofibroblasts (central to the onset of hepatic fibrosis)[36]
- Prevention of cholestasis[36]

Given its multitude of hepatoprotective effects, silymarin administration should be considered in dogs and cats with necro-inflammatory hepatobiliary disease, chronic hepatopathies, and particularly in toxic hepatopathies such as *Amanita* mushroom toxicity for which it is indicated.[5, 28]

IMPROVING SILYBIN BIOAVAILABILITY WITH PHYTOSOME TECHNOLOGY

The bioavailability of polyphenols in silybin can be significantly increased when complexed with phosphatidylcholine.[28] This method, involving the creation of 'phytosomes', has proven to be a breakthrough to increase the efficacy of poorly absorbed plant-based polyphenols.[8, 38]

Phytosomes are formed by bonding silybin molecules (isolated from standardised silymarin) to phosphatidylcholine (PC), a phospholipid preparation.[35] The PC molecules facilitate the passage of silybin polyphenols across the outer cell membrane of the intestinal epithelium, resulting in increased absorption in the bloodstream and significantly greater bioavailability in the liver.[1, 8] This vastly increases its efficacy compared with standard silymarin extracts.[38]

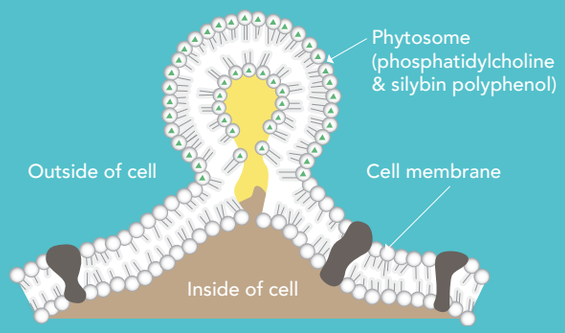


Figure 10. Mechanism of cellular incorporation of phytosomes.

THE ISSUE OF SILYMARIN'S BIOAVAILABILITY

Despite silymarin's undeniable value as a cytoprotective agent in the management of hepatobiliary disease, its effectiveness is limited by its poor solubility in water, rapid metabolism and low bioavailability when given orally, as the polyphenols in silymarin are ineffectively absorbed across the intestinal mucosa.[5, 10, 35, 36, 37]

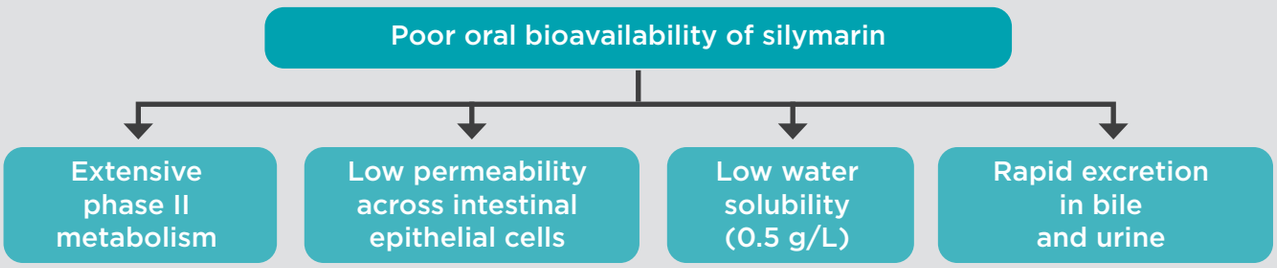


Figure 11. Key factors contributing to the poor oral bioavailability of silymarin

Oral administration of silybin in a phosphatidylcholine complex (SPC) results in greater bioavailability compared with a standard silymarin extract.[39]

In a randomised crossover study involving 16 healthy beagles, each group received either SPC or a commercially available silymarin extract, each containing equivalent amounts of silybin.

Plasma levels of silybin were up to 4.4 times higher in dogs given a silybin phosphatidylcholine complex vs conventional milk thistle extract.

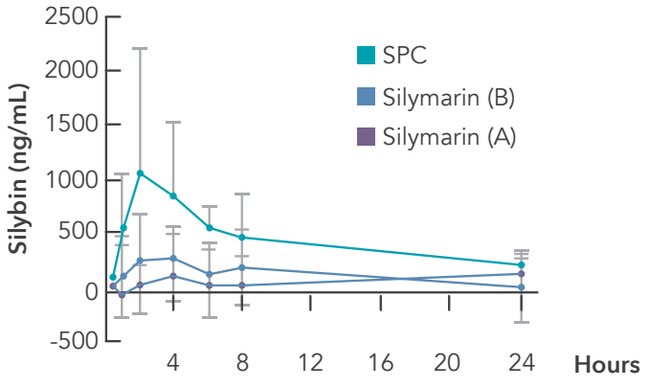


Figure 12. Silybin plasma concentration time course after dosing with SPC/silymarin extract. Values represent mean values ± standard deviation of measured levels.

Efficacy of SAMe + silybin-phosphatidylcholine complex combination for the prevention of chemotherapy-induced hepatopathies in tumour bearing dogs[40]

Increases in liver enzyme activity in 86% of dogs receiving CCNU chemotherapy (lomustine) can occur, resulting in potential treatment delays or the early discontinuation of treatment.

In a prospective randomised study, 50 dogs with lymphoma, mast cell tumour, or histiocytic sarcoma were randomly assigned to one of two groups:

- Group A received treatment with CCNU in conjunction with a SAMe + silybin-phosphatidylcholine complex (SPC) combination product.
- Group B received treatment with CCNU (lomustine) alone

Increased liver enzyme activity occurred in 84% of dogs receiving CCNU alone compared to 68% of dogs on concurrent SAMe + SPC therapy. Dogs receiving CCNU alone had significantly greater increases in ALT, AST, ALKP and bilirubin, and a significantly greater decrease in serum cholesterol concentrations than dogs receiving concurrent SAMe + SPC.

Dogs receiving CCNU alone were also substantially more likely to have treatment delayed or discontinued because of increased ALT activity.

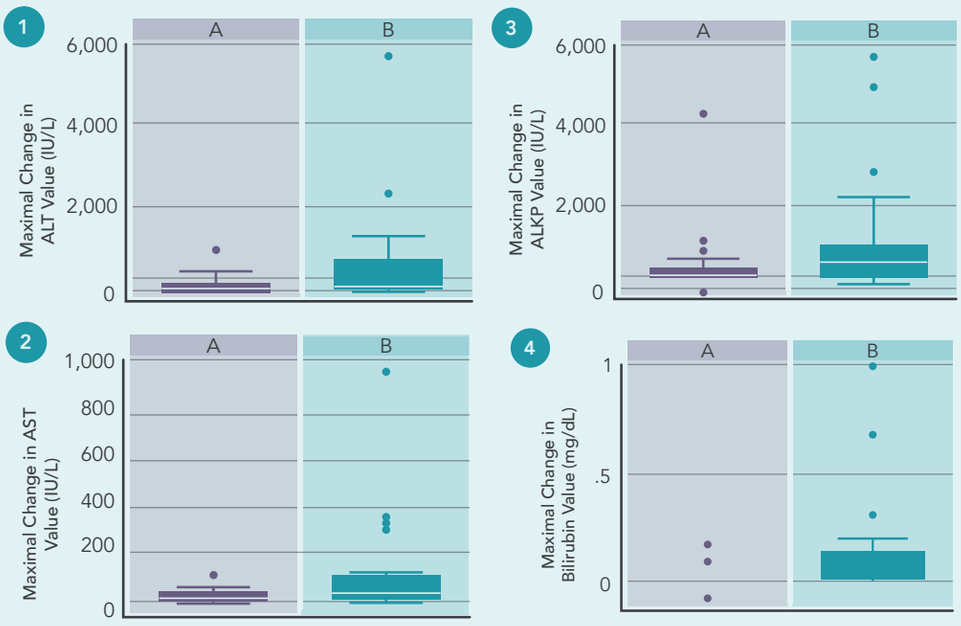


Figure 13. Box and whisker plots of serum chemistry values for Group A (SAMe + SPC treatment group) compared to Group B (CCNU alone) with regards to the maximum changes in (1) alanine aminotransferase (ALT), (2) aspartate aminotransferase (AST), (3) alkaline phosphatase (ALKP), and (4) bilirubin. Statistically significant differences were found for all four of these parameters.

NOTE: Central lines represent the median, boxes represent 25th and 75th percentiles, and whiskers represent 5th and 95th percentiles.

Results support the use of concurrent SAMe + SPC to minimise hepatocellular damage and biliary dysfunction in dogs receiving CCNU chemotherapy, thus preventing treatment delays or early cessation.

VITAMIN E: A POWERFUL ANTIOXIDANT

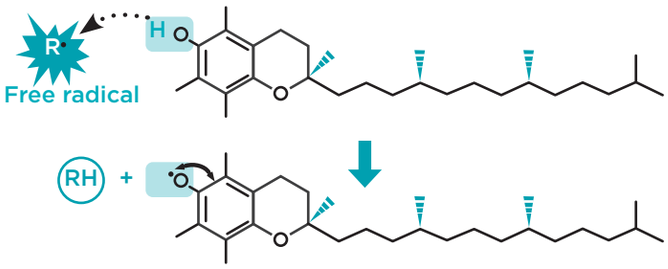


Figure 14. The antioxidant activity of vitamin E is attributed to the hydroxyl group in the tocochromanol aromatic ring, which donates hydrogen to neutralise free radicals and reactive oxygen species.[41]

Abundantly more than 'just' a micronutrient

Vitamin E is a lipid-soluble vitamin and potent endogenous antioxidant that functions as a free radical scavenger to protect membrane phospholipids from peroxidative damage.[15, 20, 28, 42] It is synthesised by plants and found primarily in food sources such as vegetable oils, nuts, seeds and grains.[18, 42]

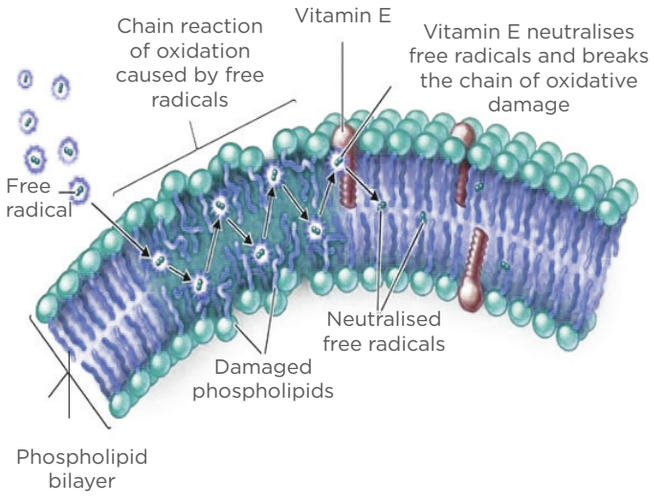


Figure 15. Vitamin E scavenges free radicals, preventing peroxidative damage in membrane phospholipids

The vitamin E family consists of eight isomers- four tocopherols and four tocotrienols of which alpha-tocopherol (or α-tocopherol) is the most bioavailable and biologically active form.[5, 18, 34, 41] The recommended oral formulation of vitamin E is commercially available as d- α –tocopherol.[5]

Aside from its powerful antioxidant properties and role in maintaining membrane integrity, the vitamin E family is also involved in various physiological processes, including immunomodulation, gene expression, regulation of cell signalling pathways that rely on reactive oxygen intermediates, and cell proliferation.[34, 41, 43]

APPLICATIONS FOR VITAMIN E IN HEPATIC DISEASE

Considering that vitamin E plays a key role in the hepatic antioxidant network alongside glutathione, supplementation has been recommended in the nutritional management of hepatobiliary disorders likely to involve oxidative membrane injury such as:[5, 34]

- **Hepatic lipidosis in cats**[15]
- **Copper and iron associated hepatopathies, along with other hepatotoxins**[3, 15, 28, 42]
- **Cholestatic hepatopathies**[5, 42]
- **Necro- inflammatory liver disease**[5]
- **Ischemia-reperfusion injury**[5]

In addition, vitamin E aids in preserving the integrity of hepatocytes and reduces the activation of hepatic stellate cells, thus acting as an antifibrotic.[10, 41] Moreover, similarly to SAMe and silymarin, vitamin E acts to replenish hepatic glutathione levels, further reducing the impact of oxidative damage on hepatocytes[41]. As such, vitamin E should be highly regarded as an adjunctive therapy in the management of liver disease in cats and dogs.

VITAMIN E IS ALSO HIGHLY EFFECTIVE AS AN ANTI-INFLAMMATORY[19, 41, 43]

Vitamin E is one of the most effective immunomodulatory nutrients, in part due to its protective capacity against the oxidation of polyunsaturated fatty acids which are enriched in membranes of immune cells. Vitamin E has been reported to inhibit the activation and release of 5 lipoxygenases, cytokines and Kupffer cells, all of which can play a significant role in contributing to inflammation in hepatocytes and thus, liver injury.

DID YOU KNOW?

Given the abundance of benefits, absence of side effects and the inexpensive nature of vitamin E, many veterinary hepatologists routinely prescribe vitamin E therapy to their liver patients.[15]

Dietary vitamin E has a beneficial effect on the oxidant status of dogs with chronic hepatitis.[44]

The effects of vitamin E supplementation were evaluated in a placebo-controlled clinical trial of 20 dogs with chronic inflammatory liver disease, treated only with a vitamin E supplemented diet for three months. Dogs were randomised into two groups and fed either an unsupplemented diet, providing approximately 0.58 IU alpha tocopherol acetate/kg bodyweight/day or a diet supplemented with additional vitamin E, providing 7 IU alpha tocopherol acetate/kg bodyweight/day for three months. No additional anti-inflammatory or antioxidant therapy was given.

Dogs were evaluated prior to, as well as at one and three months during the trial period for clinical body condition scores. Laboratory analyses such as serum biochemistry, hepatic metal content and glutathione concentrations, amongst others, were also conducted.

Although no significant changes in clinical body condition score, histological score, or hepatic metal content were identified in vitamin E supplemented dogs, significant increases in serum and hepatic vitamin E concentrations following therapy were accompanied by an increased hepatic GSH:GSSG ratio, suggestive of a reduction in oxidative stress when compared to the non-supplemented group.

A significant decrease in mean ALT concentrations in the supplemented group was also evident.

The results of this trial suggest that vitamin E supplementation has a positive effect on the oxidant status of dogs affected with chronic inflammatory liver disease.

SAMe, SILYBIN AND VITAMIN E SUPPORT LIVER HEALTH WITH AN ABUNDANCE OF BENEFITS

A. Promotes protein synthesis

B. Increases glutathione levels
Cytoprotective

C. Membrane stabilising effects

D. Antioxidant
Antifibrotic
Anti-inflammatory

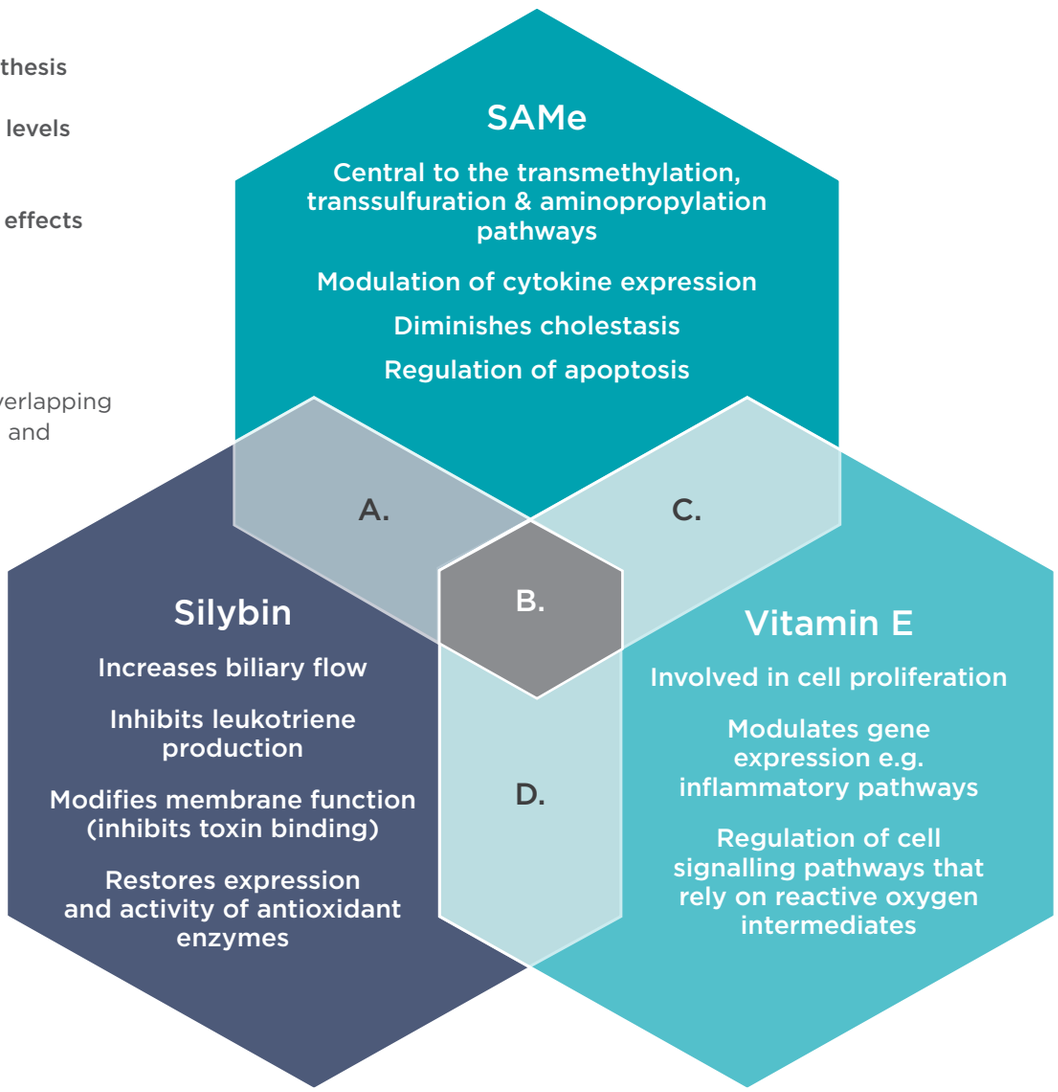


Figure 16. Unique and overlapping benefits of SAMe, silybin and vitamin E for liver health

PAW HEPATOADVANCED®: ANTIOXIDANT SUPPORT FOR DOGS & CATS WITH LIVER DISEASE

PAW HepatoAdvanced® is a convenient, chewable tablet containing a blend of bioavailable antioxidants, providing detoxification support in the management of canine and feline liver disease via the following means:

- **Supports the production of glutathione**
- **Promotes liver detoxification**
- **May protect against negative effects on the liver caused by some medications**
- **Supports liver health in pets presenting with acute liver toxicity**
- **Supports brain health in dogs**

Active ingredients	Cat & Small Dog	Medium & Large Dog
S-Adenosyl-L-methionine disulfate p-toluenesulfonate (Equivalent to SAMe)	50 mg	310 mg
D-alpha tocopherol succinate (Vitamin E)	45 IU	200 IU
Silybin Phospholipids Equivalent to silybin phosphatidylcholine (Equivalent to silybin A+B)	13 mg	90 mg

Size: 60 chewable tablets (Cat and Small Dog), 30 chewable tablets (Medium and Large Dog)
Storage: Store below 25°C in a dry place away from sunlight
Expiry: 24 months

Dosing Chart		
Weight Range	**Cat & Small Dog**	**Medium & Large Dog**
1 kg – 2.4 kg	1 chewable tablet	
2.5 kg - 9.9 kg	2 chewable tablets	
10 kg – 14.9 kg	3 chewable tablets	½ chewable tablet
15 kg – 29.9 kg		1 chewable tablet
30 kg - 59.9 kg		2 chewable tablets*

***DO NOT** exceed 2 chewable tablets per day

For optimal absorption, administer HepatoAdvanced® (as per the dosing chart above), once a day on an empty stomach.
The recommended total daily dose for dogs and cats is SAMe 10- 20mg/kg, SPC 2.7- 5.4mg/kg and vitamin E 10-15IU/kg.

HepatoAdvanced® can be used concomitantly with other common hepatic supportive treatments, such as prescription diets, ursodeoxycholic acid, anti-inflammatories, and other non- vitamin E containing nutritional supplements.

Regular re-assessment (e.g. every 1-3 months) is recommended to ensure the optimal dose is achieved to reach the desired therapeutic outcome.

FEATURES AND BENEFITS

Simple and convenient dosing in the form of a tasty chewable tablet, *with a new, smaller and easier to dose size for cats and small dogs*

Formulated with delayed release technology, enabling steady metabolism by the liver and a prolonged duration of activity

Contains a unique and stable form of S-adenosylmethionine (SAMe), a precursor to the potent antioxidant glutathione, which is hepatoprotective

Contains silybin (clinically trialled Siliphos®) in a phospholipid complex, which has been shown to provide significantly enhanced bioavailability in dogs and cats compared to standardised milk thistle

Contains vitamin E in its formulation, preventing the need for additional supplementation

WARNINGS/SAFETY

- For animal use only.
- For veterinary supply only.
- Use with caution in pregnant or lactating animals as safe use has not been established in this population
- SAMe has a wide safety margin. Side effects or overdose effects are rare, but are limited to mild gastrointestinal signs, immediate post pill nausea and food refusal.[34]
- Concomitant use of SAMe with tramadol, meperidine, dextromethorphan, pentazocine, MAOIs (selegiline), SSRIs (fluoxetine) and other anti-depressants (amitriptyline, clomipramine) may theoretically cause additive serotonergic effects. Use with caution simultaneously.[30]
- Silymarin typically has no side effects, but consider drug interactions in polymedicated patients, such as the following: antiviral drugs, drugs affected by cytochrome P450 & CYP3A4 inhibition and drugs cleared via hepatic glucuronidation.
- There are no commonly noted toxic effects derived from vitamin E supplementation, although it may inhibit the absorption of other fat- soluble vitamins when administered at high doses. Therefore, it is recommended to not exceed a total daily dose of 400IU per dog.[4,5,10,34] Vitamin E is not recommended in liver disease patients with evidence of vitamin K deficiency.[10]
- Please read the label and follow the directions for use.

HepatoAdvanced® may be used as an adjunctive therapy in conditions such as:

- Chronic hepatitis
- Hepatic lipidosis
- Cholangiohepatitis
- Paracetamol toxicity
- Hepatotoxic mushroom ingestion
- Copper related hepatopathy
- Iron overload
- Medication use including NSAIDs, phenobarbital and corticosteroids (note: does not prevent corticosteroid-induced hepatic vacuolar change)
- Metabolic hepatopathies
- Other acute or chronic hepatopathies
- Neoplasia
- Canine cognitive dysfunction
- Cirrhosis

PAW HEPATOADVANCED®: CLINICAL CASE STUDY

‘HARVEY’

8 year, 7 month old male - neutered Golden Retriever

Case history

Harvey initially presented for a Synovan injection as part of his arthritis management regime, and routine full screening bloods. No concerns were reported by the owner aside from the occasional sneeze.

Clinical examination

Harvey’s physical examination revealed no abnormalities aside from mild-moderate stiffness in range of motion on caudal extension of his coxofemoral joints, along with mild reactivity to stifle manipulation consistent with osteoarthritis.

Initial blood pathology

Full blood work revealed the following abnormalities:

- Markedly elevated ALT: 1,433 (ref range: 16 - 90 U/L)
- Mildly elevated AST: 115 (ref range: 18 - 80 U/L)
- Mildly elevated ALP: 157 (ref range: 1 - 150 U/L)
- Moderately elevated GGT: 15 (ref range: 0 - 9 U/L)

With all liver parameters elevated, moderate concerns around Harvey’s hepatocellular function were raised, prompting the need for further investigation.

Further diagnostics: abdominal ultrasonography

An abdominal ultrasound was performed 3 weeks later under sedation.

The following findings were noted:

- One small hypoechoic splenic nodule (likely benign) - well defined and with a low blood supply
- A subjectively small liver that was grossly homogenous with no overt lesions detected. The left side was difficult to image as it was deep and overlayed by a gas-filled stomach
- A clear gall bladder, with no other abnormalities detected

Differential diagnoses

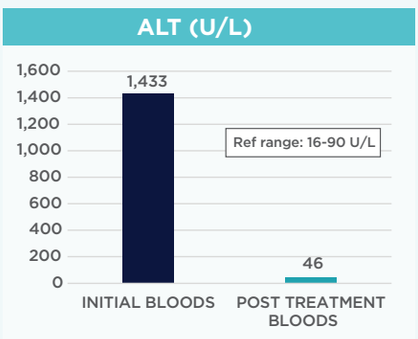
Hepatotoxins, chronic hepatitis (bacterial vs immune mediated) and neoplasia.

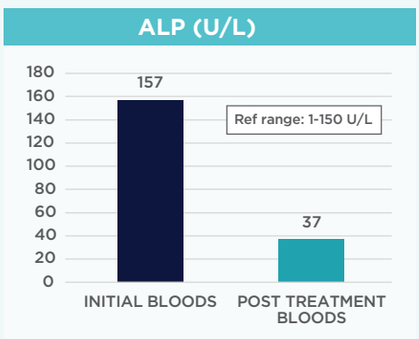
Treatment plan

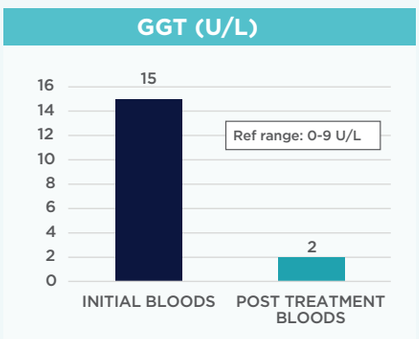
Harvey was commenced on PAW HepatoAdvanced® Medium-Large Dog at a dosage of 1.5 tablets once daily, with the view to repeat biochemistry thereafter. If liver parameters remained elevated despite therapy, the plan was to proceed with a bile acids tolerance test, with a liver biopsy as a potential next step pending the findings.

OUTCOME

Harvey presented 8 weeks later for a follow up and repeat blood work. No clinical concerns were communicated by the owner.







Following treatment with PAW HepatoAdvanced® for 8 weeks, all liver parameters were back within normal limits.*

*No repeat AST results were provided.

Introducing the PAW Practitioner Range

Developed for vets, by vets.

Learn about integrative veterinary medicine!

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