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Effect of hepatogomax on serum alkaline phosphatase, bilirubin, gamma-glutamyl transferase levels in Sprague Dawley rats cirrhosis

Pengaruh hepatogomax terhadap kadar serum alkaline phosphatase, bilirubin, gamma-glutamyl transferase pada tikus Sprague Dawley sirosis

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Abstract

Cirrhosis is the final stage of all chronic liver diseases. Complications that occur are malnutrition. Administration of Hepatogomax as an enteral formula with adequate nutrients, specifically Branched-Chain Amino Acids (BCAA) and Medium-chain Triglyceride (MCT), can reduce serum ALP, bilirubin, and GG levels. This study aimed to determine the effect of hepatogomax in different doses on serum ALP, bilirubin, and GG levels. The study used the True Experimental post-test group design. Twenty-four male rats were divided into control group K normal and K(-) cirrhotic, treatment groups P1 and P2, given TAA and hepatogomax induction, respectively, at doses of 4,87 g/200gBW/day and 14,6 g/200gBW/day. Intervention for 28 days at the PAU Laboratory, Gadjah Mada University, February 2022 to April 2022. Statistical analysis used the Kruskal Wallis and Mann Whitney Post Hoc tests. The data is the result of examining serum levels after the intervention. The results showed significant differences in ALP, bilirubin, and GGT ($p<0,05$) in the group of rats induced by TAA intervention with hepatogomax compared to those not given hepatogomax. There was no significant difference in the decrease in serum ALP levels between the K normal ($p<0,05$) and P2 ($p>0,05$) groups. Giving hepatogomax at a dose of 14,6 g/200BB/day reduced serum ALP, bilirubin, and GG levels. In conclusion, Hepatogomax decreased ALP, bilirubin, and GGT serum levels in rats with cirrhosis. The most significant decrease in serum ALP, bilirubin, and GGT levels was observed at the P2 dose.
Keywords: ALP, bilirubin, cirrhosis, hepatogomax, GGT, malnutrition

Abstrak

Sirosis merupakan tahap akhir dari semua penyakit hati kronis. Komplikasi yang terjadi adalah malnutrisi. Pemberian Hepatogomax sebagai formula enteral dengan zat gizi adekuat nutrisi spesifik *Branched-Chain Amino Acids (BCAA)* dan *Medium-chain Triglyceride (MCT)* dapat menurunkan kadar serum ALP, bilirubin, dan GGT. Penelitian betujuan untuk mengetahui pengaruh hepatogomax dalam dosis yang berbeda terhadap kadar serum ALP, bilirubin, dan GGT. Penelitian menggunakan desain *True Exsperimental post test group design*. Dua puluh empat tikus jantan dibagi menjadi: kelompok kontrol K normal dan K(-) sirosis, kelompok perlakuan P1dan P2, diberi induksi TAA dan hepatogomax masing-masing dosis 4,87 g/200gBB/hari dan 14,6 g/200gBB/hari. Pemberian intervensi selama 28 hari di Laboratorium PAU Universitas Gadjah Mada Maret 2022 sampai April 2022. Analisis statistik menggunakan uji *Kruskall Wallis* dan uji *Post Hoc Mann Whiteney*. Data adalah hasil pemeriksaan kadar serum sesudah intervensi. Hasil menunjukkan terdapat perbedaan kadar serum ALP, bilirubin dan GGT yang signifikan masing-masing ($p<0,05$) pada kelompok tikus yang diinduksi TAA intervensi hepatogomax dibandingkan dengan kelompok yang tidak diberikan hepatogomax. Tidak terdapat perbedaan

penurunan kadar serum ALP yang signifikan antara kelompok K normal (p<0,05) dan P2 (p>0,05). Pemberian hepatogomax dosis 14,6 g/200 BB/hari berpengaruh menurunkan kadar serum ALP, bilirubin, dan GGT. Kesimpulan**,** Hepatogomax berpengaruh terhadap penurunan kadar serum ALP, bilirubin, dan GGT pada kelompok tikus yang sirosis hati. Penurunan kadar serum ALP, bilirubin, dan GGT diamati paling besar pada dosis P2.
Kata Kunci: ALP, bilirubin, hepatogomax, GGT, malnutrisi, sirosis

Introduction

Chronic liver disease is one of the most severe health problems worldwide, with more than 1,2 million deaths yearly due to liver cirrhosis (Shashidhar & Nallagangula, 2019). Malnutrition is a common complication of liver cirrhosis is malnutrition. Malnutrition in cirrhosis for a long time leads to morbidity and mortality and is the final stage of all chronic liver diseases (Ruiz-Margáin et al., 2018). The prevalence of malnutrition in patients with cirrhosis is 65-90% (Shashidhar & Nallagangula, 2019).

Liver cirrhosis in Indonesia is one of the most significant causes of death, with a death rate of 48.900 people, or about 3,2% of the total deaths yearly (Yusra et al., 2020). Liver cirrhosis is associated with protein-energy malnutrition and low physical activity, which can cause sarcopenia. The incidence of protein malnutrition ranges between 20-30% of chronic liver disease patients and more than 60% of cirrhosis patients. A lack of macro energy nutrition and proteins characterizes malnutrition in cirrhosis (Abdelbasset et al., 2021).

Cirrhosis and malnutrition can cause complications with 71,3% and 41,4% mortality rates, respectively, compared to non-malnutritional patients (38,2% and 18,2%, respectively). Malnutrition occurs due to several factors, including lack of intake, absorption disorders, and hypermetabolism (Purba & Sinurat, 2018). Liver cirrhosis and its complications are health problems that are difficult to solve in Indonesia. The risk of malnutrition is higher in patients who frequently consume alcohol (*Laennec cirrhosis*), which results in liver lesions, such as fatty liver, alcoholic hepatitis, and alcoholic cirrhosis (Rashati & Eryani, 2019). This disorder occurs when the liver is injured and loses its function (Shashidhar & Nallagangula, 2019). Enteral therapy for cirrhosis disorders is administered with a hepatogomax.

Hepatogomax is an enteral formula made from soy flour, goat milk flour, coconut oil, maltodextrin, and sugar. Hepatogomax also contains high *Branched-Chain Amino Acids* (BCAA) and *Medium-chain Triglycerides* (MCT). The nutritional value of hepatogomax for energy density is 1,17 kcal/ml, protein 6,70%, fat 27,33%, and carbohydrate 65,97% with protein serenity 53,44% and with the best formulation is the comparison of soy flour and goat milk flour 45:55. (Rahmadanti et al., 2020)

Different therapeutic approaches have been used to improve nutritional status in cirrhosis, including high-protein and high-dietary supplementation with micronutrients, such as vitamins and minerals, and exercise (Ruiz-Margáin et al., 2018). Previous research has suggested that BCAA supplementation can prevent liver damage (Eguchi et al., 2021). Liver cirrhosis in vivo animal studies was conducted using *thioacetamide induction* (TAA) (Al-Attar & Al-Rethea, 2017).

Patients with malnutrition and liver cirrhosis require special therapy at a high cost. The use of commercial enteral products in hospitals can increase unit costs. The cost is less helpful in the middle society, so choosing a local food product, hepatoma, is an alternative to repair disorders and damage liver function (Choirun Nissa, Ayu Rahadiyanti, Fillah Fithra Dieny, 2019).

Enteral nutrition therapy for hepatoma products has been studied; however, the contents of BCAAs and MCTs have not been studied. Based on the above description, hepatogomax" is based on soy flour and goat milk flour, as well as the content of BCAAs and MCTs potentially against a decrease in *serum alkaline phosphatase* (ALP), *bilirubin*, and *gamma-glutamyl transferase (GGT)* levels. This study aimed to determine the effects of hepatogomax on the serum levels of ALP, bilirubin, and GGT in Sprague Dawley mice with TAA-induced cirrhosis.

Methods

The True Experimental post-test group design research was conducted from September 2021 to April 2022. The samples were tested at the

University of Gadjah Mada (UGM) in Yogyakarta. The enteral formula hepatogomax was manufactured at the Food Technology Science Laboratory, Diponegoro University. The BCCA hepatogomax examination was performed at the IPB University Laboratory. MCT examination was carried out at the UGM Integrated Research and Testing Laboratory (LPPT), and blood analysis examination in the PSPG (Food and Nutrition Study Center) UGM Yogyakarta unit using spectrophotometry techniques.

The study sample consisted of twenty-four male Sprague Dawley mice aged eight weeks weighing 150-250 grams with conditioned liver cirrhosis and induced TAA. Twenty samples plus 10%. A pure experiment. The inclusion criteria were male Sprague-Dawley rats aged 8-12 weeks weighing 150-250 g, healthy, actively moving, not experiencing disease and exclusion abnormalities, and dying during treatment. Animal destruction was stopped by administering a ketamine dose of 100 mg and burned with an incinerator.

The Diponegoro University School of Medicine approved this study (number: 14/EC/H/FK-UNDIP/II/2022). Data collection and measurement. The independent variables; Hepatogomax is an enteral formula made from soy flour, goat milk flour, coconut oil, maltodextrin, and sugar. The enteral formula was administered using a probe at 20 ml/day for 28 days. Treatment:1 dose of 4,87 g/200 g w/day, treatment 2: 14,6 g/200 g w/day, and each dose was diluted to 20 ml with a dose divided by 2x. *Alkaline serum phosphatase* (ALP) is an enzyme that catalyzes the transformation of organic phosphate into an organic phosphatase that plays an important role in the protein breakdown process. Serum bilirubin is a substance normally formed from the breakdown of red blood cells in the body. Serum *gamma-glutamyl transferase (GGT)* plays an important role in the metabolism of drugs in the heart.

Enteral formula manufacturing tools: digital scales with a density of 0.1 grams, containers, tablespoons, and mixers. Treatment of animals: rat cages, eating and drinking places, probes, and analytical scales. Serum levels of ALP, bilirubin, and GGT: reaction tube shelves, reaction tubes, centrifuges, spectrophotometry, gloves, pipettes, filters, and measuring glasses.

Ingredients of Hepatogomax enteral formula include soy flour, goat milk, coconut oil, *maltodextrin*, and sugar. *Thioacetamide (TAA)* was injected at 400 mg/kg body weight for two weeks. Animal treatment: Standard *AD-II feed* and drinking water ad libitum. Tests for serum levels of ALP, bilirubin and GGT: ALP reagents, Bilirubin, GGT. Research carried out: The hepatogomax formula was manufactured by composing the composition of each ingredient, namely soy flour, goat milk, coconut oil, maltodextrin, and sugar. All the ingredients were mixed using a blender and mixer to ensure homogeneity.

Standard *ad libitum* feeding was provided during animal adaptation. Feeding in the treatment group was given ad libitum as long as the trial animals were administered the enteral formula intervention Hepatogomax. The standard food was weighed every morning and given as much as 10% of the rat's body weight, with a maximum of 20 g/day. Weights were recorded weekly, and the rest of the feed was weighed daily. The room temperature was 20-24 C the humidity was 60%. Mice were treated with *thioacetamide* (TAA) at 400 mg/kg weight for two weeks. The injection was administered *intraperitoneally (IP).*

The administration of the intervention in the treatment group was according to the dose diluted to 20 ml, with the administration divided into 2x. The surgery lasted for 28 days. Course: Standard feeding adaptation for seven days and acclimatization, rats randomized according to group division, one normal group (KN), and three rat groups K(-): cirrhosis group without intervention, P1: cirrhose group 1, P2: cirrhosis group 2) induced with TAA 400 mg/kg weight for two weeks (14 hari). Two groups of mice with cirrhosis were administered the intervention for 28 days.

Serum ALP, bilirubin, and GGT levels Statistical data analysis was used; the results of the Shapiro Wilk test after hepatogomax intervention showed an abnormal distribution ($p<0,05$), so the non-parametric statistical test of one-way ANOVA and the Kruskal Wallis test was used.

Result and Discussion

Serum levels of ALP, bilirubin, and GGT were measured after administration of the hepatogomax intervention for 28 days. The analysis showed significant differences in the

serum levels of ALP, bilirubin, and GGT in each group (Tabel 1). Serum levels of ALP, bilirubin, and GGT in SD mice on the 28th day after administration of the intervention were lower at the dose of P2 compared to P1 and the control group that did not receive the intervention. The serum levels of ALP, bilirubin, and GGT given intervention at P2 doses of 14,6 g/200 g w/day compared with the normal group, showed almost the same results.

Table 1. The difference in serum levels of ALP, bilirubin, and GGT after hepatogomax intervention

Group Treatment		Serum Value (Mean±SD)	p-value#			
			KN	K(-)	p1	p2
ALP	KN	33,31 ± 2,94	-	0,004#	0,004#	0,318
	K(-)	60,42 ± 1,82	-	-	0,004#	0,003#
	P1	45,72 ± 1,61	-	-	-	0,003#
	P2	33,77 ± 0,75	-	-	-	-
	P*	0,000				
Bilirubin	KN	0,40 ± 0,10	-	0,004#	0,003#	0,020#
	K(-)	1,66 ± 0,17	-	-	0,003#	0,004#
	P1	1,04 ± 0,07	-	-	-	0,003#
	P2	0,59 ± 0,10	-	-	-	-
	P*	0,000				
GGT	KN	11,96 ± 0,53	-	0,004#	0,003#	0,011#
	K(-)	46,30 ± 2,17	-	-	0,004#	0,004#
	P1	31,85 ± 0,53	-	-	-	0,003#
	P2	13,97 ± 1,15	-	-	-	-
	P*	0,000				

SD: standard deviation, p*: Kruskal-Wallis test for differences in serum levels of ALP, bilirubin, and GGT; p#: Post-hoc Mann-Whitney test to determine differences between groups. KN: Normal, K(-): cirrhosis, p1: Intervention dose of 4,87 g/200 g w/day, p2: Intervention dosage of 14,6 g/200 g w/day

The results showed significant differences in ALP, bilirubin, and GGT serum levels between the treatment groups ($p < 0,05$). The homogeneity significance values showed similar variations in the ALP, *bilirubin*, and GGT data ($p > 0,05$), so *a post-hoc Mann-Whitney test* was performed to determine which groups had differences in serum ALP and GGT levels after hepatogomax intervention (Table 1). The *post-hoc Mann–Whitney* test results showed a significant difference. Serum ALP levels in the KN group were significantly different from those in the K(-) and P1 groups ($p < 0,05$). Compared to P2, the KN group showed an insignificant difference ($p > 0,05$). Group K(-), compared with P1 and P2, showed significant differences, and group P1, compared to P2, also showed significant differences ($p < 0,05$).

Serum *bilirubin* levels in the KN group were compared to those in the K(-), P1, and P2 groups. The same is true for group K(-) compared to P1 and P2. Furthermore, the group P1 compared to P2 showed a significant difference ($p < 0,05$).

Serum levels of GGT in the KN group were significantly different from those in the K(-), P1, and P2 groups. Group K(-) also showed significant differences from P1 and P2. Similarly, the P1 group showed significant differences compared with the P2 group. There is an effect of the administration of hepatogomax in lowering serum levels of ALP, *bilirubin*, and GGT based on different doses. The most significant decrease in ALP, bilirubin, and GGT serum levels was observed at P2 ($p < 0,05$).

Given the enteral formula hepatogomax during the treatment process, some SD mice showed symptoms of overindulgence, followed by weight gain. Weight gain is likely to occur due to the metabolic processes of the body and the effects of the intake of hepatogomax formula, which has a high-energy protein nutrient content, especially the content of BCAAs and MCT sources, helps in absorption metabolism, is easily digested, and can be quickly absorbed by the intestines. The control group of mice with normal K had good weight gain, whereas the cirrhosis group with K(-) had less weight gain. If not intervened for a long time, this cirrhosis condition leads to a decrease in nutritional status.

Research on cirrhotic mice without intervention resulted in weight gain, possibly because characteristic mice received the same treatment as individual cages, standard feed, aquadest, cage hygiene, and room humidity. Cirrhotic mice that did not undergo intervention experienced a lack of calories and proteins. Reduced protein energy intake in cirrhosis conditions causes protein metabolism disorders that negatively affect nutritional status, which can increase the risk of malnutrition complications in the long run if not treated. Reduced liver function resulted in mice being unable to receive a standard 20g/day feed intake with 4,1 cal energy, 1 g fat and 3,8 g protein. This study is consistent with the previous statements that regardless of any etiology, calorie protein malnutrition can develop a risk of complications and death (Park et al., 2020).

Unbalanced metabolism occurs because of inadequate intake of nutrients, hypermetabolic conditions in cirrhosis, reduced synthetic capacity of the liver, and impaired nutritional absorption. Cirrhosis is hypermetabolic with energy consumption > 120%, which causes a decrease in nutritional status to malnutrition. Hormones control the nutrient intake and metabolism that affect cirrhosis. In cirrhosis, the level of ghrelin, an *orexigenic* hormone derived from peripheral hormones, increases appetite and food intake. *Ghrelin* has a broad spectrum of other metabolic functions in glucose metabolism and weight control (Traub et al., 2021).

The normal K control group and K(-) cirrhosis group were not given intervention; the group was given only standard feed and aquades. The standard feed intake in the normal K group was acceptable. In contrast, the intake of the K(-) cirrhosis group was not acceptable at 100%, as seen from the daily feed residual rate. Each mouse's characteristics include weight differences, cage adaptation, ability to receive standard feed intake, absorption levels, and oxidative stress. It can also be affected, meaning some mice can get standard feed well. The remaining feeding is also likely due to hyperinsulinemia and insulin resistance to cirrhosis; increased insulin levels induce a feeling of satiety, leading to decreased energy intake (Traub et al., 2021).

Conditioning mice with cirrhosis with TAA induction may increase serum levels of ALP, bilirubin, and GGT due to the presence of liver metabolism by cytochrome P450 (CYP450) to form toxic metabolites, which are free radicals that bind macromolecules of the liver without accompanying nutritional therapy. Cirrhosis occurs because liver cells suffer damage to liver architecture, the accumulation of connective tissue, and there are nodules in liver tissue (Rosida, 2016).

High GGT levels are caused by inflammation and oxidative stress (Setianingrum & Padaga, 2019). High bilirubin, due to disruption of portal blood flow, leads to inhibition of bilirubin and portosystemic shunting excretion, thus increasing hemolysis (Yusra et al., 2020).

High ALP levels are caused by gallbladder blockage, bone disease, and liver metastasis (Zakaria et al., 2011). Liver cirrhosis is disorganized, and liver fibrosis is characterized by inflammation and intrahepatic biliary obstruction (Ra et al., 2019).

The intervention group P2 doses of 14.6 g/200 g w/day (ALP; p =0.318) compared to normal K did not differ. These results showed that hepatogomax at a dose of 14,6 g/200 g w/day resembled or was almost equal to that of the normal group K; thus, dose P2 was best for lowering serum levels of ALP, bilirubin and GGT in mice with cirrhosis of the liver.

ALP is an enzyme used to evaluate cholestasis function. ALP is a metalloenzyme that contains Zn as an integral part of the molecule and requires Co2+, Mg2+ or Mn2+ as its activator. The enzyme will catalyze the transformation of organic phosphate into inorganic phosphates (Silva et al., 2015).

Increased ALP activity in extrahepatic obstructions (Shashidar et al., 2019). Bilirubin is a sensitive marker for knowing the function of the bile. An increase in bilirubin leads to the inhibition of the bilirubin conjugation process and a disturbance in the excretion of conjugated bilirubin, resulting in hyperbilirubinemia (Yusra et al., 2020).

GGT is an enzyme found in liver cells, kidneys, and pancreas and plays an essential role in the metabolism of drugs in the liver. High GGT levels are associated with inflammation and oxidative stress. Serum GGT catalyzes the first step in the degradation of the extracellular antioxidant glutathione, allowing the precursor amino acids to be reused for intracellular synthesis (Setianingrum & Padaga, 2019). Liver function biomarkers such as ALP, bilirubin, and GGT are used to diagnose liver dysfunction.

The group of mice induced by TAA and given hepatogomax intervention experienced decreased serum levels of ALP, bilirubin, and GGT due to the high content of carbohydrates, protein, fat, and other nutrients and BCAAs and MCTs. Hepatogomax has a 65.97% carbohydrate nutrient composition, 6,70% protein, 27,33% fat, and 4,54 grams of BCAAs, can improve *the Fischer* ratio and muscle protein *recovery* process, and 29.26% MCT fat sources fix malnutrition cirrhosis much faster. The absorption of proteins in the body affects cells' metabolism, causing various biological responses. BCAAs and MCTs can reduce the formation of free radicals and help protect cells from damage due to free radical exposure. The BCAA content found in hepatogomax helps improve liver cirrhosis. Another factor is the standard feed, which has a protein content of 3.8 grams per day and can also maintain the balance of the rat's body weight.

Previous research has found that hepatogomax comes from pure coconut oil, soy flour, and goat milk flour. Vegetable fats, especially soybeans, are rich in phospholipids such as lecithin (*phosphatidylcholines*), which can increase the absorption of nutrients into cells through its function as a protective cell membrane. *Virgin coconut oil (VCO*) and goat milk contain *medium-chain triacylglycerol* (MCT), which has accessible digestive properties, is a quick energy source, and is not stored in body fat. Fatty delivery in MCT plays a role in managing fat malabsorption disorders in patients with cirrhosis (Rahmadanti et al., 2020).

Hepatogomax contains BCAAs consisting of the amino acids leucine, isoleucine, and valine, which are easily tolerated by the body. The results of this study found that hepatogomax had a BCAA content of 4,54 g consisting of (leucine 2,03 g, isoleucine 1,22 g, and valine 1,29 g) in humans if converted to rats to 0,082 g and the MCT content of hepatOGOMAX 4,34 g when converted into mice to 0.078 g. High carbohydrate intake in hepatogomax is helpful to help prevent hypoglycemia due to disturbances in glycogen synthesis and limited glycogen storage in the liver due to cirrhosis. Hepatogomax also has a high energy density for liver disease patients to prevent the occurrence of malnutrition as well as the presence of fluid restriction to prevent acid and oedema (Rahmadanti et al., 2020)

Previous research has shown that BCAAs can decrease ROS production by activating antioxidant mechanisms, which improves glucose metabolism via the *liver's forkhead box protein O1(FoxO1) pathway* (Iwasa et al., 2013). Hepatogomax at a dose of 14.6 g/day for 28 days may lower serum ALP, bilirubin, and GGT levels to levels equivalent to those in the normal K group. The results of chloroform fraction identification using gas-mass spectroscopy indicated the presence of BCAAs that can help repair liver cirrhosis damage.

Other studies also showed that administering hepatogomax at a dose of 14,6 g/200 g w/day decreased serum ALT, AST, and albumin levels. This study was in line with previous studies. It showed that the nutritional content of Hepatogomax P2 doses 14,6 g/200 gBB/day had energy 128,85 kcal, fat 3,89 g, protein 5,27 g, carbohydrates 19,67 g, BCAA 0,25 g and MCT 4,34 g able to improve liver function in malnourished cirrhosis mice. Another study found that animals induced with TAA had impaired liver function and significantly increased plasma transaminase, γ-glutamyltransferase (GGT), alkaline phosphatase (ALP) activity and bilirubin levels (Ra et al., 2019).

The BCAA content of 0.25 g/day and the MCT of 4.34g/day in hepatogomax dose P2 of 14.6 g/200 g w/day lowered serum ALP, bilirubin, and GG levels. The composition of *Branched-Chain Amino Acids* (BCAAs) and *Medium-chain Triglycerides* (MCTs) in hepatogomax boasts the complementary advantages of high protein serenity of milk powder and soy flour, which are 94% and 71,8%, respectively (Rahmadanti TS et al., 2020).

This study is consistent with previous studies that reported that oral intake of 10 ml/kg BCAAs in mice with liver cirrhosis may protect against liver damage mediated by *lipopolysaccharide-binding proteins* (LBP) (Eguchi et al., 2021). This study still needs to be evaluated because of the dose of P2 for daily intake if converted in humans to energy 3,639 kcal, fat 222 g, protein 55 g, carbohydrate 520 g, BCAA 14 g and MCT 12,33 g. The need for these calories is too high for the condition of the diet for liver cirrhosis, where the diet boundary of the Indonesian people is about 1800 kcal-2100 kcal (Plauth et al., 2019).

A possible mechanism is the translocation of *Enterococcus faecalis* through the restoration of the tight intestinal intersection and a decrease in *Lipopolysaccharide-binding protein* (LBP) expression in the liver, which suppresses LBP activation, toll-like receptor 4 (TLR4), and signal transduction and transcription activator 3. (STAT3). BCAAs weaken liver inflammation by suppressing the activation of the LBP pathway. BCAA deficiency in liver cirrhosis disrupts liver protein synthesis and causes muscle proteolysis and malnutrition (Eguchi et al., 2021).

This study is consistent with previous studies in which BCAAs improved nutritional status and prevented progressive liver damage in protein, glucose, fat metabolism, gene expression, insulin resistance, *and hepatocyte proliferation* (Tajiri & Shimizu, 2018). This study showed that hepatogomax with a balanced nutrient composition has anti-inflammatory, antioxidant, and other effects that can repair liver fungi. The results of this study are in line with previous studies where hepatogomax is a functional food with a composition of ingredients that already corresponds to the diet for liver cirrhosis (Rahmadanti et al., 2020).

The provision of intervention with hepatogomax requires an evaluation of the quality of the product as a functional food by applying for patent rights and paying attention to the residual fiber content in the composition of soy flour products. Giving the enteral formula in the way of the probe should not leave a residue because it can inhibit the reception of intake. The enteral formula should be 100% acceptable. It is hoped that it will provide the maximum results if applied to humans. If this study were applied to humans, then the route of administration would be as many as six times with a high-energy protein diet. Determination of this diet is necessary by considering the volume of the stomach on the day, as well as the reception of fast and proper nutritional filling to prevent the occurrence of malnutrition.

Hepatogomax is made from raw soy flour as a source of vegetable fat. Previous research has found that soy milk contains polyphenol flavonoids with antioxidant effects that significantly reduce damage to liver function, such as ALP and bilirubin levels (Uchendu et al., 2017). Previous research has shown that increased energy and calorie intake in patients with cirrhosis provides positive nitrogen balance, increased muscle mass and improved health status (Esin et al., 2017).

The administration of BCAA supplements allows the maintenance of fat-free muscle mass because of its potential to enhance the synthesis of muscle proteins without fat. BCAAs can boost damaged muscle recovery by suppressing endogenous muscle protein breakdown (Hammad et al., 2017). Lack of protein energy can lead to chronic liver disease, in which liver glycogen storage is reduced due to catabolic conditions, resulting in protein-calorie malnutrition (Esin et al., 2017).

The administration of hepatogomax intervention with the composition of nutrients in it has met the intake of nutritional substances in liver cirrhosis to prevent malnutrition and improve liver function. Therefore, hepatogomax, as an available nutrient, can be a nutrition treatment to prevent liver malnourishment.

This study has limitations in categorizing malnutrition conditions in liver cirrhosis mice; therefore, further research on histopathology and other evidence supporting the presence of malnourishment in hepatocirrosis is necessary. Other restrictions in the manufacture of products need to be filed for patent rights so that the product can be known and used in patients with malnutrition and cirrhosis. Excess calories must be modified to fit the diet for cirrhosis. The advantage of this study is that adequate nutritional content of macro-, micro-, BCAA-, and MCT-specific nutrients in hepatogomax provides a rapid absorption response to help cope with malnourished liver cirrhosis.

Conclusion

Hepatogomax dose P2 14.6 g/200 gBB/day influenced changes in ALP, bilirubin, and GGT levels in Sprague Dawley mice with cirrhosis. The group that received the intervention was lower than the group that did not.

Hepatogomax can be administered orally or by a probe with a 6-time route of administration per 150-200 ml according to the patient's cirrhosis condition.

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