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جامعة عين شمس، كلية التربية النوعية، القاهرة، مصر

تحية طيبة وبعد،،،

يسر **معامل التأثير والاستشهادات المرجعية للمجلات العلمية العربية (ارسيف – ARCIF)**، أحد مبادرات قاعدة بيانات **"معرفة"** للإنتاج والمحتوى العلمي، إعلامكم بأنه قد **أطلق التقرير السنوي التاسع للمجلات للعام 2024**.

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الجزء الثالث :

أولاً : بحوث علمية محكمة باللغة العربية :

Effect of Consuming Foods Rich in Branched-Chain Amino Acids (BCAAs) on Liver Cirrhosis in Rats Induced by Carbon Tetrachloride (CCl4)

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Effect of Consuming Foods Rich in Branched-Chain Amino Acids (BCAAs) on Liver Cirrhosis in Rats Induced by Carbon Tetrachloride (CCl4)

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Abstract

The current study aims to investigate the effective role of plant proteins rich in branched-chain amino acids (BCAAs) such as soy protein isolate, lentils, chickpeas, and lupins in the preparation of three food products (bread, pasta, and burgers) and compare them with standard BCAA-rich dietary supplements in treating rats with carbon tetrachloride (CCl_4)-induced liver cirrhosis. The chemical composition results showed a high protein content in the burger sample, followed by pasta and bread, with values of 75.05, 53.08, and 27.85g/100g of sample weight, respectively. The burger also recorded the highest BCAA value (15.23g/100g), followed by pasta (10.34g/100g), and bread (5.297g/100g). Biochemical results showed significant improvement in the groups of rats treated with BCAA-rich foods (T30, T20, T10) compared to the groups treated with the BCAA-rich dietary supplement (S30, S20, S10),

Keywords: Liver cirrhosis, legumes, BCAA, high protein foods, bread, pasta, burger.

ملخص:

العنوان : تأثير تناول الأغذية الغنية بالأحماض الأمينية المتشعبة السلسلة (BCAAs) على الفئران المصابة بتليف الكبد الناتج عن رابع كلوريد الكربون CCl4

المؤلفون : أسامة السيد مصطفى ، أماني أحمد عبد العزيز ، مها مهدي عدلي

تهدف الدراسه الحالية الي التحقق من الدور الفعال للبروتينات النباتيه الغنية بالأحماض الامينيه المتشعبة السلسلة (BCAAs) مثل (بروتين فول الصويا المعزول والعدس والحمص والترمس) لعمل ثلاث منتجات غذائيه (خبز ومكرونه وبرجر) ومقارنتها بالمكملات الغذائيه الغنية بBCAAs القياسية لعلاج الفئران المصابه بتليف الكبد المستحث برابع كلوريد الكربون (CCl4) ، أوضحت النتائج البيوكيميائية تحسنا ملحوظا في مجموعات الفئران المعالجه بالأغذية الغنيه ب (T30، T20،T10) BCAAs مقارنة بالمجموعات المعالجة بالمكمل الغذائي الغني ب BCSAs (S30 ، S20،S10)

الكلمات الدالة :تليف الكبد، البقوليات، أحماض أمينية متفرعة، أغذية مرتفعة البروتين، خبز، مكرونة، برجر.

Introduction

The liver is one of the most vital organs in the human body. It is located in the upper right quadrant of abdomen, and the liver weighs about 1.5 kilograms. The liver playes a crucial role in numerous biological processes, synthesizes proteins, and cholesterol, stores glycogen, regulates blood sugar levels, and breaks down fats. **(Betrapally 2022; Haff and Mohanty 2023; Rodriguez-Ramiro 2023)** Various factors, including viral hepatitis (B and C), metabolic disorders, autoimmune diseases, congenital anomalies, alcohol consumption, certain medications, and nonalcoholic fatty liver disease (NAFLD), can adversely affect liver health and may lead to liver cirrhosis **(Nivukoski *et al.*, 2020; Wu *et al.*, 2024).**

Liver cirrhosis is a chronic disease characterized by extensive liver damage, insufficient regeneration of liver cells, and the formation of fibrous tissue and pseudolobules **(Zheng *et al.*, 2024)**. It can result from various causes such as alcohol consumption, chronic hepatitis virus infections, autoimmune disorders, or unknown reasons. Clinically, it is marked by liver function impairment and portal hypertension, with many complications potentially arising in advanced stages, including upper gastrointestinal bleeding, ascites, and hepatocellular carcinoma **(Baumgartner *et al.*, 2021; Ginès *et al.*, 2021)**. Factors that contribute to higher morbidity and mortality rates include alcohol use, advanced age, type 2 diabetes, and being overweight **(Hsiang *et al.*, 2015)**.

The prolonged use of medications for liver cirrhosis treatment remains contentious due to potential adverse effects. Recent studies emphasize the significance of functional foods, which offer protective and therapeutic benefits through their antioxidant, anti-inflammatory, and detoxifying properties on the liver. Moreover, certain dietary supplements have shown beneficial mechanisms of action for liver diseases **(Wang *et al.*, 2023; Li *et al.*,2024).**

Branched-chain amino acids (BCAAs) encompass valine (Val), leucine (Leu), and isoleucine (Ile), play a significant role in the pathophysiological mechanisms underlying liver diseases in humans. **(Dimou *et al.*, 2022; Cuomo *et al.*, 2022)**. This class of amino acids serves as biomarkers of many diseases, like cardiovascular diseases, type 2 diabetes, obesity, and cancer **(Sivanand and Vander Heiden, 2020).**

A recent study showed that BCAAs have an effective role as pharmacological nutrients for chronic liver disease patients. A mixture of equal quantities of the BCAAs isoleucine, leucine, and valine administered via the meal can ameliorate hepatic steatosis in mice and improve not only nutritional condition but also quality and prognosis of life in liver cirrhotic patients **(Gart *et al.*, 2023; Abuelazm *et al.*, 2024; Almoselhy 2024; Román *et al.*,2024).**

Branched-chain amino acids are metabolized outside the liver, since it has been described for liver cirrhotic people **(Trillos-Almanza *et al.*, 2024)**. Low BCAAs and high aromatic amino acids (AAAs) are shared in typical abnormalities in the blood of patients with liver cirrhosis, which play a role in the pathogenesis of liver encephalopathy and muscle loss **(Varshney and Saini, 2020)**. Consequently, dietary formulations that feature a high Fisher ratio (the ratio of branched-chain amino acids to aromatic amino acids) are crucial for enhancing both the nutritional and overall health status of patients with liver cirrhosis **(Mino *et al.*,2024; Zhang *et al.*, 2024)**

Higher administration of BCAAs, as well as vegetable proteins, has brought benefits to patients with cirrhosis **(Eghtesad *et al.*, 2013)**. Optimal protein intake a day should not be less than the recommended 1.2-1.5 g/kg in dietary regimen of malnourished decompensated cirrhotic patients **(Merli *et al.*, 2019)**.

Hence, the objective of this research is to utilize certain ingredients abundant in BCAAs, including legumes (lentils,

chickpeas, lupins, and soy protein isolate), skim milk and meat, in the creation of BCAAs-rich foods like bread, pasta, and burgers. And study their effects on liver enzymes, body proteins and liver histology in experimental rats with liver cirrhosis.

MATERIALS AND METHODS

Materials

Raw materials

Lentils (*Lens culinaris*), chickpeas (*Cicer arietinum* L.), lupines (*Lupinus* spp. L.), bovine meat, and skimmed milk powder were purchased from the local market. Soy protein isolate was obtained from American FoodChem.

Chemical and other ingredients

Branched-chain amino acids (BCAA), L-leucine, L-valine and L-isoleucine in pure form are from BIOGENA GmbH, Austria. Carbon tetrachloride (CCl_4) 99.90% and carboxymethyl cellulose (CMC) obtained from Sigma Aldrich. Other used chemicals were purchased from El-Gomhoria and El Shark El Aost Companies, Egypt. Active dry yeast was obtained from the local market (Qena, Egypt).

Methods

Preparation of raw materials

Preparation of legumes (lentil, chickpea and lupine) flour

The legumes flour was prepared according to **Giami and Bekebain (1992)**, one kilogram of legume seeds was cleaned, then soaked in 2L tap water for 12 hr. Seeds were ground by using a mixer (MIENTA super blender, Model BL -721) and dried in the cabinet dryer (120°C/90 min). During drying, the ground seeds were stirred at intervals of 30 minutes to ensure uniform drying. The ground seeds were sieved to pass through a 300 mesh sieve. The obtained flour was finally packaged in sealed polyethylene bags until used.

Preparation of products

Preparation of *bread*

Bread *was prepared according to the method described by* **(Faridi *et al.*, 1989)**. *Bread making involved mixing 100 g* of dry ingredients *(5g soy protein isolate, 5g skimmed milk powder, 10g lentil flour, 70g chickpea flour and 10g lupine flour), active dry yeast* (*1% w/w) and carboxymethyl cellulose 1,50%.*

Preparation of *Pasta*

Pasta dough was prepared from different portions of dry ingredients (40g soy protein isolate, 10g skimmed milk powder, 30g lentil flour, 10g chickpea flour and 10g lupine flour), and formed using a pasta machine **(**Philips Pastamaker HR2357/05 Machine Corporation, Italy), Food Technology Dept., National Research Center, *according to the procedure reported by* **Collins and Pangloli (1997)**, *The drying process of pasta was conducted according to* **Mostafa (2020)**.

Preparation of Burger

The burger was prepared according to **Youssef *et al.* (2021)** with some modification, (*80g soy protein isolate, 15g minced meat, and 5g lupine flour*). The samples burger was frozen at-18 ± 2°C prior to analysis.

Analytical methods

Chemical composition

Chemical analysis was performed including moisture, protein, fat, crude fiber and ash, which were determined according to the **AOAC (2000)**. Total carbohydrates were calculated by difference.

Branched chain amino acids (BCAAs)

Amino acids were determined according to the method described in **AOAC (2000)**. The molar ratio of branched-chain amino acid (BCAAs) residues (Leu, Ile and Val) to aromatic

amino acid (AAAs) residues (Tyr and Phe) is known as the Fischer ratio **(Wang *et al.*, 2024)**.

Minerals determination

Mineral quantification was carried out by atomic absorption spectrophotometer (type AAnalyst 400, Perkin–Elmer, Waltham, MA, USA) after sample digestion with HCl as described by **Gupta *et al.* (2006)**.

Determination of DPPH radical scavenging activity

Radical scavenging activity of tested compounds ability was assayed using the method of **Burits and Bucar, (2000).**

Ethical Approval:

The laboratory procedures and animals were handled following the guidelines published by the Local Committee of the Faculty of Specific Education, South Valley University according to the Animal Ethical Guidelines Procedures Act with approval No (177180924).

Biological test

Experimental design

Fifty-six adult male albino rats with an average weight of 198±5 grams 4 months old were utilized in the experimental procedure. It was obtained from the Laboratory Animal House in Giza, Egypt. The rats were inspected well for any infected pathogens before starting the experimentation. All animals were acclimatized for three weeks in well-ventilated cages (7 rats for each). Rats were given a standard basal diet and provided water and libitum (Table 1). The experimentation occurred in the Laboratory Animal House, Faculty of Veterinary Medicine, Qena Governorate, Egypt. After acclimatization of three weeks, rats were divided into two main groups as follows:

The first main group: Control negative group (1): consists of 7 rats that were fed on

the basal diet during the experimental period for 10 weeks.

The second main group: consists of 49 rats that were fed on the basal diet and injected with CCl4 (1ml/Kg body weight) , dissolved in corn oil (50%, V/V) intraperitoneally 3 times/week for 3 weeks, to induce liver cirrhosi according to **Khedr and Khedr (2017)**

The second main group was divided into seven subgroups (seven rats in each) as follows:

Subgroup (1): The Positive control group was fed on the basal diet till the final experiment.

Subgroup (2)(T10): fed on the basal diet contained 200 g formulated bread diet enriched with 10 g BCAAs , 5.026 g leucine, 2.835 g isoleucine, and 2.734 g valine daily.

Subgroup (3)(T20): fed on the basal diet contained 200 g of formulated Pasta diet enriched with 20 g of BCAAs, 9.446 g of leucine, 6.002 g of isoleucine, and 5.224 g of valine daily.

Subgroup (4)(T30): fed on the basal diet contained 200 formulated burger diet enriched with 30 g BCAAs, 13.692 g leucine, 9.133 g isoleucine, and 7.638 g valine daily.

Subgroup (5)(S10): fed on the basal diet contained 10 g BCAAs, 5.026 g-Leucine, 2.835g-Isoleucine and 2.734g-Valine daily.

Subgroup (6)(S20): fed on the basal diet contained 20 g BCAAs, 9.446 g-Leucine, 6.002 g-Isoleucine and 5.224 g-Valine daily .

Subgroup (7)(S30): fed on the basal diet contained 30 g BCAAs, 13.692 g of leucine, 9.133 g of isoleucine, and 7.638 g of valine daily.

Rats body weight was calculated once a week, besides this blood sampling and liver tissues were extracted to be analyzed biochemically and histopathologically, respectively.

Rats body weights were calculated once every 2 weeks; besides this blood sampling and liver tissues were extracted to be analyzed biochemically and histopathologically, respectively.

Table 1: Nutrient and ingredient composition of the experimental diets

Ingredient(g)	Diet ingredients							
	Control		Standard BCAA group			Treatment group		
	Negative	Positive	S10	S20	S30	T10	T20	T30
Casein	200	200	189.405	179.328	169.537	144.594	93.676	49.707
L-Leucine	-	-	5.026	9.446	13.692	5.026	9.446	13.692
L-Isoleucine	-	-	2.835	6.002	9.133	2.835	6.002	9.133
L-Valine	-	-	2.734	5.224	7.638	2.734	5.224	7.638
Bread	-	-	-	-	-	200	-	-
Pasta	-	-	-	-	-	-	200	-
Burger	-	-	-	-	-	-	-	200
L-Cystine	3.000	3.000	3.000	3.000	3.000	3.000	3.000	3.000
Corn Starch	397.486	397.486	397.486	397.486	397.486	273.276	319.382	381.137
Salt mixture	35.000	35.000	35.000	35.000	35.000	35.000	35.000	35.000
Corn oil	40.000	40.000	40.000	40.000	40.000	40.000	40.000	40.000
Cellulose	50.000	50.000	50.000	50.000	50.000	50.000	50.000	50.000
Sucrose	132.000	132.000	132.000	132.000	132.000	132.000	132.000	132.000
Soy bean oil	70.000	70.000	70.000	70.000	70.000	61.365	66.638	65.331
Fiber	50.000	50.000	50.000	50.000	50.000	50.000	50.000	50.000
Mineral mix	35.000	35.000	35.000	35.000	35.000	35.000	35.000	35.000
Vitamin mix	10.000	10.000	10.000	10.000	10.000	10.000	10.000	10.000
Choline bitartrate (41.1)	2.500	2.500	2.500	2.500	2.500	2.500	2.500	2.500
Tert-but hydro quinone	0.014	0.014	0.014	0.014	0.014	0.014	0.014	0.014
Total	1000	1000	1000	1000	1000	1000	1000	1000

Where: S10= 10g BCAA, S20= 20g BCAA, S30= 30g BCAA, T10= bread sample, T20= pasta sample, T30= burger sample.

Blood samples

Blood samples were extracted for biochemical examination according to **Schermer (1967)** from all sacrificed animals of all groups under general anesthesia by using diethyl ether. The blood was obtained in clean tubes from the supraorbital venous plexus, and then serum was separated by centrifugation at 5000 rpm for 10 minutes. The resultant serum was kept frozen at -20°C until biochemical liver analysis.

Liver samples

Fresh liver samples were extracted from the sacrificed animals of all groups and then fixed in 10% neutral buffered formaldehyde for histopathological analysis.

Biochemical analysis

Liver function

- Serum liver ALT and AST activities were colorimetrically calculated according to the descriptive method by **Reitman (1957)** using a spectrophotometer.
- Alkaline phosphate (ALP) was evaluated using the colorimetric method which was expressed by **Belfield and Goldberg (1971)**.

Protein profile

- Total protein in the serum was estimated by the colorimetric method according to **Gornall *et al.* (1949)**.
- Serum albumin level was colorimetrically determined by the method) which was described by **Doumas *et al.* (1971)**.
- Globulin level in the serum was calculated via subtraction of the value of the albumin level from the value of the total protein level.
- Serum total bilirubin was colorimetrically assessed via the method of **Walter and Gerade (1970)**.

Histopathological examination

Liver specimens were collected from the rats of all existing groups; afterward, tissue specimens were fixed in 10% neutral buffered formaldehyde, passed then by dehydration in varying ascending grades of absolute alcohol, washed in xylene solution, and softened in paraffin blocks made from the paraffin waxes according to **Bancroft and Gamble (2008)**. Hematoxylin and eosin (H&E.) stained sections of 4-5µm thickness were prepared for the histopathological examinations.

Statistical analysis

The obtained results were statistically analyzed using the SPSS statistical package (Version 20) according to ***Rattanathanalerk et al. (2005)***, analysis of variance (ANOVA). Duncan's multiple range test and least significant difference (LSD) were chosen to determine any significant difference among various treatments at $p<0.05$.

RESULTS AND DISCUSSION

Nutrition quality of prepared samples

The nutrition facts of prepared samples as final products were investigated, and the obtained results are shown in Table 2 and according to the obtained results it could be noticed that, the total protein of investigated samples was 27.85, 53.08 and 75.05 g/100g for bread, pasta and burger respectively. Where, the burger sample had the most protein value with the lowest carbohydrate content it may be due to its high content of soy potein isolate such result was agreed with those obtaind by **Seke (2018); Mostafa *et al.* (2020)**, they reported that soy protein isolate contained 91.14% and 87.74% protein respectively. However, the bread sample recorded the highest values of fat and crude fiber this also reflected the higher fat and fiber content of chickpea flour as the main components of the bread formula, which was confirmed by **Kinfe *et al.* (2015)**, they found that chickpea cultivars showed higher fat (3.77 to 7.01%) and fiber (5.09 to 16.91%). Others (**Teterycz *et al.*, 2020)** explored the effects of adding legume flours on the chemical composition, of pasta and their findings indicated that a higher proportion of legume flour significantly enhanced the levels of dietary fiber, ash and protein content. In terms of BCAAs content, the burger recorded the highest value (15.23 g/100g), followed by pasta (10.34 g/100g) and then bread (5.30 g/100g). These results reflect the high BCAAs content of soy protein isolate (SPI), which ranked first as a basic component of burgers (80%) and pasta, which contained a medium percentage of SPI (40%), while the

bread formula contained a low percentage (5% SPI). Meanwhile, the total calories of prepared meals varied from 383.88 to 397.29 kcal/100g with slight differences between them. These results can also be confirmed by the study conducted by **Youssef *et al*. (2021)** in one of the studies that focused on fortifying burgers with soybeans, which proved that soy protein contains a high percentage of branched amino acids (23.00 g/100g protein), in addition to an increase in the protein content in the samples containing soy protein compared to the other samples in their study.

Table 2: Nutrition quality of prepared meals (on dry weight basis)

Components	Samples			Units
	Bread	Pasta	Burger	
Total protein	27.85±0.09	53.08±0.32	75.05±0.45	g/100g
Total fat	4.27±0.06	1.73±0.03	2.37±0.05	g/100g
Ash	3.55±0.11	3.90±0.14	3.68±0.09	g/100g
Fiber	2.46±0.06	2.28±0.05	0.71±0.02	g/100g
Total carbohydrates	61.87±0.96	39.01±0.55	18.19±0.60	g/100g
BCAAs	5.30	10.34	15.23	g/100g
Calories	397.29±12.65	383.88±13.09	394.26±11.87	kcal/100g

Bread= 5% soy protein isolate + 5% skimmed milk powder + 10% lentil flour + 70% chickpea flour + 10% lupine flour.

Pasta= 40% soy protein isolate + 10% skimmed milk powder + 30% lentil flour + 10% chickpea flour + 10% lupine flour

Burger= 80% soy protein isolate + 5% lupine flour + 15% minced meat.

Minerals content of prepared samples

The minerals content of prepared meals was investigated, and the obtained data are presented in Table 3. The obtained results indicated that, the iron content of investigated meals (bread, pasta and burger) were 6.14, 5.68 and 7.00 mg/100g respectively. Furthermore, the burger sample recorded the highest content of zinc (4.07 mg/100g) and sodium (408.33 mg/100g). According to a study conducted by **Youssef *et al*. (2021)** which proved that fortifying burgers with soy protein led to an increase in the iron content from 1.93 mg/100g to 13.70 mg/100g, while the zinc content increased from 3.88 mg/100g to 4.90 mg/100g. However, the highest value of potassium content (832.62

mg/100g) was observed by pasta sample, whereas, the bread samples recorded the highest content of magnesium (172.34 mg/100g). Generally, minerals act as activators for numerous enzymes that are essential for sustaining life **(Uddin *et al.*, 2016)**. Others **(Sun *et al.*, 2014; Mohammad *et al.*, 2012)**, methioned that, some minerals such as zinc and iron improves liver function and their deficiency can lead to a detrimental effect on liver function. As reported by **Giuberti *et al.* (2015)**, legumes have been recognized as valuable components in the formulation of snacks and baked goods, such bread, and pasta, particularly in the context of gluten-free product development **(Giuberti *et al.*, 2016)**. Thus, **Lai *et al*. (2022)** stated that, sodium restriction may reduce the palatability of food, representing a barrier to adequate nutrition intake. In a study of 120 outpatients with cirrhosis and ascites, only 31% were adherent to a 2-g-sodium diet, and adherent patients had a 20% lower daily caloric intake. When patients are prescribed a sodium-restricted diet, it should be balanced with educational resources that offer suggestions to improve diet palatability. Liberalization of sodium restriction should be considered if the patient is unable to maintain nutritional targets because of diet unpalatability. Thus, minerals play a crucial role in the metabolism of carbohydrates, fats, and proteins **(Traub *et al*., 2021)**. In addition to the important role of zinc in improving the functions of liver enzymes by reducing oxidative stress **(Mishra and Sharma, 2019)**. Given the commonality of zinc deficiency in cirrhosis, the lack of a reliable serum test, and the potential benefits, it is reasonable to supplement with 25-50 mg of oral elemental zinc daily in symptomatic patients, with careful monitoring, especially in those with chronic renal insufficiency **(Rahelić *et al*.,2006; Johnson *et al*., 2013; Merli *et al*., 2019).** A randomized controlled trial involving 79 cirrhotic patients with hepatic encephalopathy, who were unresponsive to lactulose and a protein diet of 1.0 g/kg/day, demonstrated that daily oral supplementation of zinc significantly reduced the severity of hepatic encephalopathy, improved Child-Turcotte-Pugh (CTP) scores, and enhanced quality of life

measures **(Takuma *et al*., 2010)**. Some research, including a small randomized controlled trial, indicated that oral zinc supplementation could improve taste **(Heckmann *et al*., 2005).**

In relation to magnesium element **Bémeur and Butterworth (2015)** reported that the low serum magnesium level was common in chronic liver disease and liver cirrhosis, so magnesium treatment was reported to improve hepatic enzyme levels. Also **Eshraghian *et al.* (2018)** found that the low serum magnesium level was due to decreased nutritional intake of the metal and increased excretion of magnesium due to decreased plasma level of albumin, administration of magnesiuric diuretics (furosemide), poor absorption of magnesium in the distal jejunum, and indirect effect of alcohol on renal tubules. Moreover, serum magnesium levels are often low in patients with cirrhosis, contributing to symptoms such as dysgeusia, decreased appetite, muscle cramps, and weakness **(Parisse *et al*.,2021)**. Oral magnesium supplementation may help improve appetite and taste. Magnesium can be administered via intravenous, intramuscular, or oral routes, with 400 mg of magnesium oxide commonly recommended **(Baskol *et al*., 2004; Vidot *et al*., 2014)**. While oral supplementation is convenient, it can cause or worsen diarrhea, potentially leading to further magnesium loss through stool **(Palmer *et al*., 2019)**.

Additionally, micronutrients such as sodium, magnesium, and potassium have played a significant role in liver diseases **(Ali *et al*., 2021)**. As regards potassium it was found that potassium was decreased than the normal range among cirrhotic patients among cirrhotic patients. **Chen *et al*. (2024)** found low potassium linked with liver disease patients with nonalcoholic fatty liver disease also had low potassium levels and also dietary potassium intake have an inverse association with the odds of both nonalcoholic fatty liver disease and hepatic fibrosis. Others **(Ali *et al*., 2021)**, added that patients with nonalcoholic fatty liver disease also had low potassium levels and patients with

nonalcoholic fatty liver disease had significantly lower serum potassium levels than those who did not have the liver condition.

Table 3: Minerals content of prepared meals

Components	Samples			Units
	Bread	Pasta	Burger	
Iron	6.14±0.22	5.68±0.16	7.00±0.20	mg/100g
Zinc	3.50±0.08	3.20±0.05	4.07±0.11	mg/100g
Potassium	701.47±12.87	832.62±10.82	768.19±17.04	mg/100g
Magnesium	172.34±4.65	142.52±5.01	87.51±3.11	mg/100g
Sodium	156.48±6.51	286.08±8.93	408.33±15.60	mg/100g

Bread= 5% soy protein isolate + 5% skimmed milk powder + 10% lentil flour + 70% chickpea flour + 10% lupine flour.

Pasta= 40% soy protein isolate + 10% skimmed milk powder + 30% lentil flour + 10% chickpea flour + 10% lupine flour

Burger= 80% soy protein isolate + 5% lupine flour + 15% minced meat.

Bread **Pasta** **Burger**

Antioxidant activity of prepared products

Figure 1 illustrated the antioxidant activity of final products (bread, pasta and burger). According to the obtained results the highest values of antioxidant activity (44.12 and 37.95%) were recorded by the burger and pasta samples, respectively. While a lower value (31.64%) was recorded by the bread sample. As reported by **Aharon *et al.* (2011)**, there was an 85% in total phenolic by cooking kabuli chickpea. Similarly, **Hwang *et al.* (2012)** found that boiling and steaming significantly decreased the ascorbic acid content, total phenolic, and antioxidant potential as compared with the other cooking methods. Reduced total phenolic in boiled or steamed foods has been attributed to the solvation of phenolic constituents into the cooking water **(Zhuang *et al.*, 2016)**. Also, **Xu and Chang, (2008)** reported that

free radical scavenging capacity and antioxidant activity had been found significantly ($p<0.05$) reduced after boiling in cool season edible legumes. **Rani and Khabiruddin (2016)** further demonstrated that different components of phenolic compounds significantly influence antioxidant activity to varying extents. Their research indicated that the complex presence of multiple phenolic substances in the extract contributed to a synergistic effect.

Conversely, a negative correlation was observed when phenolic compounds interacted in different ways across various assay systems. Consequently, the findings revealed that despite the impact of cooking, there remains a strong association between the phytochemical constituents and antioxidant activity in both the seed coat and cotyledon of chickpeas.

On the other side, due to meat being a source of high Fisher ratios. The antioxidant effect of animal-derived oligopeptides is mainly demonstrated by their ability to scavenge 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals and hydroxyl radicals **(Zhou *et al.*, 2009; Soltanizadeh and Mirmoghtadaie, 2014)**. Thus a healthy diet that provides enough antioxidants can prevent this problem and help the liver for a healthier condition **(Vitaglione *et al.*, 2004)**. In general, there is an important role for both branched-chain amino acids and antioxidants, as well as enriching the meal with an appropriate amount of zinc in treating liver fibrosis.

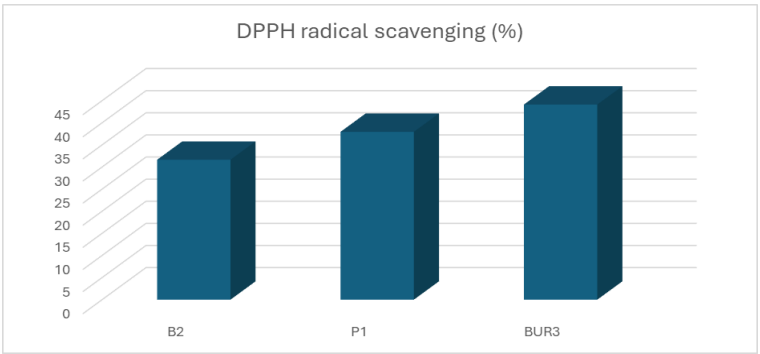

Figure 1: Antioxidant activity of final products

Biological evaluation

The effect of branched-chain amino acids in their standard form (S10, S20, S30) and branched-chain amino acids found in natural food sources (T10, T20, T30) was investigated in (bread , pasta and burger, respectively) at different concentrations of 10, 20, and 30 grams of BCAAs, either in their standard form or by obtaining the same concentrations from dietary sources on different biological parameters of experimental rats was investigated compared to the control negative group (normal rats fed on basal diet) and other induced with liver cirrhosis by CCl4 injection and fed on basal diet as the control positive group. The analysis of the biochemical blood parameters of rats permitted the estimation the performances related to diet consumption.

Effect of different Foods Rich in Branched-chain Amino Acids and standard branched-chain amino acids on serum liver functions.

Aspartate amino transferase (AST), alanine amino transferase (ALT) and alkaline phosphatase (ALP) levels in rat serum were examined and the obtained results are shown in Tables 4, 5 and 6 respectively.

According to the obtained data, (Table 4) during the experiment, the negative control group consistently showed the lowest AST enzyme levels, indicating no liver cirrhosis, while the positive control group had the highest levels, confirming liver cirrhosis. Initially, there were no significant differences between the treated groups and the negative control group.

After two weeks, a decrease in AST levels began in the treated groups, especially those receiving higher doses of branched-chain amino acids (BCAAs), with the T30 group showing the most significant reduction. This trend continued over the weeks, with the T30 and S30 groups consistently showing the most significant decreases in AST levels, followed by the T20 and S20 groups, and then the T10 and S10 groups.

By the end of the experiment at ten weeks, the treated groups maintained the lowest AST levels, confirming the long-term effectiveness of BCAA treatment in reducing liver damage and improving liver function. The higher the dose of BCAAs, the more significant the reduction in AST levels, especially in the groups treated with branched-chain amino acids in the form of food from legume sources.

Table 5. presents the effect of a diet containing naturally occurring BCAAs from natural food sources, and those present in the form of dietary supplements on alanine amino transferase (ALT). Throughout the experiment, significant differences in ALT levels were observed between the negative and positive control groups, indicating liver fibrosis in the positive control group. Initially, there were no significant differences between the treated groups and the positive control group. However, as the weeks progressed, the T30 group consistently showed the most significant decrease in ALT levels, followed by the S30, T20, S20, T10, and S10 groups. By the end of the experiment, all treated groups exhibited a significant reduction in ALT levels, demonstrating the effectiveness of branched-chain amino acids in improving liver condition. The groups treated with BCAAs in the form of food showed greater improvement compared to the groups treated with the same concentration of BCAAs in the form of standard supplements.

Table 6 demonstrated during the experiment, significant decreases in ALP levels were observed in the treated groups compared to the positive control group, indicating an improvement in liver condition. The T30 group consistently showed the most significant decrease, followed by the T20 and S30 groups. The addition of branched-chain amino acids, whether in standard or natural form, effectively reduced ALP levels, suggesting enhanced liver function and protection against damage

Generally, in the previous three tables (4, 5, and 6), data indicated that with increasing concentrations of branched-chain amino acids, liver function (AST, ALT, and ALP) improved

significantly in all treated groups, especially in those treated with branched-chain amino acids in the form of food (burger, pasta, and bread) These may have been explained by the anti-inflammatory and antioxidant properties of soy protein and its associated bioactive components might also help lower systemic inflammation and oxidative stress, both of which are key drivers of liver injury, fibrosis, and the elevation of liver enzymes like AST. Lowering oxidative stress would directly reduce hepatocellular damage, leading to decreased AST levels and overall improvement in liver function **(Li *et al*., 2015)**. Other study indicated that plant-based diets, especially those rich in polyphenols and flavonoids like those found in soy, can be protective against liver fibrosis and may even reverse some of the damage caused by chronic liver diseases **(Li *et al.*, 2024)**. Thus, a Japanese investigation revealed that a high consumption of soy products correlates with a reduced risk of liver cancer in males **(Abe *et al*., 2021)**.

Furthermore, research indicated that chickpeas mitigated lipid accumulation in steatotic liver cells in murine models. Rats that were administered chickpeas exhibited lower glycemic levels and reduced aspartate aminotransferase (AST) activity. These results underscore the significance of research focused on the functional characterization of chickpea biodiversity and its nutraceutical attributes **(Centrone *et al*., 2020)**. In a separate study conducted by **Sarhan *et al.* (2012)**, rats treated with carbon tetrachloride were provided a diet comprising 45.8% crude soy protein over an 8-week period. The inclusion of soy in their diet effectively reversed the elevation of liver enzymes and enhanced serum biochemical markers. Generally, the decrease in ALT levels in mice fed soy-derived BCAAs suggests that the soy protein and other legumes, in combination with their amino acid profiles and bioactive compounds, is protecting the liver from damage. This protection likely results from improved liver metabolism, reduced oxidative stress, and reduced inflammation, all of which contribute to lower ALT levels due to higher

antioxidant effects of isoflavones, in particular, may contribute to the normalization of ALT by preventing liver cell damage and reducing the activation of pathways that typically lead to the release of ALT into the bloodstream **(Markova *et al*., 2017; Hepburn and von Roenn, 2023)**. Soy protein has been shown to exert protective effects against liver injury and to improve bile secretion by maintaining proper liver function. The anti-inflammatory and antioxidant properties of soy, particularly its isoflavones (e.g., genistein), may play a key role in protecting the liver from the chronic inflammation that leads to cholestasis and fibrosis. The soy-derived BCAAs might also help reduce oxidative stress and inflammation in the liver, thereby normalizing ALP levels **(Holeček and Vodeničarovová, 2018)**. In general, these results are also consistent with those given by **Abdel-Daim *et al.* (2016)** when they evaluated the antioxidant effects in male mice where it showed that diet normalizes the serum concentrations of transaminases. The significant antioxidant effect could be related to the presence, in these chickpea accessions, of bioactive molecules such as carotenoids, anthocyanins, and phenols **(Summo *et al*.,2019)**. Oxidative stress and inflammation are involved in the onset and progression of numerous diseases. Therefore, phytocoumpounds, such as phenols with proven antioxidant ability, are considered health-promoting natural antioxidants **(Muscolo *et al*., 2024; Fascella *et al*.,2019)**. The obtained results are also in harmony with **Zhang *et al*. (2022)**, they studied the effects of six dietary patterns, including high-protein, low-carbohydrate, Mediterranean, calorie-restricted, and soy diets, and nighttime eating habits, on liver function and they stated that the high protein diet group revealed a significant reduction in AST levels in adults. In addition, **Li *et al*. (2024)** demonstrated that cirrhotic patients consuming late-night snacks before sleep, providing adequate protein and calories, can reduce protein energy expenditure during early morning hunger **(Nakaya *et al*., 2007)**. These results were consistent with previous reports which displayed that BCAA supplementation in cirrhotic rats or patients improves the liver

indices **(Iwasa *et al.*, 2013)**. BCAA poses to support potential benefits and positive effects to enhance liver regeneration, hepatic function albumin synthesis, and immune functions **(Nishitani *et al.*, 2005)**. Generally, the findings of our study are consistent with the evidence that protein intake affects liver function. Evidence of this is the study conducted by **Tanaka *et al.* (2016)** in which 750 mg/kg of body weight was fed, and meals rich in zinc and selenium were also fed, as well as other meals rich in antioxidants. The study showed that the combination of amino acids, zinc and antioxidants contributes better to the treatment of liver cirrhosis.

Table 4: Effect of different diets rich in branched-chain amino acids from natural food sources and in the form of standard dietary supplements on aspartate amino transferase (AST) levels in rats with liver cirrhosis (IU/L).

Groups	Aspartate Amino Transferase (AST) levels at different times (IU/L)					
	Pretreatment	2 weeks	4 weeks	6 weeks	8 weeks	10 weeks
Control groups						
Negative	140.20c±3.19	143.40e±3.37	140.20e±2.69	142.20d±5.26	139.40g±2.18	141.40g±0.35
Positive	295.60ab±5.08	292.20a±6.03	291.00a±5.86	293.20a±13.27	296.40a±4.06	294.20a±1.87
Standard BCAA groups						
S10	293.00ab±5.12	290.60a±5.44	286.40ab±4.93	281.00a±10.10	275.20b±3.72	268.00b±2.08
S20	299.00a±4.66	291.20a±5.05	281.00bc±5.51	269.60b±9.52	255.20c±4.92	238.40c±2.11
S30	297.20ab±5.03	282.40c±5.82	265.00d±5.29	246.40c±12.65	225.00e±5.90	201.20e±2.21
Treatment groups						
T10	292.00b±5.00	288.20b±4.82	283.60b±3.84	278.40a±8.62	273.00b±4.33	265.40b±2.74
T20	296.20ab±5.53	287.00b±4.77	275.40c±4.63	261.64b±11.58	245.00d±5.37	227.40d±2.06
T30	294.40ab±4.15	277.20d±5.27	258.72d±5.09	237.20c±7.72	213.00f±4.43	185.60f±2.10
LSD at 0.05	6.556	7.400	6.629	18.769	5.474	3.595

All results are expressed as Means ± SD.

Values in each column & raw which have different letters are significantly different ($p<0.05$).

Table 5: Effect of different diets rich in branched-chain amino acids from natural food sources and in the form of standard dietary supplements on alanine amino transferase (ALT) levels in rats with liver cirrhosis (IU/L).

Groups	Alanine Amino Transferase (ALT) levels at different times (IU/L)					
	Zero time	2 weeks	4 weeks	6 weeks	8 weeks	10 weeks
Control groups						
Negative	47.20b±2.24	44.00d±1.45	43.24d±2.04	45.40f±1.25	46.20f±0.98	45.20h±1.04
Positive	118.20a±4.46	120.20a±3.98	117.40a±4.26	115.60a±3.65	119.20a±2.99	116.60a±3.73
Standard BCAA groups						
S10	115.20a±4.11	112.20bc±3.38	108.20b±2.87	105.20b±3.03	102.40b±2.28	98.40b±2.69
S20	118.20a±4.25	114.52bc±4.03	108.40b±3.02	101.40bc±2.77	94.60c±3.00	86.40d±2.94
S30	117.64a±5.08	111.20bc±3.62	103.80bc±3.15	94.20d±4.11	85.20d±2.87	74.40f±2.06
Treatment groups						
T10	115.40a±4.87	111.28bc±2.76	107.58b±4.05	102.20c±4.32	97.40c±2.82	92.60c±2.53
T20	117.20a±3.08	110.48bc±3.37	104.20b±4.11	97.20cd±3.68	89.40d±3.33	79.40e±1.94
T30	115.60a±5.14	107.28c±3.00	98.40c±3.17	87.40e±3.88	74.40e±3.81	58.12g±1.55
LSD at 0.05	6.067	4.928	5.506	5.633	4.815	4.645

All results are expressed as Means ± SD.

Values in each column & raw which have different letters are significantly different ($p<0.05$).

Table 6: Effect of different diets rich in branched-chain amino acids from natural food sources and in the form of standard dietary supplements on alkaline phosphatase (ALP) levels in rats with liver cirrhosis (IU/L)

Groups	Alkaline phosphatase (ALP) levels at different times (IU/L)					
	Zero time	2 weeks	4 weeks	6 weeks	8 weeks	10 weeks
Control groups						
Negative	124.20b±3.88	127.60d±4.09	125.40f±2.43	128.16f±3.55	126.40e±5.23	130.96g±2.15
Positive	258.40a±5.86	255.40a±6.21	252.24a±4.18	253.40a±7.03	256.40a±14.67	257.20a±4.34
Standard BCAA groups						
S10	254.12a±4.33	249.40b±5.55	243.20b±4.02	236.40b±5.61	228.20b±10.03	219.80b±3.87
S20	257.20a±3.97	250.20ab±6.43	241.80c±3.57	230.20c±5.11	217.80b±7.87	202.60d±5.82
S30	253.40a±5.06	245.20bc±4.26	230.60d±4.14	215.40d±4.89	200.61c±9.26	183.20e±3.04
Treatment groups						
T10	258.20a±4.38	252.20ab±5.36	245.20b±3.46	236.80b±3.99	225.68b±12.54	212.90c±4.44
T20	256.44a±5.11	247.62abc±3.39	236.20c±5.65	222.40d±4.63	206.40c±11.09	188.40e±4.76
T30	255.68a±6.23	240.20c±4.88	225.80e±5.01	203.40e±5.81	184.20d±8.56	160.40f±4.01
LSD at 0.05	8.307	9.072	6.500	8.381	19.138	6.637

All results are expressed as Means ± SD.

Values in each column & raw which have different letters are significantly different ($p<0.05$).

Effect of different diet on protein profile and bilirubin for liver cirrhotic rats (mg/dl)

Table 7 showed the effect of different diets on protein profile and bilirubin for liver cirrhotic rats (mg/dl). From the obtained data it can be seen that the highest value of total protein (TP) was significantly recorded by the control negative group (8.34 mg/dl) followed by 7.31 mg/dl for S30 group then 7.01 mg/dl for T30 group with no significant differences between them (S30 and T30) followed by S20 and T20 groups with no significant differences between them. Conversely, the lowest value of TP (4.66 mg/dl) was recorded by the control positive group with significant differences compared to other all treated groups. Many studies recorded that BCAA administration stimulates protein synthesis in the liver, participating in improving the nutritional status and quality of life of patients with cirrhotic liver persons **(Yoshiji *et al*., 2013)**.

With regard to the albumin the highest values were recorded by the control negative followed by the T30 and S30 groups with no significant difference between them (5.59 and 4.73 mg/dl, respectively), followed by the groups (S20, T20, S10, T10 respectively) with a significant difference between each of them. BCAAs diets modulated and improved serum protein profile compared to the control positive group. These results were consistent with previous reports which displayed that BCAA supplementation improves albumin synthesis in cirrhotic rats or patients **(Iwasa *et al*., 2010)**. BCAAs induce increases in plasma albumin levels and reduce muscle wasting **(Monirujjaman *et al*., 2014)**. Thus, Short-term supplementation of BCAA taken orally prevented and avoided drop in levels of serum total protein and albumin in the perioperative period **(Takeshita *et al*., 2009)**. Where, the most suggested mechanism is that BCAAs enhance protein synthesis in the liver and other tissues through mammalian target of rapamycin (mTOR) signaling pathways. The percentage of patients with liver cirrhosis significantly returned to normal albumin levels after BCAA administration **(Lee *et al*., 2011)**. Data also indicated, there are significant differences in globulin levels among the different groups. An increase in

globulin levels was observed in some experimental groups compared to the negative control group. The negative control group recorded the highest globulin value, followed by the S30 group with no significant difference between them. Next were the T30 and S20 groups, also with no significant differences, while the S10 and T10 groups showed no significant differences compared to the positive control group. On the other hand, there are significant differences in the albumin to globulin ratio (A/G ratio) among the different groups. The A/G ratio decreased in groups suffering from liver fibrosis, reflecting a decrease in albumin synthesis and an increase in globulin synthesis. The S30, T30, S20, and T20 groups achieved the highest significant increase with no significant differences among them, followed by the S10 and T10 groups, which also showed no significant differences between them. Some experimental groups showed improvement in the A/G ratio, indicating a positive effect of the diet on this ratio. Data also refer to significant differences in total bilirubin levels among the different groups. Total bilirubin levels increased in groups suffering from liver fibrosis, indicating impaired liver function. Some experimental groups showed a decrease in total bilirubin levels, indicating the positive effect of therapeutic diets rich in branched-chain amino acids on liver function. The T30 and S30 groups showed the greatest significant decrease compared to the positive control group, with no significant differences between them, followed by the S20 group, then the T20 and S10 groups, and finally the T10 group. Generally, the beneficial effect of BCAAs was mediated by activation of hepatocyte growth factor that induces liver regeneration **(Marchesini *et al*., 2005)**. Supplementation with BCAAs, especially when associated with a high-fiber, high-protein diet, is considered a safe intervention in patients with cirrhosis, with the BCAAs contributing to the increase of muscle mass increased total serum pro tein and serum albumin levels **(Ruiz-Margáin *et al*., 2018)**. The relative increase in blood albumin in rats that received a diet rich in branched-chain amino acids from natural sources in burgers, pasta, and bread may be

due to their zinc content. This was indicated by the study of **Katayama *et al*. (2018)** many cirrhosis patients exhibited hypoz incemia, whereas blood zinc levels were associated with indi cators of nitrogen metabolism, mainly blood albumin levels, as well as several blood test parameters. Particularly, blood albumin levels were strongly associated with blood zinc levels. Thus, hypoalbuminemia detected in cirrhosis patients can be a useful indicator of zinc deficiency.

Table 7: Effect of different diet on protein profile and bilirubin for liver cirrhotic rats (mg/dl).

Groups	Protein profile and bilirubin for liver cirrhotic rats (mg/dl)				
	TP (mg/dl)	Albumin (mg/dl)	Globulin (mg/dl)	A/G ratio	Total bilirubin (mg/dl)
Control groups					
Negative	8.34a±0.33	5.59a±0.09	2.75a±0.10	2.03a±0.08	1.06f±0.04
Positive	4.66e±0.14	2.82g±0.12	1.84d±0.06	1.53d±0.05	2.87a±0.11
Standard BCAA groups					
S10	5.37d±0.23	3.35e±0.14	2.02cd±0.08	1.66c±0.04	2.02c±0.09
S20	6.56c±0.31	4.22c±0.17	2.34b±0.13	1.80b±0.05	1.69d±0.09
S30	7.31b±0.35	4.73b±0.11	2.58a±0.12	1.83b±0.08	1.25e±0.07
Treatment groups					
T10	5.05d±0.11	3.11f±0.14	1.94d±0.09	1.60c±0.07	2.44b±0.12
T20	6.19c±0.28	3.95d±0.20	2.24c±0.08	1.76b±0.09	1.87c±0.05
T30	7.01b±0.37	4.52b±0.18	2.49b±0.11	1.82b±0.06	1.36e±0.07
LSD at 0.05	0.442	0.217	0.179	0.105	0.165

All results are expressed as Means ± SD.

Values in each column & raw which have different letters are significantly different ($p<0.05$

Effect of different diet on liver malondialdehyde, glutathione peroxidase activity (GPx) and superoxide dismutase activity (SOD) for liver cirrhotic rats

As presented in Table 8. Malondialdehyde (MDA) showed a significant decrease in treated groups and standard groups compared to the MDA value of the positive group which recorded the highest value (32.22 nmol/mg protein). In contrast to the control positive group showed the lowest values (21.28 U/g tissue and 52.54 U/mL) of glutathione peroxidase (GPx) and superoxide dismutase activity (SOD) respectively. Generally, the treated groups showed a positive effect than others treated with standerd brached chain amino acids, where the lowest value of MDA (11.76 nmol/mg protein) was recorded by the control negative group followed by 13.21 nmol/mg protein which investigated by

T30 group (fed on burger sample) with no significant differences between them and with significant compared to other groups.

Also, the treated groups (T10, T20 and T30) showed higher values of GPx and SOD compared to the standard groups (S10, S20 and S30). Branched-chain amino acids (BCAAs), specifically leucine, isoleucine, and valine, have shown potential benefits in treating liver diseases, including cirrhosis. Their impact on reducing malondialdehyde (MDA) levels-an indicator of oxidative stress can be attributed to reduction of Oxidative Stress, where BCAAs appear to reduce oxidative stress in liver cells, which is a significant contributor to liver damage in cirrhosis. Elevated MDA levels reflect lipid peroxidation, a process driven by reactive oxygen species (ROS). By providing essential substrates for cellular energy production, BCAAs may reduce mitochondrial dysfunction and decrease ROS production, thus lowering MDA levels **(Kawaguchi *et al*., 2014)**.

Also, BCAAs support liver regeneration and help maintain protein synthesis in liver cells, which is often compromised in cirrhosis. By enhancing protein synthesis, BCAAs reduce catabolism and oxidative damage, potentially improving the overall antioxidant defense mechanisms in liver cells. Additionally, Leucine, one of the BCAAs, is known to activate the mammalian target of rapamycin (mTOR) pathway, which plays a role in protein synthesis and cellular growth. This activation helps in the regeneration of liver tissue and may improve cell resilience against oxidative damage, reducing markers like MDA **(Marchesini *et al*., 2005; Khedr and Khedr, 2017; Ibrahim *et al*., 2023)**.

The superiority of the diets containing legumes (especially soybeans) and containing a high BCAAs content compared to the groups fed standard BCAAs may be due to the fact that the diets containing legumes contain a high percentage of antioxidants and some important minerals (Table 3 and Figure 1, respectively) that enhance the role of branched-chain amino acids **(Díaz *et al*., 2013; Rizzo, 2020)**. It can be observed that the T30 group

achieved the best results regarding antioxidant enzymes (MDA, GPx, and SOD), followed by T20 and then T10. Which recorded the highest antioxidant activity values followed by pasta, and then bread according to Figure 1.Where, several studies have documented the antioxidant effects of isoflavones in soybeans, which can scavenge reactive oxygen species (ROS) and reduce lipid peroxidation levels (reflected by decreased MDA values). For example, in the paper by **Setchell *et al*. (2003)**, soy isoflavones were shown to act as antioxidants, effectively reducing markers of oxidative stress in experimental models.

Table 8: Effect of different diet on liver malondialdehyde, glutathione peroxidase activity (GPx) and superoxide dismutase activity (SOD) for liver cirrhotic rats.

Groups	Parameters		
	MDA (nmol/mg protein)	GPx (U/g tissue)	SOD (U/mL)
Control groups			
Negative	11.76e±0.14	125.13a±5.79	200.12a±6.32
Positive	32.22a±0.94	21.28g±0.83	52.54h±1.25
Standard BCAA groups			
S10	24.64b±0.43	28.26f±0.84	73.71g±3.08
S20	19.21d±0.81	52.35e±1.20	112.24e±3.57
S30	16.59d±0.97	80.51c±1.68	174.44c±3.47
Treatment groups			
T10	22.42c±0.36	30.23f±0.84	80.56f±1.16
T20	17.57d±0.77	58.41d±0.42	121.21d±2.64
T30	13.21e±0.80	92.83b±1.33	180.78b±3.82
LSD at 0.05	2.082	2.773	4.543

All results are expressed as Means ± SD.

Values in each column & raw which have different letters are significantly different ($p<0.05$).

MDA= malondialdehyde, GPx= glutathione peroxidase, SOD= superoxide dismutase

Effect on liver histology

Histopathologically, contrary to CCl4-induced group, both the groups treated with standard branched-chain amino acids and the groups treated with foods rich in branched-chain amino acids, especially the T30 burger group, alleviated liver fibrosis. attenuated liver cirrhosis exhibiting normal hepatocytes architecture appeared with intact nuclei; besides this blood vessel appeared slightly congested and dilated. Soya bean enriched with BCAAs encompass leucine (Leu), valine (Val), and isoleucine

(Ile) attenuated the progress in liver fibrosis and suppressed the expression of Alpha smooth muscle actin (α-SMA) as indicated in histopathological examinations Figure 2. This is agreement with **(Khedr and Khedr 2017)**, upon indicated suppressing activation of hepatic stellate cells which eventually is responsible for collagen over-secretion during liver fibrogenesis **(Ibrahim and El Din 2020)**. SPI may exert anti-fibrotic effects this is confirmed by the study of **Mercer *et al.*, (2017)** studied the effect of partial replacement of casein with SPI to treat liver fibrosis in rats fed a high-fat diet, and concluded that treated mice fed the HF/SPI diet thus had a statistically significant ($P < 0.05$) 32% reduction in the hepatic content of mRNA for the collagen gene Col1a1 compared to HF/CAS-fed mice , SPI counteracted an index of hepatic inflammatory foci , replacing casein with SPI also led to reductions in gene expression of the pro-inflammatory cytokine CXCL2 and tumor necrosis factor receptor 1 (TNFR1). Finally, nuclear content of NF-κB was highly significantly reduced ($P < 0.001$) for the HF/SPI diet compared to the HF/CAS diet suggesting reduced TNFα-signaling in the presence of SPI. We conclude that replacing casein with SPI in the HF diet opposes both liver damage and inflammation. These histological results were in agreement with a previous work proved that BCAAs supplemented had effective role in prevention of the development of liver fibrosis via using choline-deficient diet-fed db/db mice **(Iwasa *et al.*, 2013)**. Moreover, **Eguchi *et al.* (2021)** investigated that BCAAs have biological properties to suppress liver cirrhosis, including the promotion of protein synthesis and hepatocytes proliferation, simulation of immune systems, improvement of insulin resistance, inhibition of liver cancer cell proliferation and neovascularization.The prevention of liver fibrosis progression in groups of rats treated with branched-chain amino acids in the form of natural food, found in burger, pasta, and bread, as shown in images (C, D, E), may be attributed to legumes such as lentils, lupins, and soybeans, which are the most common sources of phytoestrogens. It has also been reported that soybeans contain the highest amount of Genistein (GE) **(Wasserman *et al.*,2012).**

GE contain 128 mg per 100 g of soy bean **(Hu *et al.*, 2014; Xin *et al.*, 2019)**. Previous studies **(Yoo *et al.*, 2015; Zhou *et al.*, 2021)** reported that GE alleviated liver fibrosis via activation of ECM degradation and inhibition of collagen synthesis. At the same time, the expression levels of tissue inhibitors of metalloproteinase 1 (TIMP1), procollagen type I alpha 1 (COL1A1), and hepatic transforming growth factor β (TGF-β) in mice were dramatically diminished following GE treatment. All of these findings indicated that BCAAs may have beneficial effects on the management of patients with chronic liver diseases with/without hepatocellular carcinoma.

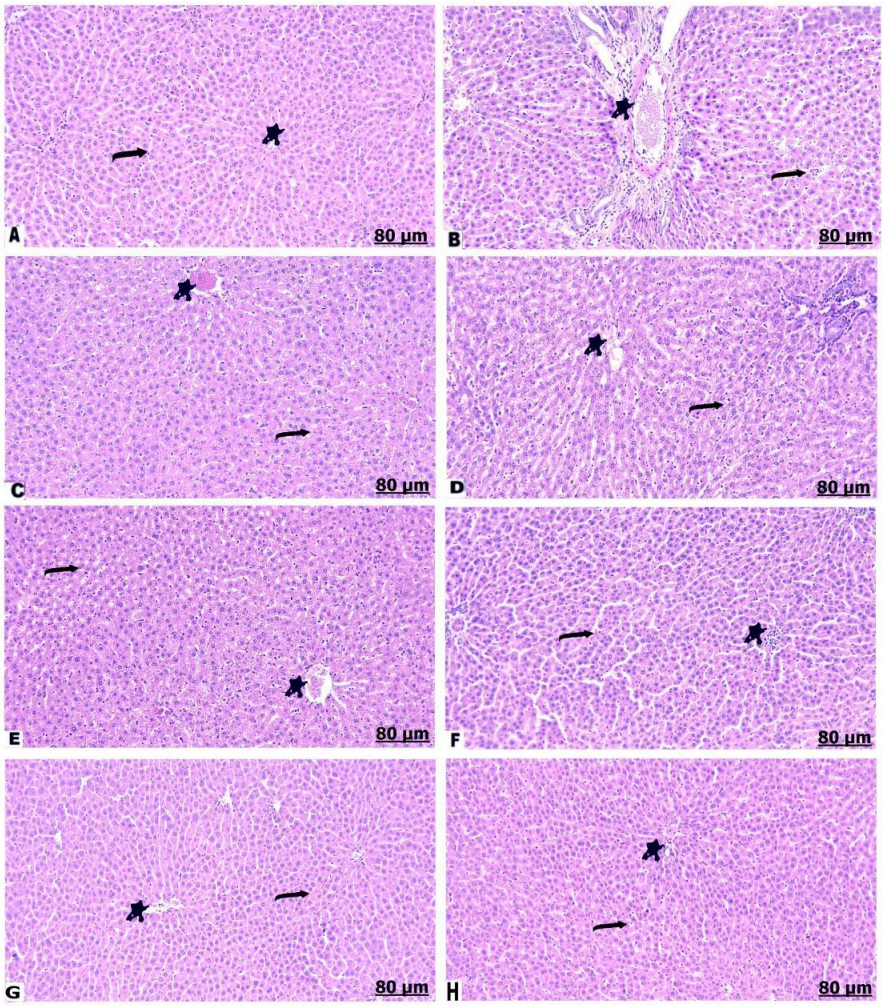

Figure 2: Light photomicrograph of H&E stained liver sections from control **(A)**, CCl4 **(B)**, CCL4+formaulated BCAAs **(C)**, CCL4+formaulated BCAAs **(D)**, CCL4+formaulated BCAAs **(E)**, CCL4+ manufactured BCAAs **(F)**, CCL4+ manufactured BCAAs **(G)** and CCL4+ manufactured BCAAs **(H)**. **A)** showing normal liver parenchyma consisted of intact blood vessels (star) and intact hepatocytes (arrow). **B)** showing thickening and fibrosis of the portal area (star) beside hemorrhage and necrosis of the hepatocytes (arrow). **C)** showing mild congestion of blood vessels (star) and vacuolization of hepatocytes (arrow). **D)** showing slightly congested blood vessels (star) and vacuolization of hepatocytes (arrow). **E)** showing minimal congestion of blood vessels (star) and vacuolar degeneration of hepatocytes and interstitial cells infiltration (arrow). **F)** showing mild dilatation of blood sinusoids (arrow) and focal aggregation of lymphocytes (star). **G)** showing normal hepatocytes (arrow) with slight congestion of central vein (star). **H)** showing mild hepatic vacuolation (arrow) and mild perivascular infiltration (star). **(bar= 80 µm)**

Conclusion

From the current study it could be concluded that, the diet containing high levels of BCAAs has an effective role in improving liver function similarly to the role played by standard BCAA in improving health status and reducing liver cirrhosis in infected rats, in addition to improving blood serum protein in all groups of expermintal rats with liver cirrhosis that were fed a diet high in BCAAs, whether standard or obtained from prepared meals (bread, pasta and burger), compared to the positive control group.

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