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Study the Hepatoprotective Effect of Curcumin against Cyclosporine A-Induced Liver Injury in Pediatric Age Group Patients

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Abstract: **Background:** Cyclosporin A is a frequently prescribed immunosuppressive medication for administration to pediatric patients. While highly efficient to preventing organ rejection, cyclosporin A may also cause adverse consequences, such as liver damage. Therefore, the utilization of curcumin is regarded to promote the enhancement of the quality of life in pediatric patients by virtue of its anti-inflammatory as well as antioxidant characteristics in bolstering liver function. **Aim:** This study contributed to the analysis of curcumin's effectiveness in protecting of pediatric patients from cyclosporine A-induced liver injury. **Patients and methods:** A total of 93 paediatric patients with cyclosporine A-induced liver injury, aged between 1 and 13 years, were recruited for the study. Clinical and demographic data were gathered from different hospitals in Iraq between 5 January 2022 and 14 October 2023. In order to achieve the study objective, the efficacy of curcumin in preventing paediatric patients with liver injury was evaluated by measuring serum alanine transaminase (ALT) and aspartate transaminase (AST) levels of patients. **Results:** The present study demonstrates the hepatoprotective effect of curcumin against cyclosporine A-induced liver injury in paediatrics. Cryptogenic causes were the most prevalent in children, accounting for 36.56% of cases. Jaundice was the most symptomatic presentation in children, occurring in 73.12% of cases.

With regard to the outcomes of curcumin administration, we observed that the mean AST (IU/L) was 52.96 ± 40.26, while the mean ALT (IU/L) was 39.86 ± 26.54. Additionally, the mean bilirubin (mg/dL) was 2.03 ± 1.10. The mean ± standard deviation values were as follows: albumin (g/dL), 3.52 ± 0.20; creatinine (mg/dL), 0.94 ± 0.14; and bilirubin (mg/dL), 2.03 ± 1.10. In evaluating the disease activity scores, we determined that the MELD score was 12.64 ± 2.37 and the Child-Pugh score was 5.16 ± 0.95. In terms of quality of life, the current study found that physical function had a mean score of 2.24 ± 1.33, emotional function 1.45 ± 0.88, daily activity 1.26 ± 0.21, and abdominal symptoms 1.03 ± 0.13. **Conclusions:** CsA (Cyclosporine A) is the most utilized drug for immunosuppression to avoid graft rejection and auto-immunological disorders. Nevertheless, therapeutic application leads to a number of side effects, including nephrotoxicity, cardiotoxicity, hypertension, and hepatitis. Among the treatments which have shown promising results are curcumin whose efficacy as a strong antioxidant medication has been observed in several pathophysiological ailments in children.

Keywords: Curcumin; Cyclosporine A; Liver injury; Pediatric Patients; Complications; and Health Quality - Life assessment.

1. INTRODUCTION

The liver's excessive accumulation of fat is recognized as hepatic steatosis, which occurs because of the increased intake of fatty acids in this organ [1,2]. This collection of more than 7% triacyl glycerides in hepatocyte vesicles results to hepatic steatosis [3]. Triacyl glycerides can either be obtained through food or synthesized from scratch via de novo lipogenesis [4 – 6]. However, there is evidence that, in patients suffering from non-alcoholic fatty liver disease (NAFLD), the origin of hepatic lipids includes 15.2% as being due to inadequate diets, 22.4% as originating from de novo synthesis, and 59% percent as being due to subcutaneous fat storage [7 – 10]. Liver injury is assumed to be one of the expressions of metabolic disorder, which is a serious health concern that affects 31-3% of males and 16-22% of females around the world, increasing in prevalence among obese individuals by as much as 60-80%. In addition, the improvement of insulin sensitivity, along with a decrease of up to 40% of intrahepatic triacylglycerides within two weeks, has been reported by some experts as a result of body weight reduction associated with a healthy diet and/or exercise regime [11,12]. However, in most instances, patients revert back to their former habits characterized by physical inactivity and poor diet. This necessitated the exploring of alternative treatments, including bioactive compounds such as curcumin (diferoylmethane), which is a polyphenolic phytochemical obtained from turmeric (Curcuma longa) rhizomes [13 – 15]. 1 mg/kg of body weight is a safe amount to consume curcumin; nonetheless, clinical studies have done tests with doses as high as 12 g/day for a period of 3 months without any reported negative effects [16]. According to published references, low levels of curcumin produce hepatoprotective effects capable of preventing liver damage [17]. Curcumin (turmeric spice) has some very important characteristics, one of which is its anti-inflammatory and antioxidant properties. A few experiments have indicated that curcumin can be used to protect the liver from harmful substances, as seen in a study done on pediatric patients who suffered from cyclosporine A-induced liver injury, where it was shown that curcumin could potentially alleviate some of the adverse effects of this drug on the liver. [18 – 20]

2. PATIENTS AND METHODS

2.1. Study design

A cross-sectional study was conducted on 93 patients with liver injury who were collected from different hospitals in Iraq during the period between January 5, 2022, and October 14, 2023. The study criteria included pediatric patients with liver injury whose ages ranged between 1-13 years with MELD score was above 11 and arterial oxygen pressure greater than 60 mmHg. Important exclusion criteria included having a history of any malignancy, hepatopulmonary syndrome;

pulmonary hypertension with an average pulmonary arterial pressure greater than 25 mmHg; hyperoxaluria; cystic fibrosis with FEV1 less than 40%, gallstones and/or bladder stones; use of antiplatelet and/or anticoagulant medications and administration of polyphenol supplements during last three months before study. Serum aspartate aminotransferase (AST) concentrations were obtained and recorded for all patients. This study recorded demographic and clinical data and parameters of the study participants, including age, sex, body mass index, medical history, duration of illness, educational level, and monthly family income.

2.2. Interventions and Assessment of Patients

For four months, each patient received 1,000 mg of curcumin by mouth each day, divided into two equal doses of 500 mg capsules. It was recommended that all subjects consume these supplements with morning and evening meals. Throughout the study period, subjects were instructed to retain their usual diet and level of physical activity. Weekly monitoring was carried out on the patients to identify any side effects from curcumin supplementation.

Each and every one of the patients had standard physical assessments conducted on them. By dividing weight (in kilograms) by the area of height (in meters), the body mass index was computed. 5 mL of blood samples from veins were collected following a 12-hour long fasting period overnight. In determining how bad the liver damage was, Child-Pugh scores, MELD(i), MELD, and MELD-Na scores served as major outcomes. In addition, the tests for prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR) were done as other outcomes on the study. For serum, AST, ALT, and ALP, along with albumin, creatinine, bilirubin, and sodium levels were determined using standard enzyme assays.

CLDQ is the most used scale to find out how patients feel about themselves after suffering from damage on their livers. It comprises questions about physical and emotional performance, tiredness level, anxiety, and health status concerning stomach problems, where the Chronic Liver Disease Quality of Life Questionnaire (CLDQ) has been validated many times in order to evaluate health-related quality of life among children living with chronic liver illnesses. High scores on the CLDQ reflect improved quality of life, whereas low scores demonstrate deteriorating quality of life. Any score above five would usually be classified as high, hence demonstrating good quality, while anything below three is considered low, hence indicating poor quality.

3. RESULTS

Table 1: Basics characteristics of participants observed in this study.

Characteristics	No. of patients [93]	Percentage [%]
Age		
1 – 4	21	22.58%
5 – 8	32	34.41%
9 – 13	40	43.01%
Sex		
Male	45	48.39%
Female	48	51.61%
BMI, Kg/m2		
Underweight	5	5.38%
Normal weight	54	58.06%
Overweight	20	21.51%
Obesity	14	15.05%
Medical history of illness		
Yes	18	19.35%
No	75	80.65%
Duration of illness, years	4.20 ± 2.56	

Education status of parents		
Primary	17	18.28%
Secondary	30	32.26%
Undergraduate or postgraduate	46	49.46%
The monthly income of the family		
< 560	28	30.11%
561 – 830	30	32.26%
> 830	35	37.63%

Table 2: Distribution of participants according to symptoms.

Symptoms	**No. of patients [93]**	**Percentage [%]**
Jaundice	68	73.12%
Abdominal pain	43	46.24%
Nausea and vomiting	32	34.41%
Fatigue	60	64.52%
Pale stools	24	25.81%
Dark urine	19	20.43%
Itching	8	8.60%
Poor appetite	29	31.18%

Table 3: Distribution of participants according to Causes of liver injury.

Causes	**No. of patients [93]**	**Percentage [%]**
Cryptogenic	34	36.56%
Autoimmune	29	31.18%
Hepatitis B virus	13	13.98%
Hepatitis C virus	7	7.53%
Primary sclerosing cholangitis	5	5.38%
Portal vein thrombosis	5	5.38%
Fatty liver	0	0.0%

Table 4: Determining of biochemical measurements in patients who underwent curcumin treatment.

	Curcumin treatment	
Variables	**Before**	**After Curcumin intervention, four months**
Aspartate aminotransferase, AST (IU/L)	62.83 ± 59.77	52.96 ± 40.26
alanine aminotransferase, ALT (IU/L)	47.17 ± 42.75	39.86 ± 26.54
Alkaline phosphatase (IU/L)	337.64 ± 194.39	275.46 ± 116.65
Bilirubin (mg/dl)	2.62 ± 1.51	2.03 ± 1.10
Albumin (g/dl)	3.84 ± 0.41	3.52 ± 0.20
Creatinine (mg/dl)	0.96 ± 0.20	0.94 ± 0.14
Sodium (mmol/L)	140.16 ± 3.14	137.95 ± 3.09
Prothrombin time, PT	16.40 ± 2.11	15.75 ± 2.61
International normalized ratio, INR	1.60 ± 0.43	1.33 ± 0.41

Table 5: Assessment of disease activity scores at patients in terms of before and after curcumin intervention.

Variables	*Period*	*Scores*
MELD(i) score	Before	16.28 ± 2.46
	After	11.20 ± 3.02
MELD score	Before	15.47 ± 3.01
	After	12.64 ± 2.37
MELD-Na score	Before	15.49 ± 4.26
	After	12.66 ± 2.31
Child-Pugh score	Before	8.95 ± 0.53
	After	5.16 ± 0.95

Table 6: Performing of Chronic Liver Disease Questionnaire (CLDQ) at children's patients in before and after curcumin intervention.

Items	*Before*	*After*
Physical function	*5.48* ± 1.34	*2.24* ± 1.33
Psychological function	*6.28* ± 0.67	*2.01* ± 0.55
Emotional function	*5.39* ± 1.56	*1.45* ± 0.88
Fatigue	*4.93* ± 0.92	*2.83* ± 0.38
Abdominal symptoms	*5.85* ± 0.74	*1.03* ± 0.13
Daily activity	*5.44* ± 1.84	*1.26* ± 0.21

4. DISCUSSION

According to the hepatoprotective effect of curcumin against cyclosporine A-induced liver injury in pediatric patients [21]. In recent years, curcumin has taken centre stage as a drug of choice for therapy and shows possibilities for averting and treating various health issues, including diabetes, cancers including respiratory diseases, and heart-related conditions like stroke, high blood pressure, and metabolic syndrome [22,23]. Moreover, the ability of curcumin to protect the liver has been suggested, and it is effective in treating various liver ailments like hepatitis, non-alcoholic fatty liver disease (NAFLD), liver tumours caused by drugs abuse or other factors like cirrhosis of bile duct or sclerosing cholangitis. The study described here is, to our knowledge, the first randomized, double-blind, placebo-controlled trial assessing the effects of curcumin on patients suffering from liver cirrhosis. Our findings showed that curcumin supplementation resulted into significant decreases in levels of ALP, bilirubin, and INR.

Additionally, PT was reduced significantly by the administration of curcumin. Our results showed also that curcumin supplementation induced a great decrease in disease activity scores and severity of liver diseases [18,19,20,24]. Those findings correlated well with previous findings, where it was revealed that curcumin could moderate liver disorders and had a favorable impact on experimental and animal models of liver injury. Likewise, our research was in agreement with research by the Americans, which indicated that curcumin helped reshape the liver of persons having metabolic disorders among kids. Besides, few studies involving liver-afflicted youngsters have confirmed that curcumin lowered portal vein girth while increasing its flow rate and enhancing liver ultrasound features [25 – 27]. It so happened that these resulted in an overall improvement of disease state. There are findings that curcumin is a stronger scavenger of free radicals than vitamin E; this means it fights oxidative stress better. It also prevents hepatic injury by stimulating farnesoid-X receptor expression and activity in the liver, thus inhibiting hepatic steatosis. According to our investigation, curcumin supplementation resulted in considerable alterations in levels of serum AST, ALT, albumin, creatinine, sodium, and PTT.

Furthermore, other studies indicated that there were significant reductions in serum ALT and AST concentrations after taking curcumin; however, no noticeable change was observed on the

part of serum ALP as well as total bilirubin levels. Moreover, the Child-Pugh and MELD scores have been used widely to predict outcomes for liver patients [28]. In most cases, according to a study conducted in Germany concerning this issue, these two indices were able to provide almost identical prognoses, hence making them reliable indicators of disease severity among liver patients. The formulation of supplements could also affect the study findings. Curcumin is generally believed to have low bioavailability due to its hydrophobic characteristics; on the other hand, nanoparticles formulations enhance curcuminoids absorption and increase their therapeutic effectiveness [29,30,31]. In spite of witnessing the positive impact of curcumin supplementation in reducing serum levels of ALP, bilirubin, INR, and PT. Also, the disease activity scores and severity level of patients suffering from liver.

5. CONCLUSION

Curcumin has strong anti-inflammatory and antioxidant properties and has shown promise in protecting the liver against damage induced by cyclosporine A. Therefore, curcumin is an important therapeutic agent that helps prevent cyclosporine A from harming young people by reducing inflammation, oxidative stress, and liver cell injury. This indicates its importance for treating drug-induced liver injury in young people since it can boost liver function and promote regeneration. Due to that, beneficial effects of curcumin have been noted in reducing disease activity scores and severity of cirrhosis in individuals suffering from liver injury, which contribute to improve of quality - life health.

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