Hepato toxic or hepato protective: A review of hepatic effects of *Citrullus colocynthis*

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**Abstract**

*Citrullus colocynthis* (CCT) is a medicinal herb known for its multiple pharmaceutical actions. The trend of its use in therapeutics and research has been increased over the time. It is very important to know its toxicity potential as it is being marketed in many areas of the world. The objective of this review was to evaluate the hepatic effects of CCT. For review, original research papers were searched using primary sources available on selected data bases and using specific key terms followed by a manual search into the secondary sources like review articles and books. The bibliographies of all the selected articles or review papers were searched manually to find the relevant literature. Literature shows conflicting data regarding hepatic effect of *Citrullus colocynthis*. It can be hepatotoxic when used in higher doses or longer durations. Seed extracts are better tolerated than pulp by the experimental animals. However, further research is needed to identify and evaluate the hepatotoxic constituents of CCT. Inspite of the growing evidence regarding its medicinal value, there is dearth of any review of the hepatic effects of Colocynth reported to date. This review will provide a comprehensive overview of the hepatic protection or toxicity offered by *Citrullus colocynthis*.

**Keywords:** *Citrullus colocynthis*, colocynth, Tumbah, phyto toxicity, Hepatic

**Introduction**

*Citrullus colocynthis* (L.) Schard (Fig. 1), one of the four species of the desert vine, related to genus Cucurbitacae, is a perennial herb with a tuberous taproot [1]. It is also known as colocynth or bitter apple in English, Kolokinthe in German, Colocinte in French [2, 3], al-Hanzal in Arabic and tumba in Urdu [4]. It is also named as thymbre or earth gall [4]. It is widely distributed in the arid areas extending from the west coast of northern Africa, eastwards touching the northward to Mediterranean Sea [5].

Colocynth seeds have a historical background for its nutritional use when African tribes in Sahara used to make food from its seeds [5]. Colocynth seeds contains linolenic acid, linoleic acid, oleic acid, palmitic acid, stearic acid, arachdonic acid [6]. It has also been considered as a potential oil harvest [7]. Among the various fatty acids, major proportion (66.6%) is constituted by Linoleic acid. It has also been considered as a potential oil harvest. It is known to have flavanoids, alkaloids, glycosides, terpenoids [8] colocynthisides and cucurbitacins [6], amino acids, carbohydrates, phenols, saponins, glycosides, tannins, triterpenoid [8].

In addition to the nutritional value of its seeds, different parts of the plant have been investigated since long to evaluate its medicinal potential. It is known to have anti diabetic [6, 18, 19], beta cell regenerative [9], alpha cell hyperplastic(14), insulinitropic [15, 19], anti-neuropathic pain [17], antioxidant [18], anti inflammatory [19-21], hypolipidemic [22, 23], anti cancer [24, 25], hepato protectivity [26, 27], antifungal [28-30], anti candidal [31, 32], antimicrobial [33], scorpion envenomation [34], hair tonic in Alopecia [35-36], insecticidal [37], anti-ulcer [38], and anti-fertility effects [39-41]. It is known to be a hydragogoue artic used in constipation, hepatic congestion. It’s pulp for constipation, fever and worms; root for cough and asthma; seed oil for snake bites, bowel complaints, and hair growth [42]. Fruit part is carminative, purgatives, anti pyretics, antihelminthic and also used in tumors, ascities, asthma, bronchitis, elephantisism tuberculous glans of neck and spleenomegaly. Its roots have been used in mastitis, rheumatigia, viseromagaly in children and jaundice [43].

**Fig 1:** *Citrullus colocynthis* (Teixeira De-Silva and Hussain, 2017)
Its active principle is said to be glucoside colocynthin \[42\]. It also contains citrulluin, citrullene and citrullinic acid. The peel free flesh of the ripe fruits contains a bitter oil, citbittol and a di-hydric alcohol, citrullool in the dried pulp \[43\]. It is normally considered that phytochemicals are safe which, however, is not the case. Herbs are known to cause drug induced liver injury (DILI). The damage is related to self medication and poor vigilance related to use of herbal medicine \[44, 45\]. It is known that the pulp of Citrullus is poisonous in excessive doses \[42, 46\]. Citrullus is known to have toxic effects on female reproductive system \[47\], heart \[48\], kidneys and liver \[49\]. Cases of rectorrahgia \[50\], colitis \[51\] and bloody diarrhea \[52\] have also been reported after Citrullus ingestion. It is also known to cause carcinogenicity \[53\], while on the other hand, its anticancer effect has also been documented \[24\]. However, a gross conflict exists regarding hepatoprotective and hepatotoxic effects of Citrullus.

**Methodology**

**Objective**

The objectives of this review were to see the hepatic effects of toxicity of *Citrullus colocynthis* and to identify gaps for further research in this area.

**Data Collection**

Meticulous strategy regarding data sources, study section and data extraction was used for the collection of evidence. Literature search was done in two phases. In phase 1, original research papers were searched using primary sources available on selected data bases and using specific key terms followed by a scoping search into the secondary sources like review articles, conference proceedings and books. In phase 2, the bibliographies of all the selected articles or review papers were searched manually to find the relevant literature.

**Data Sources**

Research articles were retrieved using specific data basis which included: Google Scholar, Google, pubmed, Medline, Proquest. Data was also collected from secondary sources like journal of Ayurveda or herbal medicine available in local library. All the sources were searched using key words of *Citrullus colocynthis* or *Colocynth* OR *Tumbah* OR *Bitter Apple* AND *Toxicity* OR *phyto-toxicity* AND *Hepatic*.

**Study Selection**

Specified inclusion and exclusion criteria was used to maximize the value of review through the collection of articles which were found to be relevant. Search was performed by the authors individually. All data collected was merged and any duplication was removed from the pool. The studies identified were then organized for abstraction and critical appraisal. The inclusion criteria were pre decided. Original research papers based on animal or human trials for the evaluation of either the histological changes of liver or liver function markers or both due to treatment with any part of the plant of *Citrullus colocynthis*, published in journals in English were included in the review.

**Data Extraction**

All the selected articles were read critically and detailed description of the results along with the experimental animals, part of plant, type of extract, dosage, route and duration of the study was included.

**Results**

All researches have been produced from some areas of Asia including Iran (4studies), India (3), Saudi Arabia (3), Iraq (2), Egypt (1), Jordan (1), UAE (2), Algeria (1) whereas only one study is produced from Europe, Germany. (Table 1, Fig. 2). Search found 18 studies (Table 2) in which different experimental animals like mice (2 studies), rabbits (2 studies) and rats (14 studies) were used. Twelve studies documented the hepatotoxicity of CCT while six studies have shown either non toxic nature or hepatoprotective nature of CCT. Different doses of various parts of *Citrullus colocynthis* like pulp (4 studies), full fruit (9), Pulp and seed (2) seeds (1) leave (1 study) were used in the experiments. Most of the studies evaluated markers of liver function like AST, ALT, ALP along with the morphological changes. In addition to it, two only abstracts were found which are not included in the data extraction. Hepato toxicity of Citrullus.

<table>
<thead>
<tr>
<th>Year</th>
<th>No</th>
<th>Authors</th>
<th>Country</th>
<th>Journal</th>
</tr>
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<tbody>
<tr>
<td>2017</td>
<td>1</td>
<td>Shafaei et al</td>
<td>Algeria</td>
<td>International Journal of Pharmacognosy and Phytochemical Research</td>
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<td>Al-Gerwi et al</td>
<td>Egypt</td>
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<td>2012</td>
<td>3</td>
<td>Shafaei et al</td>
<td>Iran</td>
<td>Journal of medicinal plant research</td>
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<tr>
<td></td>
<td></td>
<td>Dar et al</td>
<td>India</td>
<td>International research of biological and pharmaceutical research</td>
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<tr>
<td></td>
<td></td>
<td>Dar et al</td>
<td>India</td>
<td>American Journal of Plant Sciences</td>
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<td>2011</td>
<td>1</td>
<td>Khatibi</td>
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<td>Journal of Agricultural Sciences</td>
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<td>Khalil et al</td>
<td>Jordan</td>
<td>American Journal of Biochemistry and Biotechnology</td>
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<td></td>
<td></td>
<td>Alabadi and Al-Ali</td>
<td>Iraq</td>
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<td>2009</td>
<td>1</td>
<td>Atole et al</td>
<td>India</td>
<td>Veterinary World</td>
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<td>2006</td>
<td>1</td>
<td>Deghani and PajnehShahin</td>
<td>Iran</td>
<td>Iranian journal of pharmacology and therapeutics</td>
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<td>2004</td>
<td>1</td>
<td>Al-Ghathi et al</td>
<td>UAE</td>
<td>Molecular and cellular biochemistry</td>
</tr>
<tr>
<td>2002</td>
<td>1</td>
<td>Barth et al</td>
<td>Germany</td>
<td>Experimental and Toxicological Pathology</td>
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<tr>
<td>2001</td>
<td>1</td>
<td>Adam et al</td>
<td>SA</td>
<td>Small Ruminant research</td>
</tr>
<tr>
<td>2000</td>
<td>2</td>
<td>Diwan et al</td>
<td>Iraq</td>
<td>Eastern Mediterranean Health Journal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Al-Yahya et al</td>
<td>SA</td>
<td>Filoterapia</td>
</tr>
<tr>
<td>1994</td>
<td>1</td>
<td>Wafsi</td>
<td>UAE</td>
<td>Journal of Herbs, Spices and Medicinal Plants</td>
</tr>
<tr>
<td>1989</td>
<td>1</td>
<td>Shah et al</td>
<td>SA</td>
<td>Phytotherapy</td>
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</table>
In 1989, Shah et al. evaluated the toxicity profile of 6 plants used as traditional medicine in Arab, which included *Citrullus colocynthis*. They found CCT to be maximally lethal with percentage lethality of 45% and highest mortality. The mortality rate was 40, 60 and 100% in mice fed 500 mg/kg, 1 g/kg and 3 g/kg. After acute toxicity, animals were found to have diarrhea, increased respiratory rate, increased motor activity, tremors and even convulsions and death. Chronic intake of 100mg/kg caused significant increase in liver weight but weight of heart lung, spleen, kidney and testis was not changed significantly. Wasfi [55] observed hepatorenal toxicity of 800mg/kg CCT pulp and leaves.

Two studies examined the effect of CCT rich diets. Al-Yahya et al. [56] examined the toxicity of diet having 10% CCT and 10% Nerium Oleander for 3 and 6 weeks. They found raised levels of AST and ALT at both time bounds, suggesting liver damage. Adam et al. [57] used crude powder of CCT as 10% of diet in rats for 3 and 6 weeks. After 3 weeks, mild hepatic congestion and degenerative changes in livers were observed. After 6 weeks of treatment, necrosis and cytoplasmic fatty vacuolation of centrilobular hepatocytes were observed in liver along with significant rise in AST and ALT.

Diwan et al. [5] used saponin extract as 200 mg/kg and examined livers after 48 hours. There was necrosis, central venous congestion and hemorrhages in liver samples. They also observed acute toxicity of CCT with 50, 100, 150, 250, 350 and 600 mg/kg of saponin extract showing high rate of mortality in groups fed doses higher than 150mg/kg. They observed dose dependent effect on appetite, gait, activity and diarrhea.

Deghani and Panjeh Shahin [59] used alcoholic extract of CCT as 50, 100, 200, 400 mg/kg for 2 weeks intraperitoneally and observed liver damage showing sinusoidal and central venous congestion, Inflammation, hemorrhages, lymphocytic and leukocytic infiltration and fibrosis at 200-400mg/kg. However, fibrosis was evident particularly at 400mg/kg dose.

CCT induced hepatotoxicity in also observed in rabbits. Shafaei et al. [60] studied the effect of CCT on rabbit liver tissues. They used 100 and 200 mg/kg of CCT pulp and seed extracts for one month in rabbits weighing 3kg. Animals taking higher dose of pulp extract didn’t survive. Severe damage to the histological architecture of liver was observed along with kidneys. However, seed extract induced minor intestinal effects. Likewise, Soufane et al. [61] observed raised liver enzymes at 5th, 10th and 14th days of treatment with CCT 131mg/kg but no change in liver weight was observed.

Long term use of CCT extract is more deleterious even at lower doses. In evaluation of subchronic haematotoxicity and histotoxicity of CCT, Elgerwi and colleagues used CCT (1/4th of LD50) collected from three areas of Libya. After oral administration of 100 or 162mg/dl pulp extract every week for 10 weeks, they observed necrosis, fibrosis, chromatolysis, vacuolar degeneration of hepatocytes, central venous congestion, sinusoidal congestion, Inflammation with marked infiltration of lymphocytes and macrophages, focal hemorrhages, hypertrophy of kuffer cells in rat livers. They observed significantly raised liver function markers GPT, GOT and ALP. Total protein was also decreased. [61] More recently, Soufane et al. [62] used higher doses of CCT 265 mg/kg for 6 weeks and observed hepatic congestion, elevated liver enzymes, and significant reduction in liver weight.

**Hepato protective activity of Citrullus**

However, contradictory evidence also exists. Experimental studies have shown various degrees of hepato protective action of *Citrullus colocynthis*. In four studies showing hepato protective effects of CCT, whole fruit extract has been used whereas two studies have used seed only or pulp only extracts. Dar et al. evaluated the effect of CCT on polluted water [27] and paracetamol induced liver damage[26]. Dar et al. [27] gave ethanolic extract orally to rats as 100 and 200mg/kg which effectively decreased Polluted water induced raised liver enzymes and improved inflammation, necrosis and congestion in liver. In the second study they observed protective effect of CCT against paracetamol induced hepatotoxicity [26]. Paracetamol was given as 500mg/kg per oral every 72 hours for 7 days and rats were treated with 50, 100, 200 mg/kg CCT ethanolic extract. The higher dose (200mg/kg) was found to be effective in decreasing hepatocyte vacuolization and fatty change and decreasing the raised liver enzymes.

Al-Gaithi et al. [63] evaluated the effect of CCT aqueous seed extract on biochemical parameters in diabetic rats. They used doses of 0.25ml, 0.5ml and 1ml/kg of extract. No significant effect in normal rats was observed, however, significant decrease in plasma AST level was observed in diabetic rats. Likewise, Alabadi and AL-Ali [64] used 300mg/kg aqueous fruit extract in alloxan treated diabetic rats for 3 weeks and evaluated its effect on biochemical markers. They documented decrease in serum ALT and ALP levels in diabetic rats. Atole et al. [65] conducted a safety evaluation study of CCT and used 50mg/kg and 100mg/kg CCT fruit extract for 28 days in rats. They did not observe any noticeable change in liver enzymes and histological structure and have documented these doses of CCT as safe in diabetes.

Barth et al. [66] evaluated the liver toxicity of CCT extract by estimating tissue GSH, LPO levels and ROS production. However, they did not observe histological changes or liver enzymes. CCT extract in doses of 100 µg/ml reduced lipid peroxidation but this concentration could not recover CCl4 induced damage in rat liver slices.
In another study, Khalil et al. [67] have observed hepatoprotection in CCT treated diabetic rats. They used pulp only extract as 300mg/kg and observed alleviation of diabetes induced hepatic inflammation, hepatocyte vacuolation, lipid accumulation and sinusoidal damage in liver tissue of rats.

Table 2: Selected articles showing Hepatic effect of *Citrullus colocynthis*

<table>
<thead>
<tr>
<th>No</th>
<th>Study Population</th>
<th>Weight of Animals</th>
<th>Part of Plant</th>
<th>Preparation</th>
<th>Route</th>
<th>Dose</th>
<th>Duration of treatment</th>
<th>Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rats 180-210 g</td>
<td>Pulp</td>
<td>Methanolic</td>
<td>Oral</td>
<td>265mg/kg</td>
<td>For 6 weeks</td>
<td>Reduction in liver weight Elevated liver enzymes Hepatic congestion</td>
<td>Soufane et al., 2017</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Rabbits 3 kg</td>
<td>Pulp seeds</td>
<td>Pulp and seed extract</td>
<td>100, 200mg/kg</td>
<td>1 month</td>
<td>Increased glycogen content of hepatocytes in alloxanized rabbits</td>
<td>Shafaei et al., 2014</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Rats 180-210 g</td>
<td>Pulp</td>
<td>Methanolic</td>
<td>Oral</td>
<td>131mg/kg</td>
<td>24hr, 5, 10 and 14 days</td>
<td>No change in weight of liver Elevated liver enzymes</td>
<td>Soufane et al., 2013</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Rats 180-250g</td>
<td>Pulp</td>
<td>Alcoholic</td>
<td>Oral</td>
<td>100mg/kg, 162mg/kg 1/4th of LD50</td>
<td>Every week for 10 weeks</td>
<td>Necrosis, fibrosis, chromatolysis, central venous congestion, sinusoidal congestion, Inflammation, Hemorrhages, hypertrophy of kupffer cells, vacuolar degeneration of hepatocytes</td>
<td>Al-Gerwi et al., 2013</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Rabbits 3 kg</td>
<td>Pulp seeds</td>
<td>Methanolic Pulp extract and seed extract</td>
<td>100, 200mg/kg</td>
<td>1 month</td>
<td>Dilatation of sinusoids and bile ducts in pulp extract treated rats whereas no hepatorenal toxicity was observed with both doses of seed extract</td>
<td>Shafaei et al., 2012</td>
<td></td>
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<tr>
<td>6</td>
<td>Rats 200-250g</td>
<td>Fruit</td>
<td>Alcoholic</td>
<td>IP</td>
<td>50,100,200, 400mg/kg</td>
<td>Two weeks</td>
<td>Sinusoidal and Central venous congestion, Inflammation, Hemorrhages, lymphocytic and leukocytic infiltration</td>
<td>Deghani and PanjehShahin, 2006</td>
<td></td>
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<tr>
<td>7</td>
<td>Rats 60 days old</td>
<td>Seeds</td>
<td>Ethanolic</td>
<td>Incubation of liver tissue slices</td>
<td>CCT extract for incubation in doses of 10 µg/ml, 100 µg/ml</td>
<td>22 hours exposure</td>
<td>Concentrations upto 100 micrograms/ml inhibits LPO and ROS production but did not alleviate CCl4 induced liver damage</td>
<td>Barth et al., 2002</td>
<td></td>
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<tr>
<td>8</td>
<td>Rats 150±10</td>
<td>Fruit</td>
<td>Crude powder</td>
<td>Oral</td>
<td>10% diet</td>
<td>3-6 weeks</td>
<td>After 3 weeks: Mild hepatic congestion, degenerative changes, After 6 weeks: Necrosis, fatty vacuolation of centrilobular hepatocytes Significant rise in AST and ALT</td>
<td>Adam et al., 2001</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Mice 20-30g</td>
<td>Fruit</td>
<td>Methanolic Saponin extract</td>
<td>Bucco gastric cannula</td>
<td>200mg/kg</td>
<td>48 hours</td>
<td>Necrosis, Central venous congestion, Hemorrhages</td>
<td>Diwan et al., 2000</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Rats 165±10g</td>
<td>Fruit</td>
<td>10% diet</td>
<td>Oral</td>
<td>10% diet</td>
<td>3,6 weeks</td>
<td>Significant rise in AST, ALT, ASP</td>
<td>Al-Yahya et al., 2000</td>
<td></td>
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<tr>
<td>11</td>
<td>Rats 200-250g</td>
<td>Pulp Leaves</td>
<td>Chloroform and methanolic extract</td>
<td>Oral</td>
<td>800mg/kg</td>
<td>24 hours</td>
<td>Central vein dilatation and congestion Sinusoidal dilatation and congestion</td>
<td>Wasfi et al., 1994</td>
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<tr>
<td>12</td>
<td>Mice 25-30g</td>
<td>Fruit</td>
<td>Oral</td>
<td>100mg/kg</td>
<td>3 months</td>
<td>Reduction in weight of liver</td>
<td>Shah et al 1989</td>
<td></td>
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</tr>
</tbody>
</table>

Non Toxic or Hepato Protective action

| 13 | Rats 150-200g    | Fruit             | Ethanolic     | Oral        | 100, 200mg/kg | 10 days | 200mg/kg effectively decreases raised liver enzymes and Improved infalamation necrosis and congestion | Dar et al., 2012a |
| 14 | Swiss Rats 150-200g | Fruit             | Ethanolic     | Oral        | 50, 100, 200mg/kg | 7 days | Decrease vacuolization and fatty change and effectively decreases raised liver enzyme | Dar et al., 2012b |
| 15 | Rats             | Fruit             | Aqueous extract | Oral        | 300mg/kg | 3 weeks | Lowers ALP in alloxanized rats | Alabadi and Al-Ali, 2010 |
| 16 | Rats 200-250g    | Pulp              | Ethanolic     | Oral        | 1ml/kg (equivalent to 300mg/kg) | 30 days | Alleviation of hepatocyte cytoplasmic vacuolar degeneration, pyknosis, steatosis severity grade and sinusoidal damage | Khalil et al., 2010 |
| 17 | Rats 170-250g    | Seeds             | Aqueous       | Oral        | 0.25, 0.5, 1 ml/kg | 14 days | No significant effect in normal | Al-Gaithi et al., |
Discussion

History of using Folk medicine to treat various illnesses dates back to earlier times. Its only recently that herbal remedies are being analyzed for scientific validation of the toxicity profile [68]. Herbal remedies used for various purposes like psoriasis, slimming, liver tonics, rheumatism etc are well recognized for their hepatotoxicity [60]. However the scientific data about the hepatic profile of CCT in therapeutics is controversial and supports both the hepato protective and hepatotoxic effects.

Earlier researchers used higher doses of CCT as compared to the more recent studies. This change in trend looks like due to the evolving concept of toxicity potential of herbal medicines. This review shows that CCT induced hepato toxicity is dose and time dependent. Higher doses of CCT, as 800mg/kg [55], 400mg/kg and 200mg/kg [90] are more toxic. Most of the researchers documenting the antidiabetic, anti-oxidant, hypolipidemic, anti-inflammatory effect of CCT have used 50-300 mg/kg/day, wherein 300mg/kg is used for duration of 3-4 weeks and 50 mg/kg, considering a safer dose, is used for more than a month.

However, discrepancies exist regarding dose dependent effect. Shafaei et al. [70] and Soufane et al. [62] observed hepato toxicity of 200mg/kg CCT; Whereas, Dar et al. [26, 27] observed hepatoprotective effects of CCT and found 200mg/kg effective in reducing inflammation and congestion of liver in polluted water induced hepatic damage and decreased hepatic vacuolation in paracetamol induced hepatic injury. One difference between hepato protective and hepato toxic studies is the type of extract. In studies showing hepatoprotective effect, ethanolic extract was used; whereas, methanolic extract was used in most of the studies showing hepatotoxicity. Hence, it can be speculated that methanolic extracts might be hepatotoxic, however, it is a less likely justification and needs further exploration.

CCT fruit extract is considered safe if given as 50 mg or 100mg/kg when given for 28 days. [65] However, significant increase in rat liver weight was observed by Shah et al. [65] after chronic ingestion (3 months) of even 100mg/kg CCT which contradicts the finding of Soufane et al. [71] who did not observe significant change in weight of liver with 131mg/kg. This discrepancy may be due to the use of mice or longer duration of treatment. In studies showing hepto protective effect, CCT is used in different doses from 50 to 300 mg/kg. However, Soufane et al. [71] observed raised liver enzymes even at 1/10th of LD50 131mg/kg. This controversy in dose dependent effect needs further exploration. However, it is said that LD50 can vary according to animal, species, age, bedding, time of the day, ambient temperature etc. [46]

Moreover, hepato protective effect was observed in 7-10 days treatment and hepatotoxicity was observed when CCT was given for 1-6 months. However, Diwan et al. [72] have reported acute toxicity with 200 mg/kg but they used saponin extract. Saponin may be the responsible phytochemical for acute toxicity with 200 mg/kg but they used saponin extract. Hence, it can be speculated that methanolic extracts might be hepatotoxic, however, it is a less likely justification and needs further exploration.

Conclusion

Citrullus colocynthis is hepato toxic unless given in small (50-100mg/kg) doses and smaller duration. Its seed extracts are safer as compared to pulp. However, controversies exist in literature and further research is needed in this area. Isolation and evaluation of hepato toxicity of the individual constituents of Citrullus colocynthis needs to be done further at molecular level.

Declaration

There is no conflict of interest between the authors

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