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SHORT REVIEW

Hepatoprotective Activity of *Haritaki* (*Terminalia chebula* Retz): A Systematic Review

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Abstract

Terminalia chebula Retz, also referred as *Haritaki* in Sanskrit, is a widely available plant distributed all over India. *T. chebula* has been widely acknowledged for its therapeutic qualities and application in treating several kinds of diseases. This plant is part of the *Combretaceae* family and serves a crucial role in maintaining a disease-free community. The hepatoprotective qualities of *T. chebula* are widely recognized. Consequently, published literature from "Pubmed, Scopus, Cochrane database, Google Scholar" up to 2023 was used in a systematic review. With a computer-based search engine, 115 Studies in total were looked up. In the present study, *T. chebula's* hepatoprotective properties were investigated using PubMed, Scopus, Cochrane and other resources. Twelve studies that met the requirements were chosen after screening. To identify the various activities, *T. chebula* plant leaves, fruits, roots, and polymer were examined. This systematic review aimed to collect and analyze data on the efficacy of *T. chebula* as a hepatoprotective treatment from clinical trials, *in vivo* investigations, and *in vitro* experiments. The 12 studies that were chosen had significantly different study designs and resultsThe study concludes that *T. chebula* provides alternatives for several medical disciplines due to its hepatoprotective and disease-prevention qualities.

Keywords: *Terminalia chebula* Retz, Hepatoprotective, *In Vitro* Study, *In Vivo* Study, *Haritaki*

1. Introduction

The liver is the largest organ and can be harmed by a variety of factors such as bacterial infections, toxic chemicals, and drug or alcohol addiction[1]. The liver is well-known for its strong capability for regeneration and damage healing[2]. Serious clinical symptoms including jaundice and severe coagulopathy can occasionally be the result of severe and acute liver injury, and these conditions have a significant mortality rate. There are still medical activities to be completed in order to understand its pathophysiological principles and produce effective therapies for particularly severe hepatic injury[3].

Previous investigations have found a strong relationship between oxidative stress and the pathophysiology of acute liver damage[4]. Because they alter the cellular structures and macromolecules, Reactive Oxygen Species (ROS) have the potential to cause immediate harm to liver tissue[5]. Moreover, elevated ROS can damage hepatic tissue's Deoxyribonucleic Acid (DNA), activate nucleases and proteases, and alter the permeability of cellular membranes[6]. Because of this, the development of hepatoprotective or therapeutic medicines has recently faced significant obstacles related to oxidative stress and antioxidant activity[7-9]. Many groups have made efforts to produce hepatotherapeutic drugs utilizing

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herbal plants, based on the traditional use and clinical experiences[10,11].

The genus *Terminalia*, which is a member of the family *Combretaceae*[12–18], contains 200–250 species. Though plants in the *Terminalia* genus can be found in tropical areas all over the world, Southeast Asia has the most diverse plant species. The Latin word terminal is the source of the name "*Terminalia*," as these plants' leaves are found at the top of the shoots[19–25]. *Terminalia travancorensis, Terminalia alata, Terminalia procera, Terminalia paniculata, Terminalia coriacea, Terminalia myriocarpa, Terminalia manii, T. chebula, Terminalia citrine, Terminalia catappa, Terminalia bellirica, Terminalia bilata,* and *Terminalia arjuna* are among the species of this genus that have been researched. Since ancient times, several portions of the *T. chebula, T. bellerica* and *T. arjuna* species have been employed in Ayurveda[26,27]. *T. chebula* Retz (Figure 1), the most studied species in pharmacology, is indigenous to Southeast and South Asia[28,29].

The fruits of *T. chebula* possess carminative, purgative, astringent, alternative, and stomachic qualities[30,31]. Fruits are used in traditional *Ayurvedic* and *Siddha* medicines to treat a variety of conditions, including hepatomegaly, asthma, dyspepsia, dyspnea, ulcers, constipation, chronic diarrhea, malabsorption syndrome, urine discharge, skin disease, epilepsy, memory loss, cardiovascular illness, anorexia, diabetes, wound healing, antitussive, and homeostatic[32-34]. It is also used as an astringent to treat hemorrhoids, loose gums, gum bleeding, ulcers, spleen enlargements, liver problems, and skin diseases. Fruit parts are used to treat asthma and hemorrhoids[35].

Several studies on the beneficial properties of TC and chebulinic acid, no comprehensive review on hepatoprotective action has been conducted. Numerous studies have been published that show CA's hepatoprotective action; however, there has been no systematic study of TC's hepatoprotective activity, and no conclusive conclusion on the efficacy of this plant has been made. As a result, the aim of this study was to evaluate the TC's hepatoprotective activity.

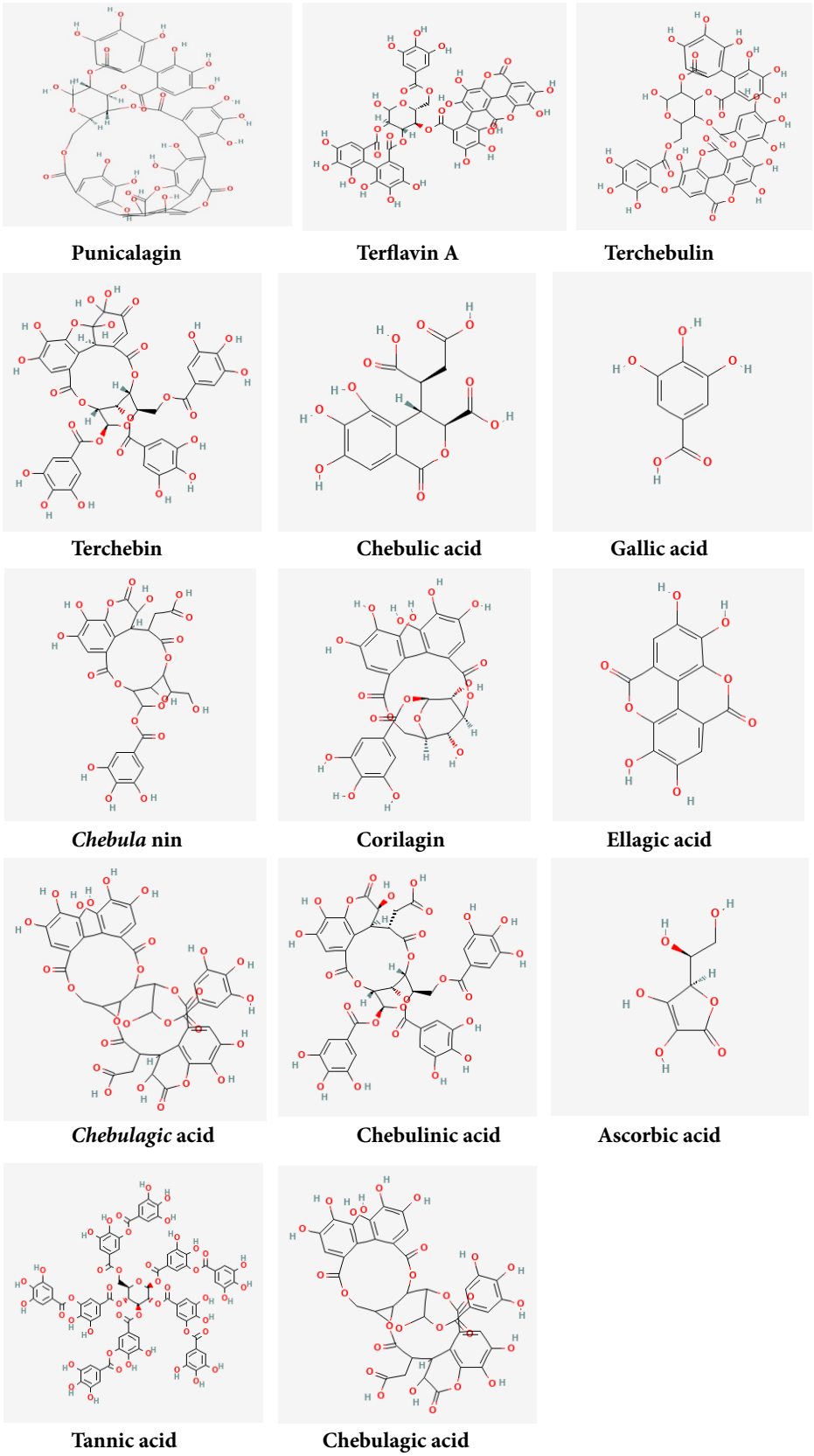
2. Chemical Composition

Punicalagin ((2, 3-(S)-hexahydroxydiphenoyl-4, 6-(S, S)-gallagyl-D-glucose), Terflavin A, Terchebulin, Terchebin(1,3,6-trigalloylglucose),terflavinsB,terflavin C, terflavin D, Punicalin, Chebulic Acid, Gallic Acid (3, 4, 5-Trihydroxybenzoic acid), Chebulanin, Corilagin, Ellagic Acid (2, 3, 7, 8-Tetrahydroxy-chromeno [5, 4, 3-cde]chromene-5, 10-dione) , *Chebula*gic acid, Chebulinic acid (1, 3, 6-Tri-O-galloyl-2, 4-chebuloyl-β-D-glucopyranoside), Chebulaginic Acid, 4-O - Methylgallic Acid, Methyl(S)-flavogallonate, Methyl Neochebulagate, Eugenol, Ascorbic acid, Tannic acid [2, 3-dihydroxy-5-({[(2R,3R,4S,5R,6R)-3, 4, 5, 6-tetrakis ({3, 4-dihydroxy-5-[(3, 4, 5-trihydroxyphenyl) carbonyloxy]phenyl}carbonyloxy) oxan-2-yl]methoxy} carbonyl)phenyl 3, 4, 5-trihydroxybenzoate], 2, 4-Chebulyl-beta-D-glucopyranose (Figure 2).

3. Material and Methods

From 2005 to September 2023, a systematic review was undertaken using the databases PubMed, Science Direct, Scopus, Proquest, Ebsco, Google, Google

Figure 1. Images of *Terminalia chebula* Retz.



Source: https://pubchem.ncbi.nlm.nih.gov

Figure 2. Chemical structure of some compounds of *Terminalia chebula* Retz.

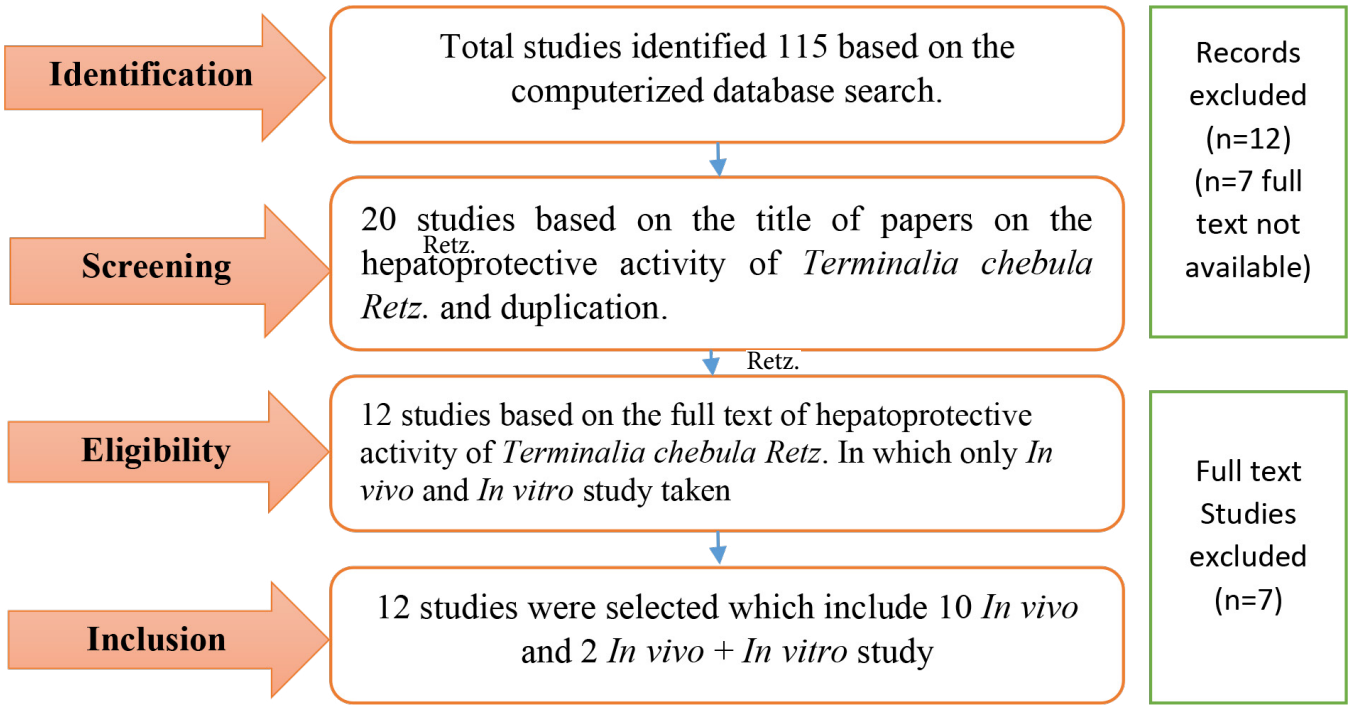


Figure 3. The PRISMA flow diagram of the study.

Table 1. Overview of publications considered in the systematic review

Sr.No.	Name of Authors	Journal and year of publication	Study type and method	Plant part used for the study	Major outcomes
1	Tasduq SA *et al.*,,	IJAPR (March 2006)	*In vivo*	Ethanolic extract of T. *chebula* (fruit) (TC extract),	In a sub-chronic (12-week) study, TC extract was found to prevent hepatotoxicity caused by the combination of rifampicin (RIF), isoniazid (INH), and pyrazinamide (PZA).
2	Sharma A *et al.*,,	Thai J Toxicology 2010; 25(2): 144-153	*In vivo*	Aqueous Extract of *Terminalia chebula* Fruit	Myrobalan's preventive activity can be attributed to the regeneration of hepatocytes and renal tubular cells even in the presence of acetaminophen. It is determined that myrobalan lowers acetaminophen hepatorenal damage in mice.
3	Sivachandran, S. *et al.*,,	International Journal of Veterinary Science (2012)	*In vivo*	Aqueous extract of *Terminalia chebula*	The current study's findings indicate that *Terminalia chebula* plant extracts could be employed as a protective agent against gentamicin-induced hepatotoxicity.
4	Rhitajit Sarkar *et al.*,	BMC Complementary and Alternative Medicine 2012, 12:144	*In vitro* and *In vivo*	Methanolic extract of *Terminalia chebula*	*Terminalia chebula* extract may include active compounds capable of reducing the toxicity caused by iron overload, making it potentially beneficial as an iron chelating medication for iron overload illnesses.

Table 1. Continued...

5	Nishanth *et al.,*	Journal of Herbs, Spices and Medicinal Plants 20(4): 402-420 (October 2014)	*In vivo*	*Terminalia chebula* fruit extract	T. *chebula* may be able to counteract 2-AAF-induced oxidative stress and drug resistance in mice hepatic tissue, hence avoiding neoplastic transition to hepatocarcinoma.
6	Tania Yeasmin *et al.,*	Journal of Bangladesh Society of Physiologist (August 2015)	*In vivo*	Paracetemol, extract of *Terminalia chebula*	*Haritaki*(*Terminalia chebula*) may possess hepatoprotective effects against paracetamol-induced liver damage. As a result, it could be used to treat liver damage induced by hepatotoxic medicines.
7	Min-Kyung Choi *et al.,*	Evidence-Based Complementary and Alternative Medicine (October 2015)	*In vivo*	*Terminalia chebula* water extract (TCW)	TCW efficiently protects the liver from both acute and severe liver injury, and the underlying mechanisms may include improved antioxidant capacity and inflammatory response control.
8	Balakrishna V *et al.,*	56 Asian J Pharm Clin Res, Vol 10, Issue 11, 2017, 55-58 56 Asian J Pharm Clin Res, Vol 10, Issue 11, 2017, 55-58 Asian Journal of Pharmaceutical and Clinical Research(July 2017)	*In vivo*	Ethanolic extract of *Terminalia chebula* fruit	The antioxidant activity of TCA is responsible for its hepatoprotective activity against ethanol induced Hepatotoxicity in Rats
9	Raheleh Ahmadi-Naji *et al.,*	Avicenna journal of phytomedicine (September 2017)	*In vivo*	Hydroalcoholic extract of T. *chebula* fruits extract	The fruit extract of T. *chebula* protects against diazinon-induced oxidative damage.
10	Srilekha E. *et al.,*	World Journal of Pharmaceutical Research (2019)	*In vivo*	Ethanolic extract of *Terminalia chebula* fruits	The ethanolic extract of *Terminalia chebula* fruit shown hepatoprotective action.
11	Xin-Hong Feng *et al.,*	Phytomedicine Volume 83, March 2021, 153479 (March 2021)	*In vitro* by DPPH radical scavenging, *In vivo*	Chebulinic Acid	Experiments in cell and two animal models yielded consistent results and provided a thorough explanation of CA's hepatoprotective properties.
12	Sarada S. *et al.,*	Biomedicine-Vol. 41 No. 2 (Supplementary issue): 2021	*In vivo*	Fruit of *Terminalia chebula* and Gallic Acid	T. *chebula* powder is more efficient than gallic acid (pure molecule) in treating high fat diet-induced hyperlipidemia, which is characterized by a decrease in antioxidant enzyme activity and increased lipid peroxidation.

Scholar, Cochrane, and Embase to locate published research publications on TC. The engine identified 115 studies (Figure 3). These included studies on various activities such as antimicrobial, antioxidant, hepatoprotective, neuroprotective, and so on.

A total of 20 studies on Hepatoprotective study. 12 available , 7 for buying.

4. Results

The studies that met the qualifying criteria i.e. only *in vivo* and *in vitro* study were selected and reviewed over. Studies that were repetitive or did not meet the inclusion criteria were eliminated. For review, full text articles were obtained by downloading the papers after each abstract was assessed independently.Studies that met the eligibility requirements were chosen for the review.

Total of 115 searched studies based on reading titles, abstract and publications, 96 were discarded because they failed to reach the eligibility criteria. 6 duplicate studies were removed from 19 studies and 12 studies were included due to matching with eligible criteria (Table 1). Out of 12 selected studies 10 were *in vivo* study and 2 study were both *in vitro* and *in vivo*.

5. Discussion

A computer-based search engine yielded 115 studies in total. The hepatoprotective activity of TC was searched using pubmed, scopus, chocrane, and other resources.

Following screening, 12 studies which met the criteria were selected. This review summarizes research on the effects of TC on hepatoprotective antioxidant components. The majority of research on TC-associated liver diseases is undertaken in animals. The plant has numerous hepatoprotective qualities, including antioxidant, analgesic, purgative, and lipid-deposition inhibitory effects. Furthermore, it improves liver function and protects against liver disease. Although a few high-quality clinical trials have been undertaken, there is insufficient information to draw conclusions about the plant's usefulness as a hepatoprotectant. Clinical studies have revealed no harmful effects connected with TC. Many papers demonstrated TC's hepatoprotective capabilities, with the majority of the activities found by the use of plant fruits. The TC fruit is one of the most commonly utilized herbal remedies in Traditional medicine prescriptions, notably for liver disorders[36].

The significance of oxidative stress in the pathophysiology of acute liver injury has been extensively described in previous research[37]. Via the disruption of cellular macromolecules and structures, High levels of Reactive Oxygen Species (ROS) can induce direct damage to liver tissue[38]. Furthermore, increased ROS can cause Deoxyribonucleic Acid (DNA) fragmentation in hepatic tissue, alter cellular membrane permeability, and activate nucleases and proteases[39]. As a result, oxidative stress and antioxidant activity are important considerations in the creation of new therapeutic or hepatoprotective drugs[40-42]. Chebulinic Acid (CA), a significant chemical component of TC fruit, shown strong activity in the screening of bioactive elements with possible hepatoprotective effects. It has also been shown to have antioxidant properties that can help protect the body from free radical damage, which causes harm to the liver.

5.1 Tasduq SA *et al*[43]

An *in vivo* investigation suggests that the advantageous function that TC (fruits) play in hepatoprotection may be due to their antioxidant qualities. This is because the utilization of antioxidative therapy is a cornerstone of the modern hepatoprotective medication development method, and oxidative stress, lipid peroxidation, and free radicals are associated to a number of liver illnesses. Research indicates that the use of an herbal preparation derived from TC (fruit) would offer a desirable therapeutic benefit in certain cases where toxicity concerns arising from repeated and long-term drug use become clinically significant (e.g., anti-TB drugs). This would also help the liver manage oxidant/antioxidant imbalance. Anti-TB drug-induced liver histopathology was reversed by TC extract treatment.

5.2 Sharma A *et al*[44]

In this *in vivo* investigation, aqueous extracts of TC were utilized to investigate the prevention of acetaminophen-induced hepatorenal toxicity in mice.

Myrobalan's antioxidant property has also been linked to its antigenotoxic potential against acetaminophen, aluminum chloride, cadmium chloride, and lead nitrate. In the root tip cells of allium cepa, myrobalan might even reverse the mitostatic effect caused by lead. Like animal cells, the root cells also feature a complex detoxification mechanism that includes catalase, SOD, and many peroxidases. Even in the presence of acetaminophen, myrobalan's preventative activity can be attributed to the regeneration of renal tubular cells and hepatocytes. The hepatorenal toxicity of acetaminophen in mice is found to be decreased by myrobalan.

5.3 Sivachandran S *et al*[45]

The study's findings demonstrated that gentamicin, when given once daily for seven days at a dosage of 80 mg/kg b.wt. i/p, significantly raised serum biochemical markers including ALT and AST while significantly lowering total protein and albumin levels. When TC aqueous extract was administered, these metrics were greatly improved. According to the current study's findings, plant extracts from TC may be used to prevent gentamicin-induced hepatotoxicity.

5.4 Rhitajit Sarkar *et al*[46]

The current study found that a 70% methanolic extract of TC can reduce hazardous iron levels in iron-overloaded mice while also preventing oxidative stress and fibrosis in the liver. The extract also has both reducing and iron chelating properties.

5.5 Nishanth *et al*[47]

This study explored the effects of TC extracts on 2-acetylaminofluorene (2-AAF)-induced hepatocellular carcinoma in mice. The 25 mg.kg1 b.w. 2-AAF medication produced liver damage and raised the expression of MDR1, ROS, and COX-2 via Akt-MAPK phosphorylation and NF-B nuclear translocation. The combination of 50 mg.kg1 TCE and 25 mg.kg1 2-AAF reduced MDR1 expression via reducing ROS generation and COX-2 expression via the Akt and MAPK signaling pathways. TC may be able to inhibit 2-AAF-induced oxidative stress and drug resistance in mouse hepatic tissue, hence avoiding neoplastic transition to hepatocarcinoma.

5.6 Tania Yeasmin *et al*[48]

According to this *In vivo* investigation, large paracetamol dosages also oxidize intracellular Glutathione (GSH), which depletes the GSH pool in liver cells and results in liver cell damage. The increased AST and ALT values in the paracetamol-treated rats in this study point to liver cell injury caused by the drug. Research on medicinal plants has shown that the active ingredients in TC enhance the activity of antioxidant enzymes, thereby protecting the liver from oxidative damage. Because TC extract can scavenge free radicals, it may offer protection against liver injury caused by paracetamol, as evidenced by the lower levels of serum AST and ALT in TCP-PCT and PCP-TCT rats.

5.7 Min-Kyung Choi *et al*[49]

The recent study illustrated the hepatoprotective advantages of TC using animal models. In models of iron-dextran injection and drug-induced toxicity from antituberculosis, TC extracts 70% methanol and 95% ethanol showed hepatoprotective effects, respectively. The current investigation modified the high dose of t-BHP (2.5 mM/kg) and provided therapy with lower doses of TC (50, 100, and 200 mg/kg) to validate the application of TC powerful hepatoprotective effects against severe liver injury.

5.8 Balakrishna V *et al*[50]

Ethanolic extract of TC was found to be effective in treating rats' ethanol-induced hepatotoxicity in the current *in vivo* study. This finding highlights the protective effect of antioxidants, which is typically brought about by the inhibition of the free radical chain reaction and the ensuing prevention of peroxidative deterioration of structural lipids in membrane organelles. Both enzymatic and non-enzymatic mechanisms, including CAT, reduced GSH, and MDL lipid peroxidation, are essential in preventing tissue damage brought on by the generation of free radicals. The plant extract may be helpful in reducing ethanol-induced hepatotoxicity, since the ethanolic TCE fruit's

hepatoprotective activity may be due to its antioxidant potential mechanism.

5.9 Raheleh Ahmadi-Naji *et al*[51]

The study's findings showed that TC fruit extract shielded male rats' livers from the hepatotoxic effects of diazinon. The antioxidant and anti-inflammatory qualities of TC fruit extract may contribute to its beneficial effects. Consequently, the fruit extract from TC can be regarded as a preventive agent against liver damage caused by free radicals after exposure to diazinon, and it can also lessen the toxic effects of diazinon in rats.

5.10 Srilekha E *et al*[52]

The investigations of ethanolic extract of fruits of TC (50mg/kg, 100mg/kg, 200mg/kg; p.o) in Ethanol induced method in rats demonstrated significant in-vivo hepatoprotective activity. The effects of TC extract were comparable to that of standard Silymarin

5.11 Xin-Hong Feng *et al*[53]

CA prevented oxidative stress caused by t-BHP in L-02 cells by upregulating the expression levels of HO-1 and NQO1, which were facilitated by Nrf2 through the MAPK signaling pathway. Mice's acute liver damage generated by CCl4 was significantly decreased by CA. In the meantime, CA promoted liver growth in zebrafish larvae that were APAP-delayed. This implies that CA would be a good candidate for a lead molecule in the development of hepatoprotective therapeutics.

5.12 Sarada S *et al*[54]

This *in vivo* study indicates that the presence of many antioxidants is responsible for the hepatoprotective effect of TC fruits. This results in pharmacological activities that include suppression of peroxidation with an oxidant-antioxidant imbalance, increased excretion of cholesterol, decreased absorption of cholesterol, decreased accumulation of cholesterol in visceral organs, inducing LDL-C and HDL-C regulation, antioxidant-mediated free radical scavenging, prevention of membrane damage, release of intracellular components, and so forth.

6. Conclusion

Classical manuscripts mention the *T. chebula*, a traditional herb with amazing medical properties. According to Ayurveda, each part of the plant, commonly referred to as panchang, has medicinal properties. Every article reviewed above demonstrated the plant's hepatoprotective qualities. Steroidal hepatoprotective medications are used more frequently, although long-term use is not advised because they impact the body's other systems. Thus, plants such as *T. chebula* can be used as an alternative remedy for a variety of health-related issues and can also cure problems in such conditions. This plant's benefits extend to agriculture, medicine, economy, and society. However, additional human trials are still needed before this plant quality may be employed widely. The current systematic research has proved the plant's hepatoprotective qualities.

7. References

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