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A Review on Hepatoprotective Activity of Commonly Consumed Vegetables

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ABSTRACT

Liver is the versatile organ of our body and plays vital role in metabolism of Carbohydrate, Protein, Lipid / Fat, Vitamin and drugs. Liver cells produce bile; it also performs excretion and detoxification. It is the site of decomposition of erythrocytes and store glycogen. Rising number of cases in Liver injury or dysfunction due to consumption of prescribed drugs, medicines that are acquired over the counter and chemicals that are used in the process of agriculture, is endemicity in developing countries. Over doses of Paracetamol, antibiotics, chemotherapeutic agents, carbon tetrachloride (CCl₄), excessive alcohol etc. contribute to hepatotoxicity. However, there is no effective drug available to stimulate and rejuvenate liver cells. Hence it is an urgent need to relook at natural sources that offer hepatoprotection. This review elucidates the list of commonly consumed seeds, root, fruit and Leafy vegetables, as food in south India and their proven hepatoprotective activity in recent times.

Keywords: hepatotoxicity; liver injury; paracetamol; carbon tetrachloride (CCl₄); thioacetamide (TAA); hepatoprotective agents.

INTRODUCTION

India is a country with cultural diversity and traditions. Region specific food habits and medical practices are observed. A variety of traditional medicinal practices such as folk/tribal medicine, Ayurveda, Siddha, Unani etc., are practiced in India and these practices take medicinal sources from medicinal plants. However, a majority of edible plants and its parts such as fruits, seeds, leaves and roots are also observed to have medicinal value substances, such as antioxidants, flavonoids, tannins and other phenolics compounds [1].

It is estimated that about 7,500 plants are used in local health traditions in; mostly, rural and tribal villages of India. Out of these, the real medicinal value of over 4,000 plants is either little known or either to unknown to the mainstream population. The classical systems of medicine such as Ayurveda, Siddha, Amchi, Unani and Tibetan use about 1,200 plants.

The liver plays vital functions in the maintenance, performance and regulating homeostasis of the body. It is involved with many biochemical pathways to growth, fight against disease, nutrient storage and supply. It also functions as a center of metabolism of nutrients such as carbohydrates, proteins and lipids and excretion of waste metabolites. The bile secreted by the liver has, among other things, plays an important role in digestion. Therefore, maintenance of a healthy liver is essential for the overall wellbeing of an individual.

Liver damage is very likely since it has to detoxicate a lot of toxic substances that are injected via food. Most of the hepatotoxic chemicals damage hepatic cells by producing reactive species. Due to excessive exposure to hepatotoxic chemicals, sometimes the free radicals generated are so high that they overpower the liver and cause jaundice, cirrhosis and fatty liver. Production of the reactive species manifests in tissue thiols depletion, lipid peroxidation, plasma membrane damage etc. resulting into severe hepatic injury [2].

India is bestowed with diverse climatic conditions, which favour region specific vegetables and their usage. In this review, various studies on fruit vegetables, leaf vegetables and pulses, that are especially consumed in the south India and their hepatoprotective activity against Paracetamol / thioacetamide / Carbon tetrachloride (CCl₄) induced Hepatotoxicity by various investigators are reviewed.

RESULTS AND DISCUSSION

Hepatoprotective Activity of Some commonly consumed vegetables (in the form of seeds, roots, leaves and fruits)

In Indian traditional medical practice a variety of food significant plants are used as preventive substances for diverse ailments. Many vegetables are consumed without the realization of the medicinal values. However, a list of plants reported to have significant hepatoprotective activity is shown in Table 1, in alphabetical order of their family, together with their scientific names, plant part consumed, type of extract used in assay, Hepatotoxicity inducer, biochemical parameters studied and references.

Biochemical Parameters studied

Most of the hepatotoxic chemicals damage liver cells mainly by inducing lipid peroxidation and other oxidative damages in liver. Estimation of the alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TB), total protein (TP), Total Glyceride (TG), albumin (ALB), glutathione (GSH), Gamma- glutamate transpeptidase (GGTP), malondialdehyde (MDA), Serum glutamate oxaloacetate transaminase (SGOT) and Serum glutamate pyruvate transaminase (SGPT), Reactive Oxygen species (ROS) such as superoxide dismutase, catalase with the levels of control animals and micrographs on histopathological changes were used in general as diagnostic tools [3].

Allium cepa L

The bulbs of onion and its extract was studied for their hepatoprotective activity by Rawat et.al. [4] against CCl₄, ethyl acetate & paracetamol and induced liver toxicity in wistar albino rats. Paracetamol or acetaminophen in larger doses produces liver necrosis after undergoing bio-activation to a toxic electrophile, N-acetyl-p-benzoquinone-imine (NAPQI) by cytochrome P450 monooxygenase (a microsomal enzyme). This alters the levels of SGOT & SGPT. Administration of carb on tetrachloride too elevated the serum levels of SGOT, SGPT, ALP and bilirubin significantly, due to its enzymatic activation of CCl₃ free radical, the structure and function of liver cells get altered. In their study they have observed that the elevated levels of biochemical parameters were significantly got reduced by the treatment with alcohol extract (AEAC) and aqueous extract (AQEAC) as they interfere with cytochrome P450 monooxygenase, as it contains saponins, carbohydrate, steroids, flavonoids, thus reducing the hepatotoxic free radicals. Histopathology of liver too showed hepatoprotective effect of these extracts.

Ige et. [5] reported the preventive effect of *Allium cepa* aqueous extract (ACE) against cadmium induced hepatotoxicity using male wistar rats as model [6-7]. They demonstrated that hepatotoxic effect of Cd is due to cumulative oxidative damage. Cadmium is observed to decrease the superoxide dismutase (SOD) and increase malondialdehyde (MDA) levels in the livers of all groups of rats exposed to Cd. Serum aspartate aminotransferase levels [8]. The commonest enzymes employed as indicators of hepatocellular damage are ALT, AST, and ALP. Damage to the liver results in increased plasma activities of these enzymes. The mechanism by which ACE ameliorates Cd-induced hepatotoxicity is its ability to maintain the integrity of the hepatocytes and scavenging ROS.

Allium sativum L

Supplemented diet of Garlic along with Vitamin-C and its hepatoprotective effect against lead induced hepatotoxicity was studied by Ajayi et.al and Senapati et.al. [9-10] on experimental rats. They observed marked increase of ALT and ALP enzyme levels and decreased level of AST, due to lead treatment, thus suggested hepatic damage. Post-lead treatment with *A. sativum* and vitamin C significantly reduced the activities of ALT and ALP and increased the activity of AST in plasma, like that of control. Lead is known to bind to the sulfhydryl groups of enzymes containing cysteine and found to form complexes with amino acids and protein. Since ALT is liver enzyme, lead will alter the level of ALT activity in the tissues by disrupting their membrane, thus discharge into blood plasma [11-12]. The reduced serum ALT and ALP activities may generally be attributed to decreased

production of these enzymes from these sources hence denotes the reversing effect of lead toxicity. Similar studies were made by Ebenyi *et.al.* [13] on Paracetamol; Md. Asaduzzaman, *et.al.* [14] on Alloxan; Nasim Ilyas, *et.al.* [15] on Isoniazid.

Amorphophallus paeoniifolius

The Methanol and aqueous extracts of elephant foot yam tuber and its Hepatoprotective act was studied by Pramod J Hurkadale *et al.* [16] on male albino-wistar rats against Paracetamol induced hepatic injury. Paracetamol hepatotoxicity is caused by the reaction metabolite N-acetyl-p-benzoquinoneimine (NAPQI), which causes oxidative stress and luthathione depletion. It is a well-known antipyretic and analgesic agent, which produces hepatic necrosis at higher doses. Pre-treatment of the rats with methanol and aqueous extract prior to paracetamol administration caused a significant reduction in the values of SGOT, SGPT, SALP and SB ($P<0.01$) almost comparable to the silymarin and Liv-52. The hepatoprotective act was confirmed by histopathological examination of the liver tissue of control and amorphophallus extract treated animals [17-20]. As the important chemical constituents of the tubers include carbohydrates, sitosterol, stigmasterol, thiamin, riboflavin [21] the report shows flavonoids and steroids may be responsible for hepatoprotective effect.

Benincasa hispida

Bort *et.al.* [22] reported the Diclofenac toxicity to hepatocytes. The hepatoprotective act of aqueous extract of winter melon (*Benincasa hispida* = BH) against Diclofenac-sodium induced hepatic injury on male albino rats was reported by Das, S.K and C. Roy [23]. It was observed that hepatoprotective effect through the modulation of antioxidant - mediated mechanism by altering serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), alkaline phosphatase (ALP), superoxide dismutase (SOD) and catalase (CAT) activities and reduced glutathione (GSH) and lipid peroxidation (LPO) levels - against diclofenac sodium - induced hepatotoxicity model in rats.

The BH pulp contains vitamin-E, beta-carotene, flavonoids and flavonols. Hence, it may be inferred that BH protected rat liver against oxidative stress as it is evidenced by the results of SGPT, SGOT, ALP, LPO, CAT, SOD and GSH activities, possibly by vitamin E, betacarotene, flavonols and flavonoids, which are present in BH pulp. Das and Roy [23] also reported hepatoprotective effect of BH against Nimesulide induced Hepatotoxicity.

Beta vulgaris

Phytochemical studies of *beet* root reveal the presence of flavonoids, carbohydrate, betaine, neobetain and anthocyanin pigments. Ranju Pal *et.al.* [24] evaluated the effect of ethanolic extract of *Beta vulgaris* (EEBV) root against CCl_4 -induced hepatic damage in rats. The hepatoprotective activity of EEBV was studied by estimating serum enzyme levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total protein and bilirubin. The treatment with EEBV is observed to ($P<0.01$) reduce the CCl_4 induced elevated serum levels of enzyme activities and bilirubin with parallel significant ($P<0.01$) increase in total protein, AST, ALT and ALP, indicating the extract could preserve the normal functional status of the liver. Histology of the liver sections of the animals treated with the extracts were also observed with the presence of normal hepatic cords, absence of necrosis and fatty infiltration, which further evidenced the hepatoprotective activity. The hepatoprotective effect of EEBV may be due to presence of its chemical contents [25-26] using leaves of *Beta vulgaris*.

Brassica juncea

Agnel Arul John *et.al.* [27] evaluated the hepatoprotective activity of aqueous extract of Mustard seeds against carbon tetrachloride (CCl_4) induced hepatic damage in albino rats [28] evaluated the leaf extract. The Lipid peroxide (LPO) and antioxidants like Superoxide dismutase (SOD) and reduced glutathione (GSH) were estimated in liver tissue homogenate. Hepatotoxicity induced rats were reported to show increased level of LPO and decreased levels of antioxidants like SOD and GSH. The activities of liver marker enzymes such as GOT, GPT, ALP, and GGT in serum were increased. On treatment with *BJ* extracts, all the biochemical changes observed in the hepatotoxicity induced rats were reversed in a dose dependent manner. It is observed that the presence of terpenoids and flavonoids are the possible reasons for hepatoprotective activity due to their free radical scavenging and antioxidant properties [28-29].

Brassica oleracea

Ethanolic extract of cabbage vegetable and its hepatoprotective activity was studied by Ahmed *et.al.* against simvastatin induced hepatotoxicity [30]. The increased levels of serum enzymes due to simvastatin treated rats were restored towards normalization in *BO*. extract (300 mg/kg/p.o and 500 mg/kg/p.o) treated animals. Further it was

observed that the hepatoprotection may be due to the presence of alkaloids, amino acids, carbohydrates, flavonoids, glycosides, phenols, proteins, saponins, steroids, tannins and terpenoids in BO extracts [31].

Carica papaya

Ethanol and aqueous extracts of *Carica papaya* has been evaluated for its anti-hepatotoxic activity by Raj Kapoor *et.al.* [32], Md. Zafor Sadeque *et.al.* [33] and Manikandaselvi *et.al.* [34] on CCl₄ induced hepatotoxicity. The activity was evaluated by using biochemical parameters such as serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin and gamma-glutamyl transpeptidase (GGTP). The histopathological change of liver sample was compared with respect to control and thus hepatoprotection activity was ascertained [35] on aqueous seed extract of *Carica papaya*.

Srinivasan Kantham [36] examined the effect of carica papaya aqueous extract on rat models of paracetamol (PCM) and thioacetamide (TAA) induced hepatic damage. Wistar strain albino rats were prophylactically treated with three doses of CPE (100, 250 and 500mg/kg, *p.o*) for 10 days and subsequently liver damage was induced. Hepatoprotective potential was evaluated by measuring biomarkers and the hepatoprotection activity was ascertained. It is speculated that the protection may be due to the presence of vitamin - C.

Citrus limon

The ethanol extract of *Lemon* fruit was evaluated for its effects on induced hepatotoxicity by CCl₄ and the ethyl acetate soluble fraction of the extract was evaluated on HepG2 cell line by Bhavsar *et.al.* [37]. It was observed that, the ethanol extract normalized the elevated levels of liver enzyme, total and direct bilirubin, due to carbon tetrachloride intoxication in rats. In the liver tissue, treatment has significantly reduced the levels of malondialdehyde (MDA), hence the lipid peroxidation, and raised the levels of antioxidant enzymes superoxide dismutase (SOD) and catalase [38]. It improved the reduced glutathione (GSH) levels in treated rats in comparison with CCl₄-intoxicated rats. Thus it may be inferred that the hepatoprotection was provided by antioxidant enzymes by their ROS activity. Casimiro *et.al.*, 2010, against acetaminophen-induced liver damage; Karaca [39], using *Citrus bergamia*.

Colocasia antiquorum

Ethanol extract obtained from the corms of *colocasia* was evaluated by Tuse *et.al.* [40] for hepatoprotective activity using paracetamol and CCl₄ intoxicated rats. The protective effect was evident from serum biochemical parameters and histopathological analysis. Ethanol extract of CA significantly ($P < 0.5$) prevented the elevation of serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) in paracetamol and CCl₄ treated rats as compared to silymarin(Control). These biochemical observations were supplemented by histopathological examination of liver sections showing the prevention of disarrangement and degeneration of hepatic cells induced by paracetamol and CCl₄. The activity may be a result of the presence of anthocyanin compounds. Furthermore, acute toxicity studies showed no signs of toxicity up to a dose level of 1000 mg/kg. Thus, it may be concluded that ethanol extract of *C. antiquorum* possesses significant hepatoprotective properties.

Colocasia esculenta (taro)

The anti-hepatotoxic and hepatoprotective studies were carried against paracetamol and CCl₄ by Bhagyashree *et.al.* [41] using *in vitro* liver slice method. The free radicals generated by CCl₄ and paracetamol cause oxidative stress as well as injury to the hepatocytes. The extent of damage caused by these free radicals and hepatoprotective efficacy was measured using the leakage of marker enzymes of liver function *viz* AST, ALT and ALP in the incubation medium. There was increase in the levels of marker enzymes indicating hepatotoxicity of these compounds. However the leaf juice of CE remarkably declined the leakage of AST, ALT and ALP in the medium indicating hepatocyte integrity. Thus it was concluded that the CE leaf juice as a whole possesses anti-hepatotoxic and hepatoprotective efficacy when tested *in vitro* using rat liver slice model [42-44].

Coriandrum sativum (Coriander)

Protective role of coriander extracts (Aqueous & Ethanolic) against lead nitrate induced oxidative stress and tissue damage in the liver was studied by Leena Kansal *et.al.* and Aga [45-46]. The study showed a significant elevation in some hepatic biochemical parameters such as AST, ALT, ACP, ALP and total cholesterol upon intoxication with lead nitrate. However, administration of aqueous coriander extract & ethanolic extract resulted in significant decrease ($p < 0.001$) of hepatic AST, ALT, ACP, ALP and total cholesterol levels. Lead administration induces overproduction of reactive oxygen species (ROS) and depletes the cellular antioxidant capacity. The active ingredients in the coriander possess antioxidant properties such as linalool and glucosides such as various β -D-glucopyranosides. These may be the reason for hepatoprotection [47-48].

Curcuma longa (Turmeric)

Mahuya sengupta *et al.* [49] evaluated the hepatoprotective effects of aqueous extract of *C. longa* against CCl_4 induced hepatotoxicity in mice and it was observed that CCl_4 administration has increased the level of SGOT, SGPT and bilirubin level in serum and intake of aqueous extract of CL has decreased the elevated levels of SGOT, SGPT and bilirubin. Administration of aqueous extract of CL also offered significant protection against the reduced nonspecific host response parameters such as morphological alteration, phagocytosis, nitric oxide release, myeloperoxidase release and intracellular killing capacity of peritoneal macrophages [50-51].

Cucumis sativus (Cucumber)

Kamalinejad [52] studied the antioxidative potential of *Cucumis sativus* on isolated rat hepatocytes against cumene hydroperoxide (CHP) induced-cytotoxicity and ROS formation. It was observed that when isolated hepatocytes were incubated with CHP, there was an initial rapid increase in ROS formation, which was prevented by aqueous extract of CS fruit. Further it was showed that aqueous extract of CS acts as a hepatoprotective and antioxidant agent against CHP-induced hepatotoxicity suggesting that antioxidants and radical scavenging components of CS fruit extract can easily cross the cell membrane and cope with the intracellular ROS formation [53-55].

Cuminum cyminum (Cumin)

Profenos, an organophosphate pesticide and its hepatotoxicity in rats was studied by Arun kumar *et al.* [56]. Further it was observed that hepatic damage induced by profenofos caused significant ($p < 0.001$) increase in marker enzymes SGPT, SGOT and serum bilirubin. Oral administration of *cumin* significantly ($p < 0.001$) lowers the levels of marker enzymes SGPT and SGOT. It also lowers serum bilirubin level. The cytoprotective properties of cumin extracts restore the cellular integrity and the essential oils of cumin play vital role to ameliorate the profenofos induced toxicity [57].

Daucus carota sativus (carrot)

The effect of carrot extract on carbon tetrachloride (CCl_4)-induced acute liver damage was evaluated by Bishayee *et al.* [58]. The increased serum enzyme levels (*viz.*, glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, lactate dehydrogenase, alkaline phosphatase, sorbitol and glutamate dehydrogenase) by CCl_4 -induction were significantly lowered due to pretreatment with the extract. The extract also decreased the elevated serum bilirubin and urea content due to CCl_4 administration. Increased activities of hepatic 5'-nucleotidase, acid phosphatase, acid ribonuclease and decreased levels of succinic dehydrogenase, glucose-6-phosphatase and cytochrome P-450 produced by CCl_4 were reversed by the extract in a dose-responsive way. Results of this study revealed that carrot could afford a significant protective action in the alleviation of CCl_4 -induced hepatocellular injury. Mani Vasudevan *et al.* [59] on *Daucus carota* seed extracts and Shoba *et al.* [60] reported similar hepatoprotective effect against Paracetamol, Isoniazid and alcohol induced hepatotoxicity. Balasubramaniam *et al.* [61] reported protective effect of carrot against lindane - induced Hepatotoxicity.

Lagenaria siceraria (Bottle guard)

Lakshmi *et al.* [62] evaluated the hepatoprotective activity of *Lagenaria siceraria* fruit extracts against CCl_4 induced hepatotoxicity in rats. The liver function biochemical parameters, liver weight and histopathological studies of the liver were studied. It is noted that in ethanol extract treated animals, the toxic effect of CCl_4 was controlled significantly by restoration of the serum of liver biochemicals to normal levels. Histology of the liver sections of the animals treated with the extracts showed the presence of normal hepatic cords, absence of necrosis and fatty infiltration, which further evidenced the hepatoprotective activity. It is generally believed that it is due to lipid peroxidation caused by carbon trichloromethyl radical ($\text{CCl}_3\cdot$). CCl_4 is biotransformed by cytochrome P-450 to the trichloromethyl-free radical that induces membrane lipid peroxidation and disturbs Ca^{2+} homeostasis to produce hepatocellular injury. The possible hepatoprotective mechanism of the extracts may be through inhibition of the cytochrome P-450 activity, prevention of the process of lipid peroxidation, stabilization of the hepatocellular membrane and enhancing the protein synthesis [63-66].

Luffa acutangula

Jadhav *et al.* [67] studied the hepatoprotective effect of hydro-alcoholic extract (HAELA) of Ridge guard, against CCl_4 and Rifampicin toxicity. Administration of standard drug- silymarin and HAELA showed significant protection against CCl_4 and rifampicin induced hepatotoxicity in rats. This may be due to the decreased levels of serum marker enzymes *viz.*, (AST, ALT, ALP and LDH) and increased total protein including the improvement in histo-architecture of liver cells of the treated groups as compared to the control group. HAELA also showed significant decrease in malondialdehyde (MDA) formation, increased activity of non-enzymatic intracellular antioxidant, glutathione and enzymatic antioxidants, catalase and superoxide dismutase. Results of this study

demonstrated that endogenous antioxidants and inhibition of lipid peroxidation of membrane contribute to hepatoprotective activity of HAELA [68-72].

Rawat *et.al.* reported a Comparison of ethyl acetate extracts of *Allium cepa* bulbs, *Luffa acutangula* fruits, *Nyctanthes arbostristis* leaves, *Swertia chirata* twigs and *Woodfordia floribunda* leaves with Silymarin for hepatoprotective activity. Hepatoprotective activity of alcoholic and aqueous extracts of fruits of *Luffa cylindrica* Linn in rats [73].

Macrotyloma uniflorum

Hepatoprotective activity of methanolic extract of *Horse gram* (MEMUS) *seed* was investigated by Parmar *et.al.* [74] against D-Galactosamine and paracetamol induced hepatotoxicity in wistar albino rats. Silymarin was used as the reference standard. The degree of protection was determined by the estimation of biochemical parameter like Serum Glutamate Pyruvate Transaminase (SGPT), Serum Glutamate Oxaloacetate Transaminase (SGOT), alkaline phosphate (ALP), Bilirubin (Direct and Total). The histopathological study further supported the hepatoprotective activity of the test extract. The dose dependant reduction in biochemical parameters as well as in morphological parameters in D-Galactosamine and paracetamol induced hepatotoxicity in rats. A number of scientific reports indicated that certain flavonoids, triterpenoids and steroids, tannins have protective effect on liver due to its antioxidant properties [75-76]. Active compound flavonoids and tannins from *Macrotyloma uniflorum* may have offered hepatoprotective activity.

***Mentha arvensis* (mint)**

Aqueous extract of *M. arvensis* (AEMA) and its protection to alcohol induced liver injury was studied by Radhika *et.al.* [77]. The ethanol and CCl₄ induction caused an elevation in the serum marker enzymes, bilirubin and Lipid peroxide levels confirming liver injury. The treatment of the animals with AEMA depicted the restoration of these parameters in serum and liver. Preliminary phytochemical screening showed the presence of flavonoids. The restoration of the hepatic functioning of the serum and tissue markers suggests the protective activity of *M. arvensis* which may be attributed to the presence of flavonoids. Kalpana Patil *et.al.* [78] on similar effect against CCl₄ induced toxicity).

Momordica charantia

An analysis of different serum enzymes including ALT, AST, ALP and LDH was carried out to evaluate the hepatoprotective and hepatocurative effects of *Momordica charantia*. The liver toxicity was induced in rabbits with administration of acetaminophen, and then *Momordica* extract was given and hepatocurative effects were observed [79]. The results indicated significant decrease in the elevated concentrations of these enzymes in acetaminophen-intoxicated rabbits. Hossain *et.al.* [80] on Alloxan induced toxicity. The hepatoprotective activity of *Momordica charantia* may be attributed due to the presence of flavonoids, ascorbic acid and other components such as saponins, tannins, triterpenes and alkaloids [81-84].

Moringa oleifera

Methanolic extract of *Moringa* leaves and its hepatoprotection against CCl₄ induced liver injury was studied by Balamurugan *et.al.* [85] on albino rats. Ruckmani *et.al.* [86] reported on Paracetamol induced toxicity. The potent hepatoprotective activity of leaves of *Moringa* was found to reduce the level of Total Bilirubin, Direct Bilirubin, SGPT and SGOT in CCl₄ treated animals. The Hepatoprotective activity of most plant materials have been attributed to the presence of flavonoid. The extracts of *Moringa* leaves have potent antioxidant activity against free radicals, prevent oxidative damage to major biomolecules and afford significant protection against oxidative damage [87-89]. Ezeonwu *et.al.* [90] reported hepatoprotective activity of Bi-Herbal ethanolic extract of *Phyllanthus Niruri* and *Moringa Oleifera* on CCl₄ Induced Hepatic Damage In Albino Rats.

***Murraya koenigii* (Curry leaf tree)**

Chronic ethanol consumption diminishes the cellular antioxidant levels through free radical induced injury causing hepatitis and cirrhosis with mortality in severe cases. The hepatoprotective activity of curry leaf plant aqueous extract against ethanol-induced hepatotoxicity in experimental animals was studied by Sadhana Sathaye *et.al.* [91]. The anti-lipid peroxidation potential (LPO), antioxidant effects on protein content, liver metabolizing enzymes viz., glutathione (GSH), superoxide dismutase (SOD), catalase (CAT) and the morphology of the cells were studied as parameters of hepatoprotection. The tannins and the carbazole alkaloids from the aqueous extract exhibited hepatoprotective activity with respect to the different parameters studied and maintained normal morphology even after ethanolic challenge to the cells as comparable to the protection offered by the standard drug L-ornithine L-aspartate (LOLA). The modulating effect of the aqueous extract and isolates on liver metabolizing enzymes,

reduction in lipid peroxidation and decreased cellular damage were found to contribute to the Hepatoprotective activity [92-94].

Musa paradisiaca

The increased liver marker enzymes due to Paracetamol induced liver injury were observed to reduce in serum when *M. paradisiaca* is fed as supplemented diet to rats [95-97]. Several tropical plant foods have been reported to have hepatoprotective properties [98-99]. This is due to their content of phytochemicals such as phenolics compounds, alkaloids, coumarins, flavonoids and lignans.

Piyush Dikshit *et.al.* [100] reported the hepatoprotective effect of stem of *Musa sapientum* (L) a cultivar of Banana, in rats intoxicated with carbon tetrachloride.

Phaseolus vulgaris

The anti-fibrotic effects of Methanolic extract of *P. vulgaris* and antioxidants in a (CCl₄) liver injury model in rats was reported by Alberto Gabriel Lopez-Reyes *et.al.* [101] and Parola *et.al.* [102]. DR Jose, rguhs.ac.in, reported on Alcohol, Paracetamol, Thioacetamide induced toxicity. Qualitative and quantitative histological analysis showed that administration of 70 mg/kg b.w. of black bean extract reduced hepatic fibrosis index by 18% compared to positive controls (P 0.006), as a result of a decrease in type I (44.3% less, P 0.03) and type IV (68.9% less, P 0.049) collagen gene expression compared to CCl₄-injured rats. Thus it is evidenced that this methanol extract ameliorates liver fibrosis and types I and IV collagen gene expression, in the animal model used. The high concentration of antioxidants of *P. vulgaris* [103-107] may have significantly decreased the expression of type I and IV collagen genes and probably also diminishes the activation of Hepatic Stellar Cells partially protecting the liver from the CCl₄ induced fibrotic effect [108].

Sesamum indicum

The hepatoprotective activity of ethanolic extract of *Sesamum indicum* seeds against hepatic injury produced by paracetamol in rats was studied by Kumar Munisha *et.al.* [109]. Administration of Paracetamol (2g/kg/day, p.o.) increased the level of serum enzyme markers while decrease in the level of Total Protein and Albumin as compared to normal control indicating acute hepatocellular damage [2]. Pre-treatment of the rats of *Sesamum indicum* (400mg/kg and 700mg/kg) prior to paracetamol administration showed a significant reduction in the level of serum enzymes, whereas increase in level of Total Protein and Albumin almost comparable to the Silymarin (25mg/kg) treated group.

Nureddin Cengiz *et.al.* [110], reported similar observations to CCl₄ induced hepatotoxicity.

Solanum lycopersicum

Weremfo *et.al.* [111] studied the level of hepatoprotection offered by the Tomato pulp which is known for its rich antioxidants [112] against CCl₄ induced hepatotoxicity. Pretreatment of rats with tomato pulp (40 mL/kg) significantly (P<0.05) lowered the respective serum AST, ALT and ALP, levels to 281.8 ± 15 U/L, 187.4 ± 6.2 U/L and 613.0 ± 42 U/L. Thus from the results it was revealed that tomato pulp significantly reduced the CCl₄ induced hepatotoxicity [113].

Solanum melongena

Five varieties of eggplant (purple colored moderate size, white-green colored moderate size, long green, green striped moderate size and pale-green colored small size, respectively, called SM1–SM5) were evaluated for total phenolic and flavonoid content, [114-116] antioxidant activity (Noda, Y., 2000) and hepatoprotection against cytotoxicity of tert-butyl hydroperoxide (t-BuOOH) in human hepatoma cell lines, HepG2, (Pannarat Akanitapichat, *et.al.* 2010). Significant correlation was reported between hepatoprotective activities and total phenolic / flavonoid content and antioxidant activities, indicating the contribution of the phenolic antioxidant present in eggplant to its hepatoprotective effect on t-BuOOH-induced toxicity.

Spinacia oleracea

The amelioration by *Spinacia oleracea* L. leaves extract against hepatosuppression induced by carbon tetrachloride (CCl₄), which was evaluated in terms of serum marker enzymes. These biochemical parameters were significantly altered by single dose of CCl₄, [117]. Pretreatment with *S. oleracea* L. prior to the administration of CCl₄, significantly restored all the serum and liver parameters nearer to the normal levels. Silymarin was used as control; Srivastava *et.al.* [118]. These indicate hepatoprotection by a possible mechanism to block the P-450 mediated CCl₄ bioactivation through selective inhibitors of ROS (reactive oxygen species).

Table 1. List of Commonly consumed Vegetables and their Hepatoprotective assay against hepatotoxic substance

S.No	Name of the Plant	Source of Family	Parts consumed	Hepato-toxicity inducing substances	Extracts studied	Histopathological and Biochemical parameters studied	References
1	<i>Allium cepa</i> /Onion	Liliaceae	Bulb, Tender leaves (Spring Onion)	CCl ₄ & Paracetamol	Aqueous & Ethanolic extract	SGOT, SGPT, ALP, Direct and total bilirubin	Riyaz Shaik <i>et al.</i> , 2012
1 a	<i>Allium cepa</i> /Onion	Liliaceae	Bulb, Tender leaves	Cadmium	Aqueous extract	ALT, AST,ALP, Total Serum & Protein malondialdehyde (MDA)	Ige <i>et al.</i> , 2011
2	<i>Allium sativum</i> /Garlic	Liliaceae	Bulbs	Lead	Garlic supplemented diet	ALT, ASP, ALP	G. O. Ajayi, <i>et.al.</i> , 2009
3	<i>Amorphophallus paeoniifolius/yam</i>	Araceae	Tubers	Paracetamol	Methanol & Aqueous extract	SGPT, SGOT ALP , Serum Bilirubin	Pramod J Hurkadle <i>et al.</i> 2012
4	<i>Benincasa hispida/winter melon</i>	Cucurbitaceae	fruits	Diclofenac sodium	aqueous extract	SGOT, SGPT, ALP, SOD, CAT, GSH, LPO	Dr. Shyamal K. Das, <i>et.al.</i> 2011
5	<i>Beta vulgaris</i> /Beetroot	Amaranthaceae	Root	CCl ₄	Ethanolic extract	AST, ALT, ALP, Total protein, Total bilirubin	Ranju Pal <i>et al</i> , 2010
6	<i>Brassica juncea</i> (Mustard seeds)	Brassicaceae	seed	CCl ₄	Aqueous extract	GOT, GPT, ALP, GGT, LPO, SOD, GSH	Agnel Arul John <i>et. al.</i> , 2011
7	<i>Brassica oleracea/ Cabbage</i>	Brassicaceae	Leaves	Simvastatin	Ethanolic extract	SGPT, SGOT, ALP, Bilirubin	M.F Ahmed <i>et. al</i> , 2012
8	<i>Carica papaya</i>	Caricaceae	Fruits	CCl ₄	Ethanol and aqueous extracts	ALT, AST, Alkaline Phosphatase, Total bilirubin & Gamma glutamate transpeptidase (GGTP)	Raj Kapoor, B. <i>et.al</i> 2002
8a	<i>Carica papaya</i>	Caricaceae	Fruits	Paracetamol & Thioacetamide	Aqueous extract	ALT, AST, ALP and bilirubin	Srinivas Kantham , 2011
9	<i>Citrus limon</i> /Lemon	Rutaceae	Fruits / Leaves	CCl ₄	Ethanol extract	ASAT, ALAT, ALP, Total and direct bilirubin	Shefalee K. Bhavsar <i>et.al.</i> 2007
10	<i>Colocasia antiquorum</i> /Colocasia	Araceae	Tender leaves, Corm	Paracetamol & CCl ₄	Ethanolic extract	SGOT, SGPT	T.A. Tuse, <i>et.al.</i> , 2009
11	<i>Colocasia esculenta /Taro</i>	Araceae	Tender leaves, Corm	CCl ₄	Aqueous extract	AST, ALT & ALP	Bhagyashree R. Patil, <i>et.al.</i> , 2009
12	<i>Coriandrum sativum/Coriander</i>	Umbelliferaeae	Seed	Lead nitrate	Aqueous & Ethanolic extract	AST, ALT, ACP, ALP, Total protein, Cholesterol	Leena Kansal <i>et. al</i> , 2011
13	<i>Curcuma longa / Turmeric</i>	Zingiberaceae	Dried Rhizome powder	CCl ₄	Aqueous extract	SGOT, SGPT, ALP, Serum bilirubin	Mahuya Sengupta <i>et al.</i> 2011
14	<i>Cucumis sativus</i> /Cucumber	Cucurbitaceae	Fruits & Seeds	Cumene hydroperoxide	Aqueous extract	reactive oxygen species (ROS)	H. Heidari, 2012
15	<i>Cuminum cyminum/Cumin seeds</i>	Apiaceae	Seed	Profenofos	Aqueous extract	SGPT, SGOT, Bilirubin	Arun kumar <i>et. al.</i> 2011
16	<i>Daucus carota sativus / Carrot</i>	Apiaceae	Leaves, Root	CCl ₄	Aqueous extract	SGOT, SGPT, ALP, Lactate dehydrogenase, Sorbitol Glutamate dehydrogenase, Serum bilirubin, Urea, Hepatic 5'-nucleotidase, Acid phosphatase, Acid ribonuclease, Succinic dehydrogenase, Glucose-6-phosphatase, Cytochrome P-450.	Bishayee A, <i>et.al.</i> , 1995
17	<i>Lagenaria</i>	Cucurbitaceae	Fruits	CCl ₄	Aqueous and	Total bilirubin, Serum	Lakshmi,

	<i>siceraria / Bottle Gourd</i>				Ethanol extract	protein, ALP, ALT, AST	BVS. <i>et. al</i> 2011
18	<i>Luffa acutangula / Ridge Gourd</i>	Cucurbitaceae	Fruits	CCl ₄ & Rifampicin	Hydro-alcoholic extract	• AST, ALT, ALP and LDH total protein	Jadhav VB, <i>et.al.</i> , 2012
19	<i>Macrotyloma uniflorum /Horse gram</i>	Fabaceae	Seed	Paracetamol & D-Galactosamine	Methanolic extract	• SGPT, SGOT, ALP, Bilirubin (Direct and Total)	H.B. Parmar <i>et. al.</i> , 2012
20	<i>Mentha arvensis / Mint</i>	Lamiaceae	Leaves and whole plant	CCl ₄ & Ethanol	Aqueous extract	• SGPT, SGOT, ALP, Total Bilirubin, Total Protein, Tissue Glycogen	Radhika <i>et. al.</i> , 2011
21	<i>Momordica charantia /Bitter Gourd</i>	Cucurbitaceae	Fruits	Acetaminophen	Aqueous extract	ALT, AST, ALP, LDH	Zahra.K. <i>et.al</i> , 2012
22	<i>Moringa oleifera /Drumstick Leaves</i>	Moringaceae	Leaves, Pod	CCl ₄	Methanolic extract	SGPT, SGOT, Total Bilirubin, Direct Bilirubin	B.Balamurugan <i>et.al.</i> , 2010
23	<i>Murraya koenigii /Curry Leaf</i>	Rutaceae	Leaves	Ethanol	Aqueous extract	• GSH, LPO, CAT, SOD, Total protein	Sadhana Sathaye <i>et. al.</i> , 2011
24	<i>Musa paradisiaca/ Banana</i>	Musaceae	Unripe & Ripe fruits	Paracetamol	Supplemented feed	• ALT, AST, Total protein, Total Glucose, Total TG, Total cholesterol, Reduced glutathione, LPO	Iweala, E.E.J., <i>et al.</i> , 2011
25	<i>Phaseolus vulgaris / Kidney Beans</i>	Fabaceae	Seed	CCl ₄	Methanolic extract	• Type I and IV, Collagen	Alberto Gabriel López-Reyes; <i>et.al.</i> , 2008
26	<i>Sesamum indicum/ Sesame seeds</i>	Pedaliaceae	Seed	Paracetamol	Ethanol extract	• SGOT, SGPT, ALP, ACP Total Bilirubin	Kumar Munish, <i>et. al.</i> , 2011
27	<i>Solanum lycopersicum /Tomato</i>	Solanaceae	Fruits	CCl ₄	Tomato pulp (Aqueous)	AST, ALT, ALP, Total bilirubin	Weremfo, A. <i>et.al.</i> , 2011
28	<i>Solanum melongena /Brinjal</i>	Solanaceae	Fruits	Tert-butyl hydroperoxide (t-BuOOH)	Methanol extract	Total phenolic, Total flavonoid	Pannarat Akanitapichat, <i>et.al</i> , 2010
29	<i>Spinacia oleracea/Spinach</i>	Chenopodiaceae	Leaves	CCl ₄	Alcohol extract	• GGT, AST, ALT, ALP, serum- bilirubin, Total protein	R.S. Gupta, <i>et. al.</i> 2006
30	<i>Vigna mungo /Black Gram</i>	Fabaceae	Seed	Ethanol	Methanolic extract	SGOT, SGPT, ALP, Total Bilirubin	Nitin <i>et. al.</i> , 2012
31	<i>Zingiber officinale /Ginger</i>	Zingiberaceae	Rhizome	Paracetamol	Aqueous extract	AST, ALT, ALP, Total bilirubin	Siham M.A. El-Shenawy <i>et al</i> 2010

The amelioration may be attributed to the combined synergistic effects of its constituents rather than to any single factor as the leaves are rich in carotenoid contents (β -carotene, lutein, zeaxanthine), ascorbic acid, (Ozturk IC, *et.al* 2009), flavonoids and *p*-caumaric acid. Bhatia *et.al*, Otari and Nilesh Kumar *et.al.* [119-121] reported Ameliorative effects of *Spinacia oleracea* L. seeds on carbon tetrachloride (CCl₄) - induced hepatotoxicity in vitro. Kang *et.al.* [122] too reported on *Spinacia* seeds.

Vigna mungo

Nitin *et.al.* [123] reported that, the hepatoprotective activity of methanolic extract of seeds of *Vigna mungo* (MEVM) against ethanol-induced hepatic damage in adult albino rats. The liver function parameters were noted to have increased (liver weight and volume), elevated serum enzyme levels (glutathione pyruvate transaminase, oxaloacetate transaminase, alkaline phosphatase and total bilirubin) and increased thiopentone upon exposure to ethanol. When Treatment with MEVM the enzymes SGPT, SGOT, ALP and BIT levels significantly decreased as compared to ethanol control group. The presence of potent diuretic such as saponins and the presence of strong antioxidants like ascorbic acid, total phenolic compounds, tannins, flavonoids etc. in the extract may be responsible for the hepatoprotective activity [124-125].

Anitha *et al.* [126] investigated and reported similar hepatoprotective result of *Vigna mungo* against CCl₄ induced hepatotoxicity. Solanki *et al.* [127] studied and recorded similar hepatoprotection by *Vigna mungo* against Acetaminophen and CCl₄ induced hepatotoxicity.

Zingiber officinale

The aqueous infusion of ginger was reported to show hepatoprotective effect on the paracetamol induced hepatotoxicity in rats [128]. The liver enzyme levels were reportedly altered and the histopathological studies revealed the tissue architecture damage due to paracetamol toxicity. However, Examination of liver tissue of rats treated with paracetamol and ginger extract and silymarin before paracetamol administration showed better hepatic architecture [129]. This hepatoprotection ability of ginger extract may be due to Zingerone, polyphenolic components, oleoresin and other antioxidants that are present in them [130-131].

Magda *et al.* and Atta *et al.* [132-133] reported similar results on CCl₄ induced Liver fibrosis; Saber *et al.* [134] studied on Adriamycin induced Hepatotoxicity and reported hepatoprotection by *Zingiber officinale*.

CONCLUSION

The review of study reiterates the fact of medicinal significance of humble vegetables that are consumed widely. The plant extracts with hepato-protective properties against hepatotoxic substances authenticate their use in folkloric medicine. These plants may offer new opportunities to the limited therapeutic options that is in the treatment of liver diseases or their symptoms, and they should be considered for future studies.

The potent hepatoprotective activities of the chemically defined molecules isolated from natural origins represent an exciting advantage in the search for effective and economical liver protective agents. However, the rich antioxidant potential of the plant origin food items need to be investigated in detail so that more liver treating drugs may be formulated in an efficient manner.

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