Review Article

Doi:

A traditional herbal in liver diseases: *Momordica charantia* L. (kudret narı/bitter/bitter melon)

Running title: A Herb in Liver Diseases: Momordica charantia L.

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Abstract
The liver is the central organ regulating the whole body's metabolism; therefore, liver diseases negatively impact all metabolic activities besides the immune system. *Momordica charantia* L. is one of the medicinal plants used in folk medicine to prevent or treat liver diseases. *M. charantia* contains compounds with antioxidant and anti-inflammatory properties; thus, it protects liver cells from free radical damage and reduces inflammation. In addition, phytochemicals of *M. charantia* can help to regulate blood sugar levels, thereby supporting metabolism and reducing fat accumulation in the liver. Previous studies indicate that *M. charantia* has the potential to enhance liver functionality while reducing the incidence of fatty liver disease. This study aimed to summarize the data from the in vivo studies investigating the hepatoprotective mechanisms of *M. charantia* L. in application doses as a future potential candidate for a dietary supplement. Due to insufficient evidence regarding its safety, the possibility of hepatotoxic effects should not be disregarded.
Keywords: Bitter melon; Hepatoprotective effect; liver diseases; *momordica charantia*; non-alcoholic fatty liver disease (NAFLD).

Introduction

The liver is responsible for several vital functions, including detoxification, protein synthesis, the production of digestive enzymes, glucose metabolism, the regulation of red blood cells, blood clotting, and control of immune function.[1] It is well demonstrated that several diseases and conditions have a frequently observed association with the liver, including hepatitis A, hepatitis B, hepatitis C, hepatitis E, alcohol-related liver diseases, autoimmune hepatitis, non-alcoholic fatty liver disease (NAFLD), drug-induced liver damage, and hepatocellular carcinoma.[2] Given the rising prevalence of liver diseases, there is a growing need for the identification of plants and plant-derived compounds that can provide hepatoprotective benefits. The studies indicate that green tea, resveratrol, milk thistle, garlic, and artichoke are among the plants that demonstrate hepatoprotective properties.[3] Although these plants exhibit hepatoprotective properties, they may also become hepatotoxic when consumed in excessive amounts. Green tea, for instance, can induce hepatotoxicity due to its content of epigallocatechin gallate (EGCG). The safe dose of EGCG has been established as less than 338 mg per day. When this threshold is exceeded, EGCG may trigger oxidative damage and potentially lead to mutations.[4] The use of herbs in the treatment of human health has a history spanning several centuries. In recent years, there has been a significant development in interest in the potential of medicinal plants for the protection and enhancement of liver health.

It is established that the fruits of the bitter *Momordica charantia* are employed in preventing or treating liver disease, particularly in Asian countries.[5] This research is thus focused on investigating the hepatoprotective effects of *M. charantia.* Due to the limited number of clinical studies investigating the hepatoprotective effects of *Momordica charantia*, this study has remained at the in vivo and in vitro levels. Although *M. charantia* has been used as a medicine for a long time, recent studies show that the alpha-momorcharin compound isolated from its seeds may cause toxicity.[6] In addition, triterpenic compounds named 22-hydroxy-23,24,24,25,26,27-pentanorcucurbit-5-en-3-one and 3,7-dioxo-23,24,25,26,27-pentanorcucurbit-5-en-22-oic acid isolated from *M. charantia* stems also caused toxicity in the HepG2 cell line.[7]

Search Strategy

Electronic literature data were used to write this traditional review. The keywords *Momordica charantia*, bitter gourd, hepatoprotective effect, bitter melon, liver health, preclinical studies, and clinical studies were searched in PubMed®, Scopus, Web of Science, Google Scholar, and EBSCOhost databases and combined using the conjunctions “AND,” “OR,” and “NOT.” Since the study focused on hepatoprotective effect, other liver diseases were not included. Every week, assessments were conducted for each database. Clinical trials and in vivo research are particularly chosen. This research is a traditional review; hence, no assessment of study quality has been accomplished.

Momordica charantia L.

Momordica charantia, commonly known as “bitter melon” or “bitter gourd,” is a species in the Cucurbitaceae family. *M. charantia* has a long history of use in traditional medicine, with applications in treating various conditions, including anemia, diabetes, intestinal parasites, digestive system diseases, skin wounds, and liver diseases.[5] In Turkish traditional medicine, an oily macerate prepared by soaking the fruits in olive oil is used to treat gastrointestinal disorders and as a wound-healing drug.[8] In India, the fruits have been traditionally utilized for a variety of therapeutic purposes, including the treatment of diabetes, psoriasis, and scabies, and abortifacient and antihelmintic effects.[9] *M. charantia* fruits are frequently utilized for jaundice in India.[10]

The pharmacological efficacy of *M. charantia* has been demonstrated by scientific studies that have investigated its diverse chemical composition and traditional medicinal uses. The studies included an investigation of the analgesic effect,[11] antidiabetic activity,[12] anti-inflammatory activity,[13] hepatoprotective activity,[14] hypolipidemic effect,[15] and wound-healing activity.[16] The present study is targeted at reviewing the literature for hepatoprotection, which is defined as the ability of a substance or treatment to protect the liver from damage or disease (Table 1).

The plant is a rich source of phytochemicals, consisting of various phytochemical groups found in different parts of the plant in varying concentrations. It has been demonstrated that the roots of *M. charantia* contain a variety of phenolic compounds, including flavonoids and triterpene saponins.[7] (Fig. 1)

Non-Alcoholic Fatty Liver Disease (NAFLD)

NAFLD has been reclassified under the umbrella name of steatotic liver diseases. Metabolic dysfunction-associated steatotic liver disease is the new name for the liver disease formerly known as NAFLD.[34] In recent times, there has been an alarming rise in the prevalence of NAFLD, which now ranks among the most common

forms of liver disease, since approximately 25% of the global population is affected by this condition. The incidence of this disease is directly proportional to the increasing prevalence of obesity.[35] NAFLD is a broad category that encompasses a spectrum of conditions, ranging from simple steatosis (hepatosteatosis) to inflammation (steatohepatitis) with or without fibrosis (non-alcoholic steatohepatitis (NASH)). Additionally, there is evidence that it is linked to the development of not only cirrhosis but also hepatocellular carcinoma (HCC).[36]

In a study utilizing a mouse model of NAFLD, the impact of *M. charantia* extract on the progression of NAFLD was examined following the administration of a high-fat diet for five days. When the experimental and control groups were compared, it was observed that blood glucose, cholesterol, and low-density lipoprotein values decreased in the experimental group fed a high-fat diet. Histological examinations also revealed an improvement in liver structure and function.[37] In a further study, the efficacy of *M. charantia* compounds on the liver was determined by isolating 3β, 7β, 25-trihydroxycucurbita-5,23(E)-dien-19-al and momordicine II triterpenic saponins, which were observed to inhibit lipid accumulation in a HepG2.[38]

The impact of protein derived from *M. charantia* fruits on NAFLD was examined in both in vitro and in vivo assays. It was observed that when HepG2 cells were pretreated with this isolated protein, it protected them from cellular changes such as steatosis. It was also demonstrated that intracellular triglyceride levels decreased and bile acid production increased. In addition, while findings such as discoloration and swelling of the liver were observed in rats fed a high-fat diet, it was observed that lipid accumulation was significantly reduced and hepatocyte growth was not observed in the groups that received *M. charantia* protein at doses of 400 and 800 mg/kg.[39]

The effect of *M. charantia* juice on NAFLD development was investigated in mice at doses of 0.5 and 5 g/kg. In the *M. charantia*-treated group, kidney area fat mass and liver weight were significantly lower than in the fat-only diet group ($p<0.05$).[40]

Alcohol-Related Liver Disease

Chronic alcohol consumption can result in a range of liver damage, from fatty liver with microvesicular steatosis to cirrhosis and HCC. Furthermore, alcohol consumption has been demonstrated to induce mitochondrial DNA damage in hepatocytes.[41] As the duration of alcohol consumption increases, there is a corresponding increase in the accumulation of lipids in hepatocytes, as well as activation of inflammatory damage, fibrogenesis, and carcinogenesis mechanisms.[42]

An 80% ethanol extract prepared from *M. charantia* fruits was investigated against alcohol-induced liver damage in mice. The results of the analyses indicated a statistically significant reduction in liver weight and in the levels of alanine aminotransferase and aspartate aminotransferase enzymes, which are biochemical markers of liver damage ($p<0.05$). Histological examinations have demonstrated a reduction in the accumulation of lipids within hepatocytes.[43]

Hepatocellular Carcinoma

HCC is the most common primary liver cancer, with an increasing incidence. Diseases such as hepatitis B, hepatitis C, and NASH, as well as alcohol, have been implicated in its etiology. Cirrhosis is known to be one of the strongest risk factors for HCC.[44]

The lectin was isolated from *M. charantia* and investigated using in vitro and in vivo methods. In the study carried out using the HepG2 cell line, increased apoptosis was observed at increasing doses ($p<0.01$). As a result of histological evaluations in mice, a significant decrease in tumor volume was also observed ($p<0.01$).[45]

Cucurbitan-type saponosides extracted from *M. charantia* fruits were assessed for their antiproliferative effects on Hep3B and HepG2 liver cell lines. The IC50 values for Caraviloside III were determined to be 16.68 μM for Hep3B and 4.12 μM for HepG2, indicating that it is the most effective saponoside. The IC50 values for the 5-fluorouracil compound, which was selected as the positive control, were determined to be 15.49 μM for Hep3B and 33.58 μM for HepG2.[46]

The in vitro and in vivo effects of MAP30 protein, isolated from *M. charantia* seeds, were evaluated in cancer cells. In vitro studies demonstrated that the compound induced cell cycle progression arrest in the HepG2 cell line at the S phase. In the mice model of liver cancer, a dose of 2 mg/kg of MAP30 was administered every two

days. Consequently, a notable reduction in tumor volume and size was observed, as evidenced by histological analysis ($p<0.05$).[47]

The administration of *M. charantia* seed oil orally to rats yielded statistically significant outcomes. These included a reduction ($p<0.05$) in the mean number, diameter, and area of dysplastic nodules in the liver and a reduction in the size of neoplastic lesions when compared to the control group.[48]

Hepatoprotective Mechanisms of *M. charantia* L.

The use of plants in natural medical treatments has a rich history, spanning thousands of years. As a result of scientific and technological progress, the efficacy and safety of herbal products can now be studied in greater detail, and these products are available in a variety of formulations. Formulation development is a crucial step in enhancing the efficacy of herbal products while reducing their potential adverse effects on the human body. The components of each herbal product may have different mechanisms of action, and it is therefore necessary to determine how these components can be used most effectively.[49]

Given that herbal extracts contain a complex mixture of phytochemicals, it is to be observed that they evince a range of pharmacological effects through a variety of mechanisms. Hazardous agents such as alcohol induce hepatocytes to damage the normal functioning of their membranes. Consequently, the activity of transaminases and alkaline phosphatase increases due to the damage.[50]

The ingestion of alcohol over an extended time can lead to the oxidation of lipids, resulting in the disruption of membrane permeability. This process involves the formation of hydroxyl ethyl radicals, which primarily target polyunsaturated fatty acids. The fractions have been demonstrated to be effective in sustaining the membrane integrity of liver cells by inhibiting alcohol-induced lipid peroxidation in the liver.[31] The oxidative mechanism is shown in Figure 2.[51]

The use of antioxidants has been shown to inhibit the progression of liver disease and improve the effectiveness of current therapies by reducing oxidative stress. Antioxidants may enhance the dissociation of Nrf2 from the complex by altering the phosphorylation of Kelch-like ECH-associated protein-1 (Keap1) or Nrf2, leading to Nrf2 activation. Activation of Nrf2 results in its translocation to the nucleus, where it interacts with the antioxidant response element. This process results in an increase in gene expression for antioxidant enzymes and phase II detoxifying enzymes, which are essential for cellular protection and recovery. Moreover, several studies have shown that certain antioxidants or plant extracts high in antioxidants are protective against hepatotoxin-induced liver injury by enhancing Nrf2 activation.[52] The oxidative mechanism is shown in Figure 3.

In unstressed conditions, the protein Keap1 represses Nrf2. However, in the presence of oxidative stress, Nrf2 is released from repression, thereby activating antioxidant genes and strengthening the cellular defense mechanism. In a study examining the hepatoprotective effects of *M. charantia* on NAFLD, serum concentrations of C-reactive protein and interleukin-6 were significantly reduced following supplementation ($p<0.05$). Similarly, SREBP-1, a principal regulator of lipogenesis and a potential contributor to the development of fatty liver, was diminished by *M. charantia* supplementation, accompanied by a reduction in FAS and ACC-1 protein expression and decreased cholesterol and TG concentrations. It has been demonstrated that inflammatory processes can induce the production of TNF-□, which may stimulate the maturation of SREBP-1 and contribute to the accumulation of lipids in hepatocytes. It can therefore be speculated that the effects of *M. charantia* on SREBP-1 and target genes are effective in reducing inflammation. These findings indicate that *M. charantia* may serve as an efficacious agent for the prevention and cure of NAFLD.[40]

The hepatoprotective properties of a formulation containing *Ferula asafoetida*, *M. charantia*, and *Nardostachys jatamansi* were examined in carbon tetrachloride-induced rats. Enzymes including glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, and alkaline phosphatases were selected as markers for the present investigation. A statistically significant decrease was observed in the levels of these enzymes ($p<0.01$).[53]

The acute toxicity of *M. charantia* L. fruits was investigated, and the LD50 value was calculated to be >5000 mg/kg. Consequently, the fruit is considered to be relatively safe.[54] Nevertheless, research indicates that bitter melon could potentially interact with hypoglycemic drug categories.[55] Furthermore, given that they exhibit CYP3A4 activity, there is a possibility of interaction with drug groups that are metabolized by this enzyme.[56, 57] The most frequently observed adverse effects are hypoglycemia and headaches.[55] It is not recommended for use during pregnancy and lactation. The study of rats demonstrated the occurrence of cardiac hypertrophy in

embryos, though no instances of lethality were observed.[58] It is important to note that a formulation prepared with *M. charantia* may potentially have adverse effects on the developing fetus.

Bioavailability

Bioavailability is one of the biggest problems in herbal products.[59] It is important to investigate technologies such as nanoparticles and phytosomes for bitter melon. Owing to the unpleasant flavor and limited bioavailability of *M. charantia*, innovative technologies such as nanoparticles and phytosomes can be utilised to enhance stability and bioavailability.[60] Nanoparticle studies have shown that herbal extracts can minimize toxicity while increasing activity.[61] The antibacterial efficacy of silver nanoparticles synthesized from the extract of *M. charantia* was examined. The nanoparticle-treated group exhibited a notable increase in activity ($p<0.005$).[62] A study on the Huh-7 liver cancer cell line showed that *M. charantia* copper-iron nanoparticles promoted apoptosis. The IC50 was determined to be 324 g/ml, and this was evaluated as effective.[63] Because they are extremely small molecules, they are likely to be hazardous. Nanoparticle safety is a contentious subject due to a lack of evidence on both acute and chronic toxicity.[64]

Discussion and Conclusion

Bitter melon (*Momordica charantia*) has a lengthy history of use in traditional medicine, spanning centuries. As the liver is responsible for numerous functions in the body, it is crucial to maintain liver health. Several pathways might cause different disorders in the liver. As a result, herbal compounds and extracts that work via a variety of pathways are critical.

Studies on the hepatoprotective effects of *M. charantia* are summarized in Table 2. The lack of clinical trials and safety limits are serious obstacles on the way from the *M. charantia* plant to medicine. This healing feature, reflected in traditional use, provides insight into modern drug development studies, elucidating the chemical structure and determining the mechanisms of action through scientific investigation. *M. charantia* can be used in combination with herbs like milk thistle and compounds that are good for the liver, such as curcumin and silymarin. It is possible to research synergistic effects.

This research aimed to assess the hepatoprotective impact of *M. charantia*. The present condition of clinical research and the formulation is both insufficient and lacking in several aspects. Moreover, another significant weakness is the lack of clinical research investigating the dosage and duration of the hepatoprotective effect.

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Table 1. Phytochemical constituents in the different parts of *M. charantia L.*

Plant part	Chemical components	Chemical groups
Root	Quercetin [17]	Flavonoid
	Kaempferol [17]	Flavonoid
	Catechin[17]	Flavonoid
	Chlorogenic acid [17]	Flavonoid
	momordicoside X	Cucurbitane-type Triterpene saponin
	3 ß, 7 ß, 25-trihydroxycucurbita-5 23(E)-dien-19-al [18]	Cucurbitane-type Triterpene saponin
	Momordicin I [18]	Cucurbitane-type Triterpene saponin
	Momoricine II [18]	Cucurbitane-type Triterpene saponin
	Kuguaglycoside G [18]	Cucurbitane-type Triterpene saponin
	Caffeic acid [19]	Phenolic compounds
	Gallic acid [19]	Phenolic compounds
	Chlorogenic acid [19]	Phenolic compounds

Leaves	Karavilagenin F [20]	Cucurbitane-type Triterpene saponin
	Karaviloside XII [20]	Cucurbitane-type Triterpene saponin
	Karaviloside XIII [20]	Cucurbitane-type Triterpene saponin
	Momordicine VI [20]	Cucurbitane-type Triterpene saponin
	Momordicine VII [20]	Cucurbitane-type Triterpene saponin
	Momoricine VIII [20]	Cucurbitane-type Triterpene saponin
	(19*R*,23*E*)-5*β*,19-epoxy-19-methoxycucurbita-6,23,25-trien-3*β*-ol [20]	Cucurbitane-type Triterpene saponin
	Kuguacin R [20]	Cucurbitane-type Triterpene saponin
Fruits	Lycopene [21]	Carotenoids
	ß-carotene [21]	Carotenoids
	Zeaxanthin [21]	Carotenoids
	Lutein [21]	Carotenoids
	Charantadiol A [22]	Triterpene saponin
	Charantagenin E [22]	Triterpene saponin
	Stigmasterol[22]	Sterols
	7,25-dihydroxycholesterol [22]	Sterols
	Goyaglycoside B [22]	Triterpene saponin
	Charantagenin D [22]	Triterpene saponin
	Kuguaglycoside C [22]	Triterpene saponin
	Momordicoside K [22]	Triterpene saponin
	Quinic acid [23]	Phenolic compounds
	Benzoic acid [23]	Phenolic compounds
	Gallic acid [23]	Phenolic compounds
Seeds	-eleostearic acid (45.60%) [24]	Fatty acids
	stearic acid (28%) [24]	Fatty acids
	oleic acid (12.45%) [24]	Fatty acids
	linoleic acid (8.90%) [24]	Fatty acids
	tr-nerolidol (61.6%) [25]	Sesquiterpene
	apiole (8.9%) [25]	Phenylpropene
	cis-dihydrocarveol (4.9%) [25]	Monoterpenoids
	germacrene D (4.4%) [25]	Sesquiterpene

Table 2. *In vivo* studies related to hepatoprotective effect of *M. charantia*

Plant part—solvent utilized	Research model	Dosage	Results
Leaves-Water [26]	CCl_4-inducedhepatotoxicity in rats	200 mg/kg and 400 mg/kg	ALT, AST, and ALP enzymes ↓ ($p<0.05$)
			SOD and CAT ↑ ($p<0.05$)
Leaves—50% ethanol [27]	CCl_4-inducedhepatotoxicity in rats	100 mg/kg and 200 mg/kg	ALT, AST ↓ ($p<0.05$),
			Histopathological findings show that there is almost no cell damage after application.
Leaves: 70% ethanol [28]	CCl_4-inducedhepatotoxicity in rats	100 mg/kg and 200 mg/kg	SGOT, SGPT, ALP enzymes, and total bilirubin were positively affected ($p<0.05$).
Juice [29]	Acetaminophen-induced liver damage in rabbits	5 ml/kg	ALT, AST, and ALP enzymes ↓ ($p<0.05$)
Fruit—95% ethanol [30]	Ammonium chloride induced liver damage in rats.	300 mg/kg	AST, ALT, and ALP enzymes ↓ ($p<0.05$)
			Decreased blood ammonia and plasma urea levels
Fruit—80% ethanol [31]	Alcohol-induced hepatotoxic rats	25, 50, and 100 mg/kg	SOD, GSH, and CAT ↑ ($p<0.05$)
Fruit-Water [14]	In restraint-stressed mice	250, 500, 750 mg/kg	According to histopathological findings, the structure of liver cells is intact and the structure of hepatic cords is clear.
			ALT AST ↓ ($p<0.05$)
Fruit—Hexane [32]	A rat model of hepatic ischemic reperfusion injury	200 mg/kg	Prevented the increase in SGOT, SGPT, ALP, LDH, and CRP levels. ($p<0.01$)
			Prevented the increase in MDA levels ($p<0.05$).
Leaves—70% methanol [33]	Cadmium-induced hepatotoxicity in rats	300 mg/kg	Cadmium caused fibrosis around the portal vein. Disintegration of the nuclei of hepatocytes was observed.
			Pretreatment with extracts revealed prominent Kupffer cells.

ALP: Alkaline phosphatases; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; SGOT: glutamate oxaloacetate transaminase; SGPT: glutamate pyruvate transaminase; SOD: Superoxide dismutase; CAT: Catalese; GSH: Glutathione; LDH: Lactate dehydrogenase; CRP: C-reactive protein; MDA: Malondialdehyde.

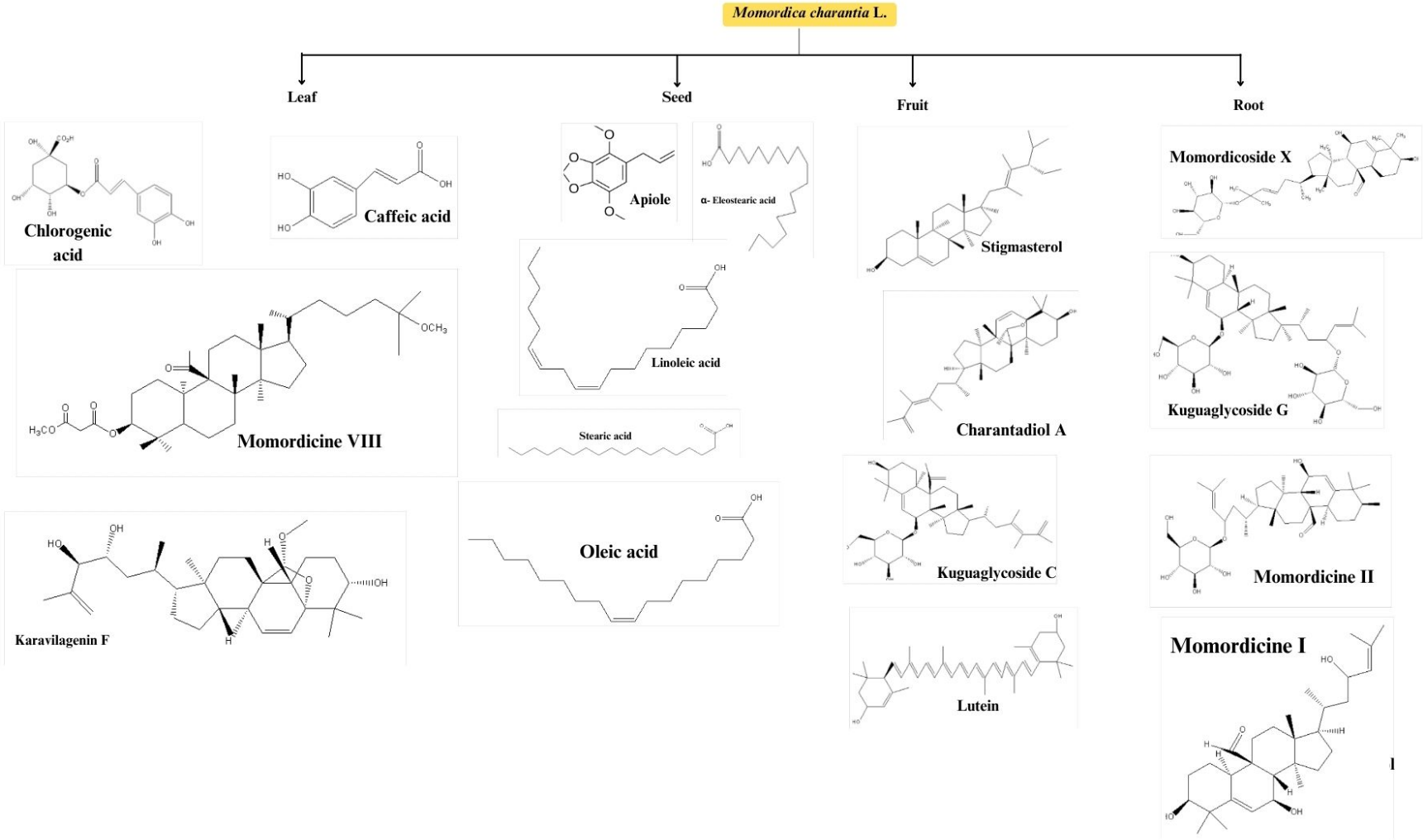

Figure 1. Molecular structure of *M. charantia* components (illustrated by the authors)

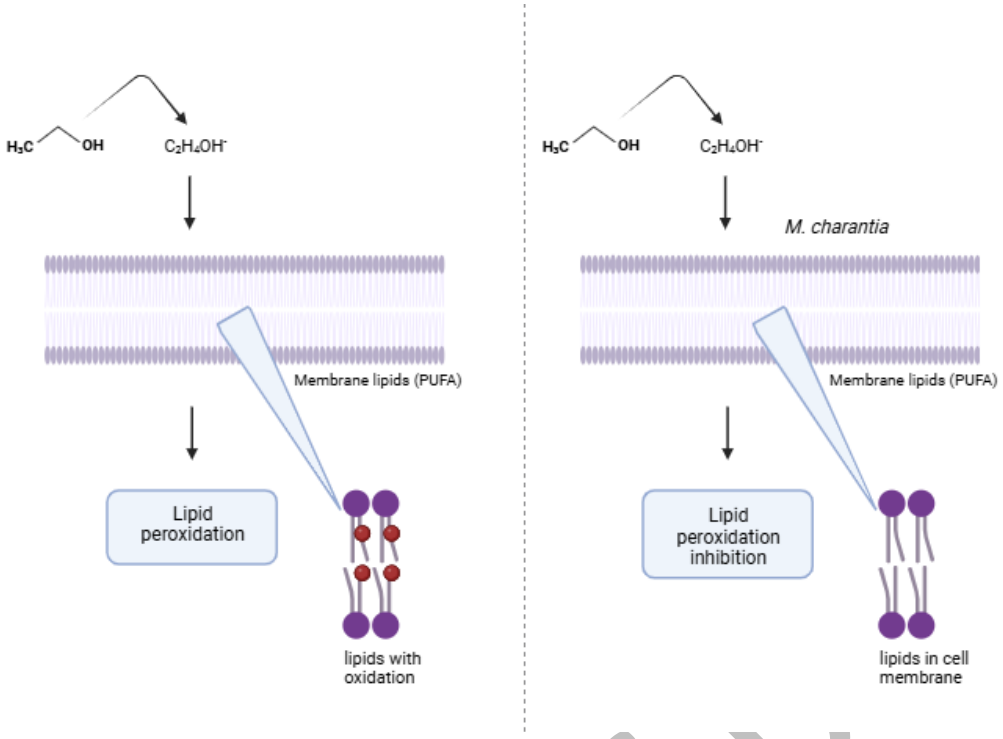

Figure 2. Antioxidant effect mechanism of M. charantia (original creations)

The effectiveness of Momordica charantia in protecting the membrane integrity of liver cells has been demonstrated by its ability to inhibit the alcohol-mediated lipid peroxidation process in the liver. (illustrated by the author)

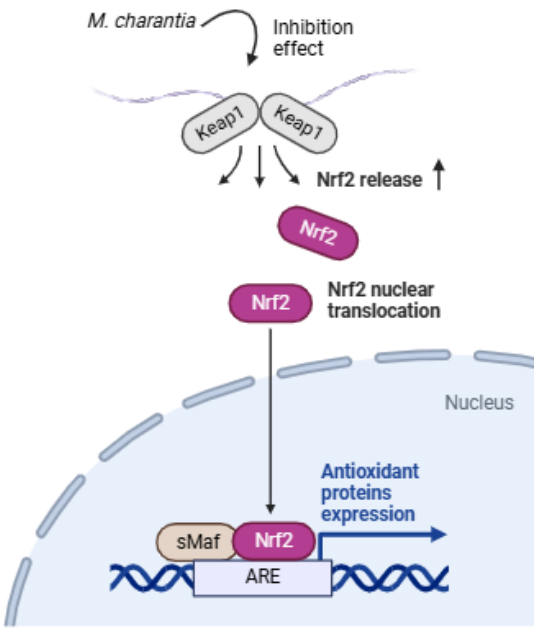

Figure 3. Antioxidative mechanisms with related Nrf2 (original creations)