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HEPATOPROTECTIVE ACTIVITY OF FENUGREEK (*TRIGONELLA FOENUM - GRAECUM*) AND GARLIC (*ALLIUM SATIVUM*) AGAINST HEPATOTOXICITY INDUCED IN DIFFERENT MICE AND RATS EXPERIMENTAL MODELS – A REVIEW

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ABSTRACT

Herbal medicine is one of the oldest forms of health care known to mankind for many generations. Various research findings have given much attention to fenugreek (*Trigonella foenum graecum*) seeds and garlic (*Allium sativum*) for their hepatoprotective effect on toxicity induced on rat liver cells. The objective of this review is to provide summarized report of the existing data on fenugreek seeds and garlic for their hepatoprotective effect in different experimental models. Various reports cited in this article represent that fenugreek seeds and garlic have hepatoprotective effect by lowering and stabilizing the biochemical parameters of liver function tests that are elevated due to liver damage. The findings showed that fenugreek seeds and garlic have a vital role in antioxidant effect, by inhibiting or scavenging free radicals prevent lipid peroxidation, hepatic protective effect and restoration of hepatic damage.

Key words: Hepatotoxicity, fenugreek seeds, garlic, hepatoprotective effect, liver.

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INTRODUCTION

Herbal medicine flourishes is the primary form of medicine for 70-80% of the world's population. Usually, herbal medicines can be formulated from a specific part of the plant such as root, leaves, fruit, flowers, and seeds. Most of the herbal medicines commonly used today are of herbal origin. Indeed, about 25% of prescription drugs containing at least one active ingredient derived from plant material (Bashar and Omar, 2011). According to WHO information, up to 90% of the population in developing countries uses plants and its products as traditional medicine for their primary health care (Yibru *et al.*, 2015). WHO has listed 21,000 herbs which are used as medicines all over the world and this magnifies the importance of herbs (WHO, 2003).

Traditional medicine is Africa's culture, future and heritage because the country has a rich bio- resource base: nearly 6,377 plant species are used in tropical Africa, more than 4,000 of these as medicinal plants. It is estimated that 90% of traditional medicine in Africa is derived from plants (WHO, 2003). Ethiopian Flora

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consists of 6000 – 7000 species distributed in about 245 plant families. Although the exact number is still unknown, about one-third of the families, have been employed in traditional medicinal practices (Tadesse, 2008).

Medicinal plants play significant role against various ailments since ancient times, as they possess therapeutic properties and pharmacological effect (Motaleb, 2011). Hepatoprotective activity of different medicinal plants was studied and evidenced by different research investigations.

Research documentation on histopathological changes and protective activity of fenugreek seeds and garlic against liver toxicity induced in mice, alloxan induced toxic effect on diabetic rats and humans were reported (Wang *et al.,* 1996).

Hepatoprotective effect was evaluated using biochemical parameters such as serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin and gamma-glutamate transpeptidase (GGTP) (Wang *et al.,* 1996; Ashraf *et al.,* 2002).

Therefore, the purpose of this review is to assess the biochemical effect of fenugreek (*Trigonella foenum-graecum*) seeds and garlic (*Allium sativum*) on its possible hepatoprotective activity on different experimental animal models.

The liver

The liver is the largest internal organ with an average weight of about 1.5 kg in human body. It is located in the right upper quadrant of the abdomen which is just below the diaphragm and it has major left and right lobes with two small inferior lobes, most of which are covered by a thin capsule and mesothelium of the visceral peritoneum (Singh *et al.,* 2011).

The capsule thickens at the hilum where the dual blood supply from the hepatic portal vein and arteries enters the liver (Junqueira and Carneiro, 2012). Almost 70-80% of the blood enter into the liver comes from the hepatic portal vein which is arising from the stomach, intestines and spleen and nearly 20-30% is supplied by the hepatic arteries (Krause, 2005).

Liver is the main organ for the metabolism and detoxification of drugs, alcohol and environmental chemicals (Singh *et al.,* 2011). It is the first internal organ to encounter a number of insults including ingested trace minerals, drugs and environmental toxicants (Xi Yang *et al.,* 2014).

Higher exposure to hepatotoxic chemicals sometimes generates free radicals that overpower the liver and causes jaundice, cirrhosis and fatty liver. Excess production of the reactive oxygen species manifests in tissue depletion, lipid peroxidation, plasma membrane damage which finally results in severe hepatic damage (Maximas H. Rose *et al.,* 2013).

Fenugreek (*Trigonella foenum-graecum*) and its medicinal values

Fenugreek is an annually grown herb which is cultivated throughout the world. The leaves and edible dried seeds of the plant are commonly used as food spices and an important component in traditional medicine. The taxonomical classification of fenugreek plant is presented in table – 1. Fenugreek seed has been reported to exhibit several pharmacological properties such as gastro-protective, hepatoprotective, anti-diabetic, reducing cholesterol, anti-carcinogenic, antioxidant, anti-nociceptive, antimicrobial and wound healing properties (Meghwal and Goswami, 2012; Shivangi Goyal *et al.,* 2016).

Phytochemistry of *Trigonella foenum-graecum*

The seed of the fenugreek plant contains many active compounds with wide pharmaceutical applications. The seeds are collected in the autumn that contains iron, vitamin A, vitamin B_1, vitamin C, phosphates, flavonoids, saponins, trigonelline alkaloids and higher concentration of fibers and protein (Wani and Kumar, 2016; Birhane, 2012).

Garlic (*Allium sativum*) and its medicinal values

Garlic (*Allium sativum*) is used worldwide as food additive, spice and medicine. The bulb portion is used as a flavoring agent and medicinal herb. Garlic can be eaten in the raw, chopped, minced, or juiced form. It has a characteristic pungent, spicy flavor that mellows and sweetens considerably with cooking (Nikolai Friesen *et al.,* 2006; Londhe *et al.,* 2011).

The traditional medical practitioners have considered garlic as an excellent medicinal plant that has a lot of therapeutic potentials (Zubair Khalid Labu *et al.,* 2013). Garlic has a broad spectrum of activities in controlling and treating diseases favor natural antioxidants. It is used for the treatment of various ailments like asthma, diabetes, cold, paralysis, forgetfulness, tremor colicky pain, chronic fever and in addition it act as anti-hypertensive and anti-rheumatic agent (Gebreselema and Mebrahtu, 2013). It has been found that garlic act as hepatoprotective agent, lowering blood pressure and cholesterol level, possessing strong antimicrobial effect and provides antioxidant protection to cells (Ajayi *et al.,* 2009).

Phytochemical constituents of *Allium sativum*

A number of bioactive substances in garlic constitute several complex sulfur-containing compounds that are rapidly absorbed, transformed and metabolized in human body. Garlic contains specific oil and water soluble compounds like thiosulfates, allicin and secondary metabolites including steroids, terpenoids, flavonoids, polyphenol and alkaloids that are responsible for its therapeutic effects (Baldi *et al.,* 1993).

Effect of Allium sativum against hepatotoxicity on the liver function test

Research findings on ethanolic extracts of garlic significantly reduced the biomarker enzymes (ALP, ALT and AST), total bilirubin and lactate dehydrogenase (LDH) of on paracetamol induced hepatotoxicity in rats (Ebenyi *et al.,* 2012; Jevas Chibuike Ozougwu *et al.,* 2014). This is because of active ingredients in garlic that is capable of free radical scavenging effect in living system.

Likewise, administration of raw garlic significantly decreased the activity of AST, ALT, ALP, gamma glutamyl transferase (GGT) and LDH compared to patients who consume alcohol with liver damage, increased permeability and necrosis of hepatocytes before treatment (Sankaran Mirunalini, 2010). In another study also showed that rats intoxicated with Galactosamine / Lipopolysaccharide (LPS) produced a significant elevation of serum tumor necrosis factor-α (TNF- α) and myeloperoxidase (MPO) which results in neutrophil infiltration (Said *et al.,* 2011). However, aqueous garlic extraction significantly reduced the elevation of serum TNF- α by inhibition of its production. The increased hepatic MPO activity due to injury was effectively reversed by pretreatment with garlic extraction (El-Beshbishy, 2008).

Antioxidant enzymes are considered to be the first line of cellular defense against oxidative damage. The antioxidant defense systems including superoxide dismutase (SOD), Catalase (CAT), and Glutathione peroxidase (GPx) activity is significantly decreased in alcoholic patients. This decrease could be due to a feedback inhibition or oxidative inactivation of the enzymes because of excess reactive oxygen species (ROS) generation. The antioxidant properties of allicin which is a major component of garlic neutralize the reactive oxygen species (Ebenyi *et al.,* 2012). Garlic also increases antioxidant action by scavenging ROS, enhancing the cellular antioxidant enzymes and increasing the glutathione in the cells.

A study carried out by Kilikdar *et al.,* (2011) reports that the activity of xanthine oxidase (XO), responsible for superoxide radicals was significantly increased in rats treated with lead. This elevated level of XO was restored to near normal activity in liver tissue when rats were pretreated with aqueous garlic extraction. This might be due to garlic having the potential to decrease the formation of ROS by controlling the activity of the antioxidant enzymes or by directly scavenging the superoxide radicals.

A significant decrease in the level of thiobarbituric acid reactive substance (TBARS) which are the end products of lipid peroxidation was observed in rat liver treated with extract of garlic as compared to paracetamol treated rats. The increase in TBARS in liver of paracetamol treated rats suggests that lipid peroxidation leading to tissue damage. Reversely, mechanism of hepatoprotection of the extract is due to its ability to reduce or prevent the lipid peroxidation (Ebenyi *et al.,* 2012).

Arti Sharma *et al.,* (2010) also reported that increase in lipid peroxidation and decrease activities of SOD, CAT, and GSH antioxidants by exposure to lead nitrate exposing the tissues to peroxidative damage. Conversely, administration of garlic prevents the hepatic tissue from getting peroxidised. This is due to significant reduction in lipid peroxidation products and partly restored the altered levels of SOD, CAT, and glutathione (GSH) antioxidant molecules. This evident also confirmed that garlic is effective since it contains antioxidant compounds called allicin.

Total serum bilirubin observed in paracetamol hepatotoxic rats suggested abnormal conjugation of bilirubin by the liver due to generalized hepatocellular damage. Conversely, total serum bilirubin was decreased after rats were treatment with silymarin and garlic extracts.

The possible mechanism of action of garlic extracts may be through their antioxidative effects. Similar reports indicate that aqueous garlic extraction significantly decreases the serum total protein and increase in serum albumin in liver tissue against CCl_4 and lead intoxication. This stabilization of serum protein level is a clear indication of garlic being related to an improvement in the functional status of the liver cells. The inhibitory role of lead in protein synthesis may be due to its damaging effect on DNA and RNA (Arti Sharma *et al.,* 2010; Sule and Arhoghro, 2016).

Additional biochemical parameters such as fasting blood glucose (FBG) serum total cholesterol (TC), triglyceride (TG), serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT) and glycogen content of liver were evaluated on alloxan induced rats. Administration of garlic significantly reduced the TC, TG, SGOT and SGPT. This reduction could have resulted from the antioxidant effect of the extracts of garlic which contains several flavonoids and beta-carotene. Besides these, the extracts also possess glycogen increasing property on the liver (Mohammad Asadujjaman *et al.,* 2012).

Another study has shown that garlic oil administration provides a protection against cyclosporine (CsA)-induced injury in the liver of rats. CsA toxicity was the result of oxidative stress. Conversely, garlic oil provides protection by enhancing antioxidant defense system and reduces lipid peroxidation. Results indicate administration of CsA alone resulted in necrosis and fatty infiltrate but these defects were ameliorated by oral administration of garlic oil (5ml/kg) with CsA 12.5 mg/kg for 28 days (Rajaa Dhunoon Marsoul *et al.,* 2016).

Effect of *Trigonella foenum-graecum* against hepatotoxicity on the liver function test

Liver enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) are reliable marker enzymes for liver function and integrity (Wang *et al.,* 1996). Studies on different experimental models have proved that its active components of Fenugreek seed has strong hepatoprotective effect against carbon tetrachloride (CCl_4) induced liver damage in rats (AI-Sultan and EI.Bahr, 2015; Said *et al.,* 2011). Other studies also revealed that potential protective effects of fenugreek seeds against acetaminophen (AC) induced hepatotoxicity and aqueous extract of germinated fenugreek seeds on Cypermetrin (CM) induced hepatotoxicity (Ibrahim and Osman, 2017; Sushma and Devasena, 2010).

The hepatoprotective effect of aqueous extract of fenugreek seeds on the hepatotoxicity induced by anticancer drug adriamycin (ADR) indicated an obvious degree of improvement which is correlated with the increase in treatment time (Sakr *et al.,* 2012). In addition, hepatoprotective activity of fenugreek seeds extract against thioacetamide (TAA) induced hepatotoxicity has been shown that the levels of liver function test (LFT)decrease after treatment with fenugreek seeds attenuate the inflammation caused by CCl_4 (Said *et al.,* 2011).

In addition acetaminophen (AC) administration caused liver dysfunction which revealed by the significant increase in aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) respectively, but after administration of fenugreek seeds significantly decreased the elevations of liver enzymes respectively. AC administration causes a decrease in total protein, albumin serum levels which restored as a result of fenugreek seeds administration; returning near to the normal values (Ibrahim and Osman, 2017). Other studies revealed that restoration of the antioxidant status and other parameters close to normal suggest that aqueous extract of germinated fenugreek seeds protects against cypermethrin (CM) and adriamycin induced hepatotoxicity (Sushma and Devasena, 2010).

Fenugreek seeds improved the histopathological and biochemical changes induced in the liver (Sakr *et al.,* 2012). Hepatotoxicity induced by carbon tetrachloride (CCl_4) after treated with fenugreek seeds, decreased the liver functional test (LFT) and displayed nearly normal architecture (AI-Sultan and EI.Bahr, 2015; Said *et al.,* 2011).

Possible mechanism of fenugreek seeds and garlic on hepatoprotective effect

Hepatotoxicity may be caused by reactive oxygen species (ROS) which resulted in reduction of hepatic antioxidant system with increase in oxidative stress. Fenugreek seeds and garlic have antioxidant effect, which helps ~~to~~ in enhancing the detoxification of foreign compounds, hepato protective effect and restoration of hepatic damage caused by hepatic induced toxic drugs (Ebenyi *et al.,* 2012).

This is because those contains active ingredients of organo sulfur compounds which are responsible for either inhibiting or scavenging free radicals and prevent lipid peroxidation in response to oxidative stress (Sankaran Mirunalini, 2010; Jevas Chibuike Ozougwu *et al.,* 2014).

Table 1: Taxonomical classification of *Trigonella foenum-graecum L.* (Meghwal and Goswami, 2012).

Kingdom	**Plantae**
Subkingdom	Tracheobionta
Super division	Spermatophyta
Division	Magnoliophyta
Class	Magnoliopsida
Order	Fabales
Family	Fabaceae (Leguminosae)
Genus	Trigonella L.
Species	foenum-graecum L.

Table 2: Taxonomical classification of *Allium sativum* [19].

Kingdom	**Plantae**
Class	Liliopsida
Subclass	Liliidae
Super order	Liliianae
Order	Amary-llidales
Family	Alliaceae
Sub family	Allioideae
Genus	Allium
Species	Sativum

Table 3: Summary on hepatoprotective effect of fenugreek (*Trigonella foenum-graecum*) seeds and garlic (*Allium sativum*) in liver function test studied by different authors.

S.N	Experimental model	Route of administration	Dose of treatment	Duration	Type plant	Biochemical parameters	References
1.	Male rats	Orally gavage	1000 mg/kg	7 days	Fenugreek	Acetaminophen induced hepatotoxicity, treated with Fenugreek seeds significantly decreased elevations in AST, ALT, and ALP.	(Ibrahim and Osman, 2017)
2.	Albino mice	Orally	0.4 gm/kg	3x/wkly/ 8 wk	Fenugreek	Treating mice with fenugreek seeds reduced the activity of AST and ALT.	(Saber *et al.*, 2009)
3	Female rats	Orally	500 mg/kg	Daily/ 3wks	Fenugreek	Thioacetamide induced hepatotoxicity, treated with aqueous fenugreek seed extract resulted in a significant increase of glutathione.	(Zargar, 2014)
4	Both sexes rats	Orally	10 gm/kg	5 wks	Fenugreek	Carbon tetrachloride induced hepatotoxicity, significant decrease was observed in serum liver test function after treated with aqueous extract of fenugreek seed compared to control group.	(Rajaa Dhunoon Marsoul *et al.*, 2016)
5	Albino rats	Orally	0.4 g/kg	3x/wk for4wks	Fenugreek	Administration of fenugreek seed extract on ARD-induced hepatotoxicity and oxidative stress shows improved the histopathological and biochemical changes.	(Sakr *et al.*, 2012)
6.	Both sexes rats	Orally	2gm/kg/d	30 days	Fenugreek	CCl_4 induced hepatotoxicity, treated with aqueous extract fenugreek seeds levels of liver function test activities decrease but their levels still higher than control and attenuation of inflammation.	(Said *et al.*, 2011)
7	Male albino rats	Orally gavage	25 mg/kg	60 days	Fenugreek	Aqueous extract of germinated fenugreek can prevent the CM-induced oxidative stress in liver. Evident from the significant reduction in LPO in liver.	(Sushma and Devasena, 2010)

8	Male Swiss albino mice	Oral gavage	100,250, 500 mg/kg	40days	Garlic	Administration of ethanol extraction of garlic to lead nitrate exposing liver tissues to shows significant reduction level of lipid peroxidation products and partly restored the altered levels of SOD, and GSH antioxidant molecules.	(Arti Sharma *et al.*, 2010)
9	Male albino rats	Orally	50mg/k g	1week	Garlic	XO free radicals was increase significantly, however treated with methanol extraction garlic restored to near normal.	(Kilikdar *et al.*, 2011)
10	Male rats	Oral gavage	5ml/ Kg/d ay	28 days	Garlic	Cyclosporine-induced increase oxidative stress. Conversely, garlic oil provides protection by enhance antioxidant defense system and reduce lipid peroxidation.	(Rajaa Dhunoon Marsoul *et al.*, 2016)
11	Albino rats of both sexes	Canular	200,400,800 mg/kg	7 days	Garlic	Ethanolic extracts of garlic produced significant reduction on the biomarker enzymes ALP, ALT, and AST, total Serum Bilirubin Level and LDH Level on paracetamol hepatotoxic liver rats.	(Ebenyi *et al.*, 2012)
12	Male albino rats	Orally	200,300 or 450mg/kg	3months	Garlic	Increase ALT, ALP, AST, total bilirubin, increase in TBARS, LDH by paracetamol, but ethanolic extracts of garlic produced significant reduction on the biomarker enzymes ALP, ALT, and AST, total Serum Bilirubin Level and LDH Level	(Jevas Chibuike Ozougwu *et al.*, 2014)
13	Alcoholi c patients	Orally	1.2 g	45days	Garlic	Administration of raw garlic significantly decreased AST, ALP, ALT, GGT, LDH and increase SOD CAT and GPx in alcoholic patients.	(Sankaran Mirunalini, 2010)
14	Male albino rats	Intraperiton eally	300 mg/kg	14 days	Garlic	Ethanolic extracts of garlic leaf reduced elevation of serum TNF- α serum MPO, AST, ALP, ALT in LPS induced hepatotoxicity rats.	(El-Beshbishy, 2008)

15	Male rats	Orally	5-10 mg/kg	21 days	Garlic	Treatment of garlic oil on liver damage induced by combined administration of ethanol and CCL_4 result in significantly decrease in ALT, AST, ALP function test.	(Wang *et al.*, 1996).
16	Wistar albino rat	Orally	100 and 200 mg/kg	25 days	Garlic	Administration of ethanol extraction of garlic on CCl4-induced liver injury shows improvement in the functional status of the liver test (Biochemicals).	(Sule and Arhoghro, 2016)

CONCLUSION

Evidences from different scientific studies involving hepatoprotective effect on different experimental models, clearly indicates that fenugreek (*Trigonella foenum-graecum*) seeds and garlic (*Allium sativum*) is showed excellent hepatoprotective activity against drug and chemical induced hepatotoxicity.

Conflict interests

The authors declare that there are no conflict interests in this article.

Authors' contributions

All authors contributed in the paper by planning, data collections, editing and reviewing and approved the final manuscript.

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