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Hepatoprotective Effect of Vitamin E

Elias Adikwu and Brambaifa Nelson

Department of Pharmacology, Faculty of Basic Medical Sciences,
College of Health Sciences, University of Port Harcourt, Choba, Rivers State, Nigeria

ABSTRACT

Drugs and some chemical agents are known to induce hepatotoxicity in humans which is of great concern to clinicians. Chemical agents are been screen daily for their hepatoprotective properties. Among these chemical agents is vitamin E which has drawn wide attention due to it reported hepatoprotective property as reported by researchers. This study collected and evaluated reports to ascertain the hepatoprotective effect of vitamin E. A comprehensive literature review on the hepatoprotective property of vitamin E in humans and animals was performed. In this review it was observed that vitamin E exhibited high hepatoprotective effect in animals but with conflicting reports in humans. In humans vitamin E was reported to be beneficial in non alcoholic steatohepatitis, in obese children with non fatty alcoholic liver disease, hepatitis B, hepatitis C and haemochromatosis. In animals it was reported to normalized hepatotoxicity induced by drugs, and some chemical agents including heavy metals. Vitamin E exhibited hepatoprotective effect and decreased oxidative stress in the liver manifested through decrease in microsomal lipid peroxidation, liver fibrosis, tumor necrosis factor, inflammation and hepatic porphyrin. It normalized levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, serum bilirubin, glutathione superoxide dimutase, lactose dehydrogenase, malondialdehyde and improved histopathological changes in the liver induced by chemical agents. Hepatoprotective property of vitamin E is attributed to it antioxidant property buried in it structure. Structurally, the side chain in the 2-position facilitates the incorporation and retention of vitamin E in biomembranes, so that the 6-position is optimal for scavenging free radicals and terminating lipid peroxidation. Furthermore, it antioxidant effect is exhibited through protection of poly unsaturated fatty acid from oxidation by reactive oxygen species, stabilization of membrane and breaking of antioxidant chains that prevent Reactive Oxygen Species damage to membranes. Vitamin E exhibited hepatoprotective effect in animals. It hepatoprotective effect in humans leaves more room for evaluation due to some discrepancies in report.

Keywords: Vitamin E, Antioxidants, Liver, Toxicity, Protection

1. INTRODUCTION

The liver is the major organ responsible for metabolism, detoxification and secretory functions in the body. Hence, it regulates various important metabolic functions in mammalian systems. Hepatic damage is associated with the distortion of these metabolic functions. The liver tissue is reported to be one of the tissues with a high regenerative capacity (Khan and Mudan, 2007). According to Rabelo *et al*. (2006) hepatocytes exhibit a very good regenerative response to several stimuli, including massive destruction of hepatic tissue by toxins, viral agents, or surgical extraction. Regeneration of the liver tissues is a result of an organized and controlled response of the liver toward tissue damage induced by toxic agents, chemical agents, trauma, infections, or post surgery resection which could induce oxidative stress in the liver. Oxidative stress can be defined as an increase in oxidants and/or a decrease in antioxidant capacity. Oxidative stress is mediated by

Corresponding Author: Elias Adikwu, Department of Pharmacology, Faculty of Basic Medical Sciences, College of Health Sciences, University of Port Harcourt, Choba, Rivers State, Nigeria

Reactive Oxygen Species (ROS) generated in liver by a number of mechanisms. ROS are small, highly reactive, oxygen-containing molecules that are naturally generated in small amounts during the body's metabolic reactions and can react with and damage complex cellular molecules such as fats, proteins, or DNA. ROS include superoxide and peroxide which normally exists in the cells as Hydrogen peroxide (H_2O_2) and Hydroxyl radical ($^{\bullet}OH$).

Superoxide, peroxide and the hydroxyl radicals are considered the primary ROS. However, because they are unstable and rapidly react with additional electrons and protons, most of these ROS are converted to water before they can damage cells (Defeng and Cederbaum, 2003; Weltman *et al*., 1998). Increase in oxidative radicals lead to decrease in enzymatic antioxidants, e.g., superoxide dismutase, catalase, glutathione peroxidase and non-enzymatic antioxidants e.g., vitamin C, vitamin E that work as scavengers for this harmful ROS. Radical-scavenging antioxidants are consumed by increased free radical activity (Bolukbas *et al*., 2005). Catalase and the Glutathione Peroxidase system help to remove hydrogen peroxide; Superoxide Dismutases (SODs) catalyze the removal of superoxide radicals (Jadhav *et al*., 2010). GSH is one of the most abundant tripeptide non-enzymatic intracellular biological antioxidant present in the liver. It is involved in the removal of free radicals such as hydrogen peroxide, superoxide anions and alkoxy radicals (Meister, 1984).

ROS induce hepatotoxicity or liver injury through a direct attack on essential biomolecules with loss of their biological functions and cell viability (Sies, 1986; Kaplowitz, 2000). Alternatively, ROS may indirectly activate redox sensitive transcription factors such as nuclear factor κB (NF-κB) (Baeuerle and Henkel, 1994) or Activator Protein-1 (AP-1) (Karin *et al*., 1997), thus triggering the production of cytotoxic, proinflammatory and/or fibrogenic mediators by Kupffer cells and other non-parenchyma cells (Tilg and Deihl, 2000). This creates room for liver apoptosis and necrosis (Esrefoglu, 2012). ROS cause lipid peroxidation of polyunsaturated fatty acid leading to disturbance in membrane structure and function (Hicman and MacDonald, 2007). Vitamin E is a natural and fat soluble antioxidant which has been reported to have hepatoprotective property. Reports have shown that vitamin E Scavenges for reactive oxygen species there by detoxifying their activities in various tissues. Researchers have reported the ability of vitamin E to inhibit or ameliorate chemicals and drugs mediated oxidative stress through ROS generation in the liver. This study reviewed reported hepatoprotective effect of vitamin E in humans and animals.

1.1. Hepatoprotective Effect of Vitamin E in Animals

Drug and chemical substances ingested by humans and animals are known to have adverse effects. Among these reported effects is hepatotoxicity. This could not be far from the involvement of the liver in drug and chemical metabolism. Continually chemical agents are being screened for hepatoprotective properties. Vitamin E is one of the agents that have received wide attention due to it reported hepatoprotective effect. Researches with animals showed that vitamin E has hepatoprotective property. It was reported that administration of vitamin E (35 mg kg^{-1} body weight) attenuated Lipopolysaccharide (10 mg kg^{-1} body) induced oxidative stress (liver damage) by reducing levels of MDA, restoring the levels of glutathione superoxide dismutase and catalase. The modulation of these biochemical parameters led to the amelioration of hepatic architecture (Bharrhan *et al*., 2010).

The ability of vitamin E to reverse or prevent chemical agents induced hepatoxicity was demonstrated by Khalifa *et al*. (2009), he and co-workers showed that 0.2g kg^{-1} day^{-1} of vitamin E normalized aspartate aminotransferase and alanine aminotransferase levels elevated by carbon tetrachloride in rats. Liu *et al*. (1995) proved that pre treatment of mice with water soluble emulsion of vitamin E significantly inhibited acute hepatic injury induced by carbon tetrachloride in mice. Fariss (1991) also reported the hepatoprotective effect of vitamin E on cadmium induced toxicity. Administration of vitamin E with carbon tetrachloride caused marked amelioration of the severity of hepatic alterations in rats induced by carbon tetrachloride. These reports agreed with the findings of Fariss *et al*. (1993). Fariss and co-reseachers revealed that administration of 100 mg kg^{-1} body weight of hemisuccinate esters of tocopherol to carbon tetrachloride intoxicated rats showed a powerful protective effect against carbon tetrachloride induced hepatotoxicity. Investigation showed that vitamin E at concentrations of 50, 100 and 225 mm produced significant hepatoprotective effect against carbon tetrachloride induced toxicity in liver cells from BRL3A cell line by lowering the leakage of intracellular enzymes, reducing the oxidation of proteins and decreasing incidence of apoptosis (Kamel *et al*., 2010).

Vitamin E has exhibited great protective ability against monosodium glutamate and chemical agents induced hepatotoxicity. Research showed that 0.2 mg kg^{-1} bwt of vitamin E coadmistered with 0.6 mg kg^{-1} bwt monosodium reduced oxidative stress and hepatotoxicity induced by monosodium glutamate in rats via

normalisation of activities of aspartate aminotransferase and alanine aminotransferase. Farombi and Onyema (2006) reported that administered vitamin E reduced lipid peroxidation in the liver of rats treated with monosodium glutamate. Vitamin E was shown to confer protection against formaldehyde and monosodium glutamate induced hepatotoxicity and oxidative stress in rats (Gulec *et al*., 2006; Onyema *et al*., 2006). Kalender *et al*. (2005) showed that oral administration of 200 mg kg^{-1} of vitamin E twice a week to diazinon intoxicated rats for 1, 4 and 7 weeks decreased diazinon induced hepatoxicity. Serum biochemical changes and histopathological changes in the liver were normalized. Similar observation was reported in mice where vitamin E ameliorated organophosphorus insecticide (diazinon) induced oxidative stress in mice liver (El-Shenawy *et al*., 2010). The hepatoprotective effect of vitamin E was also observed in melathion induced hepatotoxicity in rats. Al-Othman *et al*. (2011) evaluated the protective effect of vitamin E in melathion induced oxidative damage in the liver and kidney of rats. He and co-workers observed that vitamin E was effective in alleviating oxidative damage in liver of rats. Vitamin E was able to reverse melathion induced increase in aspartate aminotransferase and alanine aminotransferase levels in rats.

Giray *et al*. (2001) reported that pretreatment of rats with vitamin E provided significant protection against the elevation of MDA concentration in cerebral and hepatic tissues induced by cypermethrin. Atessahin *et al*. (2005) posited that treatment with vitamin E reduced sensitivity to cypermethrin induced oxidative stress in rat liver. The above observations agreed with the reports of some investigators, that administration of vitamin E may be useful in controlling the hepatotoxic effects of insecticide and chemical agents (Tokuda and Takenchi, 1995; Adal *et al*., 1999; Aldana *et al*., 2001). Vitamin E was also evaluated to be effective against clinically-used drugs-induced hepatotoxicity in animal models. Vitamin E was reported to demonstrate a remarkable hepatoprotective effect against rifampicin induced hepatotoxicity in rats. Pretreatment with vitamin E before rifampicin administration showed a significant decrease in levels of aspartate aminotransferase and alanine aminotransferase when compared with rifampicin treated rats (Awodele *et al*., 2010). Pretreatment with high dose vitamin (E 100 mg kg^{-1}) intraperitonealy for 2 months prevented both biochemical as well as histopathological evidence of hepatic damage induced by isoniazid and rifampicin when coadministered to rats. Coadministeration of amiodarone and vitamin E ameliorated amiodarone induced hepatotoxic effect in rats (Zaki and Eid, 2009). This is in agreement with the work of Kamel *et al*. (2010) who posited that vitamin E showed significant hepatoprotective effect by lowering the leakage of intracellular enzymes, reducing the oxidation of proteins and decreasing incidence of apoptosis. Administration of 6 mg kg^{-1} bwt of cisplatin to rats induced liver damage with increase peroxidation. This was inhibited by intraperitoneally administered 100 mg kg^{-1} bwt of vitamin E via significant improvement in antioxidants concentrations in treated rats (Naziroglu *et al*., 2004). In a study to evaluate the protective role of vitamin E against valporic acid induced liver damage during gestation, vitamin E 250 mg kg^{-1} and valporic acid 300 mg kg^{-1} were coadministered in days 8, 9 and 10 of gestation. It was observed that vitamin E decreased valporic acid induced perivenucular dilatation, micro vesicular steatosis, degeneration of hepatocytes and necrosis (Baran *et al*., 2004). Research showed that vitamin E offered hepatoprotective effect against 2, 3, 7 and 8 Tetrachlorodibenzo-p-Dioxin (TCDD) induced hepatotoxicity (Ghazi-Khansari *et al*., 2005).

Metallic elements like copper, lead, cadmium and iron are known to induce hepatotoxicity in experimental animal studies and clinical experiences (Venkasteswara *et al*., 2006). Studies showed that vitamin E in a dose level of 20 mg kg^{-1} administered to rats was reported to reduce copper and lead levels in serum and tissues as well as normalised aspartate aminotransferase and alanine aminotransferase levels in lead and copper intoxicated rats (Mostafa *et al*., 2010). Omara and Bagchi (1993) and Bagchi *et al*. (1993) reported that vitamin E has a protective ability against iron toxicity and iron-induced hepatic depletion of vitamin E in mice. Vitamin E may protect against liver damage, prevent fibrosis and cirrhosis progression in metal overload state (Sokol, 1996). Hepatotoxicity induced in albino mice by orally administered sodium fluoride (10 mg kg^{-1} bwt) and Aluminum chloride (200 mg kg^{-1} bwt) was reported to be reversed by treatment with oral vitamin E (2 mg kg^{-1} day^{-1}) (Chinoya *et al*., 2004). Study also revealed that treatment of rats with combined dose of 2 mg kg^{-1} of cadmium chloride subcutaneously and vitamin E 10 mg kg^{-1} orally decreased hepatotoxicity with respect to cadmium chloride treated rats (Gaurav *et al*., 2010). This is in agreement with the report of Al-Attar (2010) who administered vitamin E, 50 IU kg^{-1} body weight five times weekly. He observed improvement in biochemical and histopathological changes induced by lead, mercury, cadmium and copper

in the liver of albino rats. Vitamin E treatment reduced lipid peroxidation by 39% and increased cell viability by 12% in an acute toxicity study of ferrous sulphate in rat hepatocytes suspension (Lawrence and Bricker, 2002).

It was also reported that administration of alpha tocopherol Succinate to a rat suspension exposed to toxic cadmium concentration completely protected the hepatocytes from cadmium induced injury and lipid peroxidation (Fariss *et al*., 1991). Similar observation was reported by Rao *et al*. (2006), who observed that vitamin E supplementation ameliorated chromium and nickel induced oxidative stress in mouse liver. Vitamin E exhibited hepatoprotective potential by decreasing lipid peroxidation, hepatic porphyrin and 8 Hydroxydeoxyguanosine (8-OHDG) in the Liver of hexachlorobenzene and Iron treated mice (Horvath *et al*., 2001). Brown *et al*. (1997) showed that vitamin E, decreased hepatic fibrogensis by reducing thiobarbituric acid (an index of lipid peroxidation) and hepatic hydroxyproline in chronic iron overload rats. Antioxidant (Vitamin E) treatment during experimental hepatic fibrosis, arrested fibrogensis and completely prevented iron induced hepatic cirrhosis mainly through inhibition of non parenchymal cell proliferation induced by iron (Pietrangelo *et al*., 1995). This is in agreement with the report of Coskun *et al*. (2000), he and co workers revealed the antioxidant and hepato protective activity of vitamin E in experimental endotoxemic rats. Esodergren *et al*. (2001) evaluated the hepatoprotective effect of vitamin E and concluded that both non-enzymatic and enzymatic lipid peroxidation during experimental hepatic oxidative injury were suppressed by dietary vitamin E supplementation in rats.

Ethanol which is a known inducer of oxidative stress in the liver responded to the antioxidant (hepatoprotective) effect of vitamin E using animal model. It was observed that administration of vitamin E 400 IU to rats intoxicated with ethanol normalised thiobarbituric acid reactives, superoxide dismutase activity and restitution of liver weight. This showed that vitamin E has hepatoprotective effect against ethanol-induced acute liver injury (Morales-Gonzalez *et al*., 2006). This agreed with the report of Ramirez-Farias *et al*. (2008) who showed that short term vitamin E supplementation attenuated lipid peroxidation and protected against liver injury and dysfunction in an ethanol intoxication model. Hepatoprotective effect of vitamin E was further buttress by Sanchez *et al*. (2010). Lima and coworker showed that vitamin E attenuated hepatotoxic effect of chronic ethanol intake. Reported protective effect of vitamin E against ethanol induce hepatotoxicity by some authors is at variance with the report of Pirozhkov *et al*. (1992) who showed that vitamin E supplementation did not offer protective effect against chronic ethanol and cocaine induced hepatotoxicity. Vitamin E was also shown not to have considerable protective effect on bilirubin, transaminases, glutathione, lipid peroxidation and collagen contents in the liver of rats subjected to biliary obstruction (Pablo and Moreno, 2004). Botje *et al*. (2011) revealed that vitamin E ameliorated oxidative stress in the liver and lungs of broilers. Dietary supplementation with vitamin E at a level 6 times higher than the minimum daily requirement for guinea pigs, increased protection against hepatic lipid peroxidation without depressing endogenous antioxidant activities (Cedenas *et al*., 1995).

Comparative evaluation of vitamin E and vitamin C showed that vitamin E gave a better hepatoprotective effect than vitamin C (Uboh *et al*., 2012). Vitamin E was further shown to give a better hepatoprotective effect than cimetidine 120 mg kg^{-1} administered intraperitoneally (Tayal *et al*., 2007). The efficacy of vitamin E was shown to be enhanced when coadministered with some antioxidants or agents that have hepatoprotective properties. Combined treatment with ranitidine and vitamin E protected rat liver from rifampicin induced liver injury (Sapakal *et al*., 2011). Treatment of male rabbits with vitamin C (1 mg 100 g^{-1} body weight) and vitamin E (1 mg/100 g body weight) for 2, 4, 6 and 8 weeks ameliorated ethanol induced hepatomegaly, apoptic DNA fragmentation in hepatocytes, normalized alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and LDH activities (Shalan *et al*., 2007). In a histological examination of the protective effect of vitamin E and vitamin C in cisplatin induced hepatotoxicity, coadministeration of vitamin E (5 mg kg^{-1}) and vitamin C (8 mg kg^{-1}) to rats for 3months reduced cisplatin induced hepatotoxicity (Tarladacalisir *et al*., 2005). Co administration of vitamin E (100 mg kg^{-1} bwt) and selenium (0.1 mg kg^{-1} bwt) to albino rats reduced melathion induced hepatotoxicity by decreasing liver necrosis. Levels of aspartate aminotransferase, alanine aminotransferase and alkalinephosphatase were normalised (EL-Desoky *et al*., 2012)

Oyinbo *et al*. (2006) investigated the hepatoprotective effect of vitamin C and E on ethanol induced hepatotoxicity in rats. They reported that co administration of 200 mg vitamin C and 200 mg vitamin E for 7 days to ethanol intoxicated rats decreased hepatic

degeneration and necrosis. Significant decrease in serum transaminases and serum bilirubin was observed. Combined dose of vitamin E (200 mg kg^{-1} day^{-1}) and vitamin C (200 mg kg^{-1} day^{-1}) administered to dimethoate intoxicated guinea pigs, ameliorated dimethoate induced hepatotoxicity (A1-Awthan *et al*., 2012). The hepatoprotective effect of vitamin E increased when combined with glutathione and N-acetylcysteine. This combination reduced lipid peroxidation by 94% in iron-treated cells and 98% in iron-diethylmaleate treated cell in a suspension of rat hepatocytes (Lawrence and Bricker, 2002). These reports are at variance with the findings of Asare *et al*. (2009) who showed that coadministeration of vitamin A and E could not prevent hepatic damage in dietary Iron treated wistar rats. Vitamin E and glycine were reported to have hepatoprotective effect during the early phase of liver regeneration in rats (Parra-Vizuet *et al*., 2009).

1.2. Hepatoprotective Effect of Vitamin E in Humans

Research showed that vitamin E produced tremendous improvement when administered to patients with non alcoholic steatohepatitis and in obese children with fatty non alcoholic liver disease. This can be seen from the report of Clinical Research Network who found that 96 weeks treatment with vitamin E in non diabetic and nonalcoholic steatohepatitis patients resulted in significant improvement (Chalasani *et al*., 2008). In a randomly assigned 247 adults with non alcoholic steato hepatitis without diabetes, 84 received vitamin E at a dose of 800IU once daily for 9 weeks. It was discovered that vitamin E therapy was associated with a significant higher rate of improvement than placebo. Serum alanine, aspartate aminotransferase and hepatic steatosis, lobular inflammation were reduced (Sanyal *et al*., 2010). Vitamin E was reported to produce significant decrease in steatosis in nonalcoholic steatohepatitis patients. This agreed with the report of Chalasani *et al*. (2008) who posited that administration of vitamin E led to improvement in hepatic history in non diabetic adults with biopsy proven non alcohol steatohepatitis. An open-label pilot trial of antioxidant therapy with vitamin E at 400-1200 IU/day showed improvement in serum aminotransferase in children with non alcoholic steatohepatitis (Lavine, 2000). Hasegawa *et al*. (2001) reported improvement in non alcoholic steatohepatitis after one year of administration of vitamin E. Improvement in fibrosis was also reported after treatment with vitamin E but inflammation did not improve.

In a pilot study, 28 children with obesity related hyper transaminasemia and bright liver were treated with a low calorie diet associated with vitamin E 400 mg day^{-1} for 2 months and 100 mg day^{-1} for 3months. Result showed improvement in transaminases level and disappearance of bright liver (Vajro *et al*., 2004). In a pilot study where some obese children with non alcoholic fatty liver disease were administered vitamin E capsule at a dose of 100 mg day^{-1} for one month. It was observed that vitamin E and life style intervention produced improvement in liver function (Wang *et al*., 2008). In a prospective study where patients with non alcoholic fatty liver disease were treated with vitamin E 400mg daily and weight management programme, it was observed that vitamin E therapy is effective in ameliorating transaminasemia (Madan *et al*., 2005). In a correlating study, Ramirez-Farias *et al*. (2008) revealed that short-term antioxidant supplementation attenuated lipid peroxidation and protected against liver injury and dysfunction. It is known that patients with cystic fibrosis tend to have reduced serum concentration of vitamin E and therefore at risk of developing neurological complications associated with vitamin E deficiency. Some reported clinical trials showed that vitamin E could be of clinical benefit to patients with hepatitis B or C. Andreone *et al*. (2001), showed that 7 of 15 patients treated with vitamin E showed normalized alanine aminotransferase levels, 8 of 15 became negative for hepatitis B virus DNA and 3 of 7 HBeAg positive patients achieved seroconversion which differed significantly from placebo group. This is supported by the report of Gerner *et al*. (2008). Gerner *et al*. (2008) showed that vitamin E was well tolerated in children and adolescents with chronic hepatitis B and yielded a higher HBeAg seroconversion rate than patients treated with placebo. Among 69 children treated with vitamin E, 23.2% became negative for serum markers of viral replication (HBeAg and HBV DNA). In patients with chronic hepatitis C, high dose vitamin E significantly reduced oxidative stress but did not affect liver enzymes or histological features of liver injury (Houglum *et al*., 1997). It is known that vitamin E improved aminotransferase status in patients with various liver diseases such as hepatitis C, haemochromatosis and Wilson's disease (Herbay *et al*., 1996; 1997). In a study involving 199 patients with pulmonary tuberculosis accompanied by liver diseases receiving antitubercular therapy, inclusion into the treatment schedule of vitamin E produced hepatoprotective and antioxidant benefits (Shakun and Blikhar, 1986).

In humans it was shown that vitamin E formed synergy with some chemical agents. This can be seen from a placebo controlled double blind study by Harrison and colleagues who randomized 49 patients with biopsy-proven non alcoholic steatohepatitis. These patients

received vitamin E 1,000 IU qd, vitamin C 100 mg qd and placebo for 6 months. Biopsy revealed significant improvement in score although inflammation grade remained unchanged. A synergistic effect was observed when it was administered with Pioglitazone (Sanyal *et al*., 2004). In an open-label prospective randomized study, sixty-four patients with non alcoholic fatty liver disease were evaluated. Twenty eight patients received vitamin E plus vitamin C while 29 patients received ursodeoxycholic acid. It was found that vitamin E and C combination was effective in patient with non alcoholic fatty liver disease and was as effective as ursodeoxycholic acid (Ersoz *et al*., 2005). In a retrospective single centre study of 68 patients with non alcoholic steatohepatitis, 38 patients were administered vitamin E (400-800IU/day) and vitamin C (500-1000 mg day^{-1}) while 30 patients served as control. It was observed that vitamin E and C produced significant improvement in aminotransferases (Babich, 2010). Addition of vitamin E to interferon and ribavirin prevented the progression of fibrosis in chronic hepatitis C patients when compared with interferon and ribavirin combination (Wazir *et al*., 2008). Optimum levels of both vitamin C and vitamin E, simultaneously needed for protection against oxidative stress in the liver are much higher than the minimum daily requirements (Cedenas *et al*., 1995).

Furthermore there are some observations that are at variance with the above reports. In these observations vitamin E did not exhibit any hepatoprotective effect in humans. One of these observations was seen in a control clinical trial where vitamin E (800 IU day^{-1}) was administered to randomized 16 adults subjects for 3 months, vitamin E did not show any benefit on alanine amino transferase level (Kugelmas *et al*., 2003). Similar observation was reported when vitamin E (400 mg and 100 mg kg^{-1} day^{-1}) was administered for 2 and 3 months respectively to 28 obese children (Vajro *et al*., 2004). No beneficial effect of vitamin E on liver function in patients with mild to moderate alcoholic steatohepatitis was found (Kawanaka *et al*., 2004). Supplementation with oral vitamin E (10 mg kg^{-1} day^{-1}) for one month and 200 mg kg^{-1} day^{-1} for 3 months showed that patients with cystic fibrosis and abnormal liver function do not require increase supplement with vitamin E when compared with those with normal liver function (Stead *et al*., 1986).

1.3. Hepatoprotective Mechanism of Vitamin E

Many researchers have given explanations for the mechanism that confers hepatoprotective ability on vitamin E. Vitamin E is a lipid soluble antioxidant that scavenges for reactive oxygen species (ROS). This could be associated with it structure as reported. The structure of vitamin E makes it a highly effective antioxidant, readily donating hydrogen from the hydroxyl group on the ring structure to free radicals and rendering them inactive. Vitamin E is fat soluble and is primarily located within the phospholipids bilayer of the cell membranes where it has a major biological role in protecting polyunsaturated fats and other components of the cell membranes from oxidation by free radicals (Hicman and MacDonald, 2007).

Among the eight fat-soluble derivatives, alpha tocopherol predominates in many species and has the highest biological activity with the active site being the 6-hydroxyl group. The side chain in the 2-position facilitates the incorporation and retention of vitamin E in biomembranes, so that the 6-position is optimal for scavenging free radicals and terminating lipid peroxidation (Bjorneboe *et al*., 1990).Vitamin E has been reported to express two important functions in the membranes: preventing ROS damage in polyunsaturated fatty acids as aliposoluble antioxidant and acting against damage caused to phospholipids as a membrane-stabilizing agent (Bradford *et al*., 2003). In addition, vitamin E is known to act by breaking the antioxidant chain that prevents ROS-produced cell membrane damage (Brigelius-Flohe and Traber, 1999). Factor *et al*. (2000) demonstrated that vitamin E can directly reduce ROS production by interfering with the union between the membrane and the NADPH oxidase complex.

2. CONCLSSION

In this review it was observed that vitamin E has hepatoprotective effect in animals. It hepatoprotective effect in humans leaves more room for evaluation due to discrepancies in some reports.

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