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# Natural Remedies of Prophetic Medicine are Promising in the Management of Viral Hepatitis: Towards Better Preventive and Therapeutic Outcomes (A Review Article)

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**Abstract** Natural remedies of prophetic medicine include ajwa dates of Aliah (from Al-Madinah, Saudi Arabia), nigella sativa, costus (saussurea lappa), oral honey, sana (senna, cassia angustifolia), sanut (fennel, phoeniculum jugulare) and others. All are rich in dozens of natural antioxidant ingredients that counteract oxidative stress-induced cellular and tissue damage commonly encountered in viral hepatitis patients. Ajwa dates surprisingly reverted the malignant phenotype of hepatocellular carcinoma cells into a near normal phenotype of the normal hepatocytes. This is in an exact agreement with prophetic medicine where the prophetic hadith recommended Ajwa date fruit as a treatment and cure for toxins. Antioxidant-oxidants antagonism is the strongly suggested therapeutic mechanism. Thymoquinone, carvacrol and α-pinene are among the major antioxidants in nigella sativa. Costunolide, santamarin and dehydrocostus lactone are major antioxidants present in costus. The preventive and therapeutic benefits of such remedies to the liver include: combating hepatitis viruses, suppressing hepatitis inflammatory responses, exerting potent antioxidant effects, exerting potent antitoxic effects, exerting potent anti-fibrotic effects, exerting hepatic tissue repair, suppressing carcinogenesis, reverting hepatocellular carcinoma cells to normal or near normal phenotype and enhancing the natural immunity. All that is discussed with some detail in this review article.

***Keywords:*** *Prophetic medicine, hepatitis viruses, nutritional prophetic medicine remedies, Ajwa dates, nigella sativa, costus and oral honey*

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## 1. Introduction

Prophetic medicine is the medical knowledge gained from teachings, habits (sunnah), ahadith (sayings), deeds, and agreements by Prophet Muhammad Peace be upon him. Prophetic medicine has both preventive and therapeutic aspects. All prophetic medicine remedies are natural antioxidants even Al-hijamah (wet cupping therapy of prophetic medicine) through excretion of excess oxidants causing body clearance of such causative pathological substances. Currently, topics of prophetic medicine remedies are a fruitful arena for novel studies in the medicl literature.

Natural remedies of prophetic medicine (NRPM) include ajwa dates of Aliah (from Al-Madinah, Saudi Arabia), nigella sativa, costus (saussurea lappa), oral honey, sana (senna, cassia angustifolia), sanut (fennel, phoeniculum vulgare Mill) and other [1,2,3]. Liver cells' protection through keeping the liver cells away from toxins is an important therapeutic target in hepatic patients. The need for that increases when there is a necessity to intake a known hepatotoxic drug while liver functions are compromised e.g. in patients having viral hepatitis. In conditions of liver cell failure, almost most drugs are contraindicated for the concern regarding status of liver cells. Some NRPM can be regarded as food and as remedies e.g. oral honey. Hepatoprotection exerted by NRPM (as we will discuss below) may occur secondary to antioxidant effects, decreasing adverse or toxic effects of concomitantly administered drugs, preserving the hepatocytes structure and functions against the harmful effects of hepatotoxins, protecting hepatocytes against antimicrobials (viruses, bacteria and fungi), chemoprevention against hepatocarcinogenesis and others.

## 2. Hepatoprotective Effects of Dates and Ajwa Date Fruit Extract (Figure 1A)

Dates (Phoenix dactylifera L.) are both a fruit and a food. They are considered by many people as a natural, complete and cheap diet due to their high carbohydrates content (total sugars may be 44-88% and are mainly fructose and glucose), lipid content (0.2-0.5%), protein content (2.3-5.6%), high percentage of dietary fibers (6.4-11.5%), minerals (e.g. selenium), pectin content (0.5-3.9%) and vitamins e.g. vitamin C, and vitamins B1(thiamin), B2 (riboflavin), nicotinic acid (niacin) and vitamin A. Selenium is present in dates and activates many antioxidant enzymes, protects against carcinogenesis and enhances the functions of the immune system. Dates are a good source of antioxidants that are mainly carotenoids and phenolic substances. Palm seeds contain 14 types of fatty acids e.g. unsaturated fatty acids that include palmitoleic, oleic (41.1 to 58.8%), linoleic and linolenic acids [4,5,6,7] Dates exert beneficial effects on serum triacylglycerol and oxidative stress i.e. dates do not worsen serum glucose or lipid/lipoprotein patterns and thus can be considered as an anti-atherogenic nutrients [4,5,6]. Dates combined with nigella sativa were reported to protect the hepatocytes structure and liver functions against aflatoxin B-1-induced hepatotoxicity [8].

Oxidative stress is crucial for hepatocarcinogenesis and can be relieved by NPMR particularly Ajwa dates [9]. Ajwa date fruit was reported to revert the malignant histopathology induced by the genotoxin diethylnitrosamine to a normal histological phenotype in a dose-dependent manner via increasing antioxidants, decreasing inflammatory cytokines and counteracting the malignant phenotype [10]. Moreover, hepatotoxicity induced by dimethoate is characterized by the presence of vacuolization, necrosis, congestion, inflammation, and enlargement of the blood sinusoids in liver section. Pretreatment with date palm fruit extract prevented oxidative stress-induced hepatotoxicity and restored the liver damage induced by dimethoate (evidenced by inhibition of hepatic lipid peroxidation, improvement of antioxidant enzymes e.g. superoxide dismutase, glutathione peroxidase and catalase activities and of histopathology changes) [11]. Abdu et al. investigated the antitoxic effects of ajwa dates of Aliah (from Al-Madinah Al-Munawwarah, Saudi Arabia) against ochratoxin A. Ochratoxin A is well-known to cause global hepatocytes congestion, dilatation of the central veins and sinusoidal spaces, enlargement of periportal areas, lymphocytic infiltration, swelling and degeneration of the hepatocytes and focal necrosis. Clinically, the raised liver enzyme levels and bilirubin are usually evident. Pretreatment with ajwa date extract was reported to protect against all that and to decrease the toxicity of ochratoxin A to the minimum with absence of the above-mentioned clinical picture [12]. Moreover, Ajwa Date protected the proximal tubules and decreased the severity of the lesions. Ajwa date had protective effects against ochratoxin-induced nepherotoxicity that might lead to kidney failure [13].

Interestingly, researchers in Taibah University in Saudi Arabia were pioneering in investigating the antioxidant and tissue-protective effects of ajwa extract (dates from Al-Madinah Al-Munwwarah, Saudia Arabia) against lead acetate-induced toxicity. Lead acetate-induced toxicity caused the mitochondria to be severely swollen with disintegrated membranes in addition to severe tissue damage e.g. hepatotoxicity (hepatoportal and sinusoidal congestion, cloudy swelling & hydropic degeneration, cellular necrosis, inflammatory cellular infiltrate and cholestasis), nephrotoxicity (vascular congestion, cloudy swelling, obliteration of bowman's capsule, interstitial and tubular hemorrhage and focal tubular necrosis), cardiotoxicity (vascular congestion, cardiac muscle cloudy swelling, loss of striation and muscle necrosis) and pulmonary toxicity (congestion of alveolar capillaries, edema & thickening of alveolar walls and alveolar edema). The Ajwa date fruits extract caused hepato-protective and tissue protective effects through significant restoration of liver functions, kidney functions and levels of antioxidant enzymes [14]. Ajwa date fruits dramatically and effectively prevented and treated the acute diclofenac toxicity effects regarding the liver, lungs [15] and colon [16] where Ajwa dates prevented against the harm of drug overdosage and treated the toxicity within a short period of time. Proved therapeutic, antitoxic and nutritional benefits of Al-Alia date fruit are in agreement with their therapeutic benefits reported in prophetic medicine and the prophetic ahadeeth: "whoever eats seven ajwa date fruits in the early morning, he will not be harmed by a toxin or a magic during this day" Sahih Al-Bukhari (Explanation of Fath Al-Bari), Book: Medicine, Chapter: Medicine with dates for magic, (10/249), No. (5768) and the prophetic hadith: "In Al-Aliah Ajwa date fruit, there is a cure or an antitoxin when eaten in the early morning" Sahih Muslim (Explanation of Al-Nawawi), Book: Drinks, Chapter: The virtue of Medina dates, (7/3153), No. (5240). Alia is a cure, or it is an antidote, first reel. And and the prophetic hadith: "Ajwa date fruit if from paradise and it is a cure from toxin". Narrated by Al-Tirmidhi (2068), Al-Nasa'i in ((Al-Sunan Al-Kubra)) (6670), Ibn Majah (3455), and Ahmed (8002).

## 3. Hepatoprotective Effects of Oral Honey (Figure 1B)

Oral honey was reported to protect the liver against carbon tetrachloride-induced hepatonephrotoxicity in experimental animals. Such hepatic protection may be related to their antioxidant properties [17]. Oral honey was reported to protect the liver and kidney also against aflatoxins (chemical carcinogens of the liver) and ochratoins, to inhibit the harmful and genotoxic effects of mycotoxins and to improve the gut microflora [18].

In another study, oral honey was reported to significantly increase the elimination rate of blood ethanol, reduce the alcohol detoxication time (the time taken to attain zero blood alcohol level) and decrease the degree of alcohol intoxication (the peak blood alcohol level) by 30% and 4.4%, respectively [19]**.** Honey was reported to contain active ingredients that possess potent anti-oxidant and cancer chemopreventive activities e.g. chrysin. Chrysin was reported to abrogate early hepatocarcinogenesis and induce apoptosis in N-nitrosodiethylamine-induced preneoplastic liver nodules in the rats [20].

Moreover, co-administration of oral honey with hepatotoxic and tissue-toxic drugs e.g. pentylenetetrazole were reported to protect the liver and other tissues against drug-induced toxicity. Pentylenetetrazole is a common convulsant agent used in animal models to study the mechanisms of seizures [21]. Histological tissue analysis of Pentylenetetrazole-treated animals at 50-80 mg/kg revealed that the lungs exhibited inflammatory peribronchiolar and perialveolar infiltrates. Hepatotoxicity was manifest causing: mild loss of trabecular architecture of the hepatocytes, presence of multi-vesiculated hepatocytes (steatosis) and inflammatory infiltrates in hepatic parenchyma. Drug-induced tissue toxicity involved also the cardiac fibers (were markedly separated) and the testicular stratified epithelium of the seminal tubules (lost its normal structure with tubular epithelium loss together with absent spermatids, spermatogonia and Leydig cells). On administration of Pentylenetetrazole with oral honey, tissue protection was significant and promising. Apart from some inflammatory cardiac infiltrates, all other tissues were normal i.e. the lungs had no inflammatory infiltrates [22].

Moreover, natural honey protected the ultrastructure of the hepatocytes during experimental obstructive jaundice [23]. Supplementation of oral honey in the presence of obstructive jaundice was reported to ameliorate the bacterial translocation (predominantly detected in mesenteric lymph nodes) and improve the ileal morphology [24]. Interestingly, propolis (of honey) protected the liver cells against oxidative stress and improved hepatic histomorphology in experimental obstructive jaundice. Propolis significantly decreased the hepatocytes apoptosis, hepatocytes enlargement, canalicular dilatation and edema [25]. Both honey and propolis exerted significant antibacterial activity against staphylococcus aureus [26]. More interestingly, oral honey protected the liver and other tissues e.g. heart, brain and kidneys against trichlorfon-induced toxic effects [27]. Moreover, oral administration of honey bees royal jelly (100 and 250 mg/kg of body weight) caused a significant suppression of the mutagenic effects of cadmium in experimental animals. Interestingly, natural honey was reported to be a potential antioxidant against cadmium-induced genotoxicity and oxidative stress [28].

In healthy subjects, honey increased serum antioxidant agents as serum vitamin C concentration by 47%, beta-carotene by 3%, uric acid by 12%, and glutathione reductase by 7%. Honey increased serum iron by 20% and decreased plasma ferritin by 11%. Natural honey increased the percentage of monocytes by about 50%, and increased lymphocyte and eosinophil percentages slightly. Honey reduced serum immunoglobulin E (indicator of allergic conditions) by 34% and increased serum copper by 33% and improved liver function tests (decreased aspartate transaminase by 22% and alanine transaminase) by 18%. Honey markedly reduced lactic acid dehydrogenase by 41%, decreased creatinine kinase by 33%, and reduced fasting blood sugar by 5% [29]. In addition, total food restriction with 50% honey feeding caused a greater decrease in fasting blood glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and triacylglycerol i.e. honey feeding during total food restriction significantly modifies and ameliorates the biochemical and hematological changes observed after acute blood loss [30].

## 4. Nigella Sativa (black Cumin, Black Seed, Happah Sawdaa, Happat Al-baraka) (Figure 1C)

Nigella sativa (NS) was reported to significantly decrease hepatitis viral load, improve response to oxidative stress and improve the clinical condition and glycemic control in diabetic patients [31]. NS is a nutritional supplement that improves malnutrition associated with metabolic diseases e.g. Refsum's disease [32]. NS exerts hepatoprotective effects against hypervitaminosis A and enhances the immunological functions (potent inducer of IgG and IgM) [33]. NS exerts many therapeutic benefits against cholestatic liver injury in bile duct ligated rats possibly through attenuation of the enhanced neutrophil infiltration and oxidative stress in the liver tissue [34]. Moreover, NS exerted potent therapeutic effects and antioxidant effects against lipopolysaccharides-induced inflammation [35]. Thymoquinone (an active ingredient of NS) was recently reported to enhance the anticancer activity and reduce the hepatotoxicity of the anticancer agent (CB 1954) [36]. Thymoquinone was reported to attenuate the liver fibrosis via PI3K and TLR4 signaling pathways in activated hepatic stellate cells [37]. NS (5 mg/kg) markedly increased the weight gain and improved the glycemic control (fasting blood glucose). Histopathologically, NS partially recovered the hepatic glycogen content and protected pancreatic islet cells against streptozotocin-induced diabetes as evidenced by increased number of islets cells and islets diameter compared to control [38].

Interestingly, in healthy volunteers, NS capsule (500 mg twice daily for nine weeks) resulted in enhancing memory, attention and cognition while preserving the biochemical markers of cardiac, liver and kidney functions [39]. NS exerts potent antiviral and antimicrobial effects against hepatitis viruses, schistosoma mansoni and fungi. NS protected against murine cytomegalovirus infection [40]. During bilharziasis infection (a serious parasitic disease causing liver cirrhosis and hepatocellular carcinoma), NS protected against liver damage induced by Schistosoma mansoni where NS reduced the worm number and ova deposition, potentiated praziquantel-induced anti-schistosomiasis effects and protected liver functions during bilharzizsis. Moreover, NS was reported to exert strong biocidal effects against all the developmental stages of schistosoma parasite (miracidia, cercaria and adult worms) where NS disturbed the antioxidant enzymes of adult worms and killed them by an oxidative stress mechanism [41]**.** In addition, NS exerts potent in vivo antifungal effects [42].

NS has potent antitoxic effects. NS helped in resolution of hepato-renal toxicity induced by the toxin bromobenzene as it enhanced the hepato-renal protection mechanism, reduced disease complications and delayed disease progression. Histologically, that was evidenced by diminution of collagen fibers content and improvement

in liver and kidney architectures [43]. NS has hepatoprotective effects against isoniazide-induced hepatotoxicity in rabbits [44]. Interestingly, NS supplementation at higher doses (e.g. 1 g/kg) for 28 days caused no changes in liver functions and did not cause hepatotoxicity [45].

NS has a strong anticancer effect as methanolic extract of NS seed affected glyco-regulatory enzymes in experimental hepatocellular carcinoma and exerted chemo-preventive effects against the progression into liver malignancy. NS is a potent antioxidant (prevent loss of hepatic GSH in toluene-induced oxidative stressed) [46]. Macerated extract of NS seeds exerted protective effects against radiation-induced liver damage and tissue damage, oxidative stress and biochemical alterations due to antioxidant properties of NS extract and its ability to scavenge free radicals Velho-Pereira. Interestingly, thymoquinone attenuated diethylnitrosamine induction of hepatic carcinogenesis through antioxidant signaling [47]. Thymoquinone-rich fractions of NS were tissue-protective and greatly improved plasma antioxidant capacity and expression of antioxidant genes in hypercholesterolemic animals [48]. Thymoquinone is a relatively safe compound, particularly when given orally [49]. In addition, NS was reported to exert hepatoprotection against liver toxins. Liver sections of aflatoxin-treated animals in intoxicated mice showed inflammation, necrosis, hyperplasia of kupffer cells and infiltration of mononuclear cells, dilation of sinusoids and disruption of hepatocytes. Thymoquinone (the main active ingredient of NS at 9 mg/kg) was able to recover glutathione content of the liver tissue. Thymoquinone treatment helped to normalize liver architecture with normalizing liver functions and biochemical findings [50]. Both NS oil and thymoquinone exerted protective effects against toxicity induced by the anticancer drug cyclophosphamide and protected the liver and other tissues against chemotherapy (cyclophosphamide)-induced hepatotoxicity [51]. Thymoquinone ameliorated acute endotoxemia-induced liver dysfunction in rats [52]. NS seed oil may be a good treatment for diabetes mellaitus, obesity and metabolic syndrome as it behaves as an agonist of PPARgamma [49]. NS exerts hypoglycaemic and immunity potentiating effects of Nigella sativa L. oil in streptozotocin-induced diabetic hamsters [53]. Thymoquinone supplementation induces quinone reductase and glutathione transferase in mice liver: possible role in protection against chemical carcinogenesis and toxicity [54].

NS exerts antimutagenic effects [55] and protects against DNA damage, mutagenesis, colon carcinogenesis and liver damage induced by azoxymethane [56]. Moreover, NS inhibits the effects of 20-methylcholanthrene-induced fibrosarcoma tumorigenesis [57]. NS was reported to inhibit benzo(a)pyrene-induced forestomach carcinogenesis in mice [58]. NS was reported to protect against cisplatin-induced toxicity in rats [59]. NS was also reported to protect both the maternal liver and embryo against free radical-induced damage in diabetic animals [60]. NS induces significant hyperfibrinogenemia, significant transient prothrombin time prolongation and thrombin time reduction [61].

Medical importance of black cumin (NS) as a hepatoprotector and antitoxin was confirmed as previously reported in more than one topic in hepatology and general medicine. In prophetic medicine, NS is equally important in the prophetic teaching and the prophetic hadith: “in the black cumin, there is a cure for every disease except for death”.

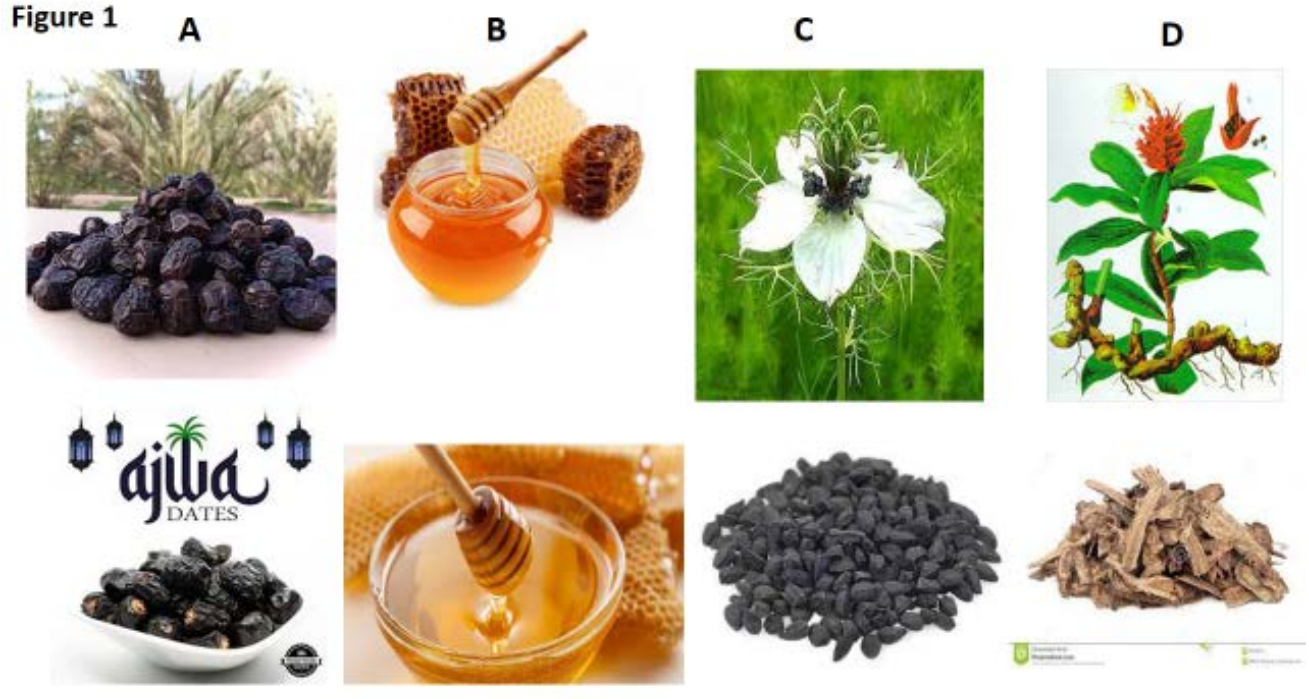


**Figure 1.** Medicinal plants of prophetic medicine exert powerful hepatoprotective effects. A. Ajwa date fruits. B. Natural honey (recommended for oral intake). C. Nigella sativa D. Costus speciosus (Saussurea lappa)

## 5. Costus (Saussurea Lappa Clarke) (Figure 1D)

Saussurea costus was reported to exhibit anti-inflammatory, anti-ulcer, anticancer and hepatoprotective activities [62]. Among the identified active components in saussurea lappa Clarke, costunolide and dehydrocostus lactone were reported to induce strong suppressive effects against the expression of HBsAg and HBeAg (a marker for hepatitis B viral genome replication in human liver cells in human hepatoma cells) [63]**.** In another study, the aqueous-methanolic extract of Saussurea lappa Clarke root was reported to protect the hepatocytes against D-galactosamine and lipopolysaccharide-induced hepatitis in mice [64]. This may be attributed to the potent antioxidant activity of the plant (probably due to the presence of chlorogenic acid) as a radical scavenger against DPPH, nitric oxide, superoxide radicals in addition to its ability to inhibit lipid peroxidation and glutathione oxidation [65].

Interestingly, costus was reported to exert anticancer activity. Dehydrocostus lactone, a medicinal plant-derived sesquiterpene lactone, was reported to induce apoptosis and endoplasmic reticulum stress in the liver cancer cells. Interestingly, there was a dramatic reduction in tumor volume (by about 50%) after 45 days of treatment [66].

## 6. Oxidative Stress, Ammonia Intoxication and Hepatic Cells Safety

Previously, El Sayed and Japanese co-researchers reported that inducing oxidative stress in cancer cells is closely related to depletion of energetics in those cancer cells [67,68,69,70]. In liver diseases, oxidative stress may be the underlying mechanism through which ammonia intoxication induces deleterious effects. Acute ammonia intoxication causes rapid (within 11 min) decrease in superoxide dismutase, catalase and glutathione peroxidase activities in the liver mitochondria, brain mitochondria, cytosol and in erythrocytes [71]. Confirmatory to that was the report by Kosenko et al. who reported that glutathione peroxidase, superoxide dismutase and catalase activities were decreased in cytosolic and mitochondrial fractions of liver and brain cells and also in blood red cells during ammonia intoxication [72,73]. Superoxide production in submitochondrial particles from the liver and brain was increased by more than 100% in both tissues. In both tissues, there was a diminished activity of the antioxidant enzymes and increased superoxide radical production that could lead to oxidative stress and cell damage, which could be involved in the mechanisms of acute ammonia toxicity [72,73].

Moreover, ammonia intoxication in vivo leads to increased formation of superoxide anion by submitochondrial particles. It also increases the activity of monoamine oxidase A (MAO-A) but not of MAO-B. Blocking NMDA receptors with MK-801 prevented ammonia-induced oxidative stress and MAO-A activation. Interestingly, ammonia intoxication did not cause $H_2O_2$ formation by mitochondria despite increased superoxide generation (due to its increased formation by the respiratory chain and by xanthine and aldehyde oxidases and decreased elimination by antioxidant enzymes). Prevention of ammonia-induced production of reactive oxygen species by MK-801 (antagonist of NMDA receptors) [71,74]. Interestingly, MK-801 was reported to prevent ammonia-induced changes in superoxide dismutase, glutathione peroxidase and catalase levels. Ammonia intoxication was reported to deplete glutathione and enhance lipid peroxidation. Taken together, this may indicate that ammonia-induced oxidative stress, changes in antioxidant enzymes and in superoxide formation in brain are mediated by excessive activation of NMDA receptors. This may support the idea that oxidative stress can play a role in the mechanism of ammonia toxicity [72,73,74]. Based on that, antioxidant ingredients in prophetic medicine remedies are quite promising in combating hyperammonemia and related liver conditions. In ammonia intoxication, ammonia-induced decrease of pyruvate (antioxidant)/lactate ratio is due to depletion of cellular glutamate by formation of glutamine (and glutathione) causing interruption of malate-aspartate shuttle (energy pathway for mitochondrial oxidation of reducing equivalents) [75]. This may decrease the pyruvate/lactate ratio in astrocytes (but not in neurons) [75,76]. This may decrease the entry of astrocytes into Krebs cycle causing decreased energy supply. Moreover, decarboxylation of pyruvate to form acetyl coenzyme A sharply decreased. Elevated ammonia concentrations also inhibit decarboxylation of alpha-ketoglutarate in the Krebs cycle causing energy failure in both neurons and astrocytes, which may cause a further decrease in energy supply in neurons and astrocytes during ammonia intoxication [75,76].

## 7. Recommendations and Future Perspectives

Careful understanding of pathophysiology of viral hepatitis, hepatic encephalopathy and liver diseases strongly supports the conclusion that NRPM may carry a big hope towards improving therapeutic outcomes for treating such diseases in light of the above-mentioned and previously published research studies.

## 8. Conclusion

Natural prophetic medicine remedies as Ajwa date fruits, nigella sativa and costus enhance the antioxidant capacity induced by Al-hijamah and antagonize oxidative stress effects conferred in liver diseases.

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## Conflict of Interest

The author declares no conflict of interest with anyone.

## Financial and Non-financial Competing Interests

The author declares that there is no financial or non-financial competing interests with any other partner. There is no financial benefits. The article is fully supported by the author.

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