



Mitochondrial Drug Delivery for the Liver Diseases: Comprehensive Review

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Article History:

Received on: 05.08.2019

Revised on: 10.11.2019

Accepted on: 18.11.2019

Keywords:

Autophagy,
Polymeric micelles,
Hepatic stellate cells,
Nanosystems,
Phytosomes

ABSTRACT

The role of mitochondria in liver targeting has been reviewed, which mainly focuses on acute and chronic. This is due to ethanol consumption, which causes liver damage. And how ethanol consumption affects liver disease. Autophagy, which explains the ROS production, in oxygen species, the changes that take place in it have been reviewed below and also helps us to understand the methods and drugs used in targeting the mitochondria differently. The mainly 2 types of targeting has been focused upon that is the active and passive targeting. The other different types of targeting are Hepatic stellate cells (HSCs) targeting, Hepatocytes, the drug is targeted, Polymeric micelles, the mitochondrial membranes are affected by the proteins, and the Nanosystems used for the delivery. The other drugs used for the study are lipophilic cation, liposomes, and the TAT peptides. The herbal treatment can also be used for the treatment of liver damage. The herbal extracts that are based on the phytosomes and the anti-oxidants that target on the hepatocytes cells.

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ISSN: 0975-7538

DOI: <https://doi.org/10.26452/ijrps.v11i1.1955>

Production and Hosted by

IJRPS | www.ijrps.com

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INTRODUCTION

The study of this article aims at the role of mitochondria in targeting liver disease on the drugs and the methods employed for the treatment of liver diseases. The metabolism of the mitochondria about the chronic hepatitis C virus. There are available different treatments. Still, the focus on the mitochondria is much effective than compared to any other form of targeting liver disease due to ethanol consumption is focused on treating different types of targeting.

After reviewing the different articles, some of the articles tell us that hepatitis is associated with severe hyperbilirubinemia, hepatic encephalopathy, and death. The RNA interference (RNAi) using short interfering RNA (siRNA) promises superior advantages to other drug development approaches given easy of design, high target selectivity, and expected low toxicity due to metabolism to natural nucleotide components by the endogenous cell system. Some of the other studies it shows on the aptamers the proteins and peptides used for treating the disease. One of the articles which say on focusing the mitochondrial targeting but only by the help of the anti-oxidants whereas the Increased oxidative stress and subsequent mitochondrial damage are important pathways for liver damage in chronic hepatitis C virus (HCV) infection; consequently, therapies that decrease mitochondrial oxidative damage may improve outcome (Gane *et al.*, 2010; Sugioka, 1994).

The article which explained to us based upon the ethanol consumption and the different type of the delivery, among which mitochondrial delivery is effective but not been explained in any of the articles referred the superoxides for the oxidation stress and

the radical formation that helps in the formation of mitochondrial targeting drug. Autophagy is the process of self-eating there are three different mechanisms which explains the three different magic bullet consideration.

It was reviewed on each device and different targeting types, namely the active targeting and passive targeting. The herbal medicines are phyto-somes and the vitamin C used for the oxidation of the lipophilic cation, and also the liposomes are used in the above article for the liver disease.

MATERIALS AND METHODS

Role of mitochondria in liver disease

It has been reported in Japan that there are about more than 1 million people who are infected from the hepatitis C virus. There are no studies carried out to know the change in the mitochondrial energy metabolism in the infected individual who is suffering from chronic liver disorder. Long back, it was noted that the mitochondrial respiration of the biopsied patients liver with the chronic hepatitis virus and liver cirrhosis. It was known that oxygen in the presence of glutamate and succinate decreased with the process of liver disease, which changes from chronic hepatitis to liver cirrhosis. It was interesting to note that cirrhosis had a more effect on the diabetic pattern in the 75-g glucose tolerance test (OGTT) later on it was seen, that the mitochondrial respiration decreased instantly in diabetic patients (Alipour *et al.*, 2007).

Different studies have been carried out to know that the dysfunction of mitochondria has a significant role in the continuation in the case of liver disease with the infection of Hepatitis C Virus. It has been reported HVC core mice that are the transgenic mice had dysfunction in the mitochondrial function and the excess production of Reactive Oxygen Species. It plays an active role in the metabolic pathway of several integrating networks. These signals damage the mitochondria indirectly or directly and cause activation of death receptors, which are mediated by the receptor pathway or the stress cascades.

The production of Reactive Oxygen Species by the MRC. Some of the oxidative reaction like mtFAO and TCA cycle they produce NADH and FADH₂, this is then reoxidized by MRC, and this causes conversion dinucleotide (NAD⁺) and flavin adenine dinucleotide (FAD) and other cycles of oxidation (Tandra *et al.*, 2011). The products of these reactions are attached for the ATP synthesis through the process of oxidative phosphorylation.

In the formed Reactive Oxygen Species, depletion

takes place for glutathione and alkylation of protein. These are involved in the different associated events with the no adaptive mitochondria, and also most of them lead to liver diseases.

One of the important mechanisms which have been taken place by the ROS is the factor for the modified lipid, and the protein component in the membrane of the mitochondria and also the lipid and protein modification takes place for the major mechanism of the injury that has been modulated by the ROS production in mitochondria. The hydrophilic, hydrophobic, structural, and the oxidative changes of the mitochondria with the alteration in the lipid-lipid and the lipid-protein with the permeability of the membrane with the transport and the receptor inactivation.

There are several roles taking place in the mitochondria, and the function of it remains as the production of adenosine triphosphate. Later the mechanisms were involved in starting series with the reactions, namely the biochemical type of results taking place in the Krebs cycle works for the transferring of electrons, which is so-called as mitochondrial respiration in the inner membrane of mitochondria. The cell survival is critical to the production and delivery of ATP rather than that of the increase in the level (Slee *et al.*, 2001). The major factors are the apoptotic death of the cell or also necrotic, which requires the completion and even initiation of these apoptoses.

Mitochondria play the chief part in the superoxide anion (O₂⁻) and also reactive oxygen species (ROS) that cause O₂⁻. Electron transport chain in the formation of O₂⁻. (Beyer, 1992). The water generation from these products are formed and the reduction in the four molecular oxygen species of the cytochrome oxidase (complex IV), this involved in the small amount of O₂ has reduction in one-electron processes, this generates the Reactive Oxygen Species is monitored by O₂⁻ hydrogen peroxide (H₂O₂) and highly reactive hydroxyl radical (HO·). The ROS Materialization takes place at the complex III by using proton moving in between ubiquinone, cytochromes b, c1, and iron-sulfur proteins in this process even complex are involved. The mitochondrial superoxide dismutase, H₂O₂, can also be transformed to O₂⁻, they diffuse from the cytoplasm to mitochondria. By the Fenton reaction, H₂O₂ can form the highly reactive hydroxyl radical (OH·), in the high iron concentration. They react with nitric oxide to form the reactive species of peroxynitrite anion (ONOO⁻). The defense mechanism neutralizes the products by the natural process. These are decayed by the production of ROS, which includes

glutathione peroxidase and phospholipid hydroperoxide glutathione peroxidase. These ROS accumulated may lead to mtDNA mutations, lipid peroxidation, protein oxidation, sometimes the whole organism is damaged (Gane et al., 2010).

Reactive Oxygen Species, these alter damage of induced function of metabolic enzyme and function of many metabolic enzymes in the matrix of mitochondria, is composed of an electron transport chain. Some of the relevant proteins lose the function of the oxidation of superoxide dismutase. The loss of activity of superoxide dismutase further compels the capacity of antioxidant, leads to oxidative stress. The mutation of the mtDNA is due to some of the degenerative diseases; these include Parkinson's disease, Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis. These drugs and the supplement of antioxidant has been applied for scavenging free radicals that mitochondria produce. These drugs hinder the mitochondria hence, the cancer cells are killed; the cells are prevented by oxidative damage; the defects are repaired. They require different strategies for the uptake of mitochondria and different pharmacotherapeutic agents (Dolezal, 2006).

There are different causative processes for liver diseases; this also leads to alteration, and stimulation of pathway that inclines to necrosis has multiple failures in the synthesis of ATP. The mitochondria likely depend on the integrity of mtDNA, the membrane lipids, lipoproteins, and antioxidants placed in the liver. The most important nitrosamine stress relies upon the mechanism and the production in the nitric oxide that linkage of proteins and thiols with the derivatives causing the enzyme inactivation of different charges and carriers. The nitrous oxide is known for the biogenesis of organelles and the respiration of mitochondria (Malhi and Gores, 2008).

The mechanisms listed above and used for stimulation of necrotic and apoptotic pathways. Whereas in the apoptosis, which includes alteration in the mitochondrial level leads to the cardiolipin and also phosphatidylcholine leads to increased transport to the mitochondria and even more driving of proapoptotic proteins. The inner and the outer membranes of the mitochondria contain many pores that are located at different contact sites where the proton gradient has been lost, and this helps in the blockage of the ATP synthesis. The permeation of the outer mitochondrial membranes have been ruptured due to the swelling, this leads to release of cytochrome C and Pro-apoptotic factor from the intermembrane space to the cytosol, splitting of the chromatin present in the nucleus and Ca²⁺ acti-

vation these are depended on the proteins (Kagan et al., 2009). whereas, the cytochrome C attaches the cytoplasmic scaffold helps in the formation of complexes influence ATP is known as "apoptosome", the signaling pro-caspase are activated. The increase in signaling of apoptotic which causes the executioner caspase activation the intercourse with these pro-caspase 2,6 and 7 to activate them and to settle them in the targeted protein sites The cell death of the apoptotic has been determined by the cytoplasmic, nuclear condensation and breaking without the loss of integrity of the membranes the phagocytic death of cell also removes them due to the inflammation. Cell death has been characterized by cytoplasmic and cell death with membrane loss.

The phagocytic cells remove the fragments of apoptotic cells by little inflammation. ATP production takes place due to two different metabolism mentioned below in the Figure 1 increased due to the mitochondrial dysfunction, and this helps in the necrotic upon the apoptotic death of cells. At the start, the injury is severe, which is rapid and leads to the depletion of the mitochondrial ATP and activates the apoptotic pathway, which has been inhibited. During this stage, there occurs necrosis that leads to swelling and follows the death of the cells, and also, the functions have been altered. This Necrotic cell death causes some of the responses in the body like inflammation and the hepatocytes sensitization at the surrounding and further damage to cells (Grattagliano et al., 2007).

The mitochondrial alteration is seen in case of the different chronic liver damage and also with that of the nonalcoholic fatty liver disease patients and hepatic C virus patients, whereas different animal studies are carried based on the following in vivo studies and the above mentioned hepatic metabolism (Simões et al., 2018).

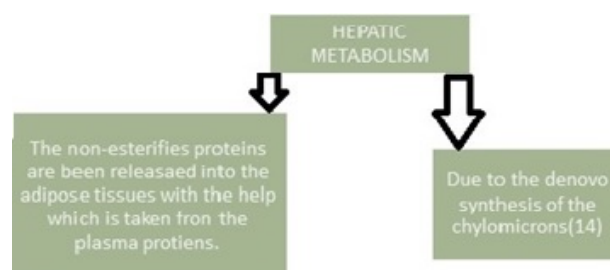


Figure 1: The different causes for the hepatic metabolism

The electron provides and migrates with the chain and influences cytochrome C oxidase (cyclooxygenase or complex IV) these in association with the oxygen and protons helps in the water formation. The superoxide anion radical is formed, which

allows the electrons to penetrate into the complex I and III. These can then be oxidized or reduced into hydrogen peroxide (H₂O₂) by manganese superoxide (MnSOD), they usually detoxify water by the glutathione peroxidase (GPx) and get reduced to glutathione (GSH). There are few numbers of Reactive oxygen species (ROS) in the mitochondria been detoxified, and this leads to a gesturing molecule. It has a major reduction in the movement involves the production of eliciting oxidative stress ([Armstrong, 2009](#)).

Role of mitochondria in the metabolism of fatty acids

The fatty acids oxidized by the beta-oxidation to acetyl-coenzyme A (CoA), oxidation takes place in the Krebs cycle forms the electrons form the nicotinamide adenine dinucleotide (NADH) and flavin-adenine dinucleotide by the process of reduction and MRC. In the matrix of mitochondria to the intracellular spaces, the electrons get coupled with the proton by the process of extrusion for the electrochemical gradients across the MIM ([Pessayre et al., 2001](#)). The ATP synthesis releases proton into the matrix and helps in the ATP production. This is stimulated by the AMPK, which activates PGC-1 α PGC-1 α with peroxisome proliferator-activated receptor α (PPAR α). The fatty acid metabolizing enzyme to induce carnitine palmitoyltransferase 1 (CPT1) acyl-CoA dehydrogenases, glucose, and β fatty acids helps in the increased mitochondrial oxidation. TFAM, the mtDNA, contributes to the transcription and translation of NRF1. Therefore, the NRF1 regulates nuclear DNA-encoded MRC proteins ([Cantó and Auwerx, 2009](#)). Liver free fatty acids (FFAs) ascend from the plasma free fatty acids and are released into the adipose tissue; they move to intestine chylomicrons and DE Novo synthesis into the hepatocytes.

There are different studies conducted for ROS and NO species that destroy the mitochondrial function by occurring after the modification of the proteome. After the modification of existing genetic information, the proteins likely involved in the dysfunction of mitochondria. The newly developed proteomic techniques are now allowed in the marking of the defects in the multi-proteins complex of the mitochondrial cell and high resolution seen in the case of the hydrophobic protein molecule and the inner membranes, so there is comprehension in the future.

Alcohol vs Liver

The transcription by ethanol metabolism and requisite of DNA activity is the PPAR- α receptor in H4IIEC3 hepatoma cells or hepatocytes expressed

in the primary cultures of rat that expresses alcohol dehydrogenase (ADH), The PPAR- α by the acetaldehyde mechanism is not identified; the acetaldehyde fails for the DNA binding. The PPAR- α protein infected by the ethanol intake, whereas RXR- α levels materials reduced; this leads to the portal vein endotoxin. The ability of PPAR- α /RXR was bond to the liver was decreased. Both of these H4IIEC3 and McA RH7777 hepatoma cells which approve with the ethanol present. There is no effect of Ethanol on CV-1 cells. Virtually the hepatoma cells of 4-methyl pyrazole bought to an end. Cyanamide that leads to an increased effect of ethanol on the expression, the acetaldehyde was involved in this ([Lluis et al., 2003](#)).

The acetaldehyde effect was allied with that of ER stress and mitochondrial glutathione stress reduction levels. It was found that the substantially increased levels in mature SREBP-1, which was fed to mice of an ethanol diet mice for about 4 weeks and also the mRNAs for FAS, malic enzyme, ATP-citrate lyase, SCD, and ACC. This recommends that ethanol metabolism leads to an increase in the hepatic lipogenesis by activating SREBP-1. In the liver adenosine, monophosphate protein kinase helps to withdraw from the fed animal with alcohol and causes alcohol exposed to the hepatoma cells. The fatty acids synthesis is increased as the movement of ACAC takes place, and also the increased malonyl CoA concentration change additional action of APMK causes the high degree of fatty acids in the liver and the SREBP-1 levels to decrease ([Lin et al., 2000](#)).

Alcoholic liver disease (ALD)

Ethanol consumption leads to liver diseases in humans is a major understanding with increased evolution leads to liver cirrhosis and fibrosis. The inflammation causes the liver induced by alcohol injury, hepatic steatosis and fibrosis lead to liver cancer. The cancer cells usually adapt them to the self-response for the activation of the protective cellular mechanism, which includes the autophagy and the biogenesis of lysosomal enzymes. And is responsible for the breakdown of the subcellular organelles and cellular proteins, which is difficult to recover from the liver injury caused due to the alcohol intake. The autophagy affects differently in acute and regular alcohol intake people ([Thomes et al., 2015](#)). There is an independent group of ethanol intake that leads to autophagy disease. Different studies show that the regular intake of ethanol to the lysosomes, which leads to increased hepatic proteins with the exposure of this ethanol seen in the case of heavy drinkers usually. The hepatic autophagy is the long term in which the mechanism

of this alcoholic lysosomal function leads to impairment. They contain nearly 50 acid hydrolase and also the autophagy components. The biogenesis of disease related to autophagy is due to the transcription of the factor EB (TFEB) (Settembre *et al.*, 2012). They are mainly generated by the rapamycin complex-1 (mTORC1).

Acute Ethanol consumption for the ROS production

The ethanol has been raised into hepatocytes been happened by the ROS production. Different experiments were carried out for various metabolism processes of ethanol for the hepatocyte action, which causes an increase in the ROS production, which that of the increase in the concentration of ethanol, this treatment has been happened due to the formation of 4- methyl pyrazole.

Chronic ethanol consumption for the ROS production

There are different studies one among them is the oxidative stress that determine the amount of ethanol present due to the tension exists the increased in the levels of ethanol in the steady-state was found to be isolated for the ROS production that was determined for the hepatocytes action in the body There are different levels of ROS production that differs from the acute intake of ethanol (Ivester *et al.*, 1995). The ethanol production ability depends on the concentration with that of the diet less levels of the incubation. This causes increased production of ROS, which causes an imbalance in the ATP production.

Increase in ethanol conflicts

Different studies have suggested that the chronic consumption of ethanol causes a decrease in the feasibility of the hepatocytes. The studies suggested that the increase in the hepatocytes causes oxidative stress due to the chronic ethanol consumption leads to ROS production seen in the mitochondria. This chronic ethanol consumption leads to a decrease in the antioxidants in the mitochondria and also the activity of glutathione peroxidase-1. This also causes mitochondrial injury due to oxidative stress. Most of the proteins have been oxidized by some of the ROS production and also the oxidative damage by the activation of proteins. Also, the detrimental effect is very high, which affects the catalytic function of the proteins. The large dose of ethanol leads to increased protein carbonyl content in the body (Grattagliano *et al.*, 1999).

Autophagy

Autophagy usually means "self-eating." It is of intracellular proteins that usually have three different

mechanisms. Mainly first is the macroautophagy, which is usually the engulfing of the large cytoplasm and the organelles of the collateral cells this forms a double vesicular membrane is called as autophagosome/ autophagic vacuole. Autophagosomes are the outer membrane that fuses with the existing membrane of the contents. Micro autophagy helps in the uptake of lysosomes present in the autolysosome, which in the content is degraded. A smaller portion of the cellular content with the lysosomal membrane with rapid hydrolysis of a molecule of water.

This plays a major role in both conditions like normal and pathologic. This is explained using the magic bullets in the Figure 2. Usually, the mitophagy removes the cells that are damaged in the mitochondria by protecting the ROS production, this protects the cell from the cell's death and also oxidative stress, and this is seen during the hepatotoxicity. Both autophagy and also mitophagy shows the same mechanism to reduce the lesions on the mitochondria. Autophagy is a cellular pathway by which cytoplasmic materials, including organelles, reach lysosomes for degradation. They usually occur due to the targeted cellular structures, nutrients deprivation, mostly the damaged mitochondria. There exists an interplay between the induce of both autophagy and the mitochondria. Mostly the mitochondria have an important role in autophagy and also during the starvation biogenesis of autophagosomes. The general autophagy is due to the decrease in ATP production and also the increase in ROS production. During the regulation of mitophagy, the removal of mitochondria takes place by the mitochondrial demand and also the quality control test of this damaged mitochondria. The ischemic condition of the liver can be treated by the chemotherapy or steatotic livers caused due to autophagy and reduce necrosis by not varying apoptosis (Green *et al.*, 2011).



Figure 2: The component that helps in the concept of magicbullet

The hepatic induced ethanol autophagy that takes place at the cellular levels has been assessed by

the ALR transfected, or it may also be called ALR-shRNA HepG2 cells. Ethanol treatment is promoted. The LC3II conversion takes place to that of p62 degradation by ALR transfection. The proteins in the ALR-shRNA cells with the proteins related to autophagy the ALR- Knockdown the mice that express the related autophagy. The ALRtransfected cells are observed in the punch fluorescent with that of the autophagy — the hepatocytes following the ethanol insult and the recombinant combine with the ALR expression by the in-vitro results. The dysfunction or the mitochondria damaged is removed by the mitophagy to maintain the healthy population of mitochondria. The outer membrane facilitates translocate of outer mitochondrial membrane (TOM) to transport the proteins into the outer mitochondrial membrane (OMM). The decrease in the mitophagy occurs due to the TOM20, a TOM complex receptor (Grattagliano *et al.*, 1999). The ALR-transfected cells usually affect the TOM20, which leads to a reduction in the EtOH treatment.

Mitochondrial-targeting therapy

The mechanism of how the drug is targeted has been mentioned in the Figure 3 has been given in a detailed diagrammatic manner.

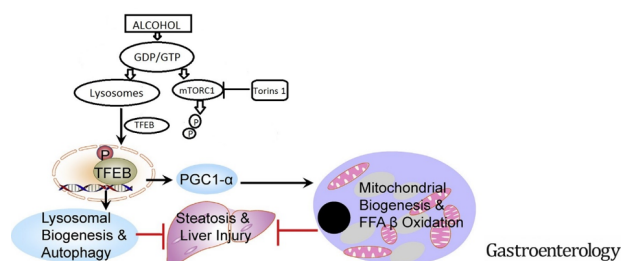


Figure 3: The mitochondria for the liver disease

Liver disease

The devices used and its applications

The drug delivery to the particular cellular compartment may lead to an increase in the therapeutic benefit and the reduction in the unwanted effects of the non-targetable tissues. The drug should show multiple actions which help in the destination of the intracellular components. There are different carriers responsible for the delivery of the drug to the liver (Yousif *et al.*, 2009). The molecule's pharmacological responses are based on the selectivity of the drug, which is required for the targeting of the mitochondria. The target of this is the little complicated as the penetration of the inner membrane of the mitochondria is difficult or may be absent. The fact is that the molecule which targets the mitochondria needs to be encapsulated into different carriers based on their different physical characteristics

of the drug that then is targeted to the specific cells to release into the mitochondria. There have been found different transporters for delivery nowadays.

The targeting into the mitochondria takes place by the two different steps mainly,

Active

This targeting usually causes the interaction of the that increases the effect of the drug (antigen-antibody or ligand-receptor) where the pharmacological activity has been seen at the sites of mitochondria.

Passive

The passive targeting is the method where the physical and the chemical property of the different system that increases the targeting or the nontargeting ration of the different contents of the drug that have features of adjusting the different physiological property of the mitochondria. As though there are different molecules delivered at the characteristic targeting sites. The synthetic polymers and some of the natural polymers like albumin, liposomes, nanoparticles, and the polymeric micelles are responsible for the cellular uptake and the trafficking of the intercellular therapeutic agents.

Lipophilic Cations

These get accumulated in the body where the lipophilic monocations triphenyl phosphonium or its methylated form which has been selectively used to transport of antioxidants namely vitamin E (James *et al.*, 2007) and ubiquinone this is used successfully for the nucleic acids of the vehiculate peptides to the mitochondria. They also embrace MitoPeroxidase, the N-acetyl cysteine-choline, and the ester of GSH-choline. A new compound that has been recently synthesized is conjugating TPP+ with TEMPOL (4-hydroxy-2, 2, 6, 6-tetramethylpiperidine-1-oxy radical), a piperidine nitroxide, termed MitoTEMPOL. The compound obtained by linking the peroxidase mimetic ebse-len with TPP+ termed MitoPeroxidase in the membranes of the mitochondria by the process of lipid peroxidation.

Liposomes

They are conventionally formed by using the phosphatidylglycerol, phosphatidylcholine, and cholesterol. They contain both lipid and water-soluble chemical antioxidants and the enzymatic antioxidants or the combination of both (Alipour *et al.*, 2007).The kuffer cells remove the liposomes by the circulation process and help the coating of the polyethylene glycol-phosphatidylethanolamine (PEG-liposomes). These types of preparations of

liposomes are pH-sensitive liposomes. The liver damage has been seen and demonstrated by the antioxidants.

The N-acetylcysteine is an encapsulated liposomal way which has a lipopolysaccharide that has a hepatic effect. The complex has hepatoprotective action that, with the help of silybin and phospholipids (Siliphos), exhibited hepatoprotective and also in some cases, the antifibrotic effect, which improves the enzyme levels in the level seen in case of NAFLD patients. They significantly affect the oxidative stress in mitochondria and also hepatic improved ATP homeostasis. A galactosylated showed a hepatoprotective action. Some liposomes help in the increase in the energy level of patients. They are also used for the anti-Leishmania drugs targeting and also immunomodulators.

TAT Peptides

For the delivery of the molecules different novel approach has been used in the conjugation of the peptides. The human immunodeficiency virus-1 has the TAT peptides to deliver the oligosaccharides (Chacinska *et al.*, 2009). There are different results for the preliminary tests.

Peptide-Based Targeting Sequences

There are the different mechanism, and the different pathway for the cytosolic and import is needed (Dolezal, 2006). N-terminus for the sequences signal of and the enabling of mitochondrial delivery. The chimeric molecule has been destined for the space of intermembrane to conjugated the nonmitochondrial. They are expressed for the synthase of the cytosol to be targeted for the mitochondria.

RESULTS AND DISCUSSION

The May fatal conditions have been considered at the time of liver targeting some of the conditions like the enzyme deficiency, and hepatom is given in the Table 1,

Passive targeting

This the targeting of the capillaries that moves into the tumor interstitium by the process of passive diffusion. They include the following factors like

1. There are about 100-200nm of fenestrations on the wall of the endothelial.
2. The IV administration shows the therapeutic effect of the nanoparticles.

Active targeting

The kuffer cells that have hepatocytes parenchyma cells have been used for this targeting. They act on the extracellular membrane and produce biochemical stimuli for the damaged liver. Hepatic stellate cells (HSCs) targeting: There is the formation of my fibroblasts that causes the insulin growth factor and stimulates the production of the collagens, and the hepatocytes have been targeted.

Hepatocytes, the drug is targeted

By using this type, the galactose the N acetyl glucosamine has been usually targeted. This helps the formation of the endocytotic uptake that is controlled by the clathrin.

Polymeric micelles

They are the most used and the novel type of drug delivery that can target both the water-soluble and the poorly water-soluble drugs. They show a prolonged action of the drug molecule. This is done by the in vivo studies, which also show prolonged circulation. Usually, the micelles are used for targeting at the site of the liver (Sugioka, 1994).

The mitochondrial membranes are affected by the proteins

The outer membrane of the mitochondria has organelles that have a pore is called as the porins in the eukaryotic cells that are found between the cytosol and the Proteins of the mitochondrial outer membrane that interacts with the apoptosis synthesis which helps to target the damaged liver. Based on the different studies conducted.

Nanosystems used for the delivery

DQAsomes

These are used as a vector for the targeting of the liver by using gene therapy. These are the complex of DNA prepared by the mixing of DNA for the DQAsomes (Guo *et al.*, 2016). They usually target the mammalian body in the mitochondria the cytoplasm across the mitochondria are helpful for the delivery of the liposomes across the gradient they have the antisense treatment for the cationic molecules with the help of the pathogen namely the gram-positive organisms. They are usually encapsulated with anti-cancer drugs like curcumin (Sharma *et al.*, 2012).

Polymer nanoparticles

Polymers like poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic-co-glycolic acid) (PLGA) and polycaprolactone (PCL) play a key role in biodegradable and biocompatible. Emulsification-solvent evaporation or nanoprecipitation are the methods used for the preparation of polymer particles. By using click chemistry, TPP and PEG are prepared (Hegarty *et al.*, 2016).

Table 1: The different types of targeting

Sl No	Types
1	Passive targeting
2	Active targeting
3	Hepatic stellate cells (HSCs) targeting
4	Hepatocytes the drug is targeted
5	Polymeric micelles
6	Mitochondrial membrane by the proteins
7	Nanosystems used for the delivery

Inorganic nanoparticles

Mitochondrial targeting nanoparticles are prepared using inorganic materials. Hydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$, HAP) shows good biocompatibility results. Apoptosis is induced once the nanoparticles enter the mitochondria of tumor cells when the mitochondrial membrane potential changes. For lung cancer cells (A549) and normal bronchial epithelial cells (16HBE), rod-shaped HAP NPs were synthesized. Liposomes, nanoparticles, polymeric micelles, and some of the other metal nanoparticles, carbon nanotubes, solid lipid nanoparticles, noisome, and dendrimers are the various types of Nanocarriers used. Poor aqueous solubility, low bioavailability, and nonspecific distribution in the body can overcome by NDDs (Torchilin, 2009).

Herbal treatment

Phytosomes

There is a substantial increase in the pharmacokinetic and pharmacological parameters, and they are used in the treatment of acute and chronic liver disease. It is also used in anti-inflammatory activity. It is prepared by using methylene chloride, dioxane and ethyl acetate with the phospholipid such as phosphatidylcholine, phosphatidylethanolamine or phosphatidylserine dissolved in the same solvent and reacts with the herbal extract. The substance obtained from the extract is lipophilic.

The free radicals have been generated due to the intake of the high amount of ethanol this leads to the radical formation, and this causes ethanol toxicity there is a subsequent decrease in the antioxidants by the defense mechanism. Also, this is known as the peroxidation of the lipids. This process may destroy the integrity of the membranes both within and the surrounding cells Research has been carried out on liver injury and the extent to which it was damaged, ultimately concluding that the main reason behind it was lipid peroxidation.

It has been established that antioxidants assist in protecting cells from any damage due to oxi-

dation and anti-oxidants of non-enzymatic type namely GSH, Vitamin C, Vitamin E (Natural scavengers) (Olutope *et al.*, 2014), May be utilized as a second level of defense against the destruction of cellular membrane out of which GSH was found to be one of the imminent nonprotein thiols for the same.

In the study performed, the concentration of GSH was deliberately reduced in alcoholic treated rats, and this significantly reduced the number of Reactive oxygen species produced and further led to the oxidation of glutathione and lipid peroxidation. It was followed by the oxidation of the reduced form of GSH into GSSG along with interaction with free radicals.

Vitamin C is an important micronutrient which is a water-soluble antioxidant and works by maintaining the normal metabolism of the body.

It undergoes reactions directly with

1. Superoxide's
2. Hydroxyl radicals,
3. Singlet oxygen and indirectly produces a synergistic effect with Tocopherol along with its regeneration (Guo *et al.*, 2016).

Vitamin E is one of the major lipid-soluble antioxidants, which is present in most cellular membranes and acts by eliminating lipid peroxidation; it decreases the concentration in ethanol. Intoxicated rat is mainly due to the utilization of anti-oxidants, or due to reduced concentration of Vitamin C and E. This eventually leads to a reduction in conversion of tocopherol radical to tocopherol (Hemilä *et al.*, 1984).

One of the major causes of alcoholic liver diseases is the role of lipids in the pathogenesis. Alcohol consumption, especially ethanol, results in hyperlipidemia in both animals and humans. Chronic consumption was found to cause hypercholesterolemia and hypertriglyceridemia (Devipriya *et al.*, 2007).

The liver is one of the most pivotal organs in the body, which regulates the lipoprotein transport of HDL and LDL in plasma as well as in cholesterol biosynthesis.

During the conversion process, VLDL is converted to LDL, which is abundant with cholesterol and related esters and commonly known as bad cholesterol. On the other hand, HDL contains a relatively lower quantity of Cholesterol, which in excess will result in hyperlipidemia.

In the intoxicated ethanol group, the levels of LDL cholesterol were found to be increased in plasma and tissue regions, whereas HDL cholesterol levels were reduced mainly attributed to an increase in hydroxy methyl glutaryl CoA reductase activity ([Shanmugam et al., 2007](#)).

Phospholipids are essential components of the biomembrane region and function as in regulating the enzymes, which are membrane-bound and decrease in these levels is mainly due to an increase in phospholipases.

It was previously proven that a chronic exposure would increase membrane phospholipase A2 function, and hence this alteration may result in the toxic effects.

CONCLUSIONS

The mitochondrial drug for the treatment of liver diseases that is more effective, which can be targeted by the hepatocytes cells and different types of delivery systems, has been employed for the study. And are mentioned with different drugs like the liposomes, Iganic cations, and the nanotechnology employed for the study.

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