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Review Article

Hepatoprotective Plants and Mechanism of Action of Various Hepatotoxicity Model: A Review.

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Abstract:
Aim: The review is objected to assembled data on medicinal plants having hepatoprotective activities and various toxicity models along with their mechanism of action. **Methodology:** Liver is an essential organ plays many characteristics functions. Demises of adults with persistent hepatic necrosis are intensified which is the main concern for days. Hepatic disorders can be engendered by any toxicity model but the prime reasons for liver injuries are drug-induced toxicity and excessive alcohol consumption. **Conclusion:** From ancient era, traditional medicine system has been used to prevent and treatment of liver cell injury. Enumerate plants are present in nature containing flavonoids that possess hepatoprotective properties

Introduction:

The liver is a vital organ which plays a fundamental role in the metabolism and excretion of xenobiotics which may result in adverse and toxic effects. Numerous toxic chemical or reactive metabolites (hepatotoxicants) which may gives birth to massive liver injuries.

Overload of drug and xenobiotic refers to liver dysfunction or liver damage (Singh et al., 2011). Chemicals that cause liver injury are called hepatotoxicants or hepatotoxins. Certain drugs may cause liver injury when introduced even within the therapeutic ranges (Willett et al., 2004).

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Hepatocytes are exposed to orally administered xenobiotics mostly without systemic modification or dilution because they flow directly to the liver by the portal venous blood. The direct mechanism of hepatotoxicity is through specific interaction of a chemical with the key cellular component and modulation of its function. The highly active anabolic metabolism that occurs within hepatocytes makes these cells especially susceptible to the adverse effect of toxicants that can act as antimetabolites or comprise mitochondrial energy production (Zarybnicky et al., 2017).

However, a mechanism that is more common involves secondary effects of toxicant interaction such as the covalent binding of reactive metabolites, collapse of ATP synthesis and regulatory ion gradients and oxidative damage leading to change in signaling transduction pathways. In liver, xenobiotics are extensively metabolized via the action of xenobiotic-metabolizing enzymes. These can generate locally reactive toxic metabolites that interact with hepatic macromolecules.

Moreover, xenobiotics metabolism can enhance the rate of reactive oxygen intermediates production such that they exceed the capacity of the protective antioxidant system (Robert et al.,2008).

Immense sophisticated medicine advances, assist the protection of liver from damage and regeneration of hepatic cells. Herbal medication is the key treatment of major hepatic complications that consist of active chemical constituent (plant extract). Nowadays, The herbal formulation is the major area of interest because of its effectiveness and vast safety profile (Chaudhary et al., 2015).

Mortality/Morbidity

Fig 1: Classification of Hepatotoxins

In the United States, per annual cases of acute liver failure are approximately 2000 moreover drug-induced accounts 50% of it whose 39% occurs due to acetaminophen, 13% are idiosyncratic reaction due to other medicines. Drugs account for 2-5 %of cases of patients hospitalized with jaundice and approximately 10% of all cases of acute hepatitis. Internationally, in the general population statisticalof incidence of adverse hepatic drug reaction still unknown.

Classification of hepatotoxins and their mechanism of action:-

(Thonda et al., 2012)

Fig 1: Classification of Hepatotoxins

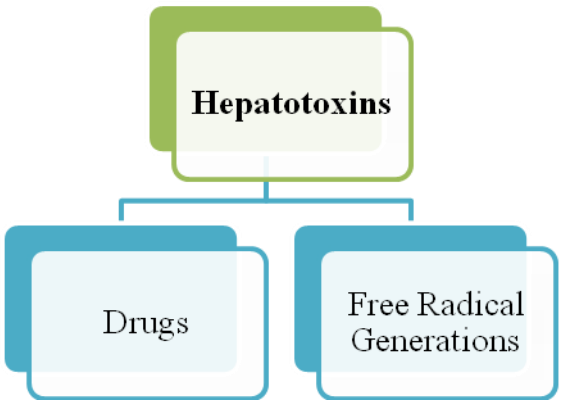


Table 1:- Mechanism of action of various toxicity model

Table 1: Mechanism of Action of various Toxicity Models

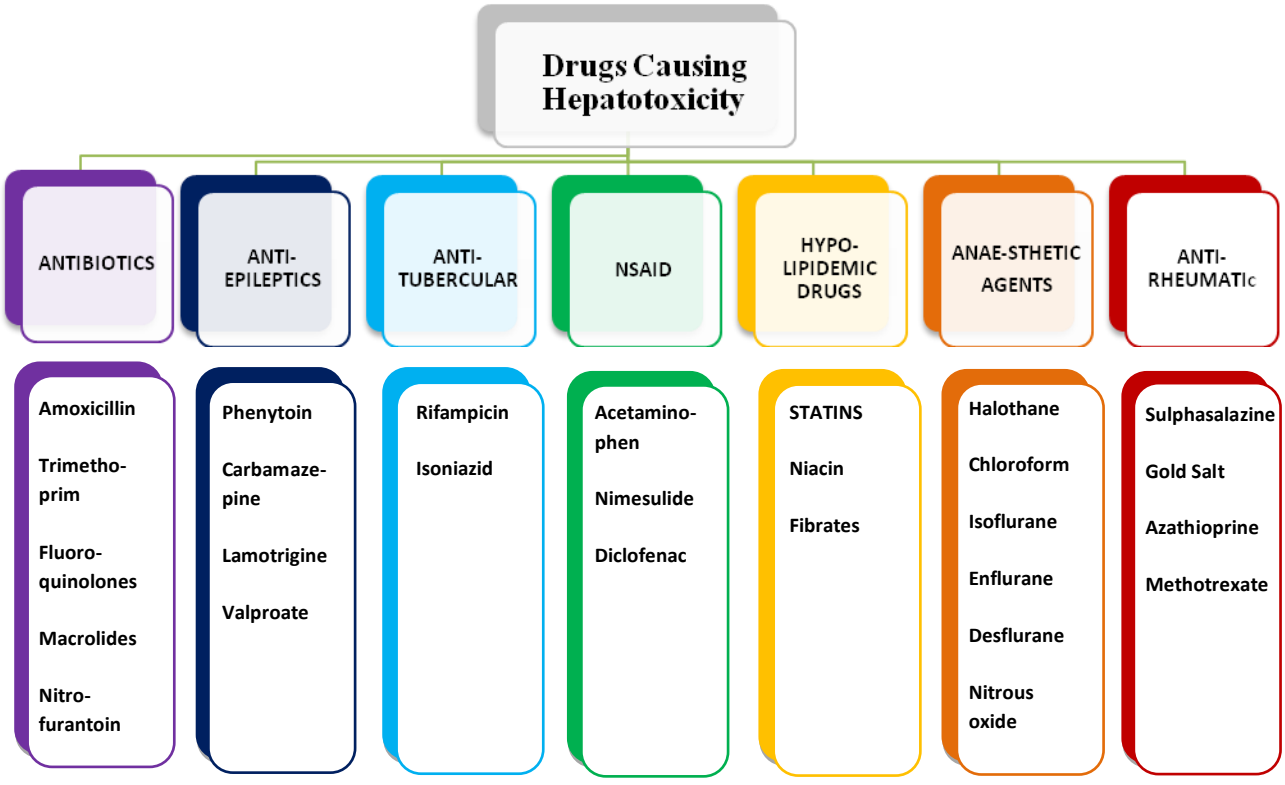
Type	Sub-type	Mechanism of action	Reference
Drug-Induced	CCl_4 Induced	When Hepatic enzymes drain into serum that leads towards necrosis. $CCl_4 \rightarrow CCl_3^- + O^-$	Bhuvaneswari et al., 2014.
	Thioacetamide Induced	Thioacetamide interrupts with the displacement of RNA from the nucleus to cytoplasm which may result in membrane injury.	Zargar et al., 2017
	Galactosamine Induced	Liver injury happens due to Hepatitis, which elevates the production of crucial uridylate nucleotides that which results in organelles injury and eventually cell death.	Lin et al., 2000
	Alcohol Induced	When oxidation process occurs in the liver emanates the production of free-oxy radicals, certainly decline the activity of antioxidant enzymes i.e.	Arteel, 2003 Padamanabhan and

		Superoxide dismutase and glutathione peroxidase. Alternatively, acetaldehyde exhibits direct damaging effect which is also formed by oxidation of ethanol.	Jangle, 2014
	Paracetamol Induced	Mechanism of toxic injury being related to mitochondrial and endoplasmic reticula leading to hepatic injury and necrosis. Necrosis of the centrilobular hepatocytes characterized by nuclear pyknosis and eosinopphilic cytoplasm following by large excessive hepatic lesion	Baskaran and Suruthi, 2016 Yoon et al., 2016
	Antitubercular Drugs Induced	Isoniazid is metabolized to monoacetyl hydrazine, which is further metabolized to a toxic product by cytochrome P450 leading to hepatotoxicity.	Padma et al., 1998
	Azathioprine Induced	Depletion of GSH leading to mitochondrial injury with necrosis.	Raza et al., 2003 Abdulla et al., 2014.
	Ranitidine	Metabolites of ranitidine results in hepatic oxidation damage as well as initiation of immuno-allergic reactions	Hemiedafried et al., 2005
Free radical generation	Superoxide(O_2^-)	During mitochondrial electron transport reaction spontaneous oxidation of O_2 occurs which is catabolized by superoxide dismutase.	Yoshikawa et al., 2009
	Hydrogen peroxide (H_2O_2)	H_2O_2 diminishes water enzymatically by catalase (in the peroxisomes) and glutathione peroxidase GSH (both in the cytosol and mitochondria).	Thonda et al., 2012
	Hydroxyl radical	Process of OH^- radical production is bipartisan (biological process) by radiolysis of H_2O and Fenton reaction.	
	Lipid peroxidation	Lipid peroxidation originated severely by oxidants such as free radicals or non-radical species that attack lipids containing carbon-carbon double bond(s), predominantly polyunsaturated fatty acids (PUFAs) that embrace hydrogen abstraction from a carbon, with oxygen insertion supervene in lipid peroxyl radicals. The lipid peroxidase is decomposed by transition metals such as iron.	Gaschler and Stockwell et al., 2017 Ayala et al., 2014

	Oxidation of proteins	Oxidative modification of protein structures are due to attack of reactive oxygen species (ROS) which results in modification of amino acid side chain, cleft of protein backbone, prompting of carbonyl derivatives moreover formation of protein complexes.	Barelli et al, 2008
	Catalase	The hydrogen peroxide formed by superoxide dismutase as well as scavenged by catalase, omnipresent heme protein that catalyzes the hydrogen peroxide into H_2O and molecular oxygen.	Berg et al., 2008

Drug causing Hepatotoxicity:- (Pandit et al.,2011)
Figure 2:- List of drugs which result in hepatotoxicity

Figure 2:- List of drugs which result in hepatotoxicity



Hepatoprotective Plants:-

***Anisochilus carnosus*:** Hepatoprotective activity was screened in ethanolic extract of stem of *Anisochilus carnosus* against tetrachloride (CCl_4) induced toxicity i.e., induced in either sex of Albino Wister rats. Two dose levels 200 and 400 mg/kg body weight. The biochemical parameter has been assayed to evaluate Liver function i.e. Serum Glutamate Pyruvate Transaminase (SGPT), Serum Glutamate oxaloacetate Transaminase

(SGOT), Alkaline Phosphate (ALT), Total Bilirubin and Total Protein. The ethanolic extract of stem of *Anisochilus carnosus* treats the hepatotoxicity and reduces the toxic effect of CCl_4 (Venkateshet al., 2011).

Asparagus racemosus: *Asparagus racemosus*has been used for hepatoprotective activity against acetaminophen, which was induced by giving gm/kg body weight was administered to rats daily P.O. *Asparagus racemosus* antioxidant property reduces all elevated levels of SGOT, SGPT, ALT, catalase (CAT), Superoxide dismutase (SOD) activity (Yakoutet al.,2015).

Azadirachta indica (neem): Leaf aqueous extract of azadirachta indica has been reported for the treatment of paracetamol induced hepatotoxicity. A single dose of 2g/kg, P.O. body weight of paracetamol causes liver necrosis. 500mg/kg body weight orally, of *Azadirachta indica* for 9 days to begin the cell recovery and descend the mountain level of AST, ALP and Glutamyl Trans-peptidase (Bhanwraet al., 2000).

Cinnamon zeyanicum: *Cinnamon zeyanicum* aerial parts aqueous extract was investigated as hepatoprotective against alcohol induced toxicity in Albino rats. 500mg/kg body weight dose of *cinnamon zeyanicum* significantly reduces SGOT, SGPT, ALP, GGT, Total Bilirubin and Total Protein. The plant extract improves liver function and also help in regeneration of liver cell (Arunet al., 2014).

Coldenia procumbens: Methanolic extract of *coldenia procumbens* linn shows antihepatotoxic activity in rats against D-galactosamine (D-GaIN). 200 mg/kg as per body weight doses significantly diminish the level of serum enzyme which is produced by D-GaIN, the comparison has been done with standard silymarin (100mg/kg). Hepatoprotective mechanism of the drug is because of its antioxidant property (Ganesh et al., 2013) (Ganesan et al., 2014).

Erythroxylum monogynum Roxb: *E. monogynum* leaves extract (Methanolic) having a dose of 100, 200 and 400mg/kg to counter the toxicity caused by 2mg/kg body weight paracetamol. Comparative has been done with standard drug i.e. silymarin (50mg/kg per B.W.). Collection of blood sample was from retro-orbital plexsus and then SGOT, SGPT, ALP, total bilirubin and total protein was assayed to check the toxicity level (Syed and Namdeo, 2013)**.**

***Ficus sycomorus* L:** Various extract of *Ficus sycomorus L.* works to encounter the N-nitrosodiethylamine (NDEA) and CCl_4induced hepatotoxicity. Activity profile of the drug depends upon which part of the plant has been selected for extract, stem bark extract shows the moderate effect and unripe fruits extract elects no effect (Samia et al., 2015).

Garcinia indica: Aqueous fruit extract of *Garcinia indica (GIE)* used against ethanol-induced hepatotoxicity.Liver necrosis was generated by introducing ethanol (5g/kg, P.O. daily) for 21 days. Two doses of GIE were administered in rats i.e.400 and 800mg/kg, standard drug silymarin (200mg/kg) for 28 days. Level of biomarkers AST, ALT, ALP, Total protein, albumin, and Triglyceride were amplifying in serum. Antioxidant parameters were ascertained in the liver like GSH, CAT, SOP, Glutathione reductase (GR), Glutathione peroxidase (GPx), Hepatic triglycerides (hTG), Marker malandialdehyde (MDA) and lipid peroxidation. 800mg/kg of *Garcinia indica* illustrates better hepatoprotective activity than 400mg/kg. GIE inhibits lipid peroxidation in liver and magnifiesendogenous antioxidant which delineates anti-hepatotoxic activity (Panda et al., 2012).

Hedyotis corymbosa: Ethanolic extract of *Hedyotis corymbosa* was screened as hepatoprotective in contrast to CCl_4induced intoxication. Raise levels of SGOT, SGPT were diminished (Chimkode et al., 2009).

Hedyotis corymbosa 50% Methanolic extract reported for treatment D-galactosamine (200mg/kg body weight, P.O.) induced hepatopathy in theexperimental animal model. Biochemical parameters were measured to evaluate the level of toxicity by AST, ALT, ALP,

CAT, ɣ-GT and Total bilirubin. Lipid peroxidation (LPO), reduced glutathione (GSH), Superoxide dismutase (SOD) and Catalase were performed to check in-vivo antioxidant activity along with histopathological examination (Gupta et al., 2012).

Hibiscus sabdariffa: *Hibiscus sabdariffa* anti-hepatotoxic activities streptozotocin diabetes-induced. Liver necrosis was inspected from histopathology studies and biochemical parameters were examined in serum. Accelerated levels of ALP, ALT, and AST in the serum of diabetic rats was refurbished to normal in *Hibiscus sabdariffa* treated rats (Adeyemi et al., 2014).

Lawsonia inermis: Paracetamol induced hepato injuries were treated by ethanolic seed extract of *Lawsonia inermis* in Wister albino rats. Toxicity was established with (750 mg/kg) paracetamol. *Lawsonia inermis* (400mg/kg) and standard reference silymarin were administered (200mg/kg) orally for 21 days/ daily by dissolving in 0.1% carboxy methyl cellulose solution. Blood was collected on the 22nd day from retro- orbital puncture. Serum was probed for biomarker enquiries like SGOT, SGPT, ALT, Total bilirubin and Total protein. *Lawsonia inermis* demonstrates hepatoprotective in nature against paracetamol induced intoxication in rats (Baskaran and Suruthi et al., 2016).

Morusnigra (mulberry): Mulberry ethanolic leave extract depicts hepatoprotective property against anti-ruhmetic drug (methotrexate). Noticeable deduction in hepG2 cells was removed after 48 hrs. A significant decrease was screened in activities of AST, ALT, ALP and LDHs. When 500mg/kg/day of mulberry ethanolic extract. Another hand, a combination of methotrexate and mulberry were injected to rat show better therapeutics results compared to asingle dose of mulberry against methotrexate hepatotoxicity (Tag, 2014).

Solanum xanthocarpum: Solanum xanthocarpum has been delclined for paracetamol induced liver damage in the experimental animal model. A single dose of paracetamol (3 g/kg) was given to induced liver toxicity. *Solanum xanthocarpum* ethanolic extract (200 and 400 mg/kg, P.O.) and Silymarin (25 mg/kg, P.O.) were introduced for 8 days once in a day. The extent of toxicity was scaled up using AST, ALT, ALP, Total protein and Total bilirubin levels. Dose 400 mg/kg of an ethanolic extract of *Solanum xanthocarpum* provides supreme shielding nearly similar to normal control and silymarin (Sivakumar et al., 2014).

Solanum nigrum: Solanum nigrum hepatoprotective activity in acute and chronic liver necrosis which is caused by Nimesulide. Measurement of liver protection was scanned by estimating ALP, SGOT, SGPT, TB level. The dose (100, 200, 300mg/kg, body weight, P.O.) of aqueous ethanolic (30:70) extract was compared with silymarin. In case of acute liver damage, dose 200 and 300 mg/kg P.O. of Solanum nigrum extract (aerial plant). 300mg/kg found to be more effective than 100 mg/kg in case of chronic hepatic necrosis (Mushtaq and Aahmad, 2013).

Targeting Drug Delivery System:-

Targeted drug delivery is thesmartest approach to deliver acomparatively higher concentration of drug only at the area of interest in the body, which often enhances the efficacy of the drug and also decline side effects (Mishraet al., 2016). A successful targeted drug delivery system follow four basic principles: Retain, Evade, Target and Release i.e requires convenient drug delivery vehicle which should load properly load the drug into it. The vehicle should have property to protect the drug from degradation into body's secretions so that it could last in blood for a long time and also could reach to the targeted site (Allem and Cullis, 2004).

Figure 3: Advantages of Targeted Drug Delivery System

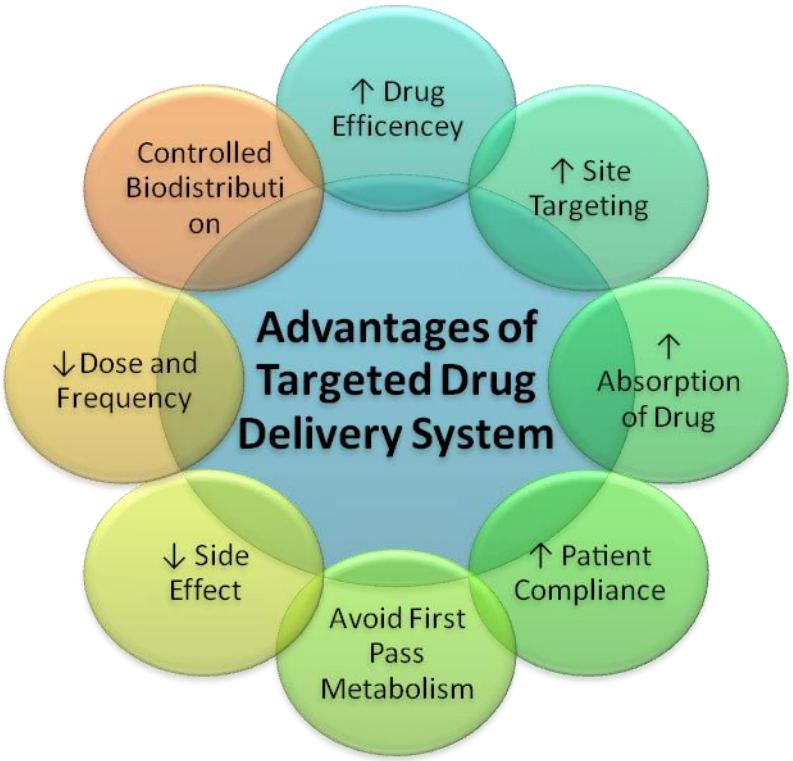


Figure 3: Advantages of Targeted Drug Delivery System

Hepatic targeted drug delivery systems (HTDDS) have attracted much more attention recently for their promising roles:

1. Increasing the efficency of pharmaceutical agents for liver,
2. Reducing drug doses,
3. Reduce the repeated administration (due to its sustained-release properties),
4. Increasing the abiovailability,
5. Stability,
6. Targeting to specific cell or organ (due to its subcellular size),
7. Significantly decreasing the toxic side effects,
8. Ability to cross the anatomical barriers such as those of stomach and intestine,
9. Showing minimal drug leakage during its passage through the stomach, intestine, and other parts of the body,
10. The delivery system is nontoxic, biocompatible, biodegradable and physically, chemically stable in the liver cells either in vivo or in vitro,
11. Having uniform sinusiod capillary distribution,

With the deepening understanding of the structure and function of the surface of cells, receptor-mediated targeted drug delivery systems have been extensively studied. In brief, the receptor-mediated targeting system is that the one functioned with ligand via (Mishra D et al., 2014)

1. Chemical coupling
2. Physical coating ways
3. Reaching the desired sites by the special interaction between the ligands in the system and the receptors on the surface of the desired organ

Ligand targeting:-

It is well known that there are many receptors present on the surface of hepatic cells. An abundant receptor which is specific to hepatic parenchymal cells is asialoglycoprotein receptors, which has the ability to recognize the galactosylated ligands, lactobionic acid ligand, asialofetuin ligand, soybean derived

sterylglucoside (SG) ligands and many more. Similarly, glycyrrhetinic acid receptors are mainly found on the sinusoidal surface of mammalian hepatocytes. It has the ability to recognize the glycyrrheyinic acid ligands (Mishra et al., 2013).

The hepatic non-parenchymal cells also have various receptors present on their surface such as mannose receptors which are located on the surface of Kupffer cells. Chemically, mannosylated albumins have received high attention because of albumin receptors present in them, which specifically recognize ligands containing N-acetyglucosamine (Kawakami et al., 2001) or L-fucose, non-reducing D-mannose (Kawakami et al., 2000; Sato et al., 2001). These receptors are mainly expressed on the surface of non-parenchymal liver cells like kupffer cells and sinusoidal endothelial cells (Ogawara, 1999).

Table 2: Represents list of receptors which are found inliver cells

Table 2: Represents list of receptors which are found on liver cells

S.no	Hepatic cells	Receptor Found	Refernce
1	Hepatocytes	Asialoglycoprotein receptor (ASGP-R)	D'Souza and Devarajan, 2015.
		IgA-receptors	S M Hsu and P L Hsu, 1980.
		Transferrin receptors (TfR 1, TfR2)	Takami and Sakaida, 2011.
		HDL receptors	Ganesan et al., 2016.
		LDL receptors	McDonald et al., 2014
		Insulin receptors	Cherringtan, 2005.
		Scavenger receptors	Ganesan et al., 2016.
2	Endothelial cells	Scavenger receptors	Li et al., 2014
		Manose/ N-acetyl glucosamine receptors	Jiang et al., 2014
		Fc receptors immune complexes	Rmirez-Garcia et al., 2013
		Hyaluronanfibronectine, denatured collagen receptors	DeLeve, 2015.
3	Hepatic stellate cells	Uroplasminogen receptors	Friedman, 1999.
		Thrombin receptors	Moss et al., 1992
		Ferritn receptors	Takami and Sakaida, 2011
		α_2-microglobulin receptors	List et al., 2014
		IGF II receptors	Schon et al., 2016.
4	Kupffer cells	LDL receptors	McDonald et al.,2014
		Mannose receptors	Jiang et al., 2014
		Galactose receptors	Wang et al., 2006
		Scavenger receptors (Class AI BI BII MARCO CD3 etc.)	Li et al., 2014

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		Fc receptors (opsonised materials, immune complexs receptors)	Ramirez-Garcia et al., 2013

Novel Drug Delivery System for Liver Targeting:

1. **Nanoparticles:-** Nanoparticles were prepared by self-assembly of the PEG-b-PMNT using the dialysis method. Redox nanoparticles have shown the protective effect against acetaminophen-induced hepatotoxicity. Lipid peroxidation level reduced due to antioxidant property, which enhances glutathione peroxidase activity and causes inhibition of O_2^-. Treatment with redox nanoparticle depicts no side effect and auspicious approach for progressing therapeutic effect(Boonruamkaew et al., 2016).

   Nanoparticles of *Embelin officinalis* and silver were developed due to its antioxidant and hepatoprotective properties against CCl_4- induced toxicity. Enormously raised enzymatic levels of Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline Phosphate (ALP), Bilirubin bring back to normal by treated it with *Embelin Officinalis* nanoparticles(Bhuvaneswari et al.,2014).

   Advantages:

   a. Due to particle size and surface properties can easily achieve both passive and active drug targeting.
   b. Nanoparticles provide control and sustain release of the drug to the specific site.
   c. Nanoparticles increase drug efficacy and reducing side effect.
   d. Particle degradation can be minimizing by choosing right matrix constituents.
   e. Attachment of a ligand provides site specific targeting.

2. **Microparticles:-**Combination of O\W emulsification- solvent evaporation method was used to develop microparticles. Glycyrrhetic Acid containing Poly(DL-lactic acid-co-glycolic acid) having an appropriate size which elicits passive targeting, high entrapment of drug in the liver and sustains drug release due to which GLA system provides long-term liver-protective effect (Onishi et al.,2006).

   Advantages:-

   a. It provides sustain and stably therapeutic effect.
   b. Improves the bioavailability and reduces the adverse effects.
   c. Decreases dose frequency and increase patient compliance

3. **Noisome:-** Niosomes were prepared by reverse phase evaporation technique for the management of acetaminophen induced hepatotoxicity in male Wister rats. Wister rats were divided into seven groups. An oral dose of N-acetylcystein (NAC) was given to animal model when oxidative stress biomarker assayed in the serum sample. Toxicity was reduced more when niosomes of NAC was given than plain NAC. Niosomes as a nano-carrier is used to improve the efficacy of NAC in case of Acetaminophe-induced liver injury (Karami et al., 2017).

   Advantages:-

   a. Hydrophilic and lipophilic both can be encapsulated
   b. Protect the drug from degradation
   c. Increase stability

d. Increase drug efficacy

4. **Liposomes:-**Liposome of N-acetylcysteine was formed by the modified dehydration-rehydration method. Investigated raised the enzymatic level of ALP and ALT found to be declined when lipo-NAC administered to Male Sprague-Dawley rats. APAP-induced toxicity was significantly decreased with Lipo-NAC as compared to conventional formulation **(**Alipour et al., 2013).

Advantages:-

a. Enhances efficacy of the drug
b. Due to encapsulation of drug, stability increases
c. Diminishes the toxicity of the encapsulated agent
d. Both water soluble and lipid soluble drugs can be loaded
e. Non-toxic, biodegradable, flexible, biocompatible

Conclusion:-

Drug molecules itself cannot attain at a specific site in this tangled cellular system of an organism. Now-a-days targeted drug delivery is a promising field having the potential for site specific drug delivery due to which quality of dose, as well as side effect declined. In recent time, According to World Health Organization statistics majority of human population is dependent on herbal sources. In this review, information has been compiled up regarding hepatoprotective plants. Certain evaluation concludes that plant extract contains flavonoids which possess anti-oxidant and anti-inflammatory activity, due to which it depicts hepatoprotective action on various toxicity models.

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