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Review

Recent developments in the understanding of NSAID-induced liver fibrosis: linking fundamental mechanisms to specific therapy ideas

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Abstract

One of the most often prescribed medicine class worldwide is that of non-steroidal anti-inflammatory drugs. NSAIDs exhibit the action of a common mechanism consisting of cyclooxygenase inhibition, the enzymes in charge of producing prostanoids. NSAIDs are primarily weak organic acids and have been connected to liver disease for multiple decades. Interstitial collagens are produced in excess and deposited in the liver's extracellular matrix, resulting in hepatic fibrosis. Only a few NSAIDs exhibit inherent dose-dependent toxicity. Dietary changes, alcohol abstinence, and antiviral drugs are examples of current therapy. Nevertheless, such etiology-driven treatment is typically inadequate in patients with late-stage fibrosis or cirrhosis. The development of practice guidelines by multidisciplinary panels of experts includes suggestions of helpful remedy options for the particular reason of liver injury, stage of fibrosis, or occurrence of co-morbidities linked to a continuing loss of liver function. We listed the causes of hepatic injuries, including NSAIDs, and the prevailing theories behind anti-fibrotic treatments.

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Introduction: Non-steroidal anti-inflammatory drugs are the most popular drugs for treating fever, pain, redness, and edema caused by inflammatory mediator production [1]. NSAIDs inhibit the cyclooxygenase (COX) enzyme, preventing the formation of prostaglandins (PGs), which are responsible for altering arachidonic acid into PGs, thromboxane, and prostacyclin [2]. Cox-1 and Cox-2 are the two known COX isoforms. The "COX-1" isoenzyme is typically present in all tissues, and its stimulation results in the creation of "PGs," which are crucial for the function of several organ systems, including securing the stomach wall and maintaining kidney function. While most tissues never release "COX-2" under physiologically normal circumstances, however, it manifests when the body is injured, which induces the synthesis of PGs [3]. Many NSAIDs are extensively and effectively used for analgesic purposes, such as reducing dental pain, primary dysmenorrhea, and postpartum pain, in addition to the cure of Rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis [4]. NSAIDs and antibacterial medicines are the most common factors behind drug-induced liver damage (DILI), and the medications most frequently reported to cause hypersensitivity responses [5] both in the population of adults and children. According to experimental data, NSAIDs can cause mitochondrial damage, a rise in dosage levels of the medicines in the hepatobiliary segments, and reacting metabolites that very strongly change proteins [6]. Consider the selective COX-2 inhibitor nimesulide, which has recently been linked to rare but severe and unexpected adverse reactions in the liver. It is commonly used to treat inflammatory and pain conditions. The chemical and the patient both contribute to the risk, just like other medications that cause idiosyncratic hepatotoxicity. Genetics or non-genetics variables, however, make this possible toxicity clinically relevant in a tiny proportion of susceptible patients. The group of NSAIDs is highly diverse in terms of side effects on the liver but is pretty uniform in terms of anti-inflammatory actions and inhibition of cyclooxygenase, which leads to prostaglandin synthesis. Most NSAIDs are regarded to be potential contributors to drug-induced hepatitis, and case reports almost universally link all NSAIDs to liver disease. It has been determined that the danger to NSAID users who additionally use other potentially hepatotoxic medications, is significantly higher than the risk that would be expected merely from adding the risks that would result from exposure to both NSAIDs and other potentially hepatotoxic drugs separately [7]. Although a large number of individuals using NSAIDs, the chance of having significant acute liver damage is low and is not a common clinical issue. The effects of NSAIDs on the liver and hepatic treatments are reviewed in this article.

NSAIDs' action mechanism and classification: There are a few schools of thought that classify NSAID effects according to the main subcellular targets. The two most often reported methods by which NSAIDs are reported to work are dependent and independent PGHS action paths.

An overview of NSAID classification is provided in the section that follows.

Structural Base Classification of NSAIDs: NSAIDs are often categorized depending on their structural makeup. The likelihood that an NSAID will cause liver damage and its chemical category are not well correlated. A list of the most popular NSAIDs is given in Table 1[8].

COX Selectivity Base Classification of NSAIDs: Arachidonic acid is bioconverted by COX enzymes, primarily COX-1 and COX-2, which are blocked by NSAIDs, into inflammatory prostanoids (prostaglandins and prostacyclin). Table 2 compares the effectiveness of NSAIDs in suppressing COX-1 and COX-2 based on their IC80 values (NSAIDs quantity that inhibits 80% activity of the enzyme) [9]. NSAIDs can be categorized into four main groups depending on their abilities to stop COX isoforms (Figure 2): (a) Non-specific, the total repressor of these two COX- 1 and COX- 2, (b) Terminators for COX-1 plus COX-2, but a partiality of COX-2; (c) strong repressors of COX-2, but along with poor inhibitory action against COX-1[9] and (d) weak blockers of two of them COX- 1 and COX- 2 [9].

Half-Life-Based Classification of NSAIDs: NSAIDs can be further subdivided into short-acting for instance diclofenac, ibuprofen, and aspirin, and long-acting for instance celecoxib and naproxen. The rapid onset of action of those with short plasma half-lives, such as ibuprofen, makes them appropriate for sharp pain. NSAIDs such as naproxen, have a longer plasma half-life, are useful for managing chronic illnesses [10].

Causes of Liver Injury: Globally, liver fibrosis is a severe health issue and a chronic condition which is caused by excess production and deposition of connective tissue proteins, particularly interstitial collagens, in the extracellular matrix of the liver [11]. It is a dynamic process that develops as a constant wound-healing response to a range of chronic stressors, including genetic disorders, autoimmune disease, Gut microbiota, mitochondrial DNA of the damaged cell, Venous obstruction, Cryptogenic and congenital liver disease, parasites, ethanol, viruses, toxins, drugs, or cholestasis [12], etc.

NSAIDs Induced Liver Toxicity: The severe negative effects of NSAIDs, such as liver damage, myocardial ischemia, gastrointestinal mucosal damage, and renal failure, restrict their use [5]. Only a few NSAIDs' clinical traits that may be linked to probable liver damage were reported here (Table 3).

Mechanisms of NSAD-Induced Liver Damage

NSAIDs' Bioactivating Effects

Oxidative Stress: In the hepatic metabolism of different NSAIDs, cytochrome P450 (CUP)-mediated oxidative biotransformation plays a significant role. The main isoforms implicated in the oxidative metabolism of several oxicams appear to be members of the CYP2C subfamily also, the effects of diclofenac on human liver microsomes and hepatocytes of rat [13]. According to recent research, CYP2C9 (P450TB) is the main isoform accelerating the liver oxidation of a large number of NSAIDs in people [14]. Specific NSIDs' hepatotoxicity may be attributed to some reactive metabolites. For instance, indomethacin, oxyphenbutazone, benoxaprofen, and phenylbutazone, which can cause lymphocyte preparations to become cytotoxic [15]. Similar to this, cultivated hepatocytes released enzymes in response to an in vitro-produced oxidative diclofenac metabolite [16], but the parent chemicals did not.

Acyl Glucuronides Formation: It has been proven that acyl glucuronides from different carboxylic NSAIDs bind

covalently to nucleophilic amino acid residues of intracellular and extra-cellular proteins. Renal clearance of conjugated NSAIDs may be compromised in elderly people. As a result, acyl glucuronides may build up, go through hydrolysis, and produce the parent product, which appears to reduce the plasma clearance of these medicines [17]. In elderly people, the recycling of acyl glucuronides may result in larger levels of the reactive acyl glucuronides and therefore higher protein adduct production.

Irreversible Binding of Protein

Protein Adduct Pathways: There are two methods for adducing proteins. The first method includes tyrosine, free cysteine thiols, or lysine residues of the proteins nucleophilically dislodging the drug's glucuronic acid moiety. The second mechanism is whereby acyl glucuronides form covalent protein adducts [18].

Adducts of plasma proteins: As a result of the acyl glucuronides' reactivity, many NSAIDs bind plasma proteins in an irreversible manner. For instance indomethacin, benoxaprofen and flufenamic acid [19], suprofen [20], diflunisal, ketoprofen [21], tolmetin, carprofen, and etodolac [22] have all been demonstrated, in vitro, to bind to albumin. In addition, several drugs in vivo formed adducts with plasma proteins while some NSAIDs have been shown to form long-lasting adducts.

Drugs Peptide Adducts: In organs exposed to medicines or their glucuronides, some investigations have looked into the production of intracellular adducts. For instance, covalent adducts of diflunisal with proteins are found in the liver, kidney, muscle, and intestine of rats treated with the medication [23], and also with the protein of urinary bladder tissue [8].

Immune-Mediated Hepatotoxicity

Immunogenicity and Antigenicity of NSAID-Modified Proteins: A molecule needs to have at least 1000 Da in molecular mass to trigger an immunological response. NSAIDs are smaller than this, however, to create a medication (hapten)-carrier conjugate that might have an impact on the immune system, they must be covalently attached to a macromolecule. Several NSAIDs can cause the development of protein adducts and trigger immunological responses that harm the tissue and cause inflammation [24].

T-cell and Antibody-Dependent Cytotoxicity : In vitro studies have supported the hypothesis that NSAIDs produce liver damage that is T-cell-mediated or antibody-dependent cell-mediated[25].

Autoimmune liver disease: Some NSAIDs have the potential to cause autoimmune hepatitis. In the case of clometacine-associated hepatitis, significant levels of non-DNA or non-smooth muscular anti-bodies are frequently present, which is common for severe active autoimmune hepatitis [26].

Metabolic Abnormalities: It is primarily based on indirect evidence that some drugs, such as Sulindac or diclofenac, may damage the liver in some susceptible persons via an aberrant metabolic pathway. This may indicate a direct toxic reaction rather than an immune-mediated mechanism in these patients given the pattern of the histological changes, the potential for dose dependency in some NSAID-induced liver reactions, and the absence of the clinical characteristics of immune allergic reactions [27].

Contraindications of NSAIDs: Patients who have salicylate or NSAID hypersensitivity, allergic reactions (urticaria, asthma, etc.), had coronary artery bypass graft surgery, or are pregnant during the third trimester should not take NSAIDs [28].

Treatment strategies for liver injury: Current therapies include removing the source of damage, such as dietary changes, alcohol abstinence, and antiviral medications. But in individuals with late-stage fibrosis or cirrhosis, such etiology-driven treatment is frequently insufficient, thus effective antifibrotic pharmacotherapeutic such as vaccination [29], anti-fibrotic drugs, anti- inflammatory treatment [30], antioxidant, inhibition of hepatocyte apoptosis, deactivation of extracellular matrix-producing cells, inhibitors of cytokine signaling [31], specific treatments for the Renin-angiotensin system [32], gene therapy and liver transplantation [33] are required.

Conclusion: Numerous acidic NSAIDs are linked to hepatocellular injury and, in rare cases, cholestatic liver damage, (induce immunological reactions, bind plasma proteins irreversibly, and lead to autoimmune hepatitis) according to the analysis of the documented NSAID-induced idiosyncratic adverse responses. However, minor liver injuries may be managed with a healthy lifestyle, while serious damage may require several treatment modalities, such as medicine to reduce inflammation and fiber production in the damaged liver, gene therapy, or liver transplantation.

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Table. 1. Characterization of NSAIDs based on their chemical structures

Carboxylic acids					**Enolic acids**	
Salicylic acids/-esters	**Acetic acids**	**Carbo- & heterocyclic acetic acids**	**Propionic acids**	**Fenamic acids**	**Pyrazolones**	**Oxicams**
Acetyl salicylic acid	**Phenylacetic acids**	Indomethacin	Ibuprofen	Flufenamic	Kebuzone	Piroxicam
Diflunisal	Diclofenac	Fentiazac	Oxaprozin	Tolfenamic	Feprazone	lsoxicam
Benorilate	Alclofenac	Etodolac	Tiaprofenic acid	Niflumic	Azapropazone	Sudoxicam
Aspirin	Fenclofenac	Zomepirac	Suprofen	Meclofenamic	Phenylbutazone	
	lbufenac	Tolmetin	Carprofen	Mefenamic	Oxyphenbutazone	
		Sulindac	Pirprofen			
		Clometacin	Ketoprofen			
		Fenclozic acid	lndoprofen			
			Benoxaprofen			
			Fenbufen			
			Fenoprofen			
			Flurbiprofen			
			Naproxen			

Table. 2. The levels of a drug's 80% COX-2 and COX-1 activity-inhibiting ratio (IC8 (values >1 indicate a greater preference for COX-1; values <1 indicate greater specificity for COX-2).

Non-selective NSAIDs	IC80 ratio COX-2/COX-1	COX-2 Selective NSAIDs	IC80 ratio COX-2/COX-1
Ketorolac[34]	294	Rofecoxib[34]	<0.05
Flurbiprofen[35]	51	Etodolac	0.04
Ketoprofen	6	Meloxicam[36]	0.09
Indomethacin[37]	4.3	Celecoxib	0.11
Aspirin[38]	3.8	Diclofenac[36]	0.23
Naproxen	3.00		
Ibuprofen[37]	2.6		
Fenoprofen	1.00		
Diflunisal	0.75		
Piroxicam	0.47		
Sulindac Sulfide[9]	0.29		

NSAID: non-steroidal anti-inflammatory drugs, IC: inhibitory concentration, COX: cyclooxygenase

Table. 3. NSAIDs which associated with liver injury.

NSAIDs	Target	Pathogenicity	Mechanism Of Action	Damage
Aspirin [35]	Inhibition of AP-1, NF-κB, MAPK cascade, L-selectin shedding	Reye's syndrome	> with a high dose	
		Acute and chronic hepatitis	Dose-dependent	low
Coxibs [39]	Kinases (Inhibition of PDK1/Akt signaling)	Acute hepatitis, mixed damage	Probably metabolic process	low
Ibuprofen [40]	Inhibition of NF-κB, MAPK cascade, Stimulation of PPAR-γ	Acute hepatitis, ductopenia	metabolic process	low
Naproxen [41]	Kinases (Inhibition of PI3k/ Akt)	Cholestatic, mixed damage	metabolic process	low
Diclofenac [42]	Leukocyte adhesion molecules (Inhibition of VLA-4 activation, L-selectin shedding)	Acute and chronic hepatitis	metabolic process	low
		Mixed damage and pure cholestasis	Immunologic	
Sulindac[43], [44]	Inhibition of NF-κB, MAPK cascade	Acute hepatitis and mixed injury	Hypersensitivity	Moderate
Oxicams [45]	inhibition of mPGES-1	Acute hepatitis, massive and submassive necrosis, cholestasis, and ductopenia	metabolic process	low
Nimesulide [46]	-	Acute hepatitis, pure cholestasis	Probably metabolic process	Moderate

NSAIDs: non-steroidal anti-inflammatory drugs, AP-1: activating protein-1, NF-κB: nuclear factor kappa B, MAPK: mitogen-activated protein kinase, PDK1: 3-phosphoinositide-dependent kinase 1, PPAR-γ: peroxisome proliferator-activated receptor-γ, PI3k: Phosphatidylinositol 3-kinases, VLA-4: very late antigen-4, mPGES-1: microsomal prostaglandin E synthase-1.

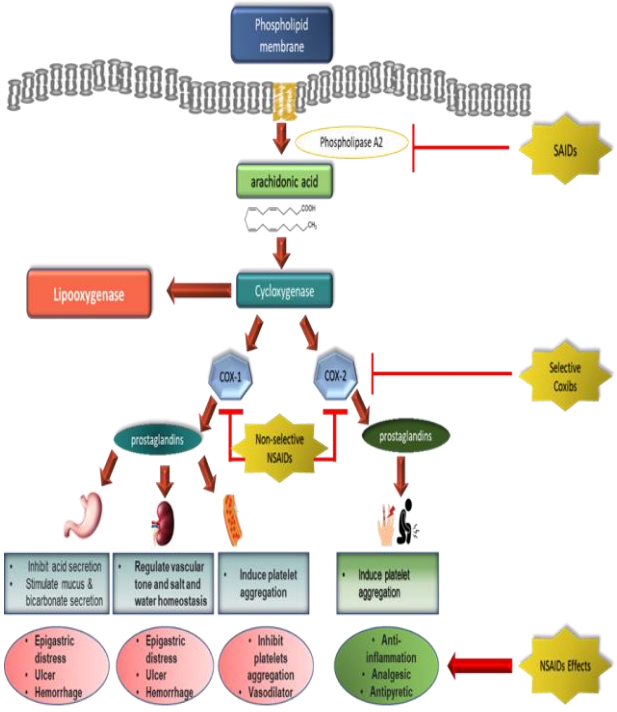

Fig. 1. Nonsteroidal anti-inflammatory medication action.

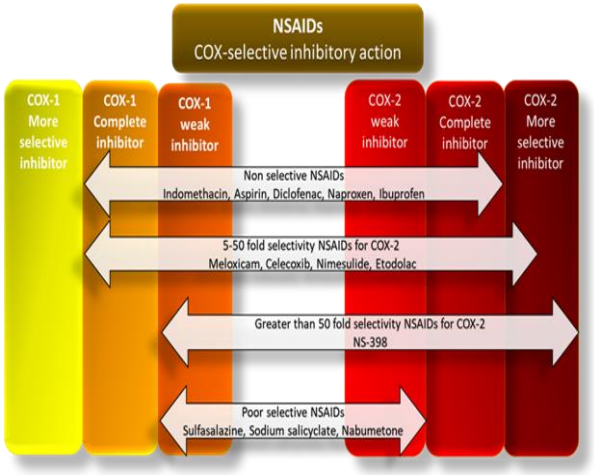

Fig. 2. NSAIDs categorization is based on COX-selective inhibitory action.

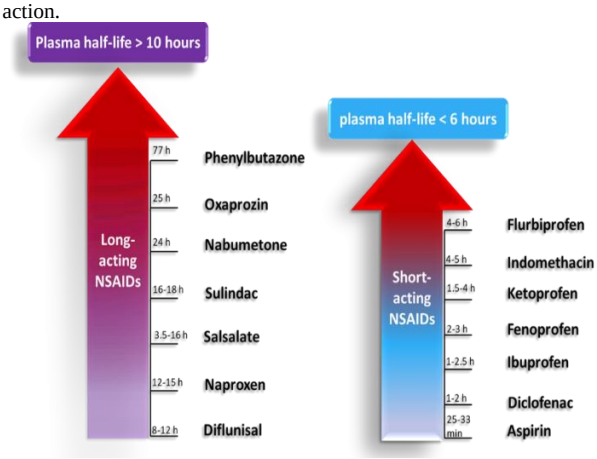

Fig. 3. NSAIDs Categorization according to their plasma ½ life

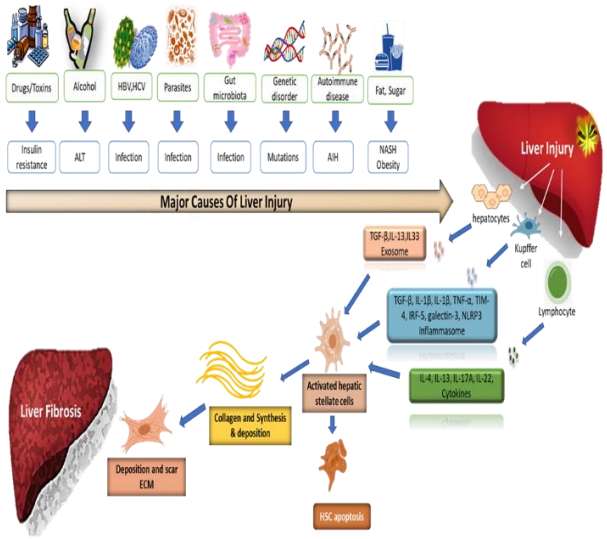

Fig. 4. Inflammation can begin and progress in the liver as a result of genetic mutation, metabolic problems, cholestasis, viral infections, parasites, medications, poisons, alcohol-causing ALD, and a broad range of different toxic substances and variables of the environment. Extreme inflammation activates hepatic stellate cells, which later change into proliferative myofibroblasts that produce an extracellular matrix, resulting in fibrosis and hepatic failure. TIM-4: T cell immunoglobulin and mucin-4, TGF-β: transforming growth factor beta, IRF-5: interferon regulatory factor-5, TNF-α: tumor necrosis factor-alpha, NLRP3: NLR family pyrin domain containing 3.

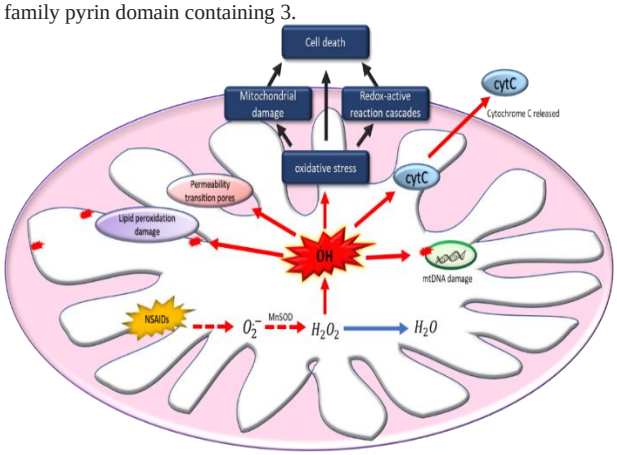

Fig. 5. Overview of the formation of reactive oxidants in mitochondria caused by NSAIDs that cause cellular damage. The majority of reactive oxygen species (ROS) are formed from superoxide (O_2^-) which is quickly transformed into H_2O_2 by superoxide dismutase (SOD2). Reactive radicals cause DNA damage, lipid peroxides, and protein carbonyls when they interact with biomolecules such as membrane lipids, proteins, and mtDNA. When the outer mitochondrial membrane becomes damaged, cytochrome C is released into the cytosol, activating the apoptotic pathway. Numerous cellular diseases are caused by the combination of all these events.

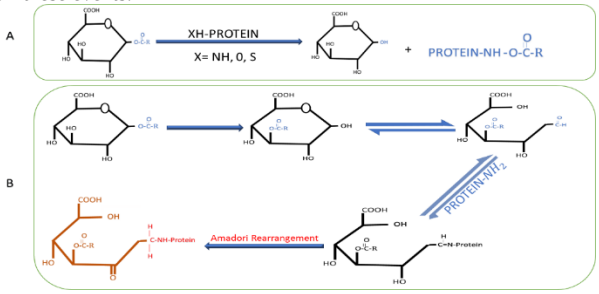

Fig. 6. Speculated pathways for the glucuronide-mediated irreversible binding of carboxylic acids to proteins. (a) Nucleophilic displacement process, resulting in the liberation of o-glucuronic acid and an acylated protein. (b) The protein that connects the adduct via the imide process and the acyl residue are connected by glucuronic acid.

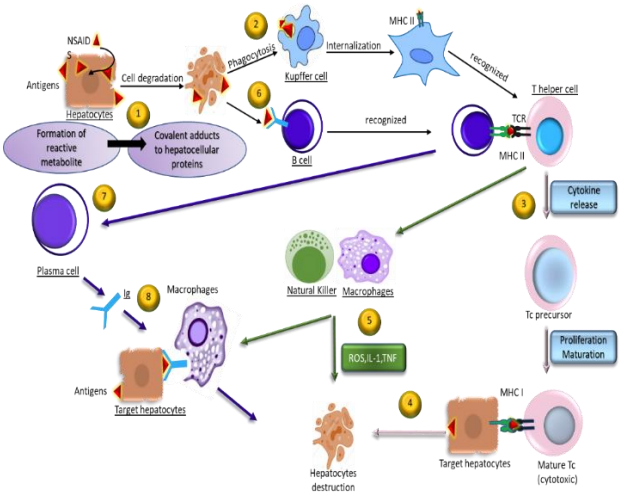

Fig. 7. Putative mechanisms and potential pathways of NSAID-induced immune-mediated hepatocyte damage. (1) After the hepatocyte is degraded, Immune system cells will have access to intracellular proteins of NSAID covalent adducts. Plasma membrane proteins may also include adducts. (2) Kupffer cells and various macrophages antigen-presenting cells, internalize NSAID-altered protein (immunogen), which is followed by the peptides being processed and presented in conjunction with MHC class II molecules. (3) B cell and cytotoxic T cell (T,) precursors are activated by cytokines, which causes their clonal proliferation and maturation into T cells. (4) T cell recognition, target cell apoptosis, and antigen-presenting cells with MHC I on the hepatocyte surface (by perforin). (5) Release of macrophage activating factor (MAF) and macrophage inhibitory factor (MIF) by T cells (MAF). Complement factors (C3a), tumor necrosis factor (TNF), Reactive oxygen species (ROS), interleukin-1 (IL-1), and various mediators are responsible for activating macrophages and destroying target cells. (6) B-cell receptor interaction, internalization, processing, and presentation of the NSAID-altered protein in association with the MHC class 2 molecule. (7) stimulation of B cells, clonal growth, and development into plasma cells that release immunoglobulins (lg). (8) Epitopes on the hepatocytes' plasma membrane are identified by certain antibodies and serve as their binding sites. Target hepatocytes are destroyed as a result of killer cells and macrophages' non-specific identification and binding via the Fc receptor, or as a result of complement activation.

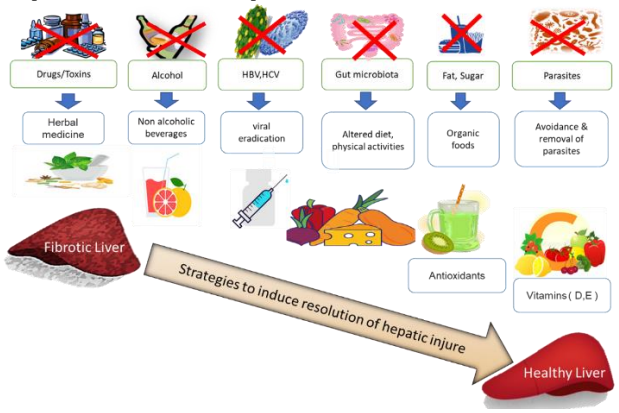

Fig. 8. Hepatic fibrosis resolution-inducing techniques.