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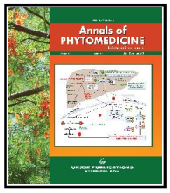

Review Article : Open Access

Hepatoprotective activity of herbal extracts and other compounds against acetaminophen-induced hepatotoxicity by various mechanisms: A narrative review

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Abstract

Paracetamol (Acetaminophen) toxicity has become an important problem worldwide. Overdoses and doses close to the usual therapeutic doses can cause acute hepatic failure. Strategies for investigating the biochemical and molecular mechanisms underlying paracetamol toxicity could provide significant benefits in treating paracetamol-induced hepatotoxicity. This review provides an innovative perspective on the role of cytochrome P450 (CYP), oxidative stress, free radicals, JNK, UDP-glucuronosyl transferase, glucuronic acid, sulfotransferase, quinone reductase, caspases, PTP1B, hepatic resident macrophages, kupffer cells, Bax/Bcl-2, mitochondrial oxidative stress, mitochondrial permeability, cytochrome c, p^{53}, Ca^{2+} channels, necrosome, glutathione-S-transferase, glutathione peroxidase, glutathione reductase, TRPM2 channels, lipid peroxidation, PARP receptors, iNOS, Nrf-2 protein, inflammation, α1-adrenoceptors, NF-κB, connexin 32, coagulation system, and liver X receptor in paracetamol-induced hepatotoxicity. Inhibitors/blockers of CYP2E1, JNK, caspase, PTP1B, Bax/Bcl-2, cytochrome c release, P53, Ca^{2+} channels, PARP, iNOS, α1-adrenoceptor, connexin 32, and activators of quinone reductase, UDP-glucuronosyl transferase, sulfotransferase, glutathione-S-transferase, glutathione reductase, TRPM2, Nrf-2 protein, and inactivators of hepatic resident macrophages, kupffer cells, necrosome, glutathione peroxidase, NF-κB, and cysteine prodrugs, antioxidants, free radical scavengers, anti-inflammatory agents, anticoagulants, liver X receptor agonists, and compounds that provide/converted into glucuronic acid are used treating paracetamol-induced hepatotoxicity.

1. Introduction

One of the most popular analgesics and antipyretics is paracetamol (Acetaminophen; *N*-acetyl-*p*-amino-phenol). It is being used by millions of people worldwide as an over-the-counter drug to its relative safety over aspirin and non-steroidal anti-inflammatory properties in terms of gastrointestinal bleeding (Bateman *et al.,* 2014; Vliegenthart *et al.,* 2015). Despite being safe, several cases of paracetamol-induced hepatotoxicity at therapeutic doses have been reported (Bartels *et al.,* 2008; Ito *et al.,* 2015; Seifert *et al.,* 2016). Paracetamol overdosage in individuals, particularly adolescents and adults with suicidal intent, can result in severe necrosis of hepatic tissue and failure.

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Moreover, paracetamol (PCM) is the only marketed product with direct hepatotoxic effect at doses close to a regular therapeutic dose and even lead to acute hepatic failure (Bernal *et al.,* 2010; Fontana, 2008). Glucuronidation and sulfation are the primary metabolic pathways of PCM that occur in the liver at therapeutic doses (Figure 1). Most of the metabolites of PCM, such as glucuronide (40-60%) and sulfonate (20-30%), are eliminated from the body through urine. Microsomal cytochrome P-450 containing mixed-function oxidase system mainly such as CYP2E1. CYP1A2 and CYP3A4 metabolize a small fraction (5-10%) of PCM to *N*-acetyl-*p*-benzoquinone imine (NAPQI), a reactive electrophilic intermediate responsible for hepatotoxicity and nephrotoxicity. NAPQI is found in trace amounts and deactivated by glutathione (GSH) at therapeutic doses of PCM. Hepatic GSH is depleted after excess doses of PCM or induction of CYP2E1 by drugs such as isoniazid leads to an increase in the levels of NAPQI that covalently binds to hepatocyte proteins and causes cell death.

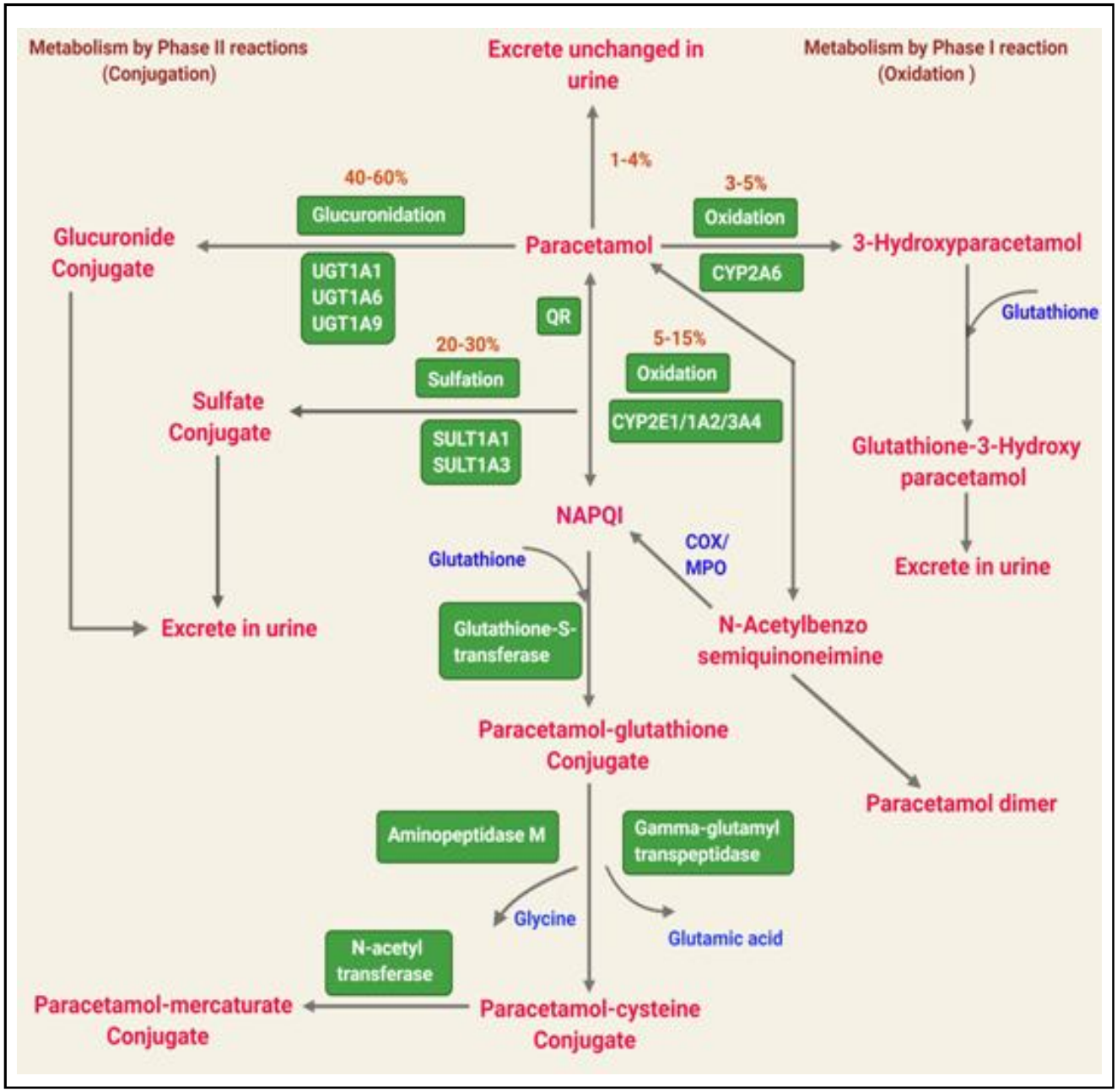

Figure 1: The overall metabolism of paracetamol at therapeutic dose. NAPQI, N-acetyl-p-benzoquinoneimine; UGT1A1, UDP-glucuronosyl transferase 1A1; UGT1A6, UDP-glucuronosyl transferase 1A6; UGT1A9, UDP-glucuronosyl transferase 1A9; SULT1A1, Sulfonyltransferase 1A1; SULT1A3, Sulfonyltransferase 1A3; CYP2E1, Cytochrome P450-2E1; CYP1A2, Cytochrome P450-1A2; CYP3A4, Cytochrome P450-3A4; CYP2A6, Cytochrome P450-2A6; QR, Quinone reductase; GSH, reduced glutathione; MPO, Myeloperoxidase.

The well-known risk factors for PCM toxicity are overdosage, malnutrition, starvation, obesity, and co-administered drugs (Figure 2).

PCM overdosage causes the saturation of glucuronidation and sulfation pathways. Malnutrition and starvation may decrease the metabolism of PCM by glucuronidation and sulfation due to depletion of GSH stores in the hepatocytes. The co-administered drugs are also significant risk factors because they are the inhibitors of glucuronidation (*e.g.*, barbiturates, antiepileptics) (Ito *et al.,* 2015), sulfation (*e.g.*, mefenamic acid, salicylic acid, and inducers of CYP enzymes (*e.g.*, acarbose, alcohol) (Thummel *et al.,* 2000). The purview of this article is to explain the biochemical and molecular mechanisms underlying PCM-induced hepatotoxicity and then empirically investigated more than 35 therapeutic targets for PCM-induced hepatotoxicity. Researchers will be able to create new, safer pharmaceutical products with PCM inorder to reduce its toxicity.

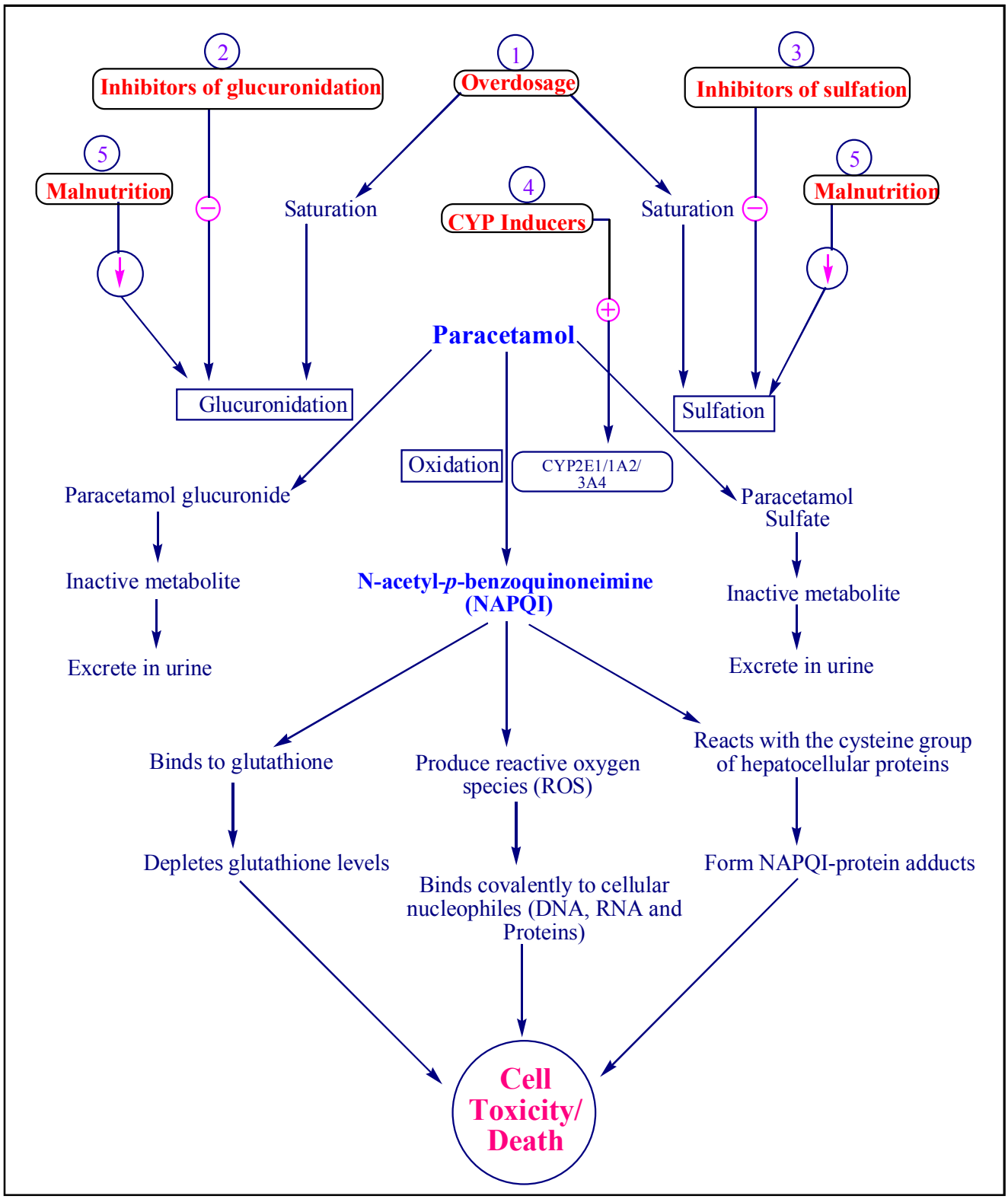

Figure 2: Paracetamol-induced hepatotoxicity and its risk factors. The toxicity is caused by 1. its toxic/overdose (saturation of glucuronidation and sulfation); 2. co-administration of paracetamol with inhibitors of glucuronidation (*e.g.*, phenobarbital, phenytoin etc..); 3. with inhibitors of sulfation (*e.g.*, mafenamic acid, salicylic acid *etc.*); 4. with inducers of CYP enzymes (e. g. alcohol, high dose of acarbose, troglitazone *etc.*); and 5 malnutrition (decreases glucuronidation and sulfation).

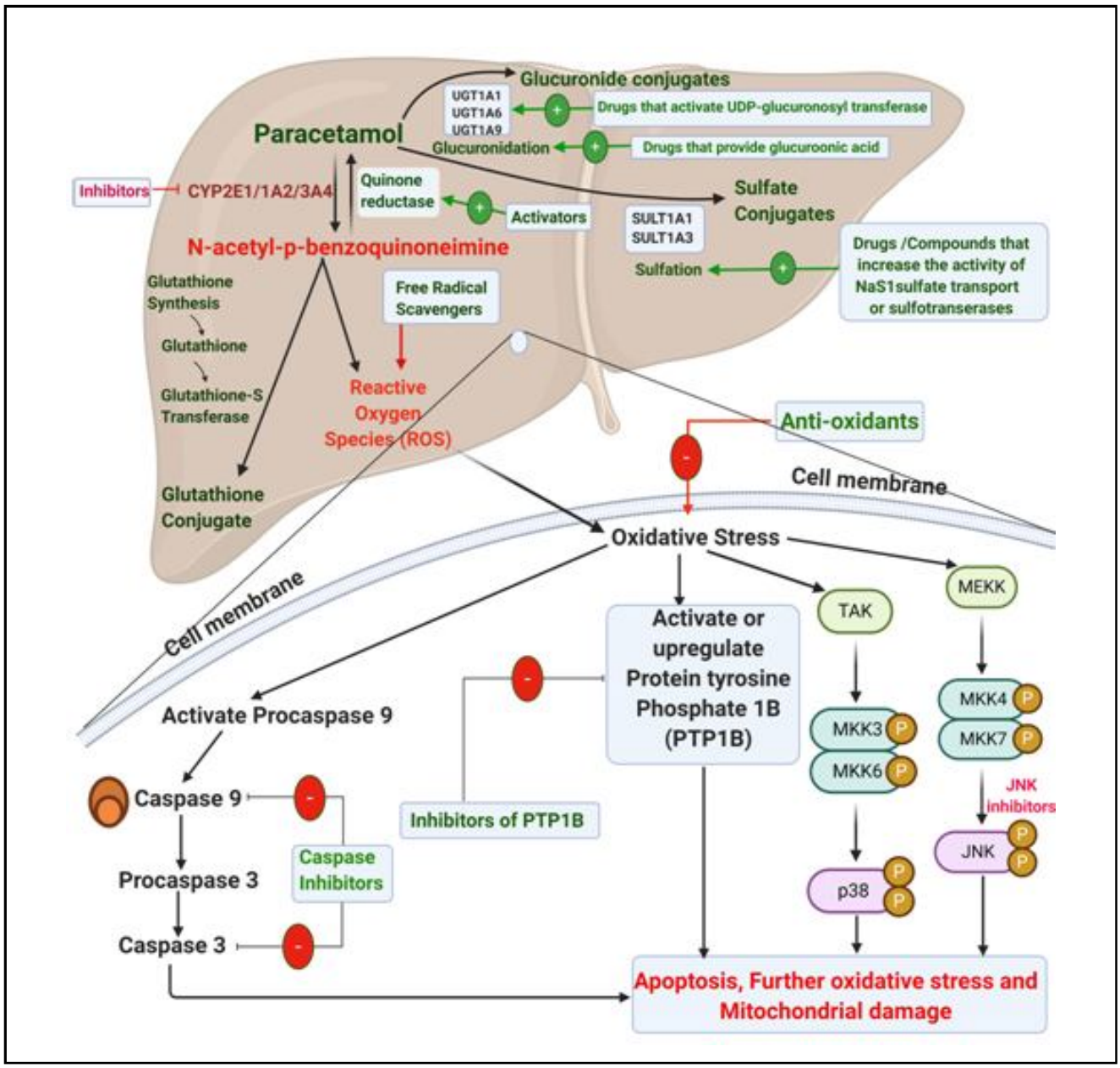

Figure 3: Cell signalling pathways and other mechanisms as therapeutic targets in paracetamol-induced hepatotoxicity. JNK, c-jun (NH2) terminal kinase; ROS, Reactive oxygen species; CYP2E1, cytochrome P450- 2E1; CYP1A2, cytochrome P450- 1A2; CYP3A4, cytochrome P450- 3A4; MEKK, MEK kinase; ASK, apoptosis signal regulating kinase and MKK, Mitogen activated protein kinase kinase; QR, quinone reductase.

2. Hepatoprotective activity of CYP2E1 inhibitors

In the liver, CYP2E1 is a membrane protein that accounts for nearly half of total hepatic CYP mRNA and 7% of total hepatic CYP protein. When catalysis is not well-coordinated, it can produce reactive oxygen species (ROS) in the active site, which can lead to lipid peroxidation, protein oxidation, and DNA oxidation. CYP2E1-dependent oxidation of PCM produces the toxic metabolite NAPQI (Figure 3). In addition to N-acetylcysteine treatment, inhibiting the CYP2E1 enzyme that produces NAPQI may be helpful in reducing PCM overdose. The formation of NAPQI was studied using selective CYP2E1 inhibitors used in human therapy. Baicalin (Jang *et al.,* 2003), ozagrel hydrochloride (Tomishima *et al.,* 2013), lupeol (Kumari and Kakkar, 2012), aminotriazole (Jing *et al.,* 2015), *Ornithogalum saundersiae* extract (Wan *et al.,* 2012), dioscin (Zhao *et al.,* 2012), *Phyllanthus urinaria* extract (Hau *et al.,* 2009), *Kigelia africana*, *Calotropis procera*, *Hibiscus sabdariffa*, and *Alchornea cordifolia* (Shon and Nam, 2004) have all been found to have inhibition of CYP2E1 alleviated PCM-induced hepatotoxicity in various animal models by reducing the formation of NAPQI. As a result, CYP2E1 could be a potential target, and CYP2E1 inhibitors could be beneficial in the treatment of PCM-induced hepatotoxicity (Table 1).

Table 1: Hepatoprotective activity of various compounds/drugs against paracetamol-induced hepatotoxicity due to CYP inhibition

Compound/drug tested and treatment schedule	Animal/tissue model used	Paracetamol dose and route of administration	Reference
CYP2E1 inhibitors			
Baicalin 300 mg/kg, p. o. after 0.5 h of PCM treatment	Mice	400 mg/kg b.w., i. p.	Jang *et al.*, 2003
Ozagrel hydrochloride 100 or 200 mg/kg, i. p. treat 30 min after PCM treatment	ICR male mice	330 mg/kg, i. p.	Tomishima *et al.*, 2013
Lupeol 150 mg/kg b.w., p. o.	Wistar rats	1 g/kg b.w., p. o.	Kumari and Kakkar, 2012
Wuzhi tablet (*Schisandra sphenanthera* extract)(175, 350, 700 mg/kg body weight BD for 3 days, i. p.)	Male C57BL/6 mice (6-8 weeks old)	400 mg/kg body weight for 3 days	Xiaomei *et al.*, 2014
Compounds that inhibit CYP2E1/ 1A2/3A4			
Ketoconazole 10 mg/kg, isoniazid 10 mg/kg, caffeine 100 mg/kg, i. p.	Male Sprague-Dawley rats (350-400 mg)	300-1822 mg/kg, i. p.	Walubo *et al.*, 2004
Caffeic acid 6 mg/kg and quercetin 10 mg/kg, p. o.	Swiss male mice and male albino wistar rats	650 mg-1g, oral	Janbaz *et al.*, 2004

Table 2: Hepatoprotective activity of compounds against parcetamol-induced hepatotoxicity due to inhibition of oxidative stress, JNK and activation of phase II metabolizing enzymes

S. No.	Compound/drug tested and treatment schedule	Animal/tissue model used	Paracetamol dose and route of administration	Reference
1.	**Inhibitors of oxidative stress or antioxidants**			
	Low doses of atorvastatin 2, 5, 20 mg/kg for 21 days, orally	Adult male albino rats 100-125 mg	500 mg/kg, oral.	Farag *et al.*, 2015
	Pterostilbene 50 mg/kg for 15 days before PCM treatment, p. o.	Male adult Sprague-Dawley rats175-220g	800 mg/kg, i. p.	El-Sayed *et al.*, 2015
	Nilotinib 25, 50 mg/kg, 2 h after PCM intoxication, i. p.	Male BALB/c mice 24-26 g	500 mg/kg, i. p.	Shaker, 2014
2.	**Free radical scavengers**			
	Curcumin 25, 50, 100 mg following PCM, i. p.	Male Sprague-Dawley rats	700 mg/kg, i. p.	Kheradpezhouh *et al.*, 2014
	β-carotene 30 mg/kg pre-treatment, once daily for 10 days, p.o.	Swiss Albino mice	400 mg/kg, orally on 10^{th} day	Manda and Bhatia, 2003
3.	**JNK inhibitors**			
	Aminotriazole 125, 250, 500 mg/kg, i. p.	Male C57 mice20-25 g body weight	350 mg/kg, i. p.	Jing *et al.*, 2015
4.	**Activators of UDP-glucuronosyl transferase**			
	Coffee 1.5% lyophilized coffee	Pregnant Wistar rats	700 mg/kg body weight, i. p.	Renata and Tasso, 2011
5.	**Compounds that provide/converting into glucuronic acid**			
	Flumazenil 0.1, 1, 10 mg/kg, i. p.	Adult Albino wistar rats (250-350 mg)	3 g/kg, i. g.	Bozogluer *et al.*, 2012
6.	**Activators of sulfotransferase**			
	Activation of liver X receptors (LXR) agonist like T0901317 10 mg/kg, i. p.	LXR α and β double knockout (LXR DKO) mice	200 mg/kg body weight, oral	Saini *et al.*, 2011

3. Hepatoprotective activity of antioxidants

An imbalance between free radicals and antioxidants in the body causes oxidative stress (Nazia *et al.,* 2022; Jyoti *et al.,* 2022). Because free radicals react so easily with other molecules, they can cause large chain chemical reactions in the body (Figure 3). High doses of atorvastatin (ATV) caused hepatic lipid peroxidation and injury. According to Farag *et al.* (2015), lower doses of ATV, on the other hand, reduced PCM-induced hepatic oxidative stress and thus attenuated PCM-induced hepatotoxicity.

Lupeol reduced oxidative stress and prevented PCM-induced hepatotoxicity when given in combination with PCM (Kumari and Kakkar, 2012). Similarly, pterostilbene (El-Sayed *et al.,* 2015), chitosan (Ozcelik *et al.,* 2014), nilotinib (Shaker, 2014), agomelatine (Karakus *et al.,* 2013), silymarin (Simeonova *et al.,* 2013), rhein (Zhao *et al.,* 2011), lactoferrin (Chodaczek *et al.,* 2007), quercetin, curcumin (Yousef *et al.,* 2010), *Boerhaavia diffusa* Linn extract (Olaleye *et al.,* 2010), *Solanum fastigiatum* leaves (Sabira *et al.,* 2008), fresh juice of tender *Azadirachta indica* leaves (Yanpallewar *et al.,* 2003). As a result, oxidative stress could be a target, and antioxidants could be helpful in treating PCM-induced hepatotoxicity (Table 2).

4. Hepatoprotective activity of free radicals or reactive oxygen species scavengers

Free radicals are chemicals with one or more unpaired electrons, making them highly unstable. To become stable, these molecules conceal electrons from another molecule, causing damage to the macromolecule. Because of physiological and metabolic functions, human body constantly produces free radicals (Vikash and Mohan, 2022; Manoj *et al.,* 2021). As a result, produced free radicals damage biomolecules like protein, lipid, and amino acids, as well as cause cell injury, which leads to a variety of diseases (Figure 3). Antioxidants can reduce the risk of various diseases by delaying the effects of free radicals. Plants are a good source of natural antioxidants, and they are considered to be safer than synthetic antioxidants. According to Jung *et al.* (2013), davallialactone (DAVA) protects against PCM-mediated hepatotoxicity by acting as a ROS scavenger. Similarly, by scavenging ROS, pioglitazone (Gaurav *et al.,* 2014), *Ornithogalum saundersiae* (Wan *et al.,* 2012), vinylic telluride (Daiana *et al.,* 2011), curcumin (Ehsan *et al.,* 2010), and carotene (Manda and Bhatia, 2003) have hepatoprotective properties against PCM-induced liver damage. As a result, ROS could be a potential target, and ROS scavengers could help treat PCM-induced hepatotoxicity (Table 2).

5. Hepatoprotective activity of JNK signalling pathway inhibitors

The c-Jun N-terminal kinases (JNKs) are members of the mitogen-activated protein kinase (MAPK) family. JNKs have an impact on the major regulators of brain functioning, immunological actions, and embryonic development, such as gene expression, cytoskeletal protein dynamics, and cell death/survival pathways. In the pathophysiology of PCM-induced hepatotoxicity in mice and humans, activation of JNK and translocation of p-JNK to mitochondria could be a critical amplification mechanism (Figure 3). JNK inhibitors, such as aminotriazole (Jing *et al.,* 2015), wuzhi tablet (Xiaomei *et al.,* 2014), ginseng (Kentaro *et al.,* 2015), leflunomide (Su *et al.,* 2008), 2-amino ethoxy diphenyl borate (Walubo *et al.,* 2004), small heterodimer partner SHP (Yong *et al.,* 2018), and chlorpromazine (Yuan *et al.,* 2019), are useful in treating PCM-hepatotoxicity. As a result, the JNK signalling pathway could be a potential target for PCM-induced hepatotoxicity, and JNK inhibitors could be beneficial (Table 2).

6. Hepatoprotective activity of UDP-glucuronosyltransferase (UGT) activators

A variety of drugs and xenobiotics can activate glucuronosyl transferases, which are found in the endoplasmic reticulum. CYP co-induces some glucuronosyltransferases. Conjugation with glucuronic acid makes lipophilic molecules much more water soluble and excretable, and is thus thought to be a detoxication pathway (Figure 3). According to Renata and Tasso, (2011), coffee consumption modulates phase II of the hepatic biotransformation system, improving the organism's detoxification ability against PCM-induced hepatotoxicity. Caffeine, on the other hand, increased the formation of PCM-glutathione conjugates, which protected the liver by activating UGT (Keith *et al.,* 2002). As a result, UGT may be a potential target, and UGT activators may alleviate PCM-hepatotoxicity (Table 2).

7. Hepatoprotective activity of glucuronic acid providers

A conjugation reaction (glucuronidation) occurs when D-glucuronic acid is added to a drug or xenobiotic as part of the detoxification process. The addition of glucuronic acid to PCM makes it water-soluble, allowing it to be excreted *via* urine. Compounds that provide/convert to glucuronic acid protect the liver from the hepatotoxic effects of PCM (Figure 3). Flumazenil is a 1, 4 imidazodiazepine derivative that has an antagonistic effect on the analgesic effect of PCM. The possible mechanism is that flumazenil reduces the hepatotoxic effects of PCM by converting to inactivated free carboxylic acid and glucuronic acid (Bozogluer *et al.,* 2012). As a result, glucuronic acid could be a potential target, and glucuronic acid providers or converters could be beneficial in the treatment of PCM-induced hepatotoxicity (Table 2).

8. Hepatoprotective activity of sulfotransferase activators

Sulfotransferase (SULT) is a phase II enzyme that transfers a sulphate group from 32-phosphoadenylyl sulphate to an acceptor's hydroxyl group. Sulfotransferase 2B1b (SULT2B1b) is involved in a number of liver-related diseases, including metabolic syndrome, chronic liver injury, and hepatocellular carcinoma (Figure 3). Hepatic nuclear factor 4 (HNF4) regulates SULT2B1b transcription, which is required for liver development and function. Compounds that stimulate sulfotransferase produce sulphate conjugates, which prevent the formation of NAPQI (Saini *et al.,* 2011). Similarly, in isolated hepatocyte studies, sodium sulphate increased the Vmax of PCM sulfotransferase activity and the formation of PCM sulphate. The combination of 2, 6-dichloro-4-nitrophenol and PCM inhibited PCM-sulfate formation *in vivo* while significantly worsening PCM hepatotoxicity in hamster hepatocytes. As a result, sulfotransferase may be a potential target, and sulfotransferase activators may be useful in the treating PCM-induced hepatotoxicity (Table 2).

9. Hepatoprotective activity of quinone reductase activators

NADPH: Quinone reductase (QR) is an enzyme which catalyses the reaction $NADPH^+ H^+ + 2$ quinone to yield $NADP^+ + 2$ semiquinone. This enzyme's three substrates are NADPH, H^+, and quinone, and its two products are $NADP^+$ and semiquinone. Quinone reductase converts NAPQI to PCM, preventing ROS formation and PCM hepatotoxicity (Figure 3). The role of QR in the protective effect of

alcohol against PCM-induced hepatotoxicity was studied. According to the findings, ethanol not only inhibited the microsomal CYP2E1-mediated formation of NAPQI from PCM, but it also accelerated the conversion of NAPQI to PCM by stimulating cytoplasmic QR activity. In the presence of dicoumarol, QR activity was inhibited, as was the conversion of NAPQI to PCM, lowering the alcohol-dependent protective effect against PCM-induced hepatic injury. Similarly, resveratrol (Sener *et al.,* 2006) and quercetin (Janbaz *et al.,* 2004) demonstrated hepatoprotective activity *via* quinone reductase activation. As a result, quinine reductase may be a potential target, and quinine reductase activators may be useful in the treatment of PCM-induced hepatotoxicity (Table 3).

Table 3: Hepatoprotective activity of compounds against parcetamol-induced hepatotoxicity due to inhibition of quinone reductase, caspase, PTP1B and modulation of Bax/Bcl-2

S. No.	Compound/drug tested and treatment schedule	Animal/tissue model used	Paracetamol dose and route of administration	Reference
1.	**Inhibitors of quinone reductase**			
	Resveratrol 30 mg/kg, i. p.	BALB-c mice	900 mg/kg body weight, i. p.	Sener *et al.,* 2006
	Quercetin 10 mg/kg, p.o.	Mice 20-25 g	1 g/kg body weight, oral	Janbaz *et al.,* 2004
2.	**Caspase inhibitors**			
	Z-VAD-CH_2F 10 mg/kg, i. p.	Male C3Heb/FeJ mice of 20-25 g body weight	100-500 mg/kg body weight, i.p.	Lawson *et al.,* 1999
	Probiotic *Enterococcus lactis* IITRHR1 0.05, 5 and 50 mg per 200 g rat body weight orally for 7 days	Male Wistar rats 200 ± 10 g body weight	1 g/kg body weight orally for 14 days	Sapna *et al.,* 2012
3.	**PTP1B inhibitors**			
	Suramin and rosiglitazone 20 mM	Hepatocytes	10 mM	Mobasher *et al.,* 2014
4.	**Modulators of Bax/Bcl-2**			
	Dioscin 5, 50, 100 mg/kg once daily for 5 days, i.g.	Hep G2 cells Kunming male mice	300 mg/kg body weight, i. p.	Zhao *et al.,* 2012
	Leflunomide 0, 0.5, 2 and 15 µM	Mouse and human liver microsomes	800 µM	Su *et al.,* 2008
	Hesperidin 100, 200 mg/kg orally for 14 days	Male Wistar rats (150-200 g) oral	750 mg/kg body weight,	Shiekh *et al.,* 2012

10. Hepatoprotective activity of caspase inhibitors

Caspases, a type of cysteine protease disassembles most cell structures during apoptosis, including the cytoskeleton, cell junctions, mitochondria, endoplasmic reticulum, Golgi apparatus, and the nucleus. Overdose of PCM could cause hepatic damage by inducing apoptotic death and inflammation in renal tubular cells, as evidenced by increased expression of caspase-3, caspase-9, NF-κB, iNOS, and Kim-1 and decreased expression of Bcl-2 (Figure 3). Lawson *et al.* (1999) reported that Z-VAD inhibited receptor-mediated apoptosis by affecting the signal transduction pathway for caspase activation (caspase inhibition). Hesperidin protected hepatotoxicity induced by PCM overdose by inhibiting apoptosis and decreasing caspase-3 (Shiekh *et al.,* 2012). Similarly, caspase inhibitors lupeol (Kumari and Kakkar, 2012), allopurinol (Nesreen *et al.,* 2016), pterostilbene (El-Sayed *et al.,* 2015), and probiotic *Enterococcus lactis* IITRHR1 (Sapna *et al.,* 2012) alleviate PCM-induced hepatotoxicity. As a result, caspases could be potential targets, and caspase inhibitors could be useful for treating PCM-induced hepatotoxicity (Table 3).

11. Hepatoprotective activity of PTP1B inhibitors

PTP1B (protein tyrosine phosphatase 1B) acts as an endoplasmic reticulum unfolded protein response regulator. It is a growth factor signalling negative regulator that influences the balance of cell survival and death (Figure 3). PCM treatment increased PTP1B expression and activated JNK and p38, decreasing survival signalling and cellular viability. Suramin inhibited the activity of PTP1B and protected the liver in human primary hepatocytes treated with PCM. Similarly, rosiglitazone (20 mM) provided hepatoprotective activity by inhibiting PTP1B activity (Mobasher *et al.,* 2014). As a result, PTP1B could be a potential target, and PTP1B inhibitors could be useful for treating PCM-induced hepatotoxicity (Table 3).

12. Hepatoprotective activity of of hepatic macrophages and kupffer cells inhibitors

Hepatic macrophages are an appealing therapeutic target for liver diseases because they play a pivotal role in liver homeostasis and the pathogenesis of liver injury. Hepatic macrophages are composed of kupffer cells derived from the foetal yolk sac and infiltrated bone marrow-derived monocytes/macrophages. PCM produces NAPQI, which activates macrophages and kupffer cells, causing them to release pro-apoptotic cytokines such as TNF-α, resulting in liver apoptosis/necrosis and hepatotoxicity (Figure 4). According to Sherryll *et al.* (1999), gadolinium chloride and dextran sulphate have hepatoprotective effects against PCM-induced hepatotoxicity due to the inactivation of hepatic macrophages and kupffer cells. As a result, hepatic macrophages and kupffer cells may be potential targets, and inhibitors of these cells may be useful for treating PCM-induced hepatotoxicity (Table 3).

13. Hepatoprotective activity of Bax/Bcl-2 modulators

Mitochondria are referred to as "cellular power houses." They also participate in various other processes, including signalling, cellular differentiation, cell death, and control of the cell division cycle and cell growth (Figure 4). Bcl-2 is a cell survival protein which is known for its role in preventing apoptosis (*via* interactions with the pro-apoptotic Bax and Bak proteins). Bcl-2 inhibits apoptosis either by sequestering proforms of caspases (a complex known as the apoptosome) or preventing the release of mitochondrial apoptogenic factors such as cytochrome c and AIF (apoptosis-inducing factor) into the cytoplasm. By increasing bcl-2 overexpression in the liver, nilotinib reduces the hepatotoxicity caused by a non-lethal dose of PCM (Shaker *et al.,* 2014).

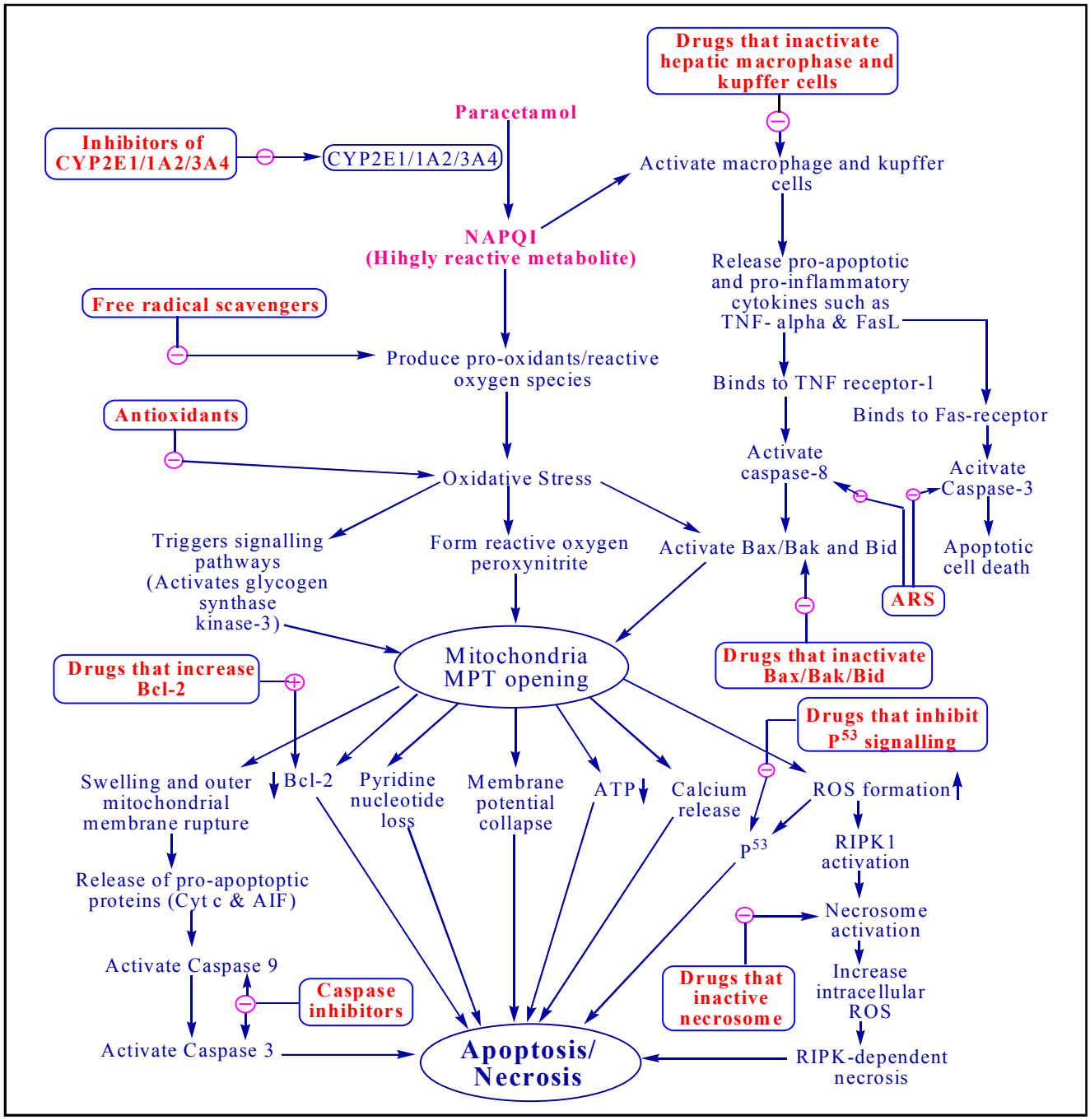

Figure 4: Therapeutic targets and pathophysiological role of mitochondrial dysfunction/damage in paracetamol-induced hepatotoxicity. NAPQI, N-acetyl-p-benzoquinoneimine; MPT, mitochondrial membrane permeability transition; ROS, Reactive oxygen species; AIF, apoptosis inducing factor; Cyt c, Cytochrome c oxidase and TNF, tumour necrosis factor; RIPK, receptor interacting protein kinase; ATP, adenosine triphosphate.

Previous research has demonstrated that schisandrol B (Yiming *et al.,* 2015), dioscin (Xiaoming *et al.,* 2012), leflunomide (Su *et al.,* 2008), hesperidin (Shiekh *et al.,* 2012), lupeol (Kumari and Kakkar, 2012), and probiotic enterococcus lactis have hepatoprotective activity in both *in vitro* and *in vivo* models due to Bax/Bcl-2 modulation. As a result, Bax/Bcl-2 may be potential targets, and modulators of Bax/Bcl-2 useful in the treating PCM-induced hepatotoxicity (Table 3).

14. Hepatoprotective activity of mitochondrial oxidative stress inhibitors

Mitochondrial structures are highly vulnerable to oxidative stress and play a pivotal role in producing ROS *via* one-electron carriers in the respiratory chain (Jyothilekshmi *et al.,* 2020). Oxidative stress can cause apoptosis. A disparity between free radical production and the antioxidant system, which maintains the organism's homeostasis, is defined as oxidative stress. NAPQI produces reactive oxygen peroxynitrile, which causes oxidative stress and hepatotoxicity by activating signalling pathways and forming reactive oxygen peroxynitrile (Figure 4). According to Banishree and Dipankar (2009), manumycin A and gliotoxin have hepatoprotective activity against PCM-induced liver damage by inhibiting mitochondrial oxidative stress. Previous research found that mito-tempo (Kuo *et al.,* 2019), DL-lipoic acid, and -tocopherol (Sudheesh *et al.,* 2013) inhibited mitochondrial oxidative stress and thus reduced PCM-induced hepatotoxicity. As a result, mitochondrial oxidative stress may be a target, and stress inhibitors may be beneficial in treating PCM-induced hepatotoxicity (Table 4).

15. Hepatoprotective activity of mitochondrial permeability transition pore (mPTP) inhibitors

The mitochondrial permeability transition pore (mPTP) is a pore that forms in the inner membrane of mitochondria in response to pathological conditions such as trauma/tissue injury (Figure 4). The opening allows the mitochondrial cell membrane's permeability to molecules smaller than 1500 Daltons to be increased. Induction of mPTP and changes in mitochondrial permeability result in mitochondrial swelling and causes apoptotic and necrotic cell death. Beyond the safe therapeutic doses, PCM causes liver toxicity via NAPQI. Recent research has revealed that mPTP plays an essential role in PCM-induced toxicity. Leflunomide (4 h after PCM dose) protected against liver necrosis by inhibiting PCM-induced activation of mPTP (Su *et al.,* 2008). According to Calivarathan *et al.* (2007), leflunomide protects against PCM-induced hepatotoxicity in mouse and human liver microsomes *via* inhibition of mPTP. As a result, mPTP may be a potential target, and mPTP inhibitors may be useful in treating PCM-induced hepatotoxicity (Table 4).

Table 4: Hepatoprotective activity of compounds against parcetamol-induced hepatotoxicity due to inhibition of mitochondrial oxidative stress, cytochrome c, p^{53}, calcium channels, lipid peroxidation and activation of glutathione-S-transferase and glutathione reductase

S. No.	Compound/drug tested and treatment schedule	Animal/tissue model used	Paracetamol dose and route of administration	Reference
1.	**Inhibitors of mitochondrial oxidative Stress**			
	DL-α-lipoic acid 100 mg/kg, p. o. and	Male Wistar rats	3 g/kg body weight, orally for	Sudheesh *et al.,* 2013
	α-tocopherol 100 mg/kg, p. o.		15 days	
	Mito-tempo 200 mg /kg after 1.5 or 3 hour of PCM treatment	Male C57BL/6J mice 8-12 weeks	300 mg/kg	Kuo *et al.,* 2019
2.	**Inhibitors of mitochondrial permeability transition pore (mPTP)**			
	Leflunomide 0, 0.5, 2 and 15 μM in liver microsomes and single injection of 30 mg/kg i.p, 4 h after PCM.	liver microsomes; Male C57BL/6 mice	800 μM in liver microsomes and 750 mg/kg in male C57BL/6 mice.	Su *et al.,* 2008
3.	**Inhibitors of cytochrome c release**			
	Lupeol 150 mg/kg for 30 consecutive days, p.o.	Male Wistar rats; Rat primary hepatocytes	1 g/kg body weight, p. o.	Kumari and Kakkar, 2012
4.	**Inhibitors of p^{53}**			
	Wuzhi tablet (*Schisandra sphenanthera* extract) 175, 350, 700 mg/kg with an interval of 12 h for 3 consecutive days.	Male C57BL/6 mice(6-8 weeks old)	Single dose of 400 mg/kg, i. p.	Xiaomei *et al.,* 2014
	Dioscin 5, 50, 100 mg/kg once daily for 5 days, i. g.	HepG2 cells Kun-ming male mice	300 mg/kg body weight, i. p.	Zhao *et al.,* 2012
5.	**Ca^{2+}-channel blockers**			
	Amlodipine 10 mg/kg/day for 14 consecutive days prior to the administration of PCM.	Adult male Wistar rats	Single oral dose of 750 mg/kg, p. o.	Nesreen *et al.,* 2016

6.	**Inactivators of necrosome**			
	Necrostatin-1 single dose of 12.5 mg/kg, i. p.	Male C57BL/6 mice 8-12 weeks old	Single i. p. dose of 800 mg/kg.	Kenji *et al.,* 2014
7.	**Activators of glutathione-S-transferase**			
	Davallialactone 10 mg/kg, p. o.	Male C57BL/6 mice	400 mg / kg body weight, i. p.	Jung *et al.,* 2013
	C2-ceramide and oltipraz 120 and 150 µmol/l	Adult male Kun-ming mice (8-week-old, 18-22 g	200 mg/kg body weight,i. p.	Ma *et al.,* 2018
8.	**Inactivators of glutathione peroxidase**			
	Coffee 1.5% lyophilized coffee	Male Wistar rats	700 mg/kg body weight, i. p.	Renata and Tasso, 2011
	Diphenyl diselenide 31 mg/kg orally for 2	Male adult		
	days	Wistar rats	2 g/kg orally after the second day.	Ethel *et al.,* 2009
9.	**Activators of glutathione reductase**			
	Nilotinib 25, 50 mg/kg 2 h after PCM intoxication, i. p.	Male BALB/c mice 24-26 g	500 mg/kg, i. p.	Shaker, 2014
	Coffee 1.5% lyophilized coffee	Male Wistar rats	700 mg/kg body weight, i. p.	Renata and Tasso, 2011
10.	**TRPM2 channel blockers**			
	Clotrimazole 50 µMACA ((N-(p-amyl-cinnamoyl) anthranilic acid -10 µM	TRMP2 knock-out mice	10-15 µM PCM containing 1.3 µM of calcium for 60 min	Kheradpezhouh *et al.,* 2010
11.	**Cysteine prodrugs**			
	Ribose cysteine 1 g/kg ,10 ml/kg 1 and 2 h after PCM, i. p.	Male CD-1 mice	600 mg/kg,15 ml/kg, i. p.	Angela *et al.,* 2015
12.	**Inhibitors of lipid peroxidation**			
	Chitosan 200 mg/kg after 15 days of PCM treatment, p. o.	Wistar rats	PCM 250 mg/kg body weight /day orally for 14 days	Ozcelik *et al.,* 2014

16. Hepatoprotective activity of cytochrome c inhibitors

Cytochrome c is a component of the mitochondrial electron transport chain. The release of cytochrome c from mitochondria into the outer mitochondrial space is a critical first step in apoptosis and necrosis (Figure 4). There are numerous mechanisms for cytochrome c release in the liver in response to various apoptotic stimuli. Kumari and Kakkar (2012) conducted a study with lupeol and found that it reduced hepatic damage by inhibiting the release of cytochrome c. It also inhibited the production of ROS and mitochondrial depolarization. Similarly, the probiotic *Enterococcus lactis* IITRHR1 (Sapna *et al.,* 2012) and leflunomide (Calivarathan *et al.,* 2007; Su *et al.,* 2008) inhibits cytochrome c release and protects against PCM-induced hepatotoxicity. As a result, cytochrome c may be a potential target, and cytochrome c inhibitors may be useful in treating PCM-induced hepatotoxicity (Table 4).

17. Hepatoprotective activity of p53 signalling pathway inhibitors

p53 is a tumour suppressor gene that encodes a protein that regulates the cell cycle. Normal cells have shallow p53 protein levels. The p53 protein can be increased in response to DNA damage and other forms of stress. It is in charge of three primary functions: growth inhibition, DNA repair, and apoptosis (Figure 4). The growth arrest stops the cell cycle from progressing, preventing the replication of damaged DNA. As a result of hepatic damage, p53 levels rise, resulting in growth arrest and apoptosis. Wuzi tablet (WZ) inhibited p53 and thus reduced PCM hepatotoxicity in a dose-dependent manner (Xiaomei *et al.,* 2014). Dioscin also inhibited PCM-induced hepatotoxicity in another study by inhibiting the p53 signalling pathway (Xiaoming *et al.,* 2012). As a result, p53 may be a potential target, and p53 inhibitors may be useful in treating PCM-induced hepatotoxicity (Table 4).

18. Hepatoprotective activity of intracellular calcium inhibitors

Regardless of the cause of the disease, hypercalcemia is a metabolic feature of patients with chronic liver disease. Toxic doses of PCM result in severe liver damage. Calcium accumulates in the nucleus and DNA before PCM. It is cleaved by enzymes into inter-nucleosome length fragments, causing necrosis of hepatocytes *in vivo* and toxic cell death *in vitro* (Figure 4). Calcium deregulation is thought to play a mechanistic role in this type of injury. Amlodipine protects against PCM-induced hepatotoxicity, demonstrating the role of calcium channels in the pathogenesis of PCM-induced hepatotoxicity (Nesreen *et al.,* 2016). Verapamil was also found to reduce calcium accumulation and DNA damage while reducing liver injury in another study. As a result, intracellular calcium may be a potential target, and calcium inhibitors may be useful in treating PCM-induced hepatotoxicity (Table 4).

19. Hepatoprotective activity of necrosome inhibitors

Necroptosis is a type of regulated necrosis caused by activation of the necrosome, a protein complex containing receptor interacting protein kinase (RIPK) 3. The RIP hemolytic interaction motif is the central domain that controls necrosome activation (RHIM). Previously, necrosis/necroptosis was thought to be an unintentional and uncontrollable cell death process. A novel concept of regulated necrosis known as RIPK-dependent necrosis or necroptosis has been discovered by recent research (Figure 4). Necrostatin, which inhibits necrosomes, is effective against PCM-induced acute liver failure (Kenji *et al.,* 2014). As a result, necrosomes may be a viable target, and necrosome inhibitors may be beneficial in treating PCM-induced hepatotoxicity (Table 4).

20. Hepatoprotective activity of glutathione-S-transferase activators

Glutathione-S-transferases (GST) are a class of functional proteins that function as both detoxification enzymes and intracellular binding proteins (Figure 5). GST catalyses the mechanism of GSH binding to electrophilic regions *via* the sulfhydryl group. The goal is to make compounds more soluble in water. Some compounds, including peroxidized lipids, are detoxified during this process, and compounds and xenobiotics are broken down. Another important function of GSH is to bind to toxins, which also serves as a mechanism for protein transport. PCM-induced toxicity is closely linked to oxidative stress. The effects of C2-ceramide and oltipraz on hepatocyte nuclear factor 1 (NF-1) and GSTA1 were studied using a PCM-induced acute liver injury mouse model. C2-ceramide could reduce NF-1 and GSTA1 expression, which exacerbated hepatic injury, whereas oltipraz could increase NF-1 and GSTA1 expression, which reduced hepatic injury (Ma *et al.,* 2018). Davallialactone (Jung *et al.,* 2013) and coffee (Renata and Tasso, 2011) have also demonstrated significant hepatoprotective activity against PCM-induced hepatotoxicity by increasing GST activity. As a result, GST may be a potential target, and GST activators may be useful in the treating PCM-induced hepatotoxicity (Table 4).

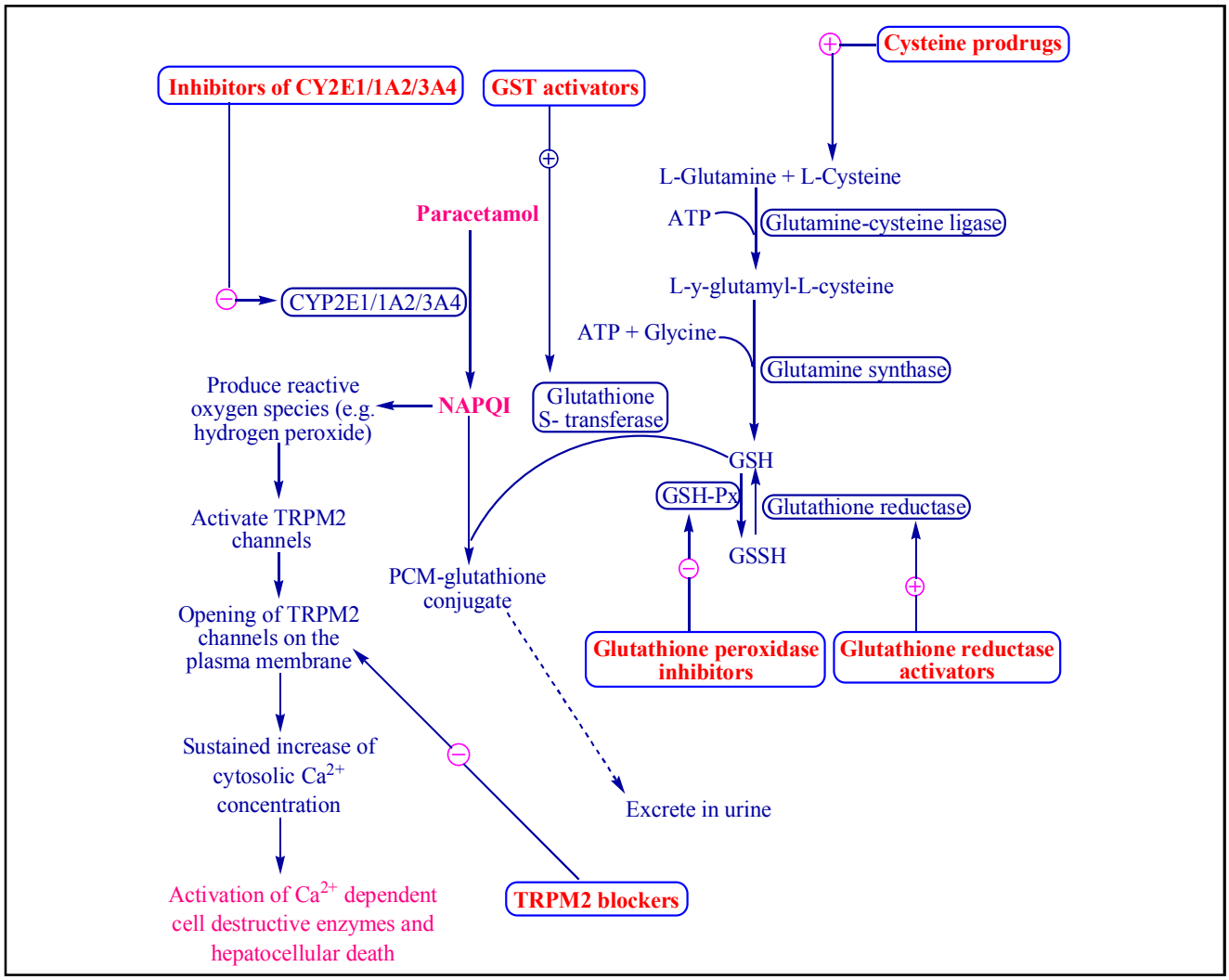

Figure 5: Glutathione system and TRPM2 channels as therapeutic targets in paracetamol-induced hepatotoxicity. GSH-Px, glutathione peroxidase; GSH, reduced glutathione; GSSH, oxidized glutathione, NAPQI, N-acetyl-p-benzoquinone imine; CYP, cytochrome P450; GST, glutathione S-transferase; TRPM2, transient receptor potential melastatin 2.

21. Hepatoprotective activity of glutathione peroxidase inhibitors

Oxidative stress plays a significant pathologic role in liver injury. Glutathione peroxidase is an antioxidant enzyme that contributes significantly to antioxidant defence. GSH and glutathione peroxidase levels are important in liver cirrhosis (Figure 5). Diphenyl diselenide (PhSe)2 protected rats from PCM-induced increases in ALT, AST, ALP, LDH, glutathione transferase, and glutathione peroxidase activities (Ethel *et al.,* 2009). In another study, daily coffee consumption reduced glutathione peroxidase activity and protected the liver (Renata and Tasso, 2011). As a result, glutathione peroxidase may be a potential target, and glutathione peroxidase inhibitors may be useful in the treating PCM-induced hepatotoxicity (Table 4).

22. Hepatoprotective activity of glutathione reductase activators

Glutathione reductase is an enzyme which catalyses the conversion of glutathione disulfide to sulfhydryl forms of glutathione, which is a critical molecule in decreasing oxidative stress and maintaining the cells reduced environment. Its levels are generally reduced in cases of liver injury (Figure 5). Lobenzarit's cytoprotective effect is mostly due to its antioxidant properties and/or ability to stimulate GSH reductase. Similarly, daily coffee consumption increased glutathione reductase activity and protected the liver (Renata and Tasso, 2011). Nilotinib also showed protective effects against PCM-induced hepatotoxicity by increasing GSH reductase activity (Shaker, 2014). As a result, glutathione reductase may be a potential target, and glutathione reductase activators may be useful in the treating PCM-induced hepatotoxicity (Table 4).

23. Hepatoprotective activity of TRMP2 channel blockers

A known consequence of PCM-induced liver toxicity is an increase in intracellular calcium concentration in hepatocytes. Calcium entry into hepatocytes in PCM overdose is mediated by transient receptor potential melanostatine 2(TRMP2) cation channels (Figure 5). TRMP2 channels play an essential role in the mechanism of PCM-induced hepatocellular death. Clotrimazole, by blocking TRMP2 channels, has hepatoprotective activity in TRMP2 knock-out mice (Kheradpezhouh *et al.,* 2014). As a result, TRMP2 channels may be a potential target, and TRMP2 channel inhibitors may be useful in the treating of PCM-induced liver toxicity (Table 4).

24. Hepatoprotective activity of cysteine providers

L-cysteine is an amino acid that aids in detoxification to prevent or reduce hepatic and renal failure (Figure 5). It also boosts GSH biosynthesis and is used to combat PCM-induced hepatic toxicity. Ribose cysteine acts as a cysteine prodrug, promoting GSH biosynthesis and protecting against PCM-induced hepatotoxicity (Angela *et al.,* 2005). Similarly, 2-methyl-thiazolidine-2, 4-dicarboxylic acid protects against PCM-induced hepatotoxicity by acting as a pro-drug and aids in GSH biosynthesis. As a result, cysteine prodrugs or compounds containing cysteine may be useful in the treating PCM-induced hepatotoxicity (Table 4).

25. Hepatoprotective activity of lipid peroxidation inhibitors

Lipid peroxidation is a chain reaction involving free radicals that results in the oxidative degradation of polyunsaturated lipids. Peroxidative events in the mitochondrial endoplasmic reticulum influence the activities of glucose 6-phosphatase, CYP, and the capacity for calcium sequestration. Furthermore, the release of hydrolytic enzymes from lysosomes and a decrease in plasma membrane fluidity can both contribute to liver damage (Figure 6). Chitosan may protect against PCM-induced hepatotoxicity by reducing lipid peroxidation, according to one study (Eda *et al.,* 2014). Silymarin, on the other hand, has a significant protective effect against PCM-induced hepatotoxicity by reducing lipid peroxidation. As a result, lipid peroxidation may be a potential target, and lipid peroxidase inhibitors may be useful in the treating PCM-induced hepatotoxicity (Table 4).

26. Hepatoprotective activity of PARP inhibitors

Poly (Adp-Ribose) Polymerase (PARP) is a protein family that involves in varied biological activities including DNA repair, genomic stability, and programmed cell death. (Figure 6). Melahat *et al.* (2015) reported that 3-aminobenzamide has hepatoprotective activity against PCM-induced hepatotoxicity caused by PARP inhibition. As a result, PARP may be a viable target, and PARP inhibitors may be beneficial in the treatment of PCM-induced hepatotoxicity (Table 5).

Table 5: Hepatoprotective activity of compounds against parcetamol-induced hepatotoxicity due to inhibition of PARP receptor, iNOS, inflammation, α_1-adrenoceptor, NF-κB, Connexin 32, and blood coagulation

S. No.	Compound/drug tested and treatment schedule	Animal/tissue model used	Paracetamol dose and route of administration	Reference
1.	**PARP receptor blockers**			
	3-aminobenzamide 20 mg/ kg exactly 1 hour after PCM treatment	Sprague-Dawley rats	PCM 1 g/kg, i. p.	Melahat *et al.,* 2015
2	**Inhibitors of iNOS**			
	Leflunomide 30 mg/kg 4 h after the PCM treatment, i. p.	Mouse and human liver microsomes; Male C57BL/6 mice	PCM 750 mg /kg, i. p.	Calivarathan *et al.,* 2007 ; Su *et al.,* 2008
	Hesperidin 100, 200 mg /kg orally for 14 days	Male Wistar rats	750 mg /kg body weight, oral	Shiekh *et al.,* 2012
3.	**Activators of Nrf-2 protein**			
	Wuzhi tablet (*Schisandra sphenanthera* extract) 350 or 750 mg/kg for 3 days	Male C57BL/6 mice (6-8 weeks old)	400 mg/kg for 6 h	Xiaomei *et al.,* 2014

	Ginsenoside Rg3 (50 mg/kg once daily for 8 consecutive days, p. o.).	H4IIE cells	500 mg/kg, i. p.	Sang and Kyung, 2013
4.	**Anti-inflammatory agents**			
	Agomelatine 40 mg/kg, 140 mg/kg N-acetylcysteine, 2g/kg PCM + 20 mg/kg agomelatine, 2 g/kg PCM + 40 mg/kg agomelatine, p. o.	Male Albino Wistar rats	2 g/kg, p. o.	Karakus *et al.,* 2013
5.	**α_1-adrenoceptor antagonists**			
	Prazosin, doxazosin, terazosin and tamsulosin ; 35.7 mmol/kg 1 h prior to PCM treatment	Male CD-1 mice	3.5 mmol/kg, i. p.	Randle *et al.,* 2008
6.	**Inhibitors of NF-κB**			
	Hesperidin 100, 200 mg/kg for 14 days, p. o.	Male Wistar rats	750 mg/kg body weight, oral	Shiekh *et al.,* 2012
	Platycodon grandiflorum saponins 15 or 30 mg/kg i.g./day for 1 week before a single injection of PCM	Male ICR Mice weighting 20-22 g (8-10 weeks old)	250 mg/kg,i. g.	Jing *et al.,* 2018
7.	**Inhibitors of connexin 32**			
	2-aminoethoxydipenyl-borate 20 mg/kg exactly after 1h of PCM treatment duration of action 48 h	C57BL/6 mice Cx32 -/- mice	1g/kg, i. p	Kuo *et al*., 2013
8.	**Anticoagulants**			
	Tranexamicacid 600 mg/kg 2 h after PCM treatment, i. p.	PAI-1 -/- mice	300 mg/kg, i. p.	Bradley *et al*., 2012
	Plasminogen activator inhibitor-1	Wild-type (WT) and PAI-1 gene knockout mice (PAI-KO)	400 mg/kg,i. p.	Bradley *et al*., 2012 Mary *et al*., 2012
9.	**Liver X receptor agonists**			
	Activation of liver X receptors (LXR) agonist like T0901317 10 mg/kg, i. p.	LXR α and β double knockout mice	200 mg /kg, i. p.	Saini *et al*., 2011

27. Hepatoprotective activity of iNOS (inducible nitric oxide synthase) inhibitors

Nitric oxide (NO) is an innate immune system effector. Endotoxin and inflammatory cytokines, for example, can activate a Ca^{2+}-independent NO synthase (NOS) in a wide range of cells, including macrophages and neutrophils. The overproduction of NO caused by the expression of this inducible NOS (iNOS) causes damage to endothelial, neuronal, and epithelial cells. Kupffer cells and neutrophils in the liver are essential sources of reactive nitrogen and oxygen species, as well as pro-inflammatory cytokines that promote oxidative stress (Figure 6). Many activated macrophages accumulate in the injured areas of the liver, releasing high levels of NO produced by iNOS and other inflammatory mediators such as TNF-α, IL-1, and reactive oxygen intermediates, all of which promote hepatotoxicity. Hesperidin has the potential to reduce oxidative stress and toxicity caused by PCM (Shiekh *et al.,* 2012). In another study, researchers discovered that leflunomide reduces iNOS expression and protects against PCM-induced hepatotoxicity in mice and human liver microsomes (Calivarathan *et al.,* 2007; Su *et al.,* 2008) . As a result, iNOS could be a viable target, and iNOS inhibitors could be useful in treating PCM-induced hepatotoxicity (Table 5).

28. Hepatoprotective activity of the protein Nrf2-Keap 1 activators

Keap1 is a molecular sensor of cellular homeostasis and oxidative stress. antioxidant-response elements (ARE) are the promoters of Nrf2, a redox-sensitive transcription factor that regulates the expression of genes whose promoters. Stress, proliferation, and inflammation are all regulated by the repressor protein Nrf2 (Figure 6). The interaction of Nrf2 with Keap1 is the primary cause of its activity (Kelch-like ECH associated protein 1). Other mechanisms of Nrf2 regulation include phosphorylation by different protein kinases, interaction with other protein partners (p21, caveolin-1) and epigenetic factors (micro-RNAs -144, -28 and -200a, and promoter methylation). Morin, a phytochemical derived from plants, increases Nrf2 signalling (Fatima *et al.,* 2015). Ginsenoside Rg3 has the ability and specificity to protect hepatocytes from NAPQI insults through GSH repl etion and coordinated gene regulation of GSH synthesis and MRP family genes by Nrf2 (Sang and Kyung, 2013). In male C57BL/6 mice, the potency of Wuzhi tablets increased Nrf2 expression while decreasing Keap 1 levels (Xiaomei *et al.,* 2014). Similarly, lophirones B and C (Najeeb *et al.,* 2018) and shikonin (Huachao *et al.,* 2019) were discovered to protect against PCM-

induced hepatotoxicity by upregulating the Nrf2-keap 1 protein. As a result, Nrf2-keap 1 proteins may be a target, and Nrf2-keap 1 protein activators may aid in the treatment of PCM-induced hepatotoxicity (Table 5).

29. Hepatoprotective activity of inflammation inhibitors

Inflammation is a critical component of the immune system's response to damage and infection. It is the body's way of alerting the immune system to heal and restore damaged tissue while also fighting off foreign bacteria and viruses. NAPQI, a reactive metabolite, causes extensive mitochondrial GSH depletion, covalent binding, severe impairment of mitochondrial function, and halt of ATP generation, culminating in ion homeostasis disruption and, as a result, oncotic necrosis (Figure 6). JNK, glycogen synthase kinase-3b (GSK-3)16, apoptosis signal-regulating kinase-1 (ASK1)17, and mixed-lineage kinase-3 (MLK3)18 are among the stress kinases that actively regulate the process. Pterostilbene protects against tissue damage due to its anti-inflammatory activity against PCM-induced hepatotoxicity (El-Sayed *et al.,* 2015). Similarly, agomelatine (Karakus *et al.,* 2013), nicotinamide (Youdan *et al.,* 2012), and gherlin were discovered to exhibit anti-inflammatory activities against PCM-induced hepatotoxicity. Another study discovered that *Hypericum perforatum* (30-300 mg/kg i.p.) and PCM (1.5 g/kg p.o) inhibited PCM-induced neutrophil recruitment and positive stress (Miriam *et al.,* 2015). Likewise, aminotriazole (Jing *et al.,* 2015) Fermented ginseng and its principal constituent compound K (Kentaro *et al.,* 2015), Ginsenoside RK1 (Jun *et al.,* 2019), Pterostilbene (Ki *et al.,* 2019), and Nilotinib (Shaker *et al.,* 2014) all shown hepatoprotective effect due to anti-inflammatory qualities. As a result, inflammation may be a possible target, and anti-inflammatory drugs may be effective in the treatment of PCM-induced hepatotoxicity (Table 5).

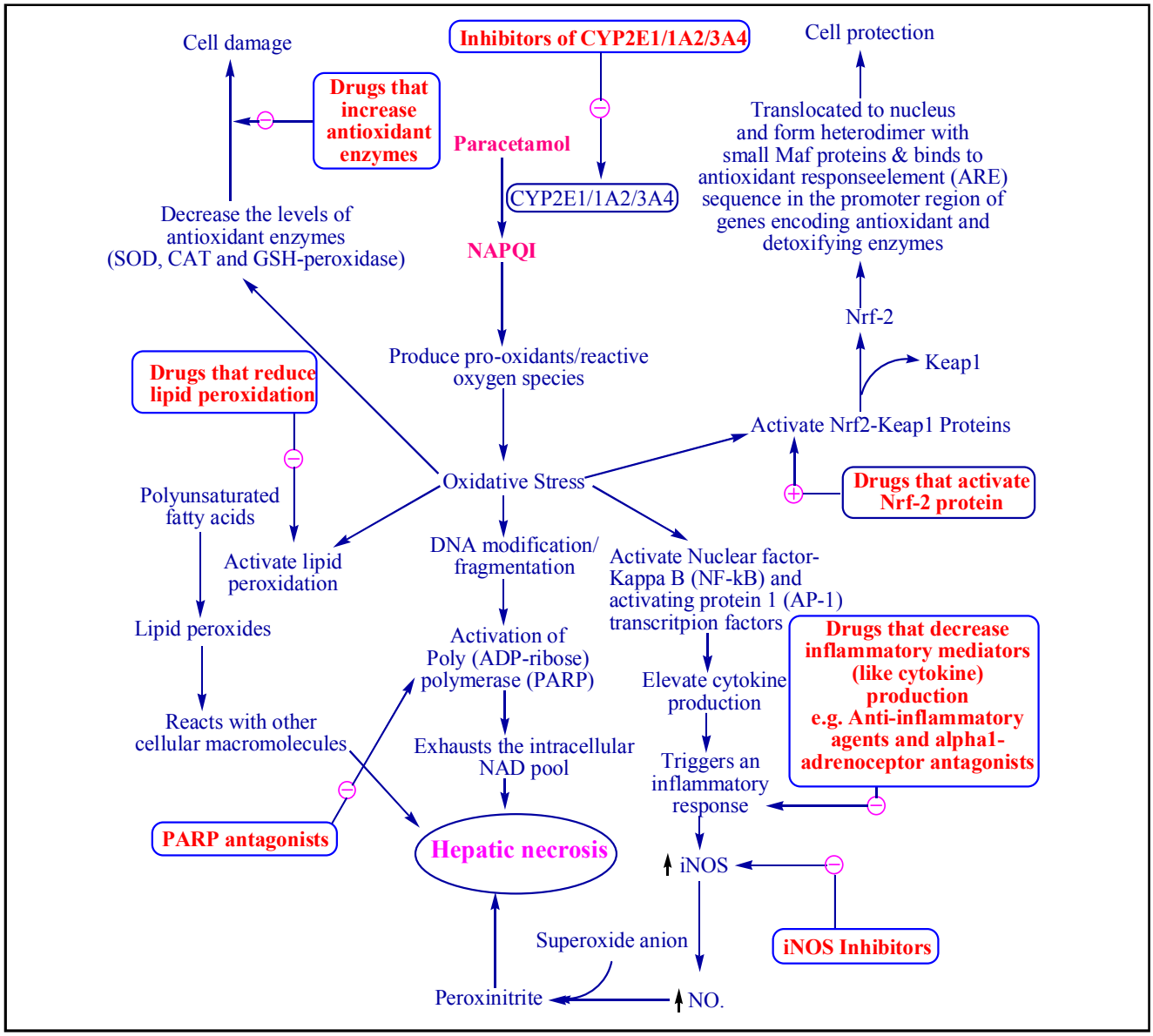

Figure 6: Lipid peroxidation, inflammation and other possible mechanisms as therapeutic targets in paracetamol-induced hepatotoxicity. iNOS, inducible nitric oxide synthase; NO, nitric oxide; NAPQI, N-acetyl-p-benzoquinoneimine.

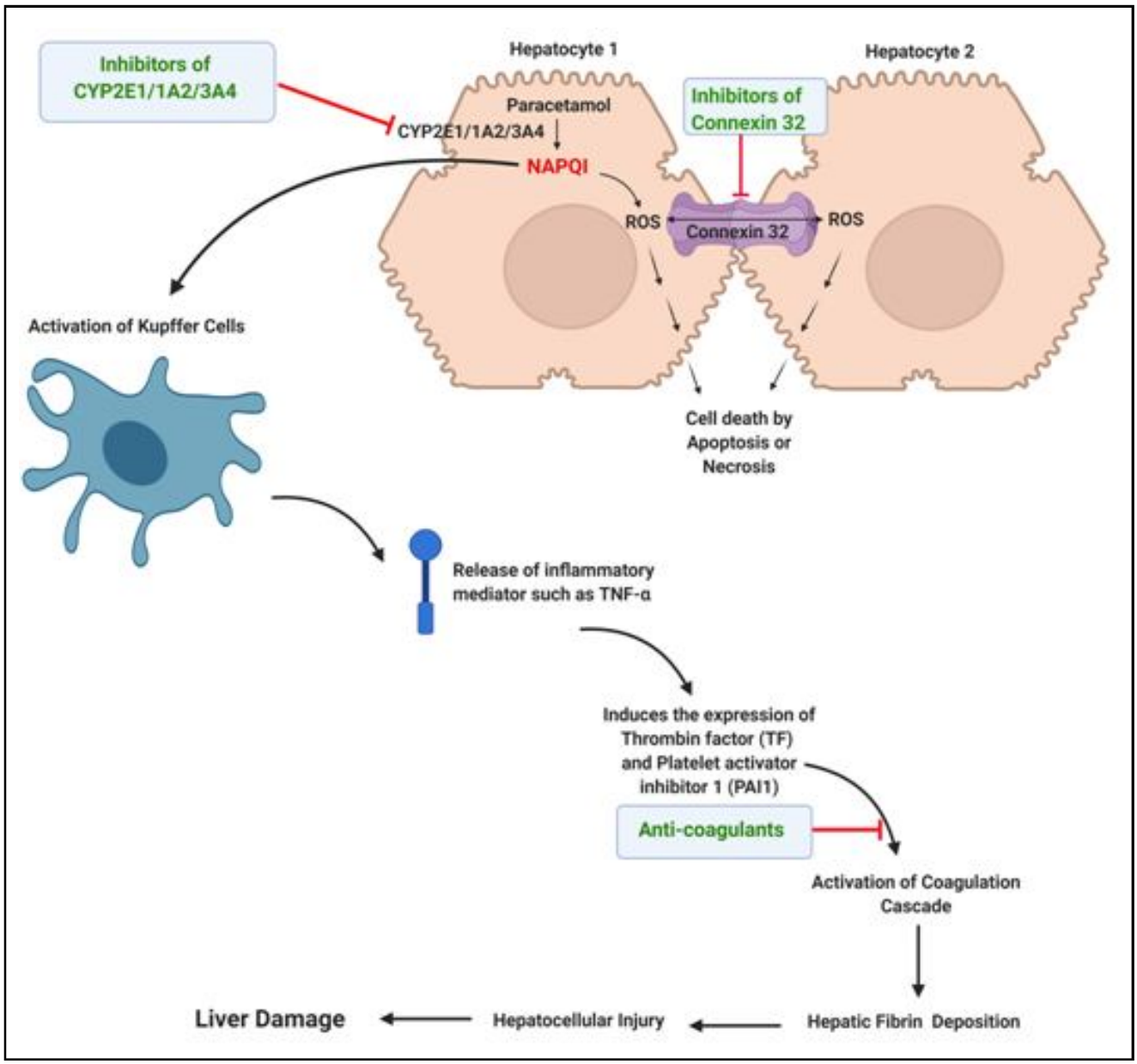

Figure 7: Connexin 32 and coagulation system as therapeutic target in paracetamol-induced hepatotoxicity. NAPQI, N-acetyl-p-benzoquinoneimine; ROS, reactive oxygen species; TNF, tumor necrosis factor; TF, tissue factor; PAI-1, plasminogen activator inhibitor-1.

30. Hepatoprotective activity of α_1-adrenoceptor inhibitors

Increased catecholamine levels may impaire hepatic perfusion in the pathophysiology of PCM-induced hepatotoxicity by (Figure 6). Doxazosin, terazosin, and tamsulosin were found to be effective against PCM-induced hepatotoxicity by decreasing α_1-adrenoreceptor blockade (Randle *et al.,* 2008). As a result, PCM-induced hepatotoxicity can be treated by compounds containing α_1–adrenoceptor inhibitors (Table 5).

31. Hepatoprotective activity of NF-κB inhibitors

The nuclear element Because of its role in the expression of pro-inflammatory genes such as cytokines (IL-1 and TNF-α), chemokines, and adhesion molecules, the NF-κB pathway is regarded as a prototypical pro-inflammatory signalling pathway (Figure 6). Caspase 3 and 9, NF-κB, iNOS, and Kim-1 expression increase during NF-κB activity, while Bcl-2 expression decreases. PCM causes hepatotoxicity by increasing caspase-3, caspase-9, NF-κB, iNOS, and Kim-1 expression while decreasing Bcl-2 expression. Hesperidin inhibited inflammation by decreasing NF-κB expression and thus exhibited hepatoprotective activity (Shiekh *et al.,* 2012). Saponins from Platycodon grandiflorum were also found to be protective by lowering NF-κB expression (Jing *et al.,* 2018). As a result, NF-κB may be a target, and compounds containing NF-κB inhibitors may be useful in the treatment of PCM-induced hepatotoxicity (Table 5).

32. Hepatoprotective activity of connexin 32 inhibitors

Connexins are the protein channels present in the gap junctions of coupled hepatocytes communicate directly and increase inflammation in liver (Figure 7). Connexin 32, a key hepatic gap junction protein, is involved in drug-induced liver damage. Kuo *et al.* (2013) discovered that 2-aminoethoxydiphenyl-borate inhibits connexin 32 and thus has hepatoprotective activity against PCM-induced hepatotoxicity. As a result, connexin 32 may be a potential target, and compounds containing connexin 32 inhibitors may be useful in treating PCM-induced hepatotoxicity (Table 5).

33. Hepatoprotective activity of coagulation system

Liver is the primary source of circulating coagulation factors. Hepatocyte TF expression accounts for the majority of liver procoagulant activity, and hepatocyte TF activates coagulation caused by liver injury (Figure 7). In various hepatotoxicities, plasminogen activator inhibitor-1 (PAI-1) gene deficiency is used to promote growth factor activation and regeneration. By preventing excessive haemorrhage and facilitating tissue repair, PAI-1 activation reduces liver injury and mortality during PCM-hepatotoxicity (Mary *et al.,* 2008). Similarly, heparin (Patricia *et al.,* 2007) and tranexamic acid (Bradley *et al.,* 2012) inhibited plasminogen activation and thus reduced PCM-induced hepatotoxicity. As a result, the coagulation system may be a potential target, and plasminogen inhibitor-containing compounds may be useful in treating PCM-induced hepatotoxicity (Table 5).

34. Hepatoprotective activity of liver X receptors

LXRs (liver X receptors) are nuclear receptor superfamily ligand-activated transcription factors. LXR isoforms are classified as alpha or beta. LXR promotes antipyretic toxic phase II conjugating enzymes like GST and SULT2A1 while compressing pro-toxic phase I CYP enzymes like CYP3A11 and CYP2E1 (Figure 3). LXR is a novel mechanism that protects the liver from PCM-induced hepatotoxicity. LXR agonists protect the liver from PCM-induced hepatotoxicity by activating antitoxic phase II conjugating enzymes such as GST and SULT2A1 while suppressing protoxic phase I P450 enzymes such as CYP2E1 (Saini *et al.,* 2011). As a result, LXR appears to be a viable target, and compounds containing LXR agonists may be beneficial in the treatment of PCM-induced hepatotoxicity (Table 5).

35. Conclusion

NAPQI, a hepatotoxic paracetamol metabolite, is primarily produced by the enzyme CYP2E1. PCM-induced hepatotoxicity may benefit from CYP2E1 inhibitors. JNKs are MAPKs (mitogen-activated protein kinase). JNK activation and p-JNK translocation to the mitochondria may play a role in the pathophysiology of PCM-induced hepatotoxicity. As a result, JNK inhibitors could be useful in treating PCM-induced hepatotoxicity. Caspases are cysteine proteases that act as primary effectors during apoptosis. PCM-induced hepatic damage is associated with an increase in caspase-3 and caspase-9 expression by inducing apoptotic death. Caspases could be potential targets, and caspase inhibitors could help treat PCM-induced hepatotoxicity. In the endoplasmic reticulum, PTP1B regulates the unfolded protein response. PCM was applied to human hepatocytes, which increased PTP1B expression and caused cell death. PTP1B inhibitors may be beneficial in the treatment of PCM-induced hepatotoxicity.

Bcl-2 is a cell survival protein best known for its ability to prevent apoptosis (*via* interactions with the pro-apoptotic Bax and Bak). By sequestering caspase proforms, which are death-inducing cysteine proteases, Bcl-2 inhibits apoptosis. In PCM-induced hepatotoxicity, Bcl-2 expression is reduced. As a result, Bax/Bcl-2 modulators may be beneficial in the treatment of PCM-induced hepatotoxicity. Cytochrome c, which is a component of the electron transport chain is found in mitochondria. The release of cytochrome c from mitochondria into the outer mitochondrial space is required for both apoptosis and necrosis. Cytochrome c release is important in PCM-induced hepatotoxicity, and Cytochrome c inhibitors may be useful in the treating PCM-induced hepatotoxicity. p53, also known as tumour protein, is a gene that encodes a protein that regulates the cell cycle and acts as a tumour suppressor. p53 protein levels are extremely low in normal cells. In conditions such as PCM-induced hepatotoxicity, DNA damage and other stress signals may increase the p53 protein. p53 may be beneficial in the treatment of PCM-induced hepatotoxicity.

Regardless of the cause, hypercalcemia is a metabolic feature of patients with chronic liver disease. Toxic doses of PCM may harm the liver severely. Calcium builds up in the nucleus and DNA, causing hepatic necrosis. As a result, intracellular calcium may be a viable target, and calcium inhibitors may be effective in treating PCM-induced hepatotoxicity. PARP is a protein family that is involved in a variety of cellular processes including DNA repair, genomic stability, and programmed cell death. PARP expression is increased in PCM-induced hepatotoxicity, implying that PARP inhibitors could be useful in treating PCM-induced hepatotoxicity. The expression of iNOS causes an increase in NO production, which damages endothelial, neuronal, and epithelial cells. Kupffer cells and neutrophils are major sources of reactive nitrogen and oxygen species, as well as pro-inflammatory cytokines, in the liver, which promote oxidative stress and liver injury. iNOS inhibitors may be beneficial in the treatment of PCM-induced hepatotoxicity. Increased catecholamine levels may contribute to the pathophysiology of PCM-induced hepatotoxicity by impairing hepatic perfusion due to 1-adrenoceptor overstimulation. As a result, α1-adrenoceptor antagonists may be effective in treating PCM-induced hepatotoxicity. Connexin 32, a critical hepatic gap junction protein, is implicated in drug-induced liver damage. Connexin 32 is involved in PCM-induced hepatotoxicity, and inhibitors of Connexin 32 may help treat it.

Quinone reductase converts NAPQI to PCM, which prevents ROS formation and PCM hepatotoxicity; thus, quinine reductase activators may be useful in the treating PCM-induced hepatotoxicity. Hepatic resident macrophages, kupffer cells, necrosome, glutathione peroxidase, NF-κB, and cysteine prodrugs, antioxidants, free radical scavengers, anti-inflammatory agents, anticoagulants, liver X receptor agonists, and compounds that activate UDP-glucuronosyl transferase, sulfotransferase, glutathione peroxidase, gluta The mechanisms and therapeutic targets discussed in this review are intended to help toxicologists, pharmacologists, and chemists develop new safer pharmaceutical products containing PCM to reduce toxicity and improve human health.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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