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REVIEW ARTICLE

Acetaminophen-Induced Hepatotoxicity in the Last 5 Years: An Update

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ABSTRACT

The global consumption of acetaminophen (APP) for pain relief and pyrexia dates back to 1883 Britain; to date, the drug is widely available over-the-counter and is marked by the WHO as an essential medicine worldwide. Overdose and APP- associated hepatotoxicity has been documented since the late 1900s, it is a global problem that continues to affect millions. The purpose of this paper is to draw attention to the mechanistic pathways of APP in terms of toxicity in the liver, biomarkers associated with APP-induced hepatotoxicity, and potential solutions to the hepatotoxicity crisis from a comparative standpoint over the past 5 years, from 2015 to 2020.

Keywords: Acetaminophen, Toxicity, Liver, Biomarker, Plant-derivative.

1. INTRODUCTION

Widely used for pain relief and pyrexia, Acetaminophen (APAP in the United States; N-acetyl-para-aminophenol (APP), and paracetamol in Britain) was synthesized by Morse in 1878 and implemented for medical indications in 1883 (Athersuch et al. 2018; Sharma & Mehta, 2014; Agarwal et al. 2020). Though steady use of the drug was not established until the 1950s, today, APP is among the most commonly used drugs on a global platform, as it is documented on the 2017 World Health Organization Model List of Essential Medicines (Athersuch et al. 2018; Sharma & Mehta, 2014). American over-the-counter APP use is ascribed to 40% of the adult population monthly; 23% of which affirm weekly use via either prescription or over-the-counter consumption (Dimitropoulos et al. 2014). Confirmation of regular consumption by greater than 60 million Americans weekly, establish the drug as the most readily used analgesic and antipyretic in the United States (U.S.) to date (Yoon et al. 2014).

Despite APP's abundant manufacturing and increased prescriptive consumption worldwide, acetaminophen hepatotoxicity remains the primary cause of acute liver failure in both the U.S. and across Europe; ready consumption is credited to a surplus of 300,000 annual U.S. hospitalizations, with about 42% of cases leading to acute liver failure due to APP overdose, a perpetual problem with onset

established in the 1990s (Yoon et al. 2014; Lancaster et al. 2015; Rubin et al. 2015). In the U.S. APP overdose leads the way, ascribing to 82,000 emergency room visits and 26,000 hospitalizations each year (Yoon et al. 2016; Rubin et al. 2016; Carreiro et al. 2019). Both 52% of individuals who consume the drug knowingly and those 48% of individuals who consume APP unknowingly are susceptible to liver failure and general liver transplantation referrals (Yoon et al. 2016). Adverse reactions associated with excess APP consumption include hepatitis, cholestasis, and asymptomatic liver enzyme increase, however, APP-induced hepatotoxicity still remains the primary cause of 48% of acute liver failure diagnoses, where 29% of acute liver failure patients due to APP ingestion undergo liver transplant with 28% of cases resulting in mortality (Yoon et al. 2016; McGill, 2016).

In an effort to comprehend, trace, and remedy the adverse reactions accompanying APP consumption, accredited researchers present evidence-based research at the molecular level in the form of biomarker identification, clinical and pharmacological pathway development, and protocols to negate APP-induced hepatotoxicity. The purpose of this paper is to present an update on APP-induced hepatotoxicity over the last 5 years in terms of pharmacology, biomarkers associated with toxicity, and remedies that currently establish viable protection against hepatotoxicity acquisition.

2. APP in the Liver

Ingestion of APP is defined by Figure I, where consumption of the drug is illustrated through the pharmacokinetic pathways of ADME – absorption, diffusion, metabolism, and excretion.

2.1. Functional APP Pharmacokinetics

APP absorption occurs following drug consumption in the duodenum as a result of its weakly acidic properties; accompanied by food, APP absorption may be further delayed (Sharma & Mehta, 2014; Yoon et al. 2016). In terms of bioavailability, APP is highly bioavailable orally at 88%; absorption and peak blood serum concentration occur within 90 minutes post consumption (Sharma & Mehta, 2014; Mazaleuskaya et al. 2015). Though the drug is not vastly bound to plasma proteins, the APP plasma half-life is approximated at 1.5-2.5 hours at recommended doses (Mazaleuskaya et al. 2015). APP diffusion (Mazaleuskaya et al. 2015) is reflected by effective plasma translocation, were APP volume distribution is approximated by 1 L/kg of plasma (Rumack, 2002). Recommended dose consumption of APP results in 85-90% metabolism by glucuronidation/sulfation, which is excreted into the urine; 2% of APP is evacuated unchanged via urine, and less than 10% is metabolized by CYP1E1, a cytochrome p450 component, into the reactive *N*-acetyl-*p*-benzoquinone imine (NAPQI) metabolite (Mazaleuskaya et al. 2016; Beger et al. 2015). In individuals without co-morbidities who consume the recommended APP dose, NAPQI is quickly converted to non-toxic metabolites via glutathione (Beger et al. 2015).

The three main pathways that govern APP metabolism are: (i) the conjugation with sulfate, (ii) conjugation with glucuronide, and metabolism (iii) via the use of cytochrome P-450 (CYP) oxidase enzyme system (Bartlett, 2004). Metabolic reactions (i) and (ii) govern approximately 90% of the consumed APP dose producing harmless metabolites, whereas metabolic reaction (iii) governs around 5% of the ingested dose and is attributed to the production of the active toxic metabolite *n*-acetyl-

p-benzoquinone imine (NAPQI) (Bartlett, 2004; McClain et al. 1999; Hinson et al. 2009). Under standardized APP dose consumption, NAPQI is detoxified hepatocellularly by glutathione reserves; however, excessive APP consumption results in the supersaturation of pathways (i) and (ii), which require a surplus of cytochrome P-450 to negate superfluous APP levels (McClain et al. 1999; Beger et al. 2015). Once the generation of NAPQI supersedes the hepatic ability to eliminate NAPQI, as observed in individuals with depleted glutathione (GSH) levels, APP overdose, chronic alcohol consumption, and malnutrition, the substance has the ability to react with protein sulfhydryl groups thereby generating protein adduct with predominant binding of cysteine-sulfhydral groups, which leads to mitochondrial dysfunction and ultimately cellular death, including innate liver immune system modulation (McClain et al. 1999; Jaeschke et al. 2011; Beger et al. 2015).

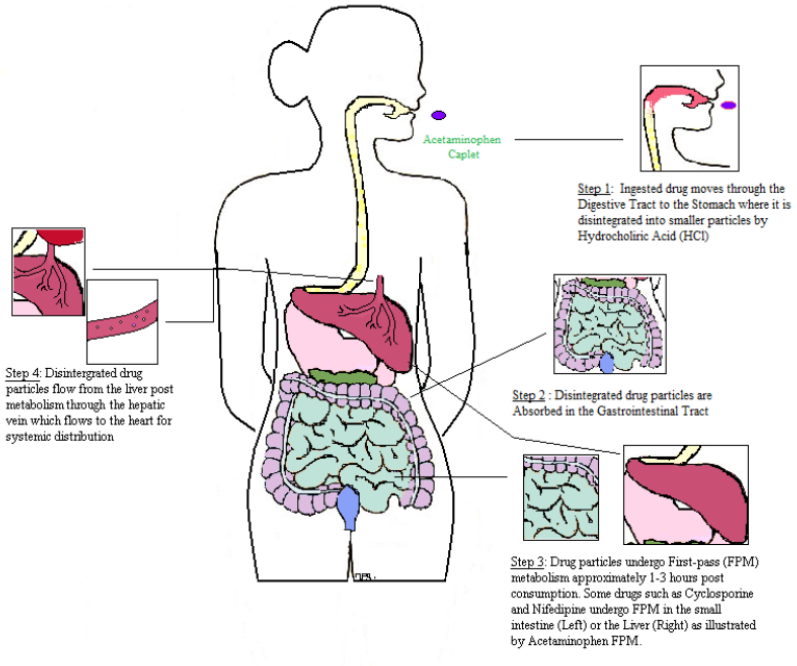

Figure 1: Visual illustration of the four primary steps observed in acetaminophen metabolism located in various regions of the body. Upon consumption, acetaminophen moves through the digestive tract to the stomach as an intact unit (Step 1). It is then disintegrated by hydrochloric acid (HCl) into minute particles to facilitate absorption with ease which takes place in the gastrointestinal tract (Step 2). Disintegrated acetaminophen particles then typically move to the liver and undergo first-pass metabolism, however, other drugs can also undergo first-pass metabolism in the small intestine (Step 3). Finally, acetaminophen particles move through the hepatic vein which directs flow into the heart, thereby facilitating acetaminophen drug flow into systemic circulation and eventually throughout the body (Step 4).

The elimination half-life of APP is about 2h post oral consumption, 8 hours with prandial APP consumption due to a decreased terminal phase, and a 4-5-hour half-life in individuals with no co-morbidities (Baraka et al. 1990).

2.2. Functional APP Pharmacodynamics

To date exceeding over 100 year, the precise mechanism of action (MOA) of APP still remains undetermined (Sharma & Mehta, 2014; Agarwal et al. 2020; Mazaleuskaya et al. 2015). Literary evidence supports multiple central mechanisms, which include APP's ef-

fect on prostaglandin production and effects on serotonergic, opioid, nitric oxide, and cannabinoid pathways with probable combinatory inter-pathway relationships (Sharma & Mehta, 2014). As of 2005, three predominant MOA theories coexist: (i) acetaminophen inhibits a distinct form of cyclooxygenase and (ii) APP functions by decreasing the active oxidized form of cyclooxygenase to an inactive form thereby exhibiting no affinity for the active site of cyclooxygenase (Lucas et al. 2005). A study (Kis et al. 2005) also proposed that (iii) APP decreases the oxidized form of the COX enzyme, functionally reestablishing a catalytically inactive state. As of 2013 a comparative study, Sharma & Mehta (2014), supported prior findings of the APP MOA in terms of 3 primary mechanisms: (i) prostaglandin inhibition, (ii) serotoninergic pathway activation, and (iii) endocannabinoid enhancement. A more recent study (Mazaleuskaya et al. 2015) defined the most widely accepted APP MOA in terms of prostaglandin [PGS] synthesis inhibition; PGS are demarcated as arachidonic acid-derived lipids that mediate inflammation, fever, and pain (Mazaleuskaya et al. 2015).

2.2.1. PGS Synthesis Inhibition

Cyclooxygenase enzymes are responsible for the metabolism of arachidonic acid to prostanoids, which include prostaglandins and thromboxanes; cumulatively, they are referred to as prostaglandin H2 synthetase (PGHS) (Sharma &Mehta, 2014). There are 3 forms of PGHS that are commonly known as COX-1, COX-2, and COX-3; prostaglandin synthesizing cylooxygenase-2 (COX-2) was discovered first followed by COX-1, which was identified in canine brain, COX-3, is a COX-1 derivative (Anderson, 2008; Smith, 2009; Smith et al. 2000). Prior studies from the early 2000s (Anderson, 2008; Botting & Ayoub, 2005; Smith et al. 2000) establish the two active sites of the PGHS molecule: (i) the COX enzyme and at (ii) the POX site; the COX site functions by oxidization and consumed APP serves to reduce the oxidized substance via the POX site pathway (Anderson, 2008). This literary evidence is reiterated in Sharma & Mehta (2014), twenty years later. COX-2 serves as a competitor or facilitator of arachidonic acid for or against the active site of COX-2, which ultimately reduces the prostaglandin level (Baraka et al. 1990).

It is the conversion of arachidonic acid to the prostanoids in a two staged sequence that inhibits PGS synthesis (Sharma & Mehta, 2014; Anderson, 2008). Activation at the COX site first produces the unstable hydroperoxide intermediate prostaglandin G2 (PGG2), which is then converted to prostaglandin H2 (PGH2) at the POX site (Sharma & Mehta, 2014; Mazaleuskaya et al. 2015; Anderson, 2008). In a two-step reaction arachidonic acid obtains two molecules of diatomic oxygen (O_2) in the formation of PGG2 via the COX enzyme, PGG2 is then reduced to prostaglandin H_2 (PGH2) by gaining two electrons by means of the POX enzyme (Anderson, 2008). Though APP does not access the active site of COX-2, it is presumed that COX-2 oxidizes, as the enzymatic activity of COX depends on the oxidized COX form, which enables APP to directly interfere with PGS synthesis by reducing Fe^{4+} to Fe^{3+} at the POX site (Sharma & Mehta, 2014; Lucas et al. 2005). In undamaged cells, low levels of arachidonic acid facilitates APP as an inhibitor of PGS synthesis, though it is a weak inhibitor (Sharma & Mehta, 2014). The inhibition of peroxide-dependent COX clarifies the differential activity of APP in the brain where peroxide levels are low, as opposed to peripheral sites of inflammation, where peroxide levels

are elevated (Sharma & Mehta, 2014; Mazaleuskaya et al. 2015).

Another proposed APP MOA theory further distinguishes the drug from NSAIDS; it is presumed that while NSAIDS act on both COX-1 and COX-2, APP acts directly on the COX-1 isoenzyme derivative COX-3 (Sharma & Mehta, 2014; Anderson et al. 2008; Botting & Ayoub, 2005; Smith, 2009). COX-3 was hypothesized to be active in the central nervous system versus sites of inflammation and injury, where inhibition via APP would be justified by the absence of anti-inflammatory and anti-platelet activity while retaining its effective antipyretic and analgesic properties; however, while the study was initially conducted in canine tissues and though COX-3 does express actions that parallel COX enzymes in humans, it was founded that the COX-3 enzyme has no role in PGS physiology (Sharma & Mehta, 2014; Anderson et al.2008; Botting & Ayoub, 2005; Smith, 2009).

The central nervous system (CNS) is the principal site of APP action, it freely crosses the blood-brain-barrier; the CNS facilitates low peroxide tone, which supports an ideal environment for superior APP action (Mazaleuskaya et al. 2015). Due to the inhibitory PGS synthesis properties of APP, the drug exhibits only a mild anti-inflammatory response in the presence of low arachidonic and peroxide levels; therefore, it can squelch mild inflammation associated with dental extractions, but has little effect on chronic inflammation as seen with gout or rheumatoid arthritis (Mazaleuskaya et al. 2015). Additionally, APP blocks other peroxidase enzymes like myeloperoxidase, resulting in decreased halogenating oxidant levels characteristic of varying inflammatory disorders (Mazaleuskaya et al. 2015).

3. APP Hepatotoxicity

As of 2015, APP dosing recommendations in adults have been restricted to 325-650mg by mouth every 4-6 hrs, with a maximum daily consumption restriction of 4g/d and 2 g/d in elevated hepatotoxicity risk patients; recent 2018 guidelines now restrict max APP dosing to < 4 g/d (Sharma & Mehta, 2014; Lancaster et al. 2015; Mccrae et al. 2018). In pediatric patients, dosing is recommended at 10-15 mg/kg/d every 4-6 hrs with a restriction to 50-75 mg/kg/d as of 2015; recent 2018 guidelines still restrict pediatric consumption to ≤75 mg/kg/d with a maximum pediatric dose of < 4 g/d (Sharma & Mehta, 2014; Lancaster et al. 2015; Mccrae et al. 2018). Drug metabolism pathways vary in adults and older adults compared to APP metabolism is pediatric populations as illustrated by Mccrae et al. (2018); Mian et al. (2018); Yang et al. (2015).

Hepatotoxicity results from the formation of excessive NAPQI metabolite, Figure II, which results from increased GSH depletion, oxidative stress, and mitochondrial dysfunction that yields decreased adenosine triphosphate (ATP) stores following excess APP consumption outside of maximum dosing mandates (Yoon et al. 2016; Beger et al. 2015; Macrae et al. 2018). Specifically, adduct formation due to the interaction of mitochondrial proteins with NAPQI result in oxidative stress and the formation of reactive oxygen species inside cellular mitochondria; studies conducted by Sezgin et al. (2018) have recently localized GSH adducts and GSH depletion pathways to the CYP2E1-positive zone of the liver (Yoon et al. 2015; Beger et al. 2015; Sezgin et al. 2018. This causes mitochondrial DNA injury, which opens the mitochondrial DNA damage pore (MPT) and stops ATP production (Yoon et al. 2015; Beger et al. 2015). To

date, unelucidated mechanisms suggest early translocation of the membrane protein BAX in the outer mitochondria in combination with Bak to form pores that release intermembrane proteins like cytochrome C (Beger et al. 2015). Eventually, the combination of released mitochondrial proteins and the cessation of ATP production results in hepatic cell death, which leads to APP-induced hepatotoxicity; other mechanisms such as the formation of toxic free radicals exemplified by peroxynitrite, superoxide and nitric oxide reactions, and nitrotryrosine adduct formation outside the mitochondria also cause cell death due to ATP production cessation (Beger et al. 2015; Yoon et al. 2016).

Acute liver failure associated with APP-toxicity progresses over the course of 0-7 days post consumption with onset of hepatic encephalopathy after the development of jaundice (Lancaster et al. 2015). Graded encephalopathy is segmented into 4 grades in correlation with the Glasgow Coma Scale, where higher grades correlate with poor clinical outcomes (Lancaster et al. 2015). Grade I, the mildest form of encephalopathy, is distinguished by minor mental status changes with increasing change in mental status asterixis through encephalopathy Grade IV; Grade IV is characterized by EEG abnormalities and coma with decerebrate posturing (Lancaster et al. 2015). Outcomes of cerebral edema resulting from hyperammonemia, inflammation, loss of cerebral blood flow autoregulation, and hyponatremia are common in Grade III and IV encephalopathy patients (Lancaster et al. 2015). Additional APP-induced liver failure sequel include shock due to vasodilation, pulmonary edema, and acute renal failure (Lancaster et al. 2015).

The outcome of APP-induced hepatotoxicity varies based on multiple factors, as not all individuals who overdose on APP progress to acute liver failure; known risk factors attributed to APP-induced hepatotoxicity leading to acute liver failure includes malnutrition, fasting, and chronic liver disease among others illustrated in Lancaster et al. (2015), which deplete GSH reserves. According to Yoon et al. (2016), the essential determining factors associated with severity and development of APP hepatotoxicity is (i) APP dose and (ii) the length of time from APP ingestion to N-acetylcystesine (NAC) reversal therapy. In mice, repeated exposure to toxic APP doses result in liver fibrosis despite liver memory correction post first toxic APP dose administration (Al-Wahsh et al. 2019). It is known that pediatric and geriatric populations respond to APP toxicity differently than adults mechanistically, where evidence has shown that AAP-induced toxicity resulting in liver failure is more severe and common in women (Rubin et al. 2018). Additionally, it also affects each body system differently, as illustrated in Mian et al. (2018). Today, the specific, targeted effects of APP-induced hepatotoxicity can be traced via biomarkers across all age groups.

4. Biomarkers linked to APP Toxicity

Prognostic biomarkers are defined by the Federal Drug Administration (FDA) as a measured distinctive that reflects a patient's degree of risk to disease occurrence/ progression that is independent of treatment; a predictive biomarker categorizes patients based on their likelihood to respond positively or negatively to a given treatment (Beger et al. 2015). A diagnostic biomarker can be measured, indicating a given disease state (Beger et al. 2015). The primary prognostic biomarkers associated with liver injury include serum alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate amintransferase

(AST), γ-glutamyl transferase (GGT), lactate dehydrogenase (LDH), and in some cases, glutamate dehydrogenase (GLDH) (McGill, 2016). Though the use of primary biomarkers facilitate clinical identification of hepatic injury, clinical biomarker interpretation is time-dependent and correlates with the precise time of APP intoxication or overdose specific to ALT blood serum expression (Bolt et al. 2015; Beger et al. 2015). Lack of sensitivity and specificity of primary biomarkers and poor mechanistic understanding of APP toxicity further perpetuate incidences of APP hepto-injury and toxicity (Athersuch et al. 2018). The identification of new APP-related hepatotoxic biomarkers aim to improve patient safety and decrease drug-related toxicity attrition; global and local American programs exist to further the identification of these novel biomarkers in human hepatocytes to negate and prevent toxicity recurrence as discussed in (Weiler et al. 2015). Additionally, the key attributes of translational safety biomarkers that denote organ injury are that they are (i) more sensitive and specific, (ii) can be detected via analytical assays in translational animal species like dogs, rats, mice, or monkeys, (iii) can be detected in humans via noninvasive measurements or body fluids like blood and urine, (iv) can predict/monitor toxicity severity of histopathology in nonclinical species, (v) are organ specific and mechanistically specific in terms of toxicity, (vi) are organ tissue-specific, and are (vii) insensitive to non-toxic agitates like diet, exercise, age, toxicants, and co-morbidities (Beger et al. 2016). Within the past 20 years, novel microRNAs (miRNAs) have been discovered in association with drug-induced hepatotoxicity; Wang et al. (2009) was the first research group to discover microRNAs in correlation with APP drug-induced hepatotoxicity in 2008.

MiRNAs are defined as a short, 21-23 nucleotide RNA species that binds to mRNA with complementary sequences in a complex sequence known as the RNA-induced silencing complex (RISC); RISCs prevent translation via either (i) physical obstruction or (ii) via mRNA degradation (Athersuch et al. 2018; Beger et al. 2015; McGill & Jaeschke, 2015; McGill et al. 2012). They function in the basic cellular roles of development, cellular differentiation, proliferation, cell-cycle control, metabolism, apoptosis, and cancer; miRNAs are commonly found in body fluids like blood and urine and serve as key markers of cellular injury that can be obtained noninvasively both clinically and non-clinically (Beger et al. 2016). The mechanistic characteristics of APP-induced hepatotoxic miRNAs as well as commonly associated miRNAs are discussed in length in McGill & Jaeschke (2015) and again in children in Yang et al. (2015). The identification of drug-induced hepatotoxic biomarkers serves to elucidate drug-induced liver injury and toxicity via (i) mechanistic elucidation and (ii) the development of blood serum and urine miRNA profiles, which aid in diagnosing drug-induced liver injury and hepatotoxicity and serve as patient outcome predictors (McGill & Jaeschke, 2015).

4.1. Animal Models: APP Hepatotoxicity Biomarkers

Table 1 illustrates the cellular biomarkers associated with APP-induced hepatotoxicity noted previously over the past 15 years; these biomarkers were isolated from various translational animal species (Ishida et al. 2002; Mcgill et al. 2012; Hanawa et al. 2008; Ramachandran et al. 2010; Demirbas et al. 2011; Sun et al. 2011; Ruepp, 2002; Antoine et al. 2009; Gautam et al. 2012; Yaman et al. 2013; Williams et al. 2011; Martin-Murphy et al. 2010; van Swelm et al. 2011;

Yan et al. 2010). In terms of miRNA biomarkers isolated from animal models, Wang et al. (2009) identified an increase in miR-122 and miR-192 after toxic APP dose administration in mice in 2009; miR-122 accounts for 50% to 70% of all miRNA in human and mouse liver transcripts respectively (McGill & Jaeschke, 2015; Wolenski et al. 2016; Bala et al. 2012). Increases in miR-155, miR-146a, and miR-125b were also founded to be elevated in mice models following exposure to toxic APP levels in mice (Wang et al. 2009; Bala et al. 2012). Recent studies conducted in the past 5 years from 2015 to 2020 includes miRNA elevations in rat, monkey, and frog models. A 2016 study conducted in rats exposed to APP toxic conditions resulted in an increase in hepatotoxic miRNA biomarkers miR-122, miR-92a, miR-146b, miR-34c, miR-144, miR-451 (Bala et al. 2012). In 2017 and 2018, monkey studies revealed hepatotoxic patterns parallel to human exposure to toxic APP levels, where circulating miR-122 and miR-192 levels increased higher than ALT levels in the liver after 24 hrs, suggesting that miR-122 and miR-192 may be a more sensitive biomarker for APP-induced hepatotoxicity (Iguchi et al. 2018; Tamai et al. 2017). A study conducted in 2019 in *Xenopus laevis* embryos indicated that similar to zebrafish, the elevation of miR-122 and depletion of GSH parallel human and mice models, indicating hepatotoxicity proportional to increasing toxic levels of APP exposure (Saide et al. 2019).

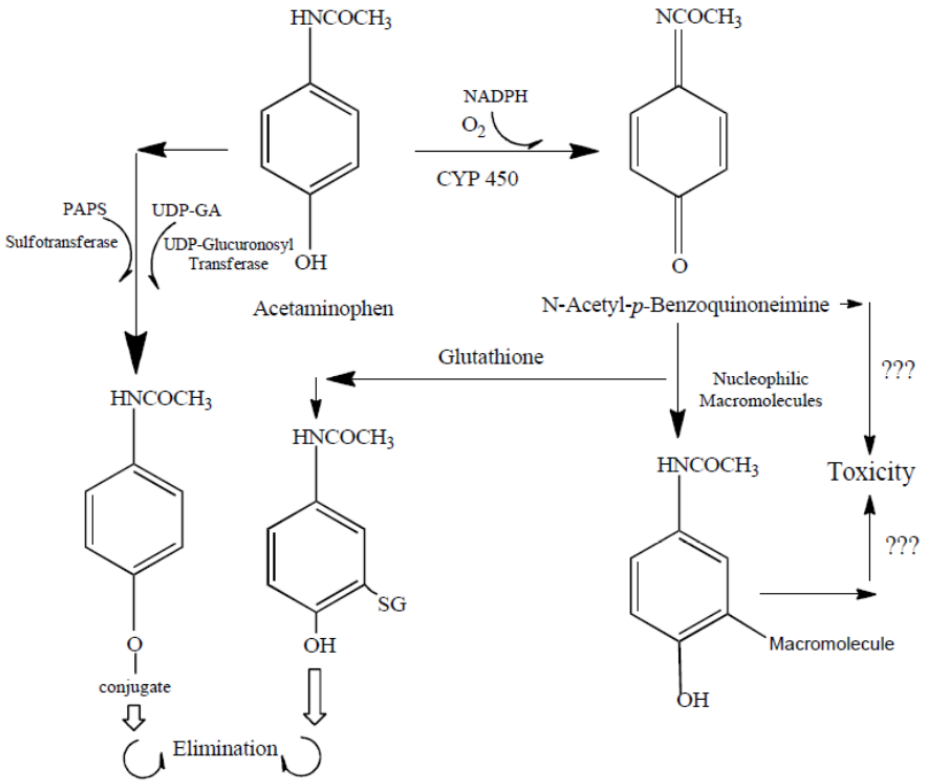

Figure 2: Pathway illustration of acetaminophen in the induction of toxicity on a molecular level (figure reproduced in part with editorial permission of Mr. Richard Doedenhoff, Journal director of Drug Metabolism and Disposition; James et al. 2003).

4.2. Human Models: APP Hepatotoxicity Biomarkers

Comparatively, Table 2 indicates the human biomarkers associated with APP-induced hepatotoxicity over the past 15 years; it is evident that significantly fewer studies have been conducted in human subjects (Fannin et al. 2009; Jetten et al. 2012; Antoine et al. 2012; Prot et al. 2011; Winnike et al. 2010; Mcgill et al. 2013). In the past 5 years from 2015 to 2020, APP biomarkers denoting hepatotoxicity has taken on a different form in human models. A study conducted by Penmetcha et al. (2019) depicted a 72 year old female in 2019 with APP-induced hepatotoxicity without the presence of exorbitant APP serum levels; labs indicated high AST and ALT levels in the absence of hepatic viruses; NAC therapy normalized liver function enzymes leading to the conclusion that APP-induced hepatotoxicity should not be ruled out despite low APP serum levels. A miRNA profile associated with APP-induced hepatotoxicity was established by Carreiro et al. in 2019; the study revealed 327 miRNAs associated with hepatotoxicity in human patients with an existing APP-induced hepatotoxic diagnosis. Specifically, miR-194-5b, miR-125b-5b, miR-193a-5b, miR-122-5p, miR21-5p, miR-27b-3p, and miR-1290 were identified to differentiate APP toxicity from other liver injury forms such as ischemic hepatitis; 12 miRNAs were associated with the most severely APP-poisoned subjects, which were reflected in miR-3646-3p, miR-412, miR-2467-3p, miR-1207-5p, miR-138-1-3p, miR-605, miR-4258, miR-372, miR-4524a-3p, miR-19b-1-5p,miR-122-5p, and miR-483-5p elevation (Carreiro et al. 2019). In 2015, human miRNAs that displayed the largest increase post exposure to APP-induced toxicity included miR-122-5p, miR-885-5p, miR-151a-3p versus the classifier model, miR-382-5p, which denoted non-APP liver injury; miR-122-5p proved to be more sensitive than ALT in correlation with hepatic injury, especially when coupled with miR-483-3p (Vliegenthart et al. 2015). An in-vitro study conducted in 2017 identified the expression of protein adducts 1 hr post exposure to APP toxic conditions, which was then accompanied by an ALT increase at the 12 and 24 hr mark; in terms of mRNAs, CYP1A2, CYP3A4 and CYP2E1 levels were founded to be decreased, while miR-122-5p, miR-378a-5p, miR-27b-3p at 6 h and miR-125b-5p at 12 h and miR-27b-3p miRNAs were increased at the 24 hr mark post toxic APP exposure (Gill et al. 2017). In children serum samples with toxic APP levels, there was a significant increase in miR-122-5p, miR-378a-5p, miR-125b-5p and miR-27b-3p, compared to healthy controls, which indicated that elevations in miRNA associated with APP toxicity represent a regulatory response that modifies CYP1A2, CYP3A4 and CYP2E1 translation due to cellular stress and cellular injury (Gill et al. 2017). Finally, elevation of miRNAs in the serum of human children post exposure to APP toxic conditions also revealed an increase in miRNAs miR-122, miR-375, miR-423-5p, miR-30d-5p, miR-125b-5p, miR-4732-5p, miR-204-5p, and miR-574-3p in 2015 (Yang et al. 2015).

5. Potential Solutions to APP Hepatotoxicity

As of 2020 with the elucidation of APP-induced toxicity pathways semi-sorted, the current trend in evidence-based research (EBR) targets treatments and preventatives of APP-induced hepatotoxicity.

Table 1: Illustrates the cellular biomarkers associated with APP-induced hepatotoxicity noted previously over the past 15 years.

Ref.	Biomarker	Indications	Model
Ishida et al. (2002)	IFN-γ	Associated with the expression of: (1)intercellular adhesion molecule 1 (2)vascular cellular adhesion molecule 1 (3)IL1, IL6 (4)tumor necrosis factor (5)monocyte hemo-attractant protein 1 (6)macrophage inflammatory protein 1 and 2 (7)KC, IP-10, MIG, Fas (8)inducible nitric oxide synthase	Wild-type BALB/c mice
McGill et al. (2012)	(1) Mitochondrial oxidative stress (2) Mitochondrial protein adducts	Mice: (1) oxidative stress (2) JNK activation (3) decrease in mitochondrial membrane potential. Rats: little to no elevation in serum GDH and ALT levels	C57Bl/6 mice; Sprague–Dawley rats
Hanawa et al. (2008)	JNK	The activation of JNK kinases resulted in: (1) decreased levels of GSH that causes hydrogen peroxide release from hepatic mitochondria. (2) JNK activation leads to decreased mitochondria redox (3) JNK translocation is the ultimate step that leads to decreased mitochondrial respiration leading to cell death	Male C57 BL/6 TNF-R1 knock-out wild-type (C57 BL/6) mice
Ramachandran et al. (2011)	(1) Mitochondrial oxidative stress (2) Centrilobular necrosis (3) DNA fragmentation (4) Glutathioninedisulphide (5) Peroxynitrite levels	Findings in the presence of animal models with protein cyclophilin D deficiency: (1) Decreased JNK activation (2) Decreased oxidant stress (3) Decreased peroxynitrite levels	Male cyclophilin D-deficient mice (*Ppif*– /– mice)
Demirbas et al. (2011)	Neopterin	AST and ALT levels correlate with neopterin level thereby indicating the extent of necrosis	Wistar rats
Sun et al. (2012)	Dityrosine	Predictor of protein oxidation resulting from APAP Hepatotoxicity →Dityrosine levels parallel APAP hepatoinjury	Wista-rImamichi rats
Ruepp et al. (2002)	(1) Mitochondrial changes (2) Decreased GSH levels (3) Hyperactive GM-CSF mRNA (4) Decreased chaperone protein performance	Fluctuation in mitochondrial morphology as a result in APAP injection at both subtoxic and toxic doses (1) Decreased Hsp10 and Hsp60 chaperone performance due to release from hepatic mitochondria to the cytoplasm (2) exacerbated GM-CSF mRNA activity as a result of APAP injection (3) resulted in centrilobular necrosis as opposed to apoptosis	Alderly Park (CD-1) male mice (fasting diets)
Antoine et al. (2009)	(1) High-mobility group box-1 proteins (HMGBPs)	Both proteins are indicators of APAP induced apoptosis and necrosis	Male CD-1 mice

	(2) Keratin-18 proteins		
Gautam et al. (2012)	(1) Glycogen (2) Cholesteryl esters (3) DNA (4) IFN-γ and TNF-α (5) IL6 and IL10	(1) Decreased glycogen (2) Increased cholesteryl ester and DNA production before ALT increase indicative of acute APAP hepatotoxicity. (3) No significant change in IFN-γ and TNF-α activity with marked decrease in IL6 and increase in IL10 activity	BALB/c mice C57BL/6 and $Nos2^{-/-}$mice
Yaman et al. (2011)	Pentraxin-3	Biomarker may act as an indicator of liver necrosis resulting from APAP injection	Inbred Wistar rat strains
Williams et al. (2011)	Nalp-3	Biomarker may initiate the release of DAMP proteins as a result of APAP induced hepatic injury	male ASC−/−, caspase-1−/−, Nalp3−/-, C57BL/6 mice
Martin-Murphy et al. (2012)	Kupffer cell activation	Kumpffer cell activation marks the onset of APAP toxicity followed by the release of HMGBPs, DAMP molecules, and Heat Shock proteins	Female C57Bl/6J mice
van Swelm et al. (2011)	Superoxide dismultase-1 (SOD-1)	(1) SOD-1 proves to be a strong and efficient biomarker of APAP hepatotoxicity detectable by urinary analysis (2) High levels of plasma ALT levels, GSTs, carbonic anhydrase 3, and regulcalcin were also found as less sensitive biomarkers	Male FVB mice
Yan et al. (2010)	(1) Mitochondrial oxidative Stress (2) Fluctuation in LDH activity (3) Necrosis (4) Cellular death	(1) 5 mM APAP treatment induced cellular death (necrosis) with 21% oxygen marked by 84% loss of LDH (2) A decrease in oxygen levels marked a decrease in the LDH activity loss	Male C57BL/6 mice

Bibliometric studies conducted by Zyoud et al. (2016) and Zyoud et al. (2014) indicate tangible data that relay the increased literature output regarding APP toxicity across the world, where the United States (U.S.) dominates among other countries. Globally, studies from differing countries offer EBR that documents hepato-protective edibles that combat APP-induced liver failure. A study conducted by Mohammadzadeh et al. in 2015 Iran addresses the potential of fenugreek seed powder as a means to reduce oxidative stress that occurs during the APP-induced hepatotoxicity pathway; the study observed a decrease in malondialdehyde and hydrogen peroxide levels in rats that were fed a combination of APP and fenugreek over the control. Another study conducted in 2018 Iran proposed the use of Metadonine, a common agent used to treat alcohol-induced hepatotoxicity as a potential intervention for APP-induced hepatotoxicity in mice, findings indicated that Metadonine is comparable to NAC in that it significantly decreased ALT, AST, and ALP while attenuating oxidative stress by lipid peroxidation suppression and reduced GSH depletion prevention due to APP toxic conditions (Minaiyan et al. 2018).

A study conducted in 2018 Korea assessed the use of *Gastrodia elata Blume* (GEB, tian ma), a traditional Asian herb commonly used to treat obesity, epilepsy,

asthma, inflammation, and depression as an intervention for APP-induced hepatotoxicity prevention; findings indicated that GEB pre-treatments decreased cellular necrosis and pro-inflammatory cytokines in the liver and kidney, a decrease in TUNEL-positive cells and oxidative stress markers like malondialdehyde, and a decrease in CYP2E1 and N-acetyl-beta-D-glucosaminidase indicated the use of GEB as a preventative of APP-induced liver and kidney injury in rat models (Seok et al. 2018). A 2017 Egyptian study identified a decreased in APP-induced oxidative damage via the use of *Moringa peregrina,* a wild tree that grows in the Egyptian eastern desert mountains; conclusions yielded that despite the increased APP-induced liver enzyme elevation, the wild tree extract reversed APP-induced toxicity by malondialdehyde suppression, glutathione peroxidase normalization, and cellular antioxidant stimulation noted by increased GSH (Azim et al. 2017). A study in 2018 China implemented the use of American Ginseng Berry (AGB) as a potential APP-induced hepato-protective in mice; findings indicate that pretreatment with AGB relieved APP-induced hepato-injury as observed via decreased ALT, AST, tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β), and nuclear transcription factor-κB (NF-κB p65) in liver tissues (Xu et al. 2018). Finally, studies in the U.S. conducted by Farooq et al. (2017) and More et al. (2017) found that aspartate functions via NMDA to suppress TLR4 and NLRP3 mediated pro-inflammatory signals in APP-induced hepatic and renal failure, where aspartic acid can be used as a therapeutic agent for APP-induced hepatotoxicity; ψ-GSH was founded to be a safer and superiorly effective alternative to NAC treatment respectively.

Table 2: indicates the human biomarkers associated with APP-induced hepatotoxicity over the past 15 years.

Ref.	Biomarker	Indications	Model
Fannin et al. (2010)	(1) genes involved in oxidative phosphorylation/mitochondrial function (2) serum lactate	(1) down regulation of 35 genes involved in oxidative phosphorylation/mitochondrial function pathways (2) increased in serum lactate after >48hrs toxic APP dose exposure	Peripheral blood from 6 healthy human adults
Jetten et al. (2012)	(1) ALT (2) total bilirubin (3) alkaline phosphatase (4) gamma glutamyl transpeptidase (5) lactate dehydrogenase (6) albumin (7) miRNAs	(1) Expression of miR-19a, miR-19b and miR-374a (2) Urine: APAP as mother compound, APAP-glucuronide, APAP-sulfate, cysteine-APAP and N-acetylcysteine-APAP; 23 masses identified (3) Plasma: all biomarkers increased at various time points of APP exposure	Plasma and Urine from 7 healthy adult humans, 1 of whom is a smoker After low dose APP exposure
Antoine et al. (2012)	(1) Keratin-18 (FL-K18) (2) High Mobility Group Box-1 (HMGB1)	(1) apoptosis and necrosis related K18 and total HMGB1 increase (2) presence of acetylated-HMGB1 (inflammatory-derived) variant	Serum or plasma from 84 adults with acute liver injury due to APP toxicity

		in the sera of APAP overdose patients	enrolled in Kansas Medical Center, aged >16 yrs
Prot et al. (2011)	(1) Actin, tubulin, coronin 1b (2) Glutathione and NAPQI (3) cytosolic calcium (4) Lipid Metabolism Genes (5) Lipid Production Enzymes	(1) decrease in actin, tubulin and coronin- (2) synthesis at the protein levels involved in cytoskeleton (3) depletion of the glutathione cell stock led to covalent binding of NAPQI leading to cell death (4) Increase in cytosolic calcium concentration correlated with cell death signal (5) downregulation of lipid metabolism genes: GPD1, GPAM, DAK; up-regulation of IGFBP-1 (6) lipid production enzymes: leukotriene A-4 hydrolase, short-branched chain specific acyl-CoA dehydrogenase, and hydroxymethylglutaryl-CoA synthase were still upregulated	Human HepG2/C3A cells cultivated in a biochip exposed to APP toxic conditions
Winnike et al. (2010)	(1) serum Alanine (2) Aminotransferase (ALT) (3) serumAspartate aminotransferase (AST) (4) serumα-glutathione-S-transferase	(1) increase in ALT, AST, alpha GSH transferase	Serum/plasma from71 healthy human men and women, aged 18–55 years
McGill et al. (2013)	(1) Acylcarnitine in serum	(1) acylcarnitine levels did not change significantly over time after APAP overdosing conditions	Human patient volunteers diagnosed with APP overdose recruited from the University of Kansas Hospital in Kansas City, KS, USA or Banner Good Samaritan Health Center in Phoenix, AZ, USA.

In terms of miRNA, newly emerging studies found the emergence of cellular and cytosolic miRNAs to be hepatoprotective. A study conducted in 2015 Germany found that miR-125b-5p functions as a regulator of cell death that attenuates APP-induced hepatotoxicity in mice and human liver cells; this attenuation occurs via direct regulation of kelch-like ECH-associated protein 1, which results in the increased expression of nuclear factor-E2-related factor 2 known to regulate acute liver failure (Yang et al. 2016). A study from 2020 China found that miR-338-3p was significantly upregulated after intraperitoneal APP administration in mice; specifically, miR-338-3p augmentation reduced hepato-injury due to APP toxic conditions via proinflammatory cytokine inhibition and activation of inflamma-

tory signaling due to nuclear factor kappa-B (NF-kB)/mitogen-activated protein kinase (MAPK) signaling pathways (Zhang et al. 2020). A study in 2018 China and the U.S. found that 4 miRNAs, hsa-miR-224-5p, hsa-miR-320a, hsa-miR-449a, and hsa-miR-877-5p suppressed drug metabolizing enzymes involved in APP-induced hepato-injury via downregulating HNF1A, HNF4A and NR1I2 expression in human hepatocytes suggesting hepto-protectivity (Yu et al. 2018). Finally, a 2017 study conducted in tandem in the U.S. and Germany found that the iconic biomarker for drug-induced hepatoxicity miRNA-122 functions in the APP detoxification pathway, with acute liver failure therapeutic potential via regulating cytochrome P450 Family 1 Subfamily A Member 2, and Subfamily E Member 1 Expression in human and mouse hepatocytes (Chowdhary et al. 2017).

6. Conclusions and Future Perspectives

The prevalence of superfluous APP consumption is among the most common cause of hepatic and renal toxicity known to date. A recent 2019 case study conducted by Penmetcha et al. (2019) denotes the prevalence of APP-induced hepatotoxic patients that present with no APP serum elevation yet fall victim to the toxic effects of the drug, underscoring the gravity and continued prevalence of APP-induced hepatotoxicity in the 21st century.

Over the past 20 years, much of the mechanistic and hepatotoxic pathways associated with APP-induced toxicity have been clearly elucidated through a global influx of EBR and literature supporting cellular function. APP-induced hepatotoxic biomarker elucidation has also become more prevalent predominantly in transient animal models, though some human models made way in the form of hepatic cell culture, biopsy acquisition, serum, urine, and plasma assessment. A 2009 study conducted by Wang et al. shed light on the first miRNA biomarker associated with APP-induced hepatotoxicity. More than 10 years later, novel miRNA biomarkers involved in APP-induced toxicity continue be identified and repurposed. In the past 5 years, from 2015 to 2020, new miRNA and herbal/plant derivatives offer potential treatment and reversal agents for APP-induced hepatotoxicity from a global perspective. Continuing forward, a lingering surge in APP-induced toxicity literature is projected for the upcoming decade, especially from countries with large economies such as the United Kingdom, Australia, Japan, China, France, and the U.S. (Zyoud et al. 2016; Zyoud et al. 2014).

CONFLICT OF INTEREST

The author declares no conflicts of interest.

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