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The potency of red onion skin flavonoids in acetaminophen-induced liver injury management: A biomolecular review

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ABSTRACT

Acetaminophen is widely used as a fever and pain reliever drug. However, acetaminophen intoxication was common and responsible for thousands of acetaminophen-induced liver injury (AILI) cases worldwide. It was understood that glutathione (GSH) depletion causes a deposit of acetaminophen metabolites which are toxic to liver cells. N-acetylcysteine (NAC), used as acetaminophen intoxication therapy, has been reported to cause side effects such as nausea, vomiting, and anaphylactic reaction. This narrative review aimed to discuss other potential candidates in AILI management. The biomolecular approach was used to investigate onion skin in-depth and holistic discussion. According to the results, onion peel extract is rich in flavonoids (quercetin and kaempferol) and potentially be a candidate in the management of AILI through proposed mechanisms such as restoration of reduced glutathione (GSH), inhibition of cytochrome P450 (CYP) enzymes, upregulation of uridine 5'-diphospho-glucuronosyltransferase (UGT) enzyme, and inhibition of TLR4 activity.

Asetaminofen merupakan obat yang umum digunakan sebagai analgesik dan antipiretik. Namun demikian, kasus intoksikasi asetaminofen sering terjadi dan telah bertanggung jawab pada puluhan ribu kasus acetaminophen-induced liver injury (AILI) di dunia. AILI terjadi akibat deplesi glutation tereduksi (GSH) yang berimplikasi pada penumpukan senyawa metabolit asetaminofen dan bersifat toksik bagi sel hepar. Saat ini tatalaksana intoksikasi asetaminofen menggunakan N-acetylsistein (NAC). Namun, penggunaan NAC dilaporkan menimbulkan efek samping berupa mual, muntah, hingga reaksi anafilaktoid. Kajian pustaka ini membahas mengenai bahan lain yang dapat digunakan dalam manajemen AILI. Tujuan penulisan kajian ini adalah untuk mengkaji secara holistik mengenai potensi flavonoid di dalam kulit bawang merah pada manajemen AILI. Metode yang digunakan pada kajian pustaka ini adalah metode narrative review dengan pendekatan mekanisme biomolekuler untuk pembahasan yang lebih holistik. Berdasarkan hasil kajian, ekstrak kulit bawang merah kaya akan flavonoid (quercetin dan kaempferol) dan berpotensi menjadi kandidat dalam manajemen AILI melalui restorasi glutation tereduksi (GSH), inhibisi enzim CYPs, upregulasi enzim UDP glucuronosyl-transferase (UGT), dan inhibisi aktivitas TLR4.

INTRODUCTION

Acetaminophen (APAP, N-acetyl-p-aminophenol, or paracetamol) is a fever and pain reliever commonly used worldwide and prescribed or non-prescribed in combination drugs.[1,2,3]. Acetaminophen is an over-the-counter drug that can be bought and sold without a doctor's prescription [4,5]. Although acetaminophen is classified as safe at normal doses [6], numbers of data reported morbidity cases due to acetaminophen intoxication [5,7,8.]

Acetaminophen intoxication has been recorded annually. Out of 82,376 cases, an estimated incidence of 27.10 per 100,000 was reported in the US at costs incurred up to US$1.06 million [7]. Intentional and unintentional reasons are responsible for causing the high rate of acetaminophen intoxication. [2]. In some deliberate cases, acetaminophen is used as a medium for suicide [1,6]. Unintended cases are caused by the lack of consumer knowledge regarding hazardous consuming the combination drugs containing acetaminophen and the public perception assumes that acetaminophen is a safe drug, resulting consumers tend to ignore the recommended dose (above 4 g/day) [1,9]. Common morbidity in patients with acetaminophen intoxication is liver organ damage, a condition known as acetaminophen-induced liver injury (AILI) [5,8].

In epidemiological studies, AILI has contributed to 50% of all liver failures in America and Australia [8,10]. Liver damage acetaminophen overdose-induced is caused by the accumulation of N-acetyl-para-benzoquinone imine (NAPQI) in the liver cells. NAPQI is a toxic compound resulting from highly reactive acetaminophen metabolism [11,12]. NAPQI is usually detoxified into cysteine and mercapturic acid conjugates at tolerable doses via the glutathione-dependent pathway (GSH-dependent pathway). However, in the acetaminophen intoxication state, GSH depletion occurs in the liver, resulting in NAPQI accumulation. This condition results in oxidative reactions, ion imbalance, and mitochondrial dysfunction, all of which lead to liver cell necrosis [11,12].

GSH restoration is one of the way treatments in AILI and acetaminophen intoxication. A common agent in GSH restoration is N-acetylcysteine (NAC), which restores GSH levels by providing important compounds in GSH synthesis [9]. However, the latest evidence suggests that NAC has a narrow therapeutic range and side effects include nausea, vomiting, diarrhea, and anaphylaxis reaction [9]. Based on a previous study, the side effect rate of using NAC varies from 8.5% to 77% [13]. This fact becomes a gap in therapeutic so that another substance is needed as a GSH restorative agent (other than NAC) and a hepatoprotective agent in AILI management.

Some studies investigated other compounds besides NAC that could potentially lead to GSH restoration. Flavonoids such as quercetin and kaempferol suggest promising natural compounds that act as hepatoprotective and restore GSH cells [14,17]. Furthermore, quercetin and kaempferol are easy to find in plants commonly found, such as asparagus, lettuce, chili pepper, and onion. The most superior among these plants is onion, containing the flavonoid quercetin (45.0 mg/100 g net weight) and kaempferol (4.50 mg/100 g net weight). In addition, red onion (Allium cepa L.) has the highest flavonoid content compared to garlic and yellow onion. Interestingly, quercetin and kaempferol are more concentrated in their skin than flesh [18,21].

Based on the elucidation above, an in-depth and holistic discussion is needed to explore the potential of red onion skin flavonoids for AILI management. This narrative review aimed to investigate the potential of red onion skin holistically as a restorative and hepatoprotective agent in AILI management. In this case, a biomolecular mechanism approach is carried out to discuss therapeutic and preventive potentials by considering the pathogenesis of AILI. This narrative review is expected to be used as a reference for further studies related to the red onion skin potential or AILI in the future.

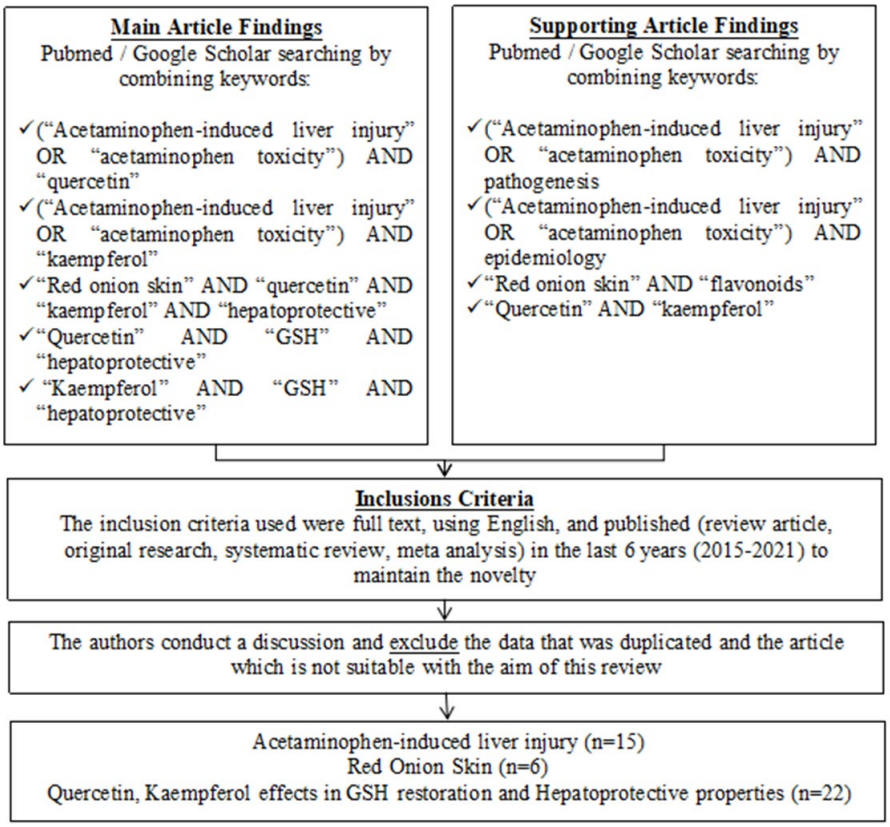

Figure 1. Data collection method
Keywords, article finding, inclusions, and exclusions criteria in this narrative review is shown in Figure 1

Data collection method

The data collection method is shown in Figure 1.

Red onion skin flavonoids and their potency

Red onion is one of the most important agricultural products worldwide. This plant belongs to the Alliaceae family and biennial plants [20]. It is claimed to have been produced 55 million each year worldwide [20]. However, red onion skin wastes cause environmental problems. This by-product cannot be used as fertilizer or animal feed since it has phytopathogenic properties and a foul odor. Therefore, it tends to be wasted and thrown away [22]. Nevertheless, the onion skin contains high levels of flavonoids, mainly in quercetin and kaempferol forms [18,20,22,23]. Quercetin (3,3', 4',5,7-pentahydroxyflavone) is one of the molecules of polyphenolic flavanols, which has antioxidant and anti-inflammatory effects [24,26]. A previous study regarding red onion reported 48 times high levels of quercetin in the skin than in the flesh [20]. Within 200 grams of red onion skin extract contained quercetin (64 mg), quercetin 3-O-β-D-glucopyranoside (3 mg), and quercetin 7-O-β-D-glucopyranoside (2 mg) [18] In addition, another type of flavonoid compound, kaempferol or 3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one, is the second most non-toxic flavonoid found in many natural products [21,27,28]. In line with quercetin, kaempferol also has several forms which are glycoside is the most common [18]. Kaempferol and quercetin are suggested to

have a beneficial bioactive effect [21,24,28].Several studies show that quercetin and kaempferol have a role as molecular hepatoprotective [15,29,33]. Both flavonoids have antioxidant and anti-inflammatory properties. Other studies suggest that quercetin and kaempferol are also potent to restore GSH [14,16,17,31,34,37].

The role of glutathione (GSH)

Glutathione is an antioxidant composed of glutamic acid, glycine, and cysteine that preserve redox balance in cells [14,38]. In the body, glutathione is usually present in reduced form (GSH) and can be transformed by glutathione peroxidase (GPx) then into its oxidized form (glutathione disulfide, GSSG). The GSH/GSSG ratio is usually greater than 10:1 in the mitochondria and cytoplasm. A reduction in this ratio suggests that oxidative stress in the cells is present [38,39]. It was clarified that GSSG facilitates toxicity and should be immediately converted back into GSH by the enzyme glutathione reductase (GSR) [39].

GSH formation is carried out through two stages of de novo synthesis involving the glutamate-cysteine ligase (GCL) enzyme complex and glutathione synthetase (GSS) [38,40]. The GCL enzyme complex facilitates the conversion of L-cysteine and L-glutamate to L-γ-glutamylcysteine through a process involving ATP. This compound will be converted into GSH with the help of the GSH synthetase (GSS) enzyme [38,39].

In accordance with the previous discussion that GSH has antioxidant properties and is also involved in the detoxification process of reactive electrophiles into xenobiotic-conjugates (GS-X) by enzyme glutathione S-transferase (GST) [38]. However, the excessive detoxification process results in decreased levels of GSH, leading to various diseases and cell damage [39,40]. This GSH depletion state also appears in acetaminophen-induced liver injury (AILI).

AILI

AILI occurs due to acetaminophen intoxication involving the specific compound, NAPQI, a reactive compound that results from the acetaminophen metabolism in liver phase I by the cytochrome P450 family 2 subfamily E member 1 (CYP2E1) enzyme [9,11]. The symptoms and signs of AILI are diverse, including nausea, vomiting, lethargy, diaphoresis, jaundice, and lactic acidosis [41]. Hereafter, if not treated properly, AILI would develop acute liver failure (ALF) and lead to death [8,10]. The proposed mechanism is NAPQI toxic to cells and leads to leakage of mitochondrial electrons to form other toxic compounds in superoxide radicals form. In turn, these superoxide radicals will undergo dismutation into hydrogen peroxide (H2O2) and oxygen (O2) by manganese superoxide dismutase (MnSOD). In addition, superoxide radicals can also react with endogenous nitric oxide (NO) and form peroxynitrite (ONOO-) [3,9,12]. Both H2O2 and ONOO- normally detoxified by GSH. In acetaminophen intoxication, GSH depletion results from accumulating H2O2 and peroxynitrite, which damages mitochondrial DNA [9,12].Increased H2O2 in the cytoplasm leads to activation of apoptosis signal-regulating kinase 1 (ASK-1). Furthermore, ASK-1 activates c-Jun N-terminal kinase (JNK), which increases reactive oxygen species (ROS) release. ROS induces a looping system that continuously activates JNK, consequently activating Bax protein [3,9,12]. The Bax/Bcl2 ratio is important in cell survivability [31]. Bax protein contributes significantly to mitochondrial damage contributing to the damage of hepatocytes. Aside from those described above, toll-like receptor [4] (TLR4) activation has also been recorded to exacerbate AILI [33]. TLR4 induces macrophages via JNK activation and leads to the release of pro-inflammatory cytokines, further exacerbating liver damage [33].

The potential of red onion skin flavonoids in AILI management

Red onion skin flavonoids as GSH restoration agent

The key to the pathogenesis of AILI is liver

GSH depletion. Accordingly, the attempt to restore GSH potentially reduces the progression of AILI. In order to restore cell GSH levels, the two dominant bioactive compounds in red onion skin, quercetin and kaempferol, are reported to have potential. Quercetin was reported to restore GSH to its normal levels in preadipocytes 3T3-L1 and human aortic endothelial cells (HAEC), which were induced by Fe2 and hydrogen peroxide (H2O2), respectively [14,35.] In previous in-vivo studies, an increase in mice liver GSH was also observed, involving administering a hepatotoxic compound, toosendanin (TSN) [36.] This statement was also confirmed in other studies using acetaminophen-induced mouse models [16,34].

In line with quercetin, kaempferol and its derivatives were reported to potentially restore liver GSH in mice models with liver injury [15,17,31]. Pretreatment of kaempferol in the acetaminophen prodrug-induced mice models significantly increased GSH [31]. This reported data indicates that kaempferol is potent to reduce the toxicity effects of acetaminophen prodrug [31]. This GSH restoration occurs due to the influence of increased expression of the complex GCL catalytic (GCLC) enzyme in both quercetin and kaempferol administration, which plays an important role in de novo GSH synthesis [31,35,37]. Accordingly, the administration of GCLC inhibitors in buthionine sulfoximine (BSO) forms demonstrated reduced GSH levels in oxidant compounds exposed [36]

Red onion skin flavonoids as hepatoprotector in AILI

Simultaneously with GSH depletion, hepatic cell necrosis occurs in AILI [9,12,41]. This necrosis cannot be distinguished from the role of the NAPQI formed by the CYPs enzyme through phase I drug metabolism in the liver [42,43]. It was reported that the administration of acetaminophen prodrug in mice induces CYP2E1 expression [31]. However, treatment with kaempferol showed the opposite result, where the protein expression was similar to the control group [31]. In accordance, quercetin inhibits CYPs enzymes, particularly CYP2E1 and CYP1A2 [29,30]. These inhibitions result in a decrease in oxidative compounds and improved energy production by mitochondria [31,34]. Furthermore, acetaminophen metabolism shifts to glucuronidation, a phase II drug metabolism process [31].

In phase II, acetaminophen is metabolized by uridine 5'-diphospho-glucuronosyltransferase (UDP-glucuronosyltransferase, UGT) and sulfotransferase (SULT) enzymes through glucuronidation and sulfation processes, respectively. UDP glucuronosyltransferase family 1 member A1 (UGT1A1) is one of the forms of UGT responsible for acetaminophen metabolism. This enzyme promotes acetaminophen conjugation to be excreted and promotes the hepatoprotective effect [31]. Furthermore, kaempferol also has beneficial bioactivity for stress-exposed cells and hepatoprotective properties. Upregulation of UGT1A1 expression and restoration of antioxidant enzymes (superoxide dismutase, glutathione-peroxidase, and catalase) were reported in the acetaminophen prodrug-induced mice models [31]. A hepatoprotective effect was also demonstrated by inhibiting Bax gene expression and decreased serum hepatic function marker, aspartate aminotransferase (AST) [31].

Activation of toll-like receptor 4 (TLR4) was involved in AILI. This gene induces macrophage activation by secreting pro-inflammatory compounds through the JNK pathway, exacerbating liver cell damage in acetaminophen intoxication. This finding has been observed in both in-vitro and in-vivo studies. [33]. Uniquely, kaempferol derivatives also have the potential to inhibit TLR4 activity. It is expected to reduce the progression of hepatocyte necrosis in AILI cases and provide a hepatoprotective effect [15,33]. The summarize of red onion skin potential flavonoids in AILI management is shown in Figure 2.

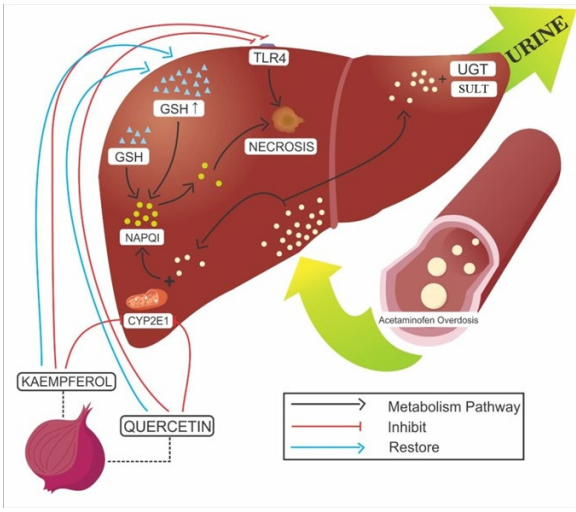

Figure 2. The potential of red onion skin flavonoids in AILI management
Acetaminophen is metabolized and conjugated by the UDP glucuronosyltransferase (UGT) and sulfotransferase (SULT) enzymes before being excreted in the urine at normal doses. The toxic compound N-acetyl-para-benzoquinone imine (NAPQI) is produced by the CYP2E1 enzyme in acetaminophen intoxication and glutathione (GSH) depletion occurs. If it continues, this will result in hepatic cell necrosis. Kaempferol and quercetin commonly found in the red onion skin extracts can potentially inhibit the CYP2E1 enzyme, inhibit the activity of TLR4, and restore GSH, which have hepatoprotective properties.

CONCLUSION

Over-dose of acetaminophen use leads to AILI, resulting in comorbidity worldwide. In this narrative review, red onion skin, agricultural wastes that are less utilized, has been proposed to have potentials in AILI management. Quercetin and kaempferol in red onion skin can restore GSH levels, inhibit CYP enzymes, and inhibit TLR4 activity, suggesting hepatoprotective properties. Nevertheless, further study of red onion skin flavonoids formulation and conducting a clinical trial are needed.

CONFLICT OF INTEREST

There is no conflict of interest in this article

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