Curcumin Benefits as Antioxidant

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Research Article

CURCUMIN BENEFITS AS ANTIOXIDANT, ANTIINFLAMATION AND ANTIAPOPTOSIS AMELIORATE PARACETAMOL TOXICITY

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ABSTRACT

Background: Paracetamol poisoning due to the use of paracetamol overdose is the most prevalent case of poisoning. Toxic metabolites from paracetamol cause glutathione depletion and lead to hepatic cell death. Curcumin, a polyphenol substrat in *Curcuma longa*, has been known to ameliorate the toxic effects of paracetamol. The mechanisms have been known are curcumin as antioxidant, anti-inflammatory, and anti-apoptotic. The curcumin protection mechanism against paracetamol poisoning will be discussed.

Methods: The journal's search for the protective effects of curcumin on paracetamol toxicity is derived from PubMed database using keyword curcumin and acetaminophen. Research on experimental animals is as the limits of the study subjects of the journal search.

Result: From a search in PubMed database, there are 15 journal titles discussing the effects of curcumin protection against paracetamol toxicity, and 11 journals selected that correspond to the research topic. Of the 11 journals selected, concluded that curcumin was found to prevent worsening of paracetamol toxicity by increasing antioxidant activity and decreasing inflammation and apoptotic.

Conclusion: Curcumin has the potential benefit to be used as a medical therapeutic for the prevention and treatment of paracetamol toxicity.

Keywords: Curcumin, Paracetamol, Antioxidants, Anti-inflammatory, Anti-apoptotic.

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BACKGROUND

Paracetamol or acetaminophen is also known as N-acetyl p-aminophenol has been used as an antipyretic and analgesic for more than 30 years. Paracetamol poisoning is the largest poisoning case according to the American Association of Poison Control Centers causes 140,000 cases of poisoning and approximately 100 mortalities in the year 2006 [1]. At therapeutic dose, paracetamol will be metabolized in the liver through a process of glucuronidation and sulfation and excreted from the cell, a small part will be metabolized by Cytochrome P450 especially CYP2E1 to N-acetyl benzoquinoneimine (NAPQI) toxic product. NAPQI will be rapidly detoxified by glutathione (GSH) and removed from the cell. An overdose of paracetamol may cause hepatic dysfunction, necrosis of hepatic cells, and hepatic organ injury [2]. GSH depletion due to the NAPQI detoxification process will occur rapidly [2-4],, so that the free NAPQI will bind to intracellular proteins and lipids as well as deoxyribonuclease acid, through covalent bonding, causing mitochondrial dysfunction, lipid peroxidation, oxidative stress, DNA fragmentation, leading to liver cell death, liver organ damage, and ending with death [2,3].

N-acetyl cysteine has been used as a paracetamol poisoning antidote, has a narrow therapeutic dose range and side effects, so an alternative therapeutic need is sought. Curcumin ((1E, 6E) -1,7-bis- (4-hydroxy-3-methoxyphenyl) -1,6-heptadien-3,5-dione), a polyphenol presents in the roots of the *Curcuma longa* plant has been used as a treatment traditional for liver disorders that are now known to be caused by oxidative stress. Curcumin has properties as antioxidants, anti-inflammatory, and anti-apoptosis that can improve the toxic effects of paracetamol overdose. This is interesting to discuss further. The review paper will gather several journals to discuss curcumin protection mechanisms in improving paracetamol toxicity.

RESEARCH METHODS

Journal searches on the benefits of curcumin as an antioxidant and anti-inflammatory to reduce the toxic effects of paracetamol derived from the PubMed database using curcumin and acetaminophen as the keywords, no years of limitation, and research on experimental animals as the limits of the study subjects.

RESULTS

Journals search in PubMed database obtained 15 journal titles, and there are 11 journals that discuss the protective effect of curcumin against paracetamol toxicity, obtained five journals that could be accessed fully, and six journals only the abstract could be accessed. All the journals that could be fully access and one of the journal abstracts will be summarized in Table 1.

DISCUSSION

The role of NAPQI in cellular damage

Reactive N-acetyl-p-benzoquinone imine (NAPQI) metabolites of paracetamol oxidation by CYP2E1 bind to the cysteine group of proteins; forming acetaminophen-protein adducts [7]. Most of the paracetamol-reactive metabolites bind through NAPQI reactions with cysteinyl sulfhydryl (-SH) groups proteins to produce 3- (cysteine-S-yl) APAP (3-Cys-A) -protein adduct, or (APAP-CYS) acetaminophen- cysteine in hepatocytes. APAP-CYS adducts are detected in mitochondria, plasma membranes, and hepatocyte cytosol [8].

NAPQI covalent binding to mitochondrial membrane proteins will inhibit mitochondrial respiration and decrease oxygen consumption trough slowing the activities of succinate dehydrogenase (respiration complex II) and NADPH dehydrogenase (respiration complex I). The decrease of oxygen consumption causes decrease in ATP production, ultimately causing cell necrosis. NAPQI covalent binding also open the mitochondrial transition pore (MTP). NAPQI in the mitochondrial increases the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) causing oxidative stress. Oxidative stress damages the regulation of cytosol calcium and mitochondrial calcium

Table 1: Several curcumin protection effects research on paracetamol toxicity

Author	Method	Result
Bulku *et al*., 2012[5] Abstract	Research on four groups of male B6C3F1 mice	Administration of curcumin: Mortality decreased; decrease of ALT serum, lipid peroxidation, and DNA fragmentation; increase of GSH, SOD, NO synthase, decrease of DNA fragmentation, Bax gene expression, caspase 3, cytochrome c, and p53; and increase of Bcl-XL
Somanawat *et al*., 2013 [2]	Research on four groups of male mice	Administration of curcumin: Decrease of AST and ALT serum, hepatic MDA, IL-12 and IL-18 serum; and increase of hepatic GSH
Li *et al*., 2013 [3]	Research on three groups of Balb-c male mice	Administration of curcumin: Reduce hepatic histologic damage; decreases of ALT serum and hepatic MDA; increases of hepatic SOD, hepatic Bax gene expression; increases of hepatic Bcl-2 gene expression; and prevent hepatic apoptosis
Soliman *et al*., 2014 [4]	Research on four groups of male rats Wistar strain	Administration of curcumin: Amelioratif hepatic histologic; decreace of ALT, AST, and urea serum; increased level of hepatic catalase antioxidants; decreased of hepatic MDA, hepatic MMP-8 expression in ihc imaging, increase of hepatic hepatic GSH, GPx, SOD, and catalase gene expression; and decrease of hepatic IL-1β, IL-8, and TNFα gene expression
Granados-Castro *et al*., 2016 [1]	Research on six groups of male CD1 mice	Administration of curcumin protecting hepatic histologic damage; decrease ALT and AST; prevent decrease in mitochondrial activity of respiratory complex I, III, and V; and prevent decrease in mitochondrial membrane potential, ATP synthesis, and aconitase activity
Kheradpezhouh *et al*., 2016 [6]	Research on Wistar mouse hepatocyte culture	Administration of curcumin inhibits TRPM2 channel activation Bay ADPR

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, MMP: Mitochondrial membrane potential, GSH: Glutathione; SOD: Superoxide dismutase, NO: Nitric oxide, MDA: Malondialdehyde, IL-12, IL-18, IL-8: Interleukin, MMP-8: Matrix metalloproteinase-8, TRPM2: Transient receptor potential melastatin 2, ADPR: Adenosine diphosphate ribose, TNF-α: Tumor necrosis factor-α

and opens the MTP. Changes in mitochondrial membranes cause translocation of the B-cell lymphoma-2 (Bcl-2)-associated-X (Bax) protein, which combines with Bcl-2 antagonist killer 1 (Bak) into the cytosol, and allow the release of intermembrane proteins such as cytochrome c, regulates cellular death programs (apoptosis), through nuclear DNA fragmentation, and p53 pathway. ROS and RNS oxidized thiols groups (structural component of MTP, causing mitochondrial potential membrane damage, then swelling and rupture of the outer membrane of mitochondria [3]).

NAPQI in the cytosol will deplete GSH, resulting in increased intracellular ROS production. ROS will be neutralized by catalase, superoxide dismutase (SOD), glutathione-S transferase (GST), and glutathione peroxidase (GPx) causing the decline of these intracellular antioxidants. ROS will activate transient receptor potential melastatin 2 (TRPM2), a nonselective Ca^{+2} permeable cation channels through intracellular adenosine diphosphate ribose (ADPR), allowing extracellular calcium to enter intracellularly, causing increase of intracellular calcium, and inducing further transition of membrane mitochondrial [6].

The role of inflammation in cellular damage

Macrophages have an important direct role in the early stage of paracetamol-induced hepatic management [9]. When activated hepatic macrophages are cells Kupffer release several molecules, i.e. hydrolytic enzymes, eicosanoids, nitric oxide, and superoxide. It also releases inflammatory cytokines, interleukin (IL)-1, IL-6, and tumor necrosis factor-α (TNF-α) [7]. Some inflammatory cytokines also increase in IL-12, IL-18 [2], IL-1β, and IL-8 regulated by matrix metalloproteinase 8 (MMP-8) [4].

Curcumin protecting toxic effects of paracetamol toxicity

Curcumin is known as antioxidant, anti-inflammatory, and anti-apoptosis. As the antioxidant, curcumin binds directly to the toxic metabolite of paracetamol and decreases the use of GSH [10], and neutralizes and scavengering the oxidant ROS and RNS. Indirectly, through the activation of nuclear factor (erythroid-derived-2)- like-2 (Nrf2) transcription factor by curcumin, the production of catalase, SOD, GST, and GPx in nucleus increase and release into cytosol (Granados-Castro *et al*., 2016) [1]. The increased level of GST stimulates GSH formation which increases the excretion of the paracetamol toxic metabolites [10]. If the free radicals are reduced, mitochondrial membrane damage and DNA fragmentation will also decrease, thus inhibiting the production of ADPR. Curcumin inhibits ADPR -mediated TRPM2 activation, thus preventing further calcium influx and kalium efflux. Preventing further intracellular calcium accumulation will prevent cell damage [6]. The decrease free radical and the binding of NAPQI by curcumin, protecting lipid peroxidation and can be demonstrated by the reduction of malondialdehyde free radicals. The increase of antioxidant levels by curcumin can be demonstrated by an increased expression of GSH mRNA, GPx mRNA, SOD mRNA, and catalase mRNA [4].

Curcumin enhances PPARα expression, known to play a major role in the immune response because it can prevent the production of inflammatory substances [11,12]. Curcumin given along with paracetamol decreases the expression of IL 1β, TNF-α, and IL-8 genes, expression of the α1-acid glycoprotein gene, enhancing the expression of the macroglobulin α-2 gene, and decreasing MMP-8 expression [4]. Curcumin also reduces serum level of IL-12 and IL-18 [2].

Curcumin decreases the expression of mRNA Bax and increases the expression of mRNA Bcl-2, thereby decreasing apoptosis induced by paracetamol. Bcl-2 protein is an anti-apoptosis factor, its activity prevents mitochondrial membrane disruption, Bax will inactivate Bcl-2 through the formation of heterodimer [3].

CONCLUSION

The toxic effects of paracetamol overdose are better understood now. Oxidative stress mechanisms and NAPQI covalent bonds with intracytosol and intramycrosome proteins play an important role. Curcumin has antioxidant and anti-inflammatory activity, is expected to be one of the natural ingredients selected for the prevention of paracetamol toxicity in patients receiving long-term and high-dose paracetamol therapy.

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