Metformin; a mini-review to its antioxidative and anti-inflammatory properties

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Introduction
Metformin, a hypoglycemic drug, is used to treat type 2 diabetes (1). It increases peripheral glucose uptake, decreases liver glucose production and suppresses insulin resistance in liver and skeletal muscle (2). Moreover, it can reduce chronic inflammation by improving metabolic activities (3). In addition to reducing chronic inflammation, it has direct anti-inflammatory (4) and antioxidant effects (5).

Materials and Methods
For this mini-review, we used a variety of sources including PubMed, Embase, Scopus and directory of open access journals (DOAJ). The search was performed by using combinations of the following key words and or their equivalents; metformin, AMP-activated protein kinase (AMPK), nuclear factor κB (NFκB), antioxidative and anti-inflammatory properties. Papers published in English as full-text articles and or as abstracts were included in this study.

Anti-inflammatory mechanism of metformin
The molecular anti-inflammatory mechanism of metformin involves the reduction of the level of nuclear factor κB (NFκB) through AMPK activation (6,7). When either the level of AMP is high or the level of ATP is low, AMPK, as an energy regulator, starts to balance metabolic homeostasis. AMPK activation leads to the activation of peroxisome proliferator-activated receptor γ co-activator α (PGC-1α). Previous studies have indicated that mitochondrial dysfunction is a result of low AMPK activation (8). The release of HMGB1 by necrotic cells raises the level of inflammatory activity. Takahiro Horiuichi was the first to demonstrate in his study that the other mechanism of metformin to reduce inflammation, which is directly
bound to alarming high mobility group box 1 (HMGB1), inhibits inflammatory factors production (7). Cerebral ischemia is a result of energy depletion and adenosine monophosphate (AMP). Inflammatory factors (NFκB, TNFa and COX2) decrease in cerebral ischemia. Furthermore, Nrf2 antioxidant pathway rises, though it is not enough to suppress inflammation and ischemia. Metformin protects cells from ischemia and inflammation by decreasing inflammatory mediators such as TNFa, NF κB and COX2. Moreover, it increases the level of Nrf2 antioxidant pathway and ATP level by activating AMPK in hippocampal neurons. AMPK triggers some intracellular signaling pathways (9). Stroke could be well treated by arterial baroreflex. The research conducted by Guo et al showed that metformin also balances the function of arterial baroreflex, enhances the level of vesicular acetylcholine transporter (VACHT) and α7nAChR expression, and finally reduces proinflammatory cytokines in brain ischemia and stroke (10). Metformin ameliorates ischemia-reperfusion injury by increasing the level of GSHPx, SOD, catalase and MDA levels in cerebrum (11). Other studies suggested that secondary brain injury caused by tobacco smoking (TS) or cigarette smoking (CS) could be treated by anti-inflammatory effect of metformin through the activation of Nrf2 that leads in turn to the maintenance of blood-brain barrier (BBB) integrity and the reduction of TS toxicity (12). Spinal cord injury (SCI), an important motor neurons disorders with high morbidity and disability, could be treated well by the anti-inflammatory and anti-apoptotic effects of metformin. The molecular anti-inflammatory mechanism of metformin increases autophagy and reduces mammalian target of rapamycin (mTOR) protein and p-p70S6K (13). Inflammatory bowel disease (IBD) refers to the chronic and recurring inflammatory conditions of the intestine and is a result of mucosal immune system dysregulation that raises the risk of colon cancer (CAC). When pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, or bacterial surface molecules like lipopolysaccharide (LPS), are exposed to intestinal epithelial cells (IECs), a complex cascade is activated that brings about an early inflammatory response and the activation of nuclear factor-kappaB (NF-κB). NF-κB signaling pathway has an important role in IBD. The activation of AMPK by metformin not only decreases the risk of IBD by ameliorating NF-κB signaling pathway in IEC but also reduces the risk of polyp growth and colon cancer (14). Previous studies have indicated that metformin has an important role in the reduction of myocardial ischemia and infarction. Metformin could effectively decrease inflammatory cytokines after induced neuropathy in diabetic rats with AMPK activation (15). Percutaneous coronary intervention (PCI) is the main strategy for the treatment of coronary artery disease. The cardio-protective mechanism of AMPK in ischemia and injury involves cellular ATP balance and storing cellular energy during ischemia (16). About 25%–30% of the patients with solid tumor, who receive cisplatin, may be exposed to the risk of nephrotoxicity. Metformin prevents cisplatin-induced nephrotoxicity by decreasing inflammatory cell and tubular cell apoptosis in NRK-52E cells, activating the AMPKa phosphorylation and rising autophagy. Li et al concluded that metformin could ameliorate tubular cell death and interstitial inflammation in cisplatin-induced nephrotoxicity (17). Another study suggests that metformin directly decreases obesity-related non-alcoholic fatty liver disease (NAFLD) by inhibiting fat deposition, and also reduces macrophages and hepatocytes inflammatory responses. Reduction of hepatic weight, inflammation and steatosis are the results of using metformin in obese individuals but it cannot change the adipocytes size. The mechanism of metformin for this change involves the reduction of liver AMPK phosphorylation, liver acetyl-CoA carboxylase phosphorylation and decreasing the level of liver c-Jun N-terminal kinase 1 (JNK1) phosphorylation and pro-inflammatory factors (17). Several studies have confirmed the role of inflammatory responses in myocardial infarction, and the significant role of neutrophil in myocardial infarction and injury. Another experimental study suggested that anti-inflammatory drugs could reduce the size of infarct. The anti-inflammatory effect of metformin, for instance, reduces heart tissue fibrosis and necrosis, post-MI infiltration of neutrophil and cardiac remodeling by AMPK activation. AMPK activation suppresses protein synthesis in heart tissue and post-MI hypertrophy (18). Hu et al have shown, for the first time, that metformin could protect cardiomyocytes against high-glucose (HG) and hypoxia/reoxygenation (H/R) injury by suppressing Jun NH2-terminal kinase (JNK) activation and raising AMPK activation (19). Metformin also impresses gastrointestinal tract by reducing inflammation. For example, it suppresses inflammatory bowel disease (IBD) by inhibiting pro-inflammatory factors (TNF-α, VEGF, IL-6, IL-8, and IL-1β), and ameliorates the expression of p-signal transducer and activator of transcription3 (STAT3) and interleukin IL-17 through the activation of AMPK that in turn prevents mTOR activation and suppresses p53 expression (20). Bal et al indicated the anti-inflammatory and anti-oxidant effect of metformin in liver injury. Pretreatment with metformin protects liver through ameliorating the level of ADAM in LPS/D-GalN-induced liver injury (21). Acute lung injury (ALI) is one of the acute respiratory distress syndromes (ARDS). ALI, associated with the elevation of endothelial permeability, damaged alveolar capillaries and the infiltration of inflammatory cytokine. The study carried out by Zhang et al, showed that LPS-induced ALI could be treated well by the anti-inflammatory effect of metformin that could in turn elevate AMPK signaling pathway and decrease NF-κB in the lungs (22). The research conducted by Vaez et al highlighted that metformin could protect ALI by enhancing the expression of TLR4, MyD88, NF-κB, and TNFα and decreasing...
MPO level (23). Pulmonary fibrosis is a side effect of radiotherapy that is used in cancer treatment. Wang et al demonstrated that metformin could suppress fibrosis, inflammatory cytokine and cells by AMPK activation. The molecular mechanism of metformin involves decreasing the expression of collagen 1a, TGF-b, pSmad2, p-Smad3 and non-small cell lung cancer cells A549 and H460 (24). The activation of AMPK by metformin could protect acute graft-versus-host disease (aGVHD) through reducing the level of T helper (Th17) and signal transducer and activator of transcription (STAT3) (5). de Araújo et al showed that the anti-inflammatory and anti-oxidant effects of metformin lead to the amelioration of bone loss (25). Also, Brownfoot et al demonstrated that metformin can be used for preeclampsia treatment. It can reduce endothelial dysfunction by ameliorating the expression of inflammatory gene and protein like vascular cell adhesion molecule-1 (VCAM-1), and vasodilating maternal vessels (26).

Conclusion
The pharmacological activities of metformin focused on improving antioxidant and anti-inflammatory properties. Modern investigation showed that AMPK activation were the main contributors to the antioxidant and anti-inflammatory effects of metformin.

Authors’ contribution
AA, SK, SHK, ME and AH were involved in drafting the manuscript and revising it critically for important intellectual content. AH revised the manuscript critically for important intellectual content. All authors read and signed the final manuscript.

Conflicts of interest
The authors declare no conflict of interest.

Ethical considerations
Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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