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Andrographolide (穿心蓮內酯) Inhibits Lipotoxicity-Induced Activation of IL-1β and the Following Inflammation in Bone Marrow-Derived Macrophages

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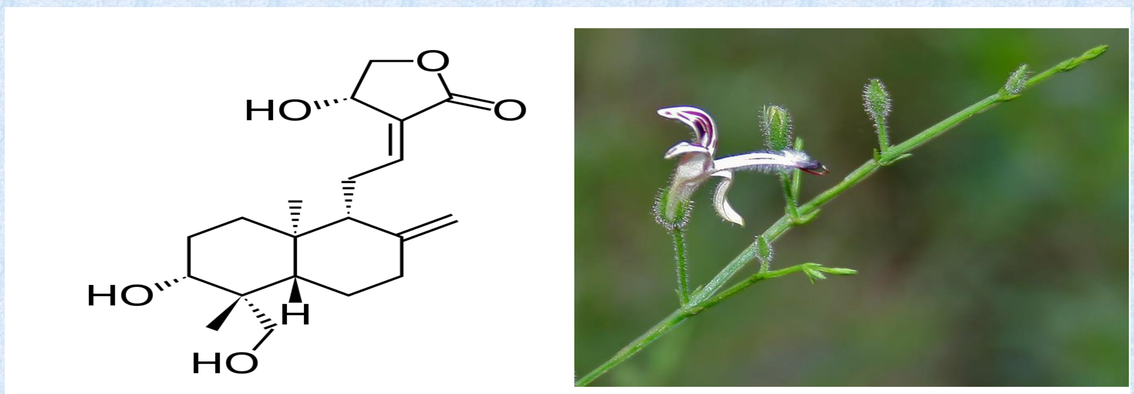
Background

Andrographolide (AND) is one of the major bioactive components of the herb Andrographis paniculata (Fig.1) and is a potent anti-inflammatory agent. Obesity leads to an excess of free fatty acids, particularly palmitic acid (PA), in the circulation and also causes the deposition of ectopic fat in nonadipose tissues, which leads to lipotoxicity, a condition closely associated with chronic inflammation.

Methods and Results

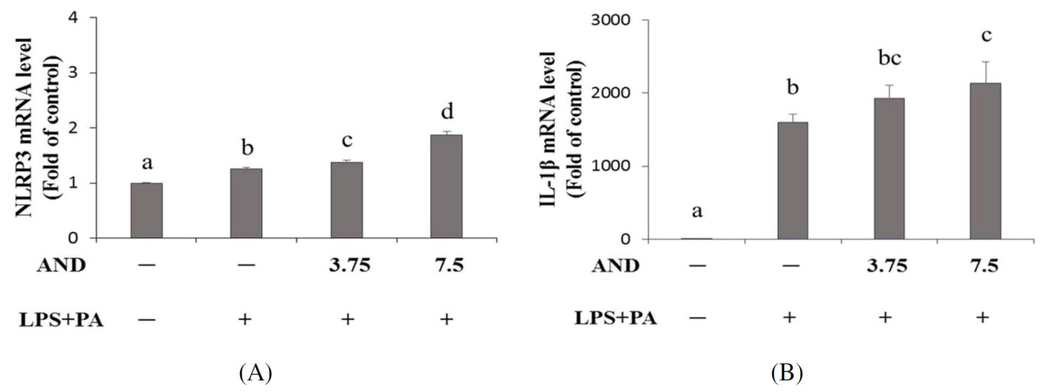
In the study, we investigated whether andrographolide could inhibit PA-induced inflammation by activating autophagy, activating the antioxidant defense system, and inhibiting the activation of IL-1β and the following inflammation. Bone marrow-derived macrophages (BMDMs) were first primed with lipopolysaccharide (LPS) and then activated with PA. LPS/PA treatment and even treated with andrographolide increased both the mRNA expression of NLRP3 and IL-1β in macrophages (Fig.2). Andrographolide inhibited the LPS/PA-induced protein expression of caspase-1 and the release of IL-1β (Fig.3). Furthermore, andrographolide attenuated LPS/PA-induced mitochondrial ROS generation(Fig.4) by first promoting autophagy (Fig. 5) and catalase activity (Fig. 6) and then inhibiting activation of the following inflammation.



(A)

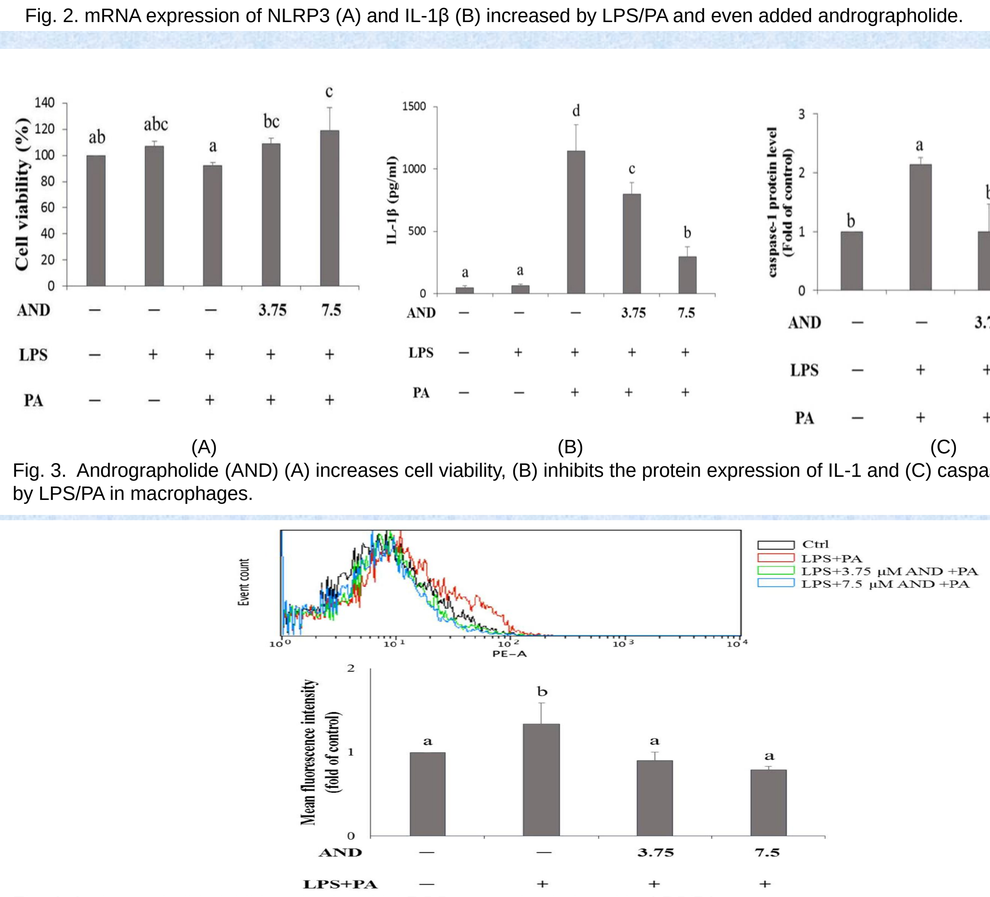
(B)

Fig. 1 (A) Andrographolide ($C_{20}H_{30}O_5$). (B) Andrographis paniculata (Wikipedia 2022)



(A) (B)

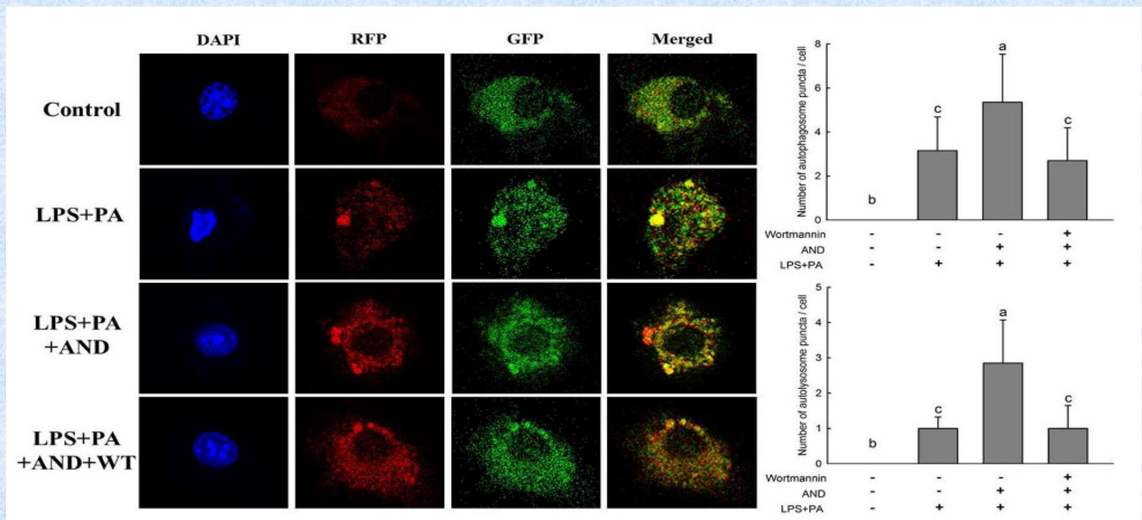
Fig. 2. mRNA expression of NLRP3 (A) and IL-1β (B) increased by LPS/PA and even added andrographolide.



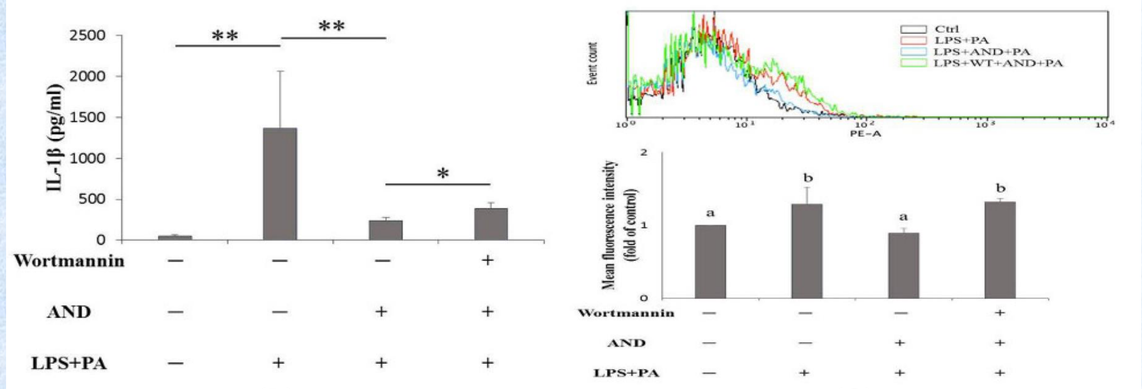
(A) (B) (C)

Fig. 3. Andrographolide (AND) (A) increases cell viability, (B) inhibits the protein expression of IL-1 and (C) caspase-1 induced by LPS/PA in macrophages.

Fig. 4. Andrographolide inhibits mitochondrial ROS generation induced by LPS/PA.

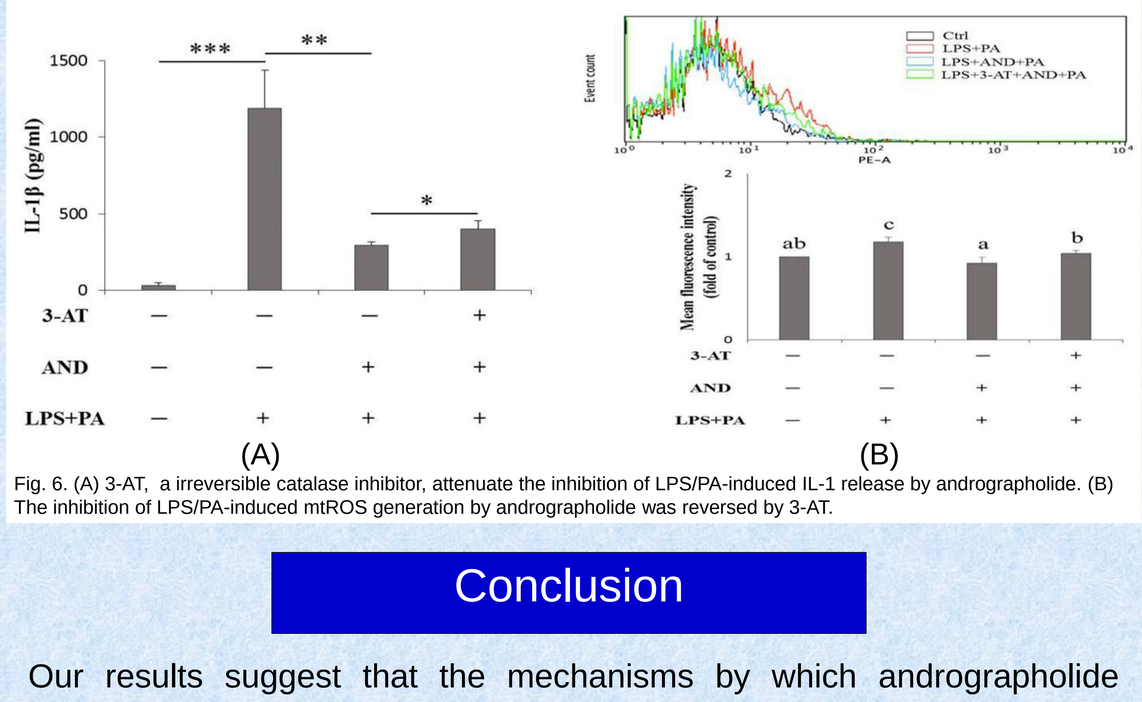


(A)



(B) (C)

Fig. 5. (A) LPS/PA treatment significantly induced autophagosome and autolysosome formation when compared with that of the control group. Addition of andrographolide further increased autophagosome formation; however, this increase was attenuated by wortmannin, an inhibitor of autophage. (B) The inhibitory effect on IL-1β was decreased by addition Wortmannin. (C) The inhibitory effect on mtROS decreased by addition of Wortannin.



(A) (B)

Fig. 6. (A) 3-AT, a irreversible catalase inhibitor, attenuate the inhibition of LPS/PA-induced IL-1 release by andrographolide. (B) The inhibition of LPS/PA-induced mtROS generation by andrographolide was reversed by 3-AT.

Conclusion

Our results suggest that the mechanisms by which andrographolide downregulates LPS/PA-induced IL-1β release and following inflammation in macrophages involve promoting autophagy and catalase activity (Fig.7). Andrographolide may thus be a candidate to prevent obesity- and lipotoxicity-driven chronic inflammation and related

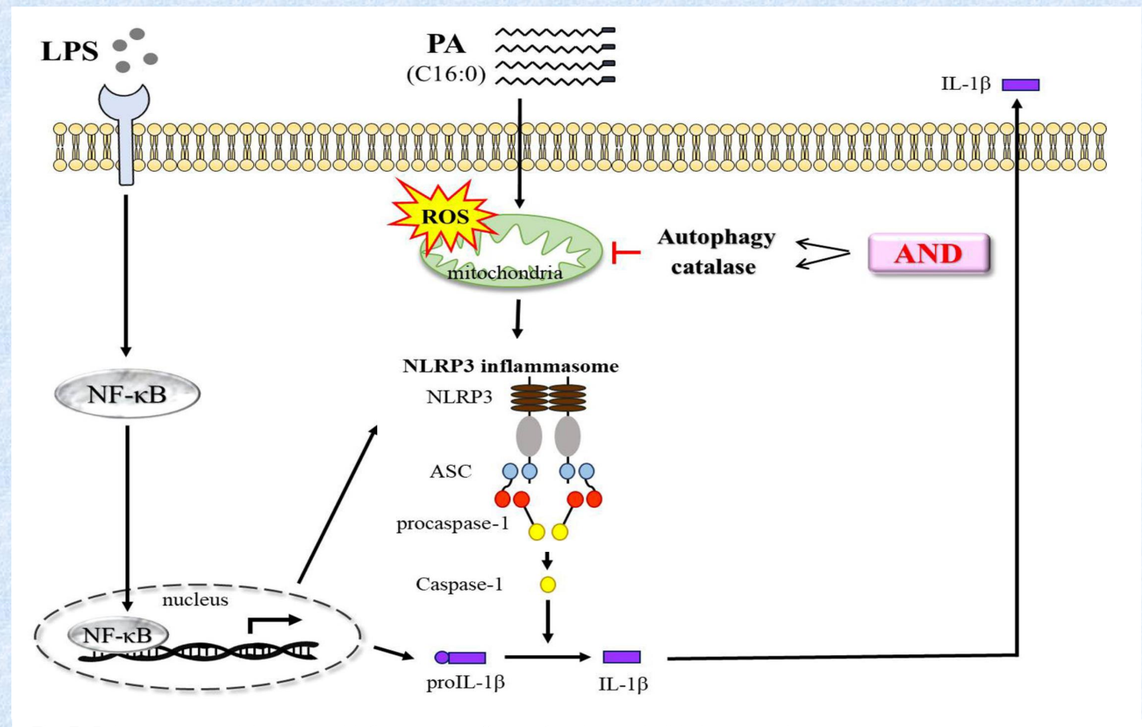


Fig. 7. Scheme summarizing the anti-inflammatory effects of andrographolide in macrophages.

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