



# Anti-inflammatory Effects and Underlying Molecular Mechanisms of Traditional Chinese Medicine

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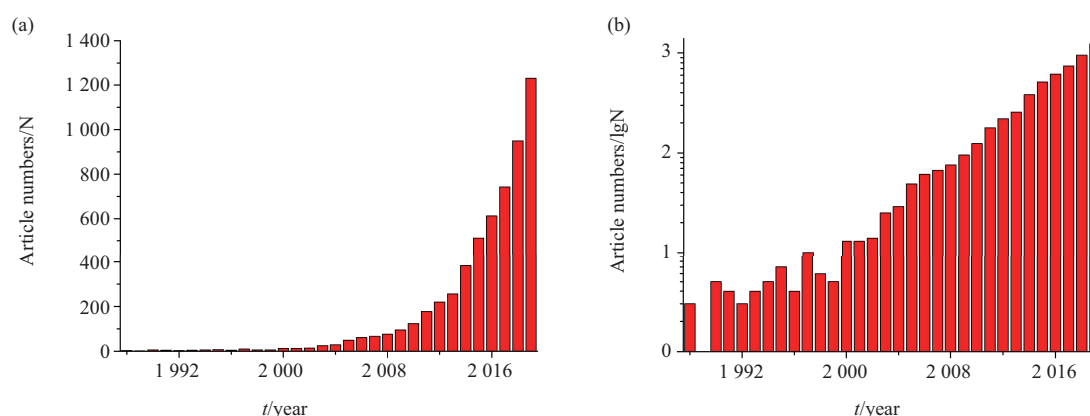
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Traditional Chinese medicines (TCMs) are great treasures in pharmacological history with records of more than 3 000 years. From ancient times to the present, TCMs of clearing heat, eliminating dampness, unblocking collaterals and removing toxins have been used in clinic to treat many infectious diseases and noninfectious chronic diseases, whose pathogenesis may involve inflammation induced by different causes. Growing evidence exhibits the

importance of TCMs and highlights the role of TCMs in the treatment of various inflammation-related diseases. The number of published articles on the treatment of inflammation with TCMs is logarithmically increasing during the recent decades (Figure 1a,b). In this special issue, the beneficial role and the molecular mechanisms of TCMs in the treatment of inflammation-related diseases were investigated or reviewed by different authors.



**Fig. 1** Changes in the number of articles published from 1988 to 2019 were searched in PubMed with the key words of inflammation and traditional Chinese medicine (a). Those are plotted in semilogarithm (b)

NF- $\kappa$ B, NLRP3/caspase-1/IL-1 $\beta$  axis, STAT and MAPK pathway, as well as Nrf2/ARE/HO-1 pathway are important in regulating inflammatory reaction. The screening of anti-inflammatory drugs, based on these targets, has become an important way to develop

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new drugs. JIANG Dai-Xun and his co-authors provide an overview of effects of cAMP-PDEs-selective TCMs on key proteins of inflammatory signaling pathways, either *via* inhibition of NF- $\kappa$ B, MAPKs (p38, ERK, or JNK), TLR, MyD88, and STAT3, or activation of Nrf2, HO-1, AMPK, and PPAR $\gamma$  (Page 659–674). They also revealed that luteolin (a phosphodiesterase 4 inhibitor) regulated VCAM-1 expression in microvascular endothelial cells through either inhibiting p65 NF- $\kappa$ B phosphorylation or promoting p85 PI3K phosphorylation (Page 675–684). LI Lin and her co-authors update the recent advances of anti-inflammatory effects of the Epimedii (yinyanghuo in Chinese) and its active compounds in a variety of diseases. The molecular mechanisms involved in anti-inflammation effects of Epimedii active compounds and its derivatives include reducing inflammatory cytokines, down-regulating NF- $\kappa$ B signaling, NLRP3/caspase-1/IL-1 $\beta$  axis, STAT signaling and MAPK pathway, as well as up-regulating Nrf2/ARE/HO-1 pathway and increasing glucocorticoid receptor and estrogen receptor signaling (Page 685–699).

In nervous system, inflammation is characterized by the excessive activation of microglia to produce inflammatory factors. The resting microglia can be induced to M1 and M2 type microglia, which have different functions. CHEN Nai-Hong and his coworker review recent studies about using TCMs to prevent ischemic cerebral damage *via* mediating microglia activation and polarization (Page 700–711). XU Shu-Jun and her colleagues clarify the mechanisms of chronic inflammation caused by microglia in Alzheimer's disease (AD), and summarize the beneficial effects of natural small-molecule compounds on maintaining immune homeostasis in AD through regulating microglial receptors and their downstream pathways (Page 712–728). CUI De-Hua and his coworkers summarize recent progress of the anti-inflammatory effect of TCMs on neurocognitive disorders including AD and Parkinson's disease (PD), and discuss the molecular mechanisms of TCMs, including the regulation on A $\beta$  generation and aggregation, tau phosphorylation, gut-brain axis and gut microbiota, autophagy, microglia polarization, extracellular space, neurogenesis and neurotransmission (Page 729–742). WANG Qiong with her colleagues review the beneficial effect of

TCMs on type 2 diabetes-related cognitive dysfunction (Page 743–761). DENG Yu-Lin and his labmates summarize the role of TCM (dragon's blood) in reducing oxidative stress levels, expression of related inflammatory factors, mitochondrial damage and alleviating irradiation-induced neuroinflammation (Page 762–767). GUO Jian-Sheng, ZENG Gui-Rong and their co-workers have investigated the ameliorating effect of *Ormosia henryi* Prain (OHP) on cognitive deficits caused by chronic stress, which is related to the molecular events of anti-inflammation in the hippocampus of CUMS mice at least (Page 768–779).

Liver is the largest substantial organ in the abdominal cavity and it provides an essential role in maintaining the basic physiological functions. TCMs have the advantages of multiple targets and small side effects in the treatment of hepatitis or liver fibrosis. HE Rong-Qiao and his labmates investigated the effect of proteolytic isozyme lmbrokinase (LK) on chronic hepatitis B, and revealed that LK could inhibit HBsAg production, decrease fibronectin and improve the state of the liver. Those data provide valuable information to understand the therapeutic role of LK as a potentially effective medicine in chronic hepatitis B treatment (Page 780–789). DENG Yu-Lin and his collaborators review the pathological mechanism of liver fibrosis and its relationship with inflammation. The application of the active herbal ingredients in TCMs, medicinal plants and traditional Chinese formulae to treat liver fibrosis, and their mechanisms of action to inhibit inflammation associated with liver fibrosis are also discussed (Page 790–808).

Metabolism-related diseases are accompanied by inflammation. MA Xiao-Feng and his coworkers summarize literatures concerning the role of fatty acid synthase (FAS) as a therapeutic target in obesity and related inflammation as well as providing evidence to support the anti-inflammation potential of TCMs with FAS inhibitory activities (Page 809–817). WU Li-Li and her collaborators summarize inflammatory molecules and pathways in relation to renal injury of diabetic nephropathy (DN), and discuss potential TCM strategies to treat DN *via* targeting inflammatory factors (Page 818–834). XU Yong and his group clarify how gut microbiota induces systemic low-grade inflammation and development of metabolic diseases. They also explore the intervention

of berberine on metabolic diseases *via* affecting the intestinal microbiota-inflammation axis (Page 835–843).

Inflammation participates in the heart and respiratory diseases. Nitric oxide (NO) and natural antioxidants can improve the longevity and synergistically eliminate the damage caused by inflammation. ZHAO Bao-Lu reviews the health protection of TCMs *via* activating Qi-blood circulation and removing blood stasis, in which NO plays an important role in the invigoration of Qi-blood circulation (Page 844–857). LI Rui-Xing and her coworkers summarize TCMs for the treatment of chronic cough in children and their anti-inflammatory mechanism. Clinical studies have found that treating children with chronic cough according to the theory of Fuyang in TCMs can obtain good curative effect (Page 858–866).

TCMs also have beneficial effect in other diseases such as osteoporosis and drug-induced skin rashes. CHEN Chang and her graduate students revealed that nobiletin improved bone microstructure by modulating bone formation *via* ROR $\alpha$ /SOST signaling in naturally aging mice (Page 867–875). HUA Qian and her colleagues found that the anti-inflammatory effect of Sanliangsan on gefitinib-induced rash was closely related to the IL-17A signaling pathway (Page 876–887).

Acupuncture and meridians are important parts of TCMs. TAN Yan and her coworkers summarize the role of acupuncture in the inhibition of microglia activation and its anti-neuroinflammation effects in AD, PD or vascular dementia (VD) (Page 888–899). The inhibition of M1 microglial activation mediated by TLRs/NF- $\kappa$ B and MAPKs pathways may be one of the key mechanisms of acupuncture's regulating neuroinflammatory response and improving cognitive impairment in AD, VD and PD. There are many

perspectives about the structures of meridians. Zhang *et al.* [1] consider that meridians are low hydraulic resistance channels (LHRC) in the human body, which can be detected using continuous flow resistance measurement and tissue hydraulic wave propagation determination methods. They observed that blockage of LHRC along the stomach meridian and the kidney meridian led to different pathological phenomena, which provided a scientific basis for the syndromes induced by meridian stasis (Page 900–912).

TCMs have the advantages of multi-components and multi-targets [2]. Their effects and mechanisms are complicated. Recently, TCMs have exhibited decent effect in the fight against coronavirus disease 2019 (COVID-19) and are considered as an effective treatment for COVID-19 [3–4]. The knowledge from this specific issue will give a better understanding of the role and mechanisms of TCMs on inflammation-related disease from the perspective of Western medicine and Chinese medicine, and pave the way for the clinical treatment of inflammation-related disease with TCMs.

## References

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Dr. Shujun Xu is a professor in Ningbo University and a visiting scholar in Stanford University. She is a council member of Zhejiang Society for Neuroscience and a committee member in Anti-aging Society of China Association of Gerontology and Geriatrics. She has been an associate editor and reviewer of Journal of Alzheimer's Disease. She has also been the reviewer of other peer-reviewed journals including Molecular Neurobiology, Neuroscience Bulletin, Science China Life Sciences, Progress in Biochemistry and Biophysics *etc.* She is interested in investigating the pathophysiology of Alzheimer's Disease (AD), the role and underlying mechanism of beneficial effects of traditional Chinese medicines including natural small-molecule compounds in the treatment of AD. She has got several National and Provincial Natural Science Foundation of China and has published more than 30 articles in the well-respected journals, including Molecular Neurobiology, Hippocampus, Journal of Alzheimer's Disease, Frontiers in Aging Neuroscience in particular. She has also got several technology awards of Zhejiang Province and Ningbo City.