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Research Progress in the Prevention and Treatment of Hyperuricemia with Gout by Traditional Chinese Medicine

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Abstract: Hyperuricaemia is a metabolic disorder whose pathogenesis is directly related to the level of uric acid in the blood. In addition, hyperuricaemia is also related to gout, diabetes mellitus and kidney disease, therefore, hyperuricaemia should be taken seriously. Traditional Chinese medicine (TCM) has unique advantages in the treatment of hyperuricaemia. In this paper, the pathogenesis of hyperuricemia and the mechanism of action of TCM in the prevention and treatment of hyperuricemia are reviewed to provide a theoretical basis for the research of anti-hyperuricemia drugs.

1. Introduction

Hyperuricemia (HUA) is characterised by supersaturation of urate in the blood, which is essentially a disorder of purine metabolism and/or reduced excretion of uric acid. Prolonged undiagnosed treatment can induce gout or gouty arthritis (Gout). Gout and gouty arthritis used to be considered the main complications of hyperuricaemia, as shown in Figure 1. However, in the observation of patients with renal disease, it has been found that hyperuricaemia may also be caused by insufficient excretion of UA due to renal failure. Evidence and scientific experiments have shown that hyperuricaemia can induce inflammation, endothelial dysfunction, as well as proliferation of vascular smooth muscle cells and activation of the renin-angiotensin system, thus inducing chronic kidney disease (CKD) and cardiovascular disease (CVD), as shown in Figure 2. The incidence of HUA is also increasing year by year with the change of lifestyle and the adjustment of dietary structure of our people [1].

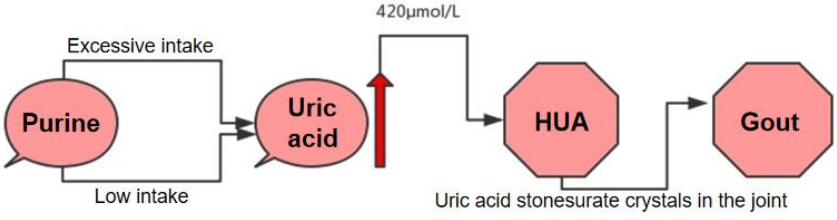

Figure 1: The process of gout caused by hyperuricemia

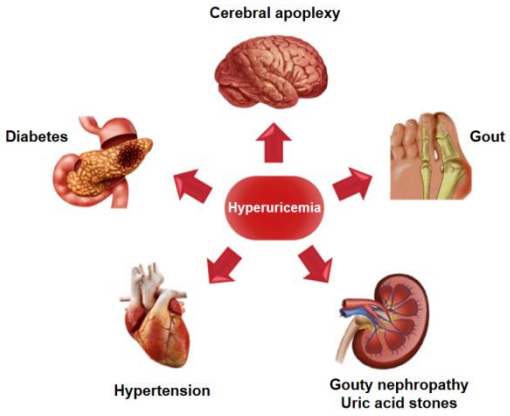

Figure 2: Complications of hyperuricemia

2. Pathogenesis

2.1. Mechanism of uric acid production

The development of hyperuricaemia is closely related to the patient's dietary habits, such as a high-purine diet, excessive fructose intake, and excessive alcohol intake. There should also be myeloproliferative disorders, or rare genetic causes such as hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency and phosphoribosyl pyrophosphate (PPRP) synthase (PRS) hyperactivity [2]. Uric acid (UA), the end product of purines, is synthesised mainly in the liver, intestine and vascular endothelium, and purines are derived from nucleotides in damaged as well as dead cells in the body [3]. These nucleotides are metabolised to xanthine, which is ultimately converted to UA by the enzyme xanthine oxidase (XO).Approximately 700 mg of UA is produced by this process each day.

2.2. Excretion mechanism of uric acid

The kidneys play a dominant role in the excretion of UA, and about 70% of the UA produced daily is excreted by the kidneys [4]. It undergoes four processes: glomerular filtration, proximal tubular reabsorption, distal tubular secretion, and post-secretory tubular reabsorption. The remaining 30% of UA is excreted from the intestine [5]. When UA production exceeds excretion, hyperuricaemia occurs, i. e. serum UA concentration > 7.0 mg/dL [6], as shown in Figure 3.

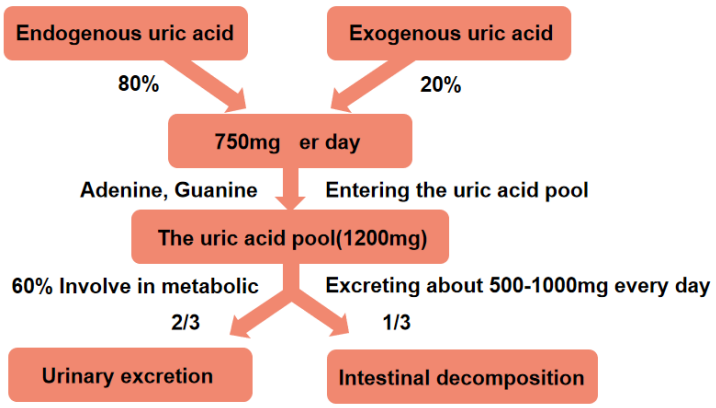

Figure 3: Excretion mechanism of uric acid

In the kidney, transmembrane transporter proteins such as ABC transporter protein G family member 2 (ABCG2), GLUT9 and URAT1 play an important role in the reabsorption and secretion of uric acid, which causes impaired uric acid excretion. Various molecules expressed in the renal proximal tubule mediate are necessary for UA exchange [7]. These molecules include, but are not limited to, glucose transporter protein 9 (GLUT9) [8], uric acid transporter protein 1 (URAT1) [9], human ATP-binding cassette subfamily G, 2 (ABCG2) [10], and organic anion transporter proteins (OATs) 1, 3, and 4 [6]. There are two different types of GLUT9, GLUT9-L located in the basolateral membrane and GLUT9-S9 located in the parietal membrane, both of which accelerate uric acid reabsorption by transporting glucose [11,12]. The transporter proteins URAT1, OAT4 and OAT1 are all expressed on the parietal membrane, with the difference that UA enters the cell by exchanging monocarboxylates with URAT1 and OAT4 on the parietal membrane [6]. The transporter proteins URAT1 and OAT4 can reabsorb filtered uric acid from glomerular filtrate into the bloodstream, which in turn passes through OAT1 located in the basolateral membrane, allowing it to uptake uric acid from the bloodstream and transport it into the tubular epithelial cells [13]. In contrast, ABCG2 consumes ATP to provide energy for the excretion of uric acid from renal tubular cells to the inner lumen [10]. OAT1 and OAT3 are located on the basolateral membrane of epithelial cells and they can transport UA from the renal mesenchyme into the epithelial cells of the proximal tubule of the kidney [14].

In the gut, genetic variation in ABCG2 reduces the function of the ABCG2 transporter and also allows for abnormal uric acid excretion, both of which trigger HUA. Uric acid deposition results in the formation of monosodium urate (MSU) crystals, which can lead to the formation of gouty nodules that trigger gout. the MSU crystals are phagocytosed by monocytes, and the body signals the formation of gout via the Toll-like receptors TLR2 and TLR4 transduction, activating NLRP3 (containing three structural domains, PYD, NACHT, and LRR) inflammatory vesicles, which promotes the maturation and secretion of cytokine precursors pro-IL-1β and IL-1β, leading to an acute attack of gouty arthritis [15].

3. Therapeutic effects and mechanisms of western drugs in HUA

3.1. Febuxostat, xanthine oxidase inhibitor

Xanthine oxidase (XOD) XOD in the liver is a key enzyme catalysing uric acid production and an important target enzyme in the treatment of hyperuricemia and gout [16].

Febuxostat is a non-purine xanthine oxidase inhibitor commonly used in the clinic and has no significant effect on the body's own purine and pyrimidine metabolism. In addition, febuxostat is able to act on both the reduced and oxidised states of xanthine oxidase, in contrast to other allopurinol products in which allopurinol glycol only inhibits the reduced state of xanthine oxidase [17]. However, its initial use may increase the frequency of acute gouty attacks and its cardiovascular safety in patients with gout is controversial [18,19].

3.2. Colchicine, an inflammatory factor inhibitor

It has been found that MSU crystals induce an inflammatory response to occur, and inflammatory mediators such as cytokines, IL-6, IL-1β, and tumour necrosis factor-α (TNF-α) can be produced in the synovial fluid and synovium during neutrophil recruitment [20]. Inflammatory factors trigger membrane disintegration, which in turn leads to joint damage [21].

The principle in the treatment of gout with colchicine is mainly to weaken leukocyte activity and phagocytosis, reduce uric acid deposition, and achieve pain relief [22]. Although treatment with this drug alone can also relieve symptoms such as gout, the overall effect is unsatisfactory and is prone

to induce adverse reactions such as abdominal pain, diarrhoea, vomiting, muscle and peripheral neuropathy, bone marrow suppression, shock, liver, kidney and other important organs damage [23], affecting the prognostic effect.

3.3. Benzbromarone, a urate anion transporter 1 inhibitor

More than 90% of uric acid is reabsorbed in the renal proximal tubule, and the rest is excreted in the urine. Uric acid transporter proteins located in the epithelial cells of the proximal tubule can mediate the reabsorption and secretion of urate, and urate anion transporter 1 (URAT1) and glucose transporter protein 9 (GLUT9) is an important factor of urate transporter proteins. Some experiments [24] demonstrated that benzbromarone inhibits urate anion transporter 1 and reduces uric acid reabsorption. However, its use is limited by drug-drug interactions and off-target toxicity, respectively [25,26]. Clinical use of benzbromarone often causes liver injury or even liver failure, so liver function should be monitored regularly during treatment with benzbromarone to reduce the risk.

4. Therapeutic effects and mechanisms of Chinese medicine on HUA

As mentioned above, in the past, Western medicine controlled the formation and excretion of uric acid through the use of drugs at various target points, which was very effective, but the side effects of the drugs were obvious. In the treatment of HUA, Chinese medicine not only has fewer side effects, but is also based on evidence-based treatment, which is more targeted and has a better prognosis.

Chinese medicine believes that elevated blood uric acid is mainly due to poor dietary habits, addicted to fat, sweet, thick and greasy, in the long run, the spleen is not healthy, ascending and descending turbid power, wet and turbid with the birth of stagnation of blood in the blood can not be discharged, the injection of joints and skin, the internal organs and six bowels. Long visible joint swelling, gouty nodules, or ulcerated flow of fat, or with gouty stones, or even lumbar pain, urinary closure, blood uric acid increase [27].

4.1. Chinese herbal medicine active ingredients

4.1.1. Total Paeony Glycosides

Total paeoniflorin (TGPF) is the main constituent of Paeonia lactiflora, and a study [28] found that TGPF may treat HUA-induced renal injury by downregulation of renal URAT1 and GLUT9 and upregulation of renal OAT1 and attenuating inflammatory responses.

4.1.2. Alcoholic extracts of Psoralea cerasifera leaves

Liang Wenjuan [29] et al. experimentally showed that Moringa oleifera leaf alcohol extract could also exert UA-lowering effects by inhibiting XO activity. Specifically, it can be reflected by the significant reduction of creatinine, urea nitrogen, and the content of IL-6 and TNF-α. However, the specific mechanism of action is still unclear.

4.1.3. Flavonoids

Flavonoids (quercetin, arnica alkaloids, silymarin, etc.) not only have biological activities such as anti-inflammatory, antibacterial, antiviral and antitumour [30,31], but also produce UA-lowering effects through inhibition of xanthine oxidase [29,32]. Chen Haiqing et al. [33] observed the effect

of quercetin on blood UA in HUA mice experimentally, and found that high doses of quercetin significantly reduced blood UA levels, increased ABCG2 protein expression, and significantly inhibited the expression of GLUT9 in the liver and intestine, suggesting that quercetin may produce UA-lowering effects by regulating the expression of GLUT9 and ABCG2 in the kidneys and intestine.

4.1.4. Horse chestnut saponin

The total saponin of A. heptaphyllum can also reduce blood UA, but with a certain dose-dependence. Zhu Lingling [34] and others proved that the total saponin of A. heptaphyllum can significantly reduce XO activity and URAT1 protein expression, and can play a role in lowering UA by inhibiting the activity of XO and lowering the expression of URAT1 protein in two pathways.

4.2. Single-flavoured Chinese medicines

4.2.1. Wei Ling Xian

Wei Ling Xian is a traditional medicine for dispelling rheumatism. Lin Fengping [35] proved through experiments that Wei Ling Xian can significantly reduce blood uric acid and increase urinary uric acid, and also found that Wei Ling Xian can reduce blood urea nitrogen and creatinine, so it is speculated that Wei Ling Xian may prevent the development of renal pathology by lowering the level of uric acid.

4.2.2. Zedoary

Zedoary has the effects of promoting water retention, seeping dampness and draining heat. Wang Jinpiao et al. [36], through rat experiments, found that the ethanol extract of zedoaria can effectively reduce UA by inhibiting XO activity, and has a certain nephroprotective effect.

4.2.3. Dioscorea villosa

Dioscorea villosa can promote dampness, dispel turbidity, expel wind and remove paralysis. Modern experimental research has found that dioscorea villosa can elevate the expression of oatplal, an organic anion transporting polypeptide, in the gastric and renal tissues of rats with hyperuricaemia model, thus increasing uric acid excretion, and can reduce the expression of URAT1 in renal tissues, reducing uric acid reabsorption and thus promoting uric acid secretion [37,38].

4.3. Traditional Chinese Medicine (TCM) Compound Formulas

4.3.1. Angelica sinensis and pain relief soup

Dang Gui Xiao Pain Tang is derived from "Qiyuan", in which Yin Chen clears heat, Qiang Wu dispels wind and promotes dampness, Atractylodes Macrocephala and Atractylodes Macrocephala are the ministerial herbs, which strengthen the spleen, dry dampness, warm the middle Jiaozhong and dissipate cold, and Scutellaria Baicalensis clears heat and dries dampness. The combination of other medicines, such as Angelica sinensis and ginseng to benefit the vital energy and replenish blood, Zhi Mu to clear heat and fire, nourish yin and moisten dryness, in order to prevent the whole formula from too much dryness and injury to the vital energy and blood, and licorice to replenish and nourish the positive vital energy. The combined application of the drugs can effectively benefit

dampness and clear heat, dredge wind and relieve pain, ensuring the elimination of pain, swelling and other symptoms.

Ma Shiwei [39] found through clinical research that the addition of angelica pain relief soup can effectively reduce blood uric acid, inhibit tumour necrosis factor-α, C-reactive protein to reduce the level of inflammation and reduce inflammation. And the therapeutic efficiency is high, and the rate of adverse reactions is low.

4.3.2. The main ingredients of Tiger Cane Gout Granules

The main ingredients of Tiger Cane Gout Granules include Qiang Wu, Tiger Cane, Yin Chen, Quan Dang Gui, Cang Zhu, Huang Bai, Sichuan Cow Knee, Poria, Ze Xie and Poria. Zhong Xiaofeng [40] observed the efficacy of Tiger Cane Gout Granules in the treatment of patients with acute gouty arthritis and found that it could significantly improve UA levels and had mild adverse reactions. Some scholars have found that Tiger Cane Gout Granules can effectively inhibit Cyr61 expression, down-regulate IL-1β, TNF-α and IL-6 expression, and attenuate the inflammatory reaction caused by sodium urate crystals [41].

4.3.3. Six-flavoured Gout Drink

Six-flavour Gout Drink is composed of six Chinese herbs: Qin Pi, Tu Fu Ling, Tiger Balm, Chinese yam, Yu Jin and Rhubarb. In the formula, Qin Pi and Tu Fu Ling play the roles of clearing the liver, dispelling dampness, removing toxins and eliminating swelling, and facilitating the joints. The rhubarb and tiger's stick play a supplementary role, so that the turbid toxin can be leaked down with the bowels. Yam strengthens the spleen and kidneys, and yujin moves Qi and activates blood circulation to relieve pain.

Zhao Hengli et al. proved experimentally that Liuwei Gout Drink could inhibit the activity of serum xanthine oxidase in quail hyperuricemia model to play a role in the treatment of HUA.

Chen Hanyu [42] used six-flavour gout drink combined with benzbromarone in the treatment of gouty arthritis, and found that the UA level of the patients was significantly reduced, and the symptoms were improved, and the mechanism may be to inhibit the activation and proliferation of the immune cells, and to regulate the high expression of the patients' peripheral blood telomere repeat sequence-binding protein 1 (TRF1) and TRF2, which can reduce the immune-inflammatory reaction.

5. Conclusion

As people's living standards continue to improve, the prevalence of HUA is gradually increasing. And HUA is one of the main factors of gout, in addition, HUA is also related to hypertension, diabetes, nephropathy and other various diseases. Therefore, lowering UA and preventing HUA can also prevent the occurrence of more other diseases.

Western medicine is mainly used to control the symptoms of gout, but the side effects caused by long-term use of western medicine will not only damage the human body, but also reduce the patient's compliance, and the disease is easy to recur if the medicine is stopped. Chinese medicine has unique efficacy in treating HUA and gout. Chinese medicine, especially Chinese medicine compound, can achieve the purpose of reducing UA and treating the disease by regulating multiple targets with multiple ingredients. However, due to the differences in the specific symptoms of patients and the consequent changes in treatment protocols, the expanded application of TCM in the prevention and treatment of HUA and gout has been limited. Therefore, further searching for safe, effective and easy-to-use proprietary Chinese medicines or single-flavour Chinese medicines from traditional Chinese medicine will become a new direction for the treatment of HUA and gout.

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