The biomarkers discovery of hyperuricemia and gout: proteomics and metabolomics

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Background. Hyperuricemia and gout are a group of disorders of purine metabolism caused by increasing production and(or) decreasing excretion of uric acid. In recent years, the incidence of hyperuricemia and gout has been increasing, which is a severe threat to people's health. Although uric acid-lowering, as well as anti-inflammatory drugs have been widely used, some drugs still have toxic side effects. At the same time, the early symptoms of asymptomatic hyperuricemia are often ignored, resulting in the loss of optimal treatment time in the disease process. By reviewing the literature, to summarize the research progress of hyperuricemia and gout on proteomics and metabolomics.
Methodology. We used professional databases including PubMed, Web of Science to conduct the literature review. This review addresses the current landscape of hyperuricemia and gout biomarkers with a focus on proteomics and metabolomics.
Results. The development of mass spectrometry-based technologies has accelerated studies on hyperuricemia and gout. Proteomic methods are used to identify relevant proteins, discover potential biomarkers and related therapeutic targets to explore the pathogenesis and provide a scientific basis for preventing, diagnosing, and treating hyperuricemia and gout. It also reveals possible relationship between hyperuricemia, gout and kidney disease, metabolic syndrome, diabetes, and hypertriglyceridemia. Metabolomics reveals the main influential pathways through small molecule metabolites, such as amino acid metabolism, lipid metabolism, or other characteristic metabolic pathways. However, the association of some potential biomarkers with gout needs to be further investigated. **Conclusions.** We suggest some possible relationships of potential biomarkers with inflammatory episodes, complement activation, and metabolic pathways. However, there are relatively few proteomic as well as metabolomic studies on hyperuricemia and gout, and some experiments are only primary screening tests, which need further in-depth study.

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15 Abstract

16 **Background.** Hyperuricemia and gout are a group of disorders of purine metabolism. In recent
17 years, the incidence of hyperuricemia and gout has been increasing, which is a severe threat to
18 people's health. Several studies on hyperuricemia and gout in proteomics and metabolomics have
19 been conducted recently. Some literature has identified biomarkers that distinguish
20 asymptomatic hyperuricemia from acute gout or remission of gout. We summarize the
21 physiological processes in which these biomarkers may be involved and their role in disease
22 progression.
23 **Methodology.** We used professional databases including PubMed, Web of Science to conduct
24 the literature review. This review addresses the current landscape of hyperuricemia and gout
25 biomarkers with a focus on proteomics and metabolomics.
26 **Results.** Proteomic methods are used to identify differentially expressed proteins to find specific
27 biomarkers. These findings may be suggestive for the diagnosis and treatment of hyperuricemia
28 and gout to explore the disease pathogenesis. The identified biomarkers may be mediators of the
29 link between hyperuricemia, gout and kidney disease, metabolic syndrome, diabetes and
30 hypertriglyceridemia. Metabolomics reveals the main influential pathways through small
31 molecule metabolites, such as amino acid metabolism, lipid metabolism, or other characteristic
32 metabolic pathways. These studies have contributed to the discovery of Chinese medicine. Some
33 traditional Chinese medicine compounds can improve the metabolic disorders of the disease.
34 **Conclusions.** We suggest some possible relationships of potential biomarkers with inflammatory
35 episodes, complement activation, and metabolic pathways. These biomarkers are able to
36 distinguish between different stages of disease development. However, there are relatively few
37 proteomic as well as metabolomic studies on hyperuricemia and gout, and some experiments are
38 only primary screening tests, which need further in-depth study.
39 **Keywords:** Hyperuricemia; gout; proteomics; metabolomics; uric acid; biomarkers

40

Introduction

41

42 For decades, patients with hyperuricemia and gout have been increasing. However, gout is a part
43 of patients with hyperuricemia(Robinson, 2018). The development of hyperuricemia is closely
44 related to metabolic syndrome (Mets)(Chen et al., 2018), chronic kidney disease(Kielstein,
45 Pontremoli&Burnier, 2020), and cardiovascular disease. Hyperuricemia generally has a serum
46 uric acid level of＞420μmol·L⁻¹ (7mg·dL⁻¹) for men and＞350μmol·L⁻¹ (6mg·dL⁻¹) for
47 women(Johnson et al., 2003). Moreover, the prevalence of hyperuricemia in men is higher than
48 in women because female gonadal hormones and anti-androgen treatment can prevent the
49 occurrence of hyperuricemia(Wan et al., 2020). In contrast, serum uric acid (SUA) levels will
50 increase in postmenopausal women. Uric acid (UA) is vital in developing hyperuricemia and
51 gout. Studies have found that high SUA levels are correlated with cardiovascular disease risk
52 factors (dyslipidemia, obesity, diabetes, renal failure, and so on) (Chales, 2019). As a risk
53 factor, it can increase the risk of death from cardiovascular disease(Borghi et al., 2018). The
54 organism generates UA through purine metabolism. When too much UA forms Monosodium
55 urate monohydrate (MSU) crystals, acute inflammation can develop into gout onset and
56 progression. The clinical manifestations of gout include asymptomatic hyperuricemia
57 (AHU)(Yip, Cohen&Pillinger, 2020) in the early stage, acute and chronic arthritis, and renal
58 impairment. About one-third of patients with hyperuricemia may develop severe kidney disease,
59 including acute and chronic urate nephropathy and urinary calculi(Sellmayr et al., 2020). In
60 addition, hyperuricemia and gout, risk factors for many conditions, can lead to many metabolic
61 disorders.

62 Omics technologies, including genomics, proteomics, metabolomics, and transcriptome, have
63 extensively promoted the development of medicine and biology(Monti et al., 2019). Marc
64 Wilkins first proposed proteomics, that is, all the proteins expressed by a genome or a
65 cell(Wilkins et al., 1996). Proteomics based on mass spectrometry(MS) is crucial for identifying
66 proteins in various diseases(Mann, 2003). At present, the methods for protein separation in
67 proteomics include two-dimensional gel electrophoresis (2-DE) (Lee, Saraygord-Afshari&Low,
68 2020), capillary electrophoresis (CE), high-performance liquid chromatography (HPLC), and
69 other methods. Then, the proteins were identified by matrix-assisted laser desorption ionization-
70 time of flight mass spectrometry (MALDI-TOF-MS), liquid chromatography-mass spectrometry
71 (LC-MS), and liquid chromatography-electrospray mass spectrometry (LC-ESI-MS), protein
72 microarray, and so on(Andrea D Weston 2004, Aslam et al., 2017). Some protein detected
73 techniques such as tandem mass tag (TMT) labeling, isobaric tag for relative and absolute
74 quantification (iTRAQ) and stable isotope labeling by amino acids in cell culture (SILAC) can
75 improve the sensitivity of MS. In recent years, proteomic studies of hyperuricemia and gout have
76 emphasized differential proteins that provide potential molecular markers for disease diagnosis.
77 Metabolomics has been widely used in various fields such as plant biology, pharmacology, and
78 medicine. Metabolomics can be divided into untargeted and targeted metabolomics according to
79 the target(Gika et al., 2014). For decades, untargeted metabolomics studies have been widely

80 used to identify broadly characterized novel substances. Targeted metabolomics, on the other
81 hand, aims to specific metabolites for study. Metabolomics analysis requires using spectroscopic
82 techniques, such as nuclear magnetic resonance (NMR), spectroscopy (VS), an MS, or a
83 combination of several methods. LC-MS has been developed as the primary technology platform
84 for metabolic profiling, such as gas chromatography-mass spectrometer (GC-MS) and 1H
85 NMR(Fraga-Corral et al., 2022). More importantly, the results of metabolomics and proteomics
86 are combined, each reflecting a different level of information to reveal different pathways of
87 disease pathogenesis and biomarkers of predictive action. Modern medicine is eventually moving
88 towards precision medicine and pursuing personalized treatment as a benchmark. The application
89 of "omics" technology reveals the physiological mechanisms and biochemical changes in human
90 systems from different perspectives and explores the metabolite changes in pathological states.
91 Integrating proteomic and metabolomic analysis, biomarkers are capable of distinguishing
92 disease abnormalities to serve as risk, diagnostic or prognostic markers as well as therapeutic
93 targets.
94 The aim of this review is to summarize the biomarkers of hyperuricemia and gout disease as well
95 as metabolic pathways. We discuss the role of some biomarkers in influencing disease
96 progression to understand the current state of research. We also summarize some types of
97 metabolic disorders present in hyperuricemia and gout, and the improvement of metabolic
98 disorders by some Chinese medicines.
99

Survey methodology

101 This review is the result of a systematic literature search on PubMed and Web of Science to find
102 articles related to the proteomics and metabolomics of hyperuricemia and gout. The search terms
103 used for the article in various combinations included "hyperuricemia and proteomics," "gout and
104 proteomics," "hyperuricemia and metabolomics," "gout and metabolomics," "gout and
105 inflammation". Meanwhile, we consulted the literature on the relationship between
106 hyperuricemia, gout and diabetes, Mets and kidney disease. The search strategy was used to
107 obtain the titles and abstracts of the relevant studies initially screened, and retrieved the full text.
108 We also reviewed the relevant references in the article to ensure comprehensive coverage and no
109 bias in the article.
110

The mechanism of hyperuricemia and gout

The production and excretion of uric acid

113 The UA synthesis-related enzyme gene mutation and the activity changes result in excessive UA
114 production. The pathways leading to increased UA production are as follows (**Figure1**).
115 Furthermore, fructose leads to the consumption of ATP and phosphate in liver metabolism and
116 the accumulation of adenosine monophosphate (AMP). Then, AMP generates inosine
117 monophosphate (IMP) under the action of AMP deaminase (AMPD), resulting in the production
118 of UA(King et al., 2018, Zou, Zhao&Wang, 2021). After the formation of UA, about 1/3 is
119 excreted from the gastrointestinal tract, and 2/3 passes through the kidney(Kielstein,

120 Pontremoli&Burnier, 2020). Reabsorption and secretion of renal tubules regulate the excretion of
121 UA, in which the proximal convoluted tubules play a dominant role. Eventually, about 90% of
122 UA is reabsorbed into the blood(Maiuolo et al., 2016). The deficiency of uricase prevents UA
123 into highly water-soluble allantoin in the kidney(Braga, Foresto-Neto&Camara, 2020).
124 Recombinant forms of uricase such as rasburicase, and PEG uricase(Otani et al., 2020) can
125 reduce the level of UA and are routinely utilized in clinical research studies. Additionally, some
126 renal urate transporters, such as URAT1, GLUT9, OAT1, OAT3, and ABCG2, are of great
127 significance in participating in the active secretion and reabsorption of urate in proximal
128 convoluted renal tubules(Alghamdi, Soliman&Nassan, 2020, Sun et al., 2021). ABCG2 can also
129 regulate urate excretion in the intestine, which is also very important for UA levels in the
130 gastrointestinal tract. Due to the urate transporter gene mutation, its structure and function
131 change, urate deposits in the kidney and causes renal impairment. Therefore, based on the urate
132 transporter gene study, clinical research drugs to reduce UA have been developed(Sun et al.,
133 2021).
134
135 **Inflammation caused by urate deposition**
136 MSU crystals form when the blood UA reaches the saturation concentration. In the early stage of
137 gout, MSU activates neutrophils to produce a large number of inflammatory cytokines.
138 Furthermore, MSU can also induce phagocytes to release many mediators, including the
139 cytokines interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), growth-
140 related oncogene α (GROα)/ CXCL1, the C-X-C chemokines (IL-8)/CXCL8, and myeloid-
141 related proteins S100A8, S100A9(Rousseau et al., 2017, Hemshekhar et al., 2020), continuously
142 drive the inflammatory response. IL-1β is well established as the primary trigger for
143 inflammation(Pillinger&Mandell, 2020). The process of IL-1β release is crucial: One is that
144 inflammatory signals induce gene expression and synthesis of the pro-IL-1β; The second is
145 exogenous ATP or reactive oxygen species (ROS), which causes the NACHT, LRR, and PYD
146 domains-containing protein 3 (NLRP3) inflammasome activation and secretion of IL-1β(Wu et
147 al., 2020).
148 MSU crystals recognize entry into macrophages and activate the NLRP3 inflammasome. NLRP3
149 inflammasome activates the cysteinyl aspartate specific proteinase-1 (caspase-1) that cleaves the
150 pro-IL-1β, producing IL-1β(Wu et al., 2019a). In mouse macrophages, extracellular ATP can
151 activate the P2X purinoreceptor 7 (P2X7R), leading to potassium ion (K +) outflow, which
152 activates the NLRP3 inflammasome and the release of IL-1β(Alessandra Piccini, 2008, Marinho
153 et al., 2020). IL-1β promotes the release of various inflammatory mediators, including TNF-α,
154 interleukin-1(IL-1), IL-6, IL-8, and other mediators, such as prostaglandin-E2 (PGE2),
155 leukotriene, intercellular cell adhesion molecule-1(ICAM-1), and ROS(Szekanecz et al., 2019,
156 Luo et al., 2020). The release of chemokines (such as IL-8/CXCL8) and adhesion factors recruits
157 polymorphonuclear leukocytes (PMNs), continues to release IL-1β, IL-8/CXCL8, S100A8,
158 S100A9, and other pro-inflammatory mediators, causing inflammation to continue, leading to
159 systemic inflammation(Rousseau et al., 2017). S100A9 could enhance neutrophils induced by

160 MSU and increase IL-8/CXCL8, IL-1, and ROS(Rousseau et al., 2017). A series of inflammatory
161 reactions revealed that IL-1β is the core of gout patients. Currently, IL-1β blockers(Otani et al.,
162 2020, Szekanecz et al., 2019) have been widely used in clinical settings to relieve inflammation
163 in gout patients.
164
165 **Proteomic study of hyperuricemia and gout**
166 **Plasma proteomics**
167 There are some proteomic studies of hyperuricemia and gout (**Table 1**). Despite the detection of
168 very low abundance proteins remains challenging, blood specimens are the most commonly
169 collected samples. Fei et al. used 2DE combined with the MALDI-TOF-MS technique to study
170 the differential proteins in serum from Uyghur patients with hyperuricemia and normal
171 population and found that complement C3, haptoglobin (Hp), complement C4, and
172 apolipoprotein A1(apo A1) expression were upregulated(Fei et al., 2012). In a follow-up study,
173 Fei et al. further analyzed the serum of Han Chinese patients with hyperuricemia by using the
174 same technique. The expression of complement C3, Hp, and α1 antitrypsin (α1-AT) was
175 upregulated, and apolipoprotein L1(apo L1) was downregulated(Fei et al., 2013). These
176 differentially expressed proteins are all roughly the same and can influence the development and
177 progression of hyperuricemia. In contrast, regional and ethnic differences can lead to different
178 protein expressions. In addition, a study demonstrated high expression of apolipoprotein A-I (apo
179 A-I) in the plasma of patients with acute gout (AG) and a proportional relationship with
180 UA(Chiang et al., 2014).
181 Together with the three aforementioned reports, these detected proteins revealed a potential link
182 between hyperuricemia and high-density lipoprotein (HDL) components. HDL has anti-
183 inflammatory, antioxidant, and complement-activating effects, and prevents thrombosis. Apo A-I
184 has cholesterol transport and anti-atherosclerotic effects and is a major HDL component.
185 Elevated levels of apo A-I during acute gouty arthritis (AGA) may be associated with
186 spontaneous remission(Georgila, Vyrla&Drakos, 2019). HDL regulates lipid metabolism and
187 influences the development of cardiovascular disease (CHD), diabetes, and other metabolic
188 disorders(Gordon&Remaley, 2017, van der Vorst, 2020). In an experiment, a rat model of
189 pregnancy-induced insulin resistance enhanced insulin sensitivity in adipose tissue after infusion
190 of apo A-I. Both TNF-α and IL-6 in rat plasma were decreased, and apo A-I could inhibit
191 inflammation(Wu et al., 2019b). Similarly, in a rabbit model, apo A-I treatment downregulated
192 the expression of serum and aortic inflammatory mediators, including ICAM-1, vascular
193 adhesion molecule-1 (VCAM-1), monocyte chemotactic protein-1, TNF-α, IL-6, and C-reactive
194 protein (CRP)(Li et al., 2017). Thus, apo A-I inhibition may contribute to the development of
195 atherosclerosis (AS) through a mechanism of chronic inflammation. Like apo A-I, apo A1
196 treatment induces a significant reduction in macrophage chemotaxis as well as inhibition of
197 monocyte recruitment in vivo, exerting an anti-inflammatory effect(Iqbal et al., 2016). Moreover,
198 α1-AT is an important serine protease inhibitor in plasma, and enhanced anti-protease activity of
199 α1-AT bound to HDL reduces TNF-α production by macrophages(Gordon et al., 2015). Hp,

200 whose primary function is through binding to free hemoglobin (Hb). Serum Hp is significantly
201 elevated in patients with coronary artery disease(Lee et al., 2013). In a clinical study, Hp with
202 high HDL-bound Hb levels led to microvascular as well as coronary artery endothelial
203 dysfunction(Asleh et al., 2019). And coronary endothelial dysfunction is one of the early stages
204 of AS manifestations. However, the direct relationship between these study indicators and
205 hyperuricemia and gout has not been elucidated yet, and further studies are needed.
206 Interestingly, two recent studies have investigated the proteomic profile of complement-
207 containing components. Shen et al. detected differential plasma proteins using label-free
208 quantitative proteomics based on HPLC-MS/MS in simple gout patients, gout with renal damage
209 patients, and non-gout patients(Shen et al., 2021a). These three groups of detected proteins have
210 processes involved in natural immune response, complement activation response, etc. More
211 importantly, among these proteins, inflammation factors gelsolin (GSN), S100A8, S100A9,
212 Alpha-1-acid glycoprotein 2(ORM2), and Annexin A1(ANXA1) were most significantly
213 associated with SUA. Consequently, this may suggest a combinatorial form of diagnosing gout
214 disease and also help establish a clinical model for gout patients. In addition, the results of Shen
215 et al. in patients with gout and gout with renal impairment suggested that complement C4A,
216 C4B, and SERPINF1 were significantly upregulated in patients with gout combined with renal
217 impairment compared to simple gout patients. To analyze the plasma protein profiles of patients
218 with AG, remission of gout (RG), and AHU, Chen and co-workers established an iTRAQ and
219 parallel reaction monitoring (PRM) based method. Authors found 11 essential proteins, including
220 Histone H2A, Histone H2B, Thrombospondin-1 (THBS1), Inter-alpha-trypsin inhibitor heavy
221 chain H4 (ITIH4), Alpha-1-acid glycoprotein 1 (ORM1), Multimerin-1(MMRN1),
222 Myeloperoxidase (MPO), Carbonic anhydrase 1(CA1), Serum albumin (ALB), Complement
223 component C8 beta chain (C8B), and Complement C2(Chen et al., 2021a). Most of the above
224 proteins are involved in the inflammatory process of gout, regulate cytokines, or enhance the
225 inflammatory response. Among them, Histone H2A, Histone H2B, and THBS1 may be potential
226 markers for distinguishing AG, RG, AHU, and healthy people. THBS1 is an extracellular matrix
227 glycoprotein that can bridge cell interaction and promote inflammation. In addition, THBS1
228 expression helps to maintain tissue homeostasis and reduce inflammation during the regression
229 of chronic inflammation (McMorrow et al., 2013, Xiaofang Tang 2020). THBS1 may be
230 involved in the regression of inflammation in patients with RG. The discovery of these proteins
231 may be a potential biomarker for the diagnosis of gout. From the proteomic characteristics of this
232 study, the research team found that complement and coagulation cascades were one of the main
233 functional pathways in the gout process. Thus, the interaction between the complement and
234 coagulation systems may influence the development of inflammation.
235 Activation of NLRP3 mediates the massive release of IL-1β and interleukin-18 (IL-18), which
236 can lead to various pathological inflammatory diseases, including AS, gout, and type 2 diabetes
237 (T2DM). Complement and the coagulation system are closely related functionally. On the one
238 hand, arousal of the complement system activates platelets and promotes coagulation. On the
239 other hand, a thrombus can activate the complement system to trigger an inflammatory response

240 further(Oncul&Afshar-Kharghan, 2020). The complement system is an essential component of
241 innate immunity and plays a role in preventing infections, among others. When the complement
242 system is activated, component C5a is a potent pro-inflammatory mediator, promoting monocyte
243 as well as neutrophil chemotaxis and activation. MSU can induce IL-1β and release
244 inflammatory cytokines by activating complement system component C5a(Khameneh et al.,
245 2017, Yu et al., 2019). The ability of complement antagonists alone to determine inflammation
246 control is limited by various factors that influence gout inflammation activation. Therefore, C5a
247 antagonists may combine with IL-1β blockers as a therapeutic target for treating inflammatory
248 diseases.
249
250 **Proteomics of other samples**
251 Urine belongs to a non-invasive collection of samples. It has certain advantages to studying urine
252 samples at the protein level. Huo et al. looked at urinary protein metabolism in patients with
253 HUA and healthy people by label-free liquid chromatography−tandem mass spectrometry
254 (LC−MS/MS) analysis (Huo et al., 2021). Through enrichment analysis of these differentially
255 expressed proteins (DEPs), plausible pathways include the processes for insulin receptor
256 recycling and lipid metabolism. Among them, V-type proton ATPase subunit B kidney isoform
257 (VATB1) and Complex factor D (CFAD or adipsin) affect insulin levels in patients with
258 hyperuricemia. Apolipoprotein C3(APOC3) may play a role in hypertriglyceridemia in patients
259 with hyperuricemia. Moreover, abnormal expression of apolipoproteins (APOC4, APOD) in the
260 plasma of gout patients(Shen et al., 2021a).
261 Triglyceride metabolism and the prevalence of T2DM are closely related to APOC3, which
262 reduces triglyceride-rich lipoproteins (TRLs) and residual uptake in the liver by inhibiting the
263 activities of lipoprotein lipase (LPL) and liver lipase (HL) (Norata et al., 2015). The
264 concentration of triglyceride can be regulated by controlling APOC3. However, it is unclear
265 whether APOC3 alone regulates triglyceride concentrations in patients with hyperuricemia.
266 Interestingly, Zewinger et al. introduced that APOC3 identified monocytes activating NLRP3
267 processes that drive IL-1β inflammatory processes leading to renal damage(Zewinger et al.,
268 2020). APOC3 could promote the inflammatory response in patients with gout and provide a
269 new target for treatment. APOD is a class of proteins that transports lipids, and arachidonic acid
270 (AA) is its common ligand. APOD exerts neuroprotective and anti-inflammatory effects by
271 stabilizing AA at the cell membrane(Rassart et al., 2020). In a cohort study, the authors
272 examined APOD expression in three intra-abdominal adipose tissues, including omental,
273 mesenteric, and round ligament (RL). In particular, with high levels of APOD in the RL depot,
274 women exhibited lower plasma insulin levels and lowered circulating pro-inflammatory PAI-1
275 and TNF-α levels(Desmarais et al., 2018). High levels of APOD may improve inflammatory
276 conditions. APOD has been shown to correlate with obesity, diabetes, and other metabolic
277 diseases. Patients with hyperuricemia and gout are accompanied by lipid metabolism disorders
278 that can promote the development of diabetes and hyperlipidemia. Adipocytes secreted fat
279 factors such as CFAD that participated in activating complement component C3a and could

280   protect β Cells. At the same time, complement C3a can enhance β Cellular insulin
281   secretion(Tafere et al., 2020). Hence, it is unsurprising that adipsin can be used as a T2DM
282   marker. Adipsin is also associated with subcutaneous fat accumulation. When adipsin
283   measurements were below BMI level, the risk of diabetes was lower (Gomez-Banoy et al.,
284   2019). In addition, it has been verified that adipocytes can affect inflammatory arthritis. Adipsin
285   is an intermediate mediator, regulating neutrophil-induced inflammatory response(Li et al.,
286   2019). Therefore, obesity can also lead to an inflammatory response in gout patients. The
287   discovery of CFAD in patients with hyperuricemia may affect the prevalence of T2DM.
288   However, hyperuricemia not only affects T2DM through CFAD but may also have other
289   mediators. However, further experimental verification is needed. APOC3 and CFAD may serve
290   as potential targets as related factors.
291   T2DM is characterized by hyperglycemia, insulin resistance, and lack of insulin secretion. As an
292   effective stimulus, Hyperglycemia is involved in NOX-mediated ROS production of endothelial
293   cells and leads to endothelial dysfunction(Meza et al., 2019). Hyperuricemia and gout patients
294   can lead to oxidative stress response and inflammatory process. Oxidative stress leads to
295   endothelial dysfunction and worsens insulin resistance(Ko et al., 2019, Yaribeygi et al., 2020).
296   According to a survey, patients with high BMI, diabetes, hypertension, and hypertriglyceridemia
297   have the highest risk of hyperuricemia(Liu et al., 2020). Hypertension, insulin resistance, and
298   high triglycerides serve as the relevant influencing factors of Mets. Additionally, a large amount
299   of fructose intake can lead to the occurrence of Mets that affects the production of metabolites
300   such as glucose, triglyceride, UA, and free fatty acids. These metabolites contribute to fat
301   accumulation, insulin resistance, and inflammation and are associated with hypertension,
302   diabetes, and hyperuricemia(Zhang, Jiao&Kong, 2017). Overall, it is possible to focus on the
303   influence of apolipoproteins and complement components on gout progression and acute
304   inflammation occurrence. Some proteins (components of HDL) could act as proteases that
305   activate complement, initiate the coagulation cascade response, and in turn, could trigger the
306   inflammatory switch. These several physiological pathways and processes are all
307   interconnected(Gordon&Remaley, 2017). Integrating multiple omics approaches to explore
308   biomarkers of hyperuricemia and Mets may be a considerable challenge.
309   Interestingly several studies investigated the proteome profiles of the synovial fluid (SF)-derived
310   exosome samples aiming to define its impact on gout progression. Chiu et al. injected sodium
311   urate crystals into the murine air pouch (resembles the synovial membrane) to induce
312   inflammation(Chiu et al., 2015). The differentially expressed proteins participated in the
313   alternative complement pathway through proteomic analysis based on an iTRAQ labeling
314   coupled with offline 2D LC-MS/MS. The results suggested that the levels of Catherine-related
315   antimicrobial peptide (CRAMP) and S100A9 were positively correlated with MSU. The authors
316   propose that activation of NALP3 inflammasome in late gout is associated with the upregulation
317   of proteins S100A9 and CRAMP. These differential proteins can be used as future therapeutic
318   targets for AG. Another study aiming to analyze the proteomics of SF-derived exosomes used
319   TMT labeled LC-MS/MS techniques. Sixty-nine differentially expressed proteins were identified

320 in gout patients, with 25 highly unique expressions, including lysozyme C, ORM1,
321 lactotransferrin, S100A9, and MPO, which may be involved in neutrophil degranulation and
322 prion disease as well as complement and coagulation cascade(Huang et al., 2022). Along the
323 same lines, Qiu et al. also found that differentially expressed genes (DEGs) were predominantly
324 enriched in the inflammatory response, S100 protein binding, in the male gout group compared
325 to the control healthy group(Qiu et al., 2021). Therefore, the inflammatory response associated
326 with differentially expressed proteins plays a vital role in gout patients.
327 According to research, MSU can stimulate neutrophils to release S100A8 and S100A9 (Sreejit et
328 al., 2020). S100A9 further enhances MSU to promote neutrophils and signaling pathways
329 (Rousseau et al., 2017). In gout patients, S100A8 and S100A9 can stimulate neutrophils to
330 produce ROS, so as to regulate inflammatory bodies and release pro-inflammatory cytokines IL-
331 1β, IL-8, IL-6, and TNF-α(Sreejit et al., 2020). Like S100A8 and S100A9, CRAMP is a
332 component of innate immunity, which plays a role in preventing pathogen infection, damage, and
333 repair as well as is related to chemotaxis and inflammatory response activation(G H
334 Gudmundsson, 1999). Interestingly, CRAMP and LL-37 have some similarities in structure and
335 function. CRAMP and LL-37 belong to antimicrobial peptides (AMPs, also known as host
336 defense peptides). CRAMP and LL-37 have some similarities in structure and function. CRAMP
337 is a functional homologue of LL-37 in mammals, and LL-37 is the form of cathelicidin protein in
338 humans(Kang et al., 2020). In inflammatory arthritis patients, CRAMP was not only up-
339 regulated but also accompanied by increased S100A8 and S100A9 proteins(Hemshekhar et al.,
340 2020, Choi et al., 2021). Although the specific physiological role of CRAMP in hyperuricemia
341 and gout is unknown, it has been confirmed that CRAMP can affect the progression of
342 inflammation. Therefore, S100A8, S100A9, and CRAMP are closely related to inflammatory
343 response and can promote the activation of the NALP3 inflammasome. These proteins may
344 provide new targets for inflammatory drug therapy in gout patients.
345
346 **The "stones" of gout**
347 Hyperuricemia may lead to severe kidney damage, such as the formation of urinary calculi. Most
348 urinary calculi are calcium stones, followed by UA stones, or can lead to calculus mixed with
349 urate and calcium oxalate. Jou et al. introduced that the protein composition of UA stones may
350 be related to the phospholipids and fatty acid pathway and inflammatory response(Jou et al.,
351 2012). These proteins may promote the formation of UA stones, and some irritants encourage
352 inflammation. In addition, whether the UA stone composition protein is consistent with the
353 protein in plasma and urine of patients with hyperuricemia and gout. In 2012, Kaneko et al.
354 measured matrix proteins in 17 different urinary stones (patients with gout and hyperuricemia).
355 They found that some proteins were detected in both CaOx stones and UA stones(Kaneko et al.,
356 2012). For the analysis of proteins, urinary stones were separated by SDS-PAGE and subjected
357 to LC-MS/MS analysis to identify the specific proteins. Osteopontin, prothrombin, protein Z, and
358 protein S were mainly identified from CaOx stones, and IgG fragments were detected in UA
359 stones. The proteins detected in the above test are a group of substances that are not similar to

360 those seen in plasma and urine samples. Identical proteins were found in CaOx and UA stones.
361 These proteins may be roughly involved in the formation of the urinary stone structure.
362 Interestingly, someone found IgG and TF10 macromolecules in the urine of patients with high
363 UA, which can have specific damaging effects on the kidney(Gao et al., 2019). However, the
364 particular influence of IgG on hyperuricemia and the kidney is not clear. In this context, Kaneko
365 and co-workers studied the matrix proteins in a gouty tophus from a patient with recurrent gout
366 via a micro-area X-ray diffractometer. Then, the authors utilized LC-MS/MS to analyze protein
367 composition and determine the composition of tophi as MSU(Kaneko et al., 2014). The proteins
368 identified in the experiment are related to inflammation and host defense. In another study, IgG
369 encapsulated MSU was found in the tophus of patients with AG. And apolipoprotein B(ApoB)
370 was detected in the mouse airbag during the anti-inflammatory process(E Ortiz-Bravo, 1993). A
371 similar study has shown that altering protein coating on MSU and M-CPPD can inhibit or
372 promote crystal-induced IL-1β inflammatory processes. Surface IgG enhances inflammatory
373 responses, while HLD, apolipoprotein A (Apo A), and apolipoprotein E(Apo E) inhibit
374 inflammatory processes (E Ortiz-Bravo 1993, Renaudin et al., 2019). The changes in the
375 inflammatory properties of the crystal by protein coating may provide a new method for treating
376 inflammation in gout patients.
377 In a follow-up study, Kaneko et al. examined a urinary stone with two layers from a male patient
378 with hyperuricemia. Then, they separated the two layers of urinary stones, and the interface was
379 detected with a micro-area X-ray diffractometer. UA is formed internally first, and then COM
380 covers UA externally. The analysis successfully identified 51 proteins with proteomic analysis
381 by LC-MS/MS. 14 were cell adhesion and cytoskeleton proteins, and 7 were metabolism-related
382 proteins. There were five defense proteins and five plasma proteins(Kaneko et al., 2018). Later,
383 there was a protein related to inflammation(S100A8) in UA, while some proteins played the role
384 of cell adhesion, self-defense, and plasma in the formation of the interface. S100A8 was
385 significantly correlated with UA(Shen et al., 2021a). MSU promotes the production of S100A8
386 and S100A9, which strengthen neutrophils and participate in inflammatory responses(Sreejit et
387 al., 2020). S100A8 and S100A9 can be used as potential targets for future research.
388

Metabolomics of hyperuricemia and gout

Amino acid metabolism

391 Here are some of the metabolic disorder pathways involved in hyperuricemia and gout (**Figure
392 2**). Several studies have the same results that amino acid metabolism is highly associated with
393 hyperuricemia and gout. Many animal models of hyperuricemia and gout have disorders of
394 amino acid metabolism. In an NMR metabolomics, the metabolite profile of a rat model of gouty
395 arthritis showed a significant increase in plasma leucine and lysine compared to the control
396 group, indicating that gouty arthritis (GA) induces disturbances in amino acid metabolism(Han et
397 al., 2016). Similarly, a urine metabolomics approach by UHPLC-ESI-QTOF-MS revealed a
398 significant disorder of tryptophan metabolism and tyrosine metabolism in a rat model of
399 hyperuricemia(Wei et al., 2018). Towards investigating the correlation between the plasma-free

400 amino acid (PFAA) profile and gout patients, an approach using HPLC-ESI-MS was applied by
401 Mahbub et al(Mahbub et al., 2017). The authors confirmed that the levels of alanine, isoleucine,
402 leucine, phenylalanine, tryptophan, and valine were positively correlated with gout. In contrast,
403 the levels of glycine and serine were negatively associated with gout. Similarly, another
404 experiment based on UPLC-MS found that gout patients involved purine metabolism and
405 branched-chain amino acids (BCAAs) metabolism. The levels of valine and leucine, and
406 phenylalanine levels in blood were increased(Huang et al., 2020). Together these studies
407 mentioned above reported that the difference and metabolism of amino acids might be related to
408 the occurrence of gout. Gout patients may have a disorder of amino acid metabolism. Following
409 a different methodological approach, Wang et al. studied the relationship between hyperuricemia
410 and amino acids. They found that cysteine, glutamine, phenylalanine, and threonine were related
411 to the changes in UA levels in hyperuricemia patients(Wang et al., 2020a). From previous
412 experiments, glycine(van Milgen, 2021) and glutamine(Otani et al., 2020) (**Figure1**) are
413 indispensable parts of the de novo synthesis of purine, and threonine is the source of glycine.
414 Likewise, these amino acids reflect the dietary habits of hyperuricemia. Glutamine is common in
415 meat, while phenylalanine and threonine are more abundant in bean products. Understanding the
416 purine production and dietary consumption of hyperuricemia and gout are helpful to the
417 prevention of diseases.
418 The transition stage of hyperuricemia and gout onset is ambiguous. The early symptoms of AHU
419 are often ignored, resulting in the loss of treatment time in the disease process. There is a gradual
420 progression from the discovery of hyperuricemia to the onset of gout. A metabolomic approach
421 based on 1H NMR spectroscopy reveals disturbing pathways in serum HUA and gout patients.
422 This study showed a more severe metabolic disorder in gout patients compared to the three
423 metabolic pathways of hyperuricemia patients, with an increase in glutamine found only in gout
424 patients(Zhang et al., 2018). LC-MS/MS was also performed by Luo et al. to screen for the
425 plasma amino acids (AAs) profile of AG and AHU(Luo et al., 2018). AG Patients consume more
426 glycine because glycine is the raw material for the de novo synthesis of purine. When serum UA
427 levels are similar, L-isoleucine, L-lysine, and L-alanine may be potential markers to distinguish
428 AG from AHU. Interestingly, when the amino acid content changes, the precipitation of MSU at
429 the limb end of AG patients is more accessible. The changes in plasma amino acids will affect
430 the generation of MSU. Different amino acid metabolic abnormalities are present in patients with
431 hyperuricemia and gout. The most significant changes in arginine metabolism were found by
432 Shen et al. Arginine biosynthesis is associated with the development of inflammation in the gout
433 process, and arginine may be a potential biomarker to differentiate between patients with
434 hyperuricemia and gout(Shen et al., 2021b). However, only focusing on the changes of amino
435 acids can't accurately distinguish between patients with AG and AHU, which may be because the
436 type and physiological function of amino acids are not evident in patients with AG and AHU.
437
438 **Other metabolic pathways**

439   Purine metabolic pathways are also closely related to the development of hyperuricemia. UA is
440   the end product of purine metabolism, and when purine nucleotide synthesis is disturbed, serum
441   UA concentration increases(Li et al., 2018). And this is followed by the formation of urate
442   crystals, which leads to the development of gout inflammation. Similar to purine metabolism,
443   other metabolic pathways are influencing hyperuricemia and gout in one way or another. The
444   untargeted metabolomic analysis of blood and stool samples collected by Bian et al. by the
445   UHPLCQ-TOF/MS method revealed the presence of abnormal glycerophospholipid metabolism
446   in the hyperuricemia animal model. The authors used chicory to modulate the related lipid
447   metabolites involved in glycerophospholipid metabolism, thereby improving hyperuricemia(Bian
448   et al., 2018). Li et al. also found significant differences in glycerophospholipid metabolism
449   between gout patients and controls(Li et al., 2018). Hyperlipidemia and obesity(Lai et al., 2021)
450   have been proved to be risk factors for hyperuricemia. It has been confirmed that BMI, waist
451   circumference, and body fat proportion are related to hyperuricemia(Rivera-Paredez et al., 2019).
452   Glycerophospholipid metabolism is strongly influenced by diet. According to a prospective
453   study, consumption of ultra-processed food (UPF)(Zhang et al., 2021) and a Western diet are
454   related to the risk for hyperuricemia. In terms of composition, UPF and Western diets generally
455   include a large amount of fat, saturated fat, sugar, and salt. These findings suggest that
456   hyperuricemia has a disorder of lipid metabolism, and a diet with high-fat content will increase
457   the risk of hyperuricemia.
458   In addition, the GA rat model involves energy metabolism as well as gut microbial metabolism.
459   Han et al. found an increase in lactate levels in plasma(Han et al., 2016). Lactic acid is a
460   common biomarker of arthritis and is seen to be elevated. At the same time, urinary levels of
461   succinate, 2-ketoglutarate, citrate, and pyruvate were elevated. Metabolites such as citrate, 2-
462   ketoglutarate, and succinate are key intermediates in the tricarboxylic acid (TCA) cycle, linking
463   lipid and amino acid metabolism. As a metabolic pathway, the TCA cycle was identified by
464   GeneGo analysis in this study by Chiu et al. Pyruvate carboxylation appears to be a novel
465   therapeutic metabolic target in GA(Chiu et al., 2015). Along the same lines, in a study exploring
466   the biomarker profile of HUA and gout, gout patients also had disturbed energy
467   metabolism(Zhang et al., 2018). Mitochondrial dysfunction alters the level of citric acid. In
468   addition, urinary levels of TMAO and hippuric acid, metabolites produced by bacteria in the
469   intestinal tract, were significantly lower in the gouty arthritis model rats compared to healthy
470   controls(Han et al., 2016). Similarly, during the acute phase of gout, the intestinal bacterial
471   metabolite hippuric acid is reduced(Liu et al., 2011). In addition, lower levels of phenylalanine in
472   the urine of gout patients(Li et al., 2018). Hyperuricemia and gout diseases disrupt the balance of
473   microbial metabolism in the gut, leading to changes in metabolites in the urine. Therefore,
474   intestinal flora metabolism will be a new direction for future research.
475   Interestingly, a noteworthy study identified primary bile acid biosynthesis as a possible new
476   metabolic pathway. UPLC-QTOF/MS was utilized for the serum metabolic profiles of metabolite
477   extracts from gout patients, and urate and bilirubin are reliable metabolites in gout
478   patients(Zhong et al., 2021). Significantly different metabolites are mainly involved in primary

479   bile acid biosynthesis, purine metabolism, and glycerophospholipid metabolism. Bile acids can
480   affect UA levels in mice by interfering with orphan nuclear receptor peroxisome proliferator-
481   activated receptor alpha (PPARα) activation of the XOD gene(Kanemitsu et al., 2017). Bilirubin
482   may be a potential biomarker. While new metabolic pathways are constantly being discovered to
483   influence the development of hyperuricemia and gout, the metabolic pathways intersect with
484   each other, thus forming large networks. More importantly, if we can further explore the network
485   metabolic key nodes, it is beneficial to discover possible biomarkers. Through this approach, it is
486   possible to know which metabolic pathways the therapeutic drugs act on and reveal the
487   pharmacological effects of the drugs.
488
489   **Chinese Medicine and metabolomics**
490   Currently, detailed drug evaluation is not possible based on the available reference indicators.
491   More and more studies are exploring the mechanisms of traditional Chinese medicine (TCM)
492   compounds for disease treatment and the efficacy of TCM through metabolomics(Wang et al.,
493   2017, Wu, Li&Zhang, 2019). Another study aimed to explore the effect of Gout Party on plasma
494   metabolic profiles in a rat model of AGA by UHPLC-Q-TOF/MS(Wang et al., 2019). Compared
495   to controls, the Gout Party treatment group affected 14 biomarkers, with the main pathways
496   involved being fatty acid metabolism, bile acid metabolism, amino acid metabolism, and energy
497   metabolism pathways. Not only that, but it also effectively reduced the release of inflammatory
498   factors IL-6 and IL-8, exerting an anti-inflammatory effect. Another similar study investigated a
499   mouse model of hyperuricemia by UPLC-ESI-Q-TOF/MS metabolomics. Chen et al. presented
500   that Tongfengxiaofang (TFXF) could regulate various disorders of arginine biosynthesis,
501   galactose metabolism, pyrimidine metabolism, glycerophospholipid metabolism, tryptophan
502   metabolism, and TCA cycle caused by hyperuricemia(Chen et al., 2021b). In addition, not only
503   the effects of drugs for disease treatment are studied by metabolomics, but also the comparative
504   efficacy of a large class of Chinese medicine prescription composed can be compared for
505   performance assessment. Shan et al. performed UPLC-Q-TOF/MS untargeted metabolomics to
506   investigate the effect of Ermiao wan categorized formulas (ECFs) on a model of high fructose
507   combined with potassium oxonate (HFCPO)-induced hyperuricemia(Shan et al., 2021). ECFs
508   included Ermiao wan (2 MW), Sanmiao wan (3 MW), and Simiao wan (4 MW). The results
509   showed that 2 MW, 3 MW, and 4 MW could partially modulate the disturbed lipid metabolic
510   pathway. More importantly, 4 MW was superior to 2 MW and 3 MW in interfering with the
511   disturbance of TCA metabolism and purine metabolism induced by hyperuricemia.
512   Lipidomics, an important branch of metabolomics, has recently become a hot research topic and
513   independent histology in biology. Due to the continuous development of technology, lipidomics
514   can identify individual lipid molecule species, and the integration studies with genomics and
515   metabolomics can uncover the complete picture of diseases(Tabassum&Ripatti, 2021, Wang et
516   al., 2020b). By metabolomics followed by transcriptomics, a model of diosgenin on potassium
517   oxonate (PO)-induced hyperuricemia was studied by UHPLC-MS combined with 1H NMR(Tan
518   et al., 2020). There were 53 altered metabolites in plasma and urine metabolomics, 19 of which

519   were lipids, mainly involved in the TCA cycle, lipid metabolism, amino acid metabolism, and
520   pyrimidine metabolism. Subsequently, genes affecting the cell cycle and energy metabolism
521   were identified in transcriptomics. Since metabolomics provides an understanding of the overall
522   changes in metabolism, it is suitable for the therapeutic evaluation of multi-targeted features of
523   herbal compounding. Therefore, studying metabolomics provides a deep dissection of the
524   organism's metabolites to identify the effective pathways through which drugs affect the disease.
525   It can be said that lipidomics can provide insight into the lipid metabolic pathways of
526   hyperuricemia and combine with other omics such as transcriptomics to understand the disease
527   development process from all levels. The combination of transcriptomics has elucidated the
528   genes affecting hyperuricemia from different perspectives, providing a basis for studying the
529   pathogenesis of hyperuricemia.
530

Conclusions

532   Gout is treated clinically with urate-lowering therapy (ULT), such as allopurinol, UA excreting
533   drugs, and uricase. In addition, anti-inflammatory treatment with drugs such as colchicine is also
534   available(Dalbeth et al., 2021). However, there is an urgent need to find alternative remedies for
535   gout due to co-morbidities and the prohibition of medications. On the one hand, since a
536   proportion of patients with hyperuricemia do not have gout manifestations, and gout increases
537   the risk as uric acid levels rise, it is not possible to accurately classify the stage of the disease
538   based on UA alone as an indicator. Clinically, this stage is usually determined by imaging, but
539   there are deficiencies. And this leads to some limitations in early prevention as well as diagnosis.
540   These point to the lack of specificity of some existing biomarker tests and the need to explore
541   new validated biomarkers to diagnose the disease. On the other hand, since high SUA levels are
542   a risk factor for some metabolic diseases, especially cardiovascular diseases, they can even
543   develop into kidney disease(Pisaniello et al., 2021). Analytical techniques for studying
544   hyperuricemia and gout proteomics have evolved from 2DE-based protein extraction, followed
545   by LC-MS, to a broader range of screening methods. For quantitative protein detection, tag-
546   based methods include isotope-encoded affinity labeling, SILAC, iTRAQ, and TMT(Tian,
547   Permentier&Bischoff, 2021). In addition, the protein species of the crystalline components were
548   explored by using micro-area x-ray diffraction determination followed by infrared analysis. SDS-
549   PAGE followed by LC-MS/MS is widely used to analyze urinary stones and gouty tophus. In
550   metabolomics studies, depending on the application and instrumentation, information on small
551   molecules in liquids is obtained using spectroscopy (i.e., NMR) and MS (i.e., LC/GC-MS or
552   tandem MS) to capture solids (i.e., solid-state NMR) or using LC-MS, CE-MS, GC-MS.
553   Studies on proteomics as well as metabolomics can identify possible biomarkers and the
554   metabolic pathways involved, providing insights into disease pathogenesis and therapeutic
555   targets. Studies on diseases such as hyperuricemia and gout are still relatively small in sample
556   size. Metabolomics has much experience in exploring herbal components for the treatment of
557   hyperuricemia as well as gout and analyzing the pharmacological effects of Chinese medicine.
558   Most metabolomics studies are based on establishing animal models to reveal the

559   pharmacological effects of TCM on diseases. From the above studies, the TCA cycle in question
560   has an impact on hyperuricemia as well as in gout models. More importantly, the TCA cycle is
561   the intertwined core of other pathways such as arginine metabolism, glycerophospholipid
562   metabolism, pyrimidine metabolism, tryptophan metabolism, etc. Some metabolomic studies
563   found that hyperuricemia is associated with disorders of the primary bile acid pathway or
564   intestinal metabolism, which provides new ideas to guide the subsequent treatment. Specific
565   amino acid species can be identified and become biomarkers of the disease requires further
566   research. The metabolic pathways and the related substances involved are relatively large routes
567   and lack specificity to reflect a comprehensive disease pathogenesis profile. Therefore, further
568   studies of the main pathways and substances are needed.
569   In addition, proteomics has focused more on plasma and urine studies as well as have a portion
570   of SF samples. In urinary stone specimens, different protein types than plasma and urine are
571   reflected. And this also indicates that different sample types result in a significant difference in
572   test results. These substances may predict early AHU, AG, and complications (renal damage).
573   The proteins explored in the abovementioned studies are broadly related to inflammation or
574   involved in complement and coagulation cascade reactions. Or they may be involved in kidney
575   stone composition and influencing the development of concomitant diseases such as diabetes and
576   hyperlipidemia. They have good suggestions for the treatment of gout inflammation and
577   concomitant diseases. In proteomic studies of patients with gout and hyperuricemia,
578   apolipoproteins and related substances promote the development of several disease risk factors
579   such as hypertriglyceridemia, AS, and diabetes. The specific mechanisms linking apolipoprotein
580   and complement components to inflammatory pathway activation need to be further explored.
581   Despite the current identification of differential proteins are mainly based on proteomic
582   approaches, biomarker discovery is limited by the ability to understand the function of the
583   proteins and incomplete studies of the specific signaling pathways of the proteins. These studies
584   are not optimal for biomarker discovery as most of them are preliminary screening tests and are
585   only associated with changes in specific biochemical associations of hyperuricemia and gout.
586   More importantly, the protein targets lack specificity and require multiple approaches for
587   validation.
588   Considerably fewer researches integrated data from multiple omics. A single proteomic or
589   metabolomic study is insufficient but requires the integration of genetic epigenomics,
590   transcriptomics, genomics, and other multifaceted findings(Bodofsky et al., 2020). Multi-omics
591   data analysis has become the focus of many disease studies to understand the pathogenesis of
592   disease processes comprehensively. In the next five or even ten years, find specific biomarkers
593   through the role of high-resolution technology. With multi-omics data integration, humankind
594   will thoroughly understand hyperuricemia and gout disease progression. More importantly, it is
595   hoped that the management protocols for AHU and gout interval will be better improved, and a
596   staged approach to treatment will be established(Dalbeth et al., 2021). Consequently, it is a
597   tremendous challenge to get biomarkers into clinical trials for application in clinical diagnosis

598 and treatment, combined with clinical laboratory automation. And this will allow better
599 management of patients with hyperuricemia and gout and play a role in disease prevention.
600

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615

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617 Xinghong Wu conceived and designed the experiments, performed the experiments, prepared
618 figures and/or tables, authored or reviewed drafts of the paper, and approved the final draft.
619 Chongge You conceived and designed the experiments, performed the experiments, authored or
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623 The following information was supplied regarding data availability:
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625

626 **References**
627 Robinson PC. 2018. *Gout - An update of aetiology, genetics, co-morbidities and management.*
628   Maturitas 118:67-73 http://dx.doi.org/10.1016/j.maturitas.2018.10.012.
629 Chen YY, Kao TW, Yang HF, Chou CW, Wu CJ, Lai CH, Sun YS, Wang CC, Chen WL. 2018.
630   *The association of uric acid with the risk of metabolic syndrome, arterial hypertension or*
631   *diabetes in young subjects- An observational study.* Clinica Chimica Acta 478:68-73
632   http://dx.doi.org/10.1016/j.cca.2017.12.038.
633 Kielstein JT, Pontremoli R, Burnier M. 2020. *Management of Hyperuricemia in Patients with*
634   *Chronic Kidney Disease: a Focus on Renal Protection.* Current Hypertension Reports
635   22:102 http://dx.doi.org/10.1007/s11906-020-01116-3.
636 Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S, Tuttle KR, Rodriguez-Iturbe
637   B, Herrera-Acosta J, Mazzali M. 2003. *Is there a pathogenetic role for uric acid in*
638   *hypertension and cardiovascular and renal disease?* Hypertension 41:1183-90
639   http://dx.doi.org/10.1161/01.HYP.0000069700.62727.C5.

640 Wan H, Zhang K, Wang Y, Chen Y, Zhang W, Xia F, Zhang Y, Wang N, Lu Y. 2020. *The*
641   *Associations Between Gonadal Hormones and Serum Uric Acid Levels in Men and*
642   *Postmenopausal Women With Diabetes.* Frontiers in Endocrinology 11:55
643   http://dx.doi.org/10.3389/fendo.2020.00055.
644 Chales G. 2019. *How should we manage asymptomatic hyperuricemia?* Joint, Bone, Spine:
645   Revue du Rhumatisme 86:437-443 http://dx.doi.org/10.1016/j.jbspin.2018.10.004.
646 Borghi C, Rodriguez-Artalejo F, De Backer G, Dallongeville J, Medina J, Nuevo J, Guallar E,
647   Perk J, Banegas JR, Tubach F, Roy C, Halcox JP. 2018. *Serum uric acid levels are*
648   *associated with cardiovascular risk score: A post hoc analysis of the EURIKA study.*
649   International Journal of Cardiology 253:167-173
650   http://dx.doi.org/10.1016/j.ijcard.2017.10.045.
651 Yip K, Cohen RE, Pillinger MH. 2020. *Asymptomatic hyperuricemia: is it really asymptomatic?*
652   Current Opinion in Rheumatology 32:71-79
653   http://dx.doi.org/10.1097/BOR.0000000000000679.
654 Sellmayr M, Hernandez Petzsche MR, Ma Q, Kruger N, Liapis H, Brink A, Lenz B, Angelotti ML,
655   Gnemmi V, Kuppe C, Kim H, Bindels EMJ, Tajti F, Saez-Rodriguez J, Lech M, Kramann
656   R, Romagnani P, Anders HJ, Steiger S. 2020. *Only Hyperuricemia with Crystalluria, but*
657   *not Asymptomatic Hyperuricemia, Drives Progression of Chronic Kidney Disease.*
658   Journal of the American Society of Nephrology 31:2773-2792
659   http://dx.doi.org/10.1681/ASN.2020040523.
660 Monti C, Zilocchi M, Colugnat I, Alberio T. 2019. *Proteomics turns functional.* Journal of
661   Proteomics 198:36-44 http://dx.doi.org/10.1016/j.jprot.2018.12.012.
662 Wilkins MR, Sanchez JC, Gooley AA, Appel RD, Humphery-Smith I, Hochstrasser DF, Williams
663   KL. 1996. *Progress with proteome projects: why all proteins expressed by a genome*
664   *should be identified and how to do it.* Biotechnology and Genetic Engineering Reviews
665   13:19-50 http://dx.doi.org/10.1080/02648725.1996.10647923.
666 Mann RAM. 2003. *Mass spectrometry-based proteomics.* Nature 422:198-207
667 Lee PY, Saraygord-Afshari N, Low TY. 2020. *The evolution of two-dimensional gel*
668   *electrophoresis - from proteomics to emerging alternative applications.* Journal of
669   Chromatography A 1615:460763 http://dx.doi.org/10.1016/j.chroma.2019.460763.
670 Andrea D Weston LH. 2004. *Systems biology, proteomics, and the future of health care: toward*
671   *predictive, preventative, and personalized medicine.* J Proteome Res 3:
672 Aslam B, Basit M, Nisar MA, Khurshid M, Rasool MH. 2017. *Proteomics: Technologies and*
673   *Their Applications.* Journal of Chromatographic Science 55:182-196
674   http://dx.doi.org/10.1093/chromsci/bmw167.
675 Gika HG, Theodoridis GA, Plumb RS, Wilson ID. 2014. *Current practice of liquid*
676   *chromatography-mass spectrometry in metabolomics and metabonomics.* Journal of
677   Pharmaceutical and Biomedical Analysis 87:12-25
678   http://dx.doi.org/10.1016/j.jpba.2013.06.032.
679 Fraga-Corral M, Carpena M, Garcia-Oliveira P, Pereira AG, Prieto MA, Simal-Gandara J. 2022.
680   *Analytical Metabolomics and Applications in Health, Environmental and Food Science.*
681   Critical Reviews in Analytical Chemistry 52:712-734
682   http://dx.doi.org/10.1080/10408347.2020.1823811.
683 King C, Lanaspa MA, Jensen T, Tolan DR, Sanchez-Lozada LG, Johnson RJ. 2018. *Uric Acid*
684   *as a Cause of the Metabolic Syndrome.* Contributions to Nephrology 192:88-102
685   http://dx.doi.org/10.1159/000484283.
686 Zou F, Zhao X, Wang F. 2021. *A review on the fruit components affecting uric acid level and*
687   *their underlying mechanisms.* Journal of Food Biochemistry 45:e13911
688   http://dx.doi.org/10.1111/jfbc.13911.

689   Maiuolo J, Oppedisano F, Gratteri S, Muscoli C, Mollace V. 2016. *Regulation of uric acid*
690   *metabolism and excretion.* International Journal of Cardiology 213:8-14
691   http://dx.doi.org/10.1016/j.ijcard.2015.08.109.
692   Braga TT, Foresto-Neto O, Camara NOS. 2020. *The role of uric acid in inflammasome-*
693   *mediated kidney injury.* Current Opinion in Nephrology and Hypertension 29:423-431
694   http://dx.doi.org/10.1097/MNH.0000000000000619.
695   Otani N, Ouchi M, Kudo H, Tsuruoka S, Hisatome I, Anzai N. 2020. *Recent approaches to gout*
696   *drug discovery: an update.* Expert Opinion on Drug Discovery 15:943-954
697   http://dx.doi.org/10.1080/17460441.2020.1755251.
698   Alghamdi YS, Soliman MM, Nassan MA. 2020. *Impact of Lesinurad and allopurinol on*
699   *experimental Hyperuricemia in mice: biochemical, molecular and Immunohistochemical*
700   *study.* BMC Pharmacol Toxicol 21:10 http://dx.doi.org/10.1186/s40360-020-0386-7.
701   Sun HL, Wu YW, Bian HG, Yang H, Wang H, Meng XM, Jin J. 2021. *Function of Uric Acid*
702   *Transporters and Their Inhibitors in Hyperuricaemia.* Frontiers in Pharmacology
703   12:667753 http://dx.doi.org/10.3389/fphar.2021.667753.
704   Rousseau LS, Pare G, Lachhab A, Naccache PH, Marceau F, Tessier P, Pelletier M, Fernandes
705   M. 2017. *S100A9 potentiates the activation of neutrophils by the etiological agent of*
706   *gout, monosodium urate crystals.* Journal of Leukocyte Biology 102:805-813
707   http://dx.doi.org/10.1189/jlb.3MA0117-020R.
708   Hemshekhar M, Piyadasa H, Mostafa D, Chow LNY, Halayko AJ, Mookherjee N. 2020.
709   *Cathelicidin and Calprotectin Are Disparately Altered in Murine Models of Inflammatory*
710   *Arthritis and Airway Inflammation.* Frontiers in Immunology 11:1932
711   http://dx.doi.org/10.3389/fimmu.2020.01932.
712   Pillinger MH Mandell BF. 2020. *Therapeutic approaches in the treatment of gout.* Seminars in
713   Arthritis and Rheumatism 50:S24-S30
714   http://dx.doi.org/10.1016/j.semarthrit.2020.04.010.
715   Wu M, Tian Y, Wang Q, Guo C. 2020. *Gout: a disease involved with complicated*
716   *immunoinflammatory responses: a narrative review.* Clinical Rheumatology 39:2849-
717   2859 http://dx.doi.org/10.1007/s10067-020-05090-8.
718   Wu J, Luo Y, Jiang Q, Li S, Huang W, Xiang L, Liu D, Hu Y, Wang P, Lu X, Zhang G, Wang F,
719   Meng X. 2019a. *Coptisine from Coptis chinensis blocks NLRP3 inflammasome activation*
720   *by inhibiting caspase-1.* Pharmacological Research 147:104348
721   http://dx.doi.org/10.1016/j.phrs.2019.104348.
722   Alessandra Piccini SC, Sara Tassi, Denise Lasiglié, Gianluca Fossati, Anna Rubartelli. 2008.
723   *ATP is released by monocytes stimulated with pathogen-sensing receptor ligands and*
724   *induces IL-1beta and IL-18 secretion in an autocrine way.* Proceedings of the National
725   Academy of Sciences of the United States of America Biological Sciences 105:8067-72
726   http://dx.doi.org/10.1073/pnas.0709684105.
727   Marinho Y, Marques-da-Silva C, Santana PT, Chaves MM, Tamura AS, Rangel TP, Gomes
728   ESIV, Guimaraes MZP, Coutinho-Silva R. 2020. *MSU Crystals induce sterile IL-1beta*
729   *secretion via P2X7 receptor activation and HMGB1 release.* Biochimica et Biophysica
730   Acta General Subjects 1864:129461 http://dx.doi.org/10.1016/j.bbagen.2019.129461.
731   Szekanecz Z, Szamosi S, Kovacs GE, Kocsis E, Benko S. 2019. *The NLRP3 inflammasome -*
732   *interleukin 1 pathway as a therapeutic target in gout.* Archives of Biochemistry and
733   Biophysics 670:82-93 http://dx.doi.org/10.1016/j.abb.2019.01.031.
734   Luo SF, Chin CY, Ho LJ, Tseng WY, Kuo CF, Lai JH. 2020. *Monosodium urate crystals induced*
735   *ICAM-1 expression and cell-cell adhesion in renal mesangial cells: Implications for the*
736   *pathogenesis of gouty nephropathy.* Journal of Microbiology, Immunology and Infection
737   53:23-32 http://dx.doi.org/10.1016/j.jmii.2017.12.004.

738   Fei YU, Chen ZY, Wei LI, Zhang ZX, Yao H. 2012. *Study of Differentially Expressed Serun*
739   *Proteins in Primary Hyperuricemia in Uyghur by 2-DE and MALDI-TOF-MS.*
740   Biotechnology 22:52-55
741   Fei YU, Zhao JM, Chen ZY, Wei LI. 2013. *Study of differentially expressed serum proteins in*
742   *primary hyperuricemia by two-dimentional gel electrophoresis and matrix-assisted laser*
743   *desorption/ionization time-of-flight tandem mass spectrometry.* Chinese Journal of
744   Prevention Control of Chronic Diseases 21:143-145
745   Chiang SL, Ou TT, Wu YJ, Tu HP, Lu CY, Huang CM, Kuo TM, Wang TN, Chou CH, Ko YC.
746   2014. *Increased level of MSU crystal-bound protein apolipoprotein A-I in acute gouty*
747   *arthritis.* Scandinavian Journal of Rheumatology 43:498-502
748   http://dx.doi.org/10.3109/03009742.2014.903994.
749   Georgila K, Vyrla D, Drakos E. 2019. *Apolipoprotein A-I (ApoA-I), Immunity, Inflammation and*
750   *Cancer.* Cancers 11: http://dx.doi.org/10.3390/cancers11081097.
751   Gordon SM Remaley AT. 2017. *High density lipoproteins are modulators of protease activity:*
752   *Implications in inflammation, complement activation, and atherothrombosis.*
753   Atherosclerosis 259:104-113 http://dx.doi.org/10.1016/j.atherosclerosis.2016.11.015.
754   van der Vorst EPC. 2020. *High-Density Lipoproteins and Apolipoprotein A1.* Sub-Cellular
755   Biochemistry 94:399-420 http://dx.doi.org/10.1007/978-3-030-41769-7_16.
756   Wu BJ, Sun Y, Ong KL, Li Y, Tang S, Barter PJ, Rye KA. 2019b. *Apolipoprotein A-I Protects*
757   *Against Pregnancy-Induced Insulin Resistance in Rats.* Arteriosclerosis, Thrombosis,
758   and Vascular Biology 39:1160-1171 http://dx.doi.org/10.1161/ATVBAHA.118.312282.
759   Li J, Wang W, Han L, Feng M, Lu H, Yang L, Hu X, Shi S, Jiang S, Wang Q, Ye L. 2017. *Human*
760   *apolipoprotein A-I exerts a prophylactic effect on high-fat diet-induced atherosclerosis*
761   *via inflammation inhibition in a rabbit model.* Acta Biochimica et Biophysica Sinica
762   49:149-158 http://dx.doi.org/10.1093/abbs/gmw128.
763   Iqbal AJ, Barrett TJ, Taylor L, McNeill E, Manmadhan A, Recio C, Carmineri A, Brodermann
764   MH, White GE, Cooper D, DiDonato JA, Zamanian-Daryoush M, Hazen SL, Channon
765   KM, Greaves DR, Fisher EA. 2016. *Acute exposure to apolipoprotein A1 inhibits*
766   *macrophage chemotaxis in vitro and monocyte recruitment in vivo.* Elife 5:
767   http://dx.doi.org/10.7554/eLife.15190.
768   Gordon SM, McKenzie B, Kemeh G, Sampson M, Perl S, Young NS, Fessler MB, Remaley AT.
769   2015. *Rosuvastatin Alters the Proteome of High Density Lipoproteins: Generation of*
770   *alpha-1-antitrypsin Enriched Particles with Anti-inflammatory Properties.* Molecular and
771   Cellular Proteomics 14:3247-57 http://dx.doi.org/10.1074/mcp.M115.054031.
772   Lee CW, Cheng TM, Lin CP, Pan JP. 2013. *Plasma haptoglobin concentrations are elevated in*
773   *patients with coronary artery disease.* PloS One 8:e76817
774   http://dx.doi.org/10.1371/journal.pone.0076817.
775   Asleh R, Levy AP, Levy NS, Asleh A, Goldenstein H, Segol I, Gulati R, Lerman LO, Lerman A.
776   2019. *Haptoglobin Phenotype Is Associated With High-Density Lipoprotein-Bound*
777   *Hemoglobin Content and Coronary Endothelial Dysfunction in Patients With Mild*
778   *Nonobstructive Coronary Artery Disease.* Arteriosclerosis, Thrombosis, and Vascular
779   Biology 39:774-786 http://dx.doi.org/10.1161/ATVBAHA.118.312232.
780   Shen L, Dong H, Guo Z, Zhai G, Zhang K. 2021a. *Identification of Abnormal Proteins in Plasma*
781   *from Gout Patients by LC-MS/MS.* Separations 8:
782   http://dx.doi.org/10.3390/separations8060085.
783   Chen G, Cheng J, Yu H, Huang X, Bao H, Qin L, Wang L, Song Y, Liu X, Peng A. 2021a.
784   *Quantitative proteomics by iTRAQ-PRM based reveals the new characterization for gout.*
785   Proteome Science 19:12 http://dx.doi.org/10.1186/s12953-021-00180-0.
786   McMorrow JP, Crean D, Gogarty M, Smyth A, Connolly M, Cummins E, Veale D, Fearon U, Tak
787   PP, Fitzgerald O, Murphy EP. 2013. *Tumor necrosis factor inhibition modulates*
788   *thrombospondin-1 expression in human inflammatory joint disease through altered*

789   *NR4A2 activity.* American Journal of Pathology 183:1243-1257
790   http://dx.doi.org/10.1016/j.ajpath.2013.06.029.
791 Xiaofang Tang YM, Yingjun Luo , Kiran Sriram , Zhijie Qi , Feng-Mao Lin , Yusu Gu , Chih-
792   Hung Lai , Chien-Yi Hsu , Kirk L Peterson , Kendall Van Keuren-Jensen , Patrick T
793   Fueger , Gene W Yeo , Rama Natarajan , Sheng Zhong , Zhen Bouman Chen 2020.
794   *Suppression of Endothelial AGO1 Promotes Adipose Tissue Browning and Improves*
795   *Metabolic Dysfunction.* Circulation 142:365-379
796   http://dx.doi.org/10.1161/CIRCULATIONAHA.119.041231.
797 Oncul S Afshar-Kharghan V. 2020. *The interaction between the complement system and*
798   *hemostatic factors.* Current Opinion in Hematology 27:341-352
799   http://dx.doi.org/10.1097/MOH.0000000000000605.
800 Khameneh HJ, Ho AW, Laudisi F, Derks H, Kandasamy M, Sivasankar B, Teng GG, Mortellaro
801   A. 2017. *C5a Regulates IL-1beta Production and Leukocyte Recruitment in a Murine*
802   *Model of Monosodium Urate Crystal-Induced Peritonitis.* Frontiers in Pharmacology 8:10
803   http://dx.doi.org/10.3389/fphar.2017.00010.
804 Yu S, Wang D, Huang L, Zhang Y, Luo R, Adah D, Tang Y, Zhao K, Lu B. 2019. *The*
805   *complement receptor C5aR2 promotes protein kinase R expression and contributes to*
806   *NLRP3 inflammasome activation and HMGB1 release from macrophages.* Journal of
807   Biological Chemistry 294:8384-8394 http://dx.doi.org/10.1074/jbc.RA118.006508.
808 Huo S, Wang H, Yan M, Xu P, Song T, Li C, Tian R, Chen X, Bao K, Xie Y, Xu P, Zhu W, Liu F,
809   Mao W, Shao C. 2021. *Urinary Proteomic Characteristics of Hyperuricemia and Their*
810   *Possible Links with the Occurrence of Its Concomitant Diseases.* ACS Omega 6:9500-
811   9508 http://dx.doi.org/10.1021/acsomega.0c06229.
812 Norata GD, Tsimikas S, Pirillo A, Catapano AL. 2015. *Apolipoprotein C-III: From*
813   *Pathophysiology to Pharmacology.* Trends in Pharmacological Sciences 36:675-687
814   http://dx.doi.org/10.1016/j.tips.2015.07.001.
815 Zewinger S, Reiser J, Jankowski V, Alansary D, Hahm E, Triem S, Klug M, Schunk SJ, Schmit
816   D, Kramann R, Korbel C, Ampofo E, Laschke MW, Selejan SR, Paschen A, Herter T,
817   Schuster S, Silbernagel G, Sester M, Sester U, Assmann G, Bals R, Kostner G, Jahnen-
818   Dechent W, Menger MD, Rohrer L, Marz W, Bohm M, Jankowski J, Kopf M, Latz E,
819   Niemeyer BA, Fliser D, Laufs U, Speer T. 2020. *Apolipoprotein C3 induces inflammation*
820   *and organ damage by alternative inflammasome activation.* Nature Immunology 21:30-
821   41 http://dx.doi.org/10.1038/s41590-019-0548-1.
822 Rassart E, Desmarais F, Najyb O, Bergeron KF, Mounier C. 2020. *Apolipoprotein D.* Gene
823   756:144874 http://dx.doi.org/10.1016/j.gene.2020.144874.
824 Desmarais F, Bergeron KF, Lacaille M, Lemieux I, Bergeron J, Biron S, Rassart E, Joanisse
825   DR, Mauriege P, Mounier C. 2018. *High ApoD protein level in the round ligament fat*
826   *depot of severely obese women is associated with an improved inflammatory profile.*
827   Endocrine 61:248-257 http://dx.doi.org/10.1007/s12020-018-1621-5.
828 Tafere GG, Wondafrash DZ, Zewdie KA, Assefa BT, Ayza MA. 2020. *Plasma Adipsin as a*
829   *Biomarker and Its Implication in Type 2 Diabetes Mellitus.* Diabetes, Metabolic
830   Syndrome and Obesity 13:1855-1861 http://dx.doi.org/10.2147/DMSO.S253967.
831 Gomez-Banoy N, Guseh JS, Li G, Rubio-Navarro A, Chen T, Poirier B, Putzel G, Rosselot C,
832   Pabon MA, Camporez JP, Bhambhani V, Hwang SJ, Yao C, Perry RJ, Mukherjee S,
833   Larson MG, Levy D, Dow LE, Shulman GI, Dephoure N, Garcia-Ocana A, Hao M,
834   Spiegelman BM, Ho JE, Lo JC. 2019. *Adipsin preserves beta cells in diabetic mice and*
835   *associates with protection from type 2 diabetes in humans.* Nature Medicine 25:1739-
836   1747 http://dx.doi.org/10.1038/s41591-019-0610-4.
837 Li Y, Zou W, Brestoff JR, Rohatgi N, Wu X, Atkinson JP, Harris CA, Teitelbaum SL. 2019. *Fat-*
838   *Produced Adipsin Regulates Inflammatory Arthritis.* Cell Reports 27:2809-2816 e3
839   http://dx.doi.org/10.1016/j.celrep.2019.05.032.

840 Meza CA, La Favor JD, Kim DH, Hickner RC. 2019. *Endothelial Dysfunction: Is There a*
841   *Hyperglycemia-Induced Imbalance of NOX and NOS?* International Journal of Molecular
842   Sciences 20: http://dx.doi.org/10.3390/ijms20153775.
843 Ko J, Kang HJ, Kim DA, Kim MJ, Ryu ES, Lee S, Ryu JH, Roncal C, Johnson RJ, Kang DH.
844   2019. *Uric acid induced the phenotype transition of vascular endothelial cells via*
845   *induction of oxidative stress and glycocalyx shedding.* FASEB Journal 33:13334-13345
846   http://dx.doi.org/10.1096/fj.201901148R.
847 Yaribeygi H, Sathyapalan T, Atkin SL, Sahebkar A. 2020. *Molecular Mechanisms Linking*
848   *Oxidative Stress and Diabetes Mellitus.* Oxidative Medicine and Cellular Longevity
849   2020:8609213 http://dx.doi.org/10.1155/2020/8609213.
850 Liu JH, Ma QH, Xu Y, Chen X, Pan CW. 2020. *Metabolic Syndrome and 5-Year Incident*
851   *Hyperuricemia Among Older Chinese Adults: A Community-Based Cohort Study.*
852   Diabetes, Metabolic Syndrome and Obesity 13:4191-4200
853   http://dx.doi.org/10.2147/DMSO.S278542.
854 Zhang DM, Jiao RQ, Kong LD. 2017. *High Dietary Fructose: Direct or Indirect Dangerous*
855   *Factors Disturbing Tissue and Organ Functions.* Nutrients 9:
856   http://dx.doi.org/10.3390/nu9040335.
857 Chiu CW, Chen HM, Wu TT, Shih YC, Huang KK, Tsai YF, Hsu YL, Chen SF. 2015. *Differential*
858   *proteomics of monosodium urate crystals-induced inflammatory response in dissected*
859   *murine air pouch membranes by iTRAQ technology.* Proteomics 15:3338-48
860   http://dx.doi.org/10.1002/pmic.201400626.
861 Huang Y, Liu Y, Huang Q, Sun S, Ji Z, Huang L, Li Z, Huang X, Deng W, Li T. 2022. *TMT-*
862   *Based Quantitative Proteomics Analysis of Synovial Fluid-Derived Exosomes in*
863   *Inflammatory Arthritis.* Frontiers in Immunology 13:800902
864   http://dx.doi.org/10.3389/fimmu.2022.800902.
865 Qiu K, Zeng T, Liao Y, Min J, Zhang N, Peng M, Kong W, Chen LL. 2021. *Identification of*
866   *Inflammation-Related Biomarker Pro-ADM for Male Patients With Gout by*
867   *Comprehensive Analysis.* Frontiers in Immunology 12:798719
868   http://dx.doi.org/10.3389/fimmu.2021.798719.
869 Sreejit G, Flynn MC, Patil M, Krishnamurthy P, Murphy AJ, Nagareddy PR. 2020. *S100 family*
870   *proteins in inflammation and beyond.* Advances in Clinical Chemistry 98:173-231
871   http://dx.doi.org/10.1016/bs.acc.2020.02.006.
872 G H Gudmundsson BA. 1999. *Neutrophil antibacterial peptides, multifunctional effector*
873   *molecules in the mammalian immune system.* Journal of Immunological Methods
874   232:45-54 http://dx.doi.org/10.1016/s0022-1759(99)00152-0.
875 Kang MJ, Jang AR, Park JY, Ahn JH, Lee TS, Kim DY, Jung DH, Song EJ, Hong JJ, Park JH.
876   2020. *Cathelicidin-related Antimicrobial Peptide Contributes to Host Immune Responses*
877   *Against Pulmonary Infection with Acinetobacter baumannii in Mice.* Immune Network
878   20:e25 http://dx.doi.org/10.4110/in.2020.20.e25.
879 Choi MC, Jo J, Lee M, Park J, Park Y. 2021. *Intra-Articular Administration of Cramp into Mouse*
880   *Knee Joint Exacerbates Experimental Osteoarthritis Progression.* International Journal of
881   Molecular Sciences 22: http://dx.doi.org/10.3390/ijms22073429.
882 Jou YC, Fang CY, Chen SY, Chen FH, Cheng MC, Shen CH, Liao LW, Tsai YS. 2012.
883   *Proteomic study of renal uric acid stone.* Urology 80:260-6
884   http://dx.doi.org/10.1016/j.urology.2012.02.019.
885 Kaneko K, Kobayashi R, Yasuda M, Izumi Y, Yamanobe T, Shimizu T. 2012. *Comparison of*
886   *matrix proteins in different types of urinary stone by proteomic analysis using liquid*
887   *chromatography-tandem mass spectrometry.* International Journal of Urology 19:765-72
888   http://dx.doi.org/10.1111/j.1442-2042.2012.03005.x.
889 Gao Z, Zuo M, Han F, Yuan X, Sun M, Li X, Liu R, Jiang W, Zhang L, Chang B, Yang J. 2019.
890   *Renal impairment markers in type 2 diabetes patients with different types of*

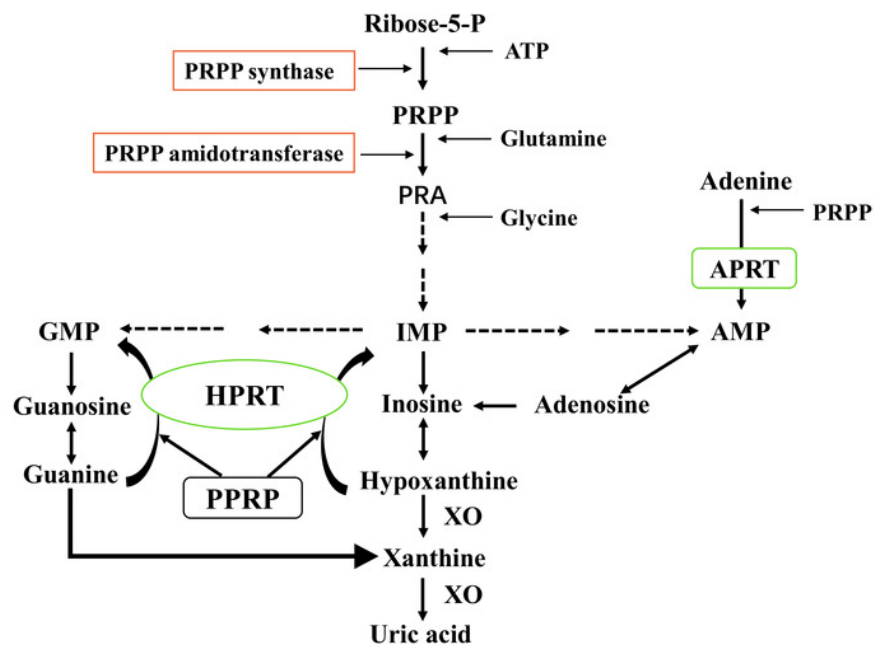
891   *hyperuricemia.* Journal of Diabetes Investigation 10:118-123
892   http://dx.doi.org/10.1111/jdi.12850.
893 Kaneko K, Iwamoto H, Yasuda M, Inazawa K, Yamaoka N, Fukuuchi T, Tamura Y, Uchida S,
894   Mawatari K, Nakagomi K, Yamada Y, Fujimori S. 2014. *Proteomic analysis to examine*
895   *the role of matrix proteins in a gouty tophus from a patient with recurrent gout.*
896   Nucleosides Nucleotides Nucleic Acids 33:199-207
897   http://dx.doi.org/10.1080/15257770.2014.880476.
898 E Ortiz-Bravo MSS, H R Schumacher Jr. 1993. *Changes in the proteins coating monosodium*
899   *urate crystals during active and subsiding inflammation. Immunogold studies of synovial*
900   *fluid from patients with gout and of fluid obtained using the rat subcutaneous air pouch*
901   *model.* Arthritis and Rheumatism 36:1274-1285
902   http://dx.doi.org/10.1002/art.1780360912.
903 E Ortiz-Bravo MSS, H R Schumacher Jr. 1993. *Changes in the proteins coating monosodium*
904   *urate crystals during active and subsiding inflammation. Immunogold studies of synovial*
905   *fluid from patients with gout and of fluid obtained using the rat subcutaneous air pouch*
906   *model.* Arthritis Rheum 36:1274-85 http://dx.doi.org/10.1002/art.1780360912.
907 Renaudin F, Sarda S, Campillo-Gimenez L, Severac C, Leger T, Charvillat C, Rey C, Liote F,
908   Camadro JM, Ea HK, Combes C. 2019. *Adsorption of Proteins on m-CPPD and Urate*
909   *Crystals Inhibits Crystal-induced Cell Responses: Study on Albumin-crystal Interaction.*
910   Journal of Functional Biomaterials 10: http://dx.doi.org/10.3390/jfb10020018.
911 Kaneko K, Kabeya M, Kondo H, Fukuuchi T, Yamaoka N, Yasuda M, Yamaguchi S. 2018.
912   *Proteomic analysis of a urinary stone with two layers composed of calcium oxalate*
913   *monohydrate and uric acid.* Nucleosides Nucleotides Nucleic Acids 37:717-723
914   http://dx.doi.org/10.1080/15257770.2018.1478095.
915 Han B, Huang H, Li Z, Gong M, Shi W, Zhu C, Gu Z, Zou Z. 2016. *Therapeutic Effects of*
916   *Chinese Medicine Herb Pair, Huzhang and Guizhi, on Monosodium Urate Crystal-*
917   *Induced Gouty Arthritis in Rats Revealed by Anti-Inflammatory Assessments and NMR-*
918   *Based Metabonomics.* Evidence-Based Complementary and Alternative Medicine
919   2016:9398435 http://dx.doi.org/10.1155/2016/9398435.
920 Wei Z, Xu C, Liu S, Song F, Liu Z, Qu X. 2018. *Metabonomics study of the effects of traditional*
921   *Chinese medicine formula Ermiaowan on hyperuricemic rats.* Journal of Separation
922   Science 41:560-570 http://dx.doi.org/10.1002/jssc.201700985.
923 Mahbub MH, Yamaguchi N, Takahashi H, Hase R, Amano H, Kobayashi-Miura M, Kanda H,
924   Fujita Y, Yamamoto H, Yamamoto M, Kikuchi S, Ikeda A, Kageyama N, Nakamura M,
925   Ishimaru Y, Sunagawa H, Tanabe T. 2017. *Alteration in plasma free amino acid levels*
926   *and its association with gout.* Environmental Health and Preventive Medicine 22:7
927   http://dx.doi.org/10.1186/s12199-017-0609-8.
928 Huang Y, Xiao M, Ou J, Lv Q, Wei Q, Chen Z, Wu J, Tu L, Jiang Y, Zhang X, Qi J, Qiu M, Cao
929   S, Gu J. 2020. *Identification of the urine and serum metabolomics signature of gout.*
930   Rheumatology (Oxford, England) 59:2960-2969
931   http://dx.doi.org/10.1093/rheumatology/keaa018.
932 Wang F, Sun L, Zong G, Gao X, Zhang H, Xiong Q, Huo S, Niu Z, Sun Q, Zeng R, Lin X. 2020a.
933   *Associations of Amino Acid and Acylcarnitine Profiles With Incident Hyperuricemia in*
934   *Middle-Aged and Older Chinese Individuals.* Arthritis Care & Research 72:1305-1314
935   http://dx.doi.org/10.1002/acr.24013.
936 van Milgen J. 2021. *The role of energy, serine, glycine, and 1-carbon units in the cost of*
937   *nitrogen excretion in mammals and birds.* Animal 15:100213
938   http://dx.doi.org/10.1016/j.animal.2021.100213.
939 Zhang Y, Zhang H, Chang D, Guo F, Pan H, Yang Y. 2018. *Metabolomics approach by (1)H*
940   *NMR spectroscopy of serum reveals progression axes for asymptomatic hyperuricemia*

941   *and gout.* Arthritis Research & Therapy 20:111 http://dx.doi.org/10.1186/s13075-018-
942   1600-5.
943 Luo Y, Wang L, Liu XY, Chen X, Song YX, Li XH, Jiang C, Peng A, Liu JY. 2018. *Plasma*
944   *profiling of amino acids distinguishes acute gout from asymptomatic hyperuricemia.*
945   Amino Acids 50:1539-1548 http://dx.doi.org/10.1007/s00726-018-2627-2.
946 Shen X, Wang C, Liang N, Liu Z, Li X, Zhu ZJ, Merriman TR, Dalbeth N, Terkeltaub R, Li C, Yin
947   H. 2021b. *Serum Metabolomics Identifies Dysregulated Pathways and Potential*
948   *Metabolic Biomarkers for Hyperuricemia and Gout.* Arthritis & Rheumatology 73:1738-
949   1748 http://dx.doi.org/10.1002/art.41733.
950 Li Q, Wei S, Wu D, Wen C, Zhou J. 2018. *Urinary Metabolomics Study of Patients with Gout*
951   *Using Gas Chromatography-Mass Spectrometry.* Biomed Research International
952   2018:3461572 http://dx.doi.org/10.1155/2018/3461572.
953 Bian M, Lin Z, Wang Y, Zhang B, Li G, Wang H. 2018. *Bioinformatic and Metabolomic Analysis*
954   *Reveal Intervention Effects of Chicory in a Quail Model of Hyperuricemia.* Evidence-
955   Based Complementary and Alternative Medicine 2018:5730385
956   http://dx.doi.org/10.1155/2018/5730385.
957 Lai CH, Huang RJ, Wong JK, Chang SW, Chung AH, Chi YC, Yu YC, Lee SD, Ting H. 2021.
958   *Confounded by obesity and modulated by urinary uric acid excretion, sleep-disordered*
959   *breathing indirectly relates to hyperuricaemia in males: A structural equation model.*
960   Journal of Sleep Research 30:e13108 http://dx.doi.org/10.1111/jsr.13108.
961 Rivera-Paredez B, Macias-Kauffer L, Fernandez-Lopez JC, Villalobos-Comparan M, Martinez-
962   Aguilar MM, de la Cruz-Montoya A, Ramirez-Salazar EG, Villamil-Ramirez H, Quiterio M,
963   Ramirez-Palacios P, Romero-Hidalgo S, Villarreal-Molina MT, Denova-Gutierrez E,
964   Flores YN, Canizales-Quinteros S, Salmeron J, Velazquez-Cruz R. 2019. *Influence of*
965   *Genetic and Non-Genetic Risk Factors for Serum Uric Acid Levels and Hyperuricemia in*
966   *Mexicans.* Nutrients 11: http://dx.doi.org/10.3390/nu11061336.
967 Zhang T, Gan S, Ye M, Meng G, Zhang Q, Liu L, Wu H, Gu Y, Zhang S, Wang Y, Wang X, Sun
968   S, Wang X, Zhou M, Jiao H, Jia Q, Song K, Wu Y, Niu K. 2021. *Association between*
969   *consumption of ultra-processed foods and hyperuricemia: TCLSIH prospective cohort*
970   *study.* Nutrition Metabolism and Cardiovascular Diseases 31:1993-2003
971   http://dx.doi.org/10.1016/j.numecd.2021.04.001.
972 Liu Y, Sun X, Di D, Quan J, Zhang J, Yang X. 2011. *A metabolic profiling analysis of*
973   *symptomatic gout in human serum and urine using high performance liquid*
974   *chromatography-diode array detector technique.* Clinica Chimica Acta 412:2132-40
975   http://dx.doi.org/10.1016/j.cca.2011.07.031.
976 Zhong Z, Huang Y, Huang Q, Zheng S, Huang Z, Deng W, Li T. 2021. *Serum metabolic profiling*
977   *analysis of gout patients based on UPLC-Q-TOF/MS.* Clinica Chimica Acta 515:52-60
978   http://dx.doi.org/10.1016/j.cca.2020.12.028.
979 Kanemitsu T, Tsurudome Y, Kusunose N, Oda M, Matsunaga N, Koyanagi S, Ohdo S. 2017.
980   *Periodic variation in bile acids controls circadian changes in uric acid via regulation of*
981   *xanthine oxidase by the orphan nuclear receptor PPARalpha.* Journal of Biological
982   Chemistry 292:21397-21406 http://dx.doi.org/10.1074/jbc.M117.791285.
983 Wang M, Chen L, Liu D, Chen H, Tang DD, Zhao YY. 2017. *Metabolomics highlights*
984   *pharmacological bioactivity and biochemical mechanism of traditional Chinese medicine.*
985   Chemico-Biological Interactions 273:133-141
986   http://dx.doi.org/10.1016/j.cbi.2017.06.011.
987 Wu G-S, Li H-K, Zhang W-D. 2019. *Metabolomics and its application in the treatment of*
988   *coronary heart disease with traditional Chinese medicine.* Chinese Journal of Natural
989   Medicines 17:321-330 http://dx.doi.org/10.1016/s1875-5364(19)30037-8.
990 Wang Y, Bi C, Pang W, Liu Y, Yuan Y, Zhao H, Zhang T, Zhao Y, Li Y. 2019. *Plasma Metabolic*
991   *Profiling Analysis of Gout Party on Acute Gout Arthritis Rats Based on UHPLC-Q-*

992   *TOF/MS Combined with Multivariate Statistical Analysis.* International Journal of
993   Molecular Sciences 20: http://dx.doi.org/10.3390/ijms20225753.
994 Chen R, Wang Q, Li Z, Wang D, Yang S, Feng Y. 2021b. *Studies on effect of Tongfengxiaofang*
995   *in HUM model mice using a UPLC‑ESI‑Q‑TOF/MS metabolomic approach.*
996   Biomedical Chromatography 35: http://dx.doi.org/10.1002/bmc.5118.
997 Shan B, Chen T, Huang B, Liu Y, Chen J. 2021. *Untargeted metabolomics reveal the*
998   *therapeutic effects of Ermiao wan categorized formulas on rats with hyperuricemia.*
999   Journal of Ethnopharmacology 281: http://dx.doi.org/10.1016/j.jep.2021.114545.
1000 Tabassum R Ripatti S. 2021. *Integrating lipidomics and genomics: emerging tools to understand*
1001   *cardiovascular diseases.* Cellular and Molecular Life Sciences 78:2565-2584
1002   http://dx.doi.org/10.1007/s00018-020-03715-4.
1003 Wang R, Li B, Lam SM, Shui G. 2020b. *Integration of lipidomics and metabolomics for in-depth*
1004   *understanding of cellular mechanism and disease progression.* Journal of Genetics and
1005   Genomics 47:69-83 http://dx.doi.org/10.1016/j.jgg.2019.11.009.
1006 Tan Y, Wang L, Gao J, Ma J, Yu H, Zhang Y, Wang T, Han L. 2020. *Multiomics Integrative*
1007   *Analysis for Discovering the Potential Mechanism of Dioscin against Hyperuricemia*
1008   *Mice.* Journal of Proteome Research 20:645-660
1009   http://dx.doi.org/10.1021/acs.jproteome.0c00584.
1010 Dalbeth N, Gosling AL, Gaffo A, Abhishek A. 2021. *Gout.* The Lancet 397:1843-1855
1011   http://dx.doi.org/10.1016/s0140-6736(21)00569-9.
1012 Pisaniello HL, Fisher MC, Farquhar H, Vargas-Santos AB, Hill CL, Stamp LK, Gaffo AL. 2021.
1013   *Efficacy and safety of gout flare prophylaxis and therapy use in people with chronic*
1014   *kidney disease: a Gout, Hyperuricemia and Crystal-Associated Disease Network (G-*
1015   *CAN)-initiated literature review.* Arthritis Research & Therapy 23:130
1016   http://dx.doi.org/10.1186/s13075-021-02416-y.
1017 Tian X, Permentier HP, Bischoff R. 2021. *Chemical isotope labeling for quantitative proteomics.*
1018   Mass Spectrometry Reviews http://dx.doi.org/10.1002/mas.21709.
1019 Bodofsky S, Merriman TR, Thomas TJ, Schlesinger N. 2020. *Advances in our understanding of*
1020   *gout as an auto-inflammatory disease.* Seminars in Arthritis and Rheumatism 50:1089-
1021   1100 http://dx.doi.org/10.1016/j.semarthrit.2020.06.015.
1022

Figure 1

De novo synthesis and salvage pathway of purine metabolism

The purine metabolism shows the first step of de novo purine synthesis mediated by the enzyme 5'-phosphoribosyl-1-pyrophosphate (PRPP) synthase, and the second step by PRPP amidotransferase. PRPP from adenosine-triphosphate (ATP) and ribose-5-phosphate is catalyzed by PRPP synthase. PRPP amidotransferase converts PRPP to ribosylamine-5-phosphate (PRA). This is then catalyzed by a series of enzymes to produce hypoxanthine nucleotides (IMP), which in turn produce adenosine monophosphate (AMP) and guanosine monophosphate (GMP). Xanthine oxidase (XO) converts hypoxanthine to xanthine and xanthine to uric acid. Meanwhile, the salvage pathway mediated by hypoxanthine phosphorybosyltransferase (HPRT) and adenine phosphorybosyltransferase (APRT). The enzyme HPRT salvages hypoxanthine to IMP and guanine to GMP. In a similar salvage pathway, APRT converts adenine to AMP.

Overview of proteomics studies in hyperuricemia and gout

We performed a detailed analysis of proteomic studies of hyperuricemia and gout including sample types, methods used, sample sizes, protein involved pathways, and key proteins.

Table 1 Overview of proteomics studies in hyperuricemia and gout

Reference	Sample	Technique	Study size	participation way	proteins	Key proteins
(Fei et al., 2012)	Serum	2-DE and MALDI-TOF-MS	Hyperuricemia:15 Control group:15	—	Complement 3, complement 4, haptoglobin, and apolipoprotein A1.	Complement 3, complement 4, haptoglobin, apolipoprotein A1.
(Fei et al., 2013)	Serum	2-DE and MALDI-TOF-MS	Hyperuricemia:15 Control group:15	—	Complement 3, haptoglobin, α1 -antitrypsin, and apolipoprotein L1.	Complement 3, haptoglobin, α1-antitrypsin, and apolipoprotein L1.
(Chiang et al., 2014)	Plasma	2-DE and MS	Male acute gouty patients:80 Male controls:129.	—	Fibrinogen gamma, transthyretin, pre-serum amyloid P component, C-reactive protein, and apolipoprotein A-I.	apolipoprotein A-I.
	Synovial fluid	LC/MS/MS	Male acute gouty patients:24	—	Fibrinogen, ORM1, ORM 2, angiotensinogen, alpha 2-macroglobulin, apolipoprotein A-I, apolipoprotein D and apolipoprotein H.	Apolipoprotein A-I
(Shen et al., 2021)	Plasma	HPLC-MS/MS	Gout patients:8; Gout patients combined with renal injury:8	These proteins participated in innate immune response, platelet degranulation, protein hydrolysis, and the classical activation pathway of complement.	In the normal control group and gout group: 32 proteins; In the gout and gout with renal injury group: 10 proteins; Correlated with SUA: GSN, S100A8, S100A9, ORM2, and ANXA1.	GSN
(Chen et al., 2021)	Plasma	iTRAQ-PRM	AG: 8; RG: 7; AHU: 7; Healthy controls: 8	The complement and coagulation cascades is one of the main functional pathways.	Eleven differentially expressed proteins such as Histone H2A, Histone H2B, Thrombospondin-1, Myeloperoxidase, complement C2, complement component C8 beta chain, ORM1, Inter-alpha-trypsin inhibitor heavy chain H4, Carbonic anhydrase 1, Serum albumin and Multimerin-1 were identified.	Histone H2A, Histone H2B and Thrombospondin-1.
(Huo et al., 2021)	Urine	Label-free LC−MS/MS	HUA:26; Healthy controls: 25	Including the processes for insulin receptor recycling and lipid metabolism.	In HUA samples: 11 proteins were found decreased and 2 proteins were found increased.	V-type proton ATPase subunit B kidney isoform, Complex factor D, apolipoprotein C3.

Table 1 Overview of proteomics studies in hyperuricemia and gout

Reference	Sample	Technique	Study size	participation way	proteins	Key proteins
(Chiu et al., 2015)	Pouch membranes	Labeling and offline 2D LC-MS/MS	—	The identified proteins were involved in an alternative complement pathway and tricarboxylic acid cycle.	Alternative complement pathway: complement component 3, complement component 8, complement component C9, complement component factor I, complement D, complement factor B, clusterin, integrin αM, and integrin β-2. Related to NALP3 inflammasome: CRAMP and S100A9.	Two upregulated proteins, S100A9 and CRAMP.
(Huang et al., 2022)	Synovial Fluid-Derived Exosomes	TMT labeled LC-MS/MS	Gout:42; Rheumatoid arthritis:30; Axial spondyloarthritis:10; Osteoarthritis :18	These proteins were significantly involved in complement and coagulation cascades, acute-phase response and citrate cycle in gout.	In gout: Sixty-nine differentially expressed proteins were found. Twenty-five proteins were found highly expressed in gout uniquely, lysozyme C, ORM1, lactotransferrin, S100A9, and myeloperoxidase.	—
(Kaneko et al., 2012)	Urinary stone	LC-MS/MS and SDS-PAGE	Gout or hyperuricemia patients:15; Urinary stones:17	some of these proteins should play an essential role in the early stage of CaOx stone formation.	In calcium oxalate monohydrate or calcium oxalate dihydrate stones, osteopontin, uromodulin, albumin, protein Z, prothrombin, protein S, hemoglobin and histone H4 were identified. In uric acid stones, uromodulin, albumin, hemoglobin, calgranulins and immunoglobin G fragments were detected. In CaOx stones and uric acid stones: Albumin, hemoglobin, uromodulin, calgranulin A and B, and histone H4 were detected.	In CaOx stones: osteopontin, prothrombin, protein Z and protein S were often identified. In UA stones: IgG fragment was detected characteristically.
(Kaneko et al., 2014)	Gouty tophus	Micro-area X-ray diffractometer and LC-MS/MS	Patients:1; Tophus:1	Many proteins relevant to inflammation and host defense were identified.	Proteomic analysis identified 134 proteins from the tophus as matrix proteins.	Immunoglobulins

Table 1 Overview of proteomics studies in hyperuricemia and gout						
Reference	Sample	Technique	Study size	participation way	proteins	Key proteins
(Kaneko et al., 2018)	A urinary stone with two layers	Micro-area X-ray diffractometer and LC-MS/MS	Patients:1; Urinary stone:1	14 of 51 were functionally categorized as cell adhesion and cytoskeleton proteins and 7 as metabolism-related proteins. There were 5 defense proteins and 5 plasma proteins.	In COM part: 48 proteins (non-muscle myosin heavy chain, uromodulin, coagulation factor II, protein S, protein Z, apolipoprotein E, and others.); In UA part: 7 proteins (S100A8, hemoglobin, albumin, and others); In the interface: 4 proteins (dermcidin, coagulation factor II, keratin 1, and osteopontin isoform OPN-b).	Proteins relevant to cell adhesion, self-defense, and plasma commonly play a major role in the generation of both COM and UA part.

5   Notes.

6   Abbreviations: 2-DE, two-dimensional gel electrophoresis; MALDI-TOF-MS, matrix-assisted laser desorption ionization-time of flight mass

7   spectrometry; MS, mass spectrometry; LC, liquid chromatography; ORM1, alpha-1-acid glycoprotein 1; ORM2, alpha-1-acid glycoprotein 2; HPLC, high-

8   performance liquid chromatography; SUA, serum uric acid; GSN, inflammation factors gelsolin; S100A8, protein S100-A8; 100A9, protein S100-A9;

9   ANXA1, annexin A1; iTRAQ-PRM, isobaric tag for relative and absolute quantification- parallel reaction monitoring; AG, acute gout; RG, remission of

10   gout; HUA, asymptomatic hyperuricemia; NALP3, NACHT, LRR, and PYD domains-containing protein 3; CRAMP, catherine-related antimicrobial

11   peptide; TMT, tandem mass tag; SDS-PAGE, sodium dodecyl sulfate-polyacrylamide gel electrophoresis; CaOx, calcium oxalate; UA, uric acid; COM,

12   calcium oxalate.

Figure 2

Some metabolic disorders pathways in hyperuricemia and gout

The network is based on the metabolic pathways and biomarkers mainly affected by hyperuricemia and gout. Metabolic processes that cause abnormalities include the tricarboxylic acid (TCA) cycle, purine metabolism, pyrimidine metabolism, glycerophospholipid metabolism, and gut microbial metabolism. Also, various amino acid metabolism disorders are common, such as tryptophan metabolism, ornithine and arginine biosynthesis in the urea cycle. Key intermediates of the TCA cycle such as citric acid, 2-ketoglutarate and succinic acid metabolites build up the entire metabolic network, making the TCA cycle an intertwining point of metabolic pathways.