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Exploration of the main active components and pharmacological mechanism of *Yerba Mate* based on network pharmacology

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Abstract

Introduction: *Yerba mate* is widely consumed in South American countries and is gaining popularity around the world. Long-term consumption of *yerba mate* has been proven to have health-care functions and therapeutic effects on many diseases; however, its underlying mechanism has not been clearly elucidated. In this research, we explored the pharmacological mechanism of *yerba mate* through a network pharmacological approach.
Material and methods: The bioactive components of *yerba mate* were screened from published literature and the Traditional Chinese Medicine System Pharmacology Database (TCMSP), and the targets and related diseases were retrieved by TCMSP. Furthermore, the component-target-disease network and protein-protein interaction (PPI) network were constructed, and combined with gene ontology (GO) functional analysis and Kyoto Encyclopaedia of Genes and Genomes (KEGG) pathway enrichment analysis to explore the pharmacological mechanism of *yerba mate*.
Results: As a result, 16 bioactive components of *yerba mate* were identified, which acted on 229 targets in total. *Yerba mate* can be used to treat 305 diseases, such as breast cancer, asthma, Alzheimer's disease, osteoarthritis, diabetes mellitus, atherosclerosis, and obesity. Protein kinase B (AKT1), signal transducer and activator of transcription 3 (STAT3), mitogen-activated protein kinase 1 (MAPK1), transcription factor AP-1 (JUN), cellular tumour antigen (p53) TP53, tumour necrosis factor (TNF), transcription factor p65 (RELA), interleukin-6 (IL6), amyloid-beta precursor protein (APP), and vascular endothelial growth factor A (VEGFA) were identified as the key targets of yerba mate playing pharmacological roles. The signalling pathways identified by KEGG pathway enrichment analysis that were most closely related to the effects of *yerba mate* included pathways in cancer, fluid shear stress and atherosclerosis, and human cytomegalovirus infection.
Conclusion: The results of our study preliminarily verify the basic pharmacological action and possible mechanism of *yerba mate* and provide a reference for the further development of its medicinal value. **(Endokrynol Pol 2022; 73 (4): 725–735)**

Key words: *yerba mate*; pharmacological mechanism; biotargets; network pharmacology

Introduction

Yerba mate is brewed from the ground, dried leaves and twigs of the *Ilex paraguariensis* A. St.-Hilaire tree, widely consumed as an infusion in South American countries [1]. Now *yerba mate* has gained worldwide popularity because of its aroma, taste, stimulation, and nutritional values [2]. It is considered that *yerba mate* may have beneficial effects on human health, including inhibiting lipogenesis and body fat accumulation [3], preventing type 2 diabetes mellitus (T2DM) [4], reducing cardiovascular risk in hypercholesterolaemic patients [5], having antioxidant [6] and anticancer [7] properties, and can be used as a new health care medicine. All the above effects can be attributed to the fact that *yerba mate* contains a variety of bioactive phytochemicals. Due to the complex interaction between multiple components and targets of *yerba mate,* it is difficult to explore the bioactive components, potential targets, and pharmacological mechanism of action of *yerba mate* by conventional methods.

With the development of bioinformatics, network pharmacol-

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ogy provides a new strategy to find the potential active components and targets of drugs, and it can reveal the relationship between drugs and diseases from a comprehensive and systematic perspective [8]. Therefore, based on the principles and methods of network pharmacology, this study aims to comprehensively explore the main bioactive components and pharmacological mechanism of *yerba mate*. We first identified the bioactive components related to *yerba mate* and matched them to relevant targets and diseases. Then we constructed a visual component-target network, component-target-disease network, and protein-protein interaction (PPI) network. In addition, we performed Kyoto Encyclopaedia of Genes and Genomes (KEGG) pathway enrichment analysis and gene ontology (GO) functional analysis on the putative targets of *yerba mate*.

Material and methods

Collection of chemical components and screening of bioactive components

The chemical components of *yerba mate* were collected from the published literature in Web of Science before 6 November 2020 and then imported into the Traditional Chinese Medicine System Pharmacology Database (TCMSP, http://lsp.nwu.edu.cn/tcmsp.php) separately [50]. The bioactive components were obtained by adjusting the ADME (absorption, distribution, metabolism, and excretion) parameters including oral bioavailability (OB) and drug-likeness (DL). Oral bioavailability reflects the percentage of the oral dose of the drug entering the systemic circulation [51]. Drug-likeness refers to the similarity of a component to a known drug [52]. In this study, the bioactive components were screed according to the threshold values of OB ≥ 30% and DL ≥ 0.18 [53].

Identification of putative targets and diseases

The screened bioactive components were imported into the TCMSP database to search for the corresponding targets. Then the target information was further checked using the UniProt database (https://www.uniprot.org/) [54] and DrugBank database (https://go.drugbank.com/) [55]. Subsequently, the target names obtained were uploaded to the UniProt database and were uniformly standardized into UniProtKB, with the species limited to "Homo sapiens". All putative targets were entered into the TCMSP database separately to further search for diseases associated with them.

PPI analysis

Protein-protein interaction analysis was performed with the STRING11.0 platform (https://string-db.org/) [56] to identify the interaction relationship between the targets. The minimum required interaction threshold was set with "highest confidence" (> 0.9) and the disconnected nodes were hidden. Data from the PPI analysis were then used for topological analysis to determine key genes.

Enrichment analysis

To further elucidate the potential pharmacological mechanism of *yerba mate*, we utilized the Metascape database (https://metascape.org/) [57] to conduct KEGG pathway enrichment analysis and GO functional analysis, with the screening criteria of $p < 0.01$. Based on the *p* value, major biological processes and metabolic pathways were selected to visualize using the EHBIO Gene Technology Platform (http://www.ehbio.com/ImageGP/) and bioinformatics online tools (http://www.bioinformatics.com.cn/).

Network construction

In this step, four integrated networks were constructed to show the relationships more intuitively between components, targets, diseases, and signalling pathways, including (1) component-target network, (2) component-target-disease network, (3) PPI network, and (4) target-pathway network. All the above networks were visualized by Cytoscape3.7.2 (https://cytoscape.org/) [58], and Cytoscape's plug-in, Network Analyzer, was then used to analyse the topological properties of these networks. The "degree" indicates the number of nodes that directly interact with a node in the network, reflecting the local connectivity and importance of a protein [59]. The targets with degree > twofold the median in the PPI network were considered to be the key genes [60].

Results

Component-target network

The flow of this network pharmacological study is illustrated in Figure 1. In total, 54 chemical components were collected from the published literature of Web of Science, and 7 of them met the screening criteria of OB ≥ 30% and DL ≥ 0.18 after being imported into the TCMSP database. Although some chemical components did not meet the criteria, there was a great deal of research on their beneficial effects on people. Therefore, nine bioactive components were supplemented, including caffeine, chlorogenic acid, oleanolic acid, rutin, theobromine, ursolic acid, 3,4-dicaffeoylquinic acid, 3,5-dicaffeoylquinic acid, and 4,5-dicaffeoylquinic acid (Tab. 1). A total of 229 targets were identified for these bioactive components in the TCMSP database. To further understand the interrelationships between these bioactive components and their corresponding targets from a holistic perspective, a component-target network was constructed as shown in Figure 1. Through the topology analysis of the network, we found that the degree of quercetin (flavonoids, degree = 148) was the highest, followed by kaempferol (flavonoids, degree = 59), luteolin (flavonoids, degree = 54), caffeine (alkaloids, degree = 52), ursolic acid (terpenoids, degree = 51), and so on. It can be seen from Table 1 that the good biological activity of *yerba mate* was mainly related to polyphenols, methylxanthine alkaloids, terpenoids, and flavonoids, and the components with more targets might play a critical role in the pharmacological function of *yerba mate*.

Component-target-disease network

Following TCMSP database-based analyses, the diseases corresponding to the targets of *yerba mate* were found to speculate the diseases that might be treated by *yerba mate*. In this step, 305 diseases were predicted, and these diseases came from 89 targets. The remaining targets had no corresponding diseases in the component-target-disease network, so it could be speculated that there are still undiscovered pathways of action in the targets of *yerba mate*. The 305 diseases included cancer, cardiovascular diseases (CVD), nervous system diseases, inflammatory

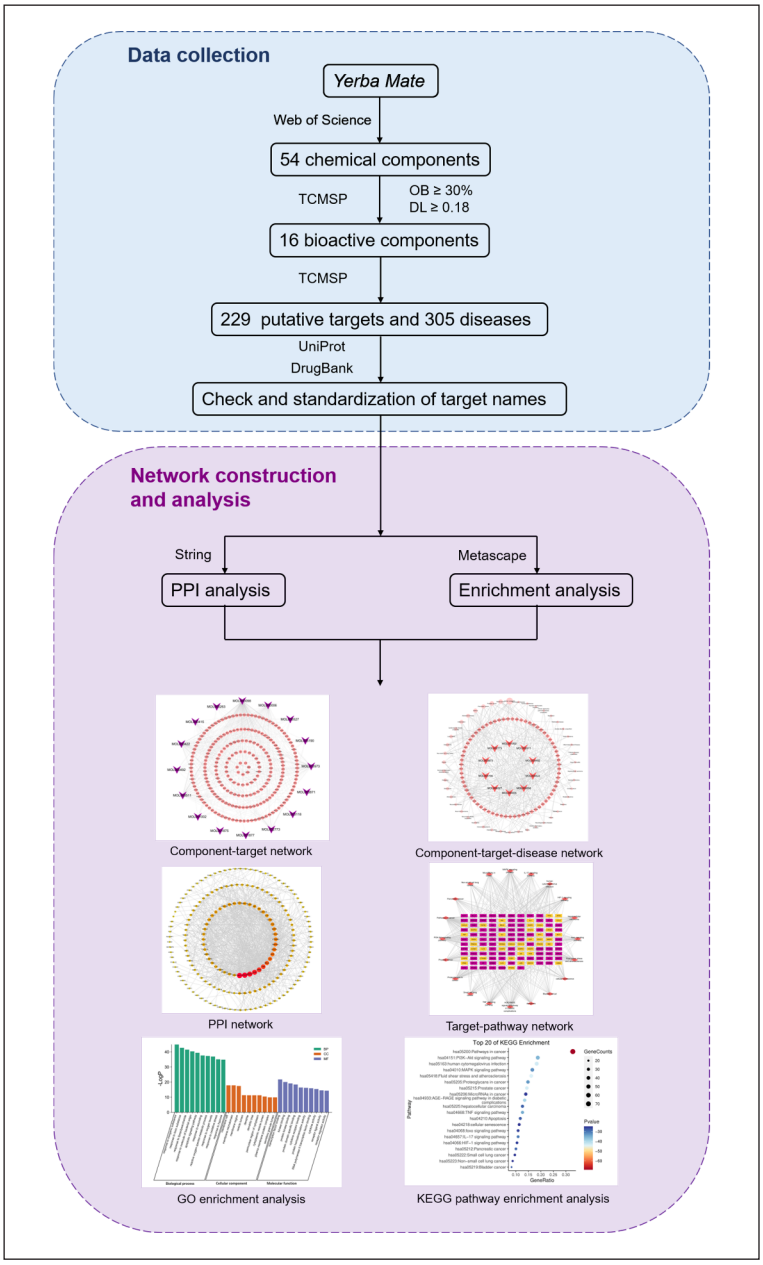

Figure 1. *Flowchart of investigating the pharmacological mechanism of yerba mate. PPI — protein-protein interaction*

Table 1. *Bioactive components of yerba mate*

Mol ID	Molecule Name	Molecular formula	OB (%)	DL	Network degree
MOL000098	Quercetin	$C_{15}H_{10}O_7$	46.43	0.28	148
MOL000422	Kaempferol	$C_{15}H_{10}O_6$	41.88	0.24	59
MOL000006	Luteolin	$C_{15}H_{10}O_6$	36.16	0.25	54
MOL003973	Caffeine	$C_8H_{10}N_4O_2$	89.46	0.08	52
MOL000511	Ursolic acid	$C_{30}H_{48}O_3$	16.77	0.75	51
MOL002773	Beta-carotene	$C_{40}H_{56}$	37.18	0.58	21
MOL000415	Rutin	$C_{27}H_{30}O_{16}$	3.20	0.68	20
MOL001002	Ellagic acid	$C_{14}H_6O_8$	43.06	0.43	10
MOL000492	Catechin	$C_{15}H_{14}O_6$	54.83	0.24	10

Table 1. *Bioactive components of yerba mate*

Mol ID	Molecule Name	Molecular formula	OB (%)	DL	Network degree
MOL006527	Theobromine	$C_7H_8N_4O_2$	69.29	0.06	9
MOL005190	Eriodictyol	$C_{15}H_{12}O_6$	71.79	0.24	8
MOL000263	Oleanolic acid	$C_{30}H_{48}O_3$	29.02	0.76	6
MOL003871	Chlorogenic acid	$C_{16}H_{18}O_9$	13.61	0.31	1
MOL003118	4,5-Dicaffeoylquinic acid	$C_{25}H_{24}O_{12}$	1.78	0.69	1
MOL001875	3,5-Dicaffeoylquinic acid	$C_{25}H_{24}O_{12}$	1.79	0.69	1
MOL001877	3,4-Dicaffeoylquinic acid	$C_{25}H_{24}O_{12}$	1.78	0.69	1

OB — oral bioavailability; DL — drug-likeness

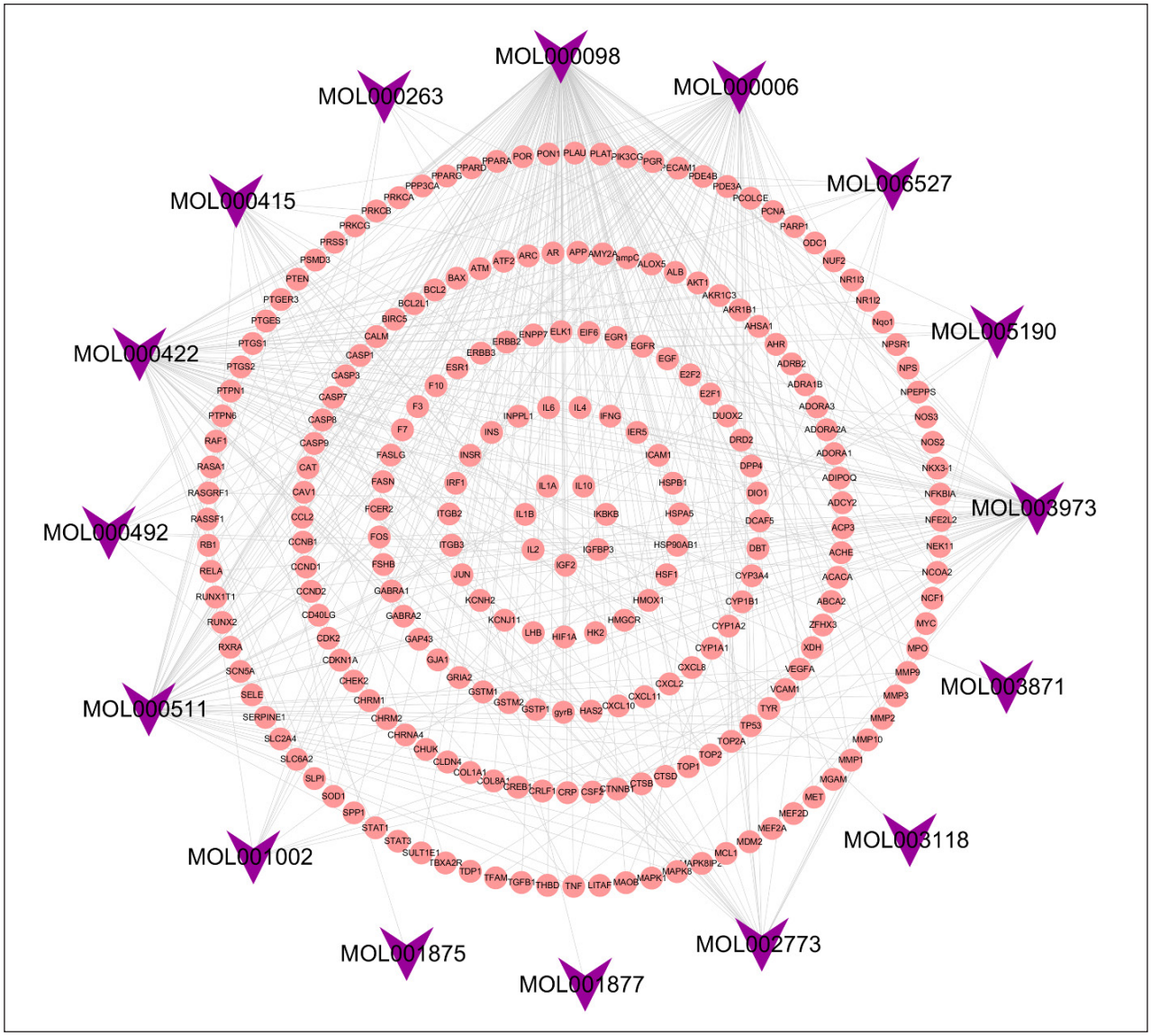

Figure 2. *Component-target network of yerba mate. Purple V-shape nodes represent the bioactive components of yerba mate, and pink circle nodes represent the corresponding targets of the components (for the List of abbreviations, see the Supplementary File)*

diseases, and so on. To more clearly show the relationship between the bioactive components, targets, and predicted diseases, we selected highly correlated bioactive components, targets, and diseases to construct a network, which contained 125 nodes (10 component nodes, 69 target nodes, and 46 disease nodes) (Fig. 2). In the

network, only disease nodes whose degree was higher than or equal to the mean value of 3 were displayed. The results of topological analysis of the network indicated that some diseases, such as breast cancer, asthma, Alzheimer's disease, osteoarthritis, diabetes mellitus, atherosclerosis, and obesity were associated with more targets, suggesting that *yerba mate* might have greater therapeutic potential for these diseases.

PPI network

The PPI network was constructed to explore the interactions between candidate targets and their roles in complex diseases (Fig. 3). After hiding the disconnected nodes, the network contained 195 nodes and 945 edges. According to the degree value from high to low, 195 nodes were arranged into three concentric circles. The innermost circle consisted of 44 key genes, which were targets with degree > twofold the median, including protein kinase B (AKT1) (degree = 45), signal transducer and activator of transcription 3 (STAT3) (degree = 44), mitogen-activated protein kinase 1 (MAPK1) (degree = 42), transcription factor AP-1 (JUN) (degree = 41), cellular tumour antigen p53 (TP53) (degree = 38), tumour necrosis factor (TNF) (degree = 36), transcription factor p65 (RELA) (degree = 32), interleukin 6 (IL6) (degree = 30), amyloid-beta precursor protein (APP) (degree = 29), vascular endothelial growth factor A (VEGFA) (degree = 28), etc. These key genes were of great significance in the treatment of *yerba mate* for various diseases.

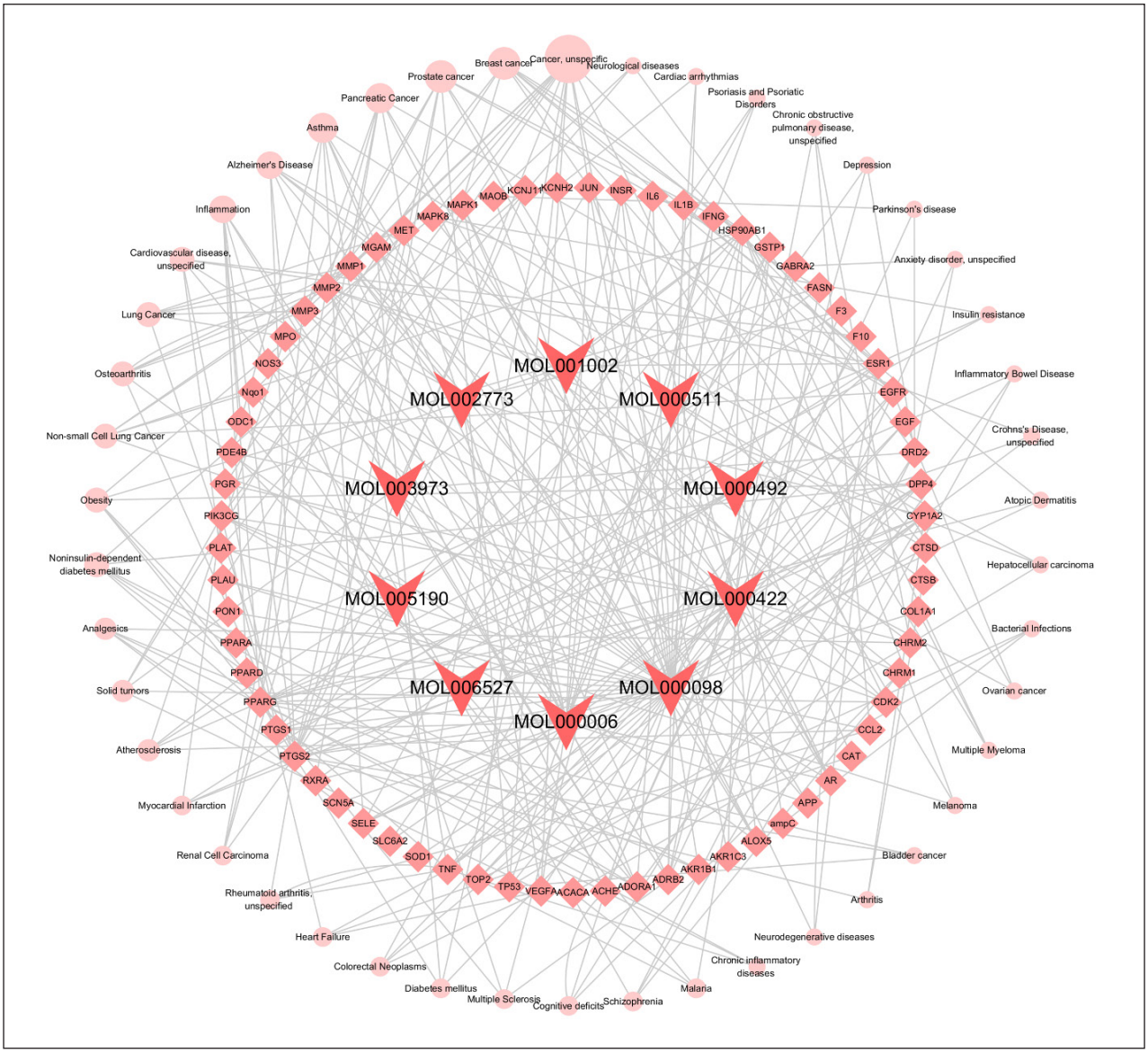

Figure 3. *Component-target-disease network. V-shaped nodes represent the bioactive components of yerba mate, the diamond nodes represent targets, and circle nodes represent diseases. The size of disease nodes is in descending order of degree values (for the List of abbreviations, see the Supplementary File)*

GO and KEGG pathway enrichment analysis

Enrichment analysis can be used to preliminarily understand the biological processes and cell components in which genes are enriched, and to predict the metabolic pathways significantly changed under experimental conditions, which is particularly important in the study of the pharmacological mechanism of drugs. GO enrichment analysis generated 2532 biological processes, 133 cellular components, and 208 molecular functions. Biological processes were mainly involved in positive regulation of nitrogen compound metabolic process and regulation of cell death; cellular components were mainly involved in membrane-enclosed lumen, extracellular space, and cytoplasm; and molecular functions were mainly involved in regulation of molecular function. As far as pathway enrichment analysis was concerned, the targets were enriched in 202 pathways, including pathways in cancer (hsa05200), fluid shear stress and atherosclerosis (hsa05418), human cytomegalovirus infection (hsa05163), prostate cancer (hsa05215), AGE-RAGE signalling pathway in diabetic complications (hsa04933), PI3K-Akt signalling pathway (hsa04151), TNF signalling pathway (hsa04668), proteoglycans in cancer (hsa05205), MAPK signalling pathway (hsa04010), IL-17 signalling pathway (hsa04657), and so on. The results of above enrichment analysis were arranged in ascending order according to Log *p* value. We selected the top 10 items of biological processes, cell components, and molecular functions, respectively, and the top 20 KEGG pathways, which are shown in Figure 4. After

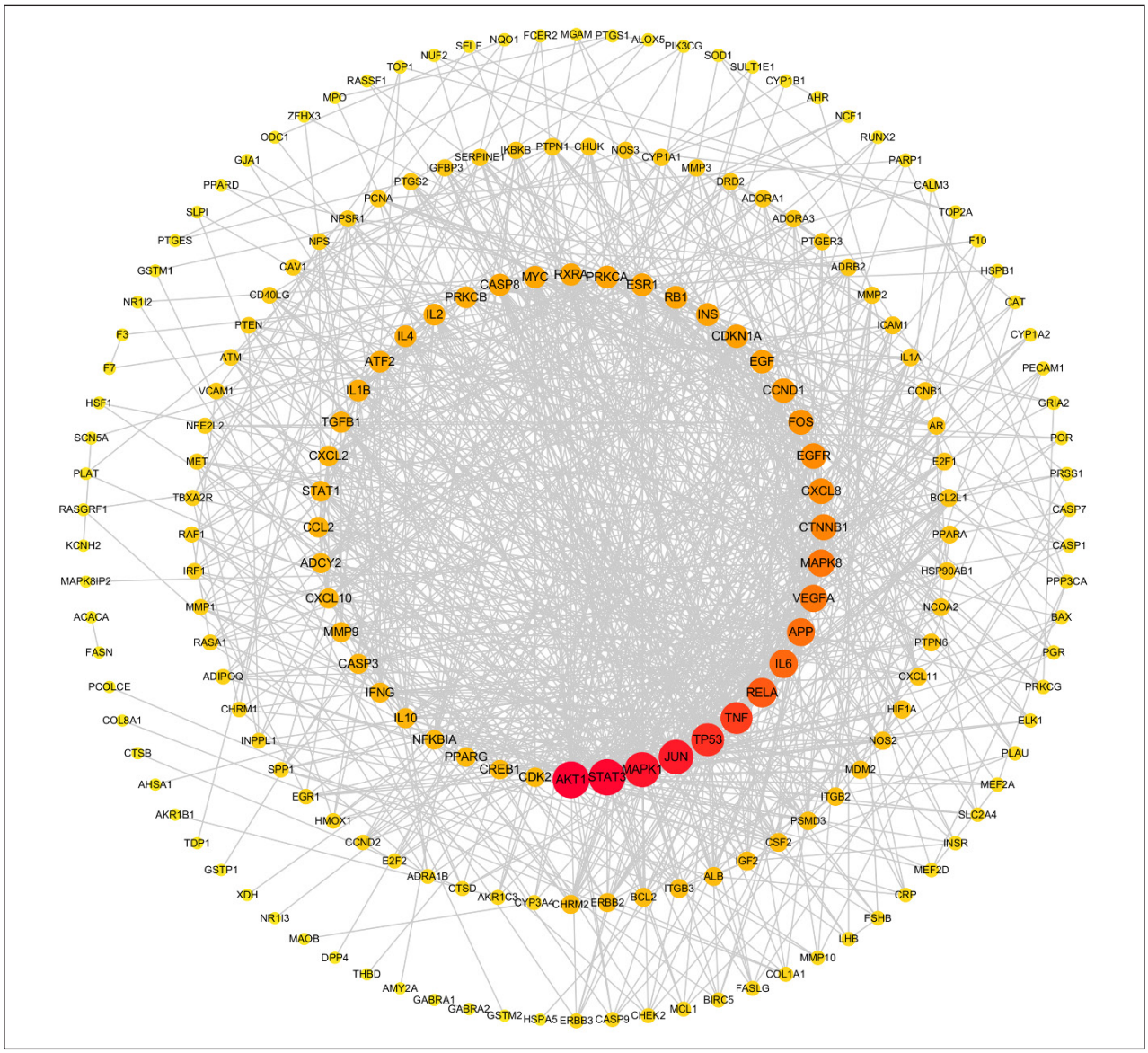

Figure 4. *Protein-protein interaction (PPI) network of the putative targets of yerba mate. The node sizes change from large to small and the colours change from red to yellow in descending order according to the degree values of nodes. The circle at the centre of the network is composed of key genes (for the List of abbreviations, see the Supplementary File)*

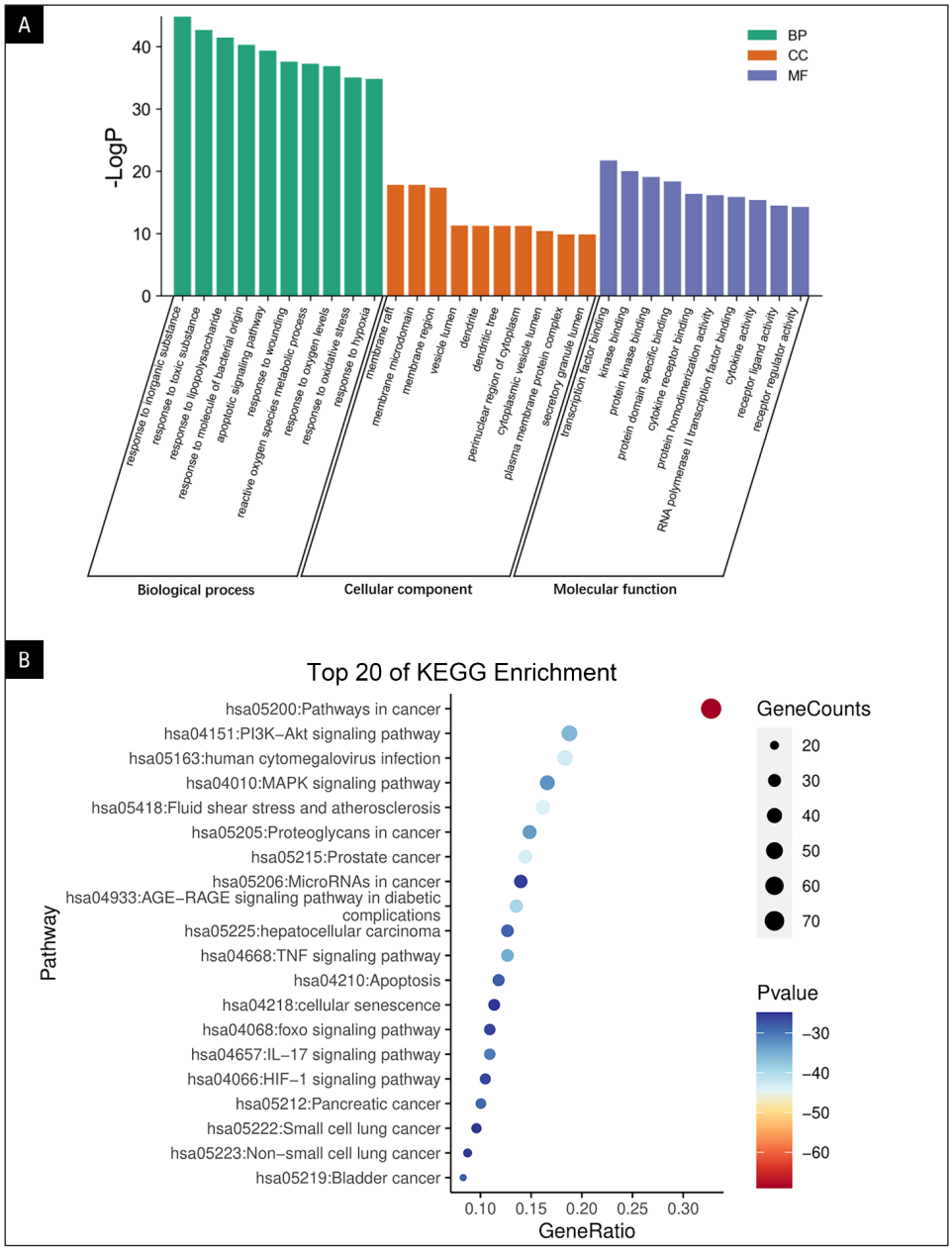

Figure 5. *Enrichment analysis of putative targets.* **A**. *Gene ontology (GO) enrichment analysis. The top 10 items of biological process, cellular component and molecular function are shown in the figure.* **B.** *Kyoto Encyclopaedia of Genes and Genomes (KEGG) pathway enrichment analysis. The size of the bubbles represents the gene counts enriched in the pathway, and the colour of the bubbles from red to blue indicates that the absolute value of the p value changes in descending order*

sorting out the pathways and the targets enriched in these pathways, we constructed a target-pathway network to show the specific relationship between targets and pathways (Fig. 5).

Discussion

Visualization analysis of the network model is one of the main methods of network pharmacology, which can predict the pharmacological mechanisms of drugs by interpreting the complex biological network relationships among drugs, active components, targets, and diseases [9]. In the present research, we constructed a component-target network and component-target-disease network based on TCMSP database. By constructing a component-target network, it could be seen that *yerba mate* exerted its biological activity mainly through polyphenols, methylxanthine alkaloids, terpenoids, and flavonoids. Among them, polyphenols, such as chlorogenic acid and ellagic acid, and methylxanthine alkaloids, represented by caffeine and theobromine, are the main sources of the antioxidant property of *yerba mate*

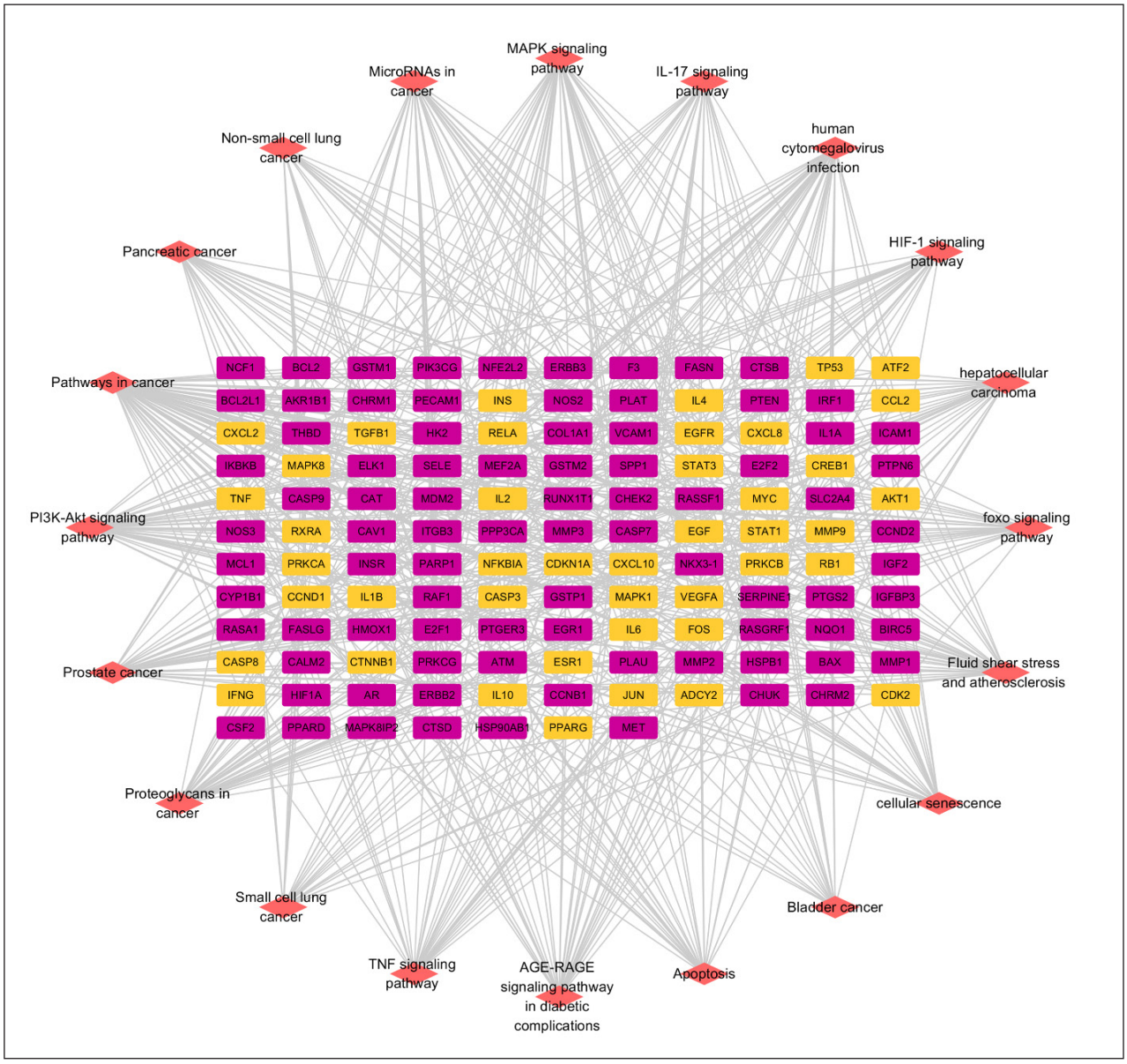

Figure 6. *Target-pathway network. The diamond nodes represent the top 20 pathways in the Kyoto Encyclopaedia of Genes and Genomes (KEGG) pathway enrichment analysis. The rectangular nodes represent the targets enriched in the top 20 pathways, and the key genes are highlighted in yellow (for the List of abbreviations, see the Supplementary File)*

[1, 10]. Regular consumption of *yerba mate* tea, which provides the body with abundant relatively stable antioxidants, may help prevent oxidative stress-related diseases [11]. Oleanolic acid and ursolic acid are typical pentacyclic triterpenes with preventive and anti-cancer activities, which are regarded as lead compounds in the development of new anti-cancer drugs [12–14]. Similarly, flavonoids, including rutin, quercetin, kaempferol, etc., also have antioxidant, anti-inflammatory, antiviral, and other pharmacological effects [15–18].

As revealed in the topology data of the component-target-disease network, *yerba mate* had its main regulatory effects on breast cancer, asthma, Alzheimer's disease, osteoarthritis, diabetes mellitus, atherosclerosis, and obesity, which was consistent with previous studies. For instance, a case-control study conducted by Ronco et al. confirmed the protective effects of *yerba mate*, high intakes of which reduced the risk of breast cancer in Uruguayan women [19]. Cross-sectional studies indicated that people who regularly drank high excess free fructose beverages could increase their likelihood of developing asthma and (in young people) were more likely to develop osteoarthritis [20–22]. An in vitro study demonstrated that phenolics (mainly chlorogenic acids and caffeic acid) in *yerba mate* could exert a potent antiglycation effect and inhibit the formation of advanced glycation end products, which might explain to some extent how excessive consumption of free

fructose could lead to asthma and osteoarthritis, and had guiding significance for treatment [23]. *Yerba mate* was perceived as a promising agent for the prevention and treatment of diabetes; many animal experiments demonstrated that *yerba mate* could not only improve metabolic disturbances and insulin resistance, but also help reduce obesity [24, 25]. In addition, *yerba mate* can also prevent atherosclerosis through multiple ways, which effectively protect against cardiovascular and cerebrovascular diseases. *Yerba mate* treatment has been shown to reduce the production of reactive oxygen species and enhanced endothelial nitric oxide synthase concentration [26, 27]. This result indicated that *yerba mate* could regulate blood fat and endothelial function, thereby inhibiting the occurrence of atherosclerosis. On the other hand, Balsan et al. [28] compared the effects of *yerba mate* and green tea on paraoxonase-1 (PON-1) levels in obese and dyslipidaemic patients, and found that the consumption of *yerba mate* could increase the level of PON-1, an enzyme with antioxidant effects in serum, and increased cholesterol in high-density lipoprotein, once again confirming the protective effect of *yerba mate* on atherosclerotic diseases.

Based on the results of topological analysis of the PPI network, AKT1, STAT3, MAPK1, JUN, TP53, TNF, RELA, IL6, APP, and VEGFA were identified as the key genes of *yerba mate* playing pharmacological roles. Some of the key genes have been representatively validated in extensive studies. For example, AKT1 is a proto-oncogene whose amplification is present in most cancers [29]. It not only affects the proliferation and apoptosis of tumour cells, but also plays a significant role in tumour invasion and metastasis [30]. Prior studies have demonstrated that the overexpression and activation of AKT1 has an important influence on the occurrence of various malignant tumours such as breast cancer, gastric cancer, lung cancer, and head and neck squamous cell carcinoma [30–33]. In recent years, targeted therapy of inhibiting AKT1 has become a focus of anti-cancer research. STAT3 is an important signalling protein that is engaged in regulating cell proliferation, survival, and apoptosis under normal physiological conditions [34]. When overexpressed or overactivated, STAT3 can lead to human diseases, such as cancer and inflammatory diseases. Strikingly, STAT3 is overexpressed and/or constitutively activated in approximately 70% of human solid and haematological tumours [35]. In inflammatory diseases, pro-inflammatory cytokines such as IL-6, IL-10, TNF-α, and other cytokines are effective drivers of STAT3 activation, thus affecting the occurrence and pathological process of inflammatory diseases. Research showed that phosphorylated STAT3 was significantly increased in chondrocytes using IL-6 to simulate the inflammatory conditions that initiated osteoarthritis, and STAT3 signalling was involved in the production and activation of IL-6-induced extracellular matrix degrading enzymes, resulting in cartilage degradation [36]. STAT3 binds to the promoter, encodes proteins according to intracellular inflammatory genes, and then releases them to the outside of the cell, thereby amplifying the inflammatory response and playing an important role in airway inflammation and remodelling in asthma [37]. VEGFA, a member of the VEGF family, has attracted extensive attention due to its role in regulating angiogenesis in homeostasis and disease processes. According to a recent study by Saukkonen et al., serum VEGFA levels were significantly higher in prediabetic and diabetic individuals than in individuals with normal blood glucose [38]. Similarly, a cross-sectional study by Sun et al. revealed that serum VEGF levels were elevated in patients with impaired glucose tolerance and in those with T2DM, and increased serum VEGFA levels were positively correlated with insulin resistance [39]. Obesity and dyslipidaemia are both risk factors for atherosclerosis. Studies have found that VEGFA levels are increased in overweight and obese people, and anti-VEGFA antibodies can inhibit fat formation while inhibiting angiogenesis, suggesting that VEGFA is beneficial to regulate fat production and control obesity [40, 41]. Furthermore, higher circulating VEGFA levels may supplement atherosclerotic ischaemia by promoting neovascularization in target organs, thereby contributing to reducing the risk of CVD [42].

Combined with the key genes obtained in the PPI network and the subsequent GO enrichment analysis results, we speculated that the bioactive components of *yerba mate* may affect the cytological components of membrane-enclosed lumen, extracellular space, and cytoplasm by regulating these key genes, thereby regulating molecular functions and ultimately influencing the disease processes. Among the signalling pathways presented in KEGG pathway enrichment, the three prominent pathways with top significance were pathways in cancer, fluid shear stress, and atherosclerosis, human cytomegalovirus infection. Pathways in cancer are ranked first among KEGG pathways and are considered to be specifically related to tumours [43]. This suggests again that *yerba mate* may have positive therapeutic implications for tumours, and genes in these pathways may be potential targets for *yerba mate* in the treatment of tumours. Fluid shear stress and atherosclerosis pathway is strongly associated with oxidative stress, inflammatory response, atherosclerosis, and cell migration. The action pattern of the fluid shear stress and atherosclerosis pathway is similar to that of biological signals. Shear stress acts on the mechanoreceptors on endothelial cells and activates a series of related signalling pathways, resulting in vascular deformation in areas of unstable blood

flow or low shear stress [44]. Human cytomegalovirus is by far the most complex human herpesvirus, which establishes a lifetime incubation period in the host after primary infection [45]. A growing body of data suggests that life-long persistent infection of human cytomegalovirus is a potential and critical risk factor for cancer and CVD [45–49]. Recognizing *yerba mate*'s regulation of the human cytomegalovirus pathway may increase preventive approaches and therapeutic measures for virus-related diseases.

Despite these findings, there were still some limitations in our study. Due to the limited databases used in this study, further pharmacokinetic tests are necessary to verify the pharmacological mechanism of *yerba mate* in the future.

Conclusions

Taken together, this study is the first to explore and obtain the bioactive components, key pathogenic targets, and regulatory signal pathways of *yerba mate* by utilizing the network pharmacology method and preliminarily verifying the basic pharmacological effects and related mechanisms of *yerba mate*, which lays a good foundation for further research. We found that the bioactive components of *yerba mate* play a potential therapeutic role in cancer, cardiovascular and cerebrovascular diseases, nervous system diseases, and inflammatory diseases by regulating AKT1, STAT3, MAPK1, and other key genes. Thus, it can be inferred that *yerba mate* has high medicinal value. It is expected that our study will provide reference for the development and clinical application of *yerba mate* as a medicinal resource.

Authors' contributions

Z.Y. and Z.Z. conceived the idea of this article. H.F., H.M., L.L., and Y.Y. prepared and organized all the data. Z.Y. analysed the data and wrote the original manuscript. Z.Z. and Z.F. participated in revising the data and improving manuscript writing. F.W., B.D., M.K., H.S., Y.L., and R.Z. contributed to the tables, software application, and visualization. S.Y. and Z.Z. supervised the findings of this work. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

Ethical approval and consent to participate

Not applicable.

Conflict of interest

The authors declare no conflict of interest

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