ISSN 1948-5204 (online)

World Journal of *Gastrointestinal Oncology*

World J Gastrointest Oncol 2023 January 15; 15(1): 1-214

Published by Baishideng Publishing Group Inc

WJGO

World Journal of Gastrointestinal Oncology

Contents

Monthly Volume 15 Number 1 January 15, 2023

REVIEW

MINIREVIEWS

ORIGINAL ARTICLE

Basic Study

Clinical and Translational Research

Case Control Study

Retrospective Study

World Journal of Gastrointestinal Oncology

Monthly Volume 15 Number 1 January 15, 2023

Contents

World Journal of Gastrointestinal Oncology

Monthly Volume 15 Number 1 January 15, 2023

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Oncology*, Jing He, PhD, Research Fellow, Department of Pediatric Surgery, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou 510623, Guangdong Province, China. hejing198374@gmail.com

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

INDEXING/ABSTRACTING

The *WJGO* is now abstracted and indexed in PubMed, PubMed Central, Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJGO* as 3.404; IF without journal self cites: 3.357; 5-year IF: 3.250; Journal Citation Indicator: 0.53; Ranking: 162 among 245 journals in oncology; Quartile category: Q3; Ranking: 59 among 93 journals in gastroenterology and hepatology; and Quartile category: Q3. The *WJGO*'s CiteScore for 2021 is 3.6 and Scopus CiteScore rank 2021: Gastroenterology is 72/149; Oncology is 203/360.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Xiang-Di Zhang*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Jia-Ru Fan*.

NAME OF JOURNAL
World Journal of Gastrointestinal Oncology

ISSN
ISSN 1948-5204 (online)

LAUNCH DATE
February 15, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Monjur Ahmed, Florin Burada

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-5204/editorialboard.htm

PUBLICATION DATE
January 15, 2023

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Gastrointestinal Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Oncol 2023 January 15; 15(1): 36-54

DOI: 10.4251/wjgo.v15.i1.36

ISSN 1948-5204 (online)

REVIEW

Traditional Chinese medicine for transformation of gastric precancerous lesions to gastric cancer: A critical review

Yi-Lin Zhong, Peng-Qian Wang, Dan-Li Hao, Feng Sui, Feng-Bin Zhang, Bing Li

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Cheng TH, Taiwan; Zhang GL, China

Received: September 20, 2022
Peer-review started: September 20, 2022
First decision: November 15, 2022
Revised: December 6, 2022
Accepted: December 27, 2022
Article in press: December 27, 2022
Published online: January 15, 2023

Yi-Lin Zhong, Peng-Qian Wang, Dan-Li Hao, Feng Sui, Bing Li, Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing 100700, China

Feng-Bin Zhang, Department of Gastroenterology, The Fourth Hospital of Hebei Medical University, Shijiazhuang 050011, Hebei Province, China

Corresponding author: Bing Li, MD, Associate Research Scientist, Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, No. 16 Nanxiaojie, Dongzhimennei, Beijing 100700, China. libingtcm@163.com

Abstract

Gastric cancer (GC) is a common gastrointestinal tumor. Gastric precancerous lesions (GPL) are the last pathological stage before normal gastric mucosa transforms into GC. However, preventing the transformation from GPL to GC remains a challenge. Traditional Chinese medicine (TCM) has been used to treat gastric disease for millennia. A series of TCM formulas and active compounds have shown therapeutic effects in both GC and GPL. This article reviews recent progress on the herbal drugs and pharmacological mechanisms of TCM in preventing the transformation from GPL to GC, especially focusing on anti-inflammatory, anti-angiogenesis, proliferation, and apoptosis. This review may provide a meaningful reference for the prevention of the transformation from GPL to GC using TCM.

Key Words: Gastric cancer; Gastric precancerous lesions; Traditional Chinese medicine; Formulas; Pharmacological mechanism; Inflammation-cancer transformation

Core Tip: Precancerous lesions are precursors of gastric cancer (GC). The molecular mechanism of the transformation of precancerous lesions into GC remains unclear. This article reviews the mechanism of traditional Chinese medicine in the treatment of precancerous lesions and GC, and describes the relationship between the molecular mechanisms of Chinese medicine in treating these two pathological stages, providing a research idea for blocking GC progression through the gastric precancerous lesion stage.

Citation: Zhong YL, Wang PQ, Hao DL, Sui F, Zhang FB, Li B. Traditional Chinese medicine for transformation of gastric precancerous lesions to gastric cancer: A critical review. *World J Gastrointest Oncol* 2023; 15(1): 36-54
URL: https://www.wjgnet.com/1948-5204/full/v15/i1/36.htm
DOI: https://dx.doi.org/10.4251/wjgo.v15.i1.36

INTRODUCTION

Gastric cancer (GC) is the fifth most commonly diagnosed cancer and the fourth leading cause of cancer-related death worldwide[1]. The direct cause of high mortality in GC is that early GC may occur without any specific symptoms and cannot be treated promptly[2]. Therefore, it is particularly important to prevent GC in early stage[3]. In the 19th century, Virchow proposed "the origin of cancer as a site of chronic inflammation"[4]. Mostly, gastric carcinogenesis is a chronic pathological process, from chronic superficial gastritis, atrophic gastritis, intestinal metaplasia (IM), gastric epithelial dysplasia (GED), to GC, which was demonstrated as the typical process of "inflammation-cancer transformation"[5]. IM and GED are the main pathological stages of gastric precancerous lesions (GPL)[6]. GPL is the last stage before the occurrence of GC. Once this stage is attained, the probability of GC increases by at least 10-fold[7,8]. Therefore, intervention of at the GPL stage and reversal of malignant transformation are of great importance for the prevention of GC. Currently, there is no recommended treatment for GPL in western medicine[9]. The only therapeutic treatment, endoscopic mucosal dissection, is applicable to cases of severe dysplasia and early GC[10]. *Helicobacter pylori* (*H. pylori*) eradication and supplementation with vitamins and minerals exert a positive effect on the treatment of GC; however, the current research is not sufficient to support their therapeutic effects on GPL[11].

Inflammation, angiogenesis, and proliferation are the three most important histological features of the transformation from GPL to GC[12-14]. Chronic inflammation is the core driver of GC[15,16]. Inflammation promotes angiogenesis, and its progression depends on the speed of angiogenesis[17,18]. Simultaneously, inflammatory cells are almost inseparable from tumor cells, and the proliferation of tumor cells is directly related to the promotion of inflammation[19]. Moreover, the microenvironment created by tumors can promote further proliferation of inflammatory cells[20]. Angiogenesis can also promote the proliferation of tumor cells[21]. Furthermore, the establishment of a large number of new blood vessels also means that the tumor is about to transition from the dormant to the malignant stage [22]. An important feature is that when the diameter of the tumor tissue is larger than 1-2 mm, it relies heavily on neovascularization to deliver nutrients and clear metabolic wastes in tumor cells[23]. Clinically, tumor angiogenesis is believed to be directly proportional to tumor malignancy[24]. Seeking drugs that regulate the proliferation, inflammation, and angiogenesis of GPL and GC may be a promising avenue for improving clinical efficacy and further drug discovery.

GPL is generally defined as "stomach distension" and "stomach pain", according to traditional Chinese medicine (TCM) theory, with symptoms including fatigue and weakness, dizziness and wasting, grayish-yellow face, and a pale and dark tongue. TCM has been used for millennia to treat GPL. A series classical formula (fangjis) was documented in Treatise on Febrile Diseases, and Prescriptions of the Pharmacy Bureausuch, and showed curative effects for GPL. For example, the sijunzi decoction, which can be dated back to 1151 AD, was effective in treating both precancerous lesions[25,26] and GC[27,28]. Currently, a variety of traditional Chinese patent medicines, such as the Weiqi decoction[29], WeiFuChun (WFC)[30], and Weipixiao (WPX)[31] have been developed for GPL. Many clinical studies have also suggested that TCM can hinder the transformation process of inflammation and cancer, treat precancerous lesions and early GC, and improve the progression of advanced GC (Table 1). For instance, WFC is a Chinese herbal compound approved by the National Medical Products Administration to treat GPL. Clinical trials have shown that WFC can significantly improve the pathological conditions of patients with GPL compared to vitamin C, especially in the case of atrophy or IM[16]. Moreover, with the advantages of TCM in precancerous lesions and GC, TCM has received increasing attention, and a growing number of clinical studies have been registered at ClinicalTrials.gov, such as the Jianpi Yangzheng Xiaozheng decoction (NCT03823248) and Yiqi Wenyang Jiedu decoction (NCT05229809).

Many experimental studies have investigated the efficacy and mechanisms of TCM. For example, WFC can increase the secretion of pepsin by inhibiting the MAPK signaling pathway, thereby regulating the weight of rats with GPL and improving histopathological changes in the gastric mucosa[32]. Another study showed that Ginsenoside Rb1 (GRb1), which is contained in WFC, can prevent the occurrence and progression of GPLs by reducing the protein expression and nuclear translocation of β-catenin, interfering with the interaction of β-catenin/TCF4, and inhibiting the transcriptional activity of downstream genes, including c-myc, Cyclin D1 and Birc5[33]. Therefore, it is important to study the effect of TCM on GPL to improve the clinical efficacy and transformation of drug research and development (R&D). In this study, we summarize the mechanisms and targets of TCM in the treatment of GPL and GC, with a particular focus on their action in the processes of inflammation, angiogenesis, cell proliferation, and apoptosis.

Table 1 Clinical trials of traditional Chinese medicine in treating gastric cancer and precancerous lesions

Pathological stages	Ref.	Clinical drugs	Clinical sample size	Intervention	Control	Treatment duration	Outcome measures
GPL	Deng *et al* [125], 2012	Weining Granules	120	Weining Granules	Weifuchun tablets	6 mo	Overall response; gastroscopically-determined response; pathologically-confirmed response; eradication of Hp; microvessel density in the gastric mucosa; VEGF; IL-2; IL-6; T lymphocyte subsets; immunoglobulins; symptom scores; QOL; adverse reactions
	Bian *et al*[16], 2021	Weifuchun (WFC)	120	WFC tablets	Vitacoenzyme tablets	6 mo	Histopathology of gastric tissues; intestinal microbiota; sensitivity and specifcity of diferent intestinal microbiota
	Li *et al*[126], 2006	Weiansan (WAS)	76	Weiansan	Weifuchun tablets	24 wk	Inflammation of gastric mucosa; degree of glandular atrophy; IM and dysplasia; Hp infection
	NCT03823248	MoLuoDan and Sanchi powder	480	Moluodan combined with Sanchi powder	Folic acid tablets	24 wk	The disappearance rate of dysplasia; Histopathological score; endoscopic findings score; main symptom score; the patient-reported outcome scale integrals
GC	Pan *et al*[128], 2020	Jianpi Yangzheng Xiaozheng decoction	210	Chemotherapy combined with JPYZXZ decoction	Chemotherapy	24 wk	One-year survival rate; progression-free survival; overall survival; immune related hematology test; objective response rate; tumor makers; TCM syndrome points; fatigue scale; QOL scale
	Xu *et al*[129], 2013	Wei Chang'An	399	Chemotherapy combined with Wei Chang'An decoction	Continuously	3 mo or more	Survival trends; survival time
	Shu *et al* [130], 2019	Yiqi Huayu Jiedu decoction	489	Chemotherapy combined with YHJD	Chemotherapy	6 mo or more	Disease-free survival rate; 5-yr survival rate; QOL; TCM symptoms
	NCT05229809	Yiqi Wenyang Jiedu prescription	212	Yiqi Wenyang Jiedu prescription	Simulation agent of Yiqi Wenyang Jiedu prescription	24 wk	Two-year disease-free survival rate; disease-free survival; overall survival; cumulative annual recurrence and metastasis rate for 1-3 yr; cumulative annual survival rate for 1-3 yr; Indexes related to fat distribution; visceral adiposity Index; tumor marker; peripheral blood inflammatory index; prognostic nutritional index; QOL of the patient; evaluation of the patient's symptoms; medication compliance; percentage of participants with adverse events

GPL: Gastric precancerous lesions; GC: Gastric cancer; WFC: Weifuchun; WAS: Weiansan; TCM: Traditional Chinese medicine; QOL: Quality of life; VEGF: Vascular endothelial growth factor.

MECHANISM OF TCM IN THE TREATMENT OF GPL

The GPL stage is a critical stage in the development of GC. The intervention goal of GPL is to reverse malignant transformation and block the progression to GC. However, the molecular mechanisms underlying GPL have not yet been fully elucidated. Many TCMs have been shown to be effective in the treatment of GPL, focusing on the regulation of proliferation and apoptosis, anti-inflammation, and inhibition of angiogenesis (Tables 2 and 3, Figure 1).

Regulating proliferation and apoptosis related to GPL

In GPL and GC, the imbalance between proliferation and apoptosis of gastric epithelial cells may be the direct cause of malignant progression[34]. The PI3K/Akt/mTOR signaling pathway can regulate growth in normal cells and in cancers, and the activation of the Akt pathway through PI3K is directly related to tumorigenesis[35]. Pathological changes in the PI3K/Akt/mTOR pathway usually include downregulation of the tumor suppressor gene PTEN, abnormal activation of PI3K, and overexpression/hyperactivation of Akt[36]. Erianin, which is one of the most important natural compounds in Dendrobium, can be directly extracted from Dendrobium. Moreover, dendrobium species are widely used to treat various digestive diseases. Wang *et al*[37] confirmed that Erianin can significantly reduce

Table 2 *In vitro* and *in vivo* protective effects of active components of Chinese herbal medicine on gastric precancerous lesions and gastric cancer

Pathological stages	Effect	No.	Ref.	Active component	Animal/cells	Pathways/targets
Gastric precancerous lesions (GPL)	Anti-proliferation inducing apoptosis	c1	Wang *et al*[37], 2021	Erianin	GES-1 cell	HRAS-PI3K-Akt↓; p-Gsk3β, MDM2, p21, CyclinD1↓
		c2	Zhu *et al*[38], 2021	Epigallocatechin gallate	Male Wistar rats, PLGC model	PI3K/Akt/mTOR↓; PTEN↑; PI3K, Akt, mTOR↓
		c3	Zeng *et al*[33], 2021	Ginsenoside Rb1	Sprague-Dawley rats, PLGC model	β-catenin/TCF4↓; c-myc, cyclin, Birc5↓
		c4	Lv *et al*[131], 2022	Ginsenoside Rg3	Male Sprague-Dawley rats, PLGC model GPL cell	TIGAR, G6PDH, NADP, GSH↓; ROS ↑
	Anti-inflammatory	c5	Liu *et al*[50], 2020	Calycosin	Male (SD) rats, PLGC model	Integrinβ1/NF-κB/DARPP-32; Integrinβ1, NF-κB, DARPP-32↑; STAT3↓
	Anti-angiogenesis	c5	Liu *et al*[50], 2020	Calycosin	Male (SD) rats, PLGC model	Integrinβ1/NF-κB/DARPP-32; Integrinβ1, NF-κB, DARPP-32↑; STAT3↓
		c6	Gao *et al*[58], 2022	Atractylenolide III	Female SD rats, Gastric Precancerous, Lesions Model	HIF-1α, VEGF-A, DLL4↓
		c4	Zeng *et al*[120], 2022	Ginsenoside Rg3	Male Sprague Dawley rats, PLGC modelAGS cell, HGC-27 cell	GLUT1, GLUT4↓
	Inhibit glycolysis	c4	Liu *et al*[63], 2020	Ginsenoside Rg3	Male Atp4a/ C57Bl/6 mice, PLGC model	PI3K/Akt/mTOR↓; PI3K/Akt/miRNA-21↓; PI3K, AKT, mTOR, HIF-1α, miRNA-21↓; caspase-3↑
		c7	Zhang *et al*[65], 2018	Astragaloside IV	Male Sprague-Dawley rats, PLGC model	LDHA, MCT1, MCT4, HIF-1α, CD147, TIGAR↓; miRNA-34a, p53↑
	Improvement of EMT	C8	Liao *et al*[68], 2023	Gallic acid	GES-1 cell, MC cells	Wnt/β-catenin↓
	Induce autophagy	c7	Cai *et al*[44], 2018	Astragaloside IV	Sprague Dawley rats, PLGC model	Bcl-2/Bax, p53, Beclin1, p62, ATG5, ATG12↓; caspase3↑
GC	Anti-proliferation inducing apoptosis	c9	Xu *et al*[74], 2021	Naringin	SNU-1 cell, GES-1 cell	PI3K/Akt↓; PI3K, Akt, Bcl-2↓; caspase 3, Bax↑
		c10	Yang *et al*[132], 2016	Epigallocatechin-3-gallate	SGC-7901 cells, Nude mouse tumour xenograft model	Wnt/β-catenin↓; GSK3b, β-catenin↓
		c11	Lee *et al*[75], 2018	Pectolinarigenin	AGS cell, MKN28 cell	PI3K/Akt/mTOR↓; PI3K, p-Akt, mTOR, p-p70S6K, p-4EBP1↓
		c10	Fu *et al*[133], 2019	Epigallocatechin-3-gallate	SGC7901 cell	VEGF, HIF-1α↓
		c12	Wang *et al*[77], 2020	Aloin	HGC-27 cell, BGC-823 cell	Akt/mTOR, Stat3, NF-κB↓; NOX2, ROS, Akt, mTOR, Stat3, IκBα, p65↓
		c13	Chen *et al*[109], 2020	Betulinic acid	BGC-823 cells, MNK45 cells	NF-κB, VASP↓
		c14	Geng *et al*[134], 2018	Usnic acid	BGC823 cell, SGC7901 cell	Bax, LC3-II↑; Bcl-2, p62↓
		c15	Xu *et al*[135], 2020	T-17	SGC-7901, AGS cell, MGC-803 cell, BGC-823 cell, NCI-N87 cell,HUVEC cell	JNK, Bcl-2↑
		c16	Liu *et al*[81], 2015	Ponicidin	MKN28 cell	JAK2/STAT3↓; Bcl-2, VEGF, VEGFR2, JAK2 STAT3↓; Bax, caspase-3↑
		c17	Chen *et al*[136], 2012	Tanshinone IIA	MKN45 cell, SGC7901 cell	cyto-c, Bax, Caspase-9↑; Bcl-2↓
		c18	Yang *et al*[52],	Tomentosin	GCCs cell, AGS cell	IL-6, TNF-α, IL-1, IL-8, Bcl-2↓; Bax↑

		2020			
	c19	Sun *et al*[137], 2007	Swainsonine	SGC-7901 cell, BALB/c nu/nu mice, GC model	p53, Bcl-2↓; cmyc↑
	c20	Tang *et al*[82], 2019	Micheliolide	AGS cell, N87 cell	IL-6, STAT3, cyclinD1, Mcl-1, MMP-2↓
	c21	Li *et al*[138], 2013	Andrographolide	BGC-823 cell	Bax, caspasase-3↑; Bcl-2↓
	c22	Liu *et al*[139], 2016	Curcumin	SGC7901 cell, GES-1 cell	c-Myc/H19↓; c-Myc, H19↓; p53↑
	c23	Lee *et al*[140], 2016	Quercetin	NOD/SCID mice, PLGC model SNU719 cell, MKN74 cells	p53, p21, Bax, Puma, caspase-3, caspase-9, PARP↑
	c4	Aziz *et al*[121], 2016	Ginsenoside Rg3	SGC-7901 cell	Caspases-3, caspase-8, caspase-9, PARP, SP1↑; HSF1, FUT4↓
	c24	Saralamma *et al* [141], 2015	Poncirin	AGS cells	Fasl, caspase-8, caspase-3, PARP↑
Anti-inflammatory	c18	Yang *et al*[52], 2020	Tomentosin	GCCs cell, AGS cell	IL-6, TNF-α, IL-1, IL-8, Bcl-2↓; Bax↑
	c25	Tharmalingam *et al*[115], 2016	Piperine	AGS cell	β-catenin, IL-8↓
	c26	Su *et al*[53], 2019	Artemisinin	SGC-7901 cell, GES-1 cells, C57BL/6 J mice	NF-κB↓; IL-8, IL-6, TNF-α, IL-1β, COX-2, p-IκBα↓; IκBα↑
	c27	Han *et al*[54], 2015	Rosmarinic acid	MKN45 cell	IL-6/STAT3↓; IL-6, IL-1β, TNF-α, TNFsR-1, HIF-1α, miRNA-155-5p↓; IL-10↑
	c28	Sun and Meng [55], 2022	Scutellarin	AGS cell, albino Wistar rats, GC modelr	TNF-α, IL-1β, IL-2↓
Anti-angiogenesis	c4	Li and Qu[89], 2019	Ginsenoside Rg3	BGC823 cell	HIF 1α, VEGF↓
Inhibit glycolysis	C29	Wang *et al*[142], 2022	Licochalcone A	MKN45 cell, SGC7901cell, GES-1 cell	Akt/HK2↓; Akt, HK2↓
	C30	Chen *et al*[96], 2015	Baicalein	AGS cell	PTEN/Akt/HIF-1α↓; HK2, LDH-A, PDK1, Akt, HIF-1α↓; PTEN↑
	C31	Wang *et al*[142], 2022	Helichrysetin	MGC803 cell, HCT-8 cell	mTOR/p70S6K/c-Myc/PDHK1↓; mTOR/p70S6K, c-Myc, PDHK1↓
	C27	Han *et al*[54], 2015	Rosmarinic acid	MKN45 cell	IL-6/STAT3↓; IL-6, IL-1β, TNF-α, TNFsR-1, HIF-1α, miRNA-155-5p↓; IL-10↑
Improvement of EMT	C32	Wang *et al*[99], 2022	Poria acid	AGS cell, MKN-28 cell	E-cadherin↑; N-cadherin, Vimentin↓
	C33	Zang *et al*[143], 2017	Luteolin	NCI-N87 cell, MKN28 cell, Hs-746T cell	E-cadherin↑; N-cadherin, vimentin, Snail↓
	c34	Zhou *et al*[108], 2019	Crocin	AGS cell, HGC-27 cell, GES-1 cell	miR-320/KLF5/HIF-1α; KLF5/HIF-1α; KLF5, HIF-1α↓; miR-320↑
	c7	Zhu and Wen, 2020[144], 2018	Astragaloside IV	BGC-823 cell, MKN-74 cell, GES-1 cell	PI3K/Akt/NF-κB↓; TGF-β1↓
Regulate immune function	c35	Zhuang *et al* [105], 2020	Sophoridine	MFC cell, RAW264.7 cell	iNOS, IFN-β, IL-12α, Granzyme-B, TNF-α, Perforin↑; Arg-1, CD206, IL-10, PD-1, Tim-3, Lag-3, CCR2↓
	C36	Lu *et al*, 2021[104]	Oleanolic acid	MKN-45, Jurkat T cell	IL-1β/ NF-κB /TET3↓; PD-L1↓
Induce autophagy	c11	Lee *et al*, 2018[75]	Pectolinarigenin	AGS cell, MKN28 cell	PI3K/Akt/mTOR↓; PI3K, p-Akt, mTOR, mTOR, p-p70S6K, p-4EBP1↓
	c14	Geng *et al*[134], 2018	Usnic acid	BGC823 cell, SGC7901 cell	Bax, LC3-II↑; Bcl-2, p62↓
	c15	Xu *et al*[135], 2020	T-17	SGC-7901, AGS, MGC-803, BGC-823, NCI-N87, HUVEC cell	JNK, Bcl-2↑
Inhibits migration,	c12	Wang *et al*[77],	Aloin	HGC-27 cell, BGC-823 cell	Akt/mTOR, Stat3, NF-κB↓; NOX2,

and invasion		2020			ROS, Akt, mTOR, Stat3, IκBα, p65↓
	c13	Chen *et al*[109] , 2020	Betulinic acid	BGC-823 cells, MNK45 cells	NF-κB, VASP↓
	c34	Zhou *et al*[108], 2019	Crocin	AGS cell, HGC-27 cell, GES-1 cell	miR-320/KLF5/HIF-1α; KLF5/HIF-1α; KLF5, HIF-1α↓; miR-320↑
	c37	Cai *et al*[110], 2018	18β-glycyrrhetinic acid	SGC-7901 cell	ROS/PKC-α/ERK↓; ROS, PKC-α, ERK↓
	c30	Yan *et al*[111], 2015	Baicalein	SGC7901 Cell, MGC803 cell	MMP-2, mmp-9, p38↓
Anti-*Helicobacter pylori*	c25	Tharmalingam *et al*[115], 2016	Piperine	AGS cell lines	β-catenin, IL-8↓
	c26	Su *et al*[53], 2019	Artemisinin	SGC-7901 cell, GES-1 cells	NF-κB↓; IL-8, IL-6, TNF-α, IL-1β, COX-2, p-IκBα↓; IκBα↑
	c28	Sun and Meng [55], 2022	Scutellarin	(AGS) cell, albino Wistar rats, GC model	TNF-α, IL-1β, IL-2↓

GPL: Gastric precancerous lesions; GC: Gastric cancer; EMT: Epithelial-mesenchymal transformation; NF-κB: Noncanonical nuclear factor-kappaB; TNF-α: Tumour necrosis factor alpha; IL: Interleukin; HIF-1α: Hypoxia-inducible factor 1α.

Harvey rat sarcoma viral oncogene homolog (HRAS), thereby inhibiting the downstream PI3K/Akt signal pathway; hence, it plays a role in the treatment of precancerous lesions. Green tea polyphenols have been recognized for their anti-GC effects. Epigalocatein gallate is the main component of green tea polyphenols. Similarly, Zhu *et al*[38] found that epigallocatechin gallate inhibits the downstream PI3K/Akt/mTOR signaling pathway by promoting PTEN expression. This process achieves a balance between cell proliferation and apoptosis. The Wnt/β-catenin signaling pathway is a conserved pathway that plays an important role in maintaining intracellular homeostasis[39]. Inappropriate activation of the Wnt/β-catenin signaling pathway often occurs in GPL gastric epithelial cells, which may be one of the reasons for the transition from GPL to GC[40,41]. Weipixiao is a TCM compound that is found in Radix Astragali, Radix Pseudostellariae, Rhizoma Atractylodis Macrocephalae, Radix Salviae Miltiorrhiz, Herba Hedyotis Diffusae, and other TCMs. It is widely used for the management of GPL in clinical practice. Zeng *et al*[33] found that Weipixiao can inhibit cell proliferation and induce apoptosis by inhibiting abnormal activation of the Wnt/β-catenin signaling pathway, while GRb1 can inhibit β-catenin protein expression. Downstream targets, such as c-myc, Cyclin D1, Lgr5, MMP-7, and Birc5, in this pathway are inhibited. Autophagy is an intracellular catabolic process[42]. Current research shows that promoting autophagy in the early stages of tumorigenesis has a positive significance in cancer treatment[43]. The Chinese medicine monomer, Astragaloside IV (As-IV), regulates autophagy by mediating the Ambra1/Beclin1 complex[44].

Regulating inflammation signaling pathways of GPL

Inflammation is the key to the progression of GPL to GC. Currently, it is generally believed that the noncanonical nuclear factor-kappaB (NF-κB) and STAT3 signaling pathways are the two major signaling pathways that connect inflammation and cancer, and they link inflammation and cancer through synergistic action[45,46]. As one of the most important signaling pathways in the inflammatory response[47], the NF-κB signaling pathway can lead to the transcriptional activation of many pro-inflammatory mediators, including tumour necrosis factor alpha (TNF-α), interleukin-8 (IL-8), and IL-6 [48]. Because it also regulates cell proliferation, angiogenesis, metabolism, inflammation, and cell migration and is in the key position of these mechanism-related pathways, it is not difficult to explain why this pathway has become the most important bridge connecting GPL and GC[49]. Calycosin may play an anti-inflammatory role by regulating the integrin β1/NF-κB/DARPP-32 pathway and downregulating STAT3 expression[50]. The upregulated expression of vascular endothelial growth factor (VEGF) and hypoxia-inducible factor 1α (HIF-1α) in cells under hypoxic conditions lead to an inflammatory reaction[51]; therefore, WQD can play an anti-inflammatory role by inhibiting the HIF-1 signaling pathway[29].

In addition, TCM monomers and compounds can regulate various inflammatory factors. TCM monomers and compounds can also regulate a variety of inflammatory factors, including IL-6, TNF-α, IL-1, IL-8, COX-2, and IL-2. Among these, TNF-α, IL-6, and IL-8 can be regulated by more than three types of Chinese herbs. For example, TNF-α can be regulated by Tomentosin[52], artemisinin (ART)[53], rosmarinic acid (RA)[54], scutellarin (SC)[55].

Inhibition of angiogenesis signaling pathways and targets of GPL

HIF-1α binds to the target gene VEGF, and then leads to the transcription of Pro angiogenic protein, which is an important reason for the formation of new blood vessels, or neovasculogenesis[56,57].

Table 3 *In vitro* and *in vivo* protective effects of Chinese herbal compound on gastric precancerous lesions and gastric cancer

Pathological stages	Effect	No.	Ref.	Formulas	Main component	Animal/cells	Pathways/targets
GPL	Anti-proliferation inducing apoptosis	fa	Zeng *et al* [31], 2016	Weipixiao (WPX)	Radix Astragali, Radix Pseudostellariae, Rhizoma Atractylodis Macrocephalae, Radix Salviae Miltiorrhiz, Herba Hedyotis Diffusae	Male SD rats, PLGC model	Wnt/β-catenin↓; Lgr5, MMP-7, Wnt1, β-catenin↓
		fa	Zeng *et al* [145], 2018	Weipixiao (WPX)	Astragalus Membranaceus, Pseudostellaria Heterophylla, Atractylodis Macrocephalae, Curcuma zedoaria, Salvia Miltiorrhiza and Hedyotis Diffusa Willd	Male SD rats, PLGC model	Wnt/GSK3β; GSK3β↑; C-myc↓
		fb	Yin *et al*[29], 2019	Weiqi decoction (WQD)	Radix Angelicae Sinensis, Radix Astragali, Radix Codonopsis, Rhizoma Curcumae, Fructus Aurantii, Fructus Akebiae and Herba Taraxaci	Male Wistar rats, CAG with Precancerous Lesion Mode	PGE2, caspase-3↑; Ki67, HIF-1, COX-2, VEGF, VEGFR1↓
		fc	Cai *et al* [146], 2022	Sancao Tiaowei Decoction	Pseudostellariae Radix, stirbaked Atractylodis Macrocephalae Rhizoma inbran, Poria, Agrimoniae Herba, Taraxaci Herba, Hedyotis Diffusa Willd, Salviae Miltiorrhizae Radix Etrhizoma, Curcumae Rhizoma and Glycyrrhizae Radix Et Rhizoma	SD male rats, PLGC model	Hh signaling↓; Shh, Gli-1, Smo, cyclinD1, CDKN2A/p16INK4a, NF-κB P65↓; Ptch↑
		fd	Hao *et al* [147], 2022	Huazhuojiedu decoction	Artemisia capillaris Thunb, Scutellaria baicalensis Georgi, Oldenlandia diffusa Roxb, Isatis indigotica Fortune, Lobelia chinensis Lour, Pogostemon cablinBenth, Scutellaria barbata D. Don, Sophora flavescens Aiton, Coptis chinensis Franch, Gynostemma pentaphyllum Makino, and Eupatorium fortunei Turcz	Male SD rats, PLGC model	Lnc 517368↓
		fe	Xu *et al* [148], 2018	Xiao Tan He Wei Decoction	Radix bupleuri, processed rhizomapinelliae, poriacocos, coptis-chinensis, oldenlandiadiffusa, dandelion,cassia twig, rhubarb, radix paeoniae alba, radix glycyrrhizae preparata	GES-1 cell, Wistar rats, PLGC rat animal models	Bax, caspase-3↑; Bcl-2, NF-κB↓
		ff	Shen *et al* [149], 2008	Jinguo Weikang Capsule (JWC)	Tinospora root, trifoliate-orange Immature fruit, kaempfer dutchmanspipe root	SD rats, PLGC model	H-ras, EGFR, P53, c-myc↓
	Anti-inflammatory	fb	Yin *et al*[29], 2019	Weiqi decoction (WQD)	Radix Angelicae Sinensis, Radix Astragali, Radix Codonopsis, Rhizoma Curcumae, Fructus Aurantii, Fructus Akebiae, and Herba Taraxaci	Male Wistar rats, CAG with Precancerous Lesion Mode	PGE2, caspase-3↑; Ki67, HIF-1, COX-2, VEGF,VEGFR1↓
		fg	Deng *et al* [125], 2012	Weining granule	Radix Astragali Mongolici, Herba Hedyotdis, Rhizoma Curcumae Phaeocau, Fructus Lycii	Male Wistar rats, PLGC model	VEGF, IL-6, IgG↓; $CD4^+$, $CD4^+/CD8^+$, IL-2↑
	Anti-angiogenesis	fb	Yin *et al*[29], 2019	Weiqi decoction (WQD)	Radix Angelicae Sinensis, Radix Astragali, Radix Codonopsis, Rhizoma Curcumae, Fructus Aurantii, Fructus Akebiae, and Herba Taraxaci	Male Wistar rats, CAG with Precancerous Lesion Mode	PGE2, caspase 3↑; Ki67, HIF-1, COX-2, VEGF,VEGFR1↓
		fa	Zeng *et al* [59], 2018	Weipixiao (WPX)	Astragalus Membranaceus, Pseudostellaria Heterophylla, Atractylodis Macrocephalae, Curcuma zedoaria, Salvia Miltiorrhiza and Hedyotis Diffusa Willd	Male SD rats, PLGC model	ERK1/CylinD1; HIF-1α, VEGF, ERK1, CylinD1↓
		fh	Wang *et al* [150], 2020	Jinlongshe (JLS)	Rhizoma Pinelliae, Radix, Rhizome Arisaemat, Glycyrrhizaepreparata, corium stomachiumgalli, *etc.*	Male SD rats, PLGC model	Apelin, CD34↓
	Protecting gastric mucosa	fi	Yi *et al* [151], 2022	Elian granules	Curcumae Rhizoma, Salviae Miltiorrhizae Radix et Rhizoma, Angelicae Sinensis, Diels, Coptidis Rhizoma, Hedyotis Diffusa, Codonopsis Radix, Atractylodis Macrocephalae Rhizoma,	Male SD rats, PLGC model	MAPK; JNK, p38↑

					Glycyrrhizae Radix et Rhizoma, Pinelliae Rhizoma, Citri Reticulatae Pericarpium, Poria		
		fj	Wang *et al* [32], 2020	WeiFuChun (WFC)	Radix Ginseng Rubra (red ginseng), Rabdosia amethystoides H. Hara, and fried Fructus Aurantii	Male SD rats, PLGC model	MAPK; VEGF, FOXO4, AKT, TP53, FAS, MAPK8, MAPK11, MAPK14↓
	Inhibit glycolysis	fa	Cai *et al*[64], 2019	Weipixiao (WPX)	Astragalus, Radix Pseudostellariae, Atractylodes macrocephala, Salvia miltiorrhiza Bge, Oldenlandia diffusa(Willd.)Roxb	Male SD rats, PLGC model	miRNA-34a/PI3K/AKT/Mtor; LDHA, CD147, MCT4, PI3K, AKT, mTOR, HIF-1α, miRNA-34a↓
		fk	Liu *et al* [152], 2019	Weipiling (WPL)	Hedysarum multijugum Maxim, Pseudostellaria heterophylla Pax, Atractylodes macrocephala Koidz, Poria cocos Wolf, Panax notoginseng F.H. Chen, Curcuma zedoaria, Roscoe,Hedyotis diffusa Willd,Hericium erinaceus Pers	Male Atp4a-/-C57Bl/6 mice	mTOR/HIF-1α↓; CDX2, MUC2, ki-67, PTEN and p53, mTOR, HIF-1a, AMPK↓; TSC1, TSC2↑
	Improvement of EMT	fl	Li *et al* [69], 2022	Manpixiao decoction	Heterophylla falsestarwort root, root of red rooted salvia, drug solomonseal, common perilla stem, largehead atractylodes rhizome, corydalis ambigua, japanese apricot fruit, citron, rose, villous amomum fruit, spreading hedyotis herb, liquorice	Wistar male rats, PLGC model	EGFR-PI3K-AKT↓; EGFR, β-catenin, N-cadherin protein↓
GC	Anti-proliferation inducing apoptosis	fm	He *et al*[76], 2020	Weifufang	Astragalus, Codonopsis pilosula, Atractylodes macrocephala, Poria cocos, Nutgrass Galingale Rhizome, Radix Curcumae, Sappan Wood, Rhizoma Curcumae, Zaoxiu Paris Root Rhizoma Paridis, Barbed Skullcap Herb, Ligustrum lucidum, South Dodder Seed, Oldenlandia, Liquorice Root, Chicken's Gizzard-membrane, fry malt, and fry Rice-grain Sprout	BALB/c-nu nude mice, BGC-823 cell, Nude mice with xenografts	PTEN↑
		fn	Fang *et al* [153], 2021	Huosu Yangwei (HSYW)	Huoxiang, Zisugeng, Baizhu, Zhike, Doukou, Foshou, Wumei, Shengjiang, Dazao, Gancao, Huangqi, Dihuang, Mudanpi, Tianhuafen, Danggui, Chuanxiong, Ezhu, Gouqizi, Huanglian, Dangsheng, and Pugongying	Male Balb/c mice, PLGC model	DNAJB4, CALD1, AKR1C1, CST1, CASP1, PREX1, SOCS3, PRDM1
		fo	Yuan *et al* [154], 2020	Jianpi Yangzheng Xiaozheng (JPYZXZ) decoction	Radix astragali, Radix codonopsis pilosulae, Rhizoma Sparganiiand Rhizoma Curcumae	HGC-27 cells ,THP-1 cell, MFC cell	PI3Kγ, NF-κB, AKT, p-C/EBPβ, IL-10↓; IL-1β, TNF-α, IL-12p↑
		fg	Deng *et al* [92], 2019	Weining granule	Radix Astragali Mongolici and Herba Hedyotdis Rhizoma Curcumae Phaeocaulis,Fructus Lycii	Male Wistar rats, PLGC model	Bcl-2, VEGF↓; caspase-3, PTEN↑
	Anti-inflammatory	fp	Li *et al* [155], 2021	Guiqi Baizhu prescription	Astragali radix, Atractylodis macrocephalae, Angelicae,Paeoniae radix alba, Pericarpium citri reticulatae, Rhubarb, Glycyrrhizae	MKN-45 cell, SGC-7901 cell, BGC-823 cell, GES-1cell	HER2, PD-L1↑
	Anti-angiogenesis	fg	Deng *et al* [92], 2019	Weining granule	Radix Astragali Mongolici and Herba Hedyotdis Rhizoma Curcumae Phaeocaulis, Fructus Lycii	Male Wistar rats, PLGC model	Bcl-2, VEGF↓; caspase-3, PTEN↑
	Improvement of EMT	fq	Liu *et al* [100], 2020	Babao Dan	Natural bezoar, snake gall, antelope horn, pearl, musk, and Panax notoginseng	AGS cell, MGC803 cell	TGF-b/Smad↓; TGF-b1, p-Smad2/3↓
		fo	Yuan *et al* [154], 2020	Jianpi Yangzheng Xiaozheng (JPYZXZ) decoction	Radix astragali, Radix codonopsis pilosulae, Rhizoma Sparganiiand Rhizoma Curcumae	HGC-27 cells, THP-1 cell, MFC cell	PI3Kγ, NF-κB, AKT, p-C/EBPβ, IL-10↓; IL-1β, TNF-α, IL-12p↑
	Inhibits migration, and	fr	Chen *et al*	Yangzheng Sanjie	Astragali Radix, Scutellariae Barbatae, Herba, Arisaematis Rhizoma	MKN-45 cell	EGFR, miR-7↑

	invasion	[112], 2018	Decoction (YZSJD)	Preparatum, Citri Sarcodactylis, Fructus, Cremastrae Pseudobulbus and Curcumae Longae, Rhizoma

SD: Sprague Dawley; GPL: Gastric precancerous lesions; GC: Gastric cancer; EMT: Epithelial-mesenchymal transformation; NF-κB: Noncanonical nuclear factor-kappa B.

Therefore, stabilizing the HIF-1α/VEGF pathway is of great significance for improving angiogenesis under hypoxic conditions. A study showed that early angiogenesis in GPL tissue is accompanied by HIF-1α and VEGF-A activation[58]. Both atractylenolide III (ATIII)[58] and WPX[59] can inhibit the HIF-1α/VEGF signaling pathway, and WPX can also inhibit the downstream targets of the pathway, such as ERK1/Cyclin D1. It then plays a role in angiogenesis inhibition.

OTHER MECHANISMS OF ACTION IN THE TREATMENT OF GPL

Regulate GPL related metabolism

Metabolic disorder is a hallmark of GC, the most significant of which are disorders of glucose metabolism[60]. In contrast to normal cells, GC cells preferentially choose glycolysis as the main way to obtain energy, even under conditions of sufficient oxygen[61]. The rapid proliferation of GC cells depends largely on glycolysis[62]. Studies have found that glycolysis also occurs in GPL; therefore, glycolysis is likely to be one of the key points in the transition from GPL to GC[63]. Ginsenoside Rg3 (GRg3) blocks glycolysis by inhibiting the PI3K/AKT pathway and downregulating downstream miRNA-21[63], whereas WPX inhibits the PI3K/AKT/mTOR pathway by upregulating upstream miRNA-34a, and then blocks glycolysis[64]. Interestingly, both WPX and As-IV can regulate LDHA, MCT4, HIF-1α, and CD147 targets inhibits glycolysis[65].

Reverse GPL related epithelial-mesenchymal transition

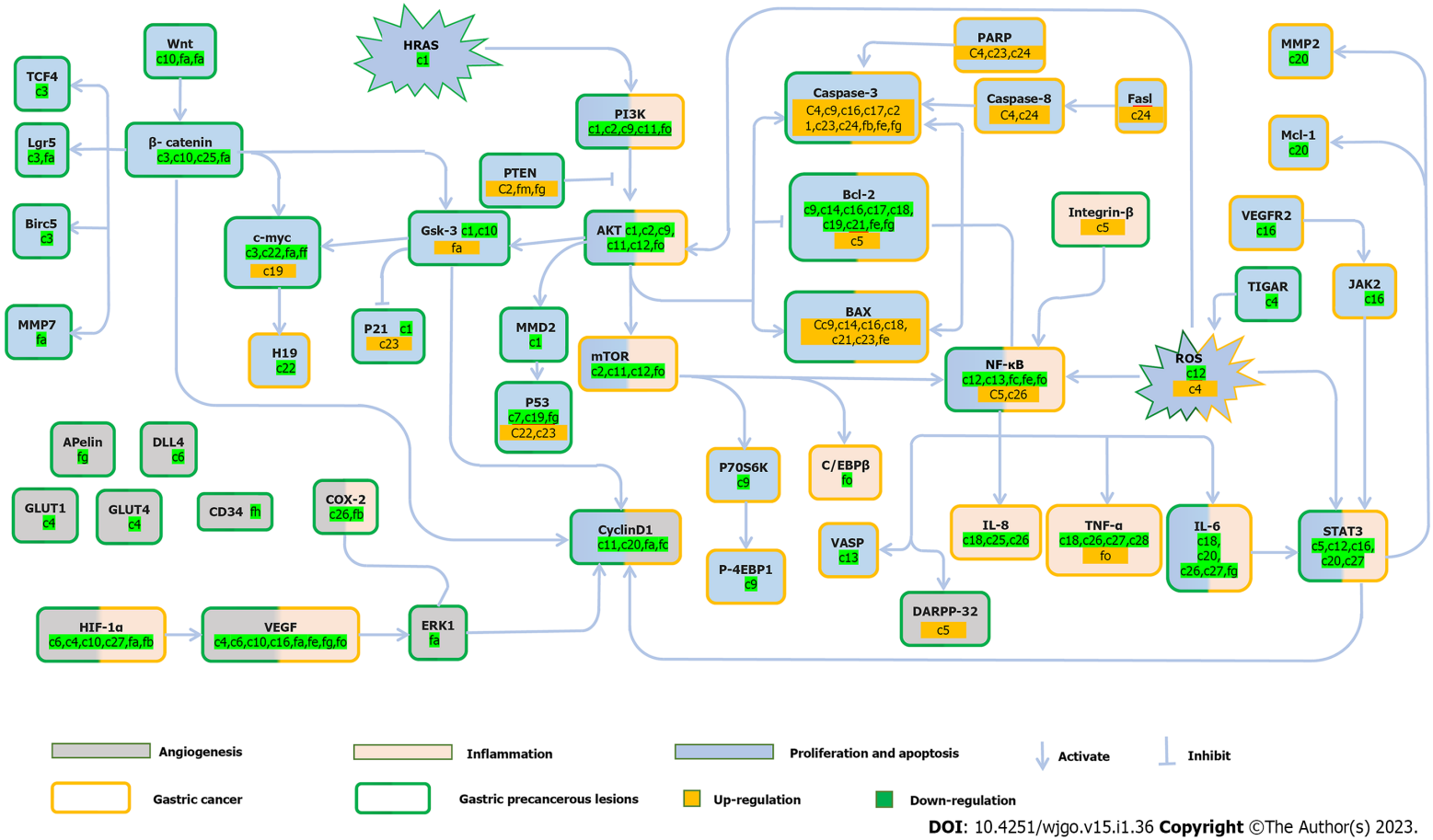
Epithelial-mesenchymal transformation (EMT) refers to the transformation of epithelial cells into mesenchymal cells under specific conditions. EMT is a physiological process that occurs during tissue self-repair[66]. When it is out of control, it may lead to fibrosis, angiogenesis, loss of normal organ function, and cancer, making it one of the key characteristics of GC[67]. Gallic acid (GA) is found in many TCMs. As early as 1552 AD, the Compendium of Materia Medica recorded the method for obtaining GA and its medicinal properties. Liao *et al*[68] found that GA can inhibit the EMT process by downregulating the Wnt/β-catenin signaling pathway, thereby inhibiting the malignant proliferation of MC cells and finally achieving the goal of treating GPL. The Manpixiao Decoction is a compound used in Chinese medicine. Li *et al*[69] confirmed that this compound could inhibit the progression of PLGC by reducing the occurrence of systemic inflammatory reactions in the local gastric mucosa and inhibiting the EGFR-PI3K-AKT related EMT pathway.

MECHANISM OF TCM IN THE TREATMENT OF GC

A variety of TCM formulas and active compounds have been demonstrated to be effective in the treatment of GC, mainly involving the regulation of proliferation, apoptosis, and inflammation (Tables 2 and 3, Figure 1).

Regulating proliferation and apoptosis related to GC

The imbalance between cell proliferation and apoptosis destroys tissue homeostasis and promotes tumor occurrence[70]. Therefore, regulating the proliferation and apoptosis of GC cells is an important therapeutic strategy for preventing GC progression[71]. In GC, the PI3K/AKT/mTOR pathway is often activated, and this pathway plays a role in promoting cancer progression[72]. Multiple targets of this pathway have been shown to be mutated or otherwise dysregulated during tumorigenesis[73]. Naringin and pectinarigenin (PEC) can inhibit the PI3K/Akt signaling pathway, and PEC can also inhibit downstream mTOR[74,75]. Weifufang promoted the upregulation of PTEN and inhibited the PI3K/Akt signaling pathway[76]. Aloin (ALO) inhibits the Akt/mTOR signaling pathway mediated by NOX2-ROS[77]. They can both play a role in inhibiting cell formation. Recent studies have shown that the STAT signaling pathway has a strong carcinogenic potential, which can promote proliferation and has an extremely significant anti-apoptotic effect[78,79]. Therefore, dysregulation of the STAT3 signaling pathway is common in GC[80]. Ponicidin can induce apoptosis in MKN28 cells, which may be related to the inhibition of the VEGFR2-mediated JAK2-STAT3 signaling pathway[81]. The study showed that micheliolide inhibited the growth of GC *in vitro* and *in vivo*, and this effect was related to downregulation expression of IL-6 and thus inhibition of the STAT3 pathway[82]. ALO can inhibit cell prolif-



DOI: 10.4251/wjgo.v15.i1.36

Figure 1 A diagram of pathway targets of traditional Chinese medicine formulas and compounds for gastric precancerous lesions and gastric cancer. Targets involved in angiogenesis, inflammation, and proliferation and apoptosis were labelled grey, pink, and blue, respectively. Border of targets regulated in gastric precancerous lesions and gastric cancer stage were painted into green and yellow, respectively. The traditional Chinese medicine formulas and compounds regulating each target were labeled as "c" and "f", respectively. Red and green background of "c" and "f" represent up- and down-regulation of the target, respectively. The details of number of these formulas and compounds were shown in Tables 2 and 3. HRAS: Harvey rat sarcoma viral oncogene homolog; HIF-1α: Hypoxia-inducible factor 1α; VEGF: Vascular endothelial growth factor; NF-KB: Noncanonical nuclear factor-kappaB; TNF-α: Tumour necrosis factor alpha; IL: Interleukin.

eration by inhibiting the NOX2-ROS mediated Stat3 signal pathway[77].

Anti-Inflammation related signaling pathways and targets of GC

The occurrence of GC is mostly the result of inflammation, and blocking the inflammatory signaling pathway is essential for the treatment of GC[83]. During GC, continuous activation of NF-κB leads to chronic inflammation and further tumorigenesis. ART and its derivatives can be used to treat GC

caused by *H. pylori* infection by downregulating inflammatory factors and inhibiting the NF-κB signaling pathway *in vivo*. The STAT3 signaling pathway plays an important role in the development of inflammation-related GC, and its activation can induce tumors to promote inflammation[84,85]. RA can downregulate the anti-inflammatory factor IL-10 and upregulate pro-inflammatory cytokines such as TNF-α and IL-1β Expression of. Inhibition of IL-6/STAT3 pathway[54].

Inhibition of angiogenesis signaling pathways and targets of GC

Without angiogenesis, it is difficult to achieve large-scale proliferation and invasion of GC cells[86]. Angiogenesis in GC is regulated by a variety of angiogenic or anti-angiogenic factors[87]. For example, VEGF is the most representative promoter of angiogenesis. Currently, it is considered one of the most promising targets for the treatment of GC[88]. Therefore, Weining granules inhibit angiogenesis by downregulating VEGF expression[89]. As an upstream regulator of VEGF, HIF-1α also plays a role in regulating other pro angiogenic factors and anti-angiogenic factors[90,91]. Therefore, the inhibition of HIF-1α and VEGF expression may be the direct reason for GRg3's excellent inhibition of angiogenesis [92].

OTHER MECHANISMS OF ACTION IN THE TREATMENT OF GC

Regulate GC related metabolism

Cancer is usually considered a metabolic disease because cancer cells proliferate rapidly by reprogramming their energy metabolism. Glycolysis is the main mechanism by which GC cells obtain energy[93,94]. Current research has shown that many TCMs can inhibit abnormal metabolic processes. Licochalcone A (Lic A) is an important active compound extracted from licorice that has anti-inflammatory, antibacterial, antioxidant, antitumor, and other activities. Wu *et al*[95] found that Lic A inhibits glycolysis by blocking the Akt/HK2 pathway. In nature, baicalein mainly exists in Scutellaria baicalensis Georgi and has anti-inflammatory, antibacterial, and other effects. Chen *et al*[96] found that baicalein can inhibit glycolysis by regulating the PTEN/Akt/HIF-1α signaling pathway.

Reverse GC related EMT

In the malignant progression of GC, tumor cells use the process of EMT to change their cell morphology to improve their invasiveness, metastatic ability, and drug resistance[97,98]. Therefore, the inhibition of EMT is a key factor in the treatment of GC. Wang *et al*[99] found that Poria acid can inhibit the EMT process by significantly increasing the expression of E-cadherin and inhibiting the expression of N-cadherin and Vimentin, thereby inhibiting the invasion and metastasis of GC cells. Babaodan (BBD) is a TCM compound that has been used in clinical treatment since the Ming Dynasty, (more than 400 years ago). Modern research has found that Babaodan has significant anti-tumor, anti-inflammatory, immune regulatory effects, as well as other effects. Liu *et al*[100] found that BBD can inhibit the TGF-β/Smad signaling pathway, thereby inhibiting TGF-β-induced EMT.

Improved GC related immune regulation

Compared with other therapies, immunotherapy has the characteristics of lasting remission, improving the quality of life of patients, and prolonging survival[101], which brings new hope to most patients with GC[102]. Modern experimental studies have found that many TCMs regulate immunity and eliminate immune disorders[103]. Oleanolic acid is widely found in many TCMs, such as hawthorns and black plums. Lu *et al*[104] found that OA destroyed IL-1 in GC cells β/NF-κB/TET3 axis, leading to DNA hypomethylation and downregulation of PD-L1. This suggests that OA can be used as an epigenetic modulator in GC immunotherapy. In addition, sophoridine, a monomer of TCM, regulates immune function and can act on macrophages and $CD8^+$ T cells, thus reshaping the immune microenvironment of GC[105].

Suppress GC related intrusion and migration

The invasion and migration of cancer cells play an important role in tumor metastasis, and distant metastasis of GC is a direct cause of high mortality[106,107]. A variety of Chinese herbal monomers and compounds have been used, including crocin[108], betulinic acid[109], ALO[77], 18 β-glycyrrhetinic acid [110], baicalein[111], and YangZheng Sanjie decoction[112].

Kill Helicobacter pylori

As early as 1994, *H. pylori* was identified as a carcinogen in GC[113]. Currently, it is the first type of carcinogen to be identified in GC. Reducing *H. pylori* infections is an important means of preventing and treating GC[114]. The TCM monomers piperine[115], ART[53] and SC[55] have been proven to have corresponding therapeutic potentials.

CONCLUSION

As early as 40 years ago, GC was recognized as the end result of further development of GPL[116]. Recently, knowledge of the molecular basis of GC and GPL has been accumulating rapidly[117]. However, the molecular mechanism of the transformation from GPL to GC remains unclear[118]. In this study, we reviewed the progress of TCM in treating GPL and GC, while aiming to investigate the potential therapeutic treatment of TCM on the transformation from GPL to GC.

In this review (Tables 1-3, Figure 1), we found that multiple mechanisms of TCM can be identified in the treatment of both GPL and GC. The abnormal activation of the PI3K/ATK, NF-κB, IL-6/STAT3, and HIF-1α/VEGF signaling pathways in both GPL and GC indicated that some pathological changes in GC occurred as early as in the GPL stage. Therefore, in the treatment of GC, secondary prevention should be moved to the GPL stage[119]. According to these studies, active components of TCM, such as Epigallocatechin Gallate, GRg3, AT-III and AS-IV, showed multiple therapeutic effects on both GPL and GC *via* different targets and signaling pathways. This suggests that these active ingredients may have the therapeutic potential to block the transition from GPL to GC through these targets and signaling pathways. For example, GRg3 has a significant anti-angiogenic effect in both the GPL and GC processes. In the GPL stage, GRg3 can inhibit angiogenesis by downregulating GLUT1 and GLUT4[120], and suppressing the PI3K/Akt/mTOR pathway and downstream HIF-1α[63]. In GC, GRg3 can also reduce HIF-1α, thereby reducing tumor angiogenesis[121]. This has revealed that in the process of progression from GPL to GC, the pro angiogenic effect of HIF-1α may be a theme throughout the two pathological stages. GLUT1, GLUT4, and other proteins may be potential targets for the progression of GPL to GC. In a broader perspective, the existence of the same TCM compound with obvious therapeutic effect both on GPL and GC indicate that "dual effects" in treating GC and its precancerous lesions: when TCM is used to treat GPL, it also eliminates the possibility of GC as a malignant progression.

Many cancers, including GCs, are preceded by precancers. Treating precancers to prevent GC is essential for reducing GC-associated morbidity and mortality. Effective cancer prevention is the best way to stop cancer, and TCM have been shown to be effective in preventing cancer[122]. GRb1, Notoginsenoside R1, AS-IV, GRg3, AT-III, Calycosin, and other active ingredients have shown a variety of therapeutic effects in the treatment of precancerous lesions, including anti-proliferation and apoptosis induction, anti-angiogenesis, inhibition of glycolysis, and anti-inflammatory activities, including PI3K/Akt, Wnt/β-catenin, NF-κB, and STAT3 signaling. Clinically, Chinese herbal medicines containing these active ingredients are often used to treat precancerous lesions, such as ginseng, Panax notoginseng, Atractylodes, Astragalus membranaceus, and Pseudostellariae radix. These TCMs are usually combined to form a TCM compound for the clinical treatment of precancerous lesions, such as WPX, Sancao Tiaowei decoction, and Guiqi Baizhu prescriptions. Interestingly, the mechanisms of action of these active ingredients and TCM prescriptions in the treatment of precancerous lesions are not the same, which suggests that the curative effects of TCM are not caused by single chemical entities but result from their multi-ingredient prescription[123]. Chinese medicine differs from Western medicine in that many compounds in Chinese medicine act on multiple targets simultaneously, producing significant therapeutic effects[124]. For example, WPX can regulate proliferation and apoptosis by regulating the Wnt/β-catenin and Wnt/GSK3β pathways, playing an anti-angiogenic role by inhibiting the angiogenic factors HIF-1α, VEGF, and ERK1/CylinD1 pathway, and inhibiting glycolysis by regulating the miRNA-34a/PI3K/AkT/mTOR pathway. Interestingly, the Chinese herbal monomers contained in this formula, such as GRb1, AS-IV, AT-III, and Calycosin, can also regulate proliferation, apoptosis, angiogenesis, and glycolysis, and the targets of these monomers from WPX are not exactly same as those of WPX. In this comparison, TCM compounds change the mechanism of action of a single compound through the combination of a variety of TCMs and lead the creation of a new mechanism of action. This feature is precisely an advantage of TCM in treating GPL, as these medicines block its progression to GC, and fill the gap of Western medicine in treating GPL.

Clinical trials are one of the most reliable sources of evidence that guide medical practice. Current western medicine therapy for GPL generally includes the eradication of *H. pylori*, vitamin supplements, and other treatments[10]. However, for patients with advanced GPL, such as the IM stage, whether eradication of *H. pylori* have therapeutic effects remain controversial[125]. Compared with Western medicine, TCM has a curative effect at all stages of GPL. Currently, clinical trials have confirmed that TCM can block the progression of GPL to GC[126,127]. Taking WFC as an example, compared with vitacoenzyme (Vit), the total effective rates of the WFC and Vit groups in alleviating the degree of atrophy were 80.00% and 23.33%, respectively. The total effective rates of relieving IM in the WFC and Vit groups were 73.33% and 26.67%, respectively[16]. Notably, primary outcome measures, such as overall survival and 5-year survival rates, were employed in majority of these trials. These "head-to-head" trials demonstrated the efficacy of TCM in preventing the transformation of GPL to GC. Nevertheless, compared to the various mechanisms of TCM against GPL and GC reported by experiments, the development of relevant clinical trials is still insufficient. In the future, more attention should be paid to the development of clinical trials of GPL and GC with TCM.

FOOTNOTES

Author contributions: Zhong YL and Wang PQ contributed equally to this study; Li B and Wang PQ conceptualized the study; Wang PQ and Zhong YL wrote the initial manuscript; Hao DL, Sui F, and Zhang FB participated in the preparation of key figures and tables; all authors were involved in the critical revision

Supported by the National Natural Science Foundation of China, No. 81904064; Scientific and Technological Innovation Project of China Academy of Chinese Medical Sciences, No.CI2021A03804 and No. CI2021A05052; and Fundamental Research Funds for the Central Public Welfare Research Institutes, No. ZZ14-YQ-023, No. ZXKT21017, and No. ZXKT21024.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

Country/Territory of origin: China

ORCID number: Yi-Lin Zhong 0000-0001-5713-5772; Peng-Qian Wang 0000-0003-0547-4144; Dan-Li Hao 0000-0002-1146-6557; Feng Sui 0000-0002-1948-336X; Feng-Bin Zhang 0000-0002-9606-3000; Bing Li 0000-0002-4613-1327.

S-Editor: Chen YL
L-Editor: A
P-Editor: Chen YL

REFERENCES

1 **Sung H**, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209-249 [PMID: 33538338 DOI: 10.3322/caac.21660]
2 **Zhang C**, Chen Z, Zhou X, Xu W, Wang G, Tang X, Luo L, Tu J, Zhu Y, Hu W, Xu X, Pan W. Cantharidin induces G(2)/M phase arrest and apoptosis in human gastric cancer SGC-7901 and BGC-823 cells. *Oncol Lett* 2014; **8**: 2721-2726 [PMID: 25364455 DOI: 10.3892/ol.2014.2611]
3 **Shin VY**, Ng EK, Chan VW, Kwong A, Chu KM. A three-miRNA signature as promising non-invasive diagnostic marker for gastric cancer. *Mol Cancer* 2015; **14**: 202 [PMID: 26607322 DOI: 10.1186/s12943-015-0473-3]
4 **Coussens LM**, Werb Z. Inflammation and cancer. *Nature* 2002; **420**: 860-867 [PMID: 12490959 DOI: 10.1038/nature01322]
5 **Correa P**. Human gastric carcinogenesis: a multistep and multifactorial process--First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res* 1992; **52**: 6735-6740 [PMID: 1458460]
6 **You WC**, Li JY, Blot WJ, Chang YS, Jin ML, Gail MH, Zhang L, Liu WD, Ma JL, Hu YR, Mark SD, Correa P, Fraumeni JF Jr, Xu GW. Evolution of precancerous lesions in a rural Chinese population at high risk of gastric cancer. *Int J Cancer* 1999; **83**: 615-619 [PMID: 10521796 DOI: 10.1002/(sici)1097-0215(19991126)83:5<615::aid-ijc8>3.0.co;2-l]
7 **Kim YI**, Park JY, Kim BJ, Hwang HW, Hong SA, Kim JG. Risk of metachronous gastric neoplasm occurrence during intermediate-term follow-up period after endoscopic submucosal dissection for gastric dysplasia. *Sci Rep* 2020; **10**: 6747 [PMID: 32317745 DOI: 10.1038/s41598-020-63722-0]
8 **Lin Z**, Luo M, Chen X, He X, Qian Y, Lai S, Si J, Chen S. Combined Detection of Plasma ZIC1, HOXD10 and RUNX3 Methylation is a Promising Strategy for Early Detection of Gastric Cancer and Precancerous Lesions. *J Cancer* 2017; **8**: 1038-1044 [PMID: 28529617 DOI: 10.7150/jca.18169]
9 **Zhao S**, Zhang X, Wang J, Ge J, Liu J. Endoscopic resection versus surgery for early gastric cancer and precancerous lesions: a meta-analysis. *Springerplus* 2016; **5**: 678 [PMID: 27350915 DOI: 10.1186/s40064-016-2273-7]
10 **Pimentel-Nunes P**, Libânio D, Marcos-Pinto R, Areia M, Leja M, Esposito G, Garrido M, Kikuste I, Megraud F, Matysiak-Budnik T, Annibale B, Dumonceau JM, Barros R, Fléjou JF, Carneiro F, van Hooft JE, Kuipers EJ, Dinis-Ribeiro M. Management of epithelial precancerous conditions and lesions in the stomach (MAPS II): European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter and Microbiota Study Group (EHMSG), European Society of Pathology (ESP), and Sociedade Portuguesa de Endoscopia Digestiva (SPED) guideline update 2019. *Endoscopy* 2019; **51**: 365-388 [PMID: 30841008 DOI: 10.1055/a-0859-1883]
11 **Dawsey SP**, Hollenbeck A, Schatzkin A, Abnet CC. A prospective study of vitamin and mineral supplement use and the risk of upper gastrointestinal cancers. *PLoS One* 2014; **9**: e88774 [PMID: 24558423 DOI: 10.1371/journal.pone.0088774]
12 **Balkwill F**, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet* 2001; **357**: 539-545 [PMID: 11229684 DOI: 10.1016/S0140-6736(00)04046-0]
13 **Zheng J**, Cai W, Lu X, He W, Li D, Zhong H, Yang L, Li S, Li H, Rafee S, Zhao Z, Wang Q, Pan H. Chronic stress accelerates the process of gastric precancerous lesions in rats. *J Cancer* 2021; **12**: 4121-4133 [PMID: 34093815 DOI: 10.7150/jca.52658]

14 **Scotiniotis IA**, Rokkas T, Furth EE, Rigas B, Shiff SJ. Altered gastric epithelial cell kinetics in Helicobacter pylori-associated intestinal metaplasia: implications for gastric carcinogenesis. *Int J Cancer* 2000; **85**: 192-200 [PMID: 10629077]

15 **Bockerstett KA**, DiPaolo RJ. Regulation of Gastric Carcinogenesis by Inflammatory Cytokines. *Cell Mol Gastroenterol Hepatol* 2017; **4**: 47-53 [PMID: 28560288 DOI: 10.1016/j.jcmgh.2017.03.005]

16 **Bian Y**, Chen X, Cao H, Xie D, Zhu M, Yuan N, Lu L, Lu B, Wu C, Bahaji Azami NL, Wang Z, Wang H, Zhang Y, Li K, Ye G, Sun M. A correlational study of Weifuchun and its clinical effect on intestinal flora in precancerous lesions of gastric cancer. *Chin Med* 2021; **16**: 120 [PMID: 34801051 DOI: 10.1186/s13020-021-00529-9]

17 **Subotički T**, Mitrović Ajtić O, Živković E, Diklić M, Đikić D, Tošić M, Beleslin-Čokić B, Dragojević T, Gotić M, Santibanez JF, Čokić V. VEGF Regulation of Angiogenic Factors *via* Inflammatory Signaling in Myeloproliferative Neoplasms. *Int J Mol Sci* 2021; **22** [PMID: 34206393 DOI: 10.3390/ijms22136671]

18 **Jackson JR**, Seed MP, Kircher CH, Willoughby DA, Winkler JD. The codependence of angiogenesis and chronic inflammation. *FASEB J* 1997; **11**: 457-465 [PMID: 9194526]

19 **Schetter AJ**, Heegaard NH, Harris CC. Inflammation and cancer: interweaving microRNA, free radical, cytokine and p53 pathways. *Carcinogenesis* 2010; **31**: 37-49 [PMID: 19955394 DOI: 10.1093/carcin/bgp272]

20 **Mantovani A**, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature* 2008; **454**: 436-444 [PMID: 18650914 DOI: 10.1038/nature07205]

21 **Folkman J**. Role of angiogenesis in tumor growth and metastasis. *Semin Oncol* 2002; **29**: 15-18 [PMID: 12516034 DOI: 10.1053/sonc.2002.37263]

22 **Carmeliet P**, Jain RK. Molecular mechanisms and clinical applications of angiogenesis. *Nature* 2011; **473**: 298-307 [PMID: 21593862 DOI: 10.1038/nature10144]

23 **Cao Y**. Tumor angiogenesis and molecular targets for therapy. *Front Biosci (Landmark Ed)* 2009; **14**: 3962-3973 [PMID: 19273326 DOI: 10.2741/3504]

24 **Jiang X**, Wang J, Deng X, Xiong F, Zhang S, Gong Z, Li X, Cao K, Deng H, He Y, Liao Q, Xiang B, Zhou M, Guo C, Zeng Z, Li G, Xiong W. The role of microenvironment in tumor angiogenesis. *J Exp Clin Cancer Res* 2020; **39**: 204 [PMID: 32993787 DOI: 10.1186/s13046-020-01709-5]

25 **Zhong WR**, Huang YX, Cui JP. [Clinical study on modified sijunzi decoction in treating intestinal metaplasia of gastric mucosa]. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 1997; **17**: 462-464 [PMID: 10322830]

26 **Gan D**, Xu A, Du H, Ye Y. Chinese Classical Formula Sijunzi Decoction and Chronic Atrophic Gastritis: Evidence for Treatment Approach? *Evid Based Complement Alternat Med* 2017; **2017**: 9012929 [PMID: 29138645 DOI: 10.1155/2017/9012929]

27 **Li YJ**, Liao LL, Liu P, Tang P, Wang H, Peng QH. Sijunzi Decoction Inhibits Stemness by Suppressing β-Catenin Transcriptional Activity in Gastric Cancer Cells. *Chin J Integr Med* 2022; **28**: 702-710 [PMID: 34751940 DOI: 10.1007/s11655-021-3314-9]

28 **Qian J**, Li J, Jia J, Jin X, Yu D, Guo C, Xie B, Qian L. DIFFERENT CONCENTRATIONS OF SIJUNZI DECOCTION INHIBIT PROLIFERATION AND INDUCE APOPTOSIS OF HUMAN GASTRIC CANCER SGC-7901 SIDE POPULATION. *Afr J Tradit Complement Altern Med* 2016; **13**: 145-156 [PMID: 28852730 DOI: 10.21010/ajtcam.v13i4.19]

29 **Yin J**, Yi J, Yang C, Xu B, Lin J, Hu H, Wu X, Shi H, Fei X. Weiqi Decoction Attenuated Chronic Atrophic Gastritis with Precancerous Lesion through Regulating Microcirculation Disturbance and HIF-1α Signaling Pathway. *Evid Based Complement Alternat Med* 2019; **2019**: 2651037 [PMID: 31320912 DOI: 10.1155/2019/2651037]

30 **Hao X**, Liu Y, Zhou P, Jiang Q, Yang Z, Xu M, Liu S, Zhang S, Wang Y. Integrating Network Pharmacology and Experimental Validation to Investigate the Mechanisms of Huazhuojiedu Decoction to Treat Chronic Atrophic Gastritis. *Evid Based Complement Alternat Med* 2020; **2020**: 2638362 [PMID: 33354218 DOI: 10.1155/2020/2638362]

31 **Zeng JH**, Pan HF, Liu YZ, Xu HB, Zhao ZM, Li HW, Ren JL, Chen LH, Hu X, Yan Y. Effects of Weipixiao on Wnt pathway-associated proteins in gastric mucosal epithelial cells from rats with gastric precancerous lesions. *Chin J Integr Med* 2016; **22**: 267-275 [PMID: 25877463 DOI: 10.1007/s11655-015-2131-4]

32 **Wang H**, Wu R, Xie D, Ding L, Lv X, Bian Y, Chen X, Nisma Lena BA, Wang S, Li K, Chen W, Ye G, Sun M. A Combined Phytochemistry and Network Pharmacology Approach to Reveal the Effective Substances and Mechanisms of Wei-Fu-Chun Tablet in the Treatment of Precancerous Lesions of Gastric Cancer. *Front Pharmacol* 2020; **11**: 558471 [PMID: 33381024 DOI: 10.3389/fphar.2020.558471]

33 **Zeng J**, Ma X, Zhao Z, Chen Y, Wang J, Hao Y, Yu J, Zeng Z, Chen N, Zhao M, Tang J, Gong D. Ginsenoside Rb1 Lessens Gastric Precancerous Lesions by Interfering With β-Catenin/TCF4 Interaction. *Front Pharmacol* 2021; **12**: 682713 [PMID: 34594214 DOI: 10.3389/fphar.2021.682713]

34 **Brenes F**, Ruiz B, Correa P, Hunter F, Rhamakrishnan T, Fontham E, Shi TY. Helicobacter pylori causes hyperproliferation of the gastric epithelium: pre- and post-eradication indices of proliferating cell nuclear antigen. *Am J Gastroenterol* 1993; **88**: 1870-1875 [PMID: 7901989]

35 **Zhang Y**, Kwok-Shing Ng P, Kucherlapati M, Chen F, Liu Y, Tsang YH, de Velasco G, Jeong KJ, Akbani R, Hadjipanayis A, Pantazi A, Bristow CA, Lee E, Mahadeshwar HS, Tang J, Zhang J, Yang L, Seth S, Lee S, Ren X, Song X, Sun H, Seidman J, Luquette LJ, Xi R, Chin L, Protopopov A, Westbrook TF, Shelley CS, Choueiri TK, Ittmann M, Van Waes C, Weinstein JN, Liang H, Henske EP, Godwin AK, Park PJ, Kucherlapati R, Scott KL, Mills GB, Kwiatkowski DJ, Creighton CJ. A Pan-Cancer Proteogenomic Atlas of PI3K/AKT/mTOR Pathway Alterations. *Cancer Cell* 2017; **31**: 820-832.e3 [PMID: 28528867 DOI: 10.1016/j.ccell.2017.04.013]

36 **Bonizzi A**, Truffi M, Sevieri M, Allevi R, Sitia L, Ottria R, Sorrentino L, Sottani C, Negri S, Grignani E, Mazzucchelli S, Corsi F. Everolimus Nanoformulation in Biological Nanoparticles Increases Drug Responsiveness in Resistant and Low-Responsive Breast Cancer Cell Lines. *Pharmaceutics* 2019; **11** [PMID: 31382388 DOI: 10.3390/pharmaceutics11080384]

37 **Wang Y**, Chu F, Lin J, Li Y, Johnson N, Zhang J, Gai C, Su Z, Cheng H, Wang L, Ding X. Erianin, the main active ingredient of Dendrobium chrysotoxum Lindl, inhibits precancerous lesions of gastric cancer (PLGC) through suppression of the HRAS-PI3K-AKT signaling pathway as revealed by network pharmacology and in vitro experimental verification. *J*

Ethnopharmacol 2021; **279**: 114399 [PMID: 34246740 DOI: 10.1016/j.jep.2021.114399]
38 **Zhu F**, Xu Y, Pan J, Li M, Chen F, Xie G. Epigallocatechin Gallate Protects against MNNG-Induced Precancerous Lesions of Gastric Carcinoma in Rats *via* PI3K/Akt/mTOR Pathway. *Evid Based Complement Alternat Med* 2021; **2021**: 8846813 [PMID: 33628319 DOI: 10.1155/2021/8846813]
39 **Silva-García O**, Valdez-Alarcón JJ, Baizabal-Aguirre VM. Wnt/β-Catenin Signaling as a Molecular Target by Pathogenic Bacteria. *Front Immunol* 2019; **10**: 2135 [PMID: 31611869 DOI: 10.3389/fimmu.2019.02135]
40 **Seckin Y**, Arici S, Harputluoglu M, Yonem O, Yilmaz A, Ozer H, Karincaoglu M, Demirel U. Expression of claudin-4 and beta-catenin in gastric premalignant lesions. *Acta Gastroenterol Belg* 2009; **72**: 407-412 [PMID: 20163034]
41 **Polakis P**. Wnt signaling and cancer. *Genes Dev* 2000; **14**: 1837-1851 [PMID: 10921899]
42 **Chen Y**, Henson ES, Xiao W, Huang D, McMillan-Ward EM, Israels SJ, Gibson SB. Tyrosine kinase receptor EGFR regulates the switch in cancer cells between cell survival and cell death induced by autophagy in hypoxia. *Autophagy* 2016; **12**: 1029-1046 [PMID: 27166522 DOI: 10.1080/15548627.2016.1164357]
43 **Zhao E**, Feng L, Bai L, Cui H. NUCKS promotes cell proliferation and suppresses autophagy through the mTOR-Beclin1 pathway in gastric cancer. *J Exp Clin Cancer Res* 2020; **39**: 194 [PMID: 32958058 DOI: 10.1186/s13046-020-01696-7]
44 **Cai T**, Zhang C, Zhao Z, Li S, Cai H, Chen X, Cai D, Liu W, Yan Y, Xie K, Pan H, Zeng X. The gastric mucosal protective effects of astragaloside IV in mnng-induced GPL rats. *Biomed Pharmacother* 2018; **104**: 291-299 [PMID: 29775897 DOI: 10.1016/j.biopha.2018.04.013]
45 **Zhao B**, Wang Y, Tan X, Ke K, Zheng X, Wang F, Lan S, Liao N, Cai Z, Shi Y, Zheng Y, Lai Y, Wang L, Li Q, Liu J, Huang A, Liu X. Inflammatory Micro-environment Contributes to Stemness Properties and Metastatic Potential of HCC *via* the NF-κB/miR-497/SALL4 Axis. *Mol Ther Oncolytics* 2019; **15**: 79-90 [PMID: 31650028 DOI: 10.1016/j.omto.2019.08.009]
46 **Fan Y**, Mao R, Yang J. NF-κB and STAT3 signaling pathways collaboratively link inflammation to cancer. *Protein Cell* 2013; **4**: 176-185 [PMID: 23483479 DOI: 10.1007/s13238-013-2084-3]
47 **Moser B**, Hochreiter B, Basílio J, Gleitsmann V, Panhuber A, Pardo-Garcia A, Hoesel B, Salzmann M, Resch U, Noreen M, Schmid JA. The inflammatory kinase IKKα phosphorylates and stabilizes c-Myc and enhances its activity. *Mol Cancer* 2021; **20**: 16 [PMID: 33461590 DOI: 10.1186/s12943-021-01308-8]
48 **Zheng C**, Yin Q, Wu H. Structural studies of NF-κB signaling. *Cell Res* 2011; **21**: 183-195 [PMID: 21135870 DOI: 10.1038/cr.2010.171]
49 **DiDonato JA**, Mercurio F, Karin M. NF-κB and the link between inflammation and cancer. *Immunol Rev* 2012; **246**: 379-400 [PMID: 22435567 DOI: 10.1111/j.1600-065X.2012.01099.x]
50 **Liu K**, Zhao F, Yan J, Xia Z, Jiang D, Ma P. Hispidulin: A promising flavonoid with diverse anti-cancer properties. *Life Sci* 2020; **259**: 118395 [PMID: 32905830 DOI: 10.1016/j.lfs.2020.118395]
51 **Agharahimi M**, Badisa RB, Mazzio E, Soliman KF, Goodman CB. Cocaine potentiates an inflammatory response in C6 astroglia-like cells. *Biomed Rep* 2021; **14**: 45 [PMID: 33786174 DOI: 10.3892/br.2021.1421]
52 **Yang H**, Zhao H, Dong X, Yang Z, Chang W. Tomentosin induces apoptotic pathway by blocking inflammatory mediators *via* modulation of cell proteins in AGS gastric cancer cell line. *J Biochem Mol Toxicol* 2020; **34**: e22501 [PMID: 32227673 DOI: 10.1002/jbt.22501]
53 **Su T**, Li F, Guan J, Liu L, Huang P, Wang Y, Qi X, Liu Z, Lu L, Wang D. Artemisinin and its derivatives prevent Helicobacter pylori-induced gastric carcinogenesis *via* inhibition of NF-κB signaling. *Phytomedicine* 2019; **63**: 152968 [PMID: 31280140 DOI: 10.1016/j.phymed.2019.152968]
54 **Han S**, Yang S, Cai Z, Pan D, Li Z, Huang Z, Zhang P, Zhu H, Lei L, Wang W. Anti-Warburg effect of rosmarinic acid *via* miR-155 in gastric cancer cells. *Drug Des Devel Ther* 2015; **9**: 2695-2703 [PMID: 26056431 DOI: 10.2147/DDDT.S82342]
55 **Sun J**, Meng M. Chemoprotective Effect of Scutellarin against Gastric Cancer in Rats: An in vitro and in vivo Study. *J Oleo Sci* 2022; **71**: 1003-1012 [PMID: 35781253 DOI: 10.5650/jos.ess21399]
56 **Weidemann A**, Johnson RS. Biology of HIF-1alpha. *Cell Death Differ* 2008; **15**: 621-627 [PMID: 18259201 DOI: 10.1038/cdd.2008.12]
57 **Zimna A**, Kurpisz M. Hypoxia-Inducible Factor-1 in Physiological and Pathophysiological Angiogenesis: Applications and Therapies. *Biomed Res Int* 2015; **2015**: 549412 [PMID: 26146622 DOI: 10.1155/2015/549412]
58 **Gao Y**, Wang J, Zhao M, Xia T, Liu Q, Chen N, Liao W, Zeng Z, You F, Zeng J. Atractylenolide III Attenuates Angiogenesis in Gastric Precancerous Lesions Through the Downregulation of Delta-Like Ligand 4. *Front Pharmacol* 2022; **13**: 797805 [PMID: 35846998 DOI: 10.3389/fphar.2022.797805]
59 **Zeng J**, Yan R, Pan H, You F, Cai T, Liu W, Zheng C, Zhao Z, Gong D, Chen L, Zhang Y. Weipixiao attenuate early angiogenesis in rats with gastric precancerous lesions. *BMC Complement Altern Med* 2018; **18**: 250 [PMID: 30200948 DOI: 10.1186/s12906-018-2309-3]
60 **Kroemer G**, Pouyssegur J. Tumor cell metabolism: cancer's Achilles' heel. *Cancer Cell* 2008; **13**: 472-482 [PMID: 18538731 DOI: 10.1016/j.ccr.2008.05.005]
61 **Flaveny CA**, Griffett K, El-Gendy Bel-D, Kazantzis M, Sengupta M, Amelio AL, Chatterjee A, Walker J, Solt LA, Kamenecka TM, Burris TP. Broad Anti-tumor Activity of a Small Molecule that Selectively Targets the Warburg Effect and Lipogenesis. *Cancer Cell* 2015; **28**: 42-56 [PMID: 26120082 DOI: 10.1016/j.ccell.2015.05.007]
62 **Hirayama A**, Kami K, Sugimoto M, Sugawara M, Toki N, Onozuka H, Kinoshita T, Saito N, Ochiai A, Tomita M, Esumi H, Soga T. Quantitative metabolome profiling of colon and stomach cancer microenvironment by capillary electrophoresis time-of-flight mass spectrometry. *Cancer Res* 2009; **69**: 4918-4925 [PMID: 19458066 DOI: 10.1158/0008-5472.CAN-08-4806]
63 **Liu W**, Pan HF, Yang LJ, Zhao ZM, Yuan DS, Liu YL, Lin LZ. Panax ginseng C.A. Meyer (Rg3) Ameliorates Gastric Precancerous Lesions in Atp4a(-/-) Mice *via* Inhibition of Glycolysis through PI3K/AKT/miRNA-21 Pathway. *Evid Based Complement Alternat Med* 2020; **2020**: 2672648 [PMID: 32076440 DOI: 10.1155/2020/2672648]
64 **Cai T**, Zhang C, Zeng X, Zhao Z, Yan Y, Yu X, Wu L, Lin L, Pan H. Protective effects of Weipixiao decoction against MNNG-induced gastric precancerous lesions in rats. *Biomed Pharmacother* 2019; **120**: 109427 [PMID: 31648165 DOI:

10.1016/j.biopha.2019.109427]
65 **Zhang C**, Cai T, Zeng X, Cai D, Chen Y, Huang X, Gan H, Zhuo J, Zhao Z, Pan H, Li S. Astragaloside IV reverses MNNG-induced precancerous lesions of gastric carcinoma in rats: Regulation on glycolysis through miRNA-34a/LDHA pathway. *Phytother Res* 2018; **32**: 1364-1372 [PMID: 29577459 DOI: 10.1002/ptr.6070]
66 **Dongre A**, Weinberg RA. New insights into the mechanisms of epithelial-mesenchymal transition and implications for cancer. *Nat Rev Mol Cell Biol* 2019; **20**: 69-84 [PMID: 30459476 DOI: 10.1038/s41580-018-0080-4]
67 **Roussos ET**, Keckesova Z, Haley JD, Epstein DM, Weinberg RA, Condeelis JS. AACR special conference on epithelial-mesenchymal transition and cancer progression and treatment. *Cancer Res* 2010; **70**: 7360-7364 [PMID: 20823151 DOI: 10.1158/0008-5472.CAN-10-1208]
68 **Liao W**, Wen Y, Wang J, Zhao M, Lv S, Chen N, Li Y, Wan L, Zheng Q, Mou Y, Zhao Z, Tang J, Zeng J. Gallic acid alleviates gastric precancerous lesions through inhibition of epithelial mesenchymal transition *via* Wnt/β-catenin signaling pathway. *J Ethnopharmacol* 2023; **302**: 115885 [PMID: 36328204 DOI: 10.1016/j.jep.2022.115885]
69 **Li Y**, Li T, Chen J, Zheng H, Li Y, Chu F, Wang S, Li P, Lin J, Su Z, Ding X. Manpixiao Decoction Halted the Malignant Transformation of Precancerous Lesions of Gastric Cancer: From Network Prediction to In-Vivo Verification. *Front Pharmacol* 2022; **13**: 927731 [PMID: 35991884 DOI: 10.3389/fphar.2022.927731]
70 **Galluzzi L**, Vitale I, Aaronson SA, Abrams JM, Adam D, Agostinis P, Alnemri ES, Altucci L, Amelio I, Andrews DW, Annicchiarico-Petruzzelli M, Antonov AV, Arama E, Baehrecke EH, Barlev NA, Bazan NG, Bernassola F, Bertrand MJM, Bianchi K, Blagosklonny MV, Blomgren K, Borner C, Boya P, Brenner C, Campanella M, Candi E, Carmona-Gutierrez D, Cecconi F, Chan FK, Chandel NS, Cheng EH, Chipuk JE, Cidlowski JA, Ciechanover A, Cohen GM, Conrad M, Cubillos-Ruiz JR, Czabotar PE, D'Angiolella V, Dawson TM, Dawson VL, De Laurenzi V, De Maria R, Debatin KM, DeBerardinis RJ, Deshmukh M, Di Daniele N, Di Virgilio F, Dixit VM, Dixon SJ, Duckett CS, Dynlacht BD, El-Deiry WS, Elrod JW, Fimia GM, Fulda S, García-Sáez AJ, Garg AD, Garrido C, Gavathiotis E, Golstein P, Gottlieb E, Green DR, Greene LA, Gronemeyer H, Gross A, Hajnoczky G, Hardwick JM, Harris IS, Hengartner MO, Hetz C, Ichijo H, Jäättelä M, Joseph B, Jost PJ, Juin PP, Kaiser WJ, Karin M, Kaufmann T, Kepp O, Kimchi A, Kitsis RN, Klionsky DJ, Knight RA, Kumar S, Lee SW, Lemasters JJ, Levine B, Linkermann A, Lipton SA, Lockshin RA, López-Otín C, Lowe SW, Luedde T, Lugli E, MacFarlane M, Madeo F, Malewicz M, Malorni W, Manic G, Marine JC, Martin SJ, Martinou JC, Medema JP, Mehlen P, Meier P, Melino S, Miao EA, Molkentin JD, Moll UM, Muñoz-Pinedo C, Nagata S, Nuñez G, Oberst A, Oren M, Overholtzer M, Pagano M, Panaretakis T, Pasparakis M, Penninger JM, Pereira DM, Pervaiz S, Peter ME, Piacentini M, Pinton P, Prehn JHM, Puthalakath H, Rabinovich GA, Rehm M, Rizzuto R, Rodrigues CMP, Rubinsztein DC, Rudel T, Ryan KM, Sayan E, Scorrano L, Shao F, Shi Y, Silke J, Simon HU, Sistigu A, Stockwell BR, Strasser A, Szabadkai G, Tait SWG, Tang D, Tavernarakis N, Thorburn A, Tsujimoto Y, Turk B, Vanden Berghe T, Vandenabeele P, Vander Heiden MG, Villunger A, Virgin HW, Vousden KH, Vucic D, Wagner EF, Walczak H, Wallach D, Wang Y, Wells JA, Wood W, Yuan J, Zakeri Z, Zhivotovsky B, Zitvogel L, Melino G, Kroemer G. Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018. *Cell Death Differ* 2018; **25**: 486-541 [PMID: 29362479 DOI: 10.1038/s41418-017-0012-4]
71 **Tao W**, Li Y, Zhu M, Li C, Li P. LncRNA NORAD Promotes Proliferation And Inhibits Apoptosis Of Gastric Cancer By Regulating miR-214/Akt/mTOR Axis. *Onco Targets Ther* 2019; **12**: 8841-8851 [PMID: 31802897 DOI: 10.2147/OTT.S216862]
72 **Ohtsu A**, Ajani JA, Bai YX, Bang YJ, Chung HC, Pan HM, Sahmoud T, Shen L, Yeh KH, Chin K, Muro K, Kim YH, Ferry D, Tebbutt NC, Al-Batran SE, Smith H, Costantini C, Rizvi S, Lebwohl D, Van Cutsem E. Everolimus for previously treated advanced gastric cancer: results of the randomized, double-blind, phase III GRANITE-1 study. *J Clin Oncol* 2013; **31**: 3935-3943 [PMID: 24043745 DOI: 10.1200/JCO.2012.48.3552]
73 **Will M**, Qin AC, Toy W, Yao Z, Rodrik-Outmezguine V, Schneider C, Huang X, Monian P, Jiang X, de Stanchina E, Baselga J, Liu N, Chandarlapaty S, Rosen N. Rapid induction of apoptosis by PI3K inhibitors is dependent upon their transient inhibition of RAS-ERK signaling. *Cancer Discov* 2014; **4**: 334-347 [PMID: 24436048 DOI: 10.1158/2159-8290.CD-13-0611]
74 **Xu C**, Huang X, Huang Y, Liu X, Wu M, Wang J, Duan X. Naringin induces apoptosis of gastric carcinoma cells *via* blocking the PI3K/AKT pathway and activating prodeath autophagy. *Mol Med Rep* 2021; **24** [PMID: 34490484 DOI: 10.3892/mmr.2021.12412]
75 **Lee HJ**, Venkatarame Gowda Saralamma V, Kim SM, Ha SE, Raha S, Lee WS, Kim EH, Lee SJ, Heo JD, Kim GS. Pectolinarigenin Induced Cell Cycle Arrest, Autophagy, and Apoptosis in Gastric Cancer Cell *via* PI3K/AKT/mTOR Signaling Pathway. *Nutrients* 2018; **10** [PMID: 30096805 DOI: 10.3390/nu10081043]
76 **He JQ**, Zhang SR, Li DF, Tang JY, Wang YQ, He X, Li YM, Wu H, Zhou M, Jiao J, Xiao PL. Experimental Study on the Effect of a Weifufang on Human Gastric Adenocarcinoma Cell Line BGC-823 Xenografts and PTEN Gene Expression in Nude Mice. *Cancer Biother Radiopharm* 2020; **35**: 199-207 [PMID: 31976763 DOI: 10.1089/cbr.2019.2906]
77 **Wang Z**, Tang T, Wang S, Cai T, Tao H, Zhang Q, Qi S, Qi Z. Aloin Inhibits the Proliferation and Migration of Gastric Cancer Cells by Regulating NOX2-ROS-Mediated Pro-Survival Signal Pathways. *Drug Des Devel Ther* 2020; **14**: 145-155 [PMID: 32021099 DOI: 10.2147/DDDT.S219247]
78 **Bromberg JF**, Wrzeszczynska MH, Devgan G, Zhao Y, Pestell RG, Albanese C, Darnell JE Jr. Stat3 as an oncogene. *Cell* 1999; **98**: 295-303 [PMID: 10458605 DOI: 10.1016/s0092-8674(00)81959-5]
79 **Hackermüller J**, Reiche K, Otto C, Hösler N, Blumert C, Brocke-Heidrich K, Böhlig L, Nitsche A, Kasack K, Ahnert P, Krupp W, Engeland K, Stadler PF, Horn F. Cell cycle, oncogenic and tumor suppressor pathways regulate numerous long and macro non-protein-coding RNAs. *Genome Biol* 2014; **15**: R48 [PMID: 24594072 DOI: 10.1186/gb-2014-15-3-r48]
80 **Piao JY**, Kim SJ, Kim DH, Park JH, Park SA, Han HJ, Na HK, Yoon K, Lee HN, Kim N, Hahm KB, Surh YJ. Helicobacter pylori infection induces STAT3 phosphorylation on Ser727 and autophagy in human gastric epithelial cells and mouse stomach. *Sci Rep* 2020; **10**: 15711 [PMID: 32973302 DOI: 10.1038/s41598-020-72594-3]
81 **Liu YF**, Lu YM, Qu GQ, Liu Y, Chen WX, Liao XH, Kong WM. Ponicidin induces apoptosis *via* JAK2 and STAT3 signaling pathways in gastric carcinoma. *Int J Mol Sci* 2015; **16**: 1576-1589 [PMID: 25588213 DOI: 10.3390/ijms16011576]

82 **Tang X**, Ding Q, Chen C, Chen F, Zhou X, Hong CJ, Pan W. Micheliolide inhibits gastric cancer growth in vitro and in vivo *via* blockade of the IL-6/STAT3 pathway. *Pharmazie* 2019; **74**: 175-178 [PMID: 30961685 DOI: 10.1691/ph.2019.8816]

83 **Crone SG**, Jacobsen A, Federspiel B, Bardram L, Krogh A, Lund AH, Friis-Hansen L. microRNA-146a inhibits G protein-coupled receptor-mediated activation of NF-κB by targeting CARD10 and COPS8 in gastric cancer. *Mol Cancer* 2012; **11**: 71 [PMID: 22992343 DOI: 10.1186/1476-4598-11-71]

84 **Ernst M**, Najdovska M, Grail D, Lundgren-May T, Buchert M, Tye H, Matthews VB, Armes J, Bhathal PS, Hughes NR, Marcusson EG, Karras JG, Na S, Sedgwick JD, Hertzog PJ, Jenkins BJ. STAT3 and STAT1 mediate IL-11-dependent and inflammation-associated gastric tumorigenesis in gp130 receptor mutant mice. *J Clin Invest* 2008; **118**: 1727-1738 [PMID: 18431520 DOI: 10.1172/JCI34944]

85 **Yu H**, Pardoll D, Jove R. STATs in cancer inflammation and immunity: a leading role for STAT3. *Nat Rev Cancer* 2009; **9**: 798-809 [PMID: 19851315 DOI: 10.1038/nrc2734]

86 **Tang S**, Wang D, Zhang Q, Li L. miR-218 suppresses gastric cancer cell proliferation and invasion *via* regulation of angiopoietin-2. *Exp Ther Med* 2016; **12**: 3837-3842 [PMID: 28105117 DOI: 10.3892/etm.2016.3893]

87 **Xu J**, Zheng X, Cheng KK, Chang X, Shen G, Liu M, Wang Y, Shen J, Zhang Y, He Q, Dong J, Yang Z. NMR-based metabolomics Reveals Alterations of Electro-acupuncture Stimulations on Chronic Atrophic Gastritis Rats. *Sci Rep* 2017; **7**: 45580 [PMID: 28358020 DOI: 10.1038/srep45580]

88 **Yang J**, Wang Q, Qiao C, Lin Z, Li X, Huang Y, Zhou T, Li Y, Shen B, Lv M, Feng J. Potent anti-angiogenesis and anti-tumor activity of a novel human anti-VEGF antibody, MIL60. *Cell Mol Immunol* 2014; **11**: 285-293 [PMID: 24608894 DOI: 10.1038/cmi.2014.6]

89 **Li B**, Qu G. Inhibition of the hypoxia-induced factor-1α and vascular endothelial growth factor expression through ginsenoside Rg3 in human gastric cancer cells. *J Cancer Res Ther* 2019; **15**: 1642-1646 [PMID: 31939450 DOI: 10.4103/jcrt.JCRT_77_17]

90 **Palazon A**, Tyrakis PA, Macias D, Veliça P, Rundqvist H, Fitzpatrick S, Vojnovic N, Phan AT, Loman N, Hedenfalk I, Hatschek T, Lövrot J, Foukakis T, Goldrath AW, Bergh J, Johnson RS. An HIF-1α/VEGF-A Axis in Cytotoxic T Cells Regulates Tumor Progression. *Cancer Cell* 2017; **32**: 669-683.e5 [PMID: 29136509 DOI: 10.1016/j.ccell.2017.10.003]

91 **Zhang Y**, Coleman M, Brekken RA. Perspectives on Hypoxia Signaling in Tumor Stroma. *Cancers (Basel)* 2021; **13** [PMID: 34202979 DOI: 10.3390/cancers13123070]

92 **Deng X**, Liang X, Zhou X, Jiang M, Zhao X, Fu L, Liang M, Wang X, Liang J. Protective effect and mechanisms of Weining granule on N-methyl-N'-nitro-N- nitrosoguanidine-induced gastric cancer in rats. *J Tradit Chin Med* 2019; **39**: 393-401 [PMID: 32186011]

93 **Ohshima K**, Morii E. Metabolic Reprogramming of Cancer Cells during Tumor Progression and Metastasis. *Metabolites* 2021; **11** [PMID: 33401771 DOI: 10.3390/metabo11010028]

94 **Koppenol WH**, Bounds PL, Dang CV. Otto Warburg's contributions to current concepts of cancer metabolism. *Nat Rev Cancer* 2011; **11**: 325-337 [PMID: 21508971 DOI: 10.1038/nrc3038]

95 **Wu J**, Zhang X, Wang Y, Sun Q, Chen M, Liu S, Zou X. Licochalcone A suppresses hexokinase 2-mediated tumor glycolysis in gastric cancer *via* downregulation of the Akt signaling pathway. *Oncol Rep* 2018; **39**: 1181-1190 [PMID: 29286170 DOI: 10.3892/or.2017.6155]

96 **Chen F**, Zhuang M, Zhong C, Peng J, Wang X, Li J, Chen Z, Huang Y. Baicalein reverses hypoxia-induced 5-FU resistance in gastric cancer AGS cells through suppression of glycolysis and the PTEN/Akt/HIF-1α signaling pathway. *Oncol Rep* 2015; **33**: 457-463 [PMID: 25333894 DOI: 10.3892/or.2014.3550]

97 **Junttila MR**, de Sauvage FJ. Influence of tumour micro-environment heterogeneity on therapeutic response. *Nature* 2013; **501**: 346-354 [PMID: 24048067 DOI: 10.1038/nature12626]

98 **Pastushenko I**, Blanpain C. EMT Transition States during Tumor Progression and Metastasis. *Trends Cell Biol* 2019; **29**: 212-226 [PMID: 30594349 DOI: 10.1016/j.tcb.2018.12.001]

99 **Wang H**, Luo Y, Chu Z, Ni T, Ou S, Dai X, Zhang X, Liu Y. Poria Acid, Triterpenoids Extracted from Poria cocos, Inhibits the Invasion and Metastasis of Gastric Cancer Cells. *Molecules* 2022; **27** [PMID: 35684565 DOI: 10.3390/molecules27113629]

100 **Liu J**, Chen Y, Cao Z, Guan B, Peng J, Zhan Z, Sferra TJ, Sankararaman S, Lin J. Babao Dan inhibits the migration and invasion of gastric cancer cells by suppressing epithelial-mesenchymal transition through the TGF-β/Smad pathway. *J Int Med Res* 2020; **48**: 300060520925598 [PMID: 32529872 DOI: 10.1177/0300060520925598]

101 **Mellman I**, Coukos G, Dranoff G. Cancer immunotherapy comes of age. *Nature* 2011; **480**: 480-489 [PMID: 22193102 DOI: 10.1038/nature10673]

102 **Matsueda S**, Graham DY. Immunotherapy in gastric cancer. *World J Gastroenterol* 2014; **20**: 1657-1666 [PMID: 24587645 DOI: 10.3748/wjg.v20.i7.1657]

103 **Zhang Y**, Lou Y, Wang J, Yu C, Shen W. Research Status and Molecular Mechanism of the Traditional Chinese Medicine and Antitumor Therapy Combined Strategy Based on Tumor Microenvironment. *Front Immunol* 2020; **11**: 609705 [PMID: 33552068 DOI: 10.3389/fimmu.2020.609705]

104 **Lu X**, Li Y, Yang W, Tao M, Dai Y, Xu J, Xu Q. Inhibition of NF-κB is required for oleanolic acid to downregulate PD-L1 by promoting DNA demethylation in gastric cancer cells. *J Biochem Mol Toxicol* 2021; **35**: e22621 [PMID: 32894642 DOI: 10.1002/jbt.22621]

105 **Zhuang H**, Dai X, Zhang X, Mao Z, Huang H. Sophoridine suppresses macrophage-mediated immunosuppression through TLR4/IRF3 pathway and subsequently upregulates CD8(+) T cytotoxic function against gastric cancer. *Biomed Pharmacother* 2020; **121**: 109636 [PMID: 31733580 DOI: 10.1016/j.biopha.2019.109636]

106 **Kanojia D**, Garg M, Gupta S, Gupta A, Suri A. Sperm-associated antigen 9 is a novel biomarker for colorectal cancer and is involved in tumor growth and tumorigenicity. *Am J Pathol* 2011; **178**: 1009-1020 [PMID: 21356354 DOI: 10.1016/j.ajpath.2010.11.047]

107 **Tian SB**, Yu JC, Liu YQ, Kang WM, Ma ZQ, Ye X, Yan C. MiR-30b suppresses tumor migration and invasion by targeting EIF5A2 in gastric cancer. *World J Gastroenterol* 2015; **21**: 9337-9347 [PMID: 26309359 DOI:

10.3748/wjg.v21.i31.9337]
108 **Zhou Y**, Xu Q, Shang J, Lu L, Chen G. Crocin inhibits the migration, invasion, and epithelial-mesenchymal transition of gastric cancer cells *via* miR-320/KLF5/HIF-1α signaling. *J Cell Physiol* 2019; **234**: 17876-17885 [PMID: 30851060 DOI: 10.1002/jcp.28418]
109 **Chen X**, Yuan XN, Zhang Z, Gong PJ, Yin WN, Jiang Q, Xu J, Xu XL, Gao Y, Chen WL, Chen FF, Tian YH, Wei L, Zhang JW. Betulinic acid inhibits cell proliferation and migration in gastric cancer by targeting the NF-κB/VASP pathway. *Eur J Pharmacol* 2020; **889**: 173493 [PMID: 32860808 DOI: 10.1016/j.ejphar.2020.173493]
110 **Cai H**, Chen X, Zhang J, Wang J. 18β-glycyrrhetinic acid inhibits migration and invasion of human gastric cancer cells *via* the ROS/PKC-α/ERK pathway. *J Nat Med* 2018; **72**: 252-259 [PMID: 29098529 DOI: 10.1007/s11418-017-1145-y]
111 **Yan X**, Rui X, Zhang K. Baicalein inhibits the invasion of gastric cancer cells by suppressing the activity of the p38 signaling pathway. *Oncol Rep* 2015; **33**: 737-743 [PMID: 25502212 DOI: 10.3892/or.2014.3669]
112 **Chen W**, Yu Y, Yang N, Zhu J, Li K, Li R, Su W, Luo L, Hu L, Chen G, Deng H. Effects of Yangzheng Sanjie Decoction-containing serum mediated by microRNA-7 on cell proliferation and apoptosis in gastric cancer. *Oncol Lett* 2018; **15**: 3621-3629 [PMID: 29467883 DOI: 10.3892/ol.2018.7757]
113 Schistosomes, liver flukes and Helicobacter pylori. *IARC Monogr Eval Carcinog Risks Hum* 1994; **61**: 1-241 [PMID: 7715068]
114 **Stoffel EM**, Mangu PB, Gruber SB, Hamilton SR, Kalady MF, Lau MW, Lu KH, Roach N, Limburg PJ; American Society of Clinical Oncology; European Society of Clinical Oncology. Hereditary colorectal cancer syndromes: American Society of Clinical Oncology Clinical Practice Guideline endorsement of the familial risk-colorectal cancer: European Society for Medical Oncology Clinical Practice Guidelines. *J Clin Oncol* 2015; **33**: 209-217 [PMID: 25452455 DOI: 10.1200/JCO.2014.58.1322]
115 **Tharmalingam N**, Park M, Lee MH, Woo HJ, Kim HW, Yang JY, Rhee KJ, Kim JB. Piperine treatment suppresses Helicobacter pylori toxin entry in to gastric epithelium and minimizes β-catenin mediated oncogenesis and IL-8 secretion in vitro. *Am J Transl Res* 2016; **8**: 885-898 [PMID: 27158376]
116 **Correa P**, Haenszel W, Cuello C, Tannenbaum S, Archer M. A model for gastric cancer epidemiology. *Lancet* 1975; **2**: 58-60 [PMID: 49653 DOI: 10.1016/s0140-6736(75)90498-5]
117 **Koulis A**, Buckle A, Boussioutas A. Premalignant lesions and gastric cancer: Current understanding. *World J Gastrointest Oncol* 2019; **11**: 665-678 [PMID: 31558972 DOI: 10.4251/wjgo.v11.i9.665]
118 **Yuasa Y**. Control of gut differentiation and intestinal-type gastric carcinogenesis. *Nat Rev Cancer* 2003; **3**: 592-600 [PMID: 12894247 DOI: 10.1038/nrc1141]
119 **Malik TH**, Sayahan MY, Al Ahmed HA, Hong X. Gastric Intestinal Metaplasia: An Intermediate Precancerous Lesion in the Cascade of Gastric Carcinogenesis. *J Coll Physicians Surg Pak* 2017; **27**: 166-172 [PMID: 28406776]
120 **Zeng Z**, Nian Q, Chen N, Zhao M, Zheng Q, Zhang G, Zhao Z, Chen Y, Wang J, Zeng J, Gong D, Tang J. Ginsenoside Rg3 inhibits angiogenesis in gastric precancerous lesions through downregulation of Glut1 and Glut4. *Biomed Pharmacother* 2022; **145**: 112086 [PMID: 34799220 DOI: 10.1016/j.biopha.2021.112086]
121 **Aziz F**, Wang X, Liu J, Yan Q. Ginsenoside Rg3 induces FUT4-mediated apoptosis in H. pylori CagA-treated gastric cancer cells by regulating SP1 and HSF1 expressions. *Toxicol In Vitro* 2016; **31**: 158-166 [PMID: 26427350 DOI: 10.1016/j.tiv.2015.09.025]
122 **Zhang W**, Shu H, Fang L, Tang N, Li Y, Guo B, Meng F. Cancer inhibition mechanism of lung cancer mouse model based on dye trace method. *Saudi J Biol Sci* 2020; **27**: 1155-1162 [PMID: 32256178 DOI: 10.1016/j.sjbs.2019.12.040]
123 **Cui X**, Shen YM, Jiang S, Qian DW, Shang EX, Zhu ZH, Duan JA. Comparative analysis of the main active components and hypoglycemic effects after the compatibility of Scutellariae Radix and Coptidis Rhizoma. *J Sep Sci* 2019; **42**: 1520-1527 [PMID: 30734512 DOI: 10.1002/jssc.201801204]
124 **Dong LC**, Fan YX, Yu Q, Ma J, Dong X, Li P, Li HJ. Synergistic effects of rhubarb-gardenia herb pair in cholestatic rats at pharmacodynamic and pharmacokinetic levels. *J Ethnopharmacol* 2015; **175**: 67-74 [PMID: 26376237 DOI: 10.1016/j.jep.2015.09.012]
125 **Deng X**, Liu ZW, Wu FS, Li LH, Liang J. A clinical study of weining granules in the treatment of gastric precancerous lesions. *J Tradit Chin Med* 2012; **32**: 164-172 [PMID: 22876438 DOI: 10.1016/s0254-6272(13)60006-0]
126 **Li HZ**, Wang H, Wang GQ, Liu J, Zhao SM, Chen J, Song QW, Gao W, Qi XZ, Gao Q. Treatment of gastric precancerous lesions with Weiansan. *World J Gastroenterol* 2006; **12**: 5389-5392 [PMID: 16981274 DOI: 10.3748/wjg.v12.i33.5389]
127 **Wang J**, Xu L, Shi R, Huang X, Li SW, Huang Z, Zhang G. Gastric atrophy and intestinal metaplasia before and after Helicobacter pylori eradication: a meta-analysis. *Digestion* 2011; **83**: 253-260 [PMID: 21282951 DOI: 10.1159/000280318]
128 **Pan X**, Tao H, Nie M, Liu Y, Huang P, Liu S, Sun W, Wu J, Ma T, Dai A, Lu J, Liu B, Zou X, Sun Q. A clinical study of traditional Chinese medicine prolonging the survival of advanced gastric cancer patients by regulating the immunosuppressive cell population: A study protocol for a multicenter, randomized controlled trail. *Medicine (Baltimore)* 2020; **99**: e19757 [PMID: 32311976 DOI: 10.1097/MD.0000000000019757]
129 **Xu Y**, Zhao AG, Li ZY, Zhao G, Cai Y, Zhu XH, Cao ND, Yang JK, Zheng J, Gu Y, Han YY, Zhu YJ, Yang JZ, Gao F, Wang Q. Survival benefit of traditional Chinese herbal medicine (a herbal formula for invigorating spleen) for patients with advanced gastric cancer. *Integr Cancer Ther* 2013; **12**: 414-422 [PMID: 22781545 DOI: 10.1177/1534735412450512]
130 **Shu P**, Tang H, Zhou B, Wang R, Xu Y, Shao J, Qi M, Xia Y, Huang W, Liu S. Effect of Yiqi Huayu Jiedu decoction on stages II and III gastric cancer: A multicenter, prospective, cohort study. *Medicine (Baltimore)* 2019; **98**: e17875 [PMID: 31764782 DOI: 10.1097/MD.0000000000017875]
131 **Lv S**, Chen X, Chen Y, Gong D, Mao G, Shen C, Xia T, Cheng J, Luo Z, Cheng Y, Li W, Zeng J. Ginsenoside Rg3 induces apoptosis and inhibits proliferation by down-regulating TIGAR in rats with gastric precancerous lesions. *BMC Complement Med Ther* 2022; **22**: 188 [PMID: 35840932 DOI: 10.1186/s12906-022-03669-z]
132 **Yang C**, Du W, Yang D. Inhibition of green tea polyphenol EGCG((-)-epigallocatechin-3-gallate) on the proliferation of

gastric cancer cells by suppressing canonical wnt/β-catenin signalling pathway. *Int J Food Sci Nutr* 2016; **67**: 818-827 [PMID: 27338284 DOI: 10.1080/09637486.2016.1198892]

133 **Fu JD**, Yao JJ, Wang H, Cui WG, Leng J, Ding LY, Fan KY. Effects of EGCG on proliferation and apoptosis of gastric cancer SGC7901 cells *via* down-regulation of HIF-1α and VEGF under a hypoxic state. *Eur Rev Med Pharmacol Sci* 2019; **23**: 155-161 [PMID: 30657557 DOI: 10.26355/eurrev_201901_16759]

134 **Geng X**, Zhang X, Zhou B, Zhang C, Tu J, Chen X, Wang J, Gao H, Qin G, Pan W. Usnic Acid Induces Cycle Arrest, Apoptosis, and Autophagy in Gastric Cancer Cells In Vitro and In Vivo. *Med Sci Monit* 2018; **24**: 556-566 [PMID: 29374767 DOI: 10.12659/msm.908568]

135 **Xu J**, Wang Z, Huang Y, Wang Y, Xiang L, He X. A spirostanol saponin isolated from Tupistra chinensis Baker simultaneously induces apoptosis and autophagy by regulating the JNK pathway in human gastric cancer cells. *Steroids* 2020; **164**: 108737 [PMID: 33002483 DOI: 10.1016/j.steroids.2020.108737]

136 **Chen J**, Shi DY, Liu SL, Zhong L. Tanshinone IIA induces growth inhibition and apoptosis in gastric cancer in vitro and in vivo. *Oncol Rep* 2012; **27**: 523-528 [PMID: 22038415 DOI: 10.3892/or.2011.1524]

137 **Sun JY**, Zhu MZ, Wang SW, Miao S, Xie YH, Wang JB. Inhibition of the growth of human gastric carcinoma in vivo and in vitro by swainsonine. *Phytomedicine* 2007; **14**: 353-359 [PMID: 17097281 DOI: 10.1016/j.phymed.2006.08.003]

138 **Li SG**, Wang YY, Ye ZY, Shao QS, Tao HQ, Shu LS, Zhao YF, Yang YJ, Yang J, Peng T, Han B, Huang D. Proliferative and apoptotic effects of andrographolide on the BGC-823 human gastric cancer cell line. *Chin Med J (Engl)* 2013; **126**: 3739-3744 [PMID: 24112174]

139 **Liu G**, Xiang T, Wu QF, Wang WX. Curcumin suppresses the proliferation of gastric cancer cells by downregulating H19. *Oncol Lett* 2016; **12**: 5156-5162 [PMID: 28105222 DOI: 10.3892/ol.2016.5354]

140 **Lee HH**, Lee S, Shin YS, Cho M, Kang H, Cho H. Anti-Cancer Effect of Quercetin in Xenograft Models with EBV-Associated Human Gastric Carcinoma. *Molecules* 2016; **21** [PMID: 27681719 DOI: 10.3390/molecules21101286]

141 **Saralamma VV**, Nagappan A, Hong GE, Lee HJ, Yumnam S, Raha S, Heo JD, Lee SJ, Lee WS, Kim EH, Kim GS. Poncirin Induces Apoptosis in AGS Human Gastric Cancer Cells through Extrinsic Apoptotic Pathway by up-Regulation of Fas Ligand. *Int J Mol Sci* 2015; **16**: 22676-22691 [PMID: 26393583 DOI: 10.3390/ijms160922676]

142 **Wang P**, Jin JM, Liang XH, Yu MZ, Yang C, Huang F, Wu H, Zhang BB, Fei XY, Wang ZT, Xu R, Shi HL, Wu XJ. Helichrysetin inhibits gastric cancer growth by targeting c-Myc/PDHK1 axis-mediated energy metabolism reprogramming. *Acta Pharmacol Sin* 2022; **43**: 1581-1593 [PMID: 34462561 DOI: 10.1038/s41401-021-00750-0]

143 **Zang MD**, Hu L, Fan ZY, Wang HX, Zhu ZL, Cao S, Wu XY, Li JF, Su LP, Li C, Zhu ZG, Yan M, Liu BY. Luteolin suppresses gastric cancer progression by reversing epithelial-mesenchymal transition *via* suppression of the Notch signaling pathway. *J Transl Med* 2017; **15**: 52 [PMID: 28241766 DOI: 10.1186/s12967-017-1151-6]

144 **Zhu J**, Wen K. Astragaloside IV inhibits TGF-β1-induced epithelial-mesenchymal transition through inhibition of the PI3K/Akt/NF-κB pathway in gastric cancer cells. *Phytother Res* 2018; **32**: 1289-1296 [PMID: 29480652 DOI: 10.1002/ptr.6057]

145 **Zeng J**, Guo J, Gong D, Zhang Y, You F, Liang C, Pan H, Cai T, Chen X, Chen L, Zhao Z. Weipixiao ameliorates gastric precancerous lesions in a rat's model by regulating GSK3|Â and C-myc. *J Tradit Chin Med* 2018; **38**: 705-713 [PMID: 32185987]

146 **Cai Y**, Cao Y, Cheng S, Zou L, Yang T, Zhang Y, Shou Q, Chen B, Chen W. Study on the Mechanism of Sancao Tiaowei Decoction in the Treatment of MNNG-Induced Precancerous Lesions of Gastric Carcinoma Through Hedgehog Signaling Pathway. *Front Oncol* 2022; **12**: 841553 [PMID: 35646631 DOI: 10.3389/fonc.2022.841553]

147 **Hao X**, Zhou P, Yang Z, Yang T, Wang Y. The therapeutic effect of Huazhuojiedu decoction on precancerous lesions in a gastric cancer model *via* the regulation of lnc 517368. *J Ethnopharmacol* 2022; **283**: 114635 [PMID: 34648901 DOI: 10.1016/j.jep.2021.114635]

148 **Xu J**, Shen W, Pei B, Wang X, Sun D, Li Y, Xiu L, Liu X, Lu Y, Zhang X, Yue X. Xiao Tan He Wei Decoction reverses MNNG-induced precancerous lesions of gastric carcinoma in vivo and vitro: Regulation of apoptosis through NF-κB pathway. *Biomed Pharmacother* 2018; **108**: 95-102 [PMID: 30218863 DOI: 10.1016/j.biopha.2018.09.012]

149 **Shen SW**, Yuwen Y, Zhang ZL, Dong S, Liu JT, Wang XM. Effect of Jinguo Weikang Capsule on proto-oncogene expression of gastric mucosa in rats with gastric precancerous lesions. *Chin J Integr Med* 2008; **14**: 212-216 [PMID: 18853119 DOI: 10.1007/s11655-008-0212-3]

150 **Wang X**, Xu J, Zhang X, Zhang C, Zheng W, Jiao J, Liu X, Yue X. Effects of Jinlongshe granules on gastric precancerous lesions in rats and its mechanism. *Int J Clin Exp Pathol* 2020; **13**: 846-853 [PMID: 32509055]

151 **Yi Z**, Jia Q, Lin Y, Wang Y, Cong J, Gu Z, Ling J, Cai G. Mechanism of Elian granules in the treatment of precancerous lesions of gastric cancer in rats through the MAPK signalling pathway based on network pharmacology. *Pharm Biol* 2022; **60**: 87-95 [PMID: 34962453 DOI: 10.1080/13880209.2021.2017980]

152 **Liu W**, Zhao ZM, Liu YL, Pan HF, Lin LZ. Weipiling ameliorates gastric precancerous lesions in Atp4a(-/-) mice. *BMC Complement Altern Med* 2019; **19**: 318 [PMID: 31744486 DOI: 10.1186/s12906-019-2718-y]

153 **Fang SQ**, Liu YH, Zhao KP, Zhang HX, Wang HW, Deng YH, Zhou YX, Ge GB, Ni HM, Chen QL. Transcriptional profiling and network pharmacology analysis identify the potential biomarkers from Chinese herbal formula Huosu Yangwei Formula treated gastric cancer in vivo. *Chin J Nat Med* 2021; **19**: 944-953 [PMID: 34961592 DOI: 10.1016/S1875-5364(22)60154-7]

154 **Yuan M**, Zou X, Liu S, Xu X, Wang H, Zhu M, Xie X, Wu J, Sun Q. Modified Jian-pi-yang-zheng decoction inhibits gastric cancer progression *via* the macrophage immune checkpoint PI3Kγ. *Biomed Pharmacother* 2020; **129**: 110440 [PMID: 32768942 DOI: 10.1016/j.biopha.2020.110440]

155 **Li L**, Jin XJ, Li JW, Li CH, Zhou SY, Li JJ, Feng CQ, Liu DL, Liu YQ. Systematic insight into the active constituents and mechanism of Guiqi Baizhu for the treatment of gastric cancer. *Cancer Sci* 2021; **112**: 1772-1784 [PMID: 33682294 DOI: 10.1111/cas.14851]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com