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Chapter

Chinese Medicines for Cancer Treatment from the Metabolomics Perspective

Wei Guo, Hor-Yue Tan, Ning Wang and Yibin Feng

Abstract

Cancer is one of the most prevalent diseases all over the world with poor prognosis and the development of novel therapeutic strategies is still urgently needed. The large amount of successful experiences in fighting against cancer-like diseases with Chinese medicine has suggested it as a great source of alternative treatments to human cancers. Cancer cells have been shown to own a predominantly unique metabolic phenotype to facilitate their rapid proliferation. Metabolic reprogramming is a remarkable hallmark of cancer and therapies targeting cancer metabolism can be highly specific and effective. Based on the sophisticated study of small molecule metabolites, metabolomics can provide us valuable information on dynamically metabolic responses of living systems to certain environmental condition. In this chapter, we systematically reviewed recent studies on metabolism-targeting anticancer therapies based on metabolomics in terms of glucose, lipid, amino acid, and nucleotide metabolisms and other altered metabolisms, with special emphasis on the potential of metabolic treatment with pure compounds, herb extracts, and formulations from Chinese medicines. The trends of future development of metabolism-targeting anticancer therapies were also discussed. Overall, the elucidation of the underlying molecular mechanism of metabolism-targeting pharmacologic therapies will provide us a new insight to develop novel therapeutics for cancer treatment.

Keywords: metabolomics, cancer metabolism, adjuvant therapies, Chinese medicines

1. Introduction

Despite all recent improvements in early detection and pleiotropic therapeutics, cancer is still the leading cause of death all over the world [1]. It is one of the most prevalent diseases with complex risk factors, and the mortality rate is similar to its morbidity, which reflects its poor prognosis. It has been projected that approximately 3.12 million new cases of cancer and a cancer death toll of 2.5 million will occur per year in China, which brings a huge burden on society [2]. To date, there are three conventional cancer therapies for cancer, including surgical resection, chemotherapy, and radiotherapy. However, diverse drawbacks and limitations have been observed in these cancer therapies either alone or in combination. For example, most cancer patients are not suitable to undergo the surgical resection due

to the late diagnosis and other factors. As the major therapies for cancer patients in middle and advanced stages, chemotherapy and radiotherapy have been shown to present serious side effects and complications, such as myelosuppression, hematological toxicity, cardiac damage, and liver and kidney dysfunction [1, 3]. Moreover, tumor cells have the ability to develop resistance to evade cell death, and the therapeutic efficacy of the current chemotherapeutic drugs is significantly reduced by the increasingly acquired drug resistance [4]. Therefore, it imminently deserves to develop more effective and less toxic adjuvant therapies for cancer prevention and treatment.

1.1 Cancer metabolism

It has been reported that cell metabolism has an essential role in the pathological progression of cancer and metabolic reprogramming is a remarkable hallmark of cancer [5]. Cancer cells have been shown to own a predominantly unique metabolic phenotype to facilitate their rapid proliferation, which is dramatically different from normal cells. Cancer cells tend to acquire energy via glycolysis rather than the much more efficient oxidative phosphorylation pathway even in aerobic conditions, which is the famous phenomenon of cancer called the "Warburg effect" [6]. Besides the consumption of glucose, cancer cells have also been reported to favor glutamine as a preferential fuel [7]. Accumulating evidences indicate that mutations in metabolic enzymes can promote the development of cancer. For example, mutations in the tricarboxylic acid (TCA) cycle enzyme isocitrate dehydrogenase, succinate dehydrogenase, and fumarate hydratase can affect the corresponding metabolites a-ketoglutarate, succinate, and fumarate. These changes can further affect the 2-oxoglutarate-dependent dioxygenases and then result in some cancers, such as paraganglioma and renal cell cancer [8–10]. What is more, the drug resistance of cancer cells is also shown to be associated with their metabolic alterations [11]. In this perspective, cancer metabolism has become a potentially fertile area, and therapies targeting cancer metabolism can be highly specific and effective. Nowadays metabolism-targeting anticancer therapies are drawing researchers' great attention and becoming a new therapeutics for cancer treatment [12].

1.2 Metabolomics and cancer

As a valuable complement to emerging "omics" science including genomics, transcriptomics, and proteomics, metabolomics utilizes leading-edge analytical chemistry technologies and advanced computational approaches to characterize the small endogenous and exogenous molecule metabolites in various biochemical metabolisms from complex biochemical mixtures [13]. Metabolomics can provide us a direct readout on dynamically metabolic responses of living systems to certain genetic modifications or pathophysiological stimuli [14], which has been extensively adopted in the field of disease diagnosis, pharmacodynamic evaluation, therapeutical monitoring, and drug discovery [15]. There are three main analytical chemistry platforms in metabolomics research, namely, nuclear magnetic resonance (NMR) spectroscopy, liquid chromatography mass spectrometry (LC-MS), and gas chromatography MS (GC/MS). Each platform has its own strengths and limitations. There are three main methodological approaches to analyze the small metabolites in metabolomics, namely, targeted, untargeted, and stable isotope-resolved metabolomics (SIRM). Numerous systemic reviews have shown in detail how each analytical platform and methodological approach works in metabolomics studies [16–20].

As mentioned above, cell metabolism has an essential role in the pathological progression of cancer, and metabolic reprogramming is a remarkable hallmark of cancer. In this context, it would be conducive to employ metabolomics in the field of cancer research for exploration of tumorigenesis mechanisms, diagnosis and monitoring of tumor, as well as discovery of novel anticancer therapies [21–23].

1.3 Chinese medicines and cancer treatment

Due to their various biological activities and low toxicity, natural products derived from Chinese medicines are reported to be an excellent source for anticancer drugs as a complementary and alternative approach [24]. Chinese medicines have evolved with their own unique theoretical system in Asian countries, especially China over thousands of years. Chinese medicines are usually divided into pure compounds, herb extracts, and formulations. Formulations from Chinese medicines are extensively employed in Chinese hospitals for clinical cancer treatment [25]. Numerous Chinese herb extracts have been reported to show inhibitory effects on cancers [26]. An increasing number of pure compounds derived from Chinese medicine herbs have been shown to inhibit the development of cancers through various mechanisms [27–30]. Besides, a large number of studies have revealed that Chinese medicines in combination with conventional chemotherapy and radiotherapy could increase the therapeutic efficacy and decrease the serious side effects and complications of these therapies [31, 32]. It is convinced that Chinese medicines are gaining increasing reputation and credibility as adjuvant therapies for cancer prevention and treatment.

Although Chinese medicines have been employed in cancer prevention and treatment for a long time, the underlying mechanisms on how they work remain to be fully elucidated because of their unique medical system with multicomponent nature. In accordance with the holistic perspective of Chinese medicines, metabolomics opens up a unique and novel insight into efficacy evaluation and action mechanism exploration of Chinese medicines as adjuvant therapies for cancer prevention and treatment.

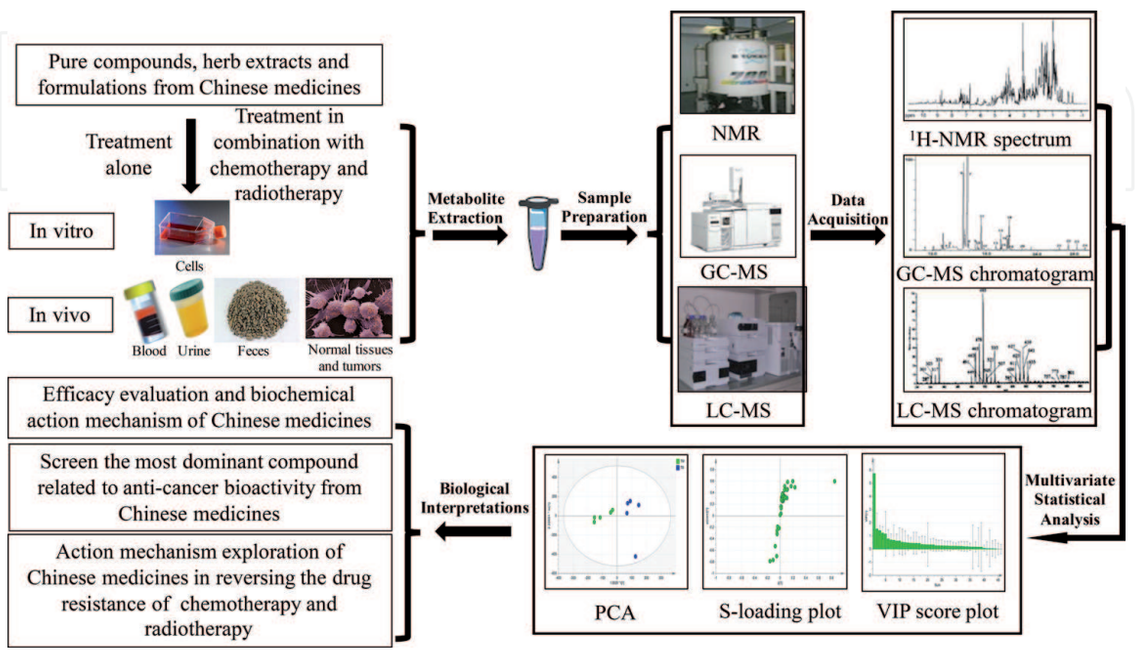

Figure 1.
The typical flowchart of metabolomics studies on antineoplastic Chinese medicines.

References	Pure compound	Cancer	Study	Method	Significantly changed metabolites or pathways	Main findings
26,700,591	Geranylgeranoic acid	Hepatoma	HuH-7 cells in vitro	UPLC/TOF/MS	GGA induced a time-dependent increase in the cellular contents of fructose 6-phosphate and decrease of fructose 1,6-diphosphate	GGA may shift HuH-7 cells from aerobic glycolysis to mitochondrial respiration through the immediate upregulation of TIGAR and SCO2 protein levels
26,160,839	Halofuginone	Colorectal cancer	HCT116 cells in vitro	UPLC-MS/MS, GC/MS and UPLC/LTQ-Orbitrap MS	Metabolomics delineated the slower rates in both glycolytic flux and glucose-derived tricarboxylic acid cycle flux	HF regulates Akt/mTORC1 signaling pathway to dampen glucose uptake and glycolysis in CRC cells
29,589,762	(−)-5-Hydroxy-equol	Hepatocellular Carcinoma	SMMC-7721 cells in vitro	1H NMR	(−)-5-Hydroxy-equol treatment significantly altered energy and amino acid metabolism	Integrated metabolomics and further verifications may facilitate the exploration of the anti-HCC mechanisms of (−)-5-hydroxy-equol
29,802,724	Nummularic acid (NA)	Prostate cancer (PCa)	DU-145 and C4-2 cells in vitro	ALEX-CIS GC–TOF-MS	The metabolism pathways related to glycolysis, TCA, and glutamine metabolisms were changed after NA treatment	NA may induce energy crisis to inhibit PCa
30,391,728	Magnoline	Prostate cancer	22RV1 cells in vitro	UPLC-MS	Magnoline markedly restored the energy metabolism, amino acid metabolism, and fatty acid metabolism	Cancer cells may result in death because of insufficient material basis to favor their rapid proliferation

References	Pure compound	Cancer	Study	Method	Significantly changed metabolites or pathways	Main findings
28,651,973	1,25-Dihydroxyvitamin D3	Prostate cancer	LNCaP cells in vitro	GC/ MS	1,25(OH)2D3 decreased glucose uptake and increased citrate/isocitrate due to TCA cycle truncation	Re-wiring glucose metabolizing pathways, and induction of a "differentiated" metabolic phenotype by 1,25(OH)2D3, may prove clinically beneficial.
26,541,605	Vitamin C	Colorectal cancer	KRAS and BRAF mutant lines and isogenic wild-type counterparts in vitro	LC-MS/MS	High levels of vitamin C increased uptake of dehydroascorbic acid (DHA) and decreased glutathione	These results provide a mechanistic rationale for exploring the therapeutic use of vitamin C for CRCs with KRAS or BRAF mutations
28,916,726	β-Lapachone	Pancreatic ductal adenocarcinoma	MiaPaCa2 cells in vitro	GC/MS and 1H NMR	β-lap treatment was found to decrease the NAD-sensitive pathways, such as glycolysis and TCA cycle	Targeting NQO1 may sensitize the treatment of β-lap
28,737,429	Diethylstilbestrol	Prostate cancer	PC3 cells in vitro	1H NMR	Lactate, phosphocreatine, and GSH were the biomarkers for DES treatment	DES upon conjugation had a more specific effect and less toxicity
28,918,937	Koningic acid	Colorectal cancer	HCT116 cells in vitro	Integrated pharmacogenomics and LC-HRMS metabolomics	Glycolysis was the highest scoring pathway only in KA-treated cells	KA efficacy is not determined by the status of individual genes but by the quantitative extent of the WE, leading to a therapeutic window in vivo

References	Pure compound	Cancer	Study	Method	Significantly changed metabolites or pathways	Main findings
30,114,709	Omega-3 polyunsaturated fatty acids	Breast cancer	MCF7 cells in vitro	GC/MS	Glycolysis and glutamine metabolism pathways were markedly reduced when treated with the combination of Rp and ω-3 PUFAs	ω-3 PUFA could increase the anti-breast cancer potential of Rp
28,198,625	Curcumin	Hepatocarcinoma	Serum from DEN-induced hepatocarcinogenesis model	GC/MS	Curcumin attenuated metabolic disorders via increasing concentration of glucose and fructose, and decreasing levels of glycine and proline	Curcumin exhibited a potent liver protective agent inhibiting chemically induced liver injury through suppressing liver cellular metabolism in the prospective application
29,448,205	6,7-Dimethoxy-1,2,3,4-tetrahydro-iso- quinoline-3-carboxylic acid	Colorectal carcinoma	Serum from DMH-induced CRC albino Wistar rat model in vivo	1H NMR	M1 exhibited to reverse the perturbed metabolism pathways in CRC condition, including glycolysis, TCA cycle, choline, phosphatidylinositol and gluconeogenesismetabolisms	M1 has the anti-CRC potential via the blockade of IL-6/JAK2/STAT3 oncogenic signaling
27,416,811	Physapubenolide	Hepatocellular carcinoma	HepG2 cells in vitro and tumor tissues and plasma from a mouse-xenograft model bearing liver carcinoma H22 cells in vivo	GC/MS	PB disturbed the metabolic pattern and significantly decreased lactate production	PB exhibits anticancer activities through suppression of glycolysis via the Akt-p53 pathway
30,322,263	Naringenin	Lung cancer	Serum from the urethane-induced lung cancer rat model in vivo	1H NMR	The glycolysis was restored to normal levels with co-therapy of Gnb and Nar	Co-therapy has the superiority over alone treatment to improve the therapeutic efficacy

References	Pure compound	Cancer	Study	Method	Significantly changed metabolites or pathways	Main findings
26,859,520	Flexibilide	Colon cancer	HCT-116 cells in vitro	UPLC/Q-TOF MS	Flexibilide exhibited the therapeutic effect on colon cancer mainly via downregulating PC biosynthesis pathway	Flexibilide exhibited the therapeutic effect on colon cancer mainly via down-regulating PC biosynthesis pathway
28,296,891	Englerin A	Clear cell renal carcinoma	A498 cells in vitro	LC-MS/MS	Englerin A significantly reversed lipid metabolism and increase ceramides levels	Ceramides may be a mediator of some of the actions of englerin A
28,948,276	Isoquercitrin	Bladder cancer	T24 cells in vitro	UPLC/Q-TOF MS	Isoquercitrin treatment was found to regulate lipid and anaerobic glycolysis	ISO influenced T24 bladder cancer cell metabolism, and this process was mainly involved in activating the AMPK pathway
28,496,003	Peiminine	Colorectal cancer	UPLC-MS and GC/MS	UPLC-MS and GC/MS	Peiminine treatment altered several metabolites, including lignocerate (24:0), oleate (18:1n9), glutamine, and glucose	Peiminine exerted the predominant therapeutic effect mainly via the metabolic regulation of lipids, amino acids, and carbohydrates
29,321,577	8u	Hepatocellular carcinoma	HepG2 cells in vitro	UPLC/Q-TOF MS	8u was found to significantly inhibit the invasion and metastasis of HepG2 cells and regulate intracellular lipid metabolism	8u could efficiently suppress the invasion and metastasis of HepG2 cells by decreasing the expression of HSP90α protein and inhibiting the PI3K/Akt signaling pathway

References	Pure compound	Cancer	Study	Method	Significantly changed metabolites or pathways	Main findings
28,125,641	Genistein and calcitriol	Osteosarcoma	MG-63 Cells in vitro	GC/MS	Co-therapy of genistein and calcitriol was found to regulate lipids and amino acids rather than energy metabolism	The promotional effects of high level of genistein on osteosarcoma could be decreased by the co-treatment of calcitriol
27,533,043	Silibinin	Prostate cancer	Tumor tissues from 22Rv1 Xenograft model in vivo	1H-NMR	Silibinin treatment did not greatly affect glucose uptake of PCa tumor but decreased the lipid synthesis	These findings further support silibinin usefulness against PCa through inhibiting hypoxia-induced signaling
26,744,170	Acyclic retinoid	Hepatocellular carcinoma	Liver tissues from mouse DEN-induced HCC model in vivo	CE-TOFMS and LC-TOFMS	ACR predominantly reversed lipogenesis but not glucose metabolism by inhibiting linoleic acid metabolites	Lipid metabolic reprogramming plays a critical role in the protective effects of ACR on HCC
30,871,192	Delta-tocotrienol	Non-small cell lung cancer	A549 and H1299 cells in vitro	1H-NMR	Cellular metabolomics analysis showed significant inhibition in the uptake of glutamine, its derivatives glutamate and glutathione, and some EAAs in both cell lines with δT treatment	δT treatment could suppress the glutamine uptake via suppressing glutamine transporters and then resulted in the induction of apoptosis and suppression of cell proliferation

References	Pure compound	Cancer	Study	Method	Significantly changed metabolites or pathways	Main findings
30,068,874	Celastrol	Colon cancer	HCT116 cells in vitro	UPLC/MS	Metabolomics analysis found celastrol changed the levels of lipid markers, carnitine and amino acids. Tryptophan was further identified as a special biomarker by targeted metabolite analysis	The suppression of IDO expression and tryptophan catabolism may be part of the mechanisms of celastrol in its cytotoxic effect against HCT116 colon cancer cells
27,754,384	Melittin	Ovarian cancer	A2780 and A2780CR cell lines in vitro	LC-MS	Melittin treatment of cisplatin-sensitive cells decreased glutamine, proline, and arginine pathways	Melittin might have some potential as an adjuvant therapy in cancer treatment
28,674,386	Chlorogenic acid and caffeic acid	Hepatocellular carcinoma	Serum from DEN-induced HCC model in vivo	16 S rRNA and LC-MS, GC/MS-MS, GC/MS	Both CaA and ChA treatment reverse 28 metabolites	The levels of ethanolamine, L-methionine, L-tyrosine, and bilirubin were associated with diminished Prevotella 9 and Lachnospiraceae incertae sedis and elevated Ruminococcaceae UCG-004
29,202,102	Resveratrol, curcumin and ursolic acid	Prostate cancer	Serum from a mouse allograft model of prostate cancer in vivo	LC-MS and GC/MS	Glutamine metabolism was regulated by the compound combinations	Compared with the individual treatment, the combined treatment has the greater antineoplastic property

References	Pure compound	Cancer	Study	Method	Significantly changed metabolites or pathways	Main findings
29,651,531		Hepatoma	SMMC7721 cells in vitro	GC/MS and LC/MS	GLA treatment diminished amino acid metabolism and elevated the metabolisms of sphingolipid, purine, and pyrimidine	GC/MS- and LC/MS-based metabolomics applied to cell culture enhanced our current understanding of the metabolic response to GLA treatment and its mechanism
26,851,007	Taurine	Breast cancer	Plasma from dimethylbenz[a] anthracene-induced breast carcinogenesis in rats in vivo	GC–TOFMS	Taurine treatment regulated 23 differential metabolites, which were associated with glucose, energy and amino acid, as well as nucleic acid metabolism	The antitumor activity of taurine in rats is mediated through altered metabolism of breast cancer cells
27,374,097	Celastrol	Acute promyelocytic leukemia	HL-60 cells in vitro and tumor tissue from mice xenograft model in vivo	UPLC-MS	Celastrol treatment regulated uridine metabolite, which further enhances apoptosis	The study firstly reveals that uridine deficiency contributes to mitochondrial apoptosis induced by celastrol in APL cells
29,787,425	Gamma-tocotrienol	Cancer	Serum from nonhuman primate models in vivo	UPLC/Q-TOF MS	GT3 could regulate the changed fatty acid beta-oxidation, amino acid and purine catabolism metabolism caused by irradiation	This initial assessment also highlights the utility of metabolomics in determining underlying physiological mechanisms responsible for the radioprotective efficacy of gamma-tocotrienol

References	Pure compound	Cancer	Study	Method	Significantly changed metabolites or pathways	Main findings
27,335,141	Fisetin	Prostate cancer	Tumor tissues from prostate cancer xenografts in vivo	HPLC/ESI–MS	Fisetin treatment was shown to downregulate secreted and intracellular hyaluronan (HA), which conferred resistance to prostate oncogenesis	Fisetin is an effective, nontoxic, potent HA synthesis inhibitor
29,978,476	Galactolipid 1,2-di-O-linolenoyl-3-O- β-galactopyranosyl-sn-glycerol	Melanoma	Serum from a syngeneic mouse model implanted with B16 melanoma in vivo	LC-MS/MS	dLGG treatment markedly elevated 12/15-LOX catalyzed oxylipin products in serum	This study shows the novel therapeutic effect of phytoagent dLGG and suggests its potential as a therapeutic agent for metastatic melanoma
30,668,340	Deoxyelephantopin	Melanoma	Kidney tissues from murine B16 metastatic allograft model in vivo	UPLC/ESI-QTOF MS	Co-therapy of DET and cisplatin could reverse the changed urea cycle metabolites and hippuric acid in renal tissues caused by cisplatin	The co-therapy of DET and cisplatin could be an effective treatment with low toxicity for melanoma

Table 1.
Summary of recent metabolomic studies on anticancer therapies of pure compounds from Chinese medicines.

Increasing excellent reviews have been focused on the application of metabolomics in the metabolic changes and the possible underlying mechanisms behind these alterations in the pathogenesis of different kinds of cancer [33–35]. Little reviews have been highlighted on the metabolism-based anticancer therapies. Since Chinese medicine has been suggested to be a great source of alternative treatments to human cancers, in this chapter we systematically reviewed recent studies from 2015 to March 2019 on metabolism-targeting anticancer therapies based on metabolomics in terms of glucose, lipid, amino acid, and nucleotide metabolisms and other altered metabolisms, with special emphasis on the potential of metabolic treatment with pure compounds, herb extracts, and formulations from Chinese medicines. The typical flowchart of metabolomics studies on antineoplastic Chinese medicines is shown in **Figure 1**. **Table 1** summarized the recent metabolomics studies on anticancer therapies of pure compounds from Chinese medicines. At the same time, the trends of future development of metabolism-targeting anticancer therapies were also discussed.

2. Review on metabolism-targeting Chinese medicine treatment on human cancers

2.1 Glucose metabolism

As mentioned above, cancer cells tend to acquire energy via glycolysis rather than the much more efficient oxidative phosphorylation pathway even in aerobic conditions. Glucose and energy metabolisms play an important role in the tumorigenesis of cancer and could be the therapeutic targets for cancer treatment. Pure compounds, herb extracts, and formulations from Chinese medicines, which target glucose and energy metabolisms, are attracting increasing attention for the development of anticancer therapies.

Geranylgeranoic acid (GGA), a kind of acyclic diterpenoids, is derived from some medicinal herbs such as turmeric. UPLC/TOF/MS-based metabolomics analysis was used to study the underlying anticancer mechanism of GGA in human hepatoma-derived HuH-7 cells [36]. It was found that GGA may shift the energetic state of HuH-7 cells from aerobic glycolysis to mitochondrial respiration, which was revealed by a time-dependent augment of fructose 6-phosphate and decline of fructose 1,6-diphosphate in HuH-7 cells after GGA treatment. Halofuginone (HF) is an active compound derived from the febrifugine which can be extracted from the Chinese herb *Dichroa febrifuga* Lour. Chen and his colleagues used the combination of UPLC-MS/MS, GC/MS, and UPLC/LTQ-Orbitrap MS metabolomics from HCT116 cells in vitro to study the anti-colorectal cancer (CRC) properties of HF [37]. They found the slower rates in the fluxes of both glycolytic and glucose-derived TCA cycle after HF treatment mainly via Akt/mTORC1 signaling pathway. (−)-5-Hydroxy-equol, as an isoflavone derived from microbial biotransformation, was shown to exhibit anti-hepatocellular carcinoma (HCC) potential. To explore the underlying mechanism, a ^{1}H NMR-based metabolomics of SMMC-7721 cells in vitro was conducted [38]. It was found that (−)-5-hydroxy-equol treatment significantly altered energy and amino acid metabolisms, which revealed that integrated metabolomics and further verifications may facilitate the exploration of the anti-HCC mechanisms of (−)-5-hydroxy-equol. Nummularic acid (NA) is a triterpenoid isolated from a medicinal plant *Fraxinus xanthoxyloides*. To explore its anticancer potential, a ALEX-CIS GC–TOF-MS-based metabolomics analysis of DU-145 and C4-2 cells in vitro was performed [39]. It was shown that the metabolism pathways related to

glycolysis, TCA, and glutamine metabolisms were changed after NA treatment, which suggested NA may induce energy crisis to inhibit prostate cancer. Magnoline is the primary compound derived from *Cortex Phellodendri amurensis*, which exhibits significant therapeutic potential for PCa. Sun et al. conducted a UPLC-MS metabolomics of 22RV1 cells in vitro on PCa [40]. It was found that magnoline markedly restored the energy metabolism, amino acid metabolism, and fatty acid metabolism, which revealed that cancer cells may result in death because of insufficient material basis to favor their rapid proliferation. 1,25-Dihydroxyvitamin D3 (1,25(OH)2D3), also known as calcitriol, is one of the bioactive forms of nutraceutical vitamin D. Recently, its metabolism-modulating effects against PCa have been reported [41]. Based on the metabolomics analysis of LNCaP cells in vitro, 1,25(OH)2D3 inhibited glucose uptake and increased citrate/isocitrate because of TCA cycle truncation. The re-wiring glucose metabolizing pathways by 1,25(OH)2D3 may prove its metabolism-modulating effects against PCa. Yun et al. found that high exposed level of vitamin C could selectively kill CRC cells harboring KRAS or BRAF mutations [42]. In detail, based on the LC-MS/MS metabolomics between KRAS and BRAF mutant lines and isogenic wild-type counterparts in vitro, high level of exposure of vitamin C could increase uptake of dehydroascorbic acid by GLUT1 transporter and then decrease glutathione, which could inactivate glyceraldehyde 3-phosphate dehydrogenase (GAPDH). β-Lapachone (β-lap), as a quinone-containing compound derived from the *lapacho* tree located in South America, is bioactivated by NAD(P)H: quinone oxidoreductase 1 (NQO1). Recently, its effects on energy metabolism due to NAD^+ depletion on pancreatic ductal adenocarcinoma (PDA) have been shown [43]. Based on the combined GC/MS and ^1H NMR metabolomics analysis of MiaPaCa2 cells in vitro, β-lap treatment was found to decrease the NAD-sensitive pathways, such as glycolysis and TCA cycle, which revealed that targeting NQO1 may sensitize the treatment of β-lap. Diethylstilbestrol (DES), as a nonsteroidal estrogen, is the pharmacological inhibitor to HIF-1a. Arminan et al. employed NMR-based metabolomics of PC3 cells in vitro to explore the metabolic responses of PCa cells to hypoxia and the treatment of DES or its polyacetal conjugate tert-DES [44]. It was shown that lactate, phosphocreatine, and glutathione were the biomarkers for DES treatment. What is more, compared with tert-DES, the cell metabolome had a more extensive impact in the free DES treatment, which revealed that DES upon conjugation had a more specific effect and less toxicity. Koningic acid (KA), as an active natural product derived from the *Trichoderma fungus*, is a selective inhibitor of GAPDH. Recently Liberti et al. employed integrated pharmacogenomics and LC-HRMS metabolomics of HCT116 cells to explore the response of KA to CRC [45]. As a result, they found that partial GAPDH suppression is more selective for highly glycolytic tumors, underscoring the potential of targeting glucose metabolism therapy could be an integral part of precision medicine. Rapamycin (Rp) is widely used in the treatment of breast cancer. However, its efficacy has been significantly reduced by the increasing drug resistance and serious metabolic disorders. Dietary omega-3 polyunsaturated fatty acids (ω-3 PUFAs) have been reported to markedly inhibit breast cancer. To explore whether combined treatment of Rp and ω-3 PUFAs has better efficacy, a GC/MS-based metabolomics of MCF7 cells in vitro was done [46]. It was found that glycolysis and glutamine metabolism pathways were markedly reduced when treated with the combination of Rp and ω-3 PUFAs, suggesting that ω-3 PUFA could increase the anti-breast cancer potential of Rp. Curcumin, as the primary bioactive compound from the spice turmeric, was found to be a potent anticancer agent [47]. In detail, based on the serum metabolomics analysis, curcumin attenuated the metabolic disorders of diethylnitrosamine (DEN)-induced

hepatocarcinogenesis by elevating the levels of glucose and fructose and reducing the levels of glycine and proline. 6,7-Dimethoxy-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid (M1) is an isoquinoline alkaloid isolated from *Mucuna pruriens* seeds. To evaluate the anti-CRC effects of M1, ^{1}H NMR-based metabolomics of serum from dimethylhydrazine (DMH)-induced CRC albino Wistar rat model in vivo was conducted [48]. As a result, M1 exhibited to reverse the perturbed metabolism pathways in CRC condition, including glycolysis, TCA cycle, choline, and phosphatidylinositol and gluconeogenesis metabolisms. Taken together, this study offered that M1 had the anti-CRC potential via the blockade of IL-6/JAK2/STAT3 oncogenic signaling. Physapubenolide (PB) is a withanolide derived from *Physalis pubescens*. Recently its potential as a promising therapeutic drug has been put forward. However, the underlying mechanism of how it works remains to be explored. Ma et al. employed GC/MS-based metabolomics of both HepG2 cells in vitro and tumor tissues and plasma from a mouse-xenograft model bearing liver carcinoma H22 cells in vivo [49]. It was found that PB reversed the disturbed metabolic pattern by markedly decreasing the lactate production, suggesting PB may exhibit anti-HCC activities through suppression of glycolysis via the Akt-p53 pathway. Gefitinib (Gnb), as a tyrosine kinase inhibitor, is widely used for the treatment of lung cancer. However, the increasing drug resistance and serious metabolic disorders have significantly reduced its efficacy. Naringenin (Nar), as flavonoid isolated from citrus fruits, has been reported to show antioxidant, antimutagenic, and anticarcinogenic activities. To explore whether co-therapy through biotin-modified nanoparticles (NPs) of Gnb and Nar, a ^{1}H NMR-based metabolomics of serum from the urethane-induced lung cancer rat model in vivo was conducted [50]. It was found that the glycolysis was restored to normal levels with co-therapy of Gnb and Nar, which showed that co-therapy had the superiority over treatment only to improve the therapeutic efficacy.

Silymarin, extracted from the seeds of milk thistle (*Silybum marianum*), has the anti-inflammation activity. To explore the mechanism of how it suppresses inflammation, a combined transcriptional profiling and GC/MS metabolomics was conducted on Huh7-TLR3 cells [51]. It was found that the glycolytic, TCA cycle, and amino acid metabolism pathways were inhibited after silymarin treatment, which revealed that silymarin may have potential in defining how metabolic pathways mediate cellular inflammation. Rhizoma Paridis saponins (RPS) are the effective parts of Rhizoma Paridis, which have been found to show strong anti-hepatocarcinoma activities. However, the anticancer mechanism remains not clear. To search for the potential biomarkers for the evaluation of treatment, ^{1}H NMR metabolomics was employed to distinguish the serum metabolic profiling of the RPS treatment group from that of the model group [52]. As a result, RPS decreased the serum levels of lactate, acetate, N-acetyl amino acid, and glutamine, which has shown that RPS was a potential anticancer drug by inhibiting the aerobic glycolysis, lipogenesis, and glutamine metabolism. As one of the rarest plants, *Camellia nitidissima Chi* was reported to have various pharmacological activities, including anti-CRC. However, its anti-CRC efficacies remained to be confirmed due to its complex components and underlying complicated mechanisms. To address these issues, Li and his colleagues employed ^{1}H NMR-based metabolomics of the intestine, kidney, and spleen from azoxymethane/dextran sodium sulfate (AOM/DSS)-induced CRC mice model [53]. They found that *C. nitidissima Chi* extracts could markedly suppress AOM/DSS-induced CRC via reversing the disturbed metabolic profiling to the normal state. What is more, compared with the water-soluble fraction of *C. nitidissima Chi*, its butanol fraction exhibited a better efficacy. Gnb was widely used in the treatment of lung carcinoma (LLC) with increasing drug resistance and serious metabolic disorders. Si Jun Zi Tang (SJZ) is a four-herb Chinese medicine

formula and has shown potential of anticancer properties. To explore the underlying mechanisms of the co-therapy of Gnb and SJZ, Li et al. conducted an integrated network pharmacology and Q-TOF LC/MS-based metabolomics of plasma from LLC-bearing mice model in vivo [54]. SJZ was shown to increase the anti-LLC effects of Gnb via restoring TCA cycle, linoleic acid metabolism, and tyrosine and tryptophan metabolism, revealing that co-therapy of Gnb and SJZ may increase the anti-LLC potential of Gnb.

2.2 Lipid metabolism

Besides the glucose and energy metabolisms having an essential role in the tumorigenesis process of cancer, it has been also reported that lipid metabolism such as de novo lipogenesis regulates the synthesis of cellular membranes and the important signaling molecules of rapidly proliferating tumor cells [55]. Targeting the lipid metabolism could be a novel therapeutics for cancer treatment. Here the recent metabolomics studies of pure compounds, herb extracts, and formulations from Chinese medicines, which target lipid metabolism, have been reviewed.

Flexibilide is a natural compound derived from the soft coral *Sinularia flexibilis* with tumor inhibitory effects. To clarify the pharmacological mechanism, a UPLC/Q-TOF MS-based metabolomics of HCT-116 cells in vitro on colon cancer was conducted [56]. It was found that flexibilide treatment greatly elevated lysophosphatidylcholine (LysoPC) and diminished phosphocholine and phosphatidylcholine (PC), revealing that flexibilide exhibited the therapeutic effect on colon cancer mainly via downregulating PC biosynthesis pathway. Englerin A is a guaiane sesquiterpene derived from the plant *Phyllanthus engleri* with potential antineoplastic property. To uncover the therapeutic role of englerin A on clear cell renal carcinoma, Batova et al. conducted a LC-MS/MS-based metabolomics of A498 cells in vitro [57]. It was found that englerin A significantly reversed lipid metabolism and increased ceramide levels. Then the increasing ceramides inhibited renal carcinoma cells. Isoquercitrin is a kind of flavonoid derived from various plants, such as *Psidium guajava* and *Fagopyrum tataricum*. It has potential antitumor activities. To decipher its therapeutic role in bladder cancer, a UPLC/Q-TOF MS-based metabolomics of T24 cells in vitro was conducted [58]. Isoquercitrin treatment was found to regulate lipid and anaerobic glycolysis via activating the AMPK pathway. Peiminine is an active substance derived from the bulbs of *Fritillaria thunbergii* with potential antineoplastic property against CRC. To investigate the molecular mechanisms of how it worked, a combined UPLC-MS- and GC/MS-based metabolomics of HCT-116 cells in vitro was used [59]. Peiminine treatment altered several metabolites, including lignocerate (24:0), oleate (18:1n9), glutamine, and glucose, indicating peiminine exerted the predominant therapeutic effect mainly via the metabolic regulation of lipids, amino acids, and carbohydrates. 8u is an acridine derivative with potential antiproliferative activity against cancer. To explore its therapeutic effects on HCC, a combined proteomics and UPLC/Q-TOF MS-based metabolomics of HepG2 cells in vitro was used [60]. 8u was found to significantly inhibit the invasion and metastasis of HepG2 cells and regulate intracellular lipid metabolism mainly via suppressing the PI3K/Akt signaling pathway. Genistein is a kind of isoflavone with antineoplastic property. However, high concentration of genistein shows promotional role in cancer. Calcitriol (1α,25(OH)2 vitamin D3) is a primary bioactive hormonal form of vitamin D3. It also shows the antitumor effect. To explore the synergism effects of co-therapy of genistein and calcitriol on osteosarcoma, a GC/MS-based metabolomics of MG-63 cells in vitro was conducted [61]. Co-therapy of genistein and calcitriol was found to regulate lipids and amino acids rather than energy metabolism. Taken together, the promotional effects of

high level of genistein on osteosarcoma could be decreased by the co-treatment of calcitriol. Silibinin, as a kind of natural flavonoid, is derived from the milk thistle (*Silybum marianum*) seeds with strong hepatoprotective activity. To clarify the pharmacological mechanism of how silibinin exerted antineoplastic property, a ^{1}H-NMR-based metabolomics of tumor tissues from 22Rv1 xenograft model in vivo was used [62]. Silibinin treatment did not greatly affect glucose uptake of PCa tumor but decreased the lipid synthesis via suppressing hypoxia-induced signaling. Acyclic retinoid (ACR), as a synthetic vitamin A-like compound, exhibits antineoplastic property against HCC. To decipher the molecular mechanisms, comprehensive cationic and lipophilic metabolomics of liver tissues from mouse DEN-induced HCC model in vivo was conducted by CE-TOFMS and LC-TOFMS [63]. ACR predominantly reversed lipogenesis but not glucose metabolism by inhibiting linoleic acid metabolites, revealing lipid metabolic reprogramming played a critical role in the protective effects of ACR on HCC.

Soft coral, *Sinularia* sp., is reported to show potential antineoplastic property. To decipher the molecular mechanisms, a MS-based metabolomics of Hep 3B cells in vitro was conducted [64]. It was found that the *Bornean Sinularia* sp. extract could regulate the sphingolipids and ceramide, revealing that the regulation of dysregulated lipids may account for the antineoplastic property of *Bornean Sinularia* sp. against HCC. *Forsythiae Fructus* (FAE), as the dry fruit of *Forsythia suspensa* (*Thunb.*) Vahl. of Oleaceae family, shows potential anticancer properties. To characterize in detail the action mechanism, Bao et al. conducted a UPLC/Q-TOF MS-based metabolomics of serum from B16-F10 melanoma-bearing mice model in vivo [65]. Aqueous extract of FAE was found to restore the disturbed metabolic profile by increasing several LysoPCs in glycerophospholipid metabolisms, revealing that the regulation of glycerophospholipid metabolisms may have an essential role in the antineoplastic property of FAE. Nutmeg is a seed of the fruit of *Myristica fragrans* with antimicrobial and anticancer activities. To explore the role of its antimicrobial activity in cancer protection, a UPLC/ESI-QTOF-MS-based metabolomics of serum from colon cancer model was investigated [66]. Nutmeg extract treatment was found to regulate lipid metabolism by decreasing four uremic toxins generated from the gut microbiota, revealing that the regulation of lipid metabolism and gut microbiota may be an effective therapy for colon cancer treatment. Volatile oil is extracted from *Saussurea lappa Decne* (VOSL), and costunolide and dehydrocostus lactone (Cos–Dehy), accounting for almost 75% of VOSL by weight, are the primary active chemical compositions of VOSL. It has been reported that they all can suppress the MCF-7cells in vitro. To characterize in detail the action mechanism of how they worked, a combined GC × GC–TOF/MS and UPLC/Q-TOF MS metabolomics of serum and urine from MCF-7 xenograft mice in vivo was conducted [67]. It was revealed that both VOSL and Cos–Dehy could relieve metabolic disturbance by decreasing glycolysis and steroid hormone metabolism and increasing unsaturated fatty acids metabolism, suggesting that VOSL is a potential therapeutics against breast cancer. Shuihonghuazi formula (SHHZF) is a famous formula which has been widely used clinically for the treatment of liver cancer. To explore its action mechanism, a DEN-induced HCC rat model was built, and a HPLC/ESI-TOF-MS-based metabolomics of plasma from this model was conducted [68]. SHHZF was found to elevate the levels of arachidonic acid-like substances and the shift of phosphatidylethanolamine (PE) to PC, revealing the reversion of the disturbed fatty acid and bile acid metabolism played an important role in the therapeutic effects of SHHZF on HCC. Qi-Yu-San-Long Decoction (QYSLD) is a classic formula, which has been widely used clinically for LLC treatment. To characterize in detail the action mechanism of how it works, a UPLC/Q-TOF MS-based metabolomics was conducted [69]. Lewis LLC mice model was firstly built, and plasma

was collected for metabolomics analysis. QYSLD was found to regulate sphingolipid metabolism, glycerophospholipid metabolism, arachidonic acid metabolism, fatty acid degradation, and steroid hormone biosynthesis. *Rhizoma Curcumae* and *Rhizoma Sparganii* (RCRS) is a famous Chinese medicine drug pair to treat hysteromyoma. To investigate the molecular mechanisms of how this drug pair works on hysteromyoma, a UPLC/Q-TOF MS-based metabolomics was conducted using the serum and urine from hysteromyoma rat model [70]. RCRS treatment characterized 16 and 18 potential biomarkers from serum and urine, respectively, which were associated with glyoxylate, dicarboxylate, and linoleic acid metabolisms.

2.3 Amino acid metabolism

As mentioned above, besides the consumption of glucose, cancer cells have also been reported to favor glutamine as a preferential fuel. Glutamine metabolism has an essential role in the pathological progression of cancer and could be a potential therapeutic option for cancer. Besides the key metabolite glutamine, it has been reported many other amino acids also play an essential role in cancer.

Delta-tocotrienol (δT) is one of the isomers of vitamin E with antineoplastic property. To explore underlying action mechanism, a ^{1}H-NMR-based metabolomics of A549 and H1299 cells in vitro was used [71]. In detail, δT treatment could suppress the glutamine uptake via suppressing glutamine transporters and then resulted in the induction of apoptosis and suppression of cell proliferation. Celastrol is a bioactive compound derived from *Trypterygium wilfordii HOOK F.* with potential antineoplastic property. To explore underlying action mechanism involved in its anti-colon cancer activity, a UPLC/MS-based metabolomics of HCT116 cells in vitro was conducted [72]. Metabolomics analysis found celastrol changed the levels of lipid markers, carnitine, and amino acids. Tryptophan was further identified as special biomarker by targeted metabolite analysis. Melittin, as a cytotoxic peptide isolated from bee venom, was shown to sensitize the response of ovarian cancer cells to cisplatin treatment. To explore an underlying action mechanism, a LC-MS metabolomics of A2780 and A2780CR cell lines in vitro was employed [73]. It was found that melittin treatment of cisplatin-sensitive cells decreased glutamine, proline, and arginine pathways. Chlorogenic acid (ChA) and caffeic acid (CaA), both as a kind of polyphenol, have shown anti-HCC activities. To decipher the molecular mechanisms, a combined 16S rRNA and metabolomics was conducted [74]. It was found that both CaA and ChA treatments reverse 28 metabolites. In detail, the levels of ethanolamine, L-methionine, L-tyrosine, and bilirubin were associated with diminished *Prevotella* 9 and *Lachnospiraceae incertae sedis* and elevated *Rumincoccaceae* UCG-004. Lodi et al. used untargeted metabolomics and metabolic flux analysis to investigate the synergistic effects of resveratrol, curcumin, and ursolic acid [75]. It was found that compared with the individual treatment, the combined treatment had the greater antineoplastic property. Mechanically, glutamine metabolism was regulated by the compound combinations.

Polyphenols are characterized as a hydroalcoholic chestnut shell extract. Sorice et al. used ^{1}H-NMR-based metabolomics of HepG2 cells in vitro to study the anti-HCC activity of polyphenols extracted from chestnut shell (PECS) [76]. PECS was found to regulate the levels of some amino acids. Annonaceous acetogenins (ACGs) are a group of C35 or C37 secondary metabolites isolated from plants in *Annonaceae*. To explore underlying action mechanism of the anti-HCC activity of ACGs, a UPLC-ESI-Q-TOF-MS-based metabolomics of SMMC 7721 cells in vitro was conducted [77]. ACG treatment could regulate the metabolisms of sphingolipid, arginine, glutathione, and proline, which further reversed the resistance of

SMMC 7721 cells to adriamycin. *Hedyotis diffusa* is a famous Chinese herbal medicine with antineoplastic property. To predict the potential underlying mechanism, a ^{1}H NMR-based metabolomics was conducted to use plasma and urine from rats bearing Walker 256 tumor [78]. *Hedyotis diffusa* treatment was found to reverse lactate, acetate, choline, 3-hydroxybutyrate, and L-glutamine in plasma as well as creatinine, L-aspartate, N-acetyl-L-aspartate, and ornithine in urine. Wang et al. developed a combined gut microbiota and metabolomics analysis to investigate the anti-CRC activity of *American ginseng* [79]. By GC/TOF-MS-based metabolomics, *American ginseng* was found to regulate the metabolisms of carbohydrates, lipids, and amino acids. By the 16S rRNA data analysis, *American ginseng* was found to inhibit the changes of microbiome community caused by azoxymethane/dextran sulfate sodium. Kushen injection (CKI) is a famous Chinese medicine preparation and widely used for treating multiple kinds of solid tumors. To evaluate the anti-HCC mechanisms of CKI, a combined network analysis and ^{1}H-NMR-based metabolomics were used [80]. Network pharmacology analysis found the primary active compounds, the potential targets, and pathways associated with the anti-HCC effects of CKI, which was further validated by metabolomics. Metabolomics analysis validated the primary pathways associated with the anti-HCC effects of CKI were amino acid metabolism and glycometabolism.

2.4 Nucleotide metabolism

To support the rapid proliferation of cancer cells, nucleic acid synthesis is shown to be accelerated. Accordingly, the anticancer therapy targeting nucleotide metabolism has obtained numerous attentions. Here the recent metabolomics studies of Chinese medicines targeting nucleotide metabolism have been reviewed.

Glaucocalyxin A (GLA) is an ent-kaurene diterpenoid derived from *Rabdosia japonica* and has shown to have antineoplastic property. To explore underlying action mechanism underlying the anti-HCC activity of GLA, a combined GC/MS- and LC/MS-based metabolomics was conducted using SMMC7721 cells in vitro [81]. It was found GLA treatment diminished amino acid metabolism and elevated the metabolisms of sphingolipid, purine, and pyrimidine. Taurine, as the most abundant free amino acid, has the antineoplastic property against breast cancer. To elucidate the mechanisms underlying the therapeutic benefits of taurine against breast cancer, a GC–TOF-MS-based metabolomics of plasma from dimethylbenz[a] anthracene-induced breast carcinogenesis in rats was conducted [82]. It was found that taurine treatment regulated 23 differential metabolites, which were associated with glucose, energy and amino acid, as well as nucleic acid metabolisms. Celastrol is a bioactive compound derived from *Trypterygium wilfordii HOOK F.* with potential antineoplastic property. To explore underlying action mechanism involved in its anti-acute promyelocytic leukemia activity, a UPLC-MS-based metabolomics of HL-60 cells in vitro and tumor tissue from mice xenograft model in vivo was conducted [83]. It was found that celastrol treatment regulated uridine metabolite, which further enhanced apoptosis. The development of radioprotector to reduce the serious side effects and complications caused by radiotherapy is important. Gamma-tocotrienol (GT3) is one of the isomers of vitamin E with antineoplastic property. To explore the radioprotective mechanism of GT3, a UPLC-QTF MS-based metabolomics of serum from nonhuman primate models in vivo was conducted [84]. It was found that GT3 could regulate the changed fatty acid beta-oxidation and amino acid and purine catabolism metabolisms caused by irradiation.

Red kidney bean, also named as *Phaseolus vulgaris L.*, possesses antineoplastic property. To evaluate its anti-melanoma activity, a combined network pharmacology and LC-MS-based metabolomics analysis was conducted using B16-F10 cells

in vitro [85]. It was found that the kernel of red kidney bean (RKBC) extract treatment markedly elevated cellular level of cGMP. Network pharmacology analysis showed that quercetin might act as the main effective ingredient of RKBC extract. Ku-jin tea (KJT) is a famous beverage derived from the leaves of the plant *Acer tataricum subsp. ginnala* with antineoplastic property. A UPLC/Q-TOF MS-based metabolomics of urine from azoxymethane-induced precancerous colorectal lesion model in rats was conducted to investigate molecular modes of inhibitory effects of KJT against CRC [86]. It was found that KJT treatment modulated amino acid and purine metabolisms, which accounted for the chemopreventive effects of KJT.

2.5 Other related metabolisms

Except for the anticancer therapies of Chinese medicine targeting the changed metabolisms mentioned above, there are also some other related metabolisms which are the targets by Chinese medicine. Fisetin is a kind of plant flavonoid with antineoplastic property. A HPLC/ESI-MS-based metabolomics of tumor tissues from PCa xenografts in vivo was conducted to explore its therapeutic benefit for PCa [87]. Fisetin treatment was shown to downregulate secreted and intracellular hyaluronan (HA), which conferred resistance to prostate oncogenesis. Yang et al. developed a LC-MS/MS-based metabolomics to study the bioefficacy of a plant galactolipid 1,2-di-O-α-linolenoyl-3-O-β-D- galactopyranosyl-sn-glycerol (dLGG) against melanoma [88]. dLGG treatment markedly elevated 12/15-LOX catalyzed oxylipin products in serum, revealing the novel therapeutic mechanism of phytoagent dLGG against melanoma. Derived from the medicinal plant *Elephantopus scaber*, deoxyelephantopin (DET) is a germacranolide sesquiterpene lactone with antineoplastic property. To study whether the co-therapy of DET and cisplatin could reduce the cisplatin-induced nephrotoxicity, a UPLC/ESI-QTOF MS-based metabolomics of kidney tissues from murine B16 metastatic allograft model in vivo was conducted [89]. It was shown that co-therapy of DET and cisplatin could reverse the changed urea cycle metabolites and hippuric acid in renal tissues caused by cisplatin, revealing that the co-therapy of DET and cisplatin could be an effective treatment with low toxicity for melanoma.

Liu et al. developed a UHPLC-MS/MS-based targeted metabolomics to evaluate the efficacy of anticancer drugs, including a traditional Chinese medicine injection Aidi injections and fluorouracil [90]. It was found that with the progression of squamous cell carcinoma of the lung, the levels of 1,3-diaminopropane, cadaverine, and N-acetylputrescine altered. The two-drug treatment alone or co-therapy reversed the levels of 1,3-diaminopropane, cadaverine, and N-acetylputrescine. The team also used this metabolomics method to evaluate the efficacy of Aidi injections on CRC [91]. It was found that Aidi injection treatment could reverse polyamine metabolism, especially agmatine and putrescine, revealing that plasma polyamine could be a biomarker for both early diagnosis and medical treatment of CRC.

3. Current perspectives and future challenges

In accordance with the holistic perspective of Chinese medicines, metabolomics can help to explain the underlying mechanisms of the anticancer effects of Chinese medicines or the reversion of the drug resistance of chemotherapy and radiotherapy. It can also help to rapidly compare the anticancer effects of multiple compounds from Chinese medicines and act as a quick preliminary platform to screen the most dominant compound related to anticancer bioactivity. Based on the metabolomics analyses of modern studies of Chinese medicines with antineoplastic properties,

the potential of metabolic treatment with pure compounds, herb extracts, and formulations from Chinese medicines is gaining numerous attentions. However, many challenges still exist in the metabolomics study of antineoplastic Chinese medicines, and there is still a long way for the wide application of metabolomics of Chinese medicines into the treatment of cancer. Firstly, it is critical to make good experimental design before starting the experiment, such as the choices of samples, analytical platforms, and methodological approaches. Secondly, it is quite essential for researchers to develop metabolomics, such as the development of data excavation and the identification and quantification of more metabolites. Thirdly, it is important for us to validate the results from metabolomics studies with more mechanical biological experiments. Fourthly, as no one single technology could achieve a comprehensive result, it is strongly suggested to combine metabolomics with some other advanced technologies for better investigation of the action mechanisms of antineoplastic Chinese medicines, such as other "omics" technologies, network pharmacology, and gut microbiome analyses. Last but not least, more attentions will be drawn to personalized treatment based on metabolomics. It has been reported that because of the interaction between genes and environment (polypharmacy, gut microbiota, xenobiotics), not all patients present the same response to drug treatment [92]. Personalized treatment has been put forward and of great importance nowadays. Although pharmacogenomics is still the only means in terms of personalized treatment, its limitation of ignoring the environmental influences has been increasingly recognized. As an alternative and complementary manner, pharmacometabolomics is an emerging "omics" and has been proposed for personalized treatment [16]. As the results of both genetic and environmental influences, pharmacometabolomics can help to understand individual phenotypic variations in drug responses by providing individual metabolic signatures of both gene-derived endogenous and environment-derived exogenous metabolites [93]. Pharmacometabolomics will offer an intriguingly avenue for personalized treatment in the future.

4. Conclusions

In this chapter, we systematically reviewed recent studies on metabolism-targeting anticancer therapies based on metabolomics in terms of glucose, lipid, amino acid, and nucleotide metabolisms and other altered metabolisms, with special emphasis on the potential of metabolic treatment with pure compounds, herb extracts, and formulations from Chinese medicines. The trends of future development of metabolism-targeting anticancer therapies were also discussed. Hopefully, we expect that through the systematic review on the recent metabolomics studies targeting Chinese medicine treatment on human cancers, more attention will be drawn to the promising candidates from the resourceful Chinese medicine as effective neoadjuvant therapies for cancer treatment clinically.

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