Bioactive Natural Leads Targeting Cancer Cell Metabolism

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Abstract

Therapeutic interest in targeting cancer metabolism has become emerging in recent years. However, a very few numbers of molecules has been identified as a potential modulator of cancer cell metabolism and are in the investigation. Therefore discovery and development of potent and selective drugs from natural sources like plants, marine organisms, or invertebrates are very essential to check the global health disaster because of cancer. To address these emerging complications potential leads from the natural origin are a judicious choice of interest. An organized and summarized evidence concerning cancer cell metabolic proteins and natural lead molecules against cancer cell metabolism with an emphasis on molecular/cellular mechanism(s) is crucial in a single podium. This chapter precisely discusses the antimetabolic potential of natural lead molecules and their mechanisms of action (MOA) against cancer cell metabolism. This complete review on different molecular mechanisms of bioactive leads will toward cancer cell metabolism support researchers in understanding the

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targetable metabolic protein and their interacting pathways, to discover safe and potent drugs for better therapeutic applications against cancer.

Keywords

Natural leads · Cancer cell metabolism · Cellular metabolic targets · Bioinformatic approaches

Abbreviations

2-PG	2-phosphoglycerate
3-PG	3-phosphoglycerate
6PGD	6-phosphogluconate dehydrogenase
ACC	Acetyl-CoA carboxylase
ACL	ATP citrate lysate
ACS	Acyl-CoA synthetases
ADR	Anticancer drug resistance
AH	Aconitase
AMPK	AMP-activated protein kinase
ATP	Adenosine triphosphate
DMAPP	Dimethylallyl diphosphate
DNA	Deoxyribonucleic acid
EGFR	Epidermal growth factor receptor
FAS	Fatty acid synthase
FH	Fumarate hydratase
G6PD	Glucose-6-phosphate dehydrogenase
GIST	Gastrointestinal stromal tumor
GLUTs	Glucose transporters
GPI	Glucose-6-phosphate isomerize
GSH	Glutathione
HIF-1α	Hypoxia-inducible factor-1α
HKs	Hexokinases
HMGCR	3-hydroxy-3-methylglutaryl-CoA reductase
HMGR	3-hydroxy-3-methylglutaryl-CoA reductase
HSF1	Heat shock factor
IDH	Isocitrate dehydrogenase
IPP	Isopentenyl pyrophosphate
LDH	Lactate dehydrogenase
LKB1	Liver kinase B1; also known as serine/threonine kinase 11—STK11
MALDI-TOF-MS	Matrix-assisted laser desorption/ionization-time-of-flight-mass spectrometry
MCTs	Monocarboxylate transporters

MDH1	Malate dehydrogenase
MFS	Major facilitator superfamily
mTOR	Mammalian target of rapamycin
NADPH	Nicotinamide adenine dinucleotide phosphate
OXPHOS	Oxidative phosphorylation
PC	Phosphatidylcholine
PDK	Pyruvate dehydrogenase
PEP	Phosphoenolpyruvate
PFKFB	6-phosphofructo-2-kinase/fructose-2, 6-bisphosphatases
PFKs	Phospho-fructokinases
PGAM1	Phosphoglycerate mutase 1
PGD	Phosphogluconate dehydrogenase
PGM	Phosphoglucomutase
PHGDH	Phosphoglycerate dehydrogenase
PKM2	Pyruvate kinase M2
PPP	Pentose phosphate pathway
QSAR	Quantitative structure-activity relationship
RNA	Ribonucleic acid
SCD-1	Stearoyl-CoA desaturase-1
SCDs	Stearoyl-CoA desaturases
SDH	Succinate dehydrogenase
SIRT3	Sirtuin 3
SLC	Solute carrier
SREBP1	Sterol regulatory element-binding protein 1
TAL	Transaldolase
TALDO1	Trans-aldolase
TCA	Tricarboxylic acid cycle
TKT	Human transketolase
TKT	Transketolase
TPI	Triosephosphate isomerase

Cell Line Details

NSCLC	Non-small-cell lung carcinoma
AsPC-1	Human pancreatic cell lines
BXPC-3	Human pancreatic cell lines
SK-BR-3	Breast cancer cells
MCF-7	Human breast adenocarcinoma cells
PC-3	Human prostate cancer cells
AGS	Human stomach adenocarcinoma cell line
PANC-1	Human pancreatic cancer cell line
MUM28	Uveal melanoma cells
OCM-1	Uveal melanoma cells
SW620	Human colorectal cancer cell line

SW480	Human colorectal cancer cell line
MDAH2774	Human ovarian cancer cells
PA-1	Human ovarian cancer cells
SKOV3	Human ovarian cancer cells
OVCAR3	Human ovarian cancer cells
HCC-LM3	Human hepatocellular carcinoma cells
H1650	Non-small cell lung cancer (NSCLC) cells
H460	Non-small cell lung cancer (NSCLC) cells
HCC827	Non-small cell lung cancer (NSCLC) cells
LY18	Human diffuse large B-cell lymphoma
LnCap	Human prostate cancer cell line
K-562	Human erythroleukemia cell line
Caco-2	Human colon cancer cells
A549	human lung adenocarcinoma cells
Ec109	Esophageal cancer cells
MIAPaCa-2	Human pancreatic adenocarcinoma
HT29	Human colon cancer cells
DLD-1	Human colon cancer cells
HCT116	Human colon cancer cells
SKBR3 cells	Human breast cancer cell line
TSCCa	Human tongue carcinoma cells
Tca8113	Human tongue carcinoma cells
NCI-H1299	Human lung cancer cells

2.1 Introduction

Reprogramming metabolism is one of the surviving techniques associated with a cancer cell. Several publications have been already reported various common traits that help in tumor cell growth and metastasis. Cancer cell requires a huge blast of energy to maintain their macromolecular biosynthesis, controlling the redox balance to support their tumor growth and progression, and reprogramming the cell metabolism is one of the reliable techniques.

In oncogenesis, tumor cells carry out aerobic glycolysis, and this metabolic rearrangement was first observed by Otto Warburg, and the phenomenon is known as "Warburg effect." In this case, to maintain the nutrient uptake and gene regulation, cancer cell undertaken a range of alterations in their intracellular metabolism and other metabolic interaction with the microenvironment (Pavlova and Thompson 2016). Over the past two decades, extensive research works have been carried out to explore deep insights into this metabolic reprogramming of cancer cells and how it provides survival and growth advantages to them by energy acquisition and biomass synthesis. Glucose and glutamine are the two major sources of glycolysis and the tricarboxylic acid cycle (TCA) process. These metabolic processes synthesize many unconventional nutrient sources from cells like ketone, lactate, ammonia, acetate, and other exogenous proteins which act as a source for ATP acquisition, biomass

synthesis for building blocks during cancer cell reaction in the frazzled microenvironment (Fig. 2.1). Therefore, targeting cancer metabolism has become a topic of research interest to achieve therapeutic benefits against cancer. Various metabolic targets have been already under exploration for their therapeutic potential, and various small molecules or drug targeting metabolism are being tested both in preclinical and clinical trials also (Luengo et al. 2017; Martinez-Outschoorn et al. 2017; Dey et al. 2019a, b, c).

Different natural products have conventionally been used to treat various human diseases (Islam et al. 2018; Debnath et al. 2012; Karuna et al. 2018; Dey et al. 2012a, b; Dey et al. 2014; Kundu et al. 2020; Sachan et al. 2020). They hold a huge bank of bioactive compounds for the new drug discovery. Natural compounds are very useful because of their wide range of pharmacophores and a high degree of stereochemistry. Natural-derived compounds are intricately appropriate candidates for the development of novel therapeutic agents because of their structural diversity, remarkable bioactivity, and significant bioavailability. Fusion with the bioinformatics tools provides deep insights about their molecular targets and, hence, simplifying the drug discovery steps. Again combining with the synthetic chemistry will generate more potent chemical entities. Various plant-based compounds are being extensively studied in various cancer models to identify the potent molecules and their mechanism of action, of which few of them also are in clinical trials (Butler et al. 2014; Seca and Pinto 2018). Among them, some natural product-inspired anticancer compounds are also available in the market (Newman and Cragg 2016). These compounds can be used alone or can be used as combination therapy along with standard drugs to promote the synergistic effect and minimize any adverse effect. On the other hand, many natural lead molecules target multiple proteins or genes and can modulate various carcinogenic pathways, hence increase the chance of success.

In this chapter, we will systematically address important metabolic proteins or enzymes, their role and also mechanism of action of various natural lead molecules (belonging to the alkaloid, phenolic, and isoprenoid group) that modulate the cancer cell metabolism and exerts the anticancer effects along with the different in silico approaches.

2.2 Global Trends in Cancer

2.2.1 General Features

Cancer is a group of diseases characterized by uncontrolled cell growth and failure to control anti-growth signals. The immortalized cells can grow beyond normal limits, metastasize, and have the potential to invade adjacent tissues and other parts of the body via the bloodstream or lymphatic system due to malfunctioning apoptosis or programmed cell death systems. The main causes of cancer include genetic mutations, carcinogens, immune system problems, lifestyle, environmental factors such as pollutants, certain viruses, and bacterial infections.

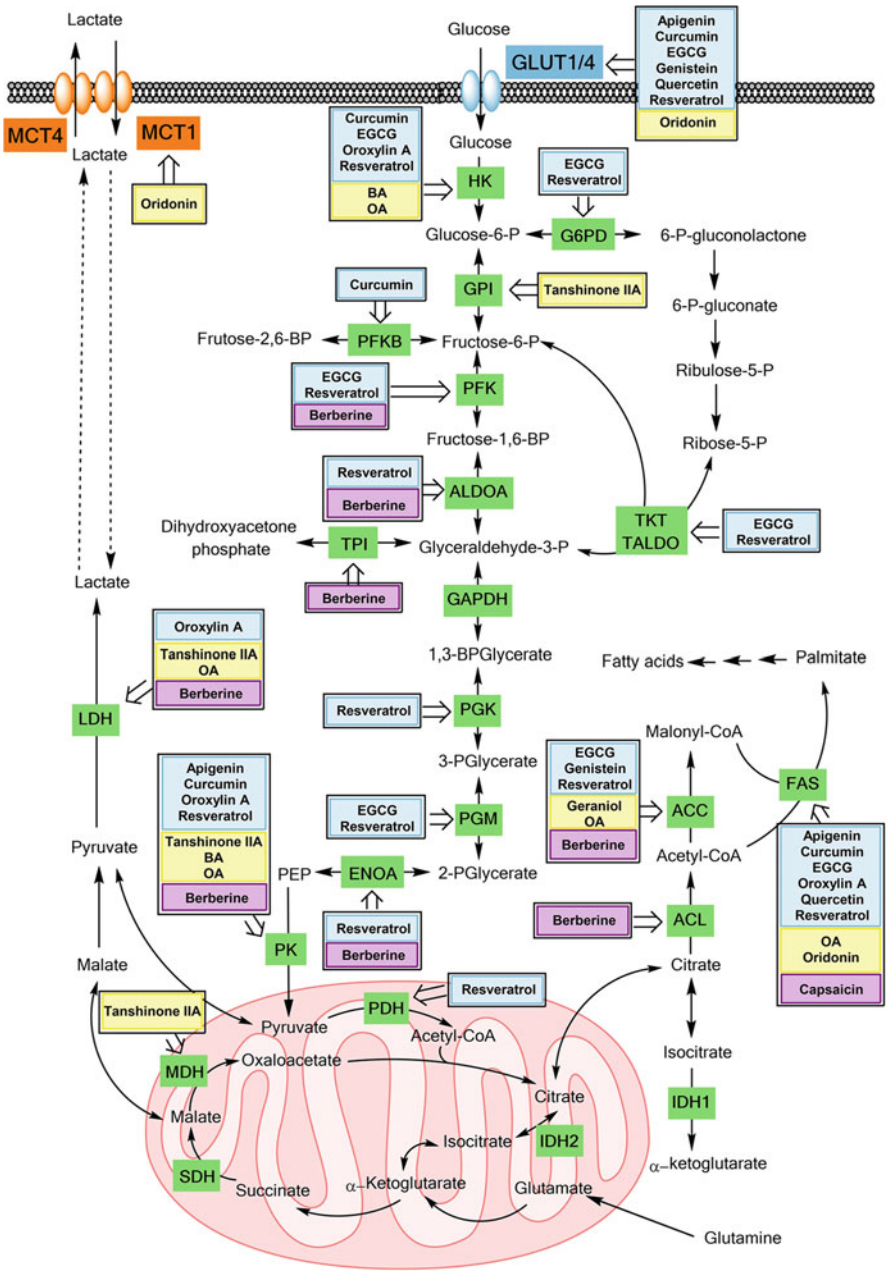

Fig. 2.1 Major metabolic signaling molecules of cancer cell metabolism pathway and the targeting natural leads. Reproduced with permission from the publisher of Guerra et al. 2018. Copyright©2018, American Chemical Society

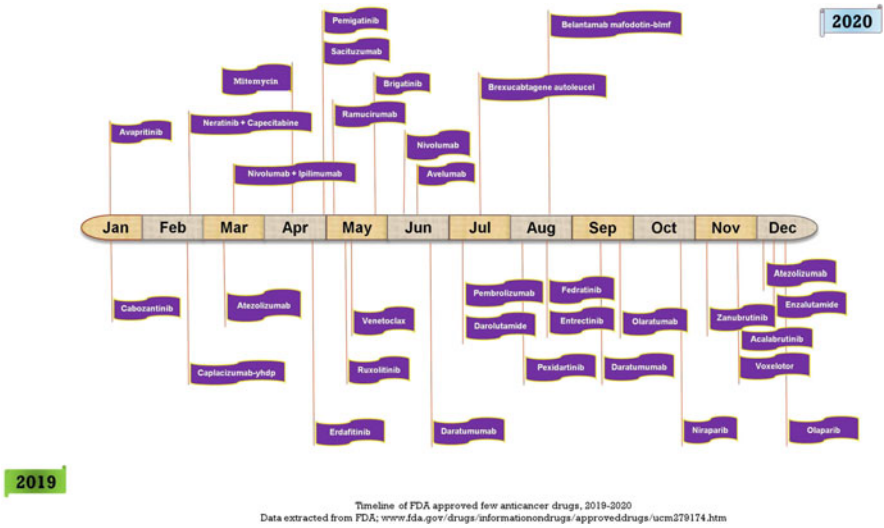

Fig. 2.2 FDA has approved certain new anticancer drugs

To combat cancer, different diagnostic approaches, including natural- and synthetic-based therapies, are being used to target cancerous cells and cancer stem cells (Block et al. 2015; Dey and Das 2013; Boohaker et al. 2012; Jeon et al. 2017; Markman et al. 2013; Thakor and Gambhir 2013). The FDA has approved certain new anticancer drugs to improve available therapeutic options (Fig. 2.2). The optimal therapeutic approach is determined by the type and stage of cancer. To date, there are ~200 different types of cancer that have been well identified, and numerous validated and effective therapies (chemotherapeutic agents, radiotherapy, surgery, hormonal drugs, complementary therapy like acupuncture, yoga, physical activity to reduce some side effects of cancer treatment, and combinations) are clinically available; however, these therapies have various limitations (Qi et al. 2010). Due to poor diagnosis and other factors, most patients are diagnosed too late to undergo surgery. Existing chemo- and radiotherapies have serious adverse effects and complications, such as diarrhea, nausea, vomiting, and alopecia, which, along with increased chemo−/radioresistance, make this a devastating and belligerent disease worldwide (Pereira et al. 2012; Qi et al. 2010). Consequently, there is a persisting requirement to develop novel, effective, and affordable anticancer drugs. One of the oldest effective strategies in drug discovery involved isolating compounds from natural sources and mimicking the active natural product. The use of medicinal plants is a common alternative for cancer treatment in many countries globally. In this regard targeting cancer energetic pathways can be a promising therapeutic approach.

2.2.2 Global Cancer Statistics

Despite technological and social development, cancer has become one of the leading causes of mortality worldwide. According to GLOBOCAN 2018, produced by the International Agency for Research on Cancer, estimations of the mortality incidence and the prevalence of major cancer types across 20 world regions have been made. The data revealed 18.1 million new cancer cases and 9.6 million cancer-associated mortalities worldwide in 2018 (Bray et al. 2018). Lung cancer is the most leading cause of cancer-associated death in both sexes. By 2030, it is projected there will be 26 million new cancer cases and 17 million cancer mortalities/year (Thun et al. 2009).

2.2.3 Chemotherapy Resistance in Cancer

Drug resistance is a common phenomenon wherein a susceptible cell becomes tolerant in the presence of a drug. Cancer is a prodigious problem for global economies and public health. Anticancer drugs, an imperative tool in medicine, are lethal to cancer cells, being designed and developed to kill cancerous cells. Resistance against chemotherapeutic drugs was first observed in the 1940s with alkylating agents, and the rapidity of the developing resistance is concerning (Cree and Charlton 2017).

Anticancer agents that kill or prevent the growth of cancer cells function by blocking DNA and RNA biosynthesis, interfering with transcription, protein synthesis, and function, and influencing hormone homeostasis. The efficacy of many, but not all, anticancer drugs is severely compromised by the emergence of anticancer drug resistance (ADR) (Housman et al. 2014). Imatinib in GIST, BRAF inhibitors in melanoma, EGFR inhibitors in NSCLC, and HER2 inhibitors in breast cancer are some examples (Cree and Charlton 2017). The six most common mechanisms of ADR are depicted in Fig. 2.3. Among them, mutations in drug targets could alter target sequences, reduction, or overexpression of targets or efflux pumps that may diminish uptake or drug efflux. Additionally, cancer cells can alter drug metabolism profiles and upregulate drug-detoxification mechanisms. Decreased susceptibility to apoptosis, changes in proliferation, and enhancement of DNA damage repair capacity can contribute to resistance development. Multiple methods of ADR confer advantages to cancer cells and allow them to grow in the presence of anticancer drugs. Thus, the number of resistant mutants increase and spread rapidly in the body.

2.3 Important Cellular Metabolic Targets

Cancer cells undertake notable metabolic reprogramming to survive and proliferate by maintaining their signaling networks and metabolic alterations (Luengo et al. 2017). These metabolic alterations actively participate in the tumor cell development and proliferation and hence positively provide growth advantages to them. These

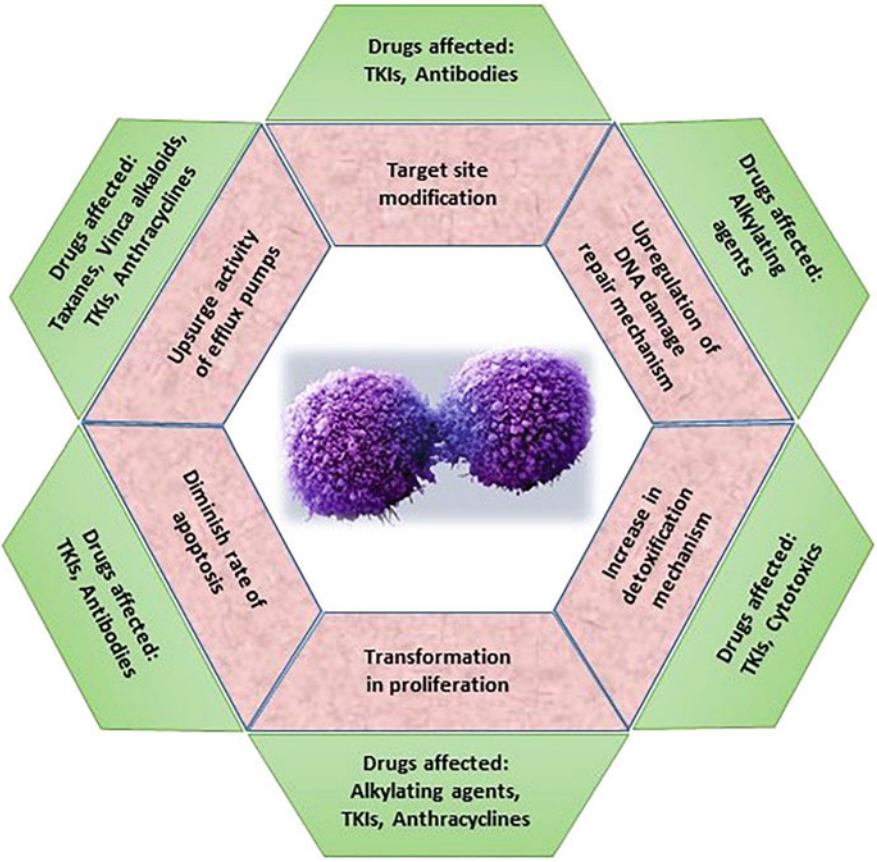

Fig. 2.3 Six most important benchmarks of anticancer drugs

changes in metabolism led us to identify and target novel therapeutic molecules in the cancer cell metabolic and bioenergetics pathway.

Glucose is the most plentiful nutrient in the blood and the main source of energy of the cell, and its metabolism is quite complex. A series of glycolytic enzymes are involved in the breakdown of glucose. Here, we will discuss those metabolic enzymes and transporters which involves in the process of cell metabolism.

2.3.1 Glucose Transporters (GLUTs)

The first rate-limiting step of glucose metabolism is the transportation of glucose across the cell membrane, and two types of hexose transporter, the family of glucose transporters (GLUTs) (Fig. 2.1) and the sodium-dependent glucose co-transporters (SGLTs), help in the glucose transportation, which is often found to be dysregulated

in some of the tumor cells (Macheda et al. 2005). These GLUTs are the part of major facilitator superfamily (MFS) with alike transmembrane anatomy, but they mainly differ from each other in tissue distribution and substrate recognition. Fourteen members constitute a human GLUT family (GLUT1–14 or SLC2A1–14) (Cao et al. 2007; Macheda et al. 2005; McBrayer et al. 2012). Among all, GLUT1 is the most abundant isoform and is frequently upregulated in most of the human cancers which are directly correlated with poor patient outcomes (Wang et al. 2017). This makes GLUT1 as a possible therapeutic target of various anticancer molecules (Barron et al. 2016).

2.3.2 Hexokinases (HKs)

Tumor cells typically undergo huge glycolytic flux and lactate production as compared to normal cells which acquire most of their energy by oxidative phosphorylation in mitochondria. This facilitates tumor cells to fast energy production, biomass synthesis and accumulation, maintenance redox balance, and cancer metastasis and invasion (Vander Heiden et al. 2009). Among all rate-limiting glycolytic enzymes, hexokinases (HKs) (Fig. 2.1) participate in the first step of glycolysis which irreversibly convert phosphorylate glucose to glucose-6-phosphate, and HK2 has been extremely expressed in the cancer cells as compared to HK1 (highly expressed in the normal cells) (Pedersen et al. 2002). This makes HK2 a novel biomarker for the cancer cells and becomes a possible therapeutic target of anticancer therapy.

2.3.3 Phospho-Fructokinases (PFKs)

Phospho-fructokinases (PFKs) (Fig. 2.1) is another important glycolytic enzyme which converts fructose-6-phosphate to fructose-1, 6-bisphosphate. Various oncogenes, hypoxia-inducible factor (HIF)-1α, and Akt inhibition can trigger the upregulation of PFK1 (Scatena et al. 2008; Yalcin et al. 2009). Again the dysfunction or altered regulation of fructose-2, 6-bisphosphate, an important allosteric activator of PFK, maintains the cellular level of PFK and hence modulates the cancer metabolism (Lincet and Icard 2015). On the other hand, a bifunctional enzyme, 6-phosphofructo-2-kinase/fructose-2, 6-bisphosphatases (PFKFB), more specifically PFKFB3, which is highly expressed in various human cancers and regulate the cell cycle, also maintain the expression of fructose-2, 6-bisphosphate (Lincet and Icard 2015). Both of these PFKs can be targeted for inhibiting the cancer cell metabolism.

2.3.4 Pyruvate Kinase M2 (PKM2)

Pyruvate kinase (PK) is the last rate-limiting glycolytic enzyme that catalyzes the conversion of phosphoenolpyruvate (PEP) to pyruvate with simultaneous production

of ATP (Dey et al. 2019a, b, c). Human PKs have four distinct isoenzymes: M1 (encoded by *PKM*; primarily present in muscle, heart, and brain), M2 (encoded by *PKM*; express in different types of cells and tissues), L (encoded by *PKLR*; mainly expressed in the liver), and R (encoded by *PKLR*; present in the erythrocytes) (Zhao et al. 2013). Cells prefer glycolysis, and oxidative phosphorylation depends on the relative expression of PKM1 and PKM2 (Fig. 2.1) (He et al. 2017). PKM2 is highly expressed in normal proliferating cells and rapidly proliferating cancer cells, whereas PKM1 is especially expressed in normal adult cells (Dayton et al. 2016). PKM2 performs both metabolic and nonmetabolic functions of cancer cells and promotes cellular growth (Yang and Lu 2015). Various cancer cells highly express PKM2 which is associated with the malignant type of tumor and poor patient outcomes (Dey et al. 2019a). Various cancer alterations of PKM2 expression are associated with drug resistance which makes PKM2 a potential therapeutic target (Zhao et al. 2013).

2.3.5 Lactate Dehydrogenase (LDH)

High production of lactate from pyruvate is one of the signatures and final glycolytic steps of cancer cells which is catalyzed by LDH (Fig. 2.1). In human tissue, two different subunits, H and M (encoded by LDHA and LDHB), form five active LDH isoenzymes (Miao et al. 2013). Among these, LDHA is abundantly expressed in the cancer cells, while knockdown or inhibition results increased mitochondrial respiration, reduced cell proliferation under hypoxic condition, decreased cellular metastasis and invasion potential, and repressed tumorigenicity (Fantin et al. 2006; Miao et al. 2013). High serum level of LDH has been directly correlated with the increased risk of colorectal, prostate, hematological, pulmonary, gynecological, and gastroesophageal cancer-associated death (Wulaningsih et al. 2015). Therefore, LDHA has become a predictive cancer biomarker and potential therapeutic target.

2.3.6 Monocarboxylate Transporters (MCTs)

MCTs (Fig. 2.1) are the member of the solute carrier (SLC) family protein and consist of 14 isoforms that exports intracellular lactate (Jones and Morris 2016). Among all MCT1–4 isoforms are mostly studied because of their importance in transporting various metabolites like lactate, pyruvate, etc. (Jones and Morris 2016). Most importantly a high expression of MCT4 is positively correlated with poor patient prognosis in various types of cancer (Bovenzi et al. 2015). Maintaining the metabolic phenotype in cancer cells makes it an attractive target or biomarker for cancer and to explore the MCTs in the pathway of anticancer therapy research.

2.3.7 Glucose-6-Phosphate Dehydrogenase (G6PD)

Various anabolic pathways like the pentose phosphate pathway (PPP; also known as the phosphogluconate pathway or the hexose monophosphate shunt) and serine biosynthesis pathway are also contributing cancer cell growth and proliferation. They also maintain the fatty acid synthesis, oxidative defense, and nucleotide biosynthesis (Patra and Hay 2014). G6PD (Fig. 2.1) is a cytosolic and first enzyme of PPP (an alternative pathway of glucose metabolism) that produces NADPH by reducing $NADP^+$. Many human cancers express a high level of G6PD which makes an attractive biomarker for cancer therapy. Some anticancer molecules are thought to control PPP by modulating the G6PD activity (Cho et al. 2018).

2.3.8 6-Phosphogluconate Dehydrogenase (6PGD)

6PGD (Fig. 2.1) is an oxidative carboxylase in the PPP and catalyzes the conversion of ribulose 5-phosphate from 6-phosphogluconate. This enzyme is highly upregulated in several cancers, and inhibition of this enzyme can lead to increased ROS production, suppression of RNA biosynthesis, and lipogenesis, which can be mediated by the inhibition of LKB1 (liver kinase B1; also known as serine/threonine kinase 11—STK11)-AMPK (AMP-activated protein kinase) (Lin et al. 2015b).

2.3.9 Transketolase (TKT) and Trans-aldolase (TALDO1)

Transketolase (encoded by TKT gene) and trans-aldolase (encoded by *TALDO1* gene) (Fig. 2.1) is an enzyme of the non-oxidative phase of PPP. Cancer cells utilize these two enzymes to produce nucleotides which will be further utilized to synthesize DNA and RNA (Patra and Hay 2014).

2.3.10 Phosphoglycerate Dehydrogenase (PHGDH)

Serine biosynthetic pathway is one of the metabolic reactions which produce non-essential amino acids, necessary for purine and GSH (glutathione) biosynthesis. PHGDH (Fig. 2.1) is an enzyme that catalyzes the first step of serine biosynthesis and highly overexpressed in various types of cancer cells (Tennant et al. 2010). This enzyme can be targeted to inhibit the growth and survival of the cancer cells with upregulated serine biosynthesis.

2.3.11 Glutaminase

Unlike glucose, glutamine, the non-essential amino acid, helps in energy generation as well as supplies nitrogen for the biosynthesis of nucleic acid and other amino

acids and helps in the growth and metabolism of tumor cells. Glutamine helps in the synthesis of GSH and an alternative source of carbon donor in lipid biosynthesis. This enzyme glutaminase (Fig. 2.1) helps in the formation of glutamate from glutamine, and hence it can be another therapeutic target for anticancer drug discovery (Tennant et al. 2010).

2.3.12 Heat Shock Factor (HSF1)

Apart from regulating the heat shock response in the eukaryotes, HSF1 (Fig. 2.1) also has some non-heat shock function which provides advantages to cancer cell growth. HSF1 enhances the glucose consumption, LDH activity, and lactate production (Dai et al. 2007). Thus downregulation or inhibition of HSF1 hinders glycolysis (Zhao et al. 2009). It has been reported that cancer cells with high expression of HSF1 get resistant to trastuzumab, and the inhibition of HSF1 sensitizes them to trastuzumab treatment. This confirms the role of HSF1 in the trastuzumab resistance, and therefore, it can be an excellent target to overcome the trastuzumab drug resistance in cancer patients.

2.3.13 Pyruvate Dehydrogenase (PDK)

Four types of PDK (Fig. 2.1) isotypes are identified so far. Typically, HIF activation initiates the overexpression of these PDKs that negatively regulate the pyruvate dehydrogenase (PDH) which converts pyruvate into acetyl-CoA and enters into the tricarboxylic acid (TCA) cycle to produce ATP (Lu et al. 2008). Inhibition of PDKs potentiates the pyruvate to acetyl-CoA production and stimulates the TCA cycle. Dichloroacetate is one of those kinds of small molecules that has already entered into the clinical trials (Saunier et al. 2016). Generally, enzymes involved in the TCA cycle (fumarate hydratase or FH; aconitase or AH; succinate dehydrogenase or SDH; and isocitrate dehydrogenase or IDH) are either mutated or deregulated in the cancer cells, and small molecules targeting those enzymes are now under examination (Luengo et al. 2017).

2.3.14 ATP Citrate Lysate (ACL)

All rapidly proliferating cells need a huge blast of lipids and steroids to continue their phospholipid bilayers synthesis and maintain signaling cascades. In the pathways of tumor progression, various enzymes that are involved in lipid biosynthesis can be served as potential therapeutic targets (Liu et al. 2017). ACL (Fig. 2.1) which is highly expressed in various tumors are directly regulated by the PI3K/Akt pathway. This enzyme links glucose and glutamine metabolism to fatty acid synthesis by converting citrate into lipogenic precursor acetyl-CoA (Chypre et al. 2012).

2.3.15 Acetyl-CoA Carboxylase (ACC)

ACC1 (Fig. 2.1) converts acetyl-CoA into malonyl-CoA in the fatty acid synthesis pathway and has been overexpressed in various cancer which is correlated to tumor progression and poor patient outcomes (Currie et al. 2013). AMPK interacts and inhibits the sterol regulatory element-binding protein 1 (SREBP1), which, in turn, phosphorylates and inactivate ACC1 (Li and Zhang 2016).

2.3.16 Fatty Acid Synthase (FAS)

FAS (Fig. 2.1) is highly expressed in various human cancers (Liu et al. 2017) and an important enzyme in lipogenesis that catalyzes the terminal step of fatty acid synthesis and converts malonyl-CoA and acetyl-CoA substrate into palmitate (Flavin et al. 2010).

2.3.17 Others

Apart from these proteins, various other proteins are highly expressed in the human tumors and also involved in fatty acid synthesis and modification, including stearoyl-CoA desaturases (SCDs) (Igal 2016) and acyl-CoA synthetases (ACS) (Currie et al. 2013). Additionally, choline and cholesterol are synthesized by choline kinase and 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), respectively, have a role in tumor development and progression, and can be considered as a potential target for anticancer drug development (Martinez-Outschoorn et al. 2017).

2.4 Natural Leads Targeting Cancer Cell Metabolism

2.4.1 Alkaloids

Alkaloids (Fig. 2.1) are the natural molecules found in plants, animals, bacteria, and fungus, having a basic nitrogen atom in their structure (except in peptide bond or amide) (Kushiro and Ebizuka 2010). In the ancient times, after the breakthrough discovery of the molecule morphine, in 1804, plants having alkaloids are being used in various traditional medicines by various ethnic groups of people in this world (Aniszewski 2007). Vinca alkaloids are the first alkaloids (discover in the 1950s) having anticancer potential against various types of human cancers (Cragg et al. 2009). In this section, we will cover major important anticancer natural lead molecules that target biosynthetic metabolic pathways.

2.4.1.1 Capsaicin

Capsaicin (*trans*-8-methyl-*N*-vanillyl-6-nonenamide) (Fig. 2.1) is a derivative of homovanillic acid and the key constituent in chili peppers that are consumed in

various cultures as a spice (Clark and Lee 2016). Because of its vast medicinal properties, capsaicin is widely explored for its anti-obesity (Kang et al. 2007), antioxidant (Galano and Martínez 2012), analgesic (Brederson et al. 2013), and anti-inflammatory properties (Kim et al. 2003). Capsaicin possesses in vitro chemopreventive and chemotherapeutic effect (Amantini et al. 2009; Jun et al. 2007; Yang et al. 2009) and antitumorigenic activity in vivo (Bhutani et al. 2007; Lu et al. 2010; Pramanik et al. 2011; Yoshitani et al. 2001; Zhang et al. 2008) against various cancers (Bley et al. 2012). In the HepG2 cell line, capsaicin notably downregulated the FAS protein levels at a 0.05–0.5 mM concentration as compared with control groups, without affecting other lipid-related proteins (like ACL and ACC) (Impheng et al. 2014). Capsaicin also suppressed intracellular triglycerides and long-chain fatty acid levels by inhibiting the synthesis of de novo fatty acid (Impheng et al. 2014). At a concentration of 150 μM, capsaicin disrupts the functionality of mitochondrial complex I and III in human pancreatic cell lines (AsPC-1 and BXPC-3) and induces the ROS generation which finally led to apoptosis (Pramanik et al. 2011).

2.4.1.2 Tetrandrine

Tetrandrine (Fig. 2.1) is a bisbenzylisoquinoline alkaloid isolated from the root of *Stephania tetrandra* S. Moore. MALDI-TOF-MS found that tetrandrine (5 ± 0.6 μg/mL) downregulated phosphoglycerate mutase 1 (PGAM1) and transaldolase (TAL) protein level and inhibited the glycolysis and pentose phosphate pathway in HepG2 cells (Cheng et al. 2010).

2.4.1.3 Piperine

Piperine (Fig. 2.1) is isolated from *Piper nigrum* Linn. In breast cancer cells (SK-BR-3), it inhibited the mRNA expression and protein level of FAS and ultimately inhibited fatty acid synthesis (Do et al. 2013).

2.4.1.4 Berberine

Reprogramming the metabolism including OXPHOS, glycolysis and fatty acid synthesis provide growth advantages to the cancer cells. Several potential targets involved in this reprogramming mechanism were investigated by various novel molecules to find a profit in cancer treatment. Among them, berberine (Fig. 2.1), an isoquinoline quaternary alkaloid isolated from the herbal plants like *Rhizoma coptidis*, is nontoxic to humans (Jantová et al. 2003). In breast cancer cells berberine treatment (36.91 μg/mL) inhibited various glycolytic enzymes like enolase α, triosephosphate isomerase (TPI) and fructose-diphosphate aldolase A (Chou et al. 2012). In MCF-7 cells the p-ACL level was decreased, while the p-ACC level was increased after berberine (2–100 μM) treatment (Tan et al. 2015). In another study on MCF-7 cells, berberine (2–50 μM) upregulated the p-PKM2 level and downregulated PFK and LDH level and shifts the metabolism toward OXPHOS (Fan et al. 2013). PKM2 activity was inhibited after berberine treatment in HeLa and HCT116 cells (Li et al. 2017c). Other metabolic proteins like 1,2-dihydroxy-3-keto-5-methylthiopentene dioxygenase, kynurenine 3-monooxygenase, succinyl-CoA:3-

ketoacid-coenzyme A transferase 1, mitochondrial/OXCT1, and triosephosphate isomerase were also differentially expressed in MCF-7 cells after berberine treatment (Chou et al. 2012).

2.4.2 Isoprenoids

Isoprenoids are plant secondary metabolites originated from the five carbon precursor's isopentenyl pyrophosphate (IPP) and its isomer dimethylallyl diphosphate (DMAPP) (Withers and Keasling 2007). Depending on the number of five-carbon skeleton, isoprenoids can be classified as monoterpenoids (C10), sesquiterpenoids (C15), diterpenoids (C20), triterpenoids (C30), and tetraterpenoids (C40) (MA Domingues et al. 2014) which have significant pharmacological activities, among which some candidates enter the clinics. For example, artemisinin (a sesquiterpene lactone) which was isolated from *Artemisia annua*, with its semi-synthetic compounds, is potent antimalarial drug (Slezakova and Ruda-Kucerova 2017). On the other hand, a diterpenoid, namely, paclitaxel, which was isolated from *Taxus brevifolia* is being used in various chemotherapeutic regimes against lung, breast, and ovarian cancer (Bernabeu et al. 2017). Nowadays plant-derived metabolites have received growing interest because of their antimetabolic activity in the anticancer pathway. Table 2.1 provides a collected list of those plant-derived isoprenoids, while some of them are mentioned below.

2.4.2.1 Oleanolic Acid

Oleanolic acid (Fig. 2.1) is an oleanane-type pentacyclic triterpenoid isolated from *Olea europaea* (family: Oleaceae) having various pharmacological activities including anticancer activity. Treatment with oleanolic acid (50–100 μg/mL) downregulated the PKM2 protein along with the concomitant increase of PKM1 which ultimately impairs glucose uptake and lactate production in the human breast cancer (MCF-7) and prostate cancer cells (PC-3) (Liu et al. 2014b, c). In these same cell lines, oleanolic acid (10–100 μg/mL) activate AMPK which, in turn, phosphorylate and inactivate 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR) and acetyl-CoA carboxylase 1 (ACC1) and downregulated fatty acid synthase (FAS) protein level which ultimately ends up into reduced fatty acid synthesis (Liu et al. 2014c). In breast cancer cells, oleanolic acid (5 μM) inhibited the glucose consumption and lactate production which was induced by high salt-mediated osmotic stress (Amara et al. 2016). Various rate-limiting glycolytic enzymes like HK, PKM2, and LDH was also downregulated after the treatment of oleanolic acid (Fig. 2.1).

2.4.2.2 Tanshinone IIA

Tanshinone IIA (Fig. 2.1) is the most important lipophilic compound found in *Salvia miltiorrhiza* Bunge roots and can inhibit tumor cell growth and proliferation by inhibiting glucose metabolism (Lin et al. 2015a). At a concentration of 5.3 μM, tanshinone IIA downregulated the glucose-6-phosphate isomerize (GPI) in human stomach adenocarcinoma AGS cell line, which ultimately inhibits the glucose

Table 2.1 Antagonistic role of isoprenoids in the bioenergetics pathways of human cancer cells

Isoprenoids	Source	Part used	Cancer cell line studied	Inhibitory concentration	Treatment time (h)	Mechanism of action	Refs.
Thymoquinone	*Nigella sativa*	Seed oil	PANC-1; MIA PaCa-2	IC_{50} values were PANC-1: 23 ± 2 μM, MIA PaCa-2: 36 ± 0.28 μM	24 h	The anticancer mechanism of thymoquinone is due to the downregulation of PKM2 protein level in PANC-1 cells which results in inhibition of PKM2 protein activity. Whereas PKM2 protein activity was increased after thymoquinone treatment in MIA PaCa-2 cells	Pandita et al. (2014)
Galbanic acid	*Ferula* genus	Roots	NIH: OVCAR-3	IC_{50} values were NIH: OVCAR-3: 37, 12.1, 10 μM	24, 48 and 72 h	Galbanic acid downregulated the mRNA expression level of both HIF1α and HIF1β in both hypoxic or normoxic conditions. In hypoxic conditions, galbanic acid downregulated GLUT1 and Eno1 expression level, whereas in the normoxic condition, it	Eskandani et al. (2015)

(continued)

Table 2.1 (continued)

Isoprenoids	Source	Part used	Cancer cell line studied	Inhibitory concentration	Treatment time (h)	Mechanism of action	Refs.
						increased the degradation of EGFR	
Andrographolide	*Andrographis paniculata* Nees	Leaves	NB4; MV-4-11	IC_{50} values were NB4: 26 μM; MV-4-11: 43 μM	72 h	In MV-4-11 cells, andrographolide downregulated the expression of ASN, ACACA, and stromal interaction molecule 1 (STIM1) protein to suppress fatty acid synthesis and lipid metabolism, respectively, which results in inhibition of cell proliferation. Andrographolide also inhibited various fatty acid contents like palmitoleic acid, oleic acid, palmitic acid, and stearic acid	Chen et al. (2017b)
Ursolic acid	Plants (thyme, lavender, marjoram, and rosemary), fruits (apple fruit peel), flowers, and berries	Whole plant or fruit peel	MCF-7; MDA-MB-231; SK-BR-3	IC_{50} values were MCF-7: 20.44 μM; MDA-MB-231: 22.9 μM; SK-BR-3: 14.58 μM	24 h	At 20 μM concentration, ursolic acid downregulated the HK2, PKM2 protein expression, and ATP, lactate production via	Lewinska et al. (2017)

						inhibiting the Akt signaling pathway which ultimately suppressed glycolysis	
US597	Ursolic acid derivative		HepG2	IC_{50} values were HepG2: 7.20 ± 2.04 μM	24 h	US597 inhibited glycolysis by downregulating the HK activity which leads to reduced ATP and lactate production	Wang et al. (2014b)
Ginsenoside 20 (S)-Rg3	*Panax ginseng*		3AO; SKOV3	Data not available	24 h	Ginsenoside 20 (S)-Rg3 suppressed glycolysis by downregulating HK2, GLUT1, PKM2, and LDH. This inhibition leads to reduced glucose consumption and lactate production. This compound inhibited the HK2 activity by downregulating the phosphorylation of STAT3	Li et al. (2015)
2-Cyano-3,12-dioxooleana-1,9-dien-28-oic imidazolide (CDDO-Im)	Oleanolic acid derivative		LiSa-2	Data not available	Data not available	Treatment with CDDO-Im inhibited the mRNA expression, protein synthesis, and gene promoter activity of FAS. As a result,	Hughes et al. (2008)

(continued)

Table 2.1 (continued)

Isoprenoids	Source	Part used	Cancer cell line studied	Inhibitory concentration	Treatment time (h)	Mechanism of action	Refs.
						fatty acid synthesis was also downregulated	
Dihydroartemisinin	Artemisinin derivative		A549, PC-3, and H1975	IC_{50} values were A549: 42.2 μM (24 h), 25.1 μM (48 h); PC-3: 35.9 μM (24 h), 25.3 μM (48 h); H1975≒60 μM	24 and 48 h	This compound suppressed the NF-□β signaling which also inhibits the GLUT1 translocation and leads to inhibition of the Warburg effect	Jiang et al. (2016)
Artesunate	Artemisinin derivative		HCT116	IC_{50} values were HCT116: 2.2 μM	24 h	Artesunate inhibited fatty acid metabolism by suppressing fatty acid biosynthetic proteins like fatty acid synthase (FASN), Acyl-CoA synthetase 5 (ACSL5), and hydroxyacyl-coenzyme A dehydrogenase (HADH)	Chen et al. (2017a)
Acetyltanshinone IIA	Tanshinone IIA derivative		SK-BR-3; MDA-MB-453	IC_{50} values were SK-BR-3: 9.17 ± 0.42 μM; MDA-MB-453: 1.97 ± 1.16 μM	24 h	This compound inhibits the lipid biosynthesis in these cancer cells by downregulating the	Guerram et al. (2015)

						key proteins ACC, p-ACL, and FAS	
Geranylgeranoic acid	Data not available	Data not available	Huh-7	Data not available	24 h	Geranylgeranoic acid inhibits fructose 6-phosphate and spermine and increases fructose 1, 6-bisphosphate, spermidine level. This compound shifts the energetic state of these cells from aerobic glycolysis to mitochondrial respiration by upregulating synthesis of cytochrome c oxidase 2 (SCO2) and TP53- induced glycolysis and apoptosis regulator (TIGAR) level	Iwao and Shidoji (2015)
Pseudolaric acid B	*Pseudolarix kaempferi* Gordon	Root bark	A549	Data not available	24 h	This compound upregulated the HK2 and GLUT1 protein level and thus increases the glucose uptake, ATP, and lactate production	Yao et al. (2017a)
Pristimerin	*Salacia cochinchinensis*	Roots	SK-BR-3	IC_{50} values were 2.4 μM	24 h	This quinone methide triterpenoid compound	Lee et al. (2013)

(continued)

Table 2.1 (continued)

Isoprenoids	Source	Part used	Cancer cell line studied	Inhibitory concentration	Treatment time (h)	Mechanism of action	Refs.
						inhibits the mRNA and protein expression of FAS and, hence, suppresses de novo fatty acid synthesis	
Cacalol	*Cacalia delphiniifolia*		MDA-MB-231; MCF-7	Data not available	48 h	Cacalol inhibits the mRNA and protein expression of FAS	Liu et al. (2011)

metabolism, intracellular ATP, and lactate production. Downregulation of malate dehydrogenase (MDH1) and L-lactate dehydrogenase B chains (LDHB) and upregulation of PCK2 by tanshinone IIA inhibited the gluconeogenesis process. In esophageal cancer cell line, Ec109, tanshinone IIA at a concentration of 0.40–1.70 μM downregulated the PKM2 mRNA and its protein expression and hence inhibited glycolysis (Zhang et al. 2016).

2.4.2.3 Geraniol

Geraniol (Fig. 2.1) is a monoterpenoid originated in the volatile oil of various aromatic plants and possesses anticancer activity (Cho et al. 2016). Geraniol inhibited the mevalonate synthesis by downregulating HMGCR activity in human breast cancer cells (MCF-7) (Duncan et al. 2004). In human prostate cancer cells (PC3), geraniol (0.25–1 μM) activated the AMPK pathway which increases the p-ACC protein level (Kim et al. 2012). In HepG2 HCC cells, geraniol inhibits fatty acid metabolism at a concentration of 50–200 μmol/L (Crespo et al. 2012; Polo and De Bravo 2006). It has entered that geraniol inhibits the HMGCR and CTP-PC cytidyl transferase which ultimately downregulated the mevalonate and phosphatidylcholine (PC) synthesis (Crespo et al. 2012).

2.4.2.4 Betulinic Acid

Betulinic acid (Fig. 2.1) is a pentacyclic lupine-triterpenoid (found mainly in outer barks of *Betula* spp.) that showed a negative impact on the tumor metabolism (Domingues et al. 2014). PKM2 protein level was suppressed after treatment with this dietary molecule in MIAPaCa-2 (25 μM) and PANC-1 (20 μM) cell line (Pandita et al. 2014). In MCF-7 and SK-BR-3 cells, betulinic acid downregulated the HK and PKM2 protein levels and inhibited the glycolysis process (Lewinska et al. 2017). In HeLa cells, betulinic acid inhibits the de novo fatty acid synthesis by downregulating the activity of SCD-1 (Potze et al. 2016).

2.4.2.5 Oridonin

This diterpenoid oridonin (Fig. 2.1) was isolated from *Rabdosia rubescens*. In colorectal cancer (SW480) cells, oridonin (1.25–20 μM) downregulated the mRNA expression and protein level of GLUT1 and MCT1 and inhibited the glucose uptake and lactate production and hence induce autophagy (Yao et al. 2017b). In uveal melanoma cells (MUM28 and OCM-1), oridonin (5 μM) suppressed the FAS protein level (Gu et al. 2015). The mRNA expression and protein level of FAS were inhibited after oridonin (5–10 μM) treatment in colorectal cancer (SW620 and SW480) cells which suppressed cellular fatty acid level (Kwan et al. 2013).

2.4.3 Phenolic Leads

These compounds comprise a major group of secondary metabolites containing hydroxylated aromatic ring system that may be flavonoids, stilbenes, phenolic acids, xanthones, and coumarins and possess various pharmacological activities

like anticancer, antibacterial, antiviral, antioxidant, and antiatherosclerotic (Han et al. 2007). The anticancer potential of different phenolic compounds boasts researchers to explore the modulation of tumor cell metabolism by this group of compounds. In this chapter, we have provided the metabolic changes in various human cancer cells governed by phenolic compounds (Table 2.2). A few phenolic compounds with antimetabolite potential are described below.

2.4.3.1 Resveratrol

Resveratrol (Fig. 2.1) is a polyphenol compound mostly found in the berries, grapes, and other food sources, having various roles in cancer cell metabolism. Treatment of resveratrol in lung cancer cells (Li et al. 2016) and hepatocellular carcinoma cells (Dai et al. 2015; Guerra et al. 2018; Iqbal and Bamezai 2012; Massimi et al. 2012) decrease the glucose uptake and lactate production. In human ovarian cancer cells (MDAH2774, PA-1, SKOV3, and OVCAR3) resveratrol treatment (50 μM) inhibits the glucose uptake by suppressing the GLUT1 membrane localization (Gwak et al. 2015; Tan et al. 2016). In HCC cells (Bel-7402 and HCC-LM3) (Dai et al. 2015), non-small cell lung cancer (NSCLC) cells (H1650, H460, and HCC827) (Li et al. 2016), and LY18 human diffuse large B-cell lymphoma (Faber et al. 2006), resveratrol inhibit the glycolysis process by inhibiting the hexokinase 2 (HK2) protein expression level. At a concentration of 10–50 μM, resveratrol inhibits the expression of glycolytic enzyme phosphofructokinase (PFK), glucose consumption, and ATP production in human breast cancer cell lines (MCF-7) (Gomez et al. 2013). In MCF-7, HeLa, and HepG2 cells, resveratrol (50 μM) inhibits PKM2 expression via downregulating mammalian target of rapamycin (mTOR) protein, which, in turn, inhibits the glycolysis and macromolecular synthesis (Iqbal and Bamezai 2012). Resveratrol also inhibits the PFK and PGAM1 expression levels in the LnCap (Narayanan et al. 2004) and LY18 lymphoma cells (Faber et al. 2006). At a concentration of 50–150 μM, resveratrol inhibits the expression of phosphogluconate dehydrogenase (PGD), G6PD, and TKT (Vanamala et al. 2011). Resveratrol decreases lactate production and increases the ATP production in colon cancer cell lines at a concentration of 10 μM for 48 h (Saunier et al. 2017). It has been also proved that resveratrol can modulate cancer cell lipid metabolism. In HCC cells, resveratrol activates AMPK expression which ultimately increases the ACC phosphorylation (Hou et al. 2008; Shin et al. 2009). Resveratrol at a concentration of 30 μM showed a protective effect against mitochondrial dysfunction, arachidonic acid, and iron-induced ROS production by AMPK-mediated inhibitory phosphorylation of GSK3β downstream of poly (ADP-ribose) polymerase-LKB1 pathway (Shin et al. 2009). Resveratrol showed antiproliferative activity toward breast cancer cells by inhibiting both FAS mRNA and protein expression (Khan et al. 2014; Pandey et al. 2011). At a concentration of 20–100 μM, resveratrol increases the arachidonic acid and its metabolite 12S-HETE concentration in breast cancer cells (MDA-MB-231 and MCF-7) (Jäger et al. 2011). In MDA-MB-231 cells, resveratrol altered lipid metabolism by increasing the ceramide level which is an important component of sphingolipids associated in cell proliferation and apoptosis. In human erythroleukemia cell line (K-562), resveratrol (50–100 μM) treatment

Table 2.2 Antagonistic role of phenolic compounds on the bioenergetics pathways of human cancer cells

Phenolic compound	Source	Part used	Cancer cell line studied	Inhibitory concentration	Treatment time (h)	Mechanism of action	Refs.
1-(+)-Acetoxypinoresinol	Extra virgin olive oil (EVOO)		SK-BR-3, MCF-7	50 μM	48 h	Inhibit the expression of the lipogenic enzyme FASN in HER2-overexpressing breast carcinoma cells	Menendez et al. (2008)
Baicalin	*Scutellaria baicalensis*	Root	AGS	NA	48 h	Under hypoxic conditions, baicalin inhibited the enzymes responsible for glycolysis such as HK2, LDH-A, and PDK1. It decreased the glucose uptake as well as the lactate production rate	Chen et al. (2015)
Bavachinin	*Psoralea corylifolia*	Seed	KB	NA	24 h	Bavachinin suppressed angiogenesis and energy metabolism of transcription of genes controlled by glut 1 and hexokinase 2 under hypoxic conditions	Nepal et al. (2012)

(continued)

Table 2.2 (continued)

Phenolic compound	Source	Part used	Cancer cell line studied	Inhibitory concentration	Treatment time (h)	Mechanism of action	Refs.
Demethoxycurcumin	*Curcuma longa*	Rhizome	LNCaP, DU145, PC-3	~20	48 h	It inhibits the expression or activity of fatty acid synthase (FASN) and acetyl-CoA carboxylase (ACC)	Hung et al. (2012)
Daidzein	*Glycine max*	NA	MCF-7, MDA-MB-231, LNCap, PC-3	LNCap: 35.2, PC-3; 100	48 h	It potentiates the glucose uptake. Increases the GLUT-1 and GLUT-4 proteins level	Uifălean et al. (2016)
Deguelin	*Mundulea sericea*	NA	H460, H1650, H1299, H520, HCC827, H1975, H358)		48 h	It decreased glucose metabolism by blocking Akt-mediated hexokinase 2 expression Inhibit lactate production	Li et al. (2017a)
Gallic acid	Gallnuts, grape seeds and skin, tea leaves	Seed, leaves	B16F10		24 h	Aldolase, pyruvate kinase, glucokinase, and α-enolase are responsible for	Liu et al. (2014a)

						glycolysis; however, GA constantly upregulated these proteins and promote cellular apoptosis in B16 melanoma cells	
Genistein	Glycine max	NA	MCF-7, MDA-MB-231 HT29 MIA PaCa-2 LNCap PC-3	IC20 0f MCF-7: 22.44 and MDA-MB-231: 11.04 IC50 LNCap: 35.2, PC-3; 100	24 h (MCF-7, MDA-MB-231) 48 h	Inhibit the GLUT1 mRNA levels and stimulate the uptake p-ACC protein (in breast and colon cancer) In prostate cancer (LNCap) increased glucose uptake rates as well as GLUT1 and GLUT4 protein levels However, in PC-3 cells glucose uptake reduced GLUT1 level decreased and GLUT4 protein levels increased	Engel et al. (2012)
Genistein derivatives Gen-27	NA	NA	MDA-MB-231, MCF-7,	MDA-MB-231: 18.48 ± 0.46, 10.10 ± 0.68, 5.34 ± 0.32	(MDA-MB-231:24,48,72), MDA-MB-	Genistein derivatives Gen-27 potentially	Tao et al. (2017)

(continued)

Table 2.2 (continued)

Phenolic compound	Source	Part used	Cancer cell line studied	Inhibitory concentration	Treatment time (h)	Mechanism of action	Refs.
			MDA-MB-468	MDA-MB-468: 19.49 ± 0.06, 11.67 ± 1.01, 3.13 ± 0.23 MCF-7: 45.43 ± 4.09,16.94 ± 0.18, 6.67 ± 0.62	468:24,48,72), MCF-7	suppressed hexokinase 2, PKM2, and LDHA protein expressions. It downregulated the lactate production as well as ATP generation	
Hesperetin	Citrus fruit	Fruit	MDA-MB-231		24 h	Hesperetin block the glucose uptake via downregulation of glucose transporter 1 (GLUT1)	Yang et al. (2013)
Hydroxytyrosol	Olive oil	NA	SW620	~20	72 h	Hydroxytyrosol inhibits the fatty acid synthase (FAS) and decreased the proliferation rate and inducing apoptosis in colon cancer cells	Notarnicola et al. (2011)
Kaempferol		NA	MCF-7 MDA-MB-	MCF-7 and MDA-MB-231: IC50 of 4 μM (1.6–9.8)	24 h	MCF-7: Kaempferol inhibits the glucose	Azevedo et al. (2015)

			231, LNCap			cellular uptake by decreasing GLUT1 MDA-MB-231: It inhibits the lipid synthesis as well as fatty acid synthase (FAS). By suppressing lactate reuptake by breast cancer cells, kaempferol may also starve cells from lactate which is responsible for cell death	
Luteolin	Extra virgin olive oil (flavonoids)	NA	MCF-7, MDA-MB-231: MIA PaCa-2, LNCap	MCF-7 and MDA-MB-231: IC50 of 4 μM (1.6–9.8)	24 h	Luteolin inhibited the oncoprotein FASN, important chemoprevention and/or management of breast cancer in which FASN highly expressed results from HER2-driven oncogenic signaling. Luteolin significantly inhibited cholesterol, phospholipid, and triglyceride	Brusselmans et al. (2005)

(continued)

Table 2.2 (continued)

Phenolic compound	Source	Part used	Cancer cell line studied	Inhibitory concentration	Treatment time (h)	Mechanism of action	Refs.
						synthesis. Luteolin also showed its potentiality in suppressing fatty acid synthesis as well as other lipid derivatives in prostate and pancreatic cell lines	
Phloretin	Flavonoid	NA	LNCap PC-3	LNCap: 25 PC-3; 39	48 h	Phloretin increased the glucose uptake via stimulation of GLUT1 and GLUT4 proteins in prostate cells (LNCap). However, when treated in PC-3 cells, it reveals the opposite effect, glucose uptake reduced via decreased sensitivity of GLUT1 proteins	Gonzalez-Menendez et al. (2014)
Osthole	*Cnidium monnieri*	Fruit	SK-OV-3	~45	48 h	Osthole inhibited the	Lin et al. (2010)

						phosphorylation of Akt and mTOR. It also suppressed the lipid synthesis as well as fatty acid synthase (FAS)	
Rosmarinic acid	*Rosmarinus officinalis*	NA	MKN45 HCT8, HCT116	240.2 μM 298.1 μmol/L 319.8 μmol/L	24 h	Rosmarinic acid interferes in the glycolytic pathway and significantly inhibits the glucose consumption as well as lactate production in both gastric and colon carcinoma	Han et al. (2015)
Scutellarein	Related flavones	NA	MDA-MB-231		24 h	Inhibition of ECAR and oxygen consumption rate (OCR)	Chen et al. (2012)
Silibinin	*Silybum marianum*	Seeds	SW480 LNCaP, 22Rv1		6 and 12 h 24 and 48 h	Silibinin generated MAP2K1/2-MAPK1/3 and suppressed PIK3CA-AKT–mTOR pathways. For this reason, endoplasmic reticulum stress was activated and glucose uptake	Raina et al. (2013)

(continued)

Table 2.2 (continued)

Phenolic compound	Source	Part used	Cancer cell line studied	Inhibitory concentration	Treatment time (h)	Mechanism of action	Refs.
						capacity reduced. Thus silibinin interferes with glucose metabolism. Silibinin significantly inhibited angiogenesis and proliferation as well as decreased FASN, HIF-1α, and ACC levels. These outcomes correlate that silibinin effectiveness against PCa through inhibiting hypoxia-induced signaling	
Wogonin	*Scutellaria baicalensis* Georgi	NA	HCT116		24 h	Wogonin markedly inhibits the expression of glycolysis-associated proteins (PDHK1, HK2, LDHA), lactate	Wang et al. (2014a)

						generation, as well as glucose uptake in a dose-dependent manner	
Xanthohumol	*Humulus lupulus*	NA	HeLa A549		48 h	Xanthohumol interacts with mitochondrial electron transfer chain complex I, potentially suppressed oxidative phosphorylation, generates reactive oxygen species, and induces apoptosis. Xanthohumol also inhibits the extracellular acidification rate	Zhang et al. (2015a)

downregulated sphingomyelin, sphingosine-1-phosphate (SIP), and upregulated transcription level of acid sphingomyelinase mRNA (ASMase) which leads to accumulation of ceramide (Mizutani et al. 2016). On the other hand, resveratrol (10 μM) treatment in human colon cancer cells (Caco-2) reduced the sphingomyelins level which results increased level of phosphatidylethanolamines and ceramides (Saunier et al. 2017).

2.4.3.2 Curcumin

Curcumin (Fig. 2.1) is a major polyphenol found in the turmeric *Curcuma longa*, which has been reported to have activity on glucose uptake, metabolism, and transport. In human A549 (15–30 μmol/L) (Liao et al. 2015) and MCF-7 (5–10 μM) cells, curcumin inhibited GLUT1 mRNA and protein expression (Vaughan et al. 2013). Interestingly curcumin treatment increased or suppressed glycolysis in the human breast cancer cells has been reported. In MCF-7 cells, curcumin (5 μM) treatment improved HK2 activity, glucose uptake, and lactate production and inhibited mitochondrial respiration (Jung et al. 2016). In MDA-MB-231 cells, curcumin (5 μM) inhibited the HK2 expression and sensitize these cells to 4-hydroxytamoxifen treatment (Geng et al. 2016). In both human breast cancer cells (SKBR-3; 5–20 μM) and HCC HepG2 cells (5–15 μg/mL), curcumin inhibited the FAS protein expression and activity (Younesian et al. 2017). Curcumin treatment (10–40 μmol/L) inhibited the expression and activity of HK2 which leads to inhibition of glucose uptake, lactate production, and ATP generation without affecting other glycolytic enzyme (PFK, LDH, and phosphoglucomutase (PGM)) activities in human colorectal cancer cells (HCT29 and HCT116) (Wang et al. 2015). Furthermore, curcumin (1–10 μM) altered AMPK activity which, in turn, downregulated the mRNA and protein expression of HK2, PFKFB3, GLUT4, and PKM2 proteins in esophageal cancer cells (Ec109) (Zhang et al. 2015b). Curcumin was also reported to inhibit the glucose uptake and lactate production by inhibiting the PKM2 expression via downregulating mTOR-HIF1α pathway in various cancer cell lines (Siddiqui et al. 2018).

2.4.3.3 Quercetin

Quercetin (Fig. 2.1) is a flavonol found in various fruits and vegetables and has been investigated its role in glucose uptake and lactate efflux in various cancer cells (Amorim et al. 2015; Moreira et al. 2013; Santos et al. 2014). Quercetin (5–100 μM) translocates GLUT1, increases its expression, but decreases its function by competitive inhibition in cholangiocarcinoma (TFK-1) and liver cancer (HepG2, Hep3B2.1-7, and HuH7) cells(Brito et al. 2016). In MCF-7 and MDA-MB-231 cells, quercetin (100 μM) competitively inhibit the GLUT1 expression (Moreira et al. 2013). Quercetin (25 μM) effectively inhibits the lipogenesis process to 38% as compared to control cells by inhibiting the enzymatic activity of FAS protein in human breast cancer (MDA-MB-231) and prostate cancer (LnCaP) cells (Brusselmans et al. 2005). In the triple-negative breast cancer model, quercetin (150–415 μM) inhibits the FAS and β-catenin levels and induced cell apoptosis (Sultan et al. 2017). In human pancreatic adenocarcinoma (MIAPaCa-2) cells,

quercetin (50 μM) inhibits glycogen synthesis (Harris et al. 2012). Quercetin (25–100 μM) has been reported to inhibit the expression and activity of FAS protein level in the HepG2 cell line (Zhao et al. 2014). In the HCC cell line, quercetin inhibits glycolysis by downregulating the HK2 and Akt/mTOR pathway (Wu et al. 2019).

2.4.3.4 Apigenin

Apigenin (Fig. 2.1) is a flavone that mostly originates in the vegetables and fruits and possesses potent anticancer activity. In human pancreatic cancer cells, apigenin (6.25–50 μM) inhibited the mRNA and protein level of GLUT1 by altering the PI3K-Akt pathway (Melstrom et al. 2008). Apigenin (10 μM) inhibited the glucose flux and ATP production by downregulating GLUT1 mRNA and protein expression without affecting other glycolytic enzymes in human lung cancer cells (Lee et al. 2016b). After apigenin exposure, both GLUT1 and GLUT4 levels were upregulated in androgen-sensitive LNCaP cells (7.1 μM), whereas in androgen-insensitive PC3 cells (15.7 μM), the GLUT1 protein expression was decreased and the expression of GLUT4 increased (Gonzalez-Menendez et al. 2014). In human colon cancer (HT29, DLD-1, and HCT116) cells, apigenin (10–40 μM) binds directly with PKM2 and altered its expression and activity and deceased glucose consumption, lactate, and ATP production (Shan et al. 2017). In breast cancer cells, specifically in epidermal growth factor receptor 2 (HER2)-overexpressing SKBR3 cells, apigenin (50 μM) significantly downregulated the FAS protein expression (Menendez et al. 2008).

2.4.3.5 Oroxylin A

Oroxylin A (Fig. 2.1) is a flavone isolated from *Oroxylum indicum* and *Scutellaria baicalensis and can modulate the glucose metabolism in various cancer cells* (Lee et al. 2016a). Oroxylin A (12.5–50 μM) inhibited the mRNA and protein expression of PDK, HK, PKM2, and LDHA in HepG2 cells under hypoxic (1% oxygen) condition rather than normoxic condition via modulating the HIF1α expression (Dai et al. 2016). Glycolysis was inhibited by oroxylin A (100–200 μM) in the human lung adenocarcinoma (A549) cells by downregulating the glycolytic protein HK2 expression (Wei et al. 2013). In MDA-MB-231 cells, oroxylin A (50–200 μM) downregulated the HK2 expression by suppressing HIF1α via sirtuin 3 (SIRT3) activation and hence inhibited glucose uptake and lactate production (Wei et al. 2015). Oroxylin A at a concentration of 12.5–50 μM modulates the TP53-induced glycolysis in HepG2 cells (Dai et al. 2013). Under hypoxic condition, oroxylin A (50–150 μM) inactivates HIF1α protein and downregulates the lipid synthesis and uptake by reprogramming fatty acid metabolism whereas decreases the intracellular fatty acid level and increases fatty acid oxidation in HCT116 cells (Ni et al. 2017).

2.4.3.6 Epigallocatechin Gallate (EGCG)

Epigallocatechin gallate (Fig. 2.1) is polyphenol mostly found in green tea with an antagonistic effect on cancer cell metabolism. EGCG (50–400 μM) downregulated the mRNA level of GLUT1, AMPK activation, and vascular endothelial growth factor (VEGF) reduction in human colon cancer cells (HT-29) (Hwang et al. 2007).

In these same cell lines, suppression of glucose uptake and upsurge of glutamine consumption was reported after EGCG (70–140 μM) treatment (Sánchez-Tena et al. 2013). In human tongue carcinoma (TSCCa and Tca8113) cells, EGCG (20–80 μM) inhibited glycolysis by downregulating the HK2 (Gao et al. 2015). EGCG (80 μM) inhibits the conversion of 3-phosphoglycerate (3-PG) to 2-phosphoglycerate (2-PG) by downregulating the expression of phosphoglycerate mutase 1 (PGAM1) in the breast (MDA-MB-231) and lung (NCI-H1299) cancer cells (Li et al. 2017b). Glucose uptake and lactate production were reduced after EGCG (10–100 μM) treatment in MCF-7 cells (Moreira et al. 2013). In MCF-7 cells, EGCG (10–40 μM) altered EGFR/PI3K/Akt/Sp-1 signaling network which ultimately inhibited the epidermal growth factor (EGF)-induced FAS expression (Yeh et al. 2003). The important constituent of cellular membrane palmitate synthesis was diminished after the downregulation of acetyl-CoA by ECGC (50 μM) treatment in human pancreatic adenocarcinoma (MIA PaCa-2) cells (Lu et al. 2015).

2.5 Bioinformatics Approaches

Traditionally, pharmacology and chemical science-based drug discovery of natural product techniques face various criticism in finding new drugs due to time constrain, a huge investment of money, and toxicity occurrence. The increasing demand for time-saving strategy to discover and develop selective and safe natural lead molecules has signaled the start of a new era of bioinformatics (Li et al. 2020). In bioinformatics analysis, it is possible by designing various computer algorithm to recognize or structurally transform a natural product, to design a lead (molecule) with the required function, and to assess its in silico therapeutic effects which further paved major foundation stone in the branch of science what is now called computer-aided drug designing or virtual screening of drugs (Fig. 2.4).

In the post-genomic era, computer-aided drug designing is one of the promising rational drug designing approaches to develop anticancer leads with plant-derived natural products or synthetic compounds that target cellular metabolic signaling networks. Multiple bioinformatics methodologies can be taken into encounter (like virtual screening, molecular docking, high-throughput screening, QSAR, pharmacophore, and modeling) to minimize the cost and time of drug identification, candidate screening, and refinement but also provide insights about the characterization of side effects and predict drug resistance (Jiang and Zhou 2005; Xia 2017). Several web-based servers or standalone softwares and online public repositories of natural product libraries are available for target identification, hit to lead generation, and lead optimization that help to understand clinical and preclinical findings. All these approaches are very useful for researchers targeting the antimetabolic lead discovery, assessment, and development.

The rise of cutting-edge technology, especially the use of high-throughput next-generation data such as metagenomic, transcriptomic, proteomics, epigenetic, ribosome profiling, and pharmacogenomics data, encompasses weighty contribution to mechanism-based drug discovery and drug repurposing (Tietz and Mitchell 2016).

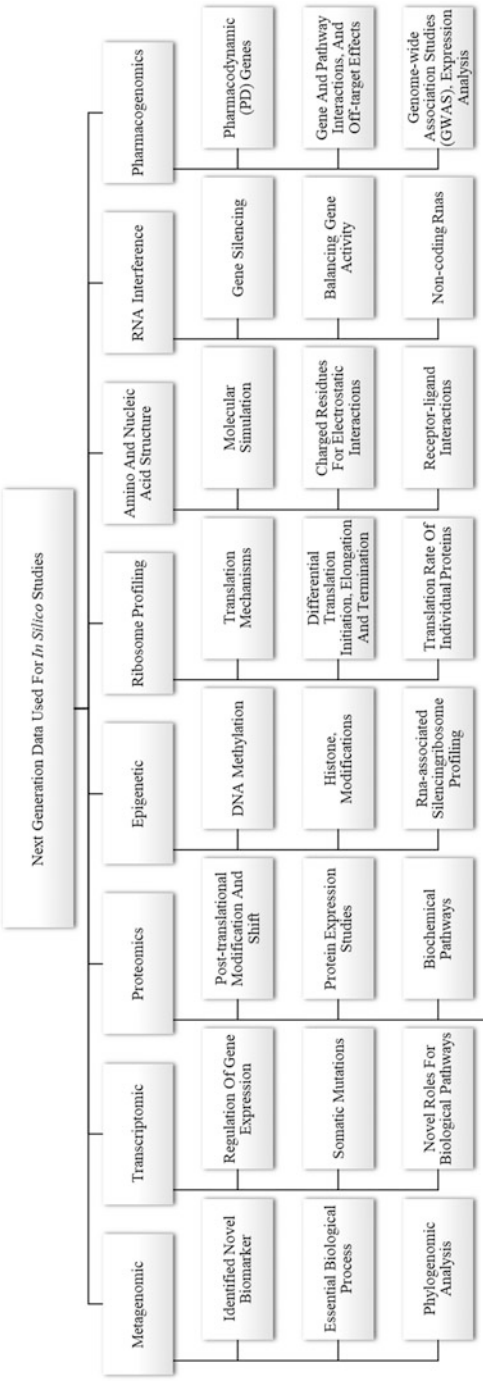

Fig. 2.4 In silico approaches for next-generation drug designing

Accumulation of amino acid and nucleotide structures, as well as the development of in silico homology modeling and molecular simulation, together with large structure databases of small molecules and metabolites, paved the way for more realistic receptor-ligand docking experiments and more informative virtual screening being uncovered biological insights whose deciphering can be the basis for scientific and economical success (Johnston et al. 2015).

2.6 Summary

Targeting cancer cell metabolism is a promising therapeutic approach that is still unexplored. In this chapter, we have highlighted many of the responsible proteins or enzymes and their modifications in the pre-carcinogenesis stage. Therefore, targeting them may be a promising strategy for chemopreventive purposes.

Identification of highly expressed or active proteins that perversely regulated the key metabolic signatures is important to develop a potential therapeutic drug. Although numerous efforts have been made for this, the effective number of lead molecules is still very low and in the preliminary stage. A promising candidate should possess toxicity against cancer cells rather than normal cells and also have favorable pharmacological profiles including stability, half-life, and bioavailability. We have reported that many natural products have been identified so far as a promising anticancer agent that targets various cancer metabolic proteins. Although these kinds of lead molecules provide many health benefits, sometimes poor pharmacokinetic properties like absorption, bioavailability is becoming a major concern that needs to explore.

Nature provides a vast source of different and diversified molecules. The rapid modernization of the screening system allows the selection and analysis of isolated natural compounds that are potent antimetabolic actions with reduced side effects. The application of synthetic chemistry and bioinformatics tools will be very much helpful to generate a more selective and less toxic lead in the distant future. Alternatively, inexpensive production of those scaffolds will make them commercially interesting.

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