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AMPK and TET2 Signaling Pathway and their Natural Activators

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Abstract

Emerging evidence suggests that sustained diabetes-associated factors such as inflammation, hyperinsulinemia, and hyperglycemia are major contributors to aberrant cell proliferation and subsequent neoplastic transformation. Epidemiological studies have also highlighted that diabetes promoting a sedentary lifestyle, with or without the direct involvement of insulin, is frequently linked to cancer. However, our knowledge regarding the molecular mechanisms that correlate hyperglycemia to oncogenic transformations remains limited. In this regard, a recent study has proved that hyperglycemia inactivates AMPK, which results in the destabilization of the TET2 and its tumour-suppressive role ultimately predisposing diabetes mellitus patients to cancer. To the management of hyperglycemia associated with oncogenesis, we need to explore a reverse pharmacology-based ethnopharmacological approach. Botanical-derived natural products are structurally and functionally more diverse with fewer or no side effects on humans. The present review discusses the molecular link between hyperglycemia and cancer progression with the effect of natural products as therapeutic agents on the hyperglycemia-cancer associated signalling pathway.

Keywords: Diabetes, Hyperglycemia, Cancer, AMPK, TET2, Natural products.

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1. Introduction

Diabetes mellitus (DM) is a multifaceted disorder associated with lipid disorder (Keiding et al., 1952), hyperinsulinemia (Diem et al., 1990; Kulkarni et al., 2003), hyperglycemia (Bhatia & Wolfsdorf, 1991), cardiovascular diseases (Finck et al., 2002), and high BMI (Logue et al., 2013). A myriad of factors can contribute to the development of DM-associated hyperglycemia such as stress, critical illness (stroke or myocardial infarction) (Capes et al., 2001), drugs [thiazides (Goldner et al., 1960), L-asparaginase (Cetin et al., 1994), octreotide (Ørskov et al., 1996), β-blockers (Haas et al., 2003), corticosteroids (Suissa et al., 2010), statins (Preiss et al., 2011)], as well as hormones (American Diabetes Association, 2014). Besides, constitutive secretion of insulin or increased expression of glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP) are also frequently associated with hyperglycemia (Golovchenko et al., 2000; Kulkarni et al., 2002; Lynn et al., 2003). Sustained hyperinsulinemia is also a familiar cause of site-specific cancer progression as it promotes increased expression of insulin receptor A (IR-A) and secretion of insulin-like growth factor 1 receptor (IGF-1 Rs) (Denley et al., 2007). It has been postulated that the development of both DM and cancer within the same individual is more likely by about 8-18% (Lee et al., 2012; Ko & Chaudhry, 2002). Collective meta-analyses of several studies have proposed that DM is usually linked with the risk of at least some form of cancer such as colorectal (Polednak 2006), bladder (Larsson et al., 2006), breast (Larsson et al., 2007), endometrium (Friberg et al., 2007), pancreatic (Ben et al., 2011), kidney (Larsson & Wolk, 2011), liver (Wang et al., 2012), gastric (Tian et al., 2012), and ovarian (Lee et al., 2013). However, despite these observations, the potential molecular links between DM and cancer are rather poorly understood and identification of common molecular targets that relate to the pathogenesis of cancer and DM remain elusive.

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The heritable covalent modifications of DNA such as methylation, acetylation, phosphorylation, and SUMOylation are often perturbed in cancer and related cellular defects (Baylin & Jones 2011). Experimental evidence suggests that the cellular metabolic fates can directly regulate the epigenome through nutrient sensors such as the AMP-activated protein kinase (AMPK) (Johnson et al., 2010; Mihaylova & Shaw 2011). Cell metabolism can affect epigenome because of several metabolites, which can act as substrates, activators, inhibitors, cofactors, or allosteric modulators of the epigenome regulating enzymes (Wong et al., 2017). Conversely, the epigenome can also modify the gene expression by altering processes such as gene transcription. AMPK is an extremely conserved protein, which senses cellular energetic stress and is also referred to as a fuel gauge of the cell. AMPK is stabilized under energetic stress particularly when an increased AMP: ATP ratio is observed (Wang et al., 2003). In a recent study, Wu and colleagues proved that hyperglycemia impedes AMPK-mediated phosphorylation of TET 2 at serine 99 residues results destabilization of TET2 and increased susceptibility for calpain-mediated proteolysis followed by dysregulation of tumour-suppressive functions and reduced 5hmC level in the CpG Island (Wu et al., 2018).

TET proteins are a member of the Fe^{++}/α-ketoglutarate-dependent dioxygenases ($Fe2^{+}$/α-KGDDs) family that includes TET1, TET2, and TET3, which are involved in the demethylation of the epigenome. TET2 is known as a tumour suppressor protein that converts 5-methylcytosine residue (5mC) to 5-hydroxymethylcytosine residue (5hmC) on CpG Island (Ito et al., 2011). In-depth investigation and understanding of metabolic glucose (metabolism)-AMPK-TET2-5hmC (epigenome) axis may decode some molecular targets which would be associated with the pathogenesis of cancer and DM. The stable form of AMPK phosphorylates numerous downstream substrates including glycogen synthase (Carling & Hardie, 1989), ACC (Hardie &

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Pan, 2002), FOXO (Greer et al., 2007), CREB (Thomson et al., 2008), raptor (Gwinn et al., 2008), and TET2 (Wu et al., 2018). AMPK phosphorylates TET2, which results in the stabilization of TET2 and prevent its calpain-mediated proteolysis (Wu et al., 2018).

Hyperglycemia is recognized when fasting and postprandial blood glucose levels are more than 125 mg/dL and 180 mg/dL, respectively (World Health Organization, 2006). Untreated hyperglycemia has been associated with several serious physiological complications including damage to the nervous systems (Rovlias & Kotsou, 2000), the peripheral vascular (Ling et al., 2003), eye (Zhang et al., 2016), lungs (Wang et al., 2016), heart (Dludla et al., 2017), and kidneys (Chowdhury et al., 2019).

The present review briefly discussed the molecular connection between the diabetes-associated factors and oncogenic progression with the therapeutic possibility of natural products. Besides that, this review also discusses the possible molecular mechanisms of how extracellular hyperglycemia can manipulate the intracellular enzymatic machinery which regulates metabolism and gene expression vis-à-vis diabetes and cancer.

2. Epidemiology and Etiology of Cancer and Diabetes Mellitus Associations

DM and cancer are often recognized as the defining disorders of the 21st century and with a remarkable global socio-economic impact. According to the World Health Organization, it is estimated that cancer and DM represent the second (9.6 million, 2018) and seventh (1.6 million, 2016) leading cause of death worldwide, respectively. The international diabetes federation has estimated that the global prevalence of DM would rise from 425 million in 2017 to 629 million in 2045 (Saeedi et al., 2019). In addition, both cancer and DM are often co-diagnosed in the same patient, which suggests that a significant increase in the cancer occurrence within diabetic patients (Polednak 2006; Larsson et al., 2006; Larsson et al., 2007; Friberg et al.,

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2007; Ben et al., 2011; Larsson & Wolk, 2011; Wang et al., 2012; Tian et al., 2012; Lee et al., 2013).

The DM-cancer association has been hypothesized to rely on various factors including insulin, IGF1, adipokines, inflammation, and hyperglycemia. The transformation of healthy cells into neoplastic phenotypes is probable through numerous genetic alterations, such as overexpression of oncogenes and/or suppression of tumour suppressor genes. The neoplastic progression of cancer cells undergoes different cellular phases such as growth, invasion, and metastasis (Barrett & Ts'o, 1978). DM can directly or indirectly promote these different aspects of neoplastic progression through several characteristic factors including hyperinsulinemia, elevated IGF1 level, cytokine imbalance, and chronic inflammation (Fig. 1).

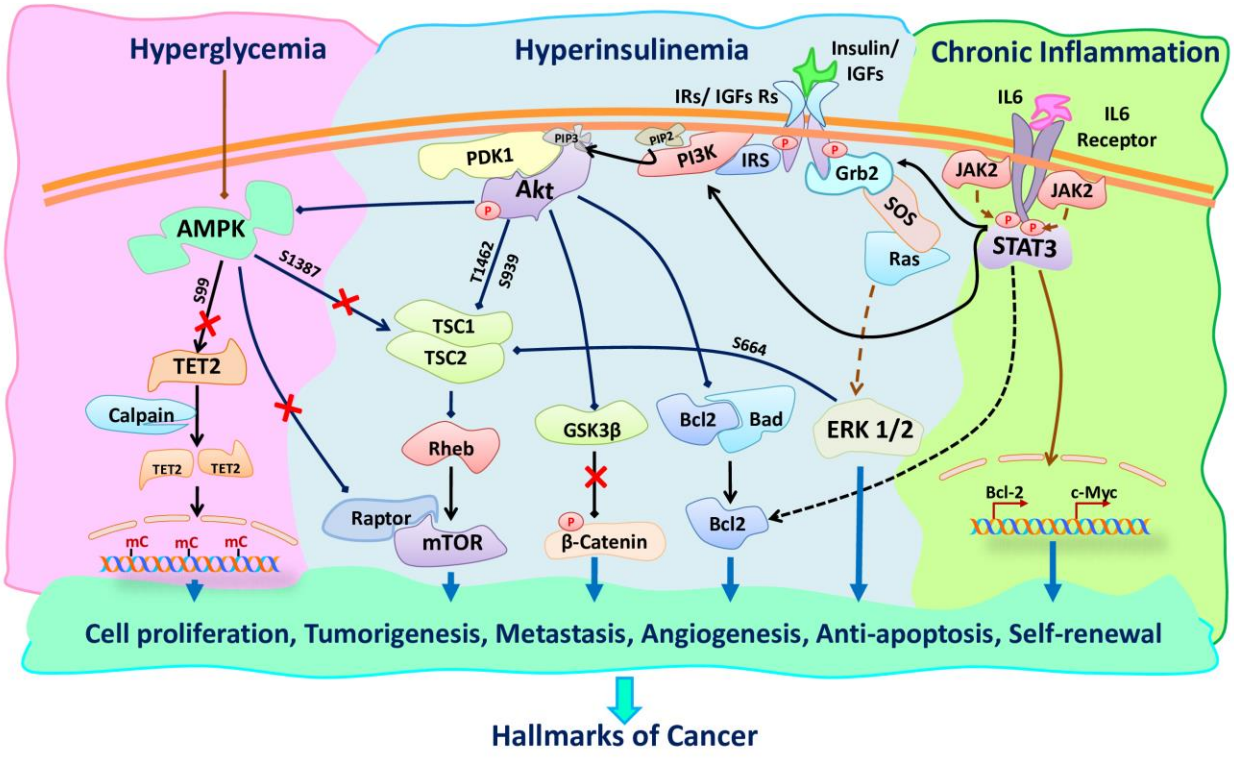

Figure 1: The cellular signalling pathways that link DM to cancer via hyperinsulinemia by over activating insulin receptors and IGF-1 leads to downstream activation of the PI3K-Akt-mTOR pathway and Ras-Raf-MEK-ERK pathway. The Akt activates, several targets like mTOR and

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Bcl2, while inhibits AMPK and β-catenin. Chronic inflammation has responses by interleukin-6 to activate STAT3 which promotes Bcl2 and c-Myc overexpression. Hyperglycemia destabilizes AMPK; so it is unable to phosphorylate TET2 and TSC1/2 complex. Unstable AMPK was also unable to inhibit raptor which regulatory-associated protein of mTOR. All these cellular cascades are cooperatively responsible for cancer progression by promoting angiogenesis, apoptosis, metastasis, and tumorigenesis.

2.1. Hyperinsulinemia

In sustained hyperinsulinemia, insulin acts as a growth-promoting factor which in combination with insulin-like growth factor-1 (IGF-1) is promote the rate of tumorigenesis (Koenuma et al., 1989; DiGiovanni et al., 2000). Approximately, 98% of serum IGF-1 is coupled with IGF-1 binding proteins (IGF-BP) which constitutes a functionally inactive form (Suikkari et al., 1988). Hyperinsulinemia also induces overexpression of IGF-1 as well as suppression of IGF-BP which results in elevation of the active form of serum IGF-1 (Kaaks et al., 2000). In humans, IRs generates two isoforms, IR-A and IR-B, and the majority of cancer cells express IR-A and IGF-1 receptors (IGFs-1Rs) on their surface (Frasca et al. 1999; Belfiore, 2007). The IR-A has a binding affinity with insulin, proinsulin, and IGF-2, and thus IR-A is efficient to induce insulin-mediated mitogenesis (Párrizas et al., 1997; Rajapaksha & Forbes 2015). An elevated level of serum IGF-1 has also been shown to increase the probability of colorectal cancer development (Palmqvist et al., 2002). Further, when insulin and IGF-1 interact with IRs and IGF-1 Rs, respectively, both activate PI3K-Akt-mTOR and Ras-Raf-MEK-ERK signalling cascade (Ceresa et al., 1997; Lee et al., 2011; Siddle 2011). Akt inhibits AMPK (Valentine et al., 2014) and glycogen synthase kinase 3β (GSK3β) (Fang et al., 2000), which now unable to

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inactivate β-catenin thereby promoting an environment of sustained cell proliferation with implications in tumour development (Kelly et al., 1995; Zhang et al., 2016). Moreover, Akt also suppresses apoptosis-induced cell death by dissociating the anti-apoptotic protein Bcl-2 (B-cell Lymphoma 2) from Bad (Datta et al., 1997). Thus, together, it can be emphasized that the sustained active forms of IRs and IGF-1Rs mediated signalling cascades can potentially augment the susceptibility to tumorigenesis (Fig. 1).

2.2. Inflammation

Elevated levels of insulin can also induce the secretion of several factors which promote the accumulation of fats in adipose tissues. The adipose cells are potent sources of inflammatory mediators including sialic acid (Prince et al., 1981), fibrinogen (Schmidt et al., 1999), IL-6 (Pradhan et al., 2001), C-reactive protein (CRP) (Freeman et al., 2002), plasminogen activator inhibitor-1 (PAI-1) (Festa et al., 2002), and TNF-α (Morris et al., 2006) that leads to the inflammation. TNF-α had shown potential physiological impacts on metabolism *via* inducing insulin resistance (Hotamisligil et al., 1993; Feinstein et al., 1993). The regular secretion of IL-6 steadily activates the IL-6 receptor and consequently activation as a signal transducer and activator of transcription protein-3 (STAT3) (Lokau et al., 2019). Inflammation-mediated over-activation of STAT3 provoked neoplastic progression and also seized host anti-tumour immunity (Lokau et al., 2019) (Fig. 1). The occurrence of leukocytes enclosed to tumor's was first observed by Rudolf Virchow representing a probable association between inflammation and tumorigenesis. T-cells and tumour-associated macrophages (TAMs) are routinely observed leucocytes near the tumour microenvironment. T-cells exhibit both tumour-promoting and tumour-suppressive attributes (Smyth et al., 2006; DeNardo et al., 2009) while TAMs frequently induce angiogenesis, tumorigenesis, invasion, and metastasis (Condeelis & Pollard 2006). The

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inflammation associated components such as TNF-α, IL-6, TAMs, and other inflammatory mediators modulate signalling pathways that are associated with tumorigenesis (Fig. 1).

2.3. Hyperglycemia

Hyperglycemia is a well understood systemic and metabolic factor that links DM to cancer. Cancer cells utilize more glucose than normal cells to fulfil their metabolic demands. Otto Warburg in the 1920s clarified that cancer cells utilize glycolysis for glucose metabolism and ATP generation instead of oxidative phosphorylation even in the hyperoxia environment (Warburg 1956). Cancer cells require more glucose for ATP generation as a prime energy source and thus they exhibit a high rate of glucose uptake, unlike their healthy counterpart. Hence, hyperglycemia facilitates tumorigenesis and cancer progression by the several direct and indirect factors thus is considered as a potential anti-tumorigenesis target (Fig. 2). Hyperglycemia links DM to cancer through increased secretion of circulating soluble factors including growth factors (insulin/IGF1) (Rajaram et al., 1997) and inflammatory cytokines (TNF-α/IL6/Adipokines) (Devaraj et al., 2005; Gonzalez et al., 2012). The majority of cancer cells constitute INRCs as these cells can efficiently uptake glucose independent of the insulin/GLUT4 pathway (Yun et al., 2009). Hyperglycemia stimulates insulin secretion, which results in hyperinsulinemia and this physiological heterogeneity leads to the hyperactivation of IR-A and IGF-1Rs which induce cellular neoplastic expansion (Rajapaksha & Forbes 2015). Metabolically active cells are also significantly involved in the generation of free radicals and other reactive species which may create mutations in DNA through oxidative damage. Sustained hyperglycemia plays a key role in neoplastic progression by promoting ROS formation, DNA mutation, DNA damage, and dysregulation of oncogenes, tumour suppressors, and DNA repair system (Pandey et al., 2011;

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Vanessa et al., 2013; Alam et al., 2015). The initiation of cancers can often be traced to mutations in oncogenes and tumour suppressor genes (Li et al., 2019).

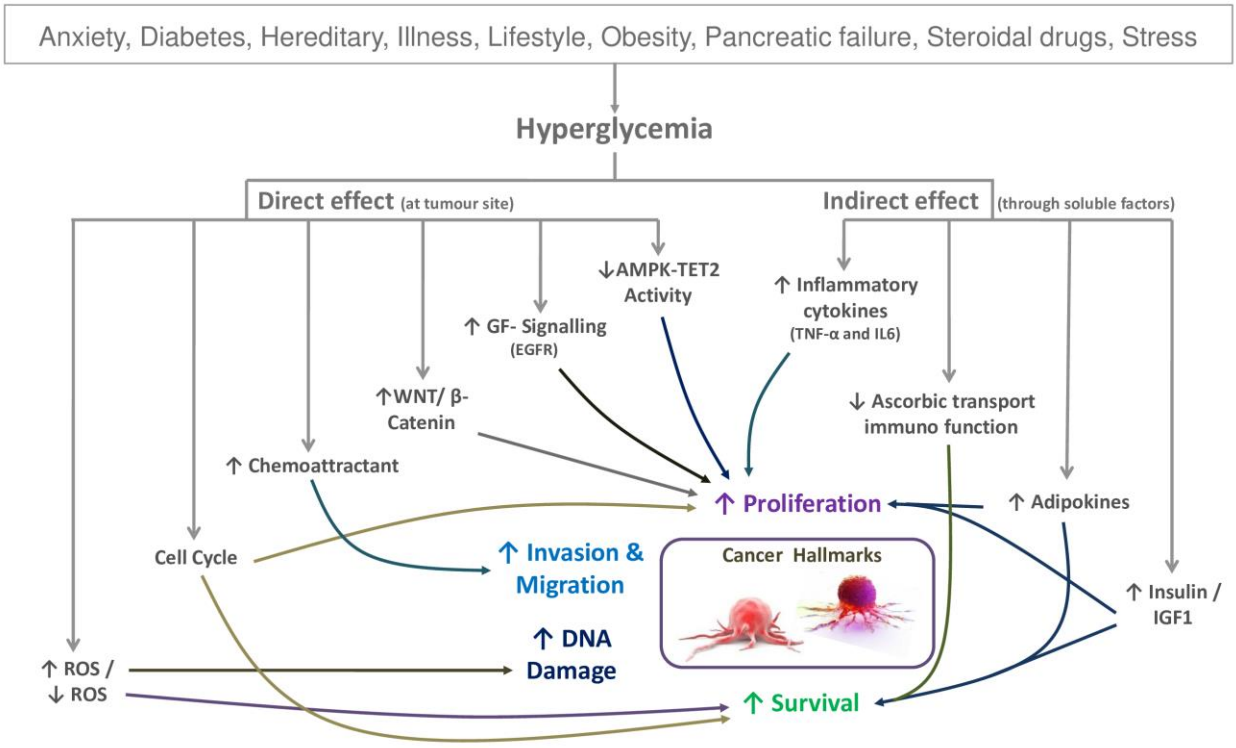

Figure 2: The physiological, genetic, social and lifestyle factors are responsible for the development of hyperglycemia. Hyperglycemia stimulates cancer hallmarks by several direct and indirect cellular mechanisms. Direct effects of hyperglycemia on tumour site: initially increases the production and accumulation of ROS to increase the rate of mutagenesis after that decreases the production of ROS to ensure survival; accelerated the rate cell cycle; elevates the secretion of chemo-attractants such as glial cell line-derived neurotrophic factor (GDNF) for invasion and migration; An over-activates the WNT/β-catenin signalling which promotes proliferation; overexpression of growth factor receptors (EGFR); destabilization of AMPK-TET2 signalling axis, results in dysregulation of 5hmC conversion and tumour-suppressive activity of TET2. The indirect effects of hyperglycemia on cancer cells mediated through the soluble factors: increased the circulatory levels of insulin/IGF1; increase the production of inflammatory cytokines TNF-α, IL6, and adipokines; and decrease ascorbic acid transportation in immune cells that minimized immunological surveillance. Both direct and indirect effects of hyperglycemia

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unite on cancer hallmarks (increased proliferation, invasion, migration, DNA damage, and survival).

Additionally, due to chronic hyperglycemia, the non-enzymatic formations of advanced glycation end (AGE) products linked with nucleic acids (Shahab et al., 2014), proteins (Haus et al., 2007), or lipids (Curtis et al., 2011) are increased. The AGEs accumulate in the tissues which can lead to DNA damage as well as and promoting inflammation (Kislinger et al., 2011), NF-kB secretions (Sousa et al., 2000), ROS formation (Alikhani et al., 2007), and overexpression AGE receptors (Stitt et al., 1997), which collectively contribute to carcinogenesis. The rate of the cell cycle is accelerated by hyperglycemia by altering the functions of key cell cycle regulatory proteins resulting in increased cellular proliferation (Masur et al., 2011). In addition, hyperglycemia activates the Wnt/β-catenin signalling cascade in neoplastically transformed cells which induce over-proliferation, promote survival, and represent one of the direct molecular mechanisms which can link hyperglycemia to cancer (Li & Siragy, 2014; Montani et al., 2016).

2.3.1. Glucose-AMPK-TET2-5hmC Signalling Axis Link between Hyperglycemia and Cancer

The main focus of this review is the contrasting impact of hyperglycemia on the AMPK-TET2 signalling axis in mechanistically distinct tissue and the probability of cancer progression. This is of significance since a recent study has observed that hyperglycemia mediated inactivation of AMPK results in the proteolysis induced destabilization of TET2 followed by dysregulation 5-hydroxy-methylcytosine (5hmC) conversion and tumour-suppressive function of TET2 which predisposes DM patients to cancer thereby suggesting a link between DM and cancer (Wu et al., 2018). The activated form of AMPK maintains optimum level intracellular ATP by modulating key proteins involved in glucose transport (Abbud et al., 2000), glycolysis (Marsin et al., 2000), by inhibiting ATP consumption processes (Onyenwoke et al., 2012), and

 doi:10.20944/preprints202204.0100.v1

tricarboxylic acid cycle (Tyszka-Czochara et al., 2018). AMPK has few upstream regulators but numerous downstream targets that enable AMPK as a central regulator of metabolism. Under energetic stress, AMP: ATP and ADP: ATP ratio is increased which activates AMPK *via* promoting phosphorylation at Thr-172 of α-subunit of AMPK and restores energy balance (Hardie & Carling, 1997). The AMPK phosphorylation is carried out by the three kinases (Serine-Threonine Kinase 11 or liver kinase B1), which are functionally active in an association with STRAD and MO25 (Woods et al., 2003), calcium/calmodulin-dependent kinase kinase 2 (CAMKKβ or CaMKK2) (Woods et al., 2005), and TGFβ-activated kinase 1 (TAK1) (Momcilovic et al., 2006). Binding of AMP or ADP to γ subunits that inhibits pThr-172 dephosphorylation mediated by protein phosphatase 2C (PP2C) (Xiao et al., 2011; Emanuelle et al., 2015) and protein phosphatase 2A (PP2A) (Ravnskjaer et al., 2006). AMPK has played a significant role in epigenetic regulation *via* phosphorylation at Ser-99 of TET2 which is involved in the demethylation of CpG Island (Wu et al., 2018). AMPK phosphorylates TET2 at Ser-99 residue that stabilizes it results in increased TET 2 activity. Due to hyperglycemia, AMPK is in an inactive form, which is inadequate to phosphorylate Ser-99 resulting in destabilization of TET2 that causes reduced transformation of 5mC to 5hmC (Fig. 3) (Wu et al., 2018). The decline of 5hmC residues is considered an epigenetic hallmark of tumorigenesis that decreases levels of TET2 expression (Ko et al., 2010; Lian et al., 2012). Further, 5hmC residues have frequently been present at the promoters and intragenic regions that lead to reduced gene expression (Wu et al., 2018; Neri et al., 2015). 5hmC residues are associated with genes that are involved in cell cycle regulation and cancer-related pathways such as MCM3, CDC73, EIF-5A, ALDH2, BNIP3, and P2RX5 (Wu et al., 2018).

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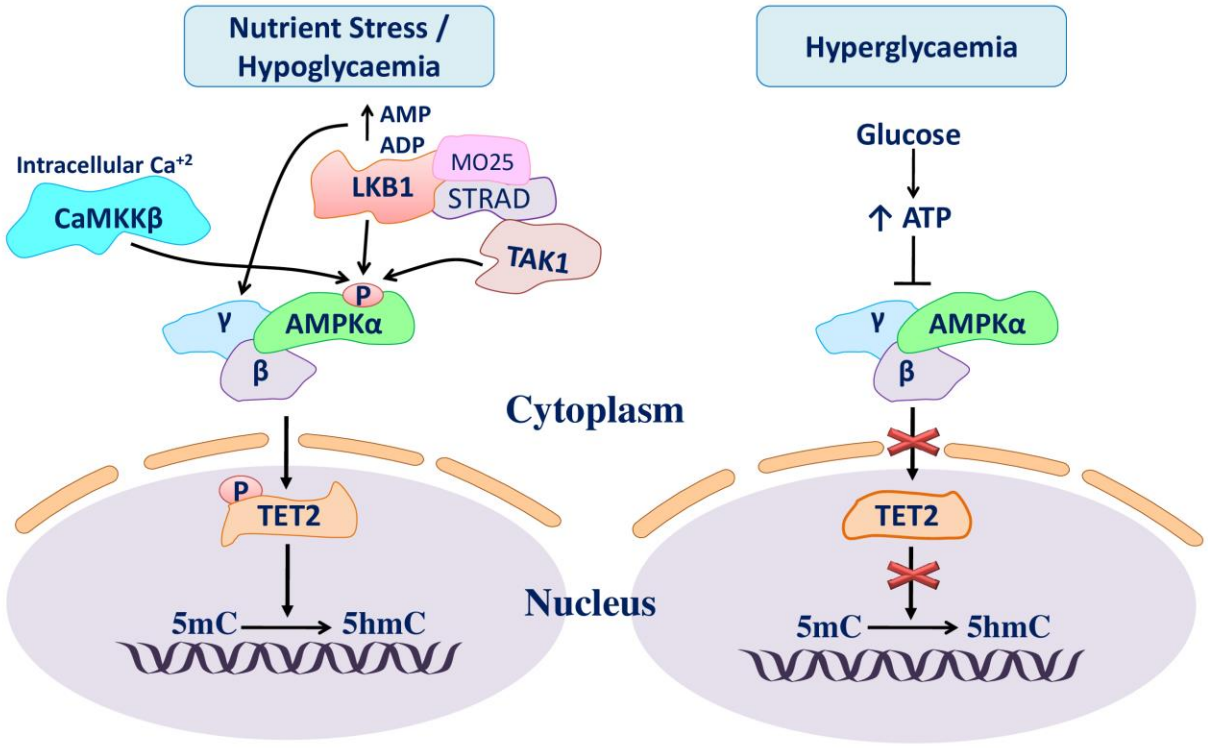

Figure 3: Intracellular glucose level modulates the activity of AMPK, which is a cellular nutrient sensor. The active form of AMPK phosphorylates and stabilized TET, which converts 5mC to 5hmC for the demethylation of CpG enrich regions. AMPK is destabilized due to hyperglycemia high intracellular ATP level; a thereby unstable form of TET2 results in halts the conversion of 5mC to 5hmC and tumour-suppressor activity.

3. Structural and Functional Insights of AMPK and TET2

AMPK is a cellular nutrient sensor, highly conserved and ubiquitously expressed in all eukaryotic species, which restores energy homeostasis at the cellular levels (Mihaylova & Shaw, 2011). Structurally AMPK is a heterotrimeric protein complex, which is composed of three subunits, catalytic α-subunit encoded by two isoforms, and regulatory β- and γ-subunit are encoded by two and three isoforms, respectively (Wang et al., 2003). The tissue-dependent expression pattern of AMPK has varied due to the occurrences of 12 different isoforms in

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mammals (Carling et al., 2013). The *N*-terminus of the α-subunits is comprised of the Kinase Domain (KD), while the C-terminus consists of important regulatory domains, known as the auto-inhibitory domain (AID) this also interact with β- and γ-subunits (Carling et al., 2013). The β-subunits have two conserved domains one is a carbohydrate-binding module (CBM) and a C terminus domain interacts with α- and γ-subunits. The γ-subunit is composed of two Bateman domains, each contains two cystathionine β-synthase repeats (CBS), which significantly recognize and bind AMP, ADP, or ATP competitively to regulate AMPK activity (Fig. 4A).

Intracellular hypoglycemia activates AMPK and downstream phosphorylation of several proteins, including TET2 which is involved in the conversion of 5mC to 5hmC. The structural insights of the TET-family (TET1-3) demonstrated that these are high molecular weight (~180- to 230-kDa) and multidomain proteins (Fig. 4B). The catalytic domain of TET consists of a cysteine-rich segment and double-stranded β helixes (DSBH, also called a jelly-roll motif) with nonconserved low-complexity insert (NCLC) in the C terminus [114]. TET specifically recognizes the 5mC at CpG Island. Fe^{+2} and *N*-oxalylglycine, a 2-oxoglutarate (α-ketoglutarate) analogue are the most preferable substrate of TET2 (Hu et al., 2013). The cysteine-rich domain is wraps around the DSBH core and stabilizes the DNA-DSBH core interaction (Hu et al., 2013). Structural investigations decipher that the core catalytic domain selectively interacts with cytosines in a CpG region context but does not bind with adjacent nucleotide bases and shows no hindrance in DNA sequences. The DNA methylation and demethylation occur in a cyclic mode with the involvement of DNA modifying enzymes (Fig. 4C). AMPK and TET2 are regulatory components of metabolism and epigenome, respectively. Disrupting metabolic regulatory system can result in impeding the epigenome regulatory component. Thus both metabolic and epigenetic

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regulatory proteins link metabolic disorder like diabetes to dysregulated genome-born disorder like cancer.

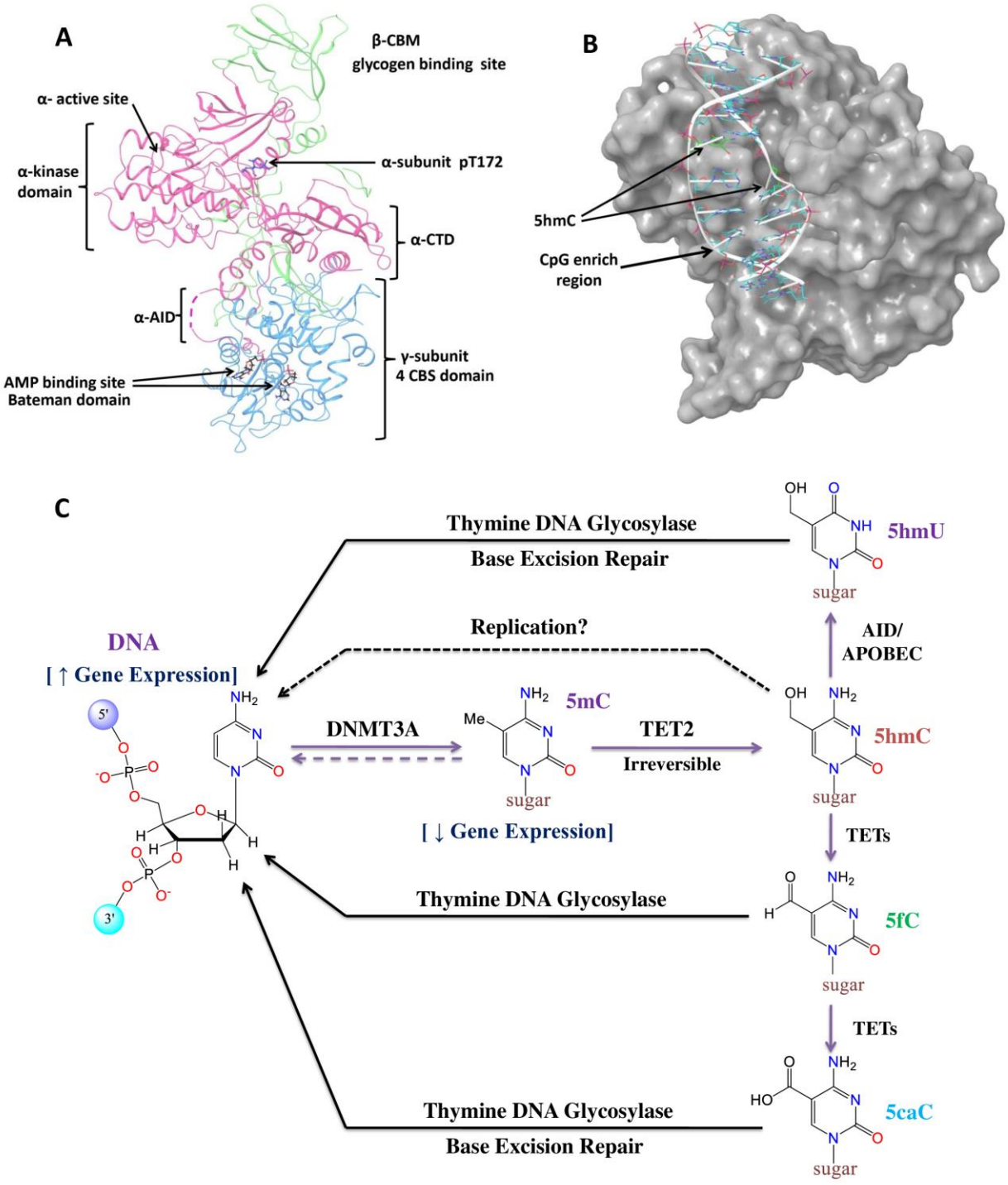

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Figure 4: A) The ribbon structural representation of AMPK (PDB entry: 6C9F), with two AMP molecules bound at γ-subunit. AMPK consist of the α subunit shown in pink, which phosphorylated on Thr172, a catalytically active kinase domain, carboxy-terminal domain (CTD), and an autoinhibitory domain (AID); the β-subunit has carbohydrate-binding site (CBS) domains, shown in green, and the γ-subunit shown in blue, it has two Bateman domain and each one has two cystathionine β-synthase repeats (CBS), that stand for allosteric modulators binding site, such as AMP, ADP, ATP. **B**) The virtual representation of the solid surface structure of human TET2 catalytic domain associated with GpC enrich DNA duplex shown in the white strand with blue nucleotide residues (PDB entry: 5DEU). 5hmC residue in the DNA demonstrated in green colour. AMPK and TET2 structure had drawn and edited using the Schrödinger suite. **C**) The diagrammatic representation of DNA methylation/demethylation cycle by a DNA methyltransferase (DNMTs)/TETs/thymine-DNA-glycosylase (TDG)/base excision repair (BER). Cytosine residues in the CpG Island can be methylated by the DNMT1 or DNMT3A/DNMT3B to transform into 5mC and the methyl group can be donated by SAM. Demethylation of 5mC residue can be done by the TETs enzymes through the 5hmC, 5fC, and 5caC residue then both 5fC and 5caC are recognized by TDG results excised oxidized cytosine residue. Due to excision of modifying cytosine that produces an abasic site which is restored by BER mechanism results in the generation of the unmodified cytosine residue. Besides that, 5hmC can be converted into 5hmU by the action of activation-induced cytidine deaminase, (AID)/apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like (APOBEC) that further transformed into unmodified cytosine residue by the TGD/BER pathway.

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4. Effect of Natural Products on AMPK-TET2 Signalling

Hyperglycemia negatively impacts the outcomes of cancer therapy by drug inactivation, chemo-resistance, and influence drug pharmacokinetics (Duan et al., 2014). The blood glucose-lowering property of hypoglycemic drugs is very crucial during cancer treatment because cancer cells are hungry for glucose. Several marketed therapeutic drugs exhibited some disadvantages in the regulation of blood glucose and related risk factors. For that, we need to investigate biocompatible chemical agents which have a high hit rate with structural diversity and the answer is natural products. The natural products have been originated and evolved by the biological system to serve as a survival function including growth regulation, metabolic and epigenetic regulation, defence from biotic and abiotic stress, and reproduction. The surrounding ecological conditions of the organism influence the structural and functional diversity of natural products. The structure and function of natural products is the outcome of a million-year evolution and still, it does continue. Natural products have been usually considered as a treasure trove for potent and novel drug designing and approximately 46% of food and drug administration (FDA) approved drugs are derived from natural products from 1981 to 2014 (Newman & Cragg (2016).

4.1. AMPK activators

The AMPK is an evolutionarily conserved energy sensor of cells; it has been activated and stabilized by metformin, which is an important drug in the treatment of DM (Luo et al., 2010). Additionally, AMPK has also been activated and stabilized by numerous plants derived natural products including salicylate and galegine (Hardie et al., 2012). Several other natural products were traditionally utilized as herbal medicines, which currently have been scientifically explored as AMPK activators, including berberine (*Coptis chinensis*), curcumin (*Curcuma*

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longa), epigallocatechin gallate (green tea), ginsenoside (*Panax ginseng*), hispidulin (snow lotus), quercetin (many fruits and vegetables), resveratrol (red grapes), and theaflavin (black tea) (Hwang et al., 2009; Lin et al., 2010) (figure 5). Many of these natural products are claimed to have anti-diabetic and anti-cancer effects.

Berberine inhibit F1 ATP synthase (Gledhill et al., 2007), resulting in inhibition of ATP production in mitochondrial. This increases AMP: ATP and/or ADP: ATP ratios which subsequently activate AMPK.

Resveratrol is a stilbenoid, a type of dietary phenolic and phytoalexin biosynthesized by several plants such as berries and peanuts in the response to injury or pathogen attack in the plants. Several scientific pieces of research suggest that there is a lack of high-quality shreds of evidence that prove a substantial impact of resveratrol on lifespan or other diseases (Sahebkar et al., 2015). There is no proof of an anti-cancerous effect of resveratrol in humans (Carter et al., 2014), but in the case of diabetes *in vivo* study support that resveratrol might prove beneficial for the improvement of insulin sensitivity (Jeyaraman et al., 2020). Some studies documented resveratrol as activator of AMPK (Ajmo et al., 2008) for the management of diabetes (Szkudelska and Szkudelski, 2010). Murase *et al.* reported that resveratrol activates AMPK *via* phosphorylation of AMPK-α and β subunits in Hepa 1-6 (mouse hepatocyte cell line) and C2C12 (mouse muscle cell line). The experimental results indicated that resveratrol (150 μM) activated 538 % of AMPK-α and 168 % of AMPK-β in Hepa 1-6 as compared to control, while 848 % of AMPK-α and 425 % of AMPK-β subunits are activated in C2C12 cells (Murase, 2011).

Obovatol is a biphenolic compound isolated from the bark of *Magnolia obovata* is therapeutically known for anti-inflammatory, nootropic, and anti-anxiety (Ma et al., 2009).

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The *in vitro* study carried out by Huh et al., (2010), proved that obovatol activates AMPK in the L6 cell line in a dose-dependent manner. In addition, the animal study of obovatol to db/db mice (oral administration for 4 weeks) reduced the level of blood glucose (Huh et al., 2010).

Nootkatone is responsible for the distinctive flavor and taste of grapefruit (*Citrus paradisi*). Although, Murase *et al*. investigated nootkatone as an activator of AMPK especially in muscle cells to promote carbohydrate and lipid metabolism (Murase *et al*.2010 and 2011a). *In vitro* screening indicated that nootkatone at (150 μM) concentration activates AMPKα (1077%) and AMPKβ (358%) than control of C2C12 muscle cells.

Nectandrin B is a type of 2,5-bis-aryl-3,4-dimethyltetrahydrofuran lignan isolated from *Myristica fragrans*, which act as a potent activator of AMPK and ACC (Oh et al., 2012).

Glabridin is a dietetic isoflavone and an important active component in *Glycyrrhiza glabra*. Lee *et al.*, 2012 revealed its therapeutic role in obesity-related metabolic disorders *via* activating AMPK. Glabridin activates AMPK by 2-fold at 30 μM concentration in the C2C12 myoblast cell line and is claimed as a potential therapeutical agent for diabetes and related metabolic syndromes (Park and Yoo, 2007).

Damulin A and ***B*** are dammarane type open-chain glycosides, isolated from *Gynostemma pentaphyllum* which act as a significant activator of AMPK evaluated using i*n vitro* studies. Both elevate the activity of AMPK in a concentration-dependent manner in L6 myotube cells (Huh et al., 2011). Besides that, there are several natural compounds are evaluated as AMPK activators, some of them are listed in Table 1.

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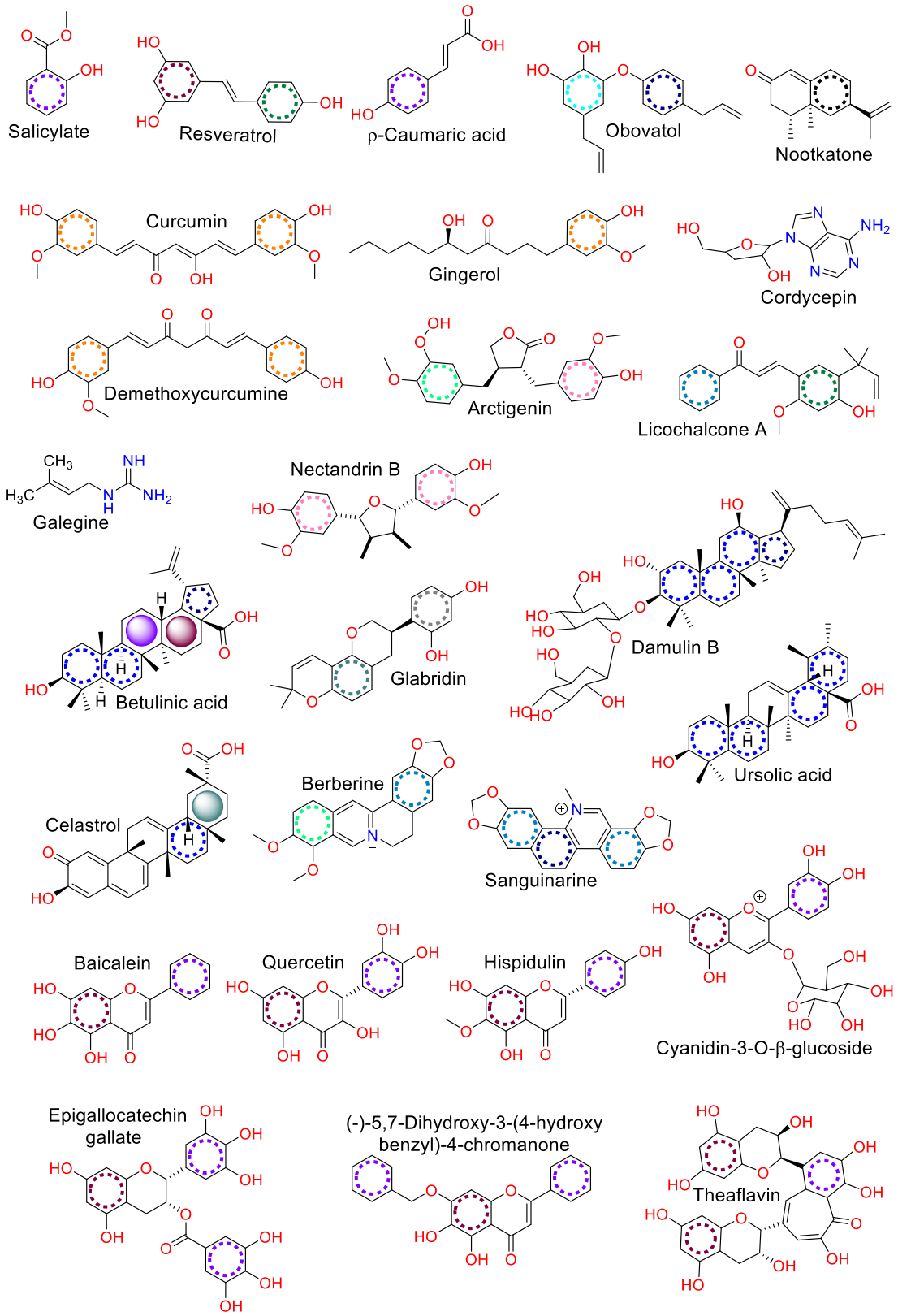

Figure 5: Natural product-derived activators of AMPK.

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4.2. TET2 activators

TET2 has not been explored much for therapeutic purposes and currently, there are no known natural or synthetic activators of TET2. Natural analogues of vitamin C (Figure 6) and α-ketoglutarate (Figure 7) can be explored as TET2 activator. Both are natural co-substrates for TET2 for oxygenation. The loss of function in TET2 is associated with the development of cancer *i.e.* myeloid malignancies. WT1, IDH1/2, and TET2 (WIT) proteins have also suppressed the development of acute myeloid leukemia (AML) (Pasca et al., 2020). Thus the small molecules that act as an agonist for WIT proteins can also help to suppress cancer development.

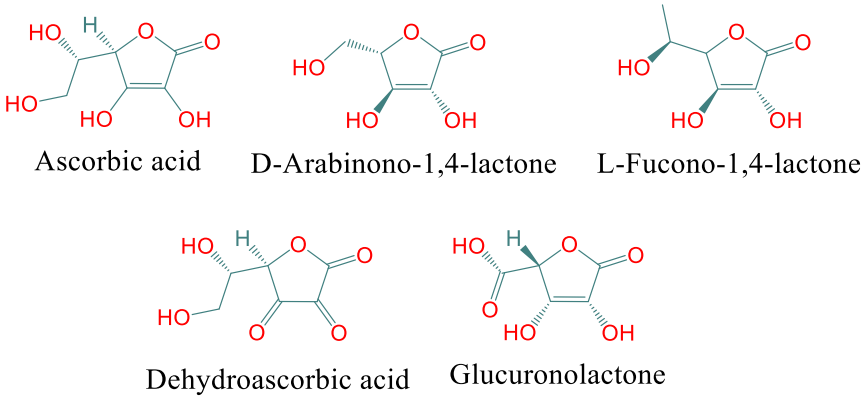

Figure 6: Natural analogues of ascorbic acid.

Table 1: List of natural products that have been evaluated as direct or indirect AMPK activator.

Compound	Bioactivity	Reference
	Direct activator	
Salicylic acid	Interact with β1 subunit and allosterically inhibit Thr172 dephosphorylation. Elevates fatty acid oxidation in HEK-293 Primary mice hepatocytes at 3 μM. Increases fat utilization in mice at 250 mg/kg.	Hawley et al., 2012
Cordycepin (*Cordyceps militaris*)	Interact with γ1 subunit to activate AMPK at 100 Mm in human cells.	Hawley et al., 2020
Sanguinarine	Interact with α1β1γ1 α1β2γ1 subunits and allosterically activates AMPK.	Choi et al., 2011

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Ethoxysanguinarine (Macleaya cordata)	Upregulate the activity of AMPK and induce autophagy in breast cancer cells.	Si et al., 2020
	Indirect activator	
Betulinic acid	Sow down lipid accumulation and lipogenesis in HepG2 at 40 μM. Restrain intracellular lipid accumulation in high fat-fed ICR mice at 5 mg/kg.	Quan et al., 2013
Ursolic acid	Inhibits adipocyte differentiation at 3T3l-1 cells at 20 μM.	He et al., 2013
Baicalein	Decreases the serum lipid in high-fat diet mice at 400 mg/kg.	Pu et al., 2012
Cyanidin-3-O-β-glucoside	Promotes fatty acid β-oxidation in HepG2 cells at1-5 μM.	Guo et al., 2012
ρ-Coumaric acid	Promotes oxidation and glucose uptake in L6 cell line at 12.5 μM.	Yoon et al., 2013
Gingerol	Promotes glucose uptake in L6 cell line at 150 μM.	Kubra et al., 2012
Licochalcone A	Inhibits triglyceride accumulation in HepG2 cells at 5-10 μM. Inhibits triglyceride accumulation in liver of High fat-fed ICR mice at 10 mg/kg.	Quan et al., 2013
(-)-5,7-Dihydroxy-3-(4-hydroxybenzyl)-4-chromanone	Phosphorylation of AMPK in IAR-20 at 10 μM.	Guo et al., 2013
Demethoxycurcumin	Inhibits human triple-negative breast cancer cells proliferation at 5 μM.	Shieh et al., 2013
Celastrol	Induce apoptosis in MCF-7 cells at 3 μM.	Kim et al., 2013
Nectandrin B	Inhibit vascular smooth muscles cells proliferation at 1-3 μM.	Nguyen et al., 2013
Arctigenin *Arctium lappa*	Inhibits Complex I of ETC.	Huang et al., 2012
Berberine *Berberis spp.*	Inhibits Complex I of ETC.	Hawley et al., 2010
Galegine *Galega officinalis*	Inhibits Complex I of ETC.	Mooney et al., 2008
Quercetin	Inhibits Complex I of ETC.	Xiao et al., 2014

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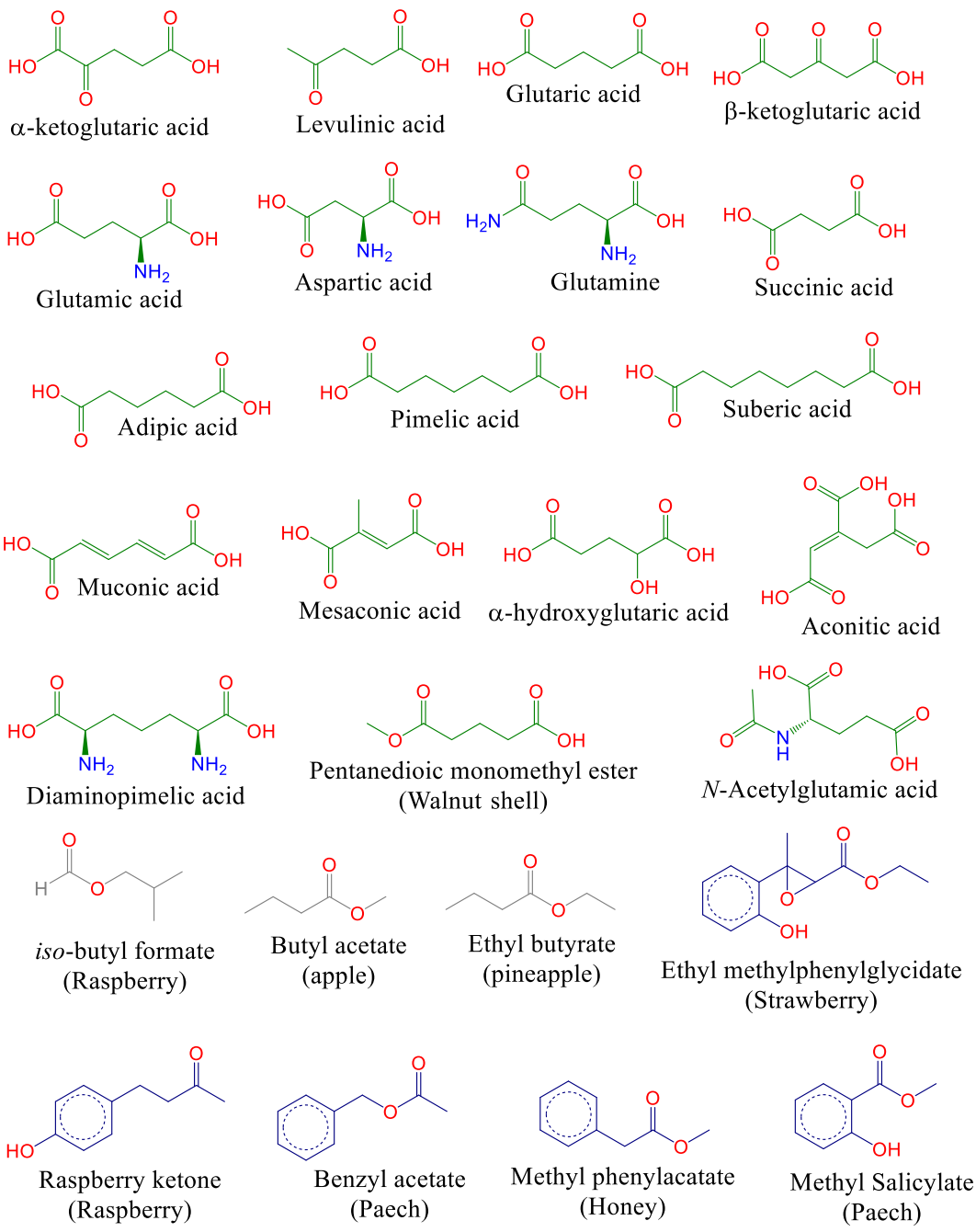

Figure 6: Natural analogues of α-ketoglutarate.

5. Conclusion and future perspective

Hyperglycemia linked diabetes to cancer *via* the glucose-AMPK-TET2-5hmC axis to regulate the expression of genes. Prolonged hyperglycemia associated with hyperinsulinemia

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may strongly support tumorigenesis through overactivation of Akt and ERK1/2 result in the AMPK destabilization, and subsequently suppressed the activity of TET2. Hyperglycemia and hyperinsulinemia together may contribute to the destabilization of the AMPK-TET 2 axis. Along with glucose (hyperglycemia), some other molecules including α-ketoglutaric acid (α-KG), oxygen, and vitamin C have directly or indirectly modulated TET2 stability. TET2 utilized oxygen and *α-ketoglutaric acid* as co-substrates for the oxygenation reactions along with vitamin C. At higher intracellular glucose results high level of ATP and *α*-ketoglutaric acid, ATP is a negative allosteric modulator of AMPK, while *α*-ketoglutarate has co-substrates for TET2. AMPK regulates the isocitrate dehydrogenase 2 (IDH2) enzyme of the TCA cycle that enhances the synthesis of α-ketoglutaric acid which has a co-substrate of TETs consequentially demethylation of CpG (Wu & Zhang, 2014; Yang et al., 2016). Besides that, AMPK regulates DNA methylation *via* increasing the S-Adenosyl Methionine (SAM) level which is substrates for DNA methyltransferase **(**DNMTs). During DNA methylation, DNMT3a and DNMT3b use SAM as a methyl donor and converted it into S-adenosylhomocysteine (SAH) which acts as a feedback inhibitor for both DNMTs activity (Cuyàs et al., 2018). For the AMPK mediated DNMTs activation, it stimulates serine hydroxymethyltransferase 2 (SHMT2) activity which subsequently increasing the SAM/SAH ratio by converting SAH to SAM (Cuyàs et al., 2018).

If we alter the biosynthesis of AMPK and TET2 natural modulators, through the inhibition of the TCA cycle, ETC inhibitors, or another mechanism then it may be facilitated to stabilize AMPK and TET2. AMPK is primarily considered as a therapeutic target for the treatment of metabolic diseases, while TET2 is for oncogenic disease. Under hyperglycemia, the alterations in the AMPK-TET2 signalling axis are associated with tumorigenesis, which may engage individually or couple with another cellular pathway. In many cancers, the kinase activity

of LKB1 is lost, results in unstable AMPK. In this condition, it might be possible to activation of AMPK by treating with some natural (berberine, salicylate, resveratrol) agents that activate AMPK (Hardie, 2016). Likewise, AMPK activators, one of the key challenges for the future is to find some molecules that activate TET2 in either AMPK dependent or independent manner. To stabilized TET2 tumour-suppressive activity by the small molecule, activators are essential for epigenome regulation. This connecting link between metabolism and epigenome may decode some unrevealed facts, which can potentially contribute to identifying novel molecular markers or targets for the treatment of DM and cancers.

Disclosure Statement

The authors have nothing to disclose.

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Author Contributions

Patil Shivprasad Suresh: Investigation, Writing and designing initial draft of manuscript. ***Rohit Sharma*****:** Supervision, Manuscript design and editing. ***Upendra Sharma***: Supervision, Manuscript design and editing. ***Yogendra Padwad***: Supervision, Manuscript design and editing.

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