Metformin: A Future Anticancerous Drug

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ABSTRACT

Metformin is a generic drug, used for treatment of type 2 diabetes mellitus. Metformin is known to activate the AMPK pathway, lower the gluconeogenesis in hepatocytes and improves the insulin signaling in some target cells, thus exhibiting the anti-hyperglycemic activity. In case of diabetes the persistent hyperglycemia, hyperinsulinemia and oxidative stress may become a favorable condition for cancerous growth. Hence the people, suffering from diabetes are more prone to cancer. On the other side it has been observed that the chance of occurrence of cancer decreases in those diabetic patients, who regularly uptake Metformin. This indicates towards the anticancerous potential of Metformin. In last decade a large number of epidemiological studies suggested a strong protective effect of metformin against a number of cancers. A large number of studies exploring the antiproliferative potential of Metformin suggested that there is not common mechanism, rather in different types of cancer it exhibit its anticancerous nature by different mechanisms. Some common mechanisms observed in different types of cancer is inhibition of mitochondrial respiratory chain complex I (NADH oxidoreductase), activation of AMPK, inhibition of mTORC1, inhibition of insulin signaling, inhibition of angiogenesis, Fas inhibition and autophagy etc. As cancer cells are highly dependent on the energy level for the continuous cell proliferation hence various studies have also suggested the inhibition of complex I to be most potential mechanism for anticancerous property of Metformin. The current review focuses upon the use of Metformin as anticancerous drug in different cancer types and putforth an explanation for Metformin as a future anticancerous drug.

KEYWORDS: Metformin, complex I, bioenergetics, cancer, therapy.

INTRODUCTION

Diabetes mellitus (DM), one of the most common life-threatening illnesses worldwide, is a group of metabolic diseases, characterized by sustained hyperglycemia. Metformin is a first-line drug used for treatment of type 2 diabetes mellitus (T2DM) (Cho et al., 2015). It is a dimethyl biguanide which is used as an anti-hyperglycaemic agent and is obtained from the plant Galega officinalis or French lilac. G. officinalis is known to be rich in a compound called Guanidine and this particular compound has a unique property of lowering the glucose levels in blood. Eventually, the extraction of this bioactive compound became the chemical basis for synthesis of metformin (Bailey, 2004). Unlike the other two derivatives of biguanide, Phenformin and Beuformin, Metformin is comparatively cost effective, more efficacious and less cytotoxic to healthy cells (Liet al., 2018). However, Phenformin and Beuformin were withdrawn from the market because they pose deleterious side effects like cardiac arrest and other heart related problems and lactic acidosis. Metformin then came into the limelight as an effective antidiabetic drug due to its superior safety profile and better efficacy (Swislocki et al., 1999; Li et al., 2018).

Thereafter, the impact of metformin as an effective antidiabetic drug sustained the clinical use and more of understanding the molecular mechanism of metformin became the necessity. Metformin is known to cause its anti-hyperglycaemic action by inhibiting the process of gluconeogenesis in liver and by increasing the activity of Insulin in certain target organs like muscle and fat tissues (Salpeter et al., 2008). A clinical research study reflects that metformin treatment in people at risk for diabetes helps to maintain body weight, improve lipid profiles, insulin resistance, and reduces new-onset diabetes by 40% compared with placebo or without treatment (Salpeter et al., 2008). Some of the anti-hyperglycaemic actions of Metformin includes increased uptake of glucose by muscles, lowering the levels of gluconeogenesis and glycogenolysis in liver, reducing the level of plasma free fatty acid, which when present at elevated levels cause insulin resistance and reducing the absorption of glucose by the intestine (Correia et al., 2008).

The molecular mechanism as far suggested by studies indicates that Metformin exerts its anti-hyperglycaemic action via activating the AMPK by increasing its phosphorylation and consequently regulating the energy homeostasis at cellular level (Hardie, 2012). Though this drug increases the phosphorylation level at AMPK level but it never affects the AMP/ATP ratio of the cell (Hardie, 2007). Some other targets of Metformin such as serine-threonine kinase 11 (STK11/LKB1), also activate AMPK through phosphorylation (Hardie, 2007). Once AMPK is activated, it causes inhibition of all ATP consumption pathways and up regulates the ATP producing pathways. Additionally, the enhanced AMPK activity leads to translocation of GLUT-4 to the membrane followed by stimulation of glycolysis, fatty acid oxidation and finally leads to inhibition of gluconeogenesis, glycogen, fatty acid and cholestrol synthesis (Correia et al., 2008). In the past few decades, a very interesting and unique target of Metformin has drawn the attention of researchers. It is found that apart from affecting the AMPK pathway, it may also target the complex I of respiratory chain enzyme (Correia et al., 2008) as well as some biological reactions which are critical for ATP generation. By doing so, it may alter the bioenergetics of cellular system. This is the reason than many of the researchers,
interested in designing the new therapy for cancer are aiming to use Metformin as a potential drug for the same.

**DIABETES AND CANCER**

A consequential link can be established between cancer and diabetes by saying that a person with diabetes is at a higher risk of developing cancer than a normal candidate, because it has been seen that patient with diabetes have elevated blood glucose levels and a higher cellular metabolism which can favor the early development of cancer along with other cellular and environmental factors, act as cancer causing agents. There are many evidences to support this connection. A group of researchers recently performed pooled analyses of 19 prospective population-based cohorts consisting of data from more than 771,297 Asians and found that diabetes was significantly associated with an elevated risk of death from overall cancer (Chen et al., 2017).

The possible biological links between diabetes mellitus and cancer includes hyperglycemia, hyperinsulinemia and fat-induced chronic inflammation, can be explained as follows.

**Hyperglycemia**

It can be proposed that normal cells can become cancerous over a period of time due to this glucose rich environment. Since the presence of high glucose level provides the enough energy to the cancerous cells for their continuous growth and proliferation and also favors the process of neoangiogenesis (Chang and Yang, 2016). However, the increased rate of cancerous cells proliferation is directly proportional to the metastasis rate and in support to that, other studies has also suggested that hyperglycemia contributes to inhibition of apoptosis, increase in the induction of metastasis as well as resistance and intolerance to chemotherapy (Duan et al., 2014). Many cancer cells are known to extensively metabolize glucose and therefore glucose metabolism inhibits apoptosis in the cancer cells by redox inactivation of cytochrome c (Vaughn and Deshmukh, 2008). It is also observed that in diabetic patients, hyperglycemia results in in massive production of ROS. This elevated ROS level is further known to trigger various mutations in the cellular DNA, which in turns contributes to initiation and progression in multistage carcinogenesis (Brownlee, 2001).

**Hyperinsulinemia**

As insulin is a growth hormone hence hyperinsulinemia and insulin resistance may be linked with uncontrolled proliferation of target cells and eventually may lead to cancer. Several studies has suggested that hyperinsulinemia promotes cancer and one of the suggested modality is that insulin has the tendency to exert its oncogenic potential by interrupting in multiple cellular signaling cascade (Arcidiacono et al., 2012). A recent study conducted in non-obese and obese people again suggested that cancer death was higher in obese people with hyperinsulinemia (Tsujimoto et al., 2017).

**High levels of Reactive Oxygen Species (ROS) and Inflammation**

Another factor which promotes development of cancer phenotype in diabetic people is high levels of ROS and chronic inflammation. This leads to imbalance in the production and restoration in levels of ROS. This imbalance leads to generation of continuous and prolonged oxidative stress in target tissue, which can cause DNA damage and
impairment of DNA repair machinery, and ultimately results in mutations and give rise to cancer (Coussens et al., 2013).

Thus there are different mechanism and factors in diabetic conditions which may eventually lead to cancer. Although, the strongest association refers to pancreas and liver (De Souza et al., 2016; Connolly et al., 2012), there are many other organs involved in carcinogenesis in diabetic patients including breast, endometrium, bladder and kidney (Liao et al., 2011; Zhang et al., 2013; Xu et al., 2017; Tseng, 2015).

METFORMIN IN DIABETES: LOWERS THE RISK OF CANCER

Recent studies suggest that there is also a significant association between the cancer incidence and anti-diabetic medications. It was observed that some medications decrease the risk of carcinogenesis and some increase that risk. The majority of studies are concern about Metformin, and its anti-neoplastic and tumor-suppressing activity. The positive effect of Metformin was found in numerous researches investigating breast, pancreas, liver, colon, ovaries and prostate tumors (Soranna et al., 2012; Li et al., 2017; Rattan et al., 2011; Evans et al., 2005; Franciosi et al., 2013; Liu et al., 2018). Though the hyperglycemia is associated with high prevalence of cancer but the diabetic patients consuming Metformin are found to have low risk of developing cancer in future. The hypothesis that Metformin reduces the risk of cancer in people with type 2 diabetes was tested and it was found that use of Metformin was associated with reduced cancer risk (Libby et al., 2009; Evans et al., 2005). Regular administration of Metformin was also found to suppress dimethyl benzathracene-induced mammary tumor progression in rats (Dilman et al., 1982; Duca et al., 2015). In current years, lots of inhibitory and therapeutic actions of Metformin on several types of human cancers have been glanced upon by various epidemiological studies. First account being a case–control study which depicted reduced risk of advancement of cancer in T2DM patients consuming Metformin was established by successive meta-analysis in which 18 observational studies in liver, colon, and pancreatic cancers were used (Evans et al., 2005; Franciosi et al., 2013). Many studies reported that Metformin suppressed colonic epithelial multiplication and decreased rectal aberrant crypt foci in colorectal cancer patients who were non-diabetic (Hosono et al., 2010). A study implicating 1,013 breast cancer patients depicted that the HER-2 positive cases were comparatively less in the group treated with Metformin rather than the non-Metformin ones (Hou et al., 2013). Inclusion to its inhibitory or preventive action, the favorable effect of Metformin on enhancement of overall survival or decrease in mortality was also remarked in liver, pancreatic, colorectal and breast cancer (Jiralerspong et al., 2009; Zhang et al., 2013; Morales and Morris, 2015). Metformin treated group was also allied to improved clinical after-effects and reduced mortality risk (Hou et al., 2013). Currentin vitro and in vivo studies further stipulate that Metformin can intensify the effects of other anti-cancer drugs, such as cisplatin, vincristine, 5-fluorouracil, and doxorubicin (Yi et al., 2017; Candido et al., 2018), making way for a combinatorial therapy with Metformin which can reduce the chemotherapy dose incancer patients. The anti-cancerous properties of Metformin have made this drug a subject of study in understanding different mechanisms at molecular and cellular levels by which it can target the cancer cells and
exert its effect by either inhibiting the cancer cells growth or by inducing apoptosis or by lowering the overall energy level of cancer cells by targeting the cellular bioenergetics.

As a part of validation, Metformin is studied in cancer cell lines of breast cancer, prostate, cancer, colorectal cancer, melanoma cancer. This in-vitro and in-vivo experiments of treating cancer cells with optimized dose of Metformin has shown different responses on different cancer type (Suissa and Azoulay, 2014; Zhuang et al., 2014, Kordes et al. 2015). Yet the exact mechanism of how it differs in different types of cancer is still a mystery. A study reveals that use of Metformin in prostate cancer patients can inhibit the tumor associated inflammation and infiltration of cancerous cells to healthy body parts thereby preventing metastasis (Liu et al., 2018). Another study shows the inhibitory role of Metformin on stromal aromatase expression and tumor progression in a rodent model of postmenopausal breast cancer (Giles et al., 2018). Preclinical studies were also done on the cell lines of different breast cancer cell types in order to evaluate the anti-cancerous effects of metformin. The cell lines on which the effect was seen are MCF-7, MDA-MB-231 (human breast adenocarcinoma cell line) and SK-BR-3 (human mammary gland metastatic adenocarcinoma cell line) (Amaral et al., 2018). The effects were seen in a dose and time dependent manner. Metformin was also found to affect the morphology, reduction in tumor size, inhibition of cell proliferation (Amaral et al., 2018).

**ANTICANCER MECHANISM OF METFORMIN**

As per the various studies, different mechanisms have been proposed till date which suggests that Metformin can be treated as future potential anticancerous drug. The different mechanisms are as follows:

**Inhibiting the insulin dependent pathway**

Metformin’s systemic action of reducing insulin and insulin like growth factors (IGF-1) in the blood might also be integrated with its anticancer action. Upregulation of insulin/IGF receptor signaling pathway leads to carcinogenesis and in this insulin/IGF-1 is involved (Drzewoski et al., 2011). With increased food consumption there is an increase in insulin production which then binds to IGF-1 and insulin receptors. Through insulin receptor substrate (IRS), the signal is conveyed to phosphoinositide 3-kinase (PI3K) and Akt/protein kinase B (PKB) that leads to indirect activation of mTORC1 (Memmott et al., 2010). Also signals from insulin receptor are received by Ras/Raf/ERK pathway that operates cellular growth. Many evidences show that the cellular metabolism changes which occur in tumor cells are linked to these pathways(Memmott et al., 2010). Enhancement in the level of circulating insulin/IGF1 and upregulation of insulin/IGF receptor signaling pathways were considered to be associated with many types of cancers. Metformin was found to decrease insulin level, inhibit insulin/IGF signaling pathways, and amend cellular metabolism in normal and cancer cells (Drzewoski et al., 2011).

**Reduction in cellular energy**

The electron transport chain (ETC) or the respiratory chain in mitochondria is known for its five major complexes involved in the transfer of electrons by complex I and ultimately ATP synthesis by the last complex, ATP synthase. Mitochondrial respiratory chain complex 1 also known as NADH: ubiquinone reductase is the first
membrane embedded complex in the ETC and is crucial for respiration and oxidative phosphorylation in mammalian cells. This complex I catalyses transfer of hydrides from NADH and also maintains high electron gradient in the intermembrane space which become source of energy in ATP synthesis. Thus complex I is the entry point for the electrons and it oxidizes the NADH, couples the electron transfer to ubiquinone in Complex II, followed by proton pumping by Complex III and IV. As the optimum energy level is critical for cancerous growth and the activity of complex I support the proliferation of cells by providing electron acceptors and regenerating oxidized cofactors. Hence, studies from past few decades emphasized on several reports of involvement of ETC and specially the Complex I, in the etiology of cancer and considering the complex I as a prominent target for cancer treatments. The mitochondrial complex I of cancer cells are targeted by small molecules which inhibits the complex I and reduce its activity. Few examples of complex I inhibitors are Metformin, Rotenone, and Piericidin (Wheaton et al., 2014; Urra et al., 2017).

Metformin is having certain chemical residues which make it positively charge; therefore, the drug interacts with the negatively charged mitochondrial membrane and enters the mitochondria. Many studies in the year 2000 showed that Metformin inhibits the activity of the complex I of mitochondrial respiratory chain (Owen et al., 2000; El-Mir et al., 2000) and thus affects the ATP level in the cells. This inhibition leads to the production of mitochondrial ROS which further lead to integrated stress response through activation of double stranded RNA activated protein kinase as the one associated with mitochondria membrane site between mitochondria and endoplasmic reticulum (Yeon and Lee, 2015; Sharma et al., 2011). This inhibition of complex I is also linked to the inhibition of fatty acid oxidation observed after Metformin treatment (Owen et al., 2000). Some of the known effects like the production of glycolytic lactate production by the intestine is also supposed to be linked to this disruption. This effect can be explained as the intestinal mucosa cells face more extensive inhibition of mitochondrial respiration due to higher local concentration of Metformin in intestine (Owen et al., 2000; El-Mir et al., 2000). Moreover, Metformin is capable of inhibiting the complex I of mitochondrial respiratory chain hence there is less demand for end product of glycolysis, eventually contribute to the reduction of gluconeogenesis and hence proving Metformin as an efficient anti-diabetic drug (El-Mir et al. 2000; Doran and Halestrap, 2000)

Metformin also indulges in inhibiting the enzymatic activity of mitochondrial glycerol 3-phosphate dehydrogenase (mG3PDH), which blocks the transport of NADH, from the cytoplasm into mitochondria (Madiraju et al., 2014; Li, M., et al., 2018). Cytosolic NADH level increases when mG3PDH gets suppressed while NAD⁺ level decrease which was actually required for lactate to pyruvate conversion (Lee et al., 2011). Thus, eventually this action halts the production of glucose from lactate cconsumptions. Increased level of cytosolic NADH also lead to enhanced pyruvate to lactate conversion. This redox status of NADH/NAD⁺ pool in the mitochondrial matrix is the one which controls the production of ROS which is the cause of energetic stress (Murphy, 2009; Shin et al., 2014). At times of low cellular energy, AMPK gets activated so that the catabolic pathway of ATP production starts and glucose uptake and utilization take place (Cao et al., 2014).
AMPK is a master regulator of cellular energy homeostasis and plays its role in cellular bioenergetics by sensing and responding to the changes in the AMP/ADP concentration with respect to ATP (He et al., 2009).

Cancer research in last few decades, reported that mitochondria are the key organelle for energy production it becomes the prime source of ATP for the cancer cells to proliferate (Wallace, 2012). Therefore, relating this ATP requirement and supplement by mitochondria has drawn the attention towards a plausible mechanism of Metformin to utilize in treatment of cancer. There are recent evidences supporting the involvement of respiratory chain complexes of mitochondria in cancer and hence Metformin could be a promising drug to target the complex I of respiratory chain in cancer cells as well (Rohlena et al., 2013; Calabrese et al., 2013; Urra et al., 2017).

However, there is an unclear logical uncertainty of whether pulling off the energy supplement via mitochondria mediated pathway can actually stop the cancer cells from proliferating, because there is another provision of energy production and supply via anaerobic pathway. Another study demonstrated that Metformin thus target the complex I of cancerous cell, but it all depends on the amount of glucose available for the cells to convert it into energy without the involvement of mitochondria (Wheaton et al., 2012). In the condition where there is plenty of glucose, Metformin has the tendency to slow down the rate of cancer cell division and henceforth slows down the growth of tumor. In the other condition when there is a shortage of glucose moiety, Metformin choses to kill the tumorous cells instead (Luengo et al., 2014). However, in depth studies are required to support this uncertainty.

**Activation of AMPK pathway**

Recent studies suggest that Metformin inhibits the activity of AMP deaminase, which eventually lead to increase in AMP levels. Increased AMP activates AMPK (Ouyang et al., 2011). Metformin induced AMPK activation leads to increased CBP and CRTC2 (transcription factors) phosphorylation resulting in disassembly of CREB co-activator complex which inhibits the gluconeogenic gene expression and thus a reduction in glucose production (Shaw et al., 2005).

In addition, increased AMP levels after the treatment of Metformin also lead to inhibition of adenylate cyclase and hence reduce the cAMP levels. This inhibits the cAMP mediated PKA pathway and suppresses the rate of gluconeogenesis (Miller et al., 2013).

A subsequent study on prostate cancer cells discovered that the antiproliferative role of Metformin is not only arbitrated by AMPK and recommended that impediment of mTOR represents an alternative pathway for Metformin action (Sahra et al., 2011). Primarily, compounds activating AMPK also inhibit the mechanistic target of rapamycin complex 1 (mTORC1) (Bolster et al., 2002; Dubbelhuis and Meijer, 2002), which is a crucial factor of anabolic metabolism that is abnormally triggered under conditions of hyperinsulinemia and obesity (Khamzina et al., 2005). Inhibition of hepatic mTORC1 signaling is dependent upon AMPK as well as tuberous sclerosis complex (TSC). TSC1 and TSC2 form an inhibiting complex to suppress the activity of mTORC1 (Inoki et al., 2003). Many studies on mouse liver tissues and primary hepatocytes show that Metformin robustly inhibits mTORC1 signaling in all these cells and tissues (Howell et al., 2016). AMPK also directly phosphorylates mTOR binding
partner protein called Raptor (scaffolding protein) which is necessary for the impediment of mTORC1 persuaded by energy stress (Gwinn et al., 2008). In inclusion to it, Kalender in 2010 mentioned that Metformin can suppress mTORC1 signaling through Ras-related GTPase, which is a self-supporting action not requiring AMPK and TSC1/2 (Insulin-independent pathway). It can be proposed that Metformin exerts its antiproliferative action and antidiabetic action through common mechanisms like activation of AMPK signaling pathway, inhibition of mTOR pathway in a dose dependent manner by involving AMPK and TSCX complex and inhibition of mitochondrial complex 1 activity as well (Howell, et al., 2017).

Other oncogenic signaling pathways rather than mTOR or AMPK are also supposed to be affected by Metformin. It was reported that Metformin reduces the proliferation and development of osteosarcoma and renal cell carcinoma cells by inhibiting Akt phosphorylation, which was linked to enhanced phosphatase and tensin (PTEN) expression (Li et al., 2018). Activation of NF-κB and Stat3 signaling in cancer stem cells is also hindered by Metformin, following to a minimized inflammatory response and impaired tumor extension (Li et al., 2018). As the induction of expression of DICER, a crucial enzyme required for regulation of microRNA biogenesis is linked to this action of Metformin (Blandino et al., 2012). Hence, microRNA expression has also been proposed to be modulated by one of the anticancer actions of Metformin.

**FAS inhibition**

Many of the cancerous cells like prostate, breast, ovarian cancers have shown an overexpression of fatty acid synthase (FAS) which is the crucial enzyme for fatty acid biosynthesis and is linked to the malignant phenotype (Xiang et al., 2004). On entering into mitochondria, Metformin inhibits the mitochondrial electron transport chain, thereby creating an imbalance in ratio of AMP to ATP and lowers energy level of cells. Some cells are able to cope up with this energy stress/energy crisis caused by Metformin by activating the AMPK pathway (Xiang et al., 2004) and reducing energy consuming functions such as protein synthesis (mTOR inhibition) and lipid synthesis (FAS inhibition). This relieves cell from energetic stress but since the cell is restricted to ‘low energy’ it leads to cytostatic effect (Pollak, 2012). In contrast to this, some tumor cells are incapable of coping up with this energetic stress caused by Metformin leading to severe cytotoxic effect. This interesting behaviour of Metformin may help it to become a potential anti cancerous compound (Statin et al., 2007).

**Affecting the aerobic glycolysis**

As already discussed that activation of AMPK is one of the mechanisms of action of Metformin against cancerous cells, this activation of AMPK expedites degradation of HIF-1α protein, which is a major transcription factor that modulates many crucial physiological pathways for cancerous proliferation (Faubert et al., 2013). This Metformin action is contrary to what actually happens in the case of inactivated AMPK, where there is a metabolic shift in cells to aerobic glycolysis and an enhancement in biomass accumulation occurs due to HIF-1α. Activated HIF-1α leads to an increased transcription of genes which are involved in glycolytic pathways, angiogenesis, resistance to apoptotic, and metabolic adaptation (Semenza, 2003). Metformin acts upon HIF-1α through suppression of mitochondrial oxygen consumption.
and shows its anti-cancerous effect (Faubert et al., 2013).

Inhibition of angiogenic factors

As an evidence, Metformin is also capable of targeting and inhibiting the pro-angiogenic factors like Tumour Necrosis Factor-a (TNF-a) and NF-kb. Recent studies suggest, at genetic level Metformin is affecting the extent of expression of different genes associated with angiogenesis, it causes short term increase in expression of Vascular Endothelial Growth Factor (VEGF), but down regulates the expression of other factors like IL-8, angiogenin, TIMP-1 (Orecchioni S., 2015).

Autophagy

Autophagy is a process of subcellular membrane rearrangement to form a double-membraned autophagosome enclosing cytoplasmic constituents and organelles, which is expedited by nutrient deficiency. Thus, autophagy is important for nutrient supply in the case of energy deficiency, and is also critical for the proper turnover and function of organelles, such as mitochondria and the ER. Metformin can enhance autophagy, as AMPK activation is known to upregulate autophagic activity through direct phosphorylation of unc51-like kinase and Beclin 1, key molecules involved in the initiation of autophagy. Few molecules involved in autophagy, such as ATG17, Beclin-1, and cathepsin B are known to be up-regulated by Metformin treatment on certain tumors (Janjetovic et al., 2011). Metformin promotes autophagy and apoptosis in esophageal squamous cell carcinoma by downregulating Stat3 signaling (Feng et al., 2014). Metformin induces autophagy and G0/G1 phase cell cycle arrest in myeloma by targeting the AMPK/mTORC1 and mTORC2 pathways (Wang et al., 2018).

EFFECT OF METFORMIN IN DIFFERENT TYPES OF CANCER

After studying the great potential of Metformin as anticancerous agent, it is being studied for its anticancer activity in different types of cancerstypes of cancers and it is observed that it shows its anti-proliferative action again a wide range of cancer types.

Breast cancer

Obesity and type 2diabetes have found to be linked with the cause of breast cancer in women. Much of the recent studies depicted that the use of Metformin as an antidiabetic drug has led to decreased risks of breast cancer in women (Soranna et al., 2012). Mammary adipose tissue inflammation leads to crown like structure formation comprising of macrophages. Studies depicted a decrease in these crown-like structures in high-weight-gain animals, who were treated with Metformin and this suggests that Metformin not only reduces hepatic lipid accumulation but also contributes to adipose-specific metabolic improvements. This effect of Metformin on whole body metabolism can be an underlying antitumor effect (Giles et al., 2018). It was also studied that the expression of aromatase the enzyme which helps in the biosynthesis of estrogen, considered as a responsible hormone for breast cancer risk in obese postmenopausal women, by the macrophages is also regulated by Metformin. Thus, Metformin reduces estrogen levels and ER signaling in tumors and thus affects the microenvironment of tumor and can be the reason of reduced growth of tumor (Giles et al., 2018).
Prostate cancer

Studies have depicted in TRAMP (Transgenic adenocarcinoma of the mouse prostate) mice Metformin can inhibit prostate cancer proliferation partially by inhibiting infiltration in tumor associated macrophages (TAM), by down regulating the levels of cyclooxygenase-2 (COX2) and subsequent production of prostaglandin E2 (PGE2) (Foretz et al., 2010; Liu et al., 2018). It was also found that ADT (Androgen deprivation therapy) induced inflammatory infiltration in prostate cancer cells was also inhibited by the action of Metformin (Liu et al., 2018). Thus, giving a scope for both ADT and Metformin coupled action to be more effective in prostate cancer treatment. Such findings are hope for a better future treatment of prostate cancer, using Metformin.

Pancreatic cancer

Type 2 diabetes mellitus is contemplated to play chief role in tumorigenesis and progression of pancreatic cancer. Resistance to insulin and enhanced insulin-like growth factor I are suggested to be the mechanisms underlying the disease onset which are common in type 2 diabetes (Li et al., 2017). Currently, many evidences have stipulated that Metformin can reduce the risk of developing pancreatic cancer in patients who concurrently also have type 2 diabetes mellitus (Li et al., 2017). Insulin/IGF-1 plays a crucial role in pancreatic cancer progression and that GPCRs are involved as autocrine-paracrine signals in this process, Metformin hinders this crosstalk between insulin/IGF-1 and GPCR signaling pathways leading to attenuation of pancreatic cancer. Activation of AMPK is the cause of this inhibitory action (Rozengurt et al., 2010). It was found that Metformin inhibits crosstalk between insulin/IGF-1 receptor and GPCR signaling systems on Ca2+

mobilization, mTORC1exhilaration, synthesis of DNA, and multiplication in a various pancreatic cancer cell lines (Kisfalvi et al., 2009). Additionally, Metformin averted carcinogen-induced pancreatic acinar cancer in hamsters perpetuated upon high-fat diets and restricted the proliferation of breast and p53 colon cancer cells in preclinical models (Schneider et al., 2001).

Thyroid cancer

34 patients with differentiated thyroid cancer taking Metformin were compared with 21 non-Metformin using patients on the anti-proliferative effect of Metformin on the differentiated thyroid cancers by Klubo-Gwiezdzinska. It was observed that tumor size was reduced, and there was a decrease in proliferation as well in the Metformin group (Kubo-Gwiezdzinska et al., 2013). p70S6K/pS6 pathway that persuades the cancer cell metabolic stress and the autophagy was also found to be triggered in presence of Metformin, later (Kubo-Gwiezdzinska et al., 2013). Experimental findings by Klubo-Gwiezdzinska on medullary thyroid cancer (MTC) cells found that patients who were treated with Metformin had a very slow cellular progression. Cyclin D1 (usually overexpressed in cancer cells) was remarkably hindered, through obstruction of mTOR/p70S6K/pS6 signaling and down-regulation of pERK. Therefore, it was concluded that Metformin can play a potential role in treating thyroid cancer.

Ovarian cancer

Various studies have shown that Metformin notably hamper the proliferation of ovarian cancer cells. This inhibition takes place either by AMPK-dependent method or AMPK-independent one (Rattan et al., 2011). Metformin causes mTOR
inhibition and also cell cycle arrest when AMPK-independent pathway comes into effect and this occurs through REDD1 and rag GTPase-dependent manner whereas in AMPK-dependent pathway many other mechanisms come into effect (Pierotti et al., 2013). Level of cyclin D1 reduces by the activated AMPK while p21 level enhances and suppression of cell cycle at G1-phase takes place. Additionally, current studies report that Metformin instigates autophagy by detection of enhanced LC3B conversion, better ATG12-ATG5 expression, and reduced p62 levels (Nazim et al., 2016). Metformin even induces unfold protein response (UPR) through protein kinase RNA-like endoplasmic reticulum kinase/eukaryotic initiation factor 2 alpha kinase pathway in OVC (Rattan et al., 2011).

Thus Metformin is found to act as a potential anticancer compound for different cancer with different mechanisms of action (Figure 1).

**CONCLUSION**

Metformin being the most widely used antidiabetic medication, now it has become an element of attraction in anticancer therapeutics. The rerouting of Metformin usage from antidiabetes to anticancer is more evident and expected to improve the cancer prognosis. Functional mitochondria are essential for energy intensive processes like proliferation. Metformin induced decrease in efficiency of mitochondria can lead to cell death in cancer due to the incapability of cancer cells to cope up with this energetic stress. Additionally, Metformin is proposed to act like an anticancerous agent by different mode of actions hence it is imperative to do the detailed analysis towards its mechanism of action in case of different cancer types. As a better understanding of this compound could be an improvement in designing a new anti-proliferative drug. Metformin should be regarded as a lead compound requiring pharmacologic optimization for oncology and increasing its anti-cancer effect by improving accumulation in neoplastic tissue.

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**Conflict of interest statement**

Authors declare no conflict of interest.

**Authors’ contributions**

SM conceptualized the draft and GS prepared the draft. AS, and SS critically reviewed the draft.

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