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Research Article

An update on the effectiveness of metformin alone and with chemotherapy drugs on tumor cells

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Abstract

Cancer and diabetes are critical risks that reveal many complications. Metformin has long been used in herbal medicine as an anti-diabetes medicine. It is one of the first-line therapies for type two (T2D that has gained use across different healthcare systems. It is the most preferred form of treatment due to its safety, being readily available, and widely used because it has fewer and affordable side effects for many users. The repurposing of metformin used in other treatments to treat cancer patients or the combination of targeted treatments with metformin can reduce the side effects of chemotherapy drugs, enhance the effectiveness, and may reduce resistance to targeted drugs. The mechanism of metformin has been demonstrated and its association with other drugs. It Inhibits cell growth and stops the cell cycle, and stimulates programmed cell death and autophagy of various cancer cells. Patients with diabetes and different kinds of malignancies such as colorectal, hepatic, and ovarian cancers have better response rates after metformin treatment. A combination of metformin and new medications has had a significant effect on those who do not receive metformin. On the other hand, prevailing evidence has greatly proved the benefit of using metformin as an adjuvant agent in medical oncology practice.

Keywords: Metformin; diabetes; cancer; chemotherapy.

1. Introduction

Malignant tumors are treated with surgery, chemotherapy, or both. Conventional chemotherapy has serious side effects such as bone marrow suppression and gastrointestinal side effects. It may not improve the patient's condition as a result of the body resisting the treatment. Repurposing some medicines such as metformin or giving it with conventional chemotherapy may reduce the side effects, decrease the body's resistance to chemotherapeutic drugs, and increase the efficacy of the targeted drugs (Deng et al., 2019).

Metformin (1,1-dimethylbiguanide hydrochloride) is one of the first-line therapies for type two, non-insulin-dependent diabetes mellitus (T2D). It reduces insulin requirement in type-1 diabetes. It is derived from galegine (2-(3-Methylbut-2-enyl) guanidine). Galegine is extracted from *Galega officinalis*. Metformin is a natural alkaloid product, which is considered as an effective medication. Diabetes mellitus treatment is conducted along with other drugs that have anti-glycaemic effects (Rena, Hardie, & Pearson, 2017).

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However, metformin has proved to be effective in treating most of the pleiotropic effects, most of the outcomes have shown that its effect is beneficial to cardiovascular and neurological treatments. Furthermore, it has a high efficiency in reducing higher rates of inflammation associated with these conditions (Peng et al., 2017).

Metformin has a low toxicity profile and is capable of targeting various major pathways of cancer treatment. Metformin contributes to its anti-neoplastic activity through suppressing of NADH dehydrogenase (complex I) and activates adenosine monophosphate protein kinase (AMPK) in the mitochondria to reduce the energy consumption of preneoplastic and neoplastic cells (Morales & Morris, 2015). Combining metformin with chemotherapy drugs increases the effectiveness of treatment in experimental animals and in vitro (Peng et al., 2017).

In this review, we summarize the mechanisms of metformin and its association with chemotherapeutic agents to yield the best tumors control and reduction of the possible adverse effects associated with targeted drugs used.

2. Mechanism of Action of metformin

Understanding the action of metformin is essential in monitoring the effect of it on the human body. Its effect on mitochondria is essential since it inhibits the electron transport system. The process, therefore, decreases Adenosine Triphosphate (ATP) and increases the levels of adenosine monophosphate (AMP). The cellular action of metformin AMP activates a protein kinase (AMPK) that further activates critical process features by energy homeostasis that occurs under energy depletion conditions. The activity of based on the AMP/ATP ratios. Metformin increases the ratio of AMP/ATP by inhibiting NADH dehydrogenase (complex I) in the inner membrane of mitochondria. AMP binds with (AMPK) (Ross, MacKintosh, & Hardie, 2016). AMPK phosphorylates that activates 6 fructokinase, and inactivates fructose-1,6-bisphosphatase and glycogen phosphorylase that inhibits gluconeogenesis and glycogen synthesis. AMPK inhibits mitochondrial glycerophosphate dehydrogenase that participates in passing NADH from cytosol to the inner membrane of the mitochondria (Fig. 1a) (Madiraju et al., 2014).

AMPK initiates phosphorylation and transcription processes with the help of salt inducible kinase 2 (SIK2). CREB activates phospho-enol pyruvate kinase (PEPCK) and glucose 6 phosphatase (G6Pase) genes that encoding the gluconeogenic enzymes (Fig. 1b) (Patel et al., 2014). AMPK is a catabolic regulator which restores energy and reduces hepatic glucose production.

Furthermore, AMPK leads to the inactivation of some vital enzymes which are essential to cellular energy such as acetyl-CoA carboxylase (ACC). Carnitine Palmitoyltransferase 1 (CPT-1) plays an essential role in lipid transport and mitochondrial oxidation. AMPK indirectly activates fatty acid B-oxidation and reduces fatty acid synthesis. AMPK inactivate and phosphorylate 3-hydroxy 3-methylglutaryl-CoA reductase (HMGCR) (Fig. 2a). HMGOR is considered a major enzyme in lipid metabolism particularly in cholesterol synthesis (Fullerton et al., 2013).

AMPK inhibits adenylcyclase that lowers cAMP production and activates 3′,5′-cyclic phosphodiesterase 4 B (PDE4B) that enhances hepatic insulin sensitivity and inactivates the glucagon function (Fig. 2b) (Hawley et al., 2010). As a result, the secretion of insulin and glucose levels reduces the blood sugar levels in the body. The process of insulin regulation is further modulated by the effect, resulting from increased insulin receptors and increased tyrosine kinase activity (Viollet et al., 2012). It improves insulin sensitivity and reduces glucose output. Furthermore, it enhances the production of glucagon-like peptide-1(GLP-1). Moreover, it has an effect on beta cells which is critical in regulating the blood sugar levels. In many cases, the expression of the GLP-1 receptor is achieved via peroxisome proliferators activated receptor (PPAR) pathway (Ma et al., 2010). The antiglycaemic effect of metformin could occur in different parts of the body. This can be attributed to decreased hepatic gluconeogenesis. The reduction can further be attributed to the reduction of glucose and reduced activation of enzymes responsible for the gluconeogenesis pathway.

3. Potential action of metformin against cancer cells

3.1 Activation of AMPK

Inhibition of cancer tumorigenesis occurs through a molecular mechanism. The AMPK activation regulates different processes within the cell. Besides, its deregulation ability has been associated with the pathogenesis of cancer. Thus, the activation process contributes to the hypoglycemic effects of metformin (Krishan, Richardson, & Sahni, 2015).

Apart from the glycemic effects, it plays a vital role in metabolic processes within the cancerous cells. Some of the critical roles that the molecule plays include inhibition of cellular proliferation and reduction of mitotic cell division. Therefore during the activation process, the AMPK induces the arrest of G1-phase during the cell cycle. It achieves this process by inhibiting the expression of cyclin D1. This is the protein that contributes to proliferation (Krishan et al., 2015).

The AMPK also hinders the action of lipogenic enzymes. Reduced effect of these enzymes will reduce the rates of fatty acids and acetyl CoA enzymes required for the formation of tumorous cells.

The other role linked to the AMPK is its ability to induce anti-inflammatory activities within the cells. This is a critical process

in ensuring that tumor formation is reduced (Faubert, Vincent, Poffenberger, & Jones, 2015). Other components responsible for the reduction of inflammatory include the tumor necrosis factor-alpha (TNFα), and vascular endothelial growth factors (VEGF). The components act along with the AMPK to ensure cell proliferation is reduced Interleukin 6 which has been identified to play a significant role in initiating processes that reduce cellular proliferation (H. Yu, Pardoll, & Jove, 2009).

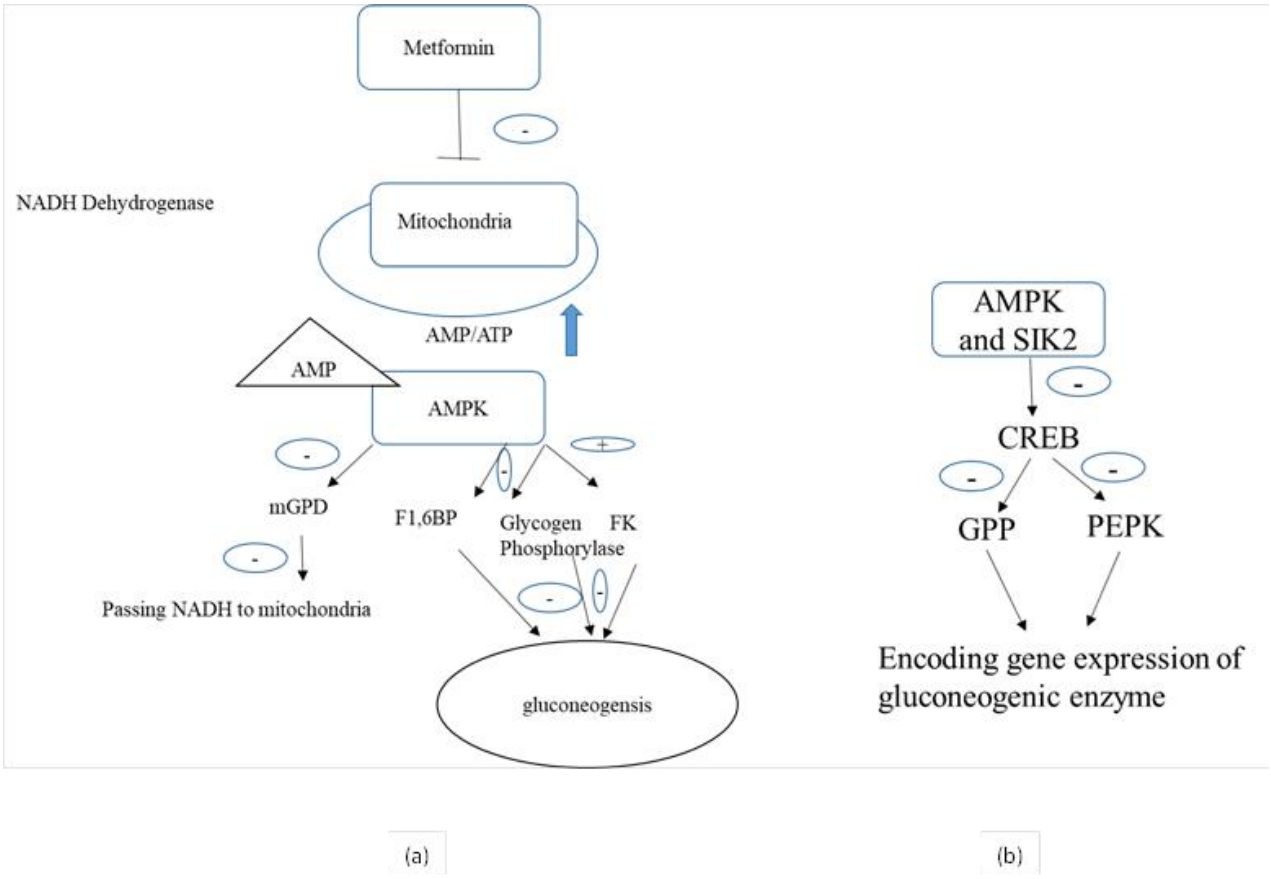

Figure 1: Metformin inhibits complex I in mitochondria and activates adenosine monophosphate kinase (AMPK) (a). AMPK activates fructokinase (FK) and inactivates fructose 1,6 bisphosphatase (F1,6BP) and glycogen phosphorylase, inhibits gluconeogenesis. AMPK inhibits mitochondrial glyceraldehyde phosphate dehydrogenase that enters NADH from the cytosol to mitochondria. **AMPK and salt-inducible kinase 2 inhibits the transcription factor (b).** cAMP response element-binding protein (CREB) is inhibited so phospho-enol pyruvate kinase (PEPK) and glucose 6 phosphatase (G6Pase) genes are not transcripted that encoding the gluconeogenic enzymes.

3.2 Mammalian Target of Rapamycin (mTOR) Inhibition

Mammalian target of rapamycin mTOR is one of the inhibitors that regulate various forms of protein synthesis and controls biochemical processes that lead to the growth and proliferation of cells. It is a member of a kinase family, phosphatidylinositol 3-kinase (PI3K). When MTOR is bound, it forms many complexes; mTOR complex 1 and mTOR complex 2 which regulates various cellular processes (Dibble & Manning, 2013). mTOR is a serine/threonine protein kinase. It ensures balance across different biochemical pathways. This helps ensure that the action mechanism initiated by metformin is achieved through a balanced set of activities that initiate cell activity. Inhibition processes similarly offer an essential form of mechanism that regulates different protein synthesis. that regulates growth, proliferation,

movement, cell survival, protein synthesis, autophagy, and transcription (Dibble & Manning, 2013; Hay & Sonenberg, 2004).

mTOR also functions as a tyrosine kinase protein which enhances insulin production, insulin-like growth factor 1, 2 (IGF1,2) receptors, and cellular energy generation. mTOR affects insulin secretion, stimulating growth factors (such as IGF-1 and IGF-2), as well as stimulating energy production within the mitochondria. It has been evident that increased activity of mTOR signals is greatly associated with several malignancies in different organs such as prostate, breast, bladder lung, brain, and kidneys. It has been proved that the leading cause of increased cancer occurrence in this context is related to the over-activity of PI3K or Akt (Guertin & Sabatini, 2005).

Increased mTOR activity leads to the promotion of cell cycle and increased protein synthesis which leads to enhanced cell proliferation. Also, mTOR poses an inhibitory effect on autophagy which leads to further tumor growth. Cell cycles are controlled via intracellular signals of PI3K / AKT / mTOR. Therefore, PI3K activates AKT, which is capable of activating CREB and mTOR.

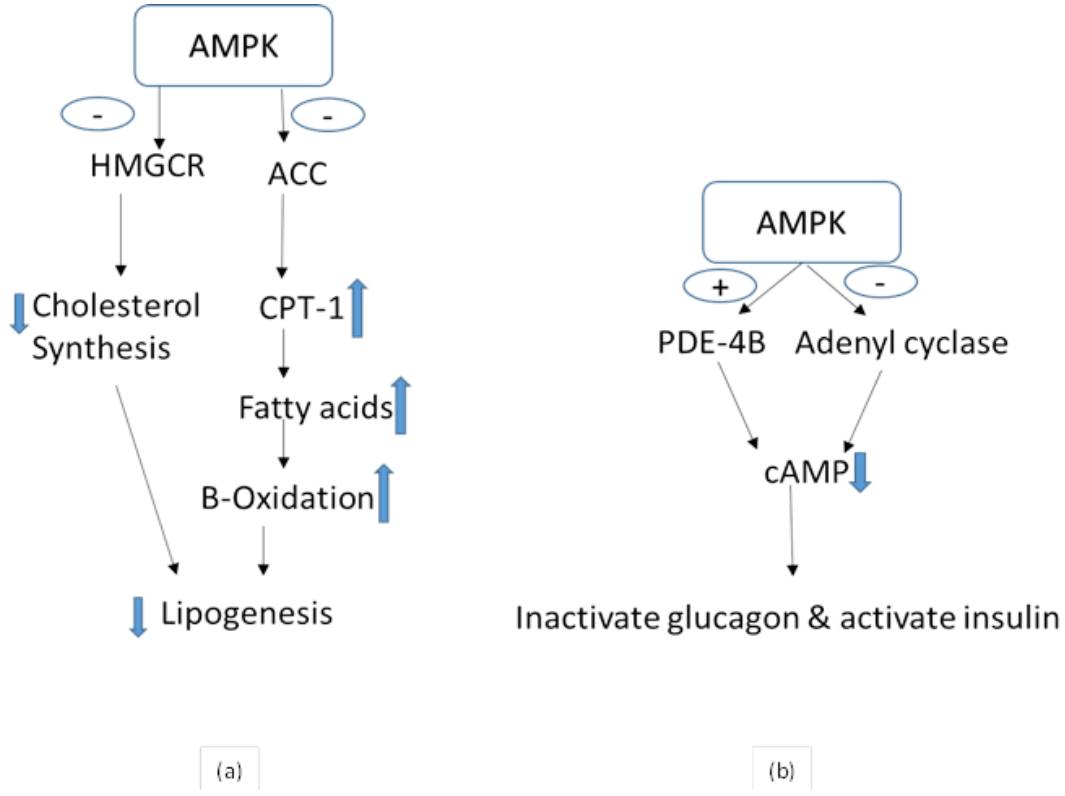

Figure 2: AMPK stimulates fatty acid oxidation and inhibits lipogenesis (a). AMPK inhibits acetyl-CoA carboxylase, an inhibitor of carnitine palmitoyltransferase 1 (CPT-1). Fatty acids transport into the inner membrane of mitochondria by CPT-1 to degrades to acetyl CoA by oxidation. AMPK inactivates 3-hydroxy 3-methylglutaryl-CoA reductase (HMGCR) that the key enzyme of cholesterol synthesis. **AMPK Lowering cAMP production (b).** AMPK inactivates adenyl cyclase and activates phosphodiesterase 4 B (PDE4B) that inhibits glucagon production and releases insulin.

Insulin recruits PI3K signals to regulate metabolism. It has been shown in several cancers that these complex mechanisms, when activated may lead to reduced apoptosis and increased further tumor cell proliferation (Peltier, O'Neill, & Schaffer, 2007; Zoncu, Efeyan, & Sabatini, 2011).

Metformin takes a central role in ensuring that the expression of mTOR is suppressed and inhibited. Downregulation of specific proteins that limit the production of different forms of growth factors is one of the venues by which the therapy is achieved. Metformin has been effective in blocking the formation of cancerous cells in the lungs and breasts. In many cases, the process is achieved

when the drug inhibits mTOR activation (Lei et al., 2017). Metformin may inhibit (mTOR) signaling by activation of AMPK which leads to suppression of cell proliferation, reduced programmed cell death as well as the arrest of cell cycles (Heckman-Stoddard, DeCensi, Sahasrabuddhe, & Ford, 2017).

Everolimus, an oral mTOR inhibitor, is an approved treatment for advanced pancreatic neuroendocrine tumors in 2011. A combination of everolimus with metformin has a potential synergistic action against cancer cells in *vivo* and in *vitro* (Y. Wang, Wei, Li, Fan, & Sun, 2015). Metformin and Everolimus together were found to significantly suppress obesity-induced tumor growth. The effect of Everolimus may be associated with insulin resistance, which causes increased blood sugar, while metformin can restore it (Y. Wang et al., 2015).

3.3 Other Signaling Pathways

Insulin is associated with many cancers. It is a growth factor, when elevated it could increase the risks of pancreatic and other cancers. Besides, it is often linked with detrimental effects on various disease outcomes. The insulin growth factor IGF-1 has a mitotic impact. Therefore, people with elevated levels of IGF-1 have higher risks of reporting many cases of epithelial cancers. A survey conducted based on populations showed a significant risk of women to breast cancer to be affected by the high concentration of IGF that those with a low concentration (Hormones & Group, 2010).

Metformin passes through the positive charge transporter in the cell membrane such as organic cation transporters (OCT), plasma monoamine transporter (PMAT) and the multidrug and toxin extrusion protein (MATE) (Zhou, Xia, & Wang, 2007). Therefore, metformin has been linked to a high ability to reduce the insulin growth factor IGF-1. Studies and reports from previous researches showed that metformin reduced circulating levels IGF in rodent models. Furthermore, the drug contributed to the activation of AMPK. AMPK plays an essential role in reducing the rates of phosphorylation of insulin-receptor substrates-1 (IRS-1). As a result, this effect contributed to a reduced mTOR cascade (Abo-Elmatty, Ahmed, Tawfik, & Helmy, 2017).

Activation of AMPK inhibits hepatic gluconeogenesis and glycogenolysis, activates musculoskeletal glucose utilization, and leads to a reduction in blood insulin level. This eventually reduces cell growth and proliferation (Cameron et al., 2016). It has been reported that media with low glucose levels have slow growth of human cancer cell lines. Furthermore, more inhibition of complex I at mitochondrial level takes place (Sahra et al., 2008), this leads to more inhibition of cancer stem-cell activity (Hirsch, Iliopoulos, Tsichlis, & Struhl, 2009), and metastasis by inhibiting matrix metalloproteinase-9 activation (Bao et al., 2012).

In vitro and *in vivo* studies have revealed the effectiveness of metformin against esophageal adenocarcinoma. This takes place through a reduction in phosphorylation steps of several receptors including; epidermal growth factor, insulin-like growth factor, angiogenesis stimulating proteins, and tissue inhibitor of metalloproteinases (TIMP-1 2) (Fujihara et al., 2015).

The other signaling pathways were featured by enzymatic process and intracellular signaling pathways initiated by Mitogen-activated kinase (MAPK). In many cases, metformin was shown to reduce different rates of growth factors. For instance, it barred the growth pathway and promoted growth inhibition components that directly reduced the rates of tumor formation in different cells in the body. The therapy also played a significant role in helping the DNA damage-inducible gene 153 (GADD153). The human epidermal growth factor receptor-2 has been noted to increase to about 30% aiming major cases of breast cancers. However, analysis and study of metformin effects were showed to suppress the levels of HER-2. The effect was often noted when the component was overexpressed. Therefore, a combination treatment of anti-HER2 and antibodies can reduce stem cell populations in HER-2 related cancers (Mallik & Chowdhury, 2018).

Metformin has an anti-angiogenic effect. Anti-angiogenic involves different drugs that block blood and nutrient supply to the tumorous cells (Rocha et al., 2011). Metformin inhibits of antiapoptotic protein expression such as Bcl-2, increases apoptotic protein such as BAX (Gao et al., 2016). Metformin phosphorlates and activates retinoblastoma protein (pRB) (tumor suppressor gene) that arrests cell cycle in G0/G1 in prostate cancer cells (Sahra et al., 2008).

Metformin acts by inhibiting and reducing the effects of different components responses of cell growth factors. It achieves this through vascular methods. Most of the cancer cells are founding tumors, and therefore targeting the vessels is essential in the destruction and inhibition of tumors. Therefore, metformin plays a crucial role in reducing the vascular catalyst and several components responsible for growth. This has been noted with the effect that the therapy has on TNF alpha and NF-Kb (Hirsch, Iliopoulos, & Struhl, 2013).

Metformin is an efficient therapy in addressing many cases of co-occurrent conditions. Apart from addressing cases of growth, it has other effects on tumors. For instance, inhibits cancer stem cells CSC Most of these cells are resistant to other cancer therapies such as chemo and radiotherapy. On the other hand, it tends to improve the response to chemotherapy treatment by initiating the tumor-infiltrating lymphocytes TIL and CD8+. It also reduces the rates at which other treatment therapies can destroy DNA by initiating a process where reactive oxygen species conduct DNA repair (Eikawa et al., 2015; Hirsch et al., 2009).

4. Anticancer effects of metformin and its combination with chemotherapeutic agents

Metformin plays a crucial role in cancer therapy patients with preexisting diabetes have a decreased risk of cancers. Cancerous cells utilize high levels of glucose for their proliferation. The risk of cancer is more prevalent among diabetic patients. On the other hand, diabetic patients treated with metformin had a better response and good results compared to those treated with other glycemic agents and insulin without metformin (Zhuang, Chan, Haugrud, & Miskimins, 2014). .The incidence of developing breast (Kim et al., 2015), ovarian (Gotlieb et al., 2008), endometrial (L. Dong et al., 2012), pancreatic (Chen et al., 2017), colon (Sui et al., 2014), prostate (Haring et al., 2017), liver (H. Dong et al., 2017), and lung cancer (Yousef & Tsiani, 2017) had better outcomes in the diabetic patients treated with metformin compared to treated with other glycemic agents without metformin.

4.1 Breast cancer

Metformin can be combined with chemotherapy treatments in breast cancer. These include doxorubicin, paclitaxel, epirubicin, and 5-fluorouracil (5-FU), carboplatin, and cyclophosphamide. The combination resulting from the products have more efficacy compared to the case when the drug can act alone (L. Dong et al., 2012; Jiralerspong et al., 2009). In a case where patients with HER+ breast cancer were studied, thiazolidinediones combined with metformin were associated with better outcomes. On the other hand, the more aggressive subtypes of breast cancer either histopathologically or molecularly showed negative outcomes (Uehara, Mitsuhashi, Tsuruoka, & Shozu, 2015). Studies have shown that when metformin is combined with paclitaxel, it leads to an AMPK activation which in turn causes an arrest of MCFF-7 and A549 cell types at different phases (Rattan, Graham, Maguire, Giri, & Shridhar, 2011; Rocha et al., 2011).

Chebowski's study on 68,000 menopausal women showed a strong link in metformin therapy diabetes and cases of breast cancer. One of the critical observation was that the case was more severe among women who were not treated with metformin (Chlebowski et al., 2012).

4.2 Ovarian and endometrial cancers (EC)

Hannah et al. (2012) noted that metformin enhanced treatment models developed to treat cases of ovarian and endometrial cancers. The combination reduced the proliferation process by regulating activities linked to the AMPK/mTOR pathway. Furthermore, the treatment reduced expression levels of hTERmRNA. Apart from lowering the proliferation process, through its antitumor effects, metformin destroys EC cells through anti-toxic impact (Lin et al., 2013). Gotlieb (Gotlieb et al., 2008) have demonstrated *in vitro* that metformin enhances ovarian cancer cell response to cisplatin and augmented its anti-cancer efficacy. Furthermore, metformin improved the reaction of endometrial cells when exposed to other therapeutic agents. The efficiency noted was as a result of a combination of chemotherapeutic agents such as cisplatin and paclitaxel. Metformin potentiates the anti-cancer effects of paclitaxel against ovarian cancers. Patients with ovarian cancer along with type 2 diabetes treated with metformin were more responsive to treatment with cisplatin than that in non-diabetic patients (S.-B. Wang, Lei, Liu, & Jia, 2017). It achieved this process by targeting different metabolic and apoptotic pathways (Gotlieb et al., 2008). It has been shown that metformin suppresses cell growth of ovarian cancer of A2780 cell type. Furthermore, it enhances the cytotoxic effect of chemotherapeutic agents such as cisplatin. *In vivo* researches has revealed that metformin reduces cell growth and angiogenesis that leads to more tumor control and less spread. A combination of metformin with paclitaxel enhances the cytotoxic effect and suppression of tumor cell growth in uterine cancers through the activation of mTOR mechanism. Further cytotoxic effects have been observed when it was combined with corticosteroids, namely dexamethasone (Hanna et al., 2012; Rattan et al., 2011).

4.3 Lung cancer

Lung cancers require intensive treatments. Metformin offers a method where a combination of different therapies can be achieved with fewer side effects. It has been observed in lung cancers, non-small cell, that metformin reduces cell proliferation and increases apoptosis. It was reported that metformin combined with paclitaxel, an improved response to diabetic patient's hat had stage IV NSCLC (Sharma, Bell, Settleman, & Haber, 2007).

A combination of metformin treatment with etoposide, cisplatin, or doxorubicin has a significant effect in reducing the rates of metabolic viability in the NCI-H460 cell line and inhibiting the growth of lung tumors. Metformin was shown to increase cisplatin cytotoxicity by suppressing different pathways such as those linked with a signal transducer. Activation of transcription-3 activity was also enhanced through an independent process unlike that initiated by the hepatic kinase B1-AMP activated protein kinase pathway in NCI-H460 human lung cancer cells. It was reported that metformin inhibits the pathway of interleukin-6 / STAT3, resulting in its abolition chemotherapeutic gefitinib resistance in lung cancer that improves the efficacy of gefitinib (Lin et al., 2013; Teixeira et al., 2013).

4.4 Colorectal cancer (CRC) and Gastric cancer

Patients treated with metformin showed a lower-rated of CRC (Liu et al., 2017) (56). Patients treated with chemotherapeutic drugs and non-metformin users showed a lower rate response to

treatment. Metformin has been shown to have a cytotoxic effect, and this corresponds to reduce risks to colorectal adenoma (Yamazaki et al., 2004). It has been observed in clinical practice that a combination of metformin with 5 fluorouracil (5-FU)has led to more control of cancer cells, and less resistance compared to treatment with 5-FU alone (Sui et al., 2014; Y. Yu et al., 2015).

Combination of metformin with some chemotherapeutic agents' i.e. cisplatin and rapamycin inhibit tumor growth and the necrosis process in gastric cancers by promoting AMPK and PTEN activity and suppress biochemical activities linked to the mTOR pathway (Lesan et al., 2014).

4.5 Hepatic cancer

Metformin has an inhibitory effect on hepatic cancer cell growth and reduces the rates of invasion of human hepatocellular carcinoma cells (HCC). Metformin reduced risks associated with other than hepatocellular carcinomas by 48% (Donadon, Balbi, Mas, Casarin, & Zanette, 2010). The combining metformin with certain chemotherapeutic agents such as cisplatin, 5-FU, and doxorubicin have led to relatively superior outcomes in patients with HCC as opposed to those who did not receive metformin. A significant reduction of liver cancer in diabetic patients treated with metformin was observed. Metformin increases the sensitivity to cisplatin through AMPK signaling pathways (Donadon et al., 2010; H. Dong et al., 2017).

Sorafenib has been used for HCC therapy since November 2007. The combination of sorafenib and metformin prevent synergistically the proliferation of cancer cells of HCC, especially in resistant cancer cells. The efficacy of tumor inhibition metformin provided the anti-inflammatory effects of sorafenib and reduce the spread of the tumor lung in liver cancer. Suppressing migration and metformin invading HCC cells by lowering the regulation of the ERK / JNK mediated nuclear factor-κB-dependent pathway, which leads to a reduction of uridylyl adenosine phosphate and MMP-9 expression (Ling et al., 2017). A combination of metformin and sorafenib inhibits the metastasis of HCC and stimulates autophagy of liver cancer by inhibiting the mTOR pathway (Ling et al., 2017).

4.6 Pancreatic cancer

High mortality rates have been reported from pancreatic duct adenocarcinoma. Metformin treatment has been found to reduce acinar-to-ductal metaplastic changes (Sui et al., 2014). On the other hand, this group has been noted to have a lower incidence of pancreatic cancer (Srivastava, 2012; Z. Wang et al., 2014). Reduced risk of cancer occurrence among patients who were diagnosed with different types of gastrointestinal tract malignancies including pancreatic cancer who were concomitantly receiving metformin therapy (Li, Li, Liu, Gou, & Wang, 2017).

Table 1: Summary of important studies of metformin combination with chemotherapeutic agents in cancer.

Study	Cancer Type	Combined Agent (s)	Response
Jiralerspong et al. (46)	Breast	Doxorubicin, paclitaxel, epirubicin, 5-fluorouracil (5-FU), carboplatin, Cyclophosphamide.	Good
Hannah et al. (51)	Ovarian, endometrial	Cisplatin, paclitaxel	
Teixeira et al., (55)	Lung	Etoposide, cisplatin, doxorubicin	
Sui X et al. (42)	Colorectal	5-fluorouracil (5-FU)	
Yu G et al. (58)	Gastric	Cisplatin, rapamycin	
Donadon V et al. (60) Ling S et al. (61)	Hepatic	Cisplatin, 5-FU, doxorubicin Sorafenib	
Haring A et al. (43)	Prostate	Gefitinib	
Rosilio C et al. (67	Leukemia	Cisplatin	Variable
Costa D et al. (68)	Neuroblastoma	Retinoic acid	Variable

4.7 Prostate cancer, thyroid carcinoma, and bladder cancer

Metformin therapy reduced viability and increased apoptosis of prostate cancer. The rate of prostate cancer development was decreased in metformin using group (Haring et al., 2017). Interestingly, in rare malignancies such as thyroid carcinomas, it has been observed a lower incidence among diabetics who were receiving metformin (Tseng, 2014). A combination of metformin and gefitinib causes anti-bladder cancer and enhances programmed cell death stronger than that compared to metformin or gefitinib alone. Gefitinib inhibits Akt signals, which inhibit mTOR, also activate AMPK with metformin. Meanwhile, researches focusing on nephrotoxicity and tubular cell apoptosis state that metformin is an excellent agent in protecting the kidneys from Acute Kidney Injury and Cisplatin-induced tubular cell apoptosis because it improves phosphorylation of AMPKα and inducing of autophagy in the organs (Deng et al., 2019).

4.8 Brain tumor and human leukemia cell line

A combination of metformin with cisplatin may lead to a

reduction in its cytotoxic effects in some malignancies such as leukemia, glial cell tumors, and tumors originating from neural crest e.g. neuroblastoma (Costa et al., 2014; Rosilio, Ben-Sahra, Bost, & Peyron, 2014).

5. Conclusion

A combination of metformin with chemotherapeutic agents enhances their anti-cancer effects and reduces undesirable side effects. Because the use of metformin in cancer treatment mainly involves aid in reducing the adverse effects of chemotherapeutic agents. The combination has the potential to reduce cell

proliferation and tumor growth has improved health among patients with breast, liver, ovarian, lung, and hepatic cancer. Clinical and laboratory studies should focus on the further understanding significance of metformin use as an adjuvant to chemotherapeutic agents.

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