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CYTOTOXIC EFFECT OF METFORMIN AND MECHANISM OF ACTION REVIEW

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Abstract:

Background
The cytotoxic impact of metformin has been reviewed in vivo and in vitro study until now the mechanism of action still not fully clear this review the aim to mentioned if metformin may be use anticancer drug mechanism of action of metformin.
Method different data about metformin effect on cancer cell line form site https://pubmed.ncbi.nlm.nih.gov
Results
There were 96 articles that collected and no other articles were identified using other sources. After examining the title and abstract, a total of 56 articles were deleted for duplication, and 24 articles were excluded. The full text of the 16 remaining studies, which detail probable effects of metformin on cancer and Clearfield mechanisms of metformin as a cytotoxic agent, was retrieved and reviewed for final inclusion.
Conclusion: current study analysis showed relationship of metformin user and cancer and summarized the mechanism as anticancer on"A MPK-dependent "impact of metformin AMPK-in dependent effects of metformin

Keywords: Metformin, cytotoxic effect, mechanism of action, cancer.

INTRODUCTION

Metformin was prescribed for treatment of patients with (type-2 diabetes mellitus T2DM). [(1)] people with diabetes disease showed elevated risk of variety of cancers[(2)]
The action of metabolism of metformin that increases skeletal muscle glucose absorption and decrease hepatic gluconeogenesis and increases skeletal muscle glucose absorption by (activating AMPK a cellular energy sensing enzyme) that maintains control cellular energy status through phosphorylation and elevated activity when ATP levels decrease and AMP levels increase. The change in the ATP:AMP ratio is used as an indicative marker of energy deficiency.[(3)]
Anti-tumorigenic effects of metformin, which require further study, might be partially due to systemic metabolic alterations, including the reduced availability of insulin[(3)].
Metformin is used off-label for the treatment of polycystic ovarian syndrome(PCO),prediabetes, hyperinsulinemia ,obesity, as well as metabolic syndrome. Diabetes was the most common diagnosis related with metformin use, followed by metabolic syndrome, according to the (NDTI) database. Obesity, polycystic ovarian syndrome, and polycystic ovary syndrome are all symptoms of polycystic ovarian syndrome. [(4)] .
Retrospective reviews that indicated increased survival rates on various type of cancer for diabetic individuals using metformin, the antidiabetic medicine is gaining a lot of attention as a potential anticancer treatment. The medicine is generating a lot of attention all through the world because of its possibility to treat/prevent several cancer, cardiovascular disease, aging, and neurological diseases.[(5)].

There is an epidemiologic relationship (Metformin and Cancer Prevention)

Several epidemiologic studies have found that diabetic people who take metformin had a decreased cancer risk than diabetics who just don't take[(6)]
Whereas many researches metformin users have a lower risk of developing cancer than non-users[(7)] other studies reviewed just few recent retrospective cohort studies in diabetic patients with breast[(8).] endometrial [(9)],prostatic [(10)]. Renal [(11)] cancers and found no clear association between uses of metformin and improved-free survival disease . These studies have some limitations, such as only a few of patients enrolled or a concentrate on a certain healthcare or ethnic grou, these studies had a shorter follow-up period, as well as lacking data on patient factors like obesity, food, and physical activity[(12).]

Considering the varied results of research on metformin use and clinical outcomes, the vast bulk of evidence points to able of metformin to increment the risk of many cancers [13].

METHOD

Different data about metformin effect on cancer cell line form site https://pubmed.ncbi.nlm.nih.gov. data base from results from the National Center for Biotechnology Information (NCBI) at the U.S. National Library of Medicine (NLM). metformin, Cancer, mechanism of action as anticancer then Filters: Abstract, studied Associated data, Books and Documents, Clinical Trial, Randomized Controlled Trial, Review, in the last 5 years - PubMe
The first author's name, publication year, technique, and findings were among the data extracted
.Incurrent review designed to aim to the reported if possible relationship metformin with Cancer and mechanisms of action metformin as anticancer cancer thus, we only included studies with in Books and Documents, Clinical Trial, Randomized Controlled Trial, Review, in the last 5 years. bias publication & restrictions : In this article, we will discuss to analyze the reported metformin and cancer & mechanisms action of metformin, thus, Only studies were included. with books and documents, clinical trial, randomized controlled trial, review, It may or may not represent all aspects of the overall organism [14]Some studies were not included in the review for reasons duplication or not meet with criteria . PRISMA 2020 flowchart for new systematic reviews including solely database and register searches [15]

RESULTS:

The database of article conducted that total 114 article collected 27 removed duplication following a review of the title and abstract Full The final article from the 16 remaining papers was received and reviewed. current study that agreement with aim of study.is (15) Figure(1) that demonstrated the distribution of data that was searched though current systemic review.
metformin could be beneficial for treatment or adjuvant for cancer treatments, according to data that reviewed epidemiological, and observational research. f found a relationship between metformin use and a lower incidence of cancer and cancer-related mortality in an observational research.[42] This review showed the metformin treatment may reduce the incidence of cancer in Type II diabetic patients in a dose–response manner,. Following then, a number more studies were conducted. In vitro studies of metformin's effect as cytotoxic effect, which reported the effect through revealed linking metformin to cancer growth inhibition and lifespan extension. a few years later showed evidence linking Metformin to lower incidence of cancer risk in diabetic patients. Its multifactorial actions of metformin have been examined at the molecular and cellular levels in various in vitro and in vivo investigations[16] diabetic patient that used the metformin showed decrease incidence occurs of cancer [19]

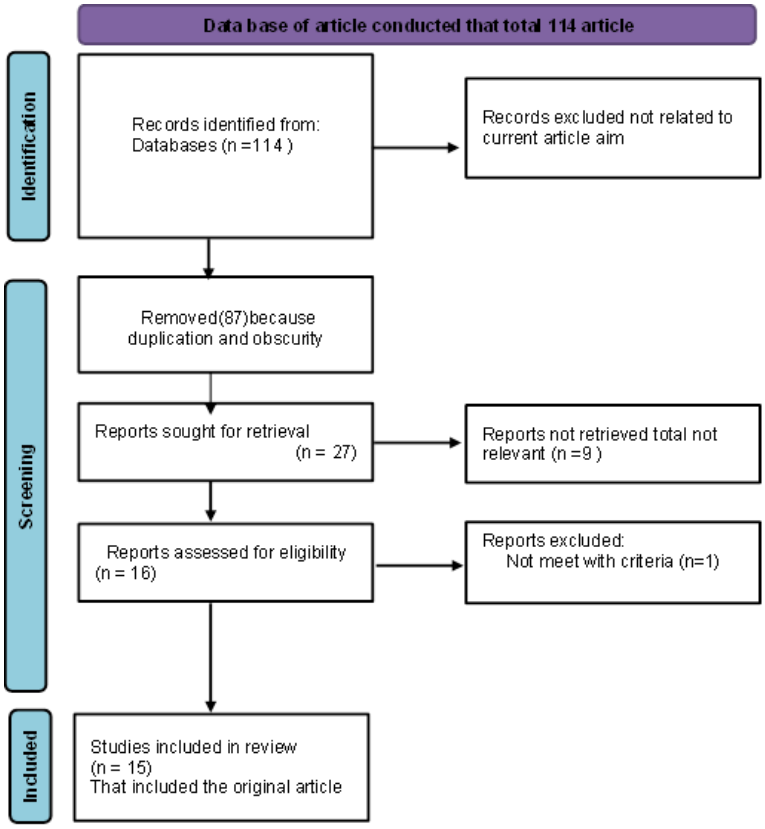

Figure (1): Demonstrated the distribution of data that was searched though current systemic review.

DISCUSSION

The first line of treatment Diabetes patient type two furthermore to its glucose-lowering effect.[43]

Metformin And Cancer(Review studies)

The reduction of hepatic glucose release is one of its key anti-diabetic actions. Animal studies published in 2001 offered the first scientific proof for Metformin anticancer effects, and a retrospectively observational study published a few years later showed evidence linking Metformin to lower cancer risk in type two diabetic patient patients. Its multifactorial anticancer actions have been examined at the molecular and cellular levels in various in vitro and in vivo investigations. Despite the fact that the majority of these investigations found Metformin to have anticancer characteristics, clinical studies and trials revealed a mixed picture of its anticancer benefits. The pleiotropic effect is highlighted in this review.[16]

frequent cancer type of men has prostatic cancer showed that diabetes patent that use metformin reduce incidence of cancer that non-user metformin therefor planning in future that has role in the treatment of prostatic cancer as mono-therapy or combined with other drugs.[17].

Diabetes and cancer are correlated with changes in insulin signaling. Many anti-diabetes treatments improve insulin signaling. Metformin has effective therapeutically in patients with leukemia, lymphomas, and multiple myeloma.[18]

over fifty years metformin use to treat type 2 diabetes. Epidemiological, and clinical research demonstrate that metformin treatment decrease the cancer occurrence in patients that suffer from diabetes .[19]

epigenetic alteration have linked to type 2 diabetes. Metformin treatment is said to affect the expression levels of a number of microRNAs, which may have anti-diabetic and anti-cancer properties.[20]

Metformin has been founded to work in conjunction with anti-cancer agents and resolve chemo- and/or radio-resistance of various types of tumors.[21]

metformin lead to a cytotoxic effect. Metformin can as direct acting on cancerscells by targeting various pathways including tumor metabolism, inflammation, angiogenesis or cancer stem cells. However, it does not seem to be sufficient to treat cancer, raising the need to be combined with other drugs.[22]

How metformin act as anticancer

Metformin has been a front line therapy for type 2 diabetes for many years. In addition to its glucose-lowering effect, metformin possesses other health-promoting effects that include reduced cancer risk and tumorigenesis. Metformin regulates AMP-activated protein kinase (AMPK) though inhibition of the mechanistic target of rapamycin complex 1 (mTORC1).[23]

Metformin is a first line medication for type II diabetes. Preclinical studies determined that metformin impairs cellular metabolism and suppresses oncogenic signaling pathways, including receptor tyrosine kinase, PI3K/Akt, and mTOR pathways. Metformin has gained interest due to its inhibitory effects on cancer stem cells.[24].

Metformin is a commonly prescribed as anti-diabetic drug, and there is among diabetic patients that it is a chemo-preventive agent against multiple cancers. Studies in pancreatic cancer cells clearly demonstrate that metformin dropped expression of Sp1, Sp3, Sp4 and Sp-regulated genes.[25]

Metformin trigger LKB1, which then trigger AMPK, due to differential effects in various tissues.[26].

There increase evidence that links modifications epigenetic to type two diabetes. Metformin may influence the activity of numerous epigenetic modifying enzymes. The levels of various microRNAs are influenced when treatment with metformin and may connect or link between anti-diabetic and anticancer activities.[27]

Metformin, drug variable and not expensive commonly used in the first-line treatment of type two diabetes, As a potential anticancer medication, it has gotten a lot of interest Metformin' had role in many signaling pathways, including AMP-activated protein kinase, mammalian target of rapamycin, insulin-like growth factor, c-Jun N-terminal kinase/mitogen-activated protein kinase (p38 MAPK), human epidermal growth factor receptor-2, and nuclear factor kappaB Metformin's cutting-edge targeting of cancer cells[28].

Metformin firstly drug that used by patient type two diabetic growing concerns on its anti-cancer effect. Glibenclamide suppress carcinogenesis through ATP-binding cassette protein super-family and ATP-sensitive potassium channels.,clinical researches reported an increased or non-significant elevated cancer occurrence risk compared with metformin users.[29]

Metformin hydrochloride exerts chemo-preventive effects on colorectal cancer Mechanisms by which metformin had anticancer properties are less understood. Findings may prove particularly meaningful in the fields of experimental and clinical oncotherapy.

Activation of adenosine monophosphate-activated protein kinase (AMPK)

AMPK-dependent impact metformin increment excitation of AMPK, An intracellular energy sensor is a device that detects the amount of energy that is present is activating by increasing the ratio of AMP/ATP, By blocking anabolic processes and encouraging catabolic processes, AMPK replenishes cellular energy levels. e.g., glycolysis and fatty acid oxidation to increase the AMP/ATP ratio[30] Metformin has also been shown to activate AMPK, which has anti-cancer properties.[31].

Both genetic and pharmacologic suppression of AMPK in lymphoma cells prevented metformin-induced growth inhibition and G0/G1 cell cycle arrest. Shi and colleagues[32]

AMPK-independent impact of metformin

mentioned that the cytotoxic effect of metformin was independent of the AMPK pathway. They used AMPK siRNA to dcrease the two catalytic subunits of AMPK, but AMPK inhibition did not block the G0/G1 cell cycle arrest induced by

metformin. Their following research revealed that metformin's effects on cell cycle arrest and cyclin D1 modification were mediated via a negative regulator of mammalian target of rapamycin (mTOR), controlled in development and DNA damage 1 [33)]

other studies exhibited that metformin-mediated Chronic inflammatory responses are suppressed Inhibition of tumor necrosis factor alpha (TNF) production in human monocytes was linked, An occurrence that was most likely unrelated to the activation of AMPK. Chronic inflammation may contribute to cancer progression, however following metformin treatment, there was no discernible change in phosphor-AMPK [(34)]

Metformin's anticancer actions are independent of the AMPK signaling pathway, according to the findings. [(35)]

Suppression of the mTOR pathway

By regulating cellular processes including biosynthesis of proteins and apoptosis, mTOR It's important for maintaining cellular energy balance. mTOR signaling is commonly triggered in malignancies and their effect positive regulation of cell proliferation and carcinogenesis in a numerous types of tumors. mTOR activation is connected to malignant tumor formation, chemotherapy resistance, and molecularly targeted therapeutic resistance, as well as a bad prognosis (36)

Metformin has been shown to inhibit the mTOR pathway in cancers like leukemia. [(37)]

Inhibition of the IGF signaling pathway

Metformin present to have characteristics anticancer via lowering IGF-1 levels, according to new findings. Metformin, an insulin-sensitizing drug, lowers IGF-1 by down-regulating insulin and insulin-binding proteins indirectly to reverse hyperinsulinemia, which could be a mechanism for metformin's anticancer effects[(38)]

Interruption of insulin receptor/IGF-1R and G protein-coupled receptor (GPCR) signaling via metformin-induced AMPK activation could be another mechanism related to IGF-1[(39)]

Other mechanism

Metformin may play a pivotal role in modulating the anti-oxidant system, including the SOD machinery, in breast cancer-derived cells. These findings could help with breast cancer clinical care and/or (targeted) treatment. (40%). The phosphorylation of the ASK1-dependent pathway, which is a key regulator of Noxa expression, was also increased by metformin and low glucose treatments. These findings suggest that apoptosis is influenced by mitochondrial dys-regulation. that was induced by the combination of low glucose and metformin [**(41)**]

Metformin is thought to improve glycemia through activating AMPK and affecting the liver[(44).]

However, recent research suggests that metformin has other organs as a target, including as the gut and intestines.[(45).]

Metformin may have a variety of cancer-related effects via diverse methods. Treatment with metformin, for example, was found to be effective in preventing cellular metastasis in EC109 esophageal squamous cell carcinoma cells [(46)] other effect on (HeLa) cervical cancer cells[(47).] Metformin increased activation of AMPK in cells other than hepatocytes will result in control of cellular proliferation[(48)]

AMPK activation in epithelial cells, such as those found in breast cancer tissue, can result in decreased proliferation, mRNA translation, and protein synthesis. [(49)]

second, chronic glucose deprivation can cause an inflammatory response and an increase in the generation of reactive oxygen species (ROS), which can damage cell membranes and nucleic acids.[(50)]

CONCLUSION

Metformin's anti-proliferative mechanisms are investigated in this study, which is a systematic review of the literature. Cytotoxic mechanisms of metformin contribution of AMPK as a potential target for anticancer therapy In conclusion, the profile of protection, the route of administration and the history for using metformin an ideal for regeneration to include other applications as well In vitro and in vivo, metformin inhibits cancer cell proliferation, The large number of clinical trials that aim to further investigate its efficacy as a potential anticancer adjuvant or treatment, as well as the large number of clinical trials that aim to further investigate its efficacy as a potential anticancer adjuvant or treatment, reflect the potential that this drug can offer and warrants the need to understand the exact mechanisms of its anticancer activity.

PERSPECTIVE ON THE FUTURE

Metformin is a safe drug and not inexpensive that has been used as an anti-diabetic medication for for a long time. The medicine is currently being used for a variety of off-label purposes, including the treatment of polycystic ovarian syndrome. More research is needed to determine metformin's cellular targets and possible anticancer applications. To uncover cellular mechanisms, more research is required.

Metformin's anticancer targets, as well as the significance of the drug's glucose-lowering properties as a potential mechanism or contributing factor, future research should focus on investigating metformin’s tissue distribution in normal and cancer cells

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