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MDPI

Review

Diabetes Mellitus and Colon Carcinogenesis: Expectation for Inhibition of Colon Carcinogenesis by Oral Hypoglycemic Drugs

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Abstract: The global deaths due to colorectal cancer and diabetes mellitus have increased by 57% and 90%, respectively. The relationship between various cancers and diabetes mellitus has been shown in multiple epidemiological studies. Hence, better management of diabetes mellitus is expected to reduce the risk of various cancers. This review focuses on colorectal cancer and aims to summarize recent findings on the antitumor effects of various oral hypoglycemic drugs on colorectal cancer and their estimated mechanisms. Of the seven classes of oral hypoglycemic agents, only metformin was found to have suppressive effects on colorectal cancer in both clinical and basic research. Clinical and basic researches on suppressing effects of glinides, dipeptidyl peptidase-4 inhibitors, thiazolidinedione, α-glucosidase inhibitors, and sodium glucose cotransporter-2 inhibitors against colon carcinogenesis have been insufficient and have not arrived at any conclusion. Therefore, further research regarding these agents is warranted. In addition, the suppressive effects of these agents in healthy subjects without diabetes should also be investigated.

Keywords: colorectal cancer; diabetes mellitus; metformin; alpha-glucosidase inhibitors; SGLT2 inhibitors; insulin-like growth factor

1. Introduction

The global deaths due to colorectal cancer (CRC) and diabetes mellitus (DM) have increased by 57% and 90%, respectively. The risk of CRC was estimated to be 27% higher in type 2 DM patients than in non-diabetic patients. Due to imbalances in lifestyles, including diet and exercise, diseases related to obesity and metabolic syndrome have increased. The number of cases of DM, especially type 2 DM, is increasing, and this trend is expected to continue in the future [1].

The relationship between DM and various cancers has been shown in many epidemiological studies [2–23], therefore, adequate DM management is expected to decrease the risk of various cancers. In fact, studies that acknowledge the carcinogenesis-inhibiting effect of several oral hypoglycemic agents currently in clinical use have increased in recent years.

This review focuses on CRC and aims to summarize the recent findings regarding the antitumor effect of various oral glycemic drugs on CRC and their estimated underlying mechanisms.

2. Diabetes Mellitus and Colorectal Cancer: Basic Introduction and Epidemiological Relevance

2.1. Diabetes Mellitus

Diabetes mellitus (DM) is a disease in which hyperglycemia presents chronically because of insulin deficiency or a decrease in the effect of insulin, where glucose tolerance is reduced. In addition to the major complications of retinal diseases, nephropathy and neuropathy, which are microvascular disorders, the development of serious complications without subjective symptoms increases, arteriosclerosis of larger vessels progresses, and the risk of heart disease increases.

DM is classified into two types, type 1 DM and type 2 DM, depending on the necessity of supplementing insulin. Type 1 DM is characterized by deficient insulin production associated with progressive destruction of pancreatic β cells, while type 2 DM is characterized by insulin dysfunction associated with environmental influences such as overeating, lack of exercise and obesity.

The number of people suffering from DM worldwide will be 629 million in 2045, compared with an estimated 426 million in 2017. In addition, the prevalence rate of DM in adult humans was 8.47% in 2017 [24]. The number of people with type 2 DM is increasing in every country and about 1 in 11 adults worldwide now have diabetes mellitus, 90% of whom have type 2 DM [25,26].

Treatment of DM is mainly by increasing insulin availability, improving insulin sensitivity, inhibiting gluconeogenesis, delaying the absorption of carbohydrate in the intestinal tract, and promoting excretion of glucose into the urine [1].

2.2. Colorectal Cancer

Colorectal cancer (CRC) is the third most commonly diagnosed cancers and the second leading cause of cancer-related global deaths [27,28]. The incidence increases with age and they usually occur in persons of 50 years old and above. Its burden is expected to increase by 60% to more than 2.2 million new cases and 1.1 million deaths due to cancer by 2030 [29].

Molecular and pathological studies on carcinogenesis of colorectum have earned much knowledge from early on as a breakthrough in genetic analysis of hereditary CRC. CRC is not caused by a single genetic abnormality, its predominant mechanism has been the multistep carcinogenesis theory, which states that colon cancer develops by the accumulation of multiple gene abnormalities [30]. Increased genomic instability due to the accumulation of genomic abnormalities is involved in carcinogenesis of various cancers including CRC. Accumulation of genomic abnormalities in CRC is classified into two types: chromosomal instability (CIN) which is accompanied by structural change of the chromosome and microsatellite instability (MIN) which is caused due to an abnormal repetitive sequence (microsatellite) of DNA in the genome without any structural change in chromosome. It has been reported that 80 to 85% of colon cancers are of the CIN type and about 15% are of the MIN type [31]. The genetic abnormality that causes MIN type is due to inactivation of the mismatch repair gene. Inactivation of cancer suppressor genes (e.g., APC, TP 53, TGFβ, etc.) and activation of oncogenes (e.g., KRAS) are also involved in colorectal carcinogenesis [1,32,33].

For early detection and early treatment, fecal occult blood test (FOBT) and endoscopy are useful. The sensitivity for CRC in the 1-day method of FOBT is 30–56% and the specificity is 96–97%; in 2-day and 3-day methods of FOBT, the sensitivity for CRC is 83–92% and the specificity is 90–96% [34–36]. FOBT is a minimally invasive simple test and is useful for screening of CRC. Endoscopy not only assesses the intestine directly but can also perform tissue biopsy and helps to perform endoscopic mucosal resection if there are abnormal lesions such as adenomatous polyps. Early stage CRC is treated with surgery, and locally advanced CRC is treated with adjuvant chemotherapy along with surgery. Neoadjuvant chemo-radiation is one of the standard treatments for rectal cancer with nodal disease [37]. Adjuvant chemotherapy schemes contain 5-fluorouracil and oxaliplatin. Metastatic CRC is treated with irinotecan or oxaliplatin combined with fluoropyrimidine and leucovorin (FOLFIRI or FOLFOX regimens) [38].

2.3. Epidemiological Relevance of Diabetes Mellitus and Colorectal Cancer Risk

In a study conducted in Taiwan with data analyzed from 36,270 DM (type 1:type 2 = 1447:34,823) patients and 145,080 subjects without DM, it was shown that the incidence of cancer at any site was significantly higher in patients with DM than in those without DM, and the risk of carcinogenesis imparted by DM was greatest in gastroenterological malignancies such as CRC, liver and pancreas as well as lung, breast and oral cancer [39,40]. In addition, various prospective cohort studies [3,7–9,12,41] and meta-analysis [5,6] have reported that the risk of various cancers increases significantly in DM-affected groups [25].

Focusing on CRC, a cohort study conducted in the United States on 850,000 diabetic patients during the period of 1960–1972 is listed as an early report on the relationship between DM and CRC. The adjusted incidence density ratio of CRC was 1.30 (95% confidence interval (CI) 1.03–1.65) for diabetic males, but no significant incidence was found for females [42]. A more recent US study observed an increased adjusted hazard ratio (HR) for CRC regardless of gender, which could be due to a change in lifestyle from the 1960s to 1990s [11].

Since the early 2000s, several cohort studies have been conducted [2,4,11,13–23], showing a significant rise in CRC risk compared to diabetes-related groups in diabetes-affected groups before the 2000s (Table 1).

Table 1. Epidemiological relevance of diabetes mellitus and risk of colorectal cancer.

References	Study	Country	Sample	Period (Years)	Risk of CRC Among DM Participants (95% CI)		
					Males	Females	Overall
Nilsen et al., 2001 [2]	Cohort	Norway	751,922	12	RR 0.66 (0.35–1.34)	RR 1.55 (1.04–2.31)	N.A.
Inoue et al., 2006 [4]	Cohort	Japan	97,771	12	HR 1.36 (1.00–1.85)	HR 0.83 (0.42–1.68)	N.A.
Jarvandi et al., 2013 [11]	Cohort	USA	484,020	12	C: HR 1.24 (1.12–1.38) R: HR 1.34 (1.14–1.57)	C: HR 1.37 (1.16–1.60) R: HR 1.43 (1.08–1.88)	C: HR 1.27 (1.17–1.39) R: HR 1.36 (1.18–1.56)
Oberaigner et al., 2014 [13]	Cohort	Austria	5,709	22	SIR 1.11 (0.81–1.49)	SIR 0.94 (0.62–1.36)	N.A.
Wang et al., 2015 [17]	Cohort	China	327,000	7	C: SIR 1.47 (1.29–1.67) R: SIR 1.25 (1.09–1.43)	C: SIR 1.33 (1.15–1.54) R: SIR 1.29 (1.10–1.51)	C: SIR 1.40 (1.27–1.55) R: SIR 1.26 (1.14–1.40)
Harding et al. 2015 [14]	Cohort	Australia	953,382	12	SIR 1.18 (1.15–1.21)	SIR 1.16 (1.13–1.20)	N.A.
Liu et al., 2015 [15]	Cohort	Sweden	380,196	47	N.A.	N.A.	C: SIR 1.33 (1.28–1.38) R: SIR 1.19 (1.13–1.25)
Dankner et al., 2016 [18]	Cohort	Israel	218,6196	11	SIR 1.45 (1.37–1.55)	SIR 1.48 (1.39–1.57)	N.A.
de Kort et al., 2016 [19]	Cohort	Netherlands	120,852	21	HR 0.95 (0.75–1.20)	HR 1.08 (0.85–1.37)	N.A.
Ballotari et al., 2017 [20]	Cohort	Italy	383,799	4	IRR 1.44 (1.25–1.55)	IRR 1.44 (1.25–2.60)	IRR 1.32 (1.12–1.55)
de Jong et al., 2017 [22]	Cohort	Netherlands	34,038	14	N.A.	N.A.	C: HR 1.40 (1.10–1.70) R: HR 0.88 (0.63–1.20)
Chen et al., 2017 [21]	Cohort	Asia	771,297	23	C: HR 1.57 (1.27–1.93) R: HR 1.26 (0.99–1.61)	C: HR 1.48 (1.20–1.81) R: HR 1.55 (1.12–2.16)	HR 1.41 (1.26–1.57)
Saarela et al., 2018 [23]	Cohort	Finland	428,326	27	C: SIR 1.29 (1.24–1.33) R: SIR 1.16 (1.10–1.21)	C: SIR 1.16 (1.12–1.20) R: SIR 1.13 (1.06–1.19)	C: SIR 1.22 (1.19–1.25) R: SIR 1.14 (1.10–1.18)

Cohort means prospective cohort. DM, diabetes mellitus; CI, confidence interval; C, colon; R, rectum; RR, relative risk; HR, hazard ratio; SIR, standardized incidence rate; IRR, incident rate ratio; N.A., not applicable.

2.4. Expectation for Reduction of Carcinogenic Risk by Diabetes Treatment, Especially Oral Hypoglycemic Drugs

Although there is no significant difference in the incidence of malignancy between type 1 DM and type 2 DM [25], type 2 DM accounts for more than 90% of the total number of diabetic patients. Considering the current situation in DM, especially type 2 DM, good control of DM by drug therapy is expected to reduce the risk of developing various malignant tumors. While treatment for type 1 DM is mainly supplementation with insulin, various oral hypoglycemic drugs are currently developed and used for type 2 DM. Recent studies have reported that various oral hypoglycemic agents, such as metformin, the preferred and most widely used pharmacological agent for type 2 DM, has tumor-suppressive properties.

3. Molecular Mechanisms of the Association between Diabetes Mellitus and Colorectal Cancer

DM and CRC share multiple risk factors, such as obesity, Western diet, sedentary lifestyle, and alcohol/tobacco use. For this reason, it is easy to imagine the theory that DM might be a causal factor for CRC development [43]. Several representative pathophysiological mechanisms, such as the insulin-like growth factor (IGF) signaling system and Wnt signaling system, have been proposed for association between DM and CRC, especially for the increased risk of developing CRC in people with DM.

3.1. The Insulin-like Growth Factor Signaling System

IGF signaling system is associated with cell proliferation, diabetes, hyperinsulinemia and obesity. IGF signaling proteins, such as IGF-1 and IGF-2, play important roles not only in cell growth and differentiation, but also in the occurrence and development of tumors. The biological effect of IGF signaling proteins are mediated by IGF-1 receptor (IGF-1R) that is structurally associated with the insulin receptor [44,45]. Ligands for IGF-1R not only include IGF-1 and IGF-2, but also insulin; ligands induce autophosphorylation of IGF-1R. This results in activation of the phosphatidylinositol 3-kinase-AKT(PI3K)/mammalian target of rapamycin (mTOR) signaling pathway and RAS protein/mitogen-activated protein Kinase (MAPK) pathway. This leads to promotion of cell proliferation and suppression of apoptosis, which leads to carcinogenesis [46]. IGF-1 is also involved in the development of angiogenesis and metastases by increasing the expression of vascular endothelial growth factor (VEGF) [47,48]. IGF-1 prevented apoptosis by inhibiting p53 and also caused angiogenesis by inducing hypoxia-inducible factor 1α (HIF1α) involved in the expression of VEGF [49,50].

In hyperinsulinemia caused by insulin resistance associated with type 2 diabetes, high insulin levels in the portal circulation upregulate the growth hormone receptor, enhance the growth hormone receptor signaling, and increase IGF-1 production [51,52].

3.2. The Wnt Signaling System

The Wnt signaling system is the fundamental mechanism that directs cells for proliferation, as a result, mutations in the Wnt signaling pathway are often associated with cancers and other diseases.

In the absence of Wnt, cytoplasmic β-catenin protein is constantly degraded by the effect of Axin complex, which is composed of Axin, the tumor suppressor adenomatous polyposis coli (APC) gene product, casein kinase 1 (CK1), and glycogen synthase kinase 3 (GSK3). CK1 and GSK3 sequentially phosphorylate the amino terminal region of β-catenin, resulting in β-catenin recognition by β-Trcp and subsequent β-catenin ubiquitination and proteasomal degradation. As a result, the transfer of β-catenin into the nucleus is inhibited, and Wnt target genes are suppressed by the DNA-bound T cell factor/lymphoid enhancer factor (TCF/LEF) family of proteins.

In the presence of Wnt, a Wnt ligand binds to a frizzled (Fz) receptor and its co-receptor, low-density lipoprotein receptor related protein 6 (LRP6) or its close relative LRP5. The Wnt-Fz-LRP5/6 complex together with the recruitment of the scaffolding dishevelled (Dvl) protein results in the recruitment of the axin complex to the receptors. These events lead to inhibition of β-catenin phosphorylation and to

the stabilization of β-catenin, which accumulates and transfers to the nucleus to form complexes with TCF/LEF and activates Wnt target gene expression [53].

Also, LRP5 appears to serve as a co-receptor in insulin signaling. The insulin receptor (IR)/LRP5 interaction could be a mode of action in the Wnt effect on Akt, ERK1/2, and GSK3 phosphorylation. The IR/LRP5 interaction acts could play a role in the pathogenesis of obesity and insulin resistance. The inducibility of this interaction is specific for the insulin receptor and is not observed with the IGF-1 receptor. Insulin and Wnt signaling interactions could also play a role in the association of these pathways in conditions like obesity, type 2 DM and cancer [54].

3.3. Glucagon-like Peptide-1

Another possible molecular mechanism linking DM and CRC includes the involvement of the hormone glucagon-like peptide-1 (GLP-1), secreted by the intestinal endocrine L cells, on the Wnt signaling pathway and the oncogenes. Because of insulin resistance, GLP-1 secretion is reduced in type 2 DM patients. Reduction of GLP-1 secretion with increased expression of proto-oncogenes, such as c-Myc, causes compensatory activation of the Wnt signaling pathway leading to intestinal cell proliferation and CRC development [55].

3.4. Gut Microbiota

There are at least 100 trillion bacteria that live in our gut system, which are known as the gut microbiome. Approximately 90% of the microbial system in healthy adults are Firmicutes and Bacteroidetes [56]. The gut microbiota can work with the host to promote health but can sometimes initiate or promote disease [57–60].

The abundance of Gram-positive bacteria that produce butyrate was reduced in patients with metabolic syndrome who were treated with vancomycin. This was correlated with impaired insulin sensitivity; results showed that reduced levels of butyrate produced in gut microbiota might lead to disease pathogenesis of type 2 diabetes [61].

Among short chain fatty acids (SCFA) produced by gut microbiota, acetic acid and butyric acid increase mucus production from intestinal mucosal goblet cells and protect intestinal tract. When the action of goblet cells is suppressed by the decrease of SCFA, this leads to a decrease in the function of the intestinal barrier, and lipopolysaccharides (LPS) produced by Gram negative bacilli, mostly Proteobacterias, transfer from the intestinal side to the lumen, where it comes in contact with blood. An increase of LPS levels in blood causes insulin resistance in insulin-sensitive organs such as skeletal muscle and liver [62]. Increased insulin resistance results in hyperinsulinemia and as a result may activate the IGF signaling system and Wnt signaling system, leading to colon carcinogenesis.

4. Suppressive Effect of Colonic Carcinogenesis by Oral Hypoglycemic Drugs

4.1. Types of Oral Hypoglycemic Drugs for Type 2 Diabetes Mellitus

There are seven classes of oral hypoglycemic drugs, which can be classified according to their respective main functions; insulin secretion promoting system for decreased insulin secretion, insulin resistance improving system for increased insulin resistance, and glucose absorption/excretion regulation system for the state of hyperglycemia.

Drugs whose main function is based upon an insulin secretion-promoting system include sulfonylureas, immediate-release insulin secretagogues (glinides), and dipeptidyl peptidase (DPP)-4 inhibitors, whereas those with main functions based upon an insulin resistance-improving system include biguanides and thiazolidinedione. Drugs whose main function is based upon a glucose absorption/excretion regulation system include alpha-glucosidase inhibitors (AGIs) and sodium-glucose cotransporter 2 (SGLT2) inhibitors.

4.2. Basic Pharmacological Action of Oral Hypoglycemic Drugs and Reports on Suppressive Effect of Colonic Carcinogenesis Risk

4.2.1. Sulfonylureas

The main effect of sulfonylureas is to increase plasma insulin concentrations. They are effective only when functional pancreatic β-cells are present. The rise in plasma insulin concentrations occurs for two reasons. Firstly, they stimulate insulin secretion by pancreatic β-cells. Secondly, they decrease hepatic clearance of insulin. Sulfonylureas have been traditionally classified into first-generation agents (tolbutamide, chlorpropamide, tolazamide, and acetohexamide) and second-generation agents (glibenclamide, glipizide, gliclazide, glimepiride, and gliquidone) [63]. Currently, the second generation is used predominantly.

We investigated cohort studies that examined various carcinogenic risks including CRC using sulfonylureas reported between 2000 and 2019. There was no report showing the effect of sulfonylureas to reduce the risk of CRC regardless of the presence or absence of significant differences [64–69]. Conversely, several studies showed that the risk of CRC slightly increases by using sulfonylureas, but to a lesser extent than insulin [70–72].

Based on these results, unfortunately, sulfonylureas seems to have no clear suppressive effect on colonic carcinogenesis.

4.2.2. Immediate-release Insulin Secretagogues (Glinides)

The main effect of glinides (repaglinide and nateglinide) is to increase the plasma insulin concentrations. The rise in plasma insulin concentrations occurs for inhibiting ATP-sensitive potassium channels in the pancreatic β-cell membrane, thus providing improved control of postprandial glucose concentrations [73].

We investigated cohort studies that examined various carcinogenic risks including CRC using glinides reported between 2000 and 2019. There are few comprehensive studies verifying the risk of cancer, including CRC, under glinides treatment [71,74]. Also, among those reports there is no clear positive effect on the risk of cancer. However, a recent in-vitro work attested that repaglinide has anti-cancer properties [75].

Due to inadequate studies, no further information is available concerning the effects of these drugs on the risk of CRC.

4.2.3. DPP-4 Inhibitors

Incretin which is an intestinal hormone, such as GLP-1, is secreted from intestinal epithelial cells with elevation of postprandial blood glucose level. GLP-1 stimulates insulin secretion and inhibits glucagon secretion, in turn increasing glucose utilization and diminishing hepatic glucose production [76]. GLP-1 in peripheral plasma is degraded by DPP-4; therefore, DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin, alogliptin, and linagliptin) increases GLP-1 in the peripheral circulation. As a result, there is a decrease in postprandial blood glucose and fasting blood glucose and HbA1c [76].

We investigated cohort studies that examined various carcinogenic risks including CRC using DPP-4 inhibitors reported between 2000 and 2019. However, there are few reports on the relationship between DPP-4 inhibitors and CRC. We found only one clinical study conducted in 2018 on the risk of colon carcinogenesis; the study reported that there was no improvement in the risk of developing colon carcinogenesis by DPP-4 inhibitors [77,78]. In in-vitro studies conducted between 2000 and 2019, there were three reports that confirmed the tumor suppressing by DPP-4 inhibitors [79–81], on the contrary, one study reported that the tumor suppressing effect could not be confirmed.

The number of reported cases is small; thus, it cannot be said whether the effect of suppressing CRC is present or absent. The DPP-4 inhibitor itself is still a novel drug and more data from both clinical and basic researches is required.

4.2.4. Biguanides

The main effect of biguanides (mainly metformin) is to inhibit hepatic gluconeogenesis and to improve peripheral utilization of glucose. However, metformin has been reported to reduce insulin sensitivity in peripheral tissues [82]. The hypoglycemic mechanism by metformin is the suppression of gluconeogenesis and the reduction of hepatic glucose production. In addition, although the contribution is small, it also reduces the absorption of glucose from the intestinal tract and the improvement of glucose uptake and utilization in skeletal muscle and adipose tissue [82]. Other recent studies have shown that metformin suppresses hepatic glucose production by antagonizing glucagon action [83], and metformin improves insulin action by adenosine monophosphate-activated protein kinase (AMPK), which suppresses acetyl-CoA carboxylase phosphorylation [84]. Metformin may also improve glucose homeostasis by interacting with the incretin axis through the action of GLP-1 [85,86].

To date, no epidemiological study was found that examined the role of metformin in the risk of colon carcinogenesis before 2000. During the period 2000 to 2019, 34 epidemiological reports were identified. Among them, 25 reports concluded that metformin was effective in reducing the risk of CRC [65,67,69,72,87–109], 8 reports concluded that there is no evidence for the involvement of metformin in CRC risk compared to the control group and other oral hypoglycemic agents [66,68,110–115], and 1 report concluded that metformin increased the risk of CRC [64].

Activation of AMPK is a major factor in the mechanism of oncogenesis by metformin (Figure 1). AMPK suppresses hepatic gluconeogenesis, promotes glucose uptake in muscle and adipose tissue, sensitizes cells to insulin, and reduces insulin levels, thereby reducing IGF-1 levels. As described above, enhancement of the IGF signaling pathway is involved in the development of various carcinomas including colon cancer. Downstream responses are downregulated by reduced signal input of the IGF-1 signaling pathway. Furthermore, AMPK also has mTOR-type suppressive action and can reduce cell proliferation signals.

Recently, in addition to simply suppressing the effect of primary carcinogenesis, metformin has been examined for suppression of postoperative recurrence [116], reduction of drug resistance, and enhancement of the effect by combination with existing chemoradiotherapy in CRC patients. Furthermore, there are also increasing number of studies [117–120] on the suppressive effect of metformin on colon carcinogenesis in non-DM patients [121,122].

4.2.5. Thiazolidinedione

The main effect of thiazolidinedione (rosiglitazone and pioglitazone) is to improve insulin sensitivity at the sites of insulin action, however, there is no action on promoting insulin secretion.

The intracellular target molecule of thiazolidinedione is a receptor-type transcription factor called peroxisome proliferator-activated receptor gamma (PPARγ), which forms heterodimers with retinoid X receptor (RXR) and is a specific DNA recognition sequence. When a thiazolidine drug binds to PPARγ/RXR heterodimer, transcription activity on DNA is increased, and various metabolic actions are exerted through the induction of target gene expression. Thiazolidine promotes cell death of obese large fat cells and increases differentiation into non-obese small fat cells through the adipocyte differentiation. As a result, insulin sensitivity is improved by reducing the factors, such as free fatty acid and TNF-α, which had lowered insulin sensitivity.

We investigated cohort studies that examined various carcinogenic risks including CRC using thiazolidine reported between 2000 and 2019. As far as we searched, no epidemiological study was found that examined thiazolidine and the risk of colon carcinogenesis. There are very few reports on basic research. One of those reports reported that the administration of a thiazolidine derivative in human cancer cell line showed an increase in apoptosis by inhibiting the DNA topoisomerase I activity [123] and a cell proliferation inhibitory effect via inactivation of NFkβ by suppressing GSK3 activity [124]. Clinical research and anti-tumor effects in further basic research is required.

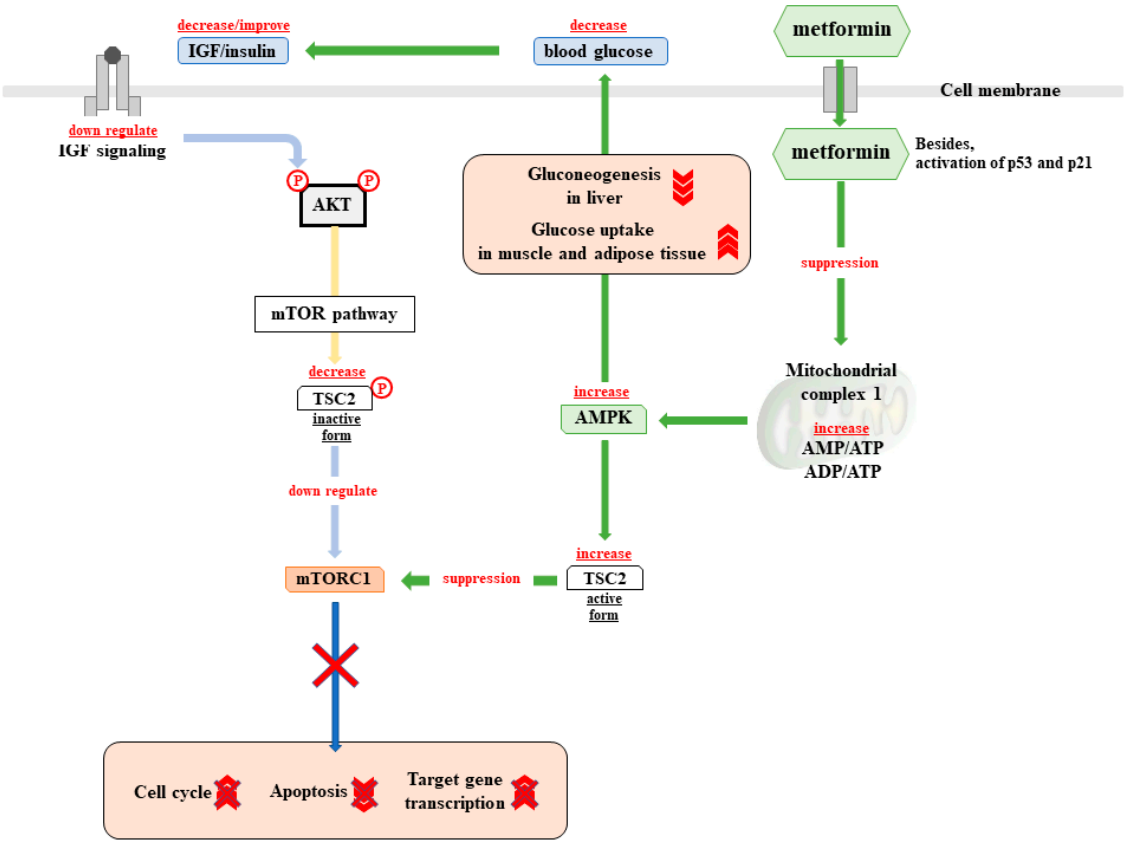

Figure 1. Effects of metformin on IGF/insulin signaling pathway. Metformin activates AMPK by inhibiting mitochondrial oxidative phosphorylation and decreasing ATP. AMPK suppresses gluconeogenesis in liver, promotes glucose uptake in muscle and adipose tissue, sensitizes cells to insulin, and reduces insulin concentration. Thereby, the activation of the entire IGF/insulin signaling pathway is suppressed. Furthermore, AMPK inhibits the activity of mTORC1 in the AKT/mTOR pathway. These actions are considered to exhibit an anti-tumor effect by suppressing cell cycle hyperregulation, canceling apoptosis suppression, and suppressing transcription enhancement of target genes. ADP, adenosine diphosphate. AMP, adenosine monophosphate. AMPK, AMP-activated protein kinase. ATP, adenosine triphosphate. IGF, insulin-like growth factor. mTORC1/2, mammalian target of rapamycin complex 1/2. TSC2, tuberous sclerosis complex 2.

4.2.6. Alpha-glucosidase Inhibitors

The main effect of alpha-glucosidase inhibitors (acarbose, miglitol and voglibose) is to retard carbohydrate digestion and reduce the rate of postprandial glucose absorption [125].

Intestinal brush border membrane-bound intestinal alpha glucosidase has the action of hydrolyzing oligosaccharides, trisaccharides and disaccharides to glucose and other monosaccharides in the small intestine. AGIs reduce the digestive rate of carbohydrates by competitively and reversibly inhibiting this enzyme, and the carbohydrates are less likely to be broken down into glucose molecules, thereby reducing postprandial hyperglycemia and hyperinsulinemia. Acarbose also inhibits pancreatic alpha-amylase, an enzyme that has the function of hydrolyzing starch to oligosaccharides in the lumen of the small intestine [125].

We investigated cohort studies that examined various carcinogenic risks including CRC using AGIs reported between 2000 and 2019. However, there are few reports on the relationship between AGIs and CRC. As far as we could search for clinical studies on the risk of colon carcinogenesis by cohort studies, only two studies were reported in 2015, and both studies reported that AGIs reduces the risk of CRC [39,126].

Although the mechanisms of anti-tumor effects, other than improvement of hyperinsulinemia, are still poorly discussed, several possibilities have been suggested. There are reports that intestinal transit time of feces is shortened in diabetic patients during AGIs administration [127], and reports show that long-term bile acid exposure of intestinal epithelia due to delayed feces induces colorectal tumorigenesis [128]. Based on the above data, it is suggested that shortening the intestinal transit time of stool by AGIs administration may reduce the risk of colorectal tumorigenesis. Further, AGIs have been reported to increase the growth inhibition of transformed cells in the colorectal mucosa and the associated butyrate levels [129]. In addition, the antineoplastic effects of AGIs have been reported, including the prevention of angiogenesis and the inhibition of tumor growth [130]. These findings suggest that AGIs can suppress colorectal tumor formation directly and indirectly [131].

Further studies in clinical research and anti-tumor effects in basic research is required.

4.2.7. SGLT2 Inhibitors

The main effect of SGLT2 inhibitors (dapagliflozin, canagliflozin and empagliflozin) is to prevent reabsorption of glucose filtered through the glomeruli and increase its urinary excretion [132,133].

Blood glucose is filtered in the glomerulus, and the filtered glucose is reabsorbed in the proximal convoluted tubule, mediated by two classes of carrier proteins: the SGLTs and the glucose transporters (GLUTs) [134]. The SGLTs are located on the luminal surface of the proximal tubule epithelium and transport glucose into the cells against the concentration gradient by transporting glucose with sodium. The SGLT1 and SGLT2 are involved in the renal reabsorption of glucose. By the actions of SGLT2 that are selectively expressed in the kidney, about 90% of the glucose filtered from blood is reabsorbed in the proximal tubule of the kidney. About 10% of glucose filtered through the action of low volumes of SGLT1 is reabsorbed in the distal tubule [135]. In patients with type 2 diabetes, renal glucose transport thresholds are increased as compared to normal individuals as a result of SGLT2 upregulation. The intrinsic risk of hypoglycemia with SGLT2 inhibitors is expected to be low, because this effect is insulin independent, and the amount of urinary glucose excretion is determined in part by blood glucose concentrations [136–139].

We investigated cohort studies that examined various carcinogenic risks including CRC using SGLT2 inhibitors reported between 2000 and 2019. As far as we could search, no clinical studies could be found that examined the relationship between SGLT2 inhibitors and CRC risk. Even in basic research, although there have been reports of suppressive effects on prostate cancer and pancreatic cancer, enough studies on CRC could not be found.

Because of the lack of adequate studies, no further information is available concerning the effect of this drug on the risk of CRC.

5. Conclusions

We examined clinical research and basic research on the colon carcinogenesis suppression effect for the past 20 years by seven groups of oral hypoglycemic drugs. Sulfonylureas did not show an effect on colon carcinogenesis in both clinical and basic research. Biguanides (mainly metformin) have been shown to suppress colon carcinogenesis in many clinical studies and basic studies, because of a long clinical application period. Further, the usefulness of the combination with existing chemotherapy and radiation therapy, post-operative relapse suppression effect has also been studied, and good results are being obtained. Therefore, it seems that the study of metformin's inhibitory effect on colon cancer is not new. There are not many clinical studies and basic studies with glinides, DDP-4 inhibitors and thiazolidinedione, and their presence or absence of colon carcinogenesis suppressive effect is unknown. Although AGIs and SGLT-2 inhibitors can be expected to suppress colon carcinogenesis, there is still insufficient information on the degree of risk reduction and its mechanism.

The improvement of clinical research and basic research on the colon carcinogenesis suppression effects by glinides, DDP-4 inhibitor, thiazolidinedione, AGIs, and SGLT-2 inhibitors are remaining

issues for future studies. Although metformin is being studied, examinations on the CRC-suppressive effect by metformin in a healthy person is also a remaining issue.

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References

1. Gonzalez, N.; Prieto, I.; Del Puerto-Nevado, L.; Portal-Nunez, S.; Ardura, J.A.; Corton, M.; Fernandez-Fernandez, B.; Aguilera, O.; Gomez-Guerrero, C.; Mas, S.; et al. 2017 update on the relationship between diabetes and colorectal cancer: Epidemiology, potential molecular mechanisms and therapeutic implications. *Oncotarget* **2017**, *8*, 18456–18485. [CrossRef]
2. Nilsen, T.I.; Vatten, L.J. Prospective study of colorectal cancer risk and physical activity, diabetes, blood glucose and BMI: Exploring the hyperinsulinaemia hypothesis. *Br. J. Cancer* **2001**, *84*, 417–422. [CrossRef]
3. Jee, S.H.; Ohrr, H.; Sull, J.W.; Yun, J.E.; Ji, M.; Samet, J.M. Fasting serum glucose level and cancer risk in Korean men and women. *JAMA* **2005**, *293*, 194–202. [CrossRef]
4. Inoue, M.; Iwasaki, M.; Otani, T.; Sasazuki, S.; Noda, M.; Tsugane, S. Diabetes mellitus and the risk of cancer: Results from a large-scale population-based cohort study in Japan. *Arch Intern. Med.* **2006**, *166*, 1871–1877. [CrossRef]
5. Noto, H.; Osame, K.; Sasazuki, T.; Noda, M. Substantially increased risk of cancer in patients with diabetes mellitus: A systematic review and meta-analysis of epidemiologic evidence in Japan. *J. Diabetes Complicat.* **2010**, *24*, 345–353. [CrossRef]
6. Noto, H.; Tsujimoto, T.; Sasazuki, T.; Noda, M. Significantly increased risk of cancer in patients with diabetes mellitus: A systematic review and meta-analysis. *Endocr. Pract.* **2011**, *17*, 616–628. [CrossRef]
7. Geraldine, N.; Marc, A.; Carla, T.; Chantal, M.; Stefaan, B.; Welcome, W.; Frank, B. Relation between diabetes, metformin treatment and the occurrence of malignancies in a Belgian primary care setting. *Diabetes Res. Clin. Pract.* **2012**, *97*, 331–336. [CrossRef]
8. Lee, M.Y.; Lin, K.D.; Hsiao, P.J.; Shin, S.J. The association of diabetes mellitus with liver, colon, lung, and prostate cancer is independent of hypertension, hyperlipidemia, and gout in Taiwanese patients. *Metabolism* **2012**, *61*, 242–249. [CrossRef]
9. Yeh, H.C.; Platz, E.A.; Wang, N.Y.; Visvanathan, K.; Helzlsouer, K.J.; Brancati, F.L. A prospective study of the associations between treated diabetes and cancer outcomes. *Diabetes Care* **2012**, *35*, 113–118. [CrossRef]
10. Zhang, P.H.; Chen, Z.W.; Lv, D.; Xu, Y.Y.; Gu, W.L.; Zhang, X.H.; Le, Y.L.; Zhu, H.H.; Zhu, Y.M. Increased risk of cancer in patients with type 2 diabetes mellitus: A retrospective cohort study in China. *BMC Public Health* **2012**, *12*, 567. [CrossRef]
11. Jarvandi, S.; Davidson, N.O.; Schootman, M. Increased risk of colorectal cancer in type 2 diabetes is independent of diet quality. *PLoS ONE* **2013**, *8*, e74616. [CrossRef]
12. Lo, S.F.; Chang, S.N.; Muo, C.H.; Chen, S.Y.; Liao, F.Y.; Dee, S.W.; Chen, P.C.; Sung, F.C. Modest increase in risk of specific types of cancer types in type 2 diabetes mellitus patients. *Int. J. Cancer* **2013**, *132*, 182–188. [CrossRef]
13. Oberaigner, W.; Ebenbichler, C.; Oberaigner, K.; Juchum, M.; Schonherr, H.R.; Lechleitner, M. Increased cancer incidence risk in type 2 diabetes mellitus: Results from a cohort study in Tyrol/Austria. *BMC Public Health* **2014**, *14*, 1058. [CrossRef]
14. Harding, J.L.; Shaw, J.E.; Peeters, A.; Cartensen, B.; Magliano, D.J. Cancer risk among people with type 1 and type 2 diabetes: Disentangling true associations, detection bias, and reverse causation. *Diabetes Care* **2015**, *38*, 264–270. [CrossRef]
15. Liu, X.; Hemminki, K.; Forsti, A.; Sundquist, K.; Sundquist, J.; Ji, J. Cancer risk in patients with type 2 diabetes mellitus and their relatives. *Int. J. Cancer* **2015**, *137*, 903–910. [CrossRef]

16. Tsilidis, K.K.; Kasimis, J.C.; Lopez, D.S.; Ntzani, E.E.; Ioannidis, J.P. Type 2 diabetes and cancer: Umbrella review of meta-analyses of observational studies. *BMJ* **2015**, *350*, g7607. [CrossRef]
17. Wang, M.; Hu, R.Y.; Wu, H.B.; Pan, J.; Gong, W.W.; Guo, L.H.; Zhong, J.M.; Fei, F.R.; Yu, M. Cancer risk among patients with type 2 diabetes mellitus: A population-based prospective study in China. *Sci. Rep.* **2015**, *5*, 11503. [CrossRef]
18. Dankner, R.; Boffetta, P.; Balicer, R.D.; Boker, L.K.; Sadeh, M.; Berlin, A.; Olmer, L.; Goldfracht, M.; Freedman, L.S. Time-Dependent Risk of Cancer After a Diabetes Diagnosis in a Cohort of 2.3 Million Adults. *Am. J. Epidemiol.* **2016**, *183*, 1098–1106. [CrossRef]
19. De Kort, S.; Simons, C.C.; van den Brandt, P.A.; Goldbohm, R.A.; Arts, I.C.; de Bruine, A.P.; Janssen-Heijnen, M.L.; Sanduleanu, S.; Masclee, A.A.; Weijenberg, M.P. Diabetes mellitus type 2 and subsite-specific colorectal cancer risk in men and women: Results from the Netherlands Cohort Study on diet and cancer. *Eur. J. Gastroenterol. Hepatol.* **2016**, *28*, 896–903. [CrossRef]
20. Ballotari, P.; Vicentini, M.; Manicardi, V.; Gallo, M.; Chiatamone Ranieri, S.; Greci, M.; Giorgi Rossi, P. Diabetes and risk of cancer incidence: Results from a population-based cohort study in northern Italy. *BMC Cancer* **2017**, *17*, 703. [CrossRef]
21. Chen, Y.; Wu, F.; Saito, E.; Lin, Y.; Song, M.; Luu, H.N.; Gupta, P.C.; Sawada, N.; Tamakoshi, A.; Shu, X.O.; et al. Association between type 2 diabetes and risk of cancer mortality: A pooled analysis of over 771,000 individuals in the Asia Cohort Consortium. *Diabetologia* **2017**, *60*, 1022–1032. [CrossRef]
22. De Jong, R.; Burden, A.M.; de Kort, S.; van Herk-Sukel, M.P.P.; Vissers, P.A.J.; Janssen, P.K.C.; Haak, H.R.; Masclee, A.A.M.; de Vries, F.; Janssen-Heijnen, M.L.G. Impact of detection bias on the risk of gastrointestinal cancer and its subsites in type 2 diabetes mellitus. *Eur. J. Cancer* **2017**, *79*, 61–71. [CrossRef]
23. Saarela, K.; Tuomilehto, J.; Sund, R.; Keskimaki, I.; Hartikainen, S.; Pukkala, E. Cancer incidence among Finnish people with type 2 diabetes during 1989-2014. *Eur. J. Epidemiol.* **2018**. [CrossRef]
24. Cho, N.H.; Shaw, J.E.; Karuranga, S.; Huang, Y.; da Rocha Fernandes, J.D.; Ohlrogge, A.W.; Malanda, B. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res. Clin. Pract.* **2018**, *138*, 271–281. [CrossRef]
25. Habib, S.L.; Rojna, M. Diabetes and risk of cancer. *ISRN Oncol.* **2013**, *2013*, 583786. [CrossRef]
26. Zheng, Y.; Ley, S.H.; Hu, F.B. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat. Rev. Endocrinol.* **2018**, *14*, 88–98. [CrossRef]
27. Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegel, R.L.; Torre, L.A.; Jemal, A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* **2018**, *68*, 394–424. [CrossRef]
28. Rawla, P.; Barsouk, A. Epidemiology of colorectal cancer: Incidence, mortality, survival, and risk factors. *Prz. Gastroenterol.* **2019**. [CrossRef]
29. Arnold, M.; Sierra, M.S.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global patterns and trends in colorectal cancer incidence and mortality. *Gut* **2017**, *66*, 683–691. [CrossRef]
30. Kinzler, K.W.; Vogelstein, B. Lessons from hereditary colorectal cancer. *Cell* **1996**, *87*, 159–170. [CrossRef]
31. Hanahan, D.; Weinberg, R.A. Hallmarks of cancer: The next generation. *Cell* **2011**, *144*, 646–674. [CrossRef] [PubMed]
32. Fearon, E.R.; Vogelstein, B. A genetic model for colorectal tumorigenesis. *Cell* **1990**, *61*, 759–767. [CrossRef]
33. Cancer Genome Atlas, N. Comprehensive molecular characterization of human colon and rectal cancer. *Nature* **2012**, *487*, 330–337. [CrossRef] [PubMed]
34. Nakama, H.; Yamamoto, M.; Kamijo, N.; Li, T.; Wei, N.; Fattah, A.S.; Zhang, B. Colonoscopic evaluation of immunochemical fecal occult blood test for detection of colorectal neoplasia. *Hepatogastroenterology* **1999**, *46*, 228–231. [PubMed]
35. Park, D.I.; Ryu, S.; Kim, Y.H.; Lee, S.H.; Lee, C.K.; Eun, C.S.; Han, D.S. Comparison of guaiac-based and quantitative immunochemical fecal occult blood testing in a population at average risk undergoing colorectal cancer screening. *Am. J. Gastroenterol.* **2010**, *105*, 2017–2025. [CrossRef]
36. Rozen, P.; Shabtai, E.I.; Liphshitz, I.; Barchana, M. Risk for colorectal cancer in elderly persons and possible methodologies for their screening. *Eur. J. Gastroenterol. Hepatol.* **2011**, *23*, 431–437. [CrossRef]
37. McCarthy, K.; Pearson, K.; Fulton, R.; Hewitt, J. Pre-operative chemoradiation for non-metastatic locally advanced rectal cancer. *Cochrane Database Syst. Rev.* **2012**, *12*, CD008368. [CrossRef]

38. Andre, T.; Boni, C.; Mounedji-Boudiaf, L.; Navarro, M.; Tabernero, J.; Hickish, T.; Topham, C.; Zaninelli, M.; Clingan, P.; Bridgewater, J.; et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N. Engl. J. Med.* **2004**, *350*, 2343–2351. [CrossRef]
39. Lin, C.M.; Huang, H.L.; Chu, F.Y.; Fan, H.C.; Chen, H.A.; Chu, D.M.; Wu, L.W.; Wang, C.C.; Chen, W.L.; Lin, S.H.; et al. Association between Gastroenterological Malignancy and Diabetes Mellitus and Anti-Diabetic Therapy: A Nationwide, Population-Based Cohort Study. *PLoS ONE* **2015**, *10*, e0125421. [CrossRef]
40. Rawla, P.; Sunkara, T.; Gaduputi, V. Epidemiology of Pancreatic Cancer: Global Trends, Etiology and Risk Factors. *World J. Oncol.* **2019**, *10*, 10–27. [CrossRef]
41. Hense, H.W.; Kajuter, H.; Wellmann, J.; Batzler, W.U. Cancer incidence in type 2 diabetes patients - first results from a feasibility study of the D2C cohort. *Diabetol. Metab. Syndr.* **2011**, *3*, 15. [CrossRef] [PubMed]
42. Will, J.C.; Galuska, D.A.; Vinicor, F.; Calle, E.E. Colorectal cancer: Another complication of diabetes mellitus? *Am. J. Epidemiol.* **1998**, *147*, 816–825. [CrossRef] [PubMed]
43. Giouleme, O.; Diamantidis, M.D.; Katsaros, M.G. Is diabetes a causal agent for colorectal cancer? Pathophysiological and molecular mechanisms. *World J. Gastroenterol.* **2011**, *17*, 444–448. [CrossRef] [PubMed]
44. Baserga, R.; Hongo, A.; Rubini, M.; Prisco, M.; Valentinis, B. The IGF-I receptor in cell growth, transformation and apoptosis. *Biochim. Biophys. Acta* **1997**, *1332*, F105–F126. [CrossRef]
45. LeRoith, D.; Werner, H.; Beitner-Johnson, D.; Roberts, C.T., Jr. Molecular and cellular aspects of the insulin-like growth factor I receptor. *Endocr. Rev.* **1995**, *16*, 143–163. [CrossRef] [PubMed]
46. Jung, H.J.; Suh, Y. Regulation of IGF-1 signaling by microRNAs. *Front. Genet.* **2014**, *5*, 472. [CrossRef] [PubMed]
47. Tran, T.T.; Gupta, N.; Goh, T.; Naigamwalla, D.; Chia, M.C.; Koohestani, N.; Mehrotra, S.; McKeown-Eyssen, G.; Giacca, A.; Bruce, W.R. Direct measure of insulin sensitivity with the hyperinsulinemic-euglycemic clamp and surrogate measures of insulin sensitivity with the oral glucose tolerance test: Correlations with aberrant crypt foci promotion in rats. *Cancer Epidemiol. Biomarkers Prev.* **2003**, *12*, 47–56.
48. Yakar, S.; Nunez, N.P.; Pennisi, P.; Brodt, P.; Sun, H.; Fallavollita, L.; Zhao, H.; Scavo, L.; Novosyadlyy, R.; Kurshan, N.; et al. Increased tumor growth in mice with diet-induced obesity: Impact of ovarian hormones. *Endocrinology* **2006**, *147*, 5826–5834. [CrossRef]
49. Gunter, M.J.; Hoover, D.R.; Yu, H.; Wassertheil-Smoller, S.; Manson, J.E.; Li, J.; Harris, T.G.; Rohan, T.E.; Xue, X.; Ho, G.Y.; et al. A prospective evaluation of insulin and insulin-like growth factor-I as risk factors for endometrial cancer. *Cancer Epidemiol. Biomarkers Prev.* **2008**, *17*, 921–929. [CrossRef]
50. Gunter, M.J.; Hoover, D.R.; Yu, H.; Wassertheil-Smoller, S.; Rohan, T.E.; Manson, J.E.; Howard, B.V.; Wylie-Rosett, J.; Anderson, G.L.; Ho, G.Y.; et al. Insulin, insulin-like growth factor-I, endogenous estradiol, and risk of colorectal cancer in postmenopausal women. *Cancer Res.* **2008**, *68*, 329–337. [CrossRef]
51. Baxter, R.C.; Bryson, J.M.; Turtle, J.R. Somatogenic receptors of rat liver: Regulation by insulin. *Endocrinology* **1980**, *107*, 1176–1181. [CrossRef] [PubMed]
52. Gallagher, E.J.; LeRoith, D. The proliferating role of insulin and insulin-like growth factors in cancer. *Trends Endocrinol. Metab.* **2010**, *21*, 610–618. [CrossRef] [PubMed]
53. MacDonald, B.T.; Tamai, K.; He, X. Wnt/beta-catenin signaling: Components, mechanisms, and diseases. *Dev. Cell* **2009**, *17*, 9–26. [CrossRef] [PubMed]
54. Palsgaard, J.; Emanuelli, B.; Winnay, J.N.; Sumara, G.; Karsenty, G.; Kahn, C.R. Cross-talk between insulin and Wnt signaling in preadipocytes: Role of Wnt co-receptor low density lipoprotein receptor-related protein-5 (LRP5). *J. Biol. Chem.* **2012**, *287*, 12016–12026. [CrossRef] [PubMed]
55. Jin, T. Why diabetes patients are more prone to the development of colon cancer? *Med. Hypotheses* **2008**, *71*, 241–244. [CrossRef] [PubMed]
56. Ellis, D.I.; Dunn, W.B.; Griffin, J.L.; Allwood, J.W.; Goodacre, R. Metabolic fingerprinting as a diagnostic tool. *Pharmacogenomics* **2007**, *8*, 1243–1266. [CrossRef] [PubMed]
57. Tringe, S.G.; Hugenholtz, P. A renaissance for the pioneering 16S rRNA gene. *Curr. Opin. Microbiol.* **2008**, *11*, 442–446. [CrossRef]
58. Atkinson, M.A.; Eisenbarth, G.S.; Michels, A.W. Type 1 diabetes. *Lancet* **2014**, *383*, 69–82. [CrossRef]
59. DeFilippis, E.M.; Givertz, M.M. Treating Diabetes in Patients with Heart Failure: Moving from Risk to Benefit. *Curr. Heart Fail Rep.* **2016**, *13*, 111–118. [CrossRef] [PubMed]
60. Aw, W.; Fukuda, S. Understanding the role of the gut ecosystem in diabetes mellitus. *J. Diabetes Investig.* **2018**, *9*, 5–12. [CrossRef] [PubMed]

61. Vrieze, A.; Out, C.; Fuentes, S.; Jonker, L.; Reuling, I.; Kootte, R.S.; van Nood, E.; Holleman, F.; Knaapen, M.; Romijn, J.A.; et al. Impact of oral vancomycin on gut microbiota, bile acid metabolism, and insulin sensitivity. *J. Hepatol.* **2014**, *60*, 824–831. [CrossRef] [PubMed]
62. Sato, J.; Kanazawa, A.; Ikeda, F.; Yoshihara, T.; Goto, H.; Abe, H.; Komiya, K.; Kawaguchi, M.; Shimizu, T.; Ogihara, T.; et al. Gut dysbiosis and detection of "live gut bacteria" in blood of Japanese patients with type 2 diabetes. *Diabetes Care* **2014**, *37*, 2343–2350. [CrossRef] [PubMed]
63. Sola, D.; Rossi, L.; Schianca, G.P.; Maffioli, P.; Bigliocca, M.; Mella, R.; Corliano, F.; Fra, G.P.; Bartoli, E.; Derosa, G. Sulfonylureas and their use in clinical practice. *Arch. Med. Sci.* **2015**, *11*, 840–848. [CrossRef] [PubMed]
64. Bodmer, M.; Becker, C.; Meier, C.; Jick, S.S.; Meier, C.R. Use of metformin is not associated with a decreased risk of colorectal cancer: A case-control analysis. *Cancer Epidemiol. Biomark. Prev.* **2012**, *21*, 280–286. [CrossRef] [PubMed]
65. Soranna, D.; Scotti, L.; Zambon, A.; Bosetti, C.; Grassi, G.; Catapano, A.; La Vecchia, C.; Mancia, G.; Corrao, G. Cancer risk associated with use of metformin and sulfonylurea in type 2 diabetes: A meta-analysis. *Oncologist* **2012**, *17*, 813–822. [CrossRef] [PubMed]
66. Qiu, H.; Rhoads, G.G.; Berlin, J.A.; Marcella, S.W.; Demissie, K. Initial metformin or sulphonylurea exposure and cancer occurrence among patients with type 2 diabetes mellitus. *Diabetes Obes. Metab.* **2013**, *15*, 349–357. [CrossRef]
67. Chen, Y.C.; Kok, V.C.; Chien, C.H.; Horng, J.T.; Tsai, J.J. Cancer risk in patients aged 30 years and above with type 2 diabetes receiving antidiabetic monotherapy: A cohort study using metformin as the comparator. *Ther. Clin. Risk Manag.* **2015**, *11*, 1315–1323. [CrossRef]
68. Mc Menamin, U.C.; Murray, L.J.; Hughes, C.M.; Cardwell, C.R. Metformin use and survival after colorectal cancer: A population-based cohort study. *Int. J. Cancer* **2016**, *138*, 369–379. [CrossRef]
69. Baglia, M.L.; Cui, Y.; Zheng, T.; Yang, G.; Li, H.; You, M.; Xu, L.; Murff, H.; Gao, Y.T.; Zheng, W.; et al. Diabetes Medication Use in Association with Survival among Patients of Breast, Colorectal, Lung, or Gastric Cancer. *Cancer Res. Treat.* **2018**. [CrossRef]
70. Currie, C.J.; Poole, C.D.; Gale, E.A. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. *Diabetologia* **2009**, *52*, 1766–1777. [CrossRef]
71. Chang, C.H.; Lin, J.W.; Wu, L.C.; Lai, M.S.; Chuang, L.M. Oral insulin secretagogues, insulin, and cancer risk in type 2 diabetes mellitus. *J. Clin. Endocrinol. Metab.* **2012**, *97*, E1170–E1175. [CrossRef] [PubMed]
72. Singh, S.; Singh, H.; Singh, P.P.; Murad, M.H.; Limburg, P.J. Antidiabetic medications and the risk of colorectal cancer in patients with diabetes mellitus: A systematic review and meta-analysis. *Cancer Epidemiol. Biomark. Prev.* **2013**, *22*, 2258–2268. [CrossRef] [PubMed]
73. Chen, M.; Hu, C.; Jia, W. Pharmacogenomics of glinides. *Pharmacogenomics* **2015**, *16*, 45–60. [CrossRef] [PubMed]
74. Simo, R.; Plana-Ripoll, O.; Puente, D.; Morros, R.; Mundet, X.; Vilca, L.M.; Hernandez, C.; Fuentes, I.; Procupet, A.; Tabernero, J.M.; et al. Impact of glucose-lowering agents on the risk of cancer in type 2 diabetic patients. The Barcelona case-control study. *PLoS ONE* **2013**, *8*, e79968. [CrossRef]
75. El Sharkawi, F.Z.; El Shemy, H.A.; Khaled, H.M. Possible anticancer activity of rosuvastatine, doxazosin, repaglinide and oxcarbazepin. *Asian Pac. J. Cancer Prev.* **2014**, *15*, 199–203. [CrossRef] [PubMed]
76. Omar, B.; Ahren, B. Pleiotropic mechanisms for the glucose-lowering action of DPP-4 inhibitors. *Diabetes* **2014**, *63*, 2196–2202. [CrossRef] [PubMed]
77. Abrahami, D.; Yin, H.; Yu, O.H.Y.; Pollak, M.N.; Azoulay, L. Incretin-based Drugs and the Incidence of Colorectal Cancer in Patients with Type 2 Diabetes. *Epidemiology* **2018**, *29*, 246–253. [CrossRef] [PubMed]
78. Karp, I.; Sivaswamy, A.; Booth, C. Does the use of incretin-based medications increase the risk of cancer in patients with type-2 diabetes mellitus? *Pharmacoepidemiol. Drug Saf.* **2019**, *28*, 489–499. [CrossRef]
79. Amritha, C.A.; Kumaravelu, P.; Chellathai, D.D. Evaluation of Anti Cancer Effects of DPP-4 Inhibitors in Colon Cancer- An Invitro Study. *J. Clin. Diagn. Res.* **2015**, *9*, FC14–FC16. [CrossRef]
80. Yorifuji, N.; Inoue, T.; Iguchi, M.; Fujiwara, K.; Kakimoto, K.; Nouda, S.; Okada, T.; Kawakami, K.; Abe, Y.; Takeuchi, T.; et al. The dipeptidyl peptidase-4 inhibitor sitagliptin suppresses mouse colon tumorigenesis in type 2 diabetic mice. *Oncol. Rep.* **2016**, *35*, 676–682. [CrossRef]

81. Fujiwara, K.; Inoue, T.; Henmi, Y.; Hirata, Y.; Naka, Y.; Hara, A.; Kakimoto, K.; Nouda, S.; Okada, T.; Kawakami, K.; et al. Sitagliptin, a dipeptidyl peptidase-4 inhibitor, suppresses CXCL5 and SDF-1 and does not accelerate intestinal neoplasia formation in Apc(Min/+) mice fed a high-fat diet. *Oncol. Lett.* **2017**, *14*, 4355–4360. [CrossRef] [PubMed]
82. Natali, A.; Ferrannini, E. Effects of metformin and thiazolidinediones on suppression of hepatic glucose production and stimulation of glucose uptake in type 2 diabetes: A systematic review. *Diabetologia* **2006**, *49*, 434–441. [CrossRef] [PubMed]
83. Miller, R.A.; Chu, Q.; Xie, J.; Foretz, M.; Viollet, B.; Birnbaum, M.J. Biguanides suppress hepatic glucagon signalling by decreasing production of cyclic AMP. *Nature* **2013**, *494*, 256–260. [CrossRef] [PubMed]
84. Fullerton, M.D.; Galic, S.; Marcinko, K.; Sikkema, S.; Pulinilkunnil, T.; Chen, Z.P.; O'Neill, H.M.; Ford, R.J.; Palanivel, R.; O'Brien, M.; et al. Single phosphorylation sites in Acc1 and Acc2 regulate lipid homeostasis and the insulin-sensitizing effects of metformin. *Nat. Med.* **2013**, *19*, 1649–1654. [CrossRef] [PubMed]
85. Maida, A.; Lamont, B.J.; Cao, X.; Drucker, D.J. Metformin regulates the incretin receptor axis via a pathway dependent on peroxisome proliferator-activated receptor-alpha in mice. *Diabetologia* **2011**, *54*, 339–349. [CrossRef] [PubMed]
86. Mulherin, A.J.; Oh, A.H.; Kim, H.; Grieco, A.; Lauffer, L.M.; Brubaker, P.L. Mechanisms underlying metformin-induced secretion of glucagon-like peptide-1 from the intestinal L cell. *Endocrinology* **2011**, *152*, 4610–4619. [CrossRef] [PubMed]
87. Lee, M.S.; Hsu, C.C.; Wahlqvist, M.L.; Tsai, H.N.; Chang, Y.H.; Huang, Y.C. Type 2 diabetes increases and metformin reduces total, colorectal, liver and pancreatic cancer incidences in Taiwanese: A representative population prospective cohort study of 800,000 individuals. *BMC Cancer* **2011**, *11*, 20. [CrossRef] [PubMed]
88. Zhang, Z.J.; Zheng, Z.J.; Kan, H.; Song, Y.; Cui, W.; Zhao, G.; Kip, K.E. Reduced risk of colorectal cancer with metformin therapy in patients with type 2 diabetes: A meta-analysis. *Diabetes Care* **2011**, *34*, 2323–2328. [CrossRef]
89. Lee, J.H.; Jeon, S.M.; Hong, S.P.; Cheon, J.H.; Kim, T.I.; Kim, W.H. Metformin use is associated with a decreased incidence of colorectal adenomas in diabetic patients with previous colorectal cancer. *Dig. Liver Dis.* **2012**, *44*, 1042–1047. [CrossRef] [PubMed]
90. Noto, H.; Goto, A.; Tsujimoto, T.; Noda, M. Cancer risk in diabetic patients treated with metformin: A systematic review and meta-analysis. *PLoS ONE* **2012**, *7*, e33411. [CrossRef]
91. Tseng, C.H. Diabetes, metformin use, and colon cancer: A population-based cohort study in Taiwan. *Eur. J. Endocrinol.* **2012**, *167*, 409–416. [CrossRef] [PubMed]
92. Franciosi, M.; Lucisano, G.; Lapice, E.; Strippoli, G.F.; Pellegrini, F.; Nicolucci, A. Metformin therapy and risk of cancer in patients with type 2 diabetes: Systematic review. *PLoS ONE* **2013**, *8*, e71583. [CrossRef] [PubMed]
93. Kanadiya, M.K.; Gohel, T.D.; Sanaka, M.R.; Thota, P.N.; Shubrook, J.H., Jr. Relationship between type-2 diabetes and use of metformin with risk of colorectal adenoma in an American population receiving colonoscopy. *J. Diabetes Complicat.* **2013**, *27*, 463–466. [CrossRef] [PubMed]
94. Zhang, P.; Li, H.; Tan, X.; Chen, L.; Wang, S. Association of metformin use with cancer incidence and mortality: A meta-analysis. *Cancer Epidemiol.* **2013**, *37*, 207–218. [CrossRef] [PubMed]
95. Cho, Y.H.; Ko, B.M.; Kim, S.H.; Myung, Y.S.; Choi, J.H.; Han, J.P.; Hong, S.J.; Jeon, S.R.; Kim, H.G.; Kim, J.O.; et al. Does metformin affect the incidence of colonic polyps and adenomas in patients with type 2 diabetes mellitus? *Intest. Res.* **2014**, *12*, 139–145. [CrossRef] [PubMed]
96. Kim, Y.H.; Noh, R.; Cho, S.Y.; Park, S.J.; Jeon, S.M.; Shin, H.D.; Kim, S.B.; Shin, J.E. Inhibitory effect of metformin therapy on the incidence of colorectal advanced adenomas in patients with diabetes. *Intest. Res.* **2015**, *13*, 145–152. [CrossRef] [PubMed]
97. Sehdev, A.; Shih, Y.C.; Vekhter, B.; Bissonnette, M.B.; Olopade, O.I.; Polite, B.N. Metformin for primary colorectal cancer prevention in patients with diabetes: A case-control study in a US population. *Cancer* **2015**, *121*, 1071–1078. [CrossRef]
98. He, X.K.; Su, T.T.; Si, J.M.; Sun, L.M. Metformin Is Associated With Slightly Reduced Risk of Colorectal Cancer and Moderate Survival Benefits in Diabetes Mellitus: A Meta-Analysis. *Medicine (Baltimore)* **2016**, *95*, e2749. [CrossRef]
99. Nie, Z.; Zhu, H.; Gu, M. Reduced colorectal cancer incidence in type 2 diabetic patients treated with metformin: A meta-analysis. *Pharm. Biol.* **2016**, *54*, 2636–2642. [CrossRef]

100. Rokkas, T.; Portincasa, P. Colon neoplasia in patients with type 2 diabetes on metformin: A meta-analysis. *Eur. J. Intern. Med.* **2016**, *33*, 60–66. [CrossRef]
101. Rosato, V.; Tavani, A.; Gracia-Lavedan, E.; Guino, E.; Castano-Vinyals, G.; Villanueva, C.M.; Kogevinas, M.; Polesel, J.; Serraino, D.; Pisa, F.E.; et al. Type 2 Diabetes, Antidiabetic Medications, and Colorectal Cancer Risk: Two Case-Control Studies from Italy and Spain. *Front. Oncol.* **2016**, *6*, 210. [CrossRef]
102. Hou, Y.C.; Hu, Q.; Huang, J.; Fang, J.Y.; Xiong, H. Metformin therapy and the risk of colorectal adenoma in patients with type 2 diabetes: A meta-analysis. *Oncotarget* **2017**, *8*, 8843–8853. [CrossRef]
103. Su, T.; Liao, B.; Dong, Y.; Peng, Z.; Zhou, Q.; Li, B.; Peng, S.; Zhang, N. [Effect of metformin on colorectal carcinoma in type 2 diabetes mellitus patients: A Markov model analysis]. *Zhonghua Wei Chang Wai Ke Za Zhi* **2017**, *20*, 689–693. [CrossRef]
104. Tian, S.; Lei, H.B.; Liu, Y.L.; Chen, Y.; Dong, W.G. The association between metformin use and colorectal cancer survival among patients with diabetes mellitus: An updated meta-analysis. *Chronic Dis. Transl. Med.* **2017**, *3*, 169–175. [CrossRef]
105. Tseng, C.H. Metformin is associated with a lower risk of colorectal cancer in Taiwanese patients with type 2 diabetes: A retrospective cohort analysis. *Diabetes Metab.* **2017**, *43*, 438–445. [CrossRef]
106. Zhu, R.C.; Rattanakorn, K.; Pham, S.; Mallam, D.; McIntyre, T.; Salifu, M.O.; Youssef, I.; McFarlane, S.I.; Vignesh, S. Survival benefits in colorectal adenocarcinoma with the use of metformin among a black diabetic inner city population. *Colorectal Cancer* **2017**, *6*, 33–41. [CrossRef]
107. Al Omari, A.; Abdelkhaleq, H.; Al-Hussaini, M.; Turfa, R.; Awad, N.; Hassan, M.M.; Alfaqih, M.A.; Garrett, C.R. Validation of the Survival Benefits of Metformin in Middle Eastern Patients With Type II Diabetes Mellitus and Colorectal Cancer. *J. Glob. Oncol.* **2018**, *4*, 1–10. [CrossRef]
108. Bradley, M.C.; Ferrara, A.; Achacoso, N.; Ehrlich, S.F.; Quesenberry, C.P., Jr.; Habel, L.A. A Cohort Study of Metformin and Colorectal Cancer Risk among Patients with Diabetes Mellitus. *Cancer Epidemiol. Biomark. Prev.* **2018**, *27*, 525–530. [CrossRef]
109. Chang, Y.T.; Tsai, H.L.; Kung, Y.T.; Yeh, Y.S.; Huang, C.W.; Ma, C.J.; Chiu, H.C.; Wang, J.Y. Dose-Dependent Relationship Between Metformin and Colorectal Cancer Occurrence Among Patients with Type 2 Diabetes-A Nationwide Cohort Study. *Transl. Oncol.* **2018**, *11*, 535–541. [CrossRef]
110. Smiechowski, B.; Azoulay, L.; Yin, H.; Pollak, M.N.; Suissa, S. The use of metformin and colorectal cancer incidence in patients with type II diabetes mellitus. *Cancer Epidemiol. Biomark. Prev.* **2013**, *22*, 1877–1883. [CrossRef]
111. Tsilidis, K.K.; Capothanassi, D.; Allen, N.E.; Rizos, E.C.; Lopez, D.S.; van Veldhoven, K.; Sacerdote, C.; Ashby, D.; Vineis, P.; Tzoulaki, I.; et al. Metformin does not affect cancer risk: A cohort study in the U.K. Clinical Practice Research Datalink analyzed like an intention-to-treat trial. *Diabetes Care* **2014**, *37*, 2522–2532. [CrossRef]
112. Kowall, B.; Stang, A.; Rathmann, W.; Kostev, K. No reduced risk of overall, colorectal, lung, breast, and prostate cancer with metformin therapy in diabetic patients: Database analyses from Germany and the UK. *Pharmacoepidemiol. Drug Saf.* **2015**, *24*, 865–874. [CrossRef]
113. Mansourian, M.; Karimi, R.; Vaseghi, G. Different effects of metformin and insulin on primary and secondary chemoprevention of colorectal adenoma in diabetes type 2: Traditional and Bayesian meta-analysis. *EXCLI J.* **2018**, *17*, 45–56. [CrossRef]
114. Vicentini, M.; Ballotari, P.; Giorgi Rossi, P.; Venturelli, F.; Sacchettini, C.; Greci, M.; Mangone, L.; Pezzarossi, A.; Manicardi, V. Effect of different glucose-lowering therapies on cancer incidence in type 2 diabetes: An observational population-based study. *Diabetes Res. Clin. Pract.* **2018**, *143*, 398–408. [CrossRef]
115. Farmer, R.E.; Ford, D.; Mathur, R.; Chaturvedi, N.; Kaplan, R.; Smeeth, L.; Bhaskaran, K. Metformin use and risk of cancer in patients with type 2 diabetes: A cohort study of primary care records using inverse probability weighting of marginal structural models. *Int. J. Epidemiol.* **2019**. [CrossRef]
116. Fransgaard, T.; Thygesen, L.C.; Gogenur, I. Metformin Increases Overall Survival in Patients with Diabetes Undergoing Surgery for Colorectal Cancer. *Ann. Surg. Oncol.* **2016**, *23*, 1569–1575. [CrossRef]
117. Zannella, V.E.; Dal Pra, A.; Muaddi, H.; McKee, T.D.; Stapleton, S.; Sykes, J.; Glicksman, R.; Chaib, S.; Zamiara, P.; Milosevic, M.; et al. Reprogramming metabolism with metformin improves tumor oxygenation and radiotherapy response. *Clin. Cancer Res* **2013**, *19*, 6741–6750. [CrossRef]

118. Jeong, Y.K.; Kim, M.S.; Lee, J.Y.; Kim, E.H.; Ha, H. Metformin Radiosensitizes p53-Deficient Colorectal Cancer Cells through Induction of G2/M Arrest and Inhibition of DNA Repair Proteins. *PLoS ONE* **2015**, *10*, e0143596. [CrossRef]
119. Miranda, V.C.; Braghiroli, M.I.; Faria, L.D.; Bariani, G.; Alex, A.; Bezerra Neto, J.E.; Capareli, F.C.; Sabbaga, J.; Lobo Dos Santos, J.F.; Hoff, P.M.; et al. Phase 2 Trial of Metformin Combined With 5-Fluorouracil in Patients With Refractory Metastatic Colorectal Cancer. *Clin. Colorectal Cancer* **2016**, *15*, 321–328.e1. [CrossRef]
120. Mussin, N.; Oh, S.C.; Lee, K.W.; Park, M.Y.; Seo, S.; Yi, N.J.; Kim, H.; Yoon, K.C.; Ahn, S.W.; Kim, H.S.; et al. Sirolimus and Metformin Synergistically Inhibits Colon Cancer In Vitro and In Vivo. *J. Korean Med. Sci.* **2017**, *32*, 1385–1395. [CrossRef]
121. Higurashi, T.; Hosono, K.; Takahashi, H.; Komiya, Y.; Umezawa, S.; Sakai, E.; Uchiyama, T.; Taniguchi, L.; Hata, Y.; Uchiyama, S.; et al. Metformin for chemoprevention of metachronous colorectal adenoma or polyps in post-polypectomy patients without diabetes: A multicentre double-blind, placebo-controlled, randomised phase 3 trial. *Lancet Oncol.* **2016**, *17*, 475–483. [CrossRef]
122. Thent, Z.C.; Zaidun, N.H.; Azmi, M.F.; Senin, M.I.; Haslan, H.; Salehuddin, R. Is Metformin a Therapeutic Paradigm for Colorectal Cancer: Insight into the Molecular Pathway? *Curr. Drug Targets* **2017**, *18*, 734–750. [CrossRef]
123. Barros, F.W.; Bezerra, D.P.; Ferreira, P.M.; Cavalcanti, B.C.; Silva, T.G.; Pitta, M.G.; de Lima Mdo, C.; Galdino, S.L.; Pitta Ida, R.; Costa-Lotufo, L.V.; et al. Inhibition of DNA topoisomerase I activity and induction of apoptosis by thiazacridine derivatives. *Toxicol. Appl. Pharmacol.* **2013**, *268*, 37–46. [CrossRef]
124. Ban, J.O.; Kwak, D.H.; Oh, J.H.; Park, E.J.; Cho, M.C.; Song, H.S.; Song, M.J.; Han, S.B.; Moon, D.C.; Kang, K.W.; et al. Suppression of NF-kappaB and GSK-3beta is involved in colon cancer cell growth inhibition by the PPAR agonist troglitazone. *Chem. Biol. Interact.* **2010**, *188*, 75–85. [CrossRef]
125. Bischoff, H. The mechanism of alpha-glucosidase inhibition in the management of diabetes. *Clin. Investig. Med.* **1995**, *18*, 303–311.
126. Tseng, Y.H.; Tsan, Y.T.; Chan, W.C.; Sheu, W.H.; Chen, P.C. Use of an alpha-Glucosidase Inhibitor and the Risk of Colorectal Cancer in Patients With Diabetes: A Nationwide, Population-Based Cohort Study. *Diabetes Care* **2015**, *38*, 2068–2074. [CrossRef]
127. Ron, Y.; Wainstein, J.; Leibovitz, A.; Monastirsky, N.; Habot, B.; Avni, Y.; Segal, R. The effect of acarbose on the colonic transit time of elderly long-term care patients with type 2 diabetes mellitus. *J. Gerontol. A Biol. Sci. Med. Sci.* **2002**, *57*, M111–M114. [CrossRef]
128. Citronberg, J.; Kantor, E.D.; Potter, J.D.; White, E. A prospective study of the effect of bowel movement frequency, constipation, and laxative use on colorectal cancer risk. *Am. J. Gastroenterol.* **2014**, *109*, 1640–1649. [CrossRef]
129. Weaver, G.A.; Tangel, C.T.; Krause, J.A.; Parfitt, M.M.; Stragand, J.J.; Jenkins, P.L.; Erb, T.A.; Davidson, R.H.; Alpern, H.D.; Guiney, W.B., Jr.; et al. Biomarkers of human colonic cell growth are influenced differently by a history of colonic neoplasia and the consumption of acarbose. *J. Nutr.* **2000**, *130*, 2718–2725. [CrossRef]
130. Pili, R.; Chang, J.; Partis, R.A.; Mueller, R.A.; Chrest, F.J.; Passaniti, A. The alpha-glucosidase I inhibitor castanospermine alters endothelial cell glycosylation, prevents angiogenesis, and inhibits tumor growth. *Cancer Res.* **1995**, *55*, 2920–2926.
131. Horibe, Y.; Adachi, S.; Ohno, T.; Goto, N.; Okuno, M.; Iwama, M.; Yamauchi, O.; Kojima, T.; Saito, K.; Ibuka, T.; et al. Alpha-glucosidase inhibitor use is associated with decreased colorectal neoplasia risk in patients with type 2 diabetes mellitus receiving colonoscopy: A retrospective study. *Oncotarget* **2017**, *8*, 97862–97870. [CrossRef]
132. Imamura, M.; Nakanishi, K.; Suzuki, T.; Ikegai, K.; Shiraki, R.; Ogiyama, T.; Murakami, T.; Kurosaki, E.; Noda, A.; Kobayashi, Y.; et al. Discovery of Ipragliflozin (ASP1941): A novel C-glucoside with benzothiophene structure as a potent and selective sodium glucose co-transporter 2 (SGLT2) inhibitor for the treatment of type 2 diabetes mellitus. *Bioorg. Med. Chem.* **2012**, *20*, 3263–3279. [CrossRef]
133. Tahrani, A.A.; Barnett, A.H.; Bailey, C.J. SGLT inhibitors in management of diabetes. *Lancet Diabetes Endocrinol.* **2013**, *1*, 140–151. [CrossRef]
134. Wright, E.M.; Loo, D.D.; Hirayama, B.A. Biology of human sodium glucose transporters. *Physiol. Rev.* **2011**, *91*, 733–794. [CrossRef]
135. Hediger, M.A.; Rhoads, D.B. Molecular physiology of sodium-glucose cotransporters. *Physiol. Rev.* **1994**, *74*, 993–1026. [CrossRef]

136. Clar, C.; Gill, J.A.; Court, R.; Waugh, N. Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes. *BMJ Open* **2012**, *2*. [CrossRef]
137. Thomson, S.C.; Rieg, T.; Miracle, C.; Mansoury, H.; Whaley, J.; Vallon, V.; Singh, P. Acute and chronic effects of SGLT2 blockade on glomerular and tubular function in the early diabetic rat. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2012**, *302*, R75–R83. [CrossRef]
138. DeFronzo, R.A.; Norton, L.; Abdul-Ghani, M. Renal, metabolic and cardiovascular considerations of SGLT2 inhibition. *Nat. Rev. Nephrol.* **2017**, *13*, 11–26. [CrossRef]
139. Briasoulis, A.; Al Dhaybi, O.; Bakris, G.L. SGLT2 Inhibitors and Mechanisms of Hypertension. *Curr. Cardiol. Rep.* **2018**, *20*, 1. [CrossRef]