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Canagliflozin: A Review with Emphasis on Pharmacological Effects

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Abstract **Review Article**

Although canagliflozin has been successfully used for the treatment of type 2 diabetes since its introduction in 2013, it has been continuing in research for the treatment of various diseases. The most common form of diabetes is type 2 diabetes and it was found that 95% of the people were suffering from this disease. Therefore, this review covers the pharmacokinetics and pharmacological effects of canagliflozin. It is hoped that this review will open the new gateways of research to achieve new rational approaches for more potent, less toxic and more therapeutically effective agents using canagliflozin.

Keywords: Canagliflozin, Diabetes Mellitus, Heart Disease.

INTRODUCTION

Canagliflozin, is a new selective oral once-daily Sodium-glucose co-transporter 2 inhibitor, was developed by Mitsubishi Tanabe Pharma (formerly Tanabe Seiyaku) and Johnson and Johnson for the treatment of type 2 diabetes. Canagliflozin is considered as a potent drug to be used for the treatment of type 2 diabetes patients. It has been approved by USFDA in March 2013 [1]. Canagliflozin is suggested as a supplement to a diet that helps to improve glycaemic control in patients with type 2 diabetes. The recommended initial dosage is 100 mg once daily taken before the first meal and may increase the dose to 300 mg Day if 100 mg/day is tolerated in patients who have GFR ≥60 ml/min/1.73 m and require additional glycemic control [2].

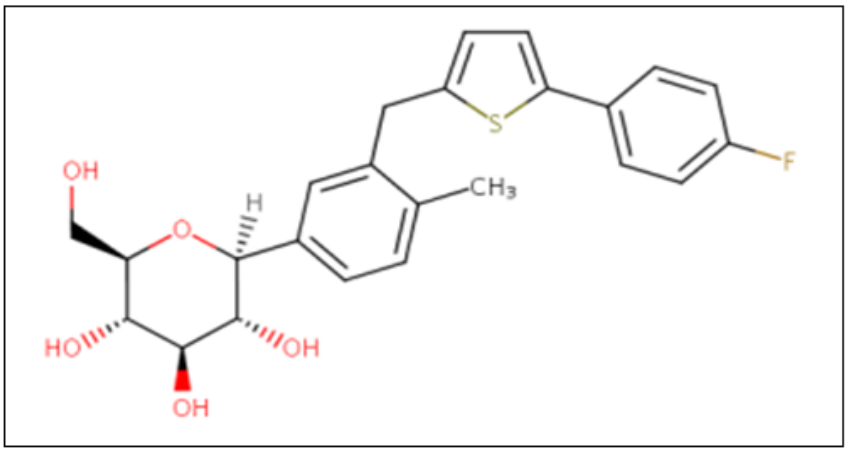

Fig-1.1: Structure of Canagliflozin

Pharmacology of canagliflozin

The all plasma glucose (PG) that is filtered at the glomerulus of the kidney is reabsorbed in the proximal tubule, with less than 1% being excreted into the urine [3**]** Reabsorption of the filtered glucose is mediated primarily by the glucose transporter protein SGLT2, SGLT2 is responsible for reabsorbing 90% of the filtered glucose in the kidney and can reabsorb nearly all glucose filtered by the glomerulus up to concentration of approximately 180 mg/dL, the renal threshold for glucose (RTG) **[**4, 6**]**. In the T2DM threshold can be increased up to 240 mg/dL [**7]**. At PG

levels exceeding the RTG, SGLT2 becomes saturated and urine glucose concentrations increase proportionately to PG levels. By inhibiting SGLT2, renal glucose reabsorption is reduced, leading to increased urine glucose excretion and a succeeding reduction in PG. The SGLT2 inhibition reduces PG in an insulin-independent manner; potentially reduce the risk for hypoglycemia [8].

PHARMACOKINETICS

Canagliflozin reaches peak plasma concentrations within 1 to 2 hours by oral administration, and steady-state levels are reached in 4 to 5 days; it has a bioavailability of 65% and is highly protein bound (99%), mainly to albumin. The single oral doses, the terminal half-life was 10.6 and 13.1 hours for canagliflozin 100 mg and 300 mg, respectively. The continued dosing, canagliflozin reduces the RTG throughout the 24-hour dosing interval, allowing for once-daily dosing. Metabolism is mainly via O-glucuronidation via uridine diphosphate glucuronosyltransferase 1A9 (UGT1A9) and uridine diphosphate glucuronosyltransferase B4 (UGT2B4) to inactive metabolites, which are eliminated by renal. Cytochrome P450 (CYP) metabolism of canagliflozin is minimal, reducing the potential for drug-drug interactions. Approximately 33% of canagliflozin metabolites are really eliminated and approximately 42% is excreted in the feces [2].

Complications with diabetes

Diabetes mellitus is a group of metabolic diseases distinguishes by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The diabetes is associated with failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels [9**]**. The nephropathy leading to renal failure; retinopathy with the potential loss of vision; peripheral neuropathy with risk of foot ulcers, amputations, and autonomic neuropathy causing gastrointestinal, genitourinary and cardiovascular symptoms complications of diabetes.Patients with diabetes have an increased prevalence of atherosclerotic cardiovascular, peripheral arterial and cerebrovascular disease. Hypertension and abnormalities of lipoprotein metabolism are often developed in people with diabetes [10]. High blood sugar levels damage the blood vessels and nerves. This causes problems in association with body organs like kidneys, nerves, feet, eyes, heart, bones, skin problems, digestive problems, sexual dysfunction, and problems with teeth and gums [11].

Effect of canagliflozin on diabetes mellitus

Diabetes mellitus (DM) is a disease distinguished by an obstruction in insulin function and insulin secretion that results in glucose intolerance and chronic hyperglycemia [42]. Canagliflozin is a sodium glucose cotransporter-2 (SGLT2) inhibitor. SGLT2 is exhibit in the proximal renal tubules and is responsible for most of the filtered glucose reabsorption from the tubular lumen. Canagliflozin reduces the reabsorption of filtered glucose and lowers the renal threshold for glucose, thereby increasing urinary glucose excretion by inhibiting SGLT2. Canagliflozin exerts its therapeutic effects in the proximal tubules of the kidneys. It is a highly selective inhibitor of SGLT2, its binding affinity to SGLT2 is 250 times greater than its binding affinity to SGLT1. The inhibition of SGLT2 in the kidney increases urinary glucose excretion, thereby decreasing blood glucose levels [22].

Effect of canagliflozin on heart disease

According to data from the World Health Organization (WHO), in the worldwide over 3 million people die from diabetes and its related complications every year, mainly due to cardiovascular disease (CVD) [12]. The toxicity of high blood glucose to the endothelium and other cells of the vessels seem to play an essential role in the development of atherosclerosis and CVD. Atherosclerosis starts a systemic inflammatory process that incriminates both cells of the immune system and those of the vessel wall. The basic pathologic lesion is atheromatous plaque. The atherogenic process develops in different stages, starting from the endothelium activation/dysfunction and resulting in plaque vulnerability and rupture [21]. SGLT2 inhibition reduces the reabsorption of glucose and therefore enhances urinary glucose excretion, consequently decreasing both fasting and postprandial hyperglycemia and preventing glucotoxicity, and therefore hyperglycemia-induced damage [40]. The scientist reported recently that canagliflozin, can activate AMPK and inhibit IL-1β-stimulated secretion of IL-6 and monocyte chemoattractant protein-1 (MCP-1) in cultured human endothelial cells, while AMPK-independent mechanisms were also recognized [13]. canagliflozin is the most potent inhibition-compared to other SGLT-2 inhibitors of production and release of inflammatory factors IL1a, IL-6 and TNF-α [13]. These effects mediated by inhibiting intracellular glycolysis, enhancing autophagy, and promoting p62-mediated IL-1 degradation **[**43**]**. Although clinical studies have proved the antihypertensive effects of canagliflozin, it finds just a borderline reduction of diastolic pressure [15]. However, canagliflozin reduces significantly heart rate. This could be attributed to a potential decrease in insulin levels as a result of the glucose-lowering effects of canagliflozin since it is conventional that insulin increases sympathetic activity [44].

Effect of canagliflozin on liver cancer growth

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide, and the second leading cause of cancer-related mortality [16]. The characteristics of HCC, including a high regularity rate and hypervascularity, have presented no satisfactory improvements in prognosis, regardless of disease etiology. Recent evidence has highlighted the inhibitory effects of antidiabetic agents on HCC [17]. However, the expression of SGLT2 in pancreatic and prostate

cancer tissues and well as the functional activity of this protein as a glucose transporter in cancer cells [18]. SGLT2-is directly suppressing pancreatic cancer growth, possibly by blocking glucose uptake. canagliflozin exclusively inhibits the growth of SGLT2-expressing liver cancers by reducing intracellular glucose uptake. Furthermore, the research found that canagliflozin impaired proangiogenic activity in SGLT2-expressing liver cancers [19]. Canagliflozin also facilitated apoptosis in Huh7 and HepG2 cells by activating caspase 3, a central enzyme in the apoptosis pathway. One of the research revealed decreases in AKT phosphorylation in canagliflozin treated cell lines. AKT is postulated to play a key role in glycolysis regulation, as well as survival, in cancer cells. Constitutively activated AKT may stimulate glucose uptake and aerobic glycolysis in human glioblastoma cells [20].

Effect of canagliflozin on memory impairment

Scopolamine is a non-selective muscarinic receptor antagonist, which blocks cholinergic signaling and pharmacologically interferes with memory performance in a temporary manner [24]. Scopolamine produces memory, cognitive impairments and then induces learning and memory obstruction including long-term and short term memory dysfunction [31]. Animals with scopolamine-induced memory impairment have been widely used to probe drugs attenuating cognitive deficits. The behavioral test showed improvement in scopolamine with canagliflozin, this could be due to improvement in memory through inhibition of AChE activities and monoamines levels in brain areas. The recent study on diabetic rats recorded AChE inhibition and amelioration of cortex monoamines by canagliflozin (10mg/kg) oral treatment [32]. Canagliflozin strongly suggested as a dual inhibitor for AChE and SGLT2 even though there is no similarity between the catalytic site of AChE and the transport channel of SGLT2. They explore molecular interactions between SGLT2 and human brain AChE with canagliflozin. The effect of Canagliflozin as compared to galantamine (GAL) treatments for two weeks on scopolamine hydrobromide (SCO) induced memory dysfunction in experimental rats and canagliflozin suggested as AChE inhibitor [22].

Effect of canagliflozin on inflammation

Inflammation is a complex biological defense response of the body to external stimuli such as pathogens, cell damage, or other stimulants [45]. Intracellular glucose metabolism plays an important role in the activation of immune cells and the outcome of inflammation. The anti-inflammatory mechanisms of canagliflozin might be mediated by enhancing autophagy, inhibiting intracellular glycolysis, and promoting p62-mediated IL-1 degradation [46]. In addition to hypoglycemic effects, the SGLT2 inhibitors might have direct anti-inflammatory effects and Canagliflozin is used for the treatment of inflammatory diseases by inhibiting intracellular glucose metabolism and promoting autophagy in immune cells. Among all SGLT2 inhibitors, Canagliflozin showed significant effects [13]. The new anti-inflammatory effects of Canagliflozin are might be useful to inhibit inflammatory damage independent of its hypoglycemic activities. Inflammation is connected with many chronic diseases including diabetes and atherosclerosis [22]. Intracellular glucose metabolism plays a pivotal role in the activation of immune cells [26]. Canagliflozin significantly impaired PFK2 expression, which is a key enzyme responsible for glycolysis and metabolic reprogramming in inflammatory macrophages. These effects suggested that Canagliflozin is useful for inflammatory diseases [37].

Effect of canagliflozin on renal function

The increased production of reactive oxygen species and reduced availability of antioxidant mechanisms can affect the renal structure and function by apoptosis, modulating cell growth and inflammatory responses [37]. The processes that have been linked to the progression of the kidney disease by early diabetic nephropathy is associated with glomerular hyperfiltration, cytokine release and tissue proliferation [45]. The inhibitors of renin-angiotensin system inhibitors are commonly used to reduce proteinuria and decrease glomerular hyperfiltration and delay the progression of diabetic nephropathy, the renin-angiotensin system blockade does not completely stop kidney disease progression and may patient pass to end-stage of renal disease [35]**.** The canagliflozin renal protective effect may be related to amelioration of hyperglycemia and decreased HbA1c observed in canagliflozin treated rats. Although, glucose-lowering action can cause to its Reno-protective effects, canagliflozin possibly apply other renal protective effects beyond glycemic control. The possible mechanism for slowing the progression of renal disease may implicate reducing oxidative stress, decreasing the release of inflammatory and apoptotic mediators thereby diminished inflammatory and apoptotic processes in the diabetic kidney. Thus, canagliflozin act as a good therapeutic agent useful to prevent or delay the progression of diabetic nephropathy. Canagliflozin inhibits renal glucose reabsorption and increases urinary glucose excretion, thus reducing plasma glucose concentration with hyperglycemia [29].

Effect of canagliflozin on retinopathy

Diabetic retinopathy is a major microvascular complication that distinguishes in many diabetics very debilitating as it may result in impaired or complete vision loss. The human diabetic's subjects are commonly suffering from the microvascular complications in different organ including the eye [27]. The pericytes in the retina have important physiological roles, such as microcirculation control, microvessel protection and other functions [28]. In the early stage of diabetic retinopathy, pericyte swelling and pericyte loss

occur, resulting in microaneurysm formation [30, 31] in the retina. The swollen pericytes lose their contractile ability, which leads to hyperperfusion in the retina. Drug-Related therapy is extremely costly for the patient who suffers from DR and financially impacts the economy. In the current therapeutic approaches, the prevention of microvascular complications is a major treatment goal; however, these therapies appear insufficient. Presently, sodium glucose cotransporter-2 (SGLT2) inhibitors canagliflozin may provide a novel therapy outwith simple glucose lowering [26].

DISCUSSION

Canagliflozin is an SGLT2 inhibitor class of the drug use for Antidiabetic drugs. Canagliflozin inhibition decreases the reabsorption of glucose and therefore increase urinary glucose excretion, therefore decreasing both fasting and postprandial hyperglycemia and preventing glucotoxicity, and hence hyperglycemia-induced damage canagliflozin, activate AMPK and inhibit IL-1β-stimulated secretion of IL-6 and monocyte chemoattractant protein-1 (MCP-1) in cultured human endothelial cells [40]. It directly suppresses pancreatic cancer growth, potentially by blocking glucose uptake. Canagliflozin mostly inhibits the growth of SGLT2-expressing liver cancers by reducing intracellular glucose uptake. Canagliflozin is used for the treatment of inflammatory diseases by inhibiting intracellular glucose metabolism and promoting autophagy in immune cells. canagliflozin act as a promising therapeutic agent useful to prevent or delay the progression of diabetic nephropathy.

CONCLUSION

Canagliflozin has a novel mechanism of action that may offer a future alternative treatment pathway for managing many diseases.

REFERENCES

1. Janssen Pharmaceuticals Inc. U.S. FDA approves canagliflozin (TA-7284) for the treatment of adult patients with type 2 diabetes. 2013.
2. Janssen Pharmaceuticals Inc. InvokanaTM (canagliflozin) tablets, for oral use: the US prescribing information. 2013.
3. Chao EC, Henry RR. SGLT2 Inhibition – a novel strategy for diabetes treatment. Nat Rev Drug Discov. 2010;9(7):551–559.
4. Wright EM. Renal Na+ glucose cotransporters. Am J Physiol Renal Physiol. 2001;280(1): F10–F18.
5. Mackenzie B, Loo DD, Panayotova-Heiermann M, Wright EM. Biophysical characteristics of the pig kidney Na+/glucose cotransporter SGLT2 reveal a common mechanism for SGLT1 and SGLT2. J Biol Chem. 1996;271(51):32678–32683.
6. Kanai Y, Lee WS, You G, Brown D, Hediger MA. The human kidney low-affinity Na+/glucose cotransporter SGLT2. Delineation of the major renal reabsorptive mechanism for D-glucose. J Clin Invest. 1994;93(1): 397–404.
7. Farber SJ, Berger EY, Earle DP. Effect of diabetes and insulin of the maximum capacity of the renal tubules to reabsorb glucose. J Clin Invest. 1951;30(2):125–129.
8. Sha S, Devineni D, Ghosh A, Polidori D, Chien S, Wexler D, Shalayda K, Demarest K, Rothenberg P. Canagliflozin, a novel inhibitor of sodium glucose co- transporter 2, dose dependently reduces calculated renal threshold for glucose excretion and increases urinary glucose excretion in healthy subjects. Diabetes, Obesity and Metabolism. 2011 Jul;13(7):669-72.
9. Triplitt CL, Reasner CA, and Isley WL, Diabetes Mellitus in Pharmacotherapy: A Pathophysiologic Approach, Eds. JT DiPiro, RL Talbert, GC Yee, GR Matzke, BG Wells, and LM Posey, 6th Ed. McGraw Hill Medical Publishing Division, New York. 2005:1333‐67.
10. American Diabetes Association: Clinical practice recommendations. Diabetes Care. 1998;21:S1‐95.
11. Stern MP, Haffner SM. Prospective assessment of metabolic control in diabetes mellitus: The complications question. JAMA. 1998;260:2896-7.
12. Wholey MH, current status in cervical carotid artery stent placement, The Journal of Cardiovascular Surgery. 2003,44(3) 331-339.
13. Mancini SJ, Boyd D, Canagliflozin inhibits interleukin-1 beta stimulated cytokine and chemokine secretion in vascular endothelial cells by AMP-activated protein kinase-dependent and -independent mechanism. 2018 (1): 5276.
14. Volker Vallon Scott C. Thomson, Targeting renal glucose reabsorption to treat hyperglycemia: the pleiotropic effects of SGLT2 inhibition. 2017 (60): 215-225.
15. Terasaki M, Hiromura M, Amelioration of hyperglycemia with a sodium-glucose cotransporter2 inhibitor prevents Macrophage-Driven Atherosclerosis through Macrophage foam cell formation suppression in type 1 and type 2 Diabetic mice.,Hatanodai, Shinagawa-Ku, Tokyo, Japan.2015.
16. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet. 2012;379:1245-55.
17. Chao EC, Henry RR. SGLT2 inhibition--a novel strategy for diabetes treatment. Nat Rev Drug Discov. 2010; 9:551-9.
18. Scafoglio C, Hirayama BA, Kepe V, Liu J, Ghezzi C, Satyamurthy N, Moatamed NA, Huang J, Koepsell H, Barrio JR, Wright EM. Functional expression of sodium-glucose transporters in cancer. ProcNatlAcadSci U S A. 2015; 112: E4111-9.
19. Kaji K, Nishimura N, Seki K, Sato S, Saikawa S, Nakanishi K, Furukawa M, Kawaratani H, Kitade M, Moriya K, Namisaki T. Sodium glucose cotransporter 2 inhibitor canagliflozin attenuates liver cancer cell growth and angiogenic activity by

inhibiting glucose uptake. International journal of cancer. 2018 Apr 15;142(8):1712-22.
20. Elstrom RL, Bauer DE, Buzzai M, Karnauskas R, Harris MH, Plas DR, Zhuang H, Cinalli RM, Alavi A, Rudin CM, Thompson CB. Akt stimulates aerobic glycolysis in cancer cells. Cancer research. 2004 Jun 1;64(11):3892-9.
21. Veldt BJ, Chen W, Heathcote EJ, Wedemeyer H, Reichen J, Hofmann WP, de Knegt RJ, Zeuzem S, Manns MP, Hansen BE, Schalm SW. Increased risk of hepatocellular carcinoma among patients with hepatitis C cirrhosis and diabetes mellitus. Hepatology. 2008 Jun;47(6):1856-62.
22. MD Rizvi S, Shakil S, Biswas D, Shakil S, Shaikh S, Bagga P, A Kamal M. Invokana (Canagliflozin) as a dual inhibitor of acetylcholinesterase and sodium glucose co-transporter 2: advancement in Alzheimer's disease-diabetes type 2 linkage via an Enzoinformatics Study. CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders). 2014 Apr 1;13(3):447-51.
23. Arafa NM, Marie MA, AlAzimi SA. Effect of canagliflozin and metformin on cortical neurotransmitters in a diabetic rat model. Chemico-biological interactions. 2016 Oct 25;258:79-88.
24. Chao EC, Henry RR. SGLT2 inhibition—a novel strategy for diabetes treatment. Nature reviews drug discovery. 2010 Jul;9(7):551.
25. Wilding JP, Norwood P, T'joen C, Bastien A, List JF, Fiedorek FT. A study of dapagliflozin in patients with type 2 diabetes receiving high doses of insulin plus insulin sensitizers: applicability of a novel insulin-independent treatment. Diabetes care. 2009 Sep 1;32(9):1656-62.
26. Lim JC, Perwick RD, Li B, Donaldson PJ. Comparison of the expression and spatial localization of glucose transporters in the rat, bovine and human lens. Experimental eye research. 2017 Aug 1;161:193-204.
27. Fowler MJ. Microvascular and macrovascular complications of diabetes. Clinical diabetes. 2008 Apr 1;26(2):77-82.
28. Kelley C, D'Amore P, Hechtman HB, Shepro D. Microvascular pericyte contractility in vitro: comparison with other cells of the vascular wall. The Journal of cell biology. 1987 Mar 1;104(3):483-90.
29. Bays H. Sodium glucose co-transporter type 2 (SGLT2) inhibitors: targeting the kidney to improve glycemic control in diabetes mellitus. Diabetes Therapy. 2013 Dec 1;4(2):195-220.
30. Kador PF, Akagi Y, Terubayashi H, Wyman M, Kinoshita JH. Prevention of pericyte ghost formation in retinal capillaries of galactose-fed dogs by aldose reductase inhibitors. Archives of ophthalmology. 1988 Aug 1;106(8):1099-102.
31. Souza AC, Bruning CA, Acker CI, Neto JS, Nogueira CW. 2-Phenylethynyl-butyltellurium enhances learning and memory impaired by scopolamine in mice. Behavioural pharmacology. 2013 Aug 1;24(4):249-54.
32. Arafaa NM, Abdel-Rahmanb M, Mahmoudc RA. Prophylactic effect of Hypericum perforatum L. extract in scopolamine rat model of cognitive dysfunction. InOpen. Conf. Proc. J 2013; 23-30.
33. Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR, UKPDS Group. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney international. 2003 Jan 1;63(1):225-32.
34. Navarro-González JF, Mora-Fernández C, De Fuentes MM, García-Pérez J. Inflammatory molecules and pathways in the pathogenesis of diabetic nephropathy. Nature Reviews Nephrology. 2011 Jun;7(6):327.
35. Scafoglio C, Hirayama BA, Kepe V, Liu J, Ghezzi C, Satyamurthy N, Moatamed NA, Huang J, Koepsell H, Barrio JR, Wright EM. Functional expression of sodium-glucose transporters in cancer. Proceedings of the National Academy of Sciences. 2015 Jul 28;112(30):E4111-9.
36. Bays H. Sodium glucose co-transporter type 2 (SGLT2) inhibitors: targeting the kidney to improve glycemic control in diabetes mellitus. Diabetes Therapy. 2013 Dec 1;4(2):195-220.
37. Kelly B, O'neill LA. Metabolic reprogramming in macrophages and dendritic cells in innate immunity. Cell research. 2015 Jul;25(7):771.
38. Inflammatory molecules and pathways in the pathogenesis of diabetic nephropathy. Nat Rev Nephrol 7: 327-340.
39. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. New England Journal of Medicine. 2001 Sep 20;345(12):851-60.
40. Kaji K, Nishimura N, Seki K, Sato S, Saikawa S, Nakanishi K, Furukawa M, Kawaratani H, Kitade M, Moriya K, Namisaki T. Sodium glucose cotransporter 2 inhibitor canagliflozin attenuates liver cancer cell growth and angiogenic activity by inhibiting glucose uptake. International journal of cancer. 2018 Apr 15;142(8):1712-22.
41. Lam JT, Martín MG, Turk E, Hirayama BA, Bosshard NU, Steinmann B, Wright EM. Missense mutations in SGLT1 cause glucose–galactose malabsorption by trafficking defects. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 1999 Feb 24;1453(2):297-303.
42. Association AD, Diagnosis and classification of diabetes mellitus, Diabetes Care 33 (Suppl. 1) (2010) S62eS69.
43. Potteaux S, Ait-Oufella H, Mallat Z. Mouse models of atherosclerosis. Drug Discovery Today: Disease Models. 2007 Dec 1;4(4):165-70.

44. Siani A, Strazzullo P, Giorgione N, De Leo A, Mancini M. Insulin-induced increase in heart rate and its prevention by propranolol. European journal of clinical pharmacology. 1990 Apr 1;38(4):393-5.
45. Ferrero- Miliani L, Nielsen OH, Andersen PS, Girardin SE. Chronic inflammation: importance of NOD2 and NALP3 in interleukin- 1β generation. Clinical & Experimental Immunology. 2007 Feb;147(2):227-35.
46. Okopień B, Buldak L, Bołdys A. Fibrates in the management of atherogenic dyslipidemia. Expert review of cardiovascular therapy. 2017 Dec 2;15(12):913-21.