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Research Article

The use of complex marketing analysis and QSPR methodology for the necessity of a drug development grounding for the treatment of type 2 diabetes mellitus with increased bioavailability

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Abstract

In order to guarantee qualitative medical and pharmaceutical care it is necessary for all participants of the process to provide consistent interconnected actions, including the use of modern approaches in pharmacotherapy, assessment of the urgent needs of the population in medicines (drugs), development and introduction of modern qualitative, safe and effective drugs into the market. Today, one of the key indicators in determining the population's need for drugs is the epidemiological indicators in a particular region and their dynamics.

In recent years, the actuality of optimal and effective approaches developing in the prevention and treatment of socially significant diseases, including diabetes mellitus (DM), has been increasingly emphasized at the global level. All actions that are proposed for the development of standardized guidelines, treatment protocols, programs for on-time detection and prevention of diabetes are aimed at forming a system of measures are patient-oriented, based on understanding the patient's problems, lifestyle, habits, income and expenses for treatment, as well as other components associated with achieving optimal results for patients.

Keywords

Type 2 diabetes mellitus, therapy, drugs, quercetin, physicochemical properties, modification, bioavailability

Introduction

Diabetes mellitus belongs to a group of metabolic diseases characterized by hyperglycemia resulting from defects of insulin secretion, insulin action, or both. Chronic hyperglycemia in diabetes is accompanied by damage, dysfunction or insufficiency of various organs and systems, including eyes, kidneys, nervous system, heart and blood vessels (Kotvitska et al. 2021).

According to the International Diabetes Federation (IDF), in 2019 one in eleven adults on the planet at the age 29–79 years is ill with diabetes, and one in five patients over 65 years old. The fact that one in two adults has undiagnosed diabetes and three out of four diabetics live in low- and middle-income countries causes much concern.

According to the regional distribution, it is determined that the largest number of people diagnosed with diabetes was recorded in 2019 in China (about 120 million people), in second place – the population of India (about 80 million people), in third place – the United States (about 30 million persons) (Kotvitska and Prokopenko 2020). The general distribution of the population with diabetes by WHO regions is shown in Fig. 1. It should be noted that IDF experts predict an increase in the population diagnosed with diabetes in all regions, with the largest increase prognosis for Africa (143% in 2045 compared to 2019), for the Middle East and North Africa – by 96%, countries of Southeast Asia – by 74% (IDF 2019; Koshovyi et al. 2021).

According to the Center for Medical Statistics of the Ministry of Health of Ukraine, as of 2019, there are 1.3 million people in the country with diabetes. However, along with each registered case there are 2–2.5 undiagnosed patients (Order of the Ministry of Health of Ukraine 2012).

In general, according to the data of the world-wide statistics, every 13 to 15 years the number of people with diabetes doubles. This mainly applies to the population with type II diabetes, which is more common among patients and is not always diagnosed. In type II diabetes, insulin is produced in insufficient quantities or there are some causes that prevent it from working effectively. It is known that this usually occurs after the age of 40 (WHO 2006). Recently, however, diagnosing type II diabetes among young patients who suffer from obesity or have a sedentary way of life is discussed more often. The problem of overweight can significantly increase the risk of developing type II diabetes. About 90% of patients with type II diabetes at the age of 16–54 years are overweight or clinically obese (Davies et al. 2018). In addition, it is emphasized that there is possible relationship between ethnicity and the risk of diabetes, in particular, it was found that people of African or Creole origin are 3 times more likely to develop diabetes, and among people from South Asia – almost 6 times higher (ADA 2018).

Diabetes mellitus is one of the three diseases that lead to disability and death in the majority of cases. According to the WHO, diabetes increases mortality by 2–3 times and reduces life expectancy. Accordingly, the problem of on-time diagnosis and the beginning of effective treatment is actual.

Taking into consideration the above mentioned information, it is actual for the modern health care system to use such pharmacotherapy schemes that will ensure the quality of life of DM patients and avoid irrational expenses of national health care systems. Based on the results of the analysis of the world-wise experience in the treatment of diabetes, we have generalized pharmacotherapy regimens and identified the main groups of drugs that are proposed to be used to ensure effective, rational and long-term hypoglycemic effect in patients with DM type II.

Objectives of the study

Justification of the necessity for the drug with increased bioavailability development for type 2 diabetes mellitus treatment using a complex marketing analysis and QSPR methodology.

Research methods

Analytical investigation of the pharmaceutical market concerning drugs used for the treatment of type II diabetes mellitus has been performed by means of content analysis of official sources of information and structural analytical restructuring. The objects of the study were drugs used for the type II diabetes treatment. Prediction of physicochemical properties of quercetin was performed using Chem 3D Ultra 9.0.

Results and discussion

Taking into consideration that the most predisposed to the disease countries with high rates of diabetes and high prognostic rates of new cases of the disease are MENA, Southeast Asia and the West Pacific, we further analyzed the pharmacotherapy regimens of diabetes in some countries of these regions.

In general, we can talk about common approaches in the pharmacotherapy of patients with type 2 diabetes, according to which the doctor takes basic measures for

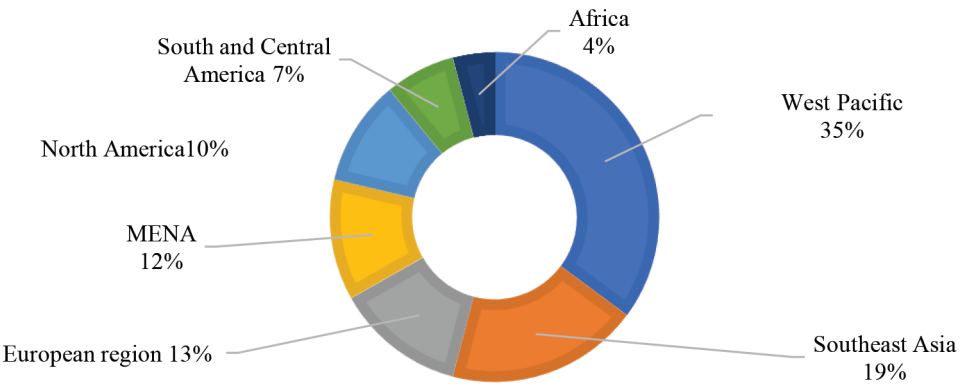

Figure 1. Distribution of the population with diabetes by regions (% of the number of patients in the world, 2019).

prevention, detection, treatment (antidiabetic therapy) and dispensary monitoring of patients. It should be noted that all the analyzed recommendations contain obligatory component of the preliminary analysis of the patient's condition before pharmacotherapy according to the following criteria: expected hypoglycemic efficacy of the drug, potential risk of hypoglycemia, contraindications or drug intolerance, duration of the disease, body mass index and age, the presence of vascular complications and concomitant pathology (Araki et al. 2020).

It has been established that hypoglycemic therapy in the analyzed countries is proposed to be carried out by a total of 9 groups of the fourth level drugs according to the PBX classification (Table 1). It is recommended to use oral forms of metformin and α-glycosidase inhibitor, or double as a monotherapy, during which insulin drugs are added to monotherapy. In case of ineffectiveness of such double therapy, triple therapy is recommended. It is noted that in India, all nine pharmacotherapeutic groups of drugs are listed in the Guidelines for the Treatment of Type 2 Diabetes (Weng et al. 2016).

Table 1. The results of a generalized analysis of approaches in the pharmacotherapy of diabetes.

ATC-code	Pharmacological group	Way of application	Presence of drugs in national recommendations / year of publication					
			USA, 2018	Japan, 2019	China, 2016	India, 2018	Korea, 2019	Ukraine, 2014
A10BA	Blood glucose lowering drugs, excl. insulins. Biguanides.	orally	+	+	+	+	+	+
A10BB	Sulfonylureas	orally		+		+	+	+
A10BF	Alpha glucosidase inhibitors	orally	+	+	+	+	+	+
A10BG	Thiazolidinediones	orally		+	+	+		+
A10BH	Dipeptidyl peptidase 4 (DPP-4) inhibitors	orally		+	+	+	+	+
A10BJ	Glucagon-like peptide-1 (GLP-1) analogues	orally	+	+	+	+	+	+
A10BK	Sodium-glucose co-transporter 2 (SGLT2) inhibitors	orally	+	+	+	+	+	
A10BX	Other blood glucose lowering drugs, excl. insulins	orally		+	+	+	+	+
A10A	Insulins and analogues	by injection			+	+	+	+

According to the American Diabetes Association recommendations, the Standard for patients with diabetes treatment provides antihyperglycemic therapy based on the determination of body mass index. For obese or overweight patients with type 2 diabetes, weight loss drugs are recommended, usually they are metformin, α-glucosidase inhibitors, sodium glucose cotransporter, glucagon-like peptide agonists, amylinmimetics.

Japanese clinical guidelines for the diabetes treatment have been revised every three years since its first publication in 2004. At present, according to the current recommendations, glucose lowering agents which belong to eight groups of the fourth level of the ATC-classification are used (Luo et al. 2020). Moreover, the recommendations emphasize that α-glucosidase inhibitors improve postprandial hyperglycemia by delaying glucose uptake, and sodium co-transporter 2 inhibitors of sodium-glucose (SGLT2) facilitate glucose excretion by inhibiting glucose reuptake by kidneys.

The analysis of publications concerning diabetes treatment among the population of **China** shows actuality of the new approach in the treatment proposed by experts, which takes into account ethnic differences characteristic for pathogenetic and clinical characteristics of diabetes, especially for people from East Asia (Mao et al. 2019). According to the profound analysis results of the recommendations of the Chinese Diabetes Society (CDS), it has been determined that it is recommended to start pharmacotherapy of type 2 diabetes with metformin monotherapy + ingibitor of α-glucosidase or stimulant of insulin secretion (ICMR 2018). In case this regimen is not effective, double or triple therapy or multiple insulin injections are prescribed. It is also emphasized that in case decrease in blood sugar levels does not occur, provided that diet is kept, it is necessary to begin treatment with metformin monotherapy. If it is not possible to prescribe metformin to the patient according to clinical indicators, it is recommended to prescribe immediately α-glucosidase inhibitors or stimulating insulin secretion drugs (Kim et al. 2019). If metformin administration is marked with a slight decrease in blood sugar, dual therapy with addition of insulin stimulators, α-glucosidase inhibitors, dipeptidyl peptidase 4 (DPP-4) inhibitors or thiazolidinediones (TZD), co-inhibitors of SGLT2), insulin, or glucagon-like peptide-1 (GLP-1) receptor agonists is prescribed.

In addition, it has been identified that α-glucosidase inhibitors are recommended in firstline therapy for patients with carbohydrate-saturated diets, which, according to the results of clinical studies, have shown a reduction of glucose (glycosylated) glycated) hemoglobin HbA1c level in blood and patient's body weight loss.

It has been determined that according to the Guidelines for the treatment of type 2 diabetes in India it is recommended to use 9 groups of the fourth level of ATC classification, and the pharmacotherapy regimen includes metformin monotherapy, metformin dual pharmacotherapy with sulfonylureas drugs, dipeptidyl peptidaze inhibitors 4, sodium-glucose cotransporter which belongs to the first-line drugs. Alpha-glucosidase inhibitors, glinides, thiazolidinedione derivatives, glucagon-like peptide receptor agonists are used as additional drugs in dual therapy with metformin drugs. And only in cases when the required level of gluten hemoglobin (HbA1c) is not achieved, it is recommended to add insulin drugs in the course of treatment.

According to the Clinical Guidelines for the Treatment of Type 2 Diabetes in **Korea**, it is recommended to start treatment with oral metformin as the first-line drug for newly diagnosed patients with diabetes (Ha and Kim 2016). If metformin is not tolerated or contraindicated, alternative monotherapy options include dipeptidyl peptidase-4 inhibitors, sodium glucose cotransporter-2 inhibitors, receptor agonists of glucagon-like peptide 1, sulfonylurea, glinidines, α-glucosidase inhibitors and insulin depending on the clinical status of the patient (Myers et al. 2017).

In **Ukraine**, medical care for patients with diabetes is provided in accordance with the Unified Clinical Protocol of primary and secondary (specialized) medical care, approved by the order of the Ministry of Health of Ukraine from 21.12.2012 № 1118 „On approval and implementation of medical and technological documents for standardization of medical care for type 2 diabetes" (ed. from 08.05.2014). According to the protocol recommendations in the pharmacotherapy of patients with type 2 diabetes, especially for overweight patients or suffering from obesity, it is recommended to use metformin as oral hypoglycemic monotherapy, which, in addition, to hypoglycemic has cardioprotective, hypolipidemic effects. Also, the use of sulfonylurea derivatives, stimulants of fast-acting insulin secretion (especially for patients with a disorderly lifestyle), α-glycosidase inhibitors, thiazolidinedione derivatives, other hypoglycemic drugs (inhibitors of the dipeptindipeptidaze 4 and agonists of glucagon-like peptide receptors are recommended for administration. An endocrinologist's consultation is obligatory when prescribing insulin therapy (State Register of Medicines of Ukraine 2022).

Thus, based on the results of the generalization, it can be affirmed about similarity in the pharmacotherapy of type 2 diabetes approaches in different countries and the actuality of the combined forms of antidiabetic drugs inclusion in the treatment regimens. Taking into consideration the WHO data on the global trend concerning „rejuvenation" of diabetes due to sedentary lifestyle, irrational and unbalanced diet, overweight and genetic predisposition among the population in most countries, it is actual to develop combined forms of drugs for the treatment of diabetes based on biguanides, sulfonylurea derivatives and α-glycosidase inhibitors.

The pathogenesis of type II diabetes, according to modern criteria, is caused by the two main disorders: the development of insulin resistance of peripheral target tissues and inadequate insulin secretion. As a result of their interaction, hyperglycemia develops, which causes oxidative stress due to glucose autoxidation, which leads to phospholipid layer damage of target tissues and β-cells plasma membranes, and it contributes to the progression of insulin resistance and reduction of secretory capabilities of the insular apparatus due to apoptosis of β-cells. By reducing the degree of oxidative stress with antioxidant therapy, it is theoretically possible not only to slow the progression of diabetic complications and insulin deficiency, but also to reduce insulin resistance, thereby contributing to better compensation of carbohydrate metabolism (Kononenko et al. 2020).

Therefore, drugs which are used as a maintenance therapy and for elimination of the disease complications are widely used. This group of drugs includes antioxidants, neuroprotectors, hepatotropics, aldose reductase inhibitors, antiplatelet, non-selective monoamine reuptake inhibitors, analgesics, anesthetics, diuretics, lipid-lowering and antiepileptic drugs. Modern antioxidant therapy is represented by various drugs (drugs of thioctic acid, alpha-tocopherol, vitamin C, selenium, etc.), which are widely used to treat not only diabetes but also other systemic diseases.

Therefore, we analyzed the data of the State Register of Medicines of Ukraine concerning the assortment of registered drugs recommended for antioxidant therapy of type II diabetes as the next stage of the study. According to the analysis results, it has been determined that for the September 2021 period, the most numerous in terms of the names number, among 106 registered drugs, are the groups of vitamin C drugs (33 names) and thioctic acid (27 names). Quercetin is represented by 6 drugs names. 71.7% of the analyzed drugs assortment were registered by domestic manufacturers, drugs registered by Germany (12.3%) take the second place in their number. In general, the assortment is represented by drugs from 8 countries. It should be noted that vitamin C and quercetin preparations are presented on the domestic market exclusively by Ukrainian manufacturers (Fig. 2).

Assortment analysis of dosage forms showed that drugs are represented in 10 different forms of manufac-

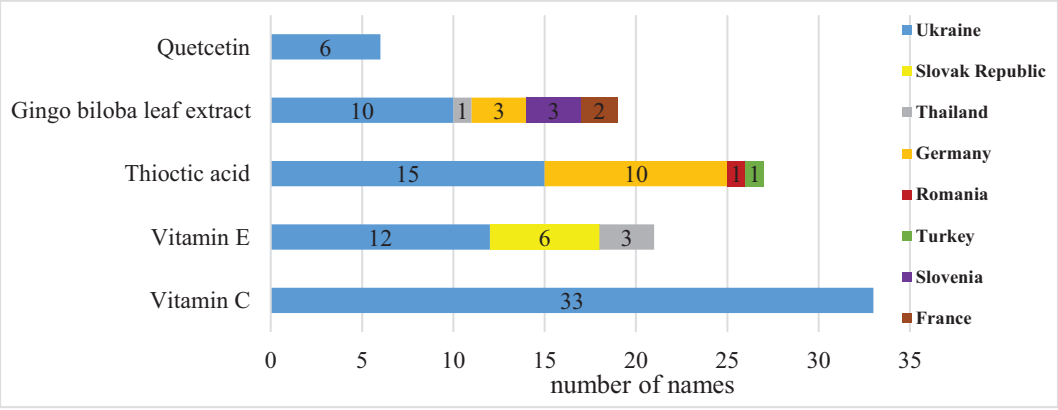

Figure 2. Distribution of drugs registered in Ukraine for antioxidant therapy by producer countries.

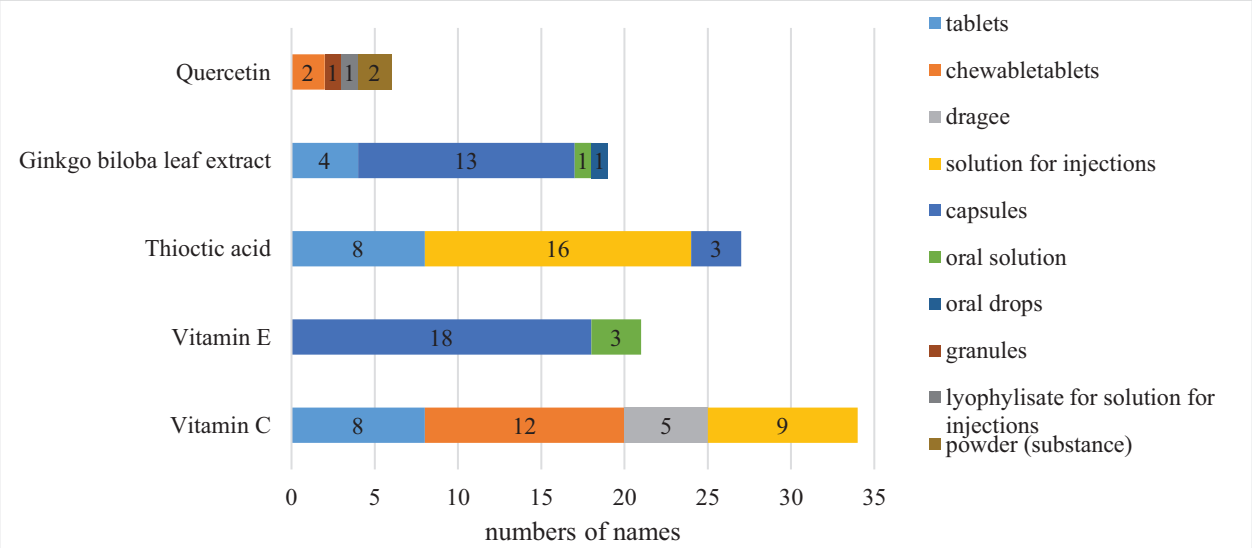

Figure 3. The structure of the drugs assortment for antioxidant therapy by dosage forms.

turing, among which the most numerous are capsules (34 names of drugs belonging to the groups of vitamin E, thioctic acid, ginkgo biloba leaf extract). Solutions for injections, taken as total, are registered in the number of 25 drugs names (belonging to the groups of vitamin C and thioctic acid), tablets – 20 names (belonging to the groups of vitamin C, thioctic acid, ginkgo biloba leaf extract). It has been noted that only quetcetin drugs, which are the least numerous, are registered in the form of powder (substance) produced by Ukrainian manufactures (Fig. 3).

The results of the literature analysis have shown that today the most promising API from the antioxidant group is quercetin, and its use reduces the risk of diabetic angiopathies progression, improves hypoglycemic control and insulin sensitivity, and has a beneficial effect on homeostasis.

Quercetin is a substance that together with cardioprotective, hepatoprotective, antisclerotic, hypoglycemic activities has an antioxidative effect. According to the prediction of antidiabetic activity of quercetin in silico, quercetin has a high degree of adhesion to glycogen phosphorylase (GP) molecules. Inhibition of glycogenolysis is a therapeutic strategy for the treatment of type II diabetes. GP catalyzes the first stage of glycogen degradation as an enzyme that limits the rate of absorption. Therefore, it will inhibit glycogenolysis, thus providing a potentially new treatment for type II diabetes. Compared with metformin, quercetin has potent antihyperglycemic properties, and the degree of interaction with the amino acid residues of the peroxis proliferator – may exceed it.

At present, there is a restriction for the use of quercetin in the composition of drugs, what is connected with its low solubility, and as a consequence, with a poor bioavailability (Kovalevska et al. 2017). According to the scientific data, the bioavailability of quercetin is in the range of 0% – 60% and depends on the dose, the dosage form which is used, individual characteristics, absorption, metabolism, elimination, etc.

Therefore, we predicted the possibility of changes in the biopharmaceutical solubility of quercetin depending on changes in physicochemical parameters using the methods of the relationship „structure / property“ (QSPR) assessment.

The results of the equilibrium constant of the deprotonation reaction determination (pKa) made it possible to conclude that quercetin is a weak pentahydric acid, which can exist in protonated form on the carboxyl oxygen atom and belongs to the compounds that contain functional groups with an active hydrogen atom (Fig. 4).

The obtained results show that quercetin is a polyprotic acid that can exist in 22 ionicmolecular forms that are in dynamic equilibrium depending on the pH of the medium. This variety can be explained by light oxidation, especially in an alkaline environment, close indicators of acidbase properties of a certain number of its functional groups. The decrease in the intensity of the ionic-molecular forms of quercetin is associated with a decrease in the content of the original quercetin due to destruction. According to the degree of intensity, we can distinguish 5 main forms by which the dissociation of quercetin occurs. Taking into consideration that the major pKa1 of quercetin is 6.38, it can be concluded that only 50% of it is available for sulubilization to bind to intestinal receptors. Therefore, it can be concluded that quercetin at physiological pH values is completely ionized and therefore unavailable for intestinal absorption. The existence of its unprotonated forms in the upper gastrointestinal tract indicates hydrophobicity and insolubility in the stomach, which can lead to its non-assimilation in the small intestine.

Lyophilicity is one of the important molecular descriptors used in the quantitative „structure / property“ study and which determines the value of the substance partition coefficient in a two-phase system (logD) and characterizes the ability to pass through the cell membrane. Determination of log D showed that at physiological parameters the pH of the gastrointestinal tract has the following values:

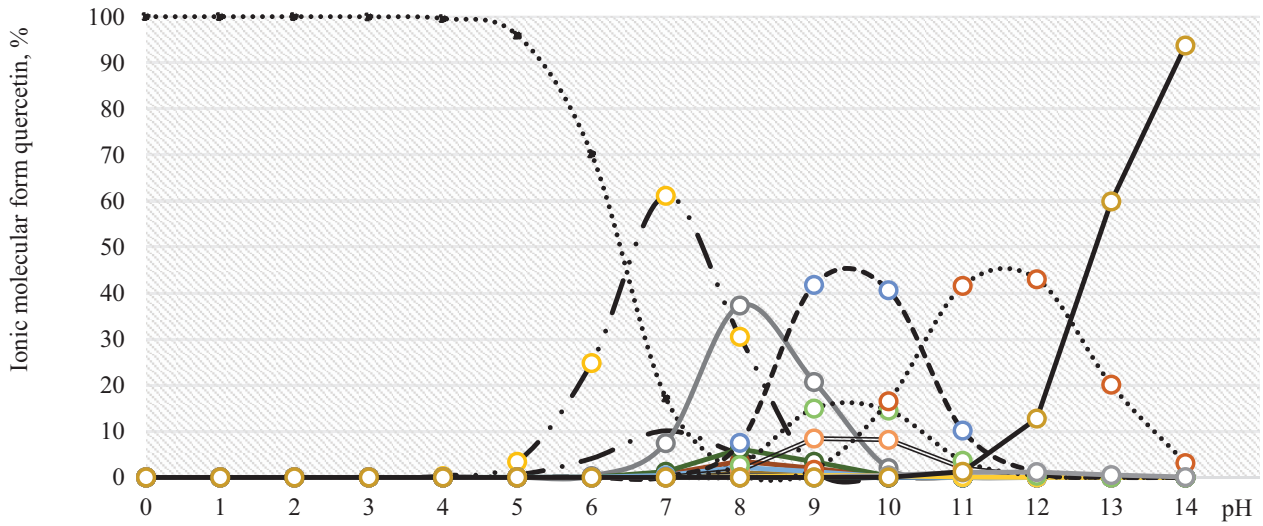

Figure 4. Diagram of the distribution of ionic-molecular forms of quercetin depending on pH.

1,2 - 2,773; 4.5 - 2.776; 6.8 - 2.32. This value of the distribution logarithm in combination with the calculated values of physicochemical descriptors indicates to a low degree of quercetin absorption.

The drug demonstrates its pharmacological effect only when it binds to specific receptors in solubilized form to overcome the intestinal barrier. That is, API for the absorption process is available only in dissolved form. Thus, solubility is the main and key parameter of bioavailability. Therefore, we investigated the solubility depending on the pH of the medium. The results of the study show that quercetin has a high solubility (log S = 0) only outside the physiological values of gastrointestinal pH (pH = 9). In the range of 1.2–7.5, the substance has negative values of logS - -2.97 - -1.98, which indicates to its hydrophobicity. Therefore, the degree of dissolution does not allow to obtain a solution of API in the stomach or its stable dispersion, which will adversely affect the absorption in the small intestine.

The next step was to determine such topological descriptors of quercetin as: molecular weight, molecule surface, number of donors and acceptors of H-bond, etc. (Table 2).

Table 2. Topological descriptors of quercetin.

Indicator	The obtained data
Molecular weight	302,238 g/mol
Hydrogen bond donors	5
Hydrogen bond acceptors	7
Melting temperature	316,0–318,0 °C
Log constant Henry	25,0301
Log P	2,11
Intestinal permeability	0,965
Polar surface area	127,45 Å^2
Gibbs energy (ΔH) (t = 298.15 K, p = 1 atm)	-606,34 kJ/mol
Number of rotating bonds	12

The obtained results (Table 2) show that the quercetin molecule complies with Lipinski's rule: the molecular weight is less than 500 Da, the logarithm of the distribution in octanol / water is less than 5, the value of H-bond acceptors does not exceed 10. It is known that there is a classification of intestinal absorption of substances depending on the polar surface area: up to 60 Å2 – high, 60–140 Å2 – satisfactory, above 140 Å2 – poor. As it can be seen from Table 2, according to the value of the polar surface area of quercetin under certain conditions, this substance can be absorbed in small intestine. But the number of rotating bonds exceeds 10, which, according to the scientific data, will ensure oral bioavailability of not more than 30%. The molecule has 3 aromatic rings, which is the limit for a satisfactory pharmacokinetic profile due to the increasing value of polar surface area and lyophilicity.

As it can be seen from Table 2, the value of the logarithm of the Henry constant, which is the ratio of the concentration of dissolved substance to its partial pressure over the solution, indicates to a poor solubility and dissociation constant. Quercetin is not a porous substance and is able to quickly reach reactivity when interacting with water. The value of the ΔH enthalpy energy indicates to the exothermic type of the reaction and possibility of heat release during the reaction, thereby indicating a decrease in the order of the system.

Molecular interaction always forms a force field, which can be described by a set of functions that characterize each type of molecular structure. To visualize the interaction of the quercetin molecule with water molecules, we used an available version of the class II molecular force field Merck (MMFF94), which is adapted for small molecules and allows calculations of their parameters. The interaction of API and the aqueous medium along with other physicochemical descriptors is controlled by the value of the molecular surface that is available to the solvent and corresponds to the volume to which the solvent sphere cannot penetrate, thus characterizing the degree of hydrophobicity of the substance.

When determining the molecular descriptors, it was found that the value of the persistent length for the strained chain did not exceed 0.6000 Å, which indicates to the molecule stiffness. Due to the visualization (Fig. 5) it is possible to observe an increase in the degree of curvature of the solid sphere of the dissolved quercetin molecule, which is available to the solvent, greater than before.

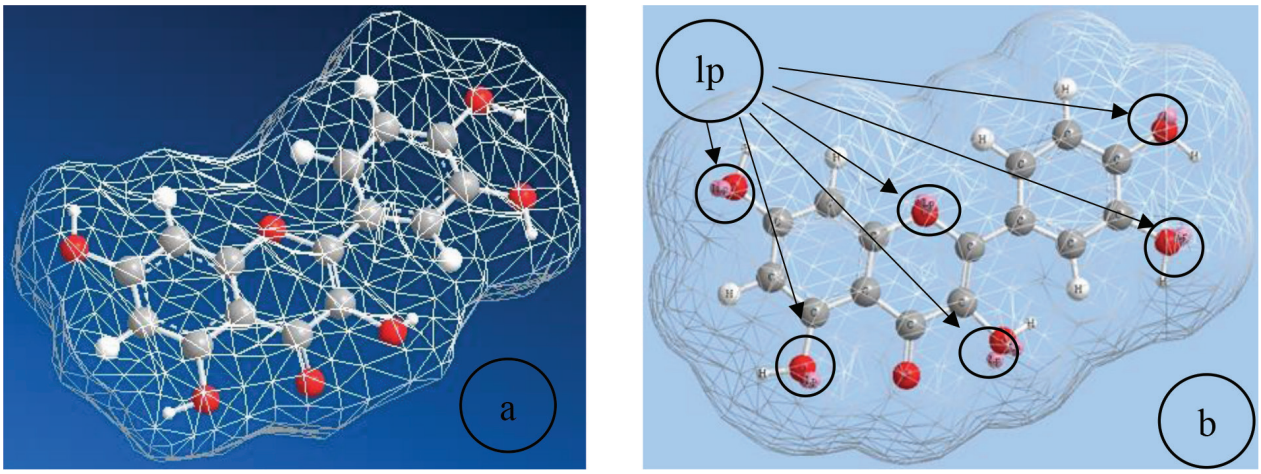

Figure 5. Structure of the quercetin molecule which takes into account the surface available for the solvent before (**a**) and after (**b**) the minimization of energy in the force field MMFF94.

The obtained data indicate the greatest possible solubility of the quercetin molecule when changing the conditions of dissolution. This conclusion confirms the presence in Fig. 5b of unshared pairs of electrons (lp) and changes in bond angles. The structure of the molecule is more dynamic, which helps to increase the degree of dissolution.

Based on the above mentioned data, it is possible to predict satisfactory bioavailability of quercetin in case of a larger contact surface formation for the compound sulubilization and the creation of conditions for the reduction of H-bond donors.

Conclusion

The performed complex analysis of the recommended treatment regimens for type 2 diabetes mellitus and the assortment of hypoglycemic drugs, allows us to make a conclusion about the similarity of approaches in pharmacotherapy of this nosology in different countries and the actuality of inclusion in the course of treatment regimens of combined antidiabetic drugs, namely on the basis of biguanides, sulfonylurea derivatives and α-glycosidase inhibitors.

According to the data of antidiabetic activity prediction, the use of quercetin may provide a potentially new treatment for type 2 diabetes. And its use as an antioxidating agent will help reduce the degree of oxidative stress, which, in its turn, will reduce the risk of diabetic angiopathies progression, improve hypoglycemic control and sensitivity to insulin. But due to its poor bioavailability it is not possible to achieve the required therapeutic activity in case of its oral administration.

In silico study was performed in order to predict the modification of the physicochemical properties of quercetin for solubility improvement. The determined value of the distribution logarithm in the octanol / water media indicates to unsatisfactory intestinal permeability. Determination of molecular descriptors of quercetin has shown that the critical parameters according to Lipinski and Weber's rule are the presence of a limiting value of H-bond donors. The analysis of functional groups and quercetin reactivity indicates to the inability to quickly achieve reactivity when interacting with water, the exothermic type of reaction and the possibility of heat release during the reaction, thereby it indicates to a decrease in the order of the system.

Based on the above mentioned information, we can make a conclusion that the bioavailability of quercetin is satisfactory in case of a larger cavity formation for the compound sulubilization and creation of conditions for H-bond donors reduction.

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