Hypoglycemic Effect of Resveratrol

Subjects: Chemistry, Medicinal

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El resveratrol (RV) es un compuesto polifenólico con propiedades antioxidantes, antiinflamatorias e hipoglucémicas. Varios estudios in vitro y en modelos animales han demostrado los efectos beneficiosos del RV; sin embargo, los resultados en humanos no son concluyentes.

glucose insulin glycated hemoglobin glycemic control

1. Introduction

Resveratrol (RV) is a kind of polyphenol, which is composed of two benzene rings and three hydroxyl groups. This structure allows RV molecules to transfer electrons to different free radicals (FR), thus reducing the damage to biomolecules. In addition, RV has anti-inflammatory effect because it can block the activation and subsequent translocation of nuclear factor kappa B (NF κ b), which is responsible for the synthesis of pro-inflammatory proteins such as tumor necrosis factor α (TNF α), interleukin-1 (IL1), interleukin-6 (IL6) and pro thrombogenic molecules [1][2][3]. RV is found in grapes, peanuts and blueberries, although the plant Polygonum cuspidatum (Mexican baboon, Japanese knot grass) is the main natural source of this compound. In the past 20 years, many studies have been carried out on the therapeutic characteristics of RV, which are realized through the signal pathways involved in the regulation of apoptosis, mitochondrial dysfunction, platelet aggregation, oxidative stress and inflammation [4][5]. In this sense, RV is an attractive compound for adjuvant treatment of chronic non communicable diseases, such as diabetes, cardiovascular disease, arthritis, neurodegenerative diseases, and even cancer [6][7].

Regarding the therapeutic effects of RV, these are strongly related to the activation of sirtuin 1 (SIRT1) and AMP-activated protein kinase (AMPK). Both proteins act as energy regulators due to their participation in metabolism and mitochondrial function, which makes them a suitable target for the treatment of metabolic diseases, such as type 2 diabetes mellitus (T2DM) [7][8].

Scientific evidence, obtained from in vitro studies and in animal models, suggests that RV has antioxidant, anti-inflammatory, and even anti-cancer properties; however, the results of clinical trials are not conclusive. In this context, some clinical trials suggest that RV exerts beneficial effects on metabolic diseases (obesity, metabolic syndrome, and diabetes), which has been evidenced by its ability to reduce the levels of lipids, glucose, and some adipokines. Furthermore, it has been observed that after RV administration, the antioxidant capacity increases and the concentrations of pro-inflammatory markers decrease [9][10][11].

Despite the above, in some investigations carried out in humans, no evidence of the therapeutic effects of RV has been found. Therefore, there is currently no consensus regarding the therapeutic benefits of RV and the dose at which they are presented, so research on this compound is still continuing [12][13].

2. Discussion

Currently, the incidence of NCDs, such as obesity, diabetes, cardiovascular diseases (CVD), and metabolic syndrome (MS), is increasing and according to the World Health Organization (WHO), is the main cause of death worldwide. The uncontrolled increase in NCDs is related to unhealthy lifestyles, such as diets rich in carbohydrates and fat, sedentary lifestyles, and tobacco and alcohol consumption [14][15][16][17][18]. For this reason, the main strategies applied for the prevention and control of these pathologies focus on achieving a change in lifestyles and improving therapeutic adherence in the population at risk [19][20][21]. However, it is well-known that the proposed strategies have not been entirely successful and the search for new therapeutic agents has been necessary, among which nutraceuticals stand out. These compounds have aroused great interest among the scientific community, including phenolic acids, stilbenes, flavonoids, lignans, and curcuminoids, which have been the object of multiple investigations aimed at understanding their role in preventing diseases and increasing longevity [22][23][24]. In this sense, RV has been widely studied. Some research suggests that its use is associated with a lower incidence and better control of a wide variety of NCDs. This occurs due to the antioxidant capacity of RV and its interaction with cell signaling pathways for the modulation of gene expression. However, other investigations show the lack of a therapeutic effect of this nutraceutical [25][26][27]. This means that researchers need to continue conducting clinical trials and analyzing existing ones to identify the efficacy and safety of RV as a complementary treatment for NCDs.

This meta-analysis contains 30 articles that study the effects of RV supplementation vs. a placebo on glucose, insulin, HbA1c, and insulin resistance (measured by the HOMA-IR index). These biochemical parameters are important for evaluating the prevention and control of metabolic diseases such as T2DM, obesity, nonalcoholic fatty liver, and MS. For this reason, they are the main biomarkers of outcome in most clinical trials evaluating the effectiveness of RV.

Our global results show that RV supplementation vs. a placebo decreases glucose and insulin levels, but has no therapeutic effect on HbA1c and HOMA-IR, which is contrary to what was found in the meta-analysis by Hausenblas et al. [28], who observed a significant decrease in HbA1c, without a considerable effect on glucose levels. In addition to this, in the study carried out by Jeyaraman et al. [29], they found that RV did not significantly improve HbA1c, glucose, and insulin levels.

Among the biochemical parameters most used in research, due to their reliability in evaluating the therapeutic efficacy of different nutraceuticals in the control of metabolic diseases, are HbA1c, insulin resistance (calculated by the HOMA-IR index), fasting glucose, and insulin. On the one hand, HbA1c is formed when glucose binds to an amino group of the β chain of hemoglobin through a non-enzymatic reaction that is influenced by the concentration of glucose in the blood, so that a state of hyperglycemia is manifested as a high percentage of HbA1c [30]. On the

other hand, it is known that insulin is the most important regulator in glucose and lipid metabolism, so insulin resistance is a distinctive feature of obesity, T2DM, and cardiovascular diseases [31].

The evidence from our meta-analysis shows that RV consumption does not improve HbA1c and insulin resistance, since, in most of the included studies, there were no significant changes in these parameters. Given the above, our results suggest that RV administration is not effective for prolonged glycemic control (around 90–120 days). However, there is considerable heterogeneity between the studies, which is attributed to the wide variation of RV dosage, duration of administration, and number of participants. Furthermore, some studies were at risk of bias in selection and blinding, due to the open and single-blind design.

Considering the general results and the influence of heterogeneity, a subgroup analysis was performed, stratifying the publications included by dose, health status, duration of intervention, and age of the participants.

2.1. Sub-Analysis by RV Dosage

After performing the stratified analysis by dose, a positive and statistically significant effect of RV on glucose levels was found at doses of 500–1000 mg/day, while the effect of RV on insulin was significant after consuming doses of less than 500 mg/day and greater than 1000 mg/day. In the systematic review and meta-analysis carried out by Zhu et al. [32], they found that, at doses of less than 100 mg/day, there are no changes in glucose levels, but higher doses (even 1 g) are capable of decreasing glucose levels, which partially coincides with our results. This is due to the fact that Zhu et al. only included subjects with T2DM, while in our study, subjects with and without T2DM were included. It has been shown that the efficacy of RV may differ according to the administered dose, because the molecular target changes. In addition, it has been proposed that RV could have a dose–response effect (hormesis), so, at low doses, it triggers a stimulating response of some metabolic pathways, and at high doses, it causes the inhibition of the same pathways [33].

SIRT1 is known to play an important role in AMPK activation to improve mitochondrial function and stimulate glucose utilization, as well as protect cells against metabolic decline. In this regard, both in vitro and in vivo studies have shown that moderate doses of RV activate SIRT1 and this, in turn, activates AMPK. In contrast, high doses activate AMPK independently of SIRT1, but do not improve mitochondrial function or protect against metabolic deterioration [34]. It has also been observed that in murine models, low doses of RV improve the insulin sensitivity and decrease its secretion by parts of the pancreatic β cells in the long term, while high doses have the same effect in the short term; however, high doses of RV cause nephrotoxicity [35].

In our meta-analysis, we found that high and low doses of RV exert similar effects on insulin levels. However, the variability in the duration of the interventions and in the health conditions of the participants does not allow us to establish if this result is due to the biological effects of RV occurring in a dose-dependent manner or a consequence of the metabolic conditions of cells, since, depending on the cellular needs, RV activates different molecules and signaling pathways, which translates into different biological effects. In addition, it should be emphasized that changes in insulin levels after RV administration, although statistically significant, do not

necessarily represent a clinically important change. Due to this, it is necessary to carry out more research on the biological effects of RV to determine if these are presented in a dose-dependent manner in humans, since, so far, many of the results in animal models have not been reproduced in humans. For this reason, it is very difficult to propose a therapeutic dose of RV.

Regarding the insulin resistance markers (HOMA-IR) and HbA1c, in this review, no significant changes were observed in these parameters, which, in addition to being consistent among most of the publications included, coincides with that reported by Zhu et al.

2.2. Sub-Analysis by Health Condition

According to the analysis by the presence or absence of T2DM, we observed that RV consumption had a positive effect on the four measured parameters (glucose, insulin, HOMA-IR, and HbA1c), in favor of the subjects with T2DM, which was consistent with the majority of the results from clinical trials conducted in diabetic subjects that were included in the meta-analysis (Abdollahi et al.; Bhatt et al.; Hoseini et al.; Javid et al.; Khodabandenlhoo et al.; Movahed et al.; and Sattarinezhad et al.). They observed a significant decrease in glycemic control markers after RV consumption in diabetic subjects. These results are consistent with the meta-analysis by Liu et al. [36], where they found that RV consumption significantly reduced glucose, insulin, insulin resistance, and HbA1c levels in participants with T2DM.

The hypoglycemic effect of RV has been attributed to its antioxidant and anti-inflammatory properties. It is known that molecular targets include SIRT1, AMPK, nuclear factor kappa β, and transcription factor Nrf2, among others [37]. It has been demonstrated in several in vitro experiments and in vivo in diabetic animal models that RV increases glucose uptake, utilization, and storage, at the same time that it restores insulin signaling pathways and increases its sensitivity [38][39][40]. The proposed mechanisms are the following:

- Increases the expression of GLUT4 (an insulin-dependent glucose transporter) and improves glucose uptake;
- Activation of SIRT1, which modulates different metabolic pathways, as follows: (i) It deacetylates the FOXO 1 protein, inhibiting its activity and suppressing the apoptosis of pancreatic β cells; (ii) it reduces the expression of the nuclear factor kappa β, which translates into a decrease in the activity of inflammation markers and oxidative stress, responsible for the production of advanced glycation end products (AGE); (iii) it activates AMPK, which regulates various intracellular processes, such as energy metabolism, mitochondrial functions, and cellular homeostasis. AMPK inactivity is correlated with insulin resistance and tissue damage caused by hyperglycemia; and (iv) it activates FOXO 3 expression, thereby suppressing the production of reactive oxygen species and improving regulation in manganese superoxide dismutase (MnSOD) expression;
- Decreases the expression of the AGE receptor (RAGE) that contributes to insulin resistance by modifying its receptor proteins, by phosphorylating the serine/threonine segment, causing insulin resistance. Therefore, the decrease in the production and activity of AGE improves insulin signaling;
- Activation of factor Nrf2, which is a transcription factor that coordinates the activation of a wide range of genes of antioxidant systems, thereby increasing the activity of the antioxidant enzymes glutathione peroxidase (GPx),

glutathione reductase (GR), superoxide dismutase (SOD), and catalase.

In the meta-analysis carried out by Liu et al. [38], non-diabetic subjects who consumed RV did not show a significant decrease in the glycemic control parameters. In this meta-analysis, we found similar results. The same has been reported in other investigations for healthy animal models. In these studies, it was has been observed that RV administration does not have a significant effect on glucose, the lipid profile, and the insulin sensitivity, although the cellular mechanisms are not entirely clear. These results can be explained considering that, in normal physiological conditions, glucose and insulin concentrations are in an acceptable range. Therefore, there are no metabolic alterations and RV consumption does not activate the molecular targets or metabolic pathways that are affected due to the presence of T2DM. In this sense, the results suggest that RV does not cause hypoglycemia in healthy people, although more quality clinical trials are required to evaluate the effects of RV consumption in healthy people.

2.3. Sub-Analysis by Duration of Intervention

Analysis by duration of the intervention (studies with an intervention < 3 months and studies with an intervention ≥ 3 months) revealed a positive effect on glucose when the intervention was less than three months. HbA1c showed a significant decrease when the intervention had a duration of more than three months, while the effect on insulin was positive in both interventions (<3 months and ≥3 months). However, the HOMA-IR index had no significant effect regarding the duration of the intervention.

The discrepancy in glucose and HbA1c results is due to the serum glucose levels reflecting a very short period of glucose metabolism and being influenced by diet in the short term. In contrast, HbA1c reflects glucose metabolism for a period ranging from 90 to 120 days, which is why it is considered a highly reliable marker of long-term glycemic control. In this regard, the results of different clinical trials included in this meta-analysis show that the intervention time plays an important role in glycemic control. Abdollahi et al. observed that the administration of 1 g/day of RV for 8 weeks is not enough to have a positive effect on HbA1C, despite lowering glucose levels, as did Thazhath et al. , who reported that 5 weeks of treatment with 1 g/day of RV has no effect on HbA1c levels in diabetic patients. On the other hand, Bhatt et al. reported that 3 months of supplementation with 250 mg/day of RV significantly reduces HbA1c, while Sattarinezhad et al. found that 500 mg/day of RV for 3 months triggers a significant decrease in HbA1C, insulin, and the HOMA-IR index.

Our results are consistent with the study by Timmers et al. [41] carried out in obese subjects. This study reported that RV consumption for a period of 30 days improves glucose homeostasis and insulin resistance because it mimics the effects of caloric restriction. Meanwhile, the meta-analysis carried out by Guo et al. [42], who evaluated the effects of VR intervention on risk factors for NCDs, showed that a 3-month intervention significantly reduces low-density lipoproteins (LDL-cholesterol) and HbA1c levels.

2.4. Sub-Analysis by Age

Three groups were formed according to the age of participants: Those (i) under 45 years old; (ii) from 45 to 59 years old; and (iii) over 60 years old. Significant changes in favor of RV were only presented for glucose, insulin, and HbA1c levels in the studies that included subjects aged 45 to 59 years, while the HOMA-IR index did not have significant changes in any group.

These results are in contrast to the findings of Crandall et al. [43] and Witte et al. [44], who found that RV administration in older adults improves the insulin sensitivity, plasma glucose, and glucose metabolism. However, in the clinical trials included in our meta-analysis, which were conducted in subjects under 45 years of age (Asghari et al.; Bo et al.; Godínez-Salas et al.; Poulsen et al.), it was observed that glycemic control markers did not change. Moreover, among clinical trials with people older than 60 years, only Hoseini et al. reported a significant change in glucose levels after an intervention with 500 mg/day of RV for 4 weeks. Most of the studies where the age of the participants ranged between 45 and 59 years found significant changes in the biomarkers of glycemic control, except those with low doses of RV (Kantartzis et al.) or short intervention periods (Dash et al.).

RV is a nutraceutical widely studied for the control of metabolic diseases due to its antioxidant and anti-inflammatory properties. Its role has been demonstrated in preclinical studies, but its effects in humans are controversial. This is probably due to its unfavorable pharmacokinetics and its low bioavailability, which could be influenced by the intestinal microbiota [45][46]. In addition, the genetic influence is an important factor for the individual response to RV [47]. RV has been shown to activate the expression of SIRT1, which is a histone deacetylase that plays a crucial role in glucose metabolism, lipids, the inflammatory process, and antioxidant defenses [48]. In vivo investigations have indicated that, in aging, the activity of SIRT1 is decreased [49, which could cause a poor response of the body to the administration of RV in older adults.

La controversia sobre los efectos biológicos del RV en humanos justifica la continuidad de la investigación, y es necesario conocer la eficacia y seguridad del RV en la prevención y tratamiento de enfermedades metabólicas de alta prevalencia, la mayoría de las cuales están relacionadas con el estrés oxidativo y el proceso inflamatorio . Otro factor importante a dilucidar son las vías metabólicas que activa y cómo influyen la edad, el estado de salud, la dosis y el momento del tratamiento.

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