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Review

Analysis of the effects of *Curcuma longa* supplementation and physical exercise in patients with diabetes: systematic review

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Abstract: Diabetes *Mellitus* is one of the most prevalent chronic diseases in the world and one of its main features is chronic hyperglycemia. Among the therapeutic forms used to control the pathology are pharmacotherapy and the use of other alternatives such as regular exercise, which participates in glycemic control and the ingestion of plant extracts with antioxidant effects in the body. Among the different plants used, curcumin is a possible plant to be used to attenuate the hyperglycemic picture triggered by Diabetes Mellitus. Some studies suggest that this plant is antioxidant and hypoglycemic. The review aimed to know the antioxidant and hypoglycemic potential of curcumin supplementation in DM. The search was performed considering articles published between 2010 to 2019, in English and Portuguese, and a theoretical survey of relevant information was conducted in the main databases of scientific publications: Virtual Health Library and its indexed databases as Pubmed, LILACS, Scielo and Scientific Electronic Library Online. The associated use Turmeric and Physical Exercise demonstrated antioxidant, anti-inflammatory and hypoglycemic activity caused by Diabetes Mellitus. We may suggest that these are potential therapeutic ways to improve the quality and survival of diabetic patients.

Keywords: diabetes; saffron; turmeric; food supplements; supplementation; physical exercise.

1. Introduction

Diabetes *Mellitus* (DM) is a metabolic disorder of multiple etiologies and multiple factors involved in its pathogenesis [1]. It is mainly characterized by chronic hyperglycemia, in which there is marked elevation of blood glucose due to the absence or ineffectiveness of insulin hormone action on cell receptors [2-4].

Type 1 DM corresponds to a minority of cases (T1DM) and is considered an inflammatory and autoimmune pathology due to the impairment in insulin production by the destruction of pancreatic β cells due to infiltration of auto-reactive T lymphocytes in the endocrine pancreas [5]. Already type 2 DM (T2DM) is increasingly prevalent, making up about 90% of cases in the world population, is characterized by resistance to the action of insulin and/or disturbances in its secretion. Thus,

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hyperglycemia is the most evident symptom in the pathology [6,7].

DM is one of the most prevalent chronic diseases in the world and is one of the greatest public health challenges of the 21st century [8,9]. The incidence of DM is increasing in both underdeveloped and developing countries. According to the International Diabetes Federation in 2015 estimated that the number of diabetic individuals aged 20 to 79 years old was 8.8% corresponding to 415 million people. If these trends continue, it is estimated that the number of people with diabetes in the year 2040 is expected to reach 642 million [7,10].

Among the several therapeutic forms used to treat and control DM, the most common are: medication (with the use of hypoglycemic agents associated or not with the administration of exogenous insulin), adequate and healthy eating and regular physical activity [11-13].

Physical activity is essential for glycemic control [11] and the reestablishment of the body's antioxidant defense in patients with diabetes. Physical exercise has been associated as a protective factor for health since the 1950s. Since then, its benefits have been associated with the reduction of chronic diseases, weight reduction in adults who exercise and the reduced risk of premature death from cardiovascular disease [14-16].

In addition to the pharmacological prescription for drug use, the use of supplementation with antioxidant compounds has also shown promising results on the maintenance of blood glucose in altered physiological conditions [17,18]. Among these dietary supplements, turmeric (Curcuma longa), which contains a natural phenolic compound widely used in foods, beverages and medicines, appears to act beneficially under glycemic control, attenuating hyperinsulinemia and Homeostasis Model Assessment Index (HOMA-IR) and the delayed onset of comorbidities often found in patients with diabetes [19-22].

Some researchers evaluate the effects of exercise after antioxidant-rich supplementation [23]. This effect is partly due to the type of exercise, frequency and intensity prescribed by physical educators [24].

Thus, the present study aims to evaluate, through literature review, the effects of turmeric consumption in the form of extract, and the practice of various types of physical exercise found in the literature on glycemic control in chronic complications of patients with DM.

2. Materials and Methods

The methodological approach of this review followed article search strategy and inclusion criteria, including the data collection and analysis phase. This systematic review was performed following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis [25].

2.1 Search Strategy and Inclusion Criteria

This systematic review study was conducted considering the articles published in the years between 2010 and 2019, in English and Portuguese. The PICO strategy [26] was used, considering studies with experimental and human diabetic model and experimental and human model that performed physical activity with the use of long curcuma longa / curcumin supplementation (P = patient), evaluated for the performance of activity. supplementation (I = intervention) to attenuate the pathology of diabetes (C = comparison of intervention or control), with the objective of verifying the physical exercise capacity together with the supplementation of Curcuma longa / curcumin in the control of diabetes mellitus (O = outcome), using the following guiding question: “What are the effects of Turmeric Supplementation associated with exercise in diabetes”.

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The study design is explained in Figure 1, with the study eligibility criteria. For studies considered to be preliminarily eligible, the full text was obtained and evaluated to verify that they met all inclusion criteria. The following inclusion criteria were used: clinical studies on the subject that showed evidence of turmeric action in animal and human model experiments.

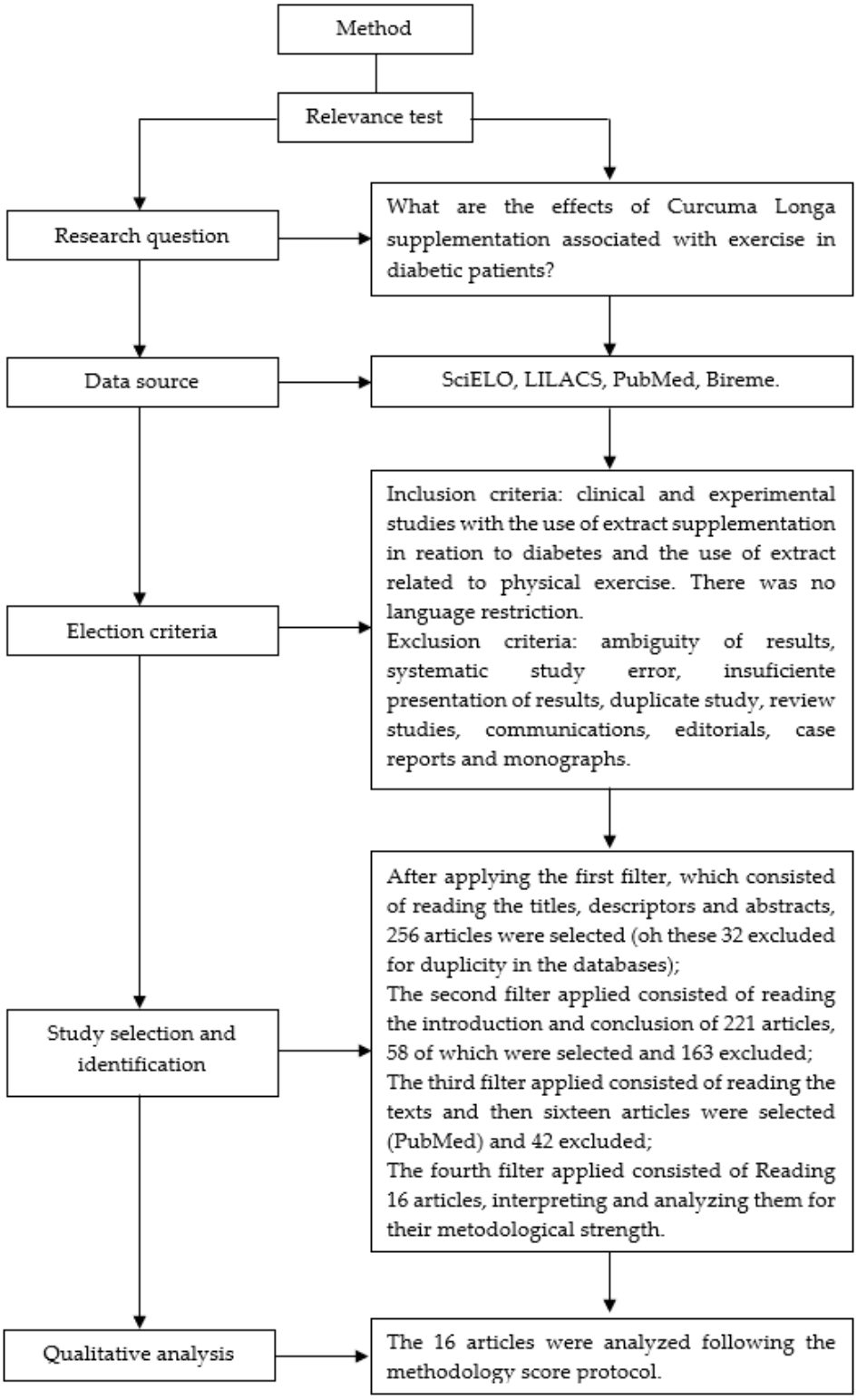

Figure 1. Research strategy flowchart and article selection.

Exclusion criteria were: ambiguous results, duplication of database-based studies, review studies, communications, case reports, summaries of scientific meetings, monographs, comments, or

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editorials.

The keywords were selected from the Health Sciences Descriptors of the VHL and MeSH (PubMed), in order to identify relevant studies in the electronic databases PubMed, SciELO and LILACS. The descriptors were "physical activity", "physical exercise", "turmeric" and "diabetes". This research was conducted from December 2017 to February 2019.

2.2 Validity of the Evaluation and Data Extraction Process

After obtaining the list of studies performed with the chosen descriptors, the relevance test was applied and each study was carefully analyzed by two eligibility reviewers (not blinded to the authors and journals), who conducted the research independently and decided in a consensual manner which studies would be selected. In case of divergence of results, a third reviewer would be consulted to resolve the study inclusion issue, as suggested in the literature.

Initially, article titles, descriptors and abstracts were identified; the first search filter was applied to select them. Subsequently, based on the results obtained, the second filter was applied by reading the introduction and conclusion of the study. If the article was considered eligible, the article was read in full and thus the third filter was applied.

In this preliminary phase, the eligible texts were evaluated for their methodological strength, representing the fourth and last relevance test filter used. At this time, the review was performed blindly to the authors and journals, in order to avoid any selection bias and possible conflicts of interest.

The studies were synthesized and distributed in a table containing the following information: author and year of publication, model, supplementation dosage and duration and results, reported in the results section of this article (According to Flowchart).

3. Results and Discussion

3.1. Turmeric Glycemic Control and Insulin Sensitivity

The World Health Organization (WHO) has been increasingly committed to encouraging the expansion of public policies that prioritize the applicability of medicinal plants in the health system [21,27]. As for the worldwide assessment of bioactive potential, it is estimated that there are around 350,000 plant species, however, less than 15% was evaluated. Therefore, it is necessary to research about new plant biomolecules, since there are a large number of plant species used by the population that remain without studies and/or without evidence of their effects on the organism [27].

Following this, there is the turmeric (Curcuma longa L.), being on the list of the National List of Medicinal Plants of Interest to the Unified Health System, being a compound highly used in world cuisine as a species of condiment as well as in therapeutic activities through popular knowledge, being scientifically proven [28]. Curcumininoid, extracted from Curcuma Longa rhizomes is the main active compound of turmeric, its yellow color is responsible for its biological actions [29,30].

Treatment with curcumin, either in its solubilized form in ethanolic extracts, incorporated in carboxymethylcellulose, or even in water is promising in the fight against diabetes by having effects on glycemic control, among them, the use of curcumin promotes the reduction of glycated hemoglobin concentration, as a consequence, a reduction in plasma glucose concentration is evidenced. Given this evidence, it is indicated as a possible drug for glycemic control [31].

There are several data in the literature indicating a wide variety of pharmacological activities for C. longa, proving anti-inflammatory, antiviral, antibacterial, antioxidant, antifungal, anticarcinogenic activities, among other therapeutic actions [20]. In the present review, among the articles selected as

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shown in Table 1 (and other studies, as follows below), oral supplementation of turmeric at a dose of 100 mg/kg and weight 200 mg/kg for sixteen weeks promoted a reduction in the concentration of blood glucose and diabetes-induced attenuation of body weight loss, as well as a strong antioxidant capacity in the retina of diabetic rats. An antiapoptotic effect was observed by increasing the expression of B-cell lymphoma protein 2 (Bcl-2) and the down regulation of associated protein X (Bax) expression in the retina of diabetic rats, where it was concluded that curcumin has great potential in the treatment of diabetic retinopathy, which is probably attributed to its hypoglycemic and antioxidant effect [32].

Table 1. Articles analyzed and selected according to pre-established inclusion criteria

Author and year	Model	Dose and Duration	Results
Nicol et al. (2015)[24]	17 men	2,5g curcumin twice a day for eccentric exercise, 2 days before and 3 days after.	↓ Ck activity, ↑ IL-6, = TNF-alpha.
Yang et al. (2018)[32]	Diabetic rats	A group received 100 mg/kg of curcumin and other group 200 mg. 16 weeks.	↓ blood glucose, ↓ body weight loss.
Rashid et al. (2017)[33]	Diabetic rats	100 mg/kg of curcumin daily for 8 weeks.	↑ inflammatory cytokines, ↑ NFkB pathway translocation, ↓ cytosolic NFkB expression, ↑ IkBa, NFkB.
Zhao et al. (2017)[34]	Diabetic and obese rats	100 mg/kg body weight during 8 weeks.	↓ apoptosis in testicular cells, ↓ Bax, ↑ expressions of Bcl-2, ↓ MDA, ↑ SOD.
Guo et al. (2018)[35]	Diabetic rats	300 mg/kg. 16 weeks.	↓ TGF-β1, ↑ Smad7 expression, ↑ AMPK, p38 and MAPK.
Kant et al. (2017)[36]	Diabetic rats	0.15% curcumin topically once a day for 19 days.	↓MDA, ↑ SOD.
Xie et al. (2018)[37]	Sprague-Dawley diabetic rats	Treated with 1.0% curcumin (weight ratio) mixed on their diet for 21 days.	↓ body weight loss, ↓ blood glucose concentration, ↓ insulin concentration, ↑ antioxidant genes.
Panahi et al. (2018)[38]	People with diabetes	500 mg/day co-administered with piperine 5 mg/day for 3 months.	↓ insulin, HbA1c and HOMA-IR ↓ glucose and Peptide C, ↓ ALT and AST.
Panahi et al. (2015)[39]	People with diabetes	1000 mg/day + piperine, 10 mg/day, 12 weeks .	↓ IMC, LDL-C, CT, TG, LDL-C and non-HDL-C, ↑ HDL-C.

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Haryuna et al. (2017)[40]	Wistar diabetic rats	Groups 3 and 4 received curcumin therapy of 200 and 400 mg/kg for 3 days. Group 5 and 6 200 and 400 mg/kg for 8 days.	↑ SOD expression in cochlear fibroblasts, ↓ ROS, ↓ NADPH, ↓ oxidase, lipoxygenase, dehydrogenous xanthine and nitric oxide synthase.
Kant et al. (2014)[41]	Diabetic rats	Curcumin (0.3%) in pluronic gel once a day for 19 days.	↑ [ ] anti-inflammatory cytokine (IL-10), ↓ Ser52, GRP78, CHOP, ↓ TNF-a, ↑ mRNA of IL-10, ↓ IL-1b; MMP-9.
Su; Wang; Chi (2017)[42]	Diabetic rats with T2DM	Received the medication for eight consecutive weeks	↑ [ ] AGL and TNF-α, ↓ FBG; AUCs, ↓ blood glucose, ↓ insulin.
Tanabe et al. (2018)[43]	Healthy men	Group 1 ingested 180 mg/day of Curcuma 7 days before isokinetic eccentric exercise. Group 2 ingested 180 mg/day– 1 CUR 7 days after isokinetic eccentric exercise.	↑ IL-8, ↓ CK.
Akazawa et al. (2018)[44]	Postmenopausal women	150 mg/day of curcumin along with aerobic exercise training for 8 weeks.	↑ flow-mediated dilation in postmenopausal women, ↑ endothelial function.
Chilelli et al. (2016)[45]	25 healthy individuals receiving Mediterranean diet and curcumin Boswellia serrata (BSE)	12 weeks	↑ TNG, ↓ Srage and NEFA, ↓ MDA.
Sugawara et al. (2012)[46]	45 women	Curcumin 150 mg/day, along with physical training with curcumin for 8 weeks.	↓ PAS, ↓ ALX, ↑VO_2 peak, ↓ LV afterload.
Takahashi et al. (2014)[47]	10 men .	90 mg of curcumin 2h before exercise and immediately after exercise for 60 min.	↑ ROMs, ↑ TRX-1, =TBARS, GSSG and GSH.

Notes. **IκBα** - nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha; **NFkB -** fator nuclear kappa B; **BAX** - associated protein X; **BCL-2** - B-cell lymphoma protein 2; **MDA** – Malonaldeído; **SOD** – superoxide dismutase; **TGF-β1** - transforming growth factor beta; **Smad 7** - induction and down-regulation of; **AMPK** - Adenosine monophosphate activated kinase; **MAPK** - mitogen actived protein kinase; **HbA1c** -

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glycated hemoglobin; **HOMA-IR** - homeostatic model assessment; **ALT**- alanina aminotransferase; **AST** - Aspartato aminotransferase; **IMC** - Body Mass Index; **LDL-C** - Low Density Lipoprotein; **CT**- Total Cholesterol; **TG** - triglycerides; **HDL-C** - High Density Lipoprotein; **ROS** - reactive oxygen species; **NADPH** - the chemically reduced form of NADP; **IL-10** - interleukins 10; **Ser52** - Phospho-eIF2a; **GRP78** - glucose-regulated protein 78; **CHOP** - C/EBP homologus protein; **TNF-a** - Tumor necrosis factor; **IL-1b** – interleukins 1b; **MMP-9** - Matrix metallopeptidase 9**; AGL**- glycosylation; **FBG** - fibrinogen-like; **AUCs** - areas under the curve**; IL-8** - interleukins 8; **CK** - Creatine kinase; **TNG** - Tumor necrosis factor; **Srage** - soluble receptor for AGE; **NEFA** - non-esterified fatty acid; **MDA** - malondialdehyde; **IL-6** - interleukins 6; **LV** – left ventricle; **ROMs** - reactive oxygen metabolites; **TRX-1** - Thioredoxin; **TBARS** - Thiobarbituric acid reactive substances**; GSSG** - glutathione disulfide; **GSH –** glutathione; **P38 -** mitogen-activated protein kinases; **mRNa** - Messenger RNA, Non HDL Cholesterol; **VO2 peak** - maximum oxygen consumption reached before stabilization of the amount of oxygen captured; **[ ]** - Concentration; ↑ - increase; ↓ - decrease; = - no change.

Oral curcumin supplementation was effective at a dose of 100mg/kg body weight at 8 weeks in improving hyperglycemia and restoring body weight in the animal model. In addition, the spleen, considered as a peripheral immune organ, showed white pulp reductions and red pulp activation in the diabetic group, thus curcumin treatment after diabetes induction restored and improved splenic tissue under conditions close to the control group [33].

Among the ways to evaluate circulating blood glucose, the oral glucose tolerance test (OGTT) is considered by WHO as the ideal method for the diagnosis of DM, both individually and in epidemiological studies. When glucose intolerance is installed, it represents an initial pathophysiological picture of the pathogenesis of T2DM and possibly may contribute to the development of cardiovascular diseases [4].

Su, Wang and Chi [42], who assessed blood glucose by the glucose tolerance test and found that 30 min after curcumin supplementation decreased blood glucose after the 4th week, while blood glucose between 60 to 120 minutes reductions up to week 4 compared to the other groups, at week 8 observed glycemic controls in both groups. In the insulin tolerance test showed that in the same period the concentration of FBG in the curcumin group was lower than in the control group. Following subcutaneous application of insulin, it was found that blood glucose between 40 minutes and 90 minutes in the curcumin group was decreased. Thus, research has shown that curcumin treatment after 8 weeks has significantly improved metabolic parameters such as increased insulin sensitivity and increased glucose tolerance. The same study showed that curcuminoid supplementation can reduce serum atherogenic lipid levels in low-intensity lipoprotein cholesterol (LDL-C), total cholesterol (TC), and triglycerides (TG).

The studies by Panahi et al. [39] also showed benefits related to the decrease in serum lipid levels, in which the combined therapy of curcuminoids (1000 mg/day) associated with piperine (10 mg/day) was used for 12 weeks and found that TC, LDL-C, TG and lipoprotein C showed significant reductions. In addition to these effects, it was found an increase in serum concentration of high density lipoproteins HDL-C.

The American Diabetes Association used glycosylated hemoglobin (HbA1c) as a method for diagnosing prediabetes and DM. HbA1c is the standardized dosing method defined by the International Expert Committee. Values for type 1 and 2 diabetes equal to or above 6.5% are considered. HbA1c has many advantages over fasting blood glucose for the diagnosis of DM, especially the higher pre-analytical stability and lower daily variation during periods of stress or disease [11].

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The study by Panahi et al. [38] using combination therapy (500 mg/day co-administered with piperine 5 mg/day orally using capsules) or placebo for 3 months, observed a significant reduction in serum glucose concentration in both groups, as well as such as C-peptide and HbA1c after curcuminoid supplementation compared to placebo group, revealing beneficial effects regarding curcumin and piperine supplementation in glycemic parameters, as shown in the study by Su, Wang and Chi [42].

The study by Xie et al. [37], where diabetic rats were orally supplemented with curcumin, there was a marked reduction in plasma glucose concentration, plasma malondialdehyde concentration and plasma glutathione peroxidase (GSH-Px) and catalase activity (CAT), however, increased the content of superoxide dismutase (SOD) and insulin. The results show that oxidative stress in diabetic rats can be attenuated by curcumin via activation of the Keap1-Nrf2-ARE signaling pathway, as evidenced by a decrease in blood glucose concentration, as in the research by Panahi et al. [38] and an increase in the transcription of antioxidant genes.

Most studies analyzing the relationship between Curcuma longa and DM, showed that turmeric intake acted in glycemic control and normalization of insulin resistance, these effects are partly due to molecular adjustments. Therefore, turmeric has potential as a form of adjuvant therapy for patients with DM.

3.2 Intracellular and Antioxidant Effects of Curcumin

Compounds such as uric acid, ascorbic acid, reduced glutathione, α-tocopherol, sulfhydryl containing molecules, CAT, SOD, glutathione peroxicity participate in the body's antioxidant defense systems [48]. The analysis of these molecules by biochemical tests has been recommended to elucidate the functional and structural abnormalities caused by diabetes, which is related to impaired endogenous antioxidant capacity. As a consequence, there is an increase in reactive species and free radicals, especially nitrogen and oxygen. The polyol pathway, non-enzymatic glycation products is related to hyperglycemia and has been used as a possible marker related to increased free radical plasma concentration in patients with diabetes [49].

Xie et al. [37] in their study found an increase in the expression of CAT, GSH-Px, heme oxygenase 1 and NADPH dehydrogenase 1 enzymes and a decrease in SOD1 expression, thus reducing oxidative stress. It was evidenced that oxidative stress in diabetic rats can be attenuated by curcumin by activating the Keap1-Nrf2-ARE signaling pathway, which is due to the decrease in blood glucose concentration and increase in the transcription of antioxidant genes.

In the study by Haryuna et al. [40], twenty-four rats were divided into six groups, 1 as control, 2 as diabetic, 3 and 4 as diabetic who received curcumin therapy of 200 and 400 mg/kg for 3 days, and 5 and 6 as diabetics who received curcumin treatment of 200 to 400 mg for 8 days to determine SOD expression, it was detected that there was a decrease in SOD expression in the diabetic group (without curcumin treatment). Treatment of curcumin at doses of 200 and 400 mg/kg for 3 and 8 days led to a significant difference in SOD expression compared to the diabetic group (without curcumin treatment). No significant differences were found between dose and duration of expression from SOD. Curcumin has been shown to be an important antioxidant against oxidative stress in diabetes, as well as in the research by Xie et al. [37], through the expression of SOD in cochlear fibroblasts.

A study by Zhao [34], where diabetic and obese rats were treated with a daily dose of curcumin, found that curcumin treatment significantly reduced apoptosis in rat testicular cells, also showed in their molecular analysis that treatment curcumin significantly and simultaneously decreased

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oncogenic proteins that inhibit apoptosis to Bax and increased Bcl-2 expressions, increasing the Bcl-2/Bax ratio, as shown by the study by Yang et al. [32]. In addition, curcumin treatment significantly decreased malondialdehyde (MDA) and increased SOD concentration, as shown by the results of Xie et al. [37]. In conclusion, curcumin's ability to inhibit oxidative stress and modulate the Bax/Bcl-2-mediated cell death pathway reveals its potential as a therapeutic agent against diabetes.

Rashid [33], in his work, resulted in curcumin supplementation with stress-dependent cell death of the endoplasmic reticulum (ER), showed induction of eIF2α and CHOP-mediated signaling pathways, as well as increased expression of GRP78, Caspase-12, Calpain-1, phospho JNK, phospho p38 and phospho p53 in the diabetic group. Curcumin treatment in this research protected cells from inflammatory and ER damage, as well as mitochondrial apoptotic death, further suggest that curcumin has the potential to act as a therapeutic antidiabetic, antioxidant, anti-inflammatory, and antiapoptotic agent against mediated splenic damage for diabetes.

Research by Guo et al. [35] shows that orally supplemented curcumin promotes an improvement in collagen deposition in the cardiac tissue of diabetic rats. These authors showed an increase in deposition of type I and type III collagen in cardiac tissues, accompanied by a marked reduction in the production of transforming growth factor β1 (TGF-β1). Curcumin supplementation inhibited TGF-β1-induced activated protein kinase (AMPK)/p38 MAPK activation and inhibited synthesis of collagen fibroblast synthesis. These results demonstrate the beneficial function of curcumin in collagen synthesis in diabetic rats, as shown by the studies by Kant et al. [36,41].

Regarding the positive effects of turmeric intracellular changes, we observed in the research by Yang et al. [32] that neuroprotective and regulatory properties occurred in the concentration of vascular endothelial growth factor, which plays an important regulatory role in physiological vascular development.

In this sense, these studies demonstrate that curcumin is able to attenuate oxidative stress, these effects are due in part to increased expression and/or activity of antioxidant enzymes that can attenuate mitochondrial dysfunction, liver damage and reduce inflammatory processes.

3.3 Physical Exercise and Curcuma

Physical exercise is characterized by repetition of directed movements, with an increase in oxygen consumption caused by the recruitment of muscle fibers at the moment of the movement action [50]. Exercise is a subgroup of physical activity in an elaborate and oriented manner in order to maintain physical fitness. We can also define it as any muscle movement that results in strength [51].

Regular practice of physical activity when designed in the form of an appropriate training program, respecting each practitioner's biological individuality with appropriate intensity, duration, frequency and progression, will result in benefits to components related to the organism's functional health. Thus, it is able to prevent and/or mitigate the effects of degenerative chronic diseases such as hypertension, diabetes, obesity, arthrosis, osteoporosis, dyslipidemia, metabolic syndrome, among others [52].

There are few studies evaluating the effects of physical exercise associated with Turmeric supplementation. In the study by Tanabe et al. [43], the effects of oral curcumin ingested before and after eccentric exercise on markers of muscle injury and inflammation in healthy men who ingested 180 mg/day Curcuma for 7 days were observed to decrease of IL-8 after 12 hours of physical exercise.

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Creatine kinase (CK) activity was also lower between 3-6 days and 5-7 days after exercise. Thus, ingestion of curcumin after exercise can attenuate muscle damage and facilitate faster recovery.

In a study by Akazawa et al. [44], where women ingested turmeric 150 mg/day and underwent aerobic exercise training for 8 weeks, it was observed that there was an increase in flow-mediated endothelial dilation while no changes were observed in the control group. In this study it was found that curcumin intake and aerobic exercise training increase flow-mediated dilation in women, both improving age-related decline in endothelial function.

By relating physical exercise to dietary planning, Chilelli et al. [45] demonstrated that healthy male athletes who received a Mediterranean diet and supplementation with Curcumin and Boswellia serrata (BSE) after 12 weeks of exercise showed decreased fatty acids. (NEFA), MDA and total soluble receptor for (Srage) in the supplemented group. Therefore, supplementation with curcumin and BSE demonstrates positive effects on chronic glycosylation and lipid peroxidation in athletes.

For male individuals, the study by Nicol et al. [24] evaluated men who received oral curcumin supplementation at a dosage of 2.5g twice daily two days before and three days after eccentric exercise. These individuals identified that between 24 and 48 hours post-exercise, curcumin was able to reduce moderate exercise pain and small reductions in creatine kinase activity. In the same study, they found that curcumin increased interleukin-6 concentrations by 0 hours and 48 hours from baseline. However, supplementation decreased IL-6 at 24 hours after exercise. Therefore consumption of curcumin probably promotes greater efficiency in recovery and muscle performance after training.

In the study by Sugawara et al. [46], female subjects were divided into four interventions: “placebo intake”, “curcumin intake”, “placebo intake exercise”, and “curcumin intake physical training”. The dosage of curcumin or placebo (150 mg/day) was administered for 8 weeks. They observed that after the interventions, systolic blood pressure (SBP) decreased significantly in both groups, whereas aortic SBP decreased significantly only in the combination treatment group between exercise and curcumin supplementation. These studies suggest that regular endurance exercise associated with daily curcumin intake may reduce left ventricular afterload to an extent greater than monotherapy with any single intervention.

Takahashi et al. [47] conducted a study in which male participants were divided into three groups: Control (placebo), isolated (only before exercise) and double (before and immediately after exercises with curcumin supplementation). Each subject received oral administration of 90 mg curcumin or placebo 2 hours before exercise and immediately after exercise. Reactive oxygen metabolites such as ROMs and TRX- measured after exercise were significantly higher than pre-exercise values. The serum biological antioxidant potential assessed by the plasma Tbars evaluated and concentrations measured immediately after exercise were significantly elevated in the curcumin supplementation group compared with pre-exercise values. These results suggest that curcumin supplementation may attenuate stress-induced oxidation caused by exercise, increasing the antioxidant effect.

Exercise is able to promote beneficial adjustments in aerobic capacity, lipid and glycemic control as it controls insulin and glucose homeostasis, promotes increased fatty acid oxidation in the muscles and reduces blood glucose concentration in addition to attenuating systemic inflammation and improve immune cell function [53,54].

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In view of that, physical exercise can be used as an important therapeutic form in Diabetes because it is able to increase glucose uptake by skeletal muscle, using an insulin-independent pathway. In addition, physical exercise associated with Curcuma Longa supplementation improves mitochondrial activity and antioxidant defenses, thus reducing oxidative stress.

3.4 *Toxicity, Adverse Effects and Contraindication*

Studies evaluating oral toxicity in rats by continuous use of up to 0.5 g/kg *Curcuma L.* essential oil for 13 weeks and curcumin up to 10,000 ppm for 70 days did not show signs of toxicity, death and/or organ changes [55].

In humans, turmeric consumption toxicity was not observed either, but maximum doses of 8000 mg/day for up to 3 months are recommended. It is noteworthy that the excessive consumption of turmeric extract may cause drowsiness and gastrointestinal irritation, especially in individuals with hypersensitive stomach [56].

According to the Food and Agriculture Organization/World Health Organization committee, which among its activities assess toxicity for food additives and seasonings, the recommended Acceptable Daily Intake for turmeric and curcumin is 0.1 to 2.5 mg/kg in weight [57].

As with all nutritional supplementation, some studies have observed relevant adverse effects. Turmeric consumption is contraindicated for patients with gastric ulcers, hemorrhagic disorders and gallstones [56,58]. In addition, the essential oil present in turmeric, due to its stimulating action, can induce abortion when consumed in inadequate doses [58]. Thus, for pregnant women, nursing mothers and children under 4 years of age, its use is contraindicated. Individuals taking anticoagulants, antiaggregants and thrombotic agents [59] as well as those who are allergic or sensitive to turmeric or any other plant component should not use any dose of turmeric or its derivatives [56].

Overall, evidence from prospective studies on turmeric supplementation intake in relation to the risk of toxicity did not show signs of toxicity, but its consumption is contraindicated in pregnant women, infants, children under 4 years of age, with disorders hemorrahagic and gallstones and gastric ulcers. Additional long-term studies are needed to further elucidate the associations between turmeric intake / supplementation and risk of toxicity.

5. Conclusions

The results found in this research suggest that Curcuma longa supplementation has therapeutic action. Of the selected articles turmeric had some beneficial effect in diabetics as better control of blood glucose and insulin sensitivity, acting also as a protective factor of cells against inflammatory mediators.

The effects of physical exercise, associated with turmeric supplementation, were effective in attenuating oxidative stress mediated by tissue damage markers, improved recovery after exercise and antioxidant effect. These evidences suggest that the association of turmeric with physical exercise is promising as to its use for DM attenuation, and it is necessary that researchers can determine the concentration, frequency and use of turmeric to achieve the maximum effect.

6. Patents

We also wish to declare that we do not have any patents resulting from this work.

Author Contributions: Conceptualization, A.S.S.J.; methodology, A.S.S.J. and J.L.S.; formal analysis, A.S.S.J. and A.C.M.; investigation, A.S.S.J., F.J.A, A.M.O.S. and J.L.S.; data curation, A.S.S.J., F.J.A., A.M.O.S. and J.L.S.; writing—original draft preparation, A.S.S.J.; writing—review and editing, F.J.A., A.M.O.S., F.B.S, J.L.S. and A.C.M.; project administration, A.S.S.J.

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