Curcumin and insulin resistance Molecular targets and clinical evidences

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Abstract

Curcumin ((1E,6E)- 1,7-bi s(4-hyd roxy -3-m ethoxy phenyl)-1,6- hept ad iene-3,5-d ione), t he m ain co mpo nent of th e Ind ian sp ice tu rm eri c, has been used in t raditional medicine to improve diabetes and its comorbidities. Since t he last two decades, sci- entific research has shown t hat in addition to its antioxidant properties, curcumin could also work as protein homeostasis regulator and it is able to modulate other intracellular path- ways. Curcumin supp lementation has been proposed t o im prove insuli n resistance (IR) t hr oug h t he acti va tio n of t he insu li n recep t o r and its dow nstr eam pa th ways in seve ral ex perim ental models, point ing ou t t hat its cli nical use may be a good and innocuous strategy to improve IR-related d iseases . IR is assoc iated w ith many d iseases and sy nd ro m es li ke car- bohyd rate int o lerance, d iabetes, m eta bo li c sy nd ro m e, and car-

Keywords: curcumin; insulin resistance; obesity; prediabetes; diabetes

Introduction

Due to its potential to improve a broad spectrum of diseases, the interest of the scie ntific community in curcumin has signif- icantly increased during the last two decades. For many years, curcumin was just the yellow pigment, obtained from turmeric (the rhizome of Curcuma longa), used in oriental cuisine as colorant and flavoring in foods [1]. However, its use in tradi-

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diovascu lar disease . Therefo re, it is im perati ve to identify safe therapeutic interventions aimed to reduce side effects t hat could lead t he patient to leave t he t reatment. To date, many clinical t rials have been carri ed out using turmeric and curcu- min to improve metabolic syndrome, carbohydrate intoler- ance, diabetes, and obesity in individuals with IR. Resu lts so far are in conclus ive because dose , t im e of t reatm ent, and type of curcumin can change the study outcome significantly. How- ever, there is some clinical evidence suggesting a benefic ial effect of curcumin on IR. In t hi s rev iew, we d iscuss t he fac to rs th at cou ld in fl uence cu rcu m in eff ects in clini cal tri als aimed to improve IR and related d iseases , and t he co nclus io ns t hat can be draw n from results obtained so far. c

traditional medicine has attracted scientific inter est directed to elucidate the possible therap eutic effects of curcumin on the onset, development, or progression of se veral diseases. In a variety of studi es (in vitro, in vivo, or clinical), anti- inflammatory (2-4], antioxidant (5,6], a nti-carcinogenic (7-9], anti-aging (10-12], anti-infectious (13,14], neuro-protective (15,16], and car dio-protective (17,18] effe cts of curcumin have been described. Furthermore, the recently descr ibed activity of curcumin as regulator of prot ein homeostasis (i.e., the balance among protein synthesis, degrada tion, folding, and aggr ega- tion) could have deep implications in the control of several molecular mechanisms involved in preventing and/ or amelio- rating the physiopathology of a number of chronic diseases such as, some types of cancer (19-22], Parkinson's disease (23,24], Alzheimer 's disease (25,26], Huntington's disease (27], depression (28,29], arthritis (30], liver diseases (31-33], cardi- ovascular disease (17,34], pancrea titis (35,36], and those related with insulin resistance (IR) (37,38]. Therefore, cur cu- min may prevent a ging-associated protein insolubility and aggregation in cells by preventing the loss in protein homeo- stasis associated with several age-related diseases. Recently, curcumin has been found to extend lifespan in the nematode Caenorhabditis elegans by maintaining protein homeostasis [10]. Is important to remark that protein aggregation has been suggested to drive b pancreatic cells degeneration [39]. Addi- tionally, a master regulator of inflammation and stress, the nuclear transcription factor (erythroid-derived 2) related factor 2 (Nrf-2), has been involved in the protection of b pancreatic cells by decreasing inflammation in cells surrounding the pan- creatic islets [40]. Altogether, these results suggest that the beneficial effect of curcumin on IR, and potentially diabetes, could be at least partially mediated through protein homeosta- sis regulation.

IR is a physiological condition characterized by the impair- ment of the insulin activity on insulin-target tissues. Therefore, IR is often observed in skeletal muscle, adipocytes, and liver [41]. Once IR is established, there is a high risk to develop type 2 diabetes (T2DM) and/or vascular diseases [42,43]. IR is one of the two main events that seem to be critical to the onset of T2DM, the second one being a progressive decline of b-cell function and insulin production [44]. Thus, compounds that improve IR and slow down/stop progressive b-cell dysfunction are attractive candidates for prevention and treatment of IR and potentially T2DM.

A bulk of experimental and clinical evidence suggests that curcumin can acts as an alternative treatment for prevention and management of T2DM complications. For example, using rat and mouse models of IR and diabetes, it has been shown that curcumin increases insulin sensitivity by improving insulin sig- naling [37,45–47]. Additionally, curcumin administration in rats decreased glucose and glycated hemoglobin (HbA1c) levels by improving b-cell function and insulin secretion [40,48,49], improving glucose homeostasis [50,51]), suppressing gluconeo- genic enzymes [52], and by recruiting glucose transporters to the cell surface [53,54]. Nevertheless, in clinical practice, stud- ies based on turmeric and curcumin supplementation delivered controversial results. For example, in T2DM subjects, curcumin supplementation of 300 mg/day has been shown effective to reduce fasting plasma glucose (FPG) [55]. However, this effect was not observed in other clinical trials conducted with T2DM subjects [56] and in individuals with diabetic nephropathy treated with 1.5 g of curcuminoids per day [57]. This is just one example of how many factors like ethnicity, dose, type of curcu- minoids employed, and the bioavailability of curcumin are cru- cial to obtain reliable and reproducible results through a good study design. In this review, we analyze how these factors impact the results of the clinical trials using curcumin supple- mentation, available so far, in IR and IR-related diseases.

Curcumin Sources and Metabolism

Curcumin along with other phytochemicals like demethoxycur- cumin, bisdemethoxycurcumin, zingiberene, curcumenol, cur- cumol, eugenol, tetrahydrocurcumin (THC), triethylcurcumin, turmerin, turmerones, and turmeronols can be found in the turmeric obtained from the rhizome of C. longa. Compared with other related species such as Curcuma mangga, Curcuma zedoaria, Costus speciosus, Curcuma xanthorrhiza, Curcuma aromatica, Curcuma phaeocaulis, Etlingera elatior, and Zin- giber cassumunar turmeric contains the highest levels of cur- cuminoids [58]. The total amount of curcuminoids found in turmeric represents just 2–8% of the total dry weight of the rhizomes. Curcumin is the principal and most abundant curcu- minoid in turmeric (represents ~80% of total curcuminoids) and its activity is associated to most of the therapeutic effects. Other less-abundant curcuminoids isolated from turmeric are demethoxycurcumin and bisdemethoxycurcumin that comprise 17% and 3%, respectively [59].

Due to their structure, curcumoinoids are almost insoluble in aqueous solution that contributes to a poor bioavailability. After oral administration of 1 g/kg of curcumin, only negligible amounts of free curcumin could be found in the plasma of Sprague-Dawley rats and about to 75% was excreted in the feces which suggest poor absorption in the gut [60]. Holder et al. [61] showed that deuterium and tritium-labeled curcu- min, administered intravenously in a dose of 50 mg/kg, was excreted in the bile of cannulated rats and was detectable as glucoronide conjugates of THC and hexahydrocurcumin. In a later study, curcumin metabolites were analyzed by reversed- phase HPLC in the plasma from mice after oral administration of curcumin (0.1 g/kg). Interestingly, this study found that low concentrations of curcumin (0.13 lg/mL) were detected in after 15 min and the maximum level (0.22 lg/mL) was reached after 1 h. In this study, the maximum concentration in plasma (2.22 lg/mL) was reached via intraperitoneal, 15 min after the administration of the same dose of curcumin. The hydrolysis with b-glucoronidase showed that 99% of curcumin and up to 85% of THC is conjugated with glucoronide in the plasma [62]. This was confirmed later, using plasma samples from healthy people administrated with 10 and 12 g of curcumin extract [63]. These results suggest that curcumin is absorbed after oral administration, but the curcumin conjugates may be the potential metabolites that exert biological action and protec- tion by its transport to others organs, such as occurs in colo- rectal cancer [64], breast cancer [65], and diabetic rats [66].

Besides administration, the pH is another factor that influ- ences curcumin bioavailability. At neutral–basic conditions (pH ranges of 7–10) more than 90% of curcumin is degraded [58]. In

spite of its low absorption and its susceptibility to suffer structural modifications by the pH, free curcumin has been found in different tissues. For example, hepatocytes can reduce curcumin to hexahydrocurcumin and hexahydrocurcu- minol [67]. In the liver and the portal circulation, traces of free curcumin (10 8 M) and its metabolites have been found [68]. Additionally, curcumin is biotransformed to curcumin glucoronide, curcumin sulfate, THC, and hexahydrocurcumin in the intestinal tract of humans and rodents. The intestinal mucosa and kidney, as well as liver, can add glucuronidate and sulfate to curcumin [69]. To overcom bioavailability issues, new formulations of curcumin/curcuminoids have been developed. In an elegant study, Shoba et al. demonstrated that curcumin was almost undetectable in the serum of eight human volunteers 6 h after oral intake of 2 g of curcumin. However, when 1% piperine was co-administered, curcumin concentrations were significantly increased in serum (up to 1.8 lg/mL) after up to 45 min, being undetectable 1 h after intake [70]. In this sense, it is important to remark that intravenous administration of curcumin has shown the best bioavailability for curcumin distribution in animals [71]; however, this type of administration is unpractical when it comes to clinical trials since it requires daily invasive interventions. Therefore, it is important to carefully consider all these factors when an inter- vention involving curcumin is designed. Despite its poor absorption, the animal and clinical studies available in the sci- entific literature reporting some effect of curcumin in meta- bolic diseases, as IR, strongly suggest that curcumin and its metabolites can be worthy candidates for a pharmacological intervention in these kind of diseases. The fact that liver and gut, among other organs, are mainly involved in curcumin metabolism, an uptake suggests those organs as main targets of curcumin; however, several metabolites could still reach distant tissues where they can act on metabolic pathways to influence health and disease.

Curcumin Targets in Insulin Resistance

Liver, muscle, and adipose tissue are the main target organs of insulin. Therefore, many pharmacological interventions have been addressed to improve IR in these organs. In line with this, curcumin has been used for many years as coadju- vant in diabetes treatment in oriental countries with some kind of success [72–74] but only recently, scientific research has focused in identifying the molecular pathways activated by curcumin to exert its anti-diabetic effect. In Table 1, we sum- marize the potential actions of curcumin to improve IR in the main insulin target organs according to the experimental evi- dence available to date.

The beneficial effects of curcumin on IR have been widely studied in animals fed with high fat diet (HFD) or fructose [32,75–80], in genetic models of diabetes [53], in combination with HFD and streptozotocin (STZ) [78,79], and in cell lines like C2C12 mouse skeletal muscle cells [46] and adipocytes [78]. For several decades it was thought that curcumin exerts its anti-diabetic effects by acting as anti-hyperglycemic com- pound [53,76–79]. In concordance, curcumin supplementation decreases plasma glucose through several mechanisms that include the activation of glycolytic enzymes, the increased activity of hepatic glucokinase (GK) and glycogen content, and downregulation of the gluconeogenic enzymes by inhibition of glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate car- boxykinase (PEPCK) activities [53]. GK catalyzes the conver- sion of glucose to glucose-6-phosphate, and its activity is inhib- ited by the protein kinase A (PKA) and stimulated by AMP activated protein kinase (AMPK) [81]. Curcumin reduces PKA activity and activates AMPK in rat hepatocytes [56] and adipo- cytes [82], inhibits G6Pase activity and PEPCK and increases AMP kinase alpha-Thr (172) in hepatocytes [83]. Therefore, it is possible to suggest that AMPK protein could be the curcu- min's main target for the regulation of hepatic glucose homeostasis.

It is important to note that glucose homeostasis is not always achieved in this kind of experimental models after cur- cumin treatment [32,75,80]. We suggest that the time of administration, doses, and vehicle employed are critical fac- tors to achieve a significant effect on glucose levels. As can be seen in Table 1, a major problem of these studies is that sev- eral concentrations of curcumin have been used to evaluate different markers of glucose homeostasis with varying results. Additionally, sometimes curcumin is administrated with differ- ent vehicles, in order to increase its absorption that could pro- duce deleterious effects. For example, when curcumin was dis- solved in hazelnut oil, no effect on FPG, insulin, and serum lipid levels was observed [80]. This may be due to an increase in IR elicited by an oil-induced rise in free-fatty acids. There- fore, factors like dose, time of the experiment, and the type of curcumin could be crucial to obtain the desired physiological effects.

Upon IR, the pancreas produces more insulin to maintain the adequate levels of blood glucose. In IR models without hyperglycemia, curcumin is able to reduce the peak of insulin production and increases insulin sensitivity [78], while in dia- betic rats, where hyperglycemia was induced by HFD and STZ, curcumin administration has been demonstrated to increase insulin production by the pancreas [76]. This dual effect of curcumin is important as potential prediabetic treatment because it is desirable to use a compound able to increase insulin sensitivity and, at the same time, reduces the peak of insulin production by the pancreas.

In order to understand the anti-diabetic potential of curcu- min, it is important to note that curcumin can improve IR through three different mechanisms; (i) Acting at the insulin receptor level, (ii) activating the insulin pathway, and (iii) the inhibition of inflammation and oxidative stress.

Curcumin Activates Insulin Receptor

In male Sprague-Dawley rats fed with fructose to induce IR, oral administration of curcumin (15, 30, and 60 mg/kg) increased insulin receptor activity via tyrosine phosphorylation in liver homogenates [32], probably via the inhibition of protein-tyrosine phosphatase 1B (PTP1B) since this protein is considered as negative regulator of insulin signaling [84]. In line with this idea, curcumin supplementation was able to inhibit PTB1B expression in the liver, leading to a reduction in the very low-density lipoprotein (VLDL) overproduction charac- teristic of the IR stage in liver [32]. Additionally, the ability of curcumin to downregulate PTP1B expression ameliorates glomerular podocyte injury and proteinuria in rats with IR [85].

However, the role of PTP1B in IR may be tissue-specific. In skeletal muscle of insulin-resistant Zucker rats, it has been reported that PTP1B activity is decreased [86], while another study reported increased PTP1B protein levels in genetic mod- els of IR-obesity and DM [87]. These results point to the rele- vance of PTP1B as a potential therapeutic target, considering that other PTPases could participate in a tissue-specific man- ner. Additionally, it is crucial to consider that insulin signaling is activated in cancer to maintain the rate of cell growth [88,89]. PTP1B is increased in various types of cancer suggest- ing its role as stimulator of cell growth in some types of can- cers [90–92]. Nevertheless, decreased levels of PTP1B have also been observed in oesophageal cancer lesions compared with that in the surrounding normal mucosa [93]. Therefore, despite that the inhibition of PTP1B may be a promising target to treat IR, it is of seminal importance to investigate the PTP1B tissue-specific response and its chronic inhibition effects in normal and cancer cells.

Curcumin Activates Insulin Pathway

It is known that curcumin administration increases glucose uptake in muscle [46,76,94] and adipose tissue [95] but the underlying mechanism is still unclear and in consequence an active field of research. A potential target of curcumin in insu- lin signaling is the insulin receptor substrate-1 (IRS1). Upon IR, IRS1 is phosphorylated in serine and threonine residues leading to lower tyrosine kinase activity [96,97]. In diabetic rats, the reduction of IRS1 Tyr-phosphorylation is responsible for decreased activation of protein kinase B (PKB/Akt) and the extracellular signal-regulated protein kinases 1 and 2 (ERK1/ 2), exhibiting defective insulin signaling transduction [98,99]. Interestingly, in fructose-fed rats, curcumin administration of 15–60 mg/kg for four weeks enhanced insulin receptor and IRS1 Tyr phosphorylation and activated the metabolic and mitogenic pathways by phosphorylation of Akt and ERK1/2 in the liver [32]. The improvement of IR was evident as a decrease in serum VLDL and triglycerides overproduction, although FPG levels were not decreased by curcumin con- sumption in the period of treatment. Probably, higher doses and/or longer times are required to observe any beneficial effects in glucose levels. Together, these studies suggest that the primary effects of curcumin are at hepatic level, enhancing glucose metabolism.

In hepatic stellate cells (HSCs) stimulated with leptin (100 ng/mL), curcumin (5–20 lM) suppressed the leptin-activation of IRS/PI3K/Akt signaling pathway and membrane transloca- tion of the glucose transporter-4 (GLUT4). In addition, curcu- min increase GK activity by inhibiting protein kinase A (PKA) activity and increasing the AMP-activated protein kinase (AMPK) activity, leading to an augmented conversion rate of glucose to glucose-6-phosphate [56]. In differentiated cells from mouse myoblast cell line (C2C12), 3–40 lM curcumin increased glucose uptake in a dose-dependent manner. Curcu- min treatment was able to activate AMPK which phosphoryl- ates the acetyl-CoA carboxylase in Ser79 residue, without any significant effect on Akt signal. However, when C2C12 were treated with a combination of curcumin and insulin, a syner- gistic effect was observed leading to the activation of Akt sig- nal pathway and thereby cells increased insulin sensitivity more than the treatment with insulin alone [55]. Later, it was demonstrated that curcumin reduced IRS-1-Ser307 phospho- rylation in C2C12 cells with IR induced by 12-O-tetradecanoyl-phorbol-13-acetate (TPA), a protein kinase C (PKC) activator, and palmitate [46]. In addition, curcumin increased the GLUT4 expression in cell membrane in skeletal muscle cells [76] lead- ing to an increased glucose uptake. These results highlight the potential effect of curcumin as glucose homeostasis regulator, during acute and chronic insulin-associated metabolic disor- ders, by increasing glucose homeostasis in liver, improving insulin signal in liver, muscle, and adipose tissue and increas- ing glucose uptake.

Curcumin Inhibits Inflammation and Oxidative Stress in IR

Inflammation and oxidative stress have been proposed to play an important role in IR progression. However, the evidences are not conclusive so far. Obesity is considered a state of chronic low-grade inflammation where the excess of adiposity induces IR and subsequently affect the liver and muscle by releasing cytokines such as the tumor necrosis factor alpha (TNF-a), interleukins 1 and 6 (IL-1 and IL-6) through the acti- vation of c-Jun N-terminal kinase (JNK) and the nuclear factor kappa B (NF-jB) pathways [100,101]. There are many mecha- nisms by which NF-jB induces IR. NF-jB induces the expres- sion of cytokines like TNF-a, which in turn induces serine phosphorylation of IRS-1 [102], increases the expression of PTP1B [103] and the suppressor of cytokine signaling 3 (SOCS3) [104], resulting in aberrant insulin signaling and IR. Adiponectin, an anti-inflammatory protein, is known to inhibit NF-jB activation; interestingly, during obesity adiponectin levels are decreased [105,106]. Furthermore, increased pro- duction of free fatty acids (FFA) and hyperglycemia activate NF-jB activation in muscle, liver, pancreas, and adipose tissue leading to T2DM [107–110].

The inhibition of NF-jB by curcumin has been studied in several cell lines and animal models. First, it was demon- strated that 5 lM curcumin inhibited the lipopolysaccharide (LPS)-induced TNF-a and IL-1 production in a human mono- cytic macrophage cell line. This inhibition of NF-jB activation was also observed in L929 fibroblast lytic assay [111]. Using human myeloid ML-1a cells, it was reported that curcumin inhibits NF-jB activity by the stabilization of I kappa B alpha, the cytoplasmic NF-jB inhibitor [112]. Further potential tar- gets of curcumin to modulate inflammation are the downregu- lation of IjBa kinase (IKK)-b needed for NF-jB activation [113], interleukines (IL-1, IL-6, and IL-8) [114,115], the phos- phorylation of leptin receptor [116], the Wnt pathway [117], the glycogen synthase kinase (GSK) 3b [118], and c-Jun NH2 terminal kinase (JNK) [115]; moreover, the activation of adipo nectin [103] and the nuclear receptor peroxisome proliferator- activated receptor (PPAR)-c [119].

With regard to IR, curcumin was able to improve glycemic status, HbA1c, and post-prandial glucose due to an increased adiponectin production in adipose tissue and a decrease of the hepatic nuclear factor-jB activity [120]. In preadipocytes and differentiated adipocytes, that overexpress TNF-a, IL-6, and cyclooxygenase-2 (COX-2) as mediators of the inflammatory response, curcumin, as well as resveratrol treatment, inhibited NF-kappaB activation and TNF-alpha, IL-1b, IL-6, and COX-2 gene expression [121]. Moreover, curcumin administered as liposomal nanoparticles inhibited NF-jB and proinflammatory cytokines production in macrophages obtained from liver and adipose tissue of obese mice (ob/ob) [122]. In adipocytes from C57BL/6J mice fed with HFD, NF-jB and JNK expression were significantly decreased by curcumin co-treatment [78]. Using the same model, Neyrinck et al. observed substantial levels of THC in the subcutaneous adipose tissue and a decreased expression of TNF-a and IL-6, suggesting that THC is the prin- cipal metabolite that exerts anti-inflammatory actions in adi- pose tissue [123]. However, in mice fed with HFD under caloric restriction, the levels of IL-1b, IL-6, and TNFa were decreased, but the addition of curcumin or curcumin plus piperine had no further effects on beneficial effects of caloric restriction [124]. Taken together, these results suggest that anti-inflammatory mechanisms are critical for curcumin in order to exert its ben- eficial effects in chronic diseases.

Interestingly, Nanji et al. [31] reported that the antioxidant effects of curcumin go together with anti-inflammatory effects characterized by the inactivation of NF-jB and the decrease of cytokines, TNF-a and IL-12, production in an experimental model of hepatic steatosis with IR. In rats fed with HFD, plas- matic TNF-a level was found increased. Interestingly, the administration of curcumin and rosiglitazone, an antidiabetic drug, was able to restore the normal values [77]. The overpro- duction of oxidants is associated with the progression of IR [125]. There is a positive correlation between oxidative stress markers in plasma and the degree of IR [126]. Curcumin is a bifunctional compound that could acts as scavenger of intra- cellular small oxidative molecules such as hydrogen peroxide (H2O2), superoxide anion (O2) hydroxyl radical (HO•), and peroxyl radical (ROO•) [127,128] and induces the activation of Nrf2, known as the master regulator of endogenous antioxi- dant response, and downstream antioxidant genes [129]. It has been demonstrated that curcumin consumption attenuates the formation of hepatic lipoperoxydes in rats and hamsters fed with HFD [130]. Also, in STZ-induced diabetic rats, curcumin and THC administration decreased the thiobarbituric acid reactive substances (TBARS) and hydroperoxide formation in liver without altering hyperglycemia [131–133]. Additionally, curcumin increased the endogenous antioxidant glutathione (GSH) and GSH reductase activity in the liver of an experimen-tal model of IR [134] and increased the activity of superoxide dismutase (SOD), catalase (CAT), and GSH peroxidase (GPx) in erythrocytes and liver from db/db mice [53] and rats fed with

HFD [80]. It has recently been demonstrated that the reduction of oxidative stress is achieved via activation of Nrf2 and its downstream genes [79]. Although the antioxidant role of cur-cumin has been well established, recent studies point out that curcumin action is much more complex than just its antioxi- dant properties. There seems to be a dual action by the activa- tion of Nrf2 which in turn induces the NF-jB inhibition. This mechanism has also been observed with other compounds like caffeic acid, dimethyl-fumarate, and chlorogenic acid [135–137].

Clinical Trials Using Curcumin to Improve IR and IR-Associated Diseases

To date, curcumin has been clinically tested in a wide spec- trum of diseases. Turmeric and curcumin supplementation has exerted positive effects in metabolic disorders IR-related, such as obesity [138,139], metabolic syndrome [140,141], prediabe- tes [142], diabetes [55–57], and in subjects with higher risk of atherosclerosis [56] or cardiovascular disease [143,144]. How- ever, the results are controversial because many factors like the type of curcumin, the dose, and the time of the treatment may influence the outcome.

In middle-aged healthy people, a daily consumption of cur- cumin (80 mg for 4 weeks) showed a positive effect, that is, reduced plasma triglyceride levels and alanine amino transfer- ase (ALT) activity, suggesting a role in improving hepatic func- tion. These results seem to correlate with a high antioxidant activity [145]. This trial highlights the ability of curcumin to modulate liver homeostasis independently of insulin function and its possible influence in insulin sensitivity evidenced by the reduction of triglycerides. For an overview of the clinical data about curcumin supplementation in diseases related to IR, we summarized the clinical trials available to date in Table 2.

Obesity

Both, the antioxidant and anti-inflammatory properties of cur- cumin renders it a potential candidate for an alternative ther- apy in obesity. The first clinical trial in this regard was con- ducted by Mohammadi et al. through the supplementation of 1 g per day of curcumin to obese individuals. In this study, a commercial formulation of curcumin (C3 complexVR) supple- mented with 5 mg of piperine, a bioavailability-enhancer, was used. After a month of treatment, no changes were found in weight, body mass index (BMI), waist circumference, hip cir- cumference, arm circumference, or body fat; however, total triglycerides levels were significantly lowered by curcumin consumption [138]. This study suggests that one month of treatment with curcumin is not enough to produce an effect on anthropometrical traits but an improvement of the action of insulin could be attained with an acute treatment. Hypertri- glyceridemia and VLDL overproduction are common lipid abnormalities in IR [146,147]. Therefore, the downregulation of triglycerides production could be related to the improve- ment of IR. Later, an intervention was carried out with the same type and dose of curcumin in non-diabetic obese individ- uals who had either at least two risk factors for coronary heart disease (CHD) (BMI > 30 and LDL: 160–190 mg/dL) or 2: 2 CHD risk factors and LDL: 130–160 mg/dL. In this study, curcumindecreased IL-1b, IL-4, and the vascular endothelial grow factor (VEGF) in serum without changes in the interleukins IL-1, IL- 2, IL-6, IL-8, IL-10, the interferon gamma (IFNc), epidermal growth factor (EGF), monocyte chemoattractant protein 1 (MCP-1), and TNF-a levels [139]. It is important to note that these findings do not exclude a potential tissue-specific anti- inflammatory effect of curcumin. For example, in adipose tis- sue a downregulation of cytokines production in adipocytes eli- cited by curcumin treatment [121,123] has been demonstrated. Taken together, these results suggest that curcumin increases insulin-sensitizing effects, at least partially, by acting on anti- inflammatory pathways in obese subjects and this is reflected by a decrease in triglycerides levels in plasma.

Prediabetes

Prediabetes is a physiopathological state where the subject is particularly prone to develop diabetes and/or cardiovascular disease [148]. Subjects with prediabetes present higher levels of fasting plasma glucose than the normal range (100–125 mg/ dL), glucose intolerance 2 h after 75 g glucose oral intake (140–199 mg/dL) [149], and a marked IR [150]. A recent study performed in prediabetic subjects [142] showed that oral cur- cumin administration is able to improve IR measured by the homeostatic model assessment-insulin resistance (HOMA-IR) and the HOMA-b, which estimates steady-state b-cell function. Besides, after 9 months of daily treatment with 1.5 g of curcu- minoids, 19 individuals in a placebo group were diagnosed as new diabetic subjects whereas in the curcumin group, no indi- vidual progressed to diabetes. After 3 months of treatment, the group with curcumin supplementation showed a significant decrease in FPG, postprandial glucose, and HbA1c. After 9 months of treatment, body weight, waist circumference, HOMA-IR, HOMA-b, and C-peptide levels were decreased, and adiponectin concentrations were increased in the curcumin group. Therefore, this study highlights the potential of curcu- min to stabilize b-cell function and hepatic IR through the improvement of glucose homeostasis. This could be explained by a reduction of gluconeogenesis, an increase in glucose uptake and in the general metabolism in general as observed in animal several studies [53,76–79]. In addition, adiponectin levels are negatively correlated with obesity [151]. The reduc- tion of body weight by curcumin consumption may be the underlying mechanism to increase adiponectin levels [152] because it has been reported that curcumin inhibits adipogen- esis in 3T3-L1 adipocytes and prevents body weight gain in C57/BL mice fed with HFD [153].

Metabolic Syndrome

Two studies describing the effect of curcumin in patients with metabolic syndrome were recently published. It has been reported that curcumin administration (1 g of C3 complexVR) decreased LDL-cholesterol, total cholesterol, triglycerides, and lipoprotein-a (Lp-a) [140] while the serum levels of high den- sity lipoprotein-cholesterol (HDL-C) were elevated after 8 weeks in patients with metabolic syndrome diagnosed accord- ing to the National Cholesterol Education Program Adult Treatment Panel III criteria [154]. A study using higher doses of curcumin and longer time of treatment showed a similar ability of this compound to decrease plasmatic levels of lipids and to reduce HbA1c in women. Interestingly, no changes were observed in fasting glucose levels [141]. These results strengthen the idea that curcumin can improve lipid metabo- lism independently from glucose homeostasis.

Diabetes and Comorbidities

In overweight and obese subjects with T2DM, the oral intake of curcumin (300 mg/daily) decreases fasting blood glucose, HbA1c, IR index, levels of FFA, triglycerides, and the increase in LPL activity after 3 months of treatment [55]. In other study, 6 months of curcumin supplementation (1.5 g/daily) decreased serum triglycerides, uric acid, visceral fat, total body fat, and IR (assessed by HOMA-IR) in T2DM subjects. These effects were associated with a decrease in adiponectin levels and high concentrations of leptin in serum. Also, the pulse wave velocity (PWV), an indicator of arterial stiffness, was reduced. Theseresults suggest that the reduction in atherogenic risk by curcu- min consumption is not just due to the modulation of hepatic IR but also to the activation of anti-inflammatory pathways that induce a protective effect against atherosclerosis in T2DM subjects [56]. The effect of curcumin oral intake has also been evaluated in subjects with diabetic nephropathy [57]. This study shows a reduction in plasmatic levels of the

transform- ing grow factor beta (TGF-b) and IL-8 in serum, associated with less protein urinary excretion, with no detectable changes in glucose, insulin, and lipids serum levels, suggesting that curcumin preserves the anti-inflammatory effect, independ- ently of the evolution and comorbidities of the disease.

Cardiovascular Diseases

Individuals with IR have a high risk to develop cardiovascular disease. Therefore, curcumin has been used in clinical trials to prevent or ameliorate this kind of diseases. In this regard, an interesting study shows that supplementation with three doses (45, 90, or 180 mg/daily) of curcumin produce no appreciable beneficial effects on this pathology in subjects with acute coro- nary syndrome. Nevertheless, the authors suggest a trend of total cholesterol and LDL-C to increase at the highest curcu- min dose, while the supplementation with 45 mg/daily showed the opposite effect [143]. We believe that these controversial results may be due to the small sample size (15 patients pergroup), to the age and clinical record of the patients, and/or to variations in curcumin sensibility among individuals. It is important to remark that the genetic background has been poorly studied so far and we believe that this factor should be included in further research in order to fully understand the role of curcumin in health and disease. As an example of the relevance of genetic variability, the overexpression of the ATP- binding cassette transporter gene, ABCA1, is responsible for the lack of activity of curcumin in M14 melanoma cells [155].

As mentioned before, another factor that could signifi-cantly affect the outcome of this kind of trials is the type of curcumin. In an acute study, patients undergoing coronary artery bypass grafting (CABG) received curcumin capsules (4 g/day) with high amounts of demethoxycurcumin and bisde-methoxycurcumin (1:0.6:0.3) for 3 days before the scheduled surgery and continued receiving the assigned treatment until 5 days after surgery. Interestingly, under these conditions curcu-min consumption was able to decrease the incidence of in-hospital myocardial infarction (MI), C-reactive protein, plasma malondialdehyde, and N-terminal pro-B-type natriuretic pep-tide [144]. No changes in glucose and plasmatic lipids were reported in this investigation, probably due to the short time of treatment. Although curcumin does not have an effect on glu-cose levels in this short-term treatment, these results suggest that curcumin and its derivatives are able to provide preven-tive protection through anti-inflammatory and antioxidant pathways. Another mechanism could be the inhibition of human platelet activation, which was shown to be involved in myocardial ischemia [156].

Conclusions

The quest for potential innocuous pharmacological interven- tions that could be of relevance for the treatment of complex diseases and help to disclose insights into the molecular mech- anisms underlying these pathologies is an active field of biomedical research. In particular, curcumin is a natural candidate due to the multiple beneficial effects reported for this compound in vitro and in vivo. When it comes to diabetes, prevention is a really desirable intervention since the long- term effects of this disease represent a considerable economic and social burden worldwide. Therefore, a nutraceutical inter- vention with an innocuous and cheap compound like curcumin could represent a great opportunity for the prevention of these diseases. In this regard, a bulk of research performed in dif- ferent experimental models has demonstrated that curcumin is able to improve IR through different mechanisms. Among others, it is important to remark the ability of curcumin to act as a regulator of insulin signaling by the activation of a wide range of molecules including hormone receptors, transcription factors, enzymes, growth factors, cytokines, and adipokines that work synergistically to maintain glucose homeostasis. Due to the absence of very conclusive or even disappointing outcomes of multiple phase III clinical trials, it seems logic to suggest that preclinical studies in animal models are less rele- vant than we would expect. It is also important to remark that curcumin is able to improve IR but adequate results depend greatly on the kind of curcumin, time of treatment, and sample size of each particular study. Additionally, it is important to remark that one of the main limitations for a nutraceutical intervention with curcumin on diabetes is its limited bioavaila- bility. Thus, the development of chemical modified structures of curcumin with an improved absorption or the chronic co- administration of curcumin with an absorption enhancer is recommended as a promising therapy for the improvement of IR. Clinical trials need to be carried out taking into account this idea for IR and its comorbidities.

Clinical trials have highlighted the critical role of curcumin

To improve IR, with a consequent improvement of serum lipid profile including a reduction in triglycerides levels. This can be explained mainly by the activation of curcumin molecular tar- gets in the liver and adipose tissue as discussed in section and summarized briefly in the integrative Fig. 1. According to the clinical trials available to date it is possible to suggest that the positive effects of curcumin in IR can be due to: (a) Improve- ment of glucose homeostasis, (b) increased LPL activity leading to a decrease in triglycerides levels, (c) increased glucose uptake independently of insulin b-cell production, (d) Anti- inflammatory action in adipose tissue through an increase in adiponectin levels and a decrease in circulating cytokines (Fig. 2). Despite the rather encouraging results of the clinical trials available to date, it is premature to conclude a full beneficial effect of curcumin on IR, prediabetes, or diabetes. Additional studies with larger numbers of patients, longer period of treat- ment, and different genetic backgrounds are required to deter- mine a definitive improvement in the clinical conditions, delay the onset, or ameliorate the progression of T2DM.

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