La Medicina del Lavoro

Med Lav 2019; 110, Suppl 2: 22-28
DOI: 10.23749/mdl.v110i2-S.9391

Nutraceuticals in the management of type 2 diabetes

Vito De Gennaro Colonna[1,2]

[1] Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy
[2] Department of Preventive Medicine, Occupational Health Unit, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy

Key words: Nutraceuticals; type 2 diabetes; hyperglycemia; dyslipidemia

Parole chiave: Nutraceutici; diabete di tipo 2; iperglicemia; dislipidemia

Summary

Background: *The prevalence of type 2 diabetes mellitus (T2DM) is dramatically increasing worldwide. Hyperglycemia and dyslipidemia, the two major components of this metabolic disorder, lead to accelerated ath-erosclerosis, coronary heart disease, chronic kidney disease and increase in the mortality rate. In recent years a growing number of hypoglycemic drugs have become available. However, in a remarkable number of patients the disease control is not fully satisfactory. Thus the search of new antidiabetic agents with minimal side effects is mandatory. In this context, nutraceuticals (bioactive compounds mostly of plant origin) can play a positive role in the management of T2DM, also in association with hypoglycemic drugs. An interesting feature of some nutraceuticals is their ability to improve not only the glycemic control but also the lipidic profile (berberine), the antioxidant status (silymarin) or endo-thelium dependent -vasodilator function (Pycnogenol) of the patients.*

Riassunto

«Nutraceutici per il trattamento del diabete di tipo 2»*. L'incidenza del diabete mellito di tipo 2 è in drammatico aumento a livello mondiale. L'iperglicemia e la dislipidemia, due importanti componenti di questa complessa malattia del metabolismo, determinano accelerazione dell'aterosclerosi e possibile comparsa di malattia coronarica e nefropatia con aumentata incidenza di mortalità. Negli ultimi anni un crescente numero di farmaci ipoglicemizzanti è stato reso disponibile per l'utilizzo clinico. Tuttavia, in un numero consistente di pazienti il controllo della malat-tia non risulta del tutto soddisfacente. In questo contesto, l'utilizzo di nutraceutici, composti bioattivi di origine prevalentemente vegetale con minimi effetti collaterali per il paziente (purché sia individuato il corretto dosaggio) , può svolgere un ruolo terapeutico positivo. Infatti, i nutraceutici possono essere cosomministrati con i farmaci ipoglicemizzanti coadiuvandone l'azione terapeutica. Inoltre, alcuni nutraceutici possiedono l'interessante proprietà di essere in grado di migliorare, oltre il controllo gli-cemico, il profilo lipidico (berberina), di ridurre lo stress ossidativo (silimarina) e di migliorare la funzione endoteliale vasorilassante (Picnogenolo).*

Corresponding author: Vito De Gennaro Colonna, MD, PhD, Department of Clinical Sciences and Community Health, Uni-versity of Milan and Department of Preventive Medicine, Occupational Health Unit, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Via Francesco Sforza 28, 20122 Milan, Italy – Tel: +390250317017 – E-mail: vito.colonna@unimi.it

Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disorder affecting a growing number of patients all over the world. T2DM is caused by abnormal insulin activity and/or release. The two major components of this metabolic disorder, hyperglycemia and dyslipidemia, lead to accelerated atherosclerosis, coronary heart disease, chronic kidney disease and increase in the rate of mortality. Despite the availability of several hypoglycemic drugs, in a remarkable number of patients the disease control is not fully satisfactory. Thus the search of new antidiabetic agents with minimal side effects is mandatory. Nutraceuticals are nutrients and/or bioactive compounds mostly of plant origin, with possible beneficial effects on human health. Plant-derived natural agents have been widely used since ancient times for a vast variety of diseases. A growing number of nutraceuticals are currently proposed to treat metabolic disorders, including diabetes mellitus. Nutraceuticals may improve glycemic control and often exert a beneficial effect on cardiovascular risk factors linked to T2DM such as dyslipidemia and hypertension with minimal side effects. In this review we take into consideration only nutraceuticals having enough evidence regarding their efficacy and safety in T2DM patients.

Nutraceuticals in T2DM

Berberine

Berberine, an isoquinoline alkaloid, is present in several plants such as *Berberis vulgaris*, *Berberis aristata* and *Coptis chinensis* (16). It is commonly used for gastrointestinal tract infections in China. Berberine has anti-microbial, glucose- and cholesterol-lowering and antioxidant effects (16). Berberine activates AMP-activated protein kinase (AMPK), a cellular energy sensor that increases fatty acid oxidation, glucose uptake and lipolysis, while inhibiting gluconeogenesis, fatty acid synthesis and cholesterol synthesis (19).

The hypoglycaemic, lipid-lowering and antioxidant properties of berberine have been widely investigated in animal models. In impaired glucose tolerance (streptozocin-treated) rats (21), treatment with berberine for 4 weeks significantly decreased fasting blood glucose, total cholesterol, free fatty acid and apoliprotein B levels; blood glucose levels after oral glucose tolerance test were also reduced (21). In high glucose and high fat diet-induced diabetic hamsters, berberine administration for 6 weeks significantly reduced glucose and insuline levels and ameliorated glucose tolerance tests (22). Furthermore total cholesterol, low density lipoprotein cholesterol (LDL-C), free fatty acid and triglyceride levels as well as markers of oxidative stress (thiobarbituric acid-reative substance and 8-isoprostane) were also decreased (22). Berberine was found also capable to reduce body weight and adipose tissue mass as well as insulin resistance in obese db/db mice (20). In this animal model, berberine also increased energy expenditure, limited weight gain, improved cold tolerance and increased brown adipose tissue activity, suggesting a potential therapeutic role of berberine in the treatment of obesity (41).

Clinical studies confirm the hypoglycaemic and lipid-lowering effects of berberine. A pilot study was conducted in 2008 to assess the efficacy of berberine in patients with T2DM (38). Adults with newly diagnosed T2DM were treated with berberine (500 mg 3 times daily) or metformin (500 mg 3 times daily) for three months (study A). The decrease in fasting and postprandial blood glucose and hemoglobin A_{1c} was similar in patients treated with berberine or metformine. Total cholesterol and triglycerides significantly decreased only in the berberine-treated group. In study B berberine (500 mg 3 times daily for 3 months) was administered to poorly controlled T2DM on-going treated with antidiabetic drugs. Berberine in combination therapy further decreased fasting and postprandial blood glucose, hemoglobin A_{1c} , fasting insulin and homeostasis model assessment of insulin resistance (HOMA-IR). Total cholesterol and LDL-C were decreased significantly as well (38). In patients treated with berberine alone no severe gastrointestinal adverse effects were recorded. In combination therapy the adverse effects (diarrhea, constipation, flatulence, abdominal pain) disappeared in 1 week after reduction of berberine dos-

age from 500 mg to 300 mg 3 times daily. Thus, the optimal dose of berberine with minimal side effects seems to be 300 mg 3 times daily, especially in combination therapy with antidiabetic drugs. In another study, T2DM patients with dyslipidemia were treated with berberine (500 mg 2 times daily) for 3 months (40). Fasting and postprandial blood glucose, hemoglobin A_{1c}, total cholesterol, LDL-C and triglycerides were all significantly reduced in the berberine-treated group. During the period of the study no serious adverse events occurred. Only a small number of patients receiving berberine (8.7 %) experienced mild to moderate constipation. No episode of hypoglycemia was reported. In 2010, a trial with daily administration of 1000 mg berberine confirmed the hypoglycaemic action of the phytochemical (39). The fasting blood glucose- and hemoglobin A_{1c}-lowering effects of berberine were found similar to those of metformine and rosiglitazone. Berberine was also found capable to increase the percentages of peripheral blood lymphocytes that express insulin receptor (39). Berberine and rosiglitazone, a thiazolidinedione (TZD), work through different mechanisms. TZDs decrease insuline resistance by activating peroxisome proliferator-activated receptor- g(PPARg) thus increasing body weight gain. Contrary to TZD, berberine reduces the expression of PPARg, thus preventing weight gain by suppressing preadipocytes differentiation (15,42). Therefore berberine may be a good choice in overweight or obese TDM2 patients. The effect of berberine on inflammatory parameters in TDM2 patients was investigated by Chen et al (2). In newly diagnosed T2DM patients administration of berberine (300 mg 3 times daily for 8 weeks) markedly reduced C-reactive protein (CRP), tumor necrosis factor (TNF)-a and lipopolysaccharide (LPS) levels. At the end of the trial fecal *Bifidobacterium* species were significantly modified. *Bifidobacterium longum*, *Bifidobacterium adolescentis* and *Bifidobacterium infantis* correlated significantly with TNF- aand LPS levels, suggesting the capability of berberine to modulate fecal microbiota thus reducing the expression of the inflammatory parameters TNF-a and LPS (2).

Silymarin

Silymarin is a standardized extract of *Silybum marianum* (milk thistle) seeds containing several flavolignans amongst which the most important is sylibin (silibinin). Milk thistle has been used since ancient times to treat a range of liver and gallbladder disorders (hepatitis, cirrhosis and jaundice). Silymarin has antioxidant and anti-inflammatory properties. It inhibits lipid peroxidation (37), prevents glutathione depletion (34) and activates antioxidant enzymes that protect DNA from degradation (18). Concerning the anti-inflammatory effects, a strong inhibitory effect of silibin on LTB4 (leukotriene B4) formation has been demonstrated (4). Silymarin also exerts an inhibitory effect on nitric oxide (NO) production and inducible nitric oxide synthase (iNOS) gene expression (17). Inhibition of intrahepatic expression of TNF- , aINFg , interleukin (IL)-2 and IL-4 have been also demonstrated (30). The antioxidant and anti-inflammatory properties of silymarin may induce a positive effect on diabetic metabolic abnormalities. Administration of silymarin to cirrothic diabetic patients (600 mg daily) for 12 months significantly reduced fasting plasma glucose and insulin, glicosuria and daily insulin requirement (35). Serum oxaloacetic transaminase (SGOT) and glutamic pyruvic transaminase (SGPT) were also significantly improved in silymarin-treated group (35). Supporting the antioxidant effect of the compound, plasma malondialdehyde (MDA) levels were significantly decreased by silymarin treatment (35). In a 4-month trial, silymarin (200 mg 3 times daily) (11) significantly decreased fasting blood glucose, HbA_{1c}, SGOT and SGPT levels. These findings indicate that silymarin, at the dosage of 600 mg/daily, may exert antidiabetic effects also after a short administration period. The effects of silymarin on antioxidant status were reported by Ebrahimpuor Koujan in 2015 (9). T2DM patients received 140 mg silymarin, 3 times daily for 45 days. Silymarin treatment significantly increased superoxide dismutase (SOD), glutathione peroxidase (GPX) activity and total antioxidant capacity (TAC) while decreasing plasma MDA and hs-CRP levels. Contrary to berberine, silymarin seems to have no effect on lipid profile (36). No mayor side

effects have been reported for silymarin (36), thus this phytochemical may be considered as a useful complementary medication in T2DM.

Berberol

Despite the known favourable effects of berberine on glycemic control and lipidic profile, the efficacy of this phytochemical is limited by its poor oral bioavailability (3). In fact, the amount of berberine capable of crossing enterocytes is greatly reduced by a P-glycoprotein-mediated gut extrusion process (26). Silymarin is a known P-glycoprotein inhibitor (43). Thus combination of berberine with silymarin may be suitable to enhance the oral bioavailability and increase the clinical effectiveness of berberine. Berberol is a commercial nutraceutical mixture composed by

588 mg of *Berberis aristata* extract (standardized based on 85% berberine) and 105 mg of *S. marianum* extract (standardized based on 60% flavolignans) (5).

T2DM patients with suboptimal glycemic control despite the use of antidiabetic drugs were treated with Berberol for 3 months (6). At the end of the treatment HbA_{1c} ,basal insulin and HOMA-IR, total cholesterol, LDL-C and triglycerides were all significantly reduced (6). The decrease in basal insulin and HOMA-IR confirms the capability of Berberol to increase insulin sensitivity and makes this nutraceutical combination a good candidate as an adjuvant therapy in poorly controlled T2DM patients. Berberol (1000 mg/day of berberine and 210 mg/day of silymarin) was compared with berberine alone (1000 mg/day) in a 4-months clinical trial (7). Berberol demonstrated to be more effective than berberine alone in reducing HbA_{1c} while both treatments similarly reduced fasting blood glucose, total cholesterol, triglycerides, SGOT and SGPT levels (7). As regard the safety of the nutraceutical combination, no patients reported any serious adverse event (myopathy or liver toxicity). Only about 15% of patients reported a mild transient abdominal discomfort. In 2015 a clinical trial investigated the role of Berberol in diabetic and hypercholesterolemic patients intolerant to statins (8). Patients were divided into three groups (low-dose statin-treated, ezitimibe-treated and patients not treated with antihyperlipidemic drugs) and treated for 1 year with Berberol. At the end of the study fasting blood glucose, HbA_{1c} , total cholesterol and LDL-C were significantly reduced in all groups of patients without any serious side effects (8). Therefore Berberol may be suggested as a safe and effective supplement to improve the lipidic and glycemic profile of hypercholesterolemic T2DM patients intolerant to statins (8).

Curcumin

Curcumin is a polyphenol with diarylheptanoid structure derived from the rhizome of *Curcuma Longa* which is used as a spice in Asian cuisine. This phytochemical has anti-inflammatory, antioxidant, immunomodulating and anticancer properties and its effects on cancer, heart failure, T2DM and depression have been clinically investigated (33). Curcumin inhibits Nuclear factor-kB (NF-kB) signalling pathway, one of the most important pathways in the cellular and molecular mechanisms of inflammation and down-regulates the expression of TNFa, Il-1, Il-6, Il-8 and CRP (27,28). In obese diabetic rats, curcumin decreased plasma glucose and decreased insulin resistance by reducing serum free fatty acids (FFAs) and increasing fatty acid oxidation in skeletal muscle (24). In humans, curcumin (300 mg/day for 3 months) significantly reduced fasting blood glucose and HOMA-IR in overweight/obese T2DM patients (25). Serum total FFAs and triglycerides were also reduced while lipoprotein lipase (LPL) activity increased (25). These findings suggest that the hypoglycemic effect of curcumin may be at least in part related to the ability of the phytochemical to decrease serum FFAs generation, which represents one of the major factors inducing insuline resistance. In keeping with this view, *in vitro* experiments demonstrated the ability of curcumin to improve FFAs b-oxidation through upregulation of phosphorylated AMP-activated protein kinase pathway (24). Due to its low bioavailability, curcumin must be used at high dose to achieve therapeutic levels. To improve the biovailability of curcumin a formulation of curcumin as a nanomicelle structure (Nano-curcumin) has been studied (29). Administration of Nano-curcumin (80

mg/die) for 3 months to T2DM patients, significantly decreased fasting blood glucose, HbA_{1c}, triglycerides and BMI (Body Mass Index) (29). These results suggest that administration of curcumin as nanomicelle may be a promising strategy to increase curcumin bioavailability and its therapeutic efficacy.

Pycnogenol

Pycnogenol is an extract of bark from the French maritime pine (*Pinus pinaster Ait.*) standardized to 70 ± 5% procyanidins. It represents a concentrate of water-soluble polyphenols (36). Pycnogenol has strong antioxidant and anti-inflammatory effects and endothelium-dependent vasodilator activity (10,30). The improvement of endothelial-dependent vasodilator function leads to a decrease in blood pressure levels in hypertensive subjects (14,44). Another effect of Pycnogenol is inhibition of a-glucosidase. Inhibition of a-glucosidase causes decreased glucose reabsorption and postprandial hyperglycemia (13). The inhibition of a-glucosidase provided by pycnogenol is more potent than that provided by green tea extract (IC_{50} about 5 mg/ml vs IC_{50} about 20 mg/ml) (12). In 2010, Stuard et al (32) investigated benefits of Pycnogenol as an adjunctive treatment to ACE-inhibitor ramipril in metabolic syndrome patients with hypertension and microalbuminurea. Pycnogenol (150 mg daily) taken in addition to ramipril (10 mg daily) further decreased blood pressure, fasting blood glucose, HbA1c , 24 hour urinary albumin and serum creatinine. C-reactive protein (CRP) levels decreased significantly only in the pycnogenol-treated group (32). In a more recent study (1) the effects of 6 months supplementation with Pycnogenol (150 mg daily) were studied in subjects with metabolic syndrome. Pycnogenol significantly decreased blood pressure, fasting blood glucose, and triglycerides levels while increasing HDL-C levels (1). Waist circumference was significantly reduced in patients with metabolic syndrome (both males and females) treated with Pycnogenol. No side-effects due to the treatment with the phytochemical were observed. This study (1) indicates a role for Pycnogenol for improving health risk factors in patients with metabolic syndrome. To investigate the anti-diabetic effects of pycnogenol, 77 patients with T2DM (taking standard anti-diabetic drugs) were treated with 100 mg pycnogenol for 12 weeks (23). Pycnogenol significantly lowered plasma glucose levels as compared with placebo. HbA1c was also lowered; however, the difference as compared with placebo was statistically significant only for the first month of treatment. In the Pycnogenol-treated patients plasma levels of endothelin-1, a potent vasoconstrictor peptide secreted by endothelial cells, were significantly decreased, while 6-ketoprostaglandin F1a levels, the metabolite of prostacyclin (a prostaglandin with vasodilator and antithrombotic activity) were elevated compared with placebo during the entire treatment period (23). These results indicate that supplementation of Pycnogenol to conventional diabetes treatment is able to reduce glucose levels and improve endothelium-dependent vasodilator function.

Conclusions

The clinical studies so far performed with nutraceuticals have some limitations such as the limited duration of the trials and the small sample size of the enrolled patients. However, the available data indicate a promising role of some nutraceuticals in the menagement of T2DM. Berberine, silymarin and Berberol have the strongest evidence of beneficial effects in T2DM patients. In this context, an interesting feature of some nutraceuticals is the ability to improve not only the glycemic control but also the lipidic profile (berberine and Berberol), the antioxidant status (silymarin) or endothelium-dependent vasodilator function (Pycnogenol) of the patients. The dosage of the nutraceutical is an important variable. The administered dose should be sufficient to provide therapeutic activity (taking into account that natural compunds have mostly low biovalability) without or with minimal side effects. Promising strategies to increase the biovailability and the therapeutic efficacy of nutraceuticals are the co-administartion of absorption enhancers or alternative delivery systems to traditional oral formulation. In conclusion, a place for nutraceuticals in the treatment of T2DM patients is emerging. However, future well-designed clinical trials are needed to confirm the efficacy and safety of nutraceuticals in the menagement of type 2 diabetes.

No potential conflict of interest relevant to this article was reported by the authors

References

1. Belcaro G, Cornelli U, Luzzi M, et al: Pycnogenol supplementation improves health risk fac-tors in subjects with metabolic syndrome. Phytother Res 2013; 27:1572-1578
2. Chen L, Lu W, Li Y: Berberine ameliorates type-2 diabetes via modulation of bifidobacterium species, tumor necrosis factor-α and lipopolysaccharide. Int J Clin Exp Med 2016; 9: 9365-9372
3. Chen W, Miao YQ, FanDJ, et al: Bioavailability study of berberine and the enhancing effects of TPGS on intestinal absorption in rats. AAPS Pharm Sci Tech 2011; 12: 705-711
4. Dehmlow C, Murawski N, de Groot: Scavenging of reactive oxygen species and inhibition of arachidonic acid metabolism by silibinin in human cells. Life Sci 1996; 1591-1600
5. Derosa G, D'Angelo A, Romano D, Maffioli P: Effects of a combination of Berberis aristata, Silibum marianum and monacolin on lipid profile in subjects at low cardiovascular risk: a double-blind, randomized, placebo-controlled trial. Int J Mol Sci 2017; 18:E343.
6. Di Pierro F, Villanova N, Agostini F et al: Pilot study on the additive effects of berberine and oral type 2 diabetes agents for patients with suboptimal glycemic control. Diabetes Metab Syndr Obes 2012; 5: 213-217
7. Di Pierro F, Putignano P, Villanova N et al: Preliminary study about the possible glycemic clinical advantage in using a fixed combination of Berberis aristata and Silybum marianum standardized extracts versus only Berberis aristata in patients with type 2 diabetes. Clin Pharmacol 2013; 5: 167-174.
8. Di Pierro F, Bellone I, Rapacioli G, et al: Clinical role of a fixed combination of standardized Berberis aristata and Silybum marianum extracts in diabetic and hypercholesterolemic patients intolerant to statins. Diabetes Metab Syndr Obes 2015; 8: 89-96
9. Ebrahimpour Koujan S, Pourghassem Gargari B, Mobasseri M, et al: Effects of Silybum marianum (L.) Gaertn. (silymarin) extract supplementation on antioxidant status and hs-CRP in patients with type 2 diabetes mellitus: a rabdomized, triple-blind, placebo-controlled clinical trial. Phytomedicine 2015; 22: 290-296
10. Enseleit F, Sudano I, Periat D, et al: Effects of Pycnogenol on endothelial function in patients with stable coronary artery disease: a double-blind, randomized, placebo-controlled. Cross-ober study. Eur Heart J 2012; 33: 1589-1597
11. Fallah Huseini H, Larijani B, Heshmat R, et al: The efficacy of Silybum marianum (L.) Gaernt. (Silymarin) in the treatment of type II diabetes: a randomized, double-blind, placebo-controlled , clinical trial. Phytother Res 2006; 20: 1036-1039
12. Gulati OP: Pycnogenol in metabolic syndrome and related disorfers. Phytother Res 2015; 29: 949-968
13. Heacock PM, Hertzler SR, Williams JA, Wolf BW: Effects of a medical food containing an herbal alpha-glucosidase inhibitor on postprandial glycemia and insulinemia in healthy adults. J Am Diet Ass 2005; 105: 65-71
14. Hosseini S, Lee J, Sepulveda RT, et al: A randomized, double-blind, placebo-controlled, pro-spective, 16 week crossover study to determine the role of Pycnogenol in modifying blood pressure in midly hypertensive patients. Nutr Res 2001; 21: 1251-1260
15. Huang C, Zhang Y, Gong Z, et al: Berberine inhibits 3T3-L1 adipocyte differentiation trough the PPAR-gamma pathway. Biochem Biophys Res Commun 2006; 348: 571-578
16. Imanshahidi M, Hosseinzadeh H: Pharmacological and therapeutic effects of Berberis vulgaris and its active constituent, berberine. Phytother Res 2008; 22: 999-1012
17. Kang JS, Jeon YJ, Kim HM: Inhibition of inducible nitric-oxide synthase expression by si-lymarin in lipopolysaccharide-stimulated macrophages. J Pharmacol Exp Ther 2002; 302: 138-144
18. Kiruthiga PV, Shafreen RB, Pandian SK, Devi KP: Silymarin protection against major reac-tive oxygen species released by environmental toxins: exogenous H2O2 exposure in erythro-cytes. Basic Clin Pharmacol, 2007; 100: 414-419
19. Krishan DR, Richardson S, Sahni S: Adenosine monophosphate-activated kinase and its key role in catabolism: structure, regulation, biological activity and pharmacological activation. Mol Pharmacol 2015; 87: 363-377
20. Lee YS, Kim RH, Kim MJ, et al: Berberine, a natural plant product activates AMP-activated protein kinase with beneficial metabolic effects in diabetic and insulin-resistant states. Diabetes 2006; 55: 2256-2264
21. Leng SH, Lu FE, Xu LJ: Therapeutic effects of berberine in impaired glucose tolerance rats and its influence on insulin secretion. Acta Pharmacol Sin 2004; 25: 496-502
22. Liu C, Wang Z, Song Y, et al: Effects of berberine on amelioration of hyperglycemia and oxi-dative stress in high glucose and high diet-induced diabetic hamsters in vivo. Biomed Res Int 2015; 313808
23. Liu X, Wei J, Tan F, et al: Antidiabetic effects of pycnogenol french maritime pine bark extract in patients with diabetes type II. Life Sciences 2004; 75: 2505-2513.
24. Na LX, Zhang YL, Li Y et al: Curcumin improves insu-

lin resistance in skeletal muscle of rats. Cardiovasc Dis 2011; 21: 526-533
25. Na XL, Li Y, Pan HZ, et al: Curcuminoids exert glucose-lowering effect in type 2 diabetes by decreasing serum fatty acids: a double-blind, placebo controlled trial. Mol Nutr Food Res 2013; 57: 1569-1577
26. Pan GY, Wang GJ, Liu XD, et al: The involvement of P-glycoprotein in berberine absorption. Pharmacol Toxicol 2002; 91: 193-197
27. Rahimi HR, Kazemi Oskuee R: Curcumin from traditional iranian medicine to molecular med-icine. Razavi Int J Med 2014; 2: 3-4
28. Rahimi HR, Jaafari MR, Mohammadpour AH, et al: Curcumin: reintroduced therapeutic agent from traditional medicine for alcoholic liver disease. Asia Pacific J Med Tox 2015; 25-30
29. Rahimi HR, Mohammadpour AH, Dastani M, et al: The effect of nano-curcumin on HbA1C, fasting blood glucose and lipid profile in diabetic subjects: a randomized clinical trial. Avicen-na J Phitomed 2016; 6: 567-577
30. Rohdewald P: A review of the french maritime pine bark extract (Pycnogenol), a herbal medi-cation with a diverse clinical pharmacology. Int J Clin Pharmacol Ther 2002; 40: 158-168
31. Schumann J, Prockl J, Kiemer AK, et al: Silibinin protects mice from T cell-dependent liver injury. J Hepatol 2003; 39: 333-340
32. Stuard S, Belcaro G, Cesarone MR, et al: Kidney function in metabolic syndrome may be im-proved with Pycnogenol(R). Panminerva Med 2010; 52: 27-32
33. Sunagawa Y, Katanasaka Y, Hasegawa K, Morimoto T: Clinical applications of curcumin. Pharm Nutr 2015; 3: 131-135
34. Tasduq SA, Peerzada K, Koul R, et al: Biochemical manifestations of anti-tubercolosis drugs induced hepatotoxicity and the effect of silymarin. Hepatol res 2005; 31: 132-135
35. Velussi M, Cernigol AM, De Monte A, et al: Long-term (12 months) treatment with an anti-oxidant drug (silymarin) is effective on hyperinsulinemia, exogenous insulin need and malondialdehyde levels in cirrhotic diabetic patients. J Hepatol 1997; 26: 871-879
36. Voroneau l, Nistor I, Dumea R, et al: Silymarin in type 2 diabetes mellitus: a systematic re-view and meta-analysis of randomized controlled trials. J Diab Res 2016; 5147468
37. Wellington K, Adis BJ: Silymarin: a review of its clinical properties in the menagement of he-patic disorders. BioDrugs 2001; 7: 465-489
38. Yin J, Xing H, Ye J: Efficacy of berberine in patients with type 2 diabetes mellitus. Metabo-lism 2008; 57: 712-717
39. Zhang H, Wei J, Xue R, et al: Berberine lowers blood glucose in type 2 diabetes mellitus pa-tients through increasing insulin receptor expression. Metabolism 2010; 59: 285-292
40. Zhang Y, Li X, Zou D, et al: Treatment of type 2 diabetes and dyslipidemia with the natural plant alkaloid berberine. J Clin Endocr Metab 2008; 93: 2559-2565
41. Zhang Z, Zhang B, Li X, et al: Berberine activates thermogenesis in white and brown adipose tissue. Nat Commun 2014; 5: 5493
42. Zhou JY, Zhou SW, Zhang KB, et al: Chronic effects of berberine on blood, liver glucolipid metabolism and liver PPARs expression in diabetic hyperlipidemic rats. Biol Pharm Bull 2008; 31: 1169-1176
43. Zhou S, Lim LY, Chowbay B: Herbal modulation of P-glycoprotein. Drug Metab Rev 2004; 36: 57-104
44. Zibaldi S, Rohdenwald P, Park D, Watson RR: Reduction of cardiovascular risk factors in subjects with type 2 diabetes by Pycnogenol supplementation. Nutr Res 2008; 28: 315-320