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SHORT REVIEW

A Review on the Possible Therapeutic Intervention by Herbal Remedies on Antipsychotic Drugs Induced Metabolic Disorder

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Abstract

This review is the compilation of some of the natural products which are effective in treating diabetes, lipid abnormalities and cardiovascular diseases. We also discussed metabolic disorder associated with antipsychotic drugs. Currently, there are no equivocal evidence to demonstrate the effectiveness of herbal drugs in treating metabolic disorders induced by antipsychotic drugs. Therefore, there is a need of extensive research work to be carried out to explore the possibilities of therapeutic intervention of herbal drugs in antipsychotics induced metabolic disorders.

Keywords: Antipsychotic Drugs, Disorder, Herbal Drugs, Metabolism

1. Introduction

Metabolic syndrome is a disorder of energy utilization and storage, diagnosed by a co-occurrence of three out of five of the following medical conditions: abdominal (central) obesity, elevated blood pressure, elevated fasting plasma glucose, high serum triglycerides (TG), and low high-density cholesterol levels. Metabolic syndrome increases the risk of developing cardiovascular disease, particularly heart failure, and diabetes[1]. Above mentioned metabolic syndrome is mainly due to age, sex, genetic and sedentary lifestyle[1]. Besides, drugs such as antipsychotic medications are also capable of altering lipid and carbohydrate metabolism there by leading to coronary disease and atherosclerosis. Therefore, it is of importance to look into the development of new alternative therapies that can effectively reduce the metabolic side effect caused by antipsychotic drugs. It has been found that Indian system of alternative medicine (herbal drugs) has been receiving attention throughout the world because of its effectiveness and safety. Therefore, these traditional herbal medicine are being tried for several medical conditions like arthritis, jaundice, respiratory illness, hyperlipidaemia diabetes mellitus, hypertension, obesity and coronary artery disease etc. with a remarkable success rate. Similar type of metabolic condition may arise when the psychiatric patients are treated with antipsychotic drugs. This review mainly addresses the use of various traditional herbal drugs in metabolic disorder. However, this review also try to disseminate the possible therapeutic intervention by the herbal drugs on antipsychotic induced metabolic disorder[2].

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2. Herbal Drugs Commonly used for Metabolic Disorder

2.1 Aloe Vera *(Aloe barbadensis miller)*

It has been reported that there are number of plants that are effective in treating, metabolic syndrome and promoting better quality of life[3,4]. *Aloe vera (A. vera)* is one of the important plant which has been reported to have significant effect in treating person suffering from metabolic syndrome. It has also been reported that *A. vera* is one of the plants having high amount of health benefits. In another report it was shown that various extract of *A. vera* has been utilised for antihyperlipidemic, antidiabetic[5,6], antihypertensive[7], antiobesity[8], and immunomodulator[9]. The important ingredients (Aloe-emodin, aloetic-acid, anthranol, barbaloin, isobarbaloin, emodin, ester of cinnamic acid) of Aloe vera leaf, pulp and exudate contain vitamins, enzymes, minerals, hormones, asprine like compound, amino acid, steroids, saponins, sugars etc.[10]. It was shown in one of the studies that *A. vera* is capable of reducing blood glucose level by virtue of its antioxidant property[11]. In a clinical study, it was found that the levels of fasting blood glucose, triglycerides, HbA1c were decreased when a high molecular weight fraction of Aloe vera was given to 15 patients with type II diabetes mellitus uncontrolled with oral antihyperglycemic medication[12]. Based on the proof, Aloe vera concentrates can play a role in diminishing blood glucose in patients with diabetes mellitus and its complications by different mechanism, for example, decreasing gluconeogenesis and lipogenesis, just as expanding glycolysis in the liver. It has also been found that *A. vera* is capable of affecting the expression of several genes concern with glucose and lipid metabolism. One such candidate is Peroxisome Proliferator-Activated Receptors (PPAR) transcription. It is likely that some of the phytosterols present in the Aloe vera gels show significant role in the antidiabetic effect by virtue of its antihyperglycemic effect. It can be concluded that Aloe vera might be an important herbal drug which will is highly useful in diabetes associated with metabolic disorder[13].

Aloe vera gel extract containing phytosterol when administered (25microgram/kg/day) for 44 days in an obese animal model of Zuker Diabetic Fatty rat (ZDF) with type II diabetes it was found that these extract reduce the serum free fattyacid, triglycerides and total weight of abdominal fat tissue[14]. A significant changes in the accumulation of triglycerides in liver was found when *A. vera* gel was administered to alcohol induced fatty liver in C57BL/6J rats. Several studies have shown that *A. vera* can modify fat accumulation, fat size, gene expression related to lipogenisis and inflammation. It has also been found that Aloe vera contributes towards reducing the body weight by the activation of AMP activated protein kinase (AMPK) In streptozotocin (STZ) induced diabetic rat Aloe vera alcoholic extract has been shown to decrease in triglyceride level, LDL and an increase in HDL. A combinations of Aloe vera gel (500mg/kg/day) with probiotic like *Lactobasillus rhamnosus* reduce the serum triglyceride, very low-density lipoprotein (VLDL) and low density lipoprotein (LDL) level[15].

In a double blinded study 45 patient with metabolic disorder when treated with 500mg capsule of Aloe vera twice a day caused marked reduction in total cholesterol, LDL and Glucose level[16]. In an another clinical trial 50 males and 52 females when Aloe vera juice were given orally twice a day there was noticeable reduction in the blood sugar and triglycerides level[17]. Aloe vera gel powder 100 and 200 mg given to subjects in a clinical trial showed a significant decrease in blood glucose, lipid profile and blood pressure[18]. In a randomized control trial 136 obese pre-diabetic patient were given capsule containing Aloe Vera gel 147 mg for eight weeks there was a decrease in the body weight, body mass, fasting blood sugar and lipid level[19].

2.2 Cinnamon: *(Cinnamomum cassia)*

Treatment with cinnamon for 90 days lowers HbA1c level in a randomized uncontrolled trail of patient with diabetes. It was found that there was a significant reduction in both blood glucose and LDL[20]. In an uncontrolled trial when Pakistani population were treated with 1 to 6 gm daily for 40 days, it was shown that there was an ameliorative effect on markers of metabolic syndrome such as LDL, HDL and triglycerides in addition to blood glucose level[21,22]. It was further demonstrated that patients with metabolic syndrome when treated with 500mg extract for 12

weeks, there was normalisation of blood pressure and triglycerides[23].

2.3 Russian Tarragon: *(Artemisia dracunculus)*

Many studies have demonstrated that Russian tarragon extract has antidiabetic effect in cell culture studies. It has been hypothesised the effect might be due to the disruption of insulin signalling pathway which ultimately resulted in insulin resistance. In metabolic syndrome the main reason for type II diabetes might be due to insulin resistance. Further it was found in human studies that Russian tarragon can cause increase in insulin sensitivity as compare to control group. It was shown that there was no change in body fat composition in person treated with Russian tarragon[24]. The mechanism behind the Russian tarragon extract for its antihyperglycemic effect might be due to the action on muscle sensitivity or reduced hepatic glucose production which is ultimately responsible for alleviating metabolic disorder[25].

2.4 Bitter Melon: (*Momordica charantia*)

M. charantia is also well known as bitter melon, karela, or bitter gourd which is most popular in patients who are suffering from diabetes particularly in Asia and South Africa, India and east Africa[26,27]. Number of reports and clinical studies have demonstrated that bitter melon extract from fruit, seed and leaves possess many bioactive compounds that are supposed to have antihyperglycemic activity in diabetic patients and animals[28,29]. Two important chemical component from *M. charantia* are momordicine II and 3-Hydroxycucurbita-5[30]. It is one of the plant which has been extensively investigated for the treatment of diabetes. *M. charantia* is most promising plant for diabetes[31]. In an open- label uncontrolled supplementation trial it was shown that there was a significant improvement in 42 individuals who were having metabolic syndrome risk factors when given 4.8 gm lyophilised bitter gourd powder capsule[32]. In a randomized design 26 subjects were given tablets containing M. *charantia* for 4 week and it was found significant reduction in blood glucose level on diabetic patients[33]. In a multicentre double blind randomized control trial,4 groups were given capsule containing 500 mg of dried powder fruit pulp for 4 weeks which was shown to produce a significant antihyperglycemic effect[34]. In a double blind randomized control trial 40 patients with type II diabetes were given commercial herbal supplement capsule of *M. charantia* for 3 months and it was found that there was a significant reduction in HbA1c[35]. In a controlled trial 45 patients with type II diabetes were given the methanol extract of whole *M. charantia* fruit for one week and it was shown that there was a significant reduction in fasting and postprandial blood glucose level[36]. Several case series studies were conducted on the blood glucose level on type II diabetic patients who were given different extract of *M. charantia*. In one of the studies when 100 patients with type II diabetes were given fresh fruit for one time, it was found that there was a significant reduction in fasting blood glucose level in Oral glucose tolerance test (OGTT)[37]. In an another study 14 patients with type II diabetes and 6 patients with Type I diabetes were given seeds of *M. charantia* single time and found significant decline in postprandial blood glucose[38]. Further study on 18 patients with diabetes mellitus when given *M. charantia* juice from the seedless fruits single time it was found that there was a significant difference in OGTT[39]. In an another report 8 patients with type II diabetes mellitus were given powdered form of dried *M. charantia* fruit for 1 week and it was found a significant reduction in fasting blood glucose level, glycosuria and OGTT[40]. There was a significant reduction in OGTT and HbA1c level when 9 patients with type II diabetes mellitus were given fresh *M. charantia* juice for 7 to 11 weeks[41]. In a case series of 19 patients with diabetes mellitus administered polypeptide-p isolated *M. charantia* for single time and it was found that significant lessening effect in the blood glucose level[42]. The main mechanism involved in *M. charantia* might be due to the stimulation of peripheral and skeletal utilization of glucose[43,44], inhibition of glucose absorption[45–47], suppression of key gluconeogenic enzymes, stimulation of key enzyme of Hexose Monophosphate (HMP) pathway[48,49], and preservation of islet β cells and their actions[50]. Also, it was found that *M. charantia* extract reduces the activation mitogen-activated protein kinases (MAPKs)

and protect the pancreatic β cell by down regulating MAPKs and NF-kB[51].

2.5 Fenugreek: (*Trigonella foenum-graecum*)

Fenugreek is the herb predominantly cultivated in India. Fenugeek seed encompasses of fiber and protein. It was found in a study that it has hypoglycemic and hypocholesterolemic effects in humans. The effect of high soluble fiber in the fenugreek seed reduces the gastric emptying time and also reduce the post prandial blood glucose. Interestingly, the seeds also contains alkaloid trigonelline component, which is capable of reducing glycosuria[52]. It was demonstrated in a clinical trial, formula food was prepared with 10% fenugreek powder and served both diabetic and non-diabetic group while both group has been shown improved glucose tolerance[53]. In an another report 24 diabetic patients were treated with(10g/day) hot water soaked fenugreek seed for 2 months resulted in decreased level of Triglycerides, very low density lipoprotein and fasting blood glucose[54]. In one of the studies, when 10g of fenugreek per day was given as a dietary supplement, it was shown that there was a reduction in the plasma glucose, postprandial glucose and LDL[55]. In a randomized double blind, placebo- controlled clinical trial 56 patients with hyperlipidemia received 8g of fenugreek seeds powder for two months. In this study it was found that there was a significant reduction in triglycerides, total cholesterol, LDL, an increase HDL, fasting blood glucose and body mass index as compared to placebo group[56].

2.6 Blueberry Fruit: (*Cyanococcus*)

In a randomized double blind control trial 48 women received 480 ml of blueberry extract for 8 weeks and it was found there was a significant reduction in the systolic, diastolic blood pressure, increased nitric oxide level and an increased superoxide dismutase activity[57]. In an another experimental group 44 patients with metabolic syndrome was given 45g blueberry powder for 6 weeks and it was shown that there was an increase in insulin activity and endothelial function[58]. Eighteen males with the cardiovascular risk factor were given 250ml of blueberry drink and it was found there was a fall in the lipid profile, weight, markers of inflammation[59]. In a twenty seven obese insulin resistance subject blueberry (22.5gm/day) was given and it was found there is an increase in insulin sensitivity and change in the markers of inflammation, lipid profile and blood pressure[60]. In an eight weeks randomized control trial forty-eight subjects with metabolic syndrome were given 480ml of blueberry and there was decrease in the systolic, diastolic, plasma LDL and MDA[61]. In a four weeks randomized control trial sixty two patients were given 330ml of bilberry and it was found that there was a significant reduction in serum levels of C-Reactive protein, IL-6, IL-15. It has been found that berry consumption can bring about reduction of oxidative stress and also in inflammatory markers. There was a marked effect in lowering total and LDL cholesterol as well as triglycerides. Several studies have shown that berries have significant effect on decreasing blood pressure, particularly systolic blood pressure among hypertensive patients and improving the markers of endothelial function[62].

2.7 Grape Seed (*Vitis vinifera*)

Grape seed extract (GSE) contains polyphenols compound which are highly effective in prevention of cardiovascular disorders[63]. In a clinical study nine patients with metabolic syndrome received 300mg/day of GSE for four weeks. It was found that there was a significant drop in both systolic and diastolic blood pressure[64]. Most of the studies have shown that GSE has effect on endothelium dependent relaxation due to increased level of nitric oxide[65]. GSE also has potential effect on lowering LDL cholesterol and triglycerides[66]. In another randomized trial 18 patients with metabolic syndrome received GSE 150 to 300 gram/day given for 4 weeks. It was found that there was a significant effect on triglycerides, high density lipoprotein, low density lipoprotein and total cholesterol[67]. In a randomized control trial 35 patients with hyperlipidemia received GSE for 12 weeks and it was found that there was a significant positive effect on Total cholesterol, high density lipoprotein-C, Low density lipoprotein-C and triglycerides[68]. In an another study it was found that grape seed prevented hypercholesterolemia by virtue of reducing total cholesterol (37%) LDL (40%) and an elevation of HDL (23%). It was also observed that

LDL-C/HDL-C ratio and total cholesterol/HDL-C ratio reduced more than 50% thereby exhibiting an improvement in the atherosclerotic risk index[69]. Therefore, it's concluded that GSE has significant effect on prevention and treatment of atherosclerosis and cardiovascular diseases.

2.8 Neem (*Azadirachta indica*)

Neem is supposed to be an effective herbal drug in reducing lipid as well as glucose level in diabetic experimental animal studies. Several literature study in Ayurveda have shown a significant reduction in the glucose and lipid level in diabetic patients. Therefore, an experiment was conducted in rabbits treated with neem seed powder. It was found that there was a significant reduction in serum lipid levels, blood glucose and activities of serum enzymes like alkaline phosphatase, acid phosphatase, lactate dehydrogenase, liver glucose 6-phosphatase[70].

3. Prevalence of Antipsychotic Drugs Induced Metabolic Disorder

Atypical antipsychotics like risperidone, clozapine, olanazapine and quetiapine are mostly preferred drugs in the treatment of schizophrenia due to their less ability to cause extrapyramidal syndrome of millions of life. However, several reports have focused that these atypical antipsychotic drugs are associated with body weight gain, altered carbohydrate metabolism, dyslipidemia and cardiovascular accidents[71]. These kind of metabolic changes are developed within six month of starting the drug therapy[71]. The hallmark of the atypical antipsychotic drugs induced alteration in metabolism might be due to increased food intake, weight gain, hyperglycemia, lipid accumulation in adipose tissue and liver. It has been suggested that drugs like olanzapine and clozapine impair appetite regulatory signal in arcuate nucleus which leads to hyperphagia. Dopamine antagonist (D1 and D2) and 5HT agonist have been shown to reverse clozapine induced hyperphagia in animals[72,73].

In a meta-analysis of more than four lakh people, it was found that treatment of antipsychotic drugs cause high prevalence of diabetes. Antipsychotics play a major role in the etiology of diabetes mellitus though there are multifactorial reasons for this disease. Both typical and atypical antipsychotics are capable of causing diabetes as compared to general population. After treatment with antipsychotics there is a rapid raise in diabetes in patients treated with antipsychotic drugs signalling an adverse effect in carbohydrate metabolism[74]. There are several mechanisms that are postulated for the antipsychotics induced diabetes. Initially it was thought that antipsychotic induced diabetes might be due to weight gain but there are also other evidences which direct us to believe that involvement of decreased insulin sensitivity and decreased insulin secretary capacity of islet cells[75].

There are several evidences in which it was shown that the antipsychotic medication contribute to the development of hyperlipidemia in addition to the increase lipid disorder patients with severe mental illness. Dyslipidemia in one of the main side effects of atypical antipsychotics but other factors including diet eating habits, stress, heavy alcohol consumption and smoking can also cause greater chances of psychiatric patients becoming dyslipidemic[76]. It has also been found treatment with atypical antipsychotic caused elevated triglyceride and cholesterol as early as one to four months after starting the treatment and remains higher for many years. This patients are quite vulnerable to cardiovascular risk and therefore a several adjunct agent have been studied for the lipid normalising quality in this population[77].

One of the main reasons for the metabolic disorder caused by antipsychotic drugs might be due to the alteration in the metabolic pathway of lipid and carbohydrate. Therefore, several pharmacological interventions are being suggested along with the treatment of antipsychotic drugs to mitigate the metabolic abnormalities. However, this drugs also produce various adverse effects. Hence, it is important to implement possible therapeutic intervention by herbal remedies on antipsychotic drugs induced metabolic disorder.

4. Discussion

It has been shown that one of the traditional Chinese medicine Ling-Gui-Zhu-Gan decoction (LGZGD)

is capable of reducing the metabolic disorder caused by second generation antipsychotic drugs in schizophrenic patient. The author has concluded that multi-ingredient and multi-pathway nature of LGZGD and its effective mechanism are responsible for its efficacy in the treatment of metabolic disorder due second generation antipsychotic drugs in schizophrenic patient[78]. It is the only study conducted to show the effectiveness of herbal drug in treating antipsychotic induced metabolic syndrome. Recently our studies have shown that there is a high prevalence of metabolic syndrome after treating the patients with antipsychotics like haloperidol, olanzapine and risperidone[79]. As metabolic syndrome is constellation of obesity, diabetes, hyperlipidemia and may have severe and extensive coronary artery disease and asymptomatic ischemia which is not uncommon in India urban and rural population[80,81]. It requires a common drug which can targ*et al*l these features of metabolic syndrome by using a potential candidates of pharmaceutical therapeutic herbal medicine. In the present scenario most of the antipsychotic induced metabolic disorder are treated with conventional antidiabetic drug like metformin, glimepiride, vildagliptinetc. and antilipidemic drugs like statins+ fibrates are given to treat the metabolic disorder induced by antipsychotic drugs. All this above mentioned conventional antidiabetic and antilipidemic can produce severe side effects like muscle pain, blood disorder and cardiac problems etc. These side effects will have an additive effect to the adverse reaction produced by the antipsychotic drug induced metabolic disorder which will further deteriorate the quality of life of the schizophrenic patients. So for there are no reports about the usefulness of traditional medicine in treating the metabolic disorder induced by antipsychotic drugs. There is a great deal of research work can be initiated on finding the effectiveness of herbal drug in antipsychotic drugs produced metabolic syndrome. To enrich the better quality of life of psychiatric patients who are on antipsychotic drugs, the herbal drug will be a great boon if they are found to be effective in treating the metabolic disorder. Therefore, there is a need of extensive research to show the ameliorative effect of herbal drugs in metabolic disorder produced by antipsychotic drugs. In this review we have tried to disseminate the effectiveness of herbal drugs like Aloe Vera (*Aloe barbadensis miller*), Cinnamon: (*Cinnamomum cassia*), Russian tarragon: (*Artemisia dracunculus*), Bitter melon: (*Momordica charantia*), Fenugreek: (*Trigonella foenum-graecum*), Blueberry Fruit: (*Cyano coccus*), Grape seed (*Vitis vinifera*) and Neem (*Azadirachta indica*) in treating general metabolic disorders like diabetes mellitus, obesity, hyperlipidemia, hypertension and cardiovascular diseases. Therefore, there is a possibility of reduction in the symptoms of metabolic syndrome produced by antipsychotic drugs if some of the herbal drugs are administered to these patients.

5. Conclusion

The natural products are a big gold mine as a therapeutic armamentarium for several diseases like diabetes, lipid disorders and cardiovascular condition associated with metabolic disorders. Now there is a need to explore the possible therapeutic intervention by herbal drugs in the treatment of metabolic disorder induced by antipsychotic drugs.

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