11 Natural Compounds Extracted from Medicinal Plants and Their Applications in the Treatment of Diabetes and Hypertension

Pooja Rawat, Pawan Kumar Singh, and Vipin Kumar

Contents

Abstract

This chapter summarizes the natural compounds derived from various medicinal plants and their utilization in the treatment of diabetes and hypertension. Non-communicable diseases (NCDs) are accountable for causing more than 70% of all the deaths worldwide. Among NCD-caused mortalities, cardiovascular diseases account for approximately 17.7 million deaths per year, while cancers, respiratory diseases and diabetes caused 8.8 million, 3.9 million and 1.6 million deaths (World Health Organization 2017). Apart from the preventive measures, i.e., controlling the risk factors, such as unhealthy diet, use of tobacco, sedentary lifestyle and excess use of alcohol, the management of NCDs in terms of their early detection, diagnosis and treatment is very crucial for reducing the disease

P. Rawat · P. K. Singh (✉) · V. Kumar
National Innovation Foundation India, An Autonomous Body of Department of Science and Technology, Government of India, Gandhinagar, Gujarat, India
e-mail: pksinghbio@gmail.com

M. K. Swamy, M. S. Akhtar (eds.), *Natural Bio-active Compounds*,
https://doi.org/10.1007/978-981-13-7205-6_11

burden. While the synthetic compounds are being utilized for a long time, they are associated with multiple side effects. Since ancient times, the traditionally used plants have played a very significant role in primary healthcare. Several bio-active compounds isolated from the plants have been investigated scientifically and were found useful in controlling chronic diseases, including diabetes and hypertension. Many of the naturally derived compounds have also entered into the clinical trials with several being approved and launched commercially. For the treatment of chronic ailments, documented medicinal plants may therefore be utilized as the excellent tools for new and safe drug discovery.

Keywords
Natural compound · Diabetes · Hypertension · Clinical · Phytomedicine · Medicinal

11.1 Introduction

Diabetes mellitus is a metabolic chronic disorder characterized by hyperglycaemia for a long period of time. It is a heterogeneous group of disorders that affects multiple organs, such as the kidney, eyes, nervous system, etc. Currently available and used therapeutics for the management of diabetes include biguanides, DPP-4 inhibitors, α-glucosidase inhibitors, sulfonylureas/insulinotropics and thiazolidinediones (World Health Organization Model Lists of Essential Medicines). Usage of these synthetic drugs is however associated with severe harmful effects. Besides synthetic molecules, many medicinal plant-based preparations have been found efficacious in the treatment of chronic diseases and their symptoms (Amin et al. 2009; Taur and Patil 2011; Choudhary et al. 2015; Rawat et al. 2016a, b; Brahmachari et al. 2017).

Hypertension is a key reason of mortality and morbidity and is linked with coronary heart disease, cerebrovascular disease and renal disease and significantly contributes to stroke and myocardial infarction. The threshold above which hypertension should be treated to avoid long-term complications is now 140/90 mm Hg. Hypertension is a multifactorial event, which is controlled through various factors such as neurogenic regulation, renin angiotensin system, endothelials, renomedullary vasodepression, adrenal steroids, etc. Current treatments to control high blood pressure include drugs such as calcium antagonists, angiotensin II receptor blockers, peripheral adrenergic inhibitors, angiotensin-converting enzyme inhibitors (ACEIs), β-blockers, α-2 adrenergic receptor agonists and diuretics (Kalra et al. 2010). However, intake of majority of the synthetic drugs is accompanied with adverse health outcomes and therefore does not lead to effective treatment especially when taken for prolonged duration (Marshall et al. 1976; Russell 1988; Morimoto et al. 2004).

The role of plant-based medications in the treatment of numerous ailments including chronic ones is being recognized worldwide. This was made possible

through in-depth researches for understanding the mechanistic basis of the action of large number of phyto-compounds, including their target sites. Natural compounds, generally considered to be safe, have always been seen as an excellent candidate for drug discovery, which has become evident from substantial counts of drugs derived from natural sources including plants (Koehn and Carter 2005; Newman and Cragg 2016). Large numbers of traditionally used medicinal plants have been documented in classical literature and other documents, with their roles indicated in treatment of many categories of ailments such as gastrointestinal disorders (Rawat et al. 2016a, b, 2017), dengue (Singh and Rawat 2017), blood pressure (Rawat et al. 2016a, b), diabetes, obesity (Saad et al. 2017; Sudha et al. 2011), cancer (Newman and Cragg 2016), chronic inflammatory disorders, etc. With the development and advancement of technological tools, researches were conducted globally, wherein multiple biomolecules with the therapeutic efficacies have been isolated and characterized from different plant species. The outcomes of the clinical evaluation of plant-based therapeutics further confirmed their potency in human disease prevention and cure. This chapter describes several antihypertensive and antidiabetic phyto-compounds isolated from plants and evaluated for their therapeutic efficacy using in vitro as well as in vivo testing models. We found that very few of these phyto-compounds have been clinically evaluated and many preclinically validated compounds are yet to be explored in clinical trials. These phyto-molecules are the subject of further research for efficacy evaluation through clinical trials.

11.2 Applications of Plant-Derived Compounds for the Treatment of Diabetes and Hypertension

11.2.1 Antidiabetic Natural Compounds

Several plant-derived molecules have been investigated for their potential as antihyperglycaemic and their ameliorative effects on various biochemical alterations associated with diabetes at the molecular level. Common targets of some of these phyto-constituents include several intermediaries of metabolic pathways involved in maintaining glucose homeostasis in the body, viz. glycolysis, Krebs cycle, gluconeogenesis, glycogen synthesis, etc., whereas others have been found to play a functional role in the downstream signalling of insulin or function as insulinomimetics. Many researchers have reviewed the antidiabetic phyto-constituents and mechanisms of their action (Joseph and Jini 2011; Hung et al. 2012). These antidiabetic phyto-constituents have been classified into alkaloids, anthranoids, glycosides, amino acids, amines, carbohydrates, carboxylic acid derivatives, peptidoglycans, polyphenols, flavonoids and saponins (Bharti et al. 2018). Insulin therapy is an important part of diabetes treatment and is considered a must for type I diabetic patients and in many patients with type II diabetic conditions too. Secretion of insulin by pancreatic β-cells is known to regulate transport of glucose inside the cells using glucose transporter GLUT-2, through insulin-mediated signalling. Inability of pancreatic cells to secrete insulin in optimum quantity or nonresponsiveness of cells

towards the insulin-insulin receptor interaction leads to non-transport of glucose inside the cells, resulting into hyperglycaemic conditions. Majority of the antidiabetic phyto-compounds have been found to have a role in triggering insulin secretion, thereby resulting in hypoglycaemia, while some also act as insulinomimetics. Recently discovered antidiabetic natural products and their mechanisms are summarized in Table 11.1.

11.2.2 Antihypertensive Natural Compounds

Numerous antihypertensive medicinal plants have been earlier documented and investigated in in vitro and in vivo models for their traditionally known biological activities. Many traditionally used antihypertensive medicinal plants have been studied in detail for their possible mode of action and pathway involved. Scientific studies highlight the significance of medicinal plants for their ameliorative effects on symptoms of the disease. Few of the plants extracts have also been tested on human subjects in multiple clinical trials and found to be effective (Rawat et al. 2016a, b). Hypotensive action has been suggested to be mediated by several modes of actions such as antagonism of Ca^{2+} channel, inhibition of angiotensin-converting enzyme (ACE), relaxation of myocardium or involvement of α-adrenoceptor (Rawat et al. 2016a, b). Apart from plants extracts, isolation and characterization of many phyto-compounds have also been carried out. These isolated compounds have been further explored for their role in mediating the blood pressure lowering effects. Mechanisms of action have been investigated for most of the constituents as shown in Table 11.2.

11.3 Clinical Trials on Plant-Derived Natural Therapeutic Compounds

Many phyto-constituents have been clinically tested for their effectiveness. In case of diabetes, the clinical parameters monitored were blood glucose, HbA1c, insulin after administration of test molecule. For hypertension, study parameter was reduction in mean arterial pressure, diastolic blood pressure (DBP) and systolic blood pressure (SBP).

11.3.1 Clinically Evaluated Antihypertensive Phyto-compounds

11.3.1.1 Allicin

To study antihypertensive property of allicin (from *Allium sativum*), a clinical trial on 100 subjects including 60 males and 40 females (25–55 years) was conducted. The study included the subjects with SBP in range of 140–150 mm and DBP <95 mm of Hg. For extraction of allicin from *Allium sativum*, fresh garlic cloves were crushed using water leading to 100% yield of allicin and 25 g crushed garlic

Table 11.1 Antidiabetic phyto-compounds and their mechanisms of action

Compounds	Source	Study type	Outcomes/mechanisms involved	References
β-carbolines, harmane and pinoline	–	In vitro	Two- and threefold increase in insulin secretion was observed in in islets of Langerhans	Cooper et al. (2003)
Gymnemic acid IV	*Gymnema sylvestre*	In vivo	Treatment of streptozotocin diabetic mice with gymnemic acid IV (13.4 mg/kg) resulted in higher plasma insulin level	Sugihara et al. (2000)
Epigallocatechin gallate	*Camellia sinensis*	In vitro	Epigallocatechin gallate acts as insulin analog and causes decrease in phosphoenolpyruvate carboxykinase and glucose 6-phosphatase gene expression and glucose production. The compound also increases insulin receptor and insulin receptor substrate-1 activation through Tyr phosphorylation	Waltner-Law et al. (2002)
Procyanidins	*Vitis vinifera*	In vivo	Procyanidins show insulinomimetic activity in L6E9 myotubes and adipocytes (3T3-L1). The compound causes dose-dependent stimulation of glucose uptake	Pinent et al. (2004)
Lagerstroemin, flosin B, stachyurin, casuarinin, casuariin, 2, 3-(S)-hexahydroxydiphenoyl-α/β-D-glucose	*Lagerstroemia speciosa*	In vitro	Compounds show insulinomimetic activity. Surge in glucose uptake was observed on treatment. The compounds (at 100 nM) showed glucose tolerance sum of 24%, 25%, 22%, 29% and 20% equivalent to that of insulin	Bai et al. (2008)
Andrographolide	*Andrographis paniculata*	In vivo and in vitro	Intravenous glucose challenge caused significant attenuation of the increase in plasma glucose levels after andrographolide administration at 1.5 mg/kg. In in vitro studies on the soleus muscle isolated from STZ-diabetic rats, glucose uptake stimulatory effects were observed; uptake was found to be dose dependent	Yu et al. (2003)
Lactucain C, lactucaside	*Lactuca indica*	In vivo	The compound at a dose of 1 mM/kg resulted in moderate lowering of plasma glucose levels	Hou et al. (2003)

(continued)

Table 11.1 (continued)

Compounds	Source	Study type	Outcomes/mechanisms involved	References
Mulberrofuran U, moracin M-3'-O-β-D-glucopyranoside, β-sitosterol, β-sitosterol-3-O-β-glucopyranoside, ursolic acid, moracin M, kaempferol-3-O-β-glucopyranoside and quercetin-3-O-β-glucopyranoside	*Morus insignis*	In vivo	Reduction in blood glucose was observed	Basnet et al. (1993)
Trans-dehydrocrotonin	*Croton cajucara*	In vivo	Trans-dehydrocrotonin at 50 mg/kg significantly lowered the blood glucose and blood triglycerides enhanced by streptozocin and ethanol, respectively	Silva et al. (2001)
Mulinolic acid, azorellanol	*Azorella compacta*	In vivo	At 180 mg/ml, both the compounds showed significant antihyperglycaemic effect, while hyperinsulinemic effect was observed only in case of azorellanol	Fuentes et al. (2005)
Tocopherol	*Cucurbita pepo*	In vivo	Ameliorative effects on glucose, lipid dysmetabolism and plasma insulin. Oxidative markers also showed reduction in their levels. Treatment with tocopherol also improved cecal and pancreatic characteristics	Bharti et al. (2013)
Quercetin	–	In vivo	Reduction in the plasma glucose was observed in streptozocin-induced diabetic rats. The effect was found to be dose dependent. Normalization of glucose tolerance and hexokinase activity was seen at 15 mg quercetin/kg. Mechanism of action was suggested to be regeneration of the pancreatic islets and probable increase in insulin release in streptozocin-induced diabetic rats	Vessal et al. (2003)
Berberine	–	In vitro and in silico	Inhibits dipeptidyl peptidase IV with IC_{50} 13.3 μM	Al-Masri et al. (2009)

Epicatechin	–	In vitro	Increase in insulin secretion from islets of Langerhans, isolated from rats, was observed at 1 mM	Hii and Howell (1984)
Hesperidin, Naringin	*Citrus* sp.	In vivo	Compounds caused increase in plasma insulin and decline in blood glucose at 200 mg/kg. Mode of action was found to be partly by causing increase in hepatic glycolysis, increase in glycogen levels and by suppression of gluconeogenesis	Jung et al. (2004)
Mangiferin	*Mangifera indica*	In vivo	Significant lowering of fasting plasma glucose level with improvement in oral glucose tolerance at 10 and 20 mg/kg	Muruganandan et al. (2005)
Cinnamaldehyde	*Cinnamonum zeylanicum*	In vivo	Decrease in plasma glucose, decrease in glycosylated haemoglobin and increase in plasma insulin. Effects were found to be dose dependent	Subash Babu et al. (2007)
Bis(catecol glycoside) esters	*Dodecadenia grandiflora*	In vivo	Antihyperglycaemic activity was observed	Kumar et al. (2009)
4,5-di-O-caffeoylquinic acid, davidigenin, 6-demethoxycapillarisin and 2′,4′-dihydroxy-4-methoxydihydrochalcone	*Artemisia dracunculus*	In vitro	Acts as an aldose reductase (ALR2) inhibitor	Logendra et al. (2006)
Kraussianone-1 (9) and kraussianone-2	*Eriosema kraussianum*	In vivo	Significant hypoglycaemia in rats at 20–80 mg/kg. Effect was found to be dose dependent	Ojewole et al. (2006)
4-hydroxyderricin (4-HD) and xanthoangelol	*Angelica keiskei*	In vitro and in vivo	Enhancement of glucose uptake by 3T3-L1 adipocytes was observed. Reduction in blood glucose and insulin resistance in in vivo studies was observed	Enoki et al. (2007)
Apigenin-6-C-β-l-fucopyranoside	*Averrhoa carambola*	In vitro and in vivo	Compound was found to be antihyperglycaemic by causing insulin secretion and was also found to act as insulinomimetic agent	Cazarolli et al. (2009)

(continued)

Table 11.1 (continued)

Compounds	Source	Study type	Outcomes/mechanisms involved	References
Pongamol and karanjin	*Pongamia pinnata*	In vivo	At 50 mg/kg and 100 mg/kg, blood glucose levels reduced significantly by 12.8% and 22%, respectively, in case of pongamol. In case of karanjin, lowering of blood glucose level by11.7% and 20.7% ($p < 0.01$) at 50 mg/kg and 100 mg/kg, respectively. Significant inhibition of protein tyrosine phosphatase 1B was also observed	Tamrakar et al. (2008)
Kaempferol and quercetin	*Euonymus alatus*	In vitro	Glucose uptake showed a significant increase in insulin-stimulated 3T3-L1 adipocytes	Fang et al. (2008)
Kaempferol-3-O-α-l-rhamnopyranoside 3″,4″-di-E-p-coumaric acid ester and 3″-E,4″-Z-di-p-coumaric acid ester	*Machilus philippinensis*	In vitro	Inhibition of α-glucosidase was observed. IC_{50} values of 6.1 and 1.0 μM were observed in case of kaempferol-3-O-α-l-rhamnopyranoside 3″,4″-di-E-p-coumaric acid ester and 3″-E,4″-Z-di-p-coumaric acid ester, respectively	Lee et al. (2008)
Aspalathin	*Aspalathus linearis*	In vitro and in vivo	At 1–100 mM, enhancement of glucose uptake by L6 myotubes was observed, which showed dose dependency. Increase in insulin secretion in RIN-5F cells was also observed at 100 mM. Lowering of blood glucose and improvement in glucose tolerance was also observed	Kawano et al. (2009)
3′,5′-Diprenylgenistein, 6,8-diprenylgenistein, derrone and alpinumisoflavone	*Tetracera scandens*	In vitro	L6 myotubes showed significant increase in glucose-uptake. Mode of action was identified to be via 5′ AMP-activated protein kinase phosphorylation, glucose transporter 4 and glucose transporter 1 mRNA expressions and protein tyrosine phosphatase 1B inhibition	Lee et al. (2009)
Steppogenin-40-O-b-D-glucoside	*Morus alba*	In vivo	Lowering of blood glucose levels	Zhang et al. (2009)

Cinchonain Ib	*Eriobotrya japonica*	In vitro and In vivo	Enhancement in insulin secretion from INS-1 cells; however, no effects on blood glucose levels were found	Qa'dan et al. (2009)
Coagulanolide	*Withania coagulans*	In vivo	Attenuation of postprandial rise in blood glucose in normoglycaemic as well as streptozotocin-induced diabetic rats	Maurya et al. (2008)
Momordicosides Q, R and S and karaviloside XI	*Momordica charantia*	In vivo	The compounds were found to have stimulatory effects on glucose transporter 4 translocation in 3T3-L1 adipocytes as well as L6 myotubes	Tan et al. (2008)
Nerolidol-3-O-α-l-rhamnopyranosyl(1 → 4)-α-l-rhamnopyranosyl(1 → 2)-[α-l-rhamnopyranosyl(1 → 6)]-β-d-glucopyranoside	*Eriobotrya japonica*	In vivo	Reduction in blood glucose	Qa'dan et al. (2009)
Costunolide	*Costus speciosus*	In vivo	Reduction in plasma glucose, glycosylated haemoglobin, total cholesterol, triglyceride and low-density lipoproteins. The effects were found to show dose dependency. Increase in tissue glycogen, plasma insulin, high-density lipoprotein and serum protein was also seen	Eliza et al. (2009)
Stigmasterol	*Butea monosperma*	In vivo	Reduction in glucose concentrations. The effect was found to be mediated by reduction in glucose-6-phophatase and upsurge in insulin	Panda et al. (2009)
Bruceines E and D	*Brucea javanica*	In vivo	Significant lowering of blood glucose	NoorShahida et al. (2009)
Tanshinone I, IIA and 15, 16-dihydrotanshinone I	*Salvia miltiorrhiza*	In vitro	Enhancement of insulin activity and insulin receptor activation via enhanced tyrosine phosphorylation as well as activation of downstream kinases protein kinase B, extracellular signal-regulated kinases 1/2, and glycogen synthase kinase 3β	Jung et al. (2009)

(continued)

Table 11.1 (continued)

Compounds	Source	Study type	Outcomes/mechanisms involved	References
28Nor-22(R)Witha 2,6,23-trienolide	*Elephantopus scaber*	In vivo	Reduction in blood glucose and restoration of insulin levels	Daisy et al. (2009b)
Corosolic acid	*Lagerstroemia speciosa*	In vitro	Inhibition of α-glucosidase with IC_{50} value of 3.53 μg/ml	Hou et al. (2009)
Spicatanol	*Hedychium spicatum*	In vitro	Inhibition of α-glucosidase with IC_{50} value of 34.1 μM	Reddy et al. (2009)
Palbinone	*Paeonia suffruticosa*	In vitro	Levels of phospho- acetyl-CoA carboxylase, phospho- 5' AMP-activated protein kinase and phospho-glycogen synthase kinase-3β were observed to increase. The compounds stimulated dose dependent increase in glycogen synthesis and uptake of glucose	Tuan et al. (2009)
Dihydroxy gymnemic triacetate	*Gymnema sylvestre*	In vivo	Significant reduction in plasma glucose along with changes in hepatic markers, decline in glycosylated haemoglobin and increase in insulin were observed	Daisy et al. (2009a)
Swietenine	*Swietenia macrophylla*	In vitro	Increase in glucose uptake was observed	Maiti et al. (2009)
13-hydroxykompasinol A, scirpusin C, kompasinol A (2) and 3,3′,4,5,5′-pentahydroxy-trans-stilbene (5)	*Syagrus romanzoffiana*	In vitro and In vivo	13-Hydroxykompasinol A and scirpusin C inhibited α-glucosidase type IV with IC_{50} of 6.5 and 4.9 μM, respectively	Lam et al. (2008)
			Significant reduction in postprandial blood glucose level by 10.2% and 12.1% in case of kompasinol A and 3,3′,4,5,5′-pentahydroxy-trans-stilbene, respectively	

Table 11.2 Antihypertensive phyto-compounds and their mechanisms of action

Compound	Source	Type of study	Study outcomes/mechanisms involved	References
Allicin	*Allium sativum*	Clinical study	Systolic and diastolic blood pressure reduced by up to 10% (5 mmHg) in subjects supplemented with garlic-allicin	Bhardwaj et al. (2015)
S-1-propenylcysteine	*Allium sativum*	In vivo	Significant decrease (10%) in the systolic blood pressure was observed in spontaneously hypertensive rats at 3 h after administration, which got normalized within 24 h. The antihypertensive effect showed dose dependency	Ushijima et al. (2018)
Safranal and crocin	*Crocus sativus*	In vivo	Mean arterial blood pressure got substantially reduced in a dose-dependent manner in hypertensive as well as normotensive rats. Safranal (1 mg/kg) and crocin (200 mg/kg) caused 50 ± 5.2 and 51 ± 3.8 mmHg reductions in mean arterial blood pressure	Imenshahidi et al. (2010)
Bark extract standardized to 8% pinoresinol di-β-D-glucoside	*Eucommia ulmoides*	Clinical trial	Intake of 500 mg of Eucommia extract (three times daily) for 8 weeks resulted in significant reduction in blood pressure in 24 healthy subject. The extract was found to have β-adrenergic blocking activity	Greenway et al. (2011)
Delphinidin- and cyanidin-3-O-sambubiosides	*Hibiscus sabdariffa*	In vitro	Inhibitory activity against angiotensin-converting enzyme with IC_{50} values of 84.5 and 68.4 μg/mL shown by delphinidin-3-O-sambubioside and cyanidin-3-O-sambubioside, respectively. Mode of action was found to be through competitive inhibition of substrate	Ojeda et al. (2010)
Ginsenoside Rg3-enriched Korean red ginseng	*Panax quinquefolius*	Clinical study	At 3 h, significant reductions in central and brachial mean arterial pressure, central systolic and diastolic BP and brachial systolic and diastolic BP were observed in Rg3 Korean red ginseng-treated group in comparison with control group	Jovanovski et al. (2014)
Ginsenoside protopanaxatriol	–	In vivo	Antihypertensive effects were mediated by stimulation of increase in nitric oxide production, activation of endothelial nitric oxide synthase and improved vessel wall thickening	Hong et al. (2012)

(continued)

Table 11.2 (continued)

Compound	Source	Type of study	Study outcomes/mechanisms involved	References
Pycnogenol from bark extract (mixture of water-soluble procyanidins, catechin, taxifolin and phenolcarbonic acids)	*Pinus pinaster*	Clinical study	Significant fall in the systolic blood pressure was observed in mildly hypertensive patients after 8-week intake of pycnogenol at a dose of 200 mg/day. However no major effect was seen on diastolic blood pressure	Hosseini et al. (2001)
Reserpine, a root extract	*Rauwolfia serpentina*	Clinical study	Significant lowering of systolic blood pressure with intake of reserpine at 0.5 mg/day in comparison with placebo	Shamon and Perez (2009)
Procyanidin-rich cocoa	*Theobroma cacao*	In vitro	Procyanidins mediated an endothelium-dependent relaxation (EDR) of aortic endothelial cells, and significant increase in Ca^{2+}-dependent nitric oxide synthase activity was also observed, which may be probable mechanism of EDR	Karim, et al. (2000)
Epicatechin as well as procyanidins	–	In vitro	Inhibition of angiotensin-converting enzyme through competitive inhibition of the active sites	Actis-Goretta et al. (2003)
Flavanol-rich dark chocolate (DC)	–	Clinical study	Decline in blood pressure and serum low-density lipoprotein and improvement in flow-mediated dilation were observed in patients with essential hypertension. The intake of flavanol-rich dark chocolate resulted in amelioration of insulin sensitivity in patients	Grassi et al. (2005)
Forskolin (7 beta-acetoxy-8, 13-epoxy-1 alpha,6 beta,9 alpha-trihydroxy-labd-14-ene-11-one), a diterpene	*Coleus forskohlii*	In vivo and clinical study	Cerebral vasodilator activity was observed. The compound was found to act through increase in cyclic adenosine monophosphate-mediated functions and through activation of the enzyme adenylate cyclase	Wysham et al. (1986); Kramer et al. (1987)
			In patient of dilated cardiomyopathy (DCM), administration of forskolin (3 μg/kg/min) resulted into reduction in diastolic blood pressure. Improvement in left ventricular function was also seen in DCM patients after administration of forskolin (3 μg/kg/min)	

Polyphenolics including quercetin, kaempferol, catechin, quercitrin, rutin, luteolin, epicatechin, caffeic acid, chlorogenic acid and gallic acids	*Psidium guajava*	In vitro	Dose-dependent inhibition of xanthine oxidase, angiotensin-converting enzyme and Fe^{2+}-induced lipid peroxidation with IC_{50} value of 38.24 μg/mL, 21.06 μg/mL and 27.52 μg/mL, respectively	Irondi et al. (2016)
Five C-glycosylflavones, vicenin 2 (1), carlinoside (2), vicenin 1 (3), schaftoside (4) and vicenin 3 (5)	*Desmodium styracifolium*	In vitro	Inhibition of angiotensin-converting enzyme activity	Zhang et al. (2015)
3, 4-Dihydroxybenzaldehyde	*Musanga cecropioides*	In vivo	Reductions in the mean arterial blood pressure by 12.61 ± 2.45 mmHg at 2.5 mg/kg and 17.88 ± 0.73 mmHg at 10 mg/kg. Effect showed dose dependency	Ayinde et al. (2010)
Puerarin	*Pueraria lobata*	In vivo	Improvement in cerebral microcirculation, thereby causing attenuation of cerebral damage in spontaneously hypertensive rats	Wu et al. (2014)
Ellagic acid	*Punica granatum*	Ex vivo	Vasorelaxant effects on isolated rat thoracic aorta. The effect was observed to be modulated via inhibition of calcium influx and endothelium-dependent mechanisms	Yilmaz and Usta (2013)
Rhynchophylline and isorhynchophylline	*Uncaria rhynchophylla*	In vitro and ex vivo	Relaxing effects on precontracted aortic rings. Mode of action was blocking of voltage-dependent Ca^{2+} channel	Zhang et al. (2004); Zhou and Zhou (2012)
[6]-Gingerol	*Zingiber officinale*	In vitro	Mode of antihypertensive action was inhibition of angiotensin II type 1 receptor activation	Liu et al. (2013)
Coumarin, vanillic acid, p-coumaric acid, gallic acid, caffeic acid and ferulic acid	*Melothria maderaspatana*	In vivo	Lowering of systolic and diastolic blood pressure. The effect is mediated via reversal of metabolic alterations in copper, magnesium and zinc	Veeramani et al. (2012)
Isoquercitrin	*Tropaeolum majus*	In vivo	Significant lowering of mean arterial pressure, through inhibition of angiotensin II generation via angiotensin-converting enzyme	Gasparotto et al. (2011)

(continued)

Table 11.2 (continued)

Compound	Source	Type of study	Study outcomes/mechanisms involved	References
Oleanolic acid	*Viscum articulatum*	In vivo	Amelioration of dexamethasone induced increase in systolic blood pressure and cardiac lipid peroxidation level. The mode of action was its antioxidant action and nitric oxide releasing effects	Bachhav et al. (2011)
Dodoneine	*Agelanthus dodoneifolius*	Ex vivo	The compound shows hypotensive effects through L-type calcium channels blockage and its negative inotropic action	Carre et al. (2014)
Rutin (1), kaempferol 3-O-rutinoside (2) and kaempferol 3-O-glucuronide (3), (+)-catechin (4) and (-)-epicatechin (5), dihydro-5,6-dehydrokawain (6) and 5,6-dehydrokawain (7)	*Alpinia zerumbet*	Ex vivo and in vitro	Antihypertensive action of rutin is mediated via non-competitive inhibition of angiotensin II and prostaglandin E2. The compound is also reported to interfere with arachidonic acid metabolism and inhibits cyclic adenosine monophosphate phosphodiesterase and induces smooth muscle relaxation. Inhibition of noradrenaline-induced contractions in rat aortic strips was caused by quercetin. Kaempferol 3-O-glucoside inhibits angiotensin-converting enzyme activity	Mpalantinos et al. (1998)
Terpinen-4-ol	*Alpinia zerumbet*	In vivo	Decline in blood pressure in desoxycorticosterone acetate-induced hypertensive rats. The effect is via vascular smooth muscle relaxation	Lahlou et al. (2003)
Penta-O-galloyl-glucoside, casuariin and 5-desgalloylstachyurin	*Geum japonicum*	Ex vivo	Vasorelaxant effects in precontracted rat aortic rings, which was found to be mediated via nitric oxide and cyclic guanosine monophosphate	Xie et al. (2007)
Marrubenol, a diterpenoid	*Marrubium vulgare*	Ex vivo	Relaxant effects on artificially contracted rat aorta and blocking L-type calcium channels thereby inhibiting contraction of smooth muscles	El Bardai et al. (2003)
Iso-S-petasin	*Petasites formosanus*	Ex vivo	Depressant action on ventricular contraction	Esberg et al. (2003)

Praeruptorin A, a coumarin compound	*Peucedanum praeruptorum*	Ex vivo	Relaxation of aorta rings isolated from rats was observed which was mediated via endothelial nitric oxide synthase	Xu et al. (2010)
Puerarin, genistein, daidzein	*Pueraria tuberosa*	In vivo	In case of genistein, lowering of blood pressure was observed. Restoration of angiotensin-converting enzyme, protein kinase C-βII and endothelial nitric oxide synthase expression was also observed along with maintenance of renal ultrastructure	Palanisamy and Venkataraman (2013)
Piperine, an alkaloid	*Piper nigrum*	In vivo	Ameliorative effects on N-nitroarginine methyl ester-induced hypertension, through its antioxidant effects	Kumar et al. (2010)
Z-ligustilide	*Radix Angelica sinensis*	Ex vivo	Reduction of phenylephrine-induced aortic tension	Du et al. (2007)
Isoquercitrin	*Tropaeolum majus*	In vivo	In spontaneously hypertensive rats, compound showed significant reduction of mean arterial pressure and angiotensin-converting enzyme activity	Gasparotto et al. (2011)
Jujuboside B	*Zizyphi spinosi*	Ex vivo	The compound reduced endothelium-dependent vascular tension. The mechanisms involve increase in extracellular transient receptor potential cation channel-mediated Ca^{2+} influx, endothelium-dependent hyperpolarization through potassium channels and nitric oxide generation in vascular endothelial cells	Zhao et al. (2016)

was supplemented to subjects. Measurements of BP were made after 3 and 6 months. The treatment resulted in up to 5 mmHg (10%) reduction in SBP and DBP was observed (Bhardwaj et al. 2015).

11.3.1.2 Pinoresinol di-β-D-Glucoside

In a randomized placebo-controlled clinical trial, antihypertensive efficacy of *Eucommia ulmoides* was checked. Thirty healthy subjects (aged 18–60 years), with BP between 120–160 and 80–100 mmHg, were chosen for the study. Five hundred milligrams of aqueous bark extract of *E. ulmoides* (containing 8% pinoresinol di-β-D-glucoside) was administered thrice a day for 8 weeks and was found to have hypotensive action. The extract was found to act through beta-adrenergic receptors (Greenway et al. 2011).

11.3.1.3 Ginsenoside Rg3

Efficacy of ginsenoside Rg3-enriched ginseng was evaluated in a double-blind, randomized clinical trial. Twenty-three individuals including 9 males and 14 females (23–27 years) with SBP in a range of 110–116 mm Hg and DBP in a range of 68–72 mm Hg were selected. Four hundred milligrams wheat bran was used as a control along with 400 mg ginsenoside Rg3-enriched extract, which were administered to patients on two separate visits with a time gap of 7 days. After intervention, measurements of different parameters including central and branchial BP were taken at 1-h interval till 3 h. At 3 h, significant reductions in central and brachial mean arterial pressure by 4.7 mm Hg and 4.4. mm Hg, respectively, central SBP and DBP by 5 mm Hg and 3.9 mm Hg, respectively, and brachial SBP and DBP by 4.4 mm Hg and 3.6 mm Hg, respectively, were observed compared with control (Jovanovski et al. 2014). *Panax quinquefolius* is the main plant source for obtaining ginsenoside Rg3.

11.3.1.4 Pycnogenol

Pycnogenol from *Pinus pinaster* is a mixture of bioflavonoids, namely, procyanidins, taxifolin, catechin and phenolcarbonic acids. Antihypertensive effects of pycnogenol was studied in a placebo-controlled, double-blind, randomized, prospective, crossover study in mildly hypertensive patients. Eleven mildly hypertensive subjects (average age of 50 years) with SBP and/or DBP of 140–159 mm Hg and 90–99 mm Hg, respectively, were selected and supplemented with 200 mg/day of pycnogenol up to 56 days. SBP showed substantial reduction with no significant differences observed in case of DBP as compared to placebo (Hosseini et al. 2001).

11.3.1.5 Reserpine

Antihypertensive effects of reserpine have been well reported in the randomized controlled clinical trials, wherein statistically significant reduction on SBP was observed in treatment group taking 0.5 mg/day or greater of reserpine in comparison with placebo (Shamon and Perez 2009). The medicinal plant, *Rauwolfia serpentina* is the main source of reserpine.

11.3.1.6 Forskolin

The potential of forskolin (obtained from *Coleus forskohlii*), 7 beta-acetoxy-8, 13-epoxy-1 α,6 β,9 α-trihydroxy-labd-14-ene-11-one, in reducing BP was clinically evaluated in patients of dilated cardiomyopathy (DCM). Forskolin was administered at concentrations of 3 μg/kg/min and 4 μg/kg/min intravenously. At lower concentration, decline in systemic vascular resistance and diastolic pressure in left ventricular end, was observed. It also improved left ventricular function in DCM patients (Kramer et al. 1987). In another clinical trial, the antihypertensive effect of forskolin was investigated in 12 patients with congestive cardiomyopathy using the thermo-dilution catheter method. Comparative studies with dobutamine, a β-1-receptor agonist, and sodium nitroprusside, a vasodilator, were conducted. Significant reduction in SBP and DBP as well as mean pulmonary artery pressure was observed with slight increase in heart rate. Approximately 70% increase in cardiac stroke volume index was also observed (Baumann et al. 1990).

11.3.2 Clinically Evaluated Antidiabetic Phyto-compounds

11.3.2.1 Epigallocatechin Gallate

Effect of epigallocatechin (EGCG) was evaluated in obese male subjects (40–65 years), and effect on insulin resistance was evaluated. Forty-six subjects were supplemented with 400 mg EGCG, while 42 subjects were given lactose (placebo) twice daily for 8 weeks. Various parameters such as oral glucose tolerance test (OGTT) and metabolic risk factors such as waist circumference, body fat, blood pressure, body mass index, low-density cholesterol, high-density cholesterol and triglycerides were monitored before and after drug intervention. Insulin sensitivity and insulin secretion were observed to show no significant alterations. Also no substantial changes in glucose tolerance were observed. However the treatment resulted in reduction in DBP in intervention group (Brown et al. 2009).

11.3.2.2 Berberine

Antidiabetic potential of berberine was investigated in type II diabetic patients suffering with dyslipidemia. One hundred sixteen patients (age 25–70 year) were selected and administered for 3 months with per day dose of 1.0 g of berberine and the placebo. Different study parameters were analysed after 3 months. Significant reduction in plasma glucose levels, HbA1c, triglyceride, low-density lipoprotein cholesterol as well as total cholesterol was observed as compared to placebo. Both treatment and placebo groups showed increase in glucose disposal rate (Zhang et al. 2008).

11.3.2.3 Corosolic Acid

A randomized clinical trial was conducted on 10 human subjects (55–70 years) with type II diabetes with basal blood glucose levels of 140–250 mg/dl. Glucosol™, which is an extract prepared from *Lagerstroemia speciosa* leaves, was given at daily dosages of 32 and 48 mg for 2 weeks. The test extract was standardized to 1%

corosolic acid. Administration of Glucosol™ to patients decreased blood glucose levels by 30% (Judy et al. 2003). In another double-blind, placebo-controlled, cross-over study, 31 subjects (16 men and 15 women) were selected. The subjects had fasting glucose levels in the range of 110–140 mg/dl. Corosolic acid (10 mg) was administered orally, 5 min before OGTT. Lowering of glucose levels from 60 min till 120 min were observed in the treatment group (Fukushima et al. 2006).

11.4 Status of Clinically Proven Phyto-compound-Based Patents Filed Across the Globe

The clinically validated antihypertensive phyto-molecules were checked for the status of patents filed/granted on them, across the globe. Patent data was retrieved using licenced version of Derwent Innovation patent database (www.info.thomsoninnovation.com/; data accessed on 28th August 2018). Multiple patent records were found for some of the clinically proven antihypertensive phytochemicals such as reserpine, forskolin, allicin and ginsenoside, whereas very few patent applications were found for pycnogenol. In case of pinoresinol di-β-D-glucoside, no patent record was found for its application as antihypertensive. Similar searches were conducted to check the status of patents filed on clinically validated antidiabetic phyto-molecules. All the three clinically proven antidiabetic phyto-compounds, viz. EGCG, berberine and corosolic acid, were found in multiple patent applications. The numbers of patents filed on inventions encompassing role of these phyto-molecules in treatment of hypertension or diabetes is summarized in Fig. 11.1. Reserpine was observed to be used maximum numbers of times in patent applications mentioning hypertension as the treatment target. In case of antidiabetics, EGCG was used maximum numbers of times in patent applications filed across the globe.

11.5 Conclusion and Future Prospects

Phyto-medications for the cure of numerous human ailments, including chronic ones is being globally accepted and recognized. Researchers have identified mechanistic basis of the action, including target sites, for number of phyto-compounds, useful against diabetes and hypertension. One excellent example of antidiabetic drug discovery from folklore plant source is metformin, which is globally being used to treat diabetic patients, though it has some reported side effects. However, much more efforts are needed to develop a pool of phyto-compound-based herbal medications suited to tackle hypertension and diabetes, and this can be easily achieved by targeting the traditionally used codified and non-codified medicinal plants for novel drug discovery.

Antidiabetic phyto-constituents target intermediaries of metabolic pathways involved in maintaining glucose homeostasis, downstream signalling of insulin and function as insulinomimetics. In case of antihypertensive phyto-compounds,

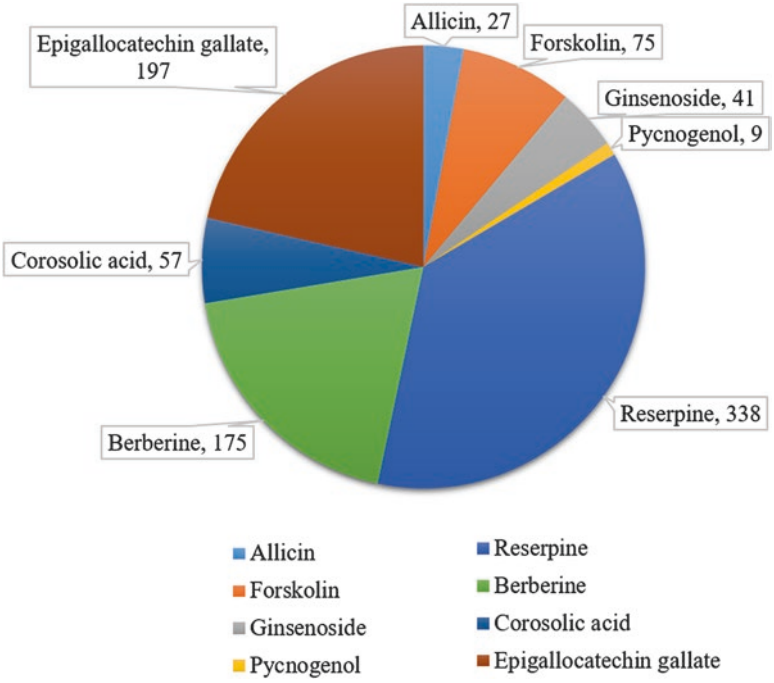

Fig. 11.1 Number of patents filed across the globe on clinically proven antihypertensive and antidiabetic phyto-constituents

hypotensive action has been suggested to be through antagonistic action on Ca^{2+} channel, ACE inhibition and α-adrenoceptor, and in some cases, the compounds have been shown to have direct relaxant effects on blood vessels. A large number of phyto-compounds have undergone preclinical validation; however, only few have been evaluated thoroughly through clinical trials. Since the plants are known to contain large number of useful compounds, researchers should also give attention on developing phyto-formulations based on whole extract and not only on pure single molecule. The non-purified plants extracts may be more useful in combating the diseases and tackling the issues of toxicity, which is generally high with single molecules. This approach may also lead to development of novel phyto-medications on fast track basis, not only as single targeted drug but also as a multifunctional therapeutics.

Acknowledgement Authors are grateful to Prof Anil Gupta, Executive Vice Chairperson, National Innovation Foundation, India, for his honorary guidance and encouragement for carrying out this research activity.

References

Actis-Goretta L, Ottaviani JI, Keen CL, Fraga CG (2003) Inhibition of angiotensin converting enzyme (ACE) activity by flavan-3-ols and procyanidins. FEBS Lett 555:597–600

Al-Masri IM, Mohammad MK, Tahaa MO (2009) Inhibition of dipeptidyl peptidase IV (DPP IV) is one of the mechanisms explaining the hypoglycemic effect of berberine. J Enzyme Inhib Med Chem 24:1061–1066

Amin A, Gali-Muhtasib H, Ocker M, Schneider-Stock R (2009) Overview of major classes of plant-derived anticancer drugs. Int J Biomed Sci 5:1–11

Ayinde BA, Omogbai EKI, Onwukaeme DN (2010) Hypotensive effects of 3, 4-dihydroxybenzaldehyde isolated from the stem bark of Musanga cecropioides. J Pharmacogn Phytother 2:4–9

Bachhav SS, Patil SD, Bhutada MS, Surana SJ (2011) Oleanolic acid prevents glucocorticoid-induced hypertension in rats. Phytother Res 25:1435–1439

Bai N, He K, Roller M (2008) Active compounds from *Lagerstroemia speciosa*, insulin-like glucose uptake-stimulatory/inhibitory and adipocyte differentiation-inhibitory activities in 3T3-L1 cells. J Agric Food Chem 56:11668–11674

Basnet P, Kadota S, Terashima S (1993) 2 new 2-arylbenzofuran derivatives from hypoglycemic activity-bearing fractions of Morus insignis. Chem Pharm Bull 41:1238–1243

Baumann G, Felix S, Sattelberger U, Klein G (1990) Cardiovascular effects of forskolin (HL 362) in patients with idiopathic congestive cardiomyopathy-A comparative study with dobutamine and sodium nitroprusside. J Cardiovasc Pharmacol 16:93–100

Bhardwaj K, Verma MK, Verma N, Bhardwaj S, Mishra S (2015) Effect of long term supplementation of active garlic allicin in reducing blood pressure in hypertensive subjects. Int J Adv Med 2:231–234

Bharti SK, Kumar A, Sharma NK, Prakash O, Jaiswal SK, Krishnan S, Gupta AK, Kumar A (2013) Tocopherol from seeds of *Cucurbita pepo* against diabetes: validation by *in vivo* experiments supported by computational docking. J Formos Med Assoc 112:676–690

Bharti SK, Krishnan S, Kumar A, Kumar A (2018) Antidiabetic phytoconstituents and their mode of action on metabolic pathways. Ther Adv Endocrinol Metab 9:81–100

Brahmachari G, Rashid K, Sil PC (2017) Discovery and development of antidiabetic agents from natural products. Elsevier, Amsterdam

Brown AL, Lane J, Coverly J, Stocks J, Jackson S, Stephen A, Bluck L, Coward A, Hendrickx H (2009) Effects of dietary supplementation with the green tea polyphenol epigallocatechin-3-gallate on insulin resistance and associated metabolic risk factors: randomized controlled trial. Br J Nutr 101:886–894

Carre G, Carreyre H, Ouedraogo M, Becq F, Bois P, Thibaudeau S, Vandebrouck C, Bescond J (2014) The hypotensive agent dodoneine inhibits L-type Ca^{2+} current with negative inotropic effect on rat heart. Eur J Pharmacol 728:119–127

Cazarolli LH, Folador P, Moresco HH, Brighente IM, Pizzolatti MG, Silva FR (2009) Stimulatory effect of apigenin-6-C-β-l-fucopyranoside on insulin secretion and glycogen synthesis. Eur J Med Chem 44:4668–4673

Choudhary M, Kumar V, Malhotra H, Singh S (2015) Medicinal plants with potential anti-arthritic activity. J Intercult Ethnopharmacol 4:147

Cooper EJ, Hudson AL, Parker CA, Morgan NG (2003) Effects of the β-carbolines, harmane and pinoline, on insulin secretion from isolated human islets of Langerhans. Eur J Pharmacol 482:189–196

Daisy P, Eliza J, Mohamed Farook KAM (2009a) A novel dihydroxy gymnemic triacetate isolated from *Gymnema sylvestre* possessing normoglycemic and hypolipidemic activity on STZ-induced diabetic rats. J Ethnopharmacol 126:339–344

Daisy P, Jasmine R, Ignacimuthu S, Murugan E (2009b) A novel steroid from *Elephantopus scaber* L. an ethnomedicinal plant with antidiabetic activity. Phytomedicine 16:252–257

Du JR, Yu Y, Yao Y, Bai B, Zong X, Lei Y, Wang CY, Qian ZM (2007) Ligustilide reduces phenylephrine induced-aortic tension *in vitro* but has no effect on systolic pressure in spontaneously hypertensive rats. Am J Chin Med 35:487–496

El Bardai S, Wibo M, Hamaide MC, Lyoussi B, Quetin-Leclercq J, Morel N (2003) Characterisation of marrubenol, a diterpene extracted from *Marrubium vulgare*, as an L-type calcium channel blocker. Br J Pharmacol 140:1211–1216

Eliza J, Daisy P, Ignacimuthu S, Duraipandiyan V (2009) Normo-glycemic and hypolipidemic effect of costunolide isolated from *Costus speciosus* (Koen ex. Retz.) Sm. in streptozotocin-induced diabetic rats. Chem Biol Interact 179:329–334

Enoki T, Ohnogi H, Nagamine K, Kudo Y, Sugiyama K, Tanabe M, Kobayashi E, Sagawa H, Kato I (2007) Antidiabetic activities of chalcones isolated from a Japanese herb, Angelica keiskei. J Agric Food Chem 55:6013–6017

Esberg L, Wang G, Lin Y, Ren J (2003) Iso-S-petasin, a hypotensive sesquiterpene from Petasites formosanus, depresses cardiac contraction and intracellular Ca^{2+} transients in adult rat ventricular myocytes. Am J Phys Cell Physiol 284:C378–C388

Fang XK, Gao J, Zhu DN (2008) Kaempferol and quercetin isolated from *Euonymus alatus* improve glucose uptake of 3T3-L1 cells without adipogenesis activity. Life Sci 82:615–622

Fuentes NL, Sagua H, Morales G, Borquez J, Martin AS, Soto J, Loyola LA (2005) Experimental antihyperglycemic effect of diterpenoids of llareta, Azorella compacta (Umbelliferae) phil in rats. Phytother Res 19:713–716

Fukushima M, Matsuyama F, Ueda N, Egawa K, Takemoto J, Kajimoto Y, Yonaha N, Miura T, Kaneko T, Nishi Y, Mitsui R (2006) Effect of corosolic acid on postchallenge plasma glucose levels. Diabetes Res Clin Pract 73:174–177

Gasparotto A, Gasparotto FM, Lourenço EL, Crestani S, Stefanello ME, Salvador MJ, da Silva-Santos JE, Marques MC, Kassuya CA (2011) Antihypertensive effects of isoquercitrin and extracts from *Tropaeolum majus* L.: evidence for the inhibition of angiotensin converting enzyme. J Ethnopharmacol 134:363–372

Grassi D, Necozione S, Lippi C, Croce G, Valeri L, Pasqualetti P, Desideri G, Blumberg JB, Ferri C (2005) Cocoa reduces blood pressure and insulin resistance and improves endothelium-dependent vasodilation in hypertensives. Hypertension 46:398–405

Greenway F, Liu Z, Yu Y, Gupta A (2011) A clinical trial testing the safety and efficacy of a standardized *Eucommia ulmoides* oliver bark extract to treat hypertension. Altern Med Rev 16:338–347

Hii CST, Howell SL (1984) Effects of epicatechin on rat islets of Langerhans. Diabetes 33:291–296

Hong SY, Kim JY, Ahn HY, Shin JH, Kwon O (2012) *Panax ginseng* extract rich in ginsenoside protopanaxatriol attenuates blood pressure elevation in spontaneously hypertensive rats by affecting the Akt-dependent phosphorylation of endothelial nitric oxide synthase. J Agric Food Chem 60:3086–3091

Hosseini S, Lee J, Sepulveda RT, Rohdewald P, Watson RR (2001) A randomized, double-blind, placebo-controlled, prospective, 16 week crossover study to determine the role of Pycnogenol in modifying blood pressure in mildly hypertensive patients. Nutr Res 21:1251–1260

Hou CC, Lin SJ, Cheng JT, Hsu FL (2003) Antidiabetic dimeric guianolides and a lignan glycoside from *Lactuca indica*. J Nat Prod 66:625–629

Hou W, Li Y, Zhang Q, Wei X, Peng A, Chen L, Wei Y (2009) Triterpene acids isolated from *Lagerstroemia speciosa* leaves as α-glucosidase inhibitors. Phytother Res 23:614–618

Hung HY, Qian K, Morris-Natschke SL, Hsu CS, Lee KH (2012) Recent discovery of plant-derived anti-diabetic natural products. Nat Prod Rep 29:580

Imenshahidi M, Hosseinzadeh H, Javadpour Y (2010) Hypotensive effect of aqueous saffron extract (*Crocus sativus* L.) and its constituents, safranal and crocin, in normotensive and hypertensive rats. Phytother Res 24:990–994

Irondi E, Agboola SO, Oboh G, Boligon AA, Athayde ML, Shode FO (2016) Guava leaves polyphenolics-rich extract inhibits vital enzymes implicated in gout and hypertension in vitro. J Intercult Ethnopharmacol 5:122

Joseph B, Jini D (2011) Insight into the hypoglycaemic effect of traditional Indian herbs used in the treatment of diabetes. Res J Med Plant 5:352–376

Jovanovski E, Bateman EA, Bhardwaj J, Fairgrieve C, Mucalo I, Jenkins AL, Vuksan V (2014) Effect of Rg3-enriched Korean red ginseng (*Panax ginseng*) on arterial stiffness and blood pressure in healthy individuals: a randomized controlled trial. J Am Soc Hypertens 8:537–541

Judy WV, Hari SP, Stogsdill WW, Judy JS, Naguib YM, Passwater R (2003) Antidiabetic activity of a standardized extract (Glucosol™) from *Lagerstroemia speciosa* leaves in Type II diabetics: a dose-dependence study. J Ethnopharmacol 87:115–117

Jung UJ, Lee MK, Jeong KS, Choi MS (2004) The hypoglycemic effects of hesperidin and naringin are partly mediated by hepatic glucose-regulating enzymes in C57BL/KsJ-db/db mice. J Nutr 134:2499–2503

Jung SH, Seol HJ, Jeon SJ, Son KH, Lee JR (2009) Insulin-sensitizing activities of tanshinones, diterpene compounds of the root of Salvia miltiorrhiza Bunge. Phytomedicine 16:327–335

Kalra S, Kalra B, Agrawal N (2010) Combination therapy in hypertension: an update. Diabetol Metab Syndr 2:44

Karim M, McCormick K, Kappagoda CT (2000) Effects of cocoa extracts on endothelium-dependent relaxation. J Nutr 130:S2105–S2108

Kawano A, Nakamura H, Hata SI, Minakawa M, Miura Y, Yagasaki K (2009) Hypoglycemic effect of aspalathin, a rooibos tea component from *Aspalathus linearis*, in type 2 diabetic model db/db mice. Phytomedicine 16:437–443

Koehn FE, Carter GT (2005) The evolving role of natural products in drug discovery. Nat Rev Drug Discov 4:206–220

Kramer W, Thormann J, Kindler M, Schlepper M (1987) Effects of forskolin on left ventricular function in dilated cardiomyopathy. Arzneimittelforschung 37:364–367

Kumar M, Rawat P, Rahuja N, Srivastava AK, Maurya R (2009) Antihyperglycemic activity of phenylpropanoyl esters of catechol glycoside and its dimers from *Dodecadenia grandiflora*. Phytochemistry 70:1448–1455

Kumar S, Saravana Kumar M, Raja B (2010) Efficacy of piperine, an alkaloidal constituent of pepper on nitric oxide, antioxidants and lipid peroxidation markers in L-NAME induced hypertensive rats. Int J Res Pharm Sci 1:300–307

Lahlou S, Leal Interaminense LF, Leal-Cardoso JH, Pinto Duarte G (2003) Antihypertensive effects of the essential oil of Alpinia zerumbet and its main constituent, terpinen-4-ol, in DOCA-salt hypertensive conscious rats. Fundam Clin Pharmacol 17:323–330

Lam SH, Chen JM, Kang CJ, Chen CH, Lee SS (2008) α-Glucosidase inhibitors from the seeds of *Syagrus romanzoffiana*. Phytochemistry 69:1173–1178

Lee SS, Lin HC, Chen CK (2008) Acylated flavonol monorhamnosides, α-glucosidase inhibitors, from Machilus philippinensis. Phytochemistry 69:2347–2353

Lee MS, Kim CH, Hoang DM, Kim BY, Sohn CB, Kim MR, Ahn JS (2009) Genistein-derivatives from Tetracera scandens stimulate glucose-uptake in L6 myotubes. Biol Pharm Bull 32:504–508

Liu Q, Liu J, Guo H, Sun S, Wang S, Zhang Y, Li S, Qiao Y (2013) 6 -gingerol: a novel AT(1) antagonist for the treatment of cardiovascular disease. Planta Med 79:322–326

Logendra S, Ribnicky DM, Yang H (2006) Bioassay-guided isolation of aldose reductase inhibitors from *Artemisia dracunculus*. Phytochemistry 67:1539–1546

Maiti A, Dewanjee S, Sahu R (2009) Isolation of hypoglycemic phytoconstituent from *Swietenia macrophylla* seeds. Phytother Res 23:1731–1733

Marshall AJ, Roberts CJC, Barritt DW (1976) Raynaud's phenomenon as side effect of beta-blockers in hypertension. Br Med J 1:1498–1499

Maurya R, Singh AB, Srivastava AK (2008) Coagulanolide, a withanolide from *Withania coagulans* fruits and antihyperglycemic activity. Bioorg Med Chem Lett 18:6534–6537

Morimoto T, Gandhi TK, Fiskio JM, Seger AC, So JW, Cook EF, Fukui T, Bates DW (2004) An evaluation of risk factors for adverse drug events associated with angiotensin-converting enzyme inhibitors. J Eval Clin Pract 10:499–509

Mpalantinos MA, Soares De Moura R, Parente JP, Kuster RM (1998) Biologically active flavonoids and kava pyrones from the aqueous extract of *Alpinia zerumbet*. Phytother Res 12:442–444

Muruganandan S, Srinivasan K, Gupta S, Gupta PK, Lal J (2005) Effect of mangiferin on hyperglycemia and atherogenicity in streptozotocin diabetic rats. J Ethnopharmacol 97:497–501

Newman DJ, Cragg GM (2016) Natural products as sources of new drugs from 1981 to 2014. J Nat Prod 79:629–661

NoorShahida A, Wong TW, Choo CY (2009) Hypoglycemic effect of quassinoids from *Brucea javanica* (L.) Merr (Simaroubaceae) seeds. J Ethnopharmacol 124:586–591

Ojeda D, Ojeda D, Jiménez-Ferrer E, Zamilpa A, Herrera-Arellano A, Tortoriello J, Alvarez L (2010) Inhibition of angiotensin converting enzyme (ACE) activity by the anthocyanins delphinidin- and cyanidin-3-O-sambubiosides from *Hibiscus sabdariffa*. J Ethnopharmacol 127:7–10

Ojewole JAO, Drewes SE, Khan F (2006) Vasodilatory and hypoglycaemic effects of two pyranoisoflavone extractives from *Eriosema kraussianum* N. E. Br. [Fabaceae] rootstock in experimental rat models. Phytochemistry 67:610–617

Palanisamy N, Venkataraman AC (2013) Beneficial effect of genistein on lowering blood pressure and kidney toxicity in fructose-fed hypertensive rats. Br J Nutr 109:1806–1812

Panda S, Jafri M, Kar A, Meheta BK (2009) Thyroid inhibitory, antiperoxidative and hypoglycemic effects of stigmasterol isolated from *Butea monosperma*. Fitoterapia 80:123–126

Pinent M, Blay M, Blade MC, Salvado MJ, Arola L, Ardevol A (2004) Grape seed-derived procyanidins have an antihyperglycemic effect in streptozotocin-induced diabetic rats and insulinomimetic activity in insulin-sensitive cell lines. Endocrinology 145:4985–4990

Qa'dan F, Verspohl EJ, Nahrstedt A, Petereit F, Matalka KZ (2009) Cinchonain Ib isolated from *Eriobotrya japonica* induces insulin secretion *in vitro* and *in vivo*. J Ethnopharmacol 124:224–227

Rawat P, Doshi R, Singh PK, Kumar V (2016a) Afflictions of enteric diseases in human population with reference to diarrhoea–a review. Biosci Biotech Res Comm 9:653–665

Rawat P, Singh PK, Kumar V (2016b) Anti-hypertensive medicinal plants and their mode of action. J Herb Med 6:107–118

Rawat P, Singh PK, Kumar V (2017) Evidence based traditional anti-diarrheal medicinal plants and their phytocompounds. Biomed Pharmacother 96:1453–1464

Reddy PP, Tiwari AK, Rao RR, Madhusudhana K, Rao VR, Ali AZ, Babu KS, Rao JM (2009) New Labdane diterpenes as intestinal α-glucosidase inhibitor from antihyperglycemic extract of *Hedychium spicatum* (Ham. Ex Smith) rhizomes. Bioorg Med Chem Lett 19:2562–2565

Russell RP (1988) Side effects of calcium channel blockers. Hypertension 11:42–44

Saad B, Zaid H, Shanak S, Kadan S (2017) Anti-diabetes and anti-obesity medicinal plants and phytochemicals: safety, efficacy, and action mechanisms. Springer, Cham

Shamon SD, Perez MI (2009) Blood pressure lowering efficacy of reserpine for primary hypertension. Cochrane Database Syst Rev 12:CD007655

Silva RM, Santos FA, Rao VS, Maciel MA, Pinto AC (2001) Blood glucose- and triglyceride-lowering effect of trans-dehydrocrotonin, a diterpene from *Croton cajucara* benth., in rats. Diabetes. Obes Metab 3:452–456

Singh PK, Rawat P (2017) Evolving herbal formulations in management of dengue fever. J Ayurveda Integr Med 8:207–210

Subash Babu P, Prabuseenivasan S, Ignacimuthu S (2007) Cinnamaldehyde-A potential antidiabetic agent. Phytomedicine 14:15–22

Sudha P, Zinjarde SS, Bhargava SY, Kumar AR (2011) Potent α-amylase inhibitory activity of Indian Ayurvedic medicinal plants. BMC Complement Altern Med 11:5

Sugihara Y, Nojima H, Matsuda H, Murakami T, Yoshikawa M, Kimura I (2000) Antihyperglycemic effects of gymnemic acid IV, a compound derived from *Gymnema sylvestre* leaves in streptozotocin-diabetic mice. J Asian Nat Prod Res 2:321–327

Tamrakar AK, Yadav PP, Tiwari P, Maurya R, Srivastava AK (2008) Identification of pongamol and karanjin as lead compounds with antihyperglycemic activity from *Pongamia pinnata* fruits. J Ethnopharmacol 118:435–439

Tan MJ, Ye JM, Turner N, Hohnen-Behrens C, Ke CQ, Tang CP, Chen T, Weiss HC, Gesing ER, Rowland A, James DE (2008) Antidiabetic activities of triterpenoids isolated from bitter melon associated with activation of the AMPK pathway. Chem Biol 15:263–273

Taur DJ, Patil RY (2011) Some medicinal plants with antiasthmatic potential: a current status. Asian Pac J Trop Biomed 1:413–418

Tuan DT, Thu NB, Nhiem NX, Ngoc TM, Yim N, Bae K (2009) Palbinone and triterpenes from Moutan Cortex (*Paeonia suffruticosa*, Paeoniaceae) stimulate glucose uptake and glycogen synthesis via activation of AMPK in insulin-resistant human HepG2 Cells. Bioorg Med Chem Lett 19:5556–5559

Ushijima M, Takashima M, Kunimura K, Kodera Y, Morihara N, Tamura K (2018) Effects of S-1-propenylcysteine, a sulfur compound in aged garlic extract, on blood pressure and peripheral circulation in spontaneously hypertensive rats. J Pharm Pharmacol 70:559–565

Veeramani C, Al-Numair KS, Chandramohan G, Alsaif MA, Alhamdan AA, Pugalendi KV (2012) Antihypertensive effect of *Melothria maderaspatana* leaf fractions on DOCA-salt-induced hypertensive rats and identification of compounds by GC-MS analysis. J Nat Med 66:302–310

Vessal M, Hemmati M, Vasei M (2003) Antidiabetic effects of quercetin in streptozocin-induced diabetic rats. Comp Biochem Physiol C 135:357–364

Waltner-Law ME, Wang XL, Law BK, Hall RK, Nawano M, Granner DK (2002) Epigallocatechin gallate, a constituent of green tea, represses hepatic glucose production. J Biol Chem 277:34933–34940

Wu XD, Wang C, Zhang ZY, Fu Y, Liu FY, Liu XH (2014) Puerarin attenuates cerebral damage by improving cerebral microcirculation in spontaneously hypertensive rats. Evid Based Complement Alternat Med 2014:408501

Wysham DG, Brotherton AF, Heistad DD (1986) Effects of forskolin on cerebral blood flow: implications for a role of adenylate cyclase. Stroke 17:1299–1303

Xie YW, Xu HX, Dong H, Fiscus RR, But PP (2007) Role of nitric oxide in the vasorelaxant and hypotensive effects of extracts and purified tannins from *Geum japonicum*. J Ethnopharmacol 109:128–133

Xu Z, Wang X, Dai Y, Kong L, Wang F, Xu H, Lu D, Song J, Hou Z (2010) (±)-Praeruptorin A enantiomers exert distinct relaxant effects on isolated rat aorta rings dependent on endothelium and nitric oxide synthesis. Chem Biol Interact 186:239–246

Yilmaz B, Usta C (2013) Ellagic acid-induced endothelium-dependent and endothelium-independent vasorelaxation in rat thoracic aortic rings and the underlying mechanism. Phytother Res 27:285–289

Yu BC, Hung CR, Chen WC, Cheng JT (2003) Antihyperglycemic effect of andrographolide in streptozotocin-induced diabetic rats. Planta Med 69:1075–1079

Zhang WB, Chen CX, Sim SM, Kwan CY (2004) *In vitro* vasodilator mechanisms of the indole alkaloids rhynchophylline and isorhynchophylline, isolated from the hook of *Uncaria rhynchophylla* (Miquel). Naunyn Schmiedeberg's Arch Pharmacol 369:232–238

Zhang Y, Li X, Zou D, Liu W, Yang J, Zhu N, Huo L, Wang M, Hong J, Wu P, Ren G (2008) Treatment of type 2 diabetes and dyslipidemia with the natural plant alkaloid berberine. J Clin Endocrinol Metab 93:2559–2565

Zhang M, Chen M, Zhang HQ, Sun S, Xia B, Wu FH (2009) *In vivo* hypoglycemic effects of phenolics from the root bark of *Morus alba*. Fitoterapia 80:475–477

Zhang YQ, Luo JG, Han C, Xu JF, Kong LY (2015) Bioassay-guided preparative separation of angiotensin-converting enzyme inhibitory C-flavone glycosides from *Desmodium styracifolium* by recycling complexation high-speed counter-current chromatography. J Pharm Biomed Anal 102:276–281

Zhao Y, Zhang X, Li J, Bian Y, Sheng M, Liu B, Fu Z, Zhang Y, Yang B (2016) Jujuboside B reduces vascular tension by increasing Ca^{2+} influx and activating endothelial nitric oxide synthase. PLoS One 11:e0149386

Zhou JY, Zhou SW (2012) Isorhynchophylline: a plant alkaloid with therapeutic potential for cardiovascular and central nervous system diseases. Fitoterapia 83:617–626