Current Topics

Recent Research in Bioactive Natural Products from Traditional Medicinal Plants

Review

Progress in Development of Interventions to Prevent Birth Defects in Diabetic Pregnancies

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Received December 24, 2018

Diabetic embryopathy is a diabetic complication, in which maternal hyperglycemia in early pregnancy causes birth defects in newborn infants. Under maternal diabetic conditions, hyperglycemia disturbs intracellular molecular activities and organelles functions. These include protein misfolding in the endoplasmic reticulum (ER), overproduction of reactive oxygen species (ROS) in mitochondria, and high levels of nitric oxide (NO). The resultant ER, oxidative, and nitrosative stresses activate apoptotic machinery to cause cell death in the embryo, ultimately resulting in developmental malformations. Based on the basic research data, efforts have been made to develop interventional strategies to alleviate the stress conditions and to reduce embryonic malformations. One of the challenges in birth defect prevention is to identify effective and safe agents to be used in pregnancy. One approach is to search and characterize naturally occurring phytochemicals, including flavonoids, curcuminoids and stilbenoids, for use in prevention of diabetic embryopathy.

Key words diabetic embryopathy; oxidative stress; endoplasmic reticulum stress; nitrosative stress; phytochemical; polyphenol

1. Introduction

Congenital birth defects are a major contribution to high rates of mortality and disability in newborn infants.[1)] In addition to genetic factors, maternal diseases are also ascribed to fetal malformations.[2)] Diabetes mellitus is accounted for nearly 6% of birth defects in diabetic pregnancies, which is twice higher than the background rate.[3,4)] The situation of the diabetic complication, known as diabetic embryopathy, is getting worse, because of rapid increase of diabetic individuals in both developed and developing counties.[5,6)] It is projected that the impact of diabetes on pregnancy will impose heavy burdens on affected individuals and families, as well as society as whole.

In diabetic pregnant women, control of blood glucose level is the first line of defense to protect embryos and fetuses.[7,8)] However, euglycemia is difficult to achieve and maintain during gestation, even in developed counties where aggressive health and clinical cares are available.[7,9)] This is largely due to unawareness of diabetic conditions before conception and early gestation, lack of willingness and effort for planned pregnancy, and delayed seeking for perinatal care.[8)]

The physiopathologic mechanism of maternal diabetes induced birth defects is complicated and not entirely understood, but we and other groups have demonstrated that it is associated with decreased cell proliferation and increased programmed cell death (apoptosis). In our previous research, we elicited that apoptosis plays a critical role with malformations in the embryos of diabetic pregnancy. The main goal of the mechanistic studies is to develop accessible, convenient, and effective prevention strategies against maternal diabetes-induced malformations. However, there are not too much research works which have been explored in the inhibitors of diabetes-induced birth defects from the natural products.

In this review we will focus on the inhibitors from herbals with preventive effects on maternal diabetes induced birth defects. Furthermore, their related mechanisms of action are summarized based on our previous research.

2. Characteristics of Structural Defects in Infants from Diabetic Pregnancies

Infants of diabetic pregnancies show various structural defects in almost every organ system, but they are most commonly seen in the central nervous and cardiovascular systems (CNS and CVS).[9–11)] In the CNS, abnormalities include excencephaly, anencephaly, and spinal bifida.[9,12)] The anomalies are results of failed fusion of the neural tube during early embryonic development, thus, called neural tube defects (NTDs). Worldwide, there are more than 300000 NTD-affected pregnancies each year, and NTDs cause significant infant mortality and childhood morbidity. One out of ten babies with NTDs will die before their first year.

The abnormalities in the CVS are also complex, including ventricular septal defects (VSD), atrial septal defects, abnormal great vessels, and hypoplastic ventricles.[4)] Congenital heart defects (CHDs) are the most common birth defects, with an incidence of four to 10 per 1000 live births. Maternal diabetes is one such nongenetic factor that significantly increases the risk of CHDs. Studies in diabetic animal models reveal the same types of CHDs as those in human diabetic pregnancies, and apoptosis, impaired cell proliferation, and

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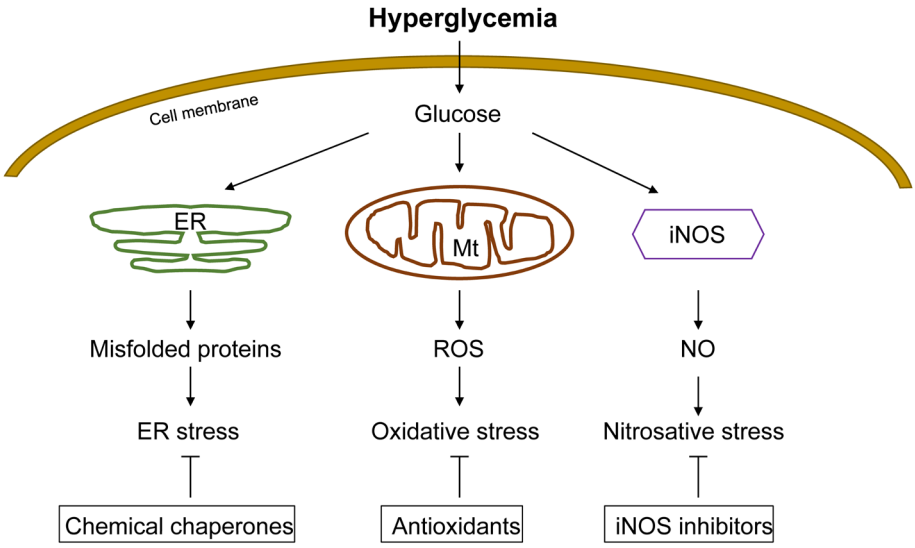

Fig. 1. Intracellular Stresses and Potential Alleviating Interventions

Hyperglycemia perturbs the endoplasmic reticulum (ER), mitochondria (Mt), and inducible nitric oxide (NO) synthase (iNOS), resulting in protein misfolding, overgeneration of reactive oxygen species (ROS), and generation of NO, and consequent ER, oxidative, and nitrosative stresses. The stress conditions can be alleviated by chemical chaperones, antioxidants, and iNOS inhibitors. (Color figure can be accessed in the online version.)

gene dysregulation are observed in the mouse hearts exposed to maternal diabetes. Our previous study demonstrated that apoptosis signal-regulating kinase 1 (ASK1) activation in maternal diabetes-induced heart defects and the signaling network downstream of ASK1 that transmits the proapoptotic, antiproliferative, and altered cell differentiation signals, leading to heart defects.[13]

Defects can be also seen in other systems, for example, craniofacial defects, renal agenesis, and eye anomalies.[12] Almost all the structural defects can be recapitulated in diabetic animal models, which provide useful systems for studies in diabetic embryopathy.[12,14]

3. Cellular and Molecular Mechanisms of Diabetic Embryopathy

Animal studies have shown that increased apoptosis is associated with malformations in the embryos of diabetic pregnancy. Apoptotic regulators, such as members of the Caspase and Bcl-2 families, have been found to be involved. The intracellular conditions that affect the apoptotic factors have been gradually unraveled.[11,15]

Hyperglycemia disrupts protein folding in endoplasmic reticulum (ER).[16] Unfolded and misfolded proteins cannot be packaged and transported to Golgi apparatus, leading to accumulation of toxic abnormal proteins the ER.[17] ER stress activates unfolded protein response (UPR), which includes a number of signaling pathways to resolve the protein folding crisis, inhibit mitosis, and stimulate apoptosis[11] (Fig. 1). Hyperglycemia induces ER stress, which is responsible for the proapoptotic JNK1/2 pathway activation, apoptosis, and NTD induction. Suppressing JNK1/2 activation by either jnk1 or jnk2 gene deletion prevents ER stress. Thus, JNK1/2 activation induced by maternal diabetes transmits the pro-apoptotic signal emanating from oxidative stress under diabetic conditions.[17]

In mitochondria, hyperglycemia disrupts the electron transport chain, leading to overproduction of reactive oxygen species (ROS) in embryonic cells.[18–21] Hyperglycemia also reduces the levels of antioxidants and antioxidative enzymes, including superoxide dismutases (SODs) and glutathione peroxidases (GPXes), resulting in oxidative stress[15,22] (Fig. 1).

Under oxidative stress, phospholipid metabolism is also disrupted. For example, arachidonic acid is normally turned into prostaglandin E by cyclooxygenase 2.[23] However, oxygen free radicals suppress this metabolic pathway and shunt it to the lipoperoxidation pathway to produce cytotoxic isoprostanes, such as 8-iso-prostaglandin F2α.[23,24] Studies has shown that over expression of an antioxidant enzyme, superoxide dismutase 1 (SOD1), in SOD1 transgenic mice, decreases maternal diabetes-induced oxidative stress and reduces embryonic malformations in diabetic pregnancies.[21]

Moreover, maternal hyperglycemia increases the expression of inducible nitric oxide (NO) synthase (iNOS), which produces high levels of NO in embryonic cells and protein nitrosylation and nitration.[25,26] Previous studies indicate that eliminating the iNOS gene in iNOS knockout mice reduces the incidence of embryonic malformations caused by maternal diabetes. The condition is known as nitrosative stress[27,28] (Fig. 1).

4. Interventions Targeting Intracellular Stress Conditions

Based on the understanding of the molecular processes in hyperglycemia-induced embryonic malformations, interventions to protect the embryos from maternal hyperglycemic insult have been explored, using diabetic pregnant animals as model systems. Agents specific for certain molecular pathways have been tested. Recent efforts have been made to identify effective and safe agents from naturally occurring products, including flavonoids, epigallocatechin-3-gallate (EGCG, **1**), quercetin (**2**), isoquercetin (**3**), spiraeoside (**4**), quercetrin (**5**) and rutin (**6**) (Fig. 2); curcuminoids, curcumin (**7**), demethoxycurcumin (**8**), bisdemethoxycurcumin (**9**) (Fig. 3), and stilbenoids, resveratrol (**10**), dihydroresveratrol (**11**), piceatannol (**12**), astringin (**13**), piceid (**14**), *etc*.[29–31] (Fig. 4).

To target oxidative stress, many antioxidants, such as Vita-

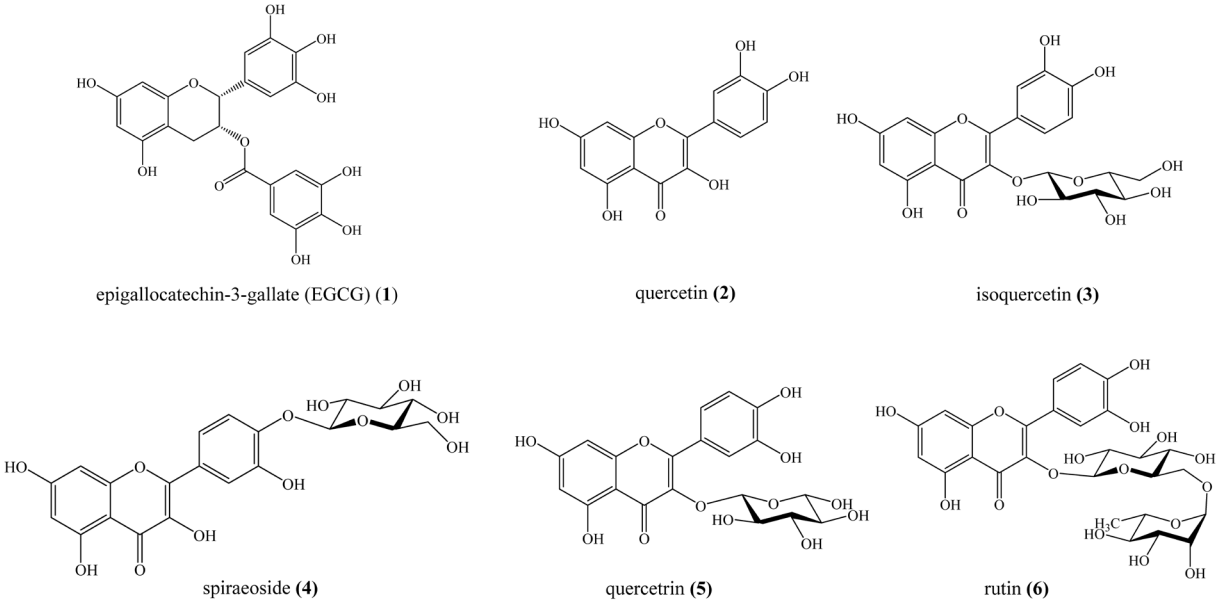

Fig. 2. Common Constituents of Flavonoids

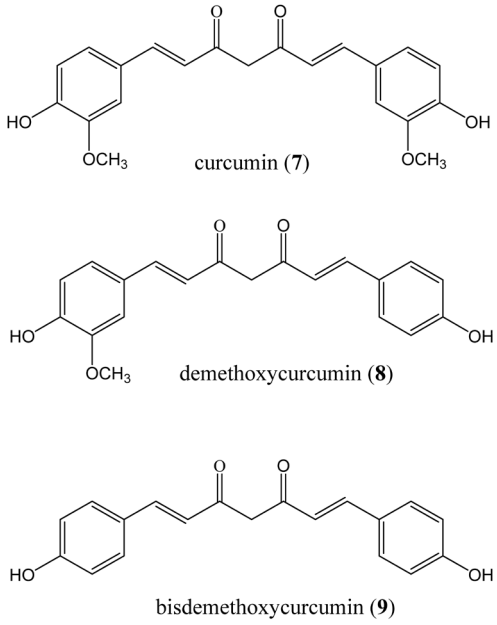

Fig. 3. Common Constituents of Curcuminoids

min C, Vitamin E, *N*-acetylcysteine, lipoic acid, and ergothioneine, have been tested and shown to decrease abnormalities, mainly NTDs, in the embryos of diabetic dams *in vivo*[32–41] (Fig. 1). Naturally occurring antioxidants have also been tested as candidate interventional agents.

Yang *et al.*[42,43] demonstrated that EGCG (**1**) from green tea has been shown to decrease embryonic malformations *in vitro* and *in vivo*. EGCG prevents hyperglycemia-induced embryopathy through inhibition of Forkhead transcription factor 3a activation, which may have been mediated *via* the activation of Akt. *In vivo* study, EGCG reduces maternal diabetes-induced NTDs formation and blocks the enhanced expression and activity of DNA methyltransferases, leading to the suppression of DNA hypermethylation. These observations suggest that EGCG, as a potential for a possible pharmacological prophylaxis, could mitigate the teratogenic effects of hyperglycemia on the developing embryo and prevent diabetes-induced NTDs.

Curcumin (**7**) from turmeric can reduce NTDs in cultured embryos in high glucose.[44] Treatment with curcumin reduced the levels of the lipid peroxidation marker, and also blocked ER stress, suggesting that curcumin supplements could reduce the negative effects of diabetes on the embryo. Punicalagin (**16**) (Fig. 4), a polyphenol compound, extracted from pomegranate fruit, which possesses antioxidant, anti-inflammatory and antitumorigenic properties, has been shown to reduce NTDs in cultured embryos by suppressing high glucose-induced lipid peroxidation marker 4-hydroxynonenal, nitrotyrosine-modified proteins, and lipid peroxides.[45] Resveratrol (**10**), antioxidant rich in grapes, berries, and peanuts, has been shown to prevent diabetes-induced oxidative stress and apoptosis in embryos, and have beneficial effects in diabetic dams, and also improved glucose and lipid profile of diabetic dams, indicating the beneficial effects in diabetic pregnancy. But its effect on reduction of embryonic malformations still needs to be further demonstrated.[46,47] Many antioxidants have been examined to prevent maternal diabetes-induced NTDs, however, the application of these antioxidants in humans remain to be further studied, because a number of clinical trials use antioxidants to alleviate similar disease conditions, such as preeclampsia and cardiovascular diseases, gained no positive results.[48–50]

To alleviate ER stress, chemical chaperones are candidate agents to enhance protein folding[51–54] (Fig. 1). Among them, 4-phenylbutyric acid (4-PBA) has been tested *in vitro* to reduce NTDs in mouse embryos.[17] It has also been shown to decrease NTDs in embryos of diabetic mic *in vivo*.[55] Many chemical chaperones can be used clinically. More work is needed to test the agents in animal models to select effective one for further translational studies.

To ameliorate nitrosative stress, an iNOS inhibitor L-N6-(1-iminoethyl)-lysine, has used in diabetic mice and shown to reduce embryonic defects[56] (Fig. 1). Naturally occurring polyphenols have the property to inhibit iNOS.[57,58] Among

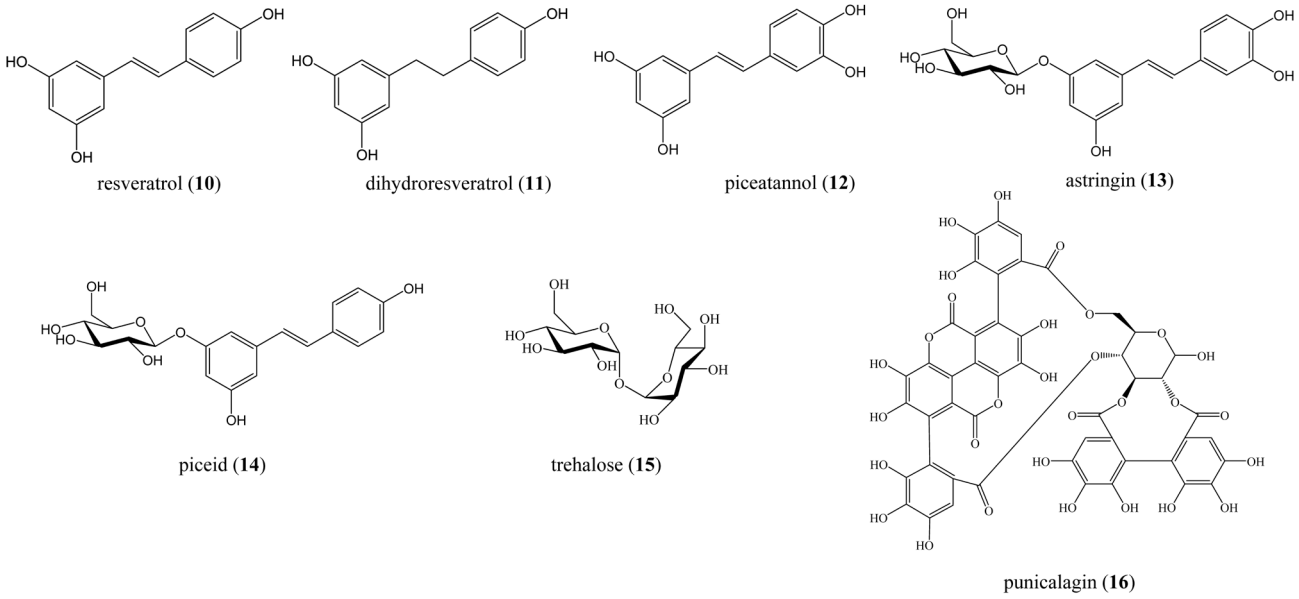

Fig. 4. Common Constituents of Stilbenoids and Other Types

them, quercetin (QC, **2**), a naturally-occurring phytochemical, appears to exert an effect on alleviation of nitrosative stress.[59] Treatment with QC in diabetic mice has been shown to reduce NTDs in the embryos.[59] These studies provide information for future pre-clinical studies to determine the effectiveness, efficacy, and safety aspects of clinical application of quercetin. Additionally, a QC derivative, quercetin-3-glucoside (isoquercetin, **3**), can also suppresses nitric oxide synthase 2 and increases superoxide dismutase 1 expression, leading to alleviation of nitrosative, oxidative, and endoplasmic reticulum stress conditions, and decrease NTDs in the embryos of diabetic mice, which may regulate expression of nitric oxide synthase 2 *via* modulating the nuclear factor-*κ*B transcription regulation system.[60]

Lipid metabolism is also a target for intervention. Myo-inositol has been used to restore the deficiency in embryos of diabetic animals.[61] Arachidonic acid has been used to inhibit ROS-induced lipid peroxidation.[32,62]

Trehalose (**15**) (Fig. 4), a natural disaccharide enriched in many fruits and vegetables, is a disaccharide of glucose and an energy source in plants and fungi. Maternal diabetes suppressed autophagy by significantly reducing LC3-II expression, autophagosome numbers, and GFP-LC3 punctate foci in neuroepithelial cells and by altering autophagy-related gene expression. Embryos from diabetic mice fed with trehalose water reversed autophagy impairment and prevented NTDs in diabetic pregnancies. Trehalose also resolved homeostatic imbalance by correcting mitochondrial defects, dysfunctional proteins, ER stress, apoptosis, and delayed neurogenesis in the neural tubes exposed to hyperglycemia. It provides evidence for the potential efficacy of trehalose as an intervention against hyperglycemia-induced NTDs.[63]

Folate, also known as Vitamin B12, is involved in multiple biochemical processes in cells, including DNA synthesis and redox regulation.[64,65] It can reduce fetal abnormalities when administered during early gestation. Supplementation of folic acid has long been a routine perinatal care to reduce adverse pregnancy outcomes.[64,65] In animal embryos cultured in high glucose, treatment with folic acid has been shown to reduce NTDs.[66] Treatment with folic acid in diabetic pregnant animals *in vivo* has also exerted similar effect on embryonic malformations.[66–68] However, it was reported recently that folic acid supplementations during pregnancies produce increased incidences of breast cancers in mouse models and inflammatory bowel diseases in the offspring. Therefore, there is an urgent and critical need for alternate candidates for preventing NTDs.

5. Conclusion and Further Research

As the number of diabetic women is fast growing, the need for interventions to prevent birth defects from diabetic pregnancies becomes urgent. Basic research has gained information about the etiology of diabetic embryopathy and explored approaches to preventions. However, to translate the basic science to human application requires vigorous tests to develop safe and effective means.

One of the approaches is to identify naturally occurring phytochemicals, in fruits, vegetables, and even traditional medicines, include flavonoids, curcuminoids, and stilbenoids.[69] These phytochemicals consist phenyl rings in their backbone and multiple reactive hydroxyl groups.[70,71] They possess antioxidative, anti-nitrosative, and anti-inflammatory properties, and thus, are candidates for dietary supplements to reduce fetal malformations in diabetic pregnancies. So far, more phytochemical study, especially for the natural products, is needed to further evaluate, based on the research underlying the molecular mechanisms of diabetic embryopathy. And more work is needed to completely delineate their pharmacodynamics and pharmacokinetics to gain information for further application in human diabetic pregnancies. And we believe further research to evaluate.

Acknowledgments The work was supported partially by the National Natural Science Foundation of China (Grant No. 81460563) and Jilin Province Science and Technology Development Projects (Grant Nos. 20160101154JC and 20190701034GH).

Conflict of Interest The authors declare no conflict of interest.

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