



PHYTOTHERAPY FOR GESTATIONAL DIABETES MELLITUS

Medjidova U.M.¹, Polukhova S.M.¹, Kazimova A.U.¹

¹ Azerbaijan Medical University, Department of Pharmacology, Baku, Azerbaijan

Abstract

This review article presents an assessment of the current knowledge of herbal medicines for the treatment of diabetic complications and their underlying mechanisms during and outside of pregnancy. Hyperglycemic status associated with diabetes leads to serious complications during pregnancy. Diabetes mellitus is a dangerous disease during pregnancy and is characterized by complications for both mother and fetus that increase the risk of morbidity. For the conservative treatment of diabetes, medications such as insulin and oral hypoglycemic agents are used, but regular exercise and adequate nutrition are important for complex treatment. For the analysis, scientific studies were used in world-renowned scientific databases - SCOPUS, PUBMED, SCIELO, NISCAIR , Google Scholar. Plant-derived antioxidants are considered as an alternative strategy to reduce oxidative damage in diabetes. The article analyzed the therapeutic effect of plant extracts such as Phyllanthus, H. rosasinensis, quercetin, and studied the effect of antioxidants such as folic acid on reducing fetal malformations associated with maternal diabetes. Some plants also have immunostimulating effect, due to which it is possible to prevent the development of a number of complications, which provokes diabetes mellitus. Scientific research shows that herbal medicine for diabetes during pregnancy can be considered adequate therapy, including safety for both the fetus and the mother. But despite a number of positive qualities of herbal medicine compared to

medicinal substances, they also have disadvantages. Therefore, during pregnancy, the use of herbal medicine as an alternative therapy requires long-term and careful study.

Key words: review, herbal medicine, diabetes, pregnancy, fetus.

Diabetic complications, without an effective therapeutic approach, are now a global and pressing medical problem. Phytotherapy - according to the World Health Organization (WHO), defined as "health practices, attitudes, knowledge and beliefs, including plant, animal and mineral based medicines, spiritual therapies, manual methods and exercises, for the treatment, diagnosis and prevention of disease and maintain well-being" [1]. The use of herbal medicines, which are defined as preparations derived from plants that appear to have therapeutic benefits, is the most popular and is used by both the general population and pregnant women around the world. The prevalence of medicinal plant use among pregnant women in the Middle East varies from 22.3% to 82.3%. [2, 3, 4, 5]. In particular, diabetes is an equally important disease during pregnancy and is characterized by complications for both mother and fetus that increase the risk of morbidity, including mortality for pregnant women, as well as their offspring [6, 7, 8]. Drugs such as insulin and oral hypoglycemic agents are used for the pharmacotherapy of diabetes, but regular exercise and an adequate diet are important for complex treatment [9, 10]. In addition, alternative therapies such as medicinal plants are widely used to reduce diabetes-induced hyperglycemia in both pregnant and non-pregnant women [11]. To obtain accessible published literature, Singh R. et al studied classic text books and peer-reviewed articles consulted by world-famous scientific databases (SCOPUS, PUBMED, SCIELO, NISCAIR, GoogleScholar). In total, 238 articles from the plant literature and review literature were reviewed, and 127 articles were selected for the study. Various medicinal plants/plant extracts containing flavonoids, alkaloids, phenolic compounds, terpenoids, saponins and phytosterol type chemical compounds have been found to be effective in treating diabetic complications. This effect may be associated with the improvement of persistent hyperglycemia, oxidative stress, and modulation of various metabolic pathways involved in the pathogenesis of diabetic complications [12]. Due to the synergistic effect of multiple herbs, herbal formulations are used in the current trend. They have great records for antioxidant, antidiabetic and hypolipidemic properties [13]. Medicinal plants play an important role in the treatment and prevention of various diseases worldwide.

The effectiveness and versatility of the action of herbal medicines, as well as the safety of their use, make phytotherapy indispensable in obstetrics and gynecology [14, 15, 16, 17, 18], including perinatology [19], where harmlessness to the fetus is a fundamental issue. . In most cases, the body of the pregnant woman and the fetus do not need intensive therapy, but only the prevention of violations of the adaptive-homeostatic reactions of the fetoplacental system. Moreover, such prevention is necessary against the background of treatment of a number of somatic diseases, complications of pregnancy and the development of fetoplacental insufficiency, with the risk of perinatal infection [20]. Circulating inflammatory cytokines such as TNF- α , IL-6, and free fatty acids have been reported to induce insulin resistance and increase metabolic complications such as obesity and other cardiovascular diseases [21]. It is important to note that the advantages of herbal remedies are good tolerability and a small number of contraindications; including efficiency, with a comparison of drugs of chemical origin. Modern phytotherapy, being an alternative to drug treatment, is becoming more and more widespread in clinical practice. Phytopreparations practically do not cause side effects and can be prescribed both as an independent treatment for a long time, and in combination with other drugs [22, 23, 24]. The results of a number of studies show that out of seven different Asian countries (2729 participants), of which 1283 (47.01%) women used one or more medicinal plants during pregnancy. The most commonly used herbal remedies were peppermint (22.8%), star anise (14.7%), olibanum (12.9%), mixer seeds (12.2%) and ginger (11.5%) . Of the 33 herbal medicinal products identified, they were classified as safe for use, five with caution, eight as potentially dangerous for use during pregnancy, and information on seven herbal medicinal products was not available in the current literature [25, 26].

Gymnema sylvestre (Retz.) R.Br. ex Sm., commonly known as Gurmar, has been proven effective against obesity and diabetes. has been clinically demonstrated and confirmed in animal models. Antidiabetic activity The content of gurmar is mainly related to gymnemic acids, gymnemasaponins and gurmarin. contained in leaves [27]. It should be noted that *Phyllanthus* species is used as a folk medicine in the treatment of diabetes. Their different gene expression can alter the production of secondary metabolites related to a specific biological property and lead to spurious drug discovery [28]. *A. cepa* may represent an interesting antihyperglycemic dietary supplement for the treatment of diabetes because it reduces the levels of serum cholesterol, triacylglycerol, and LDL cholesterol in streptozocin-induced cholesterol. diabetic rats without changes in cholesterol and HDL cholesterol levels [29].

The *H. rosa-sinensis* flower extract contains phenolic compounds and flavonoids responsible for its antioxidant activity [30]. In addition, the flowers and leaves of this plant have shown a significant hypoglycemic effect in several studies [31]. Afiune LAF et. al (2017) suggested that *H. rosa-sinensis* would have a beneficial effect on diabetic pregnancy without adverse effects on the mother or fetus. This study demonstrates the positive effects of this herbal extract in diabetic pregnant rats, both in mothers and in their offspring. And also no benefits were found in healthy rats. However, these data cannot be extrapolated to humans, as indiscriminate consumption of *H. rosa-sinensis* extract can be harmful to healthy individuals, and the use of this plant during pregnancy should be completely avoided [32]. Quercetin is an aglycone member of the flavonol family, consisting of a large number of quercetin glycoside derivatives [33]. It is believed that the hydroxyl groups on the quercetin molecule are active sites for metabolic changes in the gastrointestinal tract and blood circulation [34]. In the embryo, quercetin metabolites were modified with methyl groups and sulfonic acid esters with unchanged core rings. Modifications of quercetin at different sites with different groups can alter its biochemical properties (eg water or lipid solubility and cell membrane permeability) and biological activities (eg antinitrosative and antioxidant). In the present study, methylated quercetin Q3M was shown to have protective effects (at least antioxidant effects) in embryonic neural stem cells. Future work aims to investigate molecular interactions between quercetin derivatives and stress-related proteins such as Nos2, as well as transcription factors that regulate the expression of stress response proteins in embryonic cells. The present study demonstrates that quercetin treatment significantly reduces protein S-nitrosylation and tyrosine nitration, thereby alleviating nitrosative stress. It also reduces ROS production and oxidative stress. These effects lead to a significant reduction in apoptosis and NTD (neural tube defects) in diabetic embryos [35]. In recent years, the focus has been on Indian medicines and herbs used in the treatment of diabetes and hyperlipidemia. Although there are various approaches to reduce the negative effects of diabetes and hyperlipidemia and its secondary complications, herbal preparations are preferred due to fewer side effects and low cost. The researchers looked at 23 medicinal plants used in the treatment of diabetes mellitus and nine medicinal plants used in the treatment of hyperlipidemia. The wealth of knowledge about medicinal plants indicates great potential for research and discovery of new drugs to combat diseases, including diabetes and hyperlipidemia [36] Some plants also have immunostimulating effect, due to which it is possible to prevent the development of a number of complications, which provokes diabetes mellitus. Biologically active substances contained in medicinal products plants, have anti-inflammatory, choleric, sedative, tonic effect.

Typically used to treat diabetes mellitus multi-component fees providing comprehensive impact on the body. Low concentration active ingredients does not allow the use herbal medicine as a method that gives quick result, but mild impact, low toxicity infusions and decoctions makes it possible to choose treatment, not giving noticeable side effects. Despite this, herbal medicine, like other methods of treating sugar diabetes, should be prescribed by a doctor and carried out under his control, which makes it possible to evaluate its effectiveness and, in if necessary, make adjustments. Courses of phytotherapeutic treatment are designed from 2 weeks to 6 months depending on condition the patient and the plants used, after which It is recommended to change the composition of the herbal collection. Most often used to treat diabetes mellitus fees and decoctions, which include aralia Manchurian, Eleutherococcus senticosus, motherwort, leaves birch, currants, strawberries, mint, nettles, plantain, ginseng root, walnut, roots burdock, corn silk, flax seeds, rose hips and hawthorn [37]. Hosni et al. [8] treatment of GDM rats with cinnamaldehyde (20mg/kg) for a duration of 4 weeks

resulted in a significant increase in the weight of the pregnant diabetic rats after the reduced body weight observed due to feeding with fatty-sucrose diet. Cinnamaldehyde lowered the FINS and FBG levels compared with the untreated group. In the gestational diabetic rats administered cinnamaldehyde, liver glycogen and HDL-cholesterol significantly increased while fructosamine, triglycerides and total cholesterol levels were significantly lowered compared to the untreated gestational diabetic rats. Adiponectin levels significantly increased while leptin and TNF- α significantly reduced post-cinnamaldehyde administration [38].

The above scientific research results show that herbal medicine for diabetes during pregnancy can be viewed as an adequate therapy, including safe for both the fetus and the mother. Thus, herbal medicines can be effectively used during pregnancy accompanied by various somatic diseases. Modern phytotherapy is becoming more and more widespread in clinical practice, being an alternative to drug treatment. Therefore, many herbs are shown to have antidiabetic activity by regulating insulin secretion, insulin sensitivity to the cells, glucose abruption, etc. in order to improve the glycemic management of the patients. Addition to the glycemic control, some of the herbs illustrated effectiveness in the control of cardiovascular complications by reducing TG, cholesterol levels. However, information on the efficacy and safety of some medicinal plants is scarce. Nevertheless, more basic, and clinical research should be done to further validate the safety, effectiveness and discover more mechanisms of action of these medicinal plants. This requires further pharmacological experimental and clinical studies.

LITERATURE

- [1] World health organization. Legal status of traditional medicine and complementary/alternative medicine: a world wide review. Geneva: WHO; 2001
- [2] World Health Organization. Traditional medicine. Fact sheet Number 134. <http://www.who.int/mediacentre/factsheets/fs134/en>. Accessed 2003; 2 Feb 20153
- [3] Smeriglio A., Tomaino A., Trombetta D. Herbal Products in Pregnancy: Experimental Studies and Clinical Reports // 2014; DOI: 10.1002/ptr.5106
- [4] Karimi A., Majlesi M. Kopaei M. Herbal versus synthetic drugs; beliefs and facts // J. Nephroarmacol.; 2015; 4(1); p. 27–30
- [5] Ekor M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety // Front Pharmacol.; 2013; 4; p. 177-183 ; doi:10.3389/fphar.2013.00177
- [6] Zhao Z., Reece E. New concepts in diabetic embryopathy // Clin. Lab. Med.; 2013; 33; p. 207–33
- [7] Kautzky-Willer A., Harreiter J., Bancher-Todesca D, et al. Gestational diabetes mellitus // Wien. Klin. Wochenschr; 2016; 128 (2); p.103-12. doi: 10.1007/s00508-015-0941-1
- [8] Zhao Z. Reevaluation of Antioxidative Strategies for Birth Defect Prevention in Diabetic Pregnancies // J Biomol Res Ther.; 2016; 5(3); p. 145-155. doi: 10.4172/2167-7956.1000145
- [9] Langer O. Pharmacological treatment of gestational diabetes mellitus: point/counterpoint // Am J Obstet Gynecol.; 2018; pii: S0002-9378(18)30073-5; doi: 10.1016/j.ajog.2018.01.024
- [10] Tieu J., Coat S., Hague W., et al. Oral anti-diabetic agents for women with established diabetes impaired glucose tolerance or previous gestational diabetes planning pregnancy, or pregnant women with pre-existing diabetes // Cochrane Database Syst Rev.; 2017; 18; 10:CD007724.
- [11] Kooti, W., Farokhipour, M., Asadzadeh, Z., et al. The role of medicinal plants in the treatment of diabetes: A systematic review. // Electron. Physician; 2016; 8; p.1832–1842
- [12] Singh R., Kaur N., Kishore L., et al. Management of diabetic complications: a chemical constituents based approach // Ethnopharmacol; 2013; 150(1); p.51-70. doi: 10.1016/j.jep.2013.08.051

- [13] Sasidharan R., Hartman S., Liu Z. et al Signal Dynamics and Interactions during Flooding Stress // *Plant Physiology*; 2018; Vol. 176, Issue 2; P. 1106–1117, <https://doi.org/10.1104/pp.17.01232>
- [14] Mendoza N., Hernández C., Cornellana M. Factors determining the use of hormonal therapy and phytotherapy in Spanish postmenopausal women // *Climacteric*; 2016; 19(4); p. 375-80; doi: 10.1080/13697137.2016.1183625
- [15] Van Andel T., De Boer H., Barnes J., et al. Medicinal plants used for menstrual disorders in Latin America, the Caribbean, sub-Saharan Africa, South and Southeast Asia and their uterine properties: a review // *J Ethnopharmacol.*; 2014; 155(2); p. 992-1000
- [16] Naber K. Efficacy and safety of the phytotherapeutic drug Canephron N in prevention and treatment of urogenital and gestational disease: review of clinical experience in Eastern Europe and Central Asia // *Res. Rep. Urol.*; 2013; 4 (5); p. 39–46; doi: 10.2147/RRU.S39288
- [17] Серов В.Н., Баранов И.И., Ткаченко Л.В. и др. Оценка опыта применения комбинированного растительного препарата у беременных (многоцентровое ретроспективное наблюдательное исследование) // *Акушерство и гинекология*; 2013; №9; с. 78-84
- [18] Радзинский В.Е., Симоновская Х.Ю. Фитотерапия в акушерстве и гинекологии // *Информационный бюллетень*; (Москва) Изд. 2-е, испр. идоп. — М.: Редакция журнала Status Praesens, 2015. — 16 с. ISBN 978-5-905796-67-8
- [19] Shewamene Z., Dune T., Smith C. The use of traditional medicine in maternity care among African women in Africa and the diaspora: a systematic review. // *BMC Complement. Altern. Med.*; 2017; 17(1); p. 382-387
- [20] Mc Lay J., Pallivalappila A., Shetty A., et al. Asking the Right Question. A Comparison of Two Approaches to Gathering Data on 'Herbals Use in Survey Based Studies // 2016 <https://doi.org/10.1371/journal.pone.0150140>
- [21] Huaizhu W., Ballantyne C. Metabolic Inflammation and Insulin Resistance in Obesity // *Circ. Res.*; 2020; 126(11); p. 1549-1564; doi: 10.1161/CIRCRESAHA.119.315896
- [22] Newman D., Cragg G. Natural products as sources of new drugs from 1981 to 2014 // *J Nat Prod.*; 2016; 79(3); p. 629-661; doi: 10.1021/acs.jnatprod.5b01055.
- [23] Minghetti P., Franze S., Zaccara V., et al. Innovation in phytotherapy: is a new regulation the feasible perspective in Europe? // *Planta Med.*; 2016; 82(7); p.591-595; doi: 10.1055/s-0042-104509

- [24] WHO guidelines on developing consumer information on proper use of traditional, complementary and alternative medicine WHO; 2016 Available from: [http:// apps. who. int/ medicinedocs/ pdf/s5525e/s5525e.pdf](http://apps.who.int/medicinedocs/pdf/s5525e/s5525e.pdf)
- [25] Ahmed M., Hwang J., Choi S., et al. Safety classification of herbal medicines used among pregnant women in Asian countries: a systematic review // *BMC Complement Altern Med.*; 2017; 17(1); p. 489- 495; doi: 10.1186/s12906-017-1995-6
- [26] Kennedy D., Lupattelli A., Koren G., et al. Safety classification of herbal medicines used in pregnancy in a multinational study // *BMC Complement Altern Med.*; 2016;. 16; p. 102; doi: 10.1186/s12906-016-1079-z
- [27] Tiwari, P.; Mishra, B. N.; Sangwan, N. S. Phytochemical and Pharmacological Properties of *Gymnema818 sylvestre*: An Important Medicinal Plant. *Biomed Res. Int.* 2014, 2014, 830285
- [28] Singh A., Sharma J., Paichha C. et al., *Achyranthes aspera* (prickly chaff flower) leaves- and seeds-supplemented diets regulate growth, innate immunity, and oxidative stress in *Aeromonas hydrophila*-challenged *Labeo rohita* // *J. Appl. Aquacult.*; 2020; 32 (3); p. 250-267 <https://doi.org/10.1080/10454438.2019.1615594>
- [29] Bang M., Kim H., Cho Y. Alterations in the blood glucose, serum lipids and renal oxidative stress in diabetic rats by supplementation of onion (*Allium cepa*. Linn). // *Nutr. Res. Pract.*; 2009; 3, p. 242–246
- [30] Bhaskar A., Nithya V., Vidhya V. Phytochemical screening and in vitro antioxidant activities of the ethanolic extract of *Hibiscus rosa-sinensis* // *Ann Biol. Res.*; 2011; 2; p.653–661
- [31] Pillai S., Mini S. *Hibiscus rosasinensis* Linn. petals modulates glycogen metabolism and glucose homeostasis signalling pathway in streptozotocin-induced experimental diabetes // *Plant Foods Hum Nutr.*; 2016; 71; p.42–48; doi: 10.1007/s11130-015-0521-6
- [32] Afiune LAF., Leal-Silva T., Sinzato Y. Beneficial effects of *Hibiscusrosa-sinensis* L. Flower aqueous extract in pregnant rats with diabetes // *PLoS One.* 2017; 23;12(6):e0179785; doi: 10.1371/0179785e]
- [33] Kelly G. Quercetin. Monograph. // *Altern. Med. Rev.*; 2011; 16; p.172–94
- [34] Kaushik D., O’fallon K., Clarkson P., et al. Comparison of quercetin pharmacokinetics following oral supplementation in humans // *Jur. Food Sci.*; 2012; 77; p. 231–8
- [35] Cao L., Tan C., Meng F. Amelioration of intracellular stress and reduction of neural tube defects in embryos of diabetic mice by phytochemical quercetin // *Sci Rep.*; 2016; 18 (6); p.21491; doi: 10.1038/srep21491

- [36] Parikh N., Parikh P., Kothari C. Indigenous plant medicines for health care: treatment of Diabetes mellitus and hyperlipidemia // *Chin. J. Nat. Med.* 2014; 12(5); p. 335-44; doi: 10.1016/S1875-5364(14)60041-8
- [37] Кудабаева Х.И., Чуканова Г.Н. Влияние масляного экстракта из корней девясила в составе эрадикационной терапии на компенсацию сахарного диабета 2 типа // *Актуальные вопросы формирования здорового образа жизни, профилактики заболеваний и укрепления здоровья.* - 2009. - №1. – С. 84-8
- [38] Hosni A. A., Abdel-Moneim A.A., Abdel-Reheim E.S. et al. Cinnamaldehyde potentially attenuates gestational hyperglycemia in rats through modulation of PPAR γ , proinflammatory cytokines and oxidative stress. *Biomedicine & Pharmacotherapy* 2017, 88: 52-60. DOI: <https://doi.org/10.1016/j.biopha.2017.01.054>