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Review Article

Pharmacology for drug discovery

Synergistic and Safe Antidiabetic Effect of Polyherbal Formulation: Comprehensive Overview

Vipinchandra Bhaskarrao Pande[1], Saket Singh Chandel[2*] and Vishal Soni[3]

[1]*Department of Pharmacy, Mandsaur University, Mandsaur-458001, Madhya Pradesh, India*

[2]*Department of Pharmacology, Dr. C.V. Raman Institute of Pharmacy, Dr. C.V. Raman University, Bilaspur-495113, Chhattisgarh, India; Moblie- 9827181552; Email- singhpharma@gmail.com*

[3]*Department of Pharmacy, Mandsaur University, Mandsaur-458001, Madhya Pradesh, India*

Abstract: Diabetes is a metabolic disorder and enhances the glucose level in the blood. The synthetic antidiabetic agents are limited to the management of diabetes due to its adverse effects. The herbal medicines are the alternative and better option for the management of diabetes. Mostly Ayurvedic formulations are polyherbal formulation and impart chief role for the treatment of diabetes. The polyherbal formulation illustrates the combination of two or more herbs in formulation. The herbal components in the polyherbal formulation interacts leading to synergistic antidiabetic effect compared to the individual herb. Frequent available reports show evidence of synergistic effect of polyherbal drugs and their mechanism of action. But due to scanty availability of these reports in electronic libraries the researcher has to search the hard copies which leads to wastage of effort and time. To overcome these lacuna, this article was undertaken to scientifically review the *in vitro* and *in vivo* research studies on antidiabetic polyherbal formulations Further, the data presented in this review exploration of synergistic mechanisms of the antidiabetic polyherbal formulation will not only assist researchers to discover new phytomedicines or drug combinations but also support to avoid the possible negative synergy. Additionally, it would assist in clinical research for carrying out clinical trials to assess the efficacy of these herbal combinations and guide in understanding their synergistic mechanisms.

Keywords: Antidiabetes, Polyherbal formulation, Synergistic, Clinical study, Herbal, herb-herb combination

***Corresponding Author**

Saket Singh Chandel , Department of Pharmacology, Dr. C.V. Raman Institute of Pharmacy, Dr. C.V. Raman University, Bilaspur-495113, Chhattisgarh, India; Moblie- 9827181552

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1. INTRODUCTION

Diabetes is an enduring metabolic disorder, and it upsets all groups of people. The diabetes is depicted by high blood glucose level, inappropriate insulin action and insulin or glucose intolerance due to improper functioning of pancreatic cells. Further, the uncontrolled metabolism of carbohydrate, protein, and fat leads to hyperglycemia in blood.[1,2] It has been documented that occurrence of diabetes will be enhanced up to 629 million worldwide in 2045, and require potent medicines for the control of diabetes.[3] Chronic diabetes unpleasantly affects various organs which arise complications on eyes, kidneys, nerves, hypertension, cardiovascular disease etc. Consequently, increased level of triglyceride, total cholesterol, and low-density lipoprotein in the serum of diabetic patient are observed, while there is a decrease in high-density lipoprotein in serum.[4-5] For the management of diabetes, numerous hypoglycemic agents are available in the dosage form of chemical formulations and synthetic compounds namely sulphonylureas, metformin, alogliptin, saxagliptin, repaglinide etc. However, the uses of these medicines are limited due to associated adverse effects. The scientific paper reported an enormous number of medicinal plants to retain antidiabetic activity and used for the management of diabetes. Hence the medicinal plants/herbs/foods are good sources of alternative or complementary medicines for the management of diabetes. According to WHO, globally about 70-80% of the populations preferring traditional medicines which are obtained from the plant material and products for the treatment of hyperglycemia. The use of herbal medicines is increased over the last decade due to low side effects, easy availability, inexpensive and higher therapeutic efficacy.[6-8] The extent of therapeutic efficacy of the plant material depends upon the concentration of phytoconstituents present in it. Sometimes it has been observed that the chemical moieties are present in lower quantity in herbs and impart lower therapeutic efficacy. But the therapeutic efficacy of natural products increased by combining two or more than two herbs, and it is termed as polyherbal formulation. Polyherbal formulations may enhance the antidiabetic activity due to synergistic therapeutic properties produced by a complex compound formed by combining different plant material and consequently reducing the concentrations of single herbs. The combined extracts and formulations of the plants have been used as an antidiabetic drug rather than an individual. Hence the antidiabetic activity of polyherbal formulation suggest that there is a great demand for research to develop better and novel antidiabetic formulations. The various clinical trials illustrated that polyherbal formulation produced significant antidiabetic activity in humans.[9]Looking at the above facts, it was planned to present a comprehensive review of the existing status of research on the synergistic antidiabetic effects of polyherbal formulation and how they are effectively measured.

1.1. Synergistic effect

The interaction of two or more drugs to give a combined efficacy which is greater than the sum of their individual effect of the drugs is called a synergistic effect. The pharmaceutical science classified the synergistic property of medicines in two categories namely pharmacodynamic and pharmacokinetic synergy. The pharmacodynamic synergistic illustrates the two or more drugs that interact on the same receptors and produce higher therapeutic effects through their positive interactions. Moreover the pharmacokinetic synergistic expressed the interaction of two or more drugs leads to improved absorption, distribution, metabolism and elimination of drug causing increase in the concentration of drug in the body and enhance their therapeutic properties. It has been reported that the complex synergistic effects produced by mixing medicinal plants in complex polyherbal formulation increases the bioavailability of active components, promote therapeutic effects, and reduce toxicity.[10-12] Hence the combinations of two or more than two herbs retaining antidiabetic properties exhibit the synergistic antidiabetic potential.

1.2. Combination of medicinal plants

The polyherbal therapy is defined as an herb-herb combination, used in Ayurveda, Unani and Chinese systems of medicine. It is therapeutically used since many past years, but till date, scientific confirmation of their therapeutic benefits is missing. The therapeutic property of herb-herb combination is higher compared to a single herb. The western medicines and availability of sophisticated instruments have well developed the herb-herb combination dosage form with better efficacy and safety. Presently, the herb-herb combination therapies into certain formulas offered potential interaction effects and presented new confidence to the diabetes patient for their healing.[13] The Ayurvedic system of medicines formulated various antidiabetic formulations and each formulation containing more than two herbs. The compositions of antidiabetic Ayurvedic formulations are listed in Table 1.

Table 1: Antidiabetic Ayurvedic formulations

Marketed Ayurvedic drug	Composition of herbs
Dihar	*Syzygiumcumini, Momordicacharantia, Emblicaofficinalis, Gymnemasylvestre, Enicostemma, Azadirachtaindica, Tinosporacordifolia*and *Curcuma longa*[14]
Diabet	*Curcuma longa, Cosciniumfenestratum, Strychnospotatorum, Phyllanthusreticulatus. Tamarindusindica,* and*Tribulusterrestris*[14]
Diasol	*Eugenia jambolana, Foenumgraceum, Terminaliachebula, Quercus, infectoria, Cuminumcyminum, Taraxacumofficinale, Emblicaofficinalis, Gymnemasylvestre, Phyllanthusniruri*and*Enicostemmalittorale*[14]
Diakyur	*Cassia javanica,Cassiaauriculata, Salaciareticulata, Gymnemasylvestre, Mucunapruriens, Syzygiumjambolanum,* and *Terminaliaarjuna*[14]

1.3. Polyherbal formulation

The polyherbal formulation is defined as a formulation incorporating two or more than two herbs for the treatment of various diseases. The researchers reported that the single medicinal plants contained ample antioxidant substances like phenolic and flavonoids which are responsible for the management of diabetes. The polyherbal formulation controlled diabetes more significantly instead of the individual herb due to synergistic effect and minimum side effects of polyherbal formulation. Table 2 illustrated list of antidiabetic polyherbal formulation published in the research paper. The various studies described that the polyherbal formulation produces synergistic and improved antidiabetic effect compared to the individual herb.

Table 2 : List of scientifically reported synergistic antidiabetic polyherbal formulation

Herbal ingredients	Dosage form	Experimental protocol	Mechanism of action	References
Curcuma caesia, *Evolvulusalsinoides*, *Citrulluslanatus, Gymnemasylvestre*, *Tinosporacordifolia*, *Withaniacoagulans* and *Caesalpiniabonduc*	Suspension of extract	Alloxan induced diabetic rats	Antioxidant	15
M. indica, M. charantia, S. cuminii, A. indica, A. cepa, A. nilotica, S. cordifolia, T. foenum- gracum, G. sylvestre, C. longa, T. chebula	Churna	Streptozotocin-induced diabetic rats	Stimulate the pancreatic ß-cells directly or increase the sensitivity of the peripheral tissue to insulin, o	16
Silybummarianum, *Urticadioica* and *Boswelliaserrata*	Churna	Clinical studies	triglyceride-lowering effect of the herbal f	17
*Catharanthusroseus*and *Leucaslinifolia*	Ethanol and Aqueous extract	Alloxan induced diabetic rats (Preclinical studies)	Hhypoglycemic and antioxidant activities,	18
Syzygiumcumini, *Trigonellafoenum* and *Curcuma longa*	Churna	Clinical studies	It decreased blood glucose as well as blood pressure level in type-2 diabetic subjects	19
Strychnospotatorum, Acacia catechu, Woodfordiafruticosa, Salaciareticulata, Curcuma longa, BiophytumSenstivum, Ziziphusjujuba, CycleaPeltata, Mangiferaindica, Terminaliachebula and Cyperusrotundus	KatakakhadiradiKashayam	Streptozotocin-induced diabetes rat	Ayurvedic formulation demonstrated significant antidiabetic activity	20
Eugenia jambolana, Gymnemasylvestre, Momordicacharantia and Andrographispaniculata and Myristicafragrans	Hydroalcoholic extracts	Streptozotocin-induced diabetes rat	Antidiabetic activity of polyherbal formulation may be due to the diverse mechanism of action of each of the herbal drug present in the formulation	21
Bacopamonnieri, *Hippophaerhamnoides*, and *Dioscoreabulbifera*	Powdered	Streptozotocin-induced diabetes rat	Polyherbal formulation significantly improved cognitive deficits, increased body weight and lowered plasma glucose levels, and suggested that the bacosides, quercetin, and diosgenin present in formulation imparts the activity	22
Salaciaoblonga, *Salaciaroxburghii*, *Garciniaindica* and *Lagerstroemia parviflora*	Hydroalcoholic extract	Streptozotocin-induced diabetes rat	Polyherbal formulation produced promising antidiabetic activity but hypothesis mechanism of action has been not mentioned	23
*Mangiferaindica, Allium sativum, Psidiumguajava, Phyllanthusemblica*and *Allium cepa*	Paste of fruits	Clinical studies	Administration of polyherbal paste to diabetic patient reduced the blood glucose level, it is due to antioxidant properties of fruits	24
Glycosmispentaphylla, Tridaxprocumbens, and *Mangiferaindica*	Tablets	Streptozotocin-induced diabetes rat	Formulation possessed significant antidiabetic activity, and it may be due to the antidiabetic mechanism of the individual herbs present in the polyherbal formulation	25
Luffaacutangula and *Madhucalongifolia*	Tablets	Alloxan induced diabetes rat	Tablets exhibited antidiabetic activity due to their antioxidant property	26

Polyherbal formulation I: Gudmar, Jamunguthali, Karela bee, Haldi, Amla, Vijaysar, Tejpatra, Shilajeet, Kutki, Chitrak, Bilvapatra, Trivangabhasm, Methi, Neempatra, Pectin and guar gum Polyherbal formulation II: Gudmar, KarelaBeej, Haldi, JamunGuthali, Gudvel, Babul Ki Chal, BilvaPatra, NeemPatra, Shilajeet and Trivangabhasm	Methanol extract	Alloxan induced diabetes rat	Both the formulations significantly reduced the blood glucose level, while polyherbal formulation II demonstrated higher antidiabetic activity compared to polyherbal formulation I. This may be because of the fact that some of the herbal counterparts in the polyherbal formulation II viz. bark of babul and gravel, were not present in the polyherbal formulation I	27
*Annonasquamosa*and *Nigella sativa*	Aqueous extract	Streptozotocin-induced diabetes rat	The antidiabetic activity of polyherbal formulation due to the effect of active constituents of both plants alkaloid, phytosterols, which may be responsible for scavenging free radicals liberated by streptozotocin in diabetic rats	28
Gymnemasylvestre, Syzygiumcuimini, Pterocarpusmarsupium, Momordicacharantia, Emblicaofficinalis, Terminaliabellirica, Terminaliachebula and ShudhShilajit	Suspension of powder	Alloxan induced diabetes rat	Polyherbal formulation have potent antidiabetic activity	29
Momordicacharantia, Azadirachtaindica, Picrorhizakurroa, Ocimumsanctum, and*Zingiberofficinale*	Karnim plus	Alloxan induced diabetes rat	Karnim plus showed significant antidiabetic activity	30
*Phyllanthusemblica*and*Annonasquamosa*	Aqueous extract	Streptozotocin-induced diabetes rat	Polyherbal formulation exhibited significant antidiabetic effect by controlling the blood glucose level, and it is due to the presence of a phenolic component in the formulation	31
*Cassia auriculata, Mangiferaindica, Ficusbenghalensis, Cinnamomumtamala*and*Trichosanthesdioica*	Aqueous extract	Streptozotocin-induced diabetes rat	Polyherbal formulation exhibited promising antidiabetic activity, and it could be the regeneration of pancreatic β-cells leading to blood glucose regulation in the body	32
*Gymnemasylvestre, Trigonellafoenum*and*Phyllanthusemblica*	Aqueous extract	Streptozotocin-induced diabetes rat	The antidiabetic activity of polyherbal formulation was due to the presence of antioxidant components in the formulation	33

1.4. Future prospects

Number of research papers illustrated the significant antidiabetic activity of polyherbal formulation in different animal models. The reported polyherbal formulations are required to conduct the toxicity studies to develop the safety profile of formulations. The mechanism of action of antidiabetic activity of polyherbal formulations should be developed at the molecular level. It assures the extent of pharmacological efficacy of polyherbal formulations. Further, the pharmacokinetic and pharmacodynamic can be performed for reported polyherbal formulation. The clinical studies can be executed for polyherbal formulations having a better therapeutic and non-toxic effect. Consequently, the patent of polyherbal formulations can be processed to the patent office. The market will get a novel and better antidiabetic polyherbal formulation, and replace the synthetic antidiabetic agent associated with severe adverse effects.

2. CONCLUSION

The review summarized the synergistic effect of polyherbal formulation and also summarized their mechanism of action. The different antidiabetic polyherbal formulations are illustrated with their potency which will assist researchers to conduct further studies to give novel antidiabetic herbal agents. Consequently, the clinical benefits of multi-component combinations must be subsequently confirmed in rigorous clinical trials.

3. AUTHORS CONTRIBUTION STATEMENT

Vipinchandra Bhaskarrao Pande and Dr Saket Singh Chandel collected data from different sources and drafted the paper. Dr Vishal Soni verified the data and suggested improving the content of paper.

4. CONFLICT OF INTEREST

Conflict of interest declared none.

5. REFERENCES

1. Hammeso WW, Emiru YK, Getahun KA, Kahaliw W. Antidiabetic and antihyperlipidemic Activities of the Leaf Latex Extract of Aloe megalacantha Baker (Aloaceae) in streptozotocin-Induced Diabetic Model. Evid Based Complement Altern Med. 2019;2019: 1-9.
2. Nambirajan G, Karunanidhi K, Ganesan A, Rajendran R, Kandasamy R, Elangovan A, Thilagar S. Evaluation of antidiabetic activity of bud and flower of AvaramSenna (*Cassia auriculata* L.) in high fat diet and streptozotocin-induced diabetic rats. Biomed Pharmacother. 2018;108:1495-506. doi: 10.1016/j.biopha.2018.10.007, PMID 30372851.
3. Belayneh YM, Birhanu Z, Birru EM, Getenet G. Evaluation of in vivo antidiabetic, antidyslipidemic, and in vitro antioxidant activities of hydro methanolic root extract of *Datura stramonium* L. (Solanaceae). J Exp Pharmacol. 2019;11:29-38. doi: 10.2147/JEP.S192264, PMID 31114400.
4. Skyler JS, Bakris GL, Bonifacio E, Darsow T, Eckel RH, Groop L, Groop PH, Handelsman Y, Insel RA, Mathieu C, McElvaine AT, Palmer JP, Pugliese A, Schatz DA, Sosenko JM, Wilding JP, Ratner RE. Differentiation of diabetes by pathophysiology, natural history, and prognosis. Diabetes. 2017;66(2):241-55. doi: 10.2337/db16-0806, PMID 27980006.
5. Vijayaraghavan K. Treatment of dyslipidemia in patients with type 2 diabetes. Lipids Health Dis. 2010;9(1):144. doi: 10.1186/1476-511X-9-144, PMID 21172030.
6. Khan MF, Rawat AK, Khatoon S, Hussain MK, Mishra A, Negi DS. In vitro and in vivo antidiabetic effects of extracts of *Melia azedarach*, *Zanthoxylum alatum*, and *Tanacetumnubigenum*. Integr Med Res. 2018;7(2):176-83. doi: 10.1016/j.imr.2018.03.004, PMID 29984178.
7. Gupta RC, Chang D, SrinivasNammi A Bensoussan, Kellie Bilinski, Basil D. Roufogalis. Interactions between antidiabetic drugs and herbs: an overview of mechanisms of action and clinical implications. Diabetol Metab Syndr. 2017; 9: 59.
8. Kiran M, Bernard C, Trisha D. The use of complementary and alternative medicine among people with diabetes in Sydney. BMC Complement Altern Med. 2012;12:2.
9. Khera N, Bhatia A. Medicinal plants as natural anti-diabetic agents. Int J Pharm Sci Res. 2014;5(3):713.
10. Zhou X, Seto SW, Chang D, Kiat H, Razmovski-Naumovski VR, Chan K, Bensoussan A. Synergistic effects of Chinese herbal medicine: A comprehensive review of methodology and current research. Front Pharmacol. 2016;7:201. doi: 10.3389/fphar.2016.00201, PMID 27462269.
11. van Vuuren S, Viljoen A. Plant-based antimicrobial studies–methods and approaches to study the interaction between natural products. Planta Med. 2011;77(11):1168-82. doi: 10.1055/s-0030-1250736, PMID 21283954.
12. Williamson EM. Synergy and other interactions in phytomedicines. Phytomedicine. 2001;8(5):401-9. doi: 10.1078/0944-7113-00060, PMID 11695885.
13. Aslam MS, Ahmad MS, Mamat AS, Ahmad MZ, Salam F. An update review on polyherbal formulation: A global perspective. Syst Rev Pharm. 2016;7(1):35-41. doi: 10.5530/srp.2016.7.5.
14. Kaur M, Valecha V. Diabetes and antidiabetic herbal formulations: an alternative to allopathy. Eur J Med. 2014;6(4):226-40. doi: 10.13187/ejm.2014.6.226.
15. Mahajan SM, Baviskar DT, Chaudhari PM. Anti-diabetic activity of polyherbal formulation on alloxan induced diabetes. IOSR JPBS. 2018;13:01-6.
16. Bhattacharya B, Reddy KRC. Polyherbal ayurvedic powder effectively reduces blood sugar in streptozotocin-induced diabetic rats. pharmaceutical-sciences. 2018;80(2):253-60. doi: 10.4172/pharmaceutical-sciences.1000352.
17. Khalili N, Fereydoonzadeh R, Silymarin MR. Olibanum, and nettle, A mixed herbal formulation in the treatment of Type II diabetes: A randomized, double-blind, placebo-controlled, clinical trial. J Evid Based Integr Med. 2017;22(4):603-8.

18. Manthena SV, Arutla R, Mohan PC, Prusty B. Evaluation of antidiabetic and antioxidant activity of root extracts of herbal mixture (*Catharanthus roseus*, *Leucas linifolia*). IOSR JPBS. 2017;12(6):29-36.
19. Solanki PS, Chaudhary KV. VHKanbi, IN Patel. Effect of herbal formulation (Churn) on type 2 diabetic patients. J Pharmacogn Phytochem. 2017;6(5):307-10.
20. Azeez A, Tomy S, Ali Abdalla FMA, Suresh R, Johnson B. Antidiabetic effect of Polyherbal Formulation "KatakakhadiradiKashayam" in streptozotocin induced Diabetic rats. J Young Pharm. 2016;8(4):496-9. doi: 10.5530/jyp.2016.4.30.
21. Tripathi N, Kumar V, Acharya S. Anti-diabetic activity of a polyherbal formulation in streptozotocin induced Type 2 diabetic rats. J Nat Rem. 2016;16(4):148-52.
22. Upadhyay P, Sadhu A, Purohit S, Singh PK, Shivakumar S. Effect of a novel polyherbal formulation on diabetes induced memory deficits in rats. Clin Exp Pharmacol. 2015;5:194.
23. Subhasree N, Kamella A, Kaliappan I, Agrawal A, Dubey GP. Antidiabetic and antihyperlipidemic activities of a novel polyherbal formulation in high fat diet/streptozotocin induced diabetic rat model. IJP. Indian J Pharmacol. 2015;47(5):509-13. doi: 10.4103/0253-7613.165200, PMID 26600639.
24. Sukalingam K, Ganesan K, Ponnusamy K. Evaluation of antidiabetic activity of polyherbal formulations on Type 2 diabetic patients: A single blinded randomized study. J Int Sci. 2015;2(3):90-8.
25. Petchi RR, Vijaya C, Parasuraman S. Antidiabetic activity of polyherbal formulation in streptozotocin – nicotinamide induced diabetic Wistar rats. J Tradit Complement Med. 2014;4(2):108-17. doi: 10.4103/2225-4110.126174, PMID 24860734.
26. Singh H, Arora S, Mani M, Mahaur KK, Chandra P. Development of multicomponent formulation of herbal drugs for evaluation of Antidiabetic activity. Pharm Lett. 2014;6(1):219-23.
27. Chandel HS, Pathak A, Tailang M. Polyherbal formulations for anti diabetic therapy. Int J Pharm Pharm Sci. 2011;3:226-8.
28. Singh S, Manvi FV, Nanjwade B, Nema R. Antihyperlipidemic screening of polyherbal formulation of *Annona squamosa* and *Nigella sativa*. Int J Toxicol Pharmacol Res. 2010;2(1):1-5.
29. Mandlik RV, Desai SK, Naik SR, Sharma G, Kohli RK. Antidiabetic activity of a polyherbal formulation (DRF/AY/5001). Indian J Exp Biol. 2008;46(8):599-606. PMID 18814489.
30. Bangar OP, Jarald EE, Asghar S, Ahmad S. Antidiabetic activity of a polyherbal formulation (Karnim Plus). Int J Green Pharm. 2009;4:211-4.
31. Chaudhuri A, Sharma S. Evaluation of antidiabetic activity of polyherbal formulation in streptozotocin-induced diabetic rats. UK Journal of Pharmaceutical Biosciences. 2016;4(5):01-6. doi: 10.20510/ukjpb/4/i5/113983.
32. Majumder P, M P. Hypoglycemic activity of A novel polyherbal formulation in streptozotocin-induced diabetic rats: A therapeutic study. Asian J Pharm Clin Res. 2019;12(3):218-23. doi: 10.22159/ajpcr.2019.v12i3.29969.
33. Shah SS, Manigauha A, Dubey B. Formulation and Evaluation of Antidiabetic and antihyperlipidemic Activities of Polyherbal Formulation in streptozotocin induced diabetic rats. Pharmaceutical and Biosciences Journal. 2019;7(1):26-30. doi: 10.20510/ukjpb/7/i1/179298.