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Review Article

POLY HERBAL FORMULATIONS IN THE MANAGEMENT OF DIABETES MELLITUS: AN OVERVIEW

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A B S T R A C T

An approach for Poly Herbal Formulations (PHS) in managing Diabetes mellitus (DM) has drawn attention among numerous scientists all over the world. In spite of remarkable advancement in conventional medicine, DM relentlessly affects mankind and considered to be one of the major causes leading to morbidity and mortality all over the world. While on the other hand, PHF are attained popularity, particularly in the management of DM considering to its fewer side effects and inexpensiveness. The Indian Traditional System of Medicine (ISM) offers a diverse PHF in the treatment of this crippling disease. In this review, the authors have focused on research studies carried on PHF used for ant diabetes along with selection of plants, concept, merits and limitations of PHF.

INTRODUCTION

Over the past few decades, Diabetes mellitus (DM) is a categorized a global health peril, a lethal, slow poison that obstinately heartrending the mankind, irrespective of the gender, age, socioeconomic status and geographic location of the population[1]. According to statistics, one amongst every five persons has diabetes[2] further Type II diabetes is very common and often considered as metabolic disorder rather than a disease, accounting 90%-95% of cases[3]. Particularly in Non-insulin-dependent DM, where the body is neither capable to produce adequate insulin nor accurately use it[4]. In addition, World Health Organization (WHO) has cautioned by the year 2025 up to 300 million or even more populations will be affected by DM[5]. It has already moved into a pandemic form[2]. Although, several hypoglycaemic agents from synthetic sources were available in the market still diabetic complications remain to be a dreadful medical jeopardy[6]. Besides, conventional medicines are expensive and have severe side effects while many indigenous Indian medicinal plants have been found to be worthwhile in managing diabetes[7]. An added advantage of these medicinal plants is these are readily available and have fewer side effects[8]. Nevertheless, medicinal plants constantly served an as basic source of drugs and moreover most of the presently existing conventional medicines are originated either directly or indirectly from herbs[9]. Therefore, considerable attention has been paid on exploring natural products for the discovery of probably worthwhile targets.

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Hence there is a shift in paradigm where scientists are employing reverse pharmacology strategies based on Indian System of Medicine (ISM) like Ayurveda, Siddha, Unani, Homeopathy and Naturopathy etc., or by folklore or ethno botanical reviews in quest of new drugs[10]. In addition, these natural products comprise a plethora of bioactive molecules with multi-dimensional chemical structures that are having exceptional pharmacological actions perhaps, may lead to the discovery of new classes of safer anti-diabetic agents.

Selection of medicinal plants based on desired activity

One can attain diverse information about ISM employed in India by searching in different databases like "A Traditional Knowledge Digital Library" (TKDL) initiated by AYUSH, India. On the other hand, another database was set up by the National Medicinal Plant Board (NMPB) named it as "Indian Medicinal Plant Database" a database that includes valuable information about medicinal plants. The majority of the researchers face difficulty in identifying the plant scientific name even though they know its vernacular name while it can be overcome by simply exploring on "FRLHT" database. Other main mystification is with synonyms of plants so it can be confirmed by searching in the NAPRALERT database while it also covers ethno botanical facts, pharmacological/biochemical data of plants *In-situ, In-vitro, In-vivo* (preclinical) and human studies (clinical data). Similar kind of information is also available at the Councils databases and publications of ICMR that provides the medicinal plants used in ISM[11]. Nevertheless, Medicinal and Aromatic Plants Abstracts (MAPA) can be considered as a repository of medicinal plant information. Several other books, for instance,

"Compendium of medicinal plants" by Ram P Rastogi, "Indian Medicinal Plants: An Illustrated Dictionary" by CP Khare, "Medicinal Plants in India" in two Volumes by T Pullaiah and "Flowering Plants of Chittoor District" by K Madhav Setty provide a valid information about ethno botanical uses of plants employed in treating different diseases.

Methods employed for gathering Literature Review

A brief literature survey was carried out by exploring different data base like "PubMed" and "Google Scholar" using the different keywords like "Poly herbal formulation", "Diabetes", "Antihyperglycemic activity" and carefully selected merely PHF with anti hyperglycaemic activity. The Authors tried to include all relevant articles with PHF and summarized all the appropriate reviews in the field to acquire an overview of the selected topic.

Phyto-Constituents having Potent Anti-Diabetic activity

Secondary metabolites from medicinal plants are classified into alkaloids, terpenoids, saponins, flavonoids, phenolics, and quite a few other categories have exhibited anti-diabetic potential.

Alkaloids

Several classes of alkaloids shows anti-diabetic potential by diverse mechanism of action for instance, barberin from *Barberis aristata* acts by glucose transport[12], while major constituents from *Trigonella foenumgraecum* like trigonelline, gentianine, carpaine compounds act by either glucose transport or carbohydrate digestion and absorption[13]. DPP-IV inhibition was exhibited by Castanospermine, australine from *Castanospermum australe*[14]. Free radical scavenging action was demonstrated by Catharanthine, vindoline, vindolinene vinblastine, vincristine, from *Cathanthrus roseus*[15]. Allylpropyldisulfide from *Allium sativum* enhances glycogen synthesis, insulin secretion

Glycosides

Gymnemic acid, a well-established gymnemosides from *Gymnema sylvestre* have shown antidiabetic potential either by regeneration of pancreatic β cells or by insulin secretion[17] on other hand *C*-glycoside*s* from *Trigonella foenumgraecum* acts by glucose transport and carbohydrate metabolism[18]. Insulin secretion or glycogen synthesis was stimulated by momorcharin A and B and Momorcharaside A and B from *Momordica charantia*.[19]

Flavonoids

Most of these class drugs act by free radical scavenging activity. Besides Chrysin, Proanthocyanidins from *Vitis vinifera* shows insulinonematic activity[20]. On other hand, Kaempferitrin from *Bauhinia forficata* exhibits glycolysis[21]. In addition, Soy isoflavones from *Glycin max* acts by lipid and glucose metabolism, PPAR activation[22].

Saponins

Majority of this class drugs acts by either regeneration of pancreatic β cells or free radical scavenging for insistence, Stigmasterol, quercitol, gymnenic acid IV from *Gymnema sylvestre*[23]. whereas Diosgenin which is a steroid saponin, was evaluated in gestational diabetes mellitus showed marked improvement of glucose, insulin intolerance and upsurge hepatic glycogen content[14].

The Concept behind PHF in Management of DM

Poly herbal therapy or use of ancient traditional poly herbal formulation dates back to 5000 BC[24]. In "Ayurveda", the practice of PHF in treating various disorders was clearly mentioned. Meanwhile "Sarandghar Samhita" proposes the concept of synergism behind poly herbal formulations[24]. In majority of traditional systems, diabetes is better managed by the herbal combination instead of a single herb this might be due to synergism and efficient treatment. Each herb exhibits anti diabetic potential by diverse mechanism of action some of them regulate by insulin secretion while few control insulin resistance and others may act by enhancing glucose absorption or by antioxidant properties. In addition, few herbs act by targeting multiple sites, including enhancing insulin sensitivity, regeneration of pancreatic β cells, augment glucose utilization, aldose reductase inhibitors, α-glucosidase inhibitors and also by antioxidant property. Hence, these PHF can target several pathological events that occur during the progression of the disease. It is evident that by targeting multiple sites, diabetes treatment can be accomplished effectively and further in managing the progression of disease as well as modify the deteriorating condition of the patients. Even scientific studies on PHF have shown a synergistic effect validating its use.Nevertheless the main concept beyond any PHF may include "if a few drops of poison can shatter our body, then certainly a few drops of nectar can also revitalize it" by Sri Sri Ravi Shankar, Art of living.

Scientific Studies on few PHF with Anti-Hyperglycaemic Activity D-400

Mitra SK, *et al.,* in 1996, have screened antidiabetic activity on 'D-400' which comprises of *Balsamodendron mukul, Casearia esculentu*, *Eugenia jamboluna Lam.*, *Gymnema sylvestre* , *Momordica charantiu Linn.*, *Ocimum sanctum Linn.*, *Pterocarpus marsupium*, *Tinospora cordifolia Miers.*, and mineral like Shilajit by both alloxan and streptozotocin induced models in rats. The Authors have focused mainly the impact of formulation on the pancreas. While it showed marked improvement in the pancreas by intensification in islet number and total beta cell count and lowered blood glucose by enhancing insulin secretion either by repair or regeneration of pancreas signifying prevention of hepatic glycogenolysis[25].

Trasina

Bhattacharya SK, *et al.,* in 1997 has examined hyperglycaemia and antioxidant activity on 'Transina' (TR) formulation consists of *Eclipta alba, Ocimum sanctum, Picrorrhiza kurroa, Tinospora cordifolia, Withania somnifera, and* shilajit. The authors concluded that the anti-hyperglycaemic effect of TR may be due to pancreatic islet free radical scavenging activity, the hyperglycaemic activity of STZ being the consequence of reduction in islet SOD activity leading to the accumulation of degenerative oxidative free radicals in islet beta-cells[26].

Hyponidd

Subash B P, *et al.,* in 2004 has investigated on 'Hyponidd' a formulation comprising of the extracts of medicinal plants (*Cassia auriculata*, *Curcuma longa Enicostemma littorale*, *Emblica officinalis*, *Gymnema sylvestre*, *Eugenia jambolana*, *Momordica charantia*, *Melia azadirachta*, *Pterocarpus marsupium*, and *Tinospora cordifolia*) for antihyperglycaemic and antioxidant potential on rats. The study was carried out at two dose intervals100mg/kg and 200mg/kg) for 45days. It

exhibited reduced levels of biochemical parameters. Finally, the results concluded the activity of the formulation was effective at higher dose (200mg/kg) in reinstating the values to normal[27].

Dianex

Mutalik S, *et al.,* in 2005, has assessed hypoglycemic activity of 'Dianex' in normal as well as in streptozotocin induced diabetic mice. Dianex contain aqueous extracts of *Aegle marmelose, Azadirachta indica, Cassia auriculata*, *Curcuma longa*, Eugenia *jambolana*, *Gymnema sylvestre*, *Momordica charantia,* and *Withania somnifera* . The study was done at diverse doses of 100-500 mg/kg/day orally meanwhile toxicity studies were also carried out in acute (6 h) and sub-acute (6 weeks) studies. In both normal as well as in diabetic mice Dianex displayed significant (p <0.05) hypoglycemic activity at 250-500 mg/kg doses. No signs of toxicity were noticed in fact it showed marked development in healthy body weight. All the pathological parameters were significantly lower in diabetic mice. While, in both tested groups, the glucose tolerance was significantly (p <0.05) enhanced. Nevertheless It also showed a significant (p <0.05) antioxidant activity[28].

Ilogen-Excel

Umamaheswari S, *et al.,* in 2007, has studied anti diabetic potential of Ilogen-Excel an Ayurvedic formulation comprises of eight medicinal plants (*Andrographis paniculata, Curcuma longa, Coscinium fenestratum, Mimosa pudica, Strychnos potatorum, Salacia oblonga, Tinospora cordifolia and Vetiveli azizanioide*) in streptozotocin induced diabetic rats. The study was designed for 60 days at two dose intervals (50 mg/kg and 100 mg/kg) exhibited a significant improvement in the biochemical parameters studied[29].

MTEC

Chhanda M, *et al*., in 2007, has investigated the consequence of diabetes induced testicular oxidative stress by observing testicular peroxidase and catalase activities on MTEC. It comprises an aqueous-methanolic extracts of *Coccinia indica, Eugenia jambolana, Musa paradisiaca and Tamarindus indica* tested by using streptozotocin induced diabetic rat model. It is found to be useful in testicular disorders associated with diabetes [30].

Diamed

Pari L, *et al.,* in 2010, has conducted preclinical trials on 'Diamed' by using alloxan-induced model in the formulation consists of an aqueous extracts of *Azardirachta indica*, *Cassia auriculata* and *Momordica charantia*. The formulation was orally administered at three different dose levels for 30days. The results were extremely significant in tested biochemical parameters [31].

Diashis

Tushar KB, *et al.,* in 2010, has tested the effect of '*Diashis*', a PHF consist of eight medicinal plants, i.e., *Asphultum, Gymnema sylvestre, Holarrhena antidysenterica, Momordica charantia, Pongamia pinnata , Psoralea corylifolia*, *Syzygium cumuni and Tinospora cordifolia,* in streptozotocin induced diabetic rats. Here the authors have highlighted the impact of formulation on antioxidant enzymes and metabolic enzymes. It has shown a significant (P < 0.01) retrieval in the all biochemical parameters tested. Finally, the oxidative stress status in the liver was rectified. Further, it doesn't show any metabolic toxicity[32].

Glyoherb

Nima VT, *et al.,* in 2010, has tested Glyoherb for its antihyperglycemic, antihyperlipidemic and antioxidant potential against normal and streptozotocin-induced diabetic rats. It is a PHF manufactured by Dhanvantri Valasan, Anand, Gujarat, India comprising of well-known important medicinal plants. However, results don't show any marked improvement when compared with standard Glibenclamide (5 mg/kg) [33].

Kathakakhadiradi Kashyam

Abdul A, *et al.,* in 2016, has evaluated the antidiabetic potential of 'kathakakhadiradikashyam' (KKS) an indigenous poly herbal ayurvedic formulation in streptozotocin induced diabetes rat model. The study was performed in the 28 day continues administration. Here, the authors have focused on the percentage reduction of glucose reduction of KKS and compared with the standard drug treated group (Glibenclamide) [34].

Merits

1. Herbal formulation are better alternatives than these existing allopathic drugs
2. Normally less-toxic and inexpensive
3. Have pleiotropic effect
4. Fewer side effects

Limitations

1. Absence of an accurately designed clinical trials on humans
2. Possibilities of potential herb-herb and herb-drug interactions
3. Nonexistence of established mechanism of action
4. A lack of stringent regulatory authorities
5. Inappropriate standardization of herbal drugs
6. Ambiguous toxicological data
7. Trouble in Biomarkers estimation

CONCLUSION

Nowadays, the "Renaissance" of PHF has staging come back all over the world owing to its minimal side effects and effective treatment. Moreover, India is generally considered to be a gold mine of medicinal plants with effective TSM. A successful PHF can be developed by utilizing this ancient knowledge with reverse pharmacological strategies. Moreover, the marketed PHF exhibited a potent activity when compared to modern medicine shows a path of exploration for new approaches. Nevertheless, if we can overcome the limitations mentioned for PHF with currently available scientific tools we can develop an effective PHF in targeting not only DM but other chronic diseases as well.

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