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RESEARCH ARTICLE
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THE INFLUENCE OF AYURVEDIC HERBAL REMEDIES FOR DIABETES MELLITUS- A HOLISTIC APPROACH

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Abstract:
Diabetes is a heterogenous disease of carbohydrate metabolism characterized by hyperglycaemia with polyuria, polypepsia, and polydipsia, due to lack of secretion of insulin or resistance to insulin. Several distinct types of DM exist and are caused by a complex interaction of genetics, environmental factors and lifestyle choices. DM will likely continue to be the leading cause of morbidity and mortality in near future. It is projected that the number of individuals with DM will continue to rise in the near future.
The usual methods for diagnosing diabetes are based on various chemical tests of urine and the blood viz, Fasting Blood Glucose Level, Glucose Tolerance Test, Urinary Sugar, and Glycated Hemoglobin (HBA1c). Glucose intolerance and type 2 diabetes may also be manifestations of an underlying disorder known as the metabolic syndrome. Besides modem medicines, there are many herbal formulations placed in the market with different claims and benefits. Most of the herbal formulations are made available as solid dosage forms like capsules, tablets and powders. They are not presented as liquid orals due to risk of their sugar content. Asavas and Arishtas invention allows the manufacturer to prepare herbal composition for diabetes in the form of a liquid oral with prolonged shelf life and without disadvantage of sugar content.

Key words: Ayurvedic remedies, Diabetes mellitus, Asavas, Arishtas

Introduction

Diabetes Mellitus (DM) comprises a group of common metabolic disorders that share the phenotype of hyperglycemia. DM is the leading cause of end- stage renal disease (ERSD), non-traumatic lower extremity amputations and adult blindness. Diabetes is rising as an epidemic all over the world esp., in country like India. Increasing worldwide. The worldwide prevalence of DM has risen dramatically over the past two decades. It is believed to be one of the main criteria for deaths all over the world. Important concern of concentrating on diabetes mellitus is its prevalence particularly Type 2 diabetes is rising all over the world. Prevalence of type 2 diabetes rises with increasing age.[(1)]

More people may remain undiagnosed in our country where health concern is less. If obese people with impaired glucose tolerance (IGT) and pre-diabetic persons are included along with known diabetics all over the world, we may find billions of diabetics. Another important issue is medical expenditure on medicines, investigations, regular follow-ups, any disability occurring in between, its surgical corrections, its overall management, rehabilitation etc. is financial burden on diabetics. If one cannot afford it, life remains miserable and at risk. Major cardiovascular risk factors are usually present, before the diagnosis of type 2 diabetes as well as during the course of the disease. Hence life expectancy of diabetics has lowered undoubtedly. Diabetic Symptoms, which may arise due to pathology of insulin lack,[(2)] are Polyuria: due to the osmotic diuretic effect of glucose in the kidney tubules; Polydipsia: due to dehydration resulting from polyuria; loss of weight: The failure of Glucose and protein metabolism by the body; Polyphagia: Loss of weight causes tendency of eating more; Asthenia: Loss of body protein and diminished utilization of carbohydrates for energy.
The present invention relates to the treatment of important clinical problems like diabetes mellitus, metabolic syndrome, NAFLD wherein herbal formulations have an edge over the conventionally used synthetic drug molecules.
In an embodiment, the invention pertains to deliver the specific advantages of Asavas and Arishtas [(3)] over the conventionally used solid dosage forms. For this purpose, the invention seeks to find solution to important limiting factor of the range. The invention goes to the very fundamental aspects of fermentation procedure and identifies simple solution to overcome the issues of residual sugars.
The invention identifies specific drug potentiators to be added to the conventionally used anti-diabetic formulation of herbal origin. Once this is established the invention further worked to formulate the composition using superior process pathways The invention identifies the methods to overcome the issues related to such process pathways, the invention brought in a process, a process ingenuity leading to the development of a new product through a modification in a conventional process.
Thus, the invention provides a synergistic oral liquid herbal composition falling under the category of Asavas and Arishtas, useful for management of diabetes mellitus, metabolic syndrome, NAFLD said composition comprising a therapeutically effective amount of plant extracts, self-generated alcohol to the extent of 7 to 12% v/v and having not more than 1 to 2 % w/w of sugar content.

Aristas are excellent because it contains the highest extracts of the ingredients of the Kwath, their properties are decided on the basis of the drugs used in the preparation and thus are very useful in different medical conditions. (Bhavprakash Nighantu [Indian Materia Medica] Of SRI Bhavamisra, Commentary by Dr. K.C. Chunekar, Edited by Dr. G.S. Pandey, Chaukhambha Bharati Academy, Varanasi.2002).
Asavas & Arishta are considered unique as they have several advantages. Ayurved literature indicates that they possess better keeping quality, which is likely due to the contribution of fermentation in preservation.[(4)] The microbes involved in this process indicate this process ;enhanced therapeutic properties ,which may be due to the microbial biotransformation of the initial ingredients of Asava and Arista into more effective therapeutics as end products, improvement in the extraction of drug molecules from the herbs by alcohol-aqueous milieu, which is also produced by microbes ;improvement in drug delivery in the body, which may be at least partially due to microbial biotransformation either because of biotransformation or because of alcohol aqueous milieu. These products in general possess preservative properties, potentization of drug due to biotransformation mediated by native microbes' improvement in drug extraction and drug delivery. The potential of Asava and Arista is controlled by the profile of chemical compounds, can be modulated based on the nature of ingredients, type of fermentation and microorganisms involved. [Kumar KA, the need for developing new dosage presentation forms for traditional medicine In Indian healthcare tradition. A contemporary view, edited by Paulose KG, Murali TS, Kumar NM (Arya Vaidya Sala, Kottakal) 2002,120-28]

This oral liquid forms in the category of Asavas and Aristhas have good pharmacological actions and effect on Diabetes mellitus etc. as per the following pharmacological principle in the drug absorption

Absorption (Essentials of Medical Pharmacology, 7th Edition, 2015 K D Tripathi, Jaypee Brothers Medical Publishers (P) Ltd)

Absorption is movement of the drug from its site of administration into the circulation. Not only the fraction of the administered dose that gets absorbed, but also the rate of absorption is important. Except when given IV the drug has to cross biological membrane; absorption is governed by the above-described principles. Other factors affecting absorption are

1) Aqueous solubility- Drugs given in solid form must dissolve in the aqueous BioPhase before they are absorbed. Rate of dissolution governs rate of absorption. Obviously, a drug given as watery solution is absorbed faster than when the same is given in solid form or as oily solution.

2) Concentration-Passive diffusion depends on concentration gradient; drug given as concentrated solution is absorbed faster than from dilute solution. As in Asava, Arishta the Kwath is remained upto $1/8^{th}$ of the total volume in the preparation of the Kwath. Thus, the final extract of the drugs becomes concentrated.

3) Vascularity of the absorbing surface-Blood circulation removes the drug from the site of absorption and maintains the concentration gradient across the absorbing surface. Asava & Arishta increases the blood flow thus hastens drug absorption.

4) Route of administration –This affects drug absorption, because each route has its own peculiarities.

Oral- The effective barrier to orally administered drugs is the epithelial lining of the gastrointestinal tract, which is lipoidal. Non ionized lipid soluble drugs. e.g.ethanol are readily absorbed from stomach as well as intestine at rates proportional to their lipid: water partition coefficient. As Asava & Arishta have a limited amount of self-generated alcohol, it may help in the faster absorption.

Table No 1: List of Herbal extract use in Asava & Arista composition [(5)]

Sr. No	Name of the drug	English name	Latin name	family	Parts used
01	Aamalaki	Emblic Myrobalan, Indian gooseberry	Phyllanthus emblica Linn.	Euphorbiaceae	Fruit
02	Bibhitak	Beleric Myrobalans, Beddanut	Terminalia belerica	Combretaceae	Fruit
03	Haritaki	Morabalans	Terminalia chebula	Combretaceae	Fruit
04	Haridra	Turmeric	Curcuma longa	Zingiberaceae	Root
05	Daruharidra	Indian berberry	Berberis species	Berberidaceae	Stem
06	Vijaysar	Indian Kino tree	Pterocarpus marsupium Roxb,	Leguminosae	Stem
07	Meshshringi/Gudmar /Madhunashini /Madhuparni	Periploca of the woods	Gymnema sylvestre	Asclepiadaceae	Leaves
08	Bilwa	Beal fruit	Aegle marmelos	Rutaceae	Leaves
09	Devadaru	Himalayan cedar, pinus deodar	Cedrus deodara	Pinaceae	Stem, bark
10	Guduchi	Tinospora	Tinospora cordifolia	Menispermaceae	Stem
11	Neem	Neem tree, Margosa	Azadirachta Indica	Meliaceae	Bark, leaves
12	Palash	The forest flame	Butea frondosa Koen	Leguminosae	Fruits, seeds
13	Saptaparni	Blackboard tree	Alstonia scholaris	Apocynaceae	Stem bark, leaves
14	Pippali	Long Pepper	Piper longum	Piperaceae	Fruit
15	Ashwagandha	Winter cherry	Withania somniferra	Solanaceae	Root

And having sugar content to the extent of 1 to 2% w/w and self-generated alcohol to the extent of 7 to 12% v/v and optionally comprising powders of Woodfordia fruticosa (2 to 5%), Piper longum (0.1 to 0.3%), Elettaria cardamomum (0.1 to 0.3%), Myristica fragrans (0.1 to 0.3%) and Ammomum subulatum (0.1 to 0.3%).

In still another embodiment, the invention provides a synergistic oral liquid herbal composition falling under the category "Asavas" and "Arishtas",[(6)] useful for management of diabetes, said composition comprising a therapeutically effective amount of plant extracts, ethanol to the extent of 7 to 12% v/v

and having not more than 1 to 2% w/w of sugar content and manufactured by the process comprising the steps of:
(a) Obtaining the extract of plant parts,
(b) Adding nutrients to the extract of step (a) in a manner such that the sugar content in the culture medium does not exceed 20% w/w,
(c) Thus, the yeasts (micro-organisms) are formed capable of fermentation to the culture medium of step (b) and allowing it to ferment until the self-generated ethanol content thereof reaches 7 to 12% v/v and
(d) Obtaining the herbal composition having total sugar content of not more than 1-2 % w/w.

In an embodiment, the plant parts are obtained by cold infusion or hot decoction methods. The cold infusion method comprises the step of extracting the plant parts in water at a temperature ranging between 20 degrees to 30-degree C. The hot decoction method comprises the step of extracting the plant parts in water by heating at a temperature in the range of 60-to-90-degree C.
In still another embodiment, the nutrient in step (b) is a complex nutrient like jaggary. This nutrient is in physical forms such as solid or liquid. Further, the nutrients are added by fed batch or batch fermentation method. The nutrients are added in small amounts in regular intervals (at gradient quantities) in fed batch fermentation method. The addition of nutrients in fed batch fermentation method is such that each batch of nutrients added (each gradient) does not impart more than 5% w/w of sugar and the overall quantum of sugar added in the entire process does not exceed 20% w/w. The nutrients are added to the medium in the beginning at once in batch fermentation method
In yet another embodiment, the culture medium is incubated at a temperature ranging between 20-to-37-degree C. for more than one month upto 40-60 days in anaerobic conditions maintaining the pH of the medium from 4 to 6. For best results, the temperature is maintained at 30-degree C., the incubation is effected preferably for 4 days and the pH of the culture medium is maintained at 4-5.
As such the final sugar content in the herbal composition manufactured according to the process of the invention is not more than 1 to 2 % w/w.

The inventive steps for this invention can be divided under three major headings:
1. Identification, development of an arbitrary herbal composition comprising of well-known herbal drugs for diabetes. Each 100 ml of the finished product consists of the extract derived from the said formulation
2. The second phase of inventive steps included, identification of certain drug potentiators and identify a process pathway to incorporate the same into a liquid oral dosage form. The following drug potentiators are identified to enhance the antidiabetic activity
Woodfordia fruticosa (Flowers) 2-5 gm, Piper longum (Spike) 0.1-0.3 gm, Elettaria cardamomum (Fruits) 0.1-0.3 gm, Myristica fragrans (Fruit) 0.1-0.3 gm, Ammomum subulatum (Fruit) 0.1-0.3 gm [7]
3. Once after the selection of active herbal ingredients is affected, there is a need to develop distinct process by which the finished product shall have a lowest amount of residual sugars.

During these inventive steps a series of experiments were conducted mainly with reference to inventive step no.3.
These experiments were essentially designed on a simple biological principle that a complex sugar is reversed in to simple sugars by the microorganism to produce alcohol in any medium. When a complex sugar is added in the medium as per traditional formula, only a part of them are reversed and remained as residual sugars in the finished product
On the other hand, judicious design of the fermentation medium with simple sugars might help to overcome this problem and render the finished product virtually sugar free. Several experiments were conducted using different kinds of sugars such as Jaggery, Black Jaggery, sugarcane juice, Invert Syrup etc.[8] These studies invariably proven that the residual sugars can be controlled by means of judicious use of simple sugars in the fermentation medium.

Discussion:

1. A synergistic oral herbal composition falling under the category of "asavas" and "arishtas" formulations comprising a therapeutically effective amount of plant extracts, self-generated ethanol to the extent of 7 to 12% v/v and having not more than 1 to 3% w/w of sugar content.
2. The oral herbal composition , wherein liquid composition comprising extracts of plants selected from: [9]

a. *Momordica charantia* (2-5%),
b. *Gymenma sylvestre* (8-12%),
c. *Pterocarpus marsupium* (8-12%),
d. *Eugenia jambolana* (4-10%), and
e. *Trigonella foenumgrecum* (1-3%),

and having sugar content to the extent of 1 to 3% w/w and self-generated ethanol to the extent of 7 to 12% v/v, and, optionally, comprising extracts/powder of *Woodfordia fruticosa* (2 to 5%), *Piper longum* (0.1 to 0.3%), *Elettaria cardamomum* (0.1 to 0.3%), *Myristica fragrans* (0.1 to 0.3%) and *Ammomum subulatum* (0.1 to 0.3%).

3. The oral herbal composition , wherein the plant parts are obtained by cold infusion or hot decoction methods.
4. The oral herbal composition as , wherein the final sugar content in the herbal composition is not more than 1% w/w.
5. The oral herbal composition , wherein dosage form is selected from group consisting of Tablets, Capsules, Liquid, Powder and Granules.
6. The oral herbal composition , wherein the composition useful for management of diabetes mellitus, metabolic syndrome, Non-alcoholic Fatty Liver Disease (NAFLD)
7. A synergistic oral liquid herbal composition falling under the category "Asavas" and "Arishtas", useful for management of diabetes, said composition comprising a therapeutically effective amount of plant extracts, ethanol to the extent of 7 to 12% v/v and having not more than 1 to 3% w/w of sugar content and manufactured by the process comprising the steps of:

a. obtaining the extract of plant parts,
b. adding nutrients to the extract of step (a) in a manner such that the sugar content in the culture medium does not exceed 20% w/w,
c. adding micro-organisms capable of fermentation to the culture medium of step (b) and allowing it to ferment until the self-generated ethanol content thereof reaches 7 to 12% v/v and
d. obtaining the herbal composition having total sugar content of not more than 3% w/w.

8. The oral herbal composition , wherein the nutrient in step (b) is a complex nutrient like jaggery or simple sugar like glucose, fructose or any other hexose sugar.

Conclusion:

The invention provides a synergistic oral liquid herbal composition falling under the category of "Asavas" and "Arishtas", useful for management of diabetes mellitus, metabolic syndrome, Non-alcoholic Fatty Liver Disease (NAFLD). The present composition comprising a therapeutically effective amount of plant extracts, self-generated ethanol to the extent of 7to 12% v/v and having not more than 1 to 2 % w/w of sugar content. This process facilitates the production of fermented liquid orals virtually free from sugar and hence provides benefits to the large segment of population suffering from Diabetes mellitus and related medical conditions. This invention also provides a novel method for the manufacture of herbal compositions in liquid oral dosage form containing a limited amount of self-generated alcohol and virtually free residual sugar.

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