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WHY POLY HERBAL PREPARATION IS MORE ADVANTAGEOUS THAN TARGETED SINGLE MOLECULE BASED DRUG (S) FOR THE MANAGEMENT OF DIABETES MELLITUS

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ABSTRACT

In the context of herbal drugs gaining equal importance in the treatment of various diseases the present study dwells into the aspect of poly-herbal drugs vis-à-vis target specific single molecule to establish the advantage of one over the other. Our experimental research and through literature search has revealed that poly-herbal preparations will be more useful to certain medical problem like diabetes mellitus than target specific single molecule because diabetes is a medical problem itself as well as is also the chief pre-pondering factor for various other co-morbidities condition. The poly-herbal phyto constituents are diverse in their chemistry and so are their phyto-pharmaceutical benefits. Target specific drug can at best only address one of the etiology of the disease and not the associated co-morbidity conditions. Whereas the polyherbal drugs due to the diverse chemistry are likely to address spectrum of medical problems and hence are bound to be superior over target specific single molecule based drug. Details are presented in the article.

KEYWORDS: Polyherbal drugs, co-morbidities in diabetes, alpha glucosidase, alpha amylase.

INTRODUCTION

Diabetes mellitus can also be defined both from the symptom per see as well as from the mechanism that is involved in the pathology of the disease. Both, the pathology of the disease as well as the symptoms are inseparable in the case of diabetes. In strict sense, the etiology that is responsible for the diabetes mellitus limits itself to the high glucose burden in the blood but the symptom i.e., the high glucose burden in the blood opens the entry point for various comorbidities that are likely to spread the inimical threat to the life of the host.[1,2,3,4]

The drugs that are available today for the management of diabetes include alpha amylase and alpha glucosidase inhibitors (delay the carbohydrate metabolism and subsequent conversion of glucose) insulin etc.[5,6]

Most of the conventional drugs used in the allopathic system of medicine are single molecule driven with high target specificity. Although such drugs are useful in spontaneous reduction of glucose burden in the blood, but the remedies with broad spectrum benefits (poly herbal therapy) that are directly and indirectly connected to both the symptom of the disease as well as the etio-pathology alone can offer 'near permanent' solution to the emerging medical threat to humanity called diabetes mellitus.

Comorbidities condition in diabetes mellitus.[7,8,9]

S. no.	As classified by International classification of diseases ICD- 9
1	Myocardial infarction
2	Stroke (ischemic/hemorrhagic), nonfatal
3	Congestive heart failure
4	Stable angina
5	Transient ischemic attack
6	Peripheral vascular disease
7	Nephropathy (including ESRD)
8	Peripheral edema
9	Fracture
10	Late-stage diabetic retinopathy/ clinically significant macular edema
11	Blindness in one eye/in two eyes
12	Gastrointestinal event
13	Urinary tract infection
14	Genital infections (non-UTI)
15	Genital disorders
16	Ulcer of the skin

Therapeutic scope from herbal resource

Herbs in toto or the extracts from many select plants are proven to have multi-various therapeutic benefits starting from relieving the symptom to correcting the entire pathology to provide wellness to the body and mind.[10,11,12,13]

The herbal drugs in general are composed of innumerable phyto-active constituents from either a single plant or many plants that exist in the formulation as complex constituent; offer individualized and or synergistic benefit.

Because of the complex nature of the phyto-actives in herbal preparations, identifying the exact molecule (s) responsible for the pharmacologic effect is difficult to establish. However such difficulty in no way shall limit the obvious and undeniable therapeutic benefit of herbal drugs in general.

Allopathic drugs often target the etiopathology of the disease or target the symptom and thereby offer relief to the patient. Such compartmentalized/fragmented treatment approach followed in allopathic system of medicine although may offer spontaneous relief but seldom do any course correction that are necessary in the host system to alleviate the patient permanently from the medical problem.

From the premise of how the allopathic system of medicine and its drugs are used to address the medical problems and if we compare the above with the herbal preparations, none of the herbal preparations can be called as 'drug' in strict sense. However most of the herbal drugs are undeniably effective as proved eloquently by both the treating clinician and the patient which concur and vouch the significance of phyto-pharmacy.

India is a land of immortal tradition, ancient civilization, living philosophy and divine healing practices such as Ayurveda, Siddha, Yoga and Naturopathy. The ancient spiritual scholars of India- Siddhars and Rishis through their direct and continuous interaction with divine-ship decoded the medicinal values of several herbs, herbal concoctions, herbo-mineral-metal preparations for the treatment of almost all diseases that daunts human health, wellness and happiness.

Ancient Siddhars have further performed several miraculous feats and have lived for several thousands of years by following traditional remedies and well-disciplined lifestyle.

Diabetes- Two Headed Janus

Diabetes is not only a dangerous killer disease from the medical definition that makes our blood sweet with high level of glucose but is also tricky in many ways.

The etiology of the disease results only in one prominent symptom- hyperglycemia, but the symptom opens the flood gate for various medical problems to invade, encounter and excavate our health and happiness. Therefore the management of diabetes mellitus must be broad based and must include and involve the human system entirely and completely.

Diabetes mellitus can be called as Two Headed Janus because both the metabolic disorder that cause problem as well as the consequence symptom are equally harmful and work like two edged sword that can cut from both ends.

The uniqueness of DCOD for diabetes mellitus

DCOD is a proprietary Siddha formulation of Dr. JRK's Research & Pharmaceuticals. The formulation is comprised of 8 herbs such as

Nilavembu (Andrographis paniculata)

Naval (Syzygium cumini)

Seenthil (Tinospora cordifolia)
Pagal (Momordica charantia)
Koraikizhangu (Cyperus rotundus)
Sukku (Zingiber officinale)
Milaghu (Piper nigrum)
Adathodai (Adhatoda vasica)

All the above herbs used in DCOD are well documented in the ancient scriptures of Siddha and Ayurveda with detailed and elaborate narration on their therapeutic benefits.

Surprise and serendipity - Clinical trial of DCOD

Dr. JRK's Research and Pharmaceuticals has conducted an extensive clinical trial of DCOD in both patients with diabetes mellitus especially those who show high level of post prandial blood sugar and also those non-diabetic patients who suffer from fever and elevated body temperature due to idiopathic etiology.

The clinical trial finding has clearly shown that DCOD significantly reduced the post prandial blood sugar and offered wellness among those patients who used DCOD.

The pre-clinical laboratory evaluation of DCOD has revealed that DCOD collectively and each individual herb used in the formulation showed anti-diabetic effects such as sugar assimilation inhibition by yeast cells, alpha amylase and alpha glucosidase inhibition and finally the combination also exhibited inhibition of myeloperoxidase enzyme that cascades various inflammatory reactions in diabetic patients.

Further studies have proved that DCOD also boosts the phagocyte mediated immunity invitro indicating that DCOD would augur and augment the primary immune surveillance of the host.

In diabetic patients the phagocyte mediated immunity is quite defective and the higher expression of myeloperoxidase enzyme known to trigger various inflammatory events that may prelude degenerative complications.

Sugar assimilation by *Candida albicans*

Table 1 & 2- Macroscopic and microscopic characteristics of *Candida albicans* with reference to sugar uptake

Table- 1.

YEGM media	YEM without glucose	SDA	SDA with NIKU	SDA with Miglitol
Rich, mucoid colony	Transparent, weak, button like colony	Rich, extended mucoid colony	Sparse colony, appear weak	Improvised colony with transparent appearance

Table- 2:

0.2% glucose solution	0.2% glucose solution+1 mg/ml DCOD	0.2% glucose solution + 1mg/ml Miglitol
1. Gorged cells with well spread and rich cytoplasmic inclusions 2. Even and uniformly sized cells 3. Abundant blastospore all around the cells	1. Miniaturized cells 2. Condensed cellular inclusions showing improverished state of the cells 3. Increased vascular space	1.Miniaturized sparse cells 2. Highly condensed cellular inclusions showing impoverished sate of the cells 3. Increased vacuolar space

Table-3: Sugar assimilation inhibition assay of DCOD and individual herbs.

S. no.	Name of test material	Extent of inhibition of sugar uptake
1	Andrographis paniculata	-
2	Syzygium cumini	-
3	Tinospora cordifolia	++
4	Momordica charantia	++
5	Cyperus rotundus	+++
6	Zingiber officinale	-
7	Piper nigrum	-
8	Adhatoda vasica	++
9	Miglitol	+++
10	DCOD	++

+++ Excellent inhibition
++ Moderate inhibition
- No inhibition

Table 4: Inhibition of alpha amylase and alpha-Glucosidase.

S. no.	Sample details	IC 50 values	
		Alpha amylase	Alpha glucosidase
1	Andrographis paniculata	4 mg/ml	8 mg/ml
2.	Cyperus rotundus	2 mg/ml	3 mg/ml
3.	Justica adhatoda/ Adhatoda vasica	2 mg/ml	2 mg/ml
4.	Tinospora cordifolia	5 mg/ml	6 mg/ml
5.	Zingiber officinalae	10 mg/ml	13 mg/ml
6.	Piper nigrum	8 mg/ml	7 mg/ml
7.	Syzygium cumini	5 mg/ml	8 mg/ml
8.	Momordica charantia	6 mg/ml	6 mg/ml
9.	DCOD	0.4 mg/ml	0.6 mg/ml

Myeloperoxidase (MPO) assay

In Diabetic patients MPO may cause insulin inactivation due to the infiltration of the circulating neutrophil concentrations and that may accumulate in adipose tissues. Such situation may also lead to insulin sensitivity. The diabetic patients also known to suffer from MPO co-morbidities like atherosclerosis etc. Therefore the anti-diabetic drug if possess activity against myeloperoxidase will have very significant therapeutic value.

Table- 5: Concentration vis-à-vis time in inhibiting enzyme activity.

Time in Seconds	20 mg/ml	Time in Seconds	30 mg/ml
	% inhibition		% inhibition
0	-	0	-
20	11	20	17
40	15	40	19
60	20	60	24
80	19	80	22
100	21	100	30
120	19	120	29
140	23	140	26
180	20	180	27
200	22	200	25

Phagocytes play an important role in our primary immune surveillance.

In diabetes, due to the increased glucose burden, the phagocyte mediated immunity is in a compromise state. Our pre-clinical evaluation has shown that DCOD is very effective in boosting the phagocyte against wide spectrum of antigen/pathogen.

Table 6: Effect of DCOD on Phagocytosis.

Test products	Bacteria		Yeast		Carbon Particles	
	Phagocytic index	% Difference	Yeast	% Difference	Carbon particles	% Difference
DCOD	10	150	8	700	40	900
Untreated control	4	-	1	-	4	-

Table-7: DCOD in diabetes- Clinical trial findings.

Assesment Period In Days	Control Group		DCOD Treated Group	
	Mean+ Sd		Mean+ Sd	
	% ↓ in FBS	% ↓ in PPBS	% ↓ in FBS	% ↓ in PPBS
Day 1	3.65 ± 5.6	-0.57 ± 7.76	2.51 ± 4.77	2.39± 4.86
Day 3	2.66 ± 7.78	2.07 ± 6.19	-1.85 ± 7.64	4.58±3.57
Day 6	0.25 ± 9.56	-3.23 ± 7.68	-1.98 ± 9.36	5.95±2.42
Day 7	0.29 ± 7.06	-1.19 ± 6.06	2.25 ± 6.46	7.53±1.83

Mean Percentage reduction in blood sugar levels: (N= Treatment 12, Control 12)

Table 8: Comparison on percentage reduction in
a) Fasting blood sugar levels

Days	Control group (N=12) Mean ± SD	Test group (DCOD) (N=12) Mean ± SD	P value	Significance
ON DAY 1	3.65 ± 5.6	2.51 ± 4.77	P > 0.05	Not significant
ON DAY 3	2.66 ± 7.78	-1.85 ± 7.64	P > 0.05	Not significant
ON DAY 6	0.25 ± 9.56	-1.98 ± 9.36	P > 0.05	Not significant
ON DAY 7	0.29 ± 7.06	2.25 ± 6.46	P > 0.05	Not significant

b) Post prandial blood sugar levels

Days	Control group (N=12) Mean ± SD	Test group (DCOD) (N=12) Mean ± SD	P value	Significance
ON DAY 1	-0.57 ± 7.76	2.39± 4.86	P <0.05	Significant
ON DAY 3	2.07 ± 6.19	4.58±3.57	P <0.05	Significant
ON DAY 6	-3.23 ± 7.68	5.95±2.42	P<0.05	Significant
ON DAY 7	-1.19 ± 6.06	7.53±1.83	P< 0.05	Significant

Antipyretic effect of DCOD
Table 9: Control Group –Acetaminophen (N=10): Axillary Body Temperature.

Time point	Body temperature in Fahrenheit/In 10 patients									
	1	2	3	4	5	6	7	8	9	10
0 hour (Pre dose)	103.0	101.0	100.5	102.4	101.6	101.1	100.6	102.8	103.1	102.6
30 min post dose	102.1	100.2	94.6	101.6	100.5	100.0	99.2	101.9	101.7	101.9
1 hour post dose	101.0	98.5	94.5	100.5	99.9	98.6	95.9	100.1	100.5	99.0
Fever recurrence after dosing (hour)	4	5	8	6	8	8	9	5	5	7

Table 10: TEST GROUP (DCOD) (n=24): Axillary Body temperature.

Time point	Body temperature in Fahrenheit / In 12 patients											
	1	2	3	4	5	6	7	8	9	10	11	12
0 hour (Pre dose)	102.2	100.6	101.0	103.0	101.8	100.2	101.8	100.5	101.9	102.0	101.5	100.1
30 min post dose	102.0	100.0	100.2	104.0	101	99.8	101.1	100.0	101.1	102.5	101.1	100.8
1 hour post dose	101.2	99.5	99.8	103.5	100.5	99.0	100.9	99.2	100.2	101.6	100.0	99.9
Fever recurrence after dosing (hour)	4	6	6	3	6	6	6	6	5	3	5	6

Time point	Body temperature in Fahrenheit/ In 12 patients											
	13	14	15	16	17	18	19	20	21	22	23	24
0 hour (Pre dose)	102.7	102.0	100.5	100.9	101.1	101.6	101.0	100.2	100.2	102.5	100.7	101.7
30 min post dose	101.6	101.5	100	100.4	101.5	100.8	100.1	99.6	99.6	102.5	99.8	101.0
1 hour post dose	101	100.4	99.2	99.8	100.4	100.0	98.8	98.9	99.0	101.3	98.7	100.5
Fever recurrence after dosing (hour)	6	4	5	6	3	5	6	6	5	3	6	4

Table 11: CONTROL GROUP- Paracetamol (Mean Percentage reduction in body temperature): (n=10).

Time	Mean± SD
	% ↓ in Body temperature
At 30 min.	1.48 ± 1.56
At 1 hour	2.97 ± 1.37

Table 12: TEST GROUP: DCOD: (Mean Percentage reduction in body temperature): (n=24).

Time	Mean± SD
	% ↓ in Body temperature
At 30 min.	0.42 ± 0.52
At 1 hour	1.17 ± 0.56

Table 13: Comparison of percentage reduction in body temperature.

Time	Control group-paracetamol (N=10) Mean ± SD	Test group (DCOD) (N=24) Mean ± SD	P value	Significance
At 30 minutes	1.48 ± 1.56	0.42 ± 0.52	P<0.01	Significant
At 1 hour	2.97 ± 1.37	1.17 ± 0.56	P<0.001	Significant

The evolutionary link between body temperature and hunger

The evolution of vertebrates starting from strict oviparity to marsupial to the modern day mammals arranged in the strata viz. prototheria, metatheria and eutheria which clearly shows that the body temperature and metabolism are closely linked with each other.

In simple description, the elevated body temperature is bound to induce greater metabolism and which in turn may cause the symptom called hunger or appetite in order to replenish the much needed energy source.[14,15]

The homoeothermic (cold blooded) animals like Pisces, Amphibian and Reptilian can adapt to different temperature zones by shifting their body temperature accordingly to that of the environment. Such an adaptation helps the animal to reduce its respiration, food demand and body rhythm with great ease and resistance.[16]

Many species of fishes, members of amphibians and reptiles can afford to stay for months to years, without food and water.

Whereas the poikilothermic (warm blooded) animals cannot shift their body temperature according to the temperature of the environment in which they live. And hence the metabolic rate in these animals are quite high as they needs to continuously breakdown the food to upkeep the energy level to maintain the body temperature. The body temperature in a broader sense in warm blooded animals triggers appetite and thirst.[16]

Diabetic patients suffer from pseudo-hunger due to insufficient glucose available to the cell despite blood having high glucose. Due to the above situation the cells are always starved and that in turn trigger hunger in the patient.[17]

Due to pseudo hunger the patients are compelled to consume more food and that would results in further spiraling of blood glucose. The diabetic medication must therefore delay the conversion of complex carbohydrate to glucose, must boosts the immunity, must minimize the enzymatic expression of myeloperoxidase and retard body temperature dependent hunger.

No single allopathic drug can offer all the above therapeutic benefits. Even if the medication contains multi-various therapeutic benefits from the allopathic system of medicine, the target specificity of all such drugs with curative approach may not yield great reward in the case of diabetes mellitus because the etio-pathology of diabetes mellitus is a disorder that can be managed and cannot be corrected.

DCOD offers wide spectrum of therapeutic benefits sourced from 8 different herbs with proven therapeutic value. The synergistic benefit of the herbal drugs cannot be achieved from allopathic drugs. Further the herbal drug therapy always aims at correcting the cybernetics of human system which includes both body and mind.

To heal the body, AYUSH always adopt holistic ways of healing where the disease symptom, the underlying pathology, the lifestyle, diet regimen etc are inevitably included in the therapy. Further the evolution and eco-genomics of the human body and mind are also included in the treatment of AYUSH.[18,19]

DCOD is formulated with all essentials and fundamentals of tridosha principle of Ayurveda and Siddha, the evolutionary aspect of hunger, to address the paradigm of blood glucose burden.

DCOD doesn't approach diabetes mellitus as just a disease but it takes the patient's body and mind in totality and attempts to correct every micro event(s) singularly and collectively contributes to the disease pathology. Such remarkable, complete, body-mind involved treatment approach is available only in Ayurveda and Siddha.

DCOD is a scientifically proven, clinically tested herbal formulation which has taken 'its body-mind and soul' from Ayurveda and Siddha. DCOD as a supplement can offer medical, health and wellness benefits to diabetic patients.

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