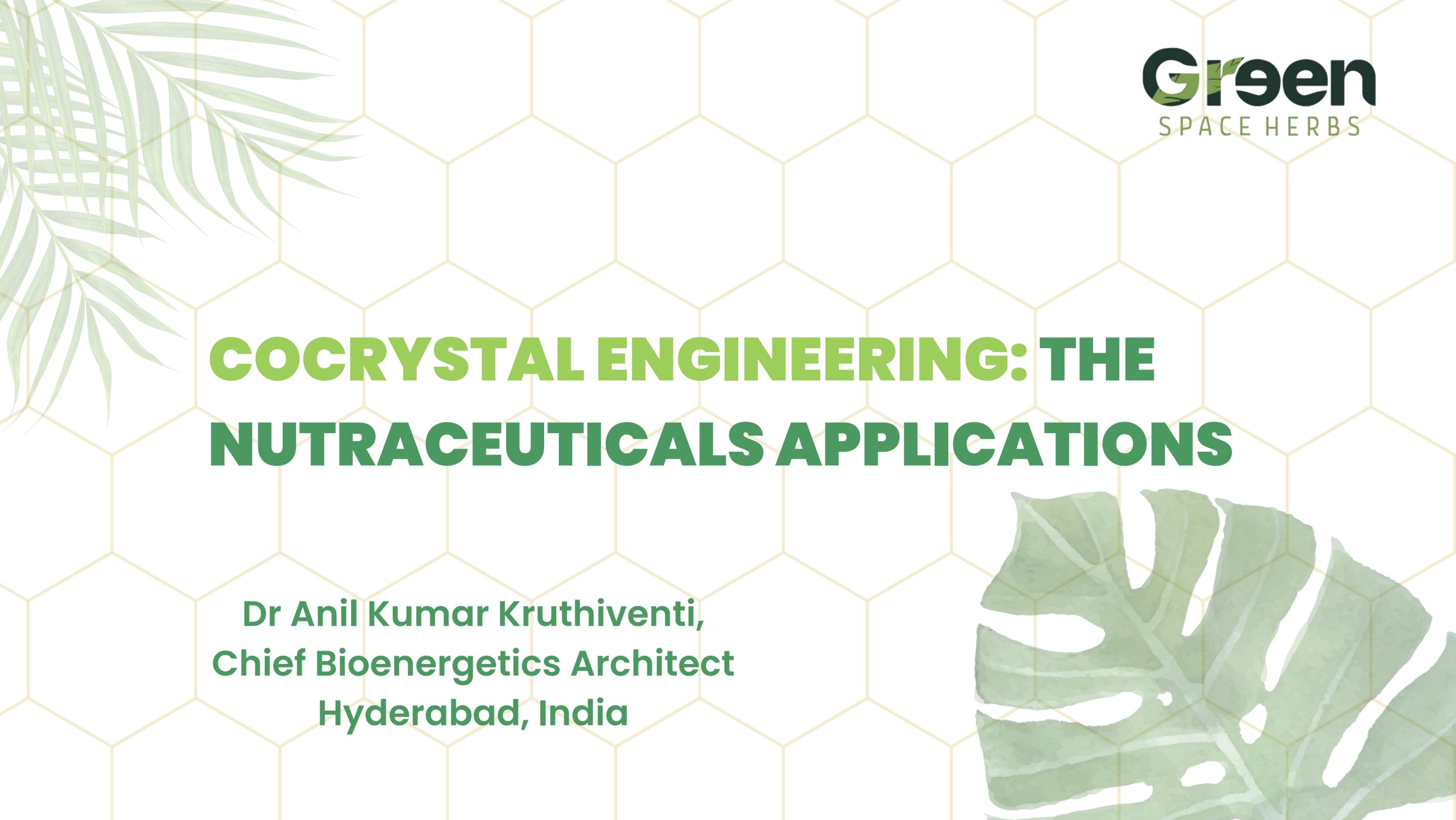


COCRYSTAL ENGINEERING: THE NUTRACEUTICALS APPLICATIONS

**Dr Anil Kumar Kruthiventi,
Chief Bioenergetics Architect
Hyderabad, India**



CAST OF CONTENTS

Nutraceuticals Unmet need



Crystal Engineering as a viable formulation strategy



Challenges in Nutraceutical Product Development



Way forward

LIFE FEW DECADES BACK AND TODAY...

Living long

Dying Short

EARLIER



Living Short

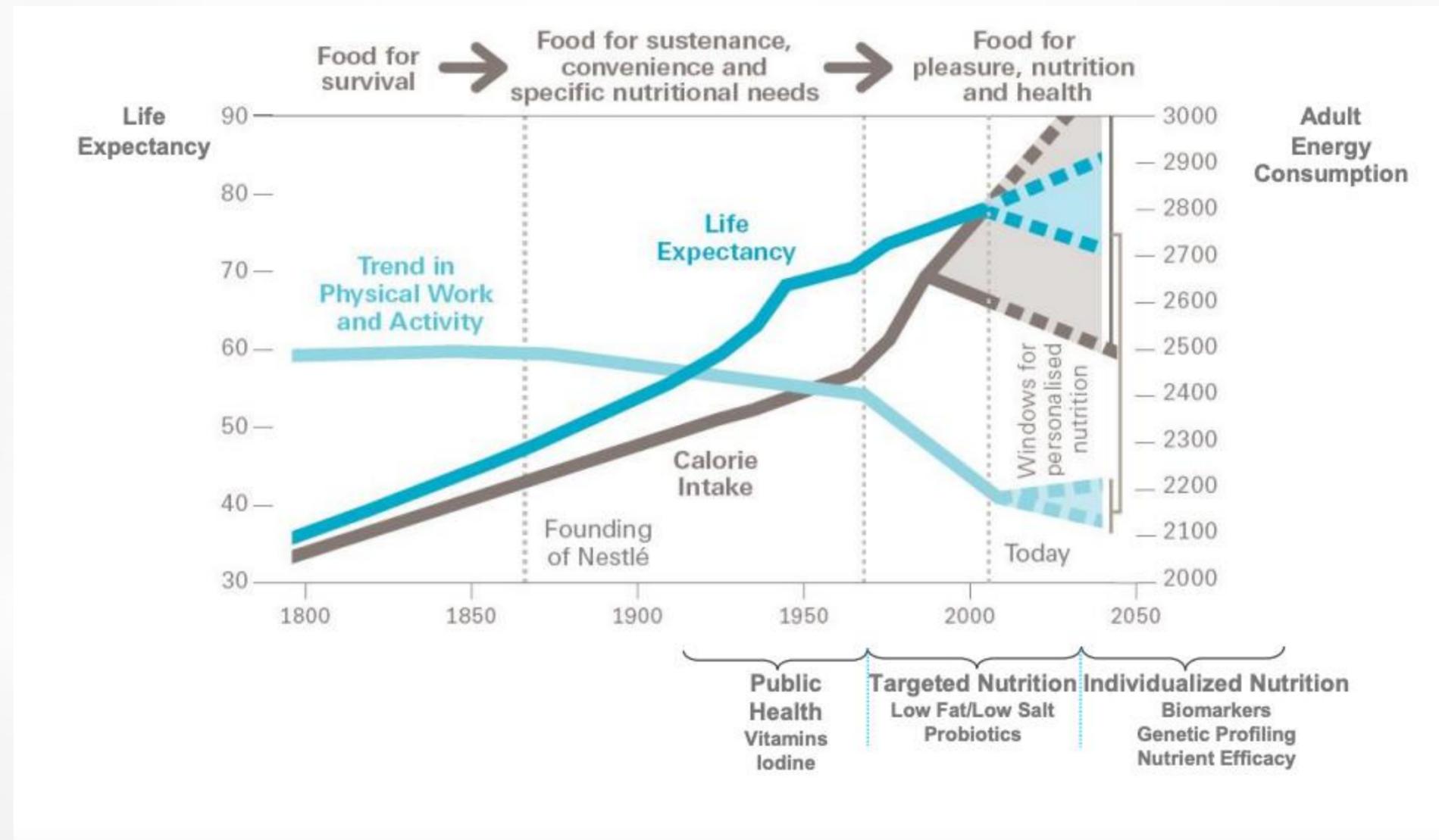
Dying Long

TODAY



Presently humans are Hrasva and are having Mandaagni and Heenasatva. Drugs too are of Heenaveerya, because Dravyasangrahana, Kala, Vidhi and Bhumi are changing due to increase in population, reduced vegetation and environmental pollution. Hence, Anupana has an important role in increasing Jataragni, Rogibala and Aushadabala.

Ref: MVR Wijayanthamala et al., Int. J. Res. Ayurveda Pharm., 7, Jan – Feb 2016.



Challenges of **Nutraceutical** **Product Development**



Nutraceuticals

Daily intake – Supplement (Anupana)
Cost becomes an important factor (RM selection and process)

Quantities required for perceivable effect usually Larger
---Taste Masking, Honeytose®, EGCG

Known for Preventive Care or as Adjuvants --- Design of a suitable clinical trial ??? Sustentials® Curcumin

Contains many active ingredients (For example: Multivitamin has 50 actives with 2-8 excipients) – Cost, Compatibility and Convenience, Traceability of ingredients, Sustentials®Curcumin & Honeytose®

Formulation Challenges (Tableting/ compressibility) – Most compounds are hygroscopic Drying poses a major challenge

Distribution strategy – Can be brought through various outlets – targeting by demographics and a specific population must

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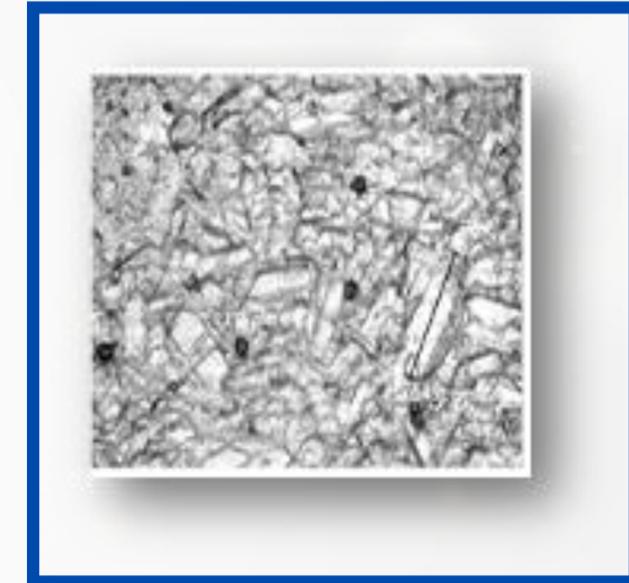
Prescription route, hence can have focussed marketing strategy

IMPROVING TASTE THROUGH **MOLECULAR COMPLEX**

- Honeytose® has 0.7 times the sweetness of Sucrose, and has a bland upfront taste profile
- Honeytose® complexed with an Oligosaccharide overcomes this bland upfront taste and provides an upfront sweetness, along with enhancement of sweetness profile, making it equal to Sucrose
- Individual sugar ingredient take long time to crystallize and absorb moisture over the time.
- Modified sugar overcome both hygroscopicity and crystallization problem.



Spray Dried sample

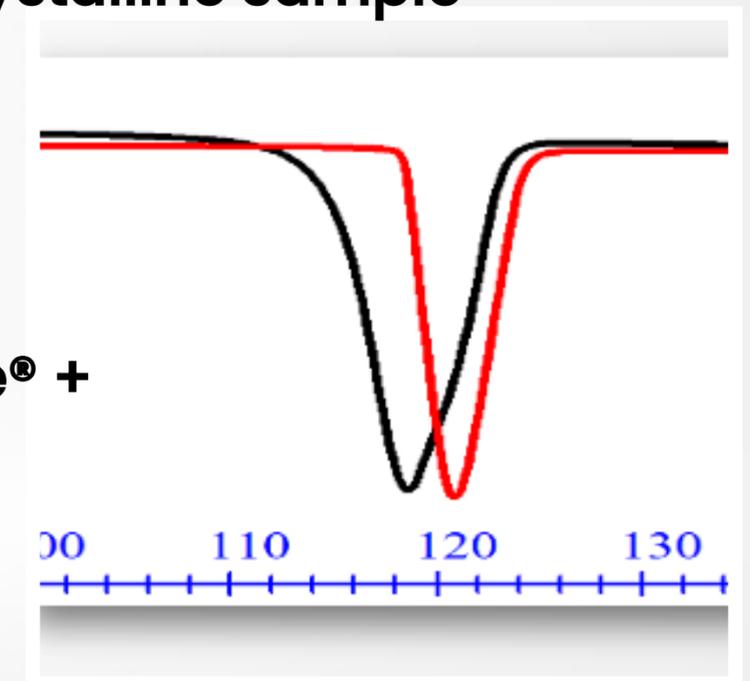


Crystalline sample



Free Flowing formulated Low Calorie Sweetener

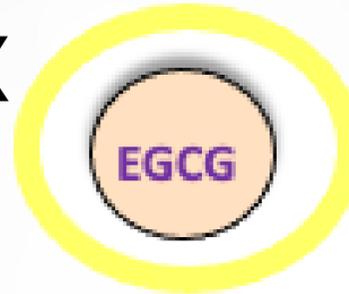
Honeytose® +



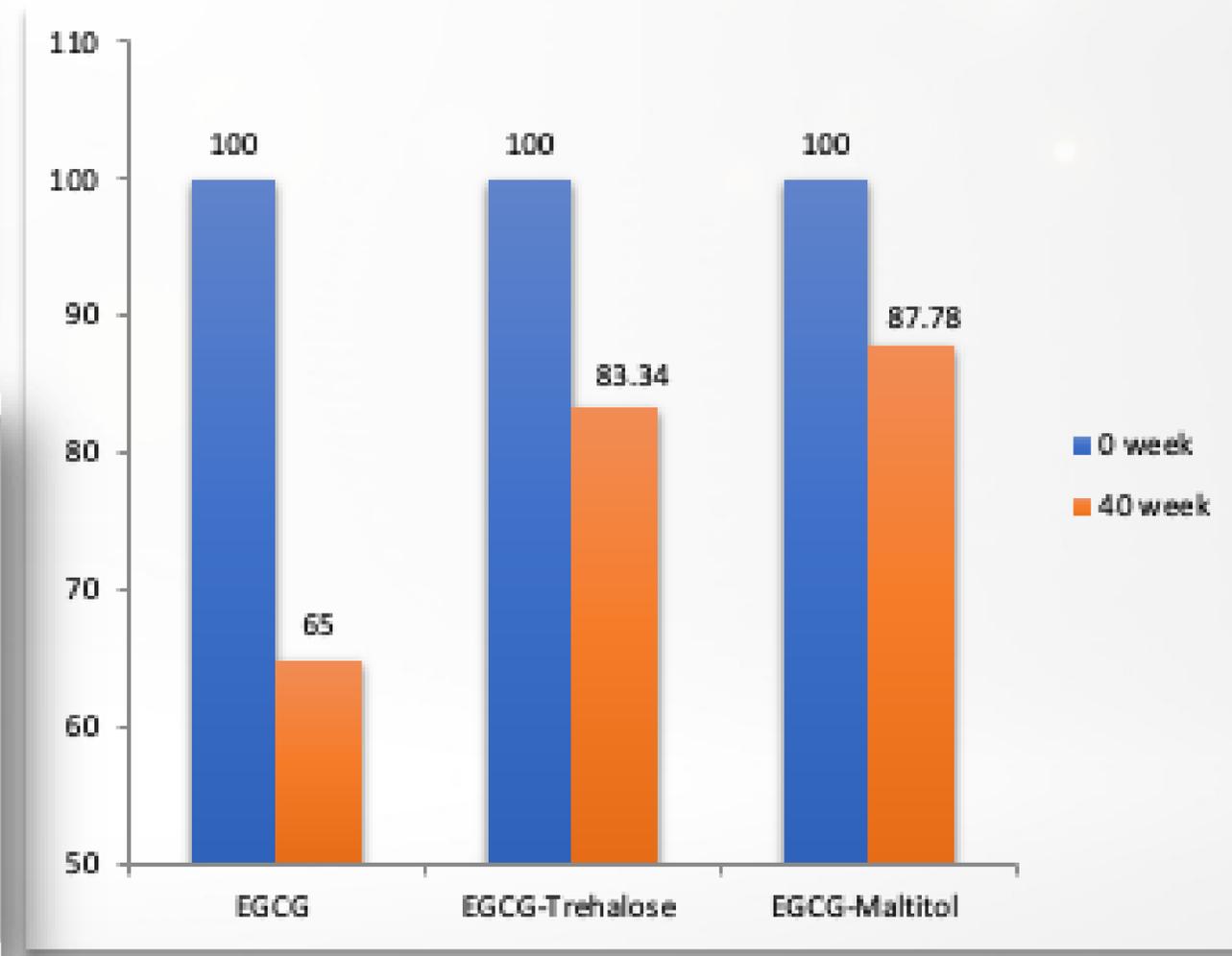
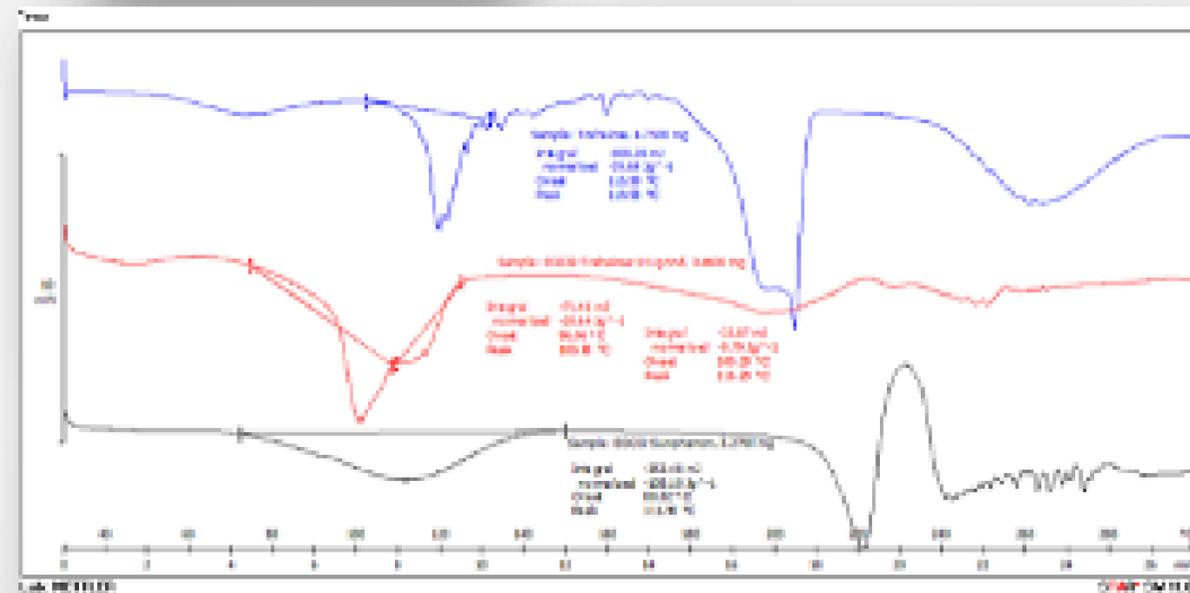
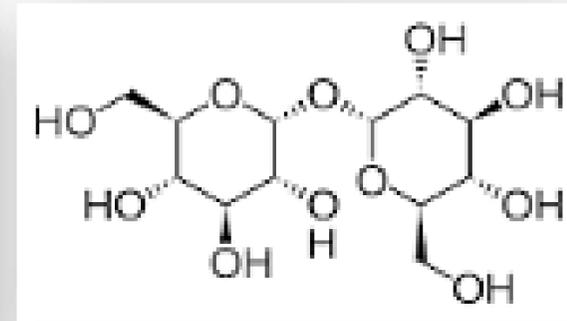
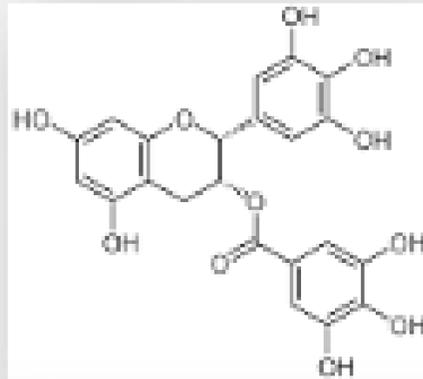
BITTERNESS MASKING USING MOLECULAR

Tastier and
better
Organoleptic
Properties

COMPLEX



Preventing
EGCG from
Degradation



Solid Solution of EGCG and Trehalose resulted in a stable and bitterness masked Green Tea Active

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Demand and Design of a Clinical Trial

- During the last 10 years or so, the decision whether to opt for a clinical trial in order to substantiate claimed health effects for a nutraceutical or food supplement product has gained strategic importance.
- Biggest driver currently compelling companies to conduct research on their products is the fact that changing regulations, particularly the relatively recent Health Claims Regulation, require manufacturers to invest in clinical trials for health claim applications if they wish to use a proprietary health claim.

- The challenges faced by researchers when designing and conducting clinical trials on nutraceuticals are manifold. Nutraceutical testing is practically a science in itself
- Health effects of nutraceuticals are often rather small and can easily be affected by heterogeneity of subjects and environmental factors. Effects may be jeopardized by confounding factors such as eating, smoking, exercise habits, etc., and they need to be reported by trial participants in diaries that should be implemented in the study setup.
- Nutraceuticals as ingredients of conventional or functional foods are provided in a delivery form very different from drugs choice of the study population
- The selection of inclusion and exclusion criteria is of utmost importance, as the condition tested may not be a disease

Inter subject Variability a major Challenge



A randomized, open label, single centre, one period, single dose, four arm bioavailability study in 28 healthy human adult male subjects, under fasting condition

Table 1: Summary of pharmacokinetic results for total curcuminoids (Group B Vs Group A)

Parameter	AUC(0-t)	AUC(0-inf)	Cmax
Least Square Mean (LSM)			
Test - B	2.7853	3.0925	2.1993
Reference - A	0.4792	2.0927	0.5240
Geometric LSM			
Test - B	16.21	22.03	9.02
Reference - A	1.61	8.11	1.69
LSM Difference			
	2.3062	0.9999	1.6753
SE Difference			
	1.1451	1.3770	0.8928
p-value (Difference)			
	0.0748	0.4951	0.0933
Geometric LSM Ratio (%)			
Test - B / Reference - A (%)	1003.61	271.79	534.03
90% Confidence Interval (%)			
Test - B vs. Reference - A			
Lower Confidence Limit	123.01	18.71	103.94
Upper Confidence Limit	8188.35	3947.26	2743.72
Inter-Subject Variability (CV %)			
	589.38	402.33	279.15
Power (%)			
	3.43	3.12	3.75

SE: Standard Error

Figure 1: Mean Concentration of total curcuminoids

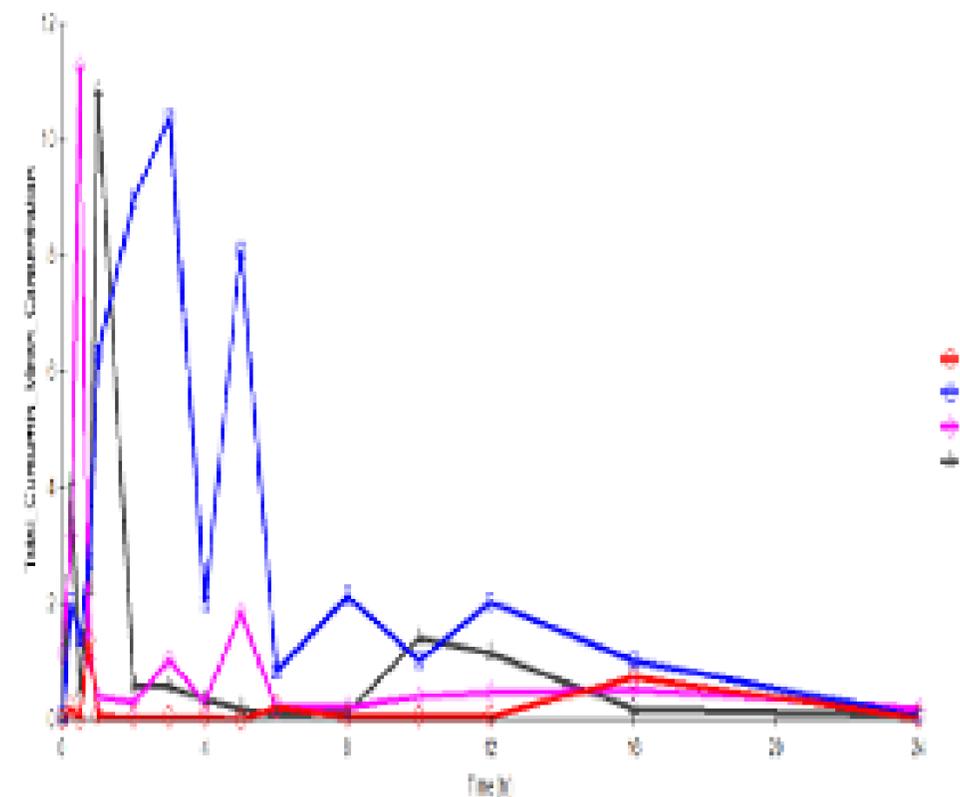


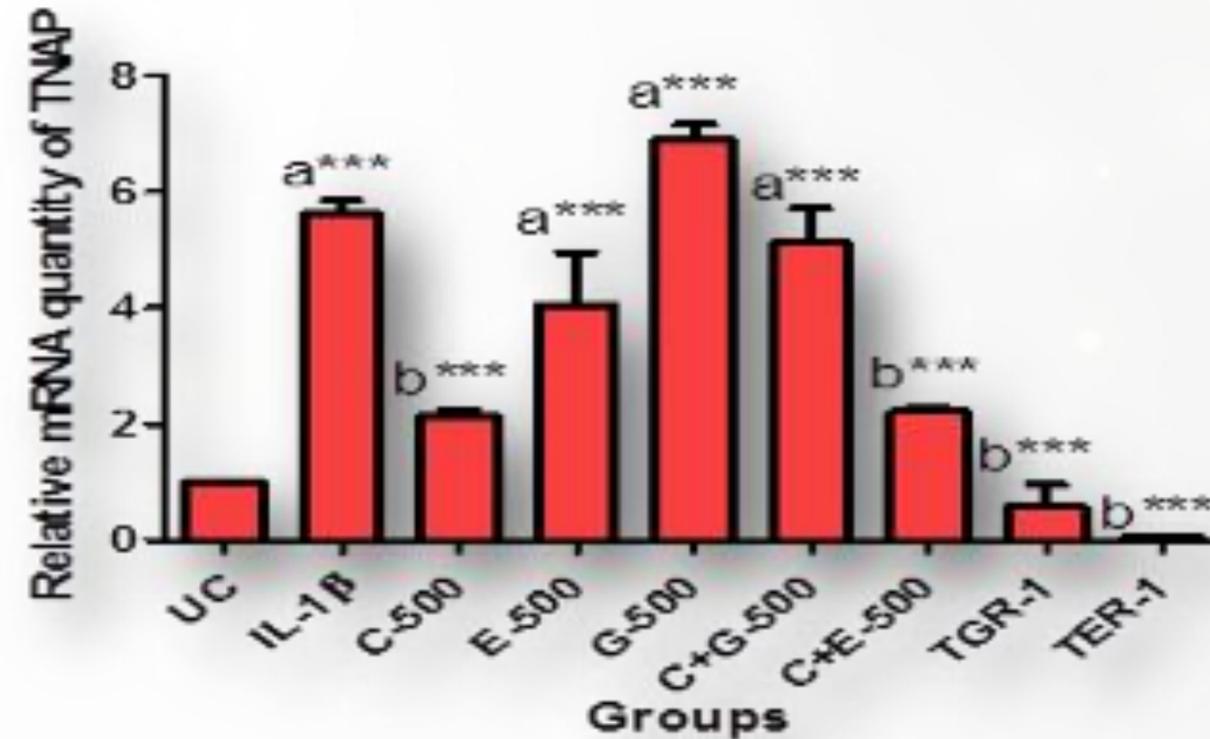
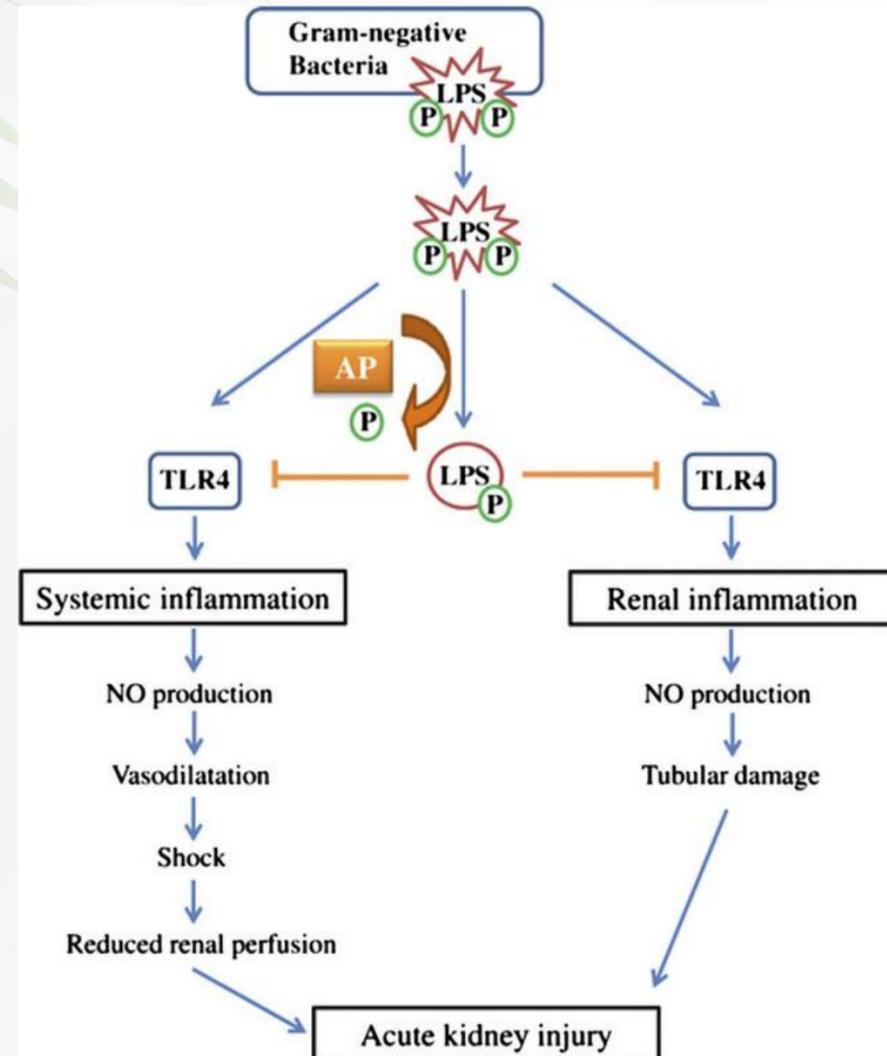
Figure 1: Concentration of Total Curcuminoids in human plasma at different time intervals after oral administration of test formulations

What it means is that – In standard approach the cohort size is significantly increased.

Alternately what we at GreenSpace Herbs are targeting is higher absorption and longer retention formulations.

Nutrigenomics study of Nutraceutical Formulations

TNAP (tissue non-specific alkaline phosphatase) is expressed in human hepatocytes and bile acids increase its activity and secretion in the bile. In addition, TNAP can be delivered from the liver in the serum, where TNAP levels are measured as a marker of cholestasis of major clinical relevance and hepatic dysfunctions. (Esteve et al., 2016). We have used TNAP as a marker to reveal tissue inflammation and metabolic stress.



UC-untreated control; LPS-Lipopolysaccharide, C-curcumin, G-Green tea extract; E-EGCG; TER & TGR- molecular complex; C+G – curcumin and green tea physical mixture; C+E – curcumin and EGCG physical mixture.

We found that molecular complexes have effectively lowered the TNAP expression as compared to individual compounds and even the simple mixture. Among all the samples and molecular complexes, TER significantly down-regulated TNAP expression at 1µg/ml, indicating strong anti-inflammatory potential probably due to synergistic action and enhanced bioavailability.

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LOW COST AS A MAJOR DRIVER IN **PRODUCT DEVELOPMENT**

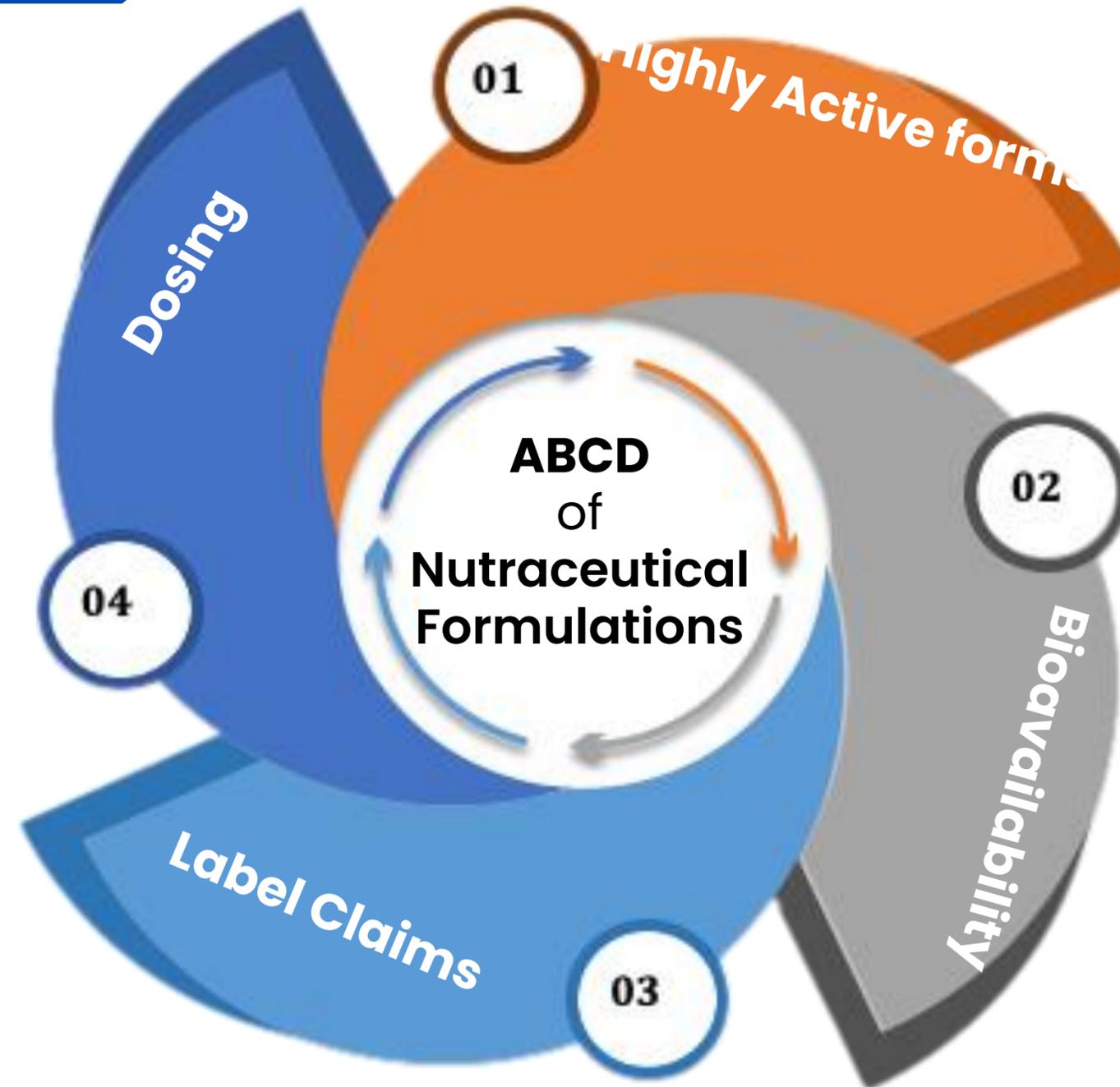


- Honeytose[®] + Oligo- A gave good flow ability and enhanced the sweetness, selection of the Oligo for scale-up was based on the cost availability of the raw materials, hence, the Oligo chosen for final product is different.
- Curcumin: EGCG was found to be better than Curcuminoids : Green Tea Extract, both from the Physiochemical and Biochemical parameters, but based on the cost of sourcing pure naturals, the later was taken forward for commercialization
- This poses challenges both from the perspective of QA (Quality Assurance) and regulatory aspects

Though FSSAI, EU and FDA are providing impetus for building the Nutraceutical Industry, they are pushing the industry, and brand owners to comply with stricter regulations. It is difficult to achieve pharmaceutical standards, for Nutra-ingredients. The nutrition industry needs to give equal importance to research on physicochemical properties and pharmacodynamic properties of active ingredients and excipients as Pharma Industries had given on developing scientific evidence for Active Pharmaceutical ingredients.

ABCD of Nutraceutical Supplements

Biomimetic Dosing to ensure high efficacy and designed action



Design Active forms and 'Synergistic' combos.

Pre-Clinical and Clinical Trials with clear endpoints

Platform technology of Solid Form Formulations for developing highly bioavailable formulations.

This effectively is ABCDEF of Nutraceuticals – Active, Bioavailable, Clinically proven, suitably Dosed, Effective Formulations

Acknowledgements

Research and BD Teams at:

- Sri Sathya Sai Institute of Higher Learning, Prashanti Nilayam, AP, India
- Dr Reddy's Institute of Life Sciences, Hyderabad
- Tata Chemicals Ltd., Innovation Centre, Pune
- Nagarjuna Fertilizers and Chemicals Ltd., Research Centre, Hyderabad

The text "THANK YOU" is centered in a large, bold, blue font. It is flanked by two solid blue horizontal bars with rounded ends, one on the left and one on the right. The background of the slide is a light, faded image of a desk with a laptop, a pen, glasses, and a plant leaf.

THANK YOU