Innovation of BioCurcuminoids and its Pharmacokinetic Study of CurcuminAura™ with regular curcuminoids

ABSTRACT

Curcuminoidsare naturally occurring phytocompound extracted from the turmeric rhizome ***Curcuma longa***, a member of the ginger (Zingiberaceae) family. Despite its long history and well-tolerated nature, curcumin has arguably not yet realised its full therapeutic potential in the prevention and treatment of human disease. This has in part been due to concerns regarding quality control (e.g. safety, purity, and other chemical attributes), poor solubility and poor absorption in the free form in the GI Tract and its rapid biotransformation to inactive metabolites thus limiting its utility as a health promoting agent and dietary supplement. This Study aims at improving the bioavailability and absorption of regular marketed curcumin 95% by formulating Bio-Curcumin trademark product

"CurcuminAura™ which contains sunflower lecithin, a powerful ingredient. Lecithin can effectively encapsulate active ingredients and promote better bioavailability and thus increase absorption, thus making it more potent in the market.

The objective of this study is to evaluate the Comparative Pharmacokinetic Study of **CurcuminAura™** with Marketed Curcumin 95.0%, in Sprague Dawley Rats by Oral Route. The study design consisted of 2 groups, each containing 4 rats per sex per group. Rats of G1, and G3 groups received dose of **CurcuminAura™, and** Curcumin 95.0% respectively by oral route. The dose volume was maintained at 10 ml/kg body weight for oral route. The dose administration was done by oral gavage.

Post dose administration, blood samples were collected from retro-orbital sinuses, under isofluorane anaesthesia at different time points. Each group, animals were divided in two sets and blood samples were collected at 30 mins, 2 and 4 hrs time points and 1, 3 and 6 hrs time points. Blank plasma was collected at 0 mins from male and female rats. Approximately 0.2 to 0.3 ml blood was collected in vials containing 1% EDTA as an anticoagulant followed by separation of plasma. Samples were stored at -80^0C and then taken for analysis. **CurcuminAura™** is standardized to 60.9% Total curcuminoids by HPLC compared to marked regular curcumin 95%, formulated to enhance bioavailability of curcuminoids. The comparison studies evident that **CurcuminAura™** has 3.8 times higher bioavailability than the reference standard. Also, in this study it is shown that the maximum absorption happens in the time line 3 hrs after feeding the drug.

***Keywords**: **CurcuminAura™, Curcumin**, Zingiberaceae, Sunflower lecithin, Pharmacokinetics, Bioavailability.*

INTRODUCTION:

With about 80 species, Curcuma is one of the larger genera in the *Zingiberaceae* family (20). It is extensively spread in Southeast Asia, Papua New Guinea, North Australia, South China, and India in the tropics. Curcuma is a rhizomatous herbaceous plant with leaf blades, leafy shoots, and

subterranean portions. The following characteristics make Curcuma easily distinguished from other *Zingiberaceae* genera: blooms borne in cincinni, subtended by bracteoles and bracts; sterile and variably colored coma bracts.

Curcuma was assigned to the Hedychieae tribe in the Burtt & Smith (7) 1972 classification, which was widely recognized for a long time. This system divided the *Zingiberaceae* family into four tribes. A new system was put forth by Kress et al. in 2002 (19) Curcuma is categorized under the tribes out of the six tribes and four subfamilies of *Zingiberaceae.*

Curcuma was divided into three sections by Baker (3): Section Hitcheniopsis (characterized by autumnal spikes from the center of the tuft of leaves; bracts are very obtuse, adnate at the sides and spreading at the tip); Section Exantha (the spikes separate from the shoot); and Section Mesantha (the spikes borne on the shoot either with or without leaves).

Traditional medicine has used turmeric, or ***Curcuma longa***, for decades. Turmeric, a spice with a strong flavor that is mostly grown from the roots of a flowering plant found in Southeast Asia and India, is also well-known for its strong anti-inflammatory and antioxidant qualities. Turmeric also lends curry its characteristic bright yellow color.

Curcumin:

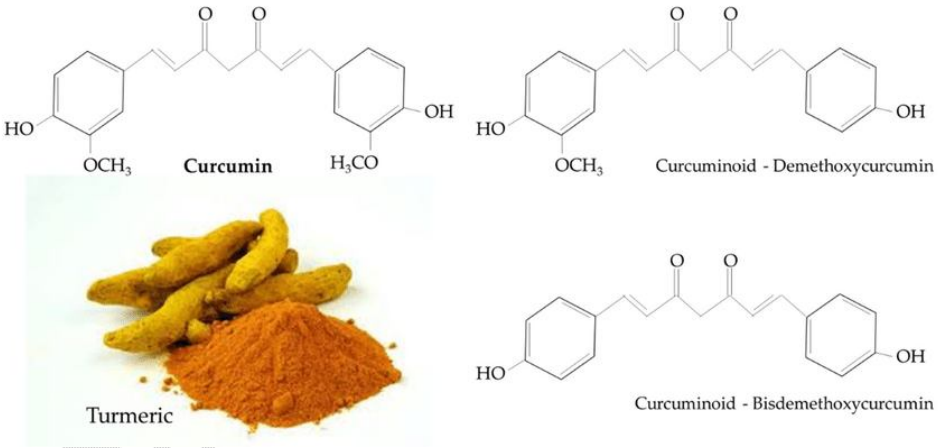

Figure 1: Structure of Curcumin

Curcumin, the main active ingredient in turmeric and the one responsible for the spice's distinctive yellow color, is a member of the Curcuminoids plant compound family. There are several types of turmeric, such as the Lakadong variety from Meghalaya, the Cuddapah variety from Andhra Pradesh, and the Alleppey type from Nizamabad. The HPLC system can identify the other active ingredients, which are DMC - Demethoxycurcumin and BDMC – Bisdemethoxycurcumin as seen in Figure 1.(5) Curcumin is a naturally occurring antioxidant that possesses anti-inflammatory properties in addition to benefits linked to age reduction, prevention of Alzheimer's disease, and possibly even relief from

depression. Turmeric's primary claim to fame is that it is frequently used to reduce inflammation; curcumin is primarily responsible for this effect.(31)

Anti-inflammatory substances like curcumin may be useful in the treatment and prevention of a number of cancer types, including colorectal, pancreatic, prostate, breast, and gastric cancers, since inflammation is connected to the growth of tumours. Curcumin may help limit the growth of tumor cells and may even stop tumors from developing in the first place, according to research carried out on mice. Diabetes and its related conditions, such as diabetic nephropathy, also known as diabetic kidney disease, which affects patients with type 1 and type 2 diabetes, may be treated and prevented with curcumin. First of all Turmeric is used as a successful treatment for a number of skin diseases, including acne, eczema (atopic dermatitis), photoaging, and psoriasis because of its anti-inflammatory, antibacterial, and antioxidant qualities. Curcumin is widely utilized in cosmetics and skin care products and has been shown to provide health advantages for kidney and eye health as well as relief from hay fever. (28)

Extraction Of Curcumin:

The most important stage in recovering curcumin from plant materials is extraction. All extraction techniques were created with a few common goals in mind, including the following: (a) recovering the compounds of interest from plant materials; (b) improving the extraction process' selectivity; (c) increasing extraction efficiency; and (d) offering a reliable and repeatable method (38). Curcumin is commonly extracted from plants using conventional extraction techniques such as solvent extraction, maceration, and Soxhlet extraction. These techniques are simple but they take a long time, are usually non-selective, and occasionally degrade materials that are sensitive to heat (38). In order to overcome these challenges, new extraction techniques have been created as more effective substitutes for traditional extraction techniques, such as supercritical liquid extraction.

Traditional techniques for curcumin extraction i.e. Solid-liquid extraction, sometimes called "maceration" or "soaking," is a well-known and frequently employed technique for extracting solid materials from a solvent. Curcumin has been extracted from plants using a wide variety of solvents, such as non-polar organic solvents and a mixture of organic solvents and water (27, 29). In order to isolate curcumin from *Curcuma longa L*., Popuri& Pagala (29) compared the extraction solvents (acetone, ethyl acetone, ethanol, methanol, and isopropanol). It was discovered that when the extraction was carried out at 30°C for 1 hour with a solid to solvent ratio of 1:8, ethanol extraction produced the maximum yield (0.26 mg/10 g). Accordingly, out of all the organic solvents used, ethanol was the most favored solvent for curcumin extraction (27), (33), (32). Furthermore, a significant factor in regulating the extraction efficiency is the solvent mixture's ethanol content (27).

German chemist Soxhlet created the Soxhlet extraction technique in 1879. It is recognized as the gold standard and reference method for the solid-liquid extraction of bioactive chemicals from plants. Several publications have reported on the extraction of curcumin from plants employing a Soxhlet extractor (12, 33). Another conventional extraction technique used to extract essential oils and bioactive substances

is steam or hydro distillation. It has been used to extract the essential oil (turmeric flavor) from raw turmeric powder or oleoresin in order to produce curcumin, or turmeric without flavor. In a study by Silva *et al.* (34), hydro-distillation produced a good yield of deodorized turmeric at a significantly lower cost than pure curcuminoid pigments. Furthermore, curcuminoids levels in deodorized turmeric were comparable to those in the control and a sample that had undergone hexane extraction for deodorization. These findings suggested that the hydro-distillation process is a productive way to extract curcuminoids or powder with minimal flavor remnants and no loss of pigment.

Novel methods for extraction of curcumin:

Supercritical fluid extraction (SFE):

Supercritical fluid extraction (SFE) is the most widely utilized non-conventional large-scale industrial technology that uses supercritical fluids as extraction solvents. One of the most widely utilized extraction solvents is supercritical carbon dioxide (CO2), which is regarded as a green solvent with no toxicity or adverse effects (15, 21). Supercritical CO2 is efficient because of its thermal and physical characteristics, which combine aspects of its gaseous and liquid forms. (4) When a gas or liquid's temperature and pressure are higher than their critical points, a supercritical fluid can be produced. (16) The SFE process is appropriate for extracting chemicals that are quickly oxidized and thermally unstable due to its mild processing temperature requirement. Because SFE requires less solvent, extracts data faster, can be automated, and enhances selectivity, it is generally considered a greener extraction technique than classic extraction. (15)

Applications/Uses Of Curcumin:

Traditional medicine makes considerable use of curcumin. The culinary, cosmetic, and pharmaceutical industries have all seen a rise in demand for it recently. Many research have looked at the uses of curcumin in health, beauty, medical, and cooking products. (10), (13), and (14).

Curcumin for medicinal purposes:

Curcumin has a long history of usage in traditional medicine as a home cure and in medicinal applications. (9) Its numerous advantageous biological and pharmacological properties, such as those that are anti-inflammatory, anti-oxidant, anti-bacterial, anti-diabetic, anti-cancer, and anti-tumor, are the main reason for its usage in a variety of medications. (10), (32), (37) Furthermore, investigations on safety evaluation revealed that curcumin is safe to use at high doses and does not have any harmful side effects. (9) Due to these biological functions that are still active and its extremely safe nature, it has been under more and more scientific scrutiny over the last few decades. Many cancer types, such as bone tumors, brain tumors, head and neck, melanoma, colon, colorectal, pancreatic, breast, prostate, ovarian, lung, and oral cancer, are treated by curcumin. (30)

Curcumin for therapeutic use

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that are anti-inflammatory, anti-oxidant, anti-bacterial, anti-diabetic, anti-cancer, and anti-tumor, are the main reason for its usage in a variety of medications. (10), (32), (37) Furthermore, investigations on safety evaluation revealed that curcumin is safe to use at high doses and does not have any harmful side effects. (9) Due to these biological functions that are still active and its extremely safe nature, it has been under more and more scientific scrutiny over the last few decades. Many cancer types, such as those of the bone, brain, head and neck, melanoma, colon, colorectal, pancreatic, breast, prostate, ovarian, lung, and oral regions, are responsive to curcumin's therapeutic activities. (26), (30) Furthermore, curcumin has been demonstrated to be a hepato-, nephron-, anti-pathogenic, antiviral, and hypoglycemic molecule. (23), (30) Because curcumin possesses anti-inflammatory, anti-infectious, and anti-oxidant properties, it has also been shown to improve wound healing through its role in collagen deposition, granulation tissue development, and tissue remodelling. (23)

Curcumin in the food industry:

Curcumin, which has a vibrant yellow-orange hue and is a natural food coloring agent that can replace artificial food coloring, has long been used in culinary applications. It improves the appearance of food and is frequently used in rice, beef, mustard, pastries, dairy goods, and canned fish (13). Moreover, curcumin can extend the shelf life of food by acting as a natural preservative. It is highly effective against a wide range of pathogens, such as *Salmonella typhimurium, Listeria monocytogenes, Staphylococcus aureus, and Escherichia coli.* (2) Research has shown that curcumin effectively preserves cooked mutton, bread, bean curd, and minced meat (22), (2). Since curcumin is extremely sensitive to acid-base reactions, it has also been suggested as a pH-sensitive indicator or sensor for tracking and informing producers, retailers, or consumers about the quality of food. Visual inspection can be used to track color changes in the sensor during food spoiling, and color analysis software can be used to quantify the color changes after canning.

Curcumin in the cosmetic industry:

Since curcumin possesses anti-inflammatory and antioxidant properties, the cosmetics industry has been using it for many years. With positive effects against UV light, aging, inflammation, hair loss, lip care, and nail care, it has demonstrated promise for a broad range of cosmetic treatments for the skin, face, hair, lips, and nails. Curcumin has anti-aging, anti-wrinkle, sunscreen, and moisture-retention qualities that make it an effective ingredient in cosmetics (18). When exposed to a variety of extreme environmental factors, including chemical pollution, UV and infrared radiation, and physical strains, curcumin easily degrades. This helps shield skin from these damaging factors by preventing the production of oxygen free radicals and lipid peroxidation. Notably, formulations containing curcumin have the ability to improve its stability and skin bioavailability (cellular absorption and penetration behavior) (11), (14). Constant curcumin administration improves the aesthetics and self-care of the skin.

Sunflower Lecithin:

Phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylinositol (PI), phosphatidic acid (PA), and other minor components including carbohydrates and triglycerides make up the majority of lecithins, which are a combination of acetone-insoluble phospholipids (21).

Lecithins are utilized in a variety of commercial applications, including food, cosmetics, pharmaceuticals, dietetics, and more, whether in their natural or modified state (25). Because of the properties of its phospholipids, this oil industry byproduct serves as a versatile addition for the production of chocolate, instant and baked goods, margarine, and mayonnaise. (8). Lecithin's primary use in the food business is related to its function as an emulsifying agent for emulsions or dispersions. (17) To make sunflower lecithin, a sunflower must be dried and then divided into three components: solids, gum, and oil. (36) A cold press technique is used to extract the lecithin from the gum.It keeps ingredients from separating and gives meals a smooth, moist texture. (12)

Pharmacokinetics And Bioavailability:

The interaction between the characteristics of pharmacodynamics (PDs) and pharmacokinetics (PKs) determines a molecule's bioavailability (BA). A number of variables, such as PKs (absorption, distribution, metabolism, and excretion; ADME) and PDs, affect how effective a drug is. The presence of xenobiotics, a meal, or a herbal treatment can alter PD responses through various synergistic and negative interactions. (6) By adjusting the ADME and physical characteristics of the active molecule, we can modify the PK and PD properties, and then adjust the BA and bioaccessibility as needed.

As nutraceuticals are complex systems with multiple components and ingredients, their disposition pattern is more intricate than that of a typical synthetic medicine molecule, which is often a single chemical entity. PK models are intended to help comprehend the medicinal moiety's disposition mechanism following absorption. The purpose of the compartment model is to offer a standardized and simple approach to characterize, evaluate, and interpret data obtained from in vivo drug disposal studies. Applications for nutraceuticals, functional foods, and drinks with particular blends of bioactive ingredients have been investigated. Such products can be marketed to certain persons, high-risk patients (with conditions like depression, diabetes, cardiovascular disease, or hypertension), people in particular age groups (such young children, adults, or the elderly), and people with particular dietary needs. In clinical practice, nutraceuticals are typically used alone or in conjunction with other nutrients to target a greater number of biochemical molecules and affect various molecular targets. Considering the variety of active molecules found in supplements and the role that food plays in influencing the release, dissolution, and ADME (absorption, metabolism, distribution, and excretion) of the active ingredients, it is assumed that nutraceuticals follow multiexponential multicompartment models (24).

METHODOLOGY:

Materials:

CurcuminAura™ Standardised to 60.9% Curcuminoids, orange to yellow colour powder, belonging to family Zingiberaceae, recommended daily dose is 500 mg,water soluble, shelf life is 3 years at 25 ± 2 °

C. Marketed Curcumin 95% was used as reference Item, Carboxymethyl cellulose (CMC) was used as a vehicle based on solubility trial, 0.1% CMC is universally accepted

Test System Details:

Sprague dawley rats were used for this study, Male and female, nulliparous and non-pregnant having weight 225-295 g for male and 190-248g female. They were obtained from the National Institute of biosciences. Rats support repeat blood collection time points;thus, they are preferred species for evaluation of pharmacokinetic profile.

METHOD

Formulation Of CurcuminAura™:

CurcuminAura™as seen in Figure 2 ;consists of Curcumin 95%, Piperine 95%, Sunflower Lecithin, and Maltodextrin as main ingredients in the formulation.

Figure 2:Image of CurcuminAura™

Analytical Comparison ofCurcuminAura™ V/S Curcumin 95% By Hplc:

CurcuminAura™, was standardized to 60.9% curcuminoids by HPLC, compared to regular marketed Curcumin 95%.

HPLC Methodology:

HPLC Analysis of Curcumin 95% and CurcuminAura™. A Shimadzu P-series HPLC with auto-sampler was operated via Lab solutions software to run the test. The machine includes a UV detector as well as PDA (Photo-Diode array) detector with a 5 µm C-18, shim-pack column of dimensions 4.6 x 250mm. The Isocratic mobile phase consisted of Acetonitrile, double distilled water and ortho-phosphoric acid. The Total run time of the analysis is 25 minutes and wavelength of detection of **CurcuminAura™** and Curcumin 95% is 420nm. The Total flow rate is, and injection volume is 20uL. Retention time of BDMC, DMC and Curcumin was observed at RT 15 16 and 18 for Standard and at RT 14, 15 and 17 **CurcuminAura™** respectively.

Materials:Acetonitrile and Methanol was of HPLC grade obtained from MERCK; Ortho-phosphoric acid was of Qualigens.

Preparation of Reference standard: Stock solution of Curcumin RS was prepared by dissolving 10 mg in 50 ml methanol.

***Preparation of Samples*:** Stock sample solution of Curcumin 95% and **CurcuminAura™**

was prepared by dissolving 10 mg in 50 ml methanol.

PHARMACOKINETIC STUDY OF CurcuminAura™ V/S CURCUMIN 95%:

Preparation of the Dose Formulation:

Initially formulation trials were conducted to find out the maximum feasible concentration and selection of suitable vehicles. For dose formulation, the required quantity of powder was weighed and triturated using mortar and pestle. A small volume of vehicle was added with continuous stirring to obtain a suspension. The exact quantity of test item and vehicle used was recorded in the raw data. All formulations were prepared fresh, before dose administration. Formulation for the reference item was prepared in a similar manner. The volume of formulation was prepared based upon the recent animal body weights.

Experimental Design:

Table 1: Depicting Experimental Design for CurcuminAura™ v/s (Marketed)Curcumin 95%

GROUP NO.	GROUP	TREATMENT	DOSE (Mg/Kg)	ANIMAL NUMBERS	
				MALE	FEMALE
G1	TEST ITEM	CurcuminAura™	110	230501-230504	230505-230508
G3	REFERENCE ITEM (MARKETED)	CURCUMIN 95%	110	230517-230520	230521-230524

Dose Administration:

Animals from group G1 received a single dose of **CurcuminAura™** at 110 mg/kg, respectively by oral route on day 1. Animals from group G3 received a single dose of marketed Curcumin 95.0% at 110 mg/kg, respectively by oral route on day 2. Dose volume was maintained at 10 ml/kg. Actual volume to be administered was calculated based on the recent body weights of each animal.

Blood Sample Collection and Plasma Separation:

As per the number of time points, animals were divided in two sets of two males and females. Post injection blood samples were withdrawn from retro-orbital sinuses, under isofluorane anaesthesia. Sampling time points were 30 mins, 2 hrs and 4 hrs and 1 hr, 3 hrs and 6 hrs. Approximately 0.2 to 0.3 ml blood was collected in vials containing 1% EDTA as an anticoagulant followed by separation of plasma. The separated plasma was transferred to pre-labelled polypropylene tubes and stored at -80°C and then bioanalyzed.

RESULTS AND DISCUSSIONS:

Analytical Comparison of CurcuminAura™ V/S Curcumin 95% By HPLC:

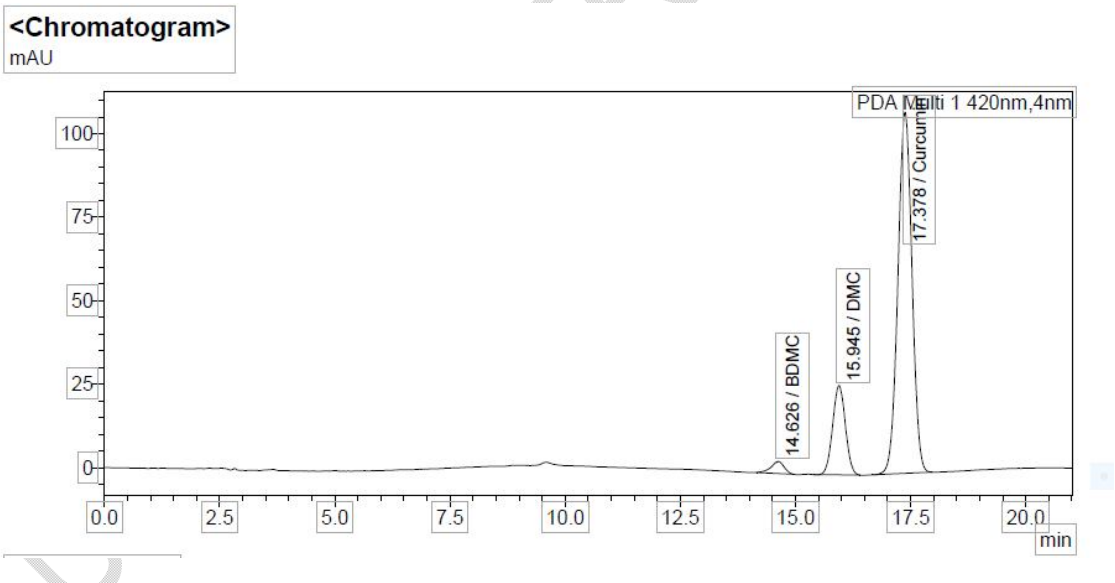


Figure 3: HPLC Chromatogram of CurcuminAura™ standardized to 60.9% curcuminoids.

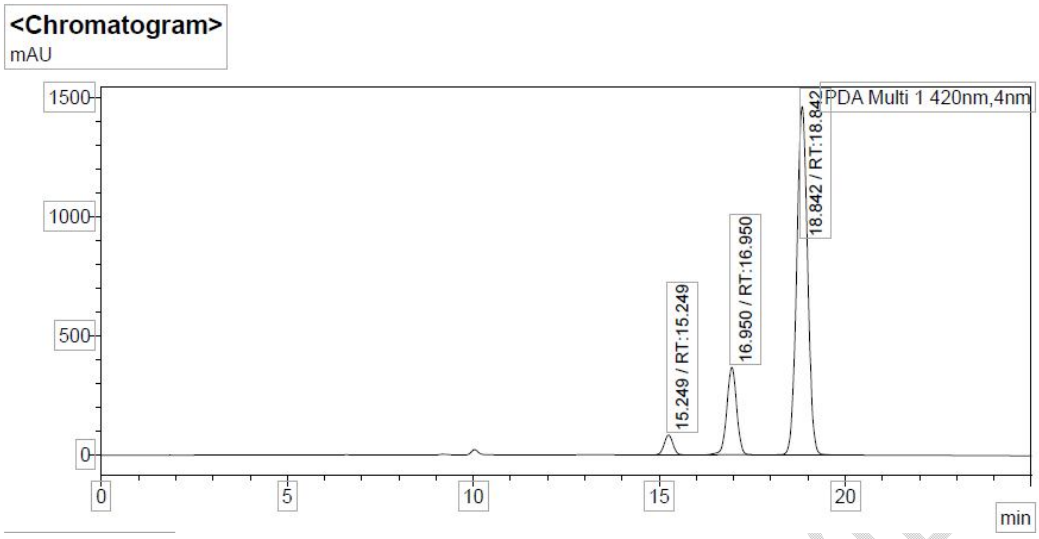


Figure 4: HPLC Chromatogram of regular marketed Curcumin 95% .

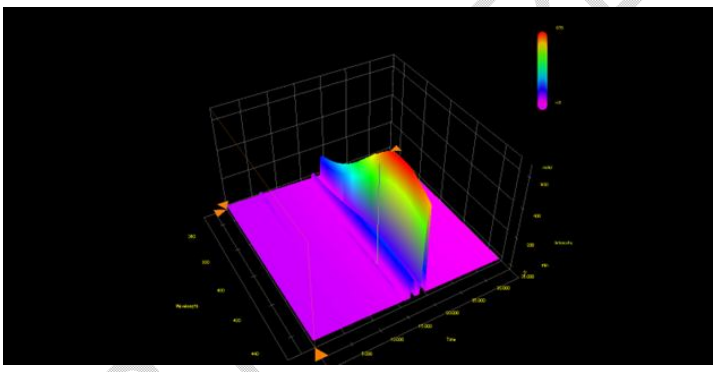


Figure 5: 3-Dimensional Image of CurcuminAura™ by HPLC.

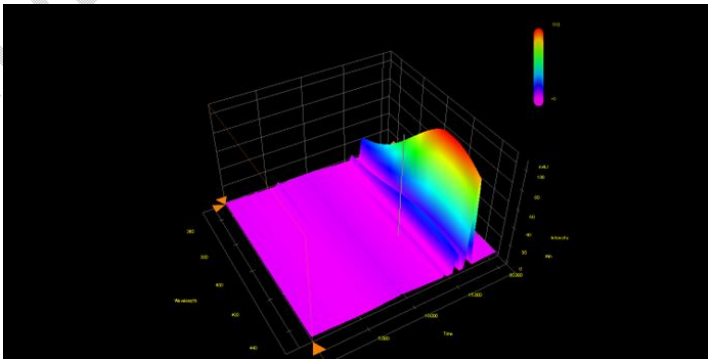


Figure 6:3-Dimensional Image of regular Marked Curcumin 95% by HPLC

CurcuminAura™ is Standardized to 60.9% Curcuminoids content by HPLC, BDMC peak is obtained at RT 14.626, BDMC Content is 1.5% , DMC peak is obtained at RT 15.945, content is 10.89%, Curcumin peak is obtained at RT 17.378, content is 48.6% by HPLC. On comparison to regular Marketed curcumin 95% which has curcumin content 70-80%, DMC 15-20%, BDMC 3-5% by HPLC as seen in figure 3, 4 , 5 and 6.

Blood Collection Time Points:

The rats were given dose of 110 mg/kg of **CurcuminAura™** and regular Curcumin. The blood collection time points by IV route were 30minutes, 1 hour, 2 hours, 3, 4 and 6 hours respectively.

Table 2: Pharmacokinetic Parameters of CurcuminAura™:

Mean/ SD/N	**Blood Time Points**			
	0 min	**30 min**	**2hr**	**4hr**
G1 Test Item (CurcuminAura™) Dose: 110 mg/kg				
Mean	0.00	93.96	69.85	33.93
SD	0.00	15.09	7.20	8.52
N	4	4	4	4
Mean/ SD/N	**Blood Time Points**			
	0 min	**1 hr**	**3hr**	**6hr**
G1 Test Item (CurcuminAura™) Dose: 110 mg/kg				
Mean	0.00	94.10	118.45	40.29
SD	0.00	20.64	112.05	9.71
N	4	4	4	4

Table 3: Pharmacokinetic Parameters of Regular Marketed Curcumin 95% :

Mean/ SD/N	Blood Time Points			
	0 min	30 min	2hr	4hr
G3 Reference Item (Curcumin 95%) Dose: 110 mg/kg				
Mean	0.00	44.27	31.94	17.58
SD	0.00	8.36	7.08	4.05
N	4	4	4	4
Mean/ SD/N	**Blood Time Points**			
	0 min	**1 hr**	**3hr**	**6hr**
G3 Reference Item (Curcumin 95%) Dose: 110 mg/kg				
Mean	0.00	44.20	31.11	15.90
SD	0.00	12.29	4.93	6.46
N	4	4	4	4

The above data shows the blood collection time points of **CurcuminAura™** v/s Regular marketed Curcumin 95%. Blood is collected at 30minutes, 1 hour, 2, 3, 4 and 6 hours after feeding the test and reference item at 110mg/kg dose to male/female rats. Maximum absorption is seen after 3 hours of feeding the test item (**CurcuminAura™**).

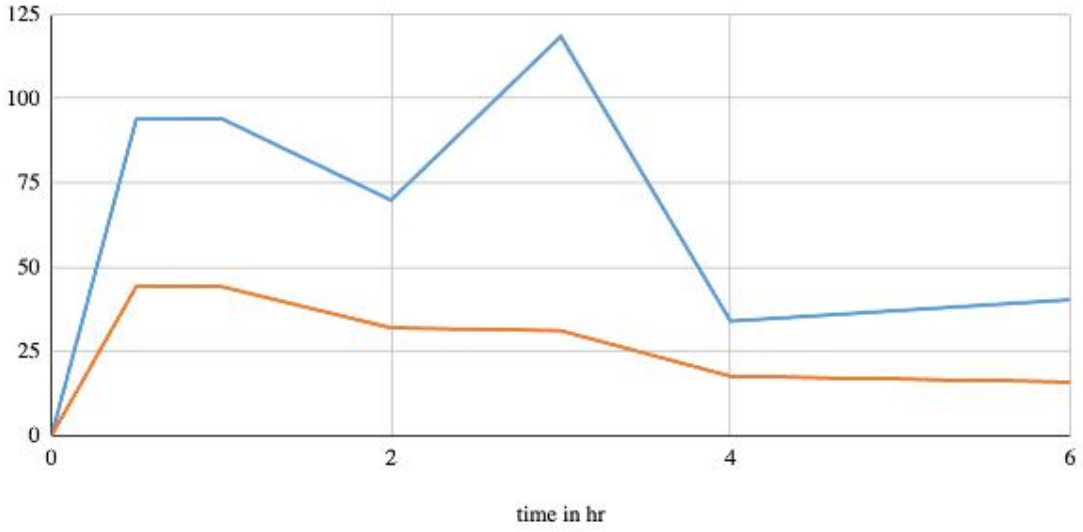
Table 4: Curcumin Absorption values in ng/ml of CurcuminAura™ and Curcumin Standard

Time in hr	0	0.5	1	2	3	4	6
CurcuminAura™	0	93.96	94.1	69.85	118.45	33.93	40.29
Curcumin 95%	0	44.27	44.2	31.94	31.11	17.58	15.9

Chart 1: Graphical representation of curcumin absorption values in ng/ml of CurcuminAura™ and Curcumin 95% standard

Blue colour represents **CurcuminAura™**

Orange colour represents Curcumin 95%



STUDY OUTCOME AND CONCLUSION:

CurcuminAura™ is the turmeric extract standardised to 60% curcuminoids content and formulated to enhance the bioavailability of the curcuminoids. This product has been tested in Rats. The comparison studies evident that **CurcuminAura™** has 3.8 times higher bioavailable than the reference standard.

Also in this study it is shown that the maximum absorption happens in the time line 3 hrs after feeding the drug.

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