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Exploratory Study of Curcumin isolated from Turmeric Curcuma Longa, the Putative Histone Deacetylase Inhibitor, as added-on strategy to antipsychotics in treating negative symptoms and Neuro-cognitive deficits in Schizophrenia

Simon Chiu*[1]; Michel Woodbury-Farina [2]; Kristen Terpstra[3]; *Vladimir Badmaev [4], Zack Cernovsky [5], Yves Bureau [6], Hana Raheb [7], Mariwan Husni [8], John Copen [9], Mujeeb Shad [10], Hou Jirui [11], Robbie Campbell [12], Zahra Khazaeipool[13] and Autumn Carriere [14]

[1,5,7,12,13].Department of Psychiatry, University of Western Ontario, London Ontario Canada; [2] Department of Psychiatry, University of Puerto Rico, San Juan PR(US), [3]Neurological Unit, St Michel's Hospital Toronto ON , [4] Medical Holdings Inc, New York, NY, USA , [6]Lawson Health Research Institute, London Ontario , [8]Northern Ontario School of Medicine ,Thunderbay Ontario Canada., [9] University of British Columbia, Victoria medical campus, Victoria BC Canada , [10]Oregon Health Sciences Centre, Portland, Oregon USA , [11]Dalian-Fusheng Natural Medicine Development Co. Ltd., China Dalian Pharma. Dalian Province, China , [14] Nipissing University Nursing Program, Faculty of Professional studies ON, Canada

ABSTRACT

Background: Growing evidence suggests epigenetic dysregulation may play a role in schizophrenia. We hypothesize that curcumin (Diferuloylmethane) extracted from Curcuma Longata, shown to function as a pan-histone deacetylease(HDAC) inhibitor, may offer potential therapeutic benefits in schizophrenia treatment.

Objective: We chose standardized Curcumin C-3 complex combined with Bioperine™: Supercumin™ to examine the efficacy of Curcumin in improving the core positive and negative symptoms and cognitive deficits in patients diagnosed as schizophrenia.

Method: We recruited community dwelling schizophrenia patients with persistent negative symptoms (Scale for Assessment of Negative Symptoms: SANS score> 30) to participate in the open-label-parallel-group-randomized study.

Results: We randomized 17 subjects (mean age: 39·9 years, male/female: 13/4) into Group 1(Supercurcumin™ daily 1 gm) and Group 2(Supercurcumin™ 4 gm daily) for 16 weeks, and 15/17 subjects completed the study. The subjects were maintained on current antipsychotic therapy. We found that Group 1 Group 2 significantly improved the total and general psychopathology sub-scales pf PANSS (Positive and Negative Symptoms scale). Within group pre- and post-treatment comparison showed standardized-mean-differences in total PANSS score and PANSS-general psychopathology were significant for Group 1 ($p < 0.003$ and $p< 0.002$) and for Group 2 ($P < 0.01$ and $p< 0.016$). We found Cohen's d-effect size favored Supercurcumin™ in PANSS-positive, PANSS-negative subscale. Both groups exhibited improvement in selected cognitive domains. Supercurcumin™ was well tolerated with no serious adverse events.

Conclusion: Our study demonstrates for the first time augmenting effects of curcumin combined with piperine in schizophrenia. Randomized controlled trials are warranted to corroborate efficacy of curcumin schizophrenia.

KEYWORDS: Curcumin; Epigenetics; Schizophrenia; positive, negative symptoms; cognition; bioperine: pepper; Histone deacetylase

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Name of the Corresponding author:

Simon Chiu *

Department of Psychiatry, University of Western Ontario, London Ontario Canada

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I. INTRODUCTION

Although the second generation of atypical antipsychotics (clozapine, olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole, cariprazine, paliperidone, arsenapine, lurisidone, and iloperidone) brings about significant improvement in positive symptoms, schizophrenia confers marked disease burden [1]. Expert consensus concludes that poor outcomes are strongly related to impaired neuro-cognition and persistent negative symptoms [2]. Persistent residual negative symptoms and decline in psychosocial functioning have sparked considerable interest to identify novel drug targets to improve treatment outcomes in schizophrenia.

There is mounting evidence that dysregulation of epigenetics signaling consisting of DNA methylation, histone modification mediated by histone deacetylase (HDAC) and non-coding micro-RNA (miRNA), plays a pivotal role in schizophrenia [3], [4], [5], [6]. Up-regulation of HDAC activities as measured with ELISA method has recently been found in lymphocytes of schizophrenia [7]. Postmortem studies in schizophrenia found evidence for altered epigenomes adversely affecting transcription of genes for maintenance of neuronal survival and repair in the hippocampus and prefrontal cortex [8], [9], and [10]. Both studies support the model of hypo-acetylation of the network of histone proteins, shifting the chromatin configuration to inactive transcription mode. The restrictive epigenome model of schizophrenia [10] predicts that HDAC inhibitors can reset the balance of histone deacetylation-acetylation in favor of the relaxed state open for transcription.

It is noteworthy that amisulpride, the atypical antipsychotic, as currently approved in Germany, Belgium, United Kingdom, Korea and China for treatment of schizophrenia [11] exhibits efficacy in inhibiting HDAC at selective HDAC isoforms :HDAC1 and HDAC3 [12]. Amisulpride belongs to the series of benzamide derivatives known as 2nd generation of HDAC inhibitors targeting selectivity at HDAC1 and HDAC3 isoforms in biochemical assays using recombinant enzyme systems [13]. Furthermore, amisulpride exhibits dual activities: 1) potent antagonist activity at striatal dopamine: DA subtypes D2/D3a, 2) potent antagonist activity at serotonin receptor subtype-7 [14], and [15]. A recent meta-analysis of randomized controlled trials in acute treatment of schizophrenia [16] showed that amisulpride ranked only second to clozapine in the efficacy measure of standardized mean differences (SMD) with 95% confidence intervals (CI) as follows: clozapine :SMD 0·88, CI:0·73–1·03; amisulpride: SMD 0·66, CL: 0·53–0·78.

These considerations inform our research group to evaluate whether curcumin,as a potent epigenetics regulator isolated from turmeric (Curcuma longata) will be beneficial in schizophrenia. Both in vivo and in vitro studies have shown that curcumin regulates multiple epigenetics pathways: HDAC (Histone Deacetylase) isoforms 1, 3, 8, HAT (histone acetyltransferase), and non-coding RNA: miRNA-22, miRNA186a and miRNA-199a [17]. In high throughput assay using HeLa nuclear extract, curcumin was found to be more potent in inhibiting HDAC than valproic acid and sodium butyrate [18]. The inhibition constant Ki of curcumin (539 nM) was comparable to Ki of Trichostatin A (504 nM). Curcumin is known for its specific neuroprotective actions in interacting with the anti-oxidant and anti-inflammatory signaling pathways, as well as modulating neuronal apoptosis network [2], [3], [17],[18], [19]. Evidence is accumulating that oxidative stress and neuro-inflammation underscore the meta-progression of schizophrenia [20]. We hypothesize that curcumin can augment anti-psychotics in improving the persistent negative symptoms and cognition deficits in schizophrenia.

Most of the clinical studies on formulated curcumin compounds focus on cancer treatment [21]. Translational studies to catalyze the therapeutic development of curcumin have met with pharmacokinetic challenges, due to relatively poor systemic bioavailability and rapid first-pass effect [22]. Pharmacokinetics studies of curcumin showed that peak serum concentration of 0.51 to 1.77 µM can be achieved with oral dosage of 4-8 gm of curcumin [23]. Curcumin, combined The black pepper extract, piperine(Isolated from Piper nigrum L.Piperaceae), a known inhibitor of hepatic and intestinal glucuronidation [24], can enhance the bioavailability of curcumin and reduce the first-pass effect. A seminal clinical study showed that concomitant administration of piperine at 20 mg with 2 gm curcumin resulted in much higher blood level of curcumin at 0.25 to 1 hr. post treatment [25]. Curcumin's systemic bioavailability measured with AUC (Area- Under- the- Curve) was increased by twenty-fold with no adverse effects in normal control subjects. Piperine can readily cross blood barrier, enhance the absorption and the brain uptake of curcumin.

The overall aim of the study is to examine the efficacy and tolerability of Curcumins in schizophrenia subjects who are only partially responding to optimal dosages of 1st and 2nd generation antipsychotics. The primary objective of our "proof-of-concept" dose-finding study of curcumin is to examine the efficacy and safety of a new standardized curcumin formulation: SupercuminTM (C-3 Complex combined with bioperine™. patented product of black pepper fruit extract manufactured by Sabinsa Corp. Piscataway, New Jersey, USA) in schizophrenia. Curcumin C3 Complex™ was first studied in colorectal cancer patients in United Kingdom [26]. The content of "Curcumin C3 complex "capsule was analyzed by HPLC (high performance liquid chromatography) and each Supercucumin™ 1000 mg-caplet contains 900 mg curcumin, 60 mg desmethoxycurcumin, and 40 mg bisdemethoxycurcumin. Caplets N J, U S A) and 5 mg Bioperine extracted from black pepper. In our study, we randomized the cohort of schizophrenic subjects into two groups who receive the oral formulation of Supercurcumin™ (C-3 complex and Bioperine) once daily for 16 weeks as follows: Group 1: 1gm Supercurcumin™ (C-3 complex and Bioperine). Group 2: 4 gm SupercurcuminTM (C-3 complex and Bioperine). The

chemical structure of curcumin and the biotransformation of curcumin are shown in the Figure 1.:

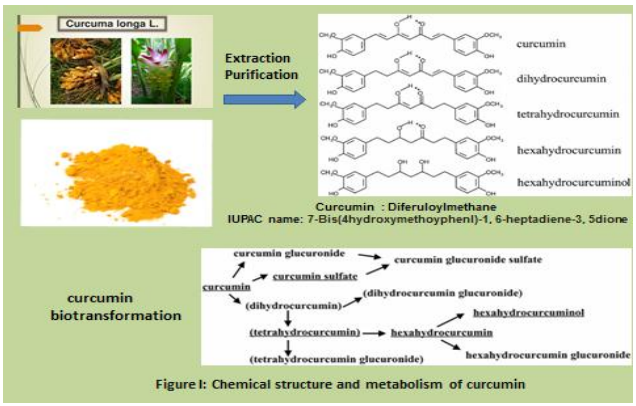

Figure I: Chemical structure and metabolism of curcumin

II. METHOD AND MATERIALS

2.a : Study design and inclusion and exclusion criteria

The study was conducted from 2009 to 2012 at an outpatient psychiatric clinic in Puerto Rico PR (US).We used pre- and post-treatment design, with each participant as the control, for the 16-week study period. They were randomized to either Group 1 or Group 2 with random number sequence. For entry to the study, the potential community-dwelling subjects ranging in age from 18 to 65 years and capable of providing informed consent were recruited to participate in the study. The subjects were required to satisfy the diagnostic criteria of schizophrenia (Diagnostic Statistical Manual of Mental Disorders: 4th Edition, American Psychiatric Association, Washington DC USA and to exhibit persistent negative symptoms as measured with SANS (Scale for the Assessment of Negative Symptoms) scale score >20. Females of reproductive age were required to submit urine pregnancy test and would be excluded if the urine test was positive. We specified the upper limit of any depressive symptoms to be no greater than 24 on the 17-item Hamilton Depression Rating Scale: HAMD scale. We stipulate that the participants were started on antipsychotic for at least 1 month and maintained on the same antipsychotic throughout the study period. We excluded participants with active and severe alcohol and substance use disorders with repeated urine positive for marijuana, cocaine, opiate amphetamine and 3, 4-methylenedioxymethamphetamine (MDMA). In view of the unusually high proportion of schizophrenic subjects who smoke cigarettes regularly, we do not exclude moderate nicotine dependence. In view of anti-inflammatory effect of curcumin, we excluded regular users of NSAID (non-steroidal anti-inflammatory drug) or allergic reaction to curcumin or pipeline. Exclusion criteria included history of cancer, recent myocardial infarction, unstable angina, severe hypertension, unstable diabetes mellitus, chronic liver disease, gallbladder disease, chronic renal disease, and recent under-/untreated GERD (gastroesophageal reflux disease), severe/untreated gastric or duodenal ulcer. We excluded neurological disorders including traumatic brain injury, cerebra-vascular disorders, and significant medical disorders. All subjects in the study received Super curcumin™ caplets obtained through the courtesy of Sabina Corp. NJ, USA, and were randomized to either Group 1 or Group 2: Group1 (1 caplet once daily) and Group 2 (4 caplets once daily) for a total of 16 weeks. They were fully explained the purpose of the study which was fully approved by an accredited community independent research ethics board Coast IRB CO USA (study protocol number; 06T-773). We monitored the safety and tolerability of the study at regular intervals according to the guidelines from Stanley Medical Research Institute MD, USA. The study was registered at the US clinical trial web site prior to the start of the study: ClinicalTrials.gov Identifier: NCT01875822

2. b. Study Protocol

During the screening phase, the subjects completed the series of medical assessment: blood pressure, pulse,12-lead EKG as required, body weight, body composition, routine blood tests :CBC, glucose and lipid profile, liver and kidney function tests and urine toxicological screen for drugs of abuse. At baseline the subjects underwent the mini-structured neuropsychiatric interview and the computerized neurocognitive test battery: CNS Vital Sign (CNS-VS) (Spanish and English version available in USA) (27) which encompasses an aggregate score: neurocognitive index and 10 neurocognitive domains: composite memory, verbal memory, visual memory, processing speed, executive function , psychomotor speed, reaction time, complex attention, cognitive flexibility and total time. The CNS-VS comprises 7 primary tests: verbal and visual memory, finger tapping, symbol digit coding, the Stroop Test, shifting attention test, continuous performance test, Trail test and Tower of London. In addition, we administered psychiatric rating scales: BPRS (Brief Psychiatric Rating Scale), PANSS (Positive and Negative Symptoms scale), and HAMD-17 item at baseline, week 4, week 8 and week 16. We used the recently revised scoring system of PANSS assigning 0 score to "no symptom" for all the subjects throughout the study period. For safety monitoring, we used Treatment-Emergent Adverse Events (TEAE) and the battery of tests of motor function: Abnormal Involuntary Movement S c a l e (AIMS).

2.c Statistical analysis :

We define the response rate towards Supercurcumin™ treatment as 30% change in the rating scales: PANSS (general score and subscales) , HAMD-17 and BPRS scores at the end of the 16-week treatment period compared to the baseline values. For within group comparison of the changes in PANSS , HAMD-17 and BPRS at 16-week treatment period compared with the baseline pre-treatment baseline, we use the paired-t-test, and non-parametric

Wilcoxin rank sum test to detect any significant difference in the rating scale. We set the significant level to be at $p < 0.5$. Furthermore, we analyzed the data using the Cohen's d effect size known to be independent of the sample size to determine the magnitude of the effect size for the changes in the therapeutic outcome measures; PANSS, HAM-17 and BPRS. For analyzing the

neurocognitive effects of curcumin, we choose the Cohen's d effect size to describe any changes in the scores on the various cognitive domains as assessed with CNS-VS neurocognitive battery of tests. For safety and adverse events, we choose the proportion of reported events in the TEAE standardized inventory of side effects in the different body systems.

III. RESULTS

At baseline, the participating subjects underwent a comprehensive physical examination, anthropometric assessment with Tanika bioimpedance-based Body image monitor: Ironman (Calif. USA). The majority of subjects were overweight as indicated by the BMI (Body Mass Index): 29.30 (S D =7.58) with no serious or untreated medical problems. Routine blood work: SMA-12 was ordered and the results were reviewed. They were diagnosed as schizophrenia for at least 5 years and living in the community. We found that their baseline neurocognitive index from CNS:VS placed them in the low average percentile scores (pooled mean score:3.85, SD= 9.13, range of percentile:1-34 %). During the period of the study, the subjects were maintained on previous dosages of antipsychotic medication : both 1st and 2nd generation of antipsychotics were used. We did not find any significant abnormalities in laboratory values of complete blood count: CBC, kidney and liver functions, glycemic control and electrolytes. We recruited 17 subjects of Latino-American descent with Diagnostic-Statistical Manual: DSM IV-R diagnosis of schizophrenia who fulfilled the inclusion criteria of residual negative symptoms with SANS score >30 at baseline, from a single outpatient academic-clinic center in Puerto Rico (USA) during the period of 2010-2012. During the 16-week study, one patient dropped out from the study due to the adverse event of hyper-sexuality. Furthermore, we failed to retrieve the database of one patient due to unexpected severe computer malfunctioning despite backup safeguard. The dropout rate was 2/17 (12%). In total, 15 patients completed the subject from baseline to week 16: 8 and 7 subjects were randomized to the respective groups: Group1: 1 gm Curcumin C-3 complex group and Group 2: curcumin C-3 Complex 4 gm group. The mean age was 39-93 yrs. (SD = 11.87 yrs., range: 25-58 yrs.). In our proof-of-concept study of C-3 complex in schizophrenia, our primary efficacy outcome is baseline-to-week-16 change in PANSS total score, and neurocognitive index. We found that for 1gm and 4gm C-3 complex groups, within-subject analysis found significant differences in PANSS total score (p<0.003: 1 gm group; p < 0.01: 4 gm group paired t-test) and PANSS general psycho-pathology subscale score (P < 0.002: 1 gm group; p< 0.016 : 4 gm group paired t-test) (**Table 1 and Table 2**).

In view of the small sample size, we further analyzed the data using the non-parametric Wilcoxon rank sum test and found similar curcumin treatment effects in terms of statistically significant differences in both PANSS total score and PANSS general pathology score at the end of the 16-week treatment period compared with the baseline scores (Table 2). The ceiling effect, and the lack of sufficient statistical power, may have explained why we failed to find statistical significance at two tailed P < 0.05 level regarding baseline-to-16 week .change in BPRS and the 17-item HAMD score.

	1g group Mean (SD)		Statistics			
Outcome Measure	Baseline	Week 16	t-value paired	p-value	Cohen d (effect size)	Wilcoxon rank sum p-value
PANSS total score	65.0 (9.8)	51.5 (14.5)	5.4	***.003**	1.2	**.027**
PANSS positive scale	14.7 (4.5)	11.8 (4.2)	1.5	.197	.7	.172
PANSS negative scale	14.5 (4.3)	13.3 (4.6)	0.7	.493	.3	.586
PANSS general psychopathology	35.8 (4.9)	26.3 (7.1)	6.2	***.002**	1.7	**.028**
BPRS	37.4 (8.4)	30.6 (8.7)	2.1	.077	.9	.051
HAM-D (17 item scale)	13.1 (9.3)	6.9 (3.9)	1.8	.127	1.0	1.38

Table 1 : Curcumin C-3 Complex effects on Symptom profile in the 1 -gm Supercucumin treatment group
PANSS: PANSS : Positive and Negative Symptoms scale; BPRS: Brief psychiatric rating scale. HAMD-17 item: Hamilton Depression Rating scale. * week-16 score statistically significant from baseline p < 0.05

	4g group Mean (SD)		Statistics			
Outcome Measure	Baseline	Week 16	t-value paired	p-value	Cohen d (effect size)	Wilcoxon rank sum p-value
PANSS total score	61.9 (11.9)	46.6 (9.4)	3.5	***.010**	1.5	**.018**
PANSS positive scale	14.4 (3.5)	10.0 (2.7)	3.5	.011	1.5	.021
PANSS negative scale	14.1 (2.9)	11.9 (4.1)	1.8	.111	.7	.121
PANSS general psychopathology	33.4 (7.0)	24.8 (4.9)	3.2	***.016**	.2	**.012**
BPRS	31.4 (5.0)	30.3 (13.0)	0.3	.770	.3	.232
HAM-D (17 item scale)	11.9 (9.0)	7.0 (4.6)	1.7	.132	.7	.115

Table 2 : Curcumin C-3 Complex effects on Symptom profile in the 4 -gm Supercucumin treatment group
PANSS: PANSS : Positive and Negative Symptoms scale; BPRS: Brief psychiatric rating scale. HAMD-17 item: Hamilton Depression Rating scale. * week-16 score statistically significant from baseline at p < 0.05

For secondary efficacy outcome, we defined the response rate of curcumin as positive change of 30% or greater compared with the baseline to evaluate the dose - dependent efficacy of C-3 complex in schizophrenia. As shown in **Figure 2**, the response rates of PANSS total score for both 4 -gm group and 1-gm group were similar for both dosages and were over 80%.For both 4-gm and 1 gm Curcumin C-3 groups, both PANSS general psychopathology and PANSS-positive subscale score showed response rates higher than 70%.

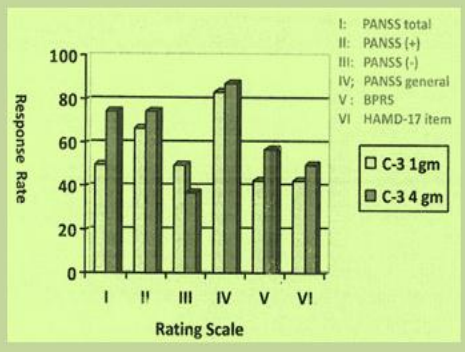

Figure 2 : Curcumin C-3 Complex Response Rate of Symptom profile in 1-gm and 4-gm Supercucumin treatment groups.
PANSS: PANSS : Positive and Negative Symptoms scale; BPRS: Brief psychiatric rating scale. HAMD-17 item: Hamilton Depression Rating scale. Response rate : >/= 30% post-treatment change compared to baseline value.

In view of the small sample size and the relative lack of statistical power, we chose to express the efficacy of curcumin in terms of Cohen's effect size independent of the sample size. Cohen's d effect size (ES) estimate is calculated by the formula as follows: the difference between baseline mean and the value at the end of the treatment period as divided by the standard deviation. We expressed the efficacy of curcumin C-3 complex with ES estimate for PANSS, Brief Psychiatric Rating scale: BPRS, and HAMD - 17 item, and Simpson Angus scale (SAS) and for Barnes Akathisia test (BAT). We repeated the psychiatric rating scales and TEAE, AIMS, SAS and at week 4, week 8 and week 16. Neurocognitive measures were repeated at the end of the 16-week period. For within-the-subject group difference, we adjusted for the correlation between the means. Effect sizes are expressed as points of Cohen's d score: d of 0.2 = small, 0.5 = medium, 0.8 and greater =large. Cohen's d statistics is independent of the sample size. As shown in **Table 1 and Table 2**, both 1 gm and 4 gm C-3 complex treatment groups produced large ES for PANSS total score and general psychopathology subscale. Medium ES were found for PANSS-positive subscale and HAMD-17item. The small ES in BPRS was somewhat unexpected for the C3 complex 4 gm group. The baseline score for PANSS negative symptom may not have been high enough to unmask the effect of curcumin. The study may not have sufficient power to detect the efficacy with respect to change in BPRS and HAM-D-17 item.

In reviewing the neurocognitive data summarized in **Table 3**, we found that for C-3 complex 1 gm group, the majority of the neurocognitive measures (8/11) improved, albeit non-significantly, over the16-week period. Similarly, for the C-3 complex 4 gm group, 9 of the 11 neurocognitive measures favored the active drug. For the 4 gm and 1 gm C-3 complex group, both reaction time and complex attention appeared to be somewhat impaired. Nevertheless, the aggregate neurocognitive index (NCI) of the C-3 complex 4 gm almost reached significance level (t =1.8, p=0.052, 1-tailed t-test). Effect size estimate favored C-3 complex treatment at 1 gm and 4 g dosages compared to baseline score when the participants were maintained on first and second generation of antipsychotics. The effect size estimates for both dosages of C-3 complex: 1 gm and 4 gm were 1.0 and 0.8, with moderate variability in the individual neurocognitive domains.C-3 complex.

	1g C-3 Complex group			4g C-3 Complex group		
Outcome Measure	Baseline mean (SD)	Week 16 mean (SD	% change (Cohen's d effect size)	Baseline mean (SD)	Week 16 mean (SD)	% change (Cohen's d effect size)
Neurocognitive Index (NCI)	2.0 (2.0)	12.0 (12.7)	+6.0 (1.0)	5.7 (12.3)	22.7 (31.2)	+17.0 (0.8)
Composite Memory	8.5 (14.3)	17.3 (14.7)	+8.8 (0.60)	15.0 (18.1)	23.6 (33.6)	+8.6 (0.32)
Verbal Memory	10.3 (13.3)	11.5 (7.6)	+1.2 (0.11)	15.1 (18.5)	26.9 (36.1)	+11.8 (0.41)
Visual Memory	11.0 (17.4)	34.3 (28.1)	+23.3 (1.0)	17.7 (20.1)	28.1 (27.4)	+10.4 (0.43)
Processing Speed	12.0 (13.8)	15.8 (19.4)	+3.8 (0.23)	19.7 (36.8)	26.4 (30.4)	+6.7 (0.20)
Executive Functioning	1.0 (0.0)	17.0 (18.5)	+16.0 (0.23)	13.4 (32.4)	22.3 (22.9)	+8.9 (0.32)
Psychomotor Speed	2.6 (1.5)	2.0 (1.0)	**-0.6 (-0.47)**	15.9 (36.7)	30.1 (37.9)	**+14.2 (0.76)**
Reaction Time	12.3 (12.4)	27.3 (24.7)	**+15.0 (-0.76)**	8.4 (11.3)	35.1 (39.9)	+26.7 (0.91)
Complex Attention	1.0 (0.0)	18.2 (25.5)	**+17.2 (-0.95)**	12.4 (30.2)	23.9 (28.4)	**+11.5 (0.39)**
Cognitive Flexibility	1.0 (0.0)	11.6 (14.9)	+10.6 (1.00)	13.4 (32.9)	21.1 (24.0)	+8.1 (0.27)
Total Time	41.3 (16.4)	29.5 (3.3)	**-11.8 (-0.89)**	46.3 (25.2)	37.9 (18.8)	**-8.4 (-0.38)**

Table 3 : Curcumin effects on Neurocognitive performance in schizophrenia subjects administered 1 gm and 4 gm Supercurcumin, showing pre- and post-treatment effects of curcumin on neurocognitive scores from VITAL-SIGN computerized Neurocognitive test battery. * statistically significant at $p < 0.05$ level.

Adjunctive treatment at 1gm and 4 gm appeared to be highly tolerated as no severe adverse events were reported. Subjective reports by the participants included decrease in irritability, level of drowsiness, memory problems, anxiety, confusion, non-specific skin irritations and chest tightness: the results of non-parametric Kendall Rank correlation coefficient (tau c) showed significant tau c coefficients ($p < 0.05$, two tailed). In examining the cardiac-metabolic profile from TEAE in our cohort of schizophrenic subjects, we did not observe any increase in BMI, changes in body composition, blood pressure and pulse (**Table 4 and Table 5)**. We are uncertain whether the one patient who reported increase in sexual activity during C-3 complex adjunctive treatment was directly related to C-3 complex. Since premorbid interpersonal relationship, difficulty has confounded the clinical presentation. The side effects were generally mild and transient. In monitoring for adverse changes in extrapyramidal motor symptoms: akathisia, Parkinsonian tremor, rigidity, and dyskinesia, we did not find any significant differences in the scores for SAS, AIMS and Barnes Akathisia test (BAT) between the 4 gm or 1 gm C-3 complex group.

	C-3:1 g group N=7		C-3: 4 g group N=8	
	Mean (SD)		Mean (SD)	
	Baseline	Wk 16	Baseline	Wk 16
Systolic BP	125.4 (10.9)	117.9 (20.0)	116.6 (17.1)	112.5 (12.8)
Diastolic BP	79.6 (6.4)	78.6 (13.1)	74.4 (5.0)	76.3 (5.2)
Pulse	72.7 (11.5)	73.6 (5.7)	73.9 (7.0)	78.0 (8.1)
Core body Temperature(Celsius)	36.4 (0.5)	36.1 (0.2)	36.1 (0.3)	36.2 (0.2)
Weight (lbs)	194.1 (51.3)	195.9 (55.7)	193.0 (64.5)	194.7 (65.7)
% fat	29.7 (8.6)	31.7 (7.7)	28.1 (10.6)	27.8 (9.9)
Waist circumference (cm)	96.0 (19.2)	100.6 (20.4)	98.3 (19.0)	100.1 (16.1)
% lean body mass	37.9 (6.4)	34.0 (4.8)	38.6 (5.6)	37.4 (5.7)
% total body water	51.2 (6.2)	49.8 (5.7)	52.5 (7.8)	51.2 (7.9)
Basal metabolic rate	1750.6 (418.7)	1721.0 (391.0)	1797.5(244.1)	1874.1 (522.9)

Table 4: Vital signs Monitoring during Supercurcumin Treatment

*Adverse events	Treatment groups	
	1 gm Supercure™	4 gm Supercure™
headache	14.3 %	.....
dizzy spells	14.3 %	.....
tinnitus	14.3 %	12.5 %
coughing sensation	14.3 %	.....
dry mouth	14.3 %	12.5
appetite increase	14.3 %	12.5
thirst sensation	14,3%	.....
libido change	\14.3% (increase)	12.5 (decrease)
sleep disturbances	14.3 %	.....

Table 5: Treatment emergent adverse events during Supercurcumin treatment:

IV. DISCUSSION

We demonstrated for the first time beneficial effects of Curcumin C-3 Complex with Bioperine (Supercurcumin™) in a cohort' of patients diagnosed as schizophrenia exhibiting marked persistent positive and negative symptoms and cognitive impairment. Our findings differ from the data from a randomized placebo-controlled study of curcumin in schizophrenia [28]. The RCT study used a different formulation of curcumin capsules (Theravalues Corporation, Tokyo, Japan) at a fixed daily oral dosage of 360 mg over 8-week period. The results showed that curcumin increased the plasma level of Brain-derived Neurotrophic factor (BDNF) compared with placebo. No difference was found between the schizophrenia group and the placebo group in either the core symptoms of schizophrenia as monitored with BPRS (Brief Psychiatric Rating scale) or the neurocognitive domains as measured with MATRICS, We interpret the discrepancy as related to the dosage regimen and the bioavailability differences in standardized formulations of curcumin used in the two studies.

Despite the small sample size and hence lack of sufficient statistic power to detect intrinsic level of significance, our effect size analysis indicates a strong positive effect of curcumin in enhancing the neurocognitive index of the CNS-VS neurocognitive battery of tests: Cohen's d effect size of 1.0 and 0.8 for C-3 complex 1 gm and 4 gm groups. **(Table 3)**. A previous study in first-episode schizophrenia reported effect size of 0.38 attributable to practice effect in subjects maintained on either risperidone or olanzapine [29]. Intriguing enough, an effect size of 0.33 has also been found in normal healthy controls administered the same battery of tests as the CNS-VS battery used in our study. The results of our pilot study indicated an adjusted effect size of 0.42-0.62 (moderate) for curcumin treatment effect in schizophrenia, after accounting for factors such as exposure, familiarity and procedural learning). Since our study cohort had severe cognitive deficits at entry to the study', our finding of curcumin exhibiting tentative cognitive enhancing effects, albeit preliminary, raise an intriguing question as to the emerging role of curcumin as potential cognitive enhancing strategy in schizophrenia.

Negative symptoms overlap considerably with the cluster of depressive symptoms in schizophrenia. Sub-syndromal depressive syndrome was found to be associated with an overall increase in the severity of positive and negative symptoms of schizophrenia [30]. Our finding on the positive effect of curcumin on sub-syndromal depressive symptoms in schizophrenia is consistent with the results of seven clinical trials of curcumin in depressive symptoms and major depressive disorder [31],[32],[33],[34],[35],[36],[37]. From analysis of the data from the cohort of 377 patients with depression, the pooled standardized mean difference (SMD) from the baseline score in Hamilton Rating Scale for Depression scores (pooled SMD -0.344, 95% confidence interval -0.558 to -0.129; P = .002) was found to be highly significant. [38]. The results provide preliminary evidence for efficacy of curcumin in ameliorating the depressive symptoms. Reduction of anxiety symptoms was reported in 3/6 of the clinical trials.

Our study with curcumin provides preliminary evidence of the cognitive enhancing effects of Supercurcumin™. Our study has certain methodological limitations: the small sample size, the lack of placebo arm, and the relatively short treatment period, in schizophrenia, the persistence of cognitive impairment rekindles debate on the controversial issue of schizophrenia as a variant of dementing process. Emil Kraepelin pioneered in conceptualizing the cognitive deficits of schizophrenia as the "Dementia Praecox' paradigm of failed neuro-regeneration [39]. A recent Genome-Wide-Association-study(GWAS) conducted by the Schizophrenia Working Group of the Psychiatric Genomics Consortium, found evidence for insidious "dementing process" underlying the cognitive deficits in schizophrenia [40]. The converging pathways derived from the 108 genetic loci hits converge upon dopamine metabolism, with functional spinoffs on three pathways: immune modulation, calcium signaling and synaptic plasticity.The mode of action of curcumin fortuitously embraces the three pathways in the GWAS study [41],[42],[43],[44].

Taken together, we interpret our positive findings of Curcumin C-3 complex in schizophrenia in the context of curcumin as the pivotal master in reprogramming the epigenetics network regulating multiple downstream signals related to neuro-inflammation, oxidative stress and synaptic plasticity. The pleotropic actions of curcumin in modulating the sensitivity of diverse neurotransmitter and signal transduction systems: dopamine, NMDA(N-methyl-D-aspartic acid) metabotropic and ionotropic receptor complex and serotonin, synergize its modulatory effects on the epigenetics circuitry in schizophrenia [45]. Curcumin distinguishes from most antipsychotics in exhibiting concomitant anti-Parkinson activity in translational genetic model of Parkinson disease [46].

V. CONCLUSION

Our preliminary study in schizophrenia shows that the novel formulation combining curcumin with piperine: black pepper: Super curcumin™, corroborates the claim that pepper increases the bioavailability of curcumin by as much as 2,000 x fold [44]. The sub-optimal pharmacokinetic profile of curcumin most likely explains the discrepant findings of studies of oral curcumin formulations in Alzheimer dementia [47]. Curcumin belongs the master regulator of multiple epigenetics targets implicated in neuro-epigenomes-driven chromatin remodeling and neuro-inflammation pathways genes, and plasticity gene [48], [49]. A recent PET imaging study with the specific HDAC ligand: [C14]-Martin stat [50] has found that schizophrenia subjects exhibited altered HDAC expression in the dorsal-lateral prefrontal cortex (DLPFC) compared with healthy control. HDAC expression positively correlated with cognitive performance scores in schizophrenia and schizoaffective disorder. For optimizing curcumin, nanotechnology can optimize targeted drug

delivery system [51], [52]. Repurposing Liposome-based-curcumin formulation (Lipocurc™, Sign Path Pharm. PA USA) from oncology to CNS disorders can be transformative approach in treatment refractory schizophrenia [45], [46]. Phase I trial of Lipocurc™ in normal healthy control subjects has demonstrated a very favorable safety profile [53]. Taken together, our preliminary study highlights pharmacological targeting of dysregulation of epigenetics signaling of HDAC inhibition [54] may be a heuristic roadmap in developing novel therapeutics in schizophrenia.

VI. ETHICS APPROVAL AND CONSENT

The study was approved by Institutional Research Ethics board USA : Aspire LLC 9320 Fuerte Drive, Suite 106 La Mesa CA 91941 USA and managed by the Lawson Health research Institute London ON Canada. We certify that study was approved by Aspire IRB LLC Calif USA and all participants signed informed consent prior to entry to the study. The study was formally registered at NIH ClinicalTrials.gov Identifier: NCT01875822. The trial registered June 2009 and completed May 2012. Informed consent was sought for publication of the aggregate data. The study protocol was reviewed and approved by the Coast Independent Review Board CO USA in Oct. 2009.

VII. AUTHOR CONTRIBUTIONS

SC ,MWF ,VB, KT, ZC contributed equally towards the design ,execution and interpretation of the results and significance of the study. All the co-authors have contributed research ideas, clinical perspectives on adjunctive treatment of schizophrenia in the context of targeting epigenetics signaling in CNS disorders. KT, ZC and HR has made special contributions in reformatting all the data and presented preliminary results of Curcumin C-3 complex study in schizophrenia at the American Psychiatric Association meeting New Research Poster session in San Francisco USA in 2013. We express special thanks to ZC, YB for their statistical expertise in statistical analysis. We would like to acknowledge the selected group of biomedical sciences trainees: KT, HR, VS, MW, ZK and AC for their robust energies in literature search, in sharing and reviewing relevant literature on epigenetics. KT, HR, VS, MW have contributed towards acquiring clinical trial skills under the dynamic leadership of MWF .

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X. CONFLICTS OF INTEREST

The authors declare no conflict of interest."

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