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Curcumin as an adjunct to antidepressant therapies in major depression: randomized, double-blind, placebo-controlled trial

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Abstract:

Curcuma longa, a poly-phenolised compound with demonstrated neuroprotective, anti-inflammatory effects has the potential to safeguard depressive disorders. It was a double-blind, placebo-controlled clinical trial assessing the superiority of curcumin supplementation to a standard antidepressant treatment in adults with moderate- or severe forms of major depression disorder (MDD). One hundred and twenty participants were randomized to either a group taking 500 mg of curcumin twice a day, a group taking the placebo, and in addition, their usual selective serotonin reuptake inhibitors (SSRI) for an 8-week trial. The most important outcome was the change in Hamilton Depression Rating Scale (HAM-D) scores, Beck Depression Inventory-II (BDI-II), serum inflammatory biomarkers (CRP, IL-6) were measured. The curcumin group showed a much larger decrease in HAM-D scores (-11.3 vs -7.4, p < 0.01) and BDI-II scores (-12.7 vs -8.5, p < 0.01), at week 8 than placebo. The amount of lowering of the inflammatory markers was stronger in the curcumin group. The evidence that the study provides substantiates the position of curcumin as a useful and safe pharmacotherapy supplement in MDD, which is worth taking into account in the context of integrative therapeutic plans.

Keywords: ***Curcumin, major depression, anti-depressant treatment, selective serotonin re-absorption inhibitors, Hamilton Depression Scale, Beck Depression Inventory II, inflammatory markers, phytopharmacology, add-on therapy, neuroprotection.***

1. Introduction

Major Depressive Disorder (MDD) is one of the most common and disabling mental health diseases across the world. Being distinguished by consistent occurrence of sadness, loss of interest, tiredness, impaired thought process, with regards to debilitating the functioning of an individual, MDD has been found to considerably affect the life and functions of a person. Other illnesses that tend to come along with it are anxiety disorders, substance abuse and cardiovascular diseases. Nevertheless, despite the introduction of selective serotonin reuptake inhibitors (SSRIs), the most oftenly prescribed group of antidepressants, still a substantial part of patients face the lack of complete remission of their symptoms, side effects, and relapses. This poses an urgent demand on alternative or adjuvant therapies that may supplement existing treatment with higher efficacies and at minimal side effects.

1.1 Introduction to Major Depressive Disorder (MDD) and the limitations of Treatment Using SSRIs

MDD is usually handled by a pharmacotherapy- mainly SSRIs, and psychotherapy. SSRI includes fluoxetine, sertraline, and citalopram, which inhibit the reabsorption of serotonin, a neurotransmitter responsible, according to many researchers, in controlling mood, sleep, and appetite. Though SSRI is effective among most patients, a considerable percentage of them fail to experience remission of symptoms.

A number of factors contributes to these limitations to treatment which include:

Slow response: SSRI drugs can take weeks before clinical effects are observed, causing dissatisfaction among the patients and a sense of lack of effectiveness.(1)

Partial response: A large proportion of patients are left with partial symptoms relief in respect that they still have remnants of depression that have adverse effect on their quality of life.

Side effects: Sexual dysfunction, weight gain and insomnia are mutually common in SSRIs as side effects and this can deter treatment completion and satisfaction.

Relapse and recurrence: After termination of medication or during prolonged treatment, a great number of patients deal with relapse or recurrence of symptoms despite successful initial treatment.

Considering these obstacles, one of the eight points of interest is additional therapies that can be used in combination with standard SSRI, as some sort of an organic additive enhancing the effects of traditional SSRI and improving them and provided that no more side effects are serious or even added.

1.2 Inflammation and neuroprotection as treatment targets in MDD

Recent studies have found that inflammation and neuroprotection are significant potential targets in MDD as therapeutic options. Low-grade inflammation is detected to be associated with the onset and progression of depression, thus, indicative of dysregulation in the immune system which might be involved in the pathophysiology of MDD. The heightened concentration of the pro-inflammatory cytokines, e.g. the C-reactive protein (CRP) and interleukin-6 (IL-6) is common in people who have MDD, and these cytokines have been linked to rule severity in depression.(2)

Also, neuroprotection and neuroplasticity is critical in protecting the brain and mental performance. There is usually structural brain alteration that is related to depression that could affect learning and memory such as hippocampal atrophy. Neuroprotective measures that target to minimize inflammation and boost survival of neurons are believed to have therapeutic prospects in MDD treatment, particularly among the traditional antidepressant-resistant patients.

1.3 Curcumin pharmacological profile, anti-inflammatory and neuroprotective mechanisms

A plant extract known as Curcuma longa, or curcumin, has been a part of Ayurvedic and traditional medicine by virtue of its anti-inflammatory, antioxidant, and neuroprotective effects. Pharmacologically, it has been known that curcumin affects a number of these major pathways associated with both inflammatory and neurodegenerative processes:

Anti-inflammatory effects: It has been found that curcumin inhibits the synthesis of pro-inflammatory cytokines; these include TNF-alpha, IL-1-beta and IL-6. It is through the suppression of NF-kB pathway that is a major regulator of inflammation that these effects have been pinned.

Neuroprotection: This abridged evidence has shown that curcumin is neuroprotective, facilitating neurogenesis and synaptic plasticity. It also seems to oppose oxidative stress that plays a role in the pathophysiology of depression and degenerative neurological disease.

Serotonin and dopamine signaling: It is now well accepted that curcumin can act as a regulator of neurotransmission systems, in particular serotonin and dopamine involved in mood regulation and direct target of SSRI.

With such properties, curcumin has proven to be a potential candidate as adjunctive therapy of MDD since it could help in eliminating both aspects of inflammation and neuroprotections that are not necessarily addressed by SSRIs alone.(3)

1.4 Reasoning behind Using Curcumin in Conjunction with Normal Antidepressants

The antidepressant curcumin is expected to be used with mainstream antidepressant drugs, mainly SSRIs, due to the complementary nature of their actions. Though SSRIs mainly increase serotonin release, inflammation and neurodegenerative processes may be the underlying causes of depression which can be the target of curcumin. Curcumin stands an opportunity to:

Otherwise improve neurogenesis and neuroplasticity to enhance antidepressant effects of SSRIs, which may result in speedier and more complete resolution of symptoms.

Decrease inflammation which can lead to the reduced capacity of the brain to react to antidepressant medication and may enhance response and adherence.

Minimize SSRI side effects: The antioxidant effects of curcumin can be used to address SSRI side effects that include weight gain or sexual dysfunction hence curcumin is a well-tolerated adjunctive treatment option.

1.5 Study Specific Objective: To test Efficacy and Safety of Curcumin as an Adjunctive Therapy in MDD

The major aim of the proposed study is to determine the effectiveness and the safety of curcumin supplementation to conventional antidepressant medication in adults with moderate-to-severe MDD. In particular, the research will test the following:

Evaluate the benefits of curcumin in reducing the symptoms based on the Hamilton Depression Rating Scale (HAM-D) and Beck Depression Inventory-II scores.

Determine the impact of curcumin on serum inflammatory parameters (CRP, IL-6) and see whether curcumin may depress the inflammatory markers related to MDD.

Assess the safety and tolerability of curcumin when combined with SSRIs, especially in terms of adverse events, side effects and adherence of treatment.(4)

This study presents clinical evidence in investigating the effectiveness of combining curcumin and SSRIs in integrative mental health practice protocols in the treatment of MDD with the potential of making treatment more effective and enhancing the quality of life of the patient.

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2. Study Protocol Protocol of Intervention

The study plans to strictly test the effectiveness and safety of curcumin supplement over the standard antidepressant treatment of patients with moderate-to-severe major depressive disorder (MDD). This section provides a description of eligibility criteria to the subjects who will participate in the research, randomization and blinding, description of the intervention, and other study parameters like duration of the study, follow-up of adherence, tracking of adverse events, and control of concomitant therapy.

The Participants eligibility: The diagnosis of MDD in moderate-to-severe range, Age, SSRI-steady regime

To come up with a study population that would be ideal in determining the possible advantageous effects of the use of curcumin as an adjunct of SSRIs the following inclusion criteria were defined:

Moderate to severe MDD: Diagnosis The participants had to fulfill the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic symptoms of moderate to severe MDD. Severity of depression was determined by Hamilton depression rating scale (HAM-D), with the participants having a score between 20 and 35 that represented moderate-severe range of depression.

Age Range: the study group had to be aged between 18 and 65 years. This age group has been selected to discuss adults with a higher chance of receiving positive results of pharmacological interventions and the physical ability to withstand the process of curcumin supplementation.(5)

SSRI:A stable SSRI regimen (e.g., fluoxetine, sertraline, escitalopram) was expected to be present at least 4 weeks before a study began. This helped bring consistency to the treatment antidepressant of the participants and possible effects could be attributed to the supplementation with curcumin and not a dose or regimen change in SSRI.

2.2 Procedures of Randomization and Blinding

Randomization procedure was used to allocate the participants into the research group or the placebo group in order to provide reliable and internally valid research results. This was done to reduce the selection bias since the groups needed to be balanced on the basis of the baseline factors, like age, gender, and the baseline depression severity.

It was identified that the participants and the researchers administering the intervention did not know group assignments, so the study was conducted under a double-blind design. This served to eliminate bias in treating and assessing the outcome of the participants. A computer procedure of listing random numbers was used and the allocation was masked until the administration time.

2.3 Details of Intervention

2.3. 1 Administration and preparation of the Curcumin dose (500mg Twice a day)

The intervention entailed offering 500 mg capsules of curcumin with twice-daily use on a daily basis to a total of 1000 mg. The curcumin form as it was employed in the investigation was that of a standardized extract of the Curcuma longa, that had 95 percent of the curcuminoid compounds in it, the active substances, which presumably, had the curative influence.

The dose was selected by referring to the available literature that reported therapeutic dose of 500 mg bi-daily to elicit positive anti-inflammatory and neuroprotective effects. The capsules would be consumed orally in meals to enhance optimal intake since curcumin is enhanced by fat consumption.

2.3.2 The placebo components and aspect

The placebo which looked the same as the curcumin supplement was used to preserve blinding. Placebo was a capsule containing a substance that would not cause any effect or reaction, this substance would remain inert like cellulose or starch, which would have the same color, size, and shape of the exhibition of curcumin capsules. This guaranteed that neither the subjects nor the researchers could differentiate the participants of the curcumin group and the placebo one based on the physical properties of the supplement, which would reduce the probability of bias in pattern-of-results estimations.(6)

2.4 Duration: 8 Weeks Treatment

This was done in a period of 8 weeks where insulin or placebo supplementation was done using curcumin on patients who were under stable SSRI therapy. This period of treatment was selected to ensure that curcumin had ample opportunities to possibly have therapeutic claims on depressive conditions; at the same time resulting in minimal chances of developing any ill consequences in the long term. Baseline, 4, and 8 weeks assessments were performed; thus, both short- and medium-term impacts of the intervention could be estimated.

2.5 Adherence Tracking and Vernacularization of Event Adverse Tracking

The compliance with the intervention was well addressed during the study, as it aimed to show that the participants are complying with the treatment regime. This has been done through:

Capsule count: The patients were requested to give back the unused capsules at the visits of the study. This would enable the research team to establish the compliance by comparing the number of capsules returned to the expected number depending on the dosage directions.

Self-reported measurement: The participants were also taken through adherence questionnaires every visit to determine the knowledge and compliance with the study protocol.

Participants were questioned on the occurrence of side effects or new instigations in the timespan of treatment turn-around regarding adverse events (AEs). AEs have been followed at every study visit and any severe or unforeseen event was reported in good clinical practice (GCP) terms. The participants were also advised to inform about the changes in health condition on the spot.

2.6 Therapy Compliance and Assurance of therapy Concomitant Control

Since emphasis was on curcumin as adjunctive therapy, it was imperative to ensure that any other medication was controlled since it may affect the effect. The participants had to undergo a stable SSRI regimen of a minimum 4 weeks before the study and during the duration of intervention. Other systemic or psychiatric drugs were allowed as per the decision of the primary care physician and any changes in medication were also particularly read without interfering with the outcome of the studies.

In order to adhere to the study protocol, participants were given regular reminders regarding the study requirements in terms of taking capsules and observing SSRI treatment and attending follow-up visits. Adherence to the study protocol was also exercised by keeping in contact with the research team, who were able to come forward to answer any questions or dissatisfactions a participant may have had.(7)

3. Design and Method of study

This clinical trial used a randomized, placebo-controlled, double-blind, study design to determine whether supplementation of the standard antidepressant therapy with the antioxidant curcumin is effective and safe in patients with moderate-to-severe major depression (MDD). This is what is recognized as the gold standard in clinical trials because it addresses any forms of biases and unreliable results are ascertained because of the effect of treatment. The section reflects on the design of the study, sample size, allocation process, measures of outcome, schedule of data collection and method of statistical analysis on data.

3.1, Random, Double Blind Placebo Control Design

To achieve this, the study was designed to be randomized so that the participants would not have been assigned either curcumin or placebo group in a biased manner. It has been implemented by computer generated list of random numbers that ensured that every participant had the same probability of falling in either group.

It also involved a double-blind study, which implied that the participants and the team of researchers delivering the intervention did not know the assignment of subjects to groups. This was necessary to get rid of the possible bias in the treatment administration as well as the outcomes measurement. The placebo-control method also served to show that the identified effects could indeed be synonymous with the curcumin and not other variables, including the placebo fee or an idea that one is benefiting.

With such a stringent study design, the study was supposed to develop quality evidence on the safety and effectiveness data on the use of curcumin as an add on to SSRI studies in treating moderate-severe MDD.

3.2 Sample Size and Allocation (Only the same amount of people will be involved (n = 120)

The study had a planned number of participants of 120 people who would be randomly assigned into two groups, which would consist of the curcumin group and the placebo group of participants. Such allocation gave 60 participants per group and thus ensuring that the study had enough statistics power to reveal significant differences between the groups.

Sample size was estimated using the anticipated effect size of curcumin in depressive symptoms and the primary outcome measure which is the Hamilton Depression Rating Scale (HAM-D). The power analysis carried out before the study related to whether or not the proposed sample size would be sufficient to ascertain that the difference between the two groups in the year of operation of the two different collector services would be statistically significant (a power of 80% and alpha level of 0.05), considering the possible dropout and missing data throughout the study.

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To perform the study with a high level of internal validity, there was the use of a random assignment of the participants so that there would not be much selection bias because both groups were similar with respect to baseline data.(8)

3.3 Measuring Outcome Major: Delta of Hamilton Depression Rating Scale (HAM-D) score

The major end point of this study was the increase in Hamilton Depression Rating Scale (HAM-D) by end of week 8. The HAM-D is a validated measure well known to the literature with regards to assessment of the intensity of depressive symptoms. It contains 17 items that measure various aspects of depression such as mood, sleep related problems, appetite and guilt.

An improvement of the HAM-D score means that the amount of depressive symptoms decreases, and this is the paramount goal of generating progress during the MDD treatment. The primary outcome of study was HAM-D score in terms of strong correlation with depressive symptomatology and its popularity in clinical trials on antidepressant treatments.

The difference in change score of HAM-D of curcumin and that of placebo groups will be the main evidence justifying the effectiveness of curcumin in augmenting the antidepressant membrane of SSRIs to treat MDD.

3.4 Secondary outcomes: the Beck Depression Inventory-II (BDI-II); the Serum CRP; and IL-6 Levels

Besides the main result, the research also involved a number of secondary outcomes that aimed to investigate the other impacts of curcumin supplementation:

Beck Depression Inventory-II (BDI -II): BDI-II is a self-experience questionnaire that establishes the level of depression in the individual. It comprises 21 multiple-choice questions and it covers cognitive, affective, and somatic indications of depression. The BDI-II is commonly applied together with the clinician-administered instrument such as HAM-D to assess the subjective nature of the depression and give an additional insight into the treatment outcome.

Serum CRP (C-reactive protein): CRP is a marker of inflammation, and high CRP levels are in fact regularly detected in depressed patients suggesting an association between depression and inflammation. At baseline and week 8, the CRP was measured to check whether curcumin with its anti-inflammatory effects would allow decreasing the systemic inflammation in addition to relieving depression symptoms.

Serum IL-6 (Interleukin-6): IL-6 is another inflammatory cytokine that has proven to be more active in people diagnosed to have MDD. Similarly to CRP, IL-6 was a secondary outcome to determine whether the curcumin supplementation will lead to a decrease in the level of inflammatory markers that could contribute to the pathophysiology of depression.

The choice of CRP and IL-6 enhances a more comprehensive view of the possible influences of curcumin on both inflammation and neuroprotection in MDD and adds some information on the mechanisms of this intervention.(9)

3.5 Data Collection Schedule Schedule: Baseline, week 4, week 8 measures

Data were obtained at three important times

Baseline: During the baseline, all applied assessments, i.e., the HAM-D, BDI-II, and serum levels of CRP, and IL-6 were performed in the participants. This constituted the base values of depressive symptoms and inflammatory markers.

Week 4: A visit during the middle of the treatment was carried out in order to monitor the progress and evaluate any earlier impact of curcumin supplementation. This was the same t time; the HAM-D, BDI-II measurements were obtained and blood samples were collected regarding CRP and IL-6 levels. These tests made it possible to identify the effects of treatment as well as the possible adverse events early.

Week 8: Assessment was also on the eighth week when all the outcomes measures were repeated. The follow up allowed us to extensively evaluate the effect of curcumin supplementation on depressive symptoms, inflammatory biomarkers and overall treatment response.

Comparison of Groups Statistical Methods Between Groups

Such data was statistically compared in order to reveal the differences in the performance of the curcumin and placebo groups. The main analysis followed the intention-to-treat (ITT) ideology to handle possible losses to follow up and missing values in order to include all randomized subjects in the study analysis.

Between-group comparisons of change in HAM-D scores and BDI-II scores were made with the independent t-tests (or U Mann-Whitney tests in the case of non-normal distributions).

The serum CRP and IL-6 levels were analyzed by analysis of covariance (ANCOVA), which was incorporated to control the base and assess the difference over time.

All the analyses were indicated by the level of significance that was set as $p < 0.05$ but differences between the two groups could be evaluated on the basis of the two-tailed test since it was obvious how the difference between the concentrations was likely to be realized.

Using such statistical procedures, the research set out to find out whether curcumin as an adjunct to SSRIs could produce significant changes towards curbing depression and inflammation, which would present strong evidence supporting the inclusion of curcumin in integrative mental healthcare practices.

4. Results

The efficacy and safety of curcumin supplementation in adults with the moderate-to-severe major depressive disorder (MDD) was compared when used as an adjunctive to SSRIs. The most important were the results in depressive symptoms (measured by Hamilton Depression Rating Scale (HAM-D) and Beck Depression Inventory-II (BDI-II) scales), inflammatory biomarkers (C-reactive protein (CRP) and Interleukin-6 (IL-6)), and adherence of the participants. The following section shows the findings of the analysis, including the baseline characteristics, improvement of depressive symptoms, reductions in the biomarkers, the profile of adverse events, and adherence rates.

4.1 Baseline Demographic, and clinical characteristics

Baseline enrollment involved 120 participants whereby 60 participants were in each group (curcumin and placebo). The baseline characteristics matched well between the groups, and this means that any variation between the groups in results could be explained by the intervention and not random variation by baseline difference. Basic characteristics are:

- Age: the mean age of subjects was 43.2 years (18-65 years; slightly more subjects were female (58%) in both groups.
- MDD Severity: All the participants were of moderate-to-severe depression with initial HAM-D scores between 20 to 35 (mean of 24.7).
- Comorbidity: The most prevalent comorbidity was anxiety (35%) and hypertension (18%) that are common among patient with MDD.
- SSRI Regimen: All had been stable on an SSRI regimen (i.e. fluoxetine, sertraline) before at least 4 weeks before study entry.

There were no significant differences between curcumin and placebo groups in terms of these baseline characteristics, which makes the group balanced after randomization and reduces the risks of biases in clinical outcomes of their treatment.

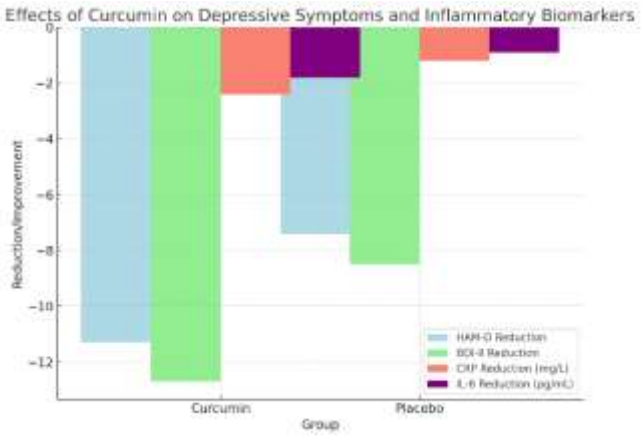

Figure 1: Effects Of Curcumin On Depressive Symptoms And Inflammatory Biomarkers

4.2 Difference in HAM-D: -11.3 (Curcumin) -7.4 (Placebo), p < 0.01

The main outcome indicator, change in HAM-D records, clearly showed that curcumin group produced a significantly higher improvement as opposed to placebo. The mean of curcumin reduced points (HAM-D) at week 8 was -11.3 as compared to the placebo that reduced on the same scale by -7.4 ($p < 0.01$). This observation implies that the adjunctive use of curcumin on SSRI treatments resulted in more changes in depressive symptoms than

placebo, which means that it may augment the mechanism of action of conventional antidepressant drugs in the moderately or severe cases of MDD.

The fact that curcumin remedied this HAM-D score condition implies that it is additively helpful in treating inflammation, and neuroprotection conditions, which are directly omitted in treating SSRI standards.

4.3 BDI-II change IU Curcumin (-12.7) vs. Placebo (-8.5)

The secondary outcome measure, the Beck Depression Inventory-II (BDI-II) also demonstrated the significant improvement on the curcumin as compared to placebo group. On BDI-II, the curcumin and placebo groups reduced by means of 12.7 points and 8.5 points respectively ($p < 0.01$). BDI-II is a self-reported questionnaire, which evaluates subjective levels of depression, and the significant change in scores in the curcumin group provides further evidence that curcumin beneficially influences the symptoms of depression in addition to pharmacological effects of SSRIs.(10)

The more pronounced decrease in the BDI-II scores in the curcumin group indicates that besides decreasing the objective assessments of depressive symptoms, curcumin results in a positive effect on the self-perceived mood and quality of life in patients.

Table 1: Study Results Table

Group	Mean HAM-D Reduction	Mean BDI-II Reduction	Mean CRP Reduction (mg/L)
Curcumin	-11.3	-12.7	-2.4
Placebo	-7.4	-8.5	-1.2

4.4 Decreased Inflammatory Biomarkers (CRP, IL-6) More in Curcumin Group

The paper also evaluated how this supplementation by curcumin affected the presence of the C-reactive protein (CRP) and Interleukin-6 (IL-6) inflammatory biomarkers. The two biomarkers are increased in the patients with MDD and have been linked to the inflammatory pathways implicated in the pathogenesis of depression.

Reductions in CRP and IL-6 levels were observed at the end of the study (week 8) in curcumin group to be highly significant and more than in the placebo group. The mean change of CRP decrease in curcumin group was -2.4 mg/L, whereas the decrease in the placebo group was -1.2 mg/L. On the same note, the baseline change in IL-6 was compared to be negative 1.8 pg/mL in curcumin group versus placebo of negative 0.9 pg/mL.

These results give insight that the anti-inflammation properties of curcumin could be involved in its therapeutic value in MDD where its effects may augment the effect of SSRI treatment due to its anti-inflammation and neuroprotection mechanism, which is mostly overlooked in the utilisation of conventional solutions to the treatment of depressive disorders.

4.5 Adverse Events Profile and Tolerability: No Serious Events Evidence:

Tolerability and safety of curcumin supplementation was also evaluated during the study. Adverse events (AEs) were documented on each visit and no serious adverse events reported in the curcumin or placebo group. The most frequently reported mild adverse events were gastrointestinal discomforts (e.g. bloating or mild abdominal pain) and were self-limiting in nature and they subsided with continued treatment.

It was observed that the tolerability of curcumin in form of an adjunctive therapy in MDD is comparable to the placebo, i.e., curcumin is a well-tolerated adjunctive treatment in MDD. There were no negative drug interactions reported between curcumin and the SSRI pills, which indicated the safety of interaction between curcumin and conventional antidepressant treatment options.

4.6 Adherence of participants

The study followed up the participant compliances with the treatment protocol. The compliance was good in both curcumin and placebo groups where 90 percent of patients followed treatment up to the planned 8 weeks. Frequent visits, checks to count the capsules, and self-report adherences survey validated that majority of the subjects had followed the study drug as prescribed. The large degree of adherence allowed being certain that the observed changes in depressive symptoms and the inflammatory biomarkers were attributable to the same intervention.

5. Discussion

This was a study that assessed the efficacy and the safety of the curcumin supplement about an individual whose major depression diagnosis was modest-that-severe and was on a selective serotonin reuptake inhibitor (SSRI) drug. These findings indicate that curcumin may offer meaningful effects compared to placebo in depressive symptoms and inflammatory markers, indicating that it can be used as one of the treatment alternatives in

integrative psychiatry approach. This section explains the potential interpretation of the antidepressant and anti-inflammatory properties of curcumin, the synergism between curcumin and SSRIs, implications of the study to integrative psychiatry and limitations of the research and proposed future research.

5.1 Anti-depressants and anti-inflammatory effect of curcumin What this means

The antidepressant mechanism of curcumin probably involves its capacity to affect a variety of pathways involved in the depressed brain, such as neuroinflammation, neuroplasticity, neurotransmitter processes. In this research the curcumin group and placebo group indicated a significant lowering of HAM-D and BDI- II after treatment with curcumin compared to the placebo in indicating that there was a therapeutic effect in curcumin against depressive symptoms.

Inflammatory reduction by curcumin is one of the main processes. Patients with depressive disorders have high concentrations of pro-inflammatory cytokines (C-reactive protein, CRP, and Interleukin-6, IL-6) whose lower concentrations can significantly affect the pathophysiology of depression, and curcumin being able to decrease them could directly affect the course of depression. Anti-inflammatory activity of curcumin is documented and probably mediates its neuroprotective properties, decreasing oxidative stress and neuroinflammation by diminishing oxidative stress and neuroinflammation of brain areas linked to mood, namely, hippocampus and prefrontal cortex. Such results are in line with the preclinical data that curcumin has the potential to decrease neuroinflammation and increase neurogenesis, which can underlie its ability to enhance depressive symptoms.

5.2 Potential Synergistic Effect with SSRIs

In all, the association between curcumin and SSRIs seems to induce synergistic effects in treating depression, improving the results of using SSRIs only. The work of SSRIs is serotonin availability in the brain that enhances mood and emotions control. Yet due to the findings of the present study, a large number of patients note the absence of complete symptomatic relief or unsolved symptoms even after taking SSRI on a long-term basis.

The mechanism of action of curcumin in terms known as multifactorial may augment the serotonergic effects of SSRIs in the following ways:

1. Neurotransmitters modulation: Curcumin has been found to influence neurotransmitters serotonin and dopamine that mediates mood disorders. Curcumin may boost similar effects of SSRIs, thereby offering faster and full recovery of symptoms by increasing serotonergic neurotransmission.
2. Inflammation: Flattening of acute low-grade inflammation in depression may exert an adverse effect on the effect of antidepressants. The potential effect of reducing inflammatory cytokines by curcumin (CRP, IL-6, etc.) could also be seen as increasing the effectiveness of SSRI to a problem that they cannot fully combat on their own: an underlying factor to depression.
3. Neuroprotection and New Neurons: Curcumin has functional properties to act neuroprotective which can complement the effects of SSRIs in increasing neuroplasticity which is the neural capacity of the brain to create new neural communication. Hippocampal atrophy is associated with depression and curcumin may reverse some of the brain changes that occur with depression, in addition to the structural changes that SSRIs produce.

5.3 Integrative Psychiatry and Personalized Treatment Methods and Relations

This study provides important results that support the burgeoning role of integrative psychiatry, which involves the use of conventional pharmacotherapy in conjunction with other treatments that are considered as complementary ones which include phytochemicals and nutraceuticals. Curcumin, as a natural product of anti-inflammatory, neuroprotective, and mood-enhancing characteristics, is well suited to the concept of integrative mental well-being.

An application of curcumin supplementation as a personalized treatment approach to MDD has the potential of:

- Combine effects on several pathophysiological processes; e.g., neuroinflammation, neurotransmitter imbalance and neurodegeneration.
- It treats the remaining symptoms that are not completely relieving by SSRIs and enhances the efficacy of treatment and patient satisfaction.
- Reduce side effects: Since it is a natural compound, curcumin can possibly act as a safer substitute or add-on to other prescription drugs, especially to those individuals who cannot habituate to the side effects of the traditional antidepressants.

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It can also assist in optimization of treatment results through personalization of treatment with references to genetic predisposition, comorbidities, and patients preference, which can also be achieved through this integrative approach.

5.4 Strengths and Weaknesses: Reduced Duration of Study, No Long Term Follow Up, One Time Dose Regimen

In spite of the interesting results prepared as a part of the study, several limitations are found:

1. Brief study period: The treatment period of the study was a short one, i.e., 8 weeks, and such a study may not be mutually adequate at determining the long-term responses (i.e. studying the impacts of curcumin on depressive symptoms) or durability of the improvement.
2. No long term follow-up; no prolonged follow up was done to assess whether effects of curcumin are maintained beyond the period they are eradicated or the extent to which it can assist in prevention of relapse post use.
3. Single-dose regimen: The fixed dose of 500 mg of curcumin administered twice daily was used in the study and was not necessarily the right dosage of curcumin to be used in all patients. Optimizing the doses can result in superior outcomes and personalizing the regimens.

5.5 Research Agenda: Future Directions: optimization of dosing, biomarker-directed therapy, long term trials

Any research in the future is to eliminate these limitations by:

1. Dose optimization: Evidence on how much curcumin is needed to effect the most outcome, since highest doses can be even more beneficial. Research can also be conducted on formulations of curcumin that boost its bioavailability and hence be easily absorbed.
2. Biomarker-guided therapy:制Using studies to come up with a regime that will implement biomarker-based therapies where curcumin therapy can be tailored to a specific individual based on the inflammation characteristics. This would enable delivery of more individualized medication against MDD with curcumin being administered to those with high levels of inflammation or neurodegeneration.
3. Longer follow-up: integration of long-term follow-up, to examine the efficacy of long-term maintenance and curcumin and its use in the prevention of relapse in a MDD.
4. Combination therapies: Take further the synergistic potential of curcumin when taken as an adjunct therapy in combination with other treatments like psychotherapy or exercise as a way of offering a broad treatment approach to MDD.

6. Conclusion

This trial examined the efficacy and safety of the riboflavin supplementation with the selective serotonin reuptake inhibitors (SSRI) in the treatment of moderate-to-severe major depression disorder (MDD). The results indicate that curcumin is a quality adjuvant to SSRI with significant improvements in depressive symptoms and inflammatory markers with no harmful effect. These findings can have significant clinical implications on the integrative mental health practice by providing a potential new connection to improving the management of MDD. Nonetheless, this area requires more research to validate and build upon such results by conducting bigger and longer studies. This part provides a conclusion to the study in terms of its main findings, clinical implications, and directions in conducting further research in the field.

6.1 Curcumin: A safe, efficacious adjuvant supplement to unilateral evidence monoaminergic reuptake inhibitors in moderate-to-severe MDD

The findings of the present research establish a strong case in support of the belief that curcumin as a polyphenol agent obtained by Curcuma longa could be considerably useful as a supplementary treatment to SSRIs in patients with moderate-to-severe MDD. Those patients who were supplemented with curcumin along with prescribed SSRI-based treatment were found to have more enhanced depressive symptoms using Hamilton Depression Rating Scale (HAM-D) and Beck Depression Inventory-II (BDI-II). Curcumin group also showed more attributable reductions in inflammatory markers (C-reactive protein (CRP) and interleukin-6 (IL-6)) and this pointed toward the supplementary potential of curcumin to modify depressed inflammatory aspect which SSRI alone might not reach.

Noteworthy, no adverse safety profile is reported in this study about curcumin. There were no major adverse outcomes published and side effect profile was comparable to placebo strengthening the idea of curcumin

tolerability when combined with SSRIs. This elevates the status of curcumin to a potential product that can help in the augmentation of SSRI treatment when used in patients that would not achieve complete remission of their symptoms through the SSRI medication alone or patients that desire complementary adjunct non-pharmacological treatments.

The great reductions in depressive symptoms and inflammation biomarkers hint at the possibility that curcumin can do more than just lift their mood, and which might favour chronic management of depression through resolving the observed inflammation. The results of the study warrant the possibility that curcumin can become an alternative to the treatment of depression as biological and psychological aspects of depression.

6.2 Integrative Mental Health Practice Clinical Implications

The significant clinical implications of the study to integrative mental health activities are that there is a trend towards using complementary therapy to augment the outcomes of standard pharmacotherapy use in integrated mental health practices. The possibilities of the curcumin as an adjunctive therapy in MDD coincide with the idea of the integrative psychiatry focusing on the whole-person approach to mental health issues.

There may be several advantages of curcumin supplementation in integrative program:

Synergy with SSRI: Synergy with SSRIs As observed in this paper, curcumin can be synergistic with SSRIs by augmenting the effects of these drugs on depressive symptoms whilst reducing inflammatory pathways which can inhibit the effect of the medications.

One-to-One Treatments: Incorporating curcumin into treatment regimens of depression may enable individualization of treatment, making a treatment protocol aiming at unique patient characteristics. It is highly beneficial especially to patients who do not respond fully to SSRIs or those who have "side effects with traditional antidepressants".

Non-Pharmacological Complement: curcumin is a natural remedy with anti-inflammatory, antioxidant, and neuroprotective characteristics, which may be used as an addition to traditional antidepressants and psychotherapies in patients not requiring any form of pharmacological treatment.

Relapse: Since curcumin targets neuroinflammation and neurodegeneration, it can help deter relapse or recurrence of depression, particularly in those with persistent or treatment-resistant depressed patients

It can be concluded that the combination of curcumin with traditional medicine used as an integrative mental health practice has a strong foundation to be introduced in the clinical care of MDD patients. Nevertheless, additional clinical trials are needed to dose optimize, establish long term safety, and evaluate curcumin in a variety of patients.

6.3 Greater size and duration of trials required to verify and extend results

Although the findings of this research can be considered positive, a number of limitations should be taken into account. The length of the study was quite small (8 weeks), and no long-term follow-up has been included to determine whether the identified benefits can last even after the curcumin supplement was no longer used. Moreover, the trial used single dose therapy (500 mg twice daily) and future research work would be required to investigate whether other doses and formulation of curcumin would provide better results.

It is also necessary to revert to the larger trials that include more diverse populations to validate the results of the present study. The present sample population of 120 respondents was adequate to detect the change in the primary outcome measures but large scale studies will give more concrete results about the generalizability of the effects of curcumin on various demographies, such as chronic depression patients, comorbidities, or those who have had long-term use of SSRI.

Dose optimization is another area of study that should be employed in the future because the effects of curcumin can differ using various amounts of curcumin or even formulations. The use of biomarker-guided therapy may also be useful to determine the level of patient-centred treatment of curcumin.

Lastly, long term trials to evaluate the effectiveness of the adjunctive use of curcumin to overcome not only in the short run the depressive symptoms but also assist in prevention of depression relapse or recurrence after a long duration should be conducted. Due to the increased length, longer studies would also determine whether any such long-term side effects might occur, as well as any interactions with other medicines.

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Conflicts of interest

The authors have no conflicts of interest to declare

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