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REVIEW

Effect of Tryptophan Restriction in the Therapy of Irritable Bowel Syndrome: a Systematic Review

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Background & Aims: The metabolic pathways of tryptophan (TRP) have been implicated in the pathophysiology of irritable bowel syndrome (IBS), positing that the strategic modulation of TRP consumption may exert regulatory effects on serotonin levels, consequently altering the clinical manifestation of IBS. This systematic review was meticulously orchestrated to evaluate the effect of TRP restriction on IBS.

Methods: A comprehensive search of the MEDLINE/PubMed, Cochrane Library, and Embase databases was conducted. Controlled trials that compared the efficacy of TRP restriction in IBS patients were scrutinized. The primary outcomes were gastrointestinal symptoms, quality of life, and pain, whereas the secondary outcomes included anxiety, mood, and safety. The risk of bias was meticulously assessed according to the guidelines recommended by the Cochrane Collaboration.

Results: A total of five trials, enrolling 135 participants, were incorporated into the qualitative synthesis. Low-TRP intake attenuated gastrointestinal discomfort and enhanced psychological well-being in IBS patients, while the effects of acute TRP depletion were controversial. Safety data from one randomized controlled trial reported no occurrence of adverse events.

Conclusion: This systematic review suggests that moderating, rather than depleting, TRP intake may potentially be a feasible and safe adjunctive treatment for patients with IBS. Future research incorporating a high-quality study design and consensus on clinical outcome measurements for IBS is warranted.

Keywords: irritable bowel syndrome, reduced tryptophan diet, acute tryptophan depletion, systematic review

Introduction

Irritable bowel syndrome (IBS) is a functional bowel disorder with recurrent abdominal pain related to defecation or a change in the frequency or appearance of stool.[1] IBS significantly reduces patients' quality of life and affects 5–10% of the population.[2] However, the pathogenesis remains unclear. Genetics and environmental factors,[3] visceral hypersensitivity,[4] gut microbiota,[5] disorder of gut brain axis[6] may be involved in pathophysiology of IBS.[7] Current treatment modalities for IBS emphasize a symptomatic approach, given the absence of definitive etiological treatments.[8]

Tryptophan (TRP) is an essential amino acid and a precursor to several bioactive compounds, including serotonin, indole, and kynurenine.[9] Serotonin, in particular, is a neurotransmitter that is well established to play a critical role in the regulation of gastrointestinal function, including gut motility and secretion.[10,11] Additionally, increasing evidence has suggested that TRP metabolism is associated with IBS and indicating that modulation of TRP intake presents a potential avenue for influencing serotonin levels and thereby impacting the symptomatology of IBS.[12–17]

The aim of this systematic review is to comprehensively examine the efficacy and safety of TRP restriction as a therapeutic option for patients with IBS by collecting all available literature.

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Methods

Information Sources

Relevant studies were identified by searching PubMed (till June 2024), EMBASE (till June 2024), and the Cochrane Central Register of Controlled trials (Issue 6 of 12, till June 2024).

Search

The search terms used for all databases were as follows: IBS and TRP. The search terms were slightly modified for different databases. In PubMed, the search query was: ("irritable bowel syndrome" [MeSH Terms] OR ("irritable" [All Fields] AND "bowel" [All Fields] AND "syndrome" [All Fields]) OR "irritable bowel syndrome" [All Fields]) AND ("tryptophan" [MeSH Terms] OR "tryptophan" [All Fields] OR "tryptophane" [All Fields] OR "tryptophan s" [All Fields] OR "tryptophanes" [All Fields] OR "tryptophans" [All Fields]). In Embase, the search query was: ("irritable bowel syndrome"/exp OR "irritable bowel syndrome" OR (irritable AND ("bowel"/exp OR bowel) AND ("syndrome"/exp OR syndrome))) AND ("tryptophan"/exp OR tryptophan). In the Cochrane Central Register of Controlled Trials, the search query was: irritable bowel syndrome and tryptophan.

Study Selection

The eligibility criteria were as follows: 1) Controlled trials compared the efficacy and tolerability of TRP restriction in the IBS patients; 2) Patients were diagnosed by Rome criteria;[18] 3) the studies had to report at least 1 of the following primary outcomes: i) Escalation in the mitigation of IBS symptomatic severity, as deduced from self-evaluative rating scales, for example, the IBS–Severity Scoring System (IBS-SSS),[19] ii) Pain or disability metrics, obtained via mechanisms including the Numeric Rating Scale (NRS),[20] or iii) Enhancements in the quality of life or overall well-being, gauged through any validated scale like the Health-Related Quality of Life–Short Form-36 (SF-36).[21] 4) Secondary outcomes featuring i) stress levels, gauged via any substantiated testing parameter, eg, the Cohen Perceived Stress Scale,[22] ii) indices of anxiety, depression, or fatigue, as measured by validated indicators such as the Hospital Anxiety and Depression Scale (HADS)[23] and iii) a discernment of the intervention's safety, determined by the tally of patients reporting adverse events or experiencing side effects.

Data Collection Process

Two independent investigators extracted the data with standardized data extraction forms. Any discrepancies were resolved by consensus. Data on patients, methods, interventions, control interventions, outcomes, and results were extracted independently from the selected studies using standardized data extraction forms.

Risk of Bias in Individual Studies

Two authors independently assessed risk of bias in the RCT studies using the risk of bias tool proposed by the Cochrane Collaboration[24] which includes the following domains: selection bias, performance bias, attrition bias, reporting bias, detection bias, and other bias. Risk of bias was assessed for each criterion as (1) low risk of bias, (2) unclear, and (3) high risk of bias. The quality of non-randomized interventional studies was assessed based on the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool.[25] Any discrepancies were resolved by consensus.

Results

Selection of Studies

A total of 509 studies were identified (Figure 1). Upon reviewing titles and abstracts, 467 studies were excluded. Additionally, 33 duplicate studies were removed. This process left 9 records for full-text examination. After reviewing these articles, 1 unrelated study, 1 review article, 1 comment, and 1 study with insufficient data were excluded. Finally, 5 studies comprising a total of 135 participants were included in the review.[15,26–29]

Study Characteristics (As shown in Table 1).

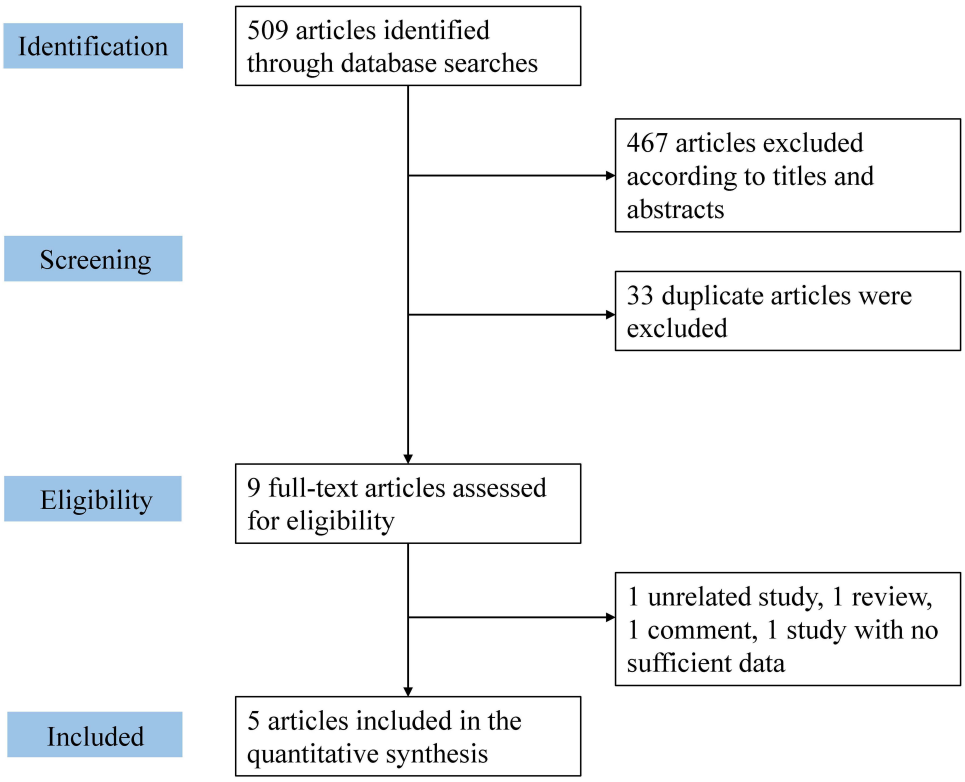

Figure 1 Flowchart of the results obtained from the literature search.

Study Regions and Diagnosis Criteria

Among the included studies, 2 originated from England, 1 from Poland, 1 from Sweden, and 1 from Ireland. The sample sizes of these studies ranged from 14 to 80 participants. IBS patients were diagnosed according to the Rome IV criteria, the Rome III criteria, and the Rome II criteria.

Study Designs

Of the 5 studies, 3 were randomized double-blind crossover studies, 1 was a randomized controlled study, and 1 was a double-blind crossover study. The study conducted by Cezary Chojnacki et al enrolled 80 patients with diarrhea-predominant IBS (IBS-D), who were randomly assigned into two groups of 40 participants each. The control group was instructed to follow a low-FODMAP diet, while the TRP restriction group received the same dietary advice with the additional restriction of TRP intake for 8 weeks. A nutritional calculator from the Kcalmar. Pro-Premium app (Hermex, Lublin, Poland) was utilized to estimate the average daily TRP intake in accordance with the guidelines from the National Institute of Public Health. Patients were provided with a diet specifically tailored to include a pre-calculated TRP content. Throughout the study, patients were continuously supervised by dietitians and meticulously maintained detailed food diaries. Caloric intake and tryptophan intake were analyzed weekly to assess adherence. In the other studies, subjects underwent an acute TRP depletion (ATD) experiment. ATD is a technique used to transiently decrease central and peripheral serotonin levels by administering a mixture devoid of TRP.[30,31] This method allows researchers to observe the effects of reduced serotonin in various neuropsychiatric disorders and provides insight into the role of serotonergic neurotransmission in IBS. In this systematic review, we consider ATD as an extreme form of TRP restriction.

Outcome Measures

Assessment of gastrointestinal symptoms utilized instruments like the Gastrointestinal Symptom Rating Scale for IBS (GSRS-IBS), Visual Analog Scales geared towards GI symptoms (VAS-GI), IBS-SSS and evaluations of visceral

Table 1 Characteristics of Included Studies

Study Year	Study design	Subjects (Sample size, Subtype of IBS; Mean age, sex)	Diagnostic criteria for IBS	Intervention	Duration	Outcome measures	Results	Adverse effects
[26] Chojnacki et al, 2023	Randomized controlled study	80 patients with IBS-D; (Mean age: 44.3 ± 11.4 Sex: 77.5% F, 22.55% M)	Rome IV criteria	Experimental Group: Reduced TRP diet + low-FODMAP diet Control Group: low-FODMAP diet	8 weeks	I. Gastrointestinal symptoms; II. Psychological status; III. TRP and its metabolites	I. A significantly greater improvement was found in the low-TRP diet group (GSRS score: 38.1% vs 49.8%; HAM-A: 38.7% vs 49.9%; HAM-D: 13.8% vs 35.0%; $p < 0.01$). II. 5-HIAA levels, as well as KYN and QA levels, were significantly reduced, while KYNA levels increased in the low-TRP diet group.	The patients did not report any side effects
[27] Kennedy et al, 2015	Double-blind crossover study	9 female patients with IBS (Mean age: 22.78 ± 1.24)	Rome III criteria	An ATD/ATI experiment	1 day	I. Gastrointestinal symptoms; II. Psychological status; III. TRP and its metabolites	I. ATD does not affect these characteristics in IBS-D patients. During ATI, patients with IBS reported greater gastrointestinal symptoms, including bloating. II. ATD significantly decreased plasma kynurenine levels.	N/A
[28] Nieuwenhoven et al, 2012	Randomized double-blind crossover study	14 IBS-D patients	N/A	An ATD/ ATI experiment	N/A	Rectal volume, adaptive relaxation, and compliance	ATD or ATI does not affect these characteristics in IBS-D patients.	N/A
[29] Shufflebotham et al, 2006	Randomized double-blind crossover study	18 IBS patients (10 patients with IBS-D,8 patients with IBS-C; Mean age: 38.1; Sex: 72% F, 28% M);	Rome II criteria	An ATD/ATI experiment	1 day	I. Gastrointestinal symptoms; II. Psychological status; III. TRP	I. Compared with the ATD day, IBS patients reported more gastrointestinal symptoms and less anxiety on the ATI day. II. IBS patients reported less anxiety on the ATI day; however, ATD and ATI did not affect mood. III. TRP concentration was decreased on the ATD day and increased on the ATI day.	N/A
[15] T O C Kilkens et al, 2004	Randomized double-blind, crossover study	14 patients with IBS-D (Mean age: 34.1; sex: 57.14% F, 42.86% M)	Rome II criteria	An ATD experiment	1 day	I. Perception of urge and pain; II. Affective memory performance; Mood; III. TRP and its metabolites	I. ATD significantly lowered the perceptual threshold for first perception; II. ATD induced a significant shift in affective memory bias towards preferential loss of positive material but no significant changes in mood. III. ATD significantly decreased plasma TRP and 5-hydroxyindole acetic acid concentrations.	N/A

Abbreviations: IBS, irritable bowel syndrome; TRP, tryptophan; F, Female; M, Male; GSRS, Gastrointestinal Symptom Rating Scale; HAM-A, Hamilton Anxiety Scale; HAM-D, Hamilton Depression Scale; ATI, Acute tryptophan increase; ATD, Acute tryptophan depletion; N/A, Not accessed.

perception. Psychological assessments incorporated the Hamilton Anxiety Scale (HAM-A), the Hamilton Depression Scale (HAM-D), the Positive and Negative Affect Schedule, the Spielberger State-Trait Anxiety Inventory (STAI-Y1), the Beck Depression Inventory (BDI), and the profile of mood states (POMS). Cognitive appraisal was administered through a memory test.

Outcomes

Gastrointestinal Symptomatology

Chojnacki et al documented a statistically significant improvement in somatic symptoms following the intervention in the group adhering to a TRP-restricted regimen (low-TRP diet). There was a notably greater relative percentage improvement in GSRS scores in the TRP-restricted group (49.8% compared to 38.1%). Additionally, there was a positive correlation between the severity of abdominal symptoms and the average TRP consumption for patients with IBS-D.

In the rest of the studies, ATD was generally employed as the TRP-restricted regimen. For example, Jonathan et al reported exacerbated gastrointestinal symptoms under acute TRP increase (ATI) conditions compared to the ATD condition in participants with IBS. On the other hand, Kilkens et al found that ATD was associated with significant increases in subjective urgency scores at lower pressure thresholds and higher overall pain scores. The perceptual threshold for initial sensation was significantly reduced during ATD compared to placebo (10.6 (1.2) vs 13.6 (0.8) mm Hg), while the thresholds for maximal tolerable discomfort did not show a significant difference (50.5 (3.6) vs 51.6 (3.3) mm Hg). The other two studies reported no impact of ATD on abdominal symptoms in IBS patients.

Psychological Status

Concurrent with improvements in GI symptoms, Chojnacki et al observed a remarkable decrease in psychological distress among the group that adhered to a reduced TRP intake. This group exhibited greater enhancements than the non-restricted cohort, with HAM-A scores at 49.9% compared to 38.7%, and HAM-D scores at 35% versus 13.8%.

In studies employing ATD as a method of TRP restriction, Jonathan et al noted diminished anxiety on the days when TRP was added back (ATI) relative to the ATD condition in subjects with IBS. Kilkens et al discovered that ATD significantly affected affective memory, skewing the retention towards negative rather than positive words, although mood parameters remained statistically unchanged. Kennedy et al did not observe an impact of ATD on psychological status, and Nieuwenhoven et al did not assess psychological status at all.

Biochemical Parameters of TRP Metabolism

In the biochemical context, Chojnacki et al measured urinary TRP and its metabolites, noting a substantial reduction in kynurenine (KYN) and quinolinic acid (QA) levels, coupled with an increase in kynurenic acid (KYNA) levels in the TRP-restricted subset. Urinary TRP concentrations also declined but not to a statistically significant extent. Complementary to these findings, Jonathan et al reported a decrease in total and free plasma TRP levels on the ATD day, with an inverse increase on the ATI day. Correspondingly, Kilkens et al reported that ATD led to a significant reduction in plasma TRP and 5-hydroxyindole acetic acid concentrations.

Safety Considerations

Safety assessment was addressed in a singular study, which reported no adverse effects in IBS individuals adhering to a TRP-restricted diet. However, further rigorously designed trials are imperative to verify the safety profile associated with TRP intake restriction.

Risk of Bias in Individual Studies

Risk of bias in individual studies is shown in Figure 2. None of the RCT studies reported adequate random sequence generation. One of the studies reported adequate allocation concealment. One study is non-blinded experimental design. All the RCTs were free of attrition bias and suspected selective reporting. The ROBIN-I checklist suggested low risk of bias of the non-RCT study included.

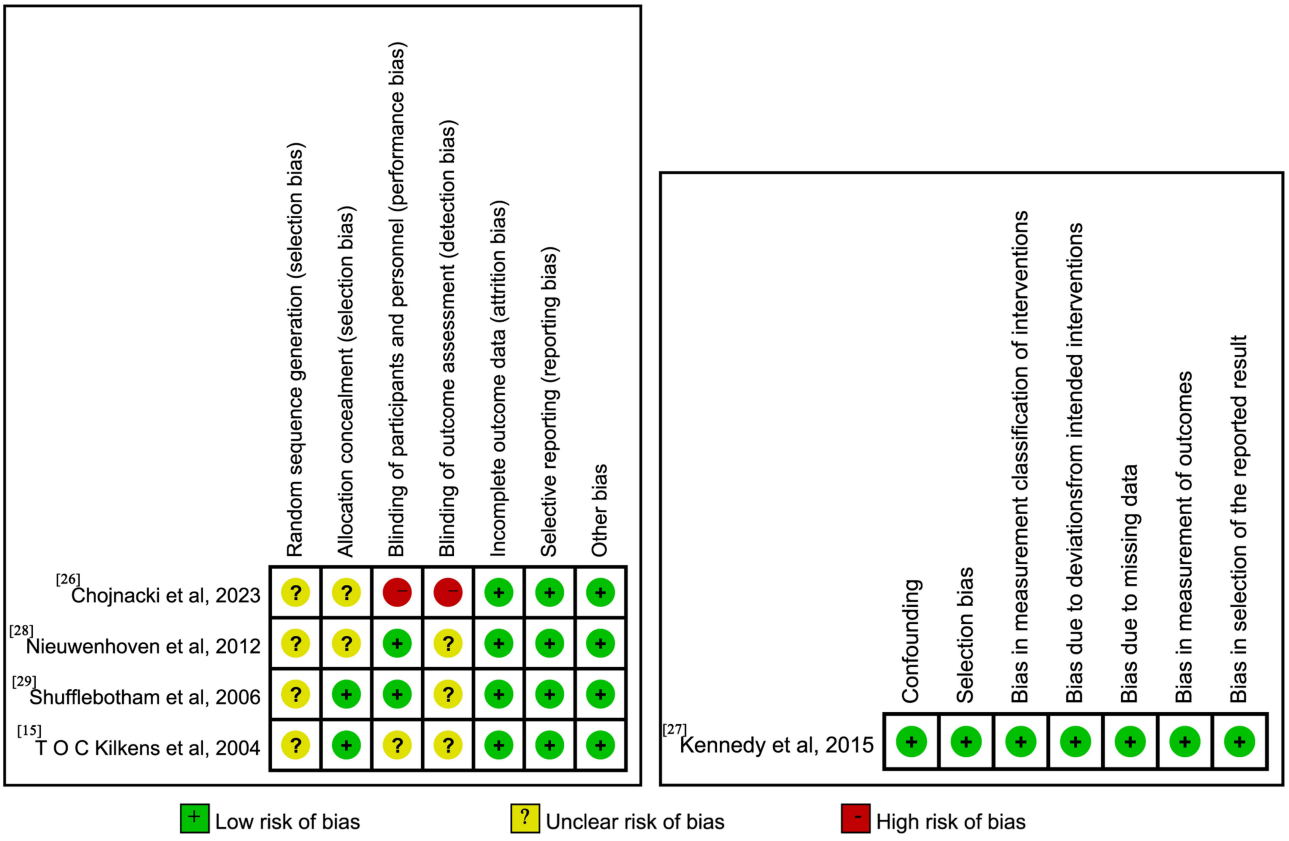

Figure 2 Risk of bias for each criterion for each included study.

Discussion

To the best of our knowledge, this is the first systematic review specifically investigating TRP restriction in IBS. Our findings suggest the notion that restricting TRP intake may lead to a significant reduction in both somatic and mental IBS symptoms.

TRP is metabolized along several pathways: i. The serotonin pathway, in which TRP is converted to serotonin, a neurotransmitter modulating gut motility and secretion.[32] ii. The kynurenine pathway, which generates metabolites involved in regulating immune responses.[33] iii. The indole pathway, where gut microbiota catabolizes TRP into indole and other metabolites, implicated in influencing the gut-brain axis and immune function.[9] Within the gastrointestinal system, TRP metabolism can impact intestinal motility, barrier function, and immune responses, all of which are critical in the pathogenesis of IBS.[34–36]

Serotonin (5-HT) is a critical neurotransmitter and signaling molecule in the gastrointestinal tract, modulating intestinal motility, secretions, and sensitivity, all of which are often dysregulated in IBS.[37] The enterochromaffin cells of the gut mucosa are the primary site of peripheral serotonin production, and it has been observed that IBS patients may have altered mucosal and plasma serotonin levels, with some presenting with increased serotonin synthesis and others with reduced levels, depending on the subtype of IBS.[38,39] The reuptake of serotonin via the serotonin reuptake transporter (SERT) is an important mechanism that terminates its action.[40] Variations in the SERT gene expression and function have been linked with IBS symptoms, indicating that serotonin's activity in the gut could be prolonged or diminished based on atypical SERT functionality.[41] Genetic polymorphisms in SERT have been studied, and some associations with IBS symptomatology have been found, but the results are not consistently replicable, suggesting a multifactorial influence on the disorder.[42–44] Moreover, the diverse range of 5-HT receptor subtypes involved in enteric neurotransmission implies multiple pathways through which serotonin can affect intestinal function.[45] Several receptor subtypes, notably the 5-HT3 and 5-HT4 receptors, are therapeutic targets,[46] with 5-HT3 antagonists being effective at

alleviating symptoms in IBS-D patients[47] and 5-HT4 agonists showing efficacy in treating IBS-C.[48] These treatments lend further credence to the connection between altered serotonergic signaling and IBS pathophysiology.

Thus, TRP restriction may regulate the serotonergic signaling pathway by reducing the synthesis of serotonin, thereby exerting a certain ameliorating effect on IBS symptoms, akin to 5-HT receptor antagonists. However, due to the incompletely elucidated mechanisms of the 5-HT signaling pathway in IBS, the effect of extreme TRP restriction (ATD) on IBS, as indicated by this systematic review, remains contentious. In addition, melatonin, synthesized from 5-HT, is a brain-gut peptide that has protective effects on the gastrointestinal tract and therapeutic effects on IBS.[49] When tryptophan is extremely restricted, the synthesis of melatonin is certainly affected. This may also be a possible reason why extreme tryptophan restriction cannot improve IBS symptoms. The degree to which TRP intake should be restricted may be key to the future clinical application of TRP restriction therapy in treating IBS.

The psychological co-morbidities of anxiety and depression in IBS are well-documented,[50] accentuating the necessity for holistic therapeutic approaches.[2,51] This review reveals nuanced effects of TRP restriction on psychological well-being, with some studies reporting decreased anxiety and depressive symptoms. Serotonin plays a significant role in regulating mood and cognition[52] and can also be the cause of mental disorders, primarily anxiety.[53] This may be one reason why TRP restriction modulates psychological status, particularly in alleviating anxiety. Interestingly, extreme TRP restriction may not effectively alleviate anxiety and could even promote it. These contrasting effects underscore the complexity of TRP's multifaceted role in psychosocial well-being. Therefore, further research is needed to determine how much TRP restriction is necessary to alleviate anxiety or improve the psychological status of IBS patients.

Furthermore, the catabolism of TRP via the kynurenine pathway yields several neuroactive compounds, with KYNA and QA traditionally associated with neuroprotective and neurotoxic effects, respectively.[54,55] KYNA is known for its neuroprotective and anti-inflammatory properties.[56] It antagonizes NMDA receptors,[57] reducing excitotoxicity and oxidative stress,[58] which are beneficial in conditions of inflammation and oxidative damage, such as IBS. By mitigating these harmful processes, KYNA can potentially alleviate IBS symptoms related to inflammation and neurogenic pain. QA is a neurotoxic metabolite that can excessively activate NMDA receptors, leading to excitotoxicity and neuronal damage.[59] Elevated levels of QA are associated with neuroinflammation,[60] which may exacerbate IBS symptoms by promoting gut-brain axis dysregulation. This can result in heightened visceral sensitivity and pain, common features of IBS.[61] KYN itself modulates immune responses and is involved in regulating gut motility.[62] Imbalances in KYN levels can disrupt these processes, potentially contributing to the dysregulated gut motility and sensitivity seen in IBS. In addition, the KYN/TRP ratio was found to be positively correlated with the severity of abdominal complaints,[63] as well as with anxiety and depressive symptoms.[64] The Increase in KYNA and reduction in KYN and QA may be another reason of TRP restriction for alleviating IBS symptoms, concomitant with neuro immunomodulatory mechanisms that are now being linked to the pathogeny of IBS.[65]

The indole pathway, primarily facilitated by gut microbiota, metabolizes tryptophan into various indole derivatives, which have significant implications for gut health and systemic physiology.[66] In this pathway, tryptophan is converted into indole and its derivatives, such as indole-3-acetic acid (IAA), indole-3-aldehyde (IAld), indole-3-propionic acid (IPA), and indole-3-lactic acid (ILA).[67] These metabolites exert diverse biological effects, influencing gut barrier function,[68] immune modulation,[69] and gut-brain axis signaling.[70] For instance, IPA is known for its neuroprotective properties[71] and its role in strengthening the gut barrier by enhancing the expression of tight junction proteins.[72] A compromised gut barrier, or "leaky gut", is a feature observed in IBS patients, which allows for the translocation of luminal antigens that can trigger immune responses and low-grade inflammation.[73] Furthermore, indole metabolites interact with the aryl hydrocarbon receptor (AhR), a ligand-activated transcription factor expressed in various tissues, including the gut.[74] Activation of AhR by IAld and other indoles influences immune responses and maintains intestinal homeostasis by regulating the production of cytokines and antimicrobial peptides.[75] However, while IAA can modulate serotonin production,[76] which is essential for regulating gut motility and visceral sensitivity, its overproduction or imbalance might contribute to the dysregulation of these processes in IBS. Therefore, the indole pathway of tryptophan metabolism produces metabolites that can act as both protective factors and potential risk factors in IBS, depending on their concentrations. This may be one of the reasons why a tryptophan-restricted diet, not depletion, can have an ameliorative effect on IBS. However, it is unfortunate that the studies included in this research did not measure the levels

of indole pathway metabolites. Further research is needed to clarify the role of the indole pathway in the regulation of IBS through a tryptophan-restricted diet.

We acknowledge that our study is not without limitations. The limited number of included studies and the heterogeneity in the quantitative methods used prevented us from conducting a meta-analysis, restricting us to qualitative analysis. Additionally, the small sample sizes and paucity of long-term follow-up data somewhat cloud the robustness of the inferences drawn. In the future, more meticulous, long-term, randomized controlled studies are needed to confirm the effect of TRP restriction on IBS. The safety profile of TRP restriction, though seemingly non-injurious based on available data, calls for a more comprehensive assessment. The idiosyncratic nature of IBS demands personalized therapeutic regimens, with TRP modulation promising but requiring rigorous validation.

Conclusion

In conclusion, our research supports the notion that TRP restriction, not depletion, may ameliorate the symptoms of IBS, indicating that the degree of TRP restriction might determine the therapy's efficacy. Future endeavors to evaluate TRP restriction in IBS must prioritize larger, methodologically robust clinical trials, longitudinal safety evaluations, and the exploration of individualized patient responses. Transparency

Data Sharing Statement

Data sharing is not applicable to this article as it is a systematic review.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that there are no financial or other relationships that might lead to a conflict of interest of the present article.

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